JIM Original Article

doi: 10.1111/joim.20080

Clonal hematopoiesis of indeterminate potential and the risk of autoimmune diseases

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Abstract. Wu H, Wei J, Yu Y, Wang N, Tan X. Clonal hematopoiesis of indeterminate potential and the risk of autoimmune diseases. *J Intern Med*. 2025;**297**:642–56.

Background. Clonal hematopoiesis of indeterminate potential (CHIP), characterized by the age-related expansion of blood cells carrying preleukemic mutations, is associated with immune aging. This study aimed to investigate the association between CHIP and established autoimmune diseases.

Methods. We analyzed baseline data from 456,692 UK Biobank participants with available whole-exome sequences. The primary outcome was 19 autoimmune disorders. Associations among any CHIP (variant allele fraction ≥2%), large CHIP clones (variant allele fraction ≥10%), and gene-specific CHIP subtypes with the incidence of autoimmune diseases were assessed using Cox regression. Mediation analysis was performed to explore the role of inflammation in the link between CHIP and autoimmune diseases.

Results. We identified 17,433 any CHIP and 11,970 large CHIP at baseline. Participants with any and large CHIP were associated with 44% and 43% higher risk for Crohn's disease, 25% and 33% higher risk for psoriasis, 13% and 14% higher risk for rheumatoid arthritis, and 35% and 55% higher risk for vasculitis, respectively. Participants with CHIP status were associated with increased levels of inflammatory markers, including white blood cell, platelets, neutrophils, and neutrophil-to-lymphocyte ratio, with overall mediation ratios of 16.3% for Crohn's disease, 7.1% for psoriasis, 23.2% for rheumatoid arthritis, and 7.2% for vasculitis.

Conclusions. CHIP was associated with an increased risk for incident multiple autoimmune diseases, including Crohn's disease, psoriasis, vasculitis, and rheumatoid arthritis, potentially mediated by elevated inflammatory levels. Future research is needed to clarify the mechanisms underlying these associations and to explore potential interventions to reduce the associated risk.

Keywords: autoimmune diseases, clonal hematopoiesis of indeterminate potential, cohort study, inflammatory level, UK Biobank

Abbreviations: CCUS, clonal cytopenia of undetermined significance; CHRS, clonal hematopoiesis risk score; CHIP, clonal hematopoiesis of indeterminate potential; GCA, giant cell arteritis; IBD, inflammatory bowel disease; IL-1β, interleukin-1 beta; INFLA score, low-grade chronic inflammation score; NLR, neutrophil-to-lymphocyte ratio; VAF, variant allele frequency; WBC, white blood cell; WES, whole-exome sequencing; WGS, whole genome sequencing

Introduction

Autoimmune diseases are multifactorial and complex, potentially affecting every organ system in the body. The adaptive immune system is tasked with distinguishing between pathogens and self-antigens; when self-tolerance fails, autoimmune diseases can arise, leading to damage of the host's tissues [1]. Recent findings estimated that approximately 10% of the population is affected by these diseases, with their burden steadily increasing over time at differing rates across various diseases [2]. Accumulated evidence

indicated genetic susceptibility and environmental triggers as major contributors to autoimmune disease risk [3]. Additionally, the immune system undergoes significant changes with advancing age, and highlighting immune aging is a critical determinant in the progression of these diseases [4]. Although experiments in mouse models have laid the groundwork for our understanding of basic immunology, these findings have largely failed to translate into effective treatments for human diseases [5]. Consequently, most autoimmune conditions remain incurable and require lifelong management.

As people age, tissues also accumulate somatic mutations [6, 7], occasionally granting selective growth advantages to certain cells [8]. When such mutations arise in hematopoietic stem cells, they can initiate a clone of cells with enhanced survival capabilities [9], leading to the expansion of this clone in the peripheral blood—a phenomenon known as clonal hematopoiesis [10]. If a cancer-associated mutation is detected in blood cells at a variant allele frequency (VAF) of 2% or greater, and no hematologic malignancy or other clonal disorder is identified, this condition is referred to as clonal hematopoiesis of indeterminate potential (CHIP) [11]. The prevalence of CHIP increases with age, affecting 10%–20% of individuals over the age of 70 [12]. Emerging evidence indicates that CHIP is a novel contributor to accelerated immune aging. Mutations associated with CHIP tend to skew hematopoietic stem cells toward myeloid over lymphoid lineages, disproportionately affecting circulating myeloid cells and impairing neutrophil functions, such as phagocytosis and the formation of extracellular traps [13, 14]. CHIP may contribute to the inflammatory processes associated with aging [15], which plays a significant role in the etiology of autoimmune diseases [16]. Therefore, CHIP may play a significant role in immune aging and the development of autoimmune diseases.

We conducted a prospective evaluation of the association between CHIP and the incidence of autoimmune diseases, investigating whether this risk is influenced by specific driver genes. This assessment leveraged newly released whole-exome sequencing (WES) data from peripheral blood samples of 450,000 participants in the UK Biobank [17]. Moreover, we studied the role of inflammatory markers in the association between CHIP and the incidence of autoimmune disease risk.

Methods

Study design and population

The UK Biobank is a large-scale cohort study initiated between 2006 and 2010, enrolling over half a million participants aged 37–73 years from 22 assessment centers across England, Scotland, and Wales. At baseline, all participants completed a comprehensive series of assessments, with detailed information available elsewhere [18]. The study was approved by the North West Multicenter Research Ethics Committee, and all participants provided written informed consent.

For the current analysis, we restricted the sample to 457,174 participants with available WES data. We excluded individuals with any prevalent hematologic malignancy, those with more than 10 third-degree relatives identified or excluded from the kinship inference process, and participants who were outliers in heterozygosity, leaving a total of 456,692 participants in the analytic cohort. Participants with baseline autoimmune diseases were excluded from each corresponding autoimmune disease cohort analysis. See Fig. S1 for additional cohort-specific information.

Exposures

The phenotypes associated with CHIP and related conditions were identified from whole blood-derived WES [19], which was conducted on the Illumina NovaSeq 6000 platform at the Regeneron Genetics Center [17]. In this study, the somatic variant calling pipeline utilized for detecting CHIP is Mutect2, a component of the Genome Analysis Toolkit [20] (Benjamin D, 2020, calling somatic SNVs and indels with Mutect2. [preprint]). Mutect2 utilizes local haplotype assembly and Bayesian modeling to identify single nucleotide alterations and small indels. The original CHIP gene list, consisting of 74 genes [21], was refined by excluding 16 genes that showed no positive association with age, were absent in myeloid cancer cases, and were not recognized as drivers of myeloid CHIP in published studies [22]. CHIP mutations were ultimately identified within a curated list of 58 genes associated with clonal hematopoiesis and myeloid malignancies, as detailed in Table S1 [19]. Based on the previously filtering criteria related to sequencing depth, variants were excluded if the total read depth was below 20, the alternate allele read depth below 5, or if there was insufficient support from

both forward and reverse reads [19]. The workflow for CHIP variant ascertainment is shown in Fig. S2.

The co-primary exposures in the study were the presence of any CHIP, identified by a conventional VAF of ≥2%, and large CHIP, defined as VAF ≥ 10%, which suggests a higher risk for more severe adverse outcomes. In addition, we conducted a separate analysis of gene-specific CHIP subtypes, focusing on the most common driver genes (DNMT3A, TET2, ASXL1, and JAK2), DNA damage repair genes (PPM1D and TP53), and spliceosome-related genes (PRPF8, SF3B1, SRSF2, U2AF1, and ZRSR2). Additional analyses tested whether the clonal hematopoiesis risk score (CHRS) was associated with incident autoimmune disease. CHRS is designed to predict the likelihood of incident myeloid malignancies in individuals with CHIP or clonal cytopenia of undetermined significance (CCUS) [23]. The detail of CHRS was provided in Supporting Information and Table S2.

Outcome ascertainment

We examined 19 common autoimmune disorders: Addison's disease, ankylosing spondylitis, coeliac disease, Type 1 diabetes, Graves' disease, Crohn's disease, ulcerative colitis, multiple sclerosis, myasthenia gravis, pernicious anemia, polymyalgia rheumatica, primary biliary cholangitis, psoriasis, rheumatoid arthritis, Sjögren's syndrome, systemic lupus erythematosus, systemic sclerosis, vasculitis, and vitiligo [2]. Although the autoimmune causes of some of these diseases are still debated, and they might be more accurately described as immune-mediated inflammatory diseases, we refer to this group collectively as autoimmune diseases for clarity and readability. Vasculitis is a broad category that encompasses several types of vascular inflammation: large vessel vasculitis (such as giant cell arteritis [GCA]), medium vessel vasculitis (such as polyarteritis nodosa), small vessel vasculitis (including microscopic polyangiitis and granulomatosis with polyangiitis), as well as cutaneous vasculitis.

For each condition, diagnoses were extracted from primary or secondary care records using diagnostic codes from the International Classification of Diseases, tenth revision (ICD-10; Table S3). The time-to-event was calculated from the date of blood draw associated with CHIP to the earliest occurrence of either autoimmune disease diagnosis, death, or the last follow-up date (October 31, 2022 for England, August 31, 2022 for Scotland, and May 31, 2022 for Wales).

Inflammatory markers

We selected inflammatory markers known to be involved in various inflammatory processes, including lymphocytes, white blood cell (WBC) count, platelet count, neutrophil count, CRP level, and the neutrophil-to-lymphocyte ratio (NLR). To address skewness and allow for meaningful group comparisons, we applied a natural logarithmic transformation to the markers and then standardized the transformed values within each group. In addition to single inflammatory markers, we calculated the low-grade chronic inflammation (INFLA) score, and a composite index used to assess overall inflammation levels (Supporting Information) [24].

Statistical analysis

Baseline characteristics were presented as means (SD) for continuous variables and percentages for categorical variables. Cox proportional hazards regression models estimated hazard ratios (HRs) and 95% confidence intervals (CIs) for the association among any CHIP, large CHIP, and each autoimmune disease risk. The proportional hazards assumption was tested using Schoenfeld residuals. The model was adjusted for multiple covariates, baseline age, sex, ethnicity, BMI, smoking status, drinking status, healthy diet score, educational level, Townsend deprivation index, and metabolic equivalent task. Kaplan–Meier curves were generated to depict cumulative incidence of autoimmune diseases. Details regarding covariates are provided in the Supporting Information.

To explore potential mechanisms linking CHIP to autoimmune diseases, we analyzed inflammatory markers. We initially used linear regression to estimate the effect of CHIP status on these markers. For those markers significantly associated with CHIP status, we further evaluated their mediating effect in the association between CHIP status and the risk of autoimmune diseases.

In supplementary analyses, we examined the association between gene-specific CHIP and autoimmune diseases. Additionally, we assessed the association between CHRS and autoimmune diseases, with CHRS analyzed both as a categorical and continuous variable. Subgroup analyses were conducted to determine whether the relationship between CHIP status and autoimmune diseases

varied by age and sex, examining potential modifying effects. Several sensitivity analyses were conducted to investigate potential sources of bias in our findings. First, we excluded participants who were potential cases of CCUS. Second, patients were excluded if they had multiple autoimmune diseases at baseline to avoid potential confounding effects from the coexistence of several autoimmune conditions. Third, events occurring within 2 years after baseline assessments were excluded to mitigate the risk of reverse causality. Fourth, we utilized the Fine and Gray models to account for the competing risks posed by deaths.

Statistical significance was defined as a two-sided $p < 0.05$, with Bonferroni correction applied for multiple comparisons. All statistical analyses were conducted using SAS version 9.4 (SAS Institute Inc.) and R version 4.3.1.

Results

Baseline characteristics

A total of 456,692 participants were included in the analysis, with 17,433 (3.82%) had any CHIP. Among all participants, DNMT3A variants was detected in 10,945 (2.40%), followed by TET2 variants in 2566 (0.47%), ASXL1 variants in 1604 (0.25%), spliceosome genes variants in 500 (0.11%) and PPM1D variants in 499 (0.11%) (Table 1; Fig. S3). The most frequent mutation in the UK Biobank population was DNMT3A:NM_022552:exon23:c.G2645A:p.R882H, with a frequency of 0.17%. A total of 1063 participants (6.10% of CHIP carriers) had mutations in more than one driver gene (Fig. S4), with mutation combinations presented in Fig. S5. Table 1 presents the characteristics of participants categorized by CHIP status. Those with any CHIP tended to be older, had higher body weight, and lower levels of education. Additionally, they were more likely to be current smokers and had healthier diets. Table S5 presents the demographic characteristics categorized by the type of autoimmune disease at the baseline visit, whereas Table S6 lists the baseline characteristics of participants with CHIP, stratified by VAF <10% versus ≥10%.

CHIP and autoimmune diseases

After excluding participants with each autoimmune disease at baseline for the corresponding analysis, we investigated the association between CHIP and the risk of developing various autoimmune diseases. During a median follow-up of 13.6 years, we observed significant associations between CHIP and several autoimmune conditions, including Crohn's disease, psoriasis, and vasculitis. Fig. 1 showed the cumulative incidence of autoimmune diseases by CHIP status. The association with rheumatoid arthritis requires cautious interpretation, as it demonstrated a p value of 0.02 in the fully adjusted model (Table 2). The presence of any CHIP or large CHIP, compared to no CHIP, was associated with a 49% and 48% higher risk of Crohn's disease, respectively. The associations were more pronounced for larger clones: CHIP with VAF ≥ 10% was linked to a 38% higher risk of psoriasis and a 58% higher risk of vasculitis. Furthermore, chip was associated with incident rheumatoid arthritis with an HRs of 1.13 (95% CI, 1.02–1.26; $p = 0.02$) for any CHIP and 1.14 (95% CI, 1.01–1.30; $p = 0.03$) for large CHIP.

Additionally, we investigated the association between CHRS and the risk of autoimmune diseases (Table S7). Each one-point increase in CHRS was associated with a higher risk of autoimmune diseases among individuals with CHIP. Subgroup analyses stratified by age and sex revealed consistent, with no significant interaction (Table S8). In sensitivity analyses, the association between CHIP and the risk of autoimmune diseases remained robust, even after excluding participants who were potential cases of CCUS, those with multiple autoimmune diseases at baseline, those diagnosed with autoimmune diseases within the first 2 years of follow-up, or when competing risk models were applied (Tables S9–S12).

Gene-specific CHIP and autoimmune diseases

The cumulative incidence of autoimmune diseases by gene-specific CHIP status is presented in Fig. 2. The results indicated that both any ASXL1 CHIP and large ASXL1 CHIP were associated with a 2.92- and 2.77-fold increased risk of developing Crohn's disease, respectively (Table 3). CHIP clones driven by mutations in TET2 and JAK2 consistently showed the strongest associations with psoriasis. JAK2 CHIP was identified as the highest risk subtype for psoriasis, with an HR of 6.05 (95% CI, 2.52–14.5) for both any CHIP and large CHIP. Additionally, mutations in spliceosome-related genes were associated with an increased risk of rheumatoid arthritis and vasculitis. However, only the association between any spliceosome gene CHIP and vasculitis remained significant after

Table 1. *Baseline characteristics of the study participants.*[a]

Characteristics	Overall	No CHIP	Any CHIP	*p* value[b]
No. of participants	456,692	439,259	17,433	
Age (years)	56.5 (8.08)	56.4 (8.09)	60.6 (6.79)	<0.0001
Sex (male, %)	208,993 (45.8)	200,980 (45.8)	8013 (46.0)	0.59
Ethnicity (%)				<0.0001
White	430,845 (94.3)	414,187 (94.3)	16,658 (95.6)	
Non-White	23,693 (5.19)	22,996 (5.24)	697 (4.00)	
Missing value	2154 (0.47)	2076 (0.47)	78 (0.45)	
Body mass index categories (%)				<0.01
Normal/underweight (<25 kg/m^2)	150,461 (33.0)	144,936 (33.0)	5525 (31.7)	
Overweight (25–30 kg/m^2)	193,662 (42.4)	186,122 (42.4)	7540 (43.3)	
Obese (≥30 kg/m^2)	110,722 (24.2)	106,426 (24.2)	4296 (24.6)	
Missing value	1847 (0.40)	1775 (0.40)	72 (0.41)	
Townson depretive index	−1.32 (3.08)	−1.30 (3.08)	−1.30 (3.10)	0.80
Education level (%)				<0.0001
College or higher	148,208 (32.5)	143,181 (32.6)	5027 (28.8)	
Any other qualification	307,914 (67.4)	295,527 (67.3)	12,387 (71.1)	
Missing value	570 (0.12)	551 (0.13)	19 (0.11)	
Metabolic equivalent task (h/week)	44.2 (44.3)	44.1 (44.3)	45.1 (44.7)	<0.01
Missing (%)	103,306 (22.6)	98,968 (22.5)	4338 (24.9)	
Smoking status (%)				<0.0001
Non-smoker	249,027 (54.5)	240,692 (54.8)	8335 (47.8)	
Ex-smoker	157,637 (34.5)	150,824 (34.3)	6813 (39.1)	
Current smoker	47,684 (10.4)	45,522 (10.4)	2162 (12.4)	
Missing value	2344 (0.51)	2221 (0.51)	123 (0.71)	
Drinking status (%)				0.58
Non-drinker	20,034 (4.39)	19,288 (4.39)	746 (4.28)	
Ex-drinker	16,266 (3.56)	15,594 (3.55)	672 (3.85)	
Current drinker	419,228 (91.8)	403,262 (91.8)	15,966 (91.6)	
Missing value	1164 (0.25)	1115 (0.25)	49 (0.28)	
Healthy diet score	3.43 (1.17)	3.43 (1.17)	3.47 (1.17)	<0.0001
Inflammation[c]				
Lymphocyte count	1.06 (0.20)	1.06 (0.20)	1.06 (0.22)	0.15
White blood cell count	2.04 (0.22)	2.03 (0.22)	2.05 (0.23)	<0.0001
Platelet count	5.51 (0.24)	5.51 (0.24)	5.52 (0.26)	<0.001
Neutrophil count	1.62 (0.26)	1.62 (0.26)	1.64 (0.27)	<0.0001
CRP	0.99 (0.65)	0.99 (0.65)	1.04 (0.66)	<0.0001
NLR	1.17 (0.28)	1.17 (0.28)	1.19 (0.30)	<0.0001
INFLA score	0.04 (6.09)	0.01 (6.08)	0.68 (6.15)	<0.0001

Abbreviations: CHIP, clonal hematopoiesis of indeterminate potential; CRP, C-reactive protein; INFLA score, low-grade chronic inflammation score; NLR, neutrophil-to-lymphocyte ratio.
[a]Continuous variables are expressed as mean (standard deviation), and categorical variables are expressed as *n* (%).
[b]Chi-squared was used for categorical variables and one-way analysis of variance for continuous variables.
[c]Inflammation was natural log transformed except INFLA score. Inflammation subset ($N = 423,187$).

Table 2. *Association of any and large (i.e., variant allele fraction ≥ 10%) clonal hematopoiesis of indeterminate potential with incident autoimmune disorders.*[a]

	Any CHIP					CHIP with VAF ≥ 10%				
		Minimally adjusted model		Fully adjusted model			Minimally adjusted model		Fully adjusted model	
	Cases	HR (95% CI)	*p* value	HR (95% CI)	*p* value	Cases	HR (95% CI)	*p* value	HR (95% CI)	*p* value
Addison's disease	280	1.35 (0.80, 2.28)[b]	0.26	1.34 (0.79, 2.25)	0.28	274	1.19 (0.61, 2.31)	0.62	1.17 (0.60, 2.28)	0.65
Ankylosing spondylitis	850	0.76 (0.52, 1.12)	0.16	0.74 (0.50, 1.09)	0.13	842	0.78 (0.49, 1.23)	0.28	0.76 (0.48, 1.20)	0.23
Coeliac disease	2219	0.83 (0.65, 1.04)	0.11	0.83 (0.66, 1.05)	0.11	2193	0.78 (0.58, 1.04)	0.09	0.78 (0.58, 1.04)	0.09
Type 1 diabetes	2592	1.08 (0.89, 1.30)	0.44	1.06 (0.88, 1.27)	0.57	2558	1.11 (0.90, 1.38)	0.34	1.09 (0.88, 1.35)	0.45
Graves' disease	3154	0.96 (0.80, 1.14)	0.64	0.94 (0.79, 1.12)	0.51	3113	0.96 (0.78, 1.19)	0.71	0.94 (0.76, 1.16)	0.57
Crohn's disease	1594	1.49 (1.20, 1.85)	<0.001**	1.44 (1.16, 1.79)	<0.001**	1566	1.48 (1.15, 1.92)	<0.001**	1.43 (1.11, 1.86)	<0.001**
Ulcerative colitis	2910	1.06 (0.88, 1.27)	0.57	1.03 (0.86, 1.24)	0.72	2871	1.04 (0.83, 1.30)	0.72	1.02 (0.82, 1.27)	0.88
Multiple sclerosis	1014	1.21 (0.89, 1.66)	0.22	1.18 (0.86, 1.61)	0.30	1001	1.24 (0.85, 1.79)	0.26	1.20 (0.83, 1.74)	0.34
Myasthenia gravis	291	0.81 (0.44, 1.48)	0.49	0.82 (0.45, 1.49)	0.51	288	0.85 (0.42, 1.73)	0.66	0.86 (0.43, 1.74)	0.68
Pernicious anemia	1966	1.00 (0.81, 1.24)	0.98	0.98 (0.80, 1.21)	0.86	1946	1.14 (0.90, 1.45)	0.28	1.11 (0.88, 1.41)	0.39
Polymyalgia rheumatica	4030	1.11 (0.97, 1.27)	0.12	1.11 (0.97, 1.27)	0.12	3958	1.12 (0.96, 1.31)	0.16	1.12 (0.95, 1.30)	0.17
Primary biliary cholangitis	306	1.07 (0.62, 1.83)	0.81	1.04 (0.61, 1.78)	0.88	297	0.56 (0.23, 1.35)	0.19	0.54 (0.22, 1.31)	0.17
Psoriasis	4500	1.29 (1.13, 1.48)	<0.001**	1.25 (1.10, 1.43)	<0.001**	4437	1.38 (1.18, 1.61)	<0.001**	1.33 (1.14, 1.55)	<0.001**
Rheumatoid arthritis	7209	1.16 (1.04, 1.29)	<0.01*	1.13 (1.02, 1.26)	0.02*	7110	1.18 (1.04, 1.33)	0.01*	1.14 (1.01, 1.30)	0.03*
Sjögren's syndrome	994	1.25 (0.94, 1.65)	0.12	1.25 (0.94, 1.65)	0.12	977	1.24 (0.89, 1.73)	0.20	1.24 (0.88, 1.73)	0.22
Systemic lupus erythematosus	574	1.25 (0.86, 1.82)	0.24	1.22 (0.84, 1.78)	0.29	565	1.27 (0.81, 1.98)	0.30	1.23 (0.79, 1.93)	0.36
Systemic sclerosis	269	1.42 (0.85, 2.36)	0.18	1.40 (0.84, 2.32)	0.20	265	1.56 (0.87, 2.79)	0.13	1.53 (0.85, 2.73)	0.15
Vasculitis	1982	1.37 (1.14, 1.64)	<0.001**	1.35 (1.12, 1.62)	<0.001**	1956	1.58 (1.29, 1.93)	**<0.0001****	1.55 (1.27, 1.90)	<0.0001**
Vitiligo	189	1.45 (0.78, 2.67)	0.24	1.45 (0.78, 2.67)	0.24	185	1.35 (0.63, 2.88)	0.44	1.35 (0.63, 2.87)	0.44

Note: Minimally adjusted model was adjusted for age, sex, and ethnicity. Fully adjusted model was additionally adjusted for BMI, smoking status, drinking status, healthy diet score, educational level, Townsend deprivation index, and metabolic equivalent task.

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

[a]Obtained by using multivariable Cox regression models in which participants without CHIP constitute the reference group.

[b]Hazard ratios (95% confidence interval) (all such values).

*p value < 0.05.

**Bonferroni corrected p value <0.0026 (i.e., 0.05/19).

Table 3. *Association of gene-specific clonal hematopoiesis of indeterminate potential (CHIP) subtypes with incident autoimmune disorders.*[a]

	Any CHIP					CHIP with VAF ≥ 10%				
		Minimally adjusted model		Fully adjusted model			Minimally adjusted model		Fully adjusted model	
	Cases	HR (95% CI)	*p* value	HR (95% CI)	*p* value	Cases	HR (95% CI)	*p* value	HR (95% CI)	*p* value
Crohn's disease										
DNMT3A	1552	1.27 (0.95, 1.71)[b]	0.11	1.24 (0.93, 1.67)	0.15	1536	1.38 (0.96, 1.99)	0.08	1.34 (0.93, 1.93)	0.11
TET2	1515	1.31 (0.69, 2.50)	0.41	1.26 (0.66, 2.43)	0.49	1513	1.25 (0.60, 2.61)	0.54	1.22 (0.58, 2.57)	0.60
ASXL1	1521	3.12 (1.87, 5.19)	<0.0001**	2.92 (1.78, 4.80)	<0.0001**	1516	7.64 (5.14, 11.4)	<0.0001**	2.77 (1.50, 5.09)	<0.001*
JAK2	1507	11.7 (4.02, 33.8)	<0.0001**	3.93 (0.62, 25.1)	0.15	1507	11.7 (4.02, 33.8)	<0.0001**	3.93 (0.62, 25.1)	0.15
PPM1D	1510	6.01 (3.08, 11.7)	<0.0001**	2.70 (1.02, 7.12)	0.04*	1508	3.11 (0.99, 9.76)	0.05*	1.98 (0.49, 7.91)	0.33
TP53	1508	4.37 (1.55, 12.4)	<0.01*	2.39 (0.60, 9.53)	0.22	1506	0.36 (0.01, 20.7)	0.62	–	
Spliceosome gene	1507	0.90 (0.13, 6.38)	0.92	0.84 (0.12, 6.00)	0.86	1507	1.06 (0.15, 7.53)	0.95	0.98 (0.14, 6.99)	0.99
Psoriasis										
DNMT3A	4387	1.10 (0.92, 1.32)	0.30	1.08 (0.90, 1.30)	0.40	4342	1.13 (0.90, 1.43)	0.28	1.11 (0.88, 1.40)	0.36
TET2	4309	1.96 (1.45, 2.64)	<0.0001**	1.85 (1.36, 2.52)	**<0.0001****	4301	1.96 (1.41, 2.74)	<0.0001**	**1.85 (1.32, 2.61)**	<0.0001**
ASXL1	4289	1.33 (0.87, 2.04)	0.19	1.16 (0.76, 1.78)	0.50	4284	1.48 (0.91, 2.40)	0.12	1.27 (0.77, 2.07)	0.35
JAK2	4272	5.66 (2.36, 13.6)	<0.0001**	6.05 (2.52, 14.5)	**<0.0001****	4272	5.66 (2.36, 13.6)	<0.0001**	6.05 (2.52, 14.5)	<0.0001**
PPM1D	4272	0.85 (0.32, 2.27)	0.75	0.79 (0.30, 2.12)	0.64	4272	1.32 (0.50, 3.51)	0.58	1.21 (0.46, 3.24)	0.70
TP53	4270	0.81 (0.20, 3.23)	0.76	0.77 (0.19, 3.06)	0.71	4270	1.03 (0.26, 4.14)	0.96	0.97 (0.24, 3.88)	0.97
Spliceosome gene	4272	1.05 (0.40, 2.81)	0.92	0.99 (0.37, 2.64)	0.98	4271	0.94 (0.30, 2.90)	0.91	0.87 (0.28, 2.69)	0.80
Rheumatoid arthritis										
DNMT3A	7061	1.12 (0.98, 1.28)	0.10	1.11 (0.97, 1.27)	0.13	6974	1.12 (0.94, 1.32)	0.21	1.10 (0.93, 1.31)	0.27
TET2	6888	1.21 (0.91, 1.61)	0.18	1.21 (0.91, 1.60)	0.20	6878	1.20 (0.87, 1.65)	0.27	1.19 (0.86, 1.63)	0.29
ASXL1	6867	1.10 (0.75, 1.60)	0.63	0.98 (0.67, 1.43)	0.90	6858	1.04 (0.66, 1.66)	0.86	0.93 (0.58, 1.47)	0.75
JAK2	6840	0.12 (0.00, 13.5)	0.37	0.05 (0.00, 91.2)	0.43	6840	0.12 (0.00, 13.5)	0.37	0.05 (0.00, 91.2)	0.43
PPM1D	6849	1.14 (0.59, 2.19)	0.70	1.07 (0.56, 2.06)	0.84	6849	1.87 (0.99, 3.54)	0.05	1.64 (0.85, 3.15)	0.14
TP53	6846	1.43 (0.65, 3.18)	0.38	1.38 (0.62, 3.07)	0.43	6846	1.92 (0.88, 4.20)	0.10	1.75 (0.78, 3.89)	0.17
Spliceosome gene	6852	2.41 (1.41, 4.11)	<0.0001**	2.02 (1.15, 3.55)	**<0.01***	6850	2.37 (1.32, 4.26)	<0.001*	1.96 (1.06, 3.64)	0.03*

(*Continued*)

Table 3. *(Continued)*

	Any CHIP					CHIP with VAF ≥ 10%				
		Minimally adjusted model		Fully adjusted model			Minimally adjusted model		Fully adjusted model	
	Cases	HR (95% CI)	*p* value	HR (95% CI)	*p* value	Cases	HR (95% CI)	*p* value	HR (95% CI)	*p* value
Vasculitis										
DNMT3A	1929	1.28 (1.01, 1.61)	**0.04***	1.27 (1.00, 1.60)	0.05*	1911	1.60 (1.22, 2.10)	<0.0001**	1.51 (1.16, 1.97)	<0.001*
TET2	1869	1.11 (0.68, 1.82)	0.67	1.11 (0.68, 1.82)	0.67	1869	1.26 (0.76, 2.09)	0.38	1.26 (0.75, 2.09)	0.38
ASXL1	1868	1.66 (0.98, 2.81)	0.06	1.56 (0.92, 2.64)	0.10	1867	2.18 (1.27, 3.75)	<0.01*	2.04 (1.19, 3.50)	<0.01*
JAK2	1857	1.70 (0.24, 12.1)	0.59	1.73 (0.24, 12.3)	0.58	1857	1.70 (0.24, 12.09)	0.59	1.73 (0.24, 12.26)	0.58
PPM1D	1862	2.35 (1.07, 5.15)	0.03	2.28 (1.04, 4.99)	0.04	1859	1.66 (0.54, 5.16)	0.38	1.59 (0.51, 4.92)	0.42
TP53	1859	2.25 (0.73, 6.91)	0.16	2.21 (0.72, 6.80)	0.16	1859	3.08 (1.05, 9.05)	0.04*	3.01 (1.02, 8.86)	0.05
Spliceosome gene	1860	3.41 (1.74, 6.69)	<0.0001**	3.26 (1.66, 6.39)	<0.0001**	1858	3.17 (1.51, 6.66)	**<0.001***	3.02 (1.44, 6.33)	<0.001*

Note: – There was not a sufficient number of participants to estimate hazard ratios. Minimally adjusted model was adjusted for age, sex, and ethnicity. Fully adjusted model was additionally adjusted for BMI, smoking status, drinking status, healthy diet score, educational level, Townsend deprivation index, and metabolic equivalent task. Spliceosome genes include PRPF8, SF3B1, SRSF2, U2AF1, and ZRSR2.

Abbreviations: CI, confidence interval; HR, hazard ratio; VAF, variant allele frequency.

[a]Obtained by using multivariable Cox regression models in which participants without CHIP constitute the reference group.

[b]Hazard ratios (95% confidence interval) (all such values).

*p value < 0.05.

**Bonferroni corrected p value < 0.00038 (i.e., 0.05/133).

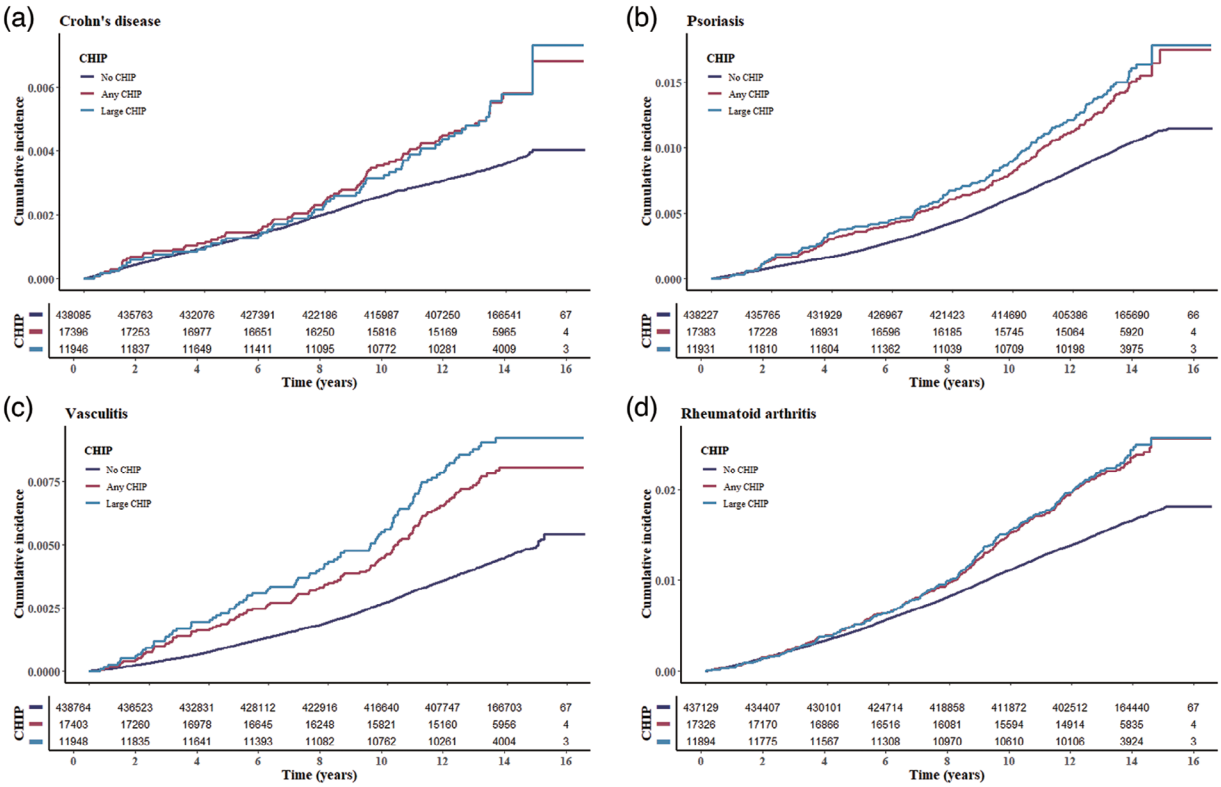

Fig. 1 ***Cumulative incidence of autoimmune diseases by CHIP Status***. *Cumulative incidence plots were constructed using the Kaplan–Meier method and represent (a) Crohn's disease, (b) psoriasis, (c) vasculitis, and (d) rheumatoid arthritis during a median follow-up of 13.6 years. CHIP indicates clonal hematopoiesis of indeterminate potential.*

Bonferroni correction, with an HR of 3.26 (95% CI, 1.66–6.39).

Exploratory analyses revealed that for those autoimmune diseases with no overall associations to CHIP, gene-specific CHIP may still be relevant (Table S13). For instance, mutations in spliceosome-related genes were associated with a higher risk of multiple sclerosis and polymyalgia rheumatica, whereas mutations in TP53 were linked to an increased risk of vitiligo. Although some of the other associations lost statistical significance after Bonferroni correction, they still point to potential insights that warrant further investigation.

CHIP and inflammatory marker levels

Participants with CHIP status were associated with increased levels of inflammatory markers, including WBC, platelets, neutrophils, NLR, and the INFLA score (Table S14). The association between gene-specific CHIP subtypes and inflammatory marker levels is presented in Table S15. In further analysis, the inflammatory markers linked to CHIP and INFLA scores played significant mediating roles in the relationship between CHIP and autoimmune diseases, with overall mediation ratios of 16.3% for Crohn's disease, 7.1% for psoriasis, 23.2% for rheumatoid arthritis, and 7.2% for vasculitis (Fig. 3). Similar mediation effects were observed in large CHIP cases. However, no mediation effect of CHIP status was found between any inflammatory markers and autoimmune diseases (data not shown).

Discussion

In this large-scale, prospective cohort study, we investigated the associations of CHIP with new-onset multiple autoimmune diseases. Our findings revealed significant associations between CHIP and the incidence of autoimmune diseases such as Crohn's disease, psoriasis, vasculitis, and

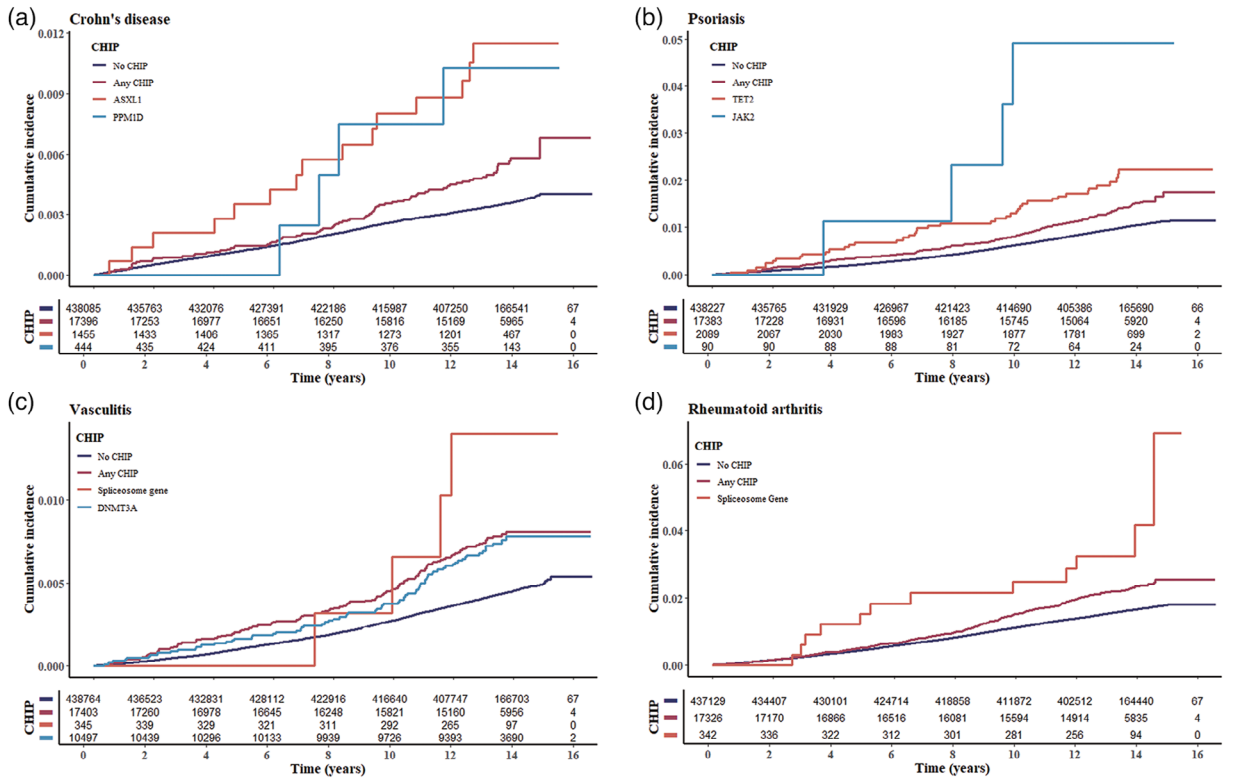

Fig. 2 ***Cumulative incidence of autoimmune diseases stratified by CHIP status and driver genes linked to autoimmune disease***. *Cumulative incidence plots were constructed using the Kaplan–Meier method and represent (a) Crohn's disease, (b) psoriasis, (c) vasculitis, and (d) rheumatoid arthritis during a median follow-up of 13.6 years. CHIP indicates clonal hematopoiesis of indeterminate potential.*

rheumatoid arthritis. Gene-specific analyses further highlighted that the elevated risk for different autoimmune diseases was primarily driven by distinct genes. Additionally, the presence of CHIP was associated with increased levels of inflammatory markers, which may mediate the link between CHIP and autoimmune diseases.

Previous studies have shown an increased prevalence of CHIP in patients with autoimmune diseases. In a cross-sectional analysis of 587 Crohn's disease patients, 441 ulcerative colitis patients, and 293 non-inflammatory bowel disease (IBD) controls, lymphoid-CHIP was found to be more prevalent in older IBD patients, whereas young Crohn's disease patients exhibited myeloid CHIP with high-risk features [25]. CHIP prevalence was also independently linked to age and vasculitis, including GCA, antibody-associated vasculitis, and Takayasu's arteritis [26]. Additionally, a UK Biobank study found that participants with clonal hematopoiesis had a 1.48-fold increased risk of incident GCA compared to those without [27]. A study involving 59 rheumatoid arthritis patients reported a CHIP prevalence of 17%, which increased to 25% in patients aged 70–79 [28]. Meanwhile, a preprint study found that large clonal hematopoiesis clones are associated with an increased risk of developing seropositive rheumatoid arthritis but have no link to seronegative rheumatoid arthritis (Corty R, 2024, Clonal Hematopoiesis and the Risk for Rheumatoid Arthritis [preprint]). This suggests that the role of CHIP in autoimmune diseases is complex, potentially being more relevant to conditions with strong immune-mediated components, such as seropositive rheumatoid arthritis, while showing a weaker association with diseases that do not rely on autoantibodies. Similarly, other studies have observed a higher prevalence of CHIP in patients with systemic sclerosis and systemic lupus erythematosus [29, 30]. However, the small sample sizes

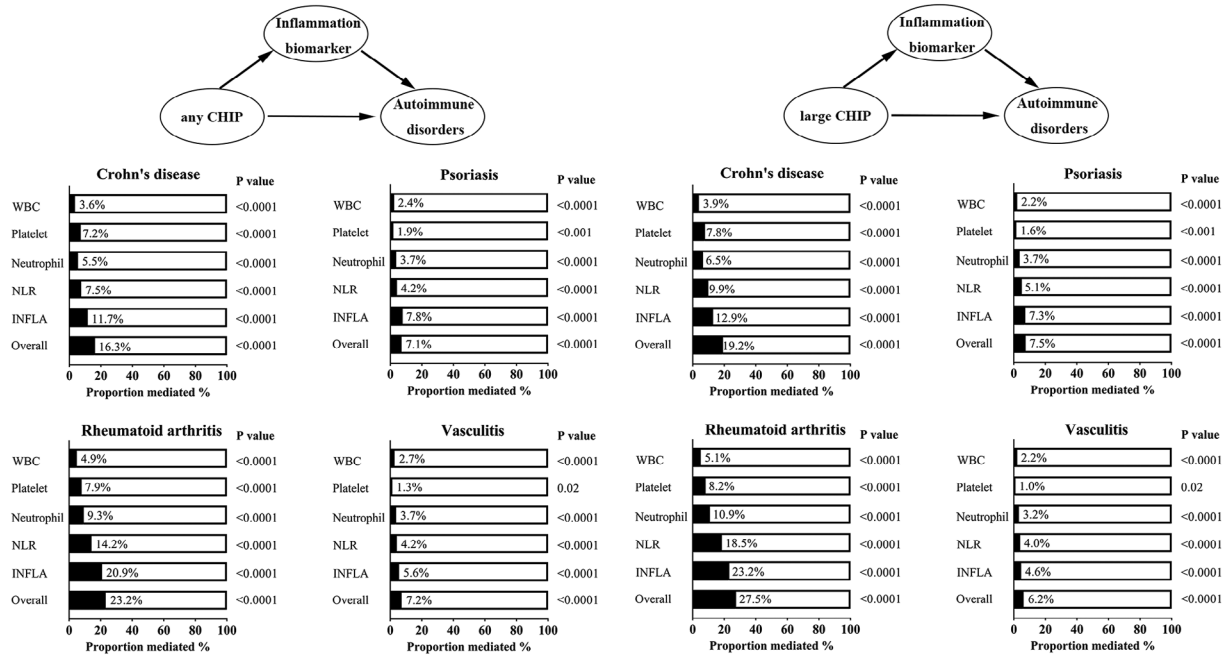

Fig. 3 ***Mediation analyses with inflammatory indicators between the association of CHIP status and autoimmune diseases***. *All models were adjusted the same as the fully adjusted model in Table 2. CHIP, clonal hematopoiesis of indeterminate potential; INFLA score, low-grade chronic inflammation score; NLR, neutrophil-to-lymphocyte ratio; WBC, white blood cell.*

and cross-sectional designs of some studies limit the ability to establish the temporal direction of these associations. Our study offers a prospective, systematic analysis of the association between CHIP and 19 autoimmune diseases, providing a clearer understanding of this link. These results suggest that CHIP is associated with an increased risk of developing autoimmune diseases, highlighting the need for further research into its role in these conditions.

The impact of CHIP on autoimmune diseases appears to vary depending on the specific driver mutation involved. Our analysis found that ASXL1 mutations in CHIP carriers were linked to the highest risk of Crohn's disease, whereas JAK2 and TET2 mutations were most associated with psoriasis. Mutations in spliceosome-related genes were tied to higher risks of vasculitis and rheumatoid arthritis. In contrast, the most common form, DNMT3A-mutant CHIP, did not show a significant association with autoimmune outcomes. Although other gene-specific CHIP subtypes were not strongly linked to autoimmune diseases, shared pathways among different CHIP mutations and autoimmune diseases may exist. Recent work suggesting the JAK2-V617F mutation promotes macrophage proliferation and glycolytic metabolism, leading to DNA replication stress and the activation of the AIM2 inflammasome [31]. Similarly, mice with heterozygous or homozygous Tet2 deficiencies exhibit increased activation of innate immune cells [21], a pattern also seen in human carriers of TET2 CHIP, who show elevated levels of circulating interleukin-1 beta (IL–1β) [32]. Preclinical evidence further indicates that spliceosome proteins, including SF3B1, SRSF2, or U2AF1, play a regulatory role in toll-like receptor-induced NF-κB activation and the production of inflammatory cytokines [33].

Given previous evidence linking dysregulated inflammation to CHIP [34, 35], we investigated whether elevated inflammation mediates the association between CHIP and autoimmune diseases. Consistent with previous studies, we found no overall association between CHIP and increased CRP levels [36–38]. However, in our current analysis, specific CHIP subtypes involving TET2, ASXL1, PPM1D, and spliceosome genes showed

a positive association with CRP, likely due to the larger sample size. Other inflammation biomarkers associated with CHIP have been found to mediate the association between CHIP and autoimmune diseases. Previous studies highlight the bidirectional relationship between CHIP and systemic inflammation in the risk of autoimmune diseases [35]. It is important to note that the occurrence of CHIP may also primarily reflect prolonged inflammation in older individuals, rather than being a direct cause of inflammation. Furthermore, many autoimmune diseases exhibit long latency periods and diagnostic delays, and the use of diagnostic codes to determine disease onset may inaccurate. Because inflammation itself can also contribute to or exacerbate certain autoimmune diseases, CHIP may simply reflect the presence of inflammation rather than directly driving disease onset. Further research is needed to better elucidate the complex relationship among CHIP, inflammation, and autoimmune diseases.

Although the mediation effects in our study reached statistical significance, some were relatively modest in magnitude, likely due to thorough adjustment for various demographic, anthropometric, and socioeconomic factors, leaving the effect sizes to represent the residual variance unexplained by these covariates. Nonetheless, the large sample size strengthens the study's ability to detect subtle associations that smaller samples might miss, aiding the development of evidence-based guidelines for broader populations. The relatively modest magnitude can also be attributed to the fact that the inflammatory biomarkers analyzed accounted for only a small portion of the total variance, indicating the potential involvement of other markers such as tumor necrosis factor-alpha, IL-1β, and interleukin-6. Furthermore, in addition to inflammation, other mechanistic pathways may also contribute to mediating the relationship between CHIP and autoimmune diseases.

Individual variations exist in the timeline of immune system aging [39], with CHIP emerging as a factor that potentially accelerates this process [40]. Autoimmune diseases often arise from the aging-related deterioration of key cellular processes in immune effector cells, such as genomic instability, mitochondrial dysfunction, impaired protein homeostasis, reduced lysosomal degradation, and decreased autophagy efficiency [4]. Specifically, aging T cells display a restricted receptor repertoire, limiting their ability to respond to new antigens and increasing the risk of self-reactivity [41]. Similarly, mature B cells show reduced adaptability in humoral responses due to impaired class switch recombination and decreased somatic hypermutation [42]. Additionally, aging impacts innate immune cells, resulting in diminished recognition of pathogen- and damage-associated molecular patterns, reduced phagocytic capacity, and dysregulated cytokine production [42]. These cumulative changes disrupt immune tolerance and promote the activation of pathogenic immune cells, which may trigger and drive the progression of autoimmune diseases. Further research is needed to elucidate the pathways driving autoimmune disease risk in individuals with CHIP.

The major strengths of this study include large sample size, extended survey periods, well-defined and validated data on confounders, as well as the use of next-generation sequencing methods to identify CHIP. However, several limitations exist. First, WES offers greater sensitivity than whole genome sequencing (WGS) for detecting coding region variants but may be less sensitive than targeted deep sequencing methods [43], suggesting that future studies should incorporate targeted sequencing to further explore these relationships. Second, CHIP status was only assessed at baseline, making it challenging to examine time-varying changes in CHIP. Third, the predominantly European ancestry and generally healthier profile of UK Biobank participants may limit the generalizability of the findings to other populations. Nonetheless, the study provides broadly applicable and robust estimates of exposure-outcome associations. Fourth, we did not account for TP53 copy number variations, as our analysis was based on WES instead of WGS, which is needed to assess copy number changes. Previous studies have shown that TP53 mutations undergo copy number gain years prior to tumor diagnosis [44], and adjusting for these variations could provide additional insights. This should be considered in future research. Lastly, causal inferences cannot be drawn from this observational study; however, this limitation was mitigated by adjusting for potential confounders and excluding participants diagnosed with autoimmune diseases within the first 2 years, ensuring the consistency of our findings.

Conclusion

The current study identifies that CHIP is associated with an increased risk of developing multiple autoimmune diseases, including Crohn's disease, psoriasis, vasculitis, and rheumatoid arthritis, potentially mediated by elevated inflammatory levels. Further research is necessary to elucidate novel mechanisms by which specific CHIP subtypes contribute to the increased risk of autoimmune diseases and to investigate potential interventions to reduce the risk.

Author contributions

Hanzhang Wu: Conceptualization; methodology; software; investigation; writing—original draft; writing—review and editing; visualization. **Jiahe Wei**: Investigation; writing—review and editing. **Yuefeng Yu**: Investigation; data curation; writing—review and editing. **Ningjian Wang**: Methodology; software; investigation; writing—original draft; writing—review and editing. **Xiao Tan**: Conceptualization; software; formal analysis; data curation; investigation; writing—original draft; writing—review and editing; supervision; project administration; funding acquisition.

Disclosure

The funders had no role in the conduct of the study; collection, management, analysis, or interpretation of the data; preparation, review, or approval of the manuscript; or decision to submit the manuscript for publication.

Conflict of interest statement

None of the authors have any potential conflicts of interest.

Funding information

ZJU 100 Young Professor Project (X.T.); Rut and Arvid Wolff Memorial Foundation (X.T., 2023-02467).

Data availability statement

The UK Biobank data are available on application (www.ukbiobank.ac.uk/). This work is based on the UK Biobank Project No. 58082.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Table S1: Driver genes and variants queried for the detection of CHIP.

Table S2: Genetic and clinical characteristics used in the clonal hematopoiesis risk score (CHRS) with corresponding score weights.

Table S3: International Classification of Diseases (ICD) used to define autoimmune diseases.

Table S4: International Classification of Diseases (ICD) used to define hematologic malignancy.

Table S5: Baseline characteristics of study participants by autoimmune disease.

Table S6: Baseline characteristics of participants carrying CHIP with VAF <10% vs.?10%.

Table S7: Association of CHRS and CHRS categories with incident autoimmune disorders.

Table S8: Stratified association of any and large (i.e. variant allele fraction?10%) clonal hematopoiesis of indeterminate potential with incident autoimmune disorders.

Table S9: Sensitivity analyses after excluding potentially CCUS cases.

Table S10: Association of any and large (i.e. variant allele fraction?10%) clonal hematopoiesis of indeterminate potential with incident autoimmune disorders, after excluding participants with had multiple autoimmune diseases at baseline.

Table S11: Sensitivity analyses after excluding incident cases during the first 2 year of follow-up.

Table S12: Association of any and large (i.e. variant allele fraction?10%) clonal hematopoiesis of indeterminate potential with incident autoimmune disorders by using competing risk regression (Fine and Gray).

Table S13: Association of gene-specific clonal hematopoiesis of indeterminate potential subtypes with incident secondary autoimmune disorders.

Table S14: Association of any and large (i.e. variant allele fraction?10%) clonal hematopoiesis of indeterminate potential with inflammatory marker levels.

Table S15: Association of gene-specific clonal hematopoiesis of indeterminate potential subtypes with inflammatory marker levels.

Figure S1: Selection of study participants in the UK Biobank Cohort.

Figure S2: Schematic of CHIP variant ascertainment workflow.

Figure S3: Number of participants per gene-specific CHIP subtype.

Figure S4: Number of different driver genes per participant.

Figure S5: Distribution of gene-specific CHIP subtypes among any CHIP carriers. UpSet plot showing a matrix layout of the number of CHIP carriers with mutations in the indicated genes. Each matrix column represents a combination of mutated driver genes. Each corresponding bar represents the number of participants with mutations in the indicated genes. ■

