Zuo *et al.*
European Journal of Medical Research (2025) 30:414
https://doi.org/10.1186/s40001-025-02639-8

European Journal of Medical Research

RESEARCH

Open Access

Association of clonal hematopoiesis of indeterminate potential with cardiometabolic multimorbidity progression and mortality: a prospective study of UK Biobank

Chenzhe Zuo[1,2,3], Dihan Fu[2,3,4], Yuanfeng Huang[5,6], Jinchen Li[5,6], Shujun Yang[2,3,4], Xunjie Cheng[2,3,4,7], Guogang Zhang[1,3,4], Tianqi Ma[2,3,4], Qunyong Peng[2,3,7*] and Yu Tan[2,3,4*]

Abstract

Background Clonal hematopoiesis of indeterminate potential (CHIP) is defined as the aging-related clonal expansion of preleukemic mutations in hematopoietic stem cells. While CHIP has been studied in cardiometabolic diseases (CMDs), its role in the long-term progression from the absence of CMD to the development of a single CMD, cardiometabolic multimorbidity (CMM), and eventual mortality remains uncertain. This study aimed to investigate the association between CHIP and gene-specific CHIP subtypes with the progression of CMD transitions.

Methods We included UK Biobank participants without CMD at baseline. The primary outcomes were the first CMD, CMM, and death. We evaluated associations between any CHIP (variant allele fraction [VAF] ≥ 2%), large CHIP (VAF ≥ 10%), and gene-specific CHIP subtypes (*DNMT3 A*, *TET2*, *ASXL1*, *JAK2*, *PPM1D/TP53* [DNA damage genes], and *SF3B1/SRSF2/U2 AF1* [spliceosome genes]) with CMD transitions via multistate model analyses. We estimated multivariable-adjusted hazard ratios (HRs) and 95% CIs with age as the time scale, and adjusted for sex, race, Townsend Deprivation Index, body mass index (BMI), smoking, alcohol, physical activity, sleep duration, and hypertension.

Results The study included 371,544 participants, with a mean age of 56.60 (± 8.03) years, and 44.2% of whom were male (CHIP: *n* = 11,570 [3.1%]; large CHIP: *n* = 7156 [1.9%]). During a median follow-up period of 14.49 years, 54,805 individuals developed at least one CMD, 8090 experienced CMM, and 26,218 died. In the fully adjusted multistate models, CHIP and large CHIP were associated with adjusted hazard ratios (HR) of 1.11 (95% CI 1.07–1.16) and 1.14 (95% CI 1.08–1.20), respectively, for transitioning from a CMD-free condition to a single CMD. The mortality risk associations were strongest, with adjusted HR of 1.45 (95% CI 1.36–1.55) and 1.64 (95% CI 1.52–1.77) for those without CMD, 1.39 (95% CI 1.26–1.54) and 1.59 (95% CI 1.41–1.79) for individuals with single CMD, and 1.58 (95% CI 1.31–1.91) and 1.61 (95% CI 1.29–2.02) for those with CMM. No significant association was observed with CMM development. Gene-specific analyses identified *DNMT3 A*, *TET2*, DNA damage genes, and spliceosome genes as the primary contributors to increased CMD risk. While CHIP showed no association with CMM progression, spliceosome genes were linked to a 1.72-fold higher risk (adjusted HR 1.72, 95% CI 1.14–2.59) of recurrent CMD events. All CHIP subtypes were

*Correspondence:
Qunyong Peng
doctorpqy@163.com
Yu Tan
tanyuu@csu.edu.cn
Full list of author information is available at the end of the article

strongly related to a heightened risk of mortality, with *JAK2* presenting the highest adjusted odds ratio at 6.79 (95% CI 4.12–11.2).

Conclusions CHIP serves as an independent risk factor for transitioning to the first CMD incidence and for mortality but is not associated with CMM development. CHIP-targeted management may represent a promising strategy for the primary prevention of CMD and for reducing mortality risk.

Keywords Cardiometabolic diseases, Clonal hematopoiesis, Multistate model, UK Biobank

Background

Cardiometabolic multimorbidity (CMM) refers to the co-occurrence of two or more cardiometabolic diseases (CMDs), including coronary heart disease (CHD), stroke, and type 2 diabetes (T2D) [1], impacting over a third of the individuals above the age of 60 [2], and significantly reduces quality of life [2, 3]. Compared to individuals with single CMD, those with CMM face a greater risk of all-cause mortality [1] and adverse outcomes [4–6]. Given the growing burden of CMM, it is necessary to investigate the factors that drive the progression of CMD, including specific disease status, as the same exposures may exert differing effects across distinct stages of CMD progression [7], from the absence of CMD to CMD, followed by CMM, and ultimately leading to death. The increase of age remains the primary risk factor for CMD incidence and progression [7–9]. Aging is typically related to chronic, systemic, low-grade inflammation in middle-aged and senior individuals, termed inflammaging. Inflammaging is involved in cardiovascular and metabolic diseases [10, 11], even though the fundamental mechanisms are not fully comprehended.

Clonal hematopoiesis of indeterminate potential (CHIP) is an age-associated condition defined by the expansion of hematopoietic cell clones, driven by mutations in hematopoietic stem cells with a survival advantage [12]. CHIP is prevalent among older individuals, affecting more than 10% of those aged over 70 [12, 13], and CHIP mutations contribute to the increased inflammation associated with aging and age-related diseases [14–16]. CHIP is primarily driven by epigenetic regulators (e.g., *DNMT3 A*, *TET2*, *ASXL1*, and *JAK2*), DNA damage genes (e.g., *TP53* and *PPM1D*), and spliceosome genes (e.g., *SRSF2*, *SF3B1*, and *U2 AF1*) [17]. Emerging evidence highlights that CHIP is connected to the development of specific CMDs in the general population, including CHD [17, 18], T2D [17, 19], and stroke [17, 20]. CHIP is also linked to all-cause mortality [17, 21], an effect that cannot be fully attributed to hematologic cancers alone and may be partly mediated by the increased risk of CMDs [21, 22]. Prior investigations have yielded contradictory outcomes concerning the relationship between CHIP and CMM risk in individuals with one specific CMD. Some research implies that CHIP, particularly involving *DNMT3 A* and *TET2* mutations, is a predictor of recurring vascular events and mortality among those with CHD and stroke [21, 23–25]. This association may be driven by CHIP-mediated enhancement of monocyte/macrophage-related chronic inflammation [26, 27] and accelerated atherosclerosis [28]. However, other studies have reported no relationship between CHIP and recurrent coronary incidents in CHD patients [29]. However, these studies vary in terms of study populations and designs, and systematic research on the connection between CHIP and CMD progression is lacking. Moreover, owing to heterogeneity in CHIP calling and study approaches, the effects of CHIP reported in previous studies are not directly comparable.

Therefore, using data from the UK Biobank, we employed a multistate model to evaluate the role of CHIP in CMD transitions among a cohort of over 371,544 individuals free of CMD at baseline. We evaluated how CHIP and its specific gene subtypes are linked to the progression from a CMD-free state to the development of CMD, subsequent CMM, and eventual mortality.

Methods

Study population

Our research utilized data sourced from the UK Biobank (https://www.ukbiobank.ac.uk/). The UK Biobank is a population-based biomedical database that includes above 500,000 participants across the United Kingdom, aged 40 to 69 years during recruitment from 2006 to 2010 [30]. This study was sanctioned by the North West Multi-Centre Research Ethics Committee, and separate ethical clearance is unnecessary for researchers operating under this approval (updated reference 21/NW/0157, 18 June 2021). Upon receiving informed consent, the participants completed questionnaires, participated in interviews, provided biological samples, and underwent physical measurements to gather phenotypic data. Additionally, the participants provided blood samples for biomarker studies, which encompass array genotyping and whole exome sequencing (WES). Health-related outcomes were derived from electronic health record linkages, with the research conducted through the UK Biobank Resource under project number 84443.

Among the 469,761 participants with available exome sequencing data (Supplemental Fig. 1), individuals were excluded if they (i) were identified as related (closer than third degree relatives; kinship coefficient >0.0884, $n=$ 34,558), (ii) had a prevalent hematologic malignancy ($n=$ 2241), or (iii) were diagnosed with CMD at baseline (definition in Supplemental Table 1, $n=$ 38,133). Participants with missing covariate data ($n=$ 23,312) were also excluded. Finally, 371,544 participants were included.

Exposures

CHIP was identified via blood-derived WES on the Illumina NovaSeq 6000 platform at the Regeneron Genetics Center (Tarrytown, New York, USA) [31, 32]. The

Table 1 Population characteristics according to CHIP status at baseline

Characteristics	Overall	CHIP status	
		No	Yes
Participants, No. (%)	371 544	359 974	11 570
Age (year), mean (SD)	56.60 (8.03)	56.47 (8.04)	60.83 (6.72)
Male, No. (%)	164 273 (44.2)	159 142 (44.2)	5 131 (44.3)
White, No. (%)	353 851 (95.2)	342 672 (95.2)	11 179 (96.6)
Townsend Deprivation Index, median (IQR)	−2.27 (−3.71, 0.25)	−2.27 (−3.71, 0.25)	−2.34 (−3.74, 0.14)
BMI (kg/m^2), mean (SD)	27.13 (4.60)	27.12 (4.61)	27.18 (4.47)
Current smoking, No. (%)	36 946 (9.9)	35 599 (9.9)	1 347 (11.6)
Alcohol consumption frequency ≥ 3 times/week, No. (%)	168 010 (45.2)	162 484 (45.1)	5 526 (47.8)
Regular physical activity, No. (%)	289 705 (78.0)	280 622 (78.0)	9 083 (78.5)
Sleep duration (h/d), mean (SD)	7.15 (1.06)	7.15 (1.06)	7.20 (1.10)
Hypertension history, No. (%)	85 700 (23.1)	82 325 (22.9)	3 375 (29.2)

BMI = body mass index, SD = standard deviation, IQR, interquartile range. Regular physical activity means at least 150 min of walking, moderate activity per week, or 75 min of vigorous activity

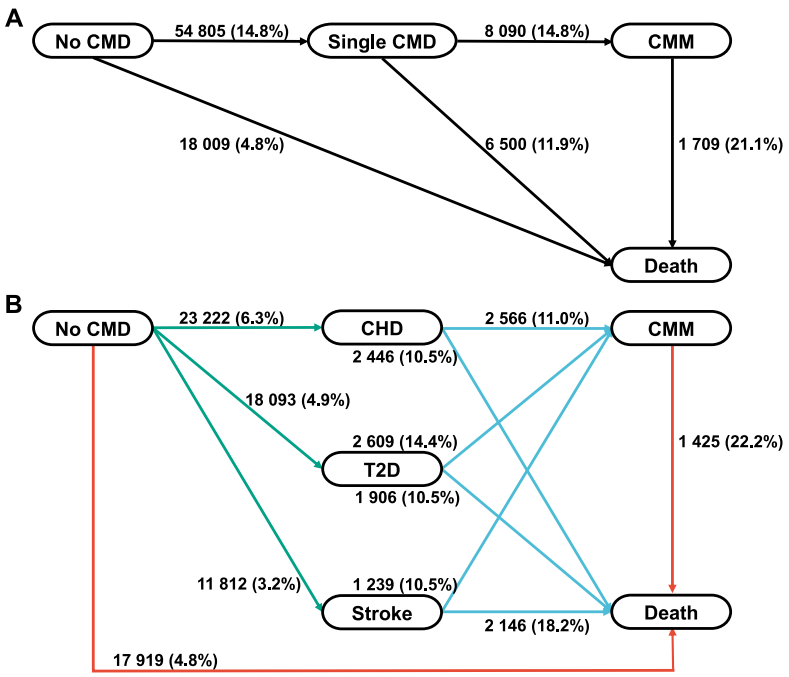

Fig. 1 Graphic schemes of CMD progression in multistate models. The numbers (percentages) of participants experiencing each transition are labeled. **A** Pattern A with 4 states and 5 transitions. A total of 371,544 participants were included in the initial state at baseline. **B** Pattern B, with 6 states and 11 transitions, included 369,776 participants at baseline. No CMD: without CHD, stroke, or T2D. CMD = cardiometabolic disease; CHD = coronary heart disease; CMM = cardiometabolic multimorbidity; T2D = type 2 diabetes

somatic variants were detected with the Genome Analysis ToolKit (GATK) Mutect2 tool [33, 34]. CHIP calling is curated as described previously [31], using a carefully compiled list of 58 genes commonly mutated in healthy individuals and myeloid malignancies (Supplemental Table 2). To decrease false-positive CHIP calls, the variants selected for further analysis met the following criteria: total read depth ≥20, minimum alternate allele depth ≥5, and variant support observed in both forward and reverse sequencing reads. The germline variants and sequencing artifacts were filtered out using methods described earlier [31].

The coprimary study exposures were the presence of any CHIP (defined as a variant allele fraction [VAF] ≥2%) [35] and a large CHIP (VAF ≥10%), as previous research indicates that CHIP variants over this threshold are more significantly connected with clinical outcomes [21, 36]. Additionally, we conducted a separate analysis of the most common gene-specific CHIP subtypes, each present in more than 10 cases across different CMD transitions, involving both any and large clones (VAF ≥10%): *DNMT3 A*, *TET2*, *ASXL1*, *JAK2*, DNA damage genes (*TP53* and *PPM1D*), and spliceosome genes (*SRSF2*, *SF3B1*, *U2 AF1*). We also assessed individuals carrying multiple CHIP variants, defined as the presence of two or more CHIP variants from the same or different genes. The VAF of multiple CHIP clones was determined based on the largest clone. The secondary analyses separately evaluated individuals with multiple CHIP (VAF ≥2%) and those with multiple large CHIP (VAF ≥10%).

Outcomes

CMD events were identified based on records of diagnoses and surgeries for inpatients (Supplemental Table 1). For each participant having specific CMD, we compare the initial recorded diagnosis date to their recruitment date to determine if the disease was present at baseline or developed during the follow-up period. Individuals who developed two or more CMDs were categorized as CMM. The dates of the initial and second CMD occurrences were used to determine first CMD and CMM, respectively. The occurrences and dates of mortality were confirmed through linkages to the National Health Service (NHS) Information Centre in England and Wales and the NHS Central Register in Scotland (latest follow-up: April 2022).

Covariates

Information on demographics (age, sex, race, and Townsend Deprivation Index), clinical factors (body mass index [BMI] and history of hypertension), and lifestyle factors (smoking status, frequency of alcohol use, physical activity levels, and sleep duration) were assessed via touchscreen questionnaires, verbal interviews, physical measurements, and diagnosis records from the UK Biobank. The Townsend Deprivation Index, reflecting the level of material deprivation within a specific area, is an official score corresponding to the output area of their post-code location, where higher values indicate greater deprivation [37]. BMI (kg/m^2) was obtained by dividing the weight (kg) by the square of height (m^2). Physical activity levels were considered to meet the 2017 UK Physical Activity Guidelines [38] if participants reported at least 150 min of walking or moderate activity weekly, or at least 75 min of vigorous activity each week. The baseline hypertension history was confirmed through the patients' diagnosis records (Supplemental Table 1).

Statistical analysis

The participants were categorized on the basis of CHIP status. Categorical variables are reported as counts (percentages, %), and continuous variables are reported as the mean/median (standard deviation [SD]/interquartile range [IQR]).

Age was used as the time scale in subsequent analyses [39]. The primary analyses were performed to test the association of CHIP with CMD progression. We used two model settings: initial models adjusted for sex and race and fully adjusted models further accounting for the Townsend deprivation index, BMI, smoking status, alcohol consumption frequency, physical activity level, sleep duration, and baseline hypertension.

First, we utilized a multistate model to evaluate the associations between CHIP and risk in all transitions from a healthy state to the first CMD, CMM, and death (Fig. 1). The multistate model extends competing risk models by analyzing not only single events but also transitions across multiple stages, capturing the dynamics of both intermediate and terminal states, which makes it ideal for complex event processes [40]. Starting with no CMD (initial state) and ending with mortality (absorbing state), we outlined five transitions in pattern A (Fig. 1A): (i) transition from no CMD to a single CMD; (ii) transition from no CMD to death; (iii) transition from a single CMD to CMM; (iv) transition from a single CMD to death; and (v) transition from CMM to death. To determine if CHIP's role was specific to particular diseases, we substituted the CMD state with 3 separate states: CHD, stroke, and T2D, creating multistate model pattern B with 11 potential transitions (Fig. 1B). Second, the Cox proportional hazards model was used to simulate transitions in the multistate model and evaluate the associations between CHIP and the first CMD, CMM, and mortality (details in Supplemental Methods). The proportional hazards assumption was verified via Kaplan–Meier curves (Supplemental Fig. 2). Third,

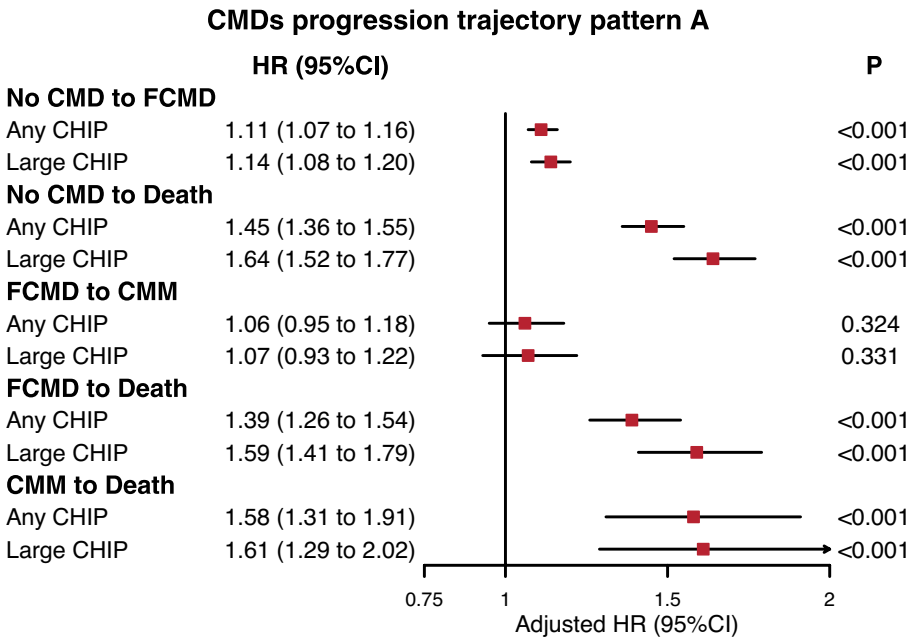

Fig. 2 Associations between CHIP and the CMD progression in multistate model pattern A. In all models, age was included as the time scale. All models represent multistate models in which participants without CHIP ($n = 359,974$) constitute the reference group. The models were adjusted for sex, race, Townsend Deprivation Index, body mass index, smoking status, alcohol consumption frequency, meeting physical activity guidelines, sleep duration, and hypertension at baseline. CHIP = clonal hematopoiesis of indeterminate potential; CI = confidence interval; FCMD = first cardiometabolic disease; CMM = cardiometabolic multimorbidity; HR = hazard ratio

to directly compare the risk levels of the baseline CHIP status for CMD, CMM, and death, we developed a multicategory outcome variable with four non-overlapping endpoint events: no events, single CMD, CMM, and death. The associations between CHIP and the multicategory outcome variable were analyzed using multinomial regression, which extends logistic regression to handle dependent variables with multiple categories. As disease dates were recorded on the basis of observation rather than exact onset, individuals could theoretically transition to two states simultaneously. We set the theoretical previous state as the recorded time point minus 0.5 days [41]. However, in multistate model pattern B, participants who were diagnosed with two or more CMDs at the same time were excluded because the sequence of disease onset is indeterminate.

The sensitivity analyses were performed to test the robustness of the findings. First, the participants who reported CMD or passed away in the first 2 years of follow-up were excluded to minimize potential reverse causality. Second, to address possible remaining confounding factors, the analytic models were further adjusted for total cholesterol, high-density lipoprotein (HDL) cholesterol, and the use of cholesterol-lowering drugs. The use of cholesterol-lowering drugs was recorded at baseline. The collection and processing techniques for the baseline blood samples, including total and HDL cholesterol measurement, have been described previously [42]. Third, the participants who simultaneously transitioned to two different states were not included. Fourth, for participants with overlapping states, the date was adjusted by subtracting 1.0 day. Finally, we investigated the continuous association between VAF and CMD progression. The VAF was set to 1% in those without CHIP and capped at 25% for CHIP, and hazard ratios were estimated for a 10% increase in VAF. The threshold for setting VAF as a continuous variable has been described elsewhere [43].

Additionally, we tested interaction terms (CHIP/large CHIP × age/sex) within the models and performed stratified analyses by sex (male vs. female) and age group (< 60 vs. ≥ 60 years) to further validate the robustness of the associations.

All analyses were performed via R software (version 4.3.1), with the mstate package used for multistate model construction [44]. A two-sided P value of < 0.05 was considered of statistically significance.

Results

CHIP frequency and baseline characteristics

The final study sample included 371,544 individuals, of whom 11.570 (3.1%) had CHIP with VAF ≥ 2% and 7156 (1.9%) had CHIP with VAF ≥ 10%. Supplemental Table 2 shows the distribution of CHIP driver variants among the participants. The most common driver was *DNMT3*

A (n = 7259; 62.7% of CHIP carriers), followed by *TET2* (n = 1859; 16.1%), *ASXL1* (n = 1139; 9.8%), DNA damage genes (*TP53* and *PPM1D*; n = 571; 4.9%), spliceosome genes (*SRSF2*, *SF3B1*, and *U2 AF1*; n = 342; 3.0%), and *JAK2* (n = 86; 0.7%). Among the 11,570 CHIP carriers, 597 (5.2%) had mutations in more than one driver gene.

Table 1 shows the baseline characteristics of the participants. The mean age when DNA samples were collected was 56.60 years. Among the participants, 164,273 (44.2%) were male and 353,851 (95.2%) were white. Compared with individuals without CHIP, CHIP carriers tended to be older, predominantly White, less socioeconomically deprived, and are more prone to being current smokers. Additionally, CHIP carriers had greater alcohol consumption, longer sleep duration, and a greater prevalence of preexisting hypertension. According to Supplemental Table 3, baseline characteristics were comparable between participants with CHIP and VAF < 10% and those with VAF ≥ 10%.

During a median follow-up duration of 14.49 years, 54,805 participants (14.8%) experienced CMD, and 18,009 (4.8%) died without CMD. Of those with CMD, 8090 developed CMM, while 6500 died from a single CMD and 1709 died with CMM (Fig. 1A). Upon examining particular diseases, 23,222 (6.3%) participants experienced CHD, 18,093 (4.9%) developed T2D, and 11,811 (3.2%) experienced stroke as their first event (Fig. 1B).

CMD progression analysis

CHIP was associated with the progression of CMD and mortality (Fig. 2). The strongest associations were observed in transitions leading to death in multistate models. Supplemental Table 4 shows that in the fully adjusted multistate models, CHIP carriers had a 45% higher risk of death in those without CMD (adjusted hazard ratio [HR] 1.45, 95% CI 1.36–1.55), 39% in those with a single CMD (adjusted HR 1.39, 95% CI 1.26–1.54), and 58% in those with CMM (adjusted HR 1.58, 95% CI 1.31–1.91). Large CHIP was related to a 64% increased risk of transitioning from no CMD to death and a 59% increased risk from single CMD to death, respectively (adjusted HR 1.64, 95% CI 1.52–1.77; adjusted HR 1.59, 95% CI 1.41–1.79, respectively). CHIP carriers without CMD were at a slightly higher risk of experiencing their first CMD (adjusted HR 1.11, 95% CI 1.07–1.16). Those with large CHIP had a 14% higher risk of developing their first CMD (adjusted HR 1.14, 95% CI 1.08–1.20). Supplemental Table 5 presents the Cox regression results for CHIP-associated CMD transitions. Aligning with the result in multistate models, CHIP carriers showed a 1.41-fold elevated risk of mortality from no CMD (adjusted HR 1.41, 95% CI 1.34–1.48). The Cox regression analysis also reveals a 1.25-fold higher risk of death progressing from a single CMD at baseline (adjusted HR 1.25, 95% CI 1.12–1.39), consistent with the multistate model findings of a 39% increased risk for the same transition (adjusted HR 1.39, 95% CI 1.26–1.54). Large CHIP was associated with even higher risk, particularly in mortality from no CMD (adjusted HR 1.59, 95% CI 1.50–1.69). These findings are consistent with the trends observed in multistate models.

In analyses focusing on particular CMDs, CHIP was linked to all transitions to the initial specific CMDs and all transitions leading to death, with the strongest association observed in death-related transitions (Fig. 3). In the fully adjusted multistate models, CHIP was related to 1.11-fold higher risk of developing first CHD (adjusted HR 1.11, 95% CI 1.04–1.19), 1.14-fold of first T2D (adjusted HR 1.14, 95% CI 1.06–1.23), and 1.11-fold of first stroke (adjusted HR 1.11, 95% CI 1.02–1.21) among all CMDs. In comparison, large CHIP was associated with higher increased risks of first CHD and first stroke development. Further, CHIP was associated with a 44% increased risk of death in individuals with CHD (adjusted HR 1.44, 95% CI 1.23–1.70), a 40% increased risk in those with T2D (adjusted HR 1.40, 95% CI 1.15–1.70), a 30% increased risk in those with stroke (adjusted HR 1.30, 95% CI 1.08–1.56), and a 56% increased risk in those with CMM (adjusted HR 1.56, 95% CI 1.27–1.92). Large CHIP was associated with a comparable or slightly higher risk. The detailed results for pattern B are presented in Supplemental Table 6.

Gene-specific analyses in the multistate model revealed that CHIP subtypes were primarily associated with transitions from a CMD-free state to single CMD, and transitions from having no CMD or a single CMD to mortality (Table 2), with similar trends observed in Cox regression models (Supplemental Table 7). The most prevalent subtype, *DNMT3 A* CHIP, was related to transitions from no CMD to one CMD, from no CMD to mortality, and from one CMD to mortality, similar to *TET2* CHIP and DNA damage genes, as shown by multistate analyses. Large *DNMT3 A*, *TET2*, and DNA damage gene CHIP subtypes were associated with even higher risks for these transitions. *ASXL1* CHIP was associated with higher mortality risk developing from no CMD or single CMD. *JAK2* CHIP carriers had a 5.73-fold greater risk of death in individuals without CMD (adjusted HR 5.73, 95% CI 3.84–8.55), which was the highest among all CHIP subtypes and the highest risk according to the Cox regression model. Spliceosome genes were the only gene-subtype that associate with all transitions. The spliceosome genes were related to a 72% increased risk of the transition from single CMD to CMM (adjusted HR 1.72, 95% CI 1.14–2.59), and were related to the highest risks with single CMD development (adjusted HR

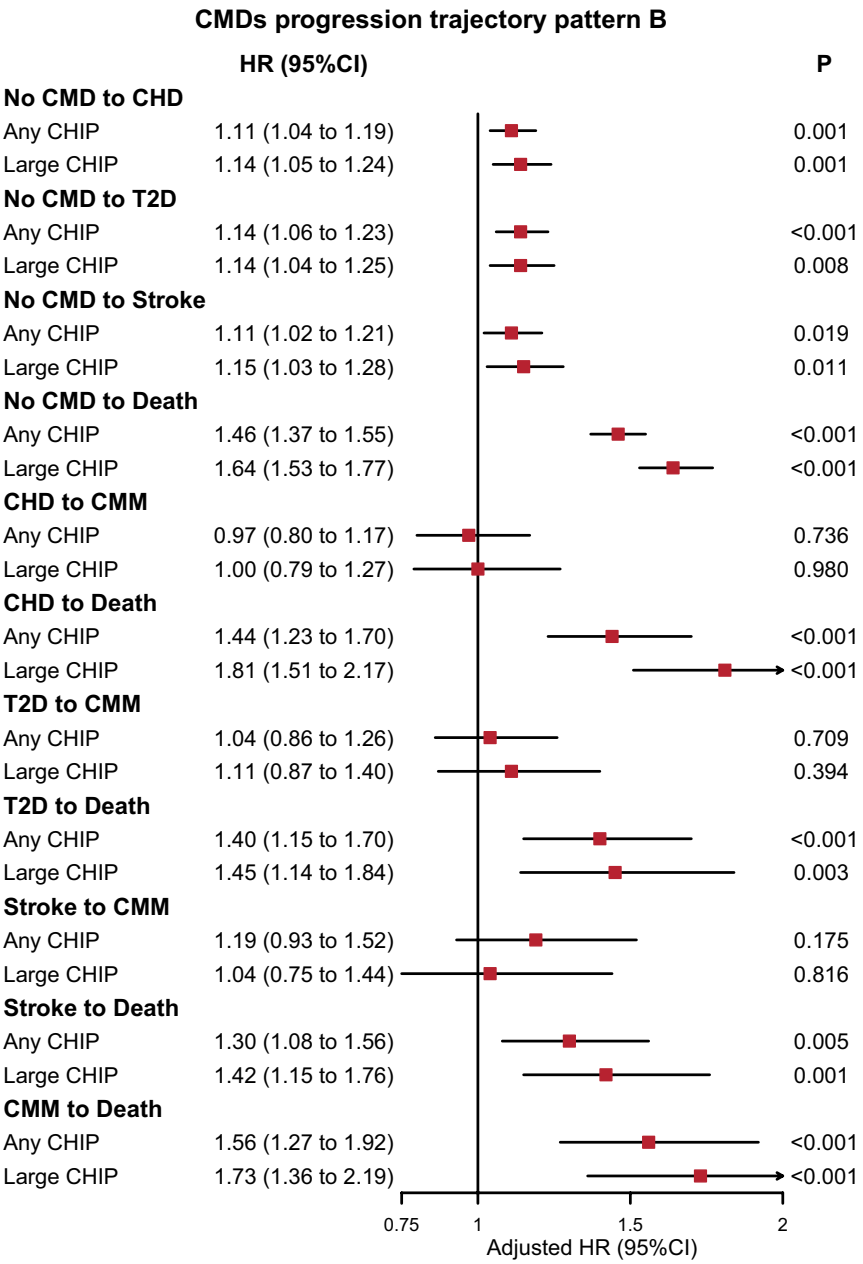

Fig. 3 Associations between CHIP and the CMD progression in multistate model pattern B. In all models, age was included as the time scale. All models represent multistate models in which participants without CHIP (n = 358 271) constitute the reference group. The models were adjusted for sex, race, Townsend Deprivation Index, body mass index, smoking status, alcohol consumption frequency, meeting physical activity guidelines, sleep duration, and hypertension at baseline. CHD = coronary heart disease; CHIP = clonal hematopoiesis of indeterminate potential; CI = confidence interval; CMM = cardiometabolic multimorbidity; HR = hazard ratio; T2D = type 2 diabetes

1.67, 95% CI 1.38–2.02), with death following first CMD (adjusted HR 3.46, 95% CI 2.53–4.72), and with death after CMM (adjusted HR 3.66, 95% CI 2.16–6.22). Carriers of any and large multiple CHIP mutations had a 116% and 199% higher risk of death following CMM, respectively. Gene-specific analyses of CHIP via Cox regression models yielded similar results (Supplemental Table 7). *ASXL1* CHIP was the only subtype associated with a greater risk of death from CMM (adjusted HR 1.74, 95% CI 1.16–2.61). *JAK2* CHIP remained the strongest predictor of death without CMD (adjusted HR 4.69, 95% CI 3.28–6.71).

Table 2 Association of gene-specific CHIP subtypes with CMDs progression in multistate model pattern A

	Any CHIP ($n = 11,570$)				CHIP with VAF ≥ 10% ($n = 7156$)			
	Model 1[a]		Model 2[b]		Model 1[a]		Model 2[b]	
	HR (95% CI)	*p*	HR (95% CI)	*p*	HR (95% CI)	*p*	HR (95% CI)	*p*
No CMD → FCMD								
DNMT3 A	1.08 (1.02, 1.14)	0.009	1.07 (1.01, 1.13)	0.018	1.07 (0.99, 1.15)	0.100	1.06 (0.98, 1.14)	0.126
TET2	1.15 (1.04, 1.28)	0.007	1.12 (1.01, 1.24)	0.028	1.23 (1.10, 1.38)	< 0.001	1.22 (1.08, 1.37)	0.001
ASXL1	1.16 (1.03, 1.32)	0.017	1.06 (0.94, 1.20)	0.333	1.12 (0.95, 1.31)	0.166	1.01 (0.86, 1.18)	0.934
JAK2	1.25 (0.78, 2.01)	0.356	1.33 (0.83, 2.15)	0.234	1.25 (0.78, 2.01)	0.356	1.33 (0.83, 2.15)	0.234
DNA damage genes	1.37 (1.16, 1.62)	< 0.001	1.30 (1.10, 1.54)	0.002	1.41 (1.14, 1.73)	0.001	1.33 (1.08, 1.64)	0.007
Spliceosome genes	1.70 (1.40, 2.05)	< 0.001	1.67 (1.38, 2.02)	< 0.001	1.85 (1.51, 2.27)	< 0.001	1.83 (1.49, 2.24)	< 0.001
No CMD → Death								
DNMT3 A	1.24 (1.13, 1.35)	< 0.001	1.21 (1.11, 1.32)	< 0.001	1.36 (1.21, 1.52)	< 0.001	1.33 (1.19, 1.49)	< 0.001
TET2	1.48 (1.27, 1.72)	< 0.001	1.49 (1.28, 1.73)	< 0.001	1.68 (1.42, 1.98)	< 0.001	1.72 (1.46, 2.03)	< 0.001
ASXL1	2.04 (1.74, 2.39)	< 0.001	1.80 (1.53, 2.11)	< 0.001	2.31 (1.92, 2.77)	< 0.001	2.01 (1.67, 2.42)	< 0.001
JAK2	5.34 (3.58, 7.97)	< 0.001	5.73 (3.84, 8.55)	< 0.001	5.34 (3.58, 7.97)	< 0.001	5.73 (3.84, 8.55)	< 0.001
DNA damage genes	2.09 (1.67, 2.63)	< 0.001	2.06 (1.64, 2.58)	< 0.001	2.20 (1.66, 2.91)	< 0.001	2.12 (1.61, 2.81)	< 0.001
Spliceosome genes	3.48 (2.78, 4.36)	< 0.001	3.36 (2.69, 4.21)	< 0.001	3.93 (3.10, 4.97)	< 0.001	3.81 (3.00, 4.82)	< 0.001
FCMD → CMM								
DNMT3 A	1.03 (0.90, 1.19)	0.652	1.03 (0.89, 1.19)	0.663	1.01 (0.83, 1.23)	0.931	1.01 (0.83, 1.22)	0.955
TET2	1.20 (0.93, 1.55)	0.164	1.19 (0.92, 1.53)	0.193	1.25 (0.94, 1.67)	0.130	1.25 (0.93, 1.66)	0.138
ASXL1	1.32 (1.00, 1.76)	0.054	1.23 (0.93, 1.64)	0.150	1.44 (1.00, 2.06)	0.047	1.32 (0.92, 1.89)	0.128
JAK2	–	–	–	–	–	–	–	–
DNA damage genes	0.63 (0.37, 1.09)	0.101	0.61 (0.35, 1.05)	0.075	0.84 (0.47, 1.52)	0.565	0.83 (0.46, 1.50)	0.534
Spliceosome genes	1.73 (1.15, 2.61)	0.009	1.72 (1.14, 2.59)	0.009	1.75 (1.14, 2.69)	0.010	1.74 (1.14, 2.68)	0.011
FCMD → Death								
DNMT3 A	1.21 (1.05, 1.40)	0.010	1.18 (1.02, 1.36)	0.026	1.34 (1.11, 1.61)	0.002	1.30 (1.08, 1.56)	0.006
TET2	1.89 (1.51, 2.36)	< 0.001	1.90 (1.52, 2.38)	< 0.001	2.11 (1.66, 2.70)	< 0.001	2.15 (1.69, 2.75)	< 0.001
ASXL1	1.58 (1.19, 2.09)	0.001	1.45 (1.09, 1.92)	0.010	2.04 (1.47, 2.84)	< 0.001	1.87 (1.35, 2.60)	< 0.001
JAK2	–	–	–	–	–	–	–	–
DNA damage genes	1.53 (1.04, 2.25)	0.031	1.43 (0.97, 2.10)	0.070	1.87 (1.21, 2.91)	0.005	1.73 (1.11, 2.68)	0.015
Spliceosome genes	3.57 (2.61, 4.87)	< 0.001	3.46 (2.53, 4.72)	< 0.001	3.41 (2.45, 4.76)	< 0.001	3.30 (2.36, 4.60)	< 0.001
CMM → Death								
DNMT3 A	1.52 (1.18, 1.97)	0.001	1.51 (1.17, 1.95)	0.002	1.54 (1.10, 2.15)	0.012	1.50 (1.07, 2.10)	0.018
TET2	1.32 (0.83, 2.10)	0.242	1.34 (0.84, 2.14)	0.215	1.44 (0.87, 2.40)	0.157	1.49 (0.89, 2.48)	0.126
ASXL1	1.55 (0.96, 2.50)	0.074	1.48 (0.91, 2.38)	0.112	–	–	–	–
JAK2	–	–	–	–	–	–	–	–
DNA damage genes	–	–	–	–	–	–	–	–
Spliceosome genes	3.37 (1.99, 5.72)	< 0.001	3.66 (2.16, 6.22)	< 0.001	3.66 (2.11, 6.33)	< 0.001	4.00 (2.30, 6.94)	< 0.001

CHIP subtypes observed in fewer than 10 cases are excluded from the analysis. In all models, age was included as the time scale. All models represent multistate models in which participants without CHIP (n = 359 974) constitute the reference group. DNA damage genes include *TP53* and *PPM1D*. Spliceosome genes include *SRSF2*, *SF3B1*, and *U2 AF1*. CHIP = clonal hematopoiesis of indeterminate potential; CI = confidence interval; FCMD = first cardiometabolic disease; CMM = cardiometabolic multimorbidity; HR = hazard ratio; VAF, variant allele frequency

[a] Model 1: adjusted for sex and race

[b] Model 2: further adjusted for Townsend Deprivation Index, body mass index, smoking status, alcohol consumption frequency, meeting physical activity guidelines, sleep duration, and hypertension at baseline

Multinomial logistic analysis

In the multinomial logistic regression, we established a multicategory outcome variable consisting of four distinct events: no events ($n = 298,730$; 80.4%), only CMD ($n = 40,215$; 10.8%), CMM ($n = 6381$; 1.7%), and death ($n = 26,218$; 7.1%). Compared to non-CHIP individuals, those with CHIP had a 6% increased odds of CMD incidence (Supplemental Table 8). The associations between

both any CHIP and large CHIP and all-cause mortality were robust (any CHIP-related odds ratio [OR] 1.46, 95% CI 1.37–1.54; large CHIP-related OR 1.67, 95% CI 1.56–1.79).

Gene-specific multinomial logistic regression analyses revealed strong associations between all CHIP subtypes and death (Supplemental Table 9). Consistent with the multistate analyses, *JAK2* ranks highest among all gene subtypes in the odds of all- cause mortality (adjusted OR 6.79, 95% CI 4.12–11.2). DNA damage genes were associated with 1.47-fold increased odds of incident CMD (adjusted OR 1.47, 95% CI 1.16–1.85). No gene-specific CHIP subtype was associated with the odds of CMM.

Sensitivity analyses

Supplemental Tables 10 and 11 display the outcomes of the sensitivity analyses. After removing 7378 participants who either reported CMDs or died within the initial 2 years of follow-up, further adjusting for total cholesterol, HDL cholesterol, and the use of cholesterol-lowering medications, excluding 2119 participants who simultaneously transitioned to two states, or altering the date calculation for participants whose time points overlap (analysis 1–4), the results remained consistent with those of the primary analyses. In analysis 5, the adjusted HRs for each CMD transition per 10% increase in CHIP clone size were 1.06 (95% CI 1.03–1.09), 1.24 (95% CI 1.19–1.29), 1.01 (95% CI 0.94–1.09), 1.21 (95% CI 1.13–1.29), and 1.36 (95% CI 1.20–1.54), respectively (Supplemental Table 12).

Stratification analysis

As shown in Supplemental Table 12, we conducted stratified analyses of the multistate model by sex and age. Among the five CMD transitions, an increased risk of death without CMD was observed in younger participants ($P_{\text{interaction}} = 0.016$) and in males ($P_{\text{interaction}} = 0.039$). These associations remained in individuals with large CHIP ($P_{\text{interaction}} = 0.035$ and 0.004, respectively). However, the associations between CHIP and other CMD transitions were not significantly different when patients were stratified by sex and age.

Discussion

Our findings suggest that CHIP independently contributes to CMD progression in middle-aged and older individuals, with its relationship with disease-specific transitions varying from CHD to stroke to T2D. These results were validated via multistate and Cox proportional hazards models and further assessed via multinomial logistic regression. We observed increased risks of CMD incidence and mortality, which were greater in individuals with larger CHIP clones, with the strongest association observed in mortality from CMM (adjusted HR 1.58, 95% CI 1.31–1.91; Supplemental Table 4). The gene-specific analyses revealed that mutations in *DNMT3 A*, *TET2*, DNA damage genes, and spliceosome genes were primarily responsible for the increased risk of CMD, with all variants strongly associated with mortality.

Our results align with those of previous studies on the relationship between CHIP incidence and the incidence of CMD alone. The population-based studies have shown that CHIP increases the risk of CHD [17, 45], stroke [17, 46–48], and T2D [17, 22]. The most recent meta-analysis by Singh et al. included 88 original studies and reported a 1.76-fold and 1.16-fold risk of CHD and stroke associated with CHIP, respectively [49]. Tobias, D.K. et al. reported an HR of 1.23 (95% CI 1.03, 1.46) for T2D risk related to CHIP by combining six prospective cohorts among 17,637 participants [22]. Similarly, our results in multistate model pattern B (Supplemental Table 6) revealed that participants with CHIP had 11, 11, and 14% higher risks of new-onset CHD, stroke, and T2D, respectively. Our findings differed slightly from those of previous studies regarding the impact of CHIP on the development of the first CMD, which could be attributed to changes in baseline characteristics, cohort composition [50, 51], and CHIP calling parameters [31]. Specifically, our main analyses excluded participants with CMD at baseline. Also, the UK Biobank population may not fully represent the general population, as the "healthy volunteer" effect could have led to an overrepresentation of healthier individuals [50]. Together, these factors suggest that our findings may be understated. Additionally, we employed a more stringent CHIP calling approach that filters variants with a minimum allele depth of ≥ 5 [31] than the criteria employed by Tobias et al. [22], which filter CHIP by a minimum allele depth of ≥ 3 and define CHIP as a VAF $\geq 10\%$ in the primary study.

Furthermore, we emphasize the critical role of CHIP in mortality risk among individuals with no CMD, a single CMD, or two or more CMDs. Our results for multistate model pattern A (Fig. 2) revealed that CHIP was associated with a 45% greater risk of death in individuals without CMD, a 39% greater risk in single CMD participants, and a 1.58-fold greater risk of death in those with CMM. The findings from multistate model pattern B showed a multivariable-adjusted CHIP-related 1.44-fold, 1.40-fold, and 1.19-fold higher risks of mortality developing from CHD, T2D, and stroke. These findings are consistent with population-based studies showing a relationship between CHIP and increased death risk [17, 21, 23, 24, 29]. A recent meta-analysis reported a 1.34-fold increased risk of all-cause mortality associated with CHIP [49], and the mortality risk in populations with incident CHD or ischemic stroke ranged from 1.11-fold to 1.28-fold [21,

23, 29]. Specifically, a study investigating the prognostic role of *DNMT3 A* and *TET2* mutations demonstrated a 1.967-fold increased risk of death among 485 patients with a history of ST-segment elevation myocardial infarction[24]. In support of the role of *DNMT3 A* and *TET2* mutations in mortality risk in CHD patients, our findings revealed that *DNMT3 A* and *TET2* were associated with a 18% and 90% increased risk of death in those with a single CMD, respectively (Table 2). Overall, our results highlight the predictive role of CHIP in mortality, regardless of CMD status.

Although CHIP is significantly associated with the incidence of single CMD and mortality risk across different disease states, we did not observe similar associations between CHIP and the transitions with CMM as the outcome. Notably, spliceosome genes were the only CHIP subtype linked to the risk of recurrent CMD incidence, with mutations in *SF3B1* and *SRSF2* likely contributing to this association through their role in increased inflammation [52, 53]. The role of CHIP in the transition from a single CMD to a CMM remains controversial. Some research in individuals with stroke or CHD indicates no significant association between CHIP and recurrent vascular events [25, 29, 54], including nonfatal stroke and myocardial infarction, which supports our findings that CHIP is not associated with CMM incidence. The lack of significant association between CHIP and CMM progression may suggest that systemic inflammation driven by CHIP predominantly accelerates the primary onset of CMDs rather than contributing to multimorbidity. Indeed, CMD patients often receive medical treatments that could potentially modulate the effects of CHIP [55]. Additionally, the presence of competing mortality risks in CMD patients might attenuate the observed risks on CMM progression. On the basis of the previous work of Singh-Manoux et al. [7], which suggested a changing role of risk factors across the CMD progression trajectory, it was rational that CHIP-related adverse effects were transition specific. However, a few other studies have shown a CHIP-related risk of recurrent cardiovascular events (HR 1.24, 95% CI 1.08–1.43) [21], as well as *DNMT3 A*- or *TET2*-related incident CMD in CHD patients [24, 25]. Therefore, further analysis with a larger sample size is warranted to provide more robust insights.

Gene-specific CHIP subtypes confer distinct risk magnitudes and mechanisms in CMD progression. For example, the *DNMT3 A* CHIP has a mixed effect on CHD. An early meta-analysis of three observational cohorts [18] reported a 1.7-fold increased risk of CHD in individuals with *DNMT3 A*. However, a recent analysis of the complete 450,000-person UK Biobank exome dataset failed to replicate this association [56]. Our gene-specific analysis in multistate models revealed a slightly higher risk of CMD incidence associated with *DNMT3 A* (adjusted HR 1.07, 95% CI 1.01–1.13; Table 2). Recent studies from prospective cohorts and biobanks revealed no associations between *DNMT3 A* and T2D [22] or stroke [46]. However, *TET2* and *ASXL1* were associated with 48% and 76% increased risks of T2D, respectively, whereas *TET2* was associated with a 1.82-fold increased risk of stroke. In contrast, our study revealed no association between *ASXL1* and CMD but identified a 1.12-fold and 1.22-fold increased risk of first-ever CMD in healthy individuals associated with any and large *TET2* (Table 2). We also found that all CHIP subtypes were strongly associated with death risk, whether due to death without CMD (Table 2) or all-cause mortality (Supplemental Table 9). *JAK2* ranks the top in the likelihood of mortality among all subtypes (Table 2, Supplemental Table 9), followed by spliceosome genes that have a 4.75-fold increased odd of all-cause mortality (Supplemental Table 9) and 3.36-fold increased risk for death without CMD (Table 2). Our findings of gene-specific CHIP risks are consistent with previous work on atherosclerotic cardiovascular disease [21], in which spliceosome genes tops in the risks of cardiovascular events (adjusted HR 2.41, 95% CI 1.45–4.00) and *JAK2* has the highest risk of mortality (adjusted HR 3.44, 95% CI 1.29–9.20). It is noteworthy that the wide CIs for *JAK2* were primarily attributed to the small number of carriers in specific CMD transitions (No CMD → FCMD: $n = 17$; No CMD → Death: $n = 24$). A similar pattern of limited sample size and wide CIs was observed for DNA damage genes and spliceosome genes. Mechanistically, *DNMT3 A* and *TET2* systemically activate inflammation and increase interleukin (IL)-6 and IL-1β signaling pathways [26, 57], whereas *JAK2* accelerates atherosclerosis, partly through activation of the AIM2 inflammasome [58]. *TP53*, a DNA damage repair gene, promotes atherosclerosis across the arterial system by inducing macrophage accumulation within atherosclerotic plaques [59]. *SF3B1* and *SRSF2* are critical components of the mRNA spliceosome, and mutations in these genes may amplify innate immune signaling, leading to increased production of circulating IL-6 and IL-18 [52, 60]. Further research is needed to elucidate the pathways underlying CMD risk in individuals with CHIP, particularly those with driver mutations in DNA damage repair or spliceosome genes.

Our analysis benefits from a large sample size and a standardized comparison of CMD and death within the same cohort, further assessing the risks associated with gene-specific CHIP mutations. Notably, CHIP exhibited pronounced associations with first CMD incidence and transitions toward death, with particularly high risks

observed for spliceosome genes in CMD and CMM development and *JAK2* in mortality, and large CHIP and CHIP subtypes are generally at higher risk. In summary, this research is the first large-scale, systematic assessment of the link between CHIP and CMD progression, showing that CHIP drives the progression of CMD and mortality, with the strongest association observed for mortality.

Currently, there is no conclusive evidence on the optimal timing and target populations for CHIP screening and intervention [61, 62]. Our stratified analysis suggested that male CHIP carriers under the age of 60 without a history of CMD are at high risk of mortality. Specifically, men are prone to elevated leukocyte activation [63] and mutations in myeloid malignancy-related genes [64], which increases their risk for all-cause mortality [21]. Our primary results also suggest that CHIP carriers with one or more CMDs are most affected. Indeed, hematopoietic stem cell mutations can occur early in life, and the speed of clonal expansion are influenced by both internal and external selective pressures. CHIP is closely linked to aging [17, 61], and its prevalence varies across sex [65] and racial groups [66]. Moreover, exposure to chemotherapy and radiotherapy can expand DNA damage-related CHIP [67–69], smoking exacerbates *ASXL1* mutations [70], and obesity may also accelerate CHIP progression [71]. CHIP itself drives telomere shortening [72] and atherogenesis [28], which in turn further promote clonal expansion. These findings suggest potential interventions to prevent the onset of CHIP, such as smoking cessation and weight loss, which could slow clonal expansion and reduce CHIP-related adverse outcomes. In addition, the CANTOS trial, which investigated the effects of canakinumab (an anti–IL-1β antibody) in participants with a history of myocardial infarction [73], revealed that those carrying *TET2* CHIP showed better prognostic outcomes and a reduced risk of major adverse cardiovascular events when treated with canakinumab, compared to participants without CHIP or those with other CHIP subtypes. This highlights the potential of precision medicine for high-risk CHIP carriers. Therefore, we emphasize the role of CHIP in mortality risk and particularly in young men without CMD. Large CHIP carriers, especially those with *TET2* mutations or mutations in DNA damage repair and spliceosome genes, may benefit the most from CHIP-targeted therapies, such as anti-IL-1β or anti-IL-6 strategies, with both cytokines potentially acting as downstream mediators of CHIP-related pathophysiology [26].

Our research has limitations. First, our study used population-scale WES to identify CHIP carriers, finding a CHIP prevalence of 3.1%, which is relatively low compared with deeper targeted sequencing studies that reported CHIP prevalence ranging from 8 to 18% [73–75]. However, participants in these studies had prior atherosclerosis, which may promote clonal hematopoiesis [28] and increase CHIP prevalence. Furthermore, a rigorous protocol was employed for CHIP identification, which minimizes false-positive calls and ensures a high-fidelity CHIP call set [31]. This approach may misclassify some individuals and reduce the sensitivity for detecting CHIP at VAF < 10%, which may lead to an underestimated CHIP prevalence. Second, the possibility of reverse causality and residual confounding cannot be excluded. However, we attempted to address reverse causality by excluding participants who developed CMD or mortality within the first two years of follow-up, and the findings remained largely unchanged. To mitigate residual confounding, we further adjusted for total cholesterol, HDL cholesterol, and the use of cholesterol-lowering medications, and the results remained stable. The results of the other sensitivity analyses also remained robust. Third, existing evidence suggests that the prevalence of CHIP and the incidence of CMD vary across different ethnic groups [2, 76]. Given that most participants in the UK Biobank are self-identified as White or of European ancestry, our findings may not be generalizable to other racial groups. Fourth, CHIP was measured only at baseline in the UK Biobank, limiting our ability to study its longitudinal dynamics. The absence of identifying developed CHIP mutations during follow-up could lead to incorrect classification of the study exposure. Fifth, the statistical power for detecting less common driver mutations is limited.

Conclusion

CHIP is a risk factor for transitioning from health to single CMD and all-cause mortality. It plays a significant role in specific CMDs and mortality, highlighting CHIP management as a possible strategy for primary and secondary prevention of CMDs.

Abbreviations

BMI	Body mass index
CHD	Coronary heart disease
CHIP	Clonal hematopoiesis of indeterminate potential
CMD	Cardiometabolic disease
CMM	Cardiometabolic multimorbidity
GATK	Genome Analysis ToolKit
HDL	High-density lipoprotein
HR	Hazard ratio
IQR	Interquartile range
NHS	National Health Service
OR	Odds ratio
SD	Standard deviation
T2D	Type 2 diabetes
VAF	Variant allele fraction
WES	Whole exome sequencing

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s40001-025-02639-8.

Additional file 1.

Acknowledgements
We acknowledge the staff and participants of the UK Biobank. UK Biobank analyses were conducted via application 84443.

Author contributions
C.Z. contributed to conceptualization, data curation, formal analysis, validation, visualization, and writing—original draft, and review and editing of the manuscript; D.F. contributed to data curation, formal analysis, investigation, resources, visualization, and writing—review and editing of the manuscript; Y.H. contributed to formal analysis, software, validation, investigation, resources, and writing—review and editing of the manuscript; J.L. contributed to data curation, formal analysis, software, resources, and writing—review and editing of the manuscript; S.Y. contributed to conceptualization, data curation, funding acquisition, validation, and writing—review and editing of the manuscript; X.C. contributed to data curation, investigation, methodology, resources, software, validation, writing—review and editing of the manuscript; G.Z. and T.M. contributed to data curation, investigation, resources, writing—review and editing of the manuscript; Q.P. contributed to conceptualization, data curation, funding acquisition, methodology, project administration, resources, supervision, writing—review and editing of the manuscript; and Y.T. contributed to conceptualization, data curation, funding acquisition, project administration, resources, supervision, writing—review and editing of the manuscript.

Funding
National Natural Science Foundation of China grant number 81873479 to G.Z., 82200470 to Y.T., and 82401853 to T.M.; Key Project of Hunan Provincial Science and Technology Innovation grant number 2020SK1013 to G.Z.; Natural Science Foundation of Hunan Province grant number 2023 JJ41010 to S.Y.; China Postdoctoral Science Foundation number GZC20242034 and 2024M753687 to T.M., and 2023M733965 to S.Y..

Availability of data and materials
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
The UK Biobank has been approved by the North West Multi-centre Research Ethics Committee as a Research Tissue Bank, and separate ethical clearance is not required for researchers under this approval (updated ref 21/NW/0157, 18 June 2021). All participants in the UK Biobank provided written informed consent.

Consent for publication
Not applicable.

Competing interest
The authors declare no competing interests.

Author details
[1]Department of Cardiovascular Medicine, the Third Xiangya Hospital, Central South University, Changsha, People's Republic of China. [2]Center of Coronary Circulation, Xiangya Hospital, Central South University, Changsha, People's Republic of China. [3]National Clinical Research Center for Geriatric Disorders, Xiangya Hospital, Central South University, Xiangya Road 87#, Changsha 410008, People's Republic of China. [4]Department of Cardiovascular Medicine, Xiangya Hospital, Central South University, Changsha, People's Republic of China. [5]Department of Geriatrics, Xiangya Hospital and Hunan Key Laboratory of Medical Genetics, School of Life Sciences, National Clinical Research Center for Geriatric Disorders, Central South University, Changsha, Hunan, China. [6]Bioinformatics Center, Xiangya Hospital & Furong Laboratory, Central South University, Changsha 410008, Hunan, China. [7]Department of Geriatric Medicine, Xiangya Hospital, Central South University, Changsha, China.

Received: 20 January 2025 Accepted: 24 April 2025
Published online: 24 May 2025

References

1. Emerging Risk Factors C, Di Angelantonio E, Kaptoge S, Wormser D, Willeit P, Butterworth AS, et al. Association of cardiometabolic multimorbidity with mortality. JAMA. 2015;314(1):52–60.
2. Cheng X, Ma T, Ouyang F, Zhang G, Bai Y. Trends in the prevalence of cardiometabolic multimorbidity in the United States, 1999–2018. Int J Environ Res Public Health. 2022;19(8):4726.
3. Makovski TT, Schmitz S, Zeegers MP, Stranges S, van den Akker M. Multimorbidity and quality of life: Systematic literature review and meta-analysis. Ageing Res Rev. 2019;53: 100903.
4. Kivimaki M, Kuosma E, Ferrie JE, Luukkonen R, Nyberg ST, Alfredsson L, et al. Overweight, obesity, and risk of cardiometabolic multimorbidity: pooled analysis of individual-level data for 120 813 adults from 16 cohort studies from the USA and Europe. Lancet Public Health. 2017;2(6):e277–85.
5. Gong L, Ma T, He L, Lin G, Zhang G, Cheng X, et al. Association between single and multiple cardiometabolic diseases and depression: A cross-sectional study of 391,083 participants from the UK biobank. Front Public Health. 2022;10: 904876.
6. Dove A, Marseglia A, Shang Y, Grande G, Vetrano DL, Laukka EJ, et al. Cardiometabolic multimorbidity accelerates cognitive decline and dementia progression. Alzheimers Dement. 2023;19(3):821–30.
7. Singh-Manoux A, Fayosse A, Sabia S, Tabak A, Shipley M, Dugravot A, et al. Clinical, socioeconomic, and behavioural factors at age 50 years and risk of cardiometabolic multimorbidity and mortality: A cohort study. PLoS Med. 2018;15(5): e1002571.
8. Karmali KN, Goff DC Jr, Ning H, Lloyd-Jones DM. A systematic examination of the 2013 ACC/AHA pooled cohort risk assessment tool for atherosclerotic cardiovascular disease. J Am Coll Cardiol. 2014;64(10):959–68.
9. North BJ, Sinclair DA. The intersection between aging and cardiovascular disease. Circ Res. 2012;110(8):1097–108.
10. Liberale L, Badimon L, Montecucco F, Luscher TF, Libby P, Camici GG. Inflammation, aging, and cardiovascular disease: JACC review topic of the week. J Am Coll Cardiol. 2022;79(8):837–47.
11. Rohm TV, Meier DT, Olefsky JM, Donath MY. Inflammation in obesity, diabetes, and related disorders. Immunity. 2022;55(1):31–55.
12. Steensma DP, Bejar R, Jaiswal S, Lindsley RC, Sekeres MA, Hasserjian RP, et al. Clonal hematopoiesis of indeterminate potential and its distinction from myelodysplastic syndromes. Blood. 2015;126(1):9–16.
13. Xie M, Lu C, Wang J, McLellan MD, Johnson KJ, Wendl MC, et al. Age-related mutations associated with clonal hematopoietic expansion and malignancies. Nat Med. 2014;20(12):1472–8.
14. Jaiswal S, Libby P. Clonal haematopoiesis: connecting ageing and inflammation in cardiovascular disease. Nat Rev Cardiol. 2020;17(3):137–44.
15. Jaiswal S, Ebert BL. Clonal hematopoiesis in human aging and disease. Science. 2019;366(6465): eaan4673.
16. Shlush LI. Age-related clonal hematopoiesis. Blood. 2018;131(5):496–504.
17. Jaiswal S, Fontanillas P, Flannick J, Manning A, Grauman PV, Mar BG, et al. Age-related clonal hematopoiesis associated with adverse outcomes. N Engl J Med. 2014;371(26):2488–98.
18. Jaiswal S, Natarajan P, Silver AJ, Gibson CJ, Bick AG, Shvartz E, et al. Clonal hematopoiesis and risk of atherosclerotic cardiovascular disease. N Engl J Med. 2017;377(2):111–21.
19. Tobias DK, Manning AK, Wessel J, Raghavan S, Westerman KE, Bick AG, et al. Clonal hematopoiesis of indeterminate potential (CHIP) and incident type 2 diabetes risk. Diabetes Care. 2023;46(11):1978–85.
20. Bhattacharya R, Zekavat SM, Haessler J, Fornage M, Raffield L, Uddin MM, et al. Clonal hematopoiesis is associated with higher risk of stroke. Stroke. 2022;53(3):788–97.
21. Gumuser ED, Schuermans A, Cho SMJ, Sporn ZA, Uddin MM, Paruchuri K, et al. Clonal hematopoiesis of indeterminate potential predicts adverse outcomes in patients with atherosclerotic cardiovascular disease. J Am Coll Cardiol. 2023;81(20):1996–2009.

22. Tobias DK, Manning AK, Wessel J, Raghavan S, Westerman KE, Bick AG, et al. Clonal hematopoiesis of indeterminate potential (CHIP) and incident type 2 diabetes risk. Diabetes Care. 2023;46(11):1978–85.
23. Arends CM, Liman TG, Strzelecka PM, Kufner A, Lowe P, Huo S, et al. Associations of clonal hematopoiesis with recurrent vascular events and death in patients with incident ischemic stroke. Blood. 2023;141(7):787–99.
24. Wang S, Hu S, Luo X, Bao X, Li J, Liu M, et al. Prevalence and prognostic significance of *DNMT3A*- and *TET2*- clonal haematopoiesis-driver mutations in patients presenting with ST-segment elevation myocardial infarction. EBioMedicine. 2022;78: 103964.
25. Opstad TB, Solheim S, Pettersen AR, Kalstad AA, Arnesen H, Seljeflot I. TERT and *TET2* genetic variants affect leukocyte telomere length and clinical outcome in coronary artery disease patients-a possible link to clonal hematopoiesis. Biomedicines. 2022;10(8):2027.
26. Fuster JJ, MacLauchlan S, Zuriaga MA, Polackal MN, Ostriker AC, Chakraborty R, et al. Clonal hematopoiesis associated with *TET2* deficiency accelerates atherosclerosis development in mice. Science. 2017;355(6327):842–7.
27. Lin AE, Bapat AC, Xiao L, Niroula A, Ye J, Wong WJ, et al. Clonal hematopoiesis of indeterminate potential with loss of *TET2* enhances risk for atrial fibrillation through Nlrp3 inflammasome activation. Circulation. 2024;149(18):1419–34.
28. Heyde A, Rohde D, McAlpine CS, Zhang S, Hoyer FF, Gerold JM, et al. Increased stem cell proliferation in atherosclerosis accelerates clonal hematopoiesis. Cell. 2021;184(5):1348–61.
29. Marston NA, Pirruccello JP, Melloni GEM, Kamanu F, Bonaca MP, Giugliano RP, et al. Clonal hematopoiesis, cardiovascular events and treatment benefit in 63,700 individuals from five TIMI randomized trials. Nat Med. 2024;30(9):2641–7.
30. Sudlow C, Gallacher J, Allen N, Beral V, Burton P, Danesh J, et al. UK biobank: an open access resource for identifying the causes of a wide range of complex diseases of middle and old age. PLoS Med. 2015;12(3): e1001779.
31. Vlasschaert C, Mack T, Heimlich JB, Niroula A, Uddin MM, Weinstock J, et al. A practical approach to curate clonal hematopoiesis of indeterminate potential in human genetic data sets. Blood. 2023;141(18):2214–23.
32. Backman JD, Li AH, Marcketta A, Sun D, Mbatchou J, Kessler MD, et al. Exome sequencing and analysis of 454,787 UK Biobank participants. Nature. 2021;599(7886):628–34.
33. Cibulskis K, Lawrence MS, Carter SL, Sivachenko A, Jaffe D, Sougnez C, et al. Sensitive detection of somatic point mutations in impure and heterogeneous cancer samples. Nat Biotechnol. 2013;31(3):213–9.
34. Benjamin D, Sato T, Cibulskis K, Getz G, Stewart C, Lichtenstein L. Calling Somatic SNVs and Indels with Mutect2. bioRxiv. 2019:861054.
35. Khoury JD, Solary E, Abla O, Akkari Y, Alaggio R, Apperley JF, et al. The 5th edition of the World Health Organization Classification of Haematolymphoid Tumours: myeloid and histiocytic/dendritic neoplasms. Leukemia. 2022;36(7):1703–19.
36. Bick AG, Pirruccello JP, Griffin GK, Gupta N, Gabriel S, Saleheen D, et al. Genetic interleukin 6 signaling deficiency attenuates cardiovascular risk in clonal hematopoiesis. Circulation. 2020;141(2):124–31.
37. Tyrrell J, Jones SE, Beaumont R, Astley CM, Lovell R, Yaghootkar H, et al. Height, body mass index, and socioeconomic status: Mendelian randomisation study in UK Biobank. BMJ. 2016;352: i582.
38. Cassidy S, Chau JY, Catt M, Bauman A, Trenell MI. Cross-sectional study of diet, physical activity, television viewing and sleep duration in 233,110 adults from the UK Biobank; the behavioural phenotype of cardiovascular disease and type 2 diabetes. BMJ Open. 2016;6(3): e010038.
39. Korn EL, Graubard BI, Midthune D. Time-to-event analysis of longitudinal follow-up of a survey: choice of the time-scale. Am J Epidemiol. 1997;145(1):72–80.
40. Putter H, Fiocco M, Geskus RB. Tutorial in biostatistics: competing risks and multi-state models. Stat Med. 2007;26(11):2389–430.
41. Han Y, Hu Y, Yu C, Guo Y, Pei P, Yang L, et al. Lifestyle, cardiometabolic disease, and multimorbidity in a prospective Chinese study. Eur Heart J. 2021;42(34):3374–84.
42. Elliott P, Peakman TC, Biobank UK. The UK Biobank sample handling and storage protocol for the collection, processing and archiving of human blood and urine. Int J Epidemiol. 2008;37(2):234–44.
43. Saadatagah S, Naderian M, Uddin M, Dikilitas O, Niroula A, Schuermans A, et al. Atrial fibrillation and clonal hematopoiesis in *TET2* and *ASXL1*. JAMA Cardiol. 2024;9(6):497–506.
44. de Wreede LC, Fiocco M, Putter H. mstate: An R package for the analysis of competing risks and multi-state models. J Stat Softw. 2011;38(7):1–30.
45. Honigberg MC, Zekavat SM, Niroula A, Griffin GK, Bick AG, Pirruccello JP, et al. Premature menopause, clonal hematopoiesis, and coronary artery disease in postmenopausal women. Circulation. 2021;143(5):410–23.
46. Bhattacharya R, Zekavat SM, Haessler J, Fornage M, Raffield L, Uddin MM, et al. Clonal hematopoiesis is associated with higher risk of stroke. Stroke. 2022;53(3):788–97.
47. Mayerhofer E, Strecker C, Becker H, Georgakis MK, Uddin MM, Hoffmann MM, et al. Prevalence and therapeutic implications of clonal hematopoiesis of indeterminate potential in young patients with stroke. Stroke. 2023;54(4):938–46.
48. Lee EJ, An HY, Lim J, Park KI, Choi SY, Jeong HY, et al. Clonal hematopoiesis and acute ischemic stroke outcomes. Ann Neurol. 2023;94(5):836–47.
49. Singh J, Li N, Ashrafi E, Thao LTP, Curtis DJ, Wood EM, et al. Clonal hematopoiesis of indeterminate potential as a prognostic factor: a systematic review and meta-analysis. Blood Adv. 2024;8(14):3771–84.
50. Fry A, Littlejohns TJ, Sudlow C, Doherty N, Adamska L, Sprosen T, et al. Comparison of sociodemographic and health-related characteristics of UK biobank participants with those of the general population. Am J Epidemiol. 2017;186(9):1026–34.
51. Kessler MD, Damask A, O'Keeffe S, Banerjee N, Li D, Watanabe K, et al. Common and rare variant associations with clonal haematopoiesis phenotypes. Nature. 2022;612(7939):301–9.
52. Pollyea DA, Harris C, Rabe JL, Hedin BR, De Arras L, Katz S, et al. Myelodysplastic syndrome-associated spliceosome gene mutations enhance innate immune signaling. Haematologica. 2019;104(9):e388–92.
53. Lee SC, North K, Kim E, Jang E, Obeng E, Lu SX, et al. Synthetic lethal and convergent biological effects of cancer-associated spliceosomal gene mutations. Cancer Cell. 2018;34(2):225–41.
54. Jiang Z, Li Y, Yan C, Zhang X, Zhang Q, Li J, et al. Clonal hematopoiesis of indeterminate potential in patients with acute coronary syndrome undergoing percutaneous coronary intervention in the absence of traditional risk factors. Clin Res Cardiol. 2023;112(4):506–17.
55. Yalcinkaya M, Liu W, Thomas LA, Olszewska M, Xiao T, Abramowicz S, et al. BRCC3-mediated NLRP3 deubiquitylation promotes inflammasome activation and atherosclerosis in *TET2* clonal hematopoiesis. Circulation. 2023;148(22):1764–77.
56. Vlasschaert C, Heimlich JB, Rauh MJ, Natarajan P, Bick AG. Interleukin-6 receptor polymorphism attenuates clonal hematopoiesis-mediated coronary artery disease risk among 451 180 individuals in the UK biobank. Circulation. 2023;147(4):358–60.
57. Sano S, Oshima K, Wang Y, MacLauchlan S, Katanasaka Y, Sano M, et al. *TET2*-mediated clonal hematopoiesis accelerates heart failure through a mechanism involving the IL-1beta/NLRP3 inflammasome. J Am Coll Cardiol. 2018;71(8):875–86.
58. Fidler TP, Xue C, Yalcinkaya M, Hardaway B, Abramowicz S, Xiao T, et al. The AIM2 inflammasome exacerbates atherosclerosis in clonal haematopoiesis. Nature. 2021;592(7853):296–301.
59. Zekavat SM, Viana-Huete V, Matesanz N, Jorshery SD, Zuriaga MA, Uddin MM, et al. *TP53*-mediated clonal hematopoiesis confers increased risk for incident atherosclerotic disease. Nat Cardiovasc Res. 2023;2:144–58.
60. Bick AG, Weinstock JS, Nandakumar SK, Fulco CP, Bao EL, Zekavat SM, et al. Inherited causes of clonal haematopoiesis in 97,691 whole genomes. Nature. 2020;586(7831):763–8.
61. Weeks LD, Ebert BL. Causes and consequences of clonal hematopoiesis. Blood. 2023;142(26):2235–46.
62. Libby P, Sidlow R, Lin AE, Gupta D, Jones LW, Moslehi J, et al. Clonal hematopoiesis: Crossroads of aging, cardiovascular disease, and cancer: JACC review topic of the week. J Am Coll Cardiol. 2019;74(4):567–77.
63. Tercan H, Cossins BC, van Deuren RC, Rutten JHW, Joosten LAB, Netea MG, et al. Association between clonal hematopoiesis driver mutations, immune cell function, and the vasculometabolic complications of obesity. J Am Heart Assoc. 2024;13(2): e031665.
64. Kamphuis P, van Zeventer IA, de Graaf AO, Salzbrunn JB, van Bergen M, Dinmohamed AG, et al. Sex differences in the spectrum of clonal hematopoiesis. Hemasphere. 2023;7(2): e832.

65. van Zeventer IA, de Graaf AO, van der Klauw MM, Vellenga E, van der Reijden BA, Schuringa JJ, et al. Peripheral blood cytopenias in the aging general population and risk of incident hematological disease and mortality. Blood Adv. 2021;5(17):3266–78.
66. Rollison DE, Howlader N, Smith MT, Strom SS, Merritt WD, Ries LA, et al. Epidemiology of myelodysplastic syndromes and chronic myeloproliferative disorders in the United States, 2001-2004, using data from the NAACCR and SEER programs. Blood. 2008;112(1):45–52.
67. Hsu JI, Dayaram T, Tovy A, De Braekeleer E, Jeong M, Wang F, et al. PPM1D Mutations Drive Clonal Hematopoiesis in Response to Cytotoxic Chemotherapy. Cell Stem Cell. 2018;23(5):700–13 e6.
68. Wong TN, Ramsingh G, Young AL, Miller CA, Touma W, Welch JS, et al. Role of TP53 mutations in the origin and evolution of therapy-related acute myeloid leukaemia. Nature. 2015;518(7540):552–5.
69. Bolton KL, Ptashkin RN, Gao T, Braunstein L, Devlin SM, Kelly D, et al. Cancer therapy shapes the fitness landscape of clonal hematopoiesis. Nat Genet. 2020;52(11):1219–26.
70. Dawoud AAZ, Tapper WJ, Cross NCP. Clonal myelopoiesis in the UK Biobank cohort: ASXL1 mutations are strongly associated with smoking. Leukemia. 2020;34(10):2660–72.
71. Pasupuleti SK, Ramdas B, Burns SS, Palam LR, Kanumuri R, Kumar R, et al. Obesity-induced inflammation exacerbates clonal hematopoiesis. J Clin Invest. 2023;133(11).
72. Nakao T, Bick AG, Taub MA, Zekavat SM, Uddin MM, Niroula A, et al. Mendelian randomization supports bidirectional causality between telomere length and clonal hematopoiesis of indeterminate potential. Sci Adv. 2022;8(14):eabl6579.
73. Svensson EC, Madar A, Campbell CD, He Y, Sultan M, Healey ML, et al. *TET2*-driven clonal hematopoiesis and response to canakinumab: An exploratory analysis of the CANTOS Randomized Clinical Trial. JAMA Cardiol. 2022;7(5):521–8.
74. Jager R, Hoke M, Mayer FJ, Boden S, Englisch C, Ay C, et al. Combined effects of clonal hematopoiesis and carotid stenosis on cardiovascular mortality. J Am Coll Cardiol. 2024;83(18):1717–27.
75. Dorsheimer L, Assmus B, Rasper T, Ortmann CA, Ecke A, Abou-El-Ardat K, et al. Association of mutations contributing to clonal hematopoiesis with prognosis in chronic ischemic heart failure. JAMA Cardiol. 2019;4(1):25–33.
76. Marnell CS, Bick A, Natarajan P. Clonal hematopoiesis of indeterminate potential (CHIP): Linking somatic mutations, hematopoiesis, chronic inflammation and cardiovascular disease. J Mol Cell Cardiol. 2021;161:98–105.

Publisher's Note