White cell count in the normal range and short and long term mortality: international comparisons of electronic health record cohorts in England and New Zealand

Supplementary Material

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**Supplementary Methods: statistical analysis**

**Acute conditions at time of white cell count measurement: CALIBER**

Total white cell counts can be affected by many factors such as infections, autoimmune diseases, medication and haematological conditions. Similar to our recent study on eosinophil counts,1 we sought to differentiate between a patient’s long-term ‘stable’ total white cell count and results obtained when the patient had an ‘acute’ condition which may alter leukocyte counts. We used other information in the electronic health record (prescriptions, diagnoses, symptoms, hospitalisations) to assess whether the patient was clinically ‘acute’ or ‘stable’ at the time of the blood test, adapting a set of criteria proposed by the eMERGE consortium (electronic Medical Records and Genomics)2 for studying genetic determinants of the stable leukocyte counts: in hospital on the date of blood test, vaccination in the previous 7 days, anaemia diagnosis within the previous 30 days, symptoms or diagnosis of infection within the previous 30 days, prior diagnosis of myelodysplastic syndrome, prior diagnosis of haemoglobinopathy, cancer chemotherapy or G-CSF within 6 months before index date, the use of drugs affecting the immune system such as methotrexate or steroids within the previous 3 months, prior diagnosis of HIV infection, prior splenectomy or prior dialysis.

**Survival analysis**

The main analysis used a Cox proportional hazards approach3 to model the association between white cell count quintiles and time to death, adjusting for the following Framingham risk factors, chosen a priori: age, sex, total: HDL cholesterol ratio, systolic blood pressure, diabetes status, and current smoking status. As it was not possible to combine the raw datasets, we used quintiles based on the CALIBER dataset for both CALIBER and PREDICT analyses. In CALIBER, the baseline hazard of the Cox model was stratified by general practice.

All analyses were done using R software (version 3.0.2),4 using the survival5 package for Cox regression. Restricted cubic splines were used to investigate the relationship between continuous variables and time-to-death as a check on the modelling assumption of linearity. We assessed the proportional hazards assumption by plotting the scaled Schoenfeld residuals against log time.3 We found that the hazard ratio varied over time (Supplementary Figure S7), so we split the follow-up time into two intervals, pre and post 6 months.

**Multiple imputation: CALIBER**

In CALIBER, the cohort consisted of individuals with a white cell count record and no prior history of cardiovascular disease, whether or not they had had a formal cardiovascular disease assessment. Total white cell count data was therefore completely observed but some people did not have records of other baseline covariates: total cholesterol, HDL cholesterol, blood pressure or smoking status. We wished to examine for interactions between total white cell count and predictor variables in their association with mortality, so we chose a method of multiple imputation which would account for these interactions. Therefore for the primary analysis we used multiple imputation using chained equations (MICE)6 with Random Forest multiple imputation.2

Random Forest is a machine learning regression method which can automatically account for non-linearities in the associations between predictor variables, and can handle large numbers of variables without encountering problems due to collinearity.3 It has been shown to perform well on test datasets derived from CALIBER,3 but can be slow on very large datasets, so we carried out the imputation within general practice, thus also accounting for between-practice variability. As Random Forest multiple imputation is a fairly new method we also performed a secondary analysis using normal-based multiple imputation in MICE. With normal-based MICE we included the general practice as a fixed effect (i.e. a categorical variable) and carried out the imputation separately by age group and sex, which accounted for interactions between these variables without requiring too many additional parameters in the imputation models.

Imputation models included all the variables in the substantive model, event indicator and time in the form of the marginal Nelson-Aalen cumulative hazard, as well as the following auxiliary variables: counts of white cell subtypes (neutrophils, basophils, eosinophils, monocytes and lymphocytes), renal function (estimated glomerular filtration rate), and diastolic blood pressure. We used 10 iterations and generated 10 imputations. We verified that the number of iterations was sufficient by inspecting plots of chain means and variances. We combined the results of analysis using Rubin's rules.
The two methods of multiple imputation used in CALIBER data (normal-based and Random Forest MICE) yielded almost identical estimates (Supplementary Figure S8).

**Multiple imputation: PREDICT**

The baseline population in PREDICT consisted of all individuals undergoing cardiovascular risk assessment in primary care. Cardiovascular risk factors were almost completely observed but about 30% of people did not have a record of total white cell count. As individuals with a measurement of white cell count would be a (possibly biased) sample, we carried out analyses both limited to those with a white cell count measurement and among the entire baseline population, using multiple imputation to handle missing values. We imputed missing values using Random Forest. Imputation models included all the variables in the substantive model, event indicator and time as the marginal Nelson-Aalen cumulative hazard. We generated 10 imputed datasets and combined the results of analysis using Rubin's rules.

Complete case analysis of PREDICT data yielded similar estimates to the main imputed analysis (Supplementary Figure S9).

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Supplementary Tables

**Supplementary Table S1. Characteristics of CALIBER and PREDICT databases**

| Data sources                                           | CALIBER (England)                                                                                                                                                                                                 | PREDICT (New Zealand)                                                                                                                                                                                                 |
|--------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Full general practice record                           | All coded data. Some free text available.                                                                                                                                                                        | No                                                                                                                                                                                                                  |
| Cardiovascular risk assessments in primary care        | Not systematically recorded                                                                                                                                                                                        | Yes                                                                                                                                                                                                                  |
| Laboratory blood tests                                 | Tests requested by GP and reported electronically, and a small number of test results entered from paper reports by the GP before electronic transfer of results was available. | All laboratory tests, including those requested by secondary care                                                                                                                                                    |
| Dispensed medication in the community                  | No                                                                                                                                                                                                               | Yes                                                                                                                                                                                                                  |
| Prescribed medication                                  | Yes                                                                                                                                                                                                               | No                                                                                                                                                                                                                  |
| Hospital admission data                                 | Yes                                                                                                                                                                                                               | Yes                                                                                                                                                                                                                  |
| Death certificate data                                  | Coded data                                                                                                                                                                                                       | Coded data and free text cause of death                                                                                                                                                                             |

**Population coverage**

| Coverage of country's population                        | General practices covering about 4% of the English population                                                                                                                                                    | Cardiovascular risk assessment from about one-third of general practices, distributed throughout the country; laboratory results for Auckland and Christchurch regions |
|--------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Number of patients                                     | 4.7 million                                                                                                                                                                                                     | 2 million with laboratory results, 400,000 with cardiovascular risk assessment                                                                                                                                       |
| Follow-up period                                       | While registered with GP                                                                                                                                                                                         | While resident in New Zealand                                                                                                                                                                                       |

**Coding**

| Primary care diagnoses                                 | Read version 2                                                                                                                                                                                                 | Not applicable                                                                                                                                                                                                     |
|--------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Hospital diagnoses                                     | WHO ICD-10                                                                                                                                                                                                       | ICD-10 Australian modification                                                                                                                                                                                        |
| Cause of death                                         | WHO ICD-10                                                                                                                                                                                                       | ICD-10 Australian modification                                                                                                                                                                                        |
| Procedures                                             | Office for Population Censuses and Surveys classification (OPCS)                                                                                                                                                   | ICD-10 Australian modification                                                                                                                                                                                        |

**Time period**

| GP data from 1990s, hospital data from 2000, cause of death from 2001 | 2002 onwards                                                                                                                                                                                                 | 2002 onwards                                                                                                                                                                                                       |
**Supplementary Table S2. Previous large studies investigating the association of total white cell count with all-cause mortality in healthy populations**

| Author, year, study name | Study population | N | events | Clinical WBC measurement? | Compare ethnic groups? | Short and long term risks? | Adjusted measure of association with total white cell count |
|--------------------------|------------------|---|--------|--------------------------|------------------------|---------------------------|-----------------------------------------------------------|
| Jee, 2005, Korean Cancer Prevention Study$^1$ | 438 500 government employees, teachers, and their dependants insured with Korea Medical Insurance Corporation | 48 757 | - | - | - | HR (95% CI) for WBC $\geq$9 vs <5 $\times 10^9$/L: Male non-smokers 1.38 (1.22, 1.56) Male smokers 1.14 (1.07, 1.21) Female non-smokers 1.20 Female smokers 1.26 (1.12, 1.41) |
| Margolis, 2005, Women’s Health Initiative Observational Study$^2$ | 66 261 women with mean follow-up 6.1 years | 1919 | - | - | - | HR 1.52 (95% CI 1.33, 1.74) for top vs bottom quartile (P for trend <0.001) |
| Kabagambe, 2011, REGARDS study$^3$ | 17 845 men and women in the Reasons for Geographic and Racial Differences in Stroke Study cohort | 1062 | - | Yes | - | HR 1.33 (95% CI 1.03, 1.72) for top vs bottom quartile in Whites (p for trend = 0.03) HR 1.13 (95% CI 0.86, 1.50) for top vs bottom quartile in Blacks (p for trend = 0.55) |
| Ruggiero, 2007, Baltimore Longitudinal Study of Aging$^4$ | 2803 people recruited from Baltimore-Washington, DC | 944 | - | - | - | HR 1.62 (95% CI 0.92, 2.85) for WBC >10 vs 3.5–6.0 $\times 10^9$/L |
| Tamakoshi, 2007, NIPPON DATA$^5$ | 6756 Japanese residents followed up from nationwide random survey | 576 | - | - | - | RR 1.61 (95% CI 1.07, 2.40) for WBC 9–10 $\times 10^9$/L vs 4–4.9 $\times 10^9$/L |
| Shankar, 2007, Blue Mountains Eye Study$^6$ | 2904 people with no prior cardiovascular disease or cancer | 575 | - | - | - | RR 1.68 (95% CI 1.35, 2.09) for top vs bottom quartile |
| Horne, 2015, JUPITER trial$^7$ | 17 197 trial participants followed for median 1.9 years | 445 | - | - | - | HR 1.0 (95% CI 0.85, 1.15) (read from graph) linear trend by tertile comparing adjusted for red cell distribution width, haematocrit, mean corpuscular volume, mean corpuscular haemoglobin concentration, high sensitivity C reactive protein and conventional cardiovascular risk factors |
| Author, year, study name | Study population | N events | Clinical WBC measurement? | Compare ethnic groups? | Short and long term risks? | Adjusted measure of association with total white cell count |
|--------------------------|------------------|----------|---------------------------|-----------------------|---------------------------|----------------------------------------------------------|
| De Labry, 1990, Normative Aging Study | 2011 healthy men in Boston | 183 | - | - | - | HR 1.16 (95% CI 1.08, 1.25) per $10^9$ higher WBC adjusted for age, cholesterol, systolic blood pressure and smoking |
| Kim, 2013, Korean elderly cohort | 9,996 men and women aged 65 or over | 118 | - | - | - | HR 1.57 (95% 0.88, 2.80) for top vs bottom quartile (P for trend <0.073) |
| Current study | 686,475 people in England (CALIBER) and 194,513 people in New Zealand (PREDICT) | 21,827 | Yes | Yes | Yes | See results in main paper |

CI, confidence interval; HR, hazard ratio; RR, relative risk. Studies are listed in descending order of number of events; results in the table are the maximally adjusted results reported in the paper.

**References for studies**

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Supplementary Table S3. Variables associated with missing white cell count status in a multivariable logistic model in PREDICT

Total number of patients = 194 498; number with missing white cell count = 55 478

| Variable                  | Comparison | Adjusted odds ratio (95% CI) † |
|---------------------------|------------|--------------------------------|
|                           | Low value  | High value                     |
| Age at assessment (years) *| 45         | 65                             | 0.80 (0.79, 0.82) |
| Diabetes                  | No         | Yes                            | 1.02 (0.99, 1.06) |
| Current smoking status    | Non-smoker | Smoker                         | 1.13 (1.10, 1.16) |
| Total: HDL cholesterol ratio *| 2.9       | 5.3                            | 0.89 (0.88, 0.91) |
| Systolic blood pressure (mmHg) *| 112       | 146                            | 1.06 (1.04, 1.08) |
| Gender                    | Male       | Female                         | 0.79 (0.77, 0.80) |
| Ethnic group              | European   | Asian                          | 0.46 (0.44, 0.48) |
|                           | European   | Indian                         | 0.44 (0.42, 0.46) |
|                           | European   | Maori                          | 1.32 (1.28, 1.36) |
|                           | European   | Other                          | 0.54 (0.50, 0.59) |
|                           | European   | Pacific                        | 0.63 (0.61, 0.65) |

* For continuous variables, comparisons were taken at the 16th and 84th centiles.
† Adjusted for all variables in the table.
## Supplementary Table S4. Acute conditions at the time of white cell count measurement in CALIBER

| Condition                                                        | < 2.95 | 2.95–5.35 | 5.35–6.25 | 6.25–7.25 | 7.25–8.65 | 8.65–10.05 | ≥ 10.05 |
|-----------------------------------------------------------------|--------|-----------|-----------|-----------|-----------|------------|---------|
| In hospital on date of blood test                               | 60 (2.2%) | 292 (0.2%) | 249 (0.2%) | 331 (0.2%) | 377 (0.3%) | 335 (0.5%) | 732 (1.2%) |
| Vaccination within previous 7 days                              | 30 (1.1%) | 136 (0.9%) | 1293 (1.0%) | 1396 (1.0%) | 1315 (1.0%) | 578 (0.8%) | 424 (0.7%) |
| Anaemia diagnosis within 30 days prior                          | 58 (2.1%) | 823 (0.6%) | 517 (0.4%) | 568 (0.4%) | 464 (0.3%) | 273 (0.4%) | 274 (0.5%) |
| Infection diagnosis within 30 days prior                        | 262 (9.6%) | 8979 (6.2%) | 8212 (6.1%) | 9111 (6.4%) | 9762 (7.3%) | 5647 (8.2%) | 6380 (10.9%) |
| Infective symptoms within 30 days prior                         | 194 (7.1%) | 6881 (4.7%) | 6559 (4.9%) | 7317 (5.2%) | 7877 (5.9%) | 4573 (6.7%) | 4909 (8.4%) |
| Prior diagnosis of myelodysplastic syndrome                     | 19 (0.7%) | 60 (0.0%) | 19 (0.0%) | 27 (0.0%) | 21 (0.0%) | 7 (0.0%) | 9 (0.0%) |
| Prior diagnosis of haemoglobinopathy                            | 20 (0.7%) | 717 (0.5%) | 483 (0.4%) | 483 (0.3%) | 440 (0.3%) | 207 (0.3%) | 190 (0.3%) |
| Chemotherapy or G-CSF within 6 months prior                     | 198 (7.3%) | 543 (0.4%) | 246 (0.2%) | 208 (0.1%) | 202 (0.2%) | 108 (0.2%) | 248 (0.4%) |
| Methotrexate within 3 months prior                              | 5 (0.2%) | 436 (0.3%) | 446 (0.3%) | 501 (0.4%) | 559 (0.4%) | 381 (0.6%) | 337 (0.6%) |
| Steroid within 3 months prior                                   | 61 (2.2%) | 1915 (1.3%) | 1973 (1.5%) | 2755 (1.9%) | 3455 (2.6%) | 2498 (3.6%) | 3719 (6.3%) |
| Other immune drug within 3 months prior                         | 73 (2.7%) | 1878 (1.3%) | 1351 (1.0%) | 1297 (0.9%) | 1311 (1.0%) | 731 (1.1%) | 723 (1.2%) |
| Prior diagnosis of cancer                                       | 436 (16.0%) | 6499 (4.5%) | 4836 (3.6%) | 4778 (3.4%) | 4176 (3.1%) | 2089 (3.0%) | 2270 (3.9%) |
| Prior splenectomy                                               | 2 (0.1%) | 64 (0.0%) | 83 (0.1%) | 146 (0.1%) | 234 (0.2%) | 190 (0.3%) | 327 (0.6%) |
| Prior diagnosis of HIV                                          | 4 (0.1%) | 61 (0.0%) | 31 (0.0%) | 14 (0.0%) | 17 (0.0%) | 14 (0.0%) | 8 (0.0%) |
| Prior dialysis                                                  | 6 (0.2%) | 37 (0.0%) | 32 (0.0%) | 34 (0.0%) | 49 (0.0%) | 28 (0.0%) | 37 (0.1%) |
| Any acute condition                                             | 925 (34.0%) | 25903 (17.7%) | 22569 (16.7%) | 24737 (17.5%) | 25438 (19.0%) | 14391 (20.9%) | 15842 (27.0%) |

G-CSF, granulocyte colony stimulating factor; HIV, human immunodeficiency virus
Supplementary Figures

**Supplementary Figure S1. Scaled Schoenfeld residuals for multiply adjusted hazard ratio for mortality comparing quintiles of total white cell count:**

Hazard ratios were adjusted for age, sex, smoking, diabetes, systolic blood pressure, ethnicity and total: HDL cholesterol ratio.

- **≤5.35 vs 6.25-7.25**
  - $\rho = 0.0092$
  - $\chi^2 = 1.66$
  - $p = 0.2$

- **7.25-8.65 vs 6.25-7.25**
  - $\rho = 0.0247$
  - $\chi^2 = 12$
  - $p = 0.00053$

- **5.35-6.25 vs 6.25-7.25**
  - $\rho = 0.0108$
  - $\chi^2 = 2.27$
  - $p = 0.13$

- **≥ 8.65 vs 6.25-7.25**
  - $\rho = 0.1386$
  - $\chi^2 = 383.64$
  - $p < 0.0001$
**Supplementary Figure S2. Multiply adjusted hazard ratios for all cause mortality by category of total white cell count, by age group: CALIBER**

Hazard ratios were adjusted for age, sex, smoking, diabetes, systolic blood pressure, ethnicity and total: HDL cholesterol ratio. P values * < 0.05, ** < 0.01, *** < 0.001

| Category of total white cell count | CALIBER | Hazard ratio (95% CI) | P value for interaction |
|------------------------------------|---------|-----------------------|------------------------|
| <2.95 age 30–45                    | -       | 8.18 (5.84, 11.45) ***| 0.21                   |
| age 45–60                           | -       | 6.37 (5.12, 7.94) ***  |                        |
| age ≥ 60                            | -       | 4.78 (4.00, 5.73) ***  | 0.038                  |
| 2.95–5.35 age 30–45                 | -       | 1.23 (1.05, 1.44) **   | 0.0074                 |
| age 45–60                           | -       | 0.96 (0.88, 1.06)      |                        |
| age ≥ 60                            | -       | 0.93 (0.88, 1.00) *    | 0.56                   |
| 5.35–6.25 age 30–45                 | -       | 0.97 (0.82, 1.15)      | 0.14                   |
| age 45–60                           | -       | 0.84 (0.77, 0.93) ***  |                        |
| age ≥ 60                            | -       | 0.88 (0.83, 0.94) ***  | 0.47                   |
| 6.25–7.25                           | -       | 1 (reference)          |                        |
| 7.25–8.65 age 30–45                 | -       | 1.14 (0.98, 1.33)      | 0.6                    |
| age 45–60                           | -       | 1.20 (1.10, 1.30) ***  |                        |
| age ≥ 60                            | -       | 1.20 (1.14, 1.27) ***  | 0.93                   |
| 8.65–10.05 age 30–45                | -       | 1.19 (1.00, 1.43)      | 0.15                   |
| age 45–60                           | -       | 1.38 (1.25, 1.53) ***  |                        |
| age ≥ 60                            | -       | 1.62 (1.52, 1.73) ***  | 0.0072                 |
| ≥ 10.05 age 30–45                   | -       | 1.61 (1.36, 1.90) ***  | <0.0001                |
| age 45–60                           | -       | 2.36 (2.16, 2.58) ***  |                        |
| age ≥ 60                            | -       | 2.56 (2.40, 2.72) ***  | 0.14                   |
**Supplementary Figure S3. Multiply adjusted hazard ratios for all cause mortality by category of total white cell count, by smoking status: CALIBER**

Hazard ratios were adjusted for age, sex, smoking, diabetes, systolic blood pressure, ethnicity and total: HDL cholesterol ratio. P values * < 0.05, ** < 0.01, *** < 0.001

| Category of total white cell count | Ex or never smokers | Current smokers | Hazard ratio (95% CI) | Hazard ratio (95% CI) |
|------------------------------------|---------------------|-----------------|-----------------------|-----------------------|
| <2.95                              | 5.24 (4.49, 6.11) ***| 7.92 (6.06, 10.37) ***|                      |                      |
| 2.95–5.35                          | 0.93 (0.88, 0.98) * | 1.23 (1.11, 1.37) ***|                      |                      |
| 5.35–6.25                          | 0.86 (0.81, 0.91) ***| 0.94 (0.85, 1.03) |                      |                      |
| 6.25–7.25                          | 1 (reference)       | 1 (reference)    |                      |                      |
| 7.25–8.65                          | 1.19 (1.12, 1.26) ***| 1.19 (1.10, 1.29) ***|                      |                      |
| 8.65–10.05                         | 1.63 (1.52, 1.75) ***| 1.36 (1.25, 1.48) ***|                      |                      |
| ≥10.05                             | 2.87 (2.68, 3.07) ***| 2.02 (1.86, 2.18) ***|                      |                      |

P value for interaction

0.0073 <0.0001 0.17 0.98 <0.0001
Supplementary Figure S4. Multiply adjusted hazard ratios for all cause mortality by category of total white cell count, by clinical state: CALIBER

Hazard ratios were adjusted for age, sex, smoking, diabetes, systolic blood pressure, ethnicity and total: HDL cholesterol ratio. P values * < 0.05, ** < 0.01, *** < 0.001

| Category of total white cell count | Stable Hazard ratio (95% CI) | Acute Hazard ratio (95% CI) | P value for interaction |
|-----------------------------------|-----------------------------|-----------------------------|------------------------|
| <2.95                             | 2.56 (2.00, 3.28) ***       | 6.62 (5.67, 7.73) ***       | <0.0001                |
| 2.95−5.35                         | 0.86 (0.81, 0.92) ***       | 1.18 (1.09, 1.28) ***       | <0.0001                |
| 5.35−6.25                         | 0.88 (0.83, 0.93) ***       | 0.89 (0.82, 0.97) *         | 0.74                   |
| 6.25−7.25                         | 1 (reference)               | 1 (reference)               |                        |
| 7.25−8.65                         | 1.21 (1.15, 1.28) ***       | 1.10 (1.02, 1.19) *         | 0.051                  |
| 8.65−10.05                        | 1.52 (1.43, 1.63) ***       | 1.31 (1.20, 1.43) ***       | 0.0047                 |
| ≥10.05                            | 2.11 (1.97, 2.25) ***       | 2.18 (2.02, 2.35) ***       | 0.49                   |
Supplementary Figure S5. Multiply adjusted hazard ratios for all cause mortality by category of total white cell count, by sex: CALIBER

Hazard ratios were adjusted for age, sex, smoking, diabetes, systolic blood pressure, ethnicity and total: HDL cholesterol ratio. P values * < 0.05, ** < 0.01, *** < 0.001

| Category of total white cell count | Men | Women | P value for interaction |
|-----------------------------------|-----|-------|-------------------------|
| <2.95                             |     |       |                         |
| 2.95−5.35                         |     |       |                         |
| 5.35−6.25                         |     |       |                         |
| 6.25−7.25                         |     |       |                         |
| 7.25−8.65                         |     |       |                         |
| 8.65−10.05                        |     |       |                         |
| ≥ 10.05                           |     |       |                         |

Hazard ratio (95% CI)

Men:
- <2.95: 5.28 (4.28, 6.52) ***
- 2.95−5.35: 1.01 (0.94, 1.08)
- 5.35−6.25: 0.88 (0.82, 0.94) ***
- 6.25−7.25: 1 (reference)
- 7.25−8.65: 1.18 (1.11, 1.26) ***
- 8.65−10.05: 1.59 (1.48, 1.71) ***
- ≥ 10.05: 2.41 (2.25, 2.58) ***

Women:
- <2.95: 5.79 (4.90, 6.83) ***
- 2.95−5.35: 0.94 (0.88, 1.01)
- 5.35−6.25: 0.88 (0.82, 0.94) ***
- 6.25−7.25: 1 (reference)
- 7.25−8.65: 1.21 (1.14, 1.29) ***
- 8.65−10.05: 1.42 (1.32, 1.53) ***
- ≥ 10.05: 2.36 (2.20, 2.53) ***
**Supplementary Figure S6. Multiply adjusted hazard ratios for all cause mortality by category of total white cell count, by ethnicity: CALIBER**

Hazard ratios were adjusted for age, sex, smoking, diabetes, systolic blood pressure, ethnicity and total: HDL cholesterol ratio. P values * < 0.05, ** < 0.01, *** < 0.001

| Category of total white cell count | CALIBER | Hazard ratio (95% CI) | P value for interaction (White as reference) |
|------------------------------------|---------|-----------------------|---------------------------------------------|
| <2.95                              | White   | 5.56 (4.81, 6.42) *** |                                             |
|                                    | Black   | 3.49 (1.41, 8.65) **  | 0.32                                        |
|                                    | South Asian | 8.58 (2.29, 32.09) ** | 0.52                                        |
|                                    | Other   | 12.73 (5.36, 30.21) ***| 0.064                                       |
| 2.95–5.35                          | White   | 0.97 (0.93, 1.03)     |                                             |
|                                    | Black   | 0.69 (0.40, 1.20)     | 0.22                                        |
|                                    | South Asian | 1.05 (0.65, 1.71)       | 0.75                                        |
|                                    | Other   | 1.04 (0.65, 1.65)     | 0.79                                        |
| 5.35–6.25                          | White   | 0.87 (0.83, 0.92) *** |                                             |
|                                    | Black   | 0.93 (0.48, 1.81)     | 0.84                                        |
|                                    | South Asian | 0.97 (0.60, 1.55)     | 0.67                                        |
|                                    | Other   | 0.94 (0.58, 1.52)     | 0.76                                        |
| 6.25–7.25                          |         | 1 (reference)         |                                             |
| 7.25–8.65                          | White   | 1.20 (1.14, 1.25) *** |                                             |
|                                    | Black   | 1.18 (0.61, 2.27)     | 0.97                                        |
|                                    | South Asian | 0.97 (0.62, 1.51)     | 0.36                                        |
|                                    | Other   | 1.49 (0.97, 2.30)     | 0.31                                        |
| 8.65–10.05                         | White   | 1.50 (1.42, 1.59) *** |                                             |
|                                    | Black   | 1.78 (0.89, 3.58)     | 0.63                                        |
|                                    | South Asian | 1.55 (0.93, 2.59)     | 0.9                                         |
|                                    | Other   | 1.51 (0.81, 2.83)     | 0.99                                        |
| ≥ 10.05                           | White   | 2.38 (2.26, 2.50) *** |                                             |
|                                    | Black   | 2.51 (1.26, 5.00) **  | 0.87                                        |
|                                    | South Asian | 2.30 (1.43, 3.69) *** | 0.89                                        |
|                                    | Other   | 3.00 (1.81, 4.98) *** | 0.36                                        |
**Supplementary Figure S7. Multiply adjusted hazard ratios for all cause mortality by category of total white cell count, by ethnicity: PREDICT**

Hazard ratios were adjusted for age, sex, smoking, diabetes, systolic blood pressure, ethnicity and total: HDL cholesterol ratio. P values * < 0.05, ** < 0.01, *** < 0.001. ‘Other’ group not shown because most categories had too few events for the calculation of hazard ratios.

| Category of total white cell count | PREDICT | Hazard ratio (95% CI) | P value for interaction (European as reference) |
|-----------------------------------|---------|-----------------------|-----------------------------------------------|
| <2.95                             | European | 6.30 (2.51, 15.79) *** |                                               |
|                                   | Asian    | 8.92 (1.14, 69.90) *   | 0.76                                          |
|                                   | Indian   | –                     |                                               |
|                                   | Maori    | –                     |                                               |
|                                   | Pacific  | 4.90 (0.68, 35.48)     | 0.82                                          |
| 2.95–5.35                         | European | 1.03 (0.75, 1.41)      |                                               |
|                                   | Asian    | 0.92 (0.40, 2.10)      | 0.79                                          |
|                                   | Indian   | 1.56 (0.68, 3.57)      | 0.35                                          |
|                                   | Maori    | 0.94 (0.62, 1.43)      | 0.73                                          |
|                                   | Pacific  | 1.65 (1.11, 2.47) *    | 0.11                                          |
| 5.35–6.25                         | European | 0.94 (0.71, 1.25)      |                                               |
|                                   | Asian    | 0.86 (0.36, 2.03)      | 0.84                                          |
|                                   | Indian   | 0.84 (0.30, 2.36)      | 0.82                                          |
|                                   | Maori    | 0.89 (0.61, 1.30)      | 0.79                                          |
|                                   | Pacific  | 1.08 (0.75, 1.56)      | 0.53                                          |
| 6.25–7.25                         | European | 1 (reference)          |                                               |
| 7.25–8.65                         | European | 1.24 (0.92, 1.67)      |                                               |
|                                   | Asian    | 1.31 (0.58, 2.97)      | 0.9                                           |
|                                   | Indian   | 0.79 (0.36, 1.73)      | 0.3                                           |
|                                   | Maori    | 1.01 (0.71, 1.44)      | 0.36                                          |
|                                   | Pacific  | 1.13 (0.82, 1.55)      | 0.67                                          |
| 8.65–10.05                        | European | 1.53 (1.12, 2.08) **   |                                               |
|                                   | Asian    | 0.99 (0.27, 3.68)      | 0.52                                          |
|                                   | Indian   | 1.03 (0.43, 2.46)      | 0.38                                          |
|                                   | Maori    | 1.22 (0.80, 1.86)      | 0.32                                          |
|                                   | Pacific  | 1.20 (0.82, 1.77)      | 0.39                                          |
| ≥10.05                            | European | 2.59 (1.90, 3.53) ***  |                                               |
|                                   | Asian    | 1.95 (0.66, 5.79)      | 0.62                                          |
|                                   | Indian   | 1.93 (0.83, 4.51)      | 0.49                                          |
|                                   | Maori    | 1.45 (1.02, 2.08) *    | 0.0024                                         |
|                                   | Pacific  | 1.28 (0.89, 1.84)      | 0.0045                                         |
Supplementary Figure S8. Multiply adjusted hazard ratios for all cause mortality by category of total white cell count, by method of multiple imputation: CALIBER

Hazard ratios were adjusted for age, sex, smoking, diabetes, systolic blood pressure, ethnicity and total: HDL cholesterol ratio. P values * < 0.05, ** < 0.01, *** < 0.001

| Category of total white cell count | Normal-based MICE | Hazard ratio (95% CI) | Random Forest MICE | Hazard ratio (95% CI) |
|-----------------------------------|-------------------|-----------------------|--------------------|-----------------------|
| <2.95                             |                   | 5.63 (4.92, 6.45) *** |                    | 5.61 (4.89, 6.43) *** |
| 2.95–5.35                         |                   | 0.97 (0.92, 1.02)     |                    | 0.97 (0.92, 1.02)     |
| 5.35–6.25                         |                   | 0.88 (0.83, 0.92) *** |                    | 0.88 (0.83, 0.92) *** |
| 6.25–7.25                         |                   | 1 (reference)         |                    | 1 (reference)         |
| 7.25–8.65                         |                   | 1.19 (1.14, 1.25) *** |                    | 1.20 (1.14, 1.25) *** |
| 8.65–10.05                        |                   | 1.50 (1.42, 1.58) *** |                    | 1.51 (1.43, 1.59) *** |
| ≥10.05                            |                   | 2.36 (2.25, 2.48) *** |                    | 2.38 (2.27, 2.51) *** |
Supplementary Figure S9. Hazard ratios for all cause mortality by category of total white cell count for complete case analysis: PREDICT

Hazard ratios were adjusted for age, sex, smoking, diabetes, systolic blood pressure, ethnicity and total: HDL cholesterol ratio. P values * < 0.05, ** < 0.01, *** < 0.001