Supplemental Material

Elements of the complete blood count associated with cardiovascular disease incidence:

Findings from the EPIC-NL cohort study

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Supplemental Information: Logistics of storage of blood samples in EPIC-NL

In the MORGEN-EPIC study, the samples were kept at room temperature for thirty minutes to three hours in the peripheral study centers, allowing slight swelling of cells and stabilization of size, after which they were stored at +5°C and transported overnight in a coolbox to the central Cryolaboratory of RIVM.

In the Prospect-EPIC study, the samples were stored at room temperature until the arrival at the central Cryolaboratory at the end of the day. During the night, the samples were stored at +5°C. The next day the samples of both studies were again kept at room temperature for at least thirty minutes and measured in a blood cell counter (Coulter counter MAXM, Coulter Electronics).

Supplemental Table 1. Outcome definitions according to ICD 9 (morbidity) and ICD 10 (mortality) codes for the definition of total CVD

ICD 9	Description	ICD 10 (cause of death)	Description	
410-414	Ischemic heart diseases	I20-I25	Ischemic heart diseases	CHD
427.5	Cardiac arrest	I46	Cardiac arrest	
428	Heart failure	I50	Heart failure	
415.1	Pulmonary embolism and infarction	I26	Pulmonary embolism	
430-438	Cerebrovascular disease	I60-I69 except I68	Cerebrovascular diseases except Cerebrovascular disorders in diseases classified elsewhere	Stroke
		G45	Transient cerebral ischemic attacks and related syndromes	
440	Atherosclerosis	I70	Atherosclerosis	
441	Aortic aneurysm and dissection	I71	Aortic aneurysm and dissection,	
442	Other aneurysm	I72	Other aneurysm	
443.9	Peripheral vascular disease, unspecified	I73	Other peripheral vascular diseases	
444	Arterial embolism and thrombosis	I74	Aerterial embolism and thrombosis	
798.1, 798.2, 798.9	Suddent death, cause unknown (except sudden infant death)	R99	Ill-defined and unknown cause of mortality	

Supplemental Table 2. Multivariate (Model 1)* hazard ratios HRs (95% confidence interval) for cardiovascular disease, stroke and coronary heart disease associated with tertiles of elements of the complete blood count, n= 14,362, EPIC-NL

			CVD			Stroke			CHD		
		N total	N cases	HR (95 %CI)	P trend[a]	N cases	HR (95 %CI)	P trend[a]	N Cases	HR (95 %CI)	P trend[a]
RBC		**14362**	**992**			**196**			**589**		
RBC (10^{12} cells/L) [b]	T1	4761	330	1 (ref)	0.44	65	1 (ref)	0.65	195	1 (ref)	0.69
	T2	4855	297	0.82 (0.69; 0.97)		48	0.62 (0.42; 0.92)		181	0.92 (0.74; 1.16)	
	T3	4746	365	0.92 (0.75; 1.12)		83	0.83 (0.54; 1.29)		213	1.05 (0.8; 1.36)	
Haematocrit (L/L)	T1	4879	293	1 (ref)	0.13	53	1 (ref)	0.05	185	1 (ref)	0.93
	T2	4646	311	1.02 (0.87; 1.20)		56	1.06 (0.73; 1.54)		183	0.93 (0.76; 1.15)	
	T3	4837	388	1.13 (0.96; 1.32)		87	1.37 (0.96; 1.95)		221	0.99 (0.81; 1.22)	
MCV (fL) [c]	T1	4769	274	1 (ref)	0.07	44	1 (ref)	**0.05**	174	1 (ref)	0.63
	T2	4797	336	1.13 (0.96; 1.32)		74	1.56 (1.08; 2.27)		194	0.98 (0.79; 1.20)	
	T3	4796	382	1.17 (0.99; 1.37)		78	1.54 (1.04; 2.26)		221	1.05 (0.85; 1.30)	
RDW (%) [d]	T1	4409	234	1 (ref)	**0.05**	51	1 (ref)	0.63	136	1 (ref)	0.27
	T2	5536	368	1.02 (0.87; 1.21)		72	0.93 (0.65; 1.34)		220	1.06 (0.85; 1.32)	
	T3	4417	390	1.17 (0.98; 1.38)		73	1.09 (0.75; 1.57)		233	1.13 (0.90; 1.42)	
WBC											
WBC (10^9 cells/L) [e]	T1	4740	247	1 (ref)	**<.0001**	41	1 (ref)	**0.02**	154	1 (ref)	**0.01**
	T2	4779	290	1.05 (0.88; 1.25)		70	1.61 (1.09; 2.36)		167	0.92 (0.74; 1.16)	
	T3	4843	455	1.45 (1.22; 1.71)		85	1.63 (1.09; 2.44)		268	1.28 (1.03; 1.59)	
Lymphocytes (109cells/L)	T1	4910	283	1 (ref)	**0.004**	60	1 (ref)	0.16	157	1 (ref)	**0.04**
	T2	4924	310	1.04 (0.89; 1.23)		58	1.00 (0.7; 1.44)		193	1.14 (0.92; 1.42)	
	T3	4528	399	1.26 (1.07; 1.48)		78	1.27 (0.89; 1.82)		239	1.26 (1.01; 1.57)	
Monocyte (109cells/L)	T1	4586	274	1 (ref)	**0.001**	54	1 (ref)	**0.03**	159	1 (ref)	0.06
	T2	4537	298	1.03 (0.87; 1.21)		54	0.99 (0.68; 1.43)		188	1.03 (0.83; 1.28)	
	T3	5239	420	1.25 (1.07; 1.47)		88	1.28 (0.91; 1.81)		242	1.18 (0.96; 1.46)	
Neutrophils (109cells/L)	T1	4626	235	1 (ref)	**0.0003**	41	1 (ref)	**0.03**	153	1 (ref)	0.10
	T2	4982	339	1.16 (0.98; 1.37)		70	1.41 (0.96; 2.07)		194	1.01 (0.81; 1.26)	
	T3	4754	418	1.36 (1.15; 1.62)		85	1.60 (1.08; 2.36)		242	1.18 (0.95; 1.47)	

Platelet

Platelet (10^{9}cells/L)	T1	4769	332	1 (ref)	0.30	63	1 (ref)	0.21	194	1 (ref)	0.62
	T2	4808	305	0.92 (0.79; 1.08)		59	0.97 (0.68; 1.38)		183	0.95 (0.77; 1.16)	
	T3	4785	355	1.07 (0.92; 1.25)		74	1.24 (0.89; 1.73)		212	1.04 (0.85; 1.27)	
Plateletcrit (L/L)	T1	4756	303	1 (ref)	0.02	61	1 (ref)	0.17	180	1 (ref)	0.30
	T2	4789	310	1.00 (0.85; 1.17)		57	0.96 (0.67; 1.38)		190	1.03 (0.84; 1.27)	
	T3	4817	379	1.19 (1.02; 1.38)		78	1.27 (0.91; 1.77)		219	1.11 (0.90; 1.35)	
MPV (fL)	T1	5022	337	1 (ref)	0.85	71	1 (ref)	0.22	200	1 (ref)	0.83
	T2	4369	293	0.95 (0.81; 1.11)		61	0.97 (0.69; 1.36)		179	1.00 (0.82; 1.23)	
	T3	4971	362	0.98 (0.84; 1.14)		64	0.81 (0.58; 1.14)		210	0.98 (0.80; 1.20)	
PDW (%) [f]	T1	4599	290	1 (ref)	0.69	52	1 (ref)	0.47	182	1 (ref)	0.57
	T2	5017	344	0.98 (0.84; 1.15)		68	1.05 (0.73; 1.51)		205	0.93 (0.76; 1.15)	
	T3	4746	358	1.01 (0.86; 1.19)		76	1.11 (0.77; 1.61)		202	0.91 (0.73; 1.12)	

*Model adjusted for age, smoking status and intensity (7 categories), body mass index (BMI, continuous), Waist-to-hip ratio (WHR, continuous), physical activity level (Cambridge index, 4 categories), educational level (low, medium, high), alcohol intake (non drinker, occasional drinker, frequent drinker). Stratified by sex and cohort center. Age is the underlying time variable. Exit age is age at first outcome of interest or censoring.

[a] p-value for trend calculated modelling the median of each parameter in each tertile as a continuous variable

[b] Red blood cells: further adjusted for haemoglobin; [c] Mean corpuscular volume; [d] Red cell distribution width: further adjusted for haemoglobin, RBC, WBC and platelet count; [e] White blood cells; [f] Platelet distribution width: further adjusted for platelet count;

Abbreviations: CVD, cardiovascular disease; CHD, coronary heart disease

Cut-off points for tertiles:

Men: RBC 4.9, 5.2; Haematocrit 0.45, 0.47; MCV 89.7, 92.7; RDW 12, 12.4; WBC 5.7, 7.0; Lymphocyte 1.7, 2.1; Monocyte 0.5, 0.6; Neutrophils 3.1, 4.1; Platelets 212, 253; Plateletcrit 0.19, 0.23; MPV 8.6, 9.3; PDW 15.6, 15.9;

Women: RBC 4.3, 4.6; Haematocrit 0.39,0.42; MCV 89.3, 92.5; RDW 11.9, 12.4; WBC 5.7, 7.1; Lymphocyte 1.7, 2.1; Monocyte 0.4, 0.5; Neutrophils 3.3, 4.4; Platelets 233, 279; Plateletcrit 0.21, 0.25; MPV 8.7, 9.4; PDW 15.5, 15.8;

Supplemental Table 3. Multivariate (Model 1)* hazard ratios HRs (95% confidence interval) for cardiovascular disease, stroke and coronary heart disease associated with tertiles of elements of the complete blood count, in participants free of cancer at baseline n= 13,820, EPIC-NL

				CVD			Stroke			CHD	
		N total	N cases	HR (95 %CI)	P trend [a]	N cases	HR (95 %CI)	P trend	N Cases	HR (95 %CI)	P trend [a]
RBC											
RBC (10^{12} cells/L) [b]	T1	4647	309	1 (ref)	0.72	61	1 (ref)	0.74	180	1 (ref)	0.41
	T2	4580	278	0.85 (0.71; 1.01)		44	0.62 (0.41; 0.94)		168	0.96 (0.76; 1.21)	
	T3	4593	351	0.96 (0.78; 1.18)		81	0.90 (0.57; 1.42)		204	1.11 (0.85; 1.46)	
Haematocrit (L/L)	T1	4671	268	1 (ref)	**0.04**	47	1 (ref)	**0.01**	168	1 (ref)	0.65
	T2	4540	305	1.08 (0.92; 1.28)		54	1.11 (0.75; 1.64)		176	0.96 (0.78; 1.20)	
	T3	4609	365	**1.19 (1.01; 1.40)**		85	**1.59 (1.1; 2.3)**		208	1.05 (0.85; 1.30)	
MCV (fL) [c]	T1	4602	259	1 (ref)	0.07	43	1 (ref)	0.06	163	1 (ref)	0.60
	T2	4623	320	1.14 (0.96; 1.34)		69	1.51 (1.03; 2.22)		184	0.99 (0.80; 1.23)	
	T3	4595	359	1.17 (0.99; 1.39)		74	1.47 (0.99; 2.18)		205	1.06 (0.85; 1.32)	
RDW (%) [d]	T1	4268	224	1 (ref)	0.09	49	1 (ref)	0.62	131	1 (ref)	0.40
	T2	4797	313	1.03 (0.86; 1.22)		60	0.93 (0.64; 1.36)		186	1.05 (0.83; 1.32)	
	T3	4755	401	1.15 (0.97; 1.36)		77	1.07 (0.74; 1.56)		235	1.10 (0.88; 1.39)	
WBC											
WBC (10^9 cells/L) [e]	T1	4530	233	1 (ref)	**<.0001**	39	1 (ref)	**0.02**	146	1 (ref)	**0.02**
	T2	4667	281	1.06 (0.89; 1.26)		67	1.58 (1.06; 2.35)		159	0.91 (0.72; 1.15)	
	T3	4623	424	**1.45 (1.21; 1.72)**		80	**1.69 (1.11; 2.55)**		247	**1.27 (1.01; 1.59)**	
Lymphocytes count	T1	4685	267	1 (ref)	**0.01**	58	1 (ref)	0.24	145	1 (ref)	**0.04**
	T2	4755	293	1.03 (0.87; 1.22)		55	0.96 (0.66; 1.40)		182	1.15 (0.92; 1.44)	
	T3	4380	378	**1.25 (1.06; 1.48)**		73	1.23 (0.85; 1.79)		225	**1.28 (1.02; 1.60)**	
Monocyte count	T1	4399	261	1 (ref)	**0.001**	54	1 (ref)	0.08	150	1 (ref)	0.06
	T2	4378	284	1.02 (0.86; 1.21)		51	0.96 (0.65; 1.42)		177	1.02 (0.82; 1.28)	
	T3	5043	393	**1.24 (1.05; 1.45)**		81	1.25 (0.87; 1.79)		225	1.18 (0.95; 1.47)	
Neutrophils count	T1	4430	221	1 (ref)	**0.001**	39	1 (ref)	**0.03**	144	1 (ref)	0.11
	T2	4791	321	1.17 (0.98; 1.39)		66	1.39 (0.93; 2.07)		181	1.01 (0.81; 1.26)	
	T3	4599	396	**1.37 (1.15; 1.63)**		81	**1.62 (1.08; 2.42)**		227	1.18 (0.94; 1.48)	

Platelet

		N	cases	HR	p-trend	cases	HR	p-trend	cases	HR	p-trend
Platelet (10^{9}cells/L)	T1	4578	310	1 (ref)	0.24	59	1 (ref)	0.23	179	1 (ref)	0.46
	T2	4618	290	0.95 (0.81; 1.11)		57	1.01 (0.7; 1.45)		171	0.96 (0.78; 1.19)	
	T3	4624	338	1.09 (0.93; 1.27)		70	1.26 (0.89; 1.78)		202	1.07 (0.87; 1.31)	
Plateletcrit (L/L)	T1	4634	289	1 (ref)	**0.02**	58	1 (ref)	0.20	168	1 (ref)	0.16
	T2	4608	293	1.01 (0.86; 1.19)		56	0.99 (0.68; 1.43)		176	1.03 (0.83; 1.28)	
	T3	4578	356	**1.20 (1.02; 1.40)**		72	1.26 (0.89; 1.79)		208	1.15 (0.93; 1.42)	
MPV (fL)	T1	4825	320	1 (ref)	0.90	66	1 (ref)	0.43	189	1 (ref)	0.84
	T2	4188	272	0.94 (0.80; 1.10)		56	0.92 (0.65; 1.32)		163	0.97 (0.78; 1.20)	
	T3	4807	346	0.98 (0.84; 1.15)		64	0.87 (0.61; 1.23)		200	0.98 (0.80; 1.20)	
PDW (%) [f]	T1	4460	276	1 (ref)	0.62	48	1 (ref)	0.26	174	1 (ref)	0.56
	T2	4821	323	0.98 (0.83; 1.15)		64	1.08 (0.74; 1.57)		188	0.90 (0.73; 1.11)	
	T3	4539	339	1.02 (0.86; 1.20)		74	1.22 (0.84; 1.79)		190	0.90 (0.72; 1.12)	

*Model adjusted for age, smoking status and intensity (7 categories), body mass index (BMI, continuous), Waist-to-hip ratio (WHR, continuous), physical activity level (Cambridge index, 4 categories), educational level (low, medium, high), alcohol intake (non drinker, occasional drinker, frequent drinker). Stratified by sex and cohort center. Age is the underlying time variable. Exit age is age at first outcome of interest or censoring.

[a] p-value for trend calculated modelling the median of each parameter in each tertile as a continuous variable

[b] Red blood cells: further adjusted for haemoglobin; [c] Mean corpuscular volume; [d] Red cell distribution width: further adjusted for haemoglobin, RBC, WBC and platelet count; [e] White blood cells; [f] Platelet distribution width: further adjusted for platelet count;

Abbreviations: CVD, cardiovascular disease; CHD, coronary heart disease

Supplemental Table 4. Multivariate (Model 2 = Model 1 further adjusted for CVD risk factors)* hazard ratios HRs (95% confidence interval) for cardiovascular disease, stroke and coronary heart disease associated with tertiles of elements of the complete blood count, in participants free of cancer at baseline n= 13,820, EPIC-NL

				CVD			Stroke			CHD	
		N total	N cases	HR (95 %CI)	P trend [a]	N cases	HR (95 %CI)	P trend	N Cases	HR (95 %CI)	P trend [a]
RBC											
	T1	4647	309	1 (ref)	0.29	61	1 (ref)	0.52	180	1 (ref)	0.82
RBC (10^{12} cells/L) [b]	T2	4580	278	0.84 (0.70; 1.00)		44	0.62 (0.41; 0.94)		168	0.93 (0.74; 1.18)	
	T3	4593	351	0.89 (0.73; 1.09)		81	0.84 (0.54; 1.33)		204	1.03 (0.78; 1.35)	
	T1	4671	268	1 (ref)	0.50	43	1 (ref)	0.10	163		0.64
Haematocrit (L/L)	T2	4540	305	1.02 (0.87; 1.21)		69	1.01 (0.68; 1.50)		184	0.92 (0.74; 1.14)	
	T3	4609	365	1.06 (0.90; 1.25)		74	1.33 (0.92; 1.94)		205	0.95 (0.77; 1.18)	
	T1	4602	259	1 (ref)	**0.01**	47	1 (ref)	**0.02**	168	1 (ref)	0.32
MCV (fL) [c]	T2	4623	320	1.17 (0.99; 1.38)		54	1.59 (1.08; 2.34)		176	1.02 (0.82; 1.27)	
	T3	4595	359	**1.24 (1.04; 1.47)**		85	**1.59 (1.06; 2.38)**		208	1.11 (0.89; 1.39)	
	T1	4268	224	1 (ref)	**0.02**	49	1 (ref)	0.52	131		0.23
RDW (%) [d]	T2	4797	313	1.06 (0.89; 1.26)		60	0.97 (0.67; 1.40)		186	1.09 (0.87; 1.37)	
	T3	4755	401	**1.22 (1.02; 1.45)**		77	1.12 (0.76; 1.64)		235	1.16 (0.91; 1.46)	
WBC											
	T1	4530	233	1 (ref)	**0.001**	39	1 (ref)	0.12	146	1 (ref)	0.11
WBC (10^9 cells/L) [e]	T2	4667	281	1.01 (0.85; 1.21)		67	1.49 (1.00; 2.23)		159	0.88 (0.70; 1.10)	
	T3	4623	424	**1.31 (1.10; 1.56)**		80	1.47 (0.97; 2.24)		247	1.15 (0.92; 1.45)	
	T1	4685	267	1 (ref)	**0.03**	58	1 (ref)	0.37	145	1 (ref)	0.10
Lymphocytes count	T2	4755	293	1.02 (0.86; 1.21)		55	0.94 (0.65; 1.37)		182	1.14 (0.91; 1.42)	
	T3	4380	378	**1.19 (1.00; 1.41)**		73	1.16 (0.80; 1.69)		225	1.21 (0.97; 1.52)	
	T1	4399	261	1 (ref)	**0.008**	54	1 (ref)	0.19	150	1 (ref)	0.12
Monocyte count	T2	4378	284	1.01 (0.86; 1.20)		51	0.95 (0.65; 1.40)		177	1.02 (0.82; 1.27)	
	T3	5043	393	**1.19 (1.01; 1.39)**		81	1.16 (0.81; 1.65)		225	1.14 (0.92; 1.42)	
	T1	4430	221	1 (ref)	**0.02**	39	1 (ref)	0.17	144	1 (ref)	0.43
Neutrophils count	T2	4791	321	1.14 (0.96; 1.36)		66	1.34 (0.90; 2.00)		181	0.99 (0.79; 1.24)	
	T3	4599	396	**1.24 (1.04; 1.48)**		81	1.39 (0.93; 2.09)		227	1.08 (0.86; 1.36)	

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Platelet											
Platelet (10^9cells/L)	T1	4578	310	1 (ref)	0.38	59	1 (ref)	0.32	179	1 (ref)	0.57
	T2	4618	290	0.94 (0.80; 1.10)		57	0.99 (0.68; 1.42)		171	0.96 (0.77; 1.18)	
	T3	4624	338	1.07 (0.91; 1.25)		70	1.22 (0.86; 1.73)		202	1.05 (0.85; 1.29)	
Plateletcrit (L/L)	T1	4634	289	1 (ref)	**0.05**	58	1 (ref)	0.30	168	1 (ref)	0.32
	T2	4608	293	1.00 (0.85; 1.18)		56	0.98 (0.68; 1.43)		176	1.04 (0.84; 1.29)	
	T3	4578	356	1.16 (0.99; 1.36)		72	1.21 (0.86; 1.71)		208	1.11 (0.90; 1.36)	
MPV (fL)	T1	4825	320	1 (ref)	0.63	66	1 (ref)	0.57	189	1 (ref)	0.20
	T2	4188	272	0.93 (0.79; 1.09)		56	1.02 (0.70; 1.49)		163	0.86 (0.70; 1.06)	
	T3	4807	346	0.93 (0.79; 1.10)		64	1.10 (0.75; 1.61)		200	0.83 (0.66; 1.03)	
PDW (%) [f]	T1	4460	276	1 (ref)	0.80	48	1 (ref)	0.38	174	1 (ref)	0.74
	T2	4821	323	0.94 (0.80; 1.10)		64	0.93 (0.65; 1.33)		188	0.97 (0.78; 1.20)	
	T3	4539	339	0.97 (0.84; 1.13)		74	0.85 (0.60; 1.21)		190	0.96 (0.79; 1.18)	

*Model adjusted for age, smoking status and intensity (7 categories), body mass index (BMI, continuous), Waist-to-hip ratio (WHR, continuous), physical activity level (Cambridge index, 4 categories), educational level (low, medium, high), alcohol intake (non drinker, occasional drinker, frequent drinker), systolic blood pressure, HDL cholesterol and diabetes. Stratified by sex and cohort center. Age is the underlying time variable. Exit age is age at first outcome of interest or censoring.

[a] p-value for trend calculated modelling the median of each parameter in each tertile as a continuous variable

[b] Red blood cells: further adjusted for haemoglobin; [c] Mean corpuscular volume; [d] Red cell distribution width: further adjusted for haemoglobin, RBC, WBC and platelet count; [e] White blood cells; [f] Platelet distribution width: further adjusted for platelet count;

Abbreviations: CVD, cardiovascular disease; CHD, coronary heart disease

Supplemental Table 5. Multivariate * hazard ratios HRs (95% confidence interval) for cardiovascular disease, stroke and coronary heart disease associated with tertiles of white blood cell subtypes adjusted for total WBC count, n= 14,362, EPIC-NL

				CVD			Stroke			CHD	
		N total	N cases	HR (95 %CI)	P trend[a]	N cases	HR (95 %CI)	P trend[a]	N Cases	HR (95 %CI)	P trend[a]
		14362	**992**			**196**			**589**		
Lymphocytes (10^9cells/L)	T1	4910	283	1 (ref)	0.52	60	1 (ref)	0.79	157	1 (ref)	0.41
	T2	4924	310	0.98 (0.83;1.16)		58	0.92 (0.63; 1.33)		193	1.10 (0.88; 1.37)	
	T3	4528	399	1.05 (0.88;1.26)		78	1.04 (0.70; 1.57)		239	1.11 (0.87; 1.42)	
Monocyte (10^9cells/L)	T1	4586	274	1 (ref)	0.09	54	1 (ref)	0.26	159	1 (ref)	0.31
	T2	4537	298	1.01 (0.85;1.19)		54	1.00 (0.68; 1.46)		188	1.01 (0.82; 1.26)	
	T3	5239	420	1.11 (0.94;1.31)		88	1.15 (0.80; 1.66)		242	1.09 (0.87; 1.35)	
Neutrophils (10^9cells/L)	T1	4626	235	1 (ref)	0.63	41	1 (ref)	0.92	153	1 (ref)	0.45
	T2	4982	339	1.03 (0.86;1.23)		70	1.21 (0.80; 1.82)		194	0.92 (0.73; 1.16)	
	T3	4754	418	0.96 (0.76;1.22)		85	1.04 (0.61; 1.79)		242	0.88 (0.65; 1.20)	

*Model adjusted for age, smoking status and intensity (7 categories), body mass index (BMI, continuous), Waist-to-hip ratio (WHR, continuous), physical activity level (Cambridge index, 4 categories), educational level (low, medium, high), alcohol intake (non drinker, occasional drinker, frequent drinker), systolic blood pressure, HDL cholesterol and diabetes. Stratified by sex and cohort center. Age is the underlying time variable. Exit age is age at first outcome of interest or censoring.

Supplemental Table 6. Multivariate (Model 1)* hazard ratios HRs (95% confidence interval) for cardiovascular disease, stroke and coronary heart disease associated with tertiles of elements of the complete blood count, after exclusion of first 2 years of follow-up n= 14,182, EPIC-NL

			CVD			Stroke			CHD	
	N total	N cases	HR (95 %CI)	P trend [a]	N cases	HR (95 %CI)	P trend	N Cases	HR (95 %CI)	P trend [a]
RBC										
RBC (10^{12} cells/L) [b]	4689	286	1 (ref)	0.38	56	1 (ref)	0.40	162	**1 (ref)**	0.61
	4809	267	0.83 (0.69; 1.00)		41	0.57 (0.37; 0.88)		162	0.98 (0.77; 1.25)	
	4684	323	0.90 (0.73; 1.11)		73	0.78 (0.48; 1.26)		183	1.07 (0.80; 1.42)	
Haematocrit (L/L)	4809	250	1 (ref)	0.06	45	1 (ref)	**0.02**	149	1 (ref)	0.48
	4657	286	1.09 (0.92; 1.29)		48	1.04 (0.69; 1.56)		166	1.02 (0.82; 1.28)	
	4716	340	**1.18 (1; 1.4)**		77	**1.53 (1.05; 2.24)**		192	1.09 (0.87; 1.36)	
MCV (fL) [c]	4721	246	1 (ref)	0.10	40	1 (ref)	**0.04**	152	1 (ref)	0.79
	4734	295	1.11 (0.94; 1.32)		60	1.44 (0.96; 2.15)		167	0.98 (0.79; 1.23)	
	4727	335	1.16 (0.97; 1.38)		70	**1.56 (1.03; 2.35)**		188	1.03 (0.82; 1.29)	
RDW (%) [d]	4365	213	1 (ref)	0.07	46	1 (ref)	0.65	123	1 (ref)	0.21
	4924	285	0.98 (0.82; 1.17)		54	0.90 (0.60; 1.33)		164	0.98 (0.77; 1.25)	
	4893	378	1.15 (0.97; 1.37)		70	1.07 (0.72; 1.57)		220	1.14 (0.89; 1.44)	
WBC										
WBC (10^9cells/L) [e]	4693	226	1 (ref)	**0.0002**	36	1 (ref)	0.09	139	1 (ref)	0.08
	4732	260	1.04 (0.87; 1.25)		66	1.73 (1.15; 2.62)		144	0.89 (0.70; 1.13)	
	4757	390	**1.38 (1.15; 1.65)**		68	1.59 (1.02; 2.45)		224	1.19 (0.94; 1.51)	
Lymphocytes (109cells/L)	4869	258	1 (ref)	**0.02**	53	1 (ref)	0.32	140	1 (ref)	0.10
	4854	271	1.01 (0.85; 1.20)		54	1.06 (0.72; 1.55)		161	1.06 (0.84; 1.34)	
	4459	347	**1.23 (1.03; 1.46)**		63	1.22 (0.82; 1.81)		206	1.21 (0.96; 1.53)	
Monocyte (109cells/L)	4538	250	1 (ref)	**0.001**	48	1 (ref)	**0.02**	144	1 (ref)	0.13
	4473	254	0.97 (0.81; 1.15)		45	0.97 (0.64; 1.47)		154	0.94 (0.74; 1.19)	
	5171	372	**1.24 (1.05; 1.47)**		77	1.41 (0.97; 2.05)		209	1.14 (0.91; 1.42)	
Neutrophils (109cells/L)	4575	212	1 (ref)	**0.003**	37	1 (ref)	0.09	135	1 (ref)	0.25
	4930	303	1.16 (0.97; 1.39)		63	1.41 (0.94; 2.12)		169	1.03 (0.82; 1.30)	
	4677	361	**1.33 (1.11; 1.59)**		70	1.52 (0.99; 2.31)		203	1.14 (0.90; 1.45)	

Platelet

Parameter	N	Cases	HR (95% CI)	p	Cases	HR (95% CI)	p	Cases	HR (95% CI)	p
Platelet (10⁹cells/L)	4709	292	1 (ref)	0.23	49	1 (ref)	**0.03**	167	1 (ref)	0.83
	4751	267	0.92 (0.78; 1.08)		51	1.08 (0.73; 1.60)		159	0.96 (0.77; 1.19)	
	4722	317	1.09 (0.93; 1.28)		70	**1.52 (1.05; 2.20)**		181	1.01 (0.81; 1.26)	
Plateletcrit (L/L)	4707	269	1 (ref)	**0.03**	49	1 (ref)	0.07	157	1 (ref)	0.45
	4720	270	0.97 (0.82; 1.15)		51	1.04 (0.70; 1.55)		160	0.98 (0.79; 1.23)	
	4755	337	**1.18 (1.00; 1.38)**		70	1.41 (0.97; 2.03)		190	1.08 (0.87; 1.34)	
MPV (fL)	4951	292	1 (ref)	0.83	58	1 (ref)	0.29	171	1 (ref)	0.89
	4316	264	0.98 (0.83; 1.16)		58	1.07 (0.75; 1.55)		153	0.99 (0.79; 1.24)	
	4915	320	0.98 (0.84; 1.15)		54	0.83 (0.57; 1.20)		183	0.98 (0.80; 1.22)	
PDW (%) [f]	4539	254	1 (ref)	0.66	46	1 (ref)	0.51	157	1 (ref)	0.62
	4958	308	1.01 (0.85; 1.19)		61	1.08 (0.73; 1.59)		176	0.94 (0.75; 1.17)	
	4685	314	1.02 (0.86; 1.21)		63	1.14 (0.77; 1.70)		174	0.91 (0.72; 1.14)	

*Model adjusted for age, smoking status and intensity (7 categories), body mass index (BMI, continuous), Waist-to-hip ratio (WHR, continuous), physical activity level (Cambridge index, 4 categories), educational level (low, medium, high), alcohol intake (non drinker, occasional drinker, frequent drinker). Stratified by sex and cohort center. Age is the underlying time variable. Exit age is age at first outcome of interest or censoring.

[a] p-value for trend calculated modelling the median of each parameter in each tertile as a continuous variable

[b] Red blood cells: further adjusted for haemoglobin; [c] Mean corpuscular volume; [d] Red cell distribution width: further adjusted for haemoglobin, RBC, WBC and platelet count; [e] White blood cells; [f] Platelet distribution width: further adjusted for platelet count;

Abbreviations: CVD, cardiovascular disease; CHD, coronary heart disease

Supplemental Table 7. Multivariate (Model 2)* hazard ratios HRs (95% confidence interval) for cardiovascular disease, stroke and coronary heart disease associated with tertiles of elements of the complete blood count, after exclusion of first 2 years of follow-up n= 14,182, EPIC-NL

			CVD			Stroke			CHD	
	N total	N cases	HR (95 %CI)	P trend [a]	N cases	HR (95 %CI)	P trend	N Cases	HR (95 %CI)	P trend[a]
RBC										
RBC (10^{12} cells/L) [b]	4689	286	1 (ref)	0.12	56	1 (ref)	0.24	162	1 (ref)	0.96
	4809	267	0.82 (0.68; 0.98)		41	0.57 (0.37; 0.88)		162	0.95 (0.75; 1.21)	
	4684	323	0.84 (0.68; 1.04)		73	0.72 (0.45; 1.17)		183	0.98 (0.74; 1.31)	
Haematocrit (L/L)	4809	250	1 (ref)	0.52	45	1 (ref)	0.16	149	1 (ref)	0.91
	4657	286	1.04 (0.87; 1.23)		48	0.95 (0.63; 1.44)		166	0.98 (0.78; 1.23)	
	4716	340	1.06 (0.89; 1.26)		77	1.29 (0.88; 1.89)		192	0.99 (0.79; 1.24)	
MCV (fL) [c]	4721	246	1 (ref)	**0.02**	40	1 (ref)	**0.01**	152	1 (ref)	0.47
	4734	295	1.14 (0.96; 1.35)		60	**1.52 (1.01; 2.27)**		167	1.01 (0.80; 1.26)	
	4727	335	**1.23 (1.03; 1.46)**		70	**1.71 (1.13; 2.60)**		188	1.08 (0.86; 1.37)	
RDW (%) [d]	4365	213	1 (ref)	**0.01**	46	1 (ref)	0.62	123	1 (ref)	0.10
	4924	285	1.01 (0.85; 1.20)		54	0.95 (0.65; 1.40)		164	1.02 (0.81; 1.29)	
	4893	378	**1.23 (1.03; 1.47)**		70	1.10 (0.74; 1.63)		220	1.20 (0.94; 1.53)	
WBC										
WBC (10^9 cells/L) [e]	4693	226	1 (ref)	**0.01**	36	1 (ref)	0.31	139	1 (ref)	0.33
	4732	260	1.00 (0.83; 1.19)		66	**1.62 (1.08; 2.45)**		144	0.85 (0.67; 1.08)	
	4757	390	**1.25 (1.04; 1.49)**		68	1.37 (0.88; 2.13)		224	1.08 (0.86; 1.38)	
Lymphocytes (109cells/L)	4869	258	1 (ref)	0.07	53	1 (ref)	0.48	140	1 (ref)	0.23
	4854	271	0.99 (0.84; 1.18)		54	1.03 (0.70; 1.52)		161	1.05 (0.83; 1.32)	
	4459	347	1.16 (0.98; 1.38)		63	1.15 (0.77; 1.70)		206	1.15 (0.91; 1.45)	
Monocyte (109cells/L)	4538	250	1 (ref)	**0.01**	48	1 (ref)	**0.04**	144	1 (ref)	0.20
	4473	254	0.96 (0.81; 1.15)		45	0.96 (0.64; 1.45)		154	0.94 (0.74; 1.18)	
	5171	372	**1.20 (1.01; 1.41)**		77	1.31 (0.90; 1.91)		209	1.11 (0.88; 1.38)	
Neutrophils (109cells/L)	4575	212	1 (ref)	**0.05**	37	1 (ref)	0.37	135	1 (ref)	0.67
	4930	303	1.13 (0.95; 1.35)		63	1.35 (0.90; 2.03)		169	1.00 (0.80; 1.27)	
	4677	361	**1.21 (1.01; 1.45)**		70	1.30 (0.85; 1.98)		203	1.05 (0.83; 1.34)	

Platelet

Platelet (10^9cells/L)	4709	292	1 (ref)	0.34	49	1 (ref)	**0.04**	167	1 (ref)	0.90
	4751	267	0.91 (0.77; 1.08)		51	1.07 (0.72; 1.58)		159	0.97 (0.78; 1.21)	
	4722	317	1.07 (0.91; 1.26)		70	**1.48 (1.02; 2.14)**		181	1.00 (0.81; 1.25)	
Plateletcrit (L/L)	4707	269	1 (ref)	0.09	49	1 (ref)	0.13	157	1 (ref)	0.62
	4720	270	0.97 (0.82; 1.15)		51	1.06 (0.71; 1.57)		160	0.98 (0.79; 1.23)	
	4755	337	1.14 (0.97; 1.34)		70	1.34 (0.92; 1.93)		190	1.05 (0.84; 1.30)	
MPV (fL)	4951	292	1 (ref)	0.75	58	1 (ref)	0.25	171	1 (ref)	0.80
	4316	264	0.98 (0.83; 1.15)		58	1.08 (0.75; 1.56)		153	0.98 (0.79; 1.23)	
	4915	320	0.97 (0.83; 1.14)		54	0.82 (0.56; 1.19)		183	0.97 (0.79; 1.20)	
PDW (%) [f]	4539	254	1 (ref)	0.62	46	1 (ref)	0.93	157	1 (ref)	0.25
	4958	308	0.96 (0.82; 1.14)		61	1.02 (0.69; 1.51)		176	0.90 (0.72; 1.12)	
	4685	314	0.94 (0.79; 1.12)		63	1.02 (0.68; 1.52)		174	0.84 (0.67; 1.06)	

*Model adjusted for age, smoking status and intensity (7 categories), body mass index (BMI, continuous), Waist-to-hip ratio (WHR, continuous), physical activity level (Cambridge index, 4 categories), educational level (low, medium, high), alcohol intake (non drinker, occasional drinker, frequent drinker), systolic blood pressure, HDL cholesterol, diabetes. Stratified by sex and cohort center. Age is the underlying time variable. Exit age is age at first outcome of interest or censoring.

[a] p-value for trend calculated modelling the median of each parameter in each tertile as a continuous variable

[b] Red blood cells: further adjusted for haemoglobin; [c] Mean corpuscular volume; [d] Red cell distribution width: further adjusted for haemoglobin, RBC, WBC and platelet count; [e] White blood cells; [f] Platelet distribution width: further adjusted for platelet count;

Abbreviations: CVD, cardiovascular disease; CHD, coronary heart disease

Supplemental Table 8. Multivariate (Model 2)* hazard ratios HRs (95% confidence interval) for cardiovascular disease, stroke and coronary heart disease associated with cohort- (and sex-) specific tertiles of elements of the complete blood count, n= 14,182, EPIC-NL

			CVD			Stroke			CHD	
	N total	N cases	HR (95 %CI)	P trend a	N cases	HR (95 %CI)	P trend	N Cases	HR (95 %CI)	P trend a
RBC										
	4772	310	1 (ref)	0.6225	58	1 (ref)	0.5846	186	1 (ref)	0.9509
RBC (10^{12} cells/L) [b]	4826	312	0.87 (0.74; 1.04)		55	0.62 (0.41; 0.92)		186	0.92 (0.74; 1.16)	
	4764	370	0.88 (0.72; 1.07)		83	0.81 (0.52; 1.26)		217	0.98 (0.75; 1.27)	
	4824	281	1 (ref)	0.0496	50	1 (ref)	0.329	176	1 (ref)	0.5725
Haematocrit (L/L)	4743	307	0.97 (0.82; 1.14)		57	0.94 (0.64; 1.37)		185	0.92 (0.75; 1.14)	
	4795	404	1.04 (0.88; 1.21)		89	1.17 (0.82; 1.67)		228	0.94 (0.76; 1.16)	
	4808	276	1 (ref)	0.0672	45	1 (ref)	0.0211	175	1 (ref)	0.3315
MCV (fL) [c]	4795	334	1.15 (0.98; 1.35)		73	1.66 (1.14; 2.42)		193	1 (0.81; 1.23)	
	4759	382	1.24 (1.05; 1.46)		78	1.62 (1.09; 2.42)		221	1.11 (0.9; 1.38)	
	4775	258	1 (ref)	0.0315	59	1 (ref)	0.6867	145	1 (ref)	0.0591
RDW (%) [d]	4937	329	1.05 (0.89; 1.24)		62	0.96 (0.67; 1.38)		201	1.14 (0.91; 1.42)	
	4650	405	1.23 (1.04; 1.45)		75	1.1 (0.76; 1.59)		243	1.24 (0.99; 1.55)	
WBC										
	4775	237	1 (ref)	<.0001	36	1 (ref)	0.1016	151	1 (ref)	0.1348
WBC (10^9 cells/L) [e]	4734	297	1.04 (0.88; 1.24)		73	1.49 (1.01; 2.21)		167	0.89 (0.71; 1.11)	
	4853	458	1.28 (1.08; 1.52)		87	1.47 (0.98; 2.21)		271	1.13 (0.9; 1.41)	
	4810	269	1 (ref)	0.0208	58	1 (ref)	0.647	151	1 (ref)	0.2169
Lymphocytes (109cells/L)	5037	321	1.02 (0.86; 1.2)		62	0.97 (0.67; 1.4)		197	1.1 (0.89; 1.37)	
	4515	402	1.15 (0.97; 1.35)		76	1.22 (0.85; 1.75)		241	1.15 (0.93; 1.44)	
	4586	274	1 (ref)	0.0001	54	1 (ref)	0.0394	159	1 (ref)	0.0552
Monocyte (109cells/L)	5640	341	1.02 (0.86; 1.19)		62	1.01 (0.69; 1.48)		213	1.01 (0.82; 1.25)	
	4136	377	1.23 (1.05; 1.44)		80	1.26 (0.89; 1.79)		217	1.17 (0.94; 1.45)	
	4781	243	1 (ref)	0.0006	44	1 (ref)	0.3129	157	1 (ref)	0.3552
Neutrophils (109cells/L)	4793	324	1.12 (0.94; 1.32)		67	1.35 (0.91; 1.98)		186	0.98 (0.79; 1.22)	
	4788	425	1.22 (1.03; 1.44)		85	1.39 (0.93; 2.06)		246	1.08 (0.86; 1.34)	

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Platelet

	4779	327	1 (ref)	0.3811	60	1 (ref)	0.2699	191	1 (ref)	0.7178
Platelet (10^{9}cells/L)	4781	309	0.93 (0.8; 1.09)		61	0.95 (0.67; 1.36)		185	0.97 (0.79; 1.19)	
	4802	356	1.04 (0.89; 1.21)		75	1.21 (0.87; 1.71)		213	1.03 (0.84; 1.26)	
	4798	301	1 (ref)	0.0099	61	1 (ref)	0.2225	179	1 (ref)	0.2733
Plateletcrit (L/L)	4774	307	1 (0.85; 1.17)		55	0.96 (0.67; 1.38)		187	1.02 (0.83; 1.26)	
	4790	384	1.17 (1.01; 1.36)		80	1.21 (0.86; 1.69)		223	1.11 (0.9; 1.36)	
	4836	331	1 (ref)	0.6803	68	1 (ref)	0.1696	198	1 (ref)	0.5319
MPV (fL)	4724	317	0.95 (0.82; 1.11)		69	0.93 (0.66; 1.31)		194	0.99 (0.81; 1.22)	
	4802	344	0.96 (0.82; 1.12)		59	0.8 (0.57; 1.12)		197	0.94 (0.76; 1.15)	
	4652	309	1 (ref)	0.8661	53	1 (ref)	0.8145	190	1 (ref)	0.1435
PDW (%) [f]	5010	345	0.98 (0.84; 1.14)		74	0.99 (0.69; 1.43)		207	0.94 (0.76; 1.15)	
	4700	338	0.92 (0.79; 1.09)		69	1.01 (0.7; 1.47)		192	0.84 (0.68; 1.04)	

*Model adjusted for age, smoking status and intensity (7 categories), body mass index (BMI, continuous), Waist-to-hip ratio (WHR, continuous), physical activity level (Cambridge index, 4 categories), educational level (low, medium, high), alcohol intake (non drinker, occasional drinker, frequent drinker), systolic blood pressure, HDL cholesterol, diabetes. Stratified by sex and cohort center. Age is the underlying time variable. Exit age is age at first outcome of interest or censoring.

[a] p-value for trend calculated modelling the median of each parameter in each tertile as a continuous variable

[b] Red blood cells: further adjusted for haemoglobin; [c] Mean corpuscular volume; [d] Red cell distribution width: further adjusted for haemoglobin, RBC, WBC and platelet count; [e] White blood cells; [f] Platelet distribution width: further adjusted for platelet count;

Abbreviations: CVD, cardiovascular disease; CHD, coronary heart disease

Supplemental Figure 1. Meta-analysis of existing studies and the present results of the association between RDW and CVD risk

Study	Event	HR (95% CI)	% Weight	Unit
CHD				
Borne et al 2014	CHD	1.12 (0.97, 1.28)	19.63	Q4 vs Q1
Chen et al 2010	CHD	1.05 (0.65, 1.68)	1.67	Q4 vs Q1
Lassale et al 2017	CHD	1.19 (0.95, 1.49)	7.45	T3 vs T1
Skjelbakken et al 2014	CHD	1.34 (1.11, 1.60)	11.29	Q5 vs Q1
Subtotal (I-squared = 0.0%, p = 0.454)		1.19 (1.08, 1.31)	40.06	
Stroke				
Chen et al 2010	Stroke	1.20 (0.80, 1.81)	2.27	Q4 vs Q1
Lappegard et al 2016	Stroke	1.37 (1.11, 1.69)	8.55	Q5 vs Q1
Lassale et al 2017	Stroke	1.10 (0.76, 1.59)	2.77	T3 vs T1
Soderholm et al 2015	Stroke	1.31 (1.11, 1.54)	14.09	Q4 vs Q1
Subtotal (I-squared = 0.0%, p = 0.758)		1.30 (1.15, 1.46)	27.67	
Total CVD				
Arbel et al 2014; Females	Total CVD	1.26 (1.03, 1.52)	9.97	>=17% vs <13%
Arbel et al 2014; Males	Total CVD	1.08 (0.82, 1.41)	5.14	>=17% vs <13%
Chen et al 2010	Total CVD	1.14 (0.83, 1.57)	3.72	Q4 vs Q1
Lassale et al 2017	Total CVD	1.22 (1.03, 1.44)	13.45	T3 vs T1
Subtotal (I-squared = 0.0%, p = 0.811)		1.20 (1.08, 1.34)	32.28	
Overall (I-squared = 0.0%, p = 0.862)		1.22 (1.15, 1.30)	100.00	

NOTE: Weights are from random effects analysis