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Clonal Hematopoiesis of Indeterminate Potential (CHIP) and Incident Type 2 Diabetes Risk

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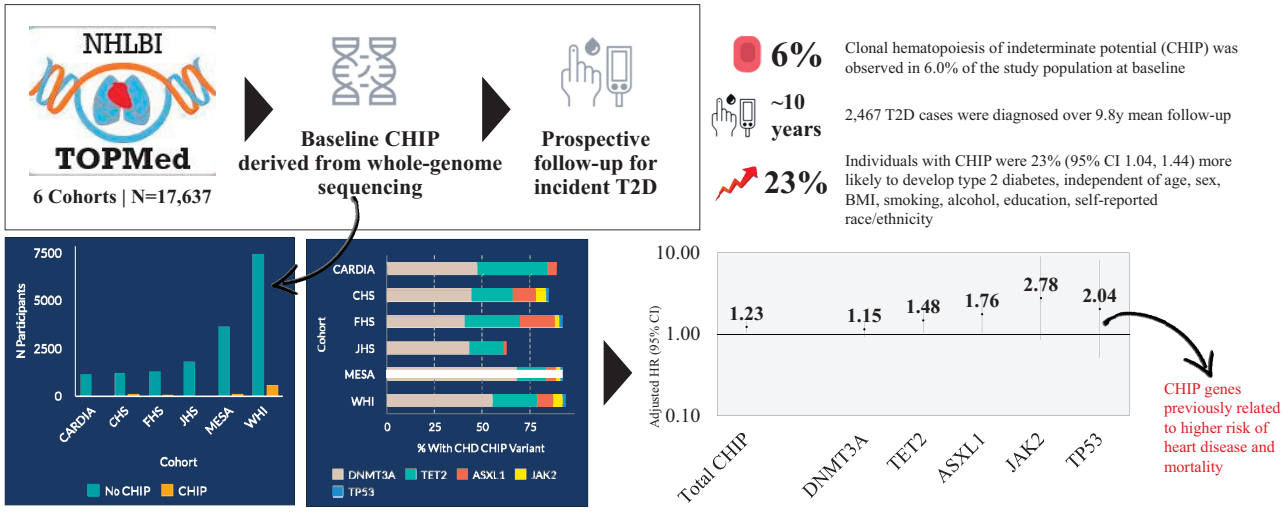

CARDIA, Coronary Artery Risk Development Study in Young Adults; CHS, Cardiovascular Health Study; CHD, coronary heart disease; FHS, Framingham Heart Study; JHS, Jackson Heart Study; HR, hazard ratio; MESA, Multi-Ethnic Study of Atherosclerosis; NHLBI, National Heart, Lung, and Blood Institute; T2D, type 2 diabetes; WHI, Women's Health Initiative; y, years.

ARTICLE HIGHLIGHTS

- Clonal hematopoiesis of indeterminate potential (CHIP) is an emerging aging-related marker of cardiometabolic outcomes and all-cause mortality risk.
- In an analysis of six prospective cohorts with a mean follow-up of 9.8 years, those with CHIP at study baseline were more likely to develop type 2 diabetes.
- CHIP mutations located on genes implicated in atherosclerotic heart disease were related to diabetes incidence, suggesting shared aging-related pathology.

ORIGINAL ARTICLE

Clonal Hematopoiesis of Indeterminate Potential (CHIP) and Incident Type 2 Diabetes Risk

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OBJECTIVE

Clonal hematopoiesis of indeterminate potential (CHIP) is an aging-related accumulation of somatic mutations in hematopoietic stem cells, leading to clonal expansion. CHIP presence has been implicated in atherosclerotic coronary heart disease (CHD) and all-cause mortality, but its association with incident type 2 diabetes (T2D) is unknown. We hypothesized that CHIP is associated with elevated risk of T2D.

RESEARCH DESIGN AND METHODS

CHIP was derived from whole-genome sequencing of blood DNA in the National Heart, Lung, and Blood Institute Trans-Omics for Precision Medicine (TOPMed) prospective cohorts. We performed analysis for 17,637 participants from six cohorts, without prior T2D, cardiovascular disease, or cancer. We evaluated baseline CHIP versus no CHIP prevalence with incident T2D, including associations with *DNMT3A*, *TET2*, *ASXL1*, *JAK2*, and *TP53* variants. We estimated multivariable-adjusted hazard ratios (HRs) and 95% CIs with adjustment for age, sex, BMI, smoking, alcohol, education, self-reported race/ethnicity, and combined cohorts' estimates via fixed-effects meta-analysis.

RESULTS

Mean (SD) age was 63.4 (11.5) years, 76% were female, and CHIP prevalence was 6.0% (*n* = 1,055) at baseline. T2D was diagnosed in *n* = 2,467 over mean follow-up of 9.8 years. Participants with CHIP had 23% (CI 1.04, 1.45) higher risk of T2D than those with no CHIP. Specifically, higher risk was for *TET2* (HR 1.48; CI 1.05, 2.08) and *ASXL1* (HR 1.76; CI 1.03, 2.99) mutations; *DNMT3A* was nonsignificant (HR 1.15; CI 0.93, 1.43). Statistical power was limited for *JAK2* and *TP53* analyses.

CONCLUSIONS

CHIP was associated with higher incidence of T2D. CHIP mutations located on genes implicated in CHD and mortality were also related to T2D, suggesting shared aging-related pathology.

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Clonal hematopoiesis of indeterminate potential (CHIP) is characterized from DNA sequencing of peripheral blood as the presence of an expansion of a somatic mutation acquired in a progenitor blood stem cell. Prevalence of one or more CHIP mutations increases notably at older ages (≥65 years) (1), and its occurrence has been associated with an approximately twofold greater risk of developing coronary heart disease (CHD), particularly for carriers of somatic mutations in *DNMT3A*, *TET2*, *ASXL1*, and *JAK2* (2,3). Cross-sectionally, among patients without prevalent heart disease, having CHIP was associated with a threefold higher coronary artery calcification score, underscoring a potential role in atherosclerotic progression (3). Although mechanisms underlying these relationships are unknown, potential pathways include increased inflammation or impaired immune function (4).

Given its strong correlation with age and CHD, CHIP may potentially be implicated in type 2 diabetes (T2D), but prior research in humans is sparse (4). Cross-sectionally, among individuals with obesity, baseline predictors of their subsequent clonal expansion rate (increase of variant allele frequency [VAF]) included insulin, HOMA of insulin resistance, and lower HDL cholesterol levels, after accounting for BMI level, suggesting a potential role of poor cardiometabolic health per se in CHIP progression, although directionality is unclear (5). Experimental mouse models of induced clonal expansion of *TET2* mutation demonstrated an acceleration of aging-induced cardiometabolic dysfunction, including greater atherosclerosis, insulin resistance, and impaired fasting glucose (6). Separately, *TET2* expansion in mice with diet-induced obesity significantly enhanced progression to insulin resistance (6), while in another case it was observed that a mouse model of obesity-driven inflammation led to greater CHIP expansion (7).

We therefore prospectively evaluated the relationship of CHIP with incident T2D in the Trans-Omics for Precision Medicine (TOPMed) program. TOPMed benefits from cohorts with high-coverage whole-genome sequencing (WGS) of stored blood samples (8), phenotyping for T2D risk factors, and longitudinal follow-up for incident T2D (9). In addition to evaluating baseline CHIP carrier status, we investigated CHIP on five previously identified CHD-related genes to identify their potential overlap with T2D risk.

RESEARCH DESIGN AND METHODS

Study Population

In our analyses we included 17,637 participants from six TOPMed cohorts that met criteria of having at least 1,000 genotyped participants with derivation of CHIP status and longitudinal follow-up for incident T2D, including the Coronary Artery Risk Development Study in Young Adults (CARDIA), Cardiovascular Health Study (CHS), Framingham Heart Study (FHS), Jackson Heart Study (JHS), Multi-Ethnic Study of Atherosclerosis (MESA), and the Women's Health Initiative (WHI) (Supplementary Fig. 1). Participants with prevalent T2D were excluded to avoid potential for reverse causation from blood draws occurring after diagnosis. We also excluded those with a history of cardiovascular disease (coronary artery disease, CHD, myocardial infarction, stroke [acute ischemic stroke, cerebrovascular accident, or acute hemorrhagic stroke]) or cancer diagnosed before blood collection, other than nonmelanoma skin cancers, based on available data in each cohort. See Supplementary Material for additional cohort-specific information. This study was approved by the respective institutional review boards of individual cohorts, and informed consent was obtained from all participants.

CHIP Derivation, T2D Ascertainment, and Covariate Data Collection

Blood DNA-derived high-coverage WGS was performed at the Broad Institute of MIT and Harvard as part of previous TOPMed research projects (10). WGS data were analyzed with GATK Mutect2 somatic variant caller, as previously described in detail (3,8); additional CHIP calling on freeze 9 was used for this publication with similar methods. CHIP was previously defined in TOPMed as the prevalence of a somatic VAF ≥2% on ≥1 of 74 prespecified driver mutations of hematopoietic stem cell expansion, and the cut point of VAF ≥10% was observed to be associated with elevated risk of developing CHD, while clonal expansion of VAF <10% carried only nominal risk (2). Thus, we adapted CHIP prevalence of ≥10% as our primary exposure of interest, with sensitivity analyses to examine the impact of VAF.

Details of the cohort-specific methods for ascertainment of T2D and related covariates have previously been published (11) and are summarized in Supplementary Material. Briefly, participants without T2D at genotyping blood draw were followed

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until date of T2D diagnosis, meeting one or more of the following criteria: fasting glucose ≥7 mmol/L, HbA_{1c} ≥6.5%, ≥11.1 mmol/L on 2-h oral glucose tolerance test, nonfasting glucose ≥11.1 mmol/L, physician-diagnosed T2D, self-reported T2D, or use of an antidiabetes medication. We harmonized phenotype data and additional covariate information from TOPMed cohorts, including age at blood draw, sex, BMI (weight in kilograms divided by the square of height in meters), waist circumference, smoking status, usual diet and alcohol intake, self-reported race/ethnicity (12), educational attainment, prediabetes status (not meeting diagnostic criteria for T2D with at least one of the following: fasting glucose between 5.6 and 7.0 mmol/L, HbA_{1c} between 5.7 and 6.5%, or between 7.8 and 11.1 mmol/L on 2-h oral glucose tolerance test), and baseline use of blood pressure or cholesterol-lowering medications. Among the cohorts a diet quality score was derived according to the Alternative Healthy Eating Index (AHEI), with collection of information on usual diet from food-frequency questionnaires (13). For cohorts with repeated assessments for any variables we used the data ascertained on or closest to blood draw.

Statistical Methods

Because a CHIP mutation can occur on more than one driver gene, we defined the exposure status as no CHIP versus at least one CHIP variant (yes/no). We further defined CHD-related CHIP as having a CHIP on one or more a priori selected genes that were previously related to incident CHD: *DNMT3A*, *TET2*, *ASXL1*, *JAK2*, or *TP53* (14). We also categorized according to the total number of CHIP mutations: noncarriers versus carriers with one CHIP gene variant or with two or more. In a sensitivity analysis, we applied a more stringent definition of CHIP, limited to variants with VAF ≥15% and ≥20%. Participants without CHIP served as the exposure reference group for all analyses.

Baseline for the analyses was date of blood draw from which CHIP was derived. Participants' follow-up was included until date of incident T2D diagnosis or last available visit—whichever came first. We used multivariable-adjusted Cox proportional hazards regression models to estimate the association of CHIP with incident T2D with stratification on age as the underlying timescale. Multivariable-adjusted models included sex (male/female), BMI (continuous), smoking status (never smoker, former, current), education (less than high school, high school or equivalent, some college, college degree or higher), and self-reported race/ethnicity (White, Black, Native American, Asian American, Hispanic, other). We adjusted for alcohol use except in the case of CHS, where this information was not available (nondrinker, light [women 1–14 g/day, men 1–28 g/day], moderate [women 15–28 g/day, men 29–42 g/day], heavy [women >28 g/day, men >42 g/day]). Indicator categories were used for missing categorical covariate data, including smoking status (<5% all cohorts) and alcohol (<1% to 40% across cohorts). BMI was missing for ∼1% and imputed as the cohort-specific median value. We cohort analyzed data separately and then combined the cohort-specific hazard ratios (HRs) and SEs using inverse variance–weighted fixed-effects meta-analyses to obtain the combined summary statistics and confirmed minimal between-study heterogeneity with I^2 values and *P* value for heterogeneity. We stratified the multivariable models by baseline characteristics to evaluate whether the association of CHIP with T2D incidence varied by baseline risk, including sex, age <60.0 vs. ≥60.0 years, BMI <30.0 vs. ≥30.0 kg/m^2, and self-reported race/ethnicity.

RESULTS

There were 17,637 participants eligible from 20,776 with data across six TOPMed cohorts (Supplementary Fig. 1). Mean (SD) for cohort participants in aggregate was 63.4 (11.5) years, ranging from 44.3 (6.5) years in CARDIA to 72.9 (5.2) years in CHS. Mean BMI was 28.4 (5.9) kg/m^2 overall, with lowest mean in CHS (26.6 [SD 4.6] kg/m^2) and highest in JHS (31.4 [7.2] kg/m^2). Of participants, 76% were female and 35% non-White, including 24% Black and 6% Hispanic.

CHIP was identified in 1,055 total participants (6.0%) overall, ranging in prevalence from 1.6% in CARDIA to 11.5% in CHS. Only 9% of these participants carried more than one CHIP mutation. Among CHIP carriers, most participants (*n* = 919 [87.1%]) carried a mutation on at least one of the five a priori defined CHD-related genes. The prevalence of CHIP accumulation was higher across older age categories, with 3.8%, 9.4%, 15.8%, and 23.1% for <70, 70–79, 80–89, and ≥90 years, respectively. Cohort-specific baseline demographics and health and lifestyle factors by CHIP status (none vs. at least one variant) are given in Table 1. Briefly, participants with CHIP were on average older but there were minimal trends for differences in lifestyle factors such as smoking status, alcohol use, BMI, or waist circumference.

Mean (SD) follow-up time from baseline blood draw was 9.8 (5.5) years, ranging from FHS with 6.2 (2.3) years to WHI with 12.2 (6.8) years. In combination, 2,467 cases of incident T2D were reported for the cohorts. The incidence rates for T2D in the non-CHIP reference groups were lowest for FHS (8.2 per 1,000 person-years) and highest for JHS (23.5 per 1,000 person-years). Results for the age- and multivariable-adjusted models of CHIP status with T2D risk are shown in Table 2. With adjustment for age, the meta-analyzed cohort estimates indicated a 22% higher risk of developing T2D (95% CI = 1.03, 1.44) for CHIP versus no CHIP. Results were similar after we additionally adjusted for sex, BMI, smoking, alcohol, race/ethnicity, and education (HR 1.23; 95% CI 1.04, 1.45), and there was minimal statistical heterogeneity between cohort estimates (I^2 = 27%, *P* = 0.23).

Among participants with prevalent CHIP at baseline, 88% were carriers of at least one a priori mutation implicated in CHD, and the relationship between CHD-CHIP and T2D was similar to that for the overall multivariable-adjusted results (HR 1.23; 95% CI 1.03, 1.46) (Fig. 1 and Supplementary Table 1). Individually, prevalence of CHD-related mutations indicated a higher T2D risk for *TET2* carriers (HR 1.48; 95% CI 1.05, 2.08) and *ASXL1* carriers (HR 1.76; 95% CI 1.03, 2.99), and possibly for *DNMT3A* carriers (HR 1.15; 95% CI 0.93, 1.43). *JAK2* and *TP53* mutations were relatively uncommon, and statistical power to assess T2D risk was low.

The multivariable-adjusted estimates for having one and two or more CHIP mutations with incident T2D risk were HR 1.23 (95% CI 1.03, 1.46) and HR 1.50 (0.80, 2.81), respectively (Supplementary Table 2). In a sensitivity analysis we implemented a higher threshold of VAF for defining CHIP and observed similar results for CHIP with VAF ≥15% compared with no CHIP (HR 1.36; 95% CI 1.11, 1.67); however, increasing the threshold to VAF ≥20% drastically reduced sample size, with only 44 total T2D cases, without indication of an association

Table 1—Baseline characteristics of NHLBI TOPMed cohort participants included in analysis, by CHIP prevalence

	CARDIA		CHS		FHS	
	No CHIP	CHIP	No CHIP	CHIP	No CHIP	CHIP
N (%)	1,168 (98.4)	19 (1.6)	1,205 (88.5)	157 (11.5)	1,299 (93.4)	92 (6.6)
Follow-up, years	10.2 (5.3)	7.9 (5.0)	6.8 (2.2)	6.6 (2.3)	6.2 (2.3)	6.1 (3.0)
Age, years	44.2 (6.5)	48.4 (8.2)	72.8 (5.1)	74.2 (5.5)	63.5 (12.7)	75.3 (9.8)
Female sex, *n* (%)	617 (52.8)	14 (73.7)	760 (63.1)	93 (59.2)	766 (59)	55 (59.8)
Race/ethnicity, *n* (%)						
Black	477 (40.8)	8 (42.1)	203 (16.8)	21 (13.4)	—	—
American Indian	—	—	—	—	—	—
Asian	—	—	—	—	—	—
Non-Hispanic White	691 (59.2)	11 (57.9)	987 (81.9)	136 (86.6)	1,298 (99.9)	92 (100)
Hispanic	—	—	15 (1.2)	—	—	—
Other	—	—	—	—	1 (0.1)	—
Education, *n* (%)						
Less than high school	253 (21.7)	5 (26.3)	320 (26.6)	56 (35.7)	71 (5.6)	21 (23.1)
High school/GED	—	—	347 (28.8)	39 (24.8)	355 (27.9)	26 (28.6)
Some college	320 (27.5)	5 (26.3)	273 (22.7)	37 (23.6)	342 (26.9)	20 (22.0)
College degree or higher	592 (50.8)	9 (47.4)	263 (21.9)	25 (15.9)	503 (39.6)	24 (26.4)
BMI, kg/m^2	28.7 (6.5)	28.6 (6.0)	26.5 (4.6)	26.7 (4.6)	27.5 (5.1)	26.3 (4.1)
Waist circumference, inches	90.1 (14.7)	91.9 (15.2)	93.9 (13.0)	95.4 (13.3)	98.0 (14.4)	96.2 (11.7)
AHEI dietary pattern score	54 (12)	57 (18)	59 (12)	58 (11)	—	—
Smoking status, *n* (%)						
Never	721 (62.4)	11 (57.9)	562 (46.7)	76 (48.4)	520 (40.0)	47 (51.1)
Past	218 (18.9)	4 (21.1)	494 (41.1)	58 (36.9)	638 (49.1)	38 (41.3)
Current	216 (18.7)	4 (21.1)	147 (12.2)	23 (14.6)	141 (10.9)	7 (7.6)
Alcohol use, *n* (%)						
Never use	232 (20.0)	2 (10.5)	—	—	68 (5.9)	4 (6.3)
Former use	256 (22.1)	3 (15.8)	—	—	82 (7.1)	6 (9.5)
Current moderate use	490 (42.2)	6 (31.6)	—	—	827 (71.5)	47 (74.6)
Current high use	182 (15.7)	8 (42.1)	—	—	179 (15.5)	6 (9.5)
Prediabetes, *n* (%)	472 (40.7)	9 (47.4)	498 (42.4)	62 (40.3)	744 (57.3)	55 (59.8)
Blood pressure med., *n* (%)	131 (11.3)	3 (15.8)	498 (41.4)	63 (40.1)	513 (39.6)	53 (58.2)
Cholesterol-lowering med., *n* (%)	69 (5.9)	1 (5.3)	64 (5.3)	8 (5.1)	404 (31.1)	26 (28.6)
Number of CHIP variants, *n* (%)						
1 variant		19 (100)		142 (90.4)		79 (85.9)
2 variants		—		15 (9.6)		9 (9.8)
3 variants		—		—		3 (3.3)
4 variants		—		—		1 (1.1)
CHD-related variant, *n* (%)		17 (89.5)		124 (80.0)		80 (87.0)
DNMTA		9 (47.4)		70 (44.6)		38 (41.3)
TET2		7 (36.8)		34 (21.7)		26 (28.3)
ASXL1		1 (5.3)		19 (12.1)		17 (18.5)
JAK2		—		8 (5.1)		2 (2.2)
TP53		—		3 (1.9)		2 (2.2)
	JHS		MESA		WHI	
	No CHIP	CHIP	No CHIP	CHIP	No CHIP	CHIP
N (%)	1,810 (96.9)	57 (3.1)	3,660 (96.1)	148 (3.9)	7,440 (92.7)	582 (7.3)
Follow-up, years	7.3 (1.7)	6.9 (1.8)	8.5 (2.3)	8.4 (2.2)	12.3 (6.8)	10.7 (6.4)
Age, years	52.3 (11.9)	63.5 (10.8)	60.2 (9.7)	66.7 (9.8)	68.1 (6.9)	70.7 (6.3)
Female sex, *n* (%)	1,140 (63.0)	33 (57.9)	1,885 (51.5)	82 (55.4)	7,440 (100)	582 (100)
Race/ethnicity, *n* (%)						
Black	1,810 (100)	57 (100)	823 (22.5)	33 (22.3)	819 (11)	48 (8.2)
American Indian	—	—	—	—	26 (0.3)	4 (0.7)

Continued on p. 1982

Table 1—Continued

	JHS		MESA		WHI	
	No CHIP	CHIP	No CHIP	CHIP	No CHIP	CHIP
Asian	—	—	499 (13.6)	14 (9.5)	130 (1.7)	7 (1.2)
Non-Hispanic White	—	—	1,541 (42.1)	75 (50.7)	6,191 (83.2)	507 (87.1)
Hispanic	—	—	797 (21.8)	26 (17.6)	223 (3.0)	11 (1.9)
Other	—	—	—	—	51 (0.7)	5 (0.9)
Education, *n* (%)						
Less than high school	191 (11.0)	6 (10.9)	530 (14.5)	17 (11.6)	377 (5.1)	29 (5.0)
High school/GED	338 (19.5)	12 (21.8)	639 (17.5)	29 (19.7)	1,398 (18.9)	104 (18.0)
Some college	1,208 (69.5)	37 (67.3)	836 (22.9)	34 (23.1)	2,839 (38.4)	231 (40.0)
College degree or higher	—	—	1,649 (45.1)	67 (45.6)	2,777 (37.6)	213 (36.9)
BMI, kg/m^2	31.4 (7.2)	30.6 (6.7)	27.9 (5.2)	28.1 (5.6)	28.4 (6.0)	28.3 (5.8)
Waist circumference, inches	99.1 (16.0)	99.2 (15.7)	96.6 (13.8)	98.9 (16.6)	87.6 (13.5)	88.4 (13.9)
AHEI dietary pattern score	—	—	—	—	52 (10)	53 (10)
Smoking status, *n* (%)						
Never	1,293 (72.1)	40 (70.2)	1,872 (51.1)	71 (48.3)	3,602 (52.8)	258 (48.1)
Past	287 (16.0)	11 (19.3)	1,322 (36.2)	63 (42.9)	2,749 (40.3)	246 (45.9)
Current	213 (11.9)	6 (10.5)	460 (12.6)	13 (8.8)	475 (7.0)	32 (6.0)
Alcohol use, *n* (%)						
Never use	429 (23.8)	17 (29.8)	706 (24.5)	28 (24.8)	547 (12.2)	38 (11.1)
Former use	442 (24.5)	20 (35.1)	741 (25.7)	28 (24.8)	877 (19.5)	78 (22.8)
Current moderate use	866 (48.1)	18 (31.6)	1,225 (42.5)	46 (40.7)	2,570 (57.3)	185 (54.1)
Current high use	64 (3.6)	2 (3.5)	213 (7.4)	11 (9.7)	494 (11.0)	41 (12)
Prediabetes, *n* (%)	768 (42.4)	33 (57.9)	531 (14.5)	17 (11.5)	2134 (28.7)	163 (28.0)
Blood pressure med., *n* (%)	740 (41.4)	35 (61.4)	1,137 (31.1)	61 (41.2)	2,474 (33.9)	203 (35.6)
Cholesterol-lowering med., *n* (%)	150 (8.4)	8 (14.0)	517 (14.1)	24 (16.2)	832 (11.4)	61 (10.7)
Number of CHIP variants, *n* (%)						
1 variant		56 (98.2)		139 (93.9)		521 (89.5)
2 variants		1 (1.8)		9 (6.1)		54 (9.3)
3 variants		—		—		5 (0.9)
4 variants		—		—		2 (0.3)
CHD-related variant, *n* (%)		50 (87.7)		132 (89.2)		516 (88.7)
DNMTA		40 (43.5)		101 (68.2)		322 (55.3)
TET2		10 (17.5)		23 (15.5)		137 (23.5)
ASXL1		1 (1.8)		8 (5.4)		48 (8.2)
JAK2		—		3 (2.0)		30 (5.2)
TP53		—		2 (1.4)		8 (1.4)

Data are means (SD) unless otherwise indicated. med., medication; NHLBI, National Heart, Lung, and Blood Institute; *N*, number of participants.

with T2D (HR 1.03; 95% CI 0.76, 1.39). In the multivariable models with stratification by baseline characteristics, we did not observe effect modification by sex, age $<$60.0 vs. $\geq$60.0 years, BMI $<$30.0 vs. $\geq$30.0 kg/m^2, or self-reported race/ethnicity, as shown in Supplementary Table 4.

CONCLUSIONS

We analyzed 17,637 participants across six TOPMed cohorts with data available for genotyping, CHIP derivation, and prospective follow-up for incident T2D. Our analyses were conducted in large longitudinal cohorts with a wide range of ages, self-reported race/ethnicities, and other demographics contributing to T2D risk status. CHIP prevalence was higher with older age at blood draw, consistent with findings of previous epidemiologic analyses (2). Participants with CHIP had a modest but significant 23% higher risk of developing T2D over nearly a decade of follow-up. Among those with a priori defined CHD-related CHIP mutations, results were similar, owing to these representing 88% of overall CHIP.

Although it is established that risk of developing T2D increases with age, reasons for deterioration in insulin sensitivity and β-cell function and mass with aging are largely unknown. In prior studies, the prevalence of clonal expansion of somatic mutations in hematopoietic stem cells was found to increase sharply at older ages, implicating CHIP in aging-related chronic diseases (2,15). Indeed, the accumulation of CHIP variants is positively associated with aging-related cancers, cardiovascular diseases, and all-cause mortality (2). Bonnefond et al. (16) also reported a higher prevalence of clonal mosaicism among patients with prevalent T2D versus without T2D, although the cross-sectional design of the study precluded the ability to delineate the temporal direction of this association. In a recent analysis in a retrospective cohort of older adults in Korea, investigators reported a positive association between CHIP and T2D incidence among 92 Korean

Table 2—Presence of CHIP mutations and risk of incident T2D among 17,637 NHLBI TOPMed participants

	No CHIP		CHIP			
	N T2D	Incidence per 1,000 PY	*N* T2D	Incidence per 1,000 PY	Age-adjusted model, HR (95% CI)	Multivariable-adjusted model, HR (95% CI)
CARDIA	119	10.0	3	20.0	2.17 (0.69, 6.85)	2.42 (0.75, 7.80)
CHS	79	9.6	11	10.6	1.15 (0.61, 2.16)	1.10 (0.58, 2.07)
FHS	66	8.2	4	7.1	0.93 (0.33, 2.63)	1.07 (0.38, 3.02)
JHS	310	23.5	12	30.4	1.19 (0.66, 2.13)	1.17 (0.65, 2.11)
MESA	472	15.2	14	11.3	0.70 (0.41, 1.20)	0.68 (0.40, 1.16)
WHI	1,268	13.9	109	17.5	1.32 (1.08, 1.61)	1.33 (1.09, 1.62)
Combined meta-analysis					1.22 (1.03, 1.44); P = 0.020, I^2 = 16% ($P_{heterogeneity}$ = 0.31)	1.23 (1.04, 1.45); P = 0.017, I^2 = 27% ($P_{heterogeneity}$ = 0.23)

NHLBI, National Heart, Lung, and Blood Institute; *N* T2D, number of participants with T2D; PY, person-years.

older adults with VAF>10% in comparison with no CHIP, but analyses were unadjusted for T2D risk factors and other potential confounders (17). Overall, we observed that the presence of CHIP, with adjustment for age and other T2D risk factors, was related to higher risk of developing T2D over follow-up, particularly for CHIP on *TET2* and *ASXL1*, previously related to atherogenic disease.

Our analysis identifies a potential shared pathophysiology of CHD and T2D that had not previously been characterized from longitudinal data. The link between T2D and CVD is well-known, as they share several upstream risk factors including age, obesity, smoking, diet, and other lifestyle factors; therefore, it is plausible that an accumulating burden of clonal expansion for certain variants precipitates both outcomes. Carriers of somatic clonal expansion mutations in *DNMT3A*, *TET2*, *ASXL1*, *JAK2*, and *TP53* genes have up to twofold higher risks of incident CHD and higher coronary artery calcification scores than noncarriers (2). Further, an animal model of *TET2* hematopoietic clonal expansion had significantly larger atherosclerotic lesions induced in comparison with controls. Additionally, experimental evidence in mice indicated that *TET2* loss-of-function mutations in bone marrow cells exacerbated obesity-related insulin resistance (6), and CHIP-enhanced IL-1β expression in white adipose tissue may have mediated these effects. Other mechanistic research also suggests that clonal expansion may promote atherosclerosis through a number of local and systemic inflammatory

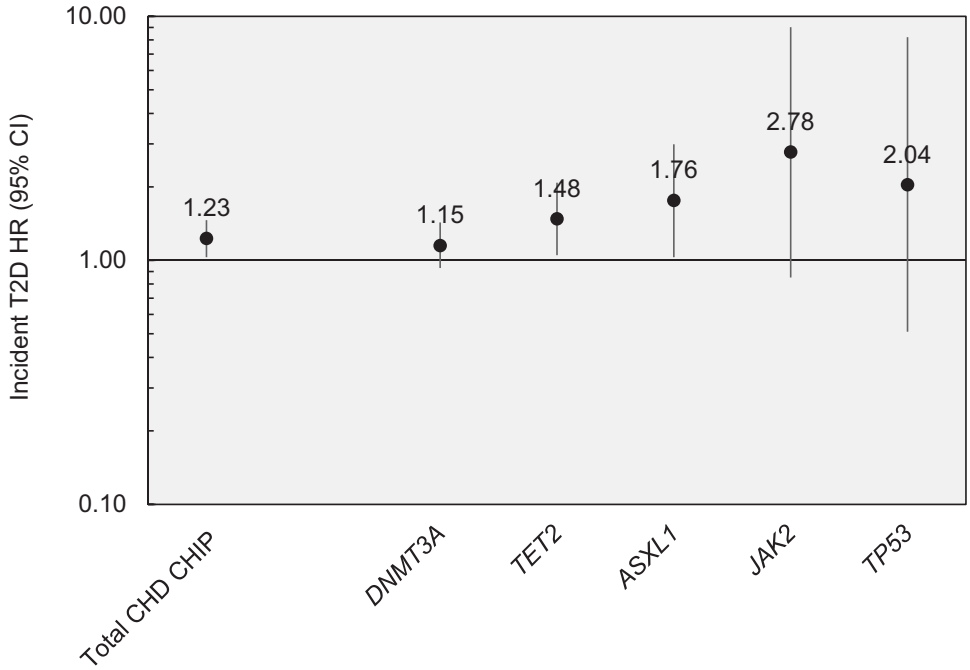

Figure 1—Presence of CHD-related CHIP mutations and risk of incident T2D among 17,637 National Heart, Lung, and Blood Institute (NHLBI) TOPMed participants. Estimates were adjusted for age (continuous), sex (male/female), BMI (continuous), smoking status (never smoker, former, current), education (less than high school, high school or equivalent, some college, college degree or higher), and self-reported race/ethnicity (White, Black, Native American, Asian American, Hispanic, other); analyses included adjustment for alcohol use for all cohorts except CHS (nondrinker, light [women 1–14 g/day, men 1–28 g/day], moderate [women 15–28 g/day, men 29–42 g/day], heavy [women >28 g/day, men >42 g/day]).

pathways (2,6,16); thus, it is plausible that inflammation serves as one potential mechanism for CHIP as a driver of aging-related chronic diseases including CHD and T2D.

Strengths of this study are the inclusion of large well-phenotyped cohorts representing diversity in age, sex, and self-reported race/ethnicity. Long-term follow-up for incident T2D outcomes allows us to establish temporality, with CHIP preceding T2D. Repeated assessments in CHIP carriers have shown that CHIP progresses over time; thus, using only a single measure we may misclassify those with VAF $<$10% at baseline. We also speculate that the CHD-related genes act upstream of T2D development, although the reverse mechanism is also plausible, whereby deterioration of glycemic control increases the likelihood of CHIP occurring; however, we carefully excluded participants with T2D, CVD, or history of cancer at baseline, and cases were identified over long-term follow-up of median $\sim$10 years from blood draw. Statistical power to detect associations with T2D risk is relatively limited for the less common driver mutations. Further, as we did not adjust for multiple comparisons in the individual gene analyses, there may be associations with T2D due to chance.

CHIP mutations located on genes previously implicated in CHD risk, but not overall CHIP, were associated with higher T2D risk. CHIP may reflect a shared pathophysiology of CHD and T2D that had not previously been characterized from longitudinal data. CHIP overall including on driver mutations previously associated with CHD was associated with development of T2D, implicating CHIP as a mediator of T2D risk through atherosclerosis-related pathways. Mechanistic research is warranted to identify the precise causal pathways underlying these observations. Further, whether CHIP or its downstream effects on atherosclerosis are modifiable is unknown. Addressing these gaps will inform potential therapies and determine whether CHIP represents a clinically targetable pathway of cardiometabolic risk.

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