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Clonal hematopoiesis of indeterminate potential, health indicators, and risk of cardiovascular diseases among patients with diabetes: a prospective cohort study

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Abstract

Background Clonal hematopoiesis of indeterminate potential (CHIP) was associated with diabetes and cardiovascular diseases (CVD). However, the effect of CHIP on CVD have not been evaluated among patients with diabetes, and whether maintaining the healthy indictors could mitigate the adverse influence was also unclear.

Methods A total of 22,239 adults from the UK Biobank with diabetes and available whole-exome sequence data, and free of CVD were included. Multivariable-adjusted Cox regressions were used to explore the associations of any CHIP (variant allele fraction ≥ 2%), large CHIP (variant allele fraction ≥ 10%), and the top 10 commonly mutated driver genes for CHIP and with risk of CVD. The joint associations between health indicators (body mass index [BMI], HbA1c, blood pressure [BP], and low-density lipoprotein cholesterol [LDL]) and CHIP were further investigated.

Results Over a median follow-up of 13.2 years, 5366 participants with diabetes developed CVD events. The hazard ratios (HRs) (95% confidence intervals [CIs]) of any CHIP and large CHIP were (1.21, 1.08–1.36) and (1.25, 1.09–1.43) for incident CVD, respectively. Significant associations between any CHIP and coronary heart disease (HR, 95%CI: 1.18, 1.03–1.36) and heart failure (1.73, 1.46–2.06) were observed, but not for stroke (1.14, 0.89–1.48). Gene-specific analyses suggested that the greatest association were for *SF3B1* (HR, 95%CI: 2.50, 1.25–5.01) and *TET2* (HR, 95%CI: 1.36, 1.07–1.77) with risk of CVD. There was no significant interaction between the four health indicators and CHIP in relation to incident CVD. Compared to patients without CHIP, those with any CHIP and ideal health indicators still exhibited significantly or nonsignificantly higher HRs (BMI: 1.18, 0.82–1.68; HbA1c: 1.12, 0.96–1.30; BP: 1.24, 1.03–1.49; LDL: 1.29, 1.09–1.53). Similar results were demonstrated using large CHIP.

Conclusions CHIP is independently associated with an increased risk of CVD in patients with diabetes, regardless of health indicator levels. Diabetic patients with CHIP but ideal health indicators still exhibited higher CVD risk compared with diabetic patients without CHIP.

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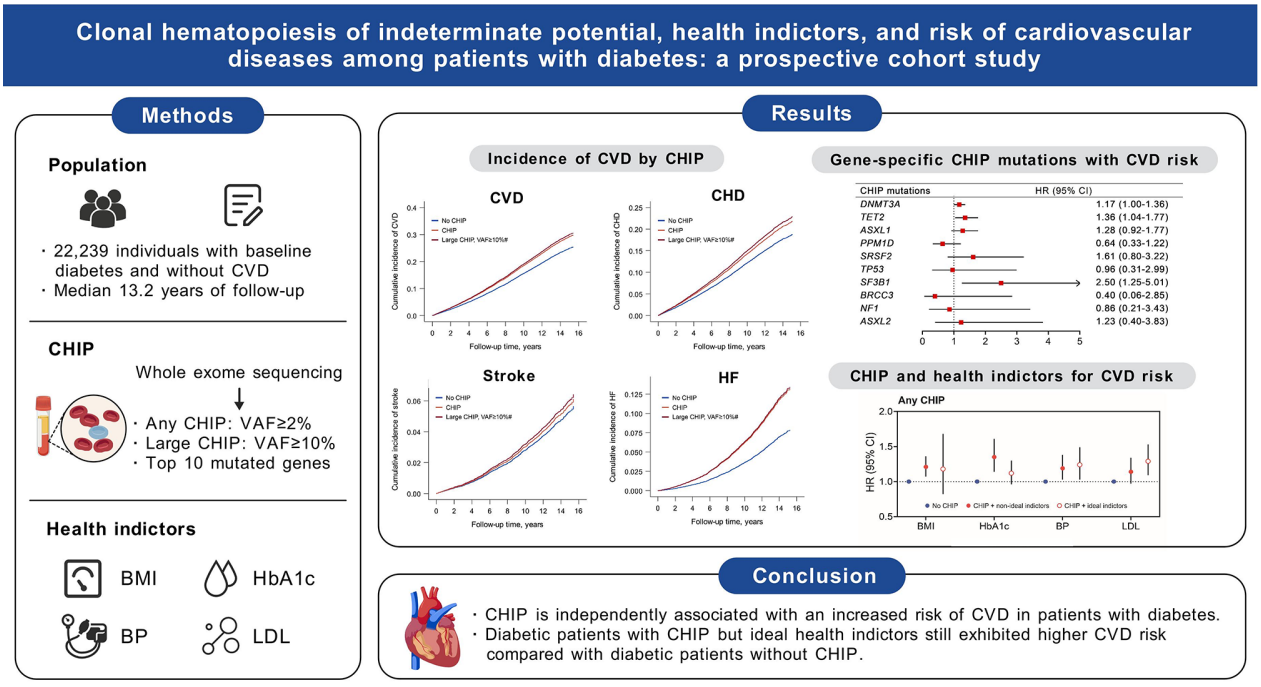
Graphic abstract



BMI, body mass index; BP, blood pressure; CHD, coronary heart disease; CHIP, chonal hematopoiesis of indeterminate; CI, confidence interval; CVD, cardiovascular disease; HF, heart failure; HR, hazard ratio; LDL, low-density lipoprotein cholesterol; VAF, variant allele frequency.

Keywords Clonal hematopoiesis of indeterminate potential, Diabetes, Cardiovascular diseases, Health indicator

Introduction

The number of people living with diabetes globally has reached 537 million in 2021, and the figure is projected to rise to 783.2 million by 2045 [1]. Cardiovascular disease (CVD) is a major complication and the leading cause of mortality among patients with diabetes. Individuals with diabetes have a two- to four-fold greater risk of developing CVD during their lifetime than those without diabetes [2]. More than half of diabetes patients would ultimately succumb to cardiovascular-related complications [3]. Thus, identifying and managing the risk factors for CVD in patients with diabetes is of paramount importance [4].

Clonal hematopoiesis of indeterminate potential (CHIP) is the clonal expansion of hematopoietic cells with preleukemic mutations in the absence of an overt cancer diagnosis [5]. As an age-related phenomenon, CHIP was estimated to affect at least 10% of individuals over the age of 65 [6]. In addition to its potential as a premalignant state in hematologic malignancy, CHIP has also been recognized as a novel risk factor for a variety of health outcomes, including diabetes [7] and CVD [8, 9]. A prospective cohort study with a mean follow-up of 9.8 years revealed that participants with CHIP had a 23% higher risk of incident type 2 diabetes than those without CHIP [7]. Close associations of CHIP with insulin resistance and impaired fasting glucose have also been reported [10]. At the same time, mounting epidemiological studies suggested positive associations between CHIP and cardiovascular conditions, including coronary artery disease [11], atherosclerosis [12], ischemic stroke [13], heart failure (HF) [12], and microvascular diseases [14]. Recent studies suggested that CHIP was associated with increased risk of CVD, potentially through the activation of the NLRP3 inflammasome pathway [8] or DNA methylation (DNAm) [15]. Moreover, patients with diabetes exhibited a state of chronic low-grade inflammation, which were the pivotal mechanisms in the development of endothelial dysfunction, atherosclerosis, and various diabetic complications [16, 17]. However, it is unclear whether the presence of CHIP-related mutations in patients with diabetes contributes to an increased risk for incident CVD.

Given that whole exome sequencing (WES) data from peripheral blood are available for 450,000 participants in the UK Biobank to detect CHIP [18], we aimed to evaluate the associations between CHIP and the risk of CVD and its subtypes among individuals with diabetes. In addition, health indicators, including body mass index (BMI), blood glucose, blood pressure (BP), and blood

lipids, remain the cornerstone in the care of patients with diabetes and significantly influence the risk of cardiovascular complications [19, 20]. Therefore, we further investigated whether maintaining ideal health indicators can offset the risk of CVD associated with CHIP among patients with diabetes.

Research design and methods

Study population

The UK Biobank is a population-based prospective cohort study that recruited more than 500 000 participants aged 40–70 years from 22 assessment centers across England, Scotland, and Wales [21]. The baseline survey was conducted from 2006 to 2010, and participants provided a wide range of health-related information through touch screen questionnaires, physical measurements, and biological samples. The UK Biobank study was approved by the North West Multicenter Research Ethics Committee (reference no. 16/NW/0274), and all participants provided informed consent.

Participants with diabetes at baseline were identified according to the previously reported methods in the UK Biobank, which encompassed an evaluation of self-reported diabetes diagnosis, prior hospital diagnosis before enrollment, use of insulin and hypoglycemic medication, or presence of HbA1c ≥ 6.5% (48 mmol/mol) at baseline [22, 23]. Among 31,126 participants who had baseline diabetes, we excluded those with missing exposure data on CHIP (n = 2,938) or who had prevalent CVD at baseline (n = 5,949), leaving 22,239 participants included in the main analyses (Supplemental file 1: Fig. 1).

Exposures

In the UK Biobank, CHIP and related phenotypes were identified via WES derived from peripheral blood samples processed on the Illumina NovaSeq 6000 platform at the Regeneron Genetics Center (Tarrytown, New York, USA) [24]. Briefly, the Mutect2 tool from the Genome Analysis Toolkit was used to detect somatic variants [25, 26]. CHIP mutations were defined based on a prespecified list of 58 genes known to be drivers of clonal hematopoiesis and myeloid malignancies, as detailed in Supplemental file 1: Table 1 [27]. To minimize false-positive CHIP calls, a series of additional postprocessing filters were used to remove variants: (1) total read depth < 20; (2) minimum read depth for the alternate allele < 5; or (3) lack of variant support in both forward and reverse sequencing reads, as described previously [27]. Participants with a variant allele frequency (VAF) < 2% were defined as no CHIP, whereas those with VAF ≥ 2% and VAF ≥ 10% were identified with any CHIP and large CHIP, respectively. A large CHIP was reported to be related to more severe adverse outcomes [27]. The top 10 most frequently mutated genes in CHIP for the current study population were as follows: *DNMT3A*, *TET2*, *ASXL1*, *PPM1D*, *SRSF2*, *TP53*, *SF3B1*, *BRCC3*, *NF1*, and *ASXL2*.

Outcomes

The primary outcome of the study was incident CVD, and the contributing outcomes were its component endpoints, including coronary heart disease (CHD), stroke, and HF [20]. The dates of disease outcomes were extracted from the death register, primary care, and hospital inpatient records and defined by the following ICD-10 codes: codes I20-I25 for CHD, codes I60-I64 and I69 for stroke (I60-I62 for hemorrhagic stroke, I63 for ischemic stroke), and codes I50 for HF [28, 29]. For each UK Biobank participant, the follow-up time was calculated from the date of their initial visit to the assessment center until the earliest occurrence of either the outcome diagnosis, death, or the end of the follow-up period (December 19, 2022).

Covariates

Four health indicators were considered in the current study: BMI, glycated hemoglobin (HbA1c), BP, and low-density lipoprotein cholesterol (LDL). These four indicators as the cardiovascular health factors were highlighted by the American Heart Association (AHA) [19], which also reflect the overall metabolic status of patients with diabetes [30, 31]. BMI was calculated as weight (kg)/height (m^2), and BMI < 25 kg/m^2 was defined as the ideal level [19]. Since the UK Biobank did not require participants to fast during blood sample collection at baseline, fasting glucose data were unavailable. Therefore, we used HbA1c to assess blood glucose levels in the population. HbA1c was measured by HPLC analysis on a Bio-Rad VARIANT II Turbo. HbA1c < 7.0% (53 mmol/mol) is recommended for tight glycemic control to reduce complications in patients with diabetes and was defined as ideal in the current study [2]. The average systolic blood pressure (SBP) and diastolic blood pressure (DBP) were calculated from two measurements, with SBP/DBP < 140/90 as the ideal level [2]. LDL was analyzed on a Beckman Coulter AU5800. LDL < 2.6 mmol/L was recommended for cardiovascular risk categories in patients with diabetes and was ideal for this study [2].

The baseline characteristics used as potential covariates included age (years), sex (male, female), ethnicity (white, other), total annual household income before tax (< £31000, ≥£31000), education (university or college degree, other), smoking status (never, previous, current), alcohol intake frequency (daily or 3–4 times/week, 1–2 times/week or 1–3 times/month, occasional or never), metabolic equivalent tasks (METs per week were calculated for all activities, including walking and moderate and vigorous activities), BMI (kg/m^2), SBP (mmHg), TC

(mmol/L), triglycerides (TG, mmol/L), cancer (yes, no), diabetes duration (years), family history of diabetes (yes, no), family history of CVD (yes, no), family history of hypertension (yes, no), use of diabetes medication (yes, no), use of cholesterol-lowering medication (yes, no), use of antihypertensive medication (yes, no), and use of aspirin (yes, no). Missing data were multiply imputed via the "mice" R package, which employs a multivariate imputation by chained equations (MICE) approach with 5 imputations [32]. We included any covariates associated with missing data, along with age, sex, and ethnicity, in stochastic regression models to predict missing variables. Each imputed dataset was analyzed separately using the same statistical model, and the results were pooled to obtain estimates.

Statistical analysis

The baseline characteristics of the study population were summarized as the mean ± standard deviation for normally distributed continuous variables, the median (lower quartile, upper quartile) for skewed distributed continuous variables, and the number (percentages) for categorical variables. Differences in characteristics between CHIP groups were compared using Student's T-test or Mann-Whitney text for continuous variables and Pearson's chi-square test for categorical variables.

Cox proportional hazards models were used to evaluate the hazard ratios (HRs) and 95% confidence intervals (CIs) for the associations of any CHIP, large CHIP, and gene-specific CHIP, with risk of incident CVD. Model 1 was adjusted for age, sex, and the first 10 principal components of genetic ancestry; Model 2 was further adjusted for ethnicity, household income, education, smoking, alcohol, MET, BMI, SBP, TC, TG, and cancer. The model for main analysis mainly incorporating the fundamental demographic characteristics and modifiable factors known to influence cardiovascular health. Given the consideration of their non-modified nature or non-directly relationship to CHIP and outcome diseases, other variables were initially excluded from the main models to avoid over-adjustment. The first 10 principal components were derived through an analysis of associated genome-wide common genotypes. For the secondary outcomes, including CHD, stroke, and HF, Bonferroni correction was applied to control for the potential Type I error rate, and p-value < 0.0167 (0.05/3) was considered statistically significant. For multiple comparisons in the gene-specific CHIP analyses, Bonferroni correction was applied and p-value < 0.005 (0.05/10) was considered statistically significant. Cumulative incidence plots were constructed using the Kaplan-Meier method to compare individuals whether exposure to CHIP for disease outcomes over time. Stratified analyses were conducted to determine the effect of CHIP on CVD across different age groups (< 60 years, ≥ 60 years), between men and women, and among individuals whether met the ideal health indicators. The stratified factor was not included in the corresponding model to avoid overadjustment. To investigate the role of health indicators in the above associations, the joint associations between CHIP and four health indicators with CVD risk were examined, with patients who had no CHIP as a reference.

Several sensitivity analyses were conducted to verify the reliability of the results. First, we restricted the follow-up time to more than 2 years to minimize the potential influence of reverse causality. Second, given the limited data on the duration of diabetes, diabetes duration was additionally adjusted for 18,342 participants. Third, we further adjusted for covariates including family history of diabetes, family history of CVD, family history of hypertension, use of diabetes medication, cholesterol-lowering medication, antihypertensive medication, and aspirin. Fourth, we set more stringent cutoff points for ideal HbA1c (< 5.7%, < 39 mmol/mol), ideal BP (< 130/80 mmHg) and ideal LDL (< 1.8 mmol/L) for the analyses. Fifth, we excluded participants who were missing data for any of the four health indicators.

All the statistical analyses were conducted using IBM SPSS Statistics (Version 26) and R software (version 4.0.1). Tests of significance were two-sided, and a P value < 0.05 was considered to indicate statistical significance, unless otherwise stated.

Results

Baseline characteristics

The study sample comprised 22,239 individuals with diabetes (mean age 58.7 ± 7.4 years, 57.8% men), of whom 977 (4.4%) had any CHIP and 700 (3.2%) had a large CHIP at baseline (Table 1). The most common CHIP driver was *DNMT3A* (58.1% of CHIP carriers), followed by *TET2* (16.5%) and *ASXL1* (10.6%) (Supplemental file 1: Table S2 and Fig. S2). The proportion of men was similar between populations with and without CHIP (59.9% of CHIP vs. 57.7% for non-CHIP, $p = 0.173$). The participants with CHIP were older, more likely to have a low household and be current or former smokers, and had a higher SBP and longer duration of diabetes than those without CHIP (all $p < 0.05$).

Associations between CHIP and the risk of incident CVD among patients with diabetes

During a median follow-up of 13.2 years, 5,366 (24.1%) patients with diabetes developed CVD. Specifically, there were 4,040 cases (18.2%) of CHD, 1,126 cases (5.1%) of stroke, and 1,808 cases (8.1%) of HF. The absolute risk of incident CVD for patients without CHIP was 23.8%, while higher in those with any CHIP and large CHIP, at 30.9%, and 31.9%, respectively (Fig. 1A). Compared with

Table 1 Baseline characteristics of UK Biobank participants with prevalent diabetes by CHIP status

Characteristics	Overall (*N* = 22,239)	Any CHIP (*N* = 977)	No CHIP (*N* = 21,262)	*P* value
Age, years	58.7 ± 7.4	61.8 ± 6.3	58.6 ± 7.5	< 0.001
Male, n (%)	12,847 (57.8)	585 (59.9)	12,262 (57.7)	0.173
White race/ethnicity, n (%)	19,165 (86.2)	881 (90.2)	18,284 (86.0)	< 0.001
High household income, n (%)	8275 (37.2)	299 (30.6)	7976 (37.5)	< 0.001
University or college degree, n (%)	5652 (25.4)	228 (23.3)	5424 (25.5)	0.127
Smoking status, n (%)				0.003
Current	2497 (11.2)	123 (12.6)	2374 (11.2)	
Former	8888 (40.0)	429 (43.9)	8459 (39.8)	
Never	10,854 (48.8)	425 (43.5)	10,429 (49.0)	
Alcohol intake frequency, n (%)				0.007
Daily or 3–4 times/week	7474 (33.6)	319 (32.7)	7155 (33.7)	
1–2 times/week or 1–3 times/month	7889 (35.5)	313 (32.0)	7576 (35.6)	
Occasional or never	6876 (30.9)	345 (35.3)	6531 (30.7)	
Metabolic equivalent task	1826.0 (810.0, 3159.0)	1892.5 (852.3, 3291.0)	1822.0 (808.5, 3152.0)	0.037
Body mass index, kg/m^2	31.2 ± 5.9	30.9 ± 5.3	31.2 ± 5.9	0.103
Systolic blood pressure, mmHg	141.9 ± 17.4	143.9 ± 17.9	141.8 ± 17.4	< 0.001
Total cholesterol, mmol/L	4.8 ± 1.1	4.7 ± 1.2	4.8 ± 1.1	0.016
Triglycerides, mmol/L	2.7 ± 1.1	2.6 ± 1.1	2.7 ± 1.1	0.398
Low-density lipoprotein, mmol/L	2.8 ± 0.9	2.7 ± 0.9	2.8 ± 0.9	0.020
HbA1c, %	7.0 ± 1.3	7.0 ± 1.2	7.0 ± 1.3	0.517
History of cancer, n (%)	2146 (9.6)	98 (10.0)	2,048 (9.6)	0.680
Diabetes duration*, years	5.4 (2.4, 10.4)	6.1 (2.6, 10.8)	5.5 (2.4, 10.4)	0.026
Family history, n (%)				
Diabetes, n (%)	9795 (44.0)	406 (41.6)	9389 (44.2)	0.109
Cardiovascular disease, n (%)	12,908 (58.0)	584 (59.8)	12,324 (58.0)	0.262
Hypertension, n (%)	10,696 (48.1)	441 (45.1)	10,255 (48.2)	0.058
Medication history, n (%)				
Insulin	3789 (17.0)	158 (16.2)	3631 (17.1)	0.472
Antihypertensive medication	11,916 (53.6)	571 (58.4)	11,345 (53.4)	0.040
Lipid-lowering medication	13,827 (62.2)	637 (65.2)	13,190 (62.0)	0.002
Aspirin	69,647 (13.9)	396 (40.5)	7886 (37.1)	0.030
CHIP mutation, n (%)				
Any CHIP	977 (4.4)	977 (100)	/	/
Large CHIP	700 (3.2)	700 (71.6)	/	/
DNMT3A	568 (2.6)	568 (58.1)	/	/
TET2	161 (0.7)	161 (16.5)	/	/
ASXL1	104 (0.5)	104 (10.6)	/	/

Data are presented as the mean ± SD, median (lower quartile, upper quartile) or n (%)

P values for differences in baseline characteristics were estimated by Student's t test or the Mann–Whitney test for continuous variables and Pearson's chi-square test

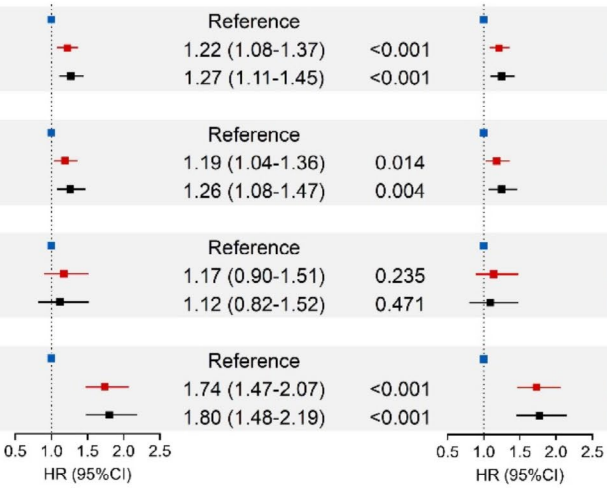
CHIP, clonal hematopoiesis of indeterminate potential; HbA1c, glycated hemoglobin

* There was total 18,342 participants with data of diabetes duration

participants without CHIP, the multivariable-adjusted HRs (95% CIs) of CVD in Model 2 were 1.21 (1.08–1.36) for individuals had any CHIP, and 1.25 (1.09–1.43) for those with large CHIP. These associations remained significant for CHD (HR, 95% CI: 1.18, 1.03–1.36 with any CHIP; and 1.25, 1.07–1.46 with large CHIP) and HF (HR, 95% CI: 1.73, 1.46–2.06 with any CHIP; and 1.77, 1.45–2.15 with large CHIP). However, there was no significant association between CHIP and stroke (HR, 95% CI: 1.14, 0.89–1.48 with any CHIP and 1.09, 0.80–1.48 with large CHIP). When considering subtypes of stroke, we observed a marginal association of any CHIP (HR, 95% CI: 1.60, 0.97–2.63) and large CHIP (HR, 95% CI: 1.72, 0.98–3.03) with hemorrhagic stroke, with p-values around 0.06 (Supplemental file 1: Table S3). However, for ischemic stroke, the HRs were lower and no significant associations were detected. The cumulative incidences of CVD, CHD, and HF were greater in individuals with any CHIP versus no CHIP, and much higher for large CHIP versus no CHIP (Fig. 1B). Exploratory analyses revealed

A

		Case (%)	Model 1	*P*	Model 2	*P*
CVD						
	No CHIP	5,064 (23.8)	Reference		Reference	
	Any CHIP	302 (30.9)	1.22 (1.08-1.37)	<0.001	1.21 (1.08-1.36)	0.002
	Large CHIP	223 (31.9)	1.27 (1.11-1.45)	<0.001	1.25 (1.09-1.43)	0.001
CHD						
	No CHIP	3,820 (18.0)	Reference		Reference	
	Any CHIP	220 (22.5)	1.19 (1.04-1.36)	0.014	1.18 (1.03-1.36)	0.015
	Large CHIP	165 (23.6)	1.26 (1.08-1.47)	0.004	1.25 (1.07-1.46)	0.005
Stroke						
	No CHIP	1,063 (5.0)	Reference		Reference	
	Any CHIP	63 (6.4)	1.17 (0.90-1.51)	0.235	1.14 (0.89-1.48)	0.304
	Large CHIP	43 (6.1)	1.12 (0.82-1.52)	0.471	1.09 (0.80-1.48)	0.582
HF						
	No CHIP	1,663 (7.8)	Reference		Reference	
	Any CHIP	145 (14.8)	1.74 (1.47-2.07)	<0.001	1.73 (1.46-2.06)	<0.001
	Large CHIP	106 (15.1)	1.80 (1.48-2.19)	<0.001	1.77 (1.45-2.15)	<0.001



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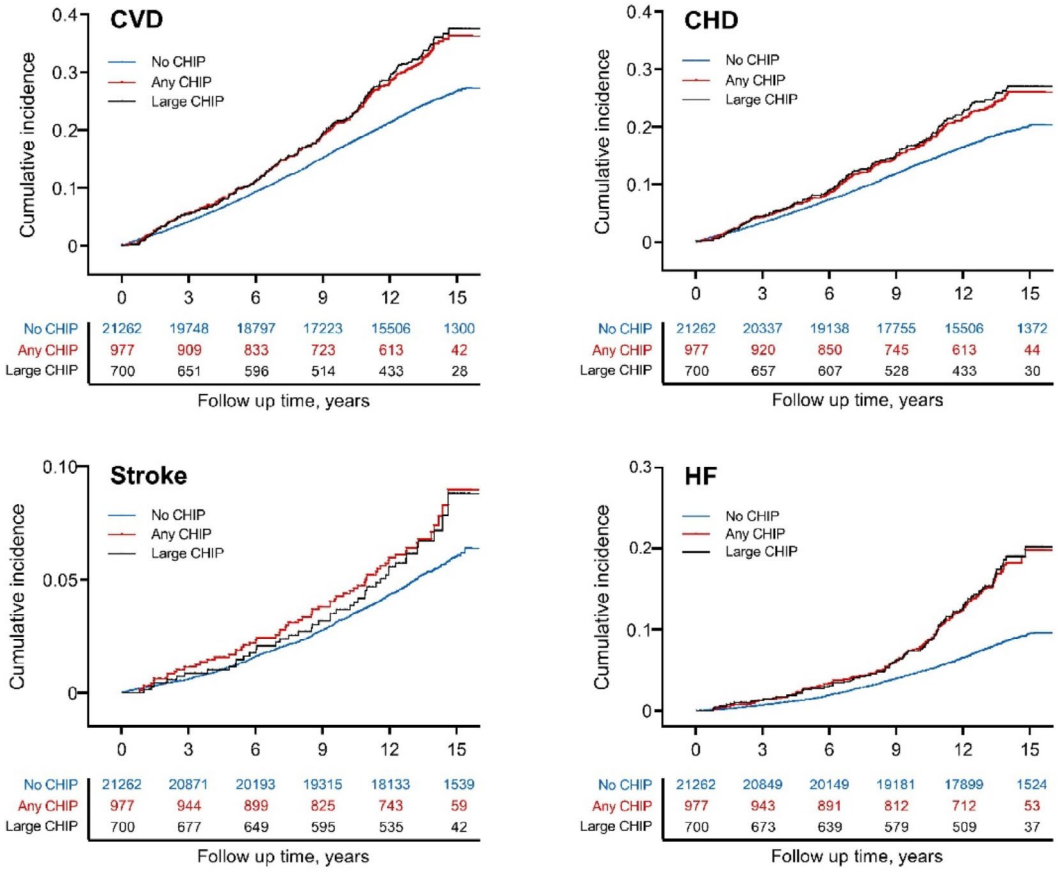

Fig. 1 (**A**) Association between CHIP and cardiovascular diseases in patients with diabetes. (**B**) Cumulative incidence curves of cardiovascular diseases according to CHIP status determined via the Kaplan–Meier method. Any CHIP: variant allele frequency ≥ 2%; large CHIP: variant allele frequency ≥ 10%. Model 1 was adjusted for age, sex, and the first 10 principal components of genetic ancestry; Model 2 was further adjusted for ethnicity, household income, education, smoking, alcohol, metabolic equivalent task, body mass index, systolic blood pressure, total cholesterol, triglycerides, and cancer. CHIP, clonal hematopoiesis of indeterminate potential; HR, hazard ratio; CI, confidence interval; CVD, cardiovascular disease; CHD, coronary heart disease; HF, heart failure. CVD was defined as the occurrence of any type of CHD, stroke, or HF. HR, hazard ratio; CI, confidence interval

that the associations of CHIP with incident events were homogeneous across subtypes based on age, sex, and health indicators (Supplemental file 1: Table S4).

Associations between gene-specific CHIP mutations and CVD risk among patients with diabetes

The associations between specific CHIP-related mutations and the risk of incident CVD among patients with diabetes are shown in Fig. 2. In the multivariable-adjusted models, both *TET2* and *SF3B1* mutations were positively associated with the occurrence of CVD (HR, 95% CI: 1.36, 1.05–1.77, $p = 0.025$, and 2.50, 1.25–5.01, $p = 0.010$, respectively), although the p-values did not reach a significance after multiple comparison adjustments. For contributory outcomes, CHIP-related mutations, including *DNMT3A* (HR 1.56, 95% CI 1.24–1.97), *TET2* (HR 2.17, 95% CI 1.52–3.10), and *SF3B1* (HR 4.43, 95% CI 1.83–10.7), were significantly associated with an increased risk of HF (all $p < 0.005$). The top 3 highest HRs for CHD and stroke with gene-specific CHIP mutations were *SF3B1*, *ASXL2*, *ASXL1*, and *SRSF2*, *NF1*, *BRCC3*, respectively. However, the relationships between gene-specific CHIP and both CHD and stroke were not significant.

Joint association between CHIP and health indicators for CVD risk among patients with diabetes

Figure 3 and Supplemental file 1: Table S5 show the joint associations between CHIP status and health indicators for incident CVD. Compared to patients without CHIP, those with any CHIP and non-ideal level of BMI (HR, 95% CI: 1.21, 1.07–1.36), HbA1c (HR, 95% CI: 1.35,

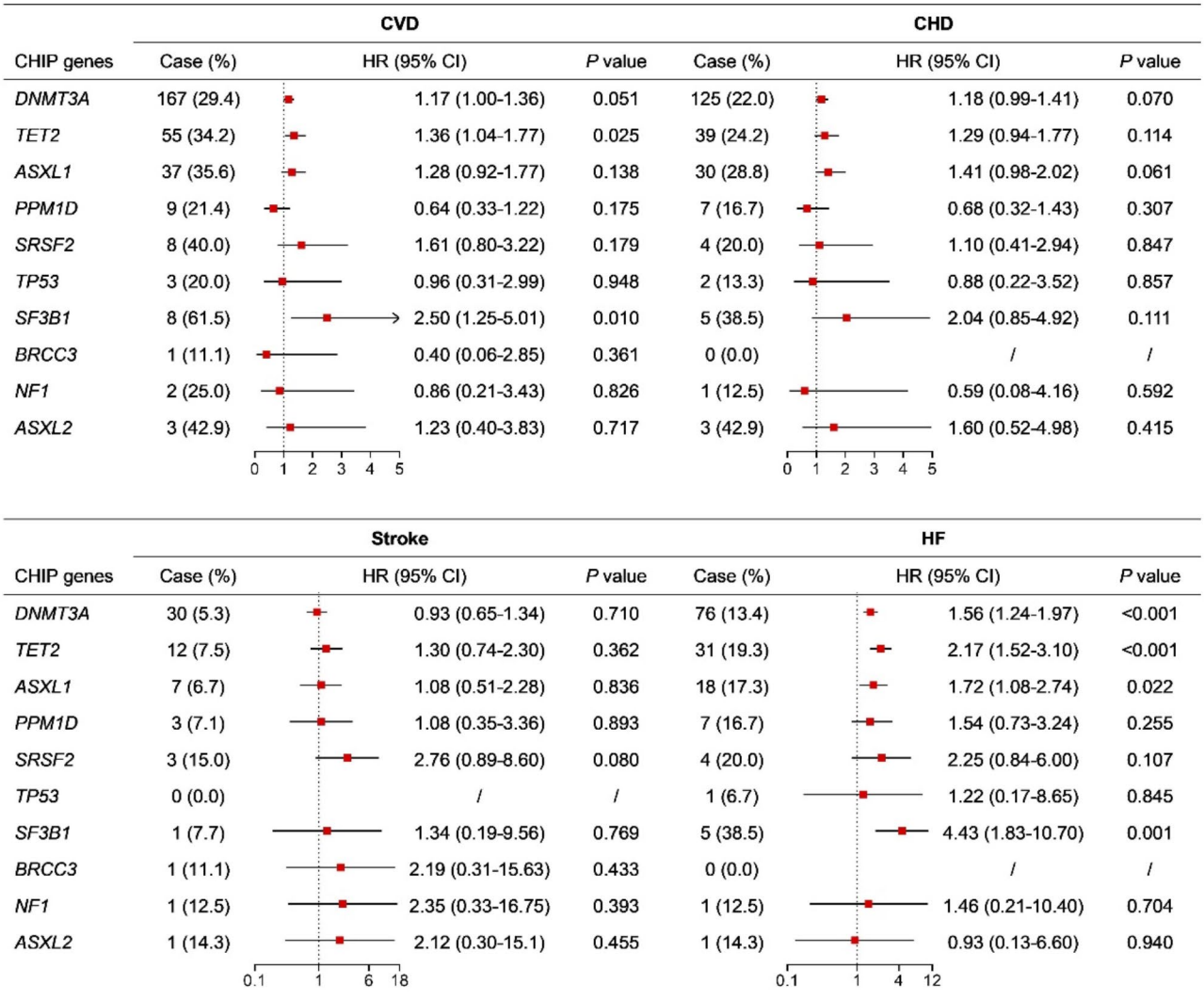

Fig. 2 Associations between driver mutations in any CHIP and cardiovascular diseases in patients with diabetes. The model was adjusted for age, sex, the first 10 principal components of genetic ancestry, ethnicity, household income, education, smoking, alcohol, metabolic equivalent task, body mass index, systolic blood pressure, total cholesterol, triglycerides, and cancer. CHIP, clonal hematopoiesis of indeterminate potential; HR, hazard ratio; CI, confidence interval; CVD, cardiovascular disease; CHD, coronary heart disease; HF, heart failure. CVD was defined as the occurrence of any type of CHD, stroke, or HF

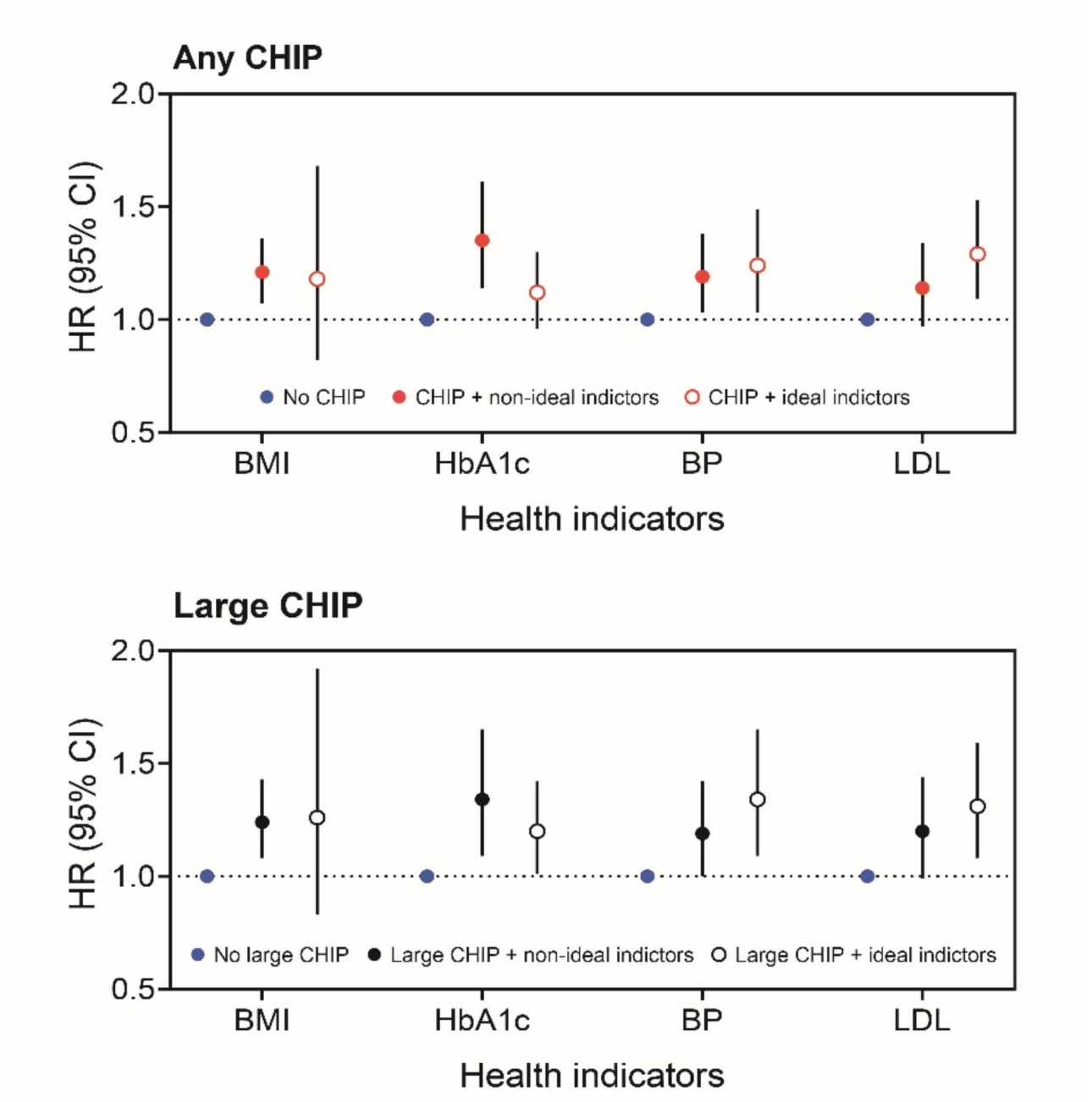

Fig. 3 Joint associations between CHIP and health indicators for the risk of cardiovascular diseases. Participants did not have CHIP were as reference. Ideal levels for health indicators: BMI < 25 kg/m^2, HbA1c < 7.0%, BP < 140/90 mmHg, and LDL < 2.6 mmol/L. Participants with a variant allele frequency ≥ 2% and < 10% (met the criterion of any CHIP but no large CHIP) were excluded from the analysis for large CHIP (n = 21,962). The model was adjusted for age, sex, the first 10 principal components of genetic ancestry, ethnicity, household income, education, smoking, alcohol, metabolic equivalent task, body mass index, systolic blood pressure, total cholesterol, triglycerides, and cancer. The confounders body mass index and systolic blood pressure were removed from the regression models for the analysis of BMI and BP, respectively. CHIP, clonal hematopoiesis of indeterminate potential; HR, hazard ratio; CI, confidence interval; BMI, body mass index; HbA1c, glycated hemoglobin; BP, blood pressure; LDL, low-density lipoprotein cholesterol

1.14–1.61), BP (HR, 95% CI: 1.19, 1.03–1.38), and LDL (HR, 95% CI: 1.14, 0.97–1.34) were associated with the increased risk of CVD. Furthermore, among individuals with CHIP who maintained ideal health indicators, the HRs remained significantly or nonsignificantly elevated compared to the no CHIP population (BMI: 1.18, 0.82–1.68, p = 0.379; HbA1c: 1.12, 0.96–1.30, p = 0.159; BP: 1.24, 1.03–1.49, p = 0.023; LDL: 1.29, 1.09–1.53, p = 0.003).

Several sensitivity analyses were performed to verify the robustness of our results. First, we restricted the follow-up time to more than 2 years, and the association between CHIP and CVD was still significant (Supplemental file 1: Table S6). In two additional adjusted models for diabetes duration, family history and medicine usage, we also found a positive relationship between the presence of CHIP and CVD risk (Supplemental file 1: Tables S7 and S8). Moreover, when a more stringent cutoff for health indicators was used, a prominent association between CHIP and CVD risk was observed for individuals with ideal HbA1c, although there was no significant interaction (Supplemental file 1: Tables S9 and S10). Furthermore, among 19,922 participants who had data for all health indicators, the results of stratified analysis and joint analysis between CHIP and health indicators remained largely unchanged (Supplemental file 1: Tables S11 and S12).

Discussion

In this prospective study of adults with diabetes, we demonstrated that CHIP was associated with an increased risk of CVD, particularly HF and CHD, but not with stroke. We also identified that specific gene mutations of CHIP, such as *TET2* and *SF3B1*, were related to CVD risk, whereas the *DNMT3A*, *TET2*, and *SF3B1* genes were linked primarily to an increased risk of HF. Moreover, health indictors including BMI, HbA1c, BP, and LDL did not significantly modify the association between CHIP and CVD. Compared to those without CHIP, diabetic patients with CHIP, even having ideal BMI, HbA1c, BP, and LDL, still exhibited a significantly or non-significantly increased risk of CVD. This finding suggests that the adverse effect of CHIP may not be effectively mitigated by maintaining ideal health indicators.

Leveraging validated human genetic instruments, for the first time, we investigated the associations of CHIP with total and specific cardiovascular diseases among patients with diabetes. In contrast to other pre-malignant entities, CHIP exerts a broader systemic influence not limited to the hematopoietic system [33]. For example, CHIP has been associated with a greater risk of type 2 diabetes [7] and CVD [9, 34] and is related to worse outcomes after arteriosclerotic events, including stroke, myocardial infarction, decompensated heart failure and cardiogenic shock [33]. CVD is widely accepted as the leading cause of morbidity and mortality in patients with diabetes [35], and both CVD and diabetes are the two major chronic diseases that manifest with increasing age. Concurrently, aging contributes to the accumulation of mutations in somatic cells, with CHIP serving as a hallmark of aging [36], which suggests the necessity of exploring the relationship between CHIP and CVD risk in the diabetic population. Our study found that patients with diabetes and CHIP have an approximately 7% higher absolute risk for developing CVD, underscoring the importance for early clinical screening and intervention in this high-risk population. Moreover, CHIP was associated with 21%, 18%, and 73% increased risks of CVD, CHD, and HF, respectively, independent of traditional risk factors. The positive association between CHIP and the risk of cardiovascular outcomes we found aligns with what has been shown in recent prospective studies among the general population [8, 37]. Prior meta-analysis indicated that CHIP was associated with 14% greater risk of stroke, however, each cohort involved in this paper did not show significant association of CHIP with stroke [38]. Among patients with diabetes, we did not observe a significant association between CHIP and stroke. These results may be due to limited confounders adjusted in previous study (age, sex, and race), different populations (general population vs. diabetic patients), and smaller sample size in our study. Moreover, the biological mechanisms underlying different stroke subtypes are varied, encompassing not only increased inflammation but also vascular rupture and thrombosis [39]. Although a study supported the positive association between CHIP and risk of ischemic stroke risk [34], the pooled effect was significant for hemorrhagic stroke, but not for ischemic stroke [38]. And within diabetic population, our findings showed no significant association between CHIP and either ischemic or hemorrhagic stroke, which warrants further confirmation in subsequent studies.

Additionally, we presented the relationship between specific gene mutations in CHIP and CVD among people with diabetes. Similar to healthy individuals, the epigenetic regulators *DNMT3A*, *TET2*, and *ASXL1* represented the top 3 mutated CHIP-associated genes in people with diabetes. We observed that the highest risks of CVD and HF were for individuals carrying CHIP mutations in *SF3B1* or *TET2*. Mutations in the *SF3B1* gene are commonly associated with abnormal RNA splicing, leading to defects in the export of mRNAs encoding genes involved in translation and cellular dysfunction. Studies have shown that patients with *SF3B1*-mutant CHIP have increased circulating levels of IL-18 [40] and an increased risk of adverse outcomes for those with established atherosclerotic cardiovascular diseases [27]. Moreover, both observational studies in the general population and animal research have indicated that *TET2* mutations, the most extensively studied mutation in CHIP, were associated with a greater risk of cardiovascular diseases and diabetes [7, 41, 42]. In addition, CHIP driven by mutations in *DNMT3A* and *ASXL1* was associated with HF risk. This finding aligns with a previous finding that *DNMT3A* was linked less strongly to CAD than to other CHIP types, such as *TET2* [27, 43], whereas *DNMT3A* mutations portended a worse prognosis in the setting of

ST-segment elevation myocardial infarction and chronic ischemic heart failure [43, 44]. Overall, the prominent association of certain genes like *SF3B1* and *TET2* with CVD in the patients with diabetes suggested that there was a clinical implication for targeted detection of mutations in CHIP genes. It allows for the precise identification of high-risk population, enabling more targeted and early intervention strategies for CVD to be implemented in diabetic patients.

The positive relationship between CHIP and CVD incidence was consistently observed across various subgroups, with no significant interactions detected between age, sex, health indicators, and CHIP. We further conducted a joint analysis of four health indicators and CHIP. Compared to individuals without CHIP, those with CHIP and had non-ideal level of health indicators exhibited a significantly higher risk of CVD, as expected. However, among patients with CHIP who achieved any one of the individual ideal health indicators, the risk of CVD remained elevated. The excess risk observed for BMI and HbA1c was non-significant, and this is probably attributed to the limited sample size and power. Interestingly, patients with CHIP and ideal LDL levels appear to have a greater increased risk of CVD than those with non-ideal LDL. It is important to note that the optimal LDL level may vary across different populations, and lower LDL levels did not necessarily correlate with a reduced risk of CVD mortality [45]. Although these indicators are essential for assessing metabolic health in patients with diabetes, capturing key aspects of glycemic control, lipid metabolism, and general health, such as BMI and BP [46], it is important to recognize that CHIP may contribute to CVD risk regardless of the health indicator status. Therefore, a comprehensive clinical management strategy that addresses not only health indicators but also CHIP is warranted. Further studies are necessary to validate our findings in diverse populations.

Considerable mechanistic studies have focused on inflammation in which CHIP mutations derived to the pathogenesis of CVD. For example, *TET2*-deficient mice had an elevated circulating levels of IL-1β and IL-6, which were the downstream mediators of the NLRP3 inflammasome, by which accelerated the development of atherosclerosis and HF [41, 42]. It was consistent for people who carried *TET2* mutation exhibit a higher level of IL-1β than non-carriers [40, 47]. More importantly, inhibition of inflammasome activation, along with the subsequent suppression of IL-1β activation, was sufficient to reverse accelerated atherosclerosis [41] and ameliorate the diminished cardiac function [48] in *TET2*-deficient mice. Furthermore, dysfunction in spliceosome components was also correlated with stronger inflammatory responses [49]. Myeloid cell lines harboring mutations in *SF3B1*, *SRSF2*, or *U2AF1* exhibit an enrichment of IL-6 mRNA [50]. In addition, epigenetic modifications, particularly DNAm, was involved in the pathogenesis of cardiovascular diseases in patients with diabetes [51–53]. Recent study evaluated the association of DNAm with CHIP, suggesting that distinct DNAm profiles were related to the impaired activity of *DNMT3A* and *TET2* [15]. Therefore, DNAm may also play a role under the relationship between CHIP and development of cardiovascular events in patients with diabetes.

Although our study benefited from next-generation sequencing, a prospective cohort of individuals with diabetes, and long-term follow-up, the results must be interpreted within the context of several limitations. First, WES offers greater sensitivity for identifying variants in coding regions than does whole-genome sequencing, although it may be less sensitive than targeted deep sequencing methods. Therefore, targeted sequencing may be a better approach to investigate these relationships in the future. Second, although careful adjustment for various confounders was performed, we acknowledged that bias from unknown and unmeasured confounding factors may still exist. Third, the primary reliance on ICD-10 codes for outcomes and diabetes ascertainment could lead to potential misclassification, and substyles for HF such as HFpEF and HFrEF could not be identified in this study. Fourth, cardiovascular disease such as atherosclerosis could accelerate the expansion of CHIP [54], indicating a reverse causation. We excluded baseline CVD cases in the main analysis and further excluded those incident CVD within the first 2 years of follow-up in the sensitivity analysis, minimizing the potential influence of reverse causation as much as possible. Fifth, the ideal health indicators may have different cutoff points depending on the study population. Although we selected additional cutoff points for the health indicators in the supplementary analysis, it is necessary to confirm our results in the future. Finally, the study population was mostly of white European descent, which limits the generalizability of our findings to other ethnicities.

Conclusions

The current study identified CHIP as a novel risk factor for incident CVD in individuals with diabetes, independent of health indicator levels. Diabetic patients with CHIP but ideal health indicators still exhibited higher residual CVD risk compared with diabetic patients without CHIP. Further research is needed to confirm our findings and explore effective preventive strategies for individuals with diabetes and CHIP.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12933-025-02626-7 .

Supplementary Material 1.

Author contributions
N.W. and Y.L. concepted this paper. Y.S., Y.Y., and Y.W. wrote the manuscript, researched the data, and reviewed/edited the manuscript. L.C., B.W., W.X. and X.T. reviewed/edited the manuscript. All the authors approved the final manuscript.

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Availability of data and materials
This study was approved by the UK Biobank (application number 77740).

Declarations

Ethics approval and consent to participate
The UK Biobank study was approved by the North West Multicenter Research Ethics Committee (reference no. 16/NW/0274), and all participants provided informed consent.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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