Philip Morris International Research & Development

APPENDIX A6.1.4.1 WBC COUNT

HEALTH EFFECTS OF SMOKING CESSATION

Short Term Health Effects

White blood cell (WBC) count

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1. BACKGROUND

It is well-established that smoking is linked to a number of diseases, particularly lung cancer, chronic obstructive pulmonary disease (COPD), and a number of forms of cardiovascular disease (CVD) [1]. It is also well-recognized that cessation of smoking reduces the risk of these diseases over time [2, 3]. For smokers who choose not to quit or who have difficulty in quitting, a possible option would be to switch to a modified risk tobacco product (MRTP). Such products may reduce the risk of smoking. This possible reduction in risk can be supported by demonstrating that one or more biological markers, or biomarkers, can be identified which return to normal levels in smokers who have switched to such products. A potential valid biomarker must meet three criteria: 1) it must be related to at least one health effect of smoking, 2) it must be related to smoking, and, as noted above, 3) it must return to levels equivalent to or close to those in a never smoker following smoking cessation. The goal of this report is to document that the biomarker white blood cell (WBC) count meets these three criteria and is thus a valid biomarker to establish the potential risk reduction for MRTPs.

White blood cells, or leukocytes, include a number of different types of cells that can be divided into two main types: granulocytes (having granules in their cytoplasm such as neutrophils, basophils, mast cells and eosinophils) and agranulocytes (characterized by the absence of cytoplasmic granules and having a one lobed nucleus and thus termed mononuclear leukocytes). Agranulocytes include monocytes and a wide range of lymphocytes (B-lymphocytes, which produce antibodies in the humoral immune response, T-lymphocytes which participate in the cell-mediated immune response, and the null group which contains natural killer cells) [4]. Most of this report will focus on total WBC count as well as neutrophil and monocyte counts. Although lymphocyte numbers are indeed reported to be consistently increased in smokers, there is often an inverse relationship between lymphocyte count and CVD as will be discussed below. Following the METHODS section, the report will first focus on the relationship of WBC count with the major smoking-related diseases. The vast majority of the published literature deals with CVD; however, there are some references dealing with both lung cancer and non-malignant respiratory disease. This will be followed by a section dealing with the association of increased WBC count in smokers. The next section will cover the effect of smoking cessation on WBC count, and finally a few articles dealing with the effect of switching to a potential MRTP will be discussed.

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2. METHODS

Three searches of the PubMed literature data base were conducted on April 2, 2015, for English language articles within the time frame of 2008 to the day the search was conducted.

Search 1: To identify articles primarily relevant to the association of WBC count and smoking and/or smoking cessation using the string: ((((((((((WBC OR PMN) AND (smokers OR smoking OR nicotine replacement OR cessation) AND ("2008"[Date - Publication]: "2015"[Date - Publication])))) AND English[Language]))) NOT HIV)) NOT eosinophil)) NOT interstitial)) NOT PAD) AND Humans[Mesh])) NOT exacerbation

Search 2: To identify articles primarily relevant to the association of WBC count and CVD using the string: (((((((((WBC OR PMN) AND ((cardiovascular disease) AND (association)) AND ("2008"[Date - Publication]: "2015"[Date - Publication])))) AND English[Language]))) NOT eosinophil) NOT HIV) NOT Exacerbation) NOT embolism) NOT PAD

Search 3: To identify articles primarily relevant to the association of WBC count to respiratory disease using the string: ((((((PMN OR WBC) AND ((respiratory disease) AND (association)) AND ("2008"[Date - Publication]: "2015"[Date - Publication])))) AND English[Language]) NOT eosinophil) NOT exacerbation) NOT embolism

Among the identified studies a set of specific criteria was applied to determine which papers should be selected for inclusion within the report.

The following inclusion criteria were applied:

1. Studies investigating the association of WBC count with CVD, lung cancer, or non-malignant respiratory disease.
2. Studies investigating the association of cigarette smoking, smoking cessation, nicotine replacement therapy (NRT), or modified risk tobacco products (MRTB) on WBC count.

The following exclusion criteria were applied:

1. Endpoint being assessed is not CVD, lung cancer, or non-malignant respiratory disease; this category includes a few studies where WBC count was not specifically correlated with smoking
2. Association of a relevant disease or smoking with markers other than generically labelled “white blood cells” or “leukocytes”, neutrophils, or monocytes
3. Population being studied is either not apparently healthy or studies that lack a control population
4. Studies involving children, infants, or neonates
5. Case studies
6. Studies on environmental tobacco smoke
7. *In vitro* or animal studies

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3. FINDINGS

The total of all three searches resulted in 716 references, 311 from Search 1, 293 from Search 2, and 112 from Search 3. Fifty-four duplicate articles were identified leaving 662 unique references. Application of the seven criteria listed above resulted in the exclusion of 239 studies from Search 1, 220 studies from Search 2, and 101 studies from Search 3 leaving a total of 102 retained articles. Table 1 presents the number of articles excluded from all three searches combined for each exclusion criterion.

Table 1. Excluded references according to exclusion criteria.

Exclusion criterion	Number of references excluded
E1. Endpoint not relevant	269
E2. Marker not relevant	88
E3. Population not apparently healthy or no control	141
E4. Children, infants or neonates	34
E5. Case studies	14
E6. Environmental tobacco smoke	4
E7. *In vitro* or animal studies	10

The four references cited in the BACKGROUND section [1-4] were added to the 102 references retained from the search resulting in a total of 106. As noted the three literature searches had a cut-off date of 2008. As a consequence, searches for each topic were conducted for relevant literature prior to 2008. The search methodology and the results will be described in each section. These literature searches resulted in the inclusion of 106 additional references resulting in the total number of 212. The numbers of references added by section were 69 for WBC count and smoking, 15 for CVD, 4 for lung cancer, 14 for COPD, 2 for smoking cessation, and 2 for WBC count and potential MRTPs.

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4. BIOMARKER-DISEASE LINK

4.1 Cardiovascular disease

A large number of epidemiological studies have investigated the association of WBC count with a variety of CVD endpoints. These studies fall into two broad groups; namely, studies where the subjects are apparently healthy and studies where the subjects have already been diagnosed with one or more CVD syndromes. The goal of the latter type of study is to investigate the association of various types of sequela, frequently mortality, with WBC count. PMI's purpose in establishing WBC count as a meaningful biomarker for the short-term health effects of smoking is to evaluate potential MRTPs. Such an evaluation is highly likely to be restricted to apparently healthy individuals. As a consequence, only studies of the first type are considered in this report.

Studies Conducted Prior to 2008

A thorough literature search was not conducted for studies prior to 2008 related to the association of WBC count with various CVD endpoints. A meta-analysis had been published by Danesh et al. in 1998 [5] covering relevant studies published before that date. This analysis pooled 19 prospective epidemiological studies that reported results for the association of WBC count with coronary heart disease (CHD) (also referred to as coronary artery disease (CAD) and ischemic heart disease (IHD)). CHD includes stable angina, unstable angina, myocardial infarction (MI) and sudden coronary death [6]. This report will focus on the seven largest studies (N>400), since all of these studies adjusted for smoking, the level of heterogeneity was quite low (χ^2_6 = 6.1), and only one of these studies involved subjects with pre-existing vascular disease (N = 747). The total number of cases in all seven studies was 5,337, about three-quarters of the total for all nineteen studies. The pooled risk ratio (highest tertile compared to lowest tertile) was 1.4 (95% CI, 1.3-1.5) and is obviously statistically significant. This can be compared to the result for all 19 studies, which included five studies with subjects with pre-existing vascular disease (HR = 1.5; 95% CI, 1.4-1.6). The mean WBC count for the highest and lowest tertiles were 8.4×10^9/L and 5.6×10^9/L. As can be seen, this meta-analysis supports a statistically significant association between WBC count and CHD.

Two reviews were identified [7, 8] that cited a number of studies conducted between 2001 and 2007 all of which confirmed the association of WBC count with CVD endpoints. In addition, a thorough, although not necessarily exhaustive, literature search had been conducted and documented in an earlier report submitted to Philip Morris International (PMI) [9] that identified seven studies published during this same period. An additional two studies were added to this group, both of which originated from the Far East, giving a total of nine. Therefore, the total number of pre-2008 references added to the report dealing with the association of WBC count with CVD, including the reference used to define CHD, was 14. The nine relevant publications are listed in Table 2.

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Table 2. Association of WBC Count with CVD – Studies 2001-2007.

Study	Year and Country	Type of Study	Study Size	Age±SD (% Male)	End-point [a]	Type of Cell [b]	RR (95% CI)	Covariates Adjusted for [c]
1. Brown [10]	2001, USA	Longitudinal (prospective), maximum 16.8 yr follow-up	8,914	30-75 (47.5)	CHD and HD mortality	WBC	RR CHD mortality (men) = 1.3 (0.9-1.8), RR CHD mortality (women) = 1.7 (1.1-2.6), RR HD mortality (men) = 1.3 (1.0-1.8), HD mortality (women) = 1.6 (1.2-2.3) [d]	Age, sex, race, smok, total C, prior CVD, stroke, diabetes, hyp status
2. Lee [11]	2001, USA	Longitudinal (prospective), 8 yr follow-up	13,555	53.9± 5.7 (44.0)	CHD, stroke	WBC	RR CHD (Caucasians) = 1.7 (1.1-2.5) (p for trend = 0.001), RR CHD (Afr. Amer.) = 1.9 (1.2-3.1) (p for trend = 0.009), RR stroke (Caucasians) = 1.9 (1.0-3.4) (p for trend = 0.04), RR stroke (Afr. Amer.) = 1.9 (1.0-3.3) (p for trend = 0.02 [e]	Age, sex ARIC field center, family income, edu, smok, alc, phys, waist girth, HDL-C, total C, diabetes, SBP, antihyp
3. Brown [12]	2004, USA	Longitudinal (prospective), median 14.6 yr follow-up	8,459	49.1± 0.4 (SE) (47.1)	CBV disease	WBC	RR (men) = 1.5 (0.7-3.5) (p for trend = 0.109), RR (women), RR = 2.7 (1.4-5.0) (p for trend = 0.002) [e]	Age, sex, race, edu, phys, BMI, smok, hyp, total C, hematocrit, prior CVD, diabetes
4. Yarnell [13]	2004, UK	Longitudinal (prospective) ca. 10 yr follow-up	4,325	45-59 (100)	IHD events	WBC	Relative odds = 2.8 (2.1-3.8) [f]	Age, study area
5. Jee [14]	2005, Korea	Longitudinal (prospective) up to 11 yr follow-up	437,454	56.8± 8.9 (25.9)	ASCVD	WBC	Hazard ratio (HR) (smoking men) = 1.4 (1.3-1.67), HR (non-smoking men) = 2.33 (1.7-3.2), HR (smoking women) = 1.20 (1.3-1.7), = HR (non-smoking women) 1.3 (1.2-1.5) [g]	Age, age^2, obesity, total C, hyp, diabetes, alc, phys, amount of smoking for smokers only

(table continues)

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Study	Year and Country	Type of Study	Study Size	Age±SD (% Male)	End-point [a]	Type of Cell [b]	RR (95% CI)	Covariates Adjusted for [c]
6. Margolis [15]	2005, US	Longitudinal (prospective) mean 6.1 yr follow-up	66,261	63.1± 7.3 (0)	CHD death, non-fatal MI, stroke	WBC	HR (CHD death) = 2.4 (1.5-3.7), HR (non-fatal MI) = 1.4 (1.1-1.8), HR (stroke) = 1.5 (1.2-1.8) (p for trend <0.001 for all)	Age, race, diabetes, hyp, total C, BMI, alc, phys, asp, fiber, fr/veg, polyunsat/sat, hormone
7. Shankar [16]	2007, Australia	Longitudinal (prospective) 7-9 yr follow-up	2,904	65.7 (41.2)	CVD mortality	WBC	RR = 2.0 (1.4-2.9) [e]	Age, sex, edu, smok, phys, asp, alc, BMI, self-rated health, diabetes, hyp, SBP, total C:HDL ratio, trigly
8. Tamakoshi [17]	2007, Japan	Longitudinal (prospective) 10 yr follow-up	6,756	52.3± 13.6 (41.0)	CVD mortality	WBC	RR (men) = 1.2 (0.4-3.4) (p = 0.9), RR (women)= 2.7 (CI, 1.0-7.5) (p = 0.08) [g]	Age, sex, BMI, smok, alc, phys, DBP, total C, HDL-C, hemoglobin A1c
9. Zakai [18]	2007, US	Longitudinal (prospective) 9.2 yr median follow-up	4,446	68± 3.8 (39)	CVD events [h]	WBC	HR (model 1) = 1.2 (1.0-1.4), HR (model 2) = 1.4 (1.2-1.6)	[i]

Notes

a. CHD – coronary heart disease, HD – heart disease, CBV – cerebrovascular, IHD – ischemic heart disease, MI – myocardial infarction, ASCVD – atherosclerotic cardiovascular diseases
b. WBC – white blood cell or leukocyte, Neu – neutrophil, Mono – monocyte
c. smok – smoking status, total C – total cholesterol levels, hyp status – hypertensivee status, edu – education, alc – alcohol intake, phys – physical activity, SBP – systolic blood pressure, antihyp – use of antihypertensive medication, asp – aspirin use, fiber – dietary fiber, fr/veg – fruit/vegetable intake, polyunsat/sat – polyunsaturated/saturated fat ratio, hormone – prior use of hormone therapy, trigly – triglyceride level, DBP – diastolic blood pressure
d. RR is for third tertile of WBC count compared to first tertile
e. RR is for fourth quartile of WBC count compared to first quartile
f. Relative odds is for fifth quintile of WBC count compared to first quintile
g. HR is for sixth sextile of WBC count compared to first sextile
h. CVD events include MI, coronary artery angioplasty or bypass grafting, angina alone, stroke alone, TIA alone, and cardiovascular death

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i. Adjustment factors for model 1 were age, sex, race, hypertension, diabetes, smoking, physical activity, BMI, total cholesterol, HDL, FVC, family history of MI, alcohol use, use of: aspirin, HMG CoA reductase inhibitors, beta blockers, or angiotensin converting enzyme inhibitors; adjustment factors for model 2 were Framingham risk factors: age, sex, race, total cholesterol, HDL, SBP, DBP, diabetes, and current smoking

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The nine studies listed in Table 2 are all prospective cohort studies and all of them relate to WBCs. Five of the studies were conducted in the US with one each in the UK, Korea, Australia, and Japan. These nine studies report a total of 23 estimates. There are a rather large number of endpoints; namely, CHD mortality (3 estimates), heart disease mortality (2), CHD (2), stroke (3), cerebrovascular disease (2), ischemic heart disease events (1), atherosclerotic cardiovascular diseases (4), non-fatal MI (1), CVD mortality (3), and CVD events (2). Although some of these are closely related, it would be impossible to combine these results into a meta-analysis. Of these 23 estimates, only four are not statistically significant (one (CHD mortality) from study number 1, one (CBV disease) from study number 3, and two (CVD mortality) from study number 8). Therefore, the results of these studies clearly support a statistically significant relationship between WBC count and various CVD endpoints. Lastly, it should be noted that the majority of these estimates provide relative risks that are close to the same magnitude as those of the Danesh meta-analysis discussed above [5].

Studies Conducted from 2008-2015

The three literature searches described above identified 44 publication reporting data on the association of WBC count with various CVD endpoints that met both the inclusion and the exclusion criteria. While checking the references in these publications an additional study was identified [19]. These studies are listed in Table 3.

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Table 3. Association of WBC count with CVD – Studies 2008-2015.

Study	Year and Country	Type of Study	Study Size	Age±SD (% Male)	End-point (a)	Type of Cell [b]	Result	Covariates Adjusted for [c]
1. Atmaca [20]	2008, Turkey	Case-control	59 cases, 51 controls	50.6± 6.8 (58.2)	CSX	WBC, Neu, Mono	WBC, 7.5±1.5 vs 6.2±1.2 (P = 0.0001); Neu, 5.1±1.1 vs 4.1± 0.8 (p = 0.0001); Mono, 0.3±0.1 vs 0.3±0.1 (P = 0.2) [d]	None
2. Cheng [21]	2008, Taiwan	Case-control	77 cases, 53 controls	64.7± 12.7 (76.9)	AMI	WBC	10.7±3.2 vs 6.7±2.0 (P<0.001) [d]	None
3. Kadoglou [22]	2008, Greece	Case-control	114 cases, 50 controls	66.9± 7.3 (54.9)	Carotid stenosis	WBC	7.2±1.9 vs 6.5±1.6 (p = 0.045) [d]	[e]
4. Lee [23]	2008, USA	Case-control	50 cases, 16 controls	58.8± 9.1 (62.1)	SA, UA, AMI	WBC	SA (N = 16), 7.2±1.9 vs 6.0±1.4 (P<0.05); UA (N = 18), 7.9±2.2 vs 6.0±1.4 (P<0.01); AMI (N = 16) 9.3±2.5 vs 6.0±1.4 (P<0.001) [d]	[f]
5. Lind [24]	2008, Sweden	Cross-sectional	1,016	70 (49.8)	BA IMT, BA IM-GSM	WBC	Univariate Spearman correlation coefficient for BA IMT = 0.05 (not significant) and for BA IM-GSM = -0.07 (P = 0.033)	[g]
6. Michos [25]	2008, Brazil	Cross-sectional	440	46.4± 6.8 (100)	CAC	WBC	6.5±1.7 vs 6.2±1.5 (p = 0.057) [d]	None
7. Rossouw [26]	2008, USA	Case-control	355 cases, 817 controls [h]	54-83 (0)	CHD	WBC	OR (per SD increase) = 1.2 (95% CI, 1.0-1.4), (p =0.01)	Age, BMI, waist-hip ratio, smok, alc, phys, diabetes, CVD history, high C, SBP, anithyp, asp, stat, assign

(table continues)

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Study	Year and Country	Type of Study	Study Size	Age±SD (% Male)	End-point (a)	Type of Cell [b]	Result	Covariates Adjusted for [c]
8. Sagastagoitia [27]	2008, Spain	Case-control	314 cases, 69 controls	65.2± 11.1 (68.1)	SA, UA	WBC	SA (N = 189), 7.3±1.9 vs 6.8±1.9 (P<0.001); UA (N = 125), 8.5±2.6 vs 6.8±1.9 (P<0.001) [d]; combined (N = 314) OR (WBC≥8.80) = 2.0 (95% CI, 1.1-3.8) (P = 0.028)	Combined OR: smok, CRP, Lp(a)
9. Sheu [28]	2008, Taiwan	Case-control	43 cases, 20 controls	62.2± 12.0 (84.1)	AMI	WBC	10.7±3.4 vs 5.8±0.9 (P<0.0001) [d]	[i]
10. Engström [29]	2009, Sweden	Longitudinal (prospective) 22.9 yr mean follow-up	16,940	43.7± 6.6 (100)	HF	WBC	HR = 1.7 (95% CI,1.3-2.3) (p for trend<0.001) [j]	Age, smok, diabetes, total C, trigly, SBP, BPM, BMI, angina, alc, phys, mar, occ
11. Halvorsen [30]	2009, Norway	Cross-sectional	5,341	65.8± 9.5 (44.2)	Plaque area, plaque echogen-icity	WBC	Plaque area: women (N = 1,613) □ 0.3 (SE, 0.5) (P = 0.57), men (N = 1592) □ 1.6 (SE, 0.57) (p = 0.004); plaque echogenicity: women (N = 1,613) OR = 1.1 (95% CI, 1.0-1.3) (p = 0.03), men (N = 1,592) OR = 1.0 (95% CI, 0.9-1.1) (P= 0.79)	Age, smok, total C, HDL-C, SBP, diabetes, CVD, treatment with lipid lowering drugs
12. Kucharska-Newton [31]	2009, USA	Longitudinal (prospective) 12.4 yr mean follow-up	14,009	45-64 (43.5)	SCD, NSCD, NF MI	WBC	SCD: RR = 2.1 (95% CI, 1.5-2.9) (P<0.001); NSCD: RR = 3.6 (95% CI, 2.3-5.5) (P<0.001); NF MI: RR = 1.7 (95% CI, 1.4-2.1) (P<0.001) [k]	Age, sex, race, ARIC center, smok, cig years of smoking
13. Lee [32]	2009, Korea	Cross-sectional	788	45.0± 12.2 (47.6)	PWV	WBC	OR = 2.7 (95% CI, 1.1-6.3) (P<0.05)	Age, sex, smok, alc, phys, BMI, MAP, FPL

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Study	Year and Country	Type of Study	Study Size	Age±SD (% Male)	End-point (a)	Type of Cell [b]	Result	Covariates Adjusted for [c]
14. Li [33]	2009, China	Case-control	93 cases, 33 controls	51.8± 8.6 (80.2)	CAE, CAD	WBC, Neu, Mono	WBC: CAE (N = 55) 7.2±1.5 vs 5.5±0.9 (P<0.01), CAD (N = 38) 6.1±1.4 vs 5.5±0.9 (P<0.01); Neu: CAE 4.5±1.7 vs 3.3±0.9 (P<0.01), CAD 3.7±1.2 vs 3.3±0.9 (P<0.01); Mono CAE 0.5±0.2 vs 0.3±0.1 (P<0.01), CAD 0.4±0.2 vs 0.3±0.1 (P<0.01) [d]	No difference among the groups for age, BMI, history of CAD, hypertension or hyperlipidemia
15. Shahzad [34]	2009, Pakistan	Case-control	93 cases, 96 controls	40-60 (100)	IHD	WBC, Neu, Mono	WBC, 9.4 vs 6.9 (P<0.001) [d]; Neu, 68% vs 57% (P<0.001); Mono, 2% vs 2% (P = 0.193)	Cases and controls matched on age
16. Thayer [35]	2009, Germany	Cross-sectional	611	41.1 (89.2)	HRV (RMSSD) [l]	WBC	Partial correlation coefficient = -0.126 (P= 0.003)	Age, sex, smok, hyp, MI, SBP, DBP, BMI, hemat, HDL, LDL, trigly, phys, norepin
17. Zurru [36]	2009, Argentina	Case-control	105 cases, 354 controls	73.0± 12 (56.4)	Ischemic stroke	WBC	Cases (N = 103) 7.6±2.1 vs controls (N = 271) 7.1±2.0 (P = 0.01) [d]	None
18. Aliberti [37]	2010, Italy	Case-control	170 cases, 4,116 controls	Cases, 62.7± 8.4 (83.5), Cont., 53.5± 18.8 (46.1)	CHD	WBC	7.6±2.0 vs 7.0±1.5 (P<0.0001) [d]	None

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Study	Year and Country	Type of Study	Study Size	Age±SD (% Male)	End-point (a)	Type of Cell [b]	Result	Covariates Adjusted for [c]
19. Chen [38]	2010, USA	Cross-sectional	5,260	55.0± 0.25 (SE), (43.8)	PAD [m]	WBC	OR = 2.3 (95% CI, 1.3-3.9) (P for trend = 0.005)	Age, sex, race, hyp, diabetes, total C, CKD, smok, homo-cysteine level
20. Kincl [39]	2010, Czech Republic	Cross-sectional	1,121	64.8 (64.2-65.4) (70.0)	CAD	WBC	Acute CAD (N = 249) 8.2 (95% CI, 7.9-8.5) vs control (N = 195) 6.7 (95% CI, 6.5-7.0) (P<0.001) [d]	None
21. Li [40]	2010, Sweden	Longitudinal (prospective) 24±5 yr follow-up	20,063	42.6± 5.6 (85.4)	ACE [n], stroke	WBC	ACE: males, HR = 1.3 (95% CI, 1.2-1.5) (P for trend <0.001); females, HR = 1.5 (95% CI, 0.9-2.5) (p for trend = 0.13); stroke: males, HR = 1.1 (95% CI, 0.9-1.3) (P for trend = 0.18): females, HR = 1.1 (95% CI, 0.6-2.0) (P for trend = 0.44) [j]	Age, smok, alc, phys, antihyp, diabetes, total C, log transformed trigly
22. Patterson [41]	2010, UK	Longitudinal (prospective) 13.4 yr median follow-up	2,208	57±4.5 (100)	CVD, CHD, ischemic stroke	WBC, Neu, Mono	WBC: CVD, HR = 1.5 (95% CI, 1.2-1.9) (P for trend <0.01); CHD, HR = 1.6 (95% CI, 1.2-2.2) (P for trend <0.01); stroke, HR = 1.3 (95% CI, 0.8-2.0) (P for trend<0.05) [k] [o]	Age, smok, SBP, BMI, total C, HDL-C, trigly, hist prem CHD
23. Pizzi [42]	2010, UK	Longitudinal (prospective) ca. 30 yr follow-up	2,951	Median 48 (69.9)	CHD mortality	WBC	RR = 0.9 (95% CI, 0.6-1.3) (P for trend = 0.60)	Sex, smok, BMI, SBP, alc

(table continues)

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Study	Year and Country	Type of Study	Study Size	Age±SD (% Male)	End-point (a)	Type of Cell [b]	Result	Covariates Adjusted for [c]
24. Bekwelem [19]	2011, USA	Longitudinal (prospective) 15.5±4.0 yr follow-up	14,485	54±6 (44.7)	HF	WBC	HR = 1.6 (95% CI, 1.3-2.0) (P for trend <0.0001) [p]	Age, race sex, edu, ARIC field center, BMI, WHR, smok, phys, hyp, diabetes, CHD, fam hist CHD, LDL-C, HDL-C, medications, trigly
25. Godsland [43]	2011, UK	Longitudinal (prospective) 21.5 yr mean follow-up	592 [q]	51.2 (100)	CVD mortality	WBC	HR (per 1 SD change in WBC) = 1.3 (95% CI, 1.0-1.7) (P = 0.06)	Age, BMI, smok, alc [r]
26. Kocaman [44]	2011, Turkey	Case-control	508 cases, 169 controls	58.2± 10.2 (70.2)	CAD	WBC, Neu, Mono	WBC: 8.1±2.5 vs 7.0±1.7; Neu: 5.1±2.3 vs 4.1±1.3; Mono: 0.6±0.2 vs 0.5±0.2 (P<0.001 for all) [d]	None
27. Konrad [45]	2011, 14 European countries	Cross-sectional	51	48.3± 4.5 (0)	FMD	WBC	r = -0.269 (p = 0.09)	None
28. Afsar [46]	2012, Turkey	Case-control	95 cases [s], 81 controls	32-84 (51.1)	Fetuin-A [t]	WBC	11.7±3.9 vs 7.5±2.2 (P<0.001) [d]	None
29. Inoue [47]	2012, Japan	Cross-sectional	8,772	49.0± 9.1 (61.2)	HR	WBC	Males (N = 5,373): OR = 1.3 (95% CI, 1.2-1.4) (P<0.0001); females (N = 3,399): OR = 1.2 (95% CI, 1.2-1.3) (P<0.0001) [u]	Age, smok, BMI, SBP, antihyp, total C, HDL-C, trigly, gly hemat, uric acid
30. Kavousi [48]	2012, Nether-lands	Longitudinal (prospective) 6.8 yr median follow-up	5,933	69.1± 8.5 (40.6)	CHD	WBC	HR = 1.8 (95% CI, 1.3-2.5) [j]	Age, sex, SBP, antihyp, total C, HDL-C, smok, diabetes

(table continues)

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Study	Year and Country	Type of Study	Study Size	Age±SD (% Male)	End-point (a)	Type of Cell [b]	Result	Covariates Adjusted for [c]
31. Korkmaz [49]	2012, Turkey	Case-control	166 cases, 118 controls	57.7± 9.2 (54.9)	CAC	WBC	OR = 1.7 (95% CI, 1.3-2.1) (P<0.001)	Age, smok
32. Nyrnes [50]	2012, Norway	Longitudinal (prospective) 10.9 yr mean follow-up	6,315	25-84 (49.0)	AF	WBC	OR = 1.4 (95% CI, 1.1-1.9) (p = 0.004) [j]	Age, sex, SBP, BMI, total C, CHD, diabetes, antihyp
33. Ortega [51]	2012, Spain	Case-control	411 cases, 389 controls	49.9 (56.0)	Carotid athero-sclerosis	WBC	OR [v] = 1.2 (95% CI, 1.1-1.3) (P<0.0001)	Age, sex
34. Pfister [52]	2012, UK	Longitudinal (prospective) 12.4 yr mean follow-up	16,011	58.0± 9.4 (44.9)	HF	WBC, Neu [w], Mono	WBC: HR [v] males (N = 7,195) 1.1 (95% CI, 1.0-1.2) (p for trend = 0.07); HR females (N = 8,816) 1.0 (95% CI, 1.0-1.1) (p for trend = 0.75); Neu: HR males 1.2 (95% CI, 1.1-1.2 (p for trend<0.0001); HR females 1.1 (95% CI, 1.0-1.1) (p for trend = 0.73); Mono HR males 0.7 (95% CI, 0.5-0.9); HR females 1.1 (95% CI, 0.8-1.5) (p for trend = 0.46)	Age, BMI, SBP, diabetes, total C, social class, edu, smok, phys
35. Phillips [53]	2012, China	Cross-sectional	1,577	59.3± 6.8 (51.2)	Carotid IMT, PWV	WBC, Neu [w]	WBC: IMT, p = 0.4; PWV, p = 0.002; Neu: IMT, p = 0.83, PWV, p = 0.001	Age, sex, edu, smok, alc, BMI, SBP, glucose, total C, trigly, CRP
36. Rienstra [54]	2012, USA	Longitudinal (prospective) 5 yr median follow-up	936	76±6 (39)	AF	WBC	HR (per 1 SD increment in WBC count) = 2.3 (95% CI, 1.1-4.8) (p = 0.02)	Age, sex, BMI, SBP, antihyp, PR interval, car mur, HF

(table continues)

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Study	Year and Country	Type of Study	Study Size	Age±SD (% Male)	End-point (a)	Type of Cell [b]	Result	Covariates Adjusted for [c]
37. Twig [55]	2012, Israel	Longitudinal (prospective) 7.51±3.86 yr follow-up	29,120	31.2± 5.5 (100)	CAD	WBC	HR = 1.8 (95% CI, 1.0-3.4) (p = 0.049) [p] [x]	Age, BMI, smok, phys, SBP, DBP, HDL, LDL, trigyl, diabetes, fam hist CAD
38. Zia [56]	2012, Sweden	Longitudinal (prospective) 13.6±3.3 yr mean follow-up	26,927	58±8 (38.3)	Stroke (CI, IH)	WBC, Neu	WBC: CI, HR = 1.4 (95% CI, 1.2-1.7) (p for trend<0.001), IH, HR = 0.7 (95% CI, 0.4-0.99) (p for trend = 0.046); Neu: CI, HR = 1.3 (95% CI, 1.1-1.5) (p for trend = 0.001), IH, HR = 0.8 (95% CI, 0.5-1.2) (p for trend = 0.20) [j]	Age, BMI, diabetes, smok, SBP, antihyp, lipid lowering drugs, alc, phys [y]
39. Balta [57]	2013, Turkey	Case-control	114 cases, 67 controls	51.6± 6.4 (67.4)	CAE, CAD	WBC, N/L [z]	WBC: CAE 7.5±1.5 vs 7.4±1.5 (p = 0.53), CAD 7.46±1.4 vs 7.4±1.5 (p = 0.69); N/L: CAE 2.4±1.2 vs 1.9±0.8 (p = 0.004); CAD 2.5± 1.3 vs 1.9±0.8 (P<0.001) [d]	None
40. Rajkumari [58]	2013, India	Case-control	27 cases, 27 controls	52.00± 11.52 (44.4)	HYP	WBC, Neu	WBC: 7.4±0.7 vs 5.2±0.5 (P<0.001) [d]; Neu: 62.0±5.0% vs 53.0±3.4% (P<0.001)	Age and sex matched
41. Tekin [59]	2013, Turkey	Case-control	107 cases, 112 controls	73.5 (36.1)	AF	WBC	OR = 1.2 (95% CI, 1.0-1.5) (p = 0.01)	Age, sex, hyp, diabetes, hyperlipodemia, smok, hemat, platelets, MPV, CAD

(table continues)

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Study	Year and Country	Type of Study	Study Size	Age±SD (% Male)	End-point (a)	Type of Cell [b]	Result	Covariates Adjusted for [c]
42. Celikbilek [60]	2014, Turkey	Case-control	120 cases, 70 controls	64.9± 12.9 (40.5)	AAIS, TIA	WBC, N/L [z]	WBC: AAIS (N = 70) 7.6 (6.4-10.5) vs 6.5 (5.7-7.7) (p = 0.006); TIA (N = 50) 6.8 (5.6-8.8) vs 6.5 (5.7-7.7) (not significant); N/L: AAIS 3.3 (2.3-4.8) vs 1.9 (1.5-2.3); TIA 2.3 (1.6-3.1) vs 1.9 (1.5-3.4) (P<0.001 for both) [d] [aa]	None
43. Cotoi [61]	2014, Sweden	Longitudinal (prospective) 16.2 yr median follow-up	664	65.6± 1.1 (40.1)	CE, stroke, CV events, CV deaths	WBC, Neu, Mono	WBC for all cases [ab]: 6.4±1.7 vs 6.0±1.5 (not significant) [d]; Neu (per 1 SD increment in Neu count): HR for CE (N = 83) 1.3 (95% CI, 1.0-1.6) (p = 0.047); HR for stroke (N = 55) 1.2 (95% CI, 0.9-1.5); HR for CV death (N = 67) 1.6 (95% CI, 1.3-2.0) (P<0.001); Mono for all cases [ab]: 0.5±0.2 vs 0.5±0.2 (p = 0.010) [d]	Age, sex, diabetes, BMI, antihyp, LDL, HDL, trigly
44. Martinsson [62]	2014, Sweden	Longitudinal (prospective) 16.5 yr mean follow-up	5079	57.6± 5.6 (41.2)	AS	WBC	HR (for 1 SD increment in WBC) = 1.1 (95% CI, 0.7-1.3) (p = 0.44)	Age, sex
45. Söderholm [63]	2014, Sweden	Longitudinal (prospective) 26.8±6.9 yr mean follow-up	19,794	44±6 (86.3)	SAH	WBC	HR = 1.3 (95% CI, 1.1-1.5) (p = 0.014) [j]	Age, sex SBP, antihyp, smok, alc, BMI, diabetes, total C, phys

Notes

a. CSX – cardiac syndrome X, AMI – acute myocardial infarction, SA – stable angina, UA – unstable angina, BA IMT – brachial artery intima media thickness, BA IM-GSM – brachial artery intima media grey scale median, CAC – coronary artery calcification, HF – heart failure, SCD – sudden cardiac death, NSCD – non-sudden cardiac death, NF MI – non-fatal myocardial infarction, PWV – pulse wave velocity, CAE – coronary artery ectasia, CAD – coronary artery disease, HRV

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– heart rate variability, IHD – ischemic heart disease, PAD – peripheral arterial disease, ACE – acute coronary events, FMD – flow mediated dilation, HR – heart rate, AF – atrial fibrillation, CI – cerebral infarction, IH – intracerebral hemorrhage, HYP – hypertension, AAIS – atherothrombotic acute ischemic stroke, TIA – transient ischemic attack, CE – cardiac events (fatal or non-fatal MI, IHD death), CV events – cerebrovascular events (CE or fatal or non-fatal stroke), AS – aortic stenosis, SAH – subarachnoid hemorrhage

b. WBC – white blood cell or leukocyte, Neu – neutrophil, Mono – monocyte

c. smok – smoking status, alc – alcohol consumption, phys – physical activity, high C – history of high cholesterol requiring medication, SBP – systolic blood pressure, antihyp – antihypertensive medication, asp – aspirin, stat – statins, assign – treatment assignment, CRP – C-reactive protein, Lp(a) – lipoprotein (a), hyp – history of hypertension, MI – history of myocardial infarction, DBP – diastolic blood pressure, hemat – haematocrit, trigly – triglycerides, norepin – urinary norepinephrine, total C – total cholesterol, BPM – blood pressure medication, mar – marital status, occ – occupation level, MAP – mean arterial pressure, FPL – fasting plasma glucose, CKD – chronic kidney disease, hist prem CHD – history of premature CHD, WHR – waist to hip ratio, gly hem – glycated haemoglobin, car mur – clinically significant cardiac murmur, MPV – mean platelet volume, CRP – C-reactive protein

d. Units 109/L+SD unless otherwise noted

e. Controls were matched to cases with respect to age, sex, and BMI

f. No significant difference between cases and controls with respect to age, sex, BMI, incidence of controlled hypertension, smoking, and family history for atherosclerotic vascular disease

g. A multiple regression analysis indicated no relationship between WBC count and BA IM-GSM ($p = 0.80$) in a model including sex, HDL-C, serum triglycerides, LDL-C, VCAM-1, e-selectin, GSSG/GSH ratio, baseline conjugated dienes (BCD)-LDL, and homocysteine

h. Both cases and controls were drawn from a prospective study designed to ascertain the risk of CHD, stroke, and venous thromboembolism associated with hormone therapy

i. There was no difference between cases and controls for sex, gender, body temperature, or creatinine level

j. HR (OR) is for fourth quartile of WBC count compared to first quartile

k. RR is for third tertile of WBC count compared to first tertile

l. RMSSD – root mean square of successive beat differences, the primary measure of HRV used in this study

m. PAD identified by an ankle brachial index (ABI) < 0.9 in either leg

n. ACE includes fatal or non-fatal MI or death from IHD

o. Neu: CVD, HR = 1.61 (95% CI, 1.2-2.1) (p for trend<0.01); CHD, HR = 1.8 (95% CI, 1.3-2.5) (p for trend<0.01); ischemic stroke, HR = 1.2 (95% CI, 0.8-2.0) (p for trend<0.05); Mono: CVD, HR = 1.1 (95% CI, 0.9-1.4), CHD 1.3 (95% CI, 1.0-1.7), ischemic stroke HR = 0.8 (95% CI, 0.5-1.3) (p for trend not significant for all endpoints); adjusted for the same covariates as for WBC [k]

p. HR is for fifth quintile of WBC count compared to first quintile

q. The original cohort consisted of 1010 males. However, the analysis was restricted to individuals who died before the end date (94 cancer deaths, 67 CVD deaths, and 57 other deaths) and 374 survivors in order to achieve age matching

r. When CVD mortality was corrected for competing causes, the HR was almost unchanged at 1.30, but the p value was 0.03

s. Cases were diagnosed with acute coronary syndrome

t. Decreased levels of the protein fetuin-A have been reported to be associated with increased vascular calcification

u. OR refers to an increase of the 3 lowest WBC quartiles to the highest quartile for every 10 beats/min increase in heart rate

v. per 1x109/L

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w. The actual correlation was for granulocytes, which include eosinophils, basophils, and mast cells; neutrophils constitute the majority of granulocytes
x. Comparison of the fourth quintile with the first quintile, adjusted for the same covariates, gave HR = 2.17 (95% CI, 1.19-3.98) (p = 0.012)
y. HR for WBC and IH not adjusted for lipid lowering medication or physical activity; HR for Neu and CI adjusted for the same covariates as above plus lymphocyte count; HR for Neu and IH adjusted for the same covariates as WBC and IH plus lymphocyte count
z. N/L – neutrophil/lymphocyte ratio
aa. Results expressed as median and interquartile range
ab. Results are related to all endpoints combined

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Of the 45 publications listed in Table 3, 7 are from Sweden and Turkey, 6 from the US, 4 from the UK, 2 each from China, Taiwan, Spain, and Norway, and 1 each from Greece, Brazil, Korea, the Netherlands, India, Israel, Japan, the Czech Republic, Italy, Argentina, Germany, Pakistan, and 14 European countries, representing an obviously wide geographic area. A large number of endpoints, approximately 30, are also represented. As a consequence, combining all of these studies in a single meta-analysis would be completely inappropriate. However, many of these endpoints can be combined under the CHD umbrella (CHD, CAD, IHD, stable and unstable angina, AMI, non-fatal MI, sudden cardiac death, and carotid atherosclerosis). This results in a total of 24 estimates from 17 studies (numbers 2, 4, 7-9, 12, 14, 15, 18, 20-22, 26, 30, 33, 37, and 39) measuring essentially the same pathology. All of these estimates resulted in a statistically significant association of various forms of CHD and WBC count with the exception of study 39 and the result for females in study 21. There are 12 estimates related to stroke contained in seven studies (numbers 17, 21, 22, 38, 42, 43, and 45). These 12 estimates relate to several different types of stroke, and there is not a consistent association of these results with WBC count. For four of the estimates there was a statistically significant association of the type of stroke being investigated with WBC count, whereas there was no significant association for the other eight estimates. Four other endpoints should be mentioned, since there were at least two estimates for each of them. There were two estimates for coronary artery calcification (CAC), publication numbers 6 and 31. The first study did not report a statistically significant association of CAC with WBC count, while the second study did. There were also two studies (13 and 35) that reported estimates for pulse wave velocity (PWV), the time taken for a pulse wave to travel from the brachial artery to the ankle (used as a measure of arterial stiffness or distensibility). Both studies reported a statistically significant association between PWV and WBC count. Study numbers 10, 24, and 34 reported four estimates for heart failure (HF). Three estimates were statistically significant. Lastly, study numbers 32, 36, and 41 each reported results for atrial fibrillation (AF). The association of AF with WBC count was significant for all three estimates.

Another difference among the publications listed in Table 3 is the type of study. There were 19 case-control studies, although eight of them neither matched cases and controls nor adjusted for any covariates; 16 longitudinal prospective studies, and ten cross-sectional study. It is important to note that all estimates from prospective studies were adjusted for a large number of covariates, as can be seen from the table. Although not shown in the table, comparison of the most highly adjusted estimate to an estimate adjusted only for age or age and sex clearly indicated a weaker association between WBC count and the endpoint being considered. Given that results from many of the case-control and cross-sectional studies have not been adjusted for covariates, the rather low p-values cited in Table 3 for such studies would probably have been attenuated by adjustment.

A number of endpoints investigated report estimates that are not statistically associated with WBC count. These are study number 5 for brachial artery intima media thickness (IMT-a measurement of the thickness of the tunica intima and tunica media, the two innermost layers of arterial walls) as well as study number 35 for carotid intima media

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thickness; study number 11 for plaque area for women and plaque echogenicity for men; study 23 for CHD mortality; publication 25 for CVD mortality; publication 27 for flow mediated dilation; study 39 for coronary artery ectasia (CAE, a rare clinical condition defined as dilatation of the coronary artery 1.5 times greater than that of an adjacent normal segment); and study 44 for arterial stenosis. Nevertheless, there is absolutely no question that WBC count is highly significantly associated with the development of CHD endpoints in complete agreement with the 1998 meta-analysis of Danesh et al. [5]. There is also evidence to support an association of WBC count with HF and AF. On the other hand, the association of WCB count with stroke is likely to be weak at best.

There were 18 estimates for neutrophils contained in ten publications. All of these estimates were statistically significant with the exception of the association with stroke (studies 22 and 43), with HF in females (study 34), with carotid IMT (study 35) and the association with intracerebral hemorrhage (study 38). Three of these estimates deal with stroke or a sub-type of stroke, supporting a weak association at best of neutrophil count and stroke as was the case with WBC count. The corresponding estimates for WBC count in these studies were also non-significant, although no separate estimate for stroke was provided in study 43. With respect to monocytes, seven studies reported 13 estimates. Only three of these were statistically significant, while ten were not statistically significant, suggesting that the monocyte cell type is probably not an appropriate leukocyte to assess risk of CVD.

There are two studies (numbers 39 and 42 [57, 60]) that use a combination of two leukocyte types to derive the neutrophil/lymphocyte (N/L) ratio. This ratio has been used extensively in recent studies investigating the association of leukocytes in CVD patients to assess the risk of subsequent events. As will be noted subsequently, there is evidence that lymphocytes are sometimes elevated in smokers compared to non-smokers [64, 65]. However, lymphocyte counts tend to be unchanged or even depressed in individuals at who develop various CVD endpoints [34, 41, 52]. As a consequence, the N/L ratio may be quite useful in identifying individuals at increased risk for CVD endpoints. This point is illustrated by the results reported by Balta et al. [57] where the association of WBC count with both CAE and CAD were not statistically significant, whereas a statistically significant association with the N/L ratio was reported for both endpoints. Despite the potentially greater sensitivity of the N/L ratio to assess CVD risk, it would not be recommended to replace WBC count to evaluate potential MRTPs. What is important here is the association of the cell type being investigated with smoking or smoking cessation (see below), and given that lymphocyte numbers are not depressed in smokers, there would be no advantage of using this biomarker.

As has been noted it is quite obvious that there is a highly significant association of WBC count with CHD, as well as a number of other endpoints. However, there is one last issue that needs to be addressed. As will be seen, WBC is significantly increased in smokers. Therefore, is WBC count independently associated with CVD or does it simply reflect the effect of smoking? It was noted above that there were 16 longitudinal prospective studies that provided 17 estimates for various CVD endpoints excluding 6 estimates for stroke. Of these 17 estimates, 13 were statistically significant. Only 3 of these estimates, 2 of which were statistically significant and 1 that was not, were not adjusted for smoking. As

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a consequence, there is ample evidence that WBC count represents a risk factor for many CVD endpoints independent of smoking.

In addition to the obvious and independent association of WBC count with various CVD endpoints, WBC count is also associated with a number of well-established risk factors for CVD. These include metabolic syndrome [66-68], platelet aggregation [69, 70] as well as platelet count [71], obesity [68, 72-76], hypertension [77, 78], triglyceride levels [73, 74, 76], the total cholesterol/HDL-C ratio [79], and type 2 diabetes [80]. Inverse associations have been reported for HDL-C [68, 75, 76], physical activity [81, 82], and adherence to a Mediterranean diet [83]. Lastly, it should be noted that a recent paper reports a highly significant association of WBC count with proprotein convertase subtilisin/kexin type 9 (PCSK9 or NARC-1(neural apoptosis-regulated convertase 1)) levels in men [84]. PCSK9 plays a major regulatory role in cholesterol homeostasis and has recently be shown to be a very powerful CVD risk factor. These findings clearly support the conclusions reached in the previous section.

4.2 Respiratory disease

Lung Cancer

Only three references meeting the inclusion and exclusion criteria were obtained from the literature search. An independent literature search was conducted using the procedures previously described, and four additional publications were found, all published prior to 2008. Because of the relatively small number of articles and the potential importance of the possible association of the utility of WBC count as a biomarker for lung cancer, each study is described below.

The first study was published by Phillips et al. in 1992 [85]. This study was a prospective study where the association of WBC count with lung cancer risk was assessed in three different cohorts; the British Regional Heart Study (BRHS), the original Multiple Risk Factor Intervention Trial (MRFIT1) and a subsequent MRFIT study, MRFIT2. All three cohorts were restricted to male subjects, and the numbers were 7,344 for the BRHS, 12,845 for MRFT1, and 7,992 for MRFIT2. Average follow-up periods were 9.7, 7, and 12 years, respectively. Case ascertainment was defined as lung cancer death for the BRHS and MRFIT2, while it was defined as lung cancer incidence in MRFIT1. A total of 309 cases were reported in all three cohorts, only four of which involved non-smokers at baseline. A highly marked increase in the risk of lung cancer associated with WBC count was observed for the BRHS and MRFT1 cohorts. The association was less marked for MRFIT2, but the result was still statistically significant. The pooled estimate for the relative odds adjusted for cig/day in all three cohorts was 1.5 ($P<0.0001$). The authors conclude that, “These results indicate that the association between leukocyte count and the risk of lung cancer is strong and independent of the amount smoked.”

The second relevant study, published in 2004 [86], was also a prospective study. A total of 7,675 participants from the Second National Health and Nutrition Examination Service (NHANES II) were followed for an average period of 16 years. The age range for this cohort was 45-85 and consisted of 47.2% males. A total of 191 deaths from lung cancer were reported during follow-up. Cox proportional hazard analysis was used to determine the association of WBC count, divided into quartiles, with lung cancer risk. The HR for

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the 4th quartile versus the 1st quartile was 4.1 (95% CI, 2.1-8.2) with adjustment for age, race, and sex. However, after further adjustment (blood pressure, heavy alcohol consumption, diabetes, education, BMI, hematocrit, current and former smoking, any and weekly aspirin use, and physical activity) the result was no longer statistically significant (HR = 1.8 (95% CI, 0.9-3.6)). The authors point out that the lack of a statistically significant association could be a consequence of the relatively small number of cases.

A small prospective study was conducted in Australia with the results being published in 2006 [87]. The subjects for this study were drawn from the Blue Mountain Eye Study. A total of 3,189 eligible subject were followed from the baseline examination (Jan. 1, 1992-Dec. 31, 1994) until Dec. 31, 2001. Average age was 63 and the cohort consisted of 42.9% males. The primary goal of this study was to assess the association of WBC count with all cancer mortality; however, lung cancer data were analyzed separately. Twenty-two deaths from lung cancer were reported during the follow-up, 11 in current smokers and 11 in former smokers. The adjusted (age, sex, education, BMI, hematocrit level, alcohol consumption, physical inactivity, smoking status, weekly aspirin use, diabetes status, and fasting glucose level) for the fourth quartile of WBC count versus the first quartile was 2.4 (95% CI, 0.6-8.6). This result is not statistically significant; however, it was a very small study, as reflected by the very wide 95% confidence interval.

In 2007, Margolis et al. examined the association of WBC count with risk of lung cancer in the Women's Health Initiative [88]. A cohort of 143,748 women, mean age 63, was followed up for a mean period of 7.8 years. During that period, 1,237 cases of incident lung cancer were diagnosed. White blood cell counts were divided into quartiles, and Cox proportional hazard analysis was used to determine the change in risk in lung cancer associated with WBC count. The HR for the 4th quartile compared to the 1st quartile was 1.6 (95% CI, 1.4-2.0) when adjusted for age, race/ethnicity, pack-years of smoking, and current and past smoking. Of the total of 1,237 cases, only 198 occurred in never smokers, and there was no association of WBC count with lung cancer in this sub-group. The HR, comparing the highest to lowest quartile, in past smokers was 1.7 (95% CI, 1.3-2.1) and was 2.0 (95%, CI, 1.2-3.3) in current smokers. The authors concluded that these results demonstrate that WBC count is associated with incident lung cancer among post-menopausal women, although it would appear that this association is restricted to current and former smokers.

The next study, also a prospective study, was published by Sprague et al. in 2008 [89]. This study utilized the Beaver Dam cohort, which consisted of 4,831 participants (age range 43-86, 43.6% male). The average follow-up period was 12.8 years. A total of 134 incident cases of lung cancer were reported during the follow-up period. Cox proportional hazard analysis was used to determine the association of WBC count with lung cancer comparing the third tertile with the first tertile. The adjusted (age, sex, pack-years of smoking, time since smoking cessation, BMI, alcohol intake, and education) HR was 2.8 (95% CI, 1.6-5.0), clearly demonstrating a statistically significant relationship between the WBC count and lung cancer. However, there is one caveat that should be mentioned. The primary goal of this research was to determine the association of incident lung cancer with physical activity, and an inverse relationship with the total physical activity index (kcal/week) was indeed observed (adjusted HR = 0.6, 95% CI, 0.4-0.9). As

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has been previously noted, there is an inverse relationship between physical activity and WBC count [81, 82]; however, the HR for the association of WBC count and incident lung cancer was not adjusted for physical activity.

dos Santos Silva et al. [90] reported on results from three prospective studies in 2010; the Northwick Park Heart Studies (NPHS)-I and -II, and the Thrombosis Prevention Trial. Only NPHS-I, however, measured WBC count. A total of 2,162 male subjects from NPHS-I with an average age of 48.1±17.9 years participated in this study. The median follow-up was 25.6 years. During this period a total of 77 lung cancer cases were reported. The fully adjusted (age, BMI, social class, alcohol consumption, serum cholesterol, pack years of smoking, never/ex/current smoking, and SBP) HR, comparing 4th quartile to the 1st quartile was 0.9 (95% CI, 0.5-1.7), clearly not a statistically significant result. Interestingly, the result obtained when the hazard ratio was adjusted only for age and smoking was almost equal to the fully adjusted HR (0.9, 95% CI, 0.5-1.6), while the HR adjusted only for age (2.2, 95% CI, 1.2-3.9) was almost equal to the HR adjusted for age and all other covariates except smoking (2.0, 95% CI, 1.1-3.7). Consequently in this study, an observed association of incident lung cancer risk with WBC count is completely attributable to the effect of smoking on WBC count.

A small case-control study published in 2012 [91] compared WBC count in 64 male non-small cell lung cancer (NSCLC) patients compared to 25 male healthy controls. Average age of the NSCLC patients was 65.6±9.9 years and 63.5±11.5 in the controls. There was a statistically significant higher level of WBC in the patients than in the controls (9.8±3.2 versus 8.4±1.9 10^9/L, p = 0.042), supporting an increase in WBC count in lung cancer.

The studies summarized above support an association of WBC count and either incident lung cancer cases or lung cancer mortality. However, not all studies provided statistically significant results. It is highly likely that a meta-analysis of the six prospective studies would yield a pooled statistically significant result.

Chronic Obstructive Pulmonary Disease

A total of nine references, published between 2008 and 2015, regarding the association of WBC count and COPD were identified by the three literature searches. PubMed was searched to identify articles published before 2008 using the terms “white blood cell” AND “COPD”, “leukocytes” AND “COPD”, “white blood cell” AND “respiratory disease”, and “leukocyte” AND “respiratory disease”. A systematic review and meta-analysis published in 2004 was retrieved that had identified studies dealing with the association of systemic inflammation and COPD from 1982-2003 [92]. Although 14 studies were included in this review, only three of them, all cross-sectional studies, related to WBC count. The pooled result for these studies was a difference of 0.9x10^9/L (95% CI, 0.4-1.4), which is statistically significant. As a consequence of this meta-analysis, the literature search was restricted to articles published after 2003. Six review articles were identified by this literature search [93-98], and any relevant articles identified in the reviews were also obtained. Only two articles published between 2004 and 2007 were identified; however, four additional articles published after 2007 were also found. These six articles plus the six reviews and the meta-analysis resulted in the

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addition of 13 additional references. Lastly, one additional reference was required to provide background information on the ECLIPSE (Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints) study, the results of which were reported by Agusti et al. (2012) [99]. Therefore, a total of 14 references were added. Because of the small number of studies published prior to 2008, all studies are summarized in Table 4 irrespective of date.

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Table 4. Association of WBC count with COPD – Studies 2014-2015

Study	Year and Country	Type of Study	Study Size	Age±SD (% Male)	Type of Cell [a]	Result	Covariates Adjusted for [b]
1. O'Donnell [100]	2004, UK	Case-control	44 cases, 21 controls (10 non-smokers, 11 smokers)	51.7±7.8 (NS[c])	Neu [d]	67.8% Neu in stage II-IV COPD (N = 17) vs 37.6% in non-smoking controls and 46.0% in healthy smokers (P<0.05)	All groups matched for age
2. Rytila [101]	2006, UK, Finland	Case-control	20 cases, 28 controls (14 non-smokers, 14 smokers)	Cases:50, non-smokers: 44, smokers: 50 (56.2)	Neu [d]	58% Neu in cases vs 30% in non-smoking controls (P<0.0001); 54% in smoking controls vs 30% in non-smoking controls (p = 0.01)	None
3. Eickhoff [102]	2008, Austria	Case-control	60 cases, 40 controls (20 non-smokers, 20 smokers)	61.4±8.8 (48)	WBC	No significant difference in WBC count between cases and either type of control	Matched for age, weight, arterial BP, total C, trigly, blood glucose
4. Roos-Engstrand [103]	2009, Sweden	Case-control	19 cases, 25 controls (12 non-smokers, 13 smokers)	64.2±5.7 (56.8)	WBC, Neu [e]	WBC: cases vs NS controls – 25 (17-30) vs 17 (11-27) 10^4/mL (not significant), cases vs S controls – 25 (17-30) vs 40 (33-49) 10^4/mL (P<0.001); Neu: no significant difference in cell number between cases and either control group [f]	None
5. Dima [104]	2010, Greece	Case-control	31 cases [g], 33 controls (17 non-smokers, 16 smokers)	49.0±2.8 (SE) (NS)	Neu [d]	Cases: 68.3 (17.0-90.5)%, NS controls: 41.3 (12.0-79.5)%, S controls 47.4 (19.1-81.3)%; (P<0.05 for both control groups) [f]	Cases and smoking controls matched for pack years

(table continues)

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Study	Year and Country	Type of Study	Study Size	Age±SD (% Male)	Type of Cell [a]	Result	Covariates Adjusted for [b]
6. He [105]	2010, China	Case-control	44 cases, 20 controls (10 non-smokers, 10 smokers)	58.7±9.3 (89.1)	Neu [d], WBC, Neu	% Neu in induced sputum increased for COPD stage II, III, and IV vs both smoking and non-smoking controls (P<0.01) and for COPD stage I vs non-smoking controls (P<0.01) [h]; no significant difference for any stage of COPD and either smoking or non-smoking controls for WBC or Neu in blood	All groups matched for age and sex
7. Biljak [106]	2011, Croatia	Case-control	109 cases, 51 controls	Cases 71 (65-76); controls 52 (46-56) [f] (NS)	WBC, Neu [i]	WBC: 9.9 (7.8-12.7) vs 6.6 (5.9-8.0) 10^9/L (P<0.0001); Neu:65 (58-75) vs 54 (50-59)% (P<0.0001) [f]	None
8. Larsson [107]	2011, Sweden	Case-control	41 cases, 151 controls	Cases 63.5±9, controls, 72±5 (40.1)	Neu	Females: cases (N = 30) 4.5 vs controls (N = 95) 3.1 10^9/L (P<0.01); males: cases (N = 11) 3.5 vs controls (N = 66) 3.1 10^9/L (not significant)	None
9. McKeever [108]	2011, USA	Cross-sectional [j]	8,381 non-smokers, 2,790 smokers [k]	Non-smokers 46.4±20.4, smokers 41.0±16.1 (42.7, 57.5)	WBC, Neu [l], Mono	All three cell types were statistically significantly related to forced expiratory volume in 1 second (FEV_1) using multivariate linear regression for quintiles of cell counts; see [m] for data	Age, sex, height, race/ethnicity, BMI, smoking status, pack years smoked
10. Agusti [99]	2012, multi-center [n]	Longitudinal (prospective) 1 yr follow-up [o]	1,758 cases, 499 controls (202 non-smokers, 297 smokers)	Cases, 63.5±7.1 (66), NS controls, 53.0±8.6 (38), S controls 55.5±8.8 (55)	WBC	Cases: 7.6 (6.3-9.0) 10^9/L, NS controls 5.8 (5.0-7.0) 10^9/L, S controls 7.1 (6.3-8.6) 10^9/L (P<0.001 for both comparisons) [f]	None

(table continues)

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Study	Year and Country	Type of Study	Study Size	Age±SD (% Male)	Type of Cell [a]	Result	Covariates Adjusted for [b]
11. Fernandez [109]	2012, Spain	Cross-sectional	106,189 non-smokers, 116,652 smokers	16-70 (73.3)	WBC	Data were provided comparing WBC count to FEV_1 by sex, three categories of BMI, and 5 age groups for a total of 90 estimates. The authors state that, "we detected significant differences for male smokers between the ages of 35 and 64 years, regardless of BMI, and for female smokers with a BMI <30 between the age of 44 and 54 years. (P<0.001)	Age, sex, BMI as noted
12. Kuhlmann [110]	2013, Sweden	Cross-sectional	888	70 (48.6)	WBC	There was an association between WBC count and FEV_1 as shown by multiple linear regression with [(per 1 SD change) = -1,6 (95% CI -3.0 to -0.3) (p = 0.02) [p]	Sex, pack years, smoking status, BMI, CRP, EGF, VCAM-1, ICAM-1
13. Steiro-poulos [111]	2013, Greece	Case-control	85 cases, 34 smoking controls	Cases, 71.5±9.8 (91.8), controls, 60.0±5.5 (100)	WBC	Cases: 10.6±1.3 10^9/L, controls: 7.1±1.9 10^9/L (P<0.001)	None
14. Wang [112]	2013, China	Case-control	70 cases, 70 controls	68.5±4.5 (58.5)	WBC	Cases: 7.3±1.3 10^9/L, controls: 6.5±1.3 10^9/L (P<0.001)	Matched for age, sex, BMI, and smoking history
15. Günay [113]	2014, Turkey	Case-control	269 cases (178 stable, 91 exacerba-tion), 50 controls	65.7±8.0 (67.7)	WBC, Neu	WBC: stable COPD 8.5±3.0 10^9/L vs control 6.3±1.6 10^9/L; Neu: stable COPD 5.3±2.1 10^9/L vs control 3.4±1.0 10^9/L (P<0.001 for both) [q]	Matched for age and sex

Notes

a. WBC – white blood cell or leukocyte, Neu – neutrophil, Mono – monocyte
b. Total C – total cholesterol, trigly – triglycerides, CRP – C-reactive protein, EGF – epidermal growth factor, VCAM-1 – vascular cell adhesion molecule 1, ICAM-1 – intercellular adhesion molecule 1
c. NS – Not specified

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d. In induced sputum
e. Both WBC and Neu obtained from bronchoalveolar lavage fluid
f. Data provided as median and interquartile range
g. COPD included 10 "reversible" cases; all COPD cases were combined for this analysis
h. Induced sputum: NS controls, %Neu = 34.4±11.4; S controls, %Neu = 46.0±9.3; COPD stage I (N = 10), %Neu = 51.2±10.9; COPD stage II (N = 10), %Neu = 62.0±12.8; COPD stage III (N = 12), %Neu = 61.8±10.9; COPD stage IV (N = 12), %Neu = 65.2±10.0
i. Segmented neutrophils
j. Taken from individuals who provided data for the NHANES III Survey
k. A total of 3163 eligible subjects were excluded because they reported being ill shortly before participating in the survey
l. Actual cell type was granulocytes
m. Non-smokers: WBC – fifth quintile, FEV_1 = -125.3 mL (95% CI, -163.1 to -87.5) compared to first quintile (reference) (p for trend<0.001); Neu – fifth quintile, FEV_1 = -119.3 mL (95% CI, -156.7 to -81.9) compared to first quintile (p for trend<0.001); Mono – fifth quintile, FEV_1 = -95.1 mL (95% CI, -130.2 to -60.1) compared to first quintile (p for trend<0.001); Smokers: WBC – fifth quintile, FEV_1 = -78.1 mL (95% CI, -138.7 to -17.6) (p for trend = 0.008); Neu – fifth quintile, FEV_1 = -68.3 mL (95% CI, -132.5 to -4.2) (p for trend = 0.018); Mono – fifth quintile, FEV_1 = -73.0 mL (95% CI, -135.2 to -10.7) (p for trend = 0.021)
n. This reference reports on data obtained from the ECLIPSE Study. ECLIPSE was conducted in 46 centers located in 12 different countries in Europe and North America [114].
o. The ECLIPSE study is projected to have a follow-up period of 3 years. However, the publication cited provides follow-up data for only one year. This period of time too short to be able to assess the prospective association of WBC count in healthy controls with risk of COPD, and these data were not presented. As a consequence, the results provided are based on baseline values and thus the study should be considered as a case-control study.
p. The association between WBC count and FEV_1 was statistically stronger in men than in women
q. Both WBC and Neu counts are statistically significantly increased in COPD patients with exacerbation compared to stable COPD patients (P<0.001)

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The 15 studies listed in Table 4 originate from nine different countries, with three from Sweden, two each from the UK, Greece, and China, and one each from Finland, Austria, Croatia, the USA, Spain, and Turkey. In addition there is one multicenter study involving 46 centers in 12 different countries. Eleven of these studies were case-control studies, although controls were not matched to controls and no adjustment was performed for five of these studies. The remaining three studies were cross-sectional. Although the study based on the ECLIPSE cohort (number 10) was designed to be a longitudinal prospective study with a follow-up of 3 years, the only usable data correlating consisted of a comparison of WBC count between cases and controls at baseline, making this a case-control study as well.

Three studies compared neutrophil percentages in COPD cases and controls in induced sputum (numbers 1, 2, and 5) and one study (number 4) measured WBC and neutrophil numbers and percentages in bronchoalveolar (BAL) fluid. Neither induced sputum nor BAL fluid are ideal sample types for clinical studies. Nonetheless, it should be noted that the three studies that investigated neutrophils in induced sputum all reported statistically significant differences between cases and controls. Seven studies (numbers 3, 6, 7, 10, 13-15) compared circulating WBC counts in cases versus controls. Two of these studies (3 and 6) did not report a significant difference in WBC counts. One of these studies (6) was quite small (N = 64), but study 3 consisted of 60 cases and 40 controls. The five remaining studies all reported a statistically significant difference ($P<0.001$) between COPD cases and controls including the study drawn from the ECLIPSE cohort. Three studies (9, 11, and 12) reported the association of circulating WBC with FEV_1. The results were statistically significant for all three studies.

Only four studies (6, 8, 9, and 15) provided results for circulating neutrophils. Three of these provided data comparing neutrophil levels in COPD patients to controls. Study 15 found a highly statistically significant difference; study 8 reported a statistically significant difference in females but not in males; while study 6 did not report a significant difference. It should be noted that study 6 reported the results for a small study that also found no difference for circulating WBC count. Study 9 reported a statistically significant association between neutrophil counts and FEV_1. Study 9 was the only study that provided data on monocytes, and this cell type was also statistically significantly associated with FEV_1.

The results tabulated in Table 4 clearly demonstrate that there is a clear association between WBC count and COPD and an inverse association with FEV_1. Therefore, WBC count has been shown to be a potentially useful biomarker for all three major smoking-related diseases.

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5. SMOKING-BIOMARKER LINK

Studies Conducted Prior to 2008

To identify relevant references related to the association of WBC count and smoking prior to 2008, a search of PubMed using the terms "white blood cell" and "smoking" as well as "leukocyte" and "smoking" was conducted for all articles prior to 2008. Secondly, all references related to two relevant articles, one published in 2007 [115] and one published in 2005 [116], were screened. Lastly, articles cited in five reviews, three published in 1987 [117-119], one in 1988 [120], and one in 2007 [121], were also obtained as well as all articles cited in the references utilized. A total of 82 references, judged to be relevant based on PubMed abstracts, were obtained for the association of WBC count and smoking. Of these, 16 articles were excluded based on the inclusion and exclusion criteria outlined above. Lastly three articles were judged to be more appropriate for other relevant aspects of WBC count. This left a total of 63 relevant articles, two of which related to the same study. These 63 references plus the five review articles led to the inclusion of an additional 68 references.

The 62 relevant pre-2008 publications related to WBC count and smoking are listed in Table 5. Of these publications 22 concerned studies conducted in the US, 14 studies conducted in the UK, 4 in Germany and Italy, 3 each in France, India, Japan, and Canada, and 1 each in Denmark, Norway, Israel, Hungary, China, Spain, and Sweden. All studies were cross-sectional.

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Table 5. Association of Smoking with WBC Count - Studies Prior to 2008.

Study	Year and Country	Type of Study	Study Size	Mean Age (±SD) or Age Range	% Male	Type of Cell [a]	Result – Units 10^9/L unless noted ±SD unless noted	Covariates Adjusted for [b]
1. Howell [122]	1970, UK	Cross-sectional	2,483	40-54	100	WBC	Elevated levels in smokers (>20 cpd) (N = 424, 7.6±2.3) compared to non-smokers (N = 606, 6.0±1.7) (P<0.0001 [c])	None
2. Corre [123]	1971, France	Cross-sectional	4,264	46-52	100	WBC	WBC elevated in smokers (N = 3,183, 6.6) compared to non-smokers (N = 1081, 5.7) (p = 0.001)	Inh [d]
3. Friedman [124]	1973, USA	Cross-sectional	86,486	15-79 [e]	44.3	WBC	Elevated in all groups of smokers compared to non-smokers (P<0.0001 [c]). See [f] for details	None
4. Okuno [125]	1973, USA	Cross-sectional	106	20-39	100	WBC	Elevated in smokers (N = 58, 6.7) compared to non-smokers (N = 48, 5.4) (p = 0.001)	None
5. Parulkar [126]	1973, India	Cross-sectional	379	20-60	100	WBC	Elevated in smokers (N = 303, 9.8±1.6) compared to non-smokers (N = 76, 7.3±1.4) (P<0.001)	None
6. Billimoria [127]	1975, UK	Cross-sectional	121	30-70	54.5	WBC	Elevated in male heavy smokers (N = 23, 8.5±0.5) compared to male non-smokers (N = 34, 5.5±0.2) (P<0.005); non-significant elevation in female heavy smokers (N = 13) compared to female non-smokers (N =24) (0.05<P<0.10)	None
7. Noble [128]	1975, USA	Cross-sectional	27	20-30	100	WBC	Elevated in smokers (N = 14, 7.6) compared to non-smokers (N = 13, 5.9) (P<0.001)	None
8. Helman [129]	1975, USA	Cross-sectional	800	20-69	43.4	WBC	Elevated in male smokers (N = 116, 8.7±1.7) compared to male non-smokers (N = 231, 7.1±1.5) and in female smokers (N = 161, 8.8±1.9) compared to female non-smokers (N = 292, 7.1±1.7) (P<0.0001)	None

(table continues)

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Study	Year and Country	Type of Study	Study Size	Mean Age (±SD) or Age Range	% Male	Type of Cell [a]	Result – Units 10^9/L unless noted ±SD unless noted	Covariates Adjusted for [b]
9. Parulkar [130]	1975, India	Cross-sectional	130	16-60	100	WBC, Neu, Mono	There was no statistically significant difference for any of the three cell types between smokers (N = 65) and non-smokers (N = 65); WBC, 8.9±2.2 vs. 6.4±2.0; Neu, 60±13% vs 64±10%; Mono, 5±4% vs 4±2%	None
10. Fisch [131]	1975, USA	Cross-sectional	14,866 [g]	18-60	0	WBC	Elevated in smokers (>1 pack/day) compared to non-smokers (P<0.0001 in all four groups [c]); see [g] for details	Age
11. Silverman [132]	1975, USA	Cross-sectional	268	36.1	40.7	WBC	Elevated in smokers (N = 153, 6.8±0.2 (SEM)) compared to non-smokers (N = 115, 6.0±0.2(SEM)) (P<0.01)	None
12. Eschwege [133]	1978, France	Cross-sectional	7,710	48-54	100	WBC	Elevated in smokers without liver disease (N = 5,317, 6.7± 0.03(SEM)) compared to non-smokers without liver disease (N = 1,952, 5.7±0.03(SEM)) ($P<10^{-9}$)	Alc [h]
13. Zalokar [134]	1981, France	Cross-sectional	16,188	43-53	100	WBC	Elevated in current smokers (inhalers) (N = 2,456, 7.3) compared to never smokers (N = 4,056, 5.7) (no p value provided)	None
14. Dodsworth [135]	1981, UK	Cross-sectional	737	18-64	57.7	WBC, Neu	Both cell types elevated in smokers (N = 153) compared to non-smokers (N = 256) (P<0.005)	None
15. Winkel [136]	1981, USA	Cross-sectional	21	24-62	52.4	WBC, Neu, Mono	WBC and Neu elevated in smokers (N = 7) compared to non-smokers (N = 14); WBC, 9.2±0.9 vs 6.8±1.1 (P<0.01); Neu, 5.9±0.9 vs 3.9±0.9; (P<0.01) monocytes were not significantly different between smokers and non-smokers (0.6±0.1 vs 0.5±0.1)	None

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Study	Year and Country	Type of Study	Study Size	Mean Age (±SD) or Age Range	% Male	Type of Cell [a]	Result – Units 10^9/L unless noted ±SD unless noted	Covariates Adjusted for [b]
16. Heinemann [137]	1982, Germany	Cross-sectional	80	NS [i]	68.7	WBC	WBC elevated in smokers (N = 50, 6.9g/L) compared to non-smokers (N = 30, 7.0 g/L) (p = 0.05)	None
17. Nancy [138]	1982, India	Cross-sectional	200	25-45	100	WBC, Neu, Mono	WBC elevated in smokers (N = 100) compared to non-smokers (N = 100); WBC, 9.2±0.2(SE) vs 7.3± 0.2(SE) (P<0.001); Neu and Mono decreased in smokers compared to non-smokers; Neu 54.7±0.8 (SE) vs 58.4± 0.7(SE) (P<0.001), Mono 2.1±0.2(SE) vs 2.7±0.2(SE) (P<0.01)	None
18. Abboud [139]	1983, Canada	Cross-sectional	54	42.8±12.7	100	Neu	Elevated in smokers with normal lung function (N = 17, 5.3±1.8) compared to non-smokers (N = 24, 3.8±0.9) (P<0.001[c])	None
19. Sparrow [140]	1984, USA	Cross-sectional	2,144	21-80	100	WBC	Elevated in smokers of >20 cpd (N = 205, 8.8±2.1) compared to never smokers (N = 466, 6.8±1.6) (P<0.001)	Age
20. Yeung [141]	1984, Canada	Cross-sectional	3,446	>20-<80	100	WBC	Elevated in current smokers compared to non-smokers (P<0.0001)	None
21. Yarnell [142]	1985, UK	Cross-sectional	688	30-69	100	WBC	Elevated in moderate smokers (N = 113, 8.4 (95% CI, 8.0-8.8)) compared to non-smokers (N = 129, 6.0 (95% CI, 5.8-6.2)) (P<0.0001 [c])	None
22. Nielsen [143]	1985, Denmark	Cross-sectional	82	21-75	41.5	WBC. Mono	Both cell types elevated in smokers (N = 41) compared to non-smokers (N = 41); WBC, 7.6±2.2 vs 5.9±1.9 (P<0.05); Mono, 0.5± 0.2 vs 0.4±0.2 (P<0.05)	None
23. Tell [144]	1985, Norway	Cross-sectional	579	12-16	50.9	WBC	Increasing trend of WBC with smoking frequency (P<0.005)	None

(table continues)

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Study	Year and Country	Type of Study	Study Size	Mean Age (±SD) or Age Range	% Male	Type of Cell [a]	Result – Units 10^9/L unless noted ±SD unless noted	Covariates Adjusted for [b]
24. Taylor [145]	1985, UK	Cross-sectional	237	25-61	100	WBC	Elevated in smokers (N = 120, 7.3 (95% CI, 6.9-7.9)) compared to never-smokers (N = 44, 5.8 (95% CI, 5.1-6.7)) (P<0.005)	None
25. Carel [146]	1985, Israel	Cross-sectional	31,331	20-80	73.0	WBC	Elevated in male smokers (N = 9,739, 8.2±1.9) compared to male non-smokers (N 13,136, 7.2±1.5) and in female smokers (N = 2,803, 7.9±1.9) compared to female non-smokers (N = 5,653, 7.1±1.6) (P<0.001 for both)	None
26. Bridges [147]	1986, USA	Cross-sectional	340	37	100	WBC, Neu, Mono	All three cell types increased in smokers (N = 170) compared to non-smokers (N = 170); WBC, 34.0%, (P<0.0001); Neu, 40.8% (P<0.0001); Mono, 23.5% (P<0.002)	None
27. Yarnell [148]	1987, UK	Cross-sectional	4,445 [j]	45-59	100	WBC	Statistically significantly elevated in moderate (15-24 cpd) smokers compared to never-smokers; see [j] for details	None
28. Knoke [149]	1987, USA	Cross-sectional	2,225	NS	100	WBC	Increasing trend of WBC count with cpd (P<0.001)	Hemat, HR
29. Ernst [150]	1987, Germany	Cross-sectional	150	40.4±6.0	100	WBC	Elevated in moderate (10-20 cpd) smokers (N = 33, 7.9±2.0) compared to non-smokers (N = 30, 5.9±2.1) (P<0.01)	None
30. Friedman [151]	1990, USA	Cross-sectional	3,468	18-30	44.8	WBC	Increasing trend of WBC count with cpd (p = 0.0001)	Age, race, edu, cent, sex, season, BMI, height, pulse rate, pro, host, mar, phys, HDL-C, BP

(table continues)

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Study	Year and Country	Type of Study	Study Size	Mean Age (±SD) or Age Range	% Male	Type of Cell [a]	Result – Units 10^9/L unless noted ±SD unless noted	Covariates Adjusted for [b]
31. Regius [152]	1990, Hungary	Cross-sectional	499	>60	42.2	WBC	Elevated in smokers (N = 112, 6.9±1.7) compared to non-smokers (N = 387, 6.1±1.6) (P<0.001)	None
32. Hansen [153]	1990, USA	Cross-sectional	12,866	35-57	100	WBC	Increasing trend of WBC count with cpd (p = 0.001)	None
33. Schwartz [154]	1991, USA	Cross-sectional	8,635	30-74	NS	WBC	Increasing trend of WBC count with cpd (p = 0.0001)	Age, race, sex, pack-years, BMI, alc, height
34. Kannel [155]	1992, USA	Cross-sectional	3,159	30-59	49.3	WBC	Elevated in smokers (N = 1,381, 7.1±1.9) compared to non-smokers (N = 1,778, 5.6±1.4) (P<0.05)	None
35. Nieto [156]	1992, USA	Cross-sectional	14,679	45-64	43.7	WBC	Elevated in Caucasian current smokers (N = 2,646, 7.7) compared to Caucasian never smokers (N = 4,182, 5.7) and in Afr. Amer. current smokers (N = 1,158, 6.3) compared to Afr. Amer. never smokers (N = 1,547, 5.2) (P<0.0001 for both)	None
36. Phillips [157]	1992, USA, UK [k]	Cross-sectional	28,181	47.3±6	100	WBC	Statistically significantly elevated in smokers compared to never smokers (results presented graphically and p value not given)	None
37. Capuano [158]	1995, Italy	Cross-sectional	1,091	25-74	47.8	WBC	Elevated in moderate (11-19 cpd) smokers (N = 121, 8.0±2.2) compared to never smokers (N = 559, 6.7±1.7) (P<0.05)	None
38. Calori [159]	1996, Italy	Cross-sectional	54 [l]	47.4±12.9	25.9	WBC	Elevated in smoking twins (N = 27, 6.2±0.9) compared to non-smoking twins (N = 27, 5.7±0.9), but result not significant (p = 0.06)	None
39. Freedman [160]	1996, USA	Cross-sectional	4,097	31-45	100	WBC	Increasing trend of WBC count with cpd (P<0.001)	None

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Study	Year and Country	Type of Study	Study Size	Mean Age (±SD) or Age Range	% Male	Type of Cell [a]	Result – Units 10^9/L unless noted ±SD unless noted	Covariates Adjusted for [b]
40. Freedman [161]	1996, USA	Cross-sectional	3,467	31-45	100	WBC, Neu, Mono	Elevated levels of all three cell types in current smokers (N = 1,526) compared to never smokers (N = 893); WBC, 7.6 vs 5.6; Neu, 4.5 vs 3.2; Mono, 0.42 vs 0.35 (P<0.001 for all three cell types)	None
41. Targher [162]	1996, Italy	Cross-sectional	90	38	100	WBC, Neu, Mono	WBC and Neu elevated in smokers (N = 42) compared to non-smokers (N = 48) (P<0.01 and <0.05, respectively); no significant change for Mono (results reported graphically)	None
42. Sunyer [163]	1996, USA	Cross-sectional	3,725	>18	100	WBC, Neu, Mono	WBC and Neu elevated in smokers (1-2 packs/day, N = 493 [m]) compared to never smokers (N = 980 [m]; WBC, 7.9±0.0(SE) vs 6.3±0.02(SE) (P<0.0001 [c]), Neu, 58.6% vs 55.8% (P<0.05); Mono depressed in 1-2 pack/day smokers compared to never smokers, 5.6% vs 5.9% (P<0.05)	None
43. Parry [164]	1997, UK	Cross-sectional	684	33.0±10.4	41.4	WBC, Neu, Mono	Elevated levels of all three cell types in current smokers (N = 210) compared to non-smokers (N = 346); WBC, 7.1 ±2.0 vs 5.5±1.2; Neu, 4.2±1.6 vs 3.2±1.1; Mono, 0.6±0.2 vs 0.4±0.2 (P<0.05 for all three cell types)	[n]
44. Celada [165]	1997, Spain	Cross-sectional	1,022	40.5±8.0	100	WBC	Elevated in smokers compared to non-smokers in a stepwise multiple regression analysis (P<0.05)	Age, HDL-C

(table continues)

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Study	Year and Country	Type of Study	Study Size	Mean Age (±SD) or Age Range	% Male	Type of Cell [a]	Result – Units 10^9/L unless noted ±SD unless noted	Covariates Adjusted for [b]
45. Bergmann [166]	1998, Germany	Cross-sectional	66	49.6±4.8	0	WBC, Neu, Mono	All three cell types were elevated in smokers (N = 33) compared to non-smokers (N = 33); WBC, 7.6±2.0 vs 6.0±1.3 (p = 0.001), Neu, 4.4±1.8 vs 3.3±0.9 (P= 0.003); Mono, 0.6±0.2 vs 0.5±0.2 (p = 0.042)	None
46. Capuano [167]	1998, Italy	Cross-sectional	147	49±11	29.2	WBC	Increasing trend of WBC count with cpd (P<0.009)	Glyc, fib, azotemia
47. Ogawa [168]	1998, Japan	Cross-sectional	1,396	20-59	100	WBC, Neu	Both WBC and Neu elevated in smokers compared to ex-smokers and non-smokers (P<0.001) (results presented graphically)	None
48. Roth [169]	1998, USA	Cross-sectional	20	33.5±7.0	70	Neu [o]	Elevated in smokers compared to non-smokers (60%) (not significant) (results presented graphically)	None
49. Fredriksson [170]	1999, Sweden	Cross-sectional	83	51.5±8.0	45.8	WBC, Neu	Both cell types were elevated in smokers (N = 33) compared to non-smokers (N = 50) (p = 0.017 and 0.006, respectively)	None
50. Woodward [171]	1999, UK	Cross-sectional	1,574	25-74	47.8	WBC	Elevated in current smokers (N = 740) compared to never smokers (N = 425) (p = 0.0001)	None
51. van Eeden [172]	2000, Canada	Cross-sectional	53	36.2±3.4	50.9	WBC, Neu	Both WBC and Neu elevated in smokers (N = 38) compared to non-smokers (N = 15); WBC, 6.8±0.3 vs 5.3±0.2; Neu, 4.2±0.2 vs 3.2±0.2 (p = 0.001, 0.003, respectively)	None
52. Yarnell [173]	2000, UK	Cross-sectional	2,188	45-59	100	WBC	Elevated in smokers, irrespective of amount smoked, compared to never smokers (P<0.0001)	None

(table continues)

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Study	Year and Country	Type of Study	Study Size	Mean Age (±SD) or Age Range	% Male	Type of Cell [a]	Result – Units 10^9/L unless noted ±SD unless noted	Covariates Adjusted for [b]
53. Chalmers [174]	2001, UK	Cross-sectional	97 [p]	36.1±9.2	53.6	Neu [q]	Elevated in asthmatic smokers (N = 31, 9.1 (6.9-17.8)) compared to asthmatic non-smokers (N = 36, 3.2 (0.8-7) (p = 0.0001)) but not in healthy smokers (N = 15, 3.6 (1.4-9.8)) compared to healthy non-smokers (N = 15, 3.0 (0.5-9.3)) [r]	None
54. Fröhlich [175]	2003, Germany	Cross-sectional	4,516	49.4±14.0	51.0	WBC	Elevated in male regular smokers(N = 609) compared to male never smokers (N = 601) (7.9 vs 6.5) and female regular smokers (N = 408) compared to female never smokers (1315) (7.8 vs 6.7) (P<0.001 for both comparisons)	Age, BMI, total C, alc, BP, edu, phys, dia, CHD, cre
55. Smith [176]	2003, UK	Cross-sectional	15,307	58.0±9.4	45.1	WBC. Mono	Both cell types elevated in males (current smokers 839, never-smokers 2,421) and females (current smokers 925, never smokers 4,721); WBC: males, 7.8 vs 6.2; females 7.4 vs 6.2; Mono: males, 0.6 vs 0.5; females 0.6 vs 0.5 (P<0.0001 for all)	Age, BMI
56. Petropoulos [177]	2004, UK	Cross-sectional	33 [s]	46.9	[t]	Neu [u]	Slightly elevated in non- smokers (N = 19) compared to smokers (N = 14) (1.1±0.9 vs 0.7±0.8), but the difference was not significant (p = 0.11)	None
57. Ishizaka [178]	2004, Japan	Cross-sectional	3,455	56.8±10.2	67.4	WBC	Elevated in current smokers (N = 1,130, 6.4±1.8) compared to never smokers (N = 1,652, 5.3±1.3) (P<0.001)	None
58. Gan [179]	2005, USA	Cross-sectional	7,685	60.1±13.2	48.2	WBC	Elevated in smokers compared to non-smokers [v] (P<0.0001 [c])	Age, sex, race, BMI, co-morbidities, and drug use

(table continues)

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Study	Year and Country	Type of Study	Study Size	Mean Age (±SD) or Age Range	% Male	Type of Cell [a]	Result – Units 10^9/L unless noted ±SD unless noted	Covariates Adjusted for [b]
59. Wanna-methee [116]	2005, UK	Cross-sectional	2,920	67.8±5.3	100	WBC	Elevated in current smokers (N = 391, 7.92 (95% CI, 7.7-8.1)) compared to never smokers (N = 873, 6.4 (95% CI, 6.3-6.5)) (P<0.0001)	Age, sex, soc, phys, alc, BMI, BP, HDL-C
60. Yasue [180]	2006, Japan	Cross-sectional	438	64.8±10.4	100	WBC, Neu	WBC and Neu elevated in current smokers (N = 210) compared to never smokers (N = 113); WBC, 6.6±1.7 vs 5.6±1.3; Neu, 3.8±1.4 vs 3.3±1.2 (p = 0.01, P<0.05, respectively)	None
61. Yen [181]	2006, China	Cross-sectional	8,374	53.5±12.1	100	WBC, Neu, Mono	All three cell types elevated in current smokers (N = 2,229) compared to never smokers (N = 5,096); WBC, 7.2 vs 6.1; Neu, 3.8 vs 3.3; Mono, 0.5 vs 0.4 (P<0.001 for all three cell types)	None
62. Lavi [115]	2007, USA	Cross-sectional	881	49.8±0.7 [w]	37.9	WBC, Neu, Mono	WBC, Neu, and Mono elevated in smokers (N = 115) compared to never-smokers (N = 452); WBC, 7.7±0.2 vs 6.6±0.1; Neu, 4.4±0.2 vs 4.0±0.1; Mono, 0.6±0.01 vs 0.5±0.01 (P<0.05 for all three cell types)	None

Notes

a. WBC – white blood cell or leukocyte, Neu – neutrophil, Mono - monocyte
b. Inh – inhalers, hemat – haematocrit, HR – heart rate, total C – total cholesterol, alc – alcohol consumption, BP – blood pressure, edu – education, phys – physical activity, dia – diabetes, CHD – congestive heart disease, cre – creatinine, soc – social class, cent – study center, pro – protein intake, host – hostility, mar – marijuana, glyc – glycemia, fib – fibrinogen
c. p value calculated from data provided
d. The difference between smokers and non-smokers was restricted to smokers who inhaled
e. See Friedman et al., 1972 [182]
f. WBC count elevated in Caucasian male smokers (N = 14,416, 8.4±2.0x10^9/L) compared to Caucasian male non-smokers (N = 8246, 7.2±1.6x10^9/L) (P<0.0001); Caucasian female smokers (N = 15,972, 8.4±2.0x10^9/L) compared to Caucasian female non-smokers (N = 18,438, 7.4±1.7x10^9/L) (P<0.0001); African American male smokers (N = 2,590, 7.2±1.9x10^9/L) compared to African American male non-smokers (N = 1,108, 6.3±1.5x10^9/L) (P<0.0001); African American female smokers (N = 2,847, 7.6±2.1x10^9/L) compared to African American female non-smokers (N = 3,199, 6.8±1.8x10^9/L) (P<0.0001); Oriental male smokers (N =651,

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7.8±1.8x10^9/L) compared to Oriental male non-smokers (N = 709, 7.0±1.6x10^9/L) (P<0.0001); and Oriental female smokers (N = 441, 7.9±1.8x10^9/L) compared to Oriental female non-smokers (N = 1,308, 7.3±1.7x10^9/L) (P<0.0001)

g. Population divided into four groups: 1) non-obese and oral contraceptive (OC) non-users (N = 9606), 2) non-obese and OC users (N = 3,399), 3) obese and OC non-users (N = 1,580), and 4) obese and OC users (N = 281). For group 1, WBC elevated in smokers of >1 pack/day (N = 2,001, 7.7±0.04(SE)x10^9/L) compared to non-smokers (N = 6,321, 6.0±0.02(SE)x10^9/L); for group 2, WBC elevated in smokers of >1 pack/day (N = 726, 8.7±0.1(SE)x10^9/L) compared to non-smokers (N = 2154, 6.90±0.04 (SE)x10^9/L); for group 3, WBC elevated in smokers of >1 pack/day (N = 278, 8.5±0.1(SE)x10^9/L) compared to non-smokers (N = 1,114, 6.6±0.05(SE)x10^9/L); for group 4, WBC elevated I smokers of >1 pack/day (N = 50, 9.7±0.5(SE)x10^9/L) compared to non-smokers (N = 202, 7.4±0.1(SE)x10^9/L)
h. For heavy drinkers (N = 150) there was no significant difference in WBC count between smokers and non-smokers
i. NS – not specified
j. Population consists of results from the Caerphilly (N = 2,253) and Speedwell (N = 2,192) studies. For the Caerphilly study WBC in moderate smokers (N = 397) = 8.1±2.0x10^9/L compared to 5.9±1.2x10^9/L for never smokers (N = 356) (P<0.0001[c]). For the Speedwell study WBC in moderate smokers (N = 336) = 8.2±2.2x10^9/L compared to 6.0±1.3x10^9/L for never smokers (N = 322) (P<0.0001[c])
k. WBC (leukocyte) numbers were obtained during a single screening examination as part of three longitudinal studies; namely, the British Regional Heart Study (UK), the Multiple Risk Factor Intervention Trial 1 (USA), and the Multiple Risk Factor Intervention Trial 2 (USA)
l. Population consisted of 27 pairs of monozygotic twins discordant for smoking
m. Each subject was checked at multiple visits: number of person visits for 1-2 pack/day smokers was 2,185 and 7709 for never smokers
n. p-value adjusted for sex, age, education, weight, allergic status, and number of hours of daylight on the day of the study
o. Obtained from bronchial lavage
p. Subjects consisted of 15 non-asthmatic non-smokers, 15 non-asthmatic smokers, 36 asthmatic non-smokers, and 31 asthmatic smokers
q. Obtained from induced sputum
r. Results expressed as median and interquartile range
s. All subjects suffered from severe chronic periodontitis
t. Cannot be determined from data provided
u. Obtained from gingival crevicular fluid
v. Smokers defined as subjects with cotinine ≥10 ng/mL, non-smokers <10 ng/mL
w. Standard error of the mean

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A total of 74 estimates related to the association of only WBC count with smoking are listed in Table 5. Seven of these studies reported the association of WBC count with the trend of increasing cpd (publications 23, 28, 30, 32, 33, 39, and 46). All of the p-values for trend were highly statistically significant (at least P<0.01). The remaining 67 estimates compared WBC counts in smokers, generally current smokers, to non-smokers, generally never-smokers. It should be noted that many of these studies also compared results in smokers to former smokers which, in general, gave results very similar to those from never-smokers. However, the fact that there is considerable evidence that WBC counts decline following smoking cessation will be discussed later in the report. These 67 estimates consistently reported an increase of about 25-30% in WBC count in smokers compared to non-smokers. Only four estimates failed to report a statistically significant increase in WBC count in smokers compared to non-smokers. Three of the studies that provided non-significant estimates were quite small. Billimoria et al. [127] (Table 5, study 6) reported a p-value between 0.05 and 0.10 for the increase in WBC count in female heavy smokers compared to female non-smokers, but the total number of subjects was only 37. Parulkar et al. [130] (study 9) also reported no statistically significant difference in WBC count between smokers and non-smokers, but the total population size was 130. Lastly, Calori et al. [159] (study 38) reported no significant difference in smoking twins compared to non-smoking twins with a total sample size of 54. Despite the absence of statistical significance, however, all three of these studies did report an increase in WBC count in smokers compared to non-smokers. One study, Eschwege et al. [133] (study 12), although quite large, reported no difference between smokers and non-smokers for heavy drinkers only. Lastly, study number 13 reported an increase in WBC counts in smokers but did not report a p-value. Not only were the remaining 62 estimates for the association of WBC count with smoking statistically significant, but 27 of these estimates had p-values<0.0001, while an additional 15 estimates had P-values≤0.001. As a consequence there is no doubt that evidence published prior to 2008 clearly establishes a very strong association between elevated WBC count and smoking.

There were 21 estimates reported for the association of neutrophil count with smoking. Four of these estimates were not statistically significant (studies 9, 48, 53, and 56). As was the case for estimates for the association of WBC count with smoking, these four estimates all related to small populations (study 9, N = 130; study 48, N = 20; study 53, N = 30; and study 56, N = 33). Moreover, three of these studies did not measure circulating neutrophils but neutrophils obtained from bronchoalveolar lavage (study 48), induced sputum (study 53), and gingival crevicular fluid (study 56). Nancy et al. [138] (study 17) reported a statistically significant decrease in neutrophil counts in smokers compared to non-smokers. The remaining 16 estimates had p-values <0.05 and generally <0.01. Lastly, there were 13 estimates for the association of monocytes with smoking. Although three of these estimates were not statistically significant, once again these were small studies (study 9, N = 130; study 15, N = 21; and study 42, N = 90). Three of the four very large studies that investigated monocytes (studies 40, 55, and 61) reported increases with P-values of <0.001, <0.0001, and <0.001, respectively. On the other hand, Nancy et al. [138] (study 17), with N = 200 and Sunyer et al. [163] (study 42), with N = 1,473, reported a statistically significant decrease in monocyte percentage in smokers compared

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to never smokers. Overall, however, there is substantial evidence that both neutrophil count and monocyte count are also significantly elevated in smokers.

Studies Conducted from 2008-2015

The 21 publications dealing with WBC count and smoking identified from the literature search plus one new article that was identified via a literature search of WBC count and smoking cessation are listed in Table 6. This list is considerably shorter than the 62 studies listed in Table 5 for at least two reasons. Obviously one reason is that the time period (8 years) is much shorter than the 37-year time period for the older studies. However, the clear-cut positive association with WBC count, as well as neutrophil and monocyte count, with smoking was well-established by 2008, and many of the publications listed in Table 6 were focused on other scientific and medical issues with WBC count being only of peripheral interest. Scientific acceptance of the association of WBC count and smoking is also reflected by the fact that these 19 publications derive from a large number of countries with 4 from Japan, 3 from the US, 2 from Germany, Italy, and Taiwan, and 1 each from China, Egypt, Greece, Israel, Kuwait, the Netherlands, Tunisia, and the UK. As was the case with the older references, all studies were cross-sectional.

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Table 6. Association of Smoking with WBC Count - Studies 2008-2015.

Study	Year and Country	Type of Study	Study Size	Mean Age (±SD) or Age Range	% Male	Type of Cell [a]	Result – Units 10^9/L unless noted ±SD unless noted	Covariates Adjusted for [b]
1. Al-Awadhi [183]	2008, Kuwait	Cross-sectional	92	31.2 [c]	59.8	WBC	Elevated in male smokers (N = 31, 8.5, range 5.1-23.7) compared to male non-smokers (N = 24, 7.1, range 5.1-9.3) (p = 0.03); no difference between female smokers (N = 18, 7.7, range = 4.6-11) and female non-smokers (N = 19, 7.5, range = 4.7-10.5) (p = 0.53)	None
2. Kung [184]	2008, Taiwan	Cross-sectional	1,169	18.6-22.8	100	WBC, Neu	WBC elevated in smokers (N = 292, 7.8±1.8) compared to non-smokers (N = 872, 7.1±1.8) (P<0.001); Neu not elevated in smokers (57.1±9.0%) compared to non-smokers (58.1±8.6%) (p = 0.084)	None
3. Otsuka [185]	2008, Japan	Cross-sectional	1,808	35-64	82.5	WBC	Elevated in male smokers (N = 503, 6.0±1.4) compared to male non-smokers (N = 989, 5.1±1.2) and in female smokers (N = 21, 5.9±1.4) compared to female non-smokers (N = 295, 4.8±1.2) (P<0.0001, <0.001, respectively [d])	None
4. Pitsavos [186]	2008, Greece	Cross-sectional	2,072 [e]	66±13.3	75.5	WBC	Increased percentage of current smokers compared to never smokers in the highest WBC tertile (38% vs 30%, P<0.001)	None
5. Bergmann [187]	2009, Germany	Cross-sectional	313	54.9± 10.8	0	WBC	Elevated in non-obese smokers (N = 6.5±1.8) compared to non- obese non-smokers (N = 113, 5.5±1.3) and in obese smokers (N = 31, 6.2±1.7) compared to obese non-smokers (N = 144, 6.1±1.5 (P<0.001, <0.01, respectively)	None

(table continues)

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Study	Year and Country	Type of Study	Study Size	Mean Age (±SD) or Age Range	% Male	Type of Cell [a]	Result – Units 10^9/L unless noted ±SD unless noted	Covariates Adjusted for [b]
6. Calapai [188]	2009, Italy	Cross-sectional	60	28.7±4.1	55.0	WBC, Neu	WBC elevated in male smokers (N = 12, 7.1± 1.4) compared to male never smokers (N = 9, 5.8±6.2) (P<0.01) and in female smokers (N = 8, 8.0±2.2) compared to female never smokers (N = 11, 5.9±1.9 (P<0.001); Neu significantly elevated in female smokers (67.4±6.1%) compared to female never smokers (58.5±11.1%) (P<0.05) but not in male smokers compared to male never-smokers	None
7. Lao [189]	2009, China	Cross-sectional	2,996	66.2	100	WBC	Elevated in current smokers (N = 837, 7.04 (95% CI. 6.9-7.2)) compared to never smokers (N = 1,266, 6.2 (95% CI, 6.1-6.3)) (P<0.001)	None
8. Steinvil [190]	2009, Israel	Cross-sectional	8,247	44.3±11	65.4	WBC. Neu	Both cell types elevated in current smokers (N = 1,469) compared to never smokers (N = 4,691); WBC, 7.5±2.0 vs 6.5±1.5 (P<0.0001 [d]); Neu, 4.5±1.6 compared to 4.0±1.1 (P<0.0001 [d])	None
9. Tseng [191]	2009, Taiwan	Cross-sectional	207	22-77	63.3	WBC	Elevated in high risk drinkers; smokers (N = 57, 6.9±1.4) compared to non-smokers (N = 48, 5.5± 1.0) (P<0.01); not significantly elevated in low risk drinkers; smokers (N = 13, 6.3±0.9) compared to non-smokers (N = 89, 6.0± 1.4) (p = 0.34 [d])	None
10. Emara [64]	2010, Egypt	Cross-sectional	40	30.6±5.6	100	WBC, Neu, Mono	WBC and Neu elevated in smokers (N = 20) compared to non-smokers (N = 20) (P<0.05); Mono levels were equal in smokers and non-smokers [f]	None
11. Hsu [65]	2010, Japan	Cross-sectional	7,562	46.7±8.1	36.2	WBC	Elevated in smokers compared to non-smokers (P<0.001) [g]	None

(table continues)

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Study	Year and Country	Type of Study	Study Size	Mean Age (±SD) or Age Range	% Male	Type of Cell [a]	Result – Units 10^9/L unless noted ±SD unless noted	Covariates Adjusted for [b]
12. Weiss [192]	2010, Austria	Cross-sectional	41	67±13	75.2	WBC	Elevated in smokers (N = 7, 7.4 (5.7-8.2)) compared to non-smokers (N = 34, 6.6 (5.8-7.2) (not significant) [h]	
13. Andreoli [193]	2011, Italy	Cross-sectional	44 [i]	31.5	59.1	WBC, Neu	Both cell types elevated in smokers (N = 22) compared to non-smokers (N = 22); WBC, 7.6±1.9 vs 6.3±1.5 (P<0.01); Neu, 4.6±1.7 vs 3.9±1.3 (P<0.05)	None
14. Frost-Pineda [194]	2011, USA	Cross-sectional	4,662	42.0± 13.2	42.1	WBC	Elevated in smokers (N = 3,509, 8.0±2.3) compared to non-smokers (N = 1,063, 6.7±1.7) (P<0.0001)	None
15. Liu [195]	2011, USA [j]						[j]	
16. de Graan [196]	2012, Nether-lands	Cross-sectional [k]	566	18-85	44.9	WBC	Elevated in smokers (N = 62, 9.1 (range 4.8-19)) compared to non-smokers (N = 214, 7.1 (range 2.3-24)) (P<0.0001) before treatment with paclitaxel; not significantly elevated in smokers (N = 75, 9.2 (range 3.4-27)) compared to non-smokers (N = 215, 8.4 (range 2.9-29)) (p = 0.4) before treatment with docetaxel [l]	None
17. Ebner [197]	2013, UK, Germany	Cross-sectional	105 [m]	63.7± 14.6	73.5	WBC	Statistically significant trend for WBC count and cotinine levels (P<0.01)	Age, BMI, Hb, eryth, cre, chol
18. Sakuragi [198]	2013, Japan	Cross-sectional	103,492, 130,431 [n]	43.0± 12.0, 44.2± 11.7	100	WBC	First group: current smokers (N = 56,529) 6.8±1.9 compared to never smokers (N = 34,298) 5.6±1.4 (P<0.01); second group: current smokers (N = 53,642) 6.8± 1.9 compared to never smokers (N = 40,748) 5.7±1.4 (P< 0.01)	None

(table continues)

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Study	Year and Country	Type of Study	Study Size	Mean Age (±SD) or Age Range	% Male	Type of Cell [a]	Result – Units 10^9/L unless noted ±SD unless noted	Covariates Adjusted for [b]
19. Snitker [199]	2013, USA	Cross-sectional	739	43.2±0.7 (SE)	51.8	WBC	Elevated in current male smokers (N = 76, 6.1±0.2 (SE)) compared to male never smokers (N = 243, 5.2±0.2 (SE)) (P<0.001); no data for females	None
20. Honda [200]	2014, Japan	Cross-sectional	266 [o]	67.6± 10.0	64.9	WBC	Elevated in current smokers (N = 103) 11.0±3.5 compared to never smokers (N = 84) 9.4±3.3 (P<0.05)	None
21. Khelifi [201]	2014, Tunisia [p]	Cross-sectional	20	39±7.8	100	WBC, Neu	WBC elevated in smoking phosphate mine workers (PMW) (N = 8, 7.9, range 6.0-8.8) compared to non-smoking PMW (N = 4, 6.0, range 5.0-10.5) (p = 0.05) and in smoking controls (N = 4, 5.8, range 5.0-6.5) compared to non-smoking controls (N = 4, 5.3, range 4.4-7.0 (p = 0.05); no difference in Neu counts between smokers and non-smokers in either group	None
22. Kawada [202]	2015, Japan	Cross-sectional	5,862	43.1±7.1	100	WBC	Elevated in current smokers <20 cig/day (N = 1,492, 7.05±0.1(SE)) compared to never smokers (N = 1,512, 6.0±0.1(SE)) (P<0.05) and in current smokers ≥20 cig/day (N = 1,266, 7.8±0.1(SE)) compared to never smokers (N = 1,512, 6.0±0.1(SE)) (P<0.05)	[q]

Notes

a. WBC – white blood cell or leukocyte, Neu – neutrophil, Mono - monocyte
b. Hb – hemoglobin, eryth – erythrocyte count, cre – creatinine, chol - cholesterol
c. There was a very large difference between the average age of smokers (37.2) and non-smokers (24.8)
d. p value calculated from data provided
e. All subjects were patients diagnosed with acute coronary syndrome (ACS)
f. Results presented graphically
g. The main goal of this publication was to determine the effect of radiation exposure on WBC count in Japanese atomic bomb survivors. A linear regression background model was established. For both males and females, smoking had the largest effect on WBC count with $\square_{smk}$ = 0.7 (95% CI, 0.5-0.9) for males and 0.7 (95% CI, 0.5-0.8) for females. Other factors included age at time of examination, BMI, indicator of infectious disease (males) and city (females)
h. Results expressed as median and interquartile range

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i. The population consisted of 2 sets of 22 monozygotic twins discordant for smoking. The fact that there were 26 males and 18 females (59.1% male) appears to be highly unusual.
j. This publication is based on the same data base (Altria Total Exposure Study) as the previous study (Frost-Pineda) [194]. The results, however, are slightly different; WBC elevated in smokers (N = 3,585, 7.6 (95% CI, 7.5-7.9)) compared to non-smokers (N = 1,077, 6.2 (95% CI, 6.1-6.4)) ($p < 0.0001$)
k. This study was a retrospective study designed to assess the effect of smoking on the pharmacokinetics and toxicities of two taxane-based drugs, paclitaxel and docetaxel. The WBC data, however, were obtained at baseline before start of treatment.
l. As indicated in the note above, the WBC data were obtained at baseline. Therefore, there is no obvious explanation for the difference between the two groups.
m. Seventy-five subjects were diagnosed with chronic heart failure, while the remaining 30 were control subjects
n. The first number represents a group enrolled in 2002 and the second, a group enrolled in 2010
o. All subjects had suffered an acute myocardial infarction; WBC data are at baseline
p. This study evaluated the effect of occupational exposure to phosphate mine dust as well as smoking. There were 12 phosphate mine workers (8 smokers and 4 non-smokers) and 8 controls (4 smokers and 4 non-smokers)
q. p value was calculated following adjustment for age and correction using the Bonferroni procedure for multiple comparisons

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The overall results for the more recent literature are completely in line with the earlier results. WBC count is clearly elevated in smokers, generally current smokers, compared to non-smokers, generally never smokers. On average, the increase is in the vicinity of 15-25%. One of the publications (study 4) reported an increased percentage in current smokers compared to never smokers in the highest WBC count quartile, while a second publication (study 18) reported a statistically significant trend for WBC count associated with increasing cotinine levels. The study by Liu et al. [195] (study 15) was based on the same data set used by Frost-Pineda et al. [194] (study 14). The results, however, were slightly different and are presented in note [j]. For the remaining 19 publications, there were 28 estimates that provided data relevant to the association of WBC counts with smoking. Of these estimates, only four were not statistically significant. Al-Awadhi [183] (study 1) reported no WBC count difference between female smokers and female non-smokers, although the difference in males was statistically significant. However, the total number of female subjects was only 37. Tseng et al [191] (study 9) reported a significant difference in WBC in "high-risk" (excessive) drinkers for smokers versus non-smokers but not in low-risk drinkers. Once again this estimate was based on a relatively small number of subjects (N = 102). Weiss et al. [192] (study 12) reported a large difference between smokers and non-smokers, but only seven smokers were included, undoubtedly explaining the lack of statistical significance. The last result that failed to reach statistical significance was rather unusual. De Grann [196] (study 16) retrospectively examined the effect of smoking on the pharmacokinetics and toxicities of two diterpene taxane drugs, paclitaxel and docetaxel (inhibitors of mitosis that are used to treat some cancers). They reported WBC count in smokers and non-smokers for both groups of subjects at baseline. For the group that was given docetaxel there was no significant difference in WBC count between smokers and non-smokers, despite there being a relatively large number of subjects (N = 289). For the group that was given paclitaxel, however, a highly significant difference ($P<0.0001$) was reported, although it was of comparable size (N = 233). The remaining 24 estimates were all statistically significant, with $P<0.0001$ for four estimates and $P<0.001$ for an additional eight estimates.

Only six estimates were reported for neutrophil counts. Three of these six estimates were not significant. Interestingly, one of these results was derived from a relatively large study (study 2, N = 1,164), while the remaining two were both derived from the same small study (number 21). There was only one estimate for monocytes (study 10), and the result was not statistically significant for this very small study (N = 40).

In conclusion there can be no doubt that in general, smoking results in a significant increase in WBC count based on a large number of estimates dating from 1970 to the present. There is also evidence suggesting that both neutrophils and monocytes are also increased in smokers compared to non-smokers. However, these data are somewhat less compelling. As a consequence, the first criterion with respect to WBC count qualifying as a biomarker for short-term health effects has been clearly satisfied.

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5.1 Smoking cessation

Studies Conducted Prior to 2008

A literature search was not carried out to identify studies dealing with WBC count and smoking cessation for studies conducted prior to 2008. A report was prepared by P.N. Lee Statistics and Computing Ltd that had identified 24 relevant studies [203]. Before discussing the results of this report, two points must be noted. First, all studies summarized in this report have determined the effect of smoking cessation on WBC count in the same group of individuals. This avoids comparison of groups of continuing smokers and quitters possibly differing on other relevant variables. Secondly, three studies were published subsequent to 2007 [204-206]. In that these studies will also be considered in the next section, they will have been double counted. However, considering the large number of studies involved, this is not anticipated to introduce any error.

The results of these 24 studies were meta-analyzed by Lee et al. in order to obtain a pooled decrease, for both WBC count and neutrophil count, associated with smoking cessation. A total of 36 estimates were available for WBC count, and the mean decrease in WBC count was -0.9 10^9/L (95% CI, -1.1 to -0.7) for the unweighted analysis and -0.8 10^9/L (95% CI, -1.0 to -0.7) for the weighted analysis. Both of these changes were highly statistically significant ($P<0.001$). Twenty-one estimates were available for neutrophil count drawn from seven studies with 20 showing a reduction. The pooled decrease was -0.7 10^9/L (95% CI, -0.9 to -0.5) for the unweighted analysis and -0.9 10^9/L (95% CI, -1.1 to -0.7) for the weighted analysis. This result is also clearly statistically significant.

A key point involving the change in WBC count following cessation is the time period required. Since the primary goal of validating WBC count as a biomarker for short term health effects of smoking is to determine the effect of switching from a conventional cigarette to an MRTP, the change in biomarker level must occur during a relatively short time scale to allow it be evaluated under practical circumstances. The data in the Lee et al. report indicate that an acute reduction takes place within the first two weeks. These data clearly support the validity of WBC count as a valid biomarker with a measurable and statistically significant decline in WBC count following smoking cessation that takes place in a short time period.

Studies Conducted from 2008-2015

Only five studies were located in the three literature searches that were conducted. One additional study, taken from the Lee et al. report, was added [204] resulting in two additional references including the Lee et al. report. In addition to these six references, six publications that were cited with respect to WBC count and smoking also provided relevant data for smoking cessation. Eleven of these references are listed in Table 7. The last reference will be discussed separately.

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Table 7. Change in WBC count following smoking cessation-Studies 2008-2015.

Study	Year and Country	Type of Study	Study Size	Age (% Male)	Type of Cell [a]	Result – Units 10^9/L unless noted ±SD unless noted	Covariates Adjusted for
1. Lao [189]	2009, China	Cross-sectional	2,996	66.2 (100)	WBC	Current smokers (N = 837, 7.0 (95% CI, 6.9-7.2)) compared to former smokers (N = 893, 6.4 (95% CI, 6.3-6.5)) (P<0.001)	None
2. Steinvil [190]	2009, Israel	Cross-sectional	8,247	44.3±11 (65.4)	WBC, Neu	WBC: current smokers (N = 1,469, 7.5±2.0) compared to former smokers (N = 2,090, 6.6±1.5) (P<0.0001 [b]); Neu: current smokers 4.5±1.6 compared to former smokers 3.9±1.1 (P<0.0001 [b])	None
3. Roethig [207]	2010, USA, South Africa	RCT [c, d]	105	43.8±6.5 (100)	WBC, Neu, Mono	WBC: smoking 8.7 (95% CI, 8.3-9.1) compared to non-smoking (3 days) 8.2 (95% CI, 7.8-8.5) (P<0.0001); Neu: smoking 57.1% (95% CI, 55.6-58.6) compared to non-smoking (3 days) 55.8% (95% CI, 54.3-57.3) (p = 0.02); Mono: 9.2% (95% CI, 8.5-9.8) compared non-smoking (3 days) 9.7% (95% CI, 9.0-10.3) (not significant)	None
4. Sorensen [204]	2010, Denmark	RCT (12 weeks)	48	20-40 (50)	Neu	Smokers (N = 48 (16 continuing, 32 baseline) 4.6±0.2(SE)) compared to abstainers (N = 26, 4.0±0.2(SE)) (P<0.01)	None
5. Yeh [205]	2010, USA	Longitudinal (prospective) [e]	10,892	45-64 (43.3)	WBC	New quitters at 3-year follow-up (N = 380) exhibited a decline of -0.5 (-0.6 to -0.3) [f] (P<0.001)	Sex, race, ARIC Study center, level of education, baseline age, phys. activity, baseline values, time between baseline and follow-up
6. Korhonen [208]	2011, USA	RCT (12 weeks) [g]	130 [h]	40.6±10.0 (0)	WBC	Abstainers (N = 58, 7.3±1.9 at baseline) compared to 6.9±1.7 at 12 weeks (not significant)	Adjustment for nicotine intake or exercise adherence did not change the results

(table continues)

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Study	Year and Country	Type of Study	Study Size	Age (% Male)	Type of Cell [a]	Result – Units 10^9/L unless noted ±SD unless noted	Covariates Adjusted for
7. Puls [206]	2011, Germany	RCT (5 weeks)	144 [i]	47.8±12.0 (43.0)	WBC	Baseline 8.4 (7.1-9.5) compared to five weeks 7.9 (6.8-8.9) [f] (p = 0.004)	None
8. Sakuragi [198]	2013, Japan	Cross-sectional	103,492, 130,431 [j]	43.0±12.0, 44.2±11.7 (100)	WBC	First group: current smokers (N = 56,529, 6.8±1.9) compared to former smokers (N = 12,665, 5.7±1.4) (P<0.01); second group: current smokers (N = 53,642, 6.8±1.9) compared to former smokers (N = 36,041, 5.8±1.4) (P< 0.01)	None
9.Snitker [199]	2013, USA	Cross-sectional	739	43.2±0.7 (SE) (51.8)	WBC	Elevated in current male smokers (N = 76, 6.1±0.2 (SE)) compared to male former smokers (N = 64, 5.5±0.2 (SE)) (P<0.04 [b]); no data for females	None
10. Honda [200]	2014, Japan	Cross-sectional	266 [k]	67.6±10.0 (64.9)	WBC	Elevated in current smokers (N = 103, 11.0±3.47) compared to former smokers (N = 79, 9.3±2.9) (P<0.05)	None
11. Kawada [202]	2015, Japan	Cross-sectional	5,862	43.1±7.1	WBC	Current smokers <20 cig/day (N = 1,492, 7.1±0.1 (SE)) compared to former smokers (1-6 yr) (N = 695, 6.0±0.1(SE)) (P<0.0001 [b]); current smokers ≥20 cig/day (N = 1,266, 7.8±0.1 (SE)) compared to former smokers (1-6yr) (6.0±0.1 (SE)) (P<0.0001 [b])	None

Notes

a. WBC – white blood cell or leukocyte, Neu – neutrophil, Mono – monocyte
b. p value calculated from data provided
c. RCT – randomized controlled trial
d. Data were obtained from three different randomized, controlled three-period crossover studies where smokers smoked a conventional cigarette, an electrically heated cigarette smoking system, and abstained from smoking
e. Data were obtained at baseline and after three years of follow up; WBC count in quitters was compared to baseline data
f. Results expressed as median and interquartile range
g. All subjects received NRT and a structured exercise program; there were four different groups varying slightly in the type of exercise program and/or counselling
h. Subjects analyzed at the end of the 12 week trial
i. All subjects were abstainers

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j. The first number represents a group enrolled in 2002 and the second, a group enrolled in 2010
k. All subjects had suffered an acute myocardial infarction; WBC data are at baseline

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The 11 studies listed in Table 7 are derived from seven different countries, four from the US, three from Japan, and one each from China, Denmark, Germany, Israel, and South Africa. Six of the studies are cross-sectional, four are randomized clinical trials (RCT), and one is a longitudinal prospective study. A total of 13 estimates for WBC in quitting smokers compared to continuing smokers were provided. Only one study (number 6) did not provide a statistically significant difference, and this was a relatively small study with 58 abstainers. Two estimates reported differences between smokers and quitters with $P<0.001$ and four estimates with $P<0.0001$. These results are completely in line with the conclusions reached by Lee et al. [203] despite the fact that a number of the studies listed in Table 7 do not represent studies where smokers and quitters were drawn from the same population. There were only three studies that reported results for neutrophils (numbers 2-4). All three reported a statistically significant decline of neutrophil counts following cessation. One study reported results for monocytes (number 3). The monocyte percentage actually increased in quitters, although the difference was not statistically significant.

These data also provide confirmation that the change in WBC count occurs rapidly. Particularly noteworthy are the results reported by Roethig et al. [207] (number 3) which indicate that a highly significant decrease ($P<0.0001$) in WBC count occurred after only three days of smoking cessation.

It is of interest to note that almost all studies, which provided data for former smokers and never smokers (numbers 1, 2, 8-11), reported a small difference between WBC counts between the two groups. For the seven estimates involved in these studies, six reported WBC count higher for former smokers compared to never smokers, and in four of the cases the difference was statistically significant. Only for Kawada et al. [202] was the result for former smokers slightly lower than that for never smokers, although the difference was not significant. Nevertheless, despite the apparent lower value for WBC count in never smokers compared to former smokers, there is no question that a significant decline in does occur following smoking cessation.

As noted above, discussion of the last publication in this group was deferred. This study, by Joseph et al. [209], deals with smoking reduction as opposed to smoking cessation. One hundred fifty-two subjects were enrolled and were randomized to either a smoking reduction (SR) group (N = 78) or a usual care (UC) group (N = 74). All subjects were smokers of at least 15 cig/day, aged 18-80, and had one of 11 cardiac disorders. The SR group received periodic counselling, and NRT was made available. The UC group received an initial brief in-person visit, and subjects were encouraged to seek smoking cessation assistance from their health care provider. The key conclusion of this study was that "smoking reduction has limited promise to significantly reduce risk in patients with heart disease." This conclusion was based on both biomarker and clinical data. However, there was a secondary analysis that analyzed data from the sub-group of subjects who reduced their smoking by at least 50% between baseline and six months (N = 43, 25 from the SR group and 18 from the UC group). These subjects had an average WBC count of 7.8 10^9/L at baseline compared to 7.2 10^9/L at the six-month time period ($P = 0.01$). Therefore, in individuals who made a meaningful reduction in smoking, WCB count was statistically significantly reduced.

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The data presented in this section clearly confirm that an increase in WBC is statistically significantly associated with smoking cessation. Moreover, at least a large percentage of the decline occurs quite rapidly.

5.2 Role in MRTP assessment

Since the goal of this analysis is to determine if WBC count is a valid biomarker for the evaluation of MRTPs, published studies that have evaluated change in WBC count for smokers who switch from a conventional cigarette to an MRTP are extremely important. Two relevant studies were identified by the literature searches that were performed, one of which was previously cited in the section covering smoking cessation [207]. Searching PubMed for additional articles was not successful. However, a search of similar articles in PubMed using the two references already identified [207, 210] located two additional relevant references. These four studies are summarized in Table 8.

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Table 8. Change in WBC count following switching to an MRTP-Studies 2008-2015.

Study	Year and Country	Type of Study	Study Size	Age (% Male)	Type of Cell [a]	Result – Units 10^9/L unless noted ±SD unless noted	Covariates Adjusted for
1. Roethig [211]	2008, USA	RCT (12 months)	97 (64 EHCSS, 33 CC) [b, c]	41.8±9.4 (46.4)	WBC	EHCSS smokers: baseline 7.5±0.2 (SE) compared to post-baseline [d] 6.6±0.7 (SE) (p = 0.0002); CC smokers: baseline 7.9±0.3 (SE) compared to post-baseline 7.8±0.1 (p = 0.74) [e]	None
2. Roethig [207]	2010, USA, South Africa	RCT [f]	105	43.8±6.5 (100)	WBC, Neu, Mono	WBC: smoking 8.7 (95% CI, 8.3-9.1) compared to EHCSS (3 days) 8.3 (95% CI, 7.9-8.7) (p = 0.0004); Neu: smoking 57.1% (95% CI, 55.6-58.6) compared to EHCSS (3 days) 55.2% (95% CI, 54.3-57.3) (not significant); Mono: 9.2% (95% CI, 8.5-9.8) compared to non-smoking (3 days) 9.3% (95% CI, 8.7-9.3) (not significant)	None
3. Flouris [212]	2012, Greece	Randomized crossover study [g]	15	36.8±9.9 (53.3)	WBC, Neu [h]	One hour after smoking both WBC and Neu count increased significantly (p = 0.004 and 0.04, respectively); no significant increase occurred 1 hour after smoking the e-cigarette (p>0.05)	None
4. Martin Leroy [210]	2012, Poland	RCT (5 weeks)	316 (237 EHCSS-K6, 79 CC) [i]	43.6±8.1 (51)	WBC, Neu	WBC: EHCSS-K6 smokers, baseline 7.1±1.73 compared to end of study 6.9±1.6 (P<0.01); Neu: EHCSS-K6 smokers, baseline 4.1±1.4 compared to end of study 3.9±1.3 (not significant, p = 0.11 [e])	None

Notes

a. WBC – white blood cell or leukocyte, Neu – neutrophil, Mono – monocyte
b. EHCSS – electrically heated cigarette smoking system, a potential MRTP, CC – conventional cigarette
c. 4 subjects in the EHCSS group and 1 subject in the CC group did not complete the study
d. Subjects were evaluated at nine different time points during the study; post-baseline represents the average of all nine measurements
e. p value calculated from data provided
f. Data were obtained from three different randomized, controlled 3-period crossover studies where smokers smoked a conventional cigarette, an electrically heated cigarette smoking system, and abstained from smoking

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g. Smokers were randomly assigned to one of three sessions – a control session, a smoking session, and an e-cigarette session. In the control session, smokers were asked to "smoke" an unlit cigarette for 30 minutes; in the smoking session, smokers were asked to smoke two cigarettes of their own brand for 30 minutes; in the e-cigarette session, smokers were asked to take puffs of an e-cigarette (Nobacco USA Mix, Nobacco GP G.P., Greece) during 30 minutes. Smokers were requested not to smoke during a week wash-out period between each session.
h. Granulocytes
i. 3 subjects in the EHCSS-K6 group and 4 subjects in the CC group did not complete the study

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Three of the four studies (numbers 1, 2, and 4) listed in Table 8 reported on the difference between baseline WBC or neutrophil counts and some time period after smokers switched from a conventional cigarette to potential MRTP. The relevant time periods ranged from three days (number 2) to 12 months (nimber1). All three studies reported changes in WBC count, and all three of the results were statistically significant. Two of these studies also reported results for neutrophils. Neither study reported a statistically significant change.Study 3 utilized a very different protocol; namely, difference in both WBC and neutrophil counts when smokers briefly used either a conventional cigarette or an e-cigarette after one week of non-smoking.Both WBC and neutrophil counts were statistically significantly increased following the smoking of two cigarettes but were not changed following smoking of an e-cigarette for a comparable time period.

With only four studies reporting data the association of potential MRTPs and WBC count, it is not possible to arrive at a definitive conclusion. Nevertheless, the results clearly support the notion that the effect of these potential MRTPs are more consistent with cessation of smoking as compared to continuing smoking.

6. CONCLUSION

The data presented in this report confirm that WBC count can be used as a fully validated biomarker with respect to assessing at least one aspect of the potential diminution of the health risks of smoking an MRTP compared to a conventional cigarette. There is a very large data set that establishes that cigarette smoking very significantly increases WBC counts. There is also a very large data set showing that there is a strong association between the level of WBC count and various CVD endpoints, particularly CHD. There is also a reasonable amount of literature confirming an association of WBC count with the other two major smoking-related diseases – lung cancer and COPD. Finally a large number of studies report a highly statistically significant decline in WBC count following smoking cessation. Moreover, this change occurs in a relatively short period of time (as little as two weeks). Lastly, although there are only a limited number of studies that have documented a decrease in WBC count when smokers switch from a conventional cigarette to a potential MRTP, these studies consistently support that WBC count does indeed decrease.

Considerably fewer studies reported on data related to change in neutrophil count or neutrophil percentage. These results were generally not only directionally similar to those for WBC count, but also gave results of similar statistical significance. Even fewer studies reported data for monocytes. Given that many of these results did not observe a change in monocyte count or percentage, there would certainly be no advantage in including data for this leukocyte type.

This report has not attempted to calculate an estimate for the size of a clinical study that would have at least 80% power to detect a meaningful change in WBC count when comparing results for an MRTP to a conventional cigarette. However, the data provided suggests that a study size of about 100 individuals should be able to detect such a change.

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7. APPENDICES

7.1 Appendix 1 References retrieved
7.2 Appendix 2 Literature excluded from search 1
7.3 Appendix 3 Literature excluded from search 2
7.4 Appendix 4 Literature excluded from search 3

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7.1 Appendix 1 References related to the included studies

1. U.S. Department of Health and Human Services. How tobacco smoke causes disease: the biology and behavioral basis for smoking-attributable disease: a report of the Surgeon General. Atlanta, GA: US Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health. 2010.
2. U.S. Department of Health and Human Services. The health benefits of smoking cessation. US Department of Health and Human Services Public Health Service Centers for Disease Control Center for Chronic Disease Prevention and Health Promotion Office on Smoking and Health. 1990;DHHS Publication No. (CDC)9O-8416.
3. Jha P, Ramasundarahettige C, Landsman V, Rostron B, Thun M, Anderson RN, et al. 21st-century hazards of smoking and benefits of cessation in the United States. N Engl J Med. 2013;368(4):341-50.
4. Miller BF, Keane Brackman C. Encyclopedia & dictionary of medicine, nursing & allied health. Philadelphia: Saunders; 2005.
5. Danesh J, Collins R, Appleby P, Peto R. Association of fibrinogen, C-reactive protein, albumin, or leukocyte count with coronary heart disease: meta-analyses of prospective studies. JAMA. 1998;279(18):1477-82.
6. Wong ND. Epidemiological studies of CHD and the evolution of preventive cardiology. Nat Rev Cardiol. 2014;11(5):276-89.
7. Madjid M, Awan I, Willerson JT, Casscells SW. Leukocyte count and coronary heart disease: implications for risk assessment. J Am Coll Cardiol. 2004;44(10):1945-56.
8. Pearson TA, Mensah GA, Alexander RW, Anderson JL, Cannon RO, 3rd, Criqui M, et al. Markers of inflammation and cardiovascular disease: application to clinical and public health practice: A statement for healthcare professionals from the Centers for Disease Control and Prevention and the American Heart Association. Circulation. 2003;107(3):499-511.
9. Sanders E. Possible pathomechanisms linking white blood count to cardiovascular disease. Edward Sanders Scientific Consulting, 2012.
10. Brown DW, Giles WH, Croft JB. White blood cell count: an independent predictor of coronary heart disease mortality among a national cohort. J Clin Epidemiol. 2001;54(3):316-22.
11. Lee CD, Folsom AR, Nieto FJ, Chambless LE, Shahar E, Wolfe DA. White blood cell count and incidence of coronary heart disease and ischemic stroke and mortality from cardiovascular disease in African-American and White men and women: atherosclerosis risk in communities study. Am J Epidemiol. 2001;154(8):758-64.

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12. Brown DW, Ford ES, Giles WH, Croft JB, Balluz LS, Mokdad AH. Associations between white blood cell count and risk for cerebrovascular disease mortality: NHANES II Mortality Study, 1976-1992. Ann Epidemiol. 2004;14(6):425-30.

13. Yarnell JW, Patterson CC, Sweetnam PM, Lowe GD. Haemostatic/inflammatory markers predict 10-year risk of IHD at least as well as lipids: the Caerphilly collaborative studies. Eur Heart J. 2004;25(12):1049-56.

14. Jee SH, Park JY, Kim HS, Lee TY, Samet JM. White blood cell count and risk for all-cause, cardiovascular, and cancer mortality in a cohort of Koreans. Am J Epidemiol. 2005;162(11):1062-9.

15. Margolis KL, Manson JE, Greenland P, Rodabough RJ, Bray PF, Safford M, et al. Leukocyte count as a predictor of cardiovascular events and mortality in postmenopausal women: the Women's Health Initiative Observational Study. Arch Intern Med. 2005;165(5):500-8.

16. Shankar A, Mitchell P, Rochtchina E, Tan J, Wang JJ. Association between circulating white blood cell count and long-term incidence of age-related macular degeneration: the Blue Mountains Eye Study. Am J Epidemiol. 2007;165(4):375-82.

17. Tamakoshi K, Toyoshima H, Yatsuya H, Matsushita K, Okamura T, Hayakawa T, et al. White blood cell count and risk of all-cause and cardiovascular mortality in nationwide sample of Japanese - Results from the NIPPON DATA90. Circ J. 2007;71(4):479-85.

18. Zakai NA, Katz R, Jenny NS, Psaty BM, Reiner AP, Schwartz SM, et al. Inflammation and hemostasis biomarkers and cardiovascular risk in the elderly: the Cardiovascular Health Study. J Thromb Haemost. 2007;5(6):1128-35.

19. Bekwelem W, Lutsey PL, Loehr LR, Agarwal SK, Astor BC, Guild C, et al. White blood cell count, C-reactive protein, and incident heart failure in the Atherosclerosis Risk in Communities (ARIC) Study. Ann Epidemiol. 2011;21(10):739-48.

20. Atmaca Y, Ozdol C, Turhan S, Vurgun K, Duzen V, Erol C. The association of elevated white blood cell count and C-reactive protein with endothelial dysfunction in cardiac syndrome X. Acta Cardiol. 2008;63(6):723-8.

21. Cheng ML, Chen CM, Gu PW, Ho HY, Chiu DT. Elevated levels of myeloperoxidase, white blood cell count and 3-chlorotyrosine in Taiwanese patients with acute myocardial infarction. Clin Biochem. 2008;41(7-8):554-60.

22. Kadoglou NP, Gerasimidis T, Golemati S, Kapelouzou A, Karayannacos PE, Liapis CD. The relationship between serum levels of vascular calcification inhibitors and carotid plaque vulnerability. J Vasc Surg. 2008;47(1):55-62.

Confidentiality Statement

Confidentiality Statement: Data and information contained in this document are considered to constitute trade secrets and confidential commercial information, and the legal protections provided to such trade secrets and confidential information are hereby claimed under the applicable provisions of United States law. No part of this document may be publicly disclosed without the written consent of Philip Morris International.

23. Lee BK, Durairaj A, Mehra A, Wenby RB, Meiselman HJ, Alexy T. Hemorheological abnormalities in stable angina and acute coronary syndromes. Clin Hemorheol Microcirc. 2008;39(1-4):43-51.

24. Lind L, Andersson J, Ronn M, Gustavsson T, Holdfelt P, Hulthe J, et al. Brachial artery intima-media thickness and echogenicity in relation to lipids and markers of oxidative stress in elderly subjects:--the prospective investigation of the vasculature in Uppsala Seniors (PIVUS) Study. Lipids. 2008;43(2):133-41.

25. Michos ED, Santos RD, Narla V, Pandey S, Meneghelo R, Carvalho JA, et al. Favorable cardiovascular risk factor profile is associated with reduced prevalence of coronary artery calcification and inflammation in asymptomatic nondiabetic white men. Prev Cardiol. 2008;11(4):189-94.

26. Rossouw JE, Cushman M, Greenland P, Lloyd-Jones DM, Bray P, Kooperberg C, et al. Inflammatory, lipid, thrombotic, and genetic markers of coronary heart disease risk in the women's health initiative trials of hormone therapy. Arch Intern Med. 2008;168(20):2245-53.

27. Sagastagoitia JD, Saez Y, Vacas M, Narvaez I, de Lafuente JP, Molinero E, et al. Acute versus chronic myocardial ischemia: a differential biological profile study. Pathophysiol Haemost Thromb. 2008;36(2):91-7.

28. Sheu JJ, Chang LT, Chiang CH, Youssef AA, Wu CJ, Lee FY, et al. Prognostic value of activated toll-like receptor-4 in monocytes following acute myocardial infarction. Int Heart J. 2008;49(1):1-11.

29. Engstrom G, Melander O, Hedblad B. Leukocyte count and incidence of hospitalizations due to heart failure. Circ Heart Fail. 2009;2(3):217-22.

30. Halvorsen DS, Johnsen SH, Mathiesen EB, Njolstad I. The association between inflammatory markers and carotid atherosclerosis is sex dependent: the Tromso Study. Cerebrovasc Dis. 2009;27(4):392-7.

31. Kucharska-Newton AM, Couper DJ, Pankow JS, Prineas RJ, Rea TD, Sotoodehnia N, et al. Hemostasis, inflammation, and fatal and nonfatal coronary heart disease: long-term follow-up of the atherosclerosis risk in communities (ARIC) cohort. Arterioscler Thromb Vasc Biol. 2009;29(12):2182-90.

32. Lee YJ, Lee JW, Kim JK, Lee JH, Kim JH, Kwon KY, et al. Elevated white blood cell count is associated with arterial stiffness. Nutr Metab Cardiovasc Dis. 2009;19(1):3-7.

33. Li JJ, Nie SP, Qian XW, Zeng HS, Zhang CY. Chronic inflammatory status in patients with coronary artery ectasia. Cytokine. 2009;46(1):61-4.

34. Shahzad F, Tawwab S, Abbas A. Relationship of white blood cell counts, haemoglobin and ESR with IHD. J Ayub Med Coll Abbottabad. 2009;21(3):59-62.

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Confidentiality Statement: Data and information contained in this document are considered to constitute trade secrets and confidential commercial information, and the legal protections provided to such trade secrets and confidential information are hereby claimed under the applicable provisions of United States law. No part of this document may be publicly disclosed without the written consent of Philip Morris International.

35. Thayer JF, Fischer JE. Heart rate variability, overnight urinary norepinephrine and C-reactive protein: evidence for the cholinergic anti-inflammatory pathway in healthy human adults. J Intern Med. 2009;265(4):439-47.

36. Zurru MC, Alonzo C, Brescacin L, Romano M, Camera LA, Waisman G, et al. Recent respiratory infection predicts atherothrombotic stroke: case-control study in a Buenos Aires healthcare system. Stroke. 2009;40(6):1986-90.

37. Aliberti G, Proietta M, Pulignano I, Del Porto F, Tammeo A, Trappolini M. Association between fibrinogen plasma levels and platelet counts in an outpatient population and in patients with coronary heart disease. Blood Coagul Fibrinolysis. 2010;21(3):216-20.

38. Chen JJ, Lin LY, Lee HH, Lai LP, Lin JL, Huang JJ, et al. Association of white blood cell count and peripheral arterial disease in patients with and without traditional risk factors. Angiology. 2010;61(4):382-7.

39. Kincl V, Panovsky R, Meluzin J, Semenka J, Groch L, Tomcikova D, et al. Association between laboratory markers and presence of coronary artery disease. Biomed Pap Med Fac Univ Palacky Olomouc Czech Repub. 2010;154(3):227-33.

40. Li C, Engstrom G, Hedblad B. Leukocyte count is associated with incidence of coronary events, but not with stroke: a prospective cohort study. Atherosclerosis. 2010;209(2):545-50.

41. Patterson CC, Smith AE, Yarnell JW, Rumley A, Ben-Shlomo Y, Lowe GD. The associations of interleukin-6 (IL-6) and downstream inflammatory markers with risk of cardiovascular disease: the Caerphilly Study. Atherosclerosis. 2010;209(2):551-7.

42. Pizzi C, De Stavola BL, Meade TW. Long-term association of routine blood count (Coulter) variables on fatal coronary heart disease: 30-year results from the first prospective Northwick Park Heart Study (NPHS-I). Int J Epidemiol. 2010;39(1):256-65.

43. Godsland IF, North BV, Johnston DG. Simple indices of inflammation as predictors of death from cancer or cardiovascular disease in a prospective cohort after two decades of follow-up. QJM. 2011;104(5):387-94.

44. Kocaman SA, Sahinarslan A, Kunak T, Balcioğlu S, Cetin M, Cemri M, et al. The particular interactions of the traditional cardiovascular risk factors with different circulating specific leukocyte subtype counts in blood: an observational study. Anadolu Kardiyol Derg. 2011;11(7):573-81.

45. Konrad T, Bar F, Schneider F, Franke S, Bohles H, Vetter G, et al. Factors influencing endothelial function in healthy pre- and post-menopausal women of the EU-RISC study. Diab Vasc Dis Res. 2011;8(3):229-36.

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46. Afsar CU, Uzun H, Yurdakul S, Muderrisoglu C, Erguney M, Demir B, et al. Association of serum fetuin-A levels with heart valve calcification and other biomarkers of inflammation among persons with acute coronary syndrome. Clin Invest Med. 2012;35(4):E206-15.

47. Inoue T, Iseki K, Iseki C, Kinjo K. Elevated resting heart rate is associated with white blood cell count in middle-aged and elderly individuals without apparent cardiovascular disease. Angiology. 2012;63(7):541-6.

48. Kavousi M, Elias-Smale S, Rutten JH, Leening MJ, Vliegenthart R, Verwoert GC, et al. Evaluation of newer risk markers for coronary heart disease risk classification: a cohort study. Ann Intern Med. 2012;156(6):438-44.

49. Korkmaz L, Kul S, Korkmaz AA, Akyuz AR, Agac MT, Erkan H, et al. Increased leucocyte count could predict coronary artery calcification in patients free of clinically apparent cardiovascular disease. Turk Kardiyol Dern Ars. 2012;40(3):223-8.

50. Nyrnes A, Njolstad I, Mathiesen EB, Wilsgaard T, Hansen JB, Skjelbakken T, et al. Inflammatory biomarkers as risk factors for future atrial fibrillation. An eleven-year follow-up of 6315 men and women: the Tromso study. Gend Med. 2012;9(6):536-47.e2.

51. Ortega E, Gilabert R, Nunez I, Cofan M, Sala-Vila A, de Groot E, et al. White blood cell count is associated with carotid and femoral atherosclerosis. Atherosclerosis. 2012;221(1):275-81.

52. Pfister R, Sharp SJ, Luben R, Wareham NJ, Khaw KT. Differential white blood cell count and incident heart failure in men and women in the EPIC-Norfolk study. Eur Heart J. 2012;33(4):523-30.

53. Phillips AC, Jiang CQ, Thomas GN, Lin JM, Yue XJ, Cheng KK, et al. White blood cell subsets are associated with carotid intima-media thickness and pulse wave velocity in an older Chinese population: the Guangzhou Biobank Cohort Study. J Hum Hypertens. 2012;26(8):485-92.

54. Rienstra M, Sun JX, Magnani JW, Sinner MF, Lubitz SA, Sullivan LM, et al. White blood cell count and risk of incident atrial fibrillation (from the Framingham Heart Study). Am J Cardiol. 2012;109(4):533-7.

55. Twig G, Afek A, Shamiss A, Derazne E, Tzur D, Gordon B, et al. White blood cell count and the risk for coronary artery disease in young adults. PLoS ONE. 2012;7(10):e47183.

56. Zia E, Melander O, Bjorkbacka H, Hedblad B, Engstrom G. Total and differential leucocyte counts in relation to incidence of stroke subtypes and mortality: a prospective cohort study. J Intern Med. 2012;272(3):298-304.

57. Balta S, Demirkol S, Celik T, Kucuk U, Unlu M, Arslan Z, et al. Association between coronary artery ectasia and neutrophil-lymphocyte ratio. Angiology. 2013;64(8):627-32.

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58. Rajkumari R, Laishram D, Thiyam J, Javan N. Hypertensive leucocytosis. J Indian Med Assoc. 2013;111(4):226-9.

59. Tekin G, Tekin YK, Sivri N, Yetkin E. Mean platelet volume in patients with nonvalvular atrial fibrillation. Blood Coagul Fibrinolysis. 2013;24(5):537-9.

60. Celikbilek A, Ismailogullari S, Zararsiz G. Neutrophil to lymphocyte ratio predicts poor prognosis in ischemic cerebrovascular disease. J Clin Lab Anal. 2014;28(1):27-31.

61. Cotoi OS, Duner P, Ko N, Hedblad B, Nilsson J, Bjorkbacka H, et al. Plasma S100A8/A9 correlates with blood neutrophil counts, traditional risk factors, and cardiovascular disease in middle-aged healthy individuals. Arterioscler Thromb Vasc Biol. 2014;34(1):202-10.

62. Martinsson A, Ostling G, Persson M, Sundquist K, Andersson C, Melander O, et al. Carotid plaque, intima-media thickness, and incident aortic stenosis: a prospective cohort study. Arterioscler Thromb Vasc Biol. 2014;34(10):2343-8.

63. Soderholm M, Zia E, Hedblad B, Engstrom G. Leukocyte count and incidence of subarachnoid haemorrhage: a prospective cohort study. BMC Neurol. 2014;14:71.

64. Emara AM, Abo El-Noor MM, Hassan NA, Wagih AA. Immunotoxicity and hematotoxicity induced by tetrachloroethylene in egyptian dry cleaning workers. Inhal Toxicol. 2010;22(2):117-24.

65. Hsu WL, Tatsukawa Y, Neriishi K, Yamada M, Cologne J, Fujiwara S. Longitudinal trends of total white blood cell and differential white blood cell counts of atomic bomb survivors. J Radiat Res. 2010;51(4):431-9.

66. Babio N, Ibarrola-Jurado N, Bullo M, Martinez-Gonzalez MA, Warnberg J, Salaverria I, et al. White blood cell counts as risk markers of developing metabolic syndrome and its components in the PREDIMED study. PLoS ONE. 2013;8(3):e58354.

67. Odagiri K, Uehara A, Mizuta I, Yamamoto M, Kurata C. Longitudinal study on white blood cell count and the incidence of metabolic syndrome. Intern Med. 2011;50(21):2491-8.

68. Gokulakrishnan K, Deepa R, Sampathkumar R, Balasubramanyam M, Mohan V. Association of leukocyte count and hsCRP with metabolic abnormalities in subjects with normal glucose tolerance (CURES - 64). J Assoc Physicians India. 2009;57:27-32.

69. Bernlochner I, Steinhubl S, Braun S, Morath T, Jaitner J, Stegherr J, et al. Association between inflammatory biomarkers and platelet aggregation in patients under chronic clopidogrel treatment. Thromb Haemost. 2010;104(6):1193-200.

70. Faraday N, Yanek LR, Vaidya D, Kral B, Qayyum R, Herrera-Galeano JE, et al. Leukocyte count is associated with increased platelet reactivity and diminished

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response to aspirin in healthy individuals with a family history of coronary artery disease. Thromb Res. 2009;124(3):311-7.

71. Santimone I, Di Castelnuovo A, De Curtis A, Spinelli M, Cugino D, Gianfagna F, et al. White blood cell count, sex and age are major determinants of heterogeneity of platelet indices in an adult general population: results from the MOLI-SANI project. Haematologica. 2011;96(8):1180-8.

72. Holz T, Thorand B, Doring A, Schneider A, Meisinger C, Koenig W. Markers of inflammation and weight change in middle-aged adults: results from the prospective MONICA/KORA S3/F3 study. Obesity (Silver Spring). 2010;18(12):2347-53.

73. Julius S, Egan BM, Kaciroti NA, Nesbitt SD, Chen AK. In prehypertension leukocytosis is associated with body mass index but not with blood pressure or incident hypertension. J Hypertens. 2014;32(2):251-9.

74. Michishita R, Shono N, Inoue T, Tsuruta T, Node K. Associations of monocytes, neutrophil count, and C-reactive protein with maximal oxygen uptake in overweight women. J Cardiol. 2008;52(3):247-53.

75. Sekitani Y, Hayashida N, Kadota K, Yamasaki H, Abiru N, Nakazato M, et al. White blood cell count and cardiovascular biomarkers of atherosclerosis. Biomarkers. 2010;15(5):454-60.

76. Waterhouse DF, Cahill RA, Sheehan F, McCreery C. Prediction of calculated future cardiovascular disease by monocyte count in an asymptomatic population. Vasc Health Risk Manag. 2008;4(1):177-87.

77. Tatsukawa Y, Hsu WL, Yamada M, Cologne JB, Suzuki G, Yamamoto H, et al. White blood cell count, especially neutrophil count, as a predictor of hypertension in a Japanese population. Hypertens Res. 2008;31(7):1391-7.

78. Tian N, Penman AD, Mawson AR, Manning RD, Jr., Flessner MF. Association between circulating specific leukocyte types and blood pressure: the atherosclerosis risk in communities (ARIC) study. J Am Soc Hypertens. 2010;4(6):272-83.

79. Ganguli D, Das N, Saha I, Sanapala KR, Chaudhuri D, Ghosh S, et al. Association between inflammatory markers and cardiovascular risk factors in women from Kolkata, W.B, India. Arq Bras Cardiol. 2011;96(1):38-46.

80. Gkrania-Klotsas E, Ye Z, Cooper AJ, Sharp SJ, Luben R, Biggs ML, et al. Differential white blood cell count and type 2 diabetes: systematic review and meta-analysis of cross-sectional and prospective studies. PLoS ONE. 2010;5(10):e13405.

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81. Klenk J, Denkinger M, Nikolaus T, Peter R, Rothenbacher D, Koenig W. Association of objectively measured physical activity with established and novel cardiovascular biomarkers in elderly subjects: every step counts. J Epidemiol Community Health. 2013;67(2):194-7.

82. Shanely RA, Nieman DC, Henson DA, Jin F, Knab AM, Sha W. Inflammation and oxidative stress are lower in physically fit and active adults. Scand J Med Sci Sports. 2013;23(2):215-23.

83. Bonaccio M, Di Castelnuovo A, De Curtis A, Costanzo S, Persichillo M, Donati MB, et al. Adherence to the Mediterranean diet is associated with lower platelet and leukocyte counts: results from the Moli-sani study. Blood. 2014;123(19):3037-44.

84. Li S, Guo YL, Xu RX, Zhang Y, Zhu CG, Sun J, et al. Association of plasma PCSK9 levels with white blood cell count and its subsets in patients with stable coronary artery disease. Atherosclerosis. 2014;234(2):441-5.

85. Phillips AN, Neaton JD, Cook DG, Grimm RH, Shaper AG. The leukocyte count and risk of lung cancer. Cancer. 1992;69(3):680-4.

86. Erlinger TP, Muntner P, Helzlsouer KJ. WBC count and the risk of cancer mortality in a national sample of U.S. adults: results from the Second National Health and Nutrition Examination Survey mortality study. Cancer Epidemiol Biomarkers Prev. 2004;13(6):1052-6.

87. Shankar A, Wang JJ, Rochtchina E, Yu MC, Kefford R, Mitchell P. Association between circulating white blood cell count and cancer mortality: a population-based cohort study. Arch Intern Med. 2006;166(2):188-94.

88. Margolis KL, Rodabough RJ, Thomson CA, Lopez AM, McTiernan A. Prospective study of leukocyte count as a predictor of incident breast, colorectal, endometrial, and lung cancer and mortality in postmenopausal women. Arch Intern Med. 2007;167(17):1837-44.

89. Sprague BL, Trentham-Dietz A, Klein BE, Klein R, Cruickshanks KJ, Lee KE, et al. Physical activity, white blood cell count, and lung cancer risk in a prospective cohort study. Cancer Epidemiol Biomarkers Prev. 2008;17(10):2714-22.

90. dos Santos Silva I, De Stavola BL, Pizzi C, Meade TW. Circulating levels of coagulation and inflammation markers and cancer risks: individual participant analysis of data from three long-term cohorts. Int J Epidemiol. 2010;39(3):699-709.

91. Gulen ST, Karadag F, Karul AB, Kilicarslan N, Ceylan E, Kuman NK, et al. Adipokines and systemic inflammation in weight-losing lung cancer patients. Lung. 2012;190(3):327-32.

Confidentiality Statement

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92. Gan WQ, Man SF, Senthilselvan A, Sin DD. Association between chronic obstructive pulmonary disease and systemic inflammation: a systematic review and a meta-analysis. Thorax. 2004;59(7):574-80.

93. Agusti A. Systemic effects of chronic obstructive pulmonary disease: what we know and what we don't know (but should). Proc Am Thorac Soc. 2007;4(7):522-5.

94. Barnes PJ. Immunology of asthma and chronic obstructive pulmonary disease. Nat Rev Immunol. 2008;8(3):183-92.

95. Gupta V, Singh D. Critical assessment of the value of sputum neutrophils. COPD. 2013;10(1):107-14.

96. Agusti A, Sin DD. Biomarkers in COPD. Clin Chest Med. 2014;35(1):131-41.

97. Shaw JG, Vaughan A, Dent AG, O'Hare PE, Goh F, Bowman RV, et al. Biomarkers of progression of chronic obstructive pulmonary disease (COPD). J Thorac Dis. 2014;6(11):1532-47.

98. Stockley RA. Biomarkers in chronic obstructive pulmonary disease: confusing or useful? Int J Chron Obstruct Pulmon Dis. 2014;9:163-77.

99. Agusti A, Edwards LD, Rennard SI, MacNee W, Tal-Singer R, Miller BE, et al. Persistent systemic inflammation is associated with poor clinical outcomes in COPD: a novel phenotype. PLoS ONE. 2012;7(5):e37483.

100. O'Donnell RA, Peebles C, Ward JA, Daraker A, Angco G, Broberg P, et al. Relationship between peripheral airway dysfunction, airway obstruction, and neutrophilic inflammation in COPD. Thorax. 2004;59(10):837-42.

101. Rytila P, Plataki M, Bucchieri F, Uddin M, Nong G, Kinnula VL, et al. Airway neutrophilia in COPD is not associated with increased neutrophil survival. Eur Respir J. 2006;28(6):1163-9.

102. Eickhoff P, Valipour A, Kiss D, Schreder M, Cekici L, Geyer K, et al. Determinants of systemic vascular function in patients with stable chronic obstructive pulmonary disease. Am J Respir Crit Care Med. 2008;178(12):1211-8.

103. Roos-Engstrand E, Ekstrand-Hammarstrom B, Pourazar J, Behndig AF, Bucht A, Blomberg A. Influence of smoking cessation on airway T lymphocyte subsets in COPD. COPD. 2009;6(2):112-20.

104. Dima E, Rovina N, Gerassimou C, Roussos C, Gratziou C. Pulmonary function tests, sputum induction, and bronchial provocation tests: diagnostic tools in the challenge of distinguishing asthma and COPD phenotypes in clinical practice. Int J Chron Obstruct Pulmon Dis. 2010;5:287-96.

105. He Z, Chen Y, Chen P, Wu G, Cai S. Local inflammation occurs before systemic inflammation in patients with COPD. Respirology. 2010;15(3):478-84.

Confidentiality Statement

Confidentiality Statement: Data and information contained in this document are considered to constitute trade secrets and confidential commercial information, and the legal protections provided to such trade secrets and confidential information are hereby claimed under the applicable provisions of United States law. No part of this document may be publicly disclosed without the written consent of Philip Morris International.

106. Biljak VR, Pancirov D, Cepelak I, Popovic-Grle S, Stjepanovic G, Grubisic TZ. Platelet count, mean platelet volume and smoking status in stable chronic obstructive pulmonary disease. Platelets. 2011;22(6):466-70.

107. Larsson S, Nordenson A, Glader P, Yoshihara S, Linden A, Slinde F. A gender difference in circulating neutrophils in malnourished patients with COPD. Int J Chron Obstruct Pulmon Dis. 2011;6:83-8.

108. McKeever T, Saha S, Fogarty AW. The association between systemic inflammatory cellular levels and lung function: a population-based study. PLoS ONE. 2011;6(7):e21593.

109. Fernandez JA, Prats JM, Artero JV, Mora AC, Farinas AV, Espinal A, et al. Systemic inflammation in 222.841 healthy employed smokers and nonsmokers: white blood cell count and relationship to spirometry. Tob Induc Dis. 2012;10(1):7.

110. Kuhlmann A, Olafsdottir IS, Lind L, Sundstrom J, Janson C. Association of biomarkers of inflammation and cell adhesion with lung function in the elderly: a population-based study. BMC Geriatr. 2013;13:82.

111. Steiropoulos P, Papanas N, Nena E, Xanthoudaki M, Goula T, Froudarakis M, et al. Mean platelet volume and platelet distribution width in patients with chronic obstructive pulmonary disease: the role of comorbidities. Angiology. 2013;64(7):535-9.

112. Wang RT, Li JY, Cao ZG, Li Y. Mean platelet volume is decreased during an acute exacerbation of chronic obstructive pulmonary disease. Respirology. 2013;18(8):1244-8.

113. Gunay E, Sarinc Ulasli S, Akar O, Ahsen A, Gunay S, Koyuncu T, et al. Neutrophil-to-lymphocyte ratio in chronic obstructive pulmonary disease: a retrospective study. Inflammation. 2014;37(2):374-80.

114. Vestbo J, Anderson W, Coxson HO, Crim C, Dawber F, Edwards L, et al. Evaluation of COPD Longitudinally to Identify Predictive Surrogate End-points (ECLIPSE). Eur Respir J. 2008;31(4):869-73.

115. Lavi S, Prasad A, Yang EH, Mathew V, Simari RD, Rihal CS, et al. Smoking is associated with epicardial coronary endothelial dysfunction and elevated white blood cell count in patients with chest pain and early coronary artery disease. Circulation. 2007;115(20):2621-7.

116. Wannamethee SG, Lowe GD, Shaper AG, Rumley A, Lennon L, Whincup PH. Associations between cigarette smoking, pipe/cigar smoking, and smoking cessation, and haemostatic and inflammatory markers for cardiovascular disease. Eur Heart J. 2005;26(17):1765-73.

117. Taylor RG. Smoking and the leucocyte count. Eur J Respir Dis. 1987;71(2):65-8.

Confidentiality Statement

Confidentiality Statement: Data and information contained in this document are considered to constitute trade secrets and confidential commercial information, and the legal protections provided to such trade secrets and confidential information are hereby claimed under the applicable provisions of United States law. No part of this document may be publicly disclosed without the written consent of Philip Morris International.

118. Ernst E, Hammerschmidt DE, Bagge U, Matrai A, Dormandy JA. Leukocytes and the risk of ischemic diseases. JAMA. 1987;257(17):2318-24.

119. Holt PG. Immune and inflammatory function in cigarette smokers. Thorax. 1987;42(4):241-9.

120. McGill HC, Jr. The cardiovascular pathology of smoking. Am Heart J. 1988;115(1 Pt 2):250-7.

121. Yanbaeva DG, Dentener MA, Creutzberg EC, Wesseling G, Wouters EFM. Systemic effects of smoking. Chest. 2007;131(5):1557-66.

122. Howell RW. Smoking habits and laboratory tests. Lancet. 1970;2(7664):152.

123. Corre F, Lellouch J, Schwartz D. Smoking and leucocyte-counts. Results of an epidemiological survey. Lancet. 1971;2(7725):632-4.

124. Friedman GD, Siegelaub AB, Seltzer CC, Feldman R, Collen MF. Smoking habits and the leukocyte count. Arch Environ Health. 1973;26(3):137-43.

125. Okuno T. Smoking and blood changes. JAMA. 1973;225(11):1387-8.

126. Parulkar VG, Barua MJ, Bhatt JV. Smoking and leucocyte counts. J Postgrad Med. 1973;19(3):132-5.

127. Billimoria JD, Pozner H, Metselaar B, Best FW, James DC. Effect of cigarette smoking on lipids, lipoproteins, blood coagulation, fibrinolysis and cellular components of human blood. Atherosclerosis. 1975;21(1):61-76.

128. Noble RC, Penny BB. Comparison of leukocyte count and function in smoking and nonsmoking young men. Infect Immun. 1975;12(3):550-5.

129. Helman N, Rubenstein LS. The effects of age, sex, and smoking on erythrocytes and leukocytes. Am J Clin Pathol. 1975;63(1):35-44.

130. Parulkar VG, Balsubramaniam P, Barua MJ, Bhatt JV. Smoking and differential leucocyte (w.b.c.) count. J Postgrad Med. 1975;21(2):75-7.

131. Fisch IR, Freedman SH. Smoking, oral contraceptives, and obesity. Effects on white blood cell count. JAMA. 1975;234(5):500-6.

132. Silverman NA, Potvin C, Alexander JC, Jr., Chretien PB. In vitro lymphocyte reactivity and T-cell levels in chronic cigarette smokers. Clin Exp Immunol. 1975;22(2):285-92.

133. Eschwege E, Papoz L, Lellouch J, Claude JR, Cubeau J, Pequignot G, et al. Blood cells and alcohol consumption with special reference to smoking habits. J Clin Pathol. 1978;31(7):654-8.

134. Zalokar JB, Richard JL, Claude JR. Leukocyte count, smoking, and myocardial infarction. N Engl J Med. 1981;304(8):465-8.

135. Dodsworth H, Dean A, Broom G. Effects of smoking and the pill on the blood count. Br J Haematol. 1981;49(3):484-8.

Confidentiality Statement

Confidentiality Statement: Data and information contained in this document are considered to constitute trade secrets and confidential commercial information, and the legal protections provided to such trade secrets and confidential information are hereby claimed under the applicable provisions of United States law. No part of this document may be publicly disclosed without the written consent of Philip Morris International.

136. Winkel P, Statland BE, Saunders AM, Osborn H, Kupperman H. Within-day physiologic variation of leukocyte types in healthy subjects as assayed by two automated leukocyte differential analyzers. Am J Clin Pathol. 1981;75(5):693-700.

137. Heinemann G, Schievelbein H, Eber S. Effect of cigarette smoking on white blood cells and erythrocyte enzymes. Arch Environ Health. 1982;37(5):261-5.

138. Nancy NR, Subramanian N, Rai UC. Effect of cigarette smoking on leucocytes in South Indians. Indian J Physiol Pharmacol. 1982;26(3):196-200.

139. Abboud RT, Johnson AJ, Richter AM, Elwood RK. Comparison of in vitro neutrophil elastase release in nonsmokers and smokers. Am Rev Respir Dis. 1983;128(3):507-10.

140. Sparrow D, Glynn RJ, Cohen M, Weiss ST. The relationship of the peripheral leukocyte count and cigarette smoking to pulmonary function among adult men. Chest. 1984;86(3):383-6.

141. Yeung MC, Buncio AD. Leukocyte count, smoking, and lung function. Am J Med. 1984;76(1):31-7.

142. Yarnell JW, Sweetnam PM, Elwood PC, Eastham R, Gilmour RA, O'Brien JR, et al. Haemostatic factors and ischaemic heart disease. The Caerphilly study. Br Heart J. 1985;53(5):483-7.

143. Nielsen H. A quantitative and qualitative study of blood monocytes in smokers. Eur J Respir Dis. 1985;66(5):327-32.

144. Tell GS, Grimm RH, Jr., Vellar OD, Theodorsen L. The relationship of white cell count, platelet count, and hematocrit to cigarette smoking in adolescents: the Oslo Youth Study. Circulation. 1985;72(5):971-4.

145. Taylor RG, Gross E, Joyce H, Holland F, Pride NB. Smoking, allergy, and the differential white blood cell count. Thorax. 1985;40(1):17-22.

146. Carel RS, Eviatar J. Factors affecting leukocyte count in healthy adults. Prev Med. 1985;14(5):607-19.

147. Bridges RB, Wyatt RJ, Rehm SR. Effects of smoking on inflammatory mediators and their relationship to pulmonary dysfunction. Eur J Respir Dis Suppl. 1986;146:145-52.

148. Yarnell JW, Sweetnam PM, Rogers S, Elwood PC, Bainton D, Baker IA, et al. Some long term effects of smoking on the haemostatic system: a report from the Caerphilly and Speedwell Collaborative Surveys. J Clin Pathol. 1987;40(8):909-13.

149. Knoke JD, Hunninghake DB, Heiss G. Physiological markers of smoking and their relation to coronary heart disease. The Lipid Research Clinics Coronary Primary Prevention Trial. Arteriosclerosis. 1987;7(5):477-82.

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Confidentiality Statement: Data and information contained in this document are considered to constitute trade secrets and confidential commercial information, and the legal protections provided to such trade secrets and confidential information are hereby claimed under the applicable provisions of United States law. No part of this document may be publicly disclosed without the written consent of Philip Morris International.

150. Ernst E, Matrai A, Schmolzl C, Magyarosy I. Dose-effect relationship between smoking and blood rheology. Br J Haematol. 1987;65(4):485-7.

151. Friedman GD, Tekawa I, Grimm RH, Manolio T, Shannon SG, Sidney S. The leucocyte count: correlates and relationship to coronary risk factors: the CARDIA study. Int J Epidemiol. 1990;19(4):889-93.

152. Regius O, Rajczy K, Gergely I, Borzsonyi L, Lengyel E, Vargha P. The effect of smoking on peripheral blood lymphocytes and on some immunological parameters in old age. Z Gerontol. 1990;23(3):163-7.

153. Hansen LK, Grimm RH, Jr., Neaton JD. The relationship of white blood cell count to other cardiovascular risk factors. Int J Epidemiol. 1990;19(4):881-8.

154. Schwartz J, Weiss ST. Host and environmental factors influencing the peripheral blood leukocyte count. Am J Epidemiol. 1991;134(12):1402-9.

155. Kannel WB, Anderson K, Wilson PW. White blood cell count and cardiovascular disease. Insights from the Framingham Study. JAMA. 1992;267(9):1253-6.

156. Nieto FJ, Szklo M, Folsom AR, Rock R, Mercuri M. Leukocyte count correlates in middle-aged adults: the Atherosclerosis Risk in Communities (ARIC) Study. Am J Epidemiol. 1992;136(5):525-37.

157. Phillips AN, Neaton JD, Cook DG, Grimm RH, Shaper AG. Leukocyte count and risk of major coronary heart disease events. Am J Epidemiol. 1992;136(1):59-70.

158. Capuano V, Lamaida N, De Martino M, Mazzotta G. Association between white blood cell count and risk factors of coronary artery disease. G Ital Cardiol. 1995;25(9):1145-52.

159. Calori G, D'Angelo A, Della Valle P, Ruotolo G, Ferini-Strambi L, Giusti C, et al. The effect of cigarette-smoking on cardiovascular risk factors: a study of monozygotic twins discordant for smoking. Thromb Haemost. 1996;75(1):14-8.

160. Freedman DS, Joesoef MR, Barboriak JJ, Stallone DD, Byers T. Correlates of leukocyte counts in men. Ann Epidemiol. 1996;6(1):74-82.

161. Freedman DS, Flanders WD, Barboriak JJ, Malarcher AM, Gates L. Cigarette smoking and leukocyte subpopulations in men. Ann Epidemiol. 1996;6(4):299-306.

162. Targher G, Seidell JC, Tonoli M, Muggeo M, De Sandre G, Cigolini M. The white blood cell count: its relationship to plasma insulin and other cardiovascular risk factors in healthy male individuals. J Intern Med. 1996;239(5):435-41.

163. Sunyer J, Munoz A, Peng Y, Margolick J, Chmiel JS, Oishi J, et al. Longitudinal relation between smoking and white blood cells. Am J Epidemiol. 1996;144(8):734-41.

Confidentiality Statement

Confidentiality Statement: Data and information contained in this document are considered to constitute trade secrets and confidential commercial information, and the legal protections provided to such trade secrets and confidential information are hereby claimed under the applicable provisions of United States law. No part of this document may be publicly disclosed without the written consent of Philip Morris International.

164. Parry H, Cohen S, Schlarb JE, Tyrrell DA, Fisher A, Russell MA, et al. Smoking, alcohol consumption, and leukocyte counts. Am J Clin Pathol. 1997;107(1):64-7.

165. Celada MM, Reguero JR, Cubero GI. The interrelationship among tobacco consumption, high-density lipoprotein cholesterol and leukocyte counts. J Cardiovasc Risk. 1997;4(4):279-81.

166. Bergmann S, Siekmeier R, Mix C, Jaross W. Even moderate cigarette smoking influences the pattern of circulating monocytes and the concentration of sICAM-1. Respir Physiol. 1998;114(3):269-75.

167. Capuano V, Lamaida N, Mazzotta G, Scotto di Quacquaro G. Relation between white blood cell count and several risk factors for coronary heart disease in patients with systemic hypertension. G Ital Cardiol. 1998;28(5):530-5.

168. Ogawa Y, Imaki M, Yoshida Y, Shibakawa M, Tanada S. An epidemiological study on the association between the total leukocyte and neutrophil counts, and risk factors of ischemic heart disease by smoking status in Japanese factory workers. Appl Human Sci. 1998;17(6):239-47.

169. Roth MD, Arora A, Barsky SH, Kleerup EC, Simmons M, Tashkin DP. Airway inflammation in young marijuana and tobacco smokers. Am J Respir Crit Care Med. 1998;157(3 Pt 1):928-37.

170. Fredriksson MI, Figueredo CM, Gustafsson A, Bergstrom KG, Asman BE. Effect of periodontitis and smoking on blood leukocytes and acute-phase proteins. J Periodontol. 1999;70(11):1355-60.

171. Woodward M, Rumley A, Tunstall-Pedoe H, Lowe GD. Associations of blood rheology and interleukin-6 with cardiovascular risk factors and prevalent cardiovascular disease. Br J Haematol. 1999;104(2):246-57.

172. van Eeden SF, Hogg JC. The response of human bone marrow to chronic cigarette smoking. Eur Respir J. 2000;15(5):915-21.

173. Yarnell JW, Sweetnam PM, Rumley A, Lowe GD. Lifestyle and hemostatic risk factors for ischemic heart disease : the Caerphilly Study. Arterioscler Thromb Vasc Biol. 2000;20(1):271-9.

174. Chalmers GW, MacLeod KJ, Thomson L, Little SA, McSharry C, Thomson NC. Smoking and airway inflammation in patients with mild asthma. Chest. 2001;120(6):1917-22.

175. Frohlich M, Sund M, Lowel H, Imhof A, Hoffmeister A, Koenig W. Independent association of various smoking characteristics with markers of systemic inflammation in men. Results from a representative sample of the general population (MONICA Augsburg Survey 1994/95). Eur Heart J. 2003;24(14):1365-72.

Confidentiality Statement

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176. Smith MR, Kinmonth AL, Luben RN, Bingham S, Day NE, Wareham NJ, et al. Smoking status and differential white cell count in men and women in the EPIC-Norfolk population. Atherosclerosis. 2003;169(2):331-7.

177. Petropoulos G, McKay IJ, Hughes FJ. The association between neutrophil numbers and interleukin-1alpha concentrations in gingival crevicular fluid of smokers and non-smokers with periodontal disease. J Clin Periodontol. 2004;31(5):390-5.

178. Ishizaka N, Ishizaka Y, Toda E, Hashimoto H, Nagai R, Yamakado M. Association between white blood cell count and carotid arteriosclerosis in Japanese smokers. Atherosclerosis. 2004;175(1):95-100.

179. Gan WQ, Man SF, Sin DD. The interactions between cigarette smoking and reduced lung function on systemic inflammation. Chest. 2005;127(2):558-64.

180. Yasue H, Hirai N, Mizuno Y, Harada E, Itoh T, Yoshimura M, et al. Low-grade inflammation, thrombogenicity, and atherogenic lipid profile in cigarette smokers. Circ J. 2006;70(1):8-13.

181. Yen ML, Yang CY, Yen BL, Ho YL, Cheng WC, Bai CH. Increased high sensitivity C-reactive protein and neutrophil count are related to increased standard cardiovascular risk factors in healthy Chinese men. Int J Cardiol. 2006;110(2):191-8.

182. Friedman GD, Seltzer CC, Siegelaub AB, Feldman R, Collen MF. Smoking among white, black, and yellow men and women. Kaiser-Permanente multiphasic health examination data, 1964-1968. Am J Epidemiol. 1972;96(1):23-35.

183. Al-Awadhi AM, AlFadhli SM, Mustafa NY, Sharma PN. Effects of cigarette smoking on hematological parameters and von Willebrand factor functional activity levels in asymptomatic male and female Arab smokers. Med Princ Pract. 2008;17(2):149-53.

184. Kung CM, Wang HL, Tseng ZL. Cigarette smoking exacerbates health problems in young men. Clin Invest Med. 2008;31(3):E138-49.

185. Otsuka R, Tamakoshi K, Wada K, Matsushita K, Ouyang P, Hotta Y, et al. Having more healthy practice was associated with low white blood cell counts in middle-aged Japanese male and female workers. Ind Health. 2008;46(4):341-7.

186. Pitsavos C, Kourlaba G, Panagiotakos DB, Tsamis E, Kogias Y, Stravopodis P, et al. Does smoking status affect the association between baseline white blood cell count and in-hospital mortality of patients presented with acute coronary syndrome? The Greek study of acute coronary syndromes (GREECS). Int J Cardiol. 2008;125(1):94-100.

187. Bergmann S, Siekmeier R. Influence of smoking and body weight on adipokines in middle aged women. Eur J Med Res. 2009;14 Suppl 4:21-6.

Confidentiality Statement

Confidentiality Statement: Data and information contained in this document are considered to constitute trade secrets and confidential commercial information, and the legal protections provided to such trade secrets and confidential information are hereby claimed under the applicable provisions of United States law. No part of this document may be publicly disclosed without the written consent of Philip Morris International.

188. Calapai G, Caputi AP, Mannucci C, Russo GA, Gregg E, Puntoni R, et al. Cardiovascular biomarkers in groups of established smokers after a decade of smoking. Basic Clin Pharmacol Toxicol. 2009;104(4):322-8.

189. Lao XQ, Jiang CQ, Zhang WS, Adab P, Lam TH, Cheng KK, et al. Smoking, smoking cessation and inflammatory markers in older Chinese men: The Guangzhou Biobank Cohort Study. Atherosclerosis. 2009;203(1):304-10.

190. Steinvil A, Berliner S, Herishanu Y, Paran Y, Justo D, Cohen M, et al. Range and determinants of white blood cell count in a large survey of Israelis without inflammation. Isr Med Assoc J. 2009;11(6):363-6.

191. Tseng YM, Tsai SM, Chen SY, Lin CC, Jin YR, Yeh WH, et al. Roles of the genetic polymorphisms of alcohol-metabolizing enzymes on the immunology in high-risk drinkers. Toxicol Sci. 2009;111(2):267-76.

192. Weiss TW, Schumacher S, Kaun C, Katsaros KM, Troseid M, Huber K, et al. Association between smoking and presence of mycoplasma pneumoniae in circulating leukocytes. Swiss Med Wkly. 2010;140:w13105.

193. Andreoli C, Gregg EO, Puntoni R, Gobbi V, Nunziata A, Bassi A. Cross-sectional study of biomarkers of exposure and biological effect on monozygotic twins discordant for smoking. Clin Chem Lab Med. 2011;49(1):137-45.

194. Frost-Pineda K, Liang Q, Liu J, Rimmer L, Jin Y, Feng S, et al. Biomarkers of potential harm among adult smokers and nonsmokers in the total exposure study. Nicotine Tob Res. 2011.

195. Liu J, Liang Q, Frost-Pineda K, Muhammad-Kah R, Rimmer L, Roethig H, et al. Relationship between biomarkers of cigarette smoke exposure and biomarkers of inflammation, oxidative stress, and platelet activation in adult cigarette smokers. Cancer Epidemiol Biomarkers Prev. 2011;20(8):1760-9.

196. de Graan AJ, Loos WJ, Friberg LE, Baker SD, van der Bol JM, van Doorn L, et al. Influence of smoking on the pharmacokinetics and toxicity profiles of taxane therapy. Clin Cancer Res. 2012;18(16):4425-32.

197. Ebner N, Foldes G, Szabo T, Tacke M, Fulster S, Sandek A, et al. Assessment of serum cotinine in patients with chronic heart failure: self-reported versus objective smoking behaviour. Clin Res Cardiol. 2013;102(2):95-101.

198. Sakuragi S, Moriguchi J, Ohashi F, Ikeda M. Reference value and annual trend of white blood cell counts among adult Japanese population. Environ Health Prev Med. 2013;18(2):143-50.

199. Snitker S, Xie K, Ryan KA, Yu D, Shuldiner AR, Mitchell BD, et al. Correlation of circulating mmp-9 with white blood cell count in humans: effect of smoking. PLoS ONE. 2013;8(6):e66277.

200. Honda T, Fujimoto K, Miyao Y, Koga H, Ishii M. Current cigarette smoking is an independent risk factor for subacute stent thrombosis in acute myocardial infarction patients. J Cardiol. 2014;63(5):358-64.

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201. Khelifi M, Zarrouk A, Nury T, Hamed H, Saguem S, Salah RB, et al. Cytokine and eicosanoid profiles of phosphate mine workers. J Toxicol Sci. 2014;39(3):465-74.

202. Kawada T. Relationships between the smoking status and plasma fibrinogen, white blood cell count and serum C-reactive protein in Japanese workers. Diabetes Metab Syndr. 2015;6(15):00023-5.

203. Lee PN, Forey BA, Fry JS, Thornton AJ, Coombs KJ. The effect of quitting smoking on white blood cell count - A review based on within-subject changes [Internet]. 2014; Available from: http://www.pnlee.co.uk/documents/refs/lee2014D.pdf (Accessed on 15 May 2014).

204. Sorensen LT, Toft BG, Rygaard J, Ladelund S, Paddon M, James T, et al. Effect of smoking, smoking cessation, and nicotine patch on wound dimension, vitamin C, and systemic markers of collagen metabolism. Surgery. 2010;148(5):982-90.

205. Yeh HC, Duncan BB, Schmidt MI, Wang NY, Brancati FL. Smoking, smoking cessation, and risk for type 2 diabetes mellitus: a cohort study. Ann Intern Med. 2010;152(1):10-7.

206. Puls M, Schroeter MR, Steier J, Stijohann L, Hasenfuss G, Konstantinides S, et al. Effect of smoking cessation on the number and adhesive properties of early outgrowth endothelial progenitor cells. Int J Cardiol. 2011;152(1):61-9.

207. Roethig HJ, Koval T, Muhammad-Kah R, Jin Y, Mendes P, Unverdorben M. Short term effects of reduced exposure to cigarette smoke on white blood cells, platelets and red blood cells in adult cigarette smokers. Regul Toxicol Pharmacol. 2010;57(2-3):333-7.

208. Korhonen T, Goodwin A, Miesmaa P, Dupuis EA, Kinnunen T. Smoking cessation program with exercise improves cardiovascular disease biomarkers in sedentary women. J Womens Health (Larchmt). 2011;20(7):1051-64.

209. Joseph AM, Hecht SS, Murphy SE, Lando H, Carmella SG, Gross M, et al. Smoking reduction fails to improve clinical and biological markers of cardiac disease: a randomized controlled trial. Nicotine Tob Res. 2008;10(3):471-81.

210. Martin Leroy C, Jarus-Dziedzic K, Ancerewicz J, Lindner D, Kulesza A, Magnette J. Reduced exposure evaluation of an Electrically Heated Cigarette Smoking System. Part 7: a one-month, randomized, ambulatory, controlled clinical study in Poland. Regul Toxicol Pharmacol. 2012;64; (2 Suppl):S74-84.

Confidentiality Statement

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211. Roethig HJ, Feng S, Liang Q, Liu J, Rees WA, Zedler BK. A 12-month, randomized, controlled study to evaluate exposure and cardiovascular risk factors in adult smokers switching from conventional cigarettes to a second-generation Electrically Heated Cigarette Smoking System. J Clin Pharmacol. 2008;48(5):580-91.

212. Flouris AD, Poulianiti KP, Chorti MS, Jamurtas AZ, Kouretas D, Owolabi EO, et al. Acute effects of electronic and tobacco cigarette smoking on complete blood count. Food Chem Toxicol. 2012;50(10):3600-3.

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7.2 Appendix 2 Excluded studies from search 1

Literature retrieved using Search 1: To identify articles primarily relevant to the association of WBC count and smoking and/or smoking cessation using the string: ((((((((((WBC OR PMN) AND (smokers OR smoking OR nicotine replacement OR cessation) AND ("2008"[Date - Publication]: "2015"[Date - Publication]))) AND English[Language]))) NOT HIV)) NOT eosinophil)) NOT interstitial)) NOT PAD) AND Humans[Mesh])) NOT exacerbation

E1. Endpoint being assessed is not CVD, lung cancer, or non-malignant respiratory disease; this category includes a few studies where WBC count was not specifically correlated with smoking

1. *Summaries for patients. Smoking, quitting smoking, and the risk for type 2 diabetes.* Ann Intern Med, 2010. **152**(1): p. I-44.
2. Alshaarawy, O., et al., *Polycyclic aromatic hydrocarbon biomarkers and serum markers of inflammation. A positive association that is more evident in men.* Environ Res, 2013. **126**: p. 98-104.
3. Arenbergerova, M., S. Gkalpakiotis, and P. Arenberger, *Effective long-term control of refractory hidradenitis suppurativa with adalimumab after failure of conventional therapy.* Int J Dermatol, 2010. **49**(12): p. 1445-9.
4. Asdie, R.H., et al., *Does insulin resistance correlate with routine blood examination? A review on erythrocytes of obese patients.* Acta Med Indones, 2009. **41**(2): p. 66-9.
5. Athanassiadi, K., E. Bagaev, and A. Haverich, *Autologous blood pleurodesis for persistent air leak.* Thorac Cardiovasc Surg, 2009. **57**(8): p. 476-9.
6. Aul, R., et al., *LPS challenge in healthy subjects: an investigation of neutrophil chemotaxis mechanisms involving CXCR1 and CXCR2.* Int Immunopharmacol, 2012. **13**(3): p. 225-31.
7. Aulinas, A., et al., *Telomere length analysis in Cushing's syndrome.* Eur J Endocrinol, 2014. **171**(1): p. 21-9.
8. Bakovic, D., et al., *The effects of low-dose epinephrine infusion on spleen size, central and hepatic circulation and circulating platelets.* Clin Physiol Funct Imaging, 2013. **33**(1): p. 30-7.
9. Banerjee, A., et al., *Neutrophilic inflammatory response and oxidative stress in premenopausal women chronically exposed to indoor air pollution from biomass burning.* Inflammation, 2012. **35**(2): p. 671-83.
10. Bartman, M.T., et al., *Long-term increases in lymphocytes and platelets in human T-lymphotropic virus type II infection.* Blood, 2008. **112**(10): p. 3995-4002.

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11. Baumeister, S.E., et al., *Predictive modeling of health care costs: do cardiovascular risk markers improve prediction?* Eur J Cardiovasc Prev Rehabil, 2010. **17**(3): p. 355-62.

12. Berrington de Gonzalez, A., et al., *Pancreatic cancer and factors associated with the insulin resistance syndrome in the Korean cancer prevention study.* Cancer Epidemiol Biomarkers Prev, 2008. **17**(2): p. 359-64.

13. Beukelman, C.J., et al., *Anti-inflammatory properties of a liposomal hydrogel with povidone-iodine (Repithel) for wound healing in vitro.* Burns, 2008. **34**(6): p. 845-55.

14. Brand, J.S., et al., *Testosterone, SHBG and differential white blood cell count in middle-aged and older men.* Maturitas, 2012. **71**(3): p. 274-8.

15. Budzinski, E.E., et al., *Pyrimidine base damage is increased in women with BRCA mutations.* Cancer Lett, 2013. **338**(2): p. 267-70.

16. Canoy, D., et al., *Weight at birth and infancy in relation to adult leukocyte count: a population-based study of 5619 men and women followed from the fetal period to adulthood.* J Clin Endocrinol Metab, 2009. **94**(6): p. 1916-22.

17. Cardoso, D.F., et al., *Influence of human T-cell lymphotropic virus type 1 (HTLV-1) Infection on laboratory parameters of patients with chronic hepatitis C virus.* Rev Inst Med Trop Sao Paulo, 2009. **51**(6): p. 325-9.

18. Caro, M.A., et al., *Risk factors for positive depression screens in hospitalized cardiac patients.* J Cardiol, 2012. **60**(1): p. 72-7.

19. Chen, W., S.R. Srinivasan, and G.S. Berenson, *Influence of birth weight on white blood cell count in biracial (black-white) children, adolescents, and young adults: the Bogalusa Heart Study.* Am J Epidemiol, 2009. **169**(2): p. 214-8.

20. Clark, J.D., 3rd, et al., *Exposure to polycyclic aromatic hydrocarbons and serum inflammatory markers of cardiovascular disease.* Environ Res, 2012. **117**: p. 132-7.

21. Cofta, S., et al., *Plasma selectins in patients with obstructive sleep apnea.* Adv Exp Med Biol, 2013. **756**: p. 113-9.

22. Cofta, S., et al., *Endothelium-derived markers and antioxidant status in the blood of obstructive sleep apnea males.* Eur J Med Res, 2009. **14 Suppl 4**: p. 49-52.

23. De Prins, S., et al., *Influence of ambient air pollution on global DNA methylation in healthy adults: a seasonal follow-up.* Environ Int, 2013. **59**: p. 418-24.

24. de Rooij, S.R., et al., *Low-grade chronic inflammation in the relationship between insulin sensitivity and cardiovascular disease (RISC) population: associations with insulin resistance and cardiometabolic risk profile.* Diabetes Care, 2009. **32**(7): p. 1295-301.

25. Du, X., et al., *U-shape association between white blood cell count and the risk of diabetes in young Chinese adults.* Diabet Med, 2009. **26**(10): p. 955-60.

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26. Ergun, S., et al., *Micronuclear and sister chromatid exchange analyses in peripheral lymphocytes of patients with oral lichen planus--a pilot study.* Oral Dis, 2009. **15**(7): p. 499-504.

27. Fan, X., et al., *Higher white blood cell counts are associated with an increased risk for metabolic syndrome and more severe psychopathology in non-diabetic patients with schizophrenia.* Schizophr Res, 2010. **118**(1-3): p. 211-7.

28. Farah, R., F. Jubran, and R. Khamisy-Farah, *Effects of statins on oxidative stress and primed polymorphonuclear leukocytes in hyperlipidemic patients.* Biotech Histochem, 2012. **87**(8): p. 519-25.

29. Franca, C.M., et al., *Macrophage migration inhibitory factor and oral cancer.* J Oral Pathol Med, 2013. **42**(5): p. 368-73.

30. Francis, S.M., et al., *Peripheral compartment innate immune response to Haemophilus influenzae and Streptococcus pneumoniae in chronic obstructive pulmonary disease patients.* Innate Immun, 2013. **19**(4): p. 428-37.

31. Friedrich, N., et al., *The association of serum prolactin concentration with inflammatory biomarkers - cross-sectional findings from the population-based Study of Health in Pomerania.* Clin Endocrinol (Oxf), 2011. **75**(4): p. 561-6.

32. Fukami, A., et al., *Factors associated with serum high mobility group box 1 (HMGB1) levels in a general population.* Metabolism, 2009. **58**(12): p. 1688-93.

33. Fumarulo, R., A. Cassano, and M.A. Mariggio, *Exogenous factors in the immunotoxicity of oral PMN.* Immunopharmacol Immunotoxicol, 2011. **33**(1): p. 1-10.

34. Gamulin, M., et al., *Cytogenetic follow-up in testicular seminoma patients exposed to adjuvant radiotherapy.* Coll Antropol, 2010. **34**(2): p. 455-65.

35. Gao, C., et al., *Potential role of diabetes mellitus in the progression of cirrhosis to hepatocellular carcinoma: a cross-sectional case-control study from Chinese patients with HBV infection.* Hepatobiliary Pancreat Dis Int, 2013. **12**(4): p. 385-93.

36. Gao, J., et al., *A case-control study on etiological factors involved in patients with burning mouth syndrome.* J Oral Pathol Med, 2009. **38**(1): p. 24-8.

37. Girdhar, A., et al., *Systemic inflammation and its response to treatment in patients with asthma.* Respir Care, 2011. **56**(6): p. 800-5.

38. Gomez, R.A., et al., *Possible predictors of poor angiogenesis after hematopoietic stem cell autograft for lower limb ischemia.* MEDICC Rev, 2012. **14**(3): p. 31-6.

39. Gopinath, B., et al., *Homocysteine, folate, vitamin B-12, and 10-y incidence of age-related macular degeneration.* Am J Clin Nutr, 2013. **98**(1): p. 129-35.

40. Guilbaud, O., et al., *Decreased immune response in alexithymic women: a cross-sectional study.* Biomed Pharmacother, 2009. **63**(4): p. 297-304.

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41. Guillemard, E., et al., *Effects of consumption of a fermented dairy product containing the probiotic Lactobacillus casei DN-114 001 on common respiratory and gastrointestinal infections in shift workers in a randomized controlled trial.* J Am Coll Nutr, 2010. **29**(5): p. 455-68.

42. Han, D.H., H.J. Lee, and S. Lim, *Smoking induced heavy metals and periodontitis: findings from the Korea National Health and Nutrition Examination Surveys 2008-2010.* J Clin Periodontol, 2013. **40**(9): p. 850-8.

43. Hanley, A.J., et al., *Association of hematological parameters with insulin resistance and beta-cell dysfunction in nondiabetic subjects.* J Clin Endocrinol Metab, 2009. **94**(10): p. 3824-32.

44. Harita, N., et al., *Increment of absolute neutrophil count in the third trimester and increased risk of small-for-gestational-age birth: Hirakata Risk Associated with Pregnancy Assessment Research (HIRAPAR).* Eur J Obstet Gynecol Reprod Biol, 2012. **164**(1): p. 30-4.

45. Heffernan, K.S., et al., *C-reactive protein and cardiac vagal activity following resistance exercise training in young African-American and white men.* Am J Physiol Regul Integr Comp Physiol, 2009. **296**(4): p. R1098-105.

46. Helmig, S., et al., *Influence of the Cyp1B1 L432V gene polymorphism and exposure to tobacco smoke on Cyp1B1 mRNA expression in human leukocytes.* Drug Metab Dispos, 2009. **37**(7): p. 1490-5.

47. Herberth, G., et al., *Maternal and cord blood miR-223 expression associates with prenatal tobacco smoke exposure and low regulatory T-cell numbers.* J Allergy Clin Immunol, 2014. **133**(2): p. 543-50.

48. Herold, C., et al., *Is there an association between comorbidities and the outcome of microvascular free tissue transfer?* J Reconstr Microsurg, 2011. **27**(2): p. 127-32.

49. Heroux, M., et al., *Dietary patterns and the risk of mortality: impact of cardiorespiratory fitness.* Int J Epidemiol, 2010. **39**(1): p. 197-209.

50. Holtfreter, B., et al., *Periodontitis is associated with endothelial dysfunction in a general population: a cross-sectional study.* PLoS One, 2013. **8**(12): p. e84603.

51. Hossain, F., et al., *Effects of pesticide use on semen quality among farmers in rural areas of Sabah, Malaysia.* J Occup Health, 2010. **52**(6): p. 353-60.

52. Hsiao, F.C., et al., *Baseline forced expiratory volume in the first second as an independent predictor of development of the metabolic syndrome.* Metabolism, 2010. **59**(6): p. 848-53.

53. Hughes, A.D., et al., *Determinants of retinal microvascular architecture in normal subjects.* Microcirculation, 2009. **16**(2): p. 159-66.

54. Jiang, H., et al., *Elevated white blood cell count is associated with higher risk of glucose metabolism disorders in middle-aged and elderly Chinese people.* Int J Environ Res Public Health, 2014. **11**(5): p. 5497-509.

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55. Jin, X., et al., *Association between Helicobacter Pylori infection and ulcerative colitis--a case control study from China.* Int J Med Sci, 2013. **10**(11): p. 1479-84.

56. Johnson, T.A., et al., *Reconstitution of circulating lymphocyte counts in FTY720-treated MS patients.* Clin Immunol, 2010. **137**(1): p. 15-20.

57. Kabagambe, E.K., et al., *Inflammation biomarkers and risk of all-cause mortality in the Reasons for Geographic And Racial Differences in Stroke cohort.* Am J Epidemiol, 2011. **174**(3): p. 284-92.

58. Kang, H.T., et al., *Relationship between employment status and obesity in a Korean elderly population, based on the 2007-2009 Korean National Health and Nutrition Examination Survey (KNHANES).* Arch Gerontol Geriatr, 2013. **57**(1): p. 54-9.

59. Kang, Y.H., et al., *Comparison of alanine aminotransferase, white blood cell count, and uric acid in their association with metabolic syndrome: a study of Korean adults.* Endocr J, 2008. **55**(6): p. 1093-102.

60. Kaplon-Cieslicka, A., et al., *Predictors of high platelet reactivity during aspirin treatment in patients with type 2 diabetes.* Kardiol Pol, 2013. **71**(9): p. 893-902.

61. Karvanen, J. and F.E. Harrell, Jr., *Visualizing covariates in proportional hazards model.* Stat Med, 2009. **28**(14): p. 1957-66.

62. Kendzia, B., et al., *Pre- and postshift levels of inflammatory biomarkers and DNA damage in non-bitumen-exposed construction workers-subpopulation of the German Human Bitumen Study.* J Toxicol Environ Health A, 2012. **75**(8-10): p. 533-43.

63. Khocht, A., et al., *Neutrophil function and periodontitis in alcohol-dependent males without medical disorders.* J Int Acad Periodontol, 2013. **15**(3): p. 68-74.

64. Kiani, A.N., et al., *Predictors of progression in atherosclerosis over 2 years in systemic lupus erythematosus.* Rheumatology (Oxford), 2011. **50**(11): p. 2071-9.

65. Kim, M., et al., *Increased oxidative stress in normal-weight postmenopausal women with metabolic syndrome compared with metabolically healthy overweight/obese individuals.* Metabolism, 2013. **62**(4): p. 554-60.

66. Klatsky, A.L., et al., *Alcohol consumption and risk of hematologic malignancies.* Ann Epidemiol, 2009. **19**(10): p. 746-53.

67. Kobrosly, R. and E. van Wijngaarden, *Associations between immunologic, inflammatory, and oxidative stress markers with severity of depressive symptoms: an analysis of the 2005-2006 National Health and Nutrition Examination Survey.* Neurotoxicology, 2010. **31**(1): p. 126-33.

68. Kozlitina, J. and C.K. Garcia, *Red blood cell size is inversely associated with leukocyte telomere length in a large multi-ethnic population.* PLoS One, 2012. **7**(12): p. e51046.

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69. Kusuma, S.K., et al., *What is the role of serological testing between stages of two-stage reconstruction of the infected prosthetic knee?* Clin Orthop Relat Res, 2011. **469**(4): p. 1002-8.

70. Lajunen, T.K., et al., *Full-length visfatin levels are associated with inflammation in women with polycystic ovary syndrome.* Eur J Clin Invest, 2012. **42**(3): p. 321-8.

71. Lavranos, G., et al., *Investigating ROS sources in male infertility: a common end for numerous pathways.* Reprod Toxicol, 2012. **34**(3): p. 298-307.

72. Lazar, Z., et al., *Exhaled breath temperature in patients with stable and exacerbated COPD.* J Breath Res, 2014. **8**(4): p. 046002.

73. Lee, J.W., et al., *Serum carcinoembryonic antigen is associated with metabolic syndrome in female Korean non-smokers.* Clin Chim Acta, 2011. **412**(7-8): p. 527-30.

74. Lee, K.M., et al., *A pilot study on the association between job stress and repeated measures of immunological biomarkers in female nurses.* Int Arch Occup Environ Health, 2010. **83**(7): p. 779-89.

75. Lee, K.S., et al., *Eating rate is associated with cardiometabolic risk factors in Korean adults.* Nutr Metab Cardiovasc Dis, 2013. **23**(7): p. 635-41.

76. Lee, Y.J., et al., *Relationship between white blood cell count and nonalcoholic fatty liver disease.* Dig Liver Dis, 2010. **42**(12): p. 888-94.

77. Leng, S.X., et al., *White blood cell counts, insulin-like growth factor-1 levels, and frailty in community-dwelling older women.* J Gerontol A Biol Sci Med Sci, 2009. **64**(4): p. 499-502.

78. Li, Y.J., et al., *Disruption of the blood-brain barrier after generalized tonic-clonic seizures correlates with cerebrospinal fluid MMP-9 levels.* J Neuroinflammation, 2013. **10**: p. 80.

79. Lohr, J., et al., *Relation of insulin-like growth factor-I and IGF binding protein 3 with markers of inflammation: results of a population-based study.* Clin Endocrinol (Oxf), 2014. **80**(1): p. 148-54.

80. Lorenzo, C., A.J. Hanley, and S.M. Haffner, *Differential white cell count and incident type 2 diabetes: the Insulin Resistance Atherosclerosis Study.* Diabetologia, 2014. **57**(1): p. 83-92.

81. Marengoni, A., et al., *Total lymphocyte count and in-hospital mortality in older persons with multimorbidity.* Aging Clin Exp Res, 2008. **20**(4): p. 290-6.

82. Martins, F.M., et al., *Oral manifestations of human T-cell lymphotropic virus infection in adult patients from Brazil.* Oral Dis, 2010. **16**(2): p. 167-71.

83. Masue, T., et al., *Associations of urinary 6-sulfatoxymelatonin with biomarkers related to cardiovascular disease in Japanese women.* Metabolism, 2012. **61**(1): p. 70-5.

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84. Meisel, P., et al., *Total tooth loss and systemic correlates of inflammation: role of obesity.* Obesity (Silver Spring), 2012. **20**(3): p. 644-50.

85. Mellenthin, L., et al., *Association between serum vitamin D concentrations and inflammatory markers in the general adult population.* Metabolism, 2014. **63**(8): p. 1056-62.

86. Mi, H., et al., *Research of correlation between the amount of leukocyte in EPS and NIH-CPSI: result from 1242 men in Fangchenggang Area in Guangxi Province.* Urology, 2012. **79**(2): p. 403-8.

87. Miller, B.J., A. Mellor, and P. Buckley, *Total and differential white blood cell counts, high-sensitivity C-reactive protein, and the metabolic syndrome in non-affective psychoses.* Brain Behav Immun, 2013. **31**: p. 82-9.

88. Moretti, E., et al., *Resistin, interleukin-6, tumor necrosis factor-alpha, and human semen parameters in the presence of leukocytospermia, smoking habit, and varicocele.* Fertil Steril, 2014. **102**(2): p. 354-60.

89. Myers, C.E., et al., *Determinants of retinal venular diameter: the Beaver Dam Eye Study.* Ophthalmology, 2012. **119**(12): p. 2563-71.

90. Na, H.Y., et al., *Sex differences in the relationship between leukocyte count and chronic kidney disease: the 2007 Korean National Health and Nutrition Examination Survey.* J Womens Health (Larchmt), 2011. **20**(1): p. 99-105.

91. Nakanishi, N., et al., *Low urine pH Is a predictor of chronic kidney disease.* Kidney Blood Press Res, 2012. **35**(2): p. 77-81.

92. Nakata, A., et al., *Is self-rated health associated with blood immune markers in healthy individuals?* Int J Behav Med, 2010. **17**(3): p. 234-42.

93. Nanba, T., et al., *Increases of the Th1/Th2 cell ratio in severe Hashimoto's disease and in the proportion of Th17 cells in intractable Graves' disease.* Thyroid, 2009. **19**(5): p. 495-501.

94. Narla, V., et al., *Coronary artery calcification and inflammation according to various metabolic syndrome definitions.* J Cardiometab Syndr, 2009. **4**(1): p. 33-9.

95. Nawrot, T.S., et al., *Telomere length and its associations with oxidized-LDL, carotid artery distensibility and smoking.* Front Biosci (Elite Ed), 2010. **2**: p. 1164-8.

96. Nolan, A., et al., *Increased production of IL-4 and IL-12p40 from bronchoalveolar lavage cells are biomarkers of Mycobacterium tuberculosis in the sputum.* PLoS One, 2013. **8**(3): p. e59461.

97. Oda, E., *High-sensitivity C-reactive protein and white blood cell count equally predict development of the metabolic syndrome in a Japanese health screening population.* Acta Diabetol, 2013. **50**(4): p. 633-8.

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98. Ogino, K., et al., *Association of serum arginase I with oxidative stress in a healthy population.* Free Radic Res, 2011. **45**(2): p. 147-55.

99. Okamura, T. and M. Watanabe, *The relationship between white blood cell count and risk of hypertension in populations with high prevalence of smoking.* Hypertens Res, 2008. **31**(7): p. 1279-81.

100. Patussi, C., et al., *Clinical assessment of oral mucositis and candidiasis compare to chemotherapic nadir in transplanted patients.* Braz Oral Res, 2014. **28**(1): p. 1-7.

101. Pellanda, L.C., et al., *Low birth weight and markers of inflammation and endothelial activation in adulthood: the ARIC study.* Int J Cardiol, 2009. **134**(3): p. 371-7.

102. Persson, M., et al., *Soluble urokinase plasminogen activator receptor in plasma is associated with incidence of CVD. Results from the Malmo Diet and Cancer Study.* Atherosclerosis, 2012. **220**(2): p. 502-5.

103. Pignatti, P., et al., *Age-related increase of airway neutrophils in older healthy nonsmoking subjects.* Rejuvenation Res, 2011. **14**(4): p. 365-70.

104. Plumb, J., et al., *Reduced glucocorticoid receptor expression and function in airway neutrophils.* Int Immunopharmacol, 2012. **12**(1): p. 26-33.

105. Puttonen, S., K. Viitasalo, and M. Harma, *Effect of shiftwork on systemic markers of inflammation.* Chronobiol Int, 2011. **28**(6): p. 528-35.

106. Riethmueller, J., et al., *Continuous vs thrice-daily ceftazidime for elective intravenous antipseudomonal therapy in cystic fibrosis.* Infection, 2009. **37**(5): p. 418-23.

107. Rihs, H.P., et al., *Modulation of oxidative DNA damage by repair enzymes XRCC1 and hOGG1.* J Toxicol Environ Health A, 2012. **75**(8-10): p. 588-96.

108. Rossi, S., et al., *A genetic variant of the anti-apoptotic protein Akt predicts natalizumab-induced lymphocytosis and post-natalizumab multiple sclerosis reactivation.* Mult Scler, 2013. **19**(1): p. 59-68.

109. Saroha, S., et al., *Lymphopenia is an independent predictor of inferior outcome in clear cell renal carcinoma.* J Urol, 2013. **189**(2): p. 454-61.

110. Sato, K.K., et al., *Elevated white blood cell count worsens proteinuria but not estimated glomerular filtration rate: the Kansai Healthcare Study.* Am J Nephrol, 2011. **34**(4): p. 324-9.

111. Schooling, C.M., *Androgen activity and markers of inflammation among men in NHANES III.* Am J Hum Biol, 2013. **25**(5): p. 622-8.

112. Shigemura, M., et al., *Levels of transferrin in bronchoalveolar lavage fluid in sarcoidosis.* Lung, 2010. **188**(2): p. 151-7.

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113. Shimauchi, T., et al., *Alterations of serum Th1 and Th2 chemokines by combination therapy of interferon-gamma and narrowband UVB in patients with mycosis fungoides.* J Dermatol Sci, 2008. **50**(3): p. 217-25.

114. Shivanaikar, S.S., M. Faizuddin, and K. Bhat, *Effect of smoking on neutrophil apoptosis in chronic periodontitis: an immunohistochemical study.* Indian J Dent Res, 2013. **24**(1): p. 147.

115. Skjelbred, C.F., et al., *Influence of GSTM1, GSTT1, GSTP1, NAT1, NAT2, EPHX1, MTR and MTHFR polymorphism on chromosomal aberration frequencies in human lymphocytes.* Carcinogenesis, 2011. **32**(3): p. 399-405.

116. So, W.Y., et al., *Risk factors in V-shaped risk associations with all-cause mortality in type 2 diabetes-The Hong Kong Diabetes Registry.* Diabetes Metab Res Rev, 2008. **24**(3): p. 238-46.

117. Spencer, B.W., et al., *Granulocyte colony stimulating factor (G-CSF) can allow treatment with clozapine in a patient with severe benign ethnic neutropaenia (BEN): a case report.* J Psychopharmacol, 2012. **26**(9): p. 1280-2.

118. Stranges, S., et al., *Additional contribution of emerging risk factors to the prediction of the risk of type 2 diabetes: evidence from the Western New York Study.* Obesity (Silver Spring), 2008. **16**(6): p. 1370-6.

119. Stuve, O., et al., *alpha4-Integrin antagonism with natalizumab: effects and adverse effects.* J Neurol, 2008. **255 Suppl 6**: p. 58-65.

120. Suarez, E.C. and N.L. Schramm-Sapyta, *Race differences in the relation of vitamins A, C, E, and beta-carotene to metabolic and inflammatory biomarkers.* Nutr Res, 2014. **34**(1): p. 1-10.

121. Sun, W.X., et al., *A decreased mean platelet volume is associated with stable and exacerbated asthma.* Respiration, 2014. **88**(1): p. 31-7.

122. Sun, X.J., et al., *Elevation of C-reactive protein and interleukin-6 in plasma of patients with aggressive periodontitis.* J Periodontal Res, 2009. **44**(3): p. 311-6.

123. Syrjala, A.M., et al., *Number of teeth and selected cardiovascular risk factors among elderly people.* Gerodontology, 2010. **27**(3): p. 189-92.

124. Tian, J.Y., et al., *Association of WBC count and glucose metabolism among Chinese population aged 40 years and over.* Diabetes Res Clin Pract, 2008. **82**(1): p. 132-8.

125. Ton, T.G., et al., *Markers of inflammation in prevalent and incident Parkinson's disease in the Cardiovascular Health Study.* Parkinsonism Relat Disord, 2012. **18**(3): p. 274-8.

126. Torab, F.C., et al., *Perforated peptic ulcer: different ethnic, climatic and fasting risk factors for morbidity in Al-ain medical district, United Arab Emirates.* Asian J Surg, 2009. **32**(2): p. 95-101.

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127. Torii, K., et al., *Tobacco smoke is related to Th17 generation with clinical implications for psoriasis patients.* Exp Dermatol, 2011. **20**(4): p. 371-3.

128. Tormo, N., et al., *Kinetics of cytomegalovirus (CMV) pp65 and IE-1-specific IFNgamma CD8+ and CD4+ T cells during episodes of viral DNAemia in allogeneic stem cell transplant recipients: potential implications for the management of active CMV infection.* J Med Virol, 2010. **82**(7): p. 1208-15.

129. Uchiyama, H., et al., *Alterations in smoking habits are associated with acute eosinophilic pneumonia.* Chest, 2008. **133**(5): p. 1174-80.

130. Uddin, M., et al., *Prosurvival activity for airway neutrophils in severe asthma.* Thorax, 2010. **65**(8): p. 684-9.

131. Ushida, Y., et al., *Combinational risk factors of metabolic syndrome identified by fuzzy neural network analysis of health-check data.* BMC Med Inform Decis Mak, 2012. **12**: p. 80.

132. Varadarajan, R., et al., *Smoking adversely affects survival in acute myeloid leukemia patients.* Int J Cancer, 2012. **130**(6): p. 1451-8.

133. Verschuur, C.A., et al., *Markers of inflammatory status are associated with hearing threshold in older people: findings from the Hertfordshire Ageing Study.* Age Ageing, 2012. **41**(1): p. 92-7.

134. Vuletic, S., et al., *SAA and PLTP activity in plasma of periodontal patients before and after full-mouth tooth extraction.* Oral Dis, 2008. **14**(6): p. 514-9.

135. Wang, K.C., et al., *Metabolomic characterization of laborers exposed to welding fumes.* Chem Res Toxicol, 2012. **25**(3): p. 676-86.

136. Wansom, D., et al., *Correlation of cellular immunity with human papillomavirus 16 status and outcome in patients with advanced oropharyngeal cancer.* Arch Otolaryngol Head Neck Surg, 2010. **136**(12): p. 1267-73.

137. Warner, J.H., et al., *Adaptive regression modeling of biomarkers of potential harm in a population of U.S. adult cigarette smokers and nonsmokers.* BMC Med Res Methodol, 2010. **10**: p. 19.

138. Wegienka, G., et al., *Within-woman change in regulatory T cells from pregnancy to the postpartum period.* J Reprod Immunol, 2011. **88**(1): p. 58-65.

139. Willems, J.M., et al., *White blood cell count and C-reactive protein are independent predictors of mortality in the oldest old.* J Gerontol A Biol Sci Med Sci, 2010. **65**(7): p. 764-8.

140. Willershausen, B., et al., *Association between chronic dental infection and acute myocardial infarction.* J Endod, 2009. **35**(5): p. 626-30.

141. Wohlfeil, M., et al., *Degree of gingivitis correlates to systemic inflammation parameters.* Clin Chim Acta, 2009. **401**(1-2): p. 105-9.

142. Wolff, H., et al., *Patients referred to an indoor air health clinic: exposure to water-damaged buildings causes an increase of lymphocytes in bronchoalveolar*

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lavage and a decrease of CD19 leucocytes in peripheral blood. Scand J Clin Lab Invest, 2009. **69**(5): p. 537-44.

143. Wu, C., et al., *Prevalence of and risk factors for asymptomatic in fl ammatory (NIH-IV) prostatitis in Chinese men.* PLoS One, 2013. **8**(8): p. e71298.

144. Wu, Y., et al., *Distribution characteristics of leukocytes in EPS and correlation with serum PSA levels: results from a Chinese male population survey.* Urology, 2013. **81**(2): p. 384-9.

145. Wuketich, S., S.A. Hienz, and C. Marosi, *Prevalence of clinically relevant oral mucositis in outpatients receiving myelosuppressive chemotherapy for solid tumors.* Support Care Cancer, 2012. **20**(1): p. 175-83.

146. Yang, X., et al., *Predicting values of lipids and white blood cell count for all-site cancer in type 2 diabetes.* Endocr Relat Cancer, 2008. **15**(2): p. 597-607.

147. Yasuda, M., et al., *Nine-year incidence and risk factors for age-related macular degeneration in a defined Japanese population the Hisayama study.* Ophthalmology, 2009. **116**(11): p. 2135-40.

148. Yeh, H.C., et al., *Smoking, smoking cessation, and risk for type 2 diabetes mellitus: a cohort study.* Ann Intern Med, 2010. **152**(1): p. 10-7.

149. Yesil, S., et al., *Predictors of amputation in diabetics with foot ulcer: single center experience in a large Turkish cohort.* Hormones (Athens), 2009. **8**(4): p. 286-95.

150. Yom-Tov, G., et al., *Clomiphene as a novel modality for the treatment of acute myeloid leukemia: A pilot phase II study.* Leuk Res, 2012. **36**(1): p. 42-5.

151. Zhang, X., et al., *Elevation of vitamin D-binding protein levels in the plasma of patients with generalized aggressive periodontitis.* J Periodontal Res, 2013. **48**(1): p. 74-9.

152. Zhao, J., et al., *Genetically predicted 17beta-estradiol and systemic inflammation in women: a separate-sample Mendelian randomisation analysis in the Guangzhou Biobank Cohort Study.* J Epidemiol Community Health, 2014. **68**(8): p. 780-5.

153. Ziora, D., S. Dworniczak, and J. Kozielski, *Induced sputum metalloproteinases and their inhibitors in relation to exhaled nitrogen oxide and sputum nitric oxides and other inflammatory cytokines in patients with chronic obstructive pulmonary disease.* J Physiol Pharmacol, 2008. **59 Suppl 6**: p. 809-17.

E2. Association of a relevant disease or smoking with markers other than generically labelled "white blood cells" or "leukocytes", neutrophils, or monocytes

1. Alman, A.C., et al., *Loss of alveolar bone due to periodontal disease exhibits a threshold on the association with coronary heart disease.* J Periodontol, 2011. **82**(9): p. 1304-13.

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2. Almanzar, G., et al., *Maternal cigarette smoking and its effect on neonatal lymphocyte subpopulations and replication.* BMC Pediatr, 2013. **13**: p. 57.

3. Asthana, A., et al., *Effects of smoking intensity and cessation on inflammatory markers in a large cohort of active smokers.* Am Heart J, 2010. **160**(3): p. 458-63.

4. Bae, U., et al., *Serum carcinoembryonic antigen level is associated with arterial stiffness in healthy Korean adult.* Clin Chim Acta, 2013. **415**: p. 286-9.

5. Braber, S., et al., *An association between neutrophils and immunoglobulin free light chains in the pathogenesis of chronic obstructive pulmonary disease.* Am J Respir Crit Care Med, 2012. **185**(8): p. 817-24.

6. Brandsma, C.A., et al., *Increased levels of (class switched) memory B cells in peripheral blood of current smokers.* Respir Res, 2009. **10**: p. 108.

7. Brozyna, S., et al., *Chemotactic mediators of Th1 T-cell trafficking in smokers and COPD patients.* COPD, 2009. **6**(1): p. 4-16.

8. Dancer, R. and D.M. Sansom, *Regulatory T cells and COPD.* Thorax, 2013. **68**(12): p. 1176-8.

9. Emerging Risk Factors, C., et al., *C-reactive protein concentration and risk of coronary heart disease, stroke, and mortality: an individual participant meta-analysis.* Lancet, 2010. **375**(9709): p. 132-40.

10. Engstrom, G., O. Melander, and B. Hedblad, *Population-based study of lung function and incidence of heart failure hospitalisations.* Thorax, 2010. **65**(7): p. 633-8.

11. Galgani, M., et al., *Imbalance of circulating dendritic cell subsets in chronic obstructive pulmonary disease.* Clin Immunol, 2010. **137**(1): p. 102-10.

12. Ge, Y., et al., *Circulating CD31+ leukocyte frequency is associated with cardiovascular risk factors.* Atherosclerosis, 2013. **229**(1): p. 228-33.

13. Hodge, G., et al., *Differential expression of pro-inflammatory cytokines in intra-epithelial T cells between trachea and bronchi distinguishes severity of COPD.* Cytokine, 2012. **60**(3): p. 843-8.

14. Holmgaard, D.B., et al., *Plasma YKL-40 and all-cause mortality in patients with chronic obstructive pulmonary disease.* BMC Pulm Med, 2013. **13**: p. 77.

15. Holmlund, A. and L. Lind, *Number of teeth is related to atherosclerotic plaque in the carotid arteries in an elderly population.* J Periodontol, 2012. **83**(3): p. 287-91.

16. Hou, C., et al., *High mobility group protein B1 (HMGB1) in Asthma: comparison of patients with chronic obstructive pulmonary disease and healthy controls.* Mol Med, 2011. **17**(7-8): p. 807-15.

17. Hou, J., et al., *Imbalance between subpopulations of regulatory T cells in COPD.* Thorax, 2013. **68**(12): p. 1131-9.

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18. Jubri, Z., et al., *Perturbation of cellular immune functions in cigarette smokers and protection by palm oil vitamin E supplementation.* Nutr J, 2013. **12**: p. 2.

19. Kitamura, H., et al., *Cross-sectional study on respiratory effect of toner-exposed work in manufacturing plants, Japan: pulmonary function, blood cells, and biochemical markers.* Hum Exp Toxicol, 2009. **28**(6-7): p. 331-8.

20. Kotani, K., et al., *Relationship between alcohol habits and hemorheology by a micro channel method in a general population.* Clin Cardiol, 2008. **31**(10): p. 488-91.

21. Lofdahl, M.J., et al., *Increased intraepithelial T-cells in stable COPD.* Respir Med, 2008. **102**(12): p. 1812-8.

22. Mallia, P., et al., *Lymphocyte subsets in experimental rhinovirus infection in chronic obstructive pulmonary disease.* Respir Med, 2014. **108**(1): p. 78-85.

23. Mobarrez, F., et al., *The effects of smoking on levels of endothelial progenitor cells and microparticles in the blood of healthy volunteers.* PLoS One, 2014. **9**(2): p. e90314.

24. Olloquequi, J., et al., *Differential lymphocyte infiltration in small airways and lung parenchyma in COPD patients.* Respir Med, 2010. **104**(9): p. 1310-8.

25. Pace, E., et al., *TLR4 up-regulation and reduced Foxp3 expression in mechanically ventilated smokers with obstructive chronic bronchitis.* COPD, 2013. **10**(2): p. 147-55.

26. Ravensberg, A.J., et al., *CD8(+) T cells characterize early smoking-related airway pathology in patients with asthma.* Respir Med, 2013. **107**(7): p. 959-66.

27. Roos-Engstrand, E., et al., *Influence of smoking cessation on airway T lymphocyte subsets in COPD.* COPD, 2009. **6**(2): p. 112-20.

28. Saliques, S., et al., *Smoking and FOS expression from blood leukocyte transcripts in patients with coronary artery disease.* Atherosclerosis, 2011. **219**(2): p. 931-6.

29. Sandal, S. and B. Yilmaz, *Genotoxic effects of chlorpyrifos, cypermethrin, endosulfan and 2,4-D on human peripheral lymphocytes cultured from smokers and nonsmokers.* Environ Toxicol, 2011. **26**(5): p. 433-42.

30. Sjaheim, T.B., et al., *Increased bronchial density of CD25+Foxp3+ regulatory T cells in occupational asthma: relationship to current smoking.* Scand J Immunol, 2013. **77**(5): p. 398-404.

31. Sugiura, H., et al., *Increased 25-hydroxycholesterol concentrations in the lungs of patients with chronic obstructive pulmonary disease.* Respirology, 2012. **17**(3): p. 533-40.

32. Torres, A.J., et al., *Reference range for T lymphocytes populations in blood donors from two different regions in Brazil.* Braz J Infect Dis, 2009. **13**(3): p. 221-5.

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33. Torres, A.J., et al., *Establishing the reference range for T lymphocytes subpopulations in adults and children from Brazil.* Rev Inst Med Trop Sao Paulo, 2013. **55**(5): p. 323-8.

34. Tracy, R.P., et al., *T-helper type 1 bias in healthy people is associated with cytomegalovirus serology and atherosclerosis: the Multi-Ethnic Study of Atherosclerosis.* J Am Heart Assoc, 2013. **2**(3): p. e000117.

35. Urbanowicz, R.A., et al., *Enhanced effector function of cytotoxic cells in the induced sputum of COPD patients.* Respir Res, 2010. **11**: p. 76.

E3. Population being studied is either not apparently healthy or studies that lack a control population

1. Akhtar, N., et al., *The role of leukocyte counts in patients with unstable angina pectoris or myocardial infarction; prognostic significance and correlation with plasma brain natriuretic peptide (BNP) levels.* J Pak Med Assoc, 2011. **61**(1): p. 51-4.

2. Angeli, F., et al., *Neutrophil count for the identification of postmenopausal hypertensive women at increased cardiovascular risk.* Obstet Gynecol, 2010. **115**(4): p. 695-703.

3. Ates, A.H., et al., *Total white blood cell count is associated with the presence, severity and extent of coronary atherosclerosis detected by dual-source multislice computed tomographic coronary angiography.* Cardiol J, 2011. **18**(4): p. 371-7.

4. Bartolone, S., et al., *White cells count in smokers affected by rheumatic diseases.* Rheumatol Int, 2012. **32**(1): p. 109-15.

5. Cortina, M.G., et al., *Monocyte count is an underlying marker of lacunar subtype of hypertensive small vessel disease.* Eur J Neurol, 2008. **15**(7): p. 671-6.

6. Dasanu, C.A. and I. Codreanu, *Persistent polyclonal B-cell lymphocytosis in chronic smokers: more than meets the eye.* Conn Med, 2012. **76**(2): p. 69-72.

7. Farah, R., R. Khamisy-Farah, and R. Shurtz-Swirski, *Calcium channel blocker effect on insulin resistance and inflammatory markers in essential hypertension patients.* Int Angiol, 2013. **32**(1): p. 85-93.

8. Farah, R., R. Shurtz-Swirski, and F. Dorlechter, *Primed polymorphonuclear leukocytes constitute a possible link between inflammation and oxidative stress in hyperlipidemic patients: effect of statins.* Minerva Cardioangiol, 2010. **58**(2): p. 175-81.

9. Floel, A., et al., *Granulocyte-colony stimulating factor (G-CSF) in stroke patients with concomitant vascular disease--a randomized controlled trial.* PLoS One, 2011. **6**(5): p. e19767.

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10. Gunaydin, S., et al., *Clinical performance and biocompatibility of hyaluronan-based heparin-bonded extracorporeal circuits in different risk cohorts.* Interact Cardiovasc Thorac Surg, 2010. **10**(3): p. 371-6.

11. Gunaydin, S., K. McCusker, and V. Vijay, *Clinical and biomaterial evaluation of a new condensed dual-function extracorporeal circuit in reoperation for coronary artery bypass surgery.* Int J Artif Organs, 2009. **32**(11): p. 802-10.

12. Jae, S.Y., et al., *Relation of cardiorespiratory fitness to inflammatory markers, fibrinolytic factors, and lipoprotein(a) in patients with type 2 diabetes mellitus.* Am J Cardiol, 2008. **102**(6): p. 700-3.

13. Kim, S.H., et al., *Factors related to the initial stroke severity of posterior circulation ischemic stroke.* Cerebrovasc Dis, 2013. **36**(1): p. 62-8.

14. Kocaman, S.A., et al., *The association of circulating monocyte count with coronary collateral growth in patients with diabetes mellitus.* Acta Diabetol, 2010. **47**(1): p. 49-54.

15. Komurcuoglu, B., et al., *Prognostic factors affecting survival in malignant pleural mesothelioma: analysis of 125 subjects.* Tumori, 2014. **100**(1): p. 55-9.

16. Lee, G.K., et al., *The long-term predictive value of the neutrophil-to-lymphocyte ratio in Type 2 diabetic patients presenting with acute myocardial infarction.* QJM, 2012. **105**(11): p. 1075-82.

17. Lee, H.K., et al., *Role of high augmentation index in spontaneous intracerebral haemorrhage.* Asian J Surg, 2010. **33**(1): p. 42-50.

18. Li, L., et al., *The combination of carotid and lower extremity ultrasonography increases the detection of atherosclerosis in type 2 diabetes patients.* J Diabetes Complications, 2012. **26**(1): p. 23-8.

19. Makris, D., et al., *Tc2 response at the onset of COPD exacerbations.* Chest, 2008. **134**(3): p. 483-8.

20. Nikanfar, M., et al., *Evaluating role of leukocytosis and high sedimentation rate as prognostic factors in acute ischemic cerebral strokes.* Pak J Biol Sci, 2012. **15**(8): p. 386-90.

21. Ose, N., et al., *Lymph node metastasis diagnosis using positron emission tomography with 2-[18F] fluoro-2-deoxy-D-glucose as a tracer and computed tomography in surgical cases of non-small cell lung cancer.* Eur J Cardiothorac Surg, 2012. **42**(1): p. 89-92.

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22. Palmerini, T., et al., *Association among leukocyte count, mortality, and bleeding in patients with non-ST-segment elevation acute coronary syndromes (from the Acute Catheterization and Urgent Intervention Triage StrategY [ACUITY] trial).* Am J Cardiol, 2013. **111**(9): p. 1237-45.

23. Rasouli, M., et al., *The multiplicative interactions of leukocyte counts with some other risk factors enhance the prognostic value for coronary artery disease.* Cardiol J, 2011. **18**(3): p. 246-53.

24. Roquer, J., et al., *Previous infection and stroke: a prospective study.* Cerebrovasc Dis, 2012. **33**(4): p. 310-5.

25. Suzuki, H., et al., *Stratification of malignant pleural mesothelioma prognosis using recursive partitioning analysis.* Lung, 2014. **192**(1): p. 191-5.

26. Terlecki, M., et al., *Acute hyperglycaemia and inflammation in patients with ST segment elevation myocardial infarction.* Kardiol Pol, 2013. **71**(3): p. 260-7.

27. Thomsen, M., et al., *Inflammatory biomarkers and exacerbations in chronic obstructive pulmonary disease.* JAMA, 2013. **309**(22): p. 2353-61.

28. Turak, O., et al., *Usefulness of the neutrophil-to-lymphocyte ratio to predict bare-metal stent restenosis.* Am J Cardiol, 2012. **110**(10): p. 1405-10.

29. Wang, T., J.H. Zhang, and X. Qin, *Analysis on death-associated factors of patients with subarachnoid hemorrhage during hospitalization.* Acta Neurochir Suppl, 2011. **110**(Pt 1): p. 219-23.

30. Zhang, B., et al., *Different independent susceptibility markers for first-ever cerebral infarction and myocardial infarction in young patients.* J Neurol, 2012. **259**(7): p. 1420-5.

E4. Studies involving children, infants, or neonates

1. Belderbos, M.E., et al., *Breastfeeding modulates neonatal innate immune responses: a prospective birth cohort study.* Pediatr Allergy Immunol, 2012. **23**(1): p. 65-74.

2. Duijts, L., et al., *Fetal growth influences lymphocyte subset counts at birth: the Generation R Study.* Neonatology, 2009. **95**(2): p. 149-56.

3. Eyrich, M., et al., *Immune function in children under chemotherapy for standard risk acute lymphoblastic leukaemia - a prospective study of 20 paediatric patients.* Br J Haematol, 2009. **147**(3): p. 360-70.

4. Keski-Nisula, L., et al., *Production of interleukin-5, -10 and interferon-gamma in cord blood is strongly associated with the season of birth.* Clin Exp Allergy, 2010. **40**(11): p. 1658-68.

5. Kovacs, G.T., et al., *Late immune recovery in children treated for malignant diseases.* Pathol Oncol Res, 2008. **14**(4): p. 391-7.

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6. Mancebo, E., et al., *Longitudinal analysis of immune function in the first 3 years of life in thymectomized neonates during cardiac surgery.* Clin Exp Immunol, 2008. **154**(3): p. 375-83.

7. Pirkola, J., et al., *Low-grade, systemic inflammation in adolescents: association with early-life factors, gender, and lifestyle.* Am J Epidemiol, 2010. **171**(1): p. 72-82.

8. Soylu, A., et al., *Resolution of chyloperitoneum in a preterm with octreotide, diet and cessation of dialysis.* Pediatr Nephrol, 2010. **25**(2): p. 363-6.

E5. Case studies

1. Del Giudice, I., et al., *Histopathological and molecular features of persistent polyclonal B-cell lymphocytosis (PPBL) with progressive splenomegaly.* Br J Haematol, 2009. **144**(5): p. 726-31.

2. Montoya, J.G., et al., *Antiviral therapy of two patients with chromosomally-integrated human herpesvirus-6A presenting with cognitive dysfunction.* J Clin Virol, 2012. **55**(1): p. 40-5.

3. Ochi, H., et al., *The persistence of drug-induced fever by teicoplanin--a case report.* Int J Clin Pharmacol Ther, 2011. **49**(5): p. 339-43.

4. Tavil, B., et al., *Linezolid-induced reversible bicytopenia in a 4-year-old boy with methicillin-resistant Staphylococcus aureus bacteremia.* Pediatr Hematol Oncol, 2008. **25**(1): p. 67-71.

5. Waki, F., et al., *Linezolid-induced pure red cell aplasia in a patient with Staphylococcus epidermidis infection after allogeneic stem cell transplantation.* Transpl Infect Dis, 2012. **14**(4): p. E1-6.

E6. Studies on environmental tobacco smoke

1. Clark, J.D., 3rd, et al., *Inflammatory markers and secondhand tobacco smoke exposure among U.S. workers.* Am J Ind Med, 2008. **51**(8): p. 626-32.

2. Dinas, P.C., et al., *Acute effects of second-hand smoke on complete blood count.* Int J Environ Health Res, 2014. **24**(1): p. 56-62.

3. Zhang, J., et al., *Secondhand tobacco smoke exposure and heart rate variability and inflammation among non-smoking construction workers: a repeated measures study.* Environ Health, 2013. **12**(1): p. 83.

E7. In vitro or animal studies

1. Dupont, A., et al., *Impairment of neutrophil reactivity to elastin peptides in COPD.* Thorax, 2013. **68**(5): p. 421-8.

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2. Gao, Z., et al., *Effect of cold-dryness on pulmonary and immunologic function in chronic obstructive pulmonary disease model rats.* J Tradit Chin Med, 2014. **34**(2): p. 221-6.

3. Lin, C.C., et al., *Induction of COX-2/PGE(2)/IL-6 is crucial for cigarette smoke extract-induced airway inflammation: Role of TLR4-dependent NADPH oxidase activation.* Free Radic Biol Med, 2010. **48**(2): p. 240-54.

4. Minematsu, N., A. Blumental-Perry, and S.D. Shapiro, *Cigarette smoke inhibits engulfment of apoptotic cells by macrophages through inhibition of actin rearrangement.* Am J Respir Cell Mol Biol, 2011. **44**(4): p. 474-82.

5. Sharma, J., et al., *Lung endothelial cell platelet-activating factor production and inflammatory cell adherence are increased in response to cigarette smoke component exposure.* Am J Physiol Lung Cell Mol Physiol, 2012. **302**(1): p. L47-55.

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7.3 Appendix 3 Excluded studies from search 2

Literature retrieved using Search 2: To identify articles primarily relevant to the association of WBC count and CVD using the string: (((((((((WBC OR PMN) AND ((cardiovascular disease) AND (association)) AND ("2008"[Date - Publication]: "2015"[Date - Publication]))) AND English[Language]))) NOT eosinophil) NOT HIV) NOT Exacerbation) NOT embolism) NOT PAD

E1. Endpoint being assessed is not CVD, lung cancer, or non-malignant respiratory disease; this category includes a few studies where WBC count was not specifically correlated with smoking

1. Adams, R.A., et al., *The effect of physical activity on haematological predictors of cardiovascular risk: evidence of a dose response.* Clin Hemorheol Microcirc, 2012. **52**(1): p. 57-65.
2. Ahmadi-Abhari, S., et al., *Seventeen year risk of all-cause and cause-specific mortality associated with C-reactive protein, fibrinogen and leukocyte count in men and women: the EPIC-Norfolk study.* Eur J Epidemiol, 2013. **28**(7): p. 541-50.
3. Allal-Elasmi, M., et al., *The measurement of circulating matrix metalloproteinase-8 and its tissue inhibitor and their association with inflammatory mediators in patients with acute coronary syndrome.* Clin Lab, 2014. **60**(6): p. 951-6.
4. Angermann, C.E., et al., *Somatic correlates of comorbid major depression in patients with systolic heart failure.* Int J Cardiol, 2011. **147**(1): p. 66-73.
5. Arruda-Olson, A.M., et al., *Association of TNFSF8 polymorphisms with peripheral neutrophil count.* Mayo Clin Proc, 2011. **86**(11): p. 1075-81.
6. Aust, G., et al., *Circulating Nampt and RBP4 levels in patients with carotid stenosis undergoing carotid endarterectomy (CEA).* Clin Chim Acta, 2011. **412**(13-14): p. 1195-200.
7. Ayala, D.E., et al., *Circadian pattern of ambulatory blood pressure in untreated hypertensive patients with and without metabolic syndrome.* Chronobiol Int, 2009. **26**(6): p. 1189-205.
8. Azab, B., et al., *Value of platelet/lymphocyte ratio as a predictor of all-cause mortality after non-ST-elevation myocardial infarction.* J Thromb Thrombolysis, 2012. **34**(3): p. 326-34.
9. Barbui, T., et al., *Thrombosis in primary myelofibrosis: incidence and risk factors.* Blood, 2010. **115**(4): p. 778-82.
10. Bassyouni, I.H., M.M. El-Wakd, and R.H. Bassyouni, *Soluble levels of osteopontin in patients with Behcet's disease: association with disease activity and vascular involvement.* J Clin Immunol, 2013. **33**(2): p. 361-7.

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11. Bayers, S., S.T. Shulman, and A.S. Paller, *Kawasaki disease: part I. Diagnosis, clinical features, and pathogenesis.* J Am Acad Dermatol, 2013. **69**(4): p. 501 e1-11; quiz 511-2.

12. Blix, K., et al., *White blood cell count measured prior to cancer development is associated with future risk of venous thromboembolism--the Tromso study.* PLoS One, 2013. **8**(9): p. e73447.

13. Bulum, T. and L. Duvnjak, *Insulin resistance in patients with type 1 diabetes: relationship with metabolic and inflammatory parameters.* Acta Clin Croat, 2013. **52**(1): p. 43-51.

14. Bulum, T., et al., *Association of hematological parameters with insulin resistance in type 1 diabetes.* Minerva Endocrinol, 2014. **39**(2): p. 119-26.

15. Chen, J.C. and J. Schwartz, *Metabolic syndrome and inflammatory responses to long-term particulate air pollutants.* Environ Health Perspect, 2008. **116**(5): p. 612-7.

16. Chim, C.S., et al., *Impact of JAK2V617F mutation on thrombosis and myeloid transformation in essential thrombocythemia: a multivariate analysis by Cox regression in 141 patients.* Hematology, 2010. **15**(4): p. 187-92.

17. Chiou, W.K., et al., *Significance and association of serum uric acid (UA) levels with components of metabolic syndrome (MS) in the elderly.* Arch Gerontol Geriatr, 2012. **55**(3): p. 724-8.

18. Connolly, G.C., et al., *Leukocytosis, thrombosis and early mortality in cancer patients initiating chemotherapy.* Thromb Res, 2010. **126**(2): p. 113-8.

19. Crosslin, D.R., et al., *Genetic variation associated with circulating monocyte count in the eMERGE Network.* Hum Mol Genet, 2013. **22**(10): p. 2119-27.

20. Duivis, H.E., et al., *Depressive symptoms and white blood cell count in coronary heart disease patients: prospective findings from the Heart and Soul Study.* Psychoneuroendocrinology, 2013. **38**(4): p. 479-87.

21. Elsenberg, E.H., et al., *Inducible cardiac ischaemia is related to a decrease in the whole-blood Toll-like receptor 2 and 4 response.* Clin Sci (Lond), 2012. **122**(11): p. 527-33.

22. Evangelopoulos, A.A., et al., *Association between serum cystatin C, monocytes and other inflammatory markers.* Intern Med J, 2012. **42**(5): p. 517-22.

23. Ferrari, M., et al., *Rhinitis is associated with a greater risk of intermittent claudication in adults.* Allergy, 2014. **69**(4): p. 472-8.

24. Fleischer, A.E., et al., *Combined clinical and laboratory testing improves diagnostic accuracy for osteomyelitis in the diabetic foot.* J Foot Ankle Surg, 2009. **48**(1): p. 39-46.

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25. Godsland, I.F. and D.G. Johnston, *Co-associations between insulin sensitivity and measures of liver function, subclinical inflammation, and hematology.* Metabolism, 2008. **57**(9): p. 1190-7.

26. Gokulakrishnan, K., et al., *Association of leukocyte count with varying degrees of glucose intolerance in Asian Indians: the Chennai Urban Rural Epidemiology Study (CURES-26).* Metab Syndr Relat Disord, 2009. **7**(3): p. 205-10.

27. Gustafsson, S., et al., *Oxidative stress and inflammatory markers in relation to circulating levels of adiponectin.* Obesity (Silver Spring), 2013. **21**(7): p. 1467-73.

28. Hamzaoui, K., et al., *VEGF and mRNA VEGF expression in CSF from Behcet's disease with neurological involvement.* J Neuroimmunol, 2009. **213**(1-2): p. 148-53.

29. Hastbacka, J., et al., *Serum matrix metalloproteinases in patients resuscitated from cardiac arrest. The association with therapeutic hypothermia.* Resuscitation, 2012. **83**(2): p. 197-201.

30. Herwadkar, A., et al., *Association between hypoparathyroidism and defective T cell immunity in 22q11.2 deletion syndrome.* J Clin Pathol, 2010. **63**(2): p. 151-5.

31. Hussain Bokhari, S.A., et al., *Non-surgical periodontal therapy lowers serum inflammatory markers: a pilot study.* J Periodontol, 2009. **80**(10): p. 1574-80.

32. Iscen, S., *Comment on association between coronary artery ectasia and neutrophil--lymphocyte ratio.* Angiology, 2013. **64**(8): p. 633.

33. Itoi, K., et al., *Relationship between diabetic macular edema and peripheral Th1/Th2 balance.* Ophthalmologica, 2008. **222**(4): p. 249-53.

34. Jeandrot, A., et al., *Serum procalcitonin and C-reactive protein concentrations to distinguish mildly infected from non-infected diabetic foot ulcers: a pilot study.* Diabetologia, 2008. **51**(2): p. 347-52.

35. Jensvoll, H., et al., *Platelet count measured prior to cancer development is a risk factor for future symptomatic venous thromboembolism: the Tromso Study.* PLoS One, 2014. **9**(3): p. e92011.

36. Justo, D., et al., *Inflammation markers in individuals with history of mental health crisis.* Inflammation, 2008. **31**(4): p. 254-9.

37. Kao, T.W., et al., *White blood cell count and psychomotor cognitive performance in the elderly.* Eur J Clin Invest, 2011. **41**(5): p. 513-20.

38. Karaman, A., M. Kadi, and F. Kara, *Sister chromatid exchange and micronucleus studies in patients with Behcet's disease.* J Cutan Pathol, 2009. **36**(8): p. 831-7.

39. Kase, S., et al., *Proliferative diabetic retinopathy with lymphocyte-rich epiretinal membrane associated with poor visual prognosis.* Invest Ophthalmol Vis Sci, 2009. **50**(12): p. 5909-12.

Confidentiality Statement

Confidentiality Statement: Data and information contained in this document are considered to constitute trade secrets and confidential commercial information, and the legal protections provided to such trade secrets and confidential information are hereby claimed under the applicable provisions of United States law. No part of this document may be publicly disclosed without the written consent of Philip Morris International.

40. Khorana, A.A., et al., *Development and validation of a predictive model for chemotherapy-associated thrombosis.* Blood, 2008. **111**(10): p. 4902-7.

41. Kim, K.I., et al., *Differential white blood cell count and all-cause mortality in the Korean elderly.* Exp Gerontol, 2013. **48**(2): p. 103-8.

42. Klein, B.E., et al., *Cross-sectional associations of blood elements, clotting factors, nephropathy, and retinal outcomes in long duration type 1 diabetes.* Ophthalmic Epidemiol, 2012. **19**(3): p. 120-6.

43. Kop, W.J., et al., *Association between depressive symptoms and fibrosis markers: the Cardiovascular Health Study.* Brain Behav Immun, 2010. **24**(2): p. 229-35.

44. Lechner, D. and A. Weltermann, *Chemotherapy-induced thrombosis: a role for microparticles and tissue factor?* Semin Thromb Hemost, 2008. **34**(2): p. 199-203.

45. Lee, Y.J., et al., *Association of serum gamma-glutamyltransferase with C-reactive protein levels and white blood cell count in Korean adults.* Clin Chem Lab Med, 2008. **46**(10): p. 1410-5.

46. Lindberg, S., et al., *Plasma neutrophil gelatinase-associated lipocalinin the general population: association with inflammation and prognosis.* Arterioscler Thromb Vasc Biol, 2014. **34**(9): p. 2135-42.

47. Lopez-Diaz, M.J., et al., *The erythrocyte sedimentation rate is associated with the development of visual complications in biopsy-proven giant cell arteritis.* Semin Arthritis Rheum, 2008. **38**(2): p. 116-23.

48. Maeda, S., et al., *A pilot study of gene expression analysis in workers with hand-arm vibration syndrome.* Ind Health, 2008. **46**(2): p. 188-93.

49. Mitka, M., *Task force: nontraditional markers add little to heart risk assessment.* JAMA, 2009. **302**(20): p. 2192-3.

50. Monteiro, A.M., et al., *Cardiovascular disease parameters in periodontitis.* J Periodontol, 2009. **80**(3): p. 378-88.

51. Oda, E. and R. Kawai, *The prevalence of metabolic syndrome and diabetes increases through the quartiles of white blood cell count in Japanese men and women.* Intern Med, 2009. **48**(13): p. 1127-34.

52. Oliveira, R., et al., *Crosstalk between inflammation, iron metabolism and endothelial function in Behcet's disease.* Clin Hemorheol Microcirc, 2014. **56**(2): p. 175-85.

53. Park, C.S., et al., *Relation between C-reactive protein, homocysteine levels, fibrinogen, and lipoprotein levels and leukocyte and platelet counts, and 10-year risk for cardiovascular disease among healthy adults in the USA.* Am J Cardiol, 2010. **105**(9): p. 1284-8.

Confidentiality Statement

Confidentiality Statement: Data and information contained in this document are considered to constitute trade secrets and confidential commercial information, and the legal protections provided to such trade secrets and confidential information are hereby claimed under the applicable provisions of United States law. No part of this document may be publicly disclosed without the written consent of Philip Morris International.

54. Patriarca, A., et al., *Is the absence of JAK2 mutation a risk factor for bleeding in essential thrombocythemia? An analysis of 106 patients.* Blood Transfus, 2010. **8**(1): p. 21-7.

55. Prizment, A.E., et al., *Association of inflammatory markers with colorectal cancer incidence in the atherosclerosis risk in communities study.* Cancer Epidemiol Biomarkers Prev, 2011. **20**(2): p. 297-307.

56. Puato, M., et al., *Atorvastatin reduces macrophage accumulation in atherosclerotic plaques: a comparison of a nonstatin-based regimen in patients undergoing carotid endarterectomy.* Stroke, 2010. **41**(6): p. 1163-8.

57. Rich, D.Q., et al., *Association between changes in air pollution levels during the Beijing Olympics and biomarkers of inflammation and thrombosis in healthy young adults.* JAMA, 2012. **307**(19): p. 2068-78.

58. Sadeghian, M.H., et al., *The association of Epstein-Barr virus infection with multiple myeloma.* Indian J Pathol Microbiol, 2011. **54**(4): p. 720-4.

59. Sahota, P., et al., *Changes in spleen size in patients with acute ischemic stroke: a pilot observational study.* Int J Stroke, 2013. **8**(2): p. 60-7.

60. Shike, H., et al., *Pyuria associated with acute Kawasaki disease and fever from other causes.* Pediatr Infect Dis J, 2009. **28**(5): p. 440-3.

61. Smolderen, K.G., et al., *Association of somatic and cognitive depressive symptoms and biomarkers in acute myocardial infarction: insights from the translational research investigating underlying disparities in acute myocardial infarction patients' health status registry.* Biol Psychiatry, 2012. **71**(1): p. 22-9.

62. Soltesz, P., et al., *Immunological features of primary anti-phospholipid syndrome in connection with endothelial dysfunction.* Rheumatology (Oxford), 2008. **47**(11): p. 1628-34.

63. Sun, W., et al., *Correlation of leukocytosis with early neurological deterioration following supratentorial intracerebral hemorrhage.* J Clin Neurosci, 2012. **19**(8): p. 1096-100.

64. Tzur, T., et al., *Can leukocyte count during the first trimester of pregnancy predict later gestational complications?* Arch Gynecol Obstet, 2013. **287**(3): p. 421-7.

65. Ulvik, A., et al., *Association of plasma B-6 vitamers with systemic markers of inflammation before and after pyridoxine treatment in patients with stable angina pectoris.* Am J Clin Nutr, 2012. **95**(5): p. 1072-8.

66. Vieira, C.L., et al., *Severe periodontitis is associated with diastolic blood pressure elevation in individuals with heterozygous familial hypercholesterolemia: a pilot study.* J Periodontol, 2011. **82**(5): p. 683-8.

67. Wada, K., et al., *Association between low birth weight and elevated white blood cell count in adulthood within a Japanese population.* Circ J, 2008. **72**(5): p. 757-63.

Confidentiality Statement

Confidentiality Statement: Data and information contained in this document are considered to constitute trade secrets and confidential commercial information, and the legal protections provided to such trade secrets and confidential information are hereby claimed under the applicable provisions of United States law. No part of this document may be publicly disclosed without the written consent of Philip Morris International.

68. Woo, S.J., et al., *Elevated systemic neutrophil count in diabetic retinopathy and diabetes: a hospital-based cross-sectional study of 30,793 Korean subjects.* Invest Ophthalmol Vis Sci, 2011. **52**(10): p. 7697-703.

69. Yorulmaz, E., et al., *Metabolic syndrome frequency in inflammatory bowel diseases.* Saudi J Gastroenterol, 2011. **17**(6): p. 376-82.

E2. Association of a relevant disease or smoking with markers other than generically labelled "white blood cells" or "leukocytes", neutrophils, or monocytes

1. Betjes, M.G., et al., *Expansion of cytolytic CD4+CD28- T cells in end-stage renal disease.* Kidney Int, 2008. **74**(6): p. 760-7.

2. Bian, C., et al., *Predictive value of the relative lymphocyte count in coronary heart disease.* Heart Vessels, 2010. **25**(6): p. 469-73.

3. Biasucci, L.M., et al., *Delayed neutrophil apoptosis in patients with unstable angina: relation to C-reactive protein and recurrence of instability.* Eur Heart J, 2009. **30**(18): p. 2220-5.

4. Brener, S.J., et al., *Diabetes mellitus, myocardial reperfusion, and outcome in patients with acute ST-elevation myocardial infarction treated with primary angioplasty (from HORIZONS AMI).* Am J Cardiol, 2012. **109**(8): p. 1111-6.

5. Chavele, K.M., et al., *Regulation of myeloperoxidase-specific T cell responses during disease remission in antineutrophil cytoplasmic antibody-associated vasculitis: the role of Treg cells and tryptophan degradation.* Arthritis Rheum, 2010. **62**(5): p. 1539-48.

6. Chertok-Shacham, E., et al., *Biomarkers of hypercoagulability and inflammation in primary hyperparathyroidism.* Med Sci Monit, 2008. **14**(12): p. CR628-32.

7. Egan, C.G., et al., *Endothelial progenitor cells and colony-forming units in rheumatoid arthritis: association with clinical characteristics.* Rheumatology (Oxford), 2008. **47**(10): p. 1484-8.

8. Gary, T., et al., *Platelet-to-lymphocyte ratio: a novel marker for critical limb ischemia in peripheral arterial occlusive disease patients.* PLoS One, 2013. **8**(7): p. e67688.

9. Gianfagna, F., et al., *Heritability, genetic correlation and linkage to the 9p21.3 region of mixed platelet-leukocyte conjugates in families with and without early myocardial infarction.* Nutr Metab Cardiovasc Dis, 2013. **23**(7): p. 684-92.

10. Heffernan, K.S., et al., *Carotid artery stiffness, high-density lipoprotein cholesterol and inflammation in men with pre-hypertension.* J Hum Hypertens, 2009. **23**(9): p. 590-6.

11. Ionita, M.G., et al., *High neutrophil numbers in human carotid atherosclerotic plaques are associated with characteristics of rupture-prone lesions.* Arterioscler Thromb Vasc Biol, 2010. **30**(9): p. 1842-8.

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12. Jia, E.Z., et al., *Helicobacter pylori infection is associated with decreased serum levels of high density lipoprotein, but not with the severity of coronary atherosclerosis.* Lipids Health Dis, 2009. **8**: p. 59.

13. Kop, W.J., et al., *Autonomic nervous system dysfunction and inflammation contribute to the increased cardiovascular mortality risk associated with depression.* Psychosom Med, 2010. **72**(7): p. 626-35.

14. Liu, X., et al., *Blood methylomics in response to arsenic exposure in a low-exposed US population.* J Expo Sci Environ Epidemiol, 2014. **24**(2): p. 145-9.

15. Lu, B., D. Parker, and C.B. Eaton, *Relationship of periodontal attachment loss to peripheral vascular disease: an analysis of NHANES 1999-2002 data.* Atherosclerosis, 2008. **200**(1): p. 199-205.

16. Mantyla, P., et al., *Acute myocardial infarction elevates serine protease activity in saliva of patients with periodontitis.* J Periodontal Res, 2012. **47**(3): p. 345-53.

17. Markus, M.R., et al., *Hepatic steatosis is associated with aortic valve sclerosis in the general population: the Study of Health in Pomerania (SHIP).* Arterioscler Thromb Vasc Biol, 2013. **33**(7): p. 1690-5.

18. Martinez-Pinna, R., et al., *Proteomic analysis of intraluminal thrombus highlights complement activation in human abdominal aortic aneurysms.* Arterioscler Thromb Vasc Biol, 2013. **33**(8): p. 2013-20.

19. Moro, F., et al., *Effects of drospirenone-ethinylestradiol and/or metformin on CD4(+)CD28(null) T lymphocytes frequency in women with hyperinsulinemia having polycystic ovary syndrome: a randomized clinical trial.* Reprod Sci, 2013. **20**(12): p. 1508-17.

20. Nunez, J., et al., *Low lymphocyte count and cardiovascular diseases.* Curr Med Chem, 2011. **18**(21): p. 3226-33.

21. Nunez, J., et al., *Low lymphocyte count in acute phase of ST-segment elevation myocardial infarction predicts long-term recurrent myocardial infarction.* Coron Artery Dis, 2010. **21**(1): p. 1-7.

22. Nunez, J., et al., *Therapeutic implications of low lymphocyte count in non-ST segment elevation acute coronary syndromes.* Eur J Intern Med, 2009. **20**(8): p. 768-74.

23. Nunez, J., et al., *Relationship between low lymphocyte count and major cardiac events in patients with acute chest pain, a non-diagnostic electrocardiogram and normal troponin levels.* Atherosclerosis, 2009. **206**(1): p. 251-7.

24. Pennings, G.J., A.S. Yong, and L. Kritharides, *Expression of EMMPRIN (CD147) on circulating platelets in vivo.* J Thromb Haemost, 2010. **8**(3): p. 472-81.

25. Phillips, A.C., et al., *Lymphocyte cell counts in middle age are positively associated with subsequent all-cause and cardiovascular mortality.* QJM, 2011. **104**(4): p. 319-24.

Confidentiality Statement

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26. Pollitt, R.A., et al., *Cumulative life course and adult socioeconomic status and markers of inflammation in adulthood.* J Epidemiol Community Health, 2008. **62**(6): p. 484-91.

27. Przybylowski, P., J. Malyszko, and J. Malyszko, *Anemia is a predictor of outcome in heart transplant recipients.* Transplant Proc, 2009. **41**(8): p. 3228-31.

28. Reina-Couto, M., et al., *Impaired resolution of inflammation in human chronic heart failure.* Eur J Clin Invest, 2014. **44**(6): p. 527-38.

29. Rudolph, V., et al., *A myeloperoxidase promoter polymorphism is independently associated with mortality in patients with impaired left ventricular function.* Free Radic Biol Med, 2009. **47**(11): p. 1584-90.

30. Salonen, I., et al., *Serum myeloperoxidase is independent of the risk factors of atherosclerosis.* Coron Artery Dis, 2012. **23**(4): p. 251-8.

31. Schaffer, A., et al., *Relationship between homocysteine and coronary artery disease. Results from a large prospective cohort study.* Thromb Res, 2014. **134**(2): p. 288-93.

32. Schooling, C.M., et al., *Parental death during childhood and adult cardiovascular risk in a developing country: the Guangzhou Biobank Cohort Study.* PLoS One, 2011. **6**(5): p. e19675.

33. Shivpuri, S., et al., *Trait anger, cynical hostility and inflammation in Latinas: variations by anger type?* Brain Behav Immun, 2011. **25**(6): p. 1256-63.

34. Sun, W., et al., *Association between HLA-DRB1, HLA-DRQB1 alleles, and CD4(+)CD28(null) T cells in a Chinese population with coronary heart disease.* Mol Biol Rep, 2011. **38**(3): p. 1675-9.

35. Tani, S., et al., *Association of body mass index with coronary plaque regression: 6-month prospective study.* J Atheroscler Thromb, 2009. **16**(3): p. 275-82.

36. Tapia-Perez, J.H., et al., *Effect of increased glucose levels on short-term outcome in hypertensive spontaneous intracerebral hemorrhage.* Clin Neurol Neurosurg, 2014. **118**: p. 37-43.

37. Vaya, A., et al., *Homocysteine levels and the metabolic syndrome in a Mediterranean population: a case-control study.* Clin Hemorheol Microcirc, 2011. **47**(1): p. 59-66.

38. West, M.J., et al., *The value of N-terminal fragment of brain natriuretic peptide and tissue inhibitor of metalloproteinase-1 levels as predictors of cardiovascular outcome in the LIPID study.* Eur Heart J, 2008. **29**(7): p. 923-31.

39. Wiernicki, I., et al., *Haptoglobin 2-1 phenotype predicts rapid growth of abdominal aortic aneurysms.* J Vasc Surg, 2010. **52**(3): p. 691-6.

40. Yao, H.C., et al., *Interleukin-2 enhances the cytotoxic activity of circulating natural killer cells in patients with chronic heart failure.* Heart Vessels, 2009. **24**(4): p. 283-6.

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41. You, Z., et al., *Tooth loss, systemic inflammation, and prevalent stroke among participants in the reasons for geographic and racial difference in stroke (REGARDS) study.* Atherosclerosis, 2009. **203**(2): p. 615-9.

42. Zhang, B., et al., *Plasma vaspin concentrations are decreased in acute coronary syndrome, but unchanged in patients without coronary lesions.* Clin Biochem, 2013. **46**(15): p. 1520-5.

43. Zhao, J., et al., *The biological effects of individual-level PM(2.5) exposure on systemic immunity and inflammatory response in traffic policemen.* Occup Environ Med, 2013. **70**(6): p. 426-31.

E3. Population being studied is either not apparently healthy or studies that lack a control population

1. Abou-Raya, S., et al., *Rheumatoid arthritis, periodontal disease and coronary artery disease.* Clin Rheumatol, 2008. **27**(4): p. 421-7.

2. Adeoye, O., et al., *Peripheral monocyte count is associated with case fatality after intracerebral hemorrhage.* J Stroke Cerebrovasc Dis, 2014. **23**(2): p. e107-11.

3. Agnihotri, S., et al., *Peripheral leukocyte counts and outcomes after intracerebral hemorrhage.* J Neuroinflammation, 2011. **8**: p. 160.

4. Akpek, M., et al., *Relation of neutrophil/lymphocyte ratio to coronary flow to in-hospital major adverse cardiac events in patients with ST-elevated myocardial infarction undergoing primary coronary intervention.* Am J Cardiol, 2012. **110**(5): p. 621-7.

5. Altun, B., et al., *The relationship between high-sensitive troponin T, neutrophil lymphocyte ratio and SYNTAX Score.* Scand J Clin Lab Invest, 2014. **74**(2): p. 108-15.

6. Angeli, F., et al., *Neutrophil count and ambulatory pulse pressure as predictors of cardiovascular adverse events in postmenopausal women with hypertension.* Am J Hypertens, 2011. **24**(5): p. 591-8.

7. Arbel, Y., et al., *Neutrophil/lymphocyte ratio is related to the severity of coronary artery disease and clinical outcome in patients undergoing angiography.* Atherosclerosis, 2012. **225**(2): p. 456-60.

8. Arbel, Y., et al., *Higher neutrophil/lymphocyte ratio is related to lower ejection fraction and higher long-term all-cause mortality in ST-elevation myocardial infarction patients.* Can J Cardiol, 2014. **30**(10): p. 1177-82.

9. Avci, A., et al., *Neutrophil/lymphocyte ratio is related to the severity of idiopathic dilated cardiomyopathy.* Scand Cardiovasc J, 2014. **48**(4): p. 202-8.

Confidentiality Statement

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10. Barbui, T., et al., *Perspectives on thrombosis in essential thrombocythemia and polycythemia vera: is leukocytosis a causative factor?* Blood, 2009. **114**(4): p. 759-63.

11. Beeftink, M.M., et al., *Relation of serum TNF-alpha and TNF-alpha genotype with delayed cerebral ischemia and outcome in subarachnoid hemorrhage.* Neurocrit Care, 2011. **15**(3): p. 405-9.

12. Benites-Zapata, V.A., et al., *Usefulness of neutrophil-to-lymphocyte ratio in risk stratification of patients with advanced heart failure.* Am J Cardiol, 2015. **115**(1): p. 57-61.

13. Berton, G., et al., *Acute-phase inflammatory markers during myocardial infarction: association with mortality and modes of death after 7 years of follow-up.* J Cardiovasc Med (Hagerstown), 2010. **11**(2): p. 111-7.

14. Brevetti, G., et al., *Prevalence of hypoechoic carotid plaques in coronary artery disease: relationship with coexistent peripheral arterial disease and leukocyte number.* Vasc Med, 2009. **14**(1): p. 13-9.

15. Brevetti, G., et al., *The prevalence of hypoechoic carotid plaques is greater in peripheral than in coronary artery disease and is related to the neutrophil count.* J Vasc Surg, 2008. **47**(3): p. 523-9.

16. Campbell, P.J., et al., *Correlation of blood counts with vascular complications in essential thrombocythemia: analysis of the prospective PT1 cohort.* Blood, 2012. **120**(7): p. 1409-11.

17. Caramazza, D., et al., *Correlation between leukocytosis and thrombosis in Philadelphia-negative chronic myeloproliferative neoplasms.* Ann Hematol, 2009. **88**(10): p. 967-71.

18. Casas-Vara, A., et al., *The obesity paradox in elderly patients with heart failure: analysis of nutritional status.* Nutrition, 2012. **28**(6): p. 616-22.

19. Cecchi, E., et al., *Effect of blood hematocrit and erythrocyte deformability on adenosine 5'-diphosphate platelet reactivity in patients with acute coronary syndromes on dual antiplatelet therapy.* Am J Cardiol, 2009. **104**(6): p. 764-8.

20. Charach, G., et al., *Usefulness of total lymphocyte count as predictor of outcome in patients with chronic heart failure.* Am J Cardiol, 2011. **107**(9): p. 1353-6.

21. Chia, S., et al., *Association of leukocyte and neutrophil counts with infarct size, left ventricular function and outcomes after percutaneous coronary intervention for ST-elevation myocardial infarction.* Am J Cardiol, 2009. **103**(3): p. 333-7.

22. Coucelo, M., et al., *JAK2V617F allele burden is associated with thrombotic mechanisms activation in polycythemia vera and essential thrombocythemia patients.* Int J Hematol, 2014. **99**(1): p. 32-40.

23. Csobay-Novak, C., et al., *Decreased plasma nociceptin/orphanin FQ levels after acute coronary syndromes.* Acta Physiol Hung, 2012. **99**(2): p. 99-110.

Confidentiality Statement

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24. de Azevedo Lucio, E., et al., *Lack of association between plasma myeloperoxidase levels and angiographic severity of coronary artery disease in patients with acute coronary syndrome.* Inflamm Res, 2011. **60**(2): p. 137-42.

25. Donohue, M.M., et al., *Higher plasma fractalkine is associated with better 6-month outcome from ischemic stroke.* Stroke, 2012. **43**(9): p. 2300-6.

26. Eisen, A., et al., *Inflammation and future risk of symptomatic heart failure in patients with stable coronary artery disease.* Am Heart J, 2014. **167**(5): p. 707-14.

27. Fertin, M., et al., *Usefulness of circulating biomarkers for the prediction of left ventricular remodeling after myocardial infarction.* Am J Cardiol, 2012. **110**(2): p. 277-83.

28. Fluri, F., et al., *Copeptin, procalcitonin and routine inflammatory markers-predictors of infection after stroke.* PLoS One, 2012. **7**(10): p. e48309.

29. Gangat, N., et al., *Leukocytosis at diagnosis and the risk of subsequent thrombosis in patients with low-risk essential thrombocythemia and polycythemia vera.* Cancer, 2009. **115**(24): p. 5740-5.

30. Gao, G., et al., *Enhanced risk profiling of implanted defibrillator shocks with circulating SCN5A mRNA splicing variants: a pilot trial.* J Am Coll Cardiol, 2014. **63**(21): p. 2261-9.

31. Girerd, N., et al., *Middle-aged men with increased waist circumference and elevated C-reactive protein level are at higher risk for postoperative atrial fibrillation following coronary artery bypass grafting surgery.* Eur Heart J, 2009. **30**(10): p. 1270-8.

32. Goupil, R., et al., *Lymphopenia and treatment-related infectious complications in ANCA-associated vasculitis.* Clin J Am Soc Nephrol, 2013. **8**(3): p. 416-23.

33. Hernandez-Leiva, E., et al., *Hemoglobin and B-type natriuretic peptide preoperative values but not inflammatory markers, are associated with postoperative morbidity in cardiac surgery: a prospective cohort analytic study.* J Cardiothorac Surg, 2013. **8**: p. 170.

34. Hong, L.F., et al., *Relation of leukocytes and its subsets counts with the severity of stable coronary artery disease in patients with diabetic mellitus.* PLoS One, 2014. **9**(3): p. e90663.

35. Hsu, C.W., et al., *White blood cell count predicts all-cause, cardiovascular disease-cause and infection-cause one-year mortality of maintenance hemodialysis patients.* Ther Apher Dial, 2010. **14**(6): p. 552-9.

36. Husser, O., et al., *White blood cell subtypes after STEMI: temporal evolution, association with cardiovascular magnetic resonance--derived infarct size and impact on outcome.* Inflammation, 2011. **34**(2): p. 73-84.

37. Ikejima, H., et al., *Effect of human peripheral monocyte subsets on coronary flow reserve in infarct-related artery in patients with primary anterior acute myocardial infarction.* Clin Exp Pharmacol Physiol, 2010. **37**(4): p. 453-9.

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38. Jia, E.Z., et al., *Severity of coronary atherosclerosis is an independent predictor of the left ventricular ejection fraction.* Clin Exp Pharmacol Physiol, 2011. **38**(2): p. 109-12.

39. Kasius, K.M., et al., *Association of platelet and leukocyte counts with delayed cerebral ischemia in aneurysmal subarachnoid hemorrhage.* Cerebrovasc Dis, 2010. **29**(6): p. 576-83.

40. Kato, A., et al., *Blood monocyte count is a predictor of total and cardiovascular mortality in hemodialysis patients.* Nephron Clin Pract, 2008. **110**(4): p. c235-43.

41. Kazmierski, R., et al., *Association of atherosclerotic risk factors with carotid adventitial thickness assessed by ultrasonography.* J Clin Ultrasound, 2009. **37**(6): p. 333-41.

42. Kim, J., et al., *Different prognostic value of white blood cell subtypes in patients with acute cerebral infarction.* Atherosclerosis, 2012. **222**(2): p. 464-7.

43. Kosuge, M., et al., *Combined prognostic utility of white blood cell count, plasma glucose, and glomerular filtration rate in patients undergoing primary stent placement for acute myocardial infarction.* Am J Cardiol, 2009. **103**(3): p. 322-7.

44. Kruger, B., et al., *Is inflammation prior to renal transplantation predictive for cardiovascular and renal outcomes?* Atherosclerosis, 2010. **210**(2): p. 637-42.

45. Kruk, M., et al., *Association of non-specific inflammatory activation with early mortality in patients with ST-elevation acute coronary syndrome treated with primary angioplasty.* Circ J, 2008. **72**(2): p. 205-11.

46. Kucukbayrak, A., et al., *Significance of bacteriuria and leukocyturia in the outpatients with heart failure.* Eur Rev Med Pharmacol Sci, 2012. **16**(6): p. 839-44.

47. Kunin, M., et al., *Peritoneal dialysis in patients with refractory congestive heart failure: potential prognostic factors.* Blood Purif, 2013. **35**(4): p. 285-94.

48. Li, D.B., et al., *Association between inflammatory mediators and angiographic morphologic features indicating thrombus formation in patients with acute myocardial infarction.* Chin Med J (Engl), 2009. **122**(15): p. 1738-42.

49. Lu, Y.C., et al., *Association between visfatin levels and coronary artery disease in patients with chronic kidney disease.* Iran J Kidney Dis, 2013. **7**(6): p. 446-52.

50. Marchetti, M. and A. Falanga, *Leukocytosis, JAK2V617F mutation, and hemostasis in myeloproliferative disorders.* Pathophysiol Haemost Thromb, 2008. **36**(3-4): p. 148-59.

51. Marfil-Alvarez, R., et al., *Acute myocardial infarct size is related to periodontitis extent and severity.* J Dent Res, 2014. **93**(10): p. 993-8.

52. Martini, R.P., et al., *Genetic variation in soluble epoxide hydrolase: association with outcome after aneurysmal subarachnoid hemorrhage.* J Neurosurg, 2014. **121**(6): p. 1359-66.

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53. McMahon, C.J., et al., *Inflammation as a predictor for delayed cerebral ischemia after aneurysmal subarachnoid haemorrhage.* J Neurointerv Surg, 2013. **5**(6): p. 512-7.

54. Milo-Cotter, O., et al., *Low lymphocyte ratio as a novel prognostic factor in acute heart failure: results from the Pre-RELAX-AHF study.* Cardiology, 2010. **117**(3): p. 190-6.

55. Moon, J.H., et al., *Decreased endothelial progenitor cells and increased serum glycated albumin are independently correlated with plaque-forming carotid artery atherosclerosis in type 2 diabetes patients without documented ischemic disease.* Circ J, 2012. **76**(9): p. 2273-9.

56. Mukamal, K.J., G.A. Wellenius, and M.A. Mittleman, *Hematologic parameters, atherosclerotic progression, and prognosis in patients with previous coronary artery bypass grafting (from the Post CABG Trial).* Am J Cardiol, 2009. **103**(3): p. 328-32.

57. Munir, T.A., M.N. Afzal, and R. Habib ur, *Baseline leukocyte count and acute coronary syndrome: predictor of adverse cardiac events, long and short-term mortality and association with traditional risk factors, cardiac biomarkers and C-reactive protein.* J Ayub Med Coll Abbottabad, 2009. **21**(3): p. 46-50.

58. Ndrepepa, G., et al., *Total leucocyte count, but not C-reactive protein, predicts 1-year mortality in patients with acute coronary syndromes treated with percutaneous coronary intervention.* Clin Sci (Lond), 2009. **116**(8): p. 651-8.

59. Nozawa, N., et al., *Association between circulating monocytes and coronary plaque progression in patients with acute myocardial infarction.* Circ J, 2010. **74**(7): p. 1384-91.

60. Nunez, J., et al., *Usefulness of the neutrophil to lymphocyte ratio in predicting long-term mortality in ST segment elevation myocardial infarction.* Am J Cardiol, 2008. **101**(6): p. 747-52.

61. Nunez, J., et al., *Effectiveness of the relative lymphocyte count to predict one-year mortality in patients with acute heart failure.* Am J Cardiol, 2011. **107**(7): p. 1034-9.

62. o Hartaigh, B., et al., *Which leukocyte subsets predict cardiovascular mortality? From the LUdwigshafen RIsk and Cardiovascular Health (LURIC) Study.* Atherosclerosis, 2012. **224**(1): p. 161-9.

63. O'Donoghue, M., et al., *Association between baseline neutrophil count, clopidogrel therapy, and clinical and angiographic outcomes in patients with ST-elevation myocardial infarction receiving fibrinolytic therapy.* Eur Heart J, 2008. **29**(8): p. 984-91.

64. Ozaydin, M., et al., *Oxidative status, inflammation, and postoperative atrial fibrillation with metoprolol vs carvedilol or carvedilol plus N-acetyl cysteine treatment.* Clin Cardiol, 2014. **37**(5): p. 300-6.

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65. Palm, F., et al., *Intracerebral haemorrhage in a population-based stroke registry (LuSSt): incidence, aetiology, functional outcome and mortality.* J Neurol, 2013. **260**(10): p. 2541-50.

66. Papa, A., et al., *Predictive value of elevated neutrophil-lymphocyte ratio on cardiac mortality in patients with stable coronary artery disease.* Clin Chim Acta, 2008. **395**(1-2): p. 27-31.

67. Papazafiropoulou, A., et al., *Plasma glucose levels and white blood cell count are related with ankle brachial index in type 2 diabetic subjects.* Hellenic J Cardiol, 2010. **51**(5): p. 402-6.

68. Park, J.T., et al., *Association of white blood cell count with metabolic syndrome in patients undergoing peritoneal dialysis.* Metabolism, 2009. **58**(10): p. 1379-85.

69. Peng, Y., et al., *Relationship between white blood cell count at admission and short term outcome in patients with acute cerebral infarction.* Clin Invest Med, 2011. **34**(4): p. E249.

70. Rabai, G., et al., *Contribution of neutrophil elastase to the lysis of obliterative thrombi in the context of their platelet and fibrin content.* Thromb Res, 2010. **126**(2): p. e94-101.

71. Rashidi, F., et al., *Does absolute neutrophilia predict early congestive heart failure after acute myocardial infarction? A cross-sectional study.* South Med J, 2008. **101**(1): p. 19-23.

72. Roe, P., et al., *Inflammation, coronary artery calcification and cardiovascular events in incident renal transplant recipients.* Atherosclerosis, 2010. **212**(2): p. 589-94.

73. Sadamasa, N., et al., *Prediction of mortality by hematological parameters on admission in patients with subarachnoid hemorrhage.* Neurol Med Chir (Tokyo), 2011. **51**(11): p. 745-8.

74. Sanchis, J., et al., *Combination of clinical risk profile, early exercise testing and circulating biomarkers for evaluation of patients with acute chest pain without ST-segment deviation or troponin elevation.* Heart, 2008. **94**(3): p. 311-5.

75. Sanjuan, R., et al., *Acute myocardial infarction: high risk ventricular tachyarrhythmias and admission glucose level in patients with and without diabetes mellitus.* Curr Diabetes Rev, 2011. **7**(2): p. 126-34.

76. Sezer, S., et al., *Body fat percentage as a risk factor for atherosclerosis but not for inflammation for hemodialysis patients: differences between genders.* J Ren Nutr, 2012. **22**(5): p. 490-8.

77. Shantsila, E., et al., *CXCR4 positive and angiogenic monocytes in myocardial infarction.* Thromb Haemost, 2013. **109**(2): p. 255-62.

78. Shen, X.H., et al., *Association of neutrophil/lymphocyte ratio with long-term mortality after ST elevation myocardial infarction treated with primary*

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percutaneous coronary intervention. Chin Med J (Engl), 2010. **123**(23): p. 3438-43.

79. Sirico, G., et al., *Echolucent femoral plaques entail higher risk of echolucent carotid plaques and a more severe inflammatory profile in peripheral arterial disease.* J Vasc Surg, 2009. **49**(2): p. 346-51.

80. Smit, J.J., et al., *Comparison of usefulness of C-reactive protein versus white blood cell count to predict outcome after primary percutaneous coronary intervention for ST elevation myocardial infarction.* Am J Cardiol, 2008. **101**(4): p. 446-51.

81. Song, S.W., et al., *Perioperative indicators of stress response and postoperative inflammatory complications in patients undergoing off-pump coronary artery bypass surgery: a prospective observational study.* Circ J, 2008. **72**(12): p. 1966-74.

82. Sood, N., et al., *The association among blood transfusions, white blood cell count, and the frequency of post-cardiothoracic surgery atrial fibrillation: a nested cohort study from the Atrial Fibrillation Suppression Trials I, II, and III.* J Cardiothorac Vasc Anesth, 2009. **23**(1): p. 22-7.

83. Tamhane, U.U., et al., *Association between admission neutrophil to lymphocyte ratio and outcomes in patients with acute coronary syndrome.* Am J Cardiol, 2008. **102**(6): p. 653-7.

84. Tani, S., et al., *Association of circulating leukocyte count with coronary atherosclerosis regression after pravastatin treatment.* Atherosclerosis, 2008. **198**(2): p. 360-5.

85. Tokgoz, S., et al., *Neutrophil lymphocyte ratio as a predictor of stroke.* J Stroke Cerebrovasc Dis, 2013. **22**(7): p. 1169-74.

86. Tompkins, C., et al., *Significance of leukocytosis after cardiac device implantation.* Am J Cardiol, 2013. **111**(11): p. 1608-12.

87. Toor, I.S., et al., *Preprocedural neutrophil count predicts outcome in patients with advanced peripheral vascular disease undergoing percutaneous transluminal angioplasty.* J Vasc Surg, 2008. **48**(6): p. 1504-8.

88. Tsai, T.H., et al., *Outcomes of patients with Killip class III acute myocardial infarction after primary percutaneous coronary intervention.* Crit Care Med, 2011. **39**(3): p. 436-42.

89. Tuttolomondo, A., et al., *Predictors of outcome in acute ischemic cerebrovascular syndromes: The GIFA study.* Int J Cardiol, 2008. **125**(3): p. 391-6.

90. Uthamalingam, S., et al., *Utility of the neutrophil to lymphocyte ratio in predicting long-term outcomes in acute decompensated heart failure.* Am J Cardiol, 2011. **107**(3): p. 433-8.

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91. Uysal, O.K., et al., *Association between uric acid and coronary collateral circulation in patients with stable coronary artery disease.* Angiology, 2014. **65**(3): p. 227-31.

92. van Diepen, S., et al., *The systemic inflammatory response syndrome in patients with ST-segment elevation myocardial infarction.* Crit Care Med, 2013. **41**(9): p. 2080-7.

93. Varma, S., et al., *Thrombotic complications of polycythemia vera.* Hematology, 2008. **13**(6): p. 319-23.

94. Wang, X., et al., *Neutrophil to lymphocyte ratio in relation to risk of all-cause mortality and cardiovascular events among patients undergoing angiography or cardiac revascularization: a meta-analysis of observational studies.* Atherosclerosis, 2014. **234**(1): p. 206-13.

95. Whiteley, W., et al., *Inflammatory markers and poor outcome after stroke: a prospective cohort study and systematic review of interleukin-6.* PLoS Med, 2009. **6**(9): p. e1000145.

96. Whiteley, W., et al., *Association of circulating inflammatory markers with recurrent vascular events after stroke: a prospective cohort study.* Stroke, 2011. **42**(1): p. 10-6.

97. Williams, B.A. and M.E. Merhige, *Association between neutrophil-lymphocyte ratio and impaired myocardial perfusion in patients with known or suspected coronary disease.* Heart Lung, 2013. **42**(6): p. 436-41.

E4. Studies involving children, infants, or neonates

1. Belisario, A.R., et al., *Coinheritance of alpha-thalassemia decreases the risk of cerebrovascular disease in a cohort of children with sickle cell anemia.* Hemoglobin, 2010. **34**(6): p. 516-29.

2. Caballero, A.E., et al., *Overweight Latino children and adolescents have marked endothelial dysfunction and subclinical vascular inflammation in association with excess body fat and insulin resistance.* Diabetes Care, 2008. **31**(3): p. 576-82.

3. Keskin, N., et al., *Elevated plasma advanced oxidation protein products in children with Henoch-Schonlein purpura.* Pediatr Nephrol, 2011. **26**(11): p. 1989-93.

4. Liu, R., et al., *Relationship between adipokines and coronary artery aneurysm in children with Kawasaki disease.* Transl Res, 2012. **160**(2): p. 131-6.

5. Palta, M., M. Sadek-Badawi, and D.P. Carlton, *Association of BPD and IVH with early neutrophil and white counts in VLBW neonates with gestational age <32 weeks.* J Perinatol, 2008. **28**(9): p. 604-10.

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6. Papadopoulou-Legbelou, K., et al., *Cardiac complications and immunophenotypic profile of infectious mononucleosis syndrome in children.* Indian Pediatr, 2012. **49**(3): p. 195-8.

7. Shah, V., et al., *Association between hematologic findings and brain injury due to neonatal hypoxic-ischemic encephalopathy.* Am J Perinatol, 2009. **26**(4): p. 295-302.

8. Singer, K., et al., *The relationship between body fat mass percentiles and inflammation in children.* Obesity (Silver Spring), 2014. **22**(5): p. 1332-6.

9. Verier, C.M., et al., *Breastfeeding in infancy is not associated with inflammatory status in healthy adolescents.* J Nutr, 2011. **141**(3): p. 411-7.

10. Wu, C.Z., et al., *Association between white blood cell count and components of metabolic syndrome.* Pediatr Int, 2009. **51**(1): p. 14-8.

E5. Case studies

1. Siddiquee, Z., et al., *Dense IgG4 plasma cell infiltrates associated with chronic infectious aortitis: implications for the diagnosis of IgG4-related disease.* Cardiovasc Pathol, 2012. **21**(6): p. 470-5.

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7.4 Appendix 4 Excluded studies from search 3

Literature retrieved using Search 3: To identify articles primarily relevant to the association of WBC count to respiratory disease using the string: ((((((PMN OR WBC) AND ((respiratory disease) AND (association)) AND ("2008"[Date - Publication]: "2015"[Date - Publication]))) AND English[Language]) NOT eosinophil) NOT exacerbation) NOT embolism

Among the identified studies a set of specific criteria was applied to determine which papers should be selected for inclusion within the report.

E1. Endpoint being assessed is not CVD, lung cancer, or non-malignant respiratory disease; this category includes a few studies where WBC count was not specifically correlated with smoking

1. Afenyi-Annan, A., et al., *Lack of Duffy antigen expression is associated with organ damage in patients with sickle cell disease.* Transfusion, 2008. **48**(5): p. 917-24.
2. Bacher, P., et al., *Antigen-specific expansion of human regulatory T cells as a major tolerance mechanism against mucosal fungi.* Mucosal Immunol, 2014. **7**(4): p. 916-28.
3. Braun, E., et al., *Is elevated red cell distribution width a prognostic predictor in adult patients with community acquired pneumonia?* BMC Infect Dis, 2014. **14**: p. 129.
4. Bwana, V., et al., *Smear positive pulmonary tuberculosis among HIV patients receiving highly active antiretroviral therapy in Dar es Salaam, Tanzania.* Tanzan J Health Res, 2011. **13**(1): p. 14-20.
5. Chen, Y.C., et al., *Toll-like receptor 2 gene polymorphisms, pulmonary tuberculosis, and natural killer cell counts.* BMC Med Genet, 2010. **11**: p. 17.
6. Chiang, T.Y., et al., *Elevated plasma matrix metalloproteinase-9 protein and its gene polymorphism in patients with community-acquired pneumonia.* Clin Chem Lab Med, 2012. **50**(3): p. 449-54.
7. Chideya, S., et al., *Isoniazid, rifampin, ethambutol, and pyrazinamide pharmacokinetics and treatment outcomes among a predominantly HIV-infected cohort of adults with tuberculosis from Botswana.* Clin Infect Dis, 2009. **48**(12): p. 1685-94.
8. Chien, Y.S., et al., *Predictors and outcomes of respiratory failure among hospitalized pneumonia patients with 2009 H1N1 influenza in Taiwan.* J Infect, 2010. **60**(2): p. 168-74.
9. Damtie, D., et al., *Common opportunistic infections and their CD4 cell correlates among HIV-infected patients attending at antiretroviral therapy clinic of Gondar University Hospital, Northwest Ethiopia.* BMC Res Notes, 2013. **6**: p. 534.

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10. Davis, J.L., et al., *Pneumocystis colonisation is common among hospitalised HIV infected patients with non-Pneumocystis pneumonia.* Thorax, 2008. **63**(4): p. 329-34.

11. de Albuquerque, Y.M., et al., *Chest radiographic findings in patients with HIV/AIDS and pulmonary tuberculosis.* Int J STD AIDS, 2013. **24**(12): p. 951-6.

12. Fox, A., et al., *Severe pandemic H1N1 2009 infection is associated with transient NK and T deficiency and aberrant CD8 responses.* PLoS One, 2012. **7**(2): p. e31535.

13. Freire, A.X., et al., *Obstructive sleep apnea and immunity: relationship of lymphocyte count and apnea hypopnea index.* South Med J, 2010. **103**(8): p. 771-4.

14. Fu, J., M.C. Tobin, and L.L. Thomas, *Neutrophil-like low-density granulocytes are elevated in patients with moderate to severe persistent asthma.* Ann Allergy Asthma Immunol, 2014. **113**(6): p. 635-640 e2.

15. Fulop, T., et al., *Screening for chronic kidney disease in the ambulatory HIV population.* Clin Nephrol, 2010. **73**(3): p. 190-6.

16. Furuhashi, K., et al., *Inflammatory markers in active pulmonary tuberculosis: association with Th1/Th2 and Tc1/Tc2 balance.* Kekkaku, 2012. **87**(1): p. 1-7.

17. Ghazanfari, T., et al., *Serum soluble Fas ligand and nitric oxide in long-term pulmonary complications induced by sulfur mustard: Sardasht-Iran Cohort Study.* Int Immunopharmacol, 2009. **9**(13-14): p. 1489-93.

18. Gleeson, M., et al., *Respiratory infection risk in athletes: association with antigen-stimulated IL-10 production and salivary IgA secretion.* Scand J Med Sci Sports, 2012. **22**(3): p. 410-7.

19. Goncalves, L.S., et al., *Factors associated with specific clinical forms of oral candidiasis in HIV-infected Brazilian adults.* Arch Oral Biol, 2013. **58**(6): p. 657-63.

20. Hardwick, R.J., et al., *beta-defensin genomic copy number is associated with HIV load and immune reconstitution in sub-saharan Africans.* J Infect Dis, 2012. **206**(7): p. 1012-9.

21. Hermans, S.M., et al., *Risk of tuberculosis after antiretroviral treatment initiation: a comparison between efavirenz and nevirapine using inverse probability weighting.* Antivir Ther, 2013. **18**(4): p. 615-22.

22. Hotz, C., et al., *Systemic involvement of acute generalized exanthematous pustulosis: a retrospective study on 58 patients.* Br J Dermatol, 2013. **169**(6): p. 1223-32.

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23. Jamaiah, I., et al., *Pneumocystis carinii (jirovecii) pneumonia (PCP): the most common opportunistic infection observed in HIV/AIDS cases at the University Malaya Medical Centre, Kuala Lumpur, Malaysia.* Southeast Asian J Trop Med Public Health, 2012. **43**(4): p. 825-31.

24. Kerkhoff, A.D., et al., *Blood neutrophil counts in HIV-infected patients with pulmonary tuberculosis: association with sputum mycobacterial load.* PLoS One, 2013. **8**(7): p. e67956.

25. Khoo, U.S., et al., *Functional role of ICAM-3 polymorphism in genetic susceptibility to SARS infection.* Hong Kong Med J, 2009. **15 Suppl 6**: p. 26-9.

26. Kumar, S., et al., *Efficacy of circulating plasma DNA as a diagnostic tool for advanced non-small cell lung cancer and its predictive utility for survival and response to chemotherapy.* Lung Cancer, 2010. **70**(2): p. 211-7.

27. Lawn, S.D., et al., *Urine lipoarabinomannan assay for tuberculosis screening before antiretroviral therapy diagnostic yield and association with immune reconstitution disease.* AIDS, 2009. **23**(14): p. 1875-80.

28. Lourda, M., et al., *Detection of IL-17A-producing peripheral blood monocytes in Langerhans cell histiocytosis patients.* Clin Immunol, 2014. **153**(1): p. 112-22.

29. Mahamid, M., et al., *Vitamin D linked to PFAPA syndrome.* Int J Pediatr Otorhinolaryngol, 2013. **77**(3): p. 362-4.

30. Millrud, C.R., et al., *Inverse immunological responses induced by allergic rhinitis and head and neck squamous cell carcinoma.* PLoS One, 2014. **9**(1): p. e86796.

31. Mirsaeidi, M., et al., *Thrombocytopenia and thrombocytosis at time of hospitalization predict mortality in patients with community-acquired pneumonia.* Chest, 2010. **137**(2): p. 416-20.

32. Muller, B.L., et al., *Inflammatory and immunogenetic markers in correlation with pulmonary tuberculosis.* J Bras Pneumol, 2013. **39**(6): p. 719-27.

33. Nguyen, D.T., et al., *Improving the diagnosis of pulmonary tuberculosis in HIV-infected individuals in Ho Chi Minh City, Viet Nam.* Int J Tuberc Lung Dis, 2011. **15**(11): p. 1528-34, i.

34. Nunes, E.A., et al., *Mycobacterium tuberculosis and nontuberculous mycobacterial isolates among patients with recent HIV infection in Mozambique.* J Bras Pneumol, 2008. **34**(10): p. 822-8.

35. Pelikan, Z., *Delayed-type asthmatic response to bronchial challenge with allergen, I: clinical features.* Ann Allergy Asthma Immunol, 2010. **104**(5): p. 394-404.

36. Pett, S.L., et al., *Predictors of bacterial pneumonia in Evaluation of Subcutaneous Interleukin-2 in a Randomized International Trial (ESPRIT).* HIV Med, 2011. **12**(4): p. 219-27.

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37. Raso, V., et al., *Association between muscle strength and the cardiopulmonary status of individuals living with HIV/AIDS.* Clinics (Sao Paulo), 2013. **68**(3): p. 359-64.

38. Ravimohan, S., et al., *Early immunologic failure is associated with early mortality among advanced HIV-infected adults initiating antiretroviral therapy with active tuberculosis.* J Infect Dis, 2013. **208**(11): p. 1784-93.

39. Routsi, C., et al., *Carbapenem-resistant versus carbapenem-susceptible Acinetobacter baumannii bacteremia in a Greek intensive care unit: risk factors, clinical features and outcomes.* Infection, 2010. **38**(3): p. 173-80.

40. Shiboski, C.H., et al., *Role of oral candidiasis in TB and HIV co-infection: AIDS Clinical Trial Group Protocol A5253.* Int J Tuberc Lung Dis, 2014. **18**(6): p. 682-8.

41. Sudfeld, C.R., et al., *Weight change at 1 mo of antiretroviral therapy and its association with subsequent mortality, morbidity, and CD4 T cell reconstitution in a Tanzanian HIV-infected adult cohort.* Am J Clin Nutr, 2013. **97**(6): p. 1278-87.

42. Thiem, U., et al., *C-reactive protein, severity of pneumonia and mortality in elderly, hospitalised patients with community-acquired pneumonia.* Age Ageing, 2009. **38**(6): p. 693-7.

43. Thwaites, G., et al., *Relationship between Mycobacterium tuberculosis genotype and the clinical phenotype of pulmonary and meningeal tuberculosis.* J Clin Microbiol, 2008. **46**(4): p. 1363-8.

44. Vamvakas, E.C. and M.A. Blajchman, *Transfusion-related mortality: the ongoing risks of allogeneic blood transfusion and the available strategies for their prevention.* Blood, 2009. **113**(15): p. 3406-17.

45. Vamvakas, E.C. and M.A. Blajchman, *Blood still kills: six strategies to further reduce allogeneic blood transfusion-related mortality.* Transfus Med Rev, 2010. **24**(2): p. 77-124.

46. Wisaksana, R., et al., *Inverse relationship of serum hepcidin levels with CD4 cell counts in HIV-infected patients selected from an Indonesian prospective cohort study.* PLoS One, 2013. **8**(11): p. e79904.

47. Yeom, J.S., et al., *Factors associated with hypoxemia in children infected with pandemic H1N1 2009 influenza virus.* Pediatr Int, 2011. **53**(5): p. 622-5.

E2. Association of a relevant disease or smoking with markers other than generically labelled “white blood cells” or “leukocytes”, neutrophils, or monocytes

1. Arrieta, O., et al., *Health-related quality of life in patients with lung cancer: validation of the Mexican-Spanish version and association with prognosis of the EORTC QLQ-LC13 questionnaire.* Lung Cancer, 2012. **77**(1): p. 205-11.

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2. Clifford, G.M., et al., *Lung cancer in the Swiss HIV Cohort Study: role of smoking, immunodeficiency and pulmonary infection.* Br J Cancer, 2012. **106**(3): p. 447-52.

3. Cusanovich, D.A., et al., *The combination of a genome-wide association study of lymphocyte count and analysis of gene expression data reveals novel asthma candidate genes.* Hum Mol Genet, 2012. **21**(9): p. 2111-23.

4. Drummond, M.B., et al., *Association between obstructive lung disease and markers of HIV infection in a high-risk cohort.* Thorax, 2012. **67**(4): p. 309-14.

5. Hara, T., et al., *Elevated serum concentrations of polymorphonuclear neutrophilic leukocyte elastase in systemic sclerosis: association with pulmonary fibrosis.* J Rheumatol, 2009. **36**(1): p. 99-105.

6. Le, D.T., et al., *A live-attenuated Listeria vaccine (ANZ-100) and a live-attenuated Listeria vaccine expressing mesothelin (CRS-207) for advanced cancers: phase I studies of safety and immune induction.* Clin Cancer Res, 2012. **18**(3): p. 858-68.

7. Lourenco, O., A. Mafalda Fonseca, and L. Taborda-Barata, *T cells in sputum of asthmatic patients are activated independently of disease severity or control.* Allergol Immunopathol (Madr), 2009. **37**(6): p. 285-92.

8. Tang, Y., et al., *Increased numbers of NK cells, NKT-like cells, and NK inhibitory receptors in peripheral blood of patients with chronic obstructive pulmonary disease.* Clin Dev Immunol, 2013. **2013**: p. 721782.

9. Ulrich, S., et al., *Increased regulatory and decreased CD8+ cytotoxic T cells in the blood of patients with idiopathic pulmonary arterial hypertension.* Respiration, 2008. **75**(3): p. 272-80.

10. Wegienka, G., et al., *Regulatory T cells vary over bleeding segments in asthmatic and non-asthmatic women.* J Reprod Immunol, 2011. **89**(2): p. 192-8.

E3. Population being studied is either not apparently healthy or studies that lack a control population

1. Blount, R.J., et al., *Ambient air pollution associated with suppressed serologic responses to Pneumocystis jirovecii in a prospective cohort of HIV-infected patients with Pneumocystis pneumonia.* PLoS One, 2013. **8**(11): p. e80795.

2. Bruske, I., et al., *Impact of ambient air pollution on the differential white blood cell count in patients with chronic pulmonary disease.* Inhal Toxicol, 2010. **22**(3): p. 245-52.

3. Garcia-Polo, C., et al., *Factors associated with high healthcare resource utilisation among COPD patients.* Respir Med, 2012. **106**(12): p. 1734-42.

4. Kang, M.H., et al., *The prognostic impact of the neutrophil-to-lymphocyte ratio in patients with small-cell lung cancer.* Br J Cancer, 2014. **111**(3): p. 452-60.

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5. Kirk, G.D., C.A. Merlo, and H.I.V.S. Lung, *HIV infection in the etiology of lung cancer: confounding, causality, and consequences.* Proc Am Thorac Soc, 2011. **8**(3): p. 326-32.

6. Meek, C.L., et al., *The relationship between the insulin-like growth factor-1 axis, weight loss, an inflammation-based score and survival in patients with inoperable non-small cell lung cancer.* Clin Nutr, 2010. **29**(2): p. 206-9.

7. Pass, H.I., et al., *Supplementary prognostic variables for pleural mesothelioma: a report from the IASLC staging committee.* J Thorac Oncol, 2014. **9**(6): p. 856-64.

8. Sarraf, K.M., et al., *Neutrophil/lymphocyte ratio and its association with survival after complete resection in non-small cell lung cancer.* J Thorac Cardiovasc Surg, 2009. **137**(2): p. 425-8.

9. Stapleton, R.D., et al., *The association between BMI and plasma cytokine levels in patients with acute lung injury.* Chest, 2010. **138**(3): p. 568-77.

10. Tang, C., et al., *Association between white blood cell count following radiation therapy with radiation pneumonitis in non-small cell lung cancer.* Int J Radiat Oncol Biol Phys, 2014. **88**(2): p. 319-25.

11. Tang, C., et al., *Lymphopenia association with gross tumor volume and lung V5 and its effects on non-small cell lung cancer patient outcomes.* Int J Radiat Oncol Biol Phys, 2014. **89**(5): p. 1084-91.

12. Teramukai, S., et al., *Pretreatment neutrophil count as an independent prognostic factor in advanced non-small-cell lung cancer: an analysis of Japan Multinational Trial Organisation LC00-03.* Eur J Cancer, 2009. **45**(11): p. 1950-8.

13. Tomita, M., et al., *Elevated preoperative inflammatory markers based on neutrophil-to-lymphocyte ratio and C-reactive protein predict poor survival in resected non-small cell lung cancer.* Anticancer Res, 2012. **32**(8): p. 3535-8.

14. Yao, Y., et al., *Pretreatment neutrophil to lymphocyte ratio is associated with response to therapy and prognosis of advanced non-small cell lung cancer patients treated with first-line platinum-based chemotherapy.* Cancer Immunol Immunother, 2013. **62**(3): p. 471-9.

E4. Studies involving children, infants, or neonates

1. Anil, N., et al., *Induced sputum nitrites correlate with FEV1 in children with cystic fibrosis.* Acta Paediatr, 2010. **99**(5): p. 711-4.

2. Duran, R., et al., *The relationship between leukemoid reaction and perinatal morbidity, mortality, and chorioamnionitis in low birth weight infants.* Int J Infect Dis, 2010. **14**(11): p. e998-1001.

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3. Feng, W.X., et al., *Tag SNP polymorphism of CCL2 and its role in clinical tuberculosis in Han Chinese pediatric population.* PLoS One, 2011. **6**(2): p. e14652.

4. Furuya, H., et al., *Clinical factors associated with severity in hospitalized children infected with avian influenza (H5N1).* Environ Health Prev Med, 2011. **16**(1): p. 64-8.

5. Harris, W.T., et al., *Transforming growth factor-beta(1) in bronchoalveolar lavage fluid from children with cystic fibrosis.* Pediatr Pulmonol, 2009. **44**(11): p. 1057-64.

6. Jose, R., et al., *Prevalence of oral and systemic manifestations in pediatric HIV cohorts with and without drug therapy.* Curr HIV Res, 2013. **11**(6): p. 498-505.

7. Kanerva, M., et al., *Microbiologic findings in acute facial palsy in children.* Otol Neurotol, 2013. **34**(7): p. e82-7.

8. Karavanaki, K., et al., *Plasma high sensitivity C-reactive protein and its relationship with cytokine levels in children with newly diagnosed type 1 diabetes and ketoacidosis.* Clin Biochem, 2012. **45**(16-17): p. 1383-8.

9. Muangchana, C., *Factors associated with diagnosis of bacterial pneumonia in children of Northern Thailand.* Southeast Asian J Trop Med Public Health, 2009. **40**(3): p. 563-9.

10. Navratil, M., et al., *Markers of systemic and lung inflammation in childhood asthma.* J Asthma, 2009. **46**(8): p. 822-8.

11. Paul, D.A., et al., *Reduced mortality and increased BPD with histological chorioamnionitis and leukocytosis in very-low-birth-weight infants.* J Perinatol, 2010. **30**(1): p. 58-62.

12. Peterson-Carmichael, S.L., et al., *Association of lower airway inflammation with physiologic findings in young children with cystic fibrosis.* Pediatr Pulmonol, 2009. **44**(5): p. 503-11.

13. Pinheiro Neto, C.D., et al., *Rhinosinusitis in HIV-infected children undergoing antiretroviral therapy.* Braz J Otorhinolaryngol, 2009. **75**(1): p. 70-5.

14. Ribeiro, L.Z., et al., *Serum mannose-binding lectin levels are linked with respiratory syncytial virus (RSV) disease.* J Clin Immunol, 2008. **28**(2): p. 166-73.

15. Sharma, G., et al., *Reduced Arylsulfatase B activity in leukocytes from cystic fibrosis patients.* Pediatr Pulmonol, 2013. **48**(3): p. 236-44.

16. Toro, A.A., et al., *Epstein-Barr virus (EBV) gene expression in interstitial pneumonitis in Brazilian human immunodeficiency virus-1-infected children: is EBV associated or not?* Pediatr Dev Pathol, 2010. **13**(3): p. 184-91.

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E5. Case Studies

1. Antonacci, N., et al., *Dyspnea and large bowel obstruction: a misleading Chilaiditi syndrome.* Am J Surg, 2011. **202**(5): p. e45-7.
2. Banh, H.L., et al., *Persistent elevation of peripheral blood myeloid cell counts associated with omalizumab therapy.* Am J Health Syst Pharm, 2012. **69**(4): p. 302-6.
3. Darling, P. and M.A. Huthwaite, *Infection-associated clozapine toxicity.* Clin Schizophr Relat Psychoses, 2011. **5**(3): p. 159-60.
4. Godoy, M.C., et al., *Organizing pneumonia as a manifestation of Pneumocystis jiroveci immune reconstitution syndrome in HIV-positive patients: report of 2 cases.* J Thorac Imaging, 2008. **23**(1): p. 39-43.
5. Olle-Goig, J.E., et al., *Profound reduction of CD4+ lymphocytes without HIV infection: two cases from the horn of Africa.* Afr Health Sci, 2012. **12**(3): p. 331-3.
6. Otsuka, T., et al., *Leflunomide-induced lung injury that developed after its withdrawal, coinciding with peripheral blood lymphocyte count decrease.* Mod Rheumatol, 2008. **18**(1): p. 96-9.
7. Prasad Goyal, J., B.S. V, and N. Kumar, *Diffuse pulmonary hemorrhage as presenting syndrome of HIV disease.* Pan Afr Med J, 2010. **5**: p. 20.
8. Teodor, A., et al., *Severe invasive listeriosis--case report.* Rev Med Chir Soc Med Nat Iasi, 2012. **116**(3): p. 808-11.

E6. Studies on environmental tobacco smoke

1. Wilson, S.E., et al., *White blood cell DNA adducts in a cohort of asthmatic children exposed to environmental tobacco smoke.* Int Arch Occup Environ Health, 2011. **84**(1): p. 19-27.

E7. In vitro or animal studies

1. Gelderman, M.P., et al., *Ultraviolet B light-exposed human platelets mediate acute lung injury in a two-event mouse model of transfusion.* Transfusion, 2011. **51**(11): p. 2343-57.
2. Gungor, N., et al., *Transcriptional profiling of the acute pulmonary inflammatory response induced by LPS: role of neutrophils.* Respir Res, 2010. **11**: p. 24.
3. Konrad, F.M., et al., *Protective effects of pentoxifylline in pulmonary inflammation are adenosine receptor A2A dependent.* FASEB J, 2013. **27**(9): p. 3524-35.
4. Srivastava, K.D., et al., *Effect of Antiasthma Simplified Herbal Medicine Intervention on neutrophil predominant airway inflammation in a ragweed*

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sensitized murine asthma model. Ann Allergy Asthma Immunol, 2014. **112**(4): p. 339-47 e1-2.

5. Voglis, S., et al., *Human neutrophil peptides and phagocytic deficiency in bronchiectatic lungs.* Am J Respir Crit Care Med, 2009. **180**(2): p. 159-66.

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