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ORIGINAL RESEARCH

Peripheral Blood Cytopenia and Risk of Cardiovascular Disease and Mortality

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BACKGROUND: Individual blood cell count abnormalities have been associated with cardiovascular disease and increased mortality. In this study, we defined a "cytopenia phenotype," reflecting bone marrow hypoproliferation, to determine if peripheral blood cytopenia is associated with increased cardiovascular disease and mortality risk.

METHODS AND RESULTS: Study participants were derived from a biracial observational cohort study, REGARDS (Reasons for Geographic and Racial Differences in Stroke), that enrolled 30 239 Black and White participants aged ≥45 years between 2003 and 2007. Median follow up was ≈9 years. The current study included 19 864 participants from REGARDS study (37.9% men, 40% Black participants) who have complete blood count available at study enrollment. We defined a cytopenia phenotype based on age-, sex-, and race-adjusted lowest fifth percentile of blood counts. Multivariable Cox proportional hazards models estimated the hazard ratios (HR) and 95% CI of cytopenia for mortality and incident cardiovascular disease in adjusted models. Mean age of the study participants was 64 years (SD:9.7). The prevalence of cytopenia was 1.9% (n=378). Cytopenia was associated with increased risk of all-cause mortality (HR, 1.73; 95% CI, 1.34–2.22) and cardiovascular disease mortality (HR, 1.56; 95% CI, 1.11–2.29). Cytopenia was associated with stroke risk in Black but not White participants (HR, 1.96 versus 0.86; *P*-interaction for race=0.08) and was not associated with coronary heart disease risk.

CONCLUSIONS: We defined a cytopenia phenotype with clinical implications for mortality and stroke risk in a large biracial and geographically diverse population. Whether generated through somatic mutations or decreased organ function, cytopenia was associated with mortality risk and was a race-specific risk factor for stroke.

Key Words: cardiovascular disease ■ cytopenia ■ mortality ■ race ■ stroke

Coronary heart disease (CHD) is the first and stroke is the fifth most common cause of death in the United States.[1] Recent studies reported associations between clonal hematopoiesis of indeterminate potential (CHIP) and CHD, stroke (collectively referred to as cardiovascular disease [CVD]) and mortality.[2,3] CHIP refers to acquired somatic mutations in driver genes in hematopoietic stem cells, leading to clonal expansion.[4,5] Over time, CHIP may progress to clonal cytopenia of undetermined significance, myelodysplastic syndrome, or acute leukemia.[6,7] Black individuals have a higher risk of CVD and associated mortality compared with White individuals. Though partly explained by traditional cardiovascular risk factors, half of the excess risk of CVD in Black individuals remains unexplained.[8] Black individuals also have a higher prevalence of anemia and leukopenia, and we speculated that this could be due partly to underlying clonal hematopoiesis, and may explain some of the Black-White differences in mortality and CVD risk.[9–12]

Anemia is associated with increased risk of cardiovascular morbidity and mortality in the general population.[13] This risk is well described in certain populations such as the elderly, those with heart failure, chronic

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CLINICAL PERSPECTIVE

What Is New?

- Cytopenia was associated with 1.7-fold increased risk of all-cause mortality and 1.6-fold higher risk of cardiovascular related mortality, with the strongest association in younger individuals aged 45 to 55 years.
- Cytopenia was associated with stroke risk in Black but not White individuals.

What Are the Clinical Implications?

- Peripheral blood count is an easily available test and can be used to predict the risk of mortality.

Nonstandard Abbreviations and Acronyms

CHIP	clonal hematopoiesis of indeterminate potential
REGARDS	Reasons for Geographic and Racial Differences in Stroke

kidney disease, and diabetes.[9,14–17] Anemia is also common in individuals presenting with acute ischemic stroke and CHD, and is associated with increased mortality.[18,19] Increased white blood cell count (WBC) and platelet count are also associated with a higher risk of CVD, likely because of underlying inflammation,[20–22] but few studies have assessed the effect of low WBC and platelet count on CVD outcomes. Further, the risk of mortality and CVD associated with cytopenia, defined by lower counts of multiple blood cell lines, has not been studied to our knowledge. Using peripheral blood cytopenia, as a marker of bone marrow hypoproliferation and possibly clonal hematopoiesis, we examined the association between cytopenia and the risk of mortality, ischemic stroke, and CHD in Black and White individuals in the REGARDS (Reasons for Geographic and Racial Differences in Stroke) study.

METHODS

The authors declare that all supporting data are available within the article and its supplementary files. Additional information can be requested by following the REGARDS study procedure for publications and presentations (https://www.uab.edu/soph/regardsstudy/researchers). The REGARDS study is a prospectively-assembled cohort of 30 239 Black and White individuals aged ≥45 years from the contiguous United States, designed to identify factors contributing to the excess stroke risk and mortality among Black US residents, and those residing in the Southeastern United States. Details of the REGARDS study design have been published previously.[23] Briefly, commercially available lists of US residents were used to recruit participants with the goal of recruiting half of the cohort from the stroke buckle (coastal North and South Carolina and coastal Georgia) and the stroke belt (remaining areas of North Carolina, South Carolina, and Georgia as well as Tennessee, Mississippi, Alabama, Louisiana, and Arkansas), and the other half from the rest of United States. Recruitment occurred between February 2003 and October 2007 through mail and telephone contact. The study included 55% women, 41% Black participants, and 56% of the participants from the Southeast United States. Exclusion criteria included self-described race other than Black or White, active treatment for cancer, medical conditions preventing long-term participation, cognitive impairment as judged by the telephone interviewer, residence in or on a waiting list for a nursing home, and inability to communicate in English. Verbal informed consent, sociodemographics and a medical history were collected over the phone, followed by an in-home visit (Examination Management Systems Incorporated, Irving, Texas) for phlebotomy, urine collection, blood pressure (BP) measurement, anthropometric measures, and written informed consent. After recruitment of 8400 participants, a complete blood count (CBC) was added to the exam.[11] The study was approved by the institutional review boards at all participating institutions, and conformed to the precepts from the Declaration of Helsinki.

Blood samples were obtained the morning of the in-home visit after a 10- to 12-hour fast. Samples were centrifuged, refrigerated and shipped the same day to the study's central laboratory at the University of Vermont. CBC was performed from intact EDTA tubes using automated cell counting on a Beckman Coulter LH 755 Hematology Workcell (Beckman Coulter, Incorporated, Fullerton, California). Coefficients of variation were 5% for leukocyte count and 3% each for hemoglobin and mean corpuscular volume between instruments and shifts. Overall, there was 90.3% success rate for obtaining a hemoglobin concentration. Levels were measured the day after sample collection on 92% of samples and within 3 days on 95.8% of samples.[11]

Study Population

The current analysis included 19 864 REGARDS participants for whom a baseline CBC at study enrollment was available. Participants with no follow-up after their initial visit (n=320), those with a pre-baseline history of stroke (for analyses of ischemic stroke, n=1068), or

CHD (for analyses of CHD, n=3225) at the time of study enrollment were excluded (Figure).

Variable Definition

Cytopenia was defined using the thresholds specified in Table 1 as presence of ≥2 of the following: (1) hemoglobin in age-, sex-, and race-specific lowest fifth percentile; (2) white cell count in race-specific lowest fifth percentile; (3) platelet count in the lowest fifth percentile, and (4) macrocytosis (mean corpuscular volume >98fL). Hemoglobin cut-offs were based on age-, sex-, and race-dependent lowest fifth percentile of the distribution because of known differences based on these parameters.[11,12,24–27] In participants with chronic kidney disease with estimated glomerular filtration rate <60 mL/min/1.73 m^2, presence of macrocytosis (mean corpuscular volume >98fL) was also needed in addition to low hemoglobin to be considered anemic. WBC thresholds were based on race-dependent distribution because of known racial differences,[12,28] while platelet count thresholds used the entire cohort because of no known age, sex, or race differences.

Race relied upon self-report. Diabetes was defined as a fasting glucose level >126 mg/dL, a nonfasting glucose level >200 mg/dL, or a self-report of current treatment for diabetes. Hypertension was defined as systolic BP >140 mm Hg and/or diastolic BP >90 mm Hg, from the average of 2 seated measures taken after a 5-minute rest or use of antihypertensive medications (as defined by self-report). Atrial fibrillation was defined using the findings from the baseline ECG or self-report of a physician diagnosis of atrial fibrillation. Left ventricular hypertrophy was assessed by using standard voltage criteria from the baseline study ECG.

Outcome Assessment

The outcomes of interest were all-cause mortality (assessed through December 31, 2016), CVD-related mortality (assessed through December 31, 2014), incident ischemic stroke (assessed through September 30, 2017) and incident CHD (assessed through December 31, 2014). Baseline vascular disease was defined as self-reported coronary, cerebrovascular, or peripheral artery disease, which included a self-report of stroke, transient ischemic attack, myocardial infarction/heart attack, coronary artery angioplasty/stenting or bypass surgery, surgery on the arteries in the neck, or leg. Participants or their proxies were contacted every 6 months to ascertain CVD events, hospitalizations, or deaths, and medical records were reviewed to confirm these events.[29] In addition, family members or contacts of study participants called the REGARDS study's toll-free numbers to report outcomes. For participants who died in the hospital, cause of death was recorded from their medical records; for those who died outside of a hospital setting, interviews with family members, death certificates, and the National Death Index were used to identify date and cause of death. Social Security Administration Master Death Files were searched to identify death events not captured using other procedures. Outcome adjudication was done by clinicians (general internists, cardiologists, and physician assistants) who underwent specific training to identify causes of death. This group reviewed causes of death and dates by examining death certificates, medical records, and other administrative databases.[29] Specific methods for assessing stroke and CHD outcomes have been previously published.[8,30]

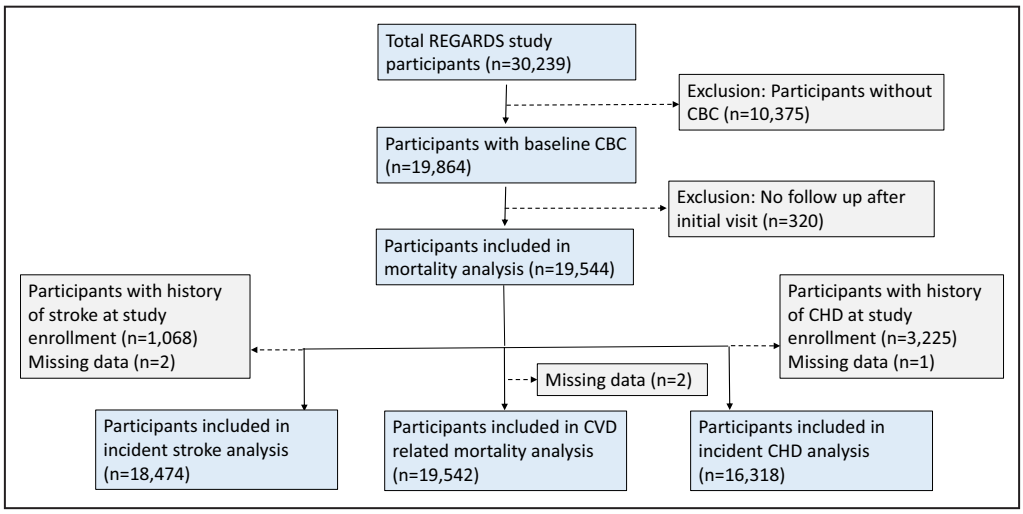

Figure. Consort diagram showing participants in each analysis.
CBC indicates complete blood count; CHD, coronary heart disease; CVD, cardiovascular disease; and REGARDS, Reasons for Geographic and Racial Differences in Stroke.

Table 1. Complete Blood Count Cutoffs Defining Cytopenia

Laboratory	Race	Sex	Age (y)	Value (mean)	Bottom 5% value
Hemoglobin, gm/dL	Black	Men	<65	14.2	11.7
			≥65	13.6	11.2
		Women	<65	12.8	10.8
			≥65	12.6	10.5
	White	Men	<65	15	13.1
			≥65	14.5	12.1
		Women	<65	13.6	11.8
			≥65	13.4	11.5
White count (×10^9/L cells)	Black			5.59	3.09
	White			6.16	3.75
Platelets (×10^9/L cells)				237.25	141

Statistical Analysis

Standard descriptive statistics were used to describe the characteristics of the study participants, using median, range, frequencies, and percentage. Associations between risk factors and cytopenia, incident ischemic stroke, CHD, overall and CVD mortality were evaluated using χ^2 tests for categorical variables and 2-tailed *t* tests for continuous variables. Cox proportional hazards models were used to calculate hazard ratios (HRs) for incident ischemic stroke, CHD and mortality associated with cytopenia using 4 models. Proportional hazards assumption was checked by visual examination of the Schoenfeld residuals.[31] Model 1 was adjusted for demographics (age, sex, race, and region), Model 2 added conventional stroke or CHD Framingham risk factors to Model 1 as appropriate. Model 3 added estimated glomerular filtration rate and C-reactive protein (CRP) to Model 2 for CHD and CVD-related mortality analysis, and estimated glomerular filtration rate, CRP, and alcohol intake for stroke. For all-cause mortality analysis, Model 3 added income, education, and rural-urban commuting areas to Model 2. In Model 4, hemoglobin as a continuous measure was added to Model 3 to determine if the associations were driven by anemia. For these analyses, a two-sided *P* value <0.05 was considered statistically significant. Differences in the association of cytopenia with outcomes by age and race were tested using cross-product interaction terms, using a *P* of <0.1 for interaction.[32] Analyses were performed with R version 3.5.3 (R Core Team, 2019, https://www.R-project.org/).

RESULTS

The study included 19 864 participants with a median follow up time of ~9 years; the study population at risk varied from 16 318 to 19 544 depending on baseline prevalence of the outcome studied (Figure). The mean age at study enrollment was 64 years (SD ±9.7). Overall, 37.9% of the cohort consisted of males, 40% were Black individuals, 59.4% residing in stroke belt/buckle. Participants who reported a baseline history of stroke or CHD at enrollment were excluded depending on the type of analysis, and hence, the study population is different for each analysis. The demographic and clinical characteristics of the participants included in each analysis can be found in Tables S1 through S5.

Prevalence of Cytopenia

The overall prevalence of cytopenia in the study cohort was 1.9% (n=378). This varied from 0.9% to 3.5% in Black individuals, 1.4% to 3.9% in White individuals, 1.6% to 3.9% in men, and 0.9% to 1.8% in women, with increasing prevalence by age (Table 2). White men aged ≥65 years had the highest prevalence of cytopenia followed by Black men ≥65 years. Characteristics of the study participants with and without cytopenia are shown in Table S1. Mean age of the study participants with cytopenia was 68 years (SD ± 10.9) and those without cytopenia was 64 years (SD ±9.7). Male participants, White individuals, never smokers or past smokers, and those with atrial fibrillation, CVD, and chronic kidney disease (assessed by estimated glomerular filtration rate and creatinine) were more likely to have cytopenia. Participants with cytopenia had lower body mass index, diastolic BP, total and LDL cholesterol, triglycerides, and CRP levels.

Cytopenia and Mortality Risk

Mortality analysis included 19 544 participants. After a median follow-up of 9.5 years (range, 0 to 13.1 years), 3933 participants died (20.1%). Of these, 1033 (5.3%) died of CVD-related causes. Characteristics of the study participants included in overall mortality analysis are shown in Table S2. Cytopenia was noted more frequently in those who died compared with those who were alive at the end of ascertainment (n=149 [3.8%] versus 225 [1.4%], *P*<0.001). Similarly, cytopenia was more prevalent in those with CVD-related mortality

Table 2. Prevalence of Cytopenia in the Study Cohort

Race	Sex	Age (y)	Number	Anemia n (%)	Leukopenia n (%)	Thrombocytopenia n (%)	Macrocytosis n (%)	Cytopenia (n, %)
Black	Men	<65	1524	74 (4.9)	94 (6.2)	91 (6.0)	69 (4.5)	29 (1.9)
		≥65	1096	55 (5.0)	55 (5.0)	120 (11.0)	59 (5.4)	38 (3.5)
	Women	<65	3148	161 (5.1)	157 (5.0)	69 (2.2)	49 (1.6)	29 (0.9)
		≥65	2242	119 (5.3)	101 (4.5)	96 (4.3)	60 (2.7)	34 (1.5)
White	Men	<65	2316	115 (5.0)	90 (3.9)	137 (5.9)	88 (3.8)	37 (1.6)
		≥65	2587	118 (4.6)	108 (4.2)	265 (10.2)	248 (9.6)	101 (3.9)
	Women	<65	3726	201 (5.4)	236 (6.3)	78 (2.1)	121 (3.3)	51 (1.4)
		≥65	3225	182 (5.6)	162 (5.0)	116 (3.6)	164 (5.1)	59 (1.8)
		Total	19 864	1025 (5.2)	1003 (5.1)	972 (4.9)	858 (4.3)	378 (1.9)

(n=36, 3.5%) compared with those who did not have CVD mortality (n=338, 1.8%), *P*<0.001 (Table S3).

Cytopenia was associated with increased risk of all-cause mortality in CVD risk factor adjusted Model 2 (HR, 1.67; 95% CI, 1.32–2.12) and extended risk factor Model 3 (HR, 1.73; 95% CI, 1.34–2.22). Cytopenia was also associated with CVD mortality in both Model 2 (HR, 1.52; 95% CI, 1.08–2.14) and in Model 3 (HR, 1.56; 95% CI, 1.11–2.19) (Table 3). The association between cytopenia and all-cause mortality remained significant after introducing hemoglobin as a continuous variable into Model 3 (HR, 1.55; 95% CI, 1.20–2.01, analysis not shown).

Cytopenia and CVD Risk

The analysis of cytopenia and ischemic stroke risk included 18 474 participants after excluding participants with baseline stroke. There were 6932 (37.5%) men, and 7266 (39.3%) Black participants. Mean baseline age was 64 years (SD ±9.7). After a median follow-up of 9.5 years (range, 0–13.1 years), 798 participants (4.3%) developed stroke. Participants who developed stroke were older, more likely to be men, had lower education and annual income, lived in rural areas, were smokers, and had more comorbidities and higher CRP (Table S4). Cytopenia was present in 349 (1.9%) participants, with no difference in the prevalence among those with (n=20, 2.5%) and without incident ischemic stroke (n=329, 1.9%), *P*=0.24.

The CHD analysis included 16 318 participants without baseline CHD who were followed for a median of 8.1 years (range, 0–10.9 years). There were 5656 (34.7%) males, and 6662 (40.8%) Black participants. Mean age at study enrollment was 63 years (SD ±9.6). There were 727 (4.3%) incident CHD events. Participants with CHD were older, more likely to be men, had lower education and annual income, were obese, smokers, and had more comorbidities (Table S5). Cytopenia was present in 287 (1.8%) participants, with no difference among those with (n=13, 1.8%) and without CHD (n=274, 1.8%), *P*=1.0.

There was no association between cytopenia and CHD or stroke risk in any model described above in the overall study population (Table 3).

Age, Cytopenia, and CVD and Mortality Risk

There was no interaction by age for cytopenia and CHD, stroke, or CVD-mortality risk (Table 4). However, there was an interaction between age and cytopenia for all-cause mortality (*P*-interaction=0.08 in Models 2 and 3). The association between cytopenia and mortality was stronger in younger individuals, with the point estimate decreasing from 6.72 (95% CI, 1.64–27.50) for participants aged 45 to 55 years, to 1.66, 2.10, 1.24, and 2.65 in those who are 55 to 65 years,

Table 3. Association of Cytopenia with CVD Outcomes and Mortality

Outcome	Hazard ratio of each event by cytopenia		
	Model 1 (demographics)	Model 2 (CVD risk factors)	Model 3 (extended risk factors)
Coronary heart disease			
Events/no cytopenia	714/16 031	683/15 197	673/14 995
Events/with cytopenia	13/287	12/281	10/276
HR (95% CI)	0.82 (0.47–1.42)	0.85 (0.48–1.51)	0.72 (0.38–1.35)
Stroke			
Events/no cytopenia	778/18 124	723/16 645	707/16 138
Events/with cytopenia	20/349	19/331	18/316
HR (95% CI)	1.13 (0.72–1.76)	1.17 (0.74–1.86)	1.18 (0.74–1.89)
All-cause mortality			
Events/no cytopenia	3783/19 169	1963/8234	1790/7481
Events/with Cytopenia	149/374	71/158	64/143
HR (95% CI)	1.63 (1.38–1.92)*	1.67 (1.32–2.12)*	1.73 (1.34–2.22)*
CVD mortality			
Events/no cytopenia	996/19 167	949/18 186	936/17 942
Events/with cytopenia	36/374	35/365	35/359
HR (95% CI)	1.38 (0.98–1.92)	1.52 (1.08–2.14)*	1.56 (1.11–2.19)*
Covariates			
Coronary heart disease			
Model 1	Age, sex, race, region		
Model 2	Model 1+smoking (current vs all others), total cholesterol (per SD), HDL cholesterol (per SD), systolic BP (per SD), taking blood pressure meds (y/n)		
Model 3	Model 2+eGFR (per SD), log CRP (per SD)		
Stroke			
Model 1	Age, sex, race, region, age*race		
Model 2	Model 1+systolic blood pressure (per SD), diabetes mellitus (yes, no), cigarette smoking (yes, no or former), prior cardiovascular disease (CHD or PVD), atrial fibrillation, left ventricular hypertrophy, use of hypertensive medications		
Model 3	Model 2+eGFR (per SD), log CRP (per SD), Alcohol (Heavy: 7+ drinks/wk for women, 14+ drinks/ wk for men; Moderate: 0 to 7 drinks/ wk for women, 0 to 14 drinks/wk for men; None: 0 drink per wk)		
All-cause mortality			
Model 1	Age, Sex, Race, Region		
Model 2	Model 1+cancer, smoking (current, former, never), diabetes mellitus, systolic blood pressure, BMI (categories), baseline CVD (stroke, CHD, PVD), eGFR (per SD)		
Model 3	Model 2 plus RUCA, Income, Education		
CVD Mortality			
Model 1	Age, sex, race, region		
Model 2	Model 1+smoking (current vs all others), total cholesterol (per SD), HDL cholesterol (per SD), systolic BP (per SD), taking blood pressure meds (yes/no)		
Model 3	Model 2+eGFR (per SD), log CRP (per SD)		

BMI indicates body mass index; BP, blood pressure; CRP, C-reactive protein; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein; HR, hazard ratio; PVD, peripheral vascular disease; and RUCA, rural-urban commuting areas.

* Indicates statistical significance.

65 to 75 years, 75 to 85 years, and >85 years, respectively in Model 3 (Table 4).

Racial Differences in Cytopenia, CVD and Mortality

While the race by cytopenia interaction term was not significant in any model for incident CHD or mortality, the interaction for cytopenia by race for stroke met our significance threshold (*P*-interaction=0.08) in Model 2. The HR of stroke for cytopenia in Black participants was 1.96 (95% CI, 1.00–3.82) as compared with 0.86 for White participants (95% CI, 0.46–1.61) (Table 5). Anemia was associated with increased risk of stroke in Black individuals with an HR of 1.57 (95% CI, 0.98–2.51) compared with HR of 0.92 (95% CI, 0.60–1.40)

Table 4. Association of Cytopenia with CVD Outcomes and Mortality by Age

Outcome		Age 45–55 y	Age 55–65 y	Age 65–75 y	Age 75–85 y	Age >85 y	$P_{interaction}$
Model 1							
CHD	Events/no cytopenia	77/3539	237/6244	255/4406	132/1678	13/164	
	Events/with cytopenia	1/45	2/94	5/75	5/61	0/12	
	HR (95% CI)	1.17 (0.16–8.41)	0.62 (0.16–2.51)	1.09 (0.45–2.65)	0.94 (0.38–2.29)	NA	0.98
Stroke	Events/no cytopenia	54/3716	240/6861	298/5207	173/2113	13/227	
	Events/with cytopenia	1/47	3/105	5/99	9/81	2/17	
	HR (95% CI)	1.88 (0.26–13.64)	0.33 (0.05–2.33)	0.94 (0.39–2.27)	1.71 (0.93–3.14)	1.48 (0.35–6.35)	0.50
Mortality	Events/no cytopenia	232/3839	903/7197	1361/5583	1099/2297	188/253	
	Events/with cytopenia	9/49	21/110	43/108	57/88	19/19	
	HR (95% CI)	3.00 (1.41–6.37)	1.71 (1.08–2.69)	1.80 (1.32–2.45)	1.42 (1.08–1.86)	1.84 (1.22–2.78)	0.38
CVD mortality	Events/no cytopenia	63/3838	230/7197	342/5583	310/2296	51/253	
	Events/with cytopenia	3/49	5/110	7/108	14/88	7/19	
	HR (95% CI)	3.12 (0.76–12.82)	2.06 (0.92–4.65)	0.96 (0.43–2.15)	1.28 (0.76–2.15)	1.70 (0.78–3.71)	0.52
Model 2							
CHD	Events/no cytopenia	68/3316	228/5923	247/4200	127/1606	13/152	
	Events/with cytopenia	1/45	2/93	5/72	4/59	0/12	
	HR (95% CI)	1.22 (0.17–8.81)	0.69 (0.17–2.78)	1.14 (0.47–2.76)	0.91 (0.34–2.46)	NA	0.98
Stroke	Events/no cytopenia	49/3375	218/6282	281/4825	163/1954	12/209	
	Events/with cytopenia	1/47	3/104	5/88	8/75	2/17	
	HR (95% CI)	1.90 (0.26–13.82)	0.35 (0.05–2.52)	0.98 (0.41–2.39)	1.68 (0.89–3.19)	1.65 (0.38–7.10)	0.57
Mortality	Events/no cytopenia	91/1132	466/3291	735/2621	580/1079	91/111	
	Events/with cytopenia	2/7	14/50	22/54	27/41	6/6	
	HR (95% CI)	7.21 (1.77–29.43)*	1.73 (0.92–3.25)	1.81 (1.20–2.75)*	1.26 (0.85–1.85)	2.77 (1.40–5.47)*	0.08*
CVD mortality	Events/no cytopenia	59/3601	218/6820	332/5326	290/2200	50/239	
	Events/with cytopenia	3/49	5/109	7/103	13/85	7/19	
	HR (95% CI)	2.95 (0.72–12.13)	2.36 (1.04–5.31)	1.01 (0.45–2.27)	1.41 (0.82–2.41)	1.76 (0.80–3.85)	0.54
Model 3							
CHD	Events/no cytopenia	67/3281	225/5848	243/4136	125/1583	13/147	
	Events/with cytopenia	1/45	1/91	5/71	3/57	0/12	
	HR (95% CI)	1.26 (0.18–9.15)	0.35 (0.05–2.51)	1.24 (0.51–3.01)	0.66 (0.21–2.07)	NA	0.78

(*Continued*)

Table 4. Continued

Outcome		Age 45–55 y	Age 55–65 y	Age 65–75 y	Age 75–85 y	Age >85 y	$P_{interaction}$
Stroke	Events/no cytopenia	49/3342	218/6202	277/4751	159/1923	12/204	
	Events/with cytopenia	1/47	3/102	5/87	7/72	2/17	
	HR (95% CI)	1.94 (0.27–14.12)	0.36 (0.05–2.57)	1.03 (0.42–2.50)	1.57 (0.80–3.07)	1.72 (0.40–7.41)	0.65
Mortality	Events/no cytopenia	85/1023	411/2967	689/2404	524/987	81/100	
	Events/with cytopenia	2/7	11/42	21/51	24/37	6/6	
	HR (95% CI)	6.72 (1.64, 27.50)*	1.66 (0.78, 3.52)	2.10 (1.37, 3.22)*	1.24 (0.82, 1.87)	2.65 (1.34, 5.26)*	0.08
CVD mortality	Events/no cytopenia	59/3563	216/6736	326/5248	286/2162	49/233	
	Events/with cytopenia	3/49	5/107	7/102	13/82	7/19	
	HR (95% CI)	2.84 (0.69, 11.71)	2.16 (0.96, 4.87)	1.15 (0.51, 2.58)	1.43 (0.84, 2.45)	1.50 (0.68, 3.29)	0.75

CHD indicates coronary heart disease; CVD, cardiovascular disease; and HR, hazard ratio.
* Indicates statistical significance.

in White individuals in Model 2 (*P*-interaction=0.09, analysis not shown).

In an analysis examining the association of individual blood cell components with the outcomes of interest, we found that low hemoglobin was associated with increased risk of CHD (HR, 2.31; 95% CI, 1.78–2.99 in Model 2), while low WBC was associated with decreased risk of CHD (HR, 0.59; 95% CI, 0.37–0.94 in Model 2). Low hemoglobin and platelet count, and increased mean corpuscular volume were all associated with increased risk of overall and CVD mortality in all the models (Table S6).

DISCUSSION

In this large biracial and geographically diverse cohort, we defined a cytopenia phenotype which was associated with overall and CVD-related mortality, and increased stroke risk in Black but not White individuals. There was a significant age-dependent association of cytopenia with mortality, with the risk of mortality being strongest in the youngest individuals with cytopenia in our cohort.

Blood cells play a major role in inflammation, atherogenesis, and thrombus formation.[33–35] Most prior research on blood cell traits and adverse outcomes focused on individual elements of the CBC in isolation, rather than cytopenia as a global marker of bone marrow function. For instance, recruitment of leukocytes and release of inflammatory cytokines characterize atherosclerosis,[35] and leukocytosis is an independent predictor of CVD and all-cause mortality.[21,36–40] Though platelets play a major role in hemostasis, association of platelet count with CVD outcomes is unclear. In an older population, a U-shaped relationship between platelet count and overall mortality was shown.[41] While the majority of these studies report an association between high blood counts and CVD and mortality, there is limited evidence on the effect of low WBC and platelet count, or low blood counts in multiple cell lines which can be representative of global bone marrow suppression/ failure. The etiology of single blood cell line abnormality is different from pancytopenia, which may reflect a clonal hematologic disorder. Hence, pancytopenia should be considered as a different clinical entity than individual cell line abnormalities.

Large cohort studies including the Framingham study, Atherosclerosis Risk in Communities study, and the Cardiovascular Health Study have examined the association of hemoglobin concentration with adverse outcomes, and both high and low hemoglobin have been associated with CVD, and mortality.[9,13,42,43] A recent study from REGARDS showed that hemoglobin concentration conferring CHD risk may be different for White and Black individuals and race specific cut offs may be more relevant clinically.[44] Though the World Health Organization criteria are often used to define anemia (men with hemoglobin <13 gm/dL and women <12 gm/dL), these criteria do not consider racial and gender/sex differences in hemoglobin and are likely insufficient to define "normal."[26,45] In our study, we defined a cytopenia phenotype in a large geographically diverse biracial cohort based on the lower fifth percentile of distribution for blood counts for age, sex, and race.

Table 5. Association of Cytopenia with CVD and Mortality by Race

Hazard ratio of each event by cytopenia										
Outcome		Model 1 (demographics)			Model 2 (CVD risk factors)			Model 3 (extended risk factors)		
Race		White	Black	P_{int}	White	Black	P_{int}	White	Black	P_{int}
CHD	Events/no cytopenia	421/9480	293/6551		404/8983	279/6214		397/8843	276/6152	
	Events/with cytopenia	8/176	5/111		7/174	5/107		6/172	4/104	
	HR (95% CI)	0.81 (0.40–1.64)	0.82 (0.34–2.00)	0.98	0.79 (0.37–1.66)	0.95 (0.39–2.32)	0.74	0.68 (0.30–1.52)	0.79 (0.29–2.12)	0.82
Stroke	Events/no cytopenia	483/10 977	295/7147		453/10 124	270/6521		447/9970	268/6452	
	Events/with cytopenia	11/231	9/118		10/220	9/111		10/217	8/108	
	HR (95% CI)	0.87 (0.48–1.59)	1.75 (0.90–3.40)	0.13	0.86 (0.46–1.61)*	1.96 (1.00–3.82)*	0.08*	0.89 (0.47–1.66)	1.85 (0.91–3.75)	0.13
All-cause mortality	Events/no cytopenia	2201/11 487	1582/7682		1144/4964	819/3270		1029/4455	761/3026	
	Events/with cytopenia	102/248	47/126		48/107	23/51		42/96	22/47	
	HR (95% CI)	1.69 (1.38–2.06)	1.51 (1.13–2.03)	0.55	1.58 (1.18–2.11)	1.90 (1.26–2.89)	0.47	1.58 (1.15–2.15)	2.10 (1.37–3.21)	0.29
CVD Mortality	Events/no cytopenia	541/11 485	455/7682		519/10 898	430/7288		511/10 732	425/7210	
	Events/with cytopenia	26/248	10/126		25/243	10/122		25/240	10/119	
	HR (95% CI)	1.60 (1.08, 2.38)	1.01 (0.54, 1.90)	0.23	1.68 (1.12, 2.52)	1.23 (0.65, 2.30)	0.40	1.74 (1.16, 2.61)	1.23 (0.66, 2.32)	0.36

CHD, coronary heart disease; CVD indicates cardiovascular disease; HR, hazard ratio; and P_{int}, *P* value for interaction.
* Indicates statistical significance.

Black individuals have a higher risk of CVD, particularly, those between ages 45 and 54 years die of stroke at a rate that is 3 times higher than White individuals.[7,46,47] The racial differences in stroke mortality are largely driven by a higher incidence of stroke in Black individuals.[9] However, traditional cardiovascular risk factors explain less than half of the racial disparity in stroke risk in Black individuals.[8] A previous REGARDS study showed that anemia is 3.3 times more common in Black individuals than White individuals, and that older age and residence in the Southeast United States are associated with anemia.[11] The genetic polymorphisms common in Black individuals such as hemoglobinopathies explain only 50% of their anemia.[25] We found that cytopenia was predictive of stroke risk in Black but not White participants, opening a new avenue of investigation to decipher the link between cytopenia and racial disparities in stroke.

CHIP has emerged as an independent risk factor for CVD and mortality.[2,3] CVD risk in CHIP is mediated by increased inflammation and atherosclerosis, characterized by release of cytokines by abnormal leukocytes.[3] In a recent study, two thirds of patients with unexplained cytopenia (mainly anemia), were found to have clonal cytopenia of undetermined significance.[48] While CHIP can lead to cytopenia in some individuals, peripheral blood cytopenia may result from other causes such as nutritional deficiency, medication effect, alcohol intake, chronic inflammation, bone marrow failure, or may reflect a poor overall health status from other organ dysfunction such as kidney or liver disease. Our study showed an increased risk of overall and CVD-related mortality with cytopenia, but we did not see an association with CHD. About half of our cohort was aged <65 years and we expect the prevalence of CHIP to be modest in this population.[2,49,50] Additionally, the REGARDS study excluded patients with active cancer at baseline. Hence, it is possible that alternate causes of cytopenia are more common than CHIP in our study participants, therefore accounting for the lack of association between cytopenia and CHD.

Our findings suggest that cytopenia, irrespective of the cause, is predictive of increased overall and CVD-related mortality. In adjusted analysis, there were no racial differences in the mortality risk associated with cytopenia. However, we found the strongest association with cytopenia in the youngest people in our cohort with ≈7-fold increased risk of overall mortality in individuals aged 45 to 55 years. The biologic basis for this association is unclear, and these estimates were limited by small sample sizes. Previous studies have shown that the association of CHIP and CHD was greater in participants with early onset CHD.[3] Cytopenia might reflect underlying clonal hematopoiesis, or a poor overall health in this age group, and necessitates further evaluation. Though CHIP has been linked to adverse CVD outcomes, translation into clinical medicine is difficult due to the cost for evaluation, lack of access to testing, unclear indications for testing and the difficulty in interpreting test results. CBC is a commonly available and low-cost test which many individuals obtain in the course of their routine clinical care. Using data from the CBC, we defined a bone marrow hypoproliferation phenotype (cytopenia) reflective of abnormal hematopoiesis which was associated with adverse outcomes. It is important to determine whether CHIP is involved in this phenotype, and further investigation of the cause is necessary to mitigate the adverse events, especially in younger individuals with cytopenia, where we found a profound increase in the risk of mortality.

Some of the limitations of our study include the fact that CBC was obtained at a single time point at study entry; we could not consider fluctuations in blood counts. We acknowledge that transient decrease in blood counts may not be associated with adverse outcomes compared with persistently low blood counts. CBC measurements in this study were obtained at an in-home visit, and hence are unlikely to be influenced by a transient acute illness or infection that might have hindered study participation. Details on the cause of cytopenia such as underlying hemoglobinopathy, inflammatory disorders, medications, or nutritional deficiencies were not available. In a smaller subset of REGARDS participants, B12 and folate deficiency were rare.[51,52] Since we adjusted for CRP level in the multivariable analysis, the possibility of inflammation contributing to cytopenia and adverse outcomes is low. Further, adjusting for hemoglobin did not change the observed associations, suggesting cytopenia is an independent phenotype to anemia. Bone marrow failure and clonal hematologic disorders causing cytopenia are relatively rare in the general population. Hence, some of our estimates are limited by low event rates. This is similar to the previous studies that showed association of CHIP with CVD,[2,3] and the few study subjects that have cytopenia have adverse CVD and mortality outcomes. The analysis was not adjusted for Charlson comorbidity index, but adjusted for medical conditions relevant to CVD, antihypertensive medications, and cancer history. In a large epidemiologic study, alcohol intake did not affect hemoglobin concentration, and serum creatinine and elevated serum inflammatory markers were associated with lower hemoglobin.[26] We have adjusted for these variables in our analysis in Model 3. The strengths of our study include a large sample size with 40% Black individuals and 62% women from a geographically diverse population with a broad age range and long follow-up. This enabled studying age-related and racial differences in the association of cytopenia with mortality and CVD risk. The study used rigorous adjudication process

to measure CVD and mortality through verification of hospital records and death registries. Additionally, all the samples were analyzed at the central laboratory using standardized procedures. In contrast to previous studies, we used age-, sex-, and race-specific cut-offs for blood counts to define cytopenia phenotype, accounting for the known differences based on age, sex, and race.

CONCLUSIONS

In this large biracial cohort, cytopenia was independently associated with increased all-cause and CVD mortality. Cytopenia was a race-specific risk factor for stroke affecting Black but not White individuals. With growing knowledge on the role of clonal hematopoiesis in CVD risk and mortality, further research is needed to determine if our phenotype of cytopenia reflects clonal hematopoiesis, or if cytopenia causes increased mortality independent of clonal hematopoiesis. Additional research is needed to explore the biologic mechanisms by which cytopenia increases mortality and identify the factors that would mitigate this risk, especially in younger individuals.

ARTICLE INFORMATION

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Supplementary Material

Tables S1–S6

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SUPPLEMENTAL MATERIAL

Table S1. Demographic and clinical characteristics of the study participants included in the analysis with and without cytopenia.

	Entire cohort	Cytopenia	No Cytopenia	P value
Entire cohort (n)	19544	374	19170	
Person-years follow-up/ 10,000	167080.1	1028337	59997653	
Follow-up in years (median, range)	9.5 (0-13.1)	8.4 (0.2-12.6)	9.5 (0-13.1)	
Age (Mean, SD)	64 (9.7)	68 (10.9)	64 (9.7)	<0.001
Sex, Male (n, %)	7399 (37.86)	204 (54.55)	7195 (37.53)	<0.001
Black Race (n, %)	7809 (39.96)	126 (33.69)	7683 (40.08)	0.014
Region (n, %)				
Rest of nation	7927 (40.56)	149 (39.84)	7778 (40.58)	0.931
Stroke Belt	6855 (35.07)	131 (35.03)	6724 (35.08)	
Stroke Buckle	4761 (24.36)	94 (25.13)	4667 (24.35)	
Annual income (n, %)				
Refused (n, %)	2522 (12.90)	59 (15.78)	2463 (12.85)	0.222
>75K (n, %)	3333 (17.05)	61 (16.31)	3272 (17.07)	
35 - 75K (n, %)	5905 (30.21)	123 (32.89)	5782 (30.16)	
20 - 34K (n, %)	4509 (23.07)	77 (20.59)	4432 (23.12)	
<20K (n, %)	3275 (16.76)	54 (14.44)	3221 (16.80)	
RUCA codes (n, %)				
Urban	13833 (70.78)	255 (76.58)	13578 (78.87)	0.782
Large rural	2148 (10.99)	46 (13.81)	2102 (12.21)	
Small rural	1129 (5.78)	23 (6.91)	1106 (6.42)	
Isolated	439 (2.25)	9 (2.7)	430 (2.5)	
Education (n, %)				
<High School (n, %)	2182 (11.16)	40 (10.70)	2142 (11.18)	0.05
High School (n, %)	5084 (26.01)	107 (28.61)	4977 (25.98)	
Some college (n, %)	5360 (27.43)	80 (21.39)	5280 (27.56)	
≥College graduate (n, %)	6903 (35.32)	147 (39.30)	6756 (35.27)	
History of smoking (n, %)				
Never	9287 (47.52)	182 (48.92)	9105 (47.67)	0.023
Past	7358 (37.65)	154 (41.40)	7204 (37.72)	
Current	2826 (14.46)	36 (9.68)	2790 (14.61)	
Co-morbidities				
Diabetes (n, %)	3907 (19.99)	80 (21.45)	3827 (20.09)	0.561
Atrial fibrillation (n, %)	1662 (8.50)	46 (12.67)	1616 (8.63)	0.009
Cardiovascular Disease (n, %)	3225 (16.50)	87 (23.71)	3138 (16.69)	<0.001
Left ventricular hypertrophy (n, %)	1682 (8.61)	38 (10.35)	1644 (8.72)	0.316
Cancer history (n, %)	1213 (6.21)	30 (18.63)	1183 (13.90)	0.11
Body mass index (mean, SD)	29 (6.3)	27 (5.8)	29 (6.3)	<0.001
Systolic BP (mean, SD)	126 (16.4)	127 (17.8)	126 (16.4)	0.945
Diastolic BP (mean, SD)	76 (9.7)	75 (11.1)	76 (9.6)	0.008

Anti-hypertensive use (n, %)	9964 (50.98)	205 (55.11)	9759 (52.99)	0.45
Total cholesterol (mean, SD)	192 (40.6)	174 (38.5)	192 (40.5)	<0.001
LDL cholesterol (mean, SD)	113 (35.2)	97 (32.0)	113 (35.2)	<0.001
HDL cholesterol (mean, sD)	53 (16.5)	54 (18.8)	53 (16.4)	0.381
Triglycerides (mean, SD)	130 (83.9)	114 (89.3)	131 (83.7)	<0.001
eGFR (mean, SD)	86 (20.3)	80 (23.1)	86 (20.2)	<0.001
Creatinine (mean, %)	1 (0.5)	1 (0.9)	1 (0.5)	<0.001
CRP (median, [25%, 75%])	2.2 (0.94-5.08)	1.56 (0.67-4.18)	2.21 (0.95-5.10)	<0.001
Blood cell counts				
Total WBC (mean, SD)	6 (2.1)	4 (4)	6 (2)	<0.001
Platelets (mean, SD)	237 (69)	162 (85.9)	239 (67.8)	<0.001
Hemoglobin (mean, SD)	14 (1.5)	13 (2.0)	14 (1.4)	<0.001
MCV (mean, SD)	90 (5.8)	94 (9.9)	90 (5.6)	<0.001

SD, standard deviation; RUCA, rural-urban commuting areas; BP, blood pressure; LDL, low-density lipoprotein; HDL, high-density lipoprotein, eGFR, estimated glomerular filtration rate; CRP, C-reactive protein; WBC, white blood cell count; MCV, mean corpuscular volume.

Table S2. Demographic and clinical characteristics of study participants included in the overall mortality analysis.

	Entire cohort	No death	Overall Mortality	P value
Entire cohort (n)	19544	15611	3933	
Person-years follow-up/ 10,000	167080.1	52456809	8569181	
Follow-up in years (median, range)	9.5 (0-13.1)	10.1 (0.1-13.1)	6.1 (0-12.3)	
Age (Mean SD)	64 (9.7)	62 (8.9)	71 (9.6)	<0.001
Sex, Male (n, %)	7399 (37.86)	5527 (35.4)	1872 (47.6)	<0.001
Race (n, %)	7809 (39.96)	6179 (39.58)	1630 (41.44)	0.035
Region (n, %)				
Rest of nation	7927 (40.56)	6290 (40.29)	1637 (41.63)	
Stroke Belt	6855 (35.07)	5466 (35.01)	1389 (35.33)	
Stroke Buckle	4761 (24.36)	3855 (24.69)	906 (23.04)	0.082
Annual income (n, %)				
Refused (n, %)	2522 (12.90)	1951 (12.50)	571 (14.52)	
>75K (n, %)	3333 (17.05)	3032 (19.42)	301 (7.65)	
35 - 75K (n, %)	5905 (30.21)	4964 (31.80)	941 (23.93)	
20 - 34K (n, %)	4509 (23.07)	3378 (21.64)	1131 (28.76)	
<20K (n, %)	3275 (16.76)	2286 (14.64)	989 (25.15)	<0.001
RUCA codes (n, %)				
Urban	13833 (70.78)	11067 (79.08)	2766 (77.81)	
Large rural	2148 (10.99)	1687 (12.06)	461 (12.97)	
Small rural	1129 (5.78)	880 (6.29)	249 (7.00)	
Isolated	439 (2.25)	360 (2.57)	79 (2.22)	0.104
Education (n, %)				
<High School (n, %)	2182 (11.16)	1421 (9.11)	761 (19.40)	
High School (n, %)	5084 (26.01)	3973 (25.46)	1111 (28.32)	
Some college (n, %)	5360 (27.43)	4332 (27.76)	1028 (26.20)	
≥College graduate (n, %)	6903 (35.32)	5880 (37.68)	1023 (26.08)	<0.001
History of smoking (n, %)				
Never	9287 (47.52)	7831 (50.35)	1456 (37.16)	
Past	7358 (37.65)	5664 (36.42)	1694 (43.24)	
Current	2826 (14.46)	2058 (13.23)	768 (19.60)	<0.001
Co-morbidities				
Diabetes (n, %)	3907 (19.99)	2687 (17.32)	1220 (31.26)	<0.001
Atrial fibrillation (n, %)	1662 (8.50)	1096 (7.18)	566 (14.86)	<0.001
Cardiovascular Disease (n, %)	3225 (16.50)	1946 (12.69)	1279 (33.34)	<0.001
Left ventricular hypertrophy (n, %)	1682 (8.61)	1235 (8.04)	447 (11.59)	<0.001
Cancer history (n, %)	1213 (6.21)	798 (12.17)	415 (19.63)	<0.001
Body mass index (mean, SD)	29 (6.3)	30 (6.2)	29 (6.5)	<0.001
Systolic BP (mean, SD)	126 (16.4)	125 (15.7)	131 (18.2)	<0.001
Diastolic BP (mean, SD)	76 (9.7)	76 (9.4)	76 (10.5)	<0.001

Anti-hypertensive use (n, %)	9964 (50.98)	7497 (50.00)	2467 (65.06)	<0.001
Total cholesterol (mean, SD)	192 (40.6)	194 (39.8)	184 (42.8)	<0.001
LDL cholesterol (mean, SD)	113 (35.2)	114 (34.7)	106 (36.3)	<0.001
HDL cholesterol (mean, sD)	53 (16.5)	54 (16.4)	51 (16.7)	<0.001
Triglycerides (mean, SD)	130 (83.9)	129 (82.2)	137 (89.8)	<0.001
eGFR (mean, SD)	86 (20.3)	89 (18.2)	75 (24.1)	<0.001
Creatinine (mean, %)	1 (0.5)	1 (0.3)	1 (0.9)	<0.001
CRP (median, [25%, 75%])	2.2 (0.94-5.08)	2.08 (0.91-4.80)	2.74 (1.14-6.51)	<0.001
Blood cell counts				
Total WBC (mean, SD)	6 (2.1)	6 (1.9)	6 (2.7)	<0.001
Platelets (mean, SD)	237 (69)	240 (67.3)	227 (74.7)	<0.001
Hemoglobin (mean, SD)	14 (1.5)	14 (1.4)	13 (1.6)	<0.001
MCV (mean, SD)	90 (5.8)	90 (5.6)	91 (6.4)	<0.001
Cytopenia	374 (1.91)	225 (1.44)	149 (3.79)	<0.001

SD, standard deviation; RUCA, rural-urban commuting areas; BP, blood pressure; LDL, low-density lipoprotein; HDL, high-density lipoprotein, eGFR, estimated glomerular filtration rate; CRP, C-reactive protein; WBC, white blood cell count; MCV, mean corpuscular volume.

Table S3. Demographic and clinical characteristics of study participants included in the CVD related mortality analysis.

	Entire cohort	No CVD mortality	CVD mortality	P value
Entire cohort (n)	19542	18509	1033	
Person-years follow-up/ 10,000	145085.9	51121852	1870786	
Follow-up in years (median, range)	8.1 (0-11)	8.2 (0.1-11)	5 (0-10.4)	
Age (Mean, SD)	64 (9.7)	64 (9.6)	71 (9.7)	<0.001
Sex, Male (n, %)	7398 (37.86)	6862 (37.07)	536 (51.89)	<0.001
Race (n, %)	7809 (39.96)	7343 (39.67)	466 (45.11)	<0.001
Region (n, %)				
Rest of nation	7926 (40.56)	7495 (40.49)	431 (41.76)	
Stroke Belt	6855 (35.08)	6485 (35.04)	370 (35.85)	
Stroke Buckle	4760 (24.36)	4529 (24.47)	231 (22.38)	0.314
Annual income (n, %)				
Refused (n, %)	2522 (12.91)	2384 (12.88)	138 (13.36)	
>75K (n, %)	3333 (17.06)	3258 (17.60)	75 (7.26)	
35 - 75K (n, %)	5904 (30.21)	5663 (30.60)	241 (23.33)	
20 - 34K (n, %)	4508 (23.07)	4203 (22.71)	305 (29.53)	
<20K (n, %)	3275 (16.76)	3001 (16.21)	274 (26.52)	<0.001
RUCA codes (n, %)				
Urban	13832 (70.78)	13095 (78.80)	737 (79.25)	
Large rural	2147 (10.99)	2031 (12.22)	116 (12.47)	
Small rural	1129 (5.78)	1071 (6.45)	58 (6.24)	
Isolated	439 (2.25)	420 (2.53)	19 (2.04)	0.813
Education (n, %)				
<High School (n, %)	2182 (11.17)	1982 (10.72)	200 (19.42)	
High School (n, %)	5084 (26.02)	4767 (25.77)	317 (30.78)	
Some college (n, %)	5358 (27.42)	5099 (27.57)	259 (25.15)	
≥College graduate (n, %)	6903 (35.32)	6649 (35.95)	254 (24.66)	<0.001
History of smoking (n, %)				
Never	9287 (47.52)	8893 (48.23)	394 (38.29)	
Past	7357 (37.65)	6903 (37.43)	454 (44.12)	
Current	2825 (14.46)	2644 (14.34)	181 (17.59)	<0.001
Co-morbidities				
Diabetes (n, %)	3906 (19.99)	3518 (19.12)	388 (38.00)	<0.001
Atrial fibrillation (n, %)	1662 (8.50)	1471 (8.14)	191 (19.08)	<0.001
Cardiovascular Disease (n, %)	3224 (16.50)	2787 (15.35)	437 (43.35)	<0.001
Left ventricular hypertrophy (n, %)	1682 (8.61)	1525 (8.38)	157 (15.56)	<0.001
Cancer history (n, %)	1213 (6.21)	1114 (13.76)	99 (17.28)	0.022
Body mass index (mean, SD)	29 (6.3)	29 (6.3)	29 (6.5)	0.714
Systolic BP (mean, SD)	126 (16.4)	126 (16.1)	133 (20.3)	<0.001

Diastolic BP (mean, SD)	76 (9.7)	76 (9.6)	76 (11.2)	0.714
Anti-hypertensive use (n, %)	9964 (50.99)	9250 (52.01)	714 (71.33)	<0.001
Total cholesterol (mean, SD)	192 (40.6)	192 (40.3)	184 (44.9)	<0.001
LDL cholesterol (mean, SD)	113 (35.2)	113 (35.0)	106 (37.4)	<0.001
HDL cholesterol (mean, sD)	53 (16.5)	53 (16.5)	49 (15.4)	<0.001
Triglycerides (mean, SD)	130 (83.9)	130 (82.6)	143 (103.4)	<0.001
eGFR (mean, SD)	86 (20.3)	87 (19.7)	72 (25.2)	<0.001
Creatinine (mean, %)	1 (0.5)	1 (0.4)	1 (1.1)	<0.001
CRP (median, [25%, 75%])	2.2 (0.94-5.08)	2.15 (0.93-5.00)	2.96 (1.28-7.21)	<0.001
Blood cell counts				
Total WBC (mean, SD)	6 (2.1)	6 (2.1)	6 (2.1)	<0.001
Platelets (mean, SD)	237 (69)	238 (68.6)	222 (73.9)	<0.001
Hemoglobin (mean, SD)	14 (1.5)	14 (1.4)	13 (1.7)	<0.001
MCV (mean, SD)	90 (5.8)	90 (5.7)	91 (6.6)	<0.001
Cytopenia	374 (1.91)	338 (1.83)	36 (3.48)	<0.001

CVD, cardiovascular disease; SD, standard deviation; RUCA, rural-urban commuting areas; BP, blood pressure; LDL, low-density lipoprotein; HDL, high-density lipoprotein, eGFR, estimated glomerular filtration rate; CRP, C-reactive protein; WBC, white blood cell count; MCV, mean corpuscular volume.

Table S4. Demographic and clinical characteristics of study participants included in the stroke analysis.

	Entire cohort	No Stroke	Incident Stroke	P value
Entire cohort (n)	18474	17676	798	
Person-years follow-up/ 10,000	156528	55659322	1512518	
Follow-up in years (median, range)	9.5 (0-13.1)	9.5 (0-13.1)	4.9 (0-12.4)	
Age (Mean, SD)	64 (9.7)	64 (9.7)	69 (9.0)	<0.001
Sex, Male (n, %)	6932 (37.52)	6575 (37.20)	357 (44.74)	<0.001
Race (n, %)	7266 (39.33)	6962 (39.39)	304 (38.10)	0.488
Region (n, %)				
Rest of nation	7489 (40.54)	7185 (40.65)	304 (38.10)	
Stroke Belt	6475 (35.05)	6187 (35.00)	288 (36.09)	
Stroke Buckle	4509 (24.41)	4303 (24.35)	206 (25.81)	0.339
Annual income (n, %)				
Refused (n, %)	2363 (12.79)	2246 (12.71)	117 (14.66)	
>75K (n, %)	3250 (17.59)	3175 (17.96)	75 (9.40)	
35 - 75K (n, %)	5677 (30.73)	5434 (30.74)	243 (30.45)	
20 - 34K (n, %)	4212 (22.80)	3995 (22.60)	217 (27.19)	
<20K (n, %)	2972 (16.09)	2826 (15.99)	146 (18.30)	<0.001
RUCA codes (n, %)				
Urban	13074 (70.77)	12526 (79.07)	548 (74.76)	
Large rural	2017 (10.92)	1913 (12.08)	104 (14.19)	
Small rural	1067 (5.78)	1005 (6.34)	62 (8.46)	
Isolated	417 (2.26)	398 (2.51)	19 (2.59)	0.028
Education (n, %)				
<High School (n, %)	1965 (10.64)	1866 (10.56)	99 (12.41)	
High School (n, %)	4767 (25.80)	4535 (25.67)	232 (29.07)	
Some college (n,%)	5082 (27.51)	4875 (27.59)	207 (25.94)	
≥College graduate (n, %)	6652 (36.01)	6392 (36.18)	260 (32.58)	0.025
History of smoking (n, %)				
Never	8863 (47.98)	8518 (48.37)	345 (43.45)	
Past	6922 (37.47)	6604 (37.50)	318 (40.05)	
Current	2618 (14.17)	2487 (14.12)	131 (16.50)	0.017
Co-morbidities				
Diabetes (n, %)	3545 (19.19)	3319 (18.9)	226 (28.5)	<0.001
Atrial fibrillation (n, %)	1509 (8.17)	1392 (8.06)	117 (14.87)	<0.001
Cardiovascular Disease (n, %)	2890 (15.64)	2660 (15.33)	230 (29.26)	<0.001
Left ventricular hypertrophy (n, %)	1551 (8.40)	1454 (8.37)	97 (12.29)	<0.001
Cancer history (n, %)	1116 (6.04)	1043 (13.46)	73 (17.76)	0.017
Body mass index (mean, SD)	29 (6.3)	29 (6.3)	29 (6.0)	0.49
Systolic BP (mean, SD)	126 (16.3)	126 (16.2)	131 (16.8)	<0.001
Diastolic BP (mean, SD)	76 (9.6)	76 (9.6)	77 (10.0)	0.017

Anti-hypertensive use (n, %)	9163 (49.6)	8651 (50.94)	512 (66.41)	<0.001
Total cholesterol (mean, SD)	192 (40.3)	192 (40.2)	190 (42.3)	0.173
LDL cholesterol (mean, SD)	113 (35)	113 (35.0)	111 (35.4)	0.056
HDL cholesterol (mean, SD)	53 (16.5)	54 (16.5)	51 (16.6)	<0.001
Triglycerides (mean, SD)	130 (82.7)	129 (82.1)	143 (94.6)	<0.001
eGFR (mean, SD)	87 (20)	87 (19.9)	81 (20.8)	<0.001
Creatinine (mean, %)	1 (0.5)	1 (0.5)	1 (0.5)	0.004
CRP (median, [25%, 75%])	2.17 (0.93-5.04)	2.14 (0.93-5.00)	2.59 (1.03-5.64)	0.003
Blood cell counts				
Total WBC (mean, SD)	6 (2.1)	6 (2.1)	6 (2.2)	<0.001
Platelets (mean, SD)	237 (68.6)	237 (68.6)	231 (68.8)	0.012
Hemoglobin (mean, SD)	14 (1.4)	14 (1.4)	14 (1.5)	0.509
MCV (mean, SD)	90 (5.7)	90 (5.7)	90 (5.7)	0.003
Cytopenia	349 (1.89)	329 (1.86)	20 (2.51)	0.24

SD, standard deviation; RUCA, rural-urban commuting areas; BP, blood pressure; LDL, low-density lipoprotein; HDL, high-density lipoprotein, eGFR, estimated glomerular filtration rate; CRP, C-reactive protein; WBC, white blood cell count; MCV, mean corpuscular volume.

Table S5. Demographic and clinical characteristics of study participants included in the coronary heart disease analysis.

	Entire Cohort	No CHD	Incident CHD	P value
Entire cohort (n)	16318	15591	727	
Total follow-up/ 10,000 person-years	120865.1	43010534	1135445	
Follow-up in years (min, median, max)	8.1 (0-10.9)	8.2 (0-10.9)	4.2 (0-10.4)	
Age (Mean, SD)	63 (9.6)	63 (9.6)	67 (9.3)	<0.001
Sex, Male (n, %)	5656 (34.66)	5300 (33.99)	356 (48.97)	<0.001
Race (n, %)	6662 (40.83)	6364 (40.82)	298 (40.99)	0.957
Region (n, %)				
Rest of nation	6645 (40.72)	6374 (40.88)	271 (37.28)	
Stroke Belt	5724 (35.08)	5441 (34.90)	283 (38.93)	
Stroke Buckle	3949 (24.20)	3776 (24.22)	173 (23.80)	0.064
Annual income (categories) (n, %)				
Refused (n, %)	2117 (12.97)	2024 (12.98)	93 (12.79)	
>75K (n, %)	2935 (17.99)	2842 (18.23)	93 (12.79)	
35 - 75K (n, %)	5012 (30.71)	4812 (30.86)	200 (27.51)	
20 - 34K (n, %)	3695 (22.64)	3508 (22.50)	187 (25.72)	
<20K (n, %)	2559 (15.68)	2405 (15.43)	154 (21.18)	<0.001
RUCA codes (n, %)				
Urban	11619 (71.20)	11112 (79.46)	507 (76.82)	
Large rural	1742 (10.68)	1650 (11.80)	92 (13.94)	
Small rural	924 (5.66)	881 (6.30)	43 (6.52)	
Isolated	360 (2.21)	342 (2.45)	18 (2.73)	0.357
Education (n, %)				
<High School (n, %)	1676 (10.27)	1556 (9.99)	120 (16.55)	
High School (n, %)	4141 (25.38)	3941 (25.29)	200 (27.59)	
Some college (n, %)	4531 (27.77)	4323 (27.74)	208 (28.69)	
College graduate and above (n, %)	5959 (36.52)	5762 (36.98)	197 (27.17)	<0.001
History of smoking (n, %)				
Never	8092 (49.59)	7802 (50.22)	290 (40.00)	
Past	5875 (36.00)	5579 (35.91)	296 (40.83)	
Current	2293 (14.05)	2154 (13.87)	139 (19.17)	<0.001
Co-morbidities				
Diabetes (n, %)	2900 (17.77)	2667 (17.22)	233 (32.23)	<0.001
Atrial fibrillation (n, %)	1095 (6.71)	1019 (6.69)	76 (10.63)	<0.001
Cardiovascular Disease (n, %)	15942 (97.7)	15237 (100)	705 (100)	<0.001
Left ventricular hypertrophy (n, %)	1278 (7.83)	1204 (7.86)	74 (10.35)	0.02
Cancer history (n, %)	921 (5.64)	858 (12.79)	63 (17.21)	0.018
Body mass index (mean, SD)	29 (6.3)	29 (6.3)	30 (6.6)	0.013
Systolic blood pressure (mean, SD)	126 (16.1)	126 (15.9)	132 (18.8)	<0.001
Diastolic BP (mean, SD)	76 (9.6)	76 (9.5)	77 (10.5)	0.4

Anti-hypertensive use (n, %)	7791 (47.74)	7344 (49.06)	447 (63.77)	<0.001
Total cholesterol (mean, SD)	195 (39.6)	195 (39.4)	193 (43.8)	0.136
LDL cholesterol (mean, SD)	115 (34.7)	115 (34.5)	114 (37.8)	0.238
HDL cholesterol (mean, SD)	54 (16.5)	54 (16.5)	50 (15.2)	<0.001
Triglycerides (mean, SD)	128 (81.6)	127 (81.1)	144 (89.5)	<0.001
eGFR (mean, SD)	88 (19.5)	88 (19.2)	81 (23.2)	<0.001
Creatinine (mean, %)	1 (0.4)	1 (0.4)	1 (0.8)	<0.001
CRP (median, (25%, 75%))	2.19 (0.93-5.0)	2.15 (0.92-4.95)	3.0 (1.24-6.17)	<0.001
Blood cell counts				
Total WBC (mean, SD)	6 (2)	6 (2.0)	6 (2.1)	<0.001
Platelets (mean, SD)	240 (69)	240 (68.9)	234 (71.7)	0.017
Hemoglobin (mean, SD)	14 (1.4)	14 (1.4)	14 (1.7)	0.444
MCV (mean, SD)	90 (5.7)	90 (5.7)	90 (6.0)	0.688
Cytopenia	287 (1.76)	274 (1.76)	13 (1.79)	1.0

CHD, coronary heart disease; SD, standard deviation; RUCA, rural-urban commuting areas; BP, blood pressure; LDL, low-density lipoprotein; HDL, high-density lipoprotein, eGFR, estimated glomerular filtration rate; CRP, C-reactive protein; WBC, white blood cell count; MCV, mean corpuscular volume.

Table S6. Association of individual blood cell component abnormalities with CVD and mortality outcomes.

		Model 1 (HR, 95% CI) (Demographics)	Model 2 (HR, 95% CI) (CVD Risk Factors)	Model 3 (HR, 95% CI) (Extended Risk factors)
Anemia				
CHD	Events/ No Cytopenia	662/15555	631/14748	621/14549
	Events/ With Cytopenia	65/763	64/730	62/722
	HR	**2.29 (1.77, 2.96)**	**2.31 (1.78, 2.99)**	**1.91 (1.45, 2.51)**
Stroke	Events/ No Cytopenia	753/17553	700/16143	693/15921
	Events/ With Cytopenia	45/919	42/832	40/825
	HR	1.28 (0.94, 1.73)	1.13 (0.83, 1.55)	1.06 (0.76, 1.46)
Overall mortality	Events/ No Cytopenia	3507/18531	1838/7977	1679/7257
	Events/ With Cytopenia	424/1011	195/414	174/366
	HR	**2.62 (2.37, 2.90)**	**1.85 (1.58, 2.15)**	**1.79 (1.52, 2.11)**
CVD mortality	Events/ No Cytopenia	912/18529	868/17589	856/17348
	Events/ With Cytopenia	120/1011	116/961	115/952
	HR	**2.73 (2.26, 3.31)**	**2.69 (2.21, 3.28)**	**1.97 (1.60, 2.42)**
Leukopenia				
CHD	Events/ No Cytopenia	707/15460	677/14652	668/14457
	Events/ With Cytopenia	20/858	18/826	15/814
	HR	**0.52 (0.33, 0.81)**	**0.59 (0.37, 0.94)**	**0.53 (0.32, 0.89)**
Stroke	Events/ No Cytopenia	763/17530	708/16089	699/15876
	Events/ With Cytopenia	35/943	34/887	34/871
	HR	0.88 (0.63, 1.24)	1.09 (0.77, 1.54)	1.15 (0.81, 1.63)
Overall mortality	Events/ No Cytopenia	3784/18558	1956/7982	1779/7242
	Events/ With Cytopenia	148/985	78/410	75/382
	HR	0.78 (0.66, 0.92)	1.04 (0.83, 1.31)	1.07 (0.85, 1.36)
CVD mortality	Events/ No Cytopenia	995/18556	948/17606	935/17372
	Events/ With Cytopenia	37/985	36/945	36/929
	HR	0.74 (0.53, 1.03)	0.94 (0.68, 1.32)	1.06 (0.76, 1.48)
Thrombocytopenia				

CHD	Events/ No Cytopenia	663/15173	637/14402	627/14212
	Events/ With Cytopenia	46/713	42/671	41/661
	HR	1.14 (0.85, 1.55)	1.10 (0.80, 1.50)	1.13 (0.82, 1.55)
Stroke	Events/ No Cytopenia	741/17083	688/15704	681/15496
	Events/ With Cytopenia	41/902	38/825	37/814
	HR	0.86 (0.62, 1.18)	0.83 (0.60, 1.15)	0.83 (0.59, 1.15)
Overall mortality	Events/ No Cytopenia	3505/18067	1811/7704	1653/6994
	Events/ With Cytopenia	331/960	173/456	160/418
	HR	**1.34 (1.19, 1.50)**	**1.38 (1.18, 1.62)**	**1.35 (1.15, 1.60)**
CVD mortality	Events/ No Cytopenia	908/18065	867/17154	857/16928
	Events/ With Cytopenia	98/960	93/911	91/898
	HR	**1.44 (1.17, 1.78)**	**1.43 (1.15, 1.78)**	**1.48 (1.19, 1.85)**
Macrocytosis				
CHD	Events/ No Cytopenia	699/15651	669/14852	658/14663
	Events/ With Cytopenia	28/647	26/607	25/590
	HR	0.85 (0.58, 1.24)	0.81 (0.54, 1.20)	0.81 (0.54, 1.22)
Stroke	Events/ No Cytopenia	753/17661	698/16230	691/16021
	Events/ With Cytopenia	44/794	43/729	41/710
	HR	1.11 (0.81, 1.50)	1.11 (0.81, 1.51)	1.09 (0.79, 1.50)
Overall mortality	Events/ No Cytopenia	3612/18675	1880/8032	1714/7300
	Events/ With Cytopenia	317/847	152/347	138/313
	HR	**1.61 (1.43, 1.81)**	**1.40 (1.18, 1.66)**	**1.50 (1.26, 1.80)**
CVD mortality	Events/ No Cytopenia	947/18673	902/17729	891/17499
	Events/ With Cytopenia	85/847	82/802	80/783
	HR	**1.61 (1.28, 2.02)**	**1.64 (1.30, 2.07)**	**1.65 (1.31, 2.09)**

CVD, cardiovascular disease; HR, hazard ratio; CI, confidence interval; CHD, coronary heart disease.