Association of Total and Differential Leukocyte Counts With Cardiovascular Disease and Mortality in the UK Biobank

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Objective—Elevated white blood cell count is associated with a higher risk of cardiovascular disease (CVD). We aimed to investigate whether specific leukocyte subpopulations, which may more closely indicate a specific inflammatory pathway, are specifically associated with CVD.

Approach and Results—Participants (478 259) from UK Biobank with data for white blood cell count were included. Death because of CVD (n=1377) and non-CVD causes (n=8987) occurred during median follow-up time of 7.0 years (interquartile range, 6.3–7.6). In Cox models, deciles of leukocyte counts (lymphocytes, monocytes, neutrophils, eosinophils, and basophils) were examined using the fifth decile as the referent group. Models were stratified by sex and adjusted for a range of classical risk factors. A sensitivity analysis excluded participants with baseline comorbidites and the first 2 years of follow-up. Men (hazard ratio [HR], 1.59; 95% confidence interval, 1.22–2.08) and women (HR, 2.15; 95% confidence interval, 1.38–3.35) in the highest decile of neutrophil count were at higher risk of CVD mortality and nonfatal CVD (men HR, 1.28; 95% confidence interval, 1.16–1.42 and women HR, 1.21; 95% confidence interval, 1.06–1.38). In the sensitivity analysis, the power to investigate CVD mortality was limited, but for both sexes combined, the linear HRs for a 1×10^9/L cell count increase in white blood cell count and neutrophils, respectively, was 1.05 (1.03–1.07) and 1.07 (1.04–1.11).

Conclusions—Among circulating leukocyte subpopulations, neutrophil count in men was most consistently associated with fatal and nonfatal CVD. Further studies of interventions that lower circulating neutrophils, such as canakinumab, are required to investigate causality.

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Key Words: cardiovascular disease ■ epidemiology ■ inflammation ■ leukocyte count ■ neutrophils

Inflammation may be a key, potentially modifiable, process in the development of cardiovascular disease (CVD).[1,2] Elevated levels of inflammatory mediators within healthy people may increase the risk of CVD. Many studies have reported that a range of different blood-based inflammatory biomarkers are associated with an increased risk of incident CVD events.[3–7] This initially led to an interest in reducing the risk of CVD by targeting patients with evidence of inflammation as illustrated by high-sensitivity C-reactive protein.[8] More recently, with genetic evidence supporting interleukin-6 pathway as causal in the development of CVD,[9] interest has emerged in directly inhibiting specific parts of the inflammatory pathway to prevent CVD.[10,11]

One of the simplest, and most commonly measured markers of the immune response and inflammation, is the total white blood cell (WBC) count. Many studies have reported that an elevated WBC is associated with higher rates of incident CVD[12–15] and non-CVD mortality.[13,16] The association between elevated WBC and elevated CVD risk may indicate that infection and inflammation are part of the pathway leading to the development of CVD. However, WBC may also reflect poor health and risk of death from any cause and therefore be a nonspecific association.

Different subpopulations of WBC (lymphocytes, neutrophils, monocytes, eosinophils, and basophils) may also be associated with CVD and non-CVD mortality.[14,17,18] In particular, elevated neutrophil counts may be associated with a higher risk of CVD in routine population data sets,[18] although the influence of clinical susceptibility bias is difficult to account for in such databases, and the influence of reverse causality requires consideration.[19] An additional consideration is that different associations in specific cell types may be suggestive of distinct pathways that lead to CVD. Although neutrophils (granulocytes that comprise the majority of circulating WBCs) can cause tissue damage, including in the

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Nonstandard Abbreviations and Acronyms	
BMI	body mass index
CI	confidence interval
CVD	cardiovascular disease
HR	hazard ratio
WBC	white blood cell count

walls of blood vessels via the formation of neutrophil extracellular traps,[20] which in turn lead to macrophage-produced interleukin precursors,[21] other white cell types such as monocytes (precursors of tissue macrophages) may also be important.[22]

To explore these associations further, we examined the association between WBC and the differential leukocyte counts with all-cause mortality, CVD mortality, and non-CVD mortality in the UK Biobank population. This is a large population-based cohort study with >500 000 participants who have no clinical indication for WBC measurement. Simultaneous comparison of differential counts with both CVD and non-CVD mortality allows specificity of the associations to be investigated. To restrict the potential for reverse casualty—ie, whereby preexisting and subclinical illness might cause changes in leukocyte counts—we also examined these associations in a sensitivity analysis.

Materials and Methods

All data and materials have been made publicly available at the UK Biobank and can be accessed at http://www.ukbiobank.ac.uk/.

UK Biobank recruited 502 655 participants (aged 37–73 years) from 22 assessment centers across the UK between April 2007 and December 2010.[23] Baseline biological measurements were recorded, and touchscreen questionnaires were administered, as described elsewhere.[1,2] UK Biobank received ethical approval from the North West Multi-centre Research Ethics Committee (REC reference: 11/NW/03820). All participants gave written informed consent before enrollment in the study, which was conducted in accord with the principles of the Declaration of Helsinki.

Smoking status was categorized into never, former, or current smoking. Ethnicity was coded as white, South Asian, black, or mixed/other, with white as the referent group. Body mass index (BMI) was calculated as (weight in kilograms per height in square meter). Area-based socioeconomic status was derived from postcode of residence, using the Townsend score.[3] WBCs were measured on fresh samples as an absolute number per unit volume, and their component leukocytes (lymphocytes, monocytes, neutrophils, eosinophils, and basophils) as absolute measures and proportions of the overall WBC; all using an automated, clinically validated, Coulter LH 750. Calibration and quality control were performed in line with the manufacturer's recommendations. Further details of these measurements can be found in the UK Biobank online showcase and protocol (http://www.ukbiobank.ac.uk).

Specific baseline comorbidities of interest were self-reported CVD (myocardial infraction, angina, stroke or transient ischemic attack), diabetes mellitus, rheumatoid arthritis, chronic kidney disease and atrial fibrillation or flutter. A category of other baseline comorbidities potentially associated with inflammation was defined as any of self-reported baseline diagnosis of peripheral vascular disease, heart failure, any malignancy, dementia, Parkinson disease, psoriasis or eczema, osteoporosis, polyarthropathies and systemic connective tissue disorders (other than rheumatoid arthritis), multiple sclerosis, chronic fatigue syndrome, chronic liver disease, endometriosis, polycystic ovarian syndrome, diverticular disease of the intestine, hypertension, depression, painful conditions, asthma, treated dyspepsia, thyroid disorders, chronic obstructive pulmonary disorder, inflammatory bowel disease or irritable bowel syndrome, alcohol problems, other psychoactive substance abuse, treated constipation, prostate disorders, glaucoma, epilepsy, migraines, chronic sinusitis, anorexia or bulimia, anxiety and other neurotic or stress-related disorders, schizophrenia, viral hepatitis, bronchiectasis, Ménière disease, and pernicious anemia.

Date and cause of death were obtained from death certificates held by the National Health Service Information Centre for participants from England and Wales and the National Health Service Central Register Scotland for participants from Scotland. There were 3 outcomes of interest in the current study; all-cause mortality, death related to CVD (primary cause of death including ICD-10 codes I20-I23, I24.1, I25.2 and I60-I64) and death unrelated to CVD (any ICD-10 codes excluding I00-I99). We also examined the association between WBC and nonfatal CVD outcomes. Nonfatal outcomes (codes I20-I23, I24.1, I25.2 and I60-I64) were ascertained from hospitalization records using record linkage to national hospitalization data. End of follow-up for the main study for each participant was recorded as the date of death or the date of end of follow-up for the assessment center attended (30/11/2015 for Scottish centers, 31/01/2016 for English or Welsh centers), whichever came first. End of follow-up for the nonfatal events analysis was the date of admission of the first CVD hospitalization or the date of end of follow-up for the assessment center attended, or the date of death, whichever came first. The period at risk per participant began on the date of their assessment. Participants who were hospitalized within 30 days of their assessment were excluded.

Statistical Analyses

The distribution of classical risk factors (age, sex, systolic blood pressure, BMI, deprivation score, smoking, ethnicity, baseline CVD, baseline diabetes mellitus, family history of CVD [mother, father, or sibling], rheumatoid arthritis, chronic kidney disease [stage 4 or 5], atrial fibrillation, and other baseline illness), and leukocyte subpopulations, were investigated by decile of WBCs. We examined the relationship between WBC and its constituents and the outcomes using restricted cubic splines of each cell count restricted to values of their mean ±4 SD and found that the deciles adequately modeled the data (Figures VII through XXIV in the online-only Data Supplement). We present the primary results on the basis of deciles. Classical risk factors were expressed as mean (SD) if symmetrically distributed, median (interquartile range) if skewed, and number (%) if categorical. Tests for trends across WBC deciles were performed using regression, a Wilcoxon test for trend, or a χ^2 test, respectively. Associations between classical risk factors, WBC, and leukocyte subpopulations with mortality outcomes were also tabulated using these methods. Correlations between WBC and its components were tested by Spearman correlation coefficients.

Associations of leukocytes with all-cause mortality, CVD mortality, and non-CVD mortality were investigated using Cox-proportional hazard models. WBC and leukocyte counts at baseline were entered into the model as absolute counts, by sex-specific deciles. The fifth decile was used as the referent group. The adjusted model included continuous terms for age, deprivation index, systolic blood pressure, and BMI and categorical variables for smoking, ethnicity, diabetes mellitus, family history of CVD, rheumatoid arthritis, atrial fibrillation, baseline CVD, and the binary composite variable for other baseline comorbidities (defined above). The results were reported as sex-specific hazard ratios (HRs) for deciles of the leukocytes, together with 95% confidence intervals. We also investigated associations of leukocytes with outcomes using the exposure as a linear variable where this was an appropriate model fit. To examine the potential role of reverse causality, a sensitivity analysis was performed that excluded those with any baseline comorbidities (diabetes mellitus, rheumatoid arthritis, atrial fibrillation, baseline CVD, and other baseline illness), and the first 2 years of follow-up. The results from this analysis had lower power; so only linear models combining sexes are presented. A further sensitivity analysis was conducted using a Fine and Gray model to adjust CVD mortality for the competing risk of non-CVD mortality (and vice versa).[4] These models did not meaningfully change HRs and so the more complex competing risk model was not utilized. We tested the interaction between smoking status and WBC and its components for cardiovascular mortality and found no significant interactions after adjusting for multiple testing.

All analyses were performed using STATA 14 (StataCorp LP). A *P* value of <0.05 was considered statistically significant.

Results

Cross-Sectional Associations

Of 502 634 people included in the study, WBC data were available in 478 279 (95.2%), lymphocytes, monocytes, neutrophils, eosinophils, and basophils in 477 401 (95.0%). There were 258 966 women and 219 313 men with WBC measured.

Participants with higher WBC count were generally older; had higher systolic blood pressure and higher BMI; and were more likely to be a smoker, have a family history of CVD, and have baseline rheumatoid arthritis, chronic kidney disease, diabetes mellitus, CVD, atrial fibrillation, or other comorbidities

Table 1. Association of WBC Count (by Deciles) With Classical Risk Factors

	≤4.87 (10^9/L)	4.87–5.41 (10^9/L)	5.41–5.88 (10^9/L)	5.88–6.29 (10^9/L)	6.29–6.69 (10^9/L)	6.69–7.10 (10^9/L)	7.10–7.60 (10^9/L)	7.60–8.20 (10^9/L)	8.20–9.18 (10^9/L)	≥9.18 (10^9/L)	*P* Value for Trend
	n=48 057	n=49 251	n=46 659	n=47 508	n=47 873	n=51 802	n=44 149	n=49 550	n=45 775	n=47 635	
Age, y	55.5±7.9	56.2±7.9	56.5±8.0	56.7±8.0	56.7±8.0	56.9±8.1	56.9±8.1	56.8±8.2	56.8±8.2	56.6±8.3	<0.0001
Male sex, n (%)	21 299 (44.3)	22 316 (45.3)	21 341 (45.7)	21 660 (45.6)	21 936 (45.8)	23 891 (46.1)	20 361 (46.1)	22 813 (46.0)	21 393 (46.7)	22 299 (46.8)	<0.001
SBP, mm Hg	136.1±19.1	137.8±19.4	138.8±19.5	139.4±19.5	139.9±19.7	140.5±19.6	140.8±19.8	141.3±19.7	141.6±19.8	141.8±19.84	<0.0001
BMI, kg/m^2	25.8±4.1	26.4±4.1	26.7±4.3	27.0±4.4	27.2±4.5	27.6±4.6	27.8±4.8	28.1±5.0	28.5±5.2	29.0±5.8	<0.0001
Deprivation (score)	−1.4±3.1	−1.5±3.0	−1.5±3.0	−1.5±3.0	−1.5±3.0	−1.4±3.0	−1.3±3.1	−1.3±3.1	−1.1±3.2	−0.6±3.3	<0.0001
Smoking, n (%)											
Never	30 236 (63.0)	29 896 (60.8)	27 647 (59.3)	27 703 (58.4)	27 413 (57.3)	28 737 (55.5)	23 886 (54.1)	25 599 (51.7)	21 999 (48.1)	19 188 (40.3)	<0.0001
Previous	15 810 (32.9)	16 980 (34.5)	16 406 (35.2)	16 785 (35.4)	17 003 (35.5)	18 492 (35.7)	15 792 (35.8)	17 635 (35.6)	15 789 (34.5)	14 607 (30.7)	
Current	1962 (4.1)	2331 (4.7)	2550 (5.5)	2966 (6.3)	3418 (7.1)	4509 (8.7)	4437 (10.1)	6257 (12.6)	7937 (17.4)	13 792 (29.0)	
Ethnicity, n (%)											
White	42 762 (89.4)	45 109 (92.0)	42 803 (92.2)	43 736 (92.5)	44 339 (93.0)	47 787 (92.7)	40 657 (92.5)	45 635 (92.5)	41 976 (92.1)	43 503 (91.8)	<0.0001
South Asian	344 (0.7)	491 (1.0)	568 (1.2)	657 (1.4)	676 (1.4)	871 (1.7)	811 (1.8)	972 (2.0)	1014 (2.2)	1090 (2.3)	
Black	2291 (4.8)	1148 (2.3)	833 (1.8)	727 (1.5)	518 (1.1)	517 (1.0)	391 (0.9)	354 (0.7)	322 (0.7)	302 (0.6)	
Other	2421 (5.1)	2302 (4.7)	2216 (4.8)	2150 (4.5)	2132 (4.5)	2382 (4.6)	2105 (4.8)	2363 (4.8)	2260 (5.0)	2490 (5.3)	
Baseline CVD, n (%)	1602 (3.3)	1947 (4.0)	2168 (4.6)	2288 (4.8)	2620 (5.5)	3154 (6.1)	2854 (6.5)	3475 (7.0)	3736 (8.2)	4667 (9.8)	<0.0001
Baseline diabetes mellitus, n (%)	1355 (2.8)	1439 (2.9)	1586 (3.4)	1810 (3.8)	2071 (4.3)	2571 (5.0)	2463 (5.6)	3138 (6.3)	3594 (7.9)	4951 (10.4)	<0.0001
Family history of CVD, n (%)	25 871 (53.8)	27 311 (55.5)	26 058 (55.8)	26 961 (56.8)	27 115 (56.6)	29 289 (56.5)	25 119 (56.9)	28 398 (57.3)	26 108 (57.0)	27 249 (57.2)	<0.0001
Rheumatoid arthritis, n (%)	499 (1.0)	473 (1.0)	479 (1.0)	538 (1.1)	470 (1.0)	492 (0.9)	469 (1.1)	580 (1.2)	574 (1.3)	778 (1.6)	<0.0001
Baseline CKD, n (%)	53 (0.1)	56 (0.1)	63 (0.1)	53 (0.1)	73 (0.2)	88 (0.2)	77 (0.2)	93 (0.2)	101 (0.2)	163 (0.3)	<0.0001
Atrial fibrillation, n (%)	260 (0.5)	313 (0.6)	282 (0.6)	328 (0.7)	355 (0.7)	413 (0.8)	350 (0.8)	398 (0.8)	414 (0.9)	449 (0.9)	<0.0001
Other baseline illness, n (%)	27 858 (58.0)	29 319 (59.5)	28 548 (61.2)	29 514 (62.1)	30 219 (63.1)	33 581 (64.8)	29 096 (65.9)	33 222 (67.0)	31 629 (69.1)	34 511 (72.4)	<0.0001
Lymphocyte count	1.4 (1.1–1.6)	1.6 (1.3–1.8)	1.7 (1.4–2.0)	1.8 (1.5–2.1)	1.9 (1.6–2.3)	2.0 (1.6–2.3)	2.0 (1.7–2.4)	2.1 (1.8–2.5)	2.3 (1.9–2.7)	2.5 (2.1–3.1)	<0.0001
Monocyte count	0.3 (0.3–0.4)	0.4 (0.3–0.5)	0.4 (0.3–0.5)	0.4 (0.3–0.5)	0.4 (0.4–0.5)	0.5 (0.4–0.6)	0.5 (0.4–0.6)	0.5 (0.4–0.6)	0.6 (0.4–0.7)	0.6 (0.5–0.8)	<0.0001
Neutrophil count	2.5 (2.1–2.8)	3.0 (2.7–3.3)	3.4 (3.1–3.6)	3.6 (3.3–3.9)	3.9 (3.6–4.3)	4.2 (3.9–4.6)	4.5 (4.2–4.9)	4.9 (4.5–5.4)	5.0 (5.0–6.0)	6.7 (6.0–7.5)	<0.0001
Eosinophil count	0.1 (0.1–0.1)	0.1 (0.1–0.2)	0.1 (0.1–0.2)	0.1 (0.1–0.2)	0.1 (0.1–0.2)	0.1 (0.1–0.2)	0.2 (0.1–0.2)	0.2 (0.1–0.3)	0.2 (0.1–0.3)	0.2 (0.1–0.3)	<0.0001
Basophil Count	0.0 (0.0–0.0)	0.0 (0.0–0.0)	0.0 (0.0–0.0)	0.0 (0.0–0.0)	0.0 (0.0–0.0)	0.0 (0.0–0.0)	0.0 (0.0–0.1)	0.0 (0.0–0.1)	0.0 (0.0–0.1)	0.0 (0.0–0.1)	<0.0001

BMI indicates body mass index; CKD, chronic kidney disease; CVD, cardiovascular disease; SBP, systolic blood pressure; and WBC, white blood cell count.

(Table 1). A higher proportion of South Asians and a lower proportion of black ethnicities were observed in high WBC deciles. Deprivation scores were higher in the extreme deciles of WBC, particularly the lowest decile. The proportion of cells that are components of WBC varied by WBC count; proportions of neutrophils increased substantially as deciles of WBC increased, proportions of lymphocytes and monocytes fell, whereas proportions of eosinophils and basophils remained broadly similar.

In correlations of leukocyte counts with each other (Table 2), higher WBC counts were driven by higher absolute numbers of every differential leukocyte count, with the correlation being particularly high for neutrophils (r=0.90). Only neutrophil percentage was positively associated with WBC, whereas every other leukocyte percentages had an inverse association with WBCs. Percentage of neutrophils was strongly inversely associated with percentage of lymphocytes (r=–0.92).

Univariable Association of Leukocytes With Mortality

Among participants with a WBC measurement, median follow-up time for all-cause mortality was 7.0 years (interquartile range, 6.3–7.6). All-cause mortality occurred in 5255 women (2.0%) and 8227 men (3.8%) in the full analysis and in 753 women (0.9%) and 1146 (1.5%) men in the sensitivity analysis. CVD mortality occurred in 428 women (0.2%) and 949 men (0.4%) in the full analysis and in 50 women (0.1%) and 107 (0.1%) men in the sensitivity analysis. Non-CVD mortality occurred in 3982 women (1.5%) and 5005 men (2.3%) in the in the full analysis, and in 626 women (0.7%) and 814 (1.1%) men in the sensitivity analysis.

Death from any cause and CVD causes were generally associated with a more adverse clinical risk profile (Table 3), including older age, male sex, higher systolic blood pressure, higher BMI, smoking, baseline CVD, diabetes mellitus, rheumatoid arthritis, chronic kidney disease, atrial fibrillation, and other baseline illness. The group who died from CVD or non-CVD causes during follow-up generally also had a lower lymphocyte count and lymphocyte proportion at baseline. In contrast, those who died from CVD or non-CVD causes during follow-up generally had slightly higher monocyte count and proportion of monocytes, and a substantially higher neutrophil count and proportion of neutrophils. The group who died from CVD or non-CVD causes also had a slightly higher eosinophil and basophil counts.

Multivariable Association of Leukocytes With All-Cause Mortality

In adjusted Cox models, total WBC, neutrophils, basophils, and monocytes showed generally J-shaped associations with all-cause mortality in both sexes (Figures 1 through 4). However, in the sensitivity analysis, these associations were generally attenuated to approximately more linear forms. For both sexes combined, the linear HRs for a 1×10^9/L cell count increase in WBC and neutrophils, respectively, was 1.06 (1.05–1.07) and 1.10 (1.07–1.12), respectively. Data were similar excluding smokers. For lymphocytes, those with low levels tended to be at far higher risk of all-cause mortality than those with elevated levels (Figure 4). The sensitivity analysis attenuated this toward the null (Table II in the online-only Data Supplement).

Multivariable Association of Leukocytes With CVD Mortality

Men in the highest decile of WBC were at greater risk of CVD mortality compared with those in the fifth decile (HR, 1.64; 95% confidence interval [CI], 1.24–2.16). Both men (HR, 1.59; 95% CI, 1.22–2.08) and women (HR, 2.15; 95% CI, 1.38–3.35) in the highest decile of neutrophil count were at greater risk of CVD mortality. Monocyte count was also associated with CVD mortality in men (HR, 1.57; 95% CI, 1.26–1.97). For both sexes combined, the linear HRs for a 1×10^9/L cell count increase in WBC and neutrophils, respectively, was 1.04 (0.97–1.11) and 1.05 (0.94–1.17), respectively.

Multivariable Association of Leukocytes With Non-CVD Mortality

U-shaped associations were found between deciles of monocytes, neutrophils, WBC, and basophils with non-CVD mortality. For WBCs and neutrophils, these associations were

Table 2. Correlations (r) of Leukocyte Variables With Each Other

	WBC	Lymphocyte Count	Lymphocyte, %	Monocyte Count	Monocyte, %	Neutrophil Count	Neutrophil, %	Eosinophil Count	Eosinophil, %	Basophil Count
Lymphocyte count	0.561	…	…	…	…	…	…	…	…	…
Lymphocyte %	–0.252	0.604	…	…	…	…	…	…	…	…
Monocyte count	0.479	0.307	–0.094	…	…	…	…	…	…	…
Monocyte %	–0.248	–0.115	0.092	0.673	…	…	…	…	…	…
Neutrophil count	0.902	0.222	–0.578	0.328	–0.344	…	…	…	…	…
Neutrophil %	0.294	–0.506	–0.919	–0.107	–0.358	0.647	…	…	…	…
Eosinophil count	0.275	0.228	–0.003	0.255	0.061	0.139	–0.184	…	…	…
Eosinophil %	–0.068	0.030	0.088	0.092	0.160	–0.179	–0.305	0.900	…	…
Basophil count	0.266	0.205	–0.014	0.184	–0.015	0.197	–0.025	0.110	0.022	…
Basophil %	–0.027	0.059	0.088	0.070	0.097	–0.089	–0.161	0.066	0.080	0.665

All r values significant at P<0.0001, except correlation of eosinophil count with lymphocyte % (P = 0.0243). WBC indicates white blood cell count.

Table 3. Association of Classical Cardiovascular Risk Factors and Leukocyte Measures With All-Cause, Cardiovascular, and Noncardiovascular Death

	Alive n=464 797	Dead n=13 482	*P* Value vs Alive	CVD Mortality (n=1377)	*P* Value vs Alive	Non-CVD Mortality (n=8987)	*P* Value vs Alive
Age, y	56.4±8.1	61.3±6.6	<0.0001	62.2±6.1	<0.0001	61.2±6.7	<0.0001
Male sex, n (%)	211 086 (45.4)	8227 (61.0)	<0.0001	949 (68.9)	<0.0001	5005 (55.7)	<0.0001
SBP, mm Hg	139.7±19.6	143.9±21.2	<0.0001	147.4±22.7	<0.0001	143.2±20.8	<0.0001
BMI, kg/m^2	27.4±4.8	28.1±5.4	<0.0001	28.7±5.5	<0.0001	27.6±5.1	<0.0001
Deprivation (score)	−1.3±3.1	−0.7±3.4	<0.0001	−0.3±3.5	<0.0001	−0.9±3.3	<0.0001
Smoking, n (%)			<0.0001		<0.0001		<0.0001
Nonsmoker	257 211 (55.4)	5103 (37.9)		476 (34.6)		3592 (40.0)	
Ex-smoker	159 641 (34.4)	5665 (42.1)		598 (43.5)		3682 (41.0)	
Current smoker	47 464 (10.2)	2696 (20.0)		301 (21.9)		1701 (19.0)	
Ethnicity, n (%)			<0.0001		0.27		<0.0001
White	425 732 (92.0)	12 590 (94.0)		1257 (92.1)		8446 (94.5)	
South Asian	7359 (1.6)	135 (1.0)		27 (2.0)		56 (0.6)	
Black	7296 (1.6)	107 (0.8)		14 (1.0)		68 (0.8)	
Other	22 253 (4.8)	568 (4.2)		67 (4.9)		368 (4.1)	
Baseline CVD	26 228 (5.6)	2286 (17.0)		440 (32.0)	<0.0001	884 (9.8)	<0.0001
Baseline diabetes	23 454 (5.0)	1786 (13.2)	<0.0001	276 (20.0)	<0.0001	855 (9.5)	<0.0001
Family history of CVD	261 530 (56.3)	7958 (59.0)	<0.0001	882 (64.1)	<0.0001	5183 (57.7)	0.0241
Rheumatoid arthritis, n (%)	5064 (1.1)	288 (2.1)	<0.0001	40 (2.9)	<0.0001	161 (1.8)	<0.0001
Baseline CKD, n (%)	676 (0.1)	144 (1.1)	<0.0001	28 (2.0)	<0.0001	57 (0.6)	<0.0001
Atrial fibrillation, n (%)	3335 (0.7)	227 (1.7)	<0.0001	40 (2.9)	<0.0001	83 (0.9)	0.0429
Other baseline illness, n (%)	306 924 (66.0)	11 275 (83.6)	<0.0001	1182 (85.8)	<0.0001	7339 (81.7)	<0.0001
WBC (10^9/L)	6.6 (5.6–7.8)	7.1 (5.9–8.6)	<0.0001	7.4 (6.2–8.9)	<0.0001	7.0 (5.8–8.4)	<0.0001
Lymphocyte %	28.6 (24.0–33.6)	26.0 (20.8–31.6)	<0.0001	25.7 (20.3–31.6)	<0.0001	26.6 (21.2–32.0)	<0.0001
Lymphocytes (10^9/L)	1.9 (1.5–2.3)	1.8 (1.4–2.3)	<0.0001	1.8 (1.5–2.3)	0.071	1.8 (1.4–2.3)	<0.0001
Monocyte %	6.8 (5.6–8.2)	7.1 (5.7–8.7)	<0.0001	7.3 (5.7–88)	<0.0001	7.0 (5.6–8.6)	<0.0001
Monocytes (10^9/L)	0.5 (0.4–0.6)	0.5 (0.4–0.6)	<0.0001	0.5 (0.4–0.7)	<0.0001	0.5 (0.4–0.6)	<0.0001
Neutrophil%	61.1 (55.6–66.4)	63.2 (57.3–69.2)	<0.0001	63.5 (56.9–69.4)	<0.0001	62.9 (57.0–68.8)	<0.0001
Neutrophils (10^9/L)	4.0 (3.3–4.9)	4.5 (3.5–5.6)	<0.0001	4.7 (3.7–5.8)	<0.0001	4.4 (3.5–5.4)	<0.0001
Eosinophil %	2.1 (1.4–3.3)	2.1 (1.3–3.2)	<0.0001	2.1 (1.3–3.2)	0.51	2.0 (1.3–3.1)	<0.0001
Eosinophils (10^9/L)	0.1 (0.1–0.2)	0.1 (0.1–0.2)	<0.0001	0.2 (0.1–0.2)	<0.0001	0.1 (0.1–0.2)	0.0158
Basophil %	0.4 (0.3–0.7)	0.4 (0.3–0.7)	0.0.15	0.4 (0.3–0.7)	0.69	0.4 (0.3–0.7)	0.0940
Basophils (10^9/L)	0.0 (0.0–0.0)	0.0 (0.0–0.1)	0.005	0.0 (0.0–0.1)	0.45	0.0 (0.0–0.1)	<0.0001

BMI, body mass index; CKD, chronic kidney disease; cardiovascular disease; SBP, systolic blood pressure; and WBC, white blood cell count.

attenuated in the sensitivity analysis. For both sexes combined, the linear HRs for a 1×10^9/L cell count increase in WBC and neutrophils, respectively, was 1.06 (1.04–1.07) and 1.10 (1.07–1.13), respectively.

Multivariable Association of Leukocytes With Nonfatal CVD

Associations between leukocyte deciles and nonfatal CVD were similar to, but generally less strong than, those with CVD mortality. Men (HR, 1.28; 95% CI, 1.16–1.42) and women (HR, 1.21; 95% CI, 1.06–1.38) in the highest decile of WBC were at greater risk of nonfatal CVD compared with those in the fifth decile (Table V online-only Data Supplement). This trend was also true of neutrophils and of monocytes among men. For both sexes combined, the linear HRs for a 1×10^9/L cell count increase in WBC and neutrophils, respectively, was 1.05 (1.03–1.07) and 1.07 (1.04–1.11), respectively. Most associations were removed in the sensitivity analysis, with the exception of high monocytes in women and low basophils in both sexes, which retained a higher risk of nonfatal CVD events.

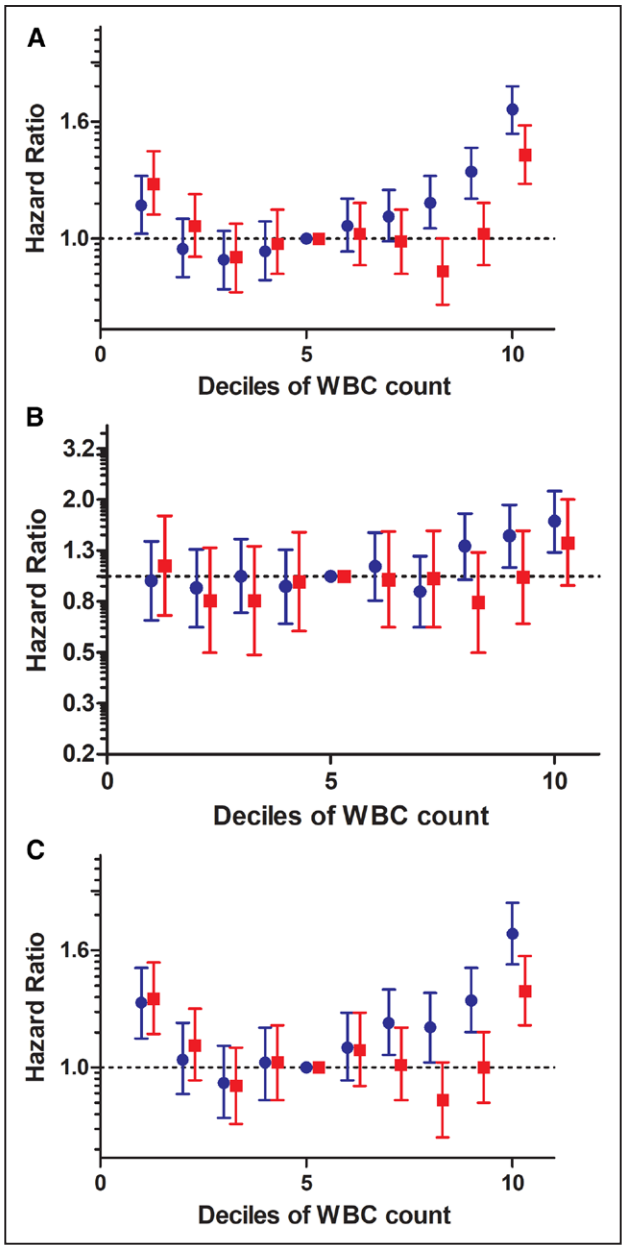

Figure 1. Association of deciles of white blood cell count (WBC) with 3 mortality outcomes (**A**, all-cause mortality; **B**, fatal cardiovascular disease [CVD], and **C**, non-CVD mortality) in all study participants, stratified by sex (blue=male; red=female).

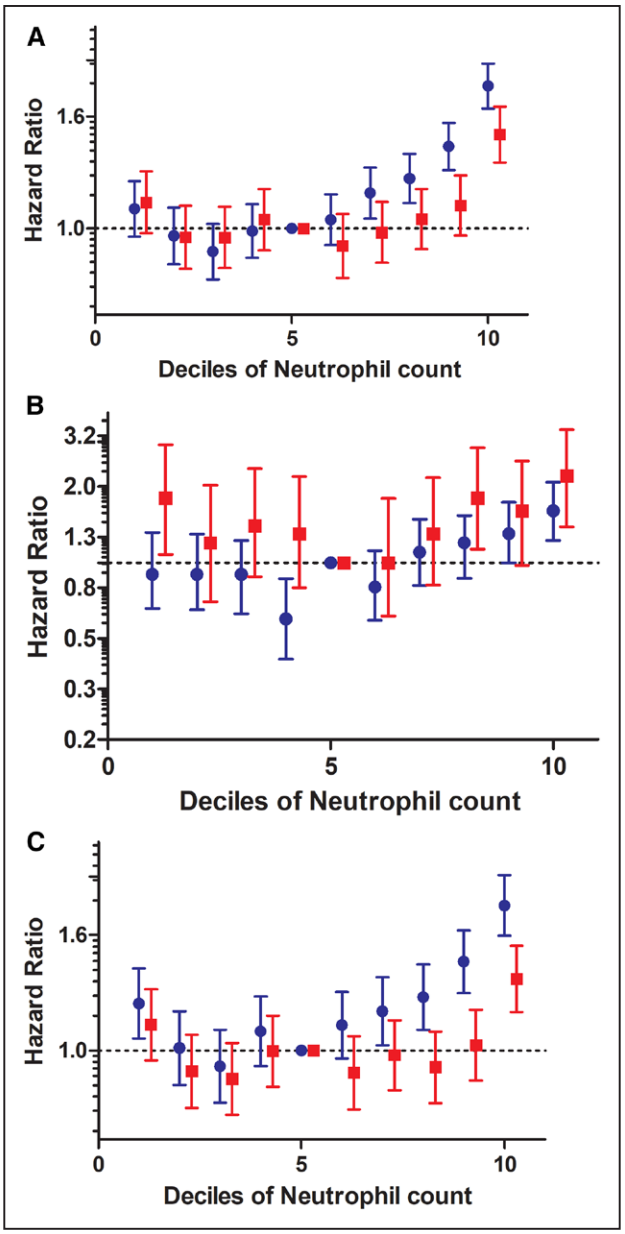

Figure 2. Association of deciles of neutrophil count with 3 mortality outcomes in all study participants (**A**, all-cause mortality; **B**, fatal cardiovascular disease [CVD]; and **C**, non-CVD mortality), stratified by sex (blue=male; red=female).

Discussion

In this large, prospectively enrolled cohort of >475 000 individuals from a general population, we found that a high WBC is associated with both CVD and non-CVD mortality, consistent with prior studies.[12–15] In addition, we report that the leukocyte subpopulations are differentially associated with CVD mortality and nonfatal CVD. Specifically, we found that higher counts of neutrophils are associated with a higher risk of CVD mortality and nonfatal CVD, in line with previous data.[14,17,18] Our data emphasize the importance of reverse causality in influencing the association between differential blood counts and outcomes. Therefore, additionally, we have shown that the association of neutrophils with nonfatal CVD remains robust to a sensitivity analysis that attempts to limit the influence of reverse causality. We could not confirm this for fatal CVD, primarily because of lack of power. The distinct association of neutrophils with CVD is of particular interest given that inhibiting the IL-1 β (interleukin 1β) pathway with canakinumab substantially reduces circulating neutrophil counts[23,24] and has been shown to prevent CVD.[25]

Our a priori hypothesis was that a specific leukocyte population might be more specifically associated with CVD mortality, in line with observations that neutrophils, macrophages, or lymphocytes might play a specific role in the immune response that causes, and results from, atherosclerosis.[19,21,26–28] In contrast to prior studies, we simultaneously examined not only the association between WBC and mortality outcomes

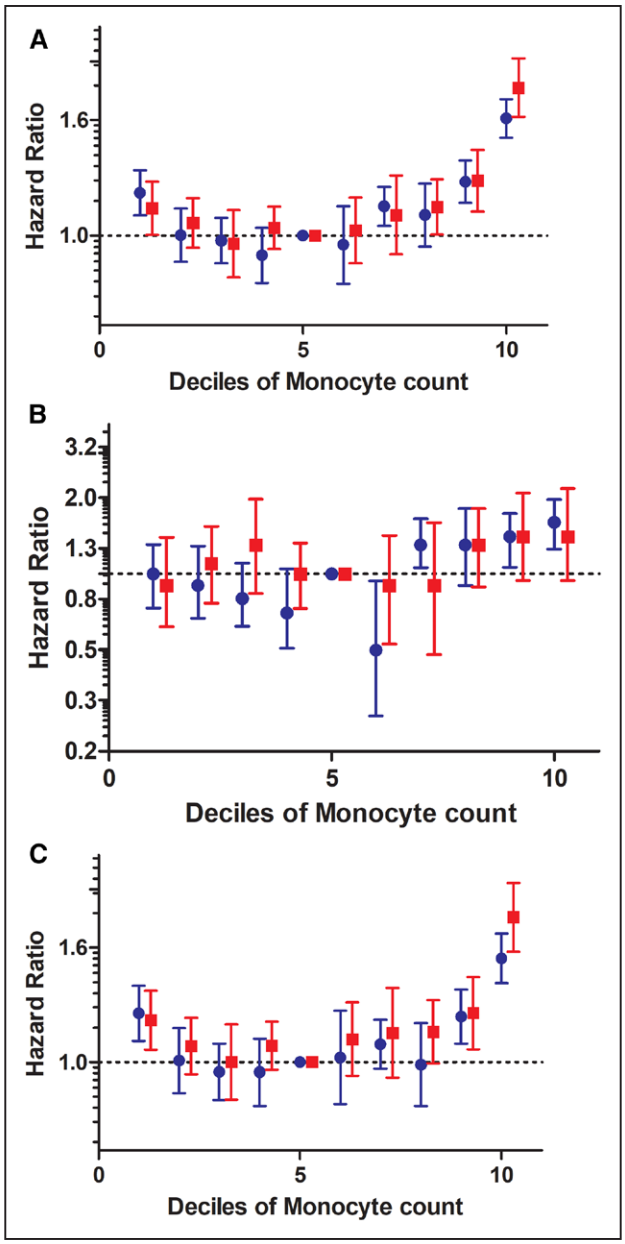

Figure 3. Association of deciles of monocyte count in all study participants with 3 mortality outcomes (**A**, all-cause mortality; **B**, fatal cardiovascular disease [CVD]; and **C**, non-CVD mortality), stratified by sex (blue=male; red=female).

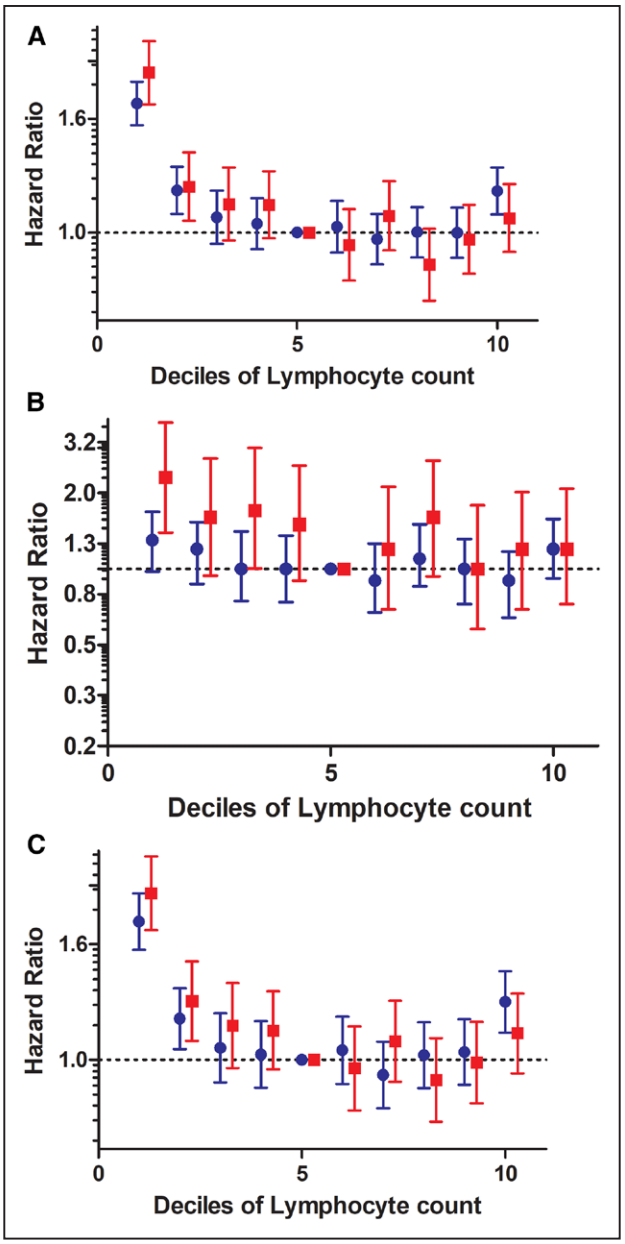

Figure 4. Association of deciles of lymphocyte count in all study participants with 3 mortality outcomes (**A**, all-cause mortality, **B**, fatal CVD; **C**, non-CVD mortality), stratified by sex (blue=male; red=female).

but also subpopulations of leukocytes. Recent data from a large cohort study has shown that WBC was associated with coronary heart disease and cancer mortality among healthy women, even after excluding those with comorbidities (CVDs, connective tissue disease, ulcerative colitis, liver disease, diabetes mellitus, or cancers) and early deaths during follow-up.[13] The association of WBC with CVD mortality among women in UK Biobank was fairly weak, but the association of neutrophils with CVD we report was strong in both sexes and is also similar to a recent large cohort study.[18] Our sensitivity analysis attenuated associations of circulating leukocyte counts with mortality outcomes. This suggests an element of reverse causality.[19] Mechanisms that explain this observation likely include the association between neutrophilia and trauma, stress, bacterial infection, smoking, and indolent cancer,[29] any of which ultimately might increase the risk of death from any cause. Likewise, lymphopenia is likely to be caused by old age, viral infection, autoimmune disease, renal failure, and immunosuppressive drugs.[30] By excluding those with a range of baseline diseases, and those who develop disease within 2 years of baseline, the present results provide models that limit the effect of baseline disease on counts themselves.

What mechanisms might explain the association of leukocytes with CVD mortality? The inflammatory hypothesis of CVD is well established.[31] Underpinning this, cellular atherosclerotic plaques appear more prone to rupture.[32] It is

hypothesized that leukocytes may play a direct role in destabilizing the plaque itself[33,34] through fibrous cap thinning, although it may be that circulating levels of leukocytes do not necessarily reflect resident cells within atherosclerotic plaques. Investigating specific differential counts, our data suggest that high circulating neutrophil levels are linearly associated with CVD mortality that occurs beyond a 2-year time horizon in ostensibly healthy people. The same does not seem to be true of other leukocytes. It is interesting that, until recently, neutrophils were a neglected leukocyte in atherosclerosis research. There are clear mechanisms that might explain why neutrophils might play an important role in causing CVD death.[35] Neutrophils interact with cholesterol crystals to produce pro-IL-1β.[20] They can form structures that bind bacteria and platelets, the end result of which is that neutrophils release nuclear material leading to cell death and thrombosis.[36] Neutrophils are, therefore, intimately linked to the inflammatory cascade, which can be promoted through a proatherogenic environment. Other environmental factors, such as smoking,[37] might also promote neutrophilia and CVD death, resulting in confounding. However, our sensitivity analysis suggests that there may be an independent association too. Inhibiting IL-1β in patients with established CVD reduces cardiovascular events[10,25] and strongly reduces circulating neutrophil counts.[26,27] Our findings suggest that further work should be done in patients without preexisting CVD to determine whether IL-1β blockers, or other modulators of the immune response to inflammation, may have a role to play in the prevention of CVD and the role of neutrophils in this context.

Higher neutrophil counts were also associated with a higher risk of non-CVD death. Here, the association may be even more complex. Specific non-CVD conditions may be linked to higher neutrophil counts through different pathways. For instance, there is evidence that people with chronic inflammatory conditions such as rheumatoid arthritis have increased risk of death beyond that caused by CVD (http://onlinelibrary.wiley.com/doi/10.1002/acr.22752/abstract). There has also been speculation that tumor-infiltrating neutrophils may be important in the prognosis of several types of cancer (https://www.sciencedirect.com/science/article/pii/S1044579X13000138). As noted above, mechanisms that may underlie the associations we observe include the influence of indolent malignancy (both solid organ and hematological) and other confounders such as inflammatory diseases and smoking. Although we corrected for as many of these as possible through multivariable analysis and sensitivity analysis, there remains a significant element of confounding and reverse causality. More work is required to examine the association between neutrophils and specific non-CVD causes of death to determine potential mechanisms underlying our findings.

Our study has many strengths. The UK Biobank includes a wide sample of the UK general population in terms of age, sex, ethnicity, and socioeconomic status and as such is not derived from health records of patients with a clinical indication for leukocyte measurement, in contrast to prior work.[18] Further strengths of the study include its large sample size, comprehensive phenotyping, and simultaneous consideration of differential leukocyte counts derived from a central laboratory measurement, also in contrast to prior work.[18] The side-by-side comparison of CVD and non-CVD mortality gives an indication of the specificity of associations, although we did not further subdivide non-CVD morality because of lack of adjudicated outcomes. It is notable that inflammatory markers seem to have a stronger association with CVD mortality than with nonfatal events.[38,39] Weaknesses include the lack of data to adjust for lipids, although the extensive adjustment model will capture much of this confounding by proxy. Lack of adjustment for medication is a further limitation, although again adjustment for comorbidity accounts for much of the association. Reverse causality is possible in any observational study, and although our results include a sensitivity analysis and an analysis excluding those with diagnosed comorbidities, we cannot exclude the potential of further reverse causality explaining some of the associations that we report.

In conclusion, we report that among leukocytes, higher neutrophil count is particularly associated with higher CVD risk in a general population. This association seems to be robust in those without comorbidity at baseline or in those who may have unrecognized disease at baseline. Further work is required to determine whether modulation of the immune responses that involve neutrophils, via canakinumab or other interventions, can lead to a reduction in CVD mortality.

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Disclosures

None.

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Highlights

- Among circulating leukocyte subpopulations, neutrophil count was most strongly, and linearly, associated with higher cardiovascular disease mortality.
- Data were robust to a sensitivity analysis excluding those with preexisting comorbidities and the first 2 years of follow-up.
- Circulating lymphocytes showed trends toward an inverse association with cardiovascular disease mortality.
- Leukocyte subpopulations also showed similar associations with non–cardiovascular disease mortality.