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## Health-related quality of life in thyroid and blood disorders

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# CHAPTER 8

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## Association between peripheral blood cell count abnormalities and health-related quality of life in the general population

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## Abstract

Complete blood cell counts, including differentials, are widely available and change on aging. Peripheral blood cell counts outside the normal range have previously been associated with increased mortality rates and a number of comorbid conditions. However, data about the association between blood cell count abnormalities, other than anemia, and health-related quality of life (HRQoL) are scarce. We investigated the association between abnormalities in (differential) blood cell counts and HRQoL in 143 191 community-dwelling individuals from the prospective population-based Lifelines cohort. HRQoL was measured using the RAND 36-Item Health Survey. Logistic regression analyses were used to determine the effect of blood cell count abnormalities on the odds of having a lower score than an age- and sex-specific reference value for each domain. Leukocytosis, neutrophilia, and a high neutrophil to lymphocyte ratio were associated with impaired HRQoL across multiple domains, both for younger and older ( $\geq 60$  years) individuals. Using multivariable models, we confirmed that these associations were independent of the potential confounding factors obesity, smoking, alcohol use, number of medications (as a measure of comorbidity), anemia, and mean corpuscular volume. The impact on HRQoL was most pronounced for high neutrophil levels. Further, high white blood cell counts proved to be a better marker for inferior HRQoL as compared to elevated high-sensitivity C-reactive protein levels. Decreased HRQoL in several domains was also observed for individuals with monocytosis, lymphocytosis, and thrombocytosis. Taken together, the present study demonstrates an association between inflammatory and myeloid-skewed blood cell counts and inferior HRQoL in community-dwelling individuals.

## Introduction

A complete blood cell count is one of the most commonly used laboratory tests, and is regarded essential in the diagnostic process of a broad variety of clinical conditions. Most electronic counters provide additional information about differential white blood cell (WBC) counts, including neutrophils, lymphocytes, monocytes, eosinophils, and basophils (1). Hemoglobin concentration and platelet count gradually decrease with advancing age, and laboratory results outside the normal reference range are more common in older individuals. Additionally, the aging hematopoietic system is known for skewing toward the myeloid lineage, whereas lymphocyte subsets gradually decrease with age (2-8).

Among the peripheral blood cell count abnormalities, anemia is extensively studied and well known for its association with increased morbidity and mortality. Moreover, older community-dwelling individuals with anemia experience inferior health-related quality of life (HRQoL) (9). Multiple studies have reported on the association between other blood cell count abnormalities and mortality, both in the general population and in the context of acute or chronic medical disorders. Increased all-cause mortality rates were detected for increased levels of total WBC count, neutrophils, monocytes, basophils, lower levels of lymphocytes, and higher neutrophil to lymphocyte ratios (NLR) (10-15). Platelet counts were associated with mortality in an U-shaped manner (16-17). In contrast, data about the association between blood cell count abnormalities, other than anemia, and HRQoL are scarce.

In this study, we aimed to assess the association between HRQoL and abnormalities in peripheral (differential) blood cell counts in a large population-based cohort.

## Materials and methods

### Lifelines cohort

This study was performed using data from the Lifelines cohort, a multidisciplinary prospective population-based cohort study examining in a unique 3-generation design the health and health-related behaviors of 167729 persons living in the north of the Netherlands. It employs a broad range of investigative procedures in assessing the biomedical, sociodemographic, behavioral, physical, and psychological factors which contribute to the health and disease of the general population, with a special focus on multimorbidity and complex genetics. Recruitment of participants was performed between December 2006 and December 2013 using different strategies (invited through general practitioner, via participating family members or self-registered). The study protocol was approved by the medical ethics review committee of the University Medical Center Groningen

and conducted in accordance with the Declaration of Helsinki. All participants provided written informed consent. The Lifelines study population is broadly representative for the population in the north of the Netherlands (18-20). For the present study, we included all participants  $\geq 18$  years.

### **Clinical examination, questionnaires, and sample processing**

After signed informed consent was received, participants received a baseline questionnaire and an invitation to a comprehensive health assessment at the Lifelines outpatient clinic. All subjects completed a self-administered questionnaire on medical history, past and current diseases, use of medication, and health behavior. Medication use was verified by a certified research assistant, and scored by anatomical therapeutic chemical code. Smoking status was defined as nonsmoker, former smoker, and current smoker (21). Alcohol intake was based on self-report and classified into ordered groups based on daily alcohol intake: 0 drinks/d (nondrinker),  $\leq 1$  drink/d (light drinker),  $>1-2$  drinks/d (moderate drinker), and  $>2$  drinks/d (heavy drinker) (22). Body weight was measured without shoes to the nearest 0.1 kg. Body mass index (BMI) was calculated by dividing weight in kilograms by the squared height in meters ( $\text{kg}/\text{m}^2$ ). Peripheral blood samples of participants were drawn after an overnight fast and processed at  $4^\circ\text{C}$  under tightly controlled and monitored conditions. For all routine clinical chemistry assays, samples were directly transported to the University Medical Center Groningen.

### **Definition of blood cell count abnormalities**

Total and differential WBC counts, hemoglobin concentration, mean corpuscular volume (MCV), and platelet counts were determined using routine procedures on a XE2100-system (Sysmex, Kobe, Japan). Local laboratory reference intervals were used to define leukopenia ( $<4.0 \times 10^9/\text{L}$ ), leukocytosis ( $>10.0 \times 10^9/\text{L}$ ), thrombocytopenia ( $<150 \times 10^9/\text{L}$ ), thrombocytosis ( $>400 \times 10^9/\text{L}$ ), neutropenia ( $<1.8 \times 10^9/\text{L}$ ), neutrophilia ( $>7.0 \times 10^9/\text{L}$ ), lymphopenia ( $<0.8 \times 10^9/\text{L}$ ), lymphocytosis ( $>3.2 \times 10^9/\text{L}$ ), monocytopenia ( $<0.3 \times 10^9/\text{L}$ ), monocytosis ( $>0.9 \times 10^9/\text{L}$ ), basophilia ( $>0.2 \times 10^9/\text{L}$ ), and eosinophilia ( $>0.4 \times 10^9/\text{L}$ ). The NLR was calculated by dividing the absolute neutrophil count by the lymphocyte count. Anemia was defined according to World Health Organization criteria: hemoglobin concentration  $<13.0$  g/dL in men and  $<12.0$  g/dL in women. High-sensitivity C-reactive protein (hs-CRP) was initially measured with CardioPhase hsCRP (Siemens, BNII, Marburg, Germany) and after 2012 on a Roche Modular P chemistry analyzer (Roche, Basel, Switzerland). Elevated hs-CRP was defined as  $>10$  mg/L.

## Health-related quality of life

HRQoL was assessed using the RAND 36-Item Health Survey, which is a commonly used generic questionnaire consisting of 36 questions related to own health status covering 8 domains (23). A weighted scoring and summation of selected items results in a score between 0 and 100 for each domain, with a higher score reflecting a better HRQoL. Since HRQoL scores are not normally distributed, we defined a sex- and age-specific cut-off value at the 25th percentile for each domain. Participants with a score lower than this value were considered to have an abnormally low score for that respective domain, as described previously (9, 24, 25).

## Statistical analysis

Data are presented as mean  $\pm$  standard deviation, median (interquartile range) or percentage. Between-group differences were evaluated using 1-way ANOVA, Kruskal-Wallis test, or  $\chi^2$  test, as appropriate. Logistic regression was used to determine the effect of blood cell count abnormalities on the odds of having a lower score than the (age- and sex-specific) value for each HRQoL domain. To account for the effect of health behavior, comorbid conditions, and different types of anemia on HRQoL, multivariable models were adjusted for smoking status (26), alcohol consumption (27), BMI (24), number of medications used (28) (as a general measure of comorbidity), presence of anemia and MCV (9). Additional multivariable models were constructed to include hs-CRP, when available. Odds ratios are reported with 95% confidence interval. For all analyses, the normal range for the respective blood cell count was used as a reference. For the NLR, individuals in the lowest (1<sup>st</sup>) and highest (5<sup>th</sup>) quintile were compared with individuals in the 2nd to 4th quintiles. In subgroup analyses, individuals <60 and  $\geq$ 60 years were evaluated separately. Statistical analyses were performed using IBM SPSS software, version 23.0 (SPSS Inc., Chicago, IL). A P value <0.05 was considered statistically significant.

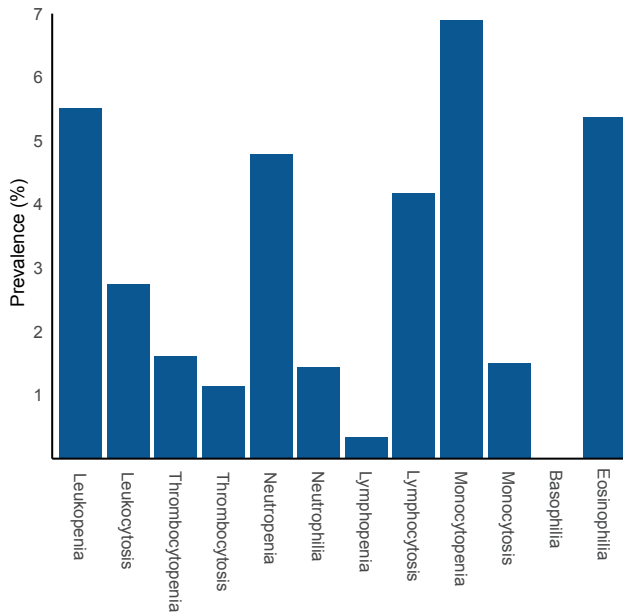
## Results

Relevant baseline characteristics for the cohort with available total WBC and platelet count (N=143191) and the cohort with complete differential WBC count (N=140890) are shown in Table 1. The overall prevalence of blood cell count abnormalities is shown in Figure 1. The prevalence of monocytopenia was the highest (6.9%), whereas basophilia was very rarely detected (0.009%) (Figure 1). The distribution of the blood cell counts and relevant baseline characteristics for individuals with and without blood cell count abnormalities are shown in Supplementary Figures 1, 2, and Table 1.

**Table 1. Baseline characteristics for participants with peripheral blood cell counts available.**

	Available platelet and total WBC count (N=143191)	Available complete differential WBC count (N=140890)
<b>Male sex (%)</b>	41.6	41.5
<b>Age (years)</b>	44.4 ± 12.8	44.4 ± 12.7
<b>BMI (kg/m<sup>2</sup>)</b>	26.0 ± 4.3	26.0 ± 4.3
<b>Smoking</b>		
Current (%)	20.9	20.5
Former (%)	32.9	33.0
Never (%)	46.2	46.5
<b>Number of medications used</b>	1 (0 – 2)	1 (0 – 2)
<b>Alcohol use</b>		
Non-drinker (%)	21.4	21.4
Light drinker (%)	50.1	50.2
Moderate drinker (%)	20.4	20.4
Heavy drinker (%)	8.1	8.1
<b>Anemia (%)</b>	4.1	4.1
<b>MCV (fL)</b>	89.9 ± 4.2	89.8 ± 4.2
<b>Recruitment</b>		
General practitioner (%)	53.8	53.7
Family (%)	32.1	32.1
Self-registered (%)	14.2	14.2
<b>WBC (10<sup>9</sup>/L)</b>	6.1 ± 1.8	
<b>Platelets (10<sup>9</sup>/L)</b>	250 ± 57	
<b>Neutrophils (10<sup>9</sup>/L)</b>		3.32 ± 1.23
<b>Lymphocytes (10<sup>9</sup>/L)</b>		2.02 ± 0.59
<b>Monocytes (10<sup>9</sup>/L)</b>		0.48 ± 0.15
<b>Basophils (10<sup>9</sup>/L)</b>		0.03 ± 0.02
<b>Eosinophils (10<sup>9</sup>/L)</b>		0.18 ± 0.13
<b>NLR</b>		1.75 ± 0.78

Data are given as mean ± SD, median (IQR) when not normally distributed, or percentage. BMI, body mass index; IQR, interquartile range; SD, standard deviation; MCV, mean corpuscular volume; NLR, neutrophil to lymphocyte ratio; WBC, white blood cell.



**Figure 1. Prevalence of blood cell count abnormalities among evaluable individuals.** The definitions of blood cell count abnormalities were based on local laboratory reference intervals, as indicated in the methods section.

## Effect of abnormal WBC and platelet counts on HRQoL

First, we evaluated whether abnormalities in total WBC and platelet counts were associated with HRQoL at younger and older age. A significantly larger proportion of individuals with leukocytosis had a score below the age- and sex-specific value, for all (<60 years) or 6 out of 8 ( $\geq 60$  years) domains (all except mental health and bodily pain), as compared to individuals with a WBC in the normal range. In contrast, individuals with leukopenia were less likely to have a score below the age- and sex-specific value in 7 (<60 years, all except role limitations due to physical functioning) or 3 ( $\geq 60$  years, physical functioning, vitality, and general health) domains (Figure 2A and 2B). For individuals <60 years with thrombocytopenia, HRQoL was slightly increased in 2 domains, whereas HRQoL was reduced for individuals with thrombocytosis in 6 (<60 years, all except social functioning and mental health) or 3 ( $\geq 60$  years, role limitations due to physical functioning, bodily pain, and general health) domains (Figure 2C and 2D). Being a possible explanation for reactive elevated platelet counts, concurrent anemia was observed in 300 of 1640 (18.3%) individuals with thrombocytosis. Absolute scores per domain for the different subgroups are given in Supplementary Table 2)

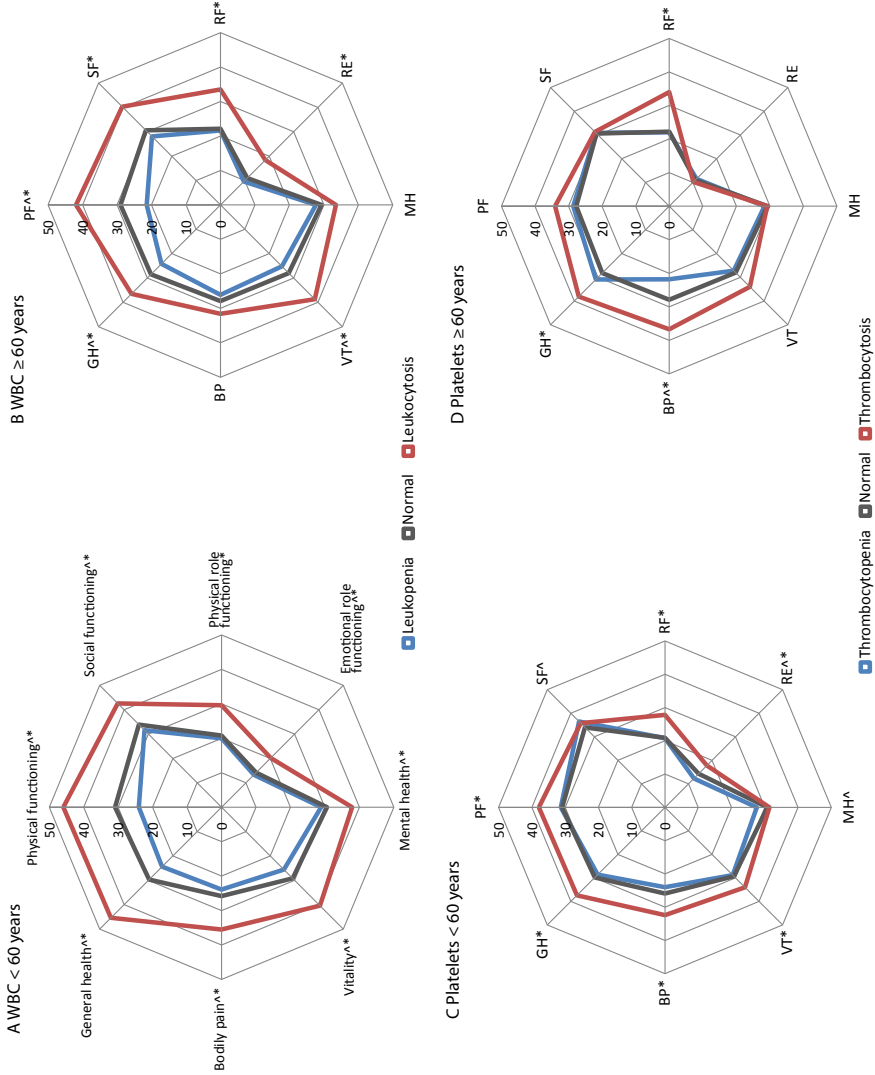


Multivariable logistic regression was performed to adjust the observed associations for BMI, smoking status, alcohol use, number of medications used, presence of anemia, and MCV (Figure 3 and Supplementary Figure 3). Leukocytosis remained strongly associated with a decreased HRQoL across all 8 domains, independent of these potential confounders. For leukopenia, an increase in HRQoL was observed for 2 domains (physical functioning and general health; Figure 3A). Thrombocytopenia remained independently associated with an increased HRQoL in 3 domains (role limitations due to emotional functioning, mental health, and bodily pain) in the multivariable model. For thrombocytosis, the association with decreased HRQoL was sustained for 2 domains (role limitations due to physical functioning and general health; Figure 3B).

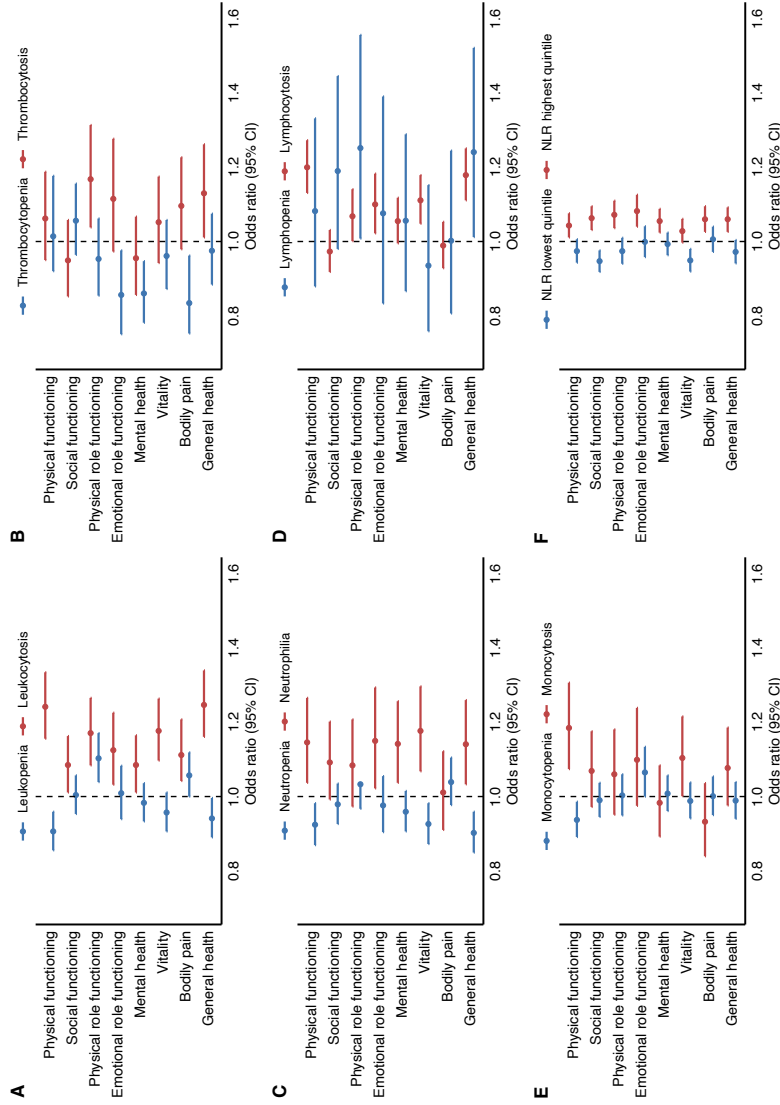
### **Effect of abnormal differential WBC counts on HRQoL**

Next, we evaluated the associations between the differential WBC count and HRQoL. Consistent with the associations observed for leukocytosis, neutrophilia (all 8 domains), lymphocytosis (all 8 domains), and monocytosis (all 8 domains) were all significantly associated with decreased HRQoL (Figure 4A–C). A significantly increased HRQoL was observed for individuals with neutropenia (all 8 domains) and monocytopenia (7 domains, all except role limitations due to emotional functioning) (Figure 4A and 4C). For individuals with lymphopenia, significantly decreased HRQoL was observed for 3 domains (social functioning, role limitations due to physical functioning, and general health; Figure 4B). Basophilia, hampered by low numbers, was not associated with HRQoL (Figure (Figure4D).4D). Individuals with eosinophilia had a slightly lower HRQoL in 5 domains (physical functioning, social functioning, role limitations due to physical functioning, vitality, and general health; Figure 4E). No major differences were observed when evaluating individuals <60 and ≥60 years separately (Supplementary Figure 4). Absolute scores per domain for the different subgroups are given in Supplementary Table 2).

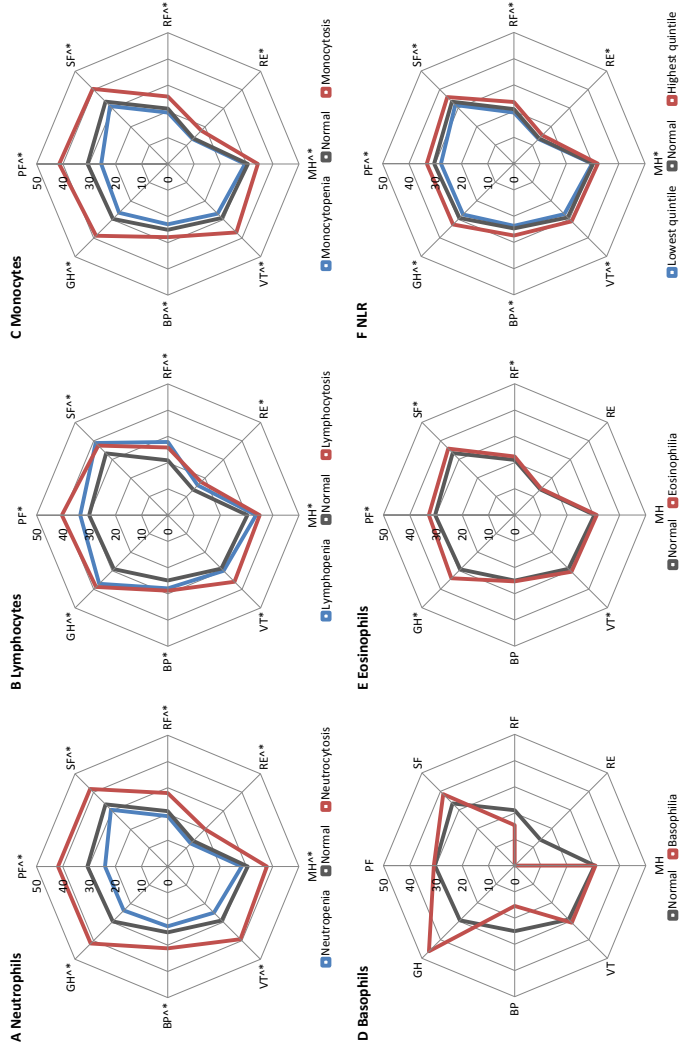
**Figure 2. Percentage of individuals, stratified according to age group and blood cell count abnormality, with a score below the age- and sex-specific cut-off values for the different domains of the RAND-36 health survey.** ^A significant difference in the proportion having a score below the age- and sex-specific cut-off value in individuals with leukopenia or thrombocytopenia as compared to individuals with a normal blood cell count. \*A significant difference in the proportion having a score below the age- and sex-specific cut-off value in individuals with leukocytosis or thrombocytosis as compared to individuals with a normal blood cell count. WBC, white blood cell



**Figure 3. Forest plots demonstrating the odds ratios for having a lower score than the (age- and sex-specific) 25th percentile cut-off per HRQoL subscale, according to blood cell count abnormality.** Logistic regression analyses included body mass index, smoking status, alcohol use, number of medications, presence of anemia and mean corpuscular volume as covariates. A blood cell count in the normal range was used as the reference group. For the NLR, the 2nd to 4th quintile was used as a reference. Circles indicate odds ratios for each cohort, with horizontal lines corresponding to 95% CI. CI, confidence interval; HROoL, health-related quality of life; NLR, neutrophil to lymphocyte ratio.



**Figure 4. Percentage of individuals with a score below the age- and sex-specific cut-off value for the different domains of the RAND-36 health survey, according to differential blood cell count abnormality.** ^A significant difference in the proportion having a score below the age- and sex-specific cut-off value in individuals with neutropenia, lymphopenia, monocytopenia, or lowest NLR quintile, as compared to individuals with a normal blood cell count. ^A significant difference in the proportion having a score below the age- and sex-specific cut-off value in individuals with neutrophilia, lymphocytosis, monocytois, basophililia, eosinophilia, or highest NLR quintile, as compared to individuals with a normal blood cell count. BP, bodily pain; GH, general health; MH, mental health; NLR, neutrophil to lymphocyte ratio; PF, physical functioning; RE, emotional role functioning; SF, social functioning; VT, vitality.



The reported associations were again evaluated in a multivariable logistic regression model, with adjustment for BMI, smoking status, alcohol use, number of medications used, presence of anemia, and MCV (Figure 3 and Supplementary Figure 3). Neutrophilia and lymphocytosis independently associated with a decreased HRQoL in 5 (all except social functioning, role limitations due to physical functioning and bodily pain), respectively 6 (all except social functioning and bodily pain) domains (Figure 3C and 3D). For individuals with monocytosis, HRQoL was affected in 2 domains (physical functioning and vitality) in the multivariable model (Figure 3E). The associations between neutropenia and improved HRQoL scores were retained for 3 domains (physical functioning, vitality, and general health; Figure 3C). For lymphopenia, the association with inferior HRQoL was retained for 2 domains (role limitations due to physical functioning and general health; Figure 3D). After adjustment for confounders, monocytopenia was significantly associated with increased HRQoL in 1 domain (physical functioning; Figure 3E).

When evaluating the differential WBC count, the NLR may be used as a measure for the relative myeloid contribution ("myeloid skewing"). A high NLR (represented by the highest quintile) was significantly associated with a lower HRQoL in all 8 domains (Figure 4F), and this effect was observed for both younger (<60 years) and older individuals ( $\geq 60$  years; Supplementary Figure 4). In multivariable logistic regression analyses, we were able to confirm this association between high NLR and inferior HRQoL in 7 domains (all except vitality; Figure 3F).

### **Peripheral blood cell counts and hs-CRP as a marker for systemic inflammation and effect on HRQoL**

Clearly, the effects on HRQoL are most pronounced for individuals with increased inflammatory blood cell counts. We questioned whether these associations were independent of hs-CRP levels, being another marker of systemic inflammation. hs-CRP levels were available for a subset of individuals with evaluable total and differential WBC counts (N=55342 and N=54383, respectively). Multivariable models were constructed with additional adjustment for hs-CRP, demonstrating that the association between leukocytosis and HRQoL was independent of hs-CRP in 4 domains (physical functioning, role limitations due to physical functioning, vitality, and general health). For the NLR, the association was independent of hs-CRP in 6 domains (all except role limitations due to physical functioning and vitality; Table 2).

Since leukocytosis and hs-CRP appear to be independent markers of decreased HRQoL, we assessed whether there was a differential effect on HRQoL for individuals with one or both markers of inflammation. Individuals were categorized based on elevated (differential) blood cell count and/or elevated hs-CRP ( $>10$  mg/L). As shown in Table 3.3, leukocytosis and elevated hs-CRP associated with inferior HRQoL as compared to normal counts for both markers. However, this effect was more pronounced for individuals with leukocytosis and

normal hs-CRP as compared to individuals with elevated hs-CRP and normal WBC count in 5 domains (social functioning, role limitations due to emotional functioning, mental health, vitality, and general health). When the effects of elevated hs-CRP and high NLR were evaluated, both associated with inferior HRQoL, although the observed associations with inferior HRQoL were stronger for elevated hs-CRP for 5 domains (physical functioning, role limitations due to physical functioning, vitality, bodily pain, and general health). Overall, individuals with a combination of both inflammatory markers (leukocytosis or NLR in the highest quintile combined with elevated hs-CRP) did not experience different HRQoL as compared to individuals having one of either markers of inflammation.

## Discussion

This is the first comprehensive study to assess the association between (differential) blood cell count abnormalities and HRQoL in community-dwelling individuals. In general, our data reveal that elevated platelet and WBC counts were associated with decreased HRQoL in multiple domains. This phenomenon was most pronounced for high neutrophil levels, being the most abundant leukocyte and myeloid cell population. Notably, these associations were observed for both younger and older individuals and were independent of the potential confounding factors obesity, smoking, alcohol use, comorbidity, presence of anemia, and MCV. Overall, the observed absolute differences in HRQoL domain scores reached the 3- to 5-point difference that was previously suggested as the minimal clinically important difference (29).

There is increasing evidence for low-grade inflammation being a common pathway underlying multiple conditions, including cardiovascular disease, cancer, diabetes, and various other health outcomes (30). In multiple previous population-based studies, proinflammatory cytokines (including IL-6 and TNF- $\alpha$ ) (31-36), acute-phase proteins (CRP and fibrinogen) (34, 35, 37-42) and erythrocyte sedimentation rate (43) were associated with decreased HRQoL or subjectively perceived health. Together with cytokines and acute-phase proteins, leukocytes are main components of the immune response in reaction to acute injury or illness. However, data about a possible link between cellular markers of inflammation (ie, leukocytosis, lymphocytosis, elevated NLR) and HRQoL are scarce. Jylhä et al (44) demonstrated that individuals with a WBC  $>6.8 \times 10^9/L$  experienced a lower self-rated health than individuals with a WBC  $\leq 4.8 \times 10^9/L$  in a sample of 4065 subjects  $\geq 71$  years. Furthermore, several studies demonstrated a negative association between WBC and well-being (45, 46). Our results are in agreement with these findings, demonstrating a clear link between leukocytosis and inferior HRQoL. In addition, we show that leukocytosis may be a better predictor of inferior HRQoL than hs-CRP.

When evaluating the differential WBC count, the effect on HRQoL was most pronounced for neutrophils. Although traditionally considered the main actors in acute inflammatory responses, there is emerging evidence for the direct contribution of neutrophils to chronic inflammatory processes (47). In addition, remodeling of the hematopoietic system in response to inflammatory signaling results in overproduction of myeloid cells (48). Indeed, reduced HRQoL was observed for individuals with higher NLR levels, reflecting relative myeloid predominance.

**Table 2. Univariable and multivariable logistic regression analyses assessing the association between increased inflammatory blood cell counts and health-related quality of life independent of hs-CRP levels.**

	Univariate		Multivariate (model 1)		Multivariate (model 2)	
	Odds ratio (95% CI)	P value	Odds ratio (95% CI)	P value	Odds ratio (95% CI)	P value
<b>Leukocytosis</b>						
Physical functioning	1.91 (1.79 – 2.03)	<0.001	1.24 (1.16 – 1.34)	<0.001	1.15 (1.02 – 1.259)	0.024
Social functioning	1.46 (1.37 – 1.56)	<0.001	1.09 (1.01 – 1.16)	0.023	1.07 (0.96 – 1.21)	0.24
Physical role functioning	1.61 (1.50 – 1.72)	<0.001	1.17 (1.08 – 1.27)	<0.001	1.17 (1.03 – 1.33)	0.014
Emotional role functioning	1.57 (1.45 – 1.70)	<0.001	1.13 (1.03 – 1.23)	0.008	1.13 (0.98 – 1.30)	0.087
Mental health	1.37 (1.29 – 1.47)	<0.001	1.09 (1.01 – 1.17)	0.024	1.07 (0.95 – 1.20)	0.27
Vitality	1.67 (1.54 – 1.76)	<0.001	1.18 (1.10 – 1.26)	<0.001	1.18 (1.05 – 1.32)	0.007
Bodily pain	1.54 (1.44 – 1.64)	<0.001	1.11 (1.04 – 1.21)	0.002	1.08 (0.91 – 1.10)	0.21
General health	1.92 (1.80 – 2.05)	<0.001	1.25 (1.16 – 1.34)	<0.001	1.21 (1.08 – 1.36)	0.002
<b>NLR highest quintile</b>						
Physical functioning	1.14 (1.11 – 1.18)	<0.001	1.04 (1.01 – 1.08)	0.009	1.06 (1.00 – 1.11)	0.043
Social functioning	1.12 (1.09 – 1.15)	<0.001	1.06 (1.03 – 1.10)	<0.001	1.10 (1.05 – 1.16)	<0.001
Physical role functioning	1.17 (1.13 – 1.21)	<0.001	1.07 (1.04 – 1.10)	<0.001	1.04 (0.98 – 1.10)	0.17
Emotional role functioning	1.15 (1.11 – 1.20)	<0.001	1.08 (1.04 – 1.13)	<0.001	1.08 (1.00 – 1.15)	0.033
Mental health	1.09 (1.06 – 1.12)	<0.001	1.06 (1.02 – 1.09)	0.001	1.07 (1.01 – 1.12)	0.016
Vitality	1.10 (1.07 – 1.14)	<0.001	1.03 (1.00 – 1.06)	0.078	1.04 (0.99 – 1.10)	0.14
Bodily pain	1.15 (1.12 – 1.19)	<0.001	1.06 (1.03 – 1.10)	<0.001	1.09 (1.03 – 1.15)	0.002
General health	1.16 (1.13 – 1.19)	<0.001	1.06 (1.03 – 1.09)	<0.001	1.06 (1.01 – 1.12)	0.025

Logistic regression analyses included body mass index, smoking status, alcohol use, number of medications used, presence of anemia and mean corpuscular volume as covariates (model 1). Model 2 was additionally adjusted for hs-CRP, when available. A WBC count in the normal range and a NLR in the 2<sup>nd</sup> to 4<sup>th</sup> quintile were used as reference group. CI, confidence interval; NLR, neutrophil to lymphocyte ratio.

**Table 3. Percentage of individuals with a score below the sex- and age-specific cut-off values for the different domains of the RAND-36 health survey according to the presence of elevated inflammatory blood cell counts and/or high hs-CRP levels.**

	PF	P value	SF	P value	RF	P value	RE	P value	MH	P value	VT	P value	BP	P value	GH	P value
<b>WBC</b>																
Normal WBC and hs-CRP (N=49015)	31.1	0.43	33.7	0.003	21.3	0.07	14.0	<0.001	30.6	<0.001	30.1	0.002	26.1	0.94	29.6	0.008
Normal WBC and high hs-CRP (N=1705)	42.9		36.9		27.6		16.0		30.6		36.8		34.7		40.1	
High WBC and normal hs-CRP (N=1300)	44.3		42.3		30.7		21.9		37.6		42.3		34.8		44.8	
High WBC and hs-CRP (N=300)	48.7		40.0		31.0		16.0		35.7		39.0		34.3		46.7	
<b>NLR</b>																
Normal NLR and hs-CRP (N=32094)	30.9	<0.001	33.4	0.50	21.1	0.004	13.7	0.21	30.1	0.95	30.0	0.001	24.7	0.005	29.5	<0.001
Normal NLR and high hs-CRP (N=901)	43.1		37.4		27.4		17.1		32.1		37.8		32.0		40.6	
High NLR and normal hs-CRP (N=9862)	33.7		36.3		23.1		15.5		32.2		32.2		27.6		32.5	
High NLR and hs-CRP (N=885)	42.5		36.9		27.6		15.6		30.2		36.0		33.3		39.8	

P values are given to compare individuals with elevated inflammatory blood cell counts and normal hs-CRP with individuals having normal blood cell counts and elevated hs-CRP (>10 mg/L). BP, bodily pain; GH, general health; MH, mental health; NLR, neutrophil to lymphocyte ratio; PF, physical functioning; RE, emotional role functioning; RF, physical role functioning; SF, social functioning; VT, vitality; WBC, white blood cell.





Thus, myeloid-skewed leukocyte counts may represent a state of chronic inflammation that is associated with HRQoL. The relation between thrombocytosis and HRQoL may have different explanations. Although anemia of iron deficiency may be underlying in a subset of individuals and was previously associated with reduced HRQoL (9), this was corrected for in multivariable analysis. Alternatively, reactive thrombocytosis may represent another phenotypic manifestation of chronic inflammation (48).

A chronic state of low-grade inflammation is increasingly recognized as a hallmark of aging. So-called "inflammaging" is used to describe the age-related increase in circulating markers of inflammation, including proinflammatory cytokines (4, 49). In contrast to anemia (9), the associations between inflammatory blood cell counts and HRQoL were observed both for younger and older ( $\geq 60$  years) individuals. Although inflammatory markers, including skewing toward the myeloid lineage (4), increase with age, the impact of inflammatory blood cell counts on HRQoL is relevant for all ages.

Multivariable analyses were corrected for comorbidities, suggesting that the association between inflammatory blood cell counts and HRQoL is not merely a reflection of recognized underlying chronic diseases. However, we cannot exclude that underlying conditions are mediating the observed associations between inflammation and HRQoL. On the other hand, inflammation may serve as a proxy for a general state of accelerated aging that includes morbidity, frailty, and otherwise unrelated adverse health outcomes, including lower HRQoL.

It should be noted that inflammatory blood cell counts may not only be a cause of impaired HRQoL but also a consequence. Chronic (physical and/or mental) stress may induce proliferation of primitive hematopoietic progenitors, giving rise to an increase in inflammatory leukocytes, including higher numbers of neutrophils, monocytes, and lymphocytes (50).

This study has some strengths and limitations. This is the first study to investigate the possible effect of (differential) blood cell count abnormalities on HRQoL. Additionally, we used information on HRQoL from a large number of participants from the general population with a wide range of age, socioeconomic status, and comorbidities. All subjects were uniformly characterized and were not aware of their blood cell count status when filling out the HRQoL questionnaire. The associations between inflammatory blood cell counts and inferior HRQoL were observed across all domains, further strengthening the observed effects. Several potential limitations should also be acknowledged. First, although the Lifelines cohort is representative of the general population in the North of the Netherlands,<sup>20</sup> this is an ethnically homogeneous population, limiting wider applicability of the results. Since this is a cross-sectional study, the analyses do not provide information about causality. Furthermore, due to the observational nature of the study, it was not possible to exclude the role of unknown or unmeasured confounding variables. Although there is a heterogeneous collection of medical

disorders which affect peripheral blood counts, we were not able to ascertain the potential underlying cause of abnormalities. Finally, we used only a single blood cell count for the analyses. As peripheral blood cell counts may fluctuate over time, multiple measurements over time may provide more accurate information.

In conclusion, the present study demonstrates an association between elevated and myeloid-skewed inflammatory blood cell counts and inferior HRQoL in community-dwelling individuals. Peripheral blood cell counts are easy to obtain and inexpensive, thereby representing an interesting alternative marker for inferior health outcomes associated with chronic inflammation, including quality of life.

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### **Data sharing statement**

The article is based on data from the Lifelines Cohort Study. Lifelines adheres to standards for data availability. The data catalogue of Lifelines is publicly accessible at [www.lifelines.nl](http://www.lifelines.nl). All international researchers can obtain data at the Lifelines research office ([research@lifelines.nl](mailto:research@lifelines.nl)), for which a fee is required.

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### **Disclosures**

The authors declare no competing interest.

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## CHAPTER 8

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	0 (0 - 1)	1 (0 - 2)	1 (0 - 2)	<0.001	0 (0 - 3)	1 (0 - 2)	1 (0 - 2)	<0.001
<b>Number of medications used</b>								
<b>Alcohol use</b>								
Non/light/ moderate/heavy	173/526/ 225/776	215/501/ 203/81	277/457/ 176/90	<0.001	216/507/ 197/81	213/503/ 204/80	230/483/ 190/96	<0.001
<b>Anemia (%)</b>	75	40	30	<0.001	9.1	43	23	<0.001
<b>MCV (fL)</b>	90.0 ± 43	89.8 ± 42	91.3 ± 46	<0.001	90.1 ± 49	89.8 ± 42	90.6 ± 42	<0.001
						<b>Normal</b>	<b>Basophilia</b>	<b>P value</b>
<b>Number</b>	9713	129056	2121			<b>140877</b>	13	
<b>Male sex (%)</b>	25.9	42.3	62.5	<0.001		41.5	46.2	0.734
<b>Age (years)</b>	43.4 ± 11.8	44.5 ± 12.8	45.4 ± 13.4	<0.001		44.4 ± 12.7	52.4 ± 8.2	0.024
<b>BMI (kg/m<sup>2</sup>)</b>	24.8 ± 3.8	26.1 ± 4.3	26.8 ± 4.8	<0.001		26.0 ± 4.3	26.3 ± 7.1	0.567
<b>Smoking</b>								
Current/former/ never	9.7/36.4/53.9	20.8/32.9/46.3	54.3/22.1/23.6	<0.001		20.5/33.0/46.5	38.5/46.2/15.4	0.066
<b>Number of medications used</b>	1 (0 - 1)	1 (0 - 2)	1 (0 - 2)	<0.001		1 (0 - 2)	1 (0 - 2)	0.978
<b>Alcohol use</b>								
Non/light/ moderate/heavy	22.9/54.4/ 18.0/47	213/50.0/ 20.5/8.2	21.3/40.9/ 22.4/2.7	<0.001		21.4/50.2 20.4/8.1	16.7/41.7/ 25.0/16.7	0.675
<b>Anemia (%)</b>	6.4	2.0	2.9	<0.001		4.1	7.7	0.520
<b>MCV (fL)</b>	89.6 ± 4.2	89.8 ± 4.2	91.2 ± 4.4	<0.001		89.8 ± 4.2	90.5 ± 8.7	0.843

	Normal	Eosinophilia	P value	1 <sup>st</sup> quintile	2 <sup>nd</sup> -4 <sup>th</sup> quintile	5 <sup>th</sup> quintile	P value
<b>Number</b>	133329	7561		28201	84714	27975	
<b>Male sex (%)</b>	41.0	49.8	<0.001	40.4	42.7	39.0	<0.001
<b>Age (years)</b>	44.4 ± 12.7	44.0 ± 13.3	0.007	43.3 ± 14.4	44.4 ± 12.5	45.4 ± 11.7	<0.001
<b>BMI (kg/m<sup>2</sup>)</b>	26.0 ± 4.3	26.0 ± 4.3	0.545	25.3 ± 3.9	26.1 ± 4.3	26.4 ± 4.7	<0.001
<b>Smoking</b>							
Current/former/ never	9.9/33.2/46.9	30.9/29.1/40.1	<0.001	18.3/34.0/47.7	20.4/33.0/46.6	22.9/32.0/45.1	<0.001
<b>Number of medications used</b>	1 (0 - 2)	1 (0 - 2)	<0.001	1 (0 - 2)	1 (0 - 2)	1 (0 - 2)	<0.001
<b>Alcohol use</b>							
Non/light/ moderate/heavy	21.4/50.4/ 20.2/7.9	20.5/46.6/ 22.6/10.3	<0.001	17.8/51.4/ 21.6/8.8	21.3/50.2/ 20.4/8.0	25.1/49.0/ 18.5/7.4	<0.001
<b>Anemia (%)</b>	3.9	0.2	0.005	3.8	4.0	5.0	<0.001
<b>MCV (fL)</b>	89.8 ± 4.2	90.1 ± 4.2	<0.001	90.0 ± 4.0	89.8 ± 4.1	89.9 ± 4.5	<0.001

Data are given as mean ± SD, median (IQR) when not normally distributed, or percentage. BMI, body mass index; IQR, interquartile range; MCV, mean corpuscular volume; SD, standard deviation.



Supplementary Table 2. Absolute scores for the different domains of the RAND-36 health survey, stratified according to differential blood cell count abnormality.

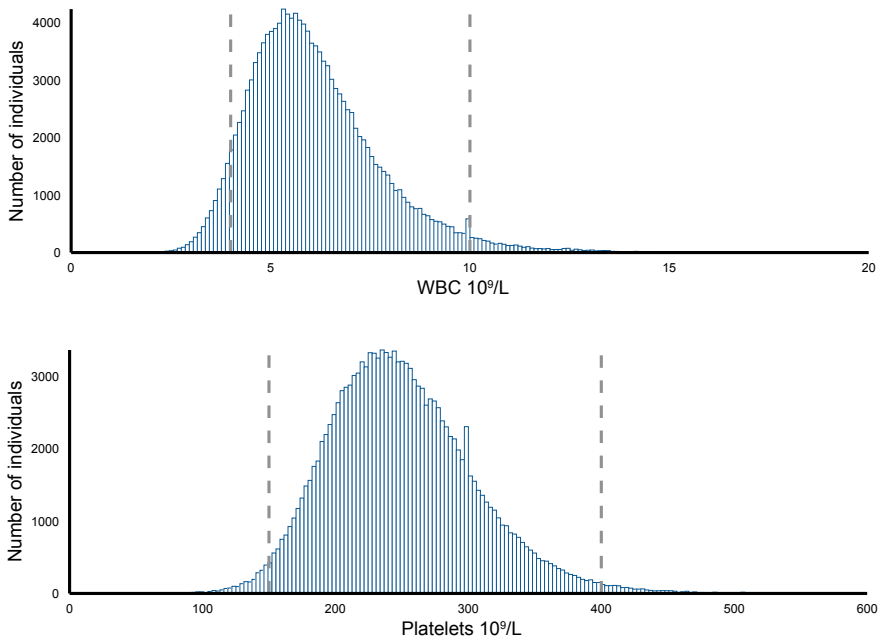
	Leukopenia		WBC in normal range		Leukocytosis	
	Mean ± SD	Median (IQR)	Mean ± SD	Median (IQR)	Mean ± SD	Median (IQR)
<b>Physical functioning</b>	92.0 ± 13.0	95.0 (90.0-100.0)	90.6 ± 14.2	95.0 (90.0-100.0)	85.2 ± 19.6	90.0 (80.0-100.0)
<b>Social functioning</b>	88.5 ± 17.3	100.0 (87.5-100.0)	87.7 ± 18.0	100.0 (75.0-100.0)	83.0 ± 21.7	87.5 (75.0-100.0)
<b>Physical role functioning</b>	87.1 ± 28.9	100.0 (100.0-100.0)	86.8 ± 29.2	100.0 (100.0-100.0)	80.2 ± 34.6	100.0 (75.0-100.0)
<b>Emotional role functioning</b>	91.6 ± 24.2	100.0 (100.0-100.0)	90.8 ± 29.2	100.0 (100.0-100.0)	86.0 ± 30.7	100.0 (100.0-100.0)
<b>Mental health</b>	80.2 ± 13.3	84.0 (72.0-88.0)	79.8 ± 13.7	84.0 (72.0-88.0)	76.6 ± 16.2	80.0 (68.0-88.0)
<b>Vitality</b>	69.6 ± 16.7	70.0 (60.0-80.0)	67.9 ± 17.0	70.0 (60.0-80.0)	62.6 ± 18.9	65.0 (50.0-75.0)
<b>Bodily pain</b>	85.6 ± 18.2	89.8 (77.6-100.0)	84.5 ± 19.0	89.8 (67.3-100.0)	79.8 ± 22.6	89.8 (67.3-100.0)
<b>General health</b>	74.3 ± 16.4	75.0 (65.0-85.0)	72.0 ± 16.6	75.0 (65.0-85.0)	65.2 ± 19.0	65.0 (55.0-80.0)
	Thrombocytopenia		Platelets in normal range		Thrombocytosis	
	Mean ± SD	Median (IQR)	Mean ± SD	Median (IQR)	Mean ± SD	Median (IQR)
<b>Physical functioning</b>	90.4 ± 14.4	95.0 (90.0-100.0)	90.6 ± 14.3	95.0 (90.0-100.0)	86.8 ± 18.1	95.0 (85.0-100.0)
<b>Social functioning</b>	88.9 ± 17.3	100.0 (87.5-100.0)	87.6 ± 18.0	100.0 (75.0-100.0)	84.1 ± 21.1	87.5 (75.0-100.0)
<b>Physical role functioning</b>	86.2 ± 30.2	100.0 (100.0-100.0)	86.7 ± 29.3	100.0 (100.0-100.0)	81.4 ± 33.8	100.0 (75.0-100.0)
<b>Emotional role functioning</b>	92.0 ± 23.5	100.0 (100.0-100.0)	90.8 ± 25.3	100.0 (100.0-100.0)	88.3 ± 28.5	100.0 (100.0-100.0)
<b>Mental health</b>	81.7 ± 13.3	84.0 (72.0-92.0)	79.7 ± 13.8	84.0 (72.0-88.0)	78.0 ± 14.9	80.0 (72.0-88.0)
<b>Vitality</b>	70.0 ± 17.1	73.3 (60.0-83.8)	67.9 ± 17.0	70.0 (60.0-80.0)	64.3 ± 18.3	65.0 (50.0-75.0)
<b>Bodily pain</b>	86.0 ± 18.4	100.0 (77.6-100.0)	84.5 ± 19.1	89.8 (67.3-100.0)	80.1 ± 22.1	89.8 (67.3-100.0)
<b>General health</b>	71.8 ± 17.0	75.0 (60.0-85.0)	72.0 ± 16.7	75.0 (65.0-85.0)	68.3 ± 19.0	70.0 (60.0-80.0)

	<b>Neutropenia</b>		<b>Neutrophils in normal range</b>		<b>Neutrophilia</b>	
	Mean ± SD	Median (IQR)	Mean ± SD	Median (IQR)	Mean ± SD	Median (IQR)
<b>Physical functioning</b>	92.3 ± 12.6	95.0 (90.0-100.0)	90.6 ± 14.3	95.0 (90.0-100.0)	86.2 ± 18.7	95.0 (80.0-100.0)
<b>Social functioning</b>	88.6 ± 17.1	100.0 (87.5-100.0)	87.6 ± 18.0	100.0 (75.0-100.0)	83.4 ± 21.6	87.5 (75.0-100.0)
<b>Physical role functioning</b>	88.1 ± 27.8	100.0 (100.0-100.0)	86.7 ± 29.3	100.0 (100.0-100.0)	81.3 ± 34.2	100.0 (75.0-100.0)
<b>Emotional role functioning</b>	91.9 ± 23.8	100.0 (100.0-100.0)	90.8 ± 25.3	100.0 (100.0-100.0)	86.2 ± 30.3	100.0 (100.0-100.0)
<b>Mental health</b>	80.3 ± 13.1	84.0 (72.0-88.0)	79.8 ± 13.7	84.0 (72.0-88.0)	76.8 ± 16.0	80.0 (68.0-88.0)
<b>Vitality</b>	69.9 ± 16.3	70.0 (60.0-80.0)	67.9 ± 17.0	70.0 (60.0-80.0)	63.2 ± 18.6	65.0 (50.0-75.0)
<b>Bodily pain</b>	85.7 ± 18.1	89.8 (77.6-100.0)	84.5 ± 19.1	89.8 (67.3-100.0)	80.7 ± 22.4	89.8 (67.3-100.0)
<b>General health</b>	74.5 ± 16.0	75.0 (65.0-85.0)	72.0 ± 16.7	75.0 (65.0-85.0)	66.6 ± 19.1	70.0 (55.0-80.0)
	<b>Lymphopenia</b>		<b>Lymphocytes in normal range</b>		<b>Lymphocytosis</b>	
	Mean ± SD	Median (IQR)	Mean ± SD	Median (IQR)	Mean ± SD	Median (IQR)
<b>Physical functioning</b>	87.2 ± 18.3	95.0 (85.0-100.0)	90.7 ± 14.1	95.0 (90.0-100.0)	87.9 ± 16.8	95.0 (85.0-100.0)
<b>Social functioning</b>	84.5 ± 21.7	100.0 (75.0-100.0)	87.8 ± 17.9	100.0 (100.0-100.0)	84.9 ± 20.5	100.0 (75.0-100.0)
<b>Physical role functioning</b>	80.9 ± 34.9	100.0 (75.0-100.0)	86.8 ± 29.2	100.0 (100.0-100.0)	83.2 ± 32.5	100.0 (75.0-100.0)
<b>Emotional role functioning</b>	88.7 ± 28.3	100.0 (100.0-100.0)	90.9 ± 25.1	100.0 (100.0-100.0)	87.6 ± 29.1	100.0 (100.0-100.0)
<b>Mental health</b>	79.9 ± 13.4	84.0 (72.0-88.0)	79.8 ± 13.6	84.0 (72.0-88.0)	77.5 ± 15.5	80.0 (68.0-88.0)
<b>Vitality</b>	67.5 ± 18.9	70.0 (55.0-80.0)	68.1 ± 17.0	70.0 (60.0-80.0)	64.6 ± 18.3	65.0 (50.0-80.0)
<b>Bodily pain</b>	82.9 ± 21.3	89.8 (67.3-100.0)	84.6 ± 19.0	89.8 (67.3-100.0)	81.9 ± 21.1	89.8 (67.3-100.0)
<b>General health</b>	67.5 ± 21.3	75.0 (55.0-80.0)	72.2 ± 16.6	75.0 (65.0-85.0)	67.7 ± 18.2	70.0 (55.0-80.0)

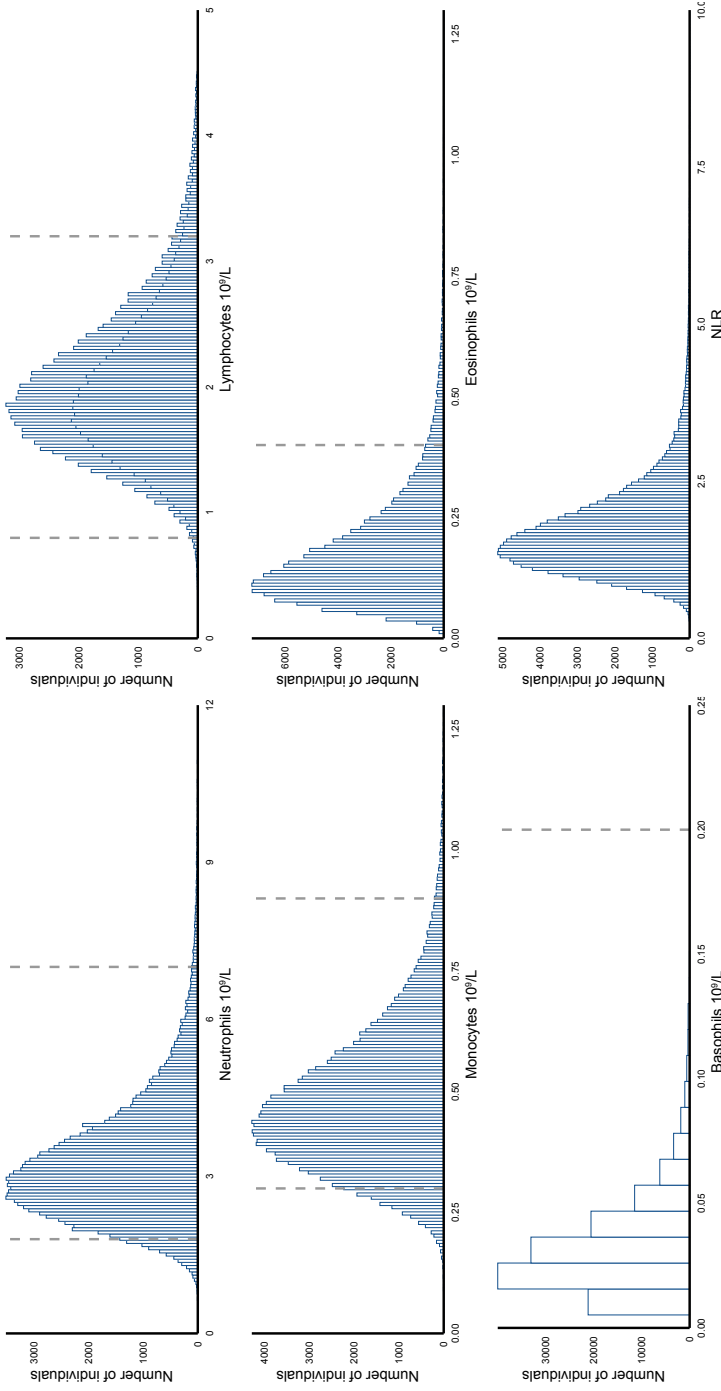


	Monocytopenia		Monocytes in normal range		Monocytosis	
	Mean ± SD	Median (IQR)	Mean ± SD	Median (IQR)	Mean ± SD	Median (IQR)
<b>Physical functioning</b>	91.9 ± 13.0	95.0 (90.0-100.0)	90.6 ± 14.3	95.0 (90.0-100.0)	86.7 ± 18.4	95.0 (85.0-100.0)
<b>Social functioning</b>	87.5 ± 18.1	100.0 (75.0-100.0)	87.7 ± 18.0	100.0 (75.0-100.0)	85.8 ± 20.2	100.0 (75.0-100.0)
<b>Physical role functioning</b>	87.6 ± 28.4	100.0 (100.0-100.0)	86.6 ± 29.4	100.0 (100.0-100.0)	83.2 ± 32.4	100.0 (75.0-100.0)
<b>Emotional role functioning</b>	91.3 ± 25.0	100.0 (100.0-100.0)	90.8 ± 25.2	100.0 (100.0-100.0)	87.8 ± 28.9	100.0 (100.0-100.0)
<b>Mental health</b>	79.5 ± 13.4	84.0 (72.0-88.0)	80.0 ± 13.7	84.0 (72.0-88.0)	76.1 ± 15.5	84.0 (72.0-92.0)
<b>Vitality</b>	67.8 ± 16.7	70.0 (60.0-80.0)	67.9 ± 17.0	70.0 (60.0-80.0)	66.1 ± 18.3	70.0 (55.0-80.0)
<b>Bodily pain</b>	85.1 ± 18.3	89.8 (77.6-100.0)	84.4 ± 19.1	89.8 (67.3-100.0)	83.1 ± 20.9	89.8 (67.3-100.0)
<b>General health</b>	73.7 ± 16.3	75.0 (65.0-85.0)	71.9 ± 16.7	75.0 (65.0-85.0)	67.5 ± 18.1	70.0 (55.0-80.0)
	NLR lowest quintile		NLR 2 <sup>nd</sup> to 4 <sup>th</sup> quintile		NLR highest quintile	
	Mean ± SD	Median (IQR)	Mean ± SD	Median (IQR)	Mean ± SD	Median (IQR)
<b>Physical functioning</b>	91.6 ± 13.4	95.0 (90.0-100.0)	90.6 ± 14.3	95.0 (90.0-100.0)	89.1 ± 15.7	95.0 (85.0-100.0)
<b>Social functioning</b>	88.3 ± 17.6	100.0 (75.0-100.0)	87.5 ± 18.2	100.0 (75.0-100.0)	86.5 ± 18.8	100.0 (75.0-100.0)
<b>Physical role functioning</b>	87.9 ± 28.0	100.0 (100.0-100.0)	86.6 ± 29.4	100.0 (100.0-100.0)	84.7 ± 31.1	100.0 (100.0-100.0)
<b>Emotional role functioning</b>	91.3 ± 24.6	100.0 (100.0-100.0)	90.7 ± 25.4	100.0 (100.0-100.0)	89.6 ± 26.8	100.0 (100.0-100.0)
<b>Mental health</b>	79.8 ± 13.6	84.0 (72.0-88.0)	79.7 ± 13.8	84.0 (72.0-88.0)	79.2 ± 14.1	84.0 (72.0-88.0)
<b>Vitality</b>	68.8 ± 16.8	70.0 (60.0-80.0)	67.7 ± 17.1	70.0 (55.0-80.0)	66.8 ± 17.4	70.0 (55.0-80.0)
<b>Bodily pain</b>	85.1 ± 18.5	89.8 (77.6-100.0)	84.5 ± 19.2	89.8 (67.3-100.0)	83.3 ± 19.9	89.8 (67.3-100.0)
<b>General health</b>	72.9 ± 16.4	75.0 (65.0-85.0)	71.8 ± 16.7	75.0 (62.5-85.0)	70.7 ± 17.3	70.0 (60.0-85.0)

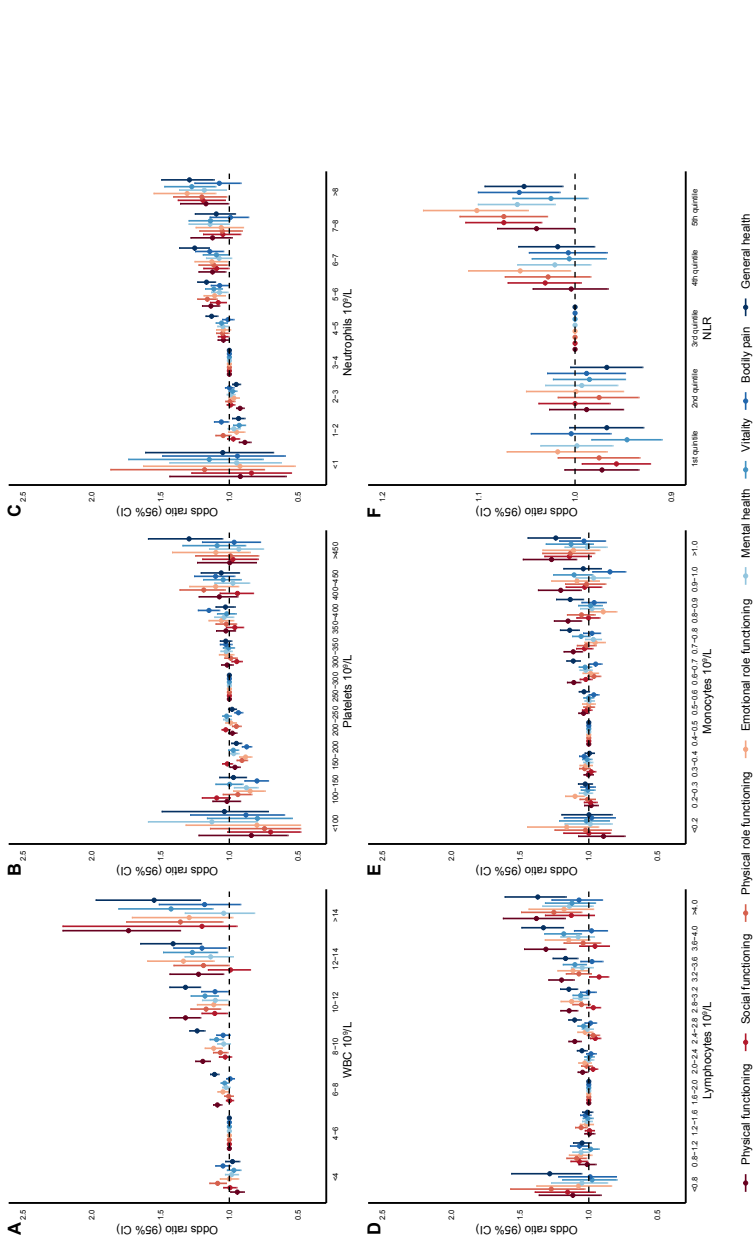
NLR, neutrophil to lymphocyte ratio; WBC, white blood cell.



**Supplementary Figure 1. Distribution of white blood cell and platelet counts in the evaluable Lifelines cohort (N=143191).** In order to improve visibility, figures were cropped at the extremes and a minor proportion of outliers in platelet count ( $>600 \times 10^9/L$ , N=52) and white blood cell count ( $>20 \times 10^9/L$ , N=34) were removed. WBC, white blood cell.



**Supplementary Figure 2. Distribution of differential white blood cell counts in the evaluable Lifelines cohort (N=140890).** In order to improve visibility, figures were cropped at the extremes and a minor proportion of outliers in neutrophil count ( $>12 \times 10^9/L$ , N=57), lymphocyte count ( $>5 \times 10^9/L$ , N=3), monocyte count ( $>1.3 \times 10^9/L$ , N=67), eosinophil count ( $>1.3 \times 10^9/L$ , N=86), basophil count ( $>0.25 \times 10^9/L$ , N=8) and neutrophil to lymphocyte ratio ( $>10$ , N=50) were removed. NLR, neutrophil to lymphocyte ratio.



**Supplementary Figure 3. Forest plots demonstrating the odds ratios for having a lower score than the (age- and sex-specific) 25th percentile cut-off per HRQoL subscale, according to different strata of blood cell counts.** Logistic regression analyses included body mass index, smoking status, alcohol use, and number of medications, presence of anemia and mean corpuscular volume as covariates. The following ranges in peripheral blood cell counts were used as the reference group: white blood cell count 4-6x10<sup>9</sup>/L; platelets 250-300x10<sup>9</sup>/L; neutrophils 3-4x10<sup>9</sup>/L; lymphocytes 1.6-2.0x10<sup>9</sup>/L; and NLR in the 3rd quintile. Circles indicate odds ratios for each domain, with horizontal lines corresponding to 95% confidence intervals. NLR, neutrophil to lymphocyte ratio; WBC, white blood cell



**Supplementary Figure 4. Percentage of individuals with a score below the age- and sex-specific cut-off value for the different domains of the RAND-36 health survey, stratified according to differential blood cell count abnormality and age group (<60 years and ≥60 years). A circumflex (∧) indicates a significant difference in the proportion below the age- and sex-specific cut-off value for individuals with neutropenia, lymphopenia, monocytopenia or lowest NLR quintile, as compared to individuals with a normal blood cell count. An asterisk (\*) indicates a significant difference in the proportion below the age- and sex-specific cut-off value for individuals with neutrophilia, lymphocytosis, monocytosis, eosinophilia or highest NLR quintile, as compared to individuals with a normal blood cell count. BP, bodily pain; GH, general health; MH, mental health; NLR, neutrophil to lymphocyte ratio; PF, physical functioning; RE, emotional role functioning; RF, social functioning; SF, vitality; WBC, white blood cell**

