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APPENDIX A6.1.4.3 SOLUBLE INTRACELLULAR ADHESION MOLECULE (SICAM)-1

HEALTH EFFECTS OF SMOKING CESSATION

Short Term Health Effects

Soluble Intracellular Adhesion Molecule (sICAM)-1

Internal Report

Mike Peck

August 20th 2015

Version: 1

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1 BACKGROUND

ICAM-1 is an endothelial adhesion molecule that binds to the leukocyte integrins, leukocyte function-associated antigen-1 (LFA-1) and Mac-1. This enables leukocytes to adhere to the endothelium as a prelude to their invasion into the subendothelium and tissues. sICAM is generated by proteolytic cleavage of membrane-bound ICAM and is measurable in plasma and serum.

Inflammation has a critical role in the pathogenesis of cardiovascular diseases (CVD), including coronary heart disease, stroke and the renal and peripheral complications of diabetes. During vascular inflammation, leukocytes attach to and migrate into and cross the vascular wall. The initial and crucial step in this process is mediated by adhesion molecules, which are expressed on leukocytes and vascular endothelial cells in response to inflammatory stimuli.

Adhesion molecules are found in 2 forms, membrane-bound and soluble. The membrane bound forms mediate leukocyte attachment and internalization. The soluble form arises as a result of shedding or enzymatic cleavage of the membrane bound form, and in some cases as alternatively spliced molecules lacking the transmembrane domain. The precise proteolytic mechanism responsible for cleavage is not fully understood. The soluble form may inhibit additional leukocyte adhesion thus having a modulating effect on leukocyte recruitment, and it is thought that soluble levels of adhesion molecules reflect differences in cellular levels.

2 METHODS

Three searches of the PubMed literature data base were conducted on August 5th 2015 for English language articles published within the time frame of 2008 to the present day.

Search 1. To identify literature that linked smoking or nicotine replacement therapy to sICAM using the search string: (sICAM OR (soluble intracellular adhesion molecule)) AND (smokers OR smoking OR nicotine replacement OR cessation) AND ("2008"[Date - Publication]: "2015"[Date - Publication]) AND English[Language]

Search 2. To identify literature reporting an association between sICAM and cardiovascular disease using the search string: (sICAM OR soluble intracellular adhesion molecule) AND ((cardiovascular disease) AND (association)) AND ("2008"[Date - Publication]: "2015"[Date - Publication]))) AND English[Language])

Search 3. To idendify literature reporting an association between sICAM and respiratory disease using the search string: (sICAM OR soluble intracellular adhesion molecule) AND ((respiratory disease) AND (association)) AND ("2008"[Date - Publication]: "2015"[Date - Publication]))) AND English[Language])

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

The following inclusion criteria was applied:

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Studies investigating the association of cigarette smoking, smoking cessation or nicotine replacement therapy (NRT) on sICAM

Studies investigating the association of sICAM with cardiovascular disease or respiratory disease

The following exclusion criteria were applied:

1. Studies that used the measurement of sICAM simply for control purposes (e.g., results were adjusted for differences in sICAM between populations, but sICAM itself was not an endpoint)
2. Studies involving dietary, pharmacological or exercise interventions in which sICAM was an endpoint, but lacking a clear link between sICAM and either a disease of relevance or smoking
3. Studies in patients with a disease not covered by the search categories (e.g., cancer, HIV infection, periodontitis) where there was no clear link between sICAM and either a disease of relevance or smoking
4. Studies of passive or parental smoking
5. Studies showing a link between sICAM and either a disease of relevance or smoking, but in a defined, narrow population (e.g., pregnant women, individuals with a particular haplotype, individuals with a specific disease) or tissue (e.g., retina, gums)
6. Studies reporting results from in vivo animal experiments
7. Studies with no caomparison between smoking and non-smoking/switching/cessation
8. sICAM not measured

The literature searches identified seven smoking-related studies that met the inclusion criteria. These are described below.

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Table 1. Search results and distribution across the exclusion criteria

	Search 1	Search 2	Search 3
Number of articles retrieved	53	121	9
Articles rejected due to:			
E1. sICAM used only as control/biomarker of exposure	1	1	
E2. sICAM lacked link to disease or smoking	4	19	
E3. Disease not covered by search categories	22	70	5
E4. Studies of passive or parental smoking	2	1	
E5. Studies in a narrow population (e.g. pregnant women)	3	14	1
E6. *In vitro* studies or studies using *in vivo* animal models	2	1	
E7. Studies in which sICAM was measured for toxicological or forensic purposes			
E8. Studies with no comparison to smoking and cessation/switching	8	9	2
Articles selected for review	11	6	1

3 BIOMARKER-DISEASE LINK

3.1 Cardiovascular disease

A number of epidemiologic studies have suggested circulating sICAM levels may be an early marker of atherosclerosis [1, 2], CVD events that reflect coronary atherosclerotic disease progression and vessel narrowing, and aortic valve calcification [3], but not events associated with acute thrombosis/vessel occlusion [4], coronary heart disease unrelated to job stress [5] and CVD risk among asymptomatic young adults [6]. In addition, elevated sICAM levels were associated with endothelial dysfunction, one of the earliest stages of the development of atherosclerosis, in adolescents [7] and in peritoneal dialysis patients compared with healthy controls [8]. Furthermore, in a study of individuals without overt CVD, sICAM levels were higher in subjects with a cluster of

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metabolic disorders (metabolic syndrome) than in individuals without metabolic syndrome [9].

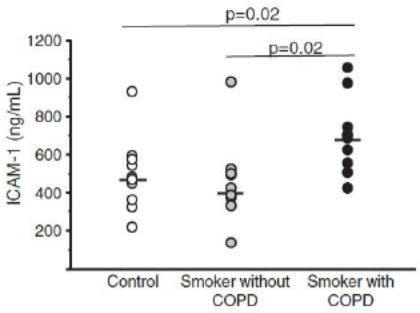
sICAM concentrations in serum/plasma have been associated with CVD in prospective epidemiologic studies, including the Women's Health Study [10], Atherosclerosis Risk in Communities (ARIC) Study [11], Physicians Health Study [12], and the British Regional Heart Study of mature adults [13].

Chronic inflammation and endothelial dysfunction may also be associated with hypertension and CVD. For example, a study of Mongolian subjects showed that hypertension and prehypertension were positively and significantly associated with higher sICAM levels after adjusting for age and gender [14].

Therefore, sICAM concentrations might be an early biomarker for the changes in the artery wall accompanying atherosclerosis, early endothelial dysfunction, or the presence of advanced plaques in the coronary and carotid arteries.

3.2 Respiratory disease

Soluble ICAM has been shown to be raised in the serum and sputum supernatant from smokers with COPD compared to non-smoking controls [15] (see figure). This finding was also reported in another study in which increased levels of sICAM were measured in the circulation of subjects with predicted FEV1 between 60% and 70% (GOLD grade II COPD) [16]. It has also been shown, however, that in subjects with severe COPD (FEV1 33% predicted, GOLD grade IV) serum levels of sICAM were lower than those from healthy non-smokers [17] suggesting an association between disease severity and levels of sICAM. Analysis of a cohort from the Framingham heart study found that high concentrations of sICAM in the serum (if the sole biomarker in the model) were associated with lower levels of FEV_1 and with higher odds for COPD among those subjects with extensive smoking histories [18]. It has also now been shown that there is an association between sICAM levels and longitudinal progression of the percentage of pulmonary emphysema [19].



Studies have shown that ICAM is overexpressed in the airway epithlium of subjects with COPD [20] and that serum levels of sICAM (and other proinflammatory mediators such as interleukin 1ß) are significantly elevated in COPD [21]. A significant relationship between sICAM-1 and the presence of COPD has also been shown [18]. One small cross-sectional study of subjects with COPD and controls without COPD illustrated a relationship between sICAM-1 and smoking after correcting for several clinically relevant covariates, including the presence of COPD [22].

4 SMOKING-BIOMARKER LINK

Inflammation plays a key role in the pathogenesis of cardiovascular disease (CVD) [23]. Cellular adhesion molecules, including ICAM, are regulated by proinflammatory cytokines and are expressed on the surface of endothelial cells. Adhesion molecules

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facilitate the adhesion and transmigration of leukocytes into the vascular endothelium and then the subendothelial space, a critical event in the initiation of atherosclerosis [24]. Elevated levels of sICAM in plasma may reflect endothelial dysfunction and ongoing atherosclerosis [23]. Previous clinical and epidemiologic studies have demonstrated that elevated levels of sICAM are associated with increased risk for CVD and CVD-related mortality [25]. The significant associations between cell adhesion molecules and CVD risk factors highlight their usefulness as biomarkers of preclinical atherosclerosis and future coronary events.One study investigated the effects of smoking and inflammation on leptin regulation in Japanese males and found that sICAM levels were significantly higher in smokers than in non-smokers in both obese and non-obese subjects (P=0.004) [26]. A second study assessed the associations of current smoking status, cumulative smoking exposure and smoking cessation with incident symptomatic peripheral artery disease over a median follow-up of 12.7 years in a cohort of 39,825 women without CVD at baseline [27]. Current smokers (<15 or ≥15 cigarettes/day) had significantly (P<0.001) higher sICAM levels than did past smokers or never smokers. sICAM levels were higher in subjects who smoked ≥15 cigarettes/day than in subjects who smoked <15 cigarettes/day (457.0 vs. 397.0 µg/mL, respectively).

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Table 2. Evidence for association between sICAM and disease.

Author	Study Period	Study Design	Study Population	Study Size; Sex, Age Distrib.	Experimental Group(s) (or Case Definition or At Risk Population)	Control Group(s) (or Controls or Median Follow-up Period)	Selection, Matching Factors
Albert et al. [4]	N/A	Population-based study	Apparently healthy women	23,984; F; mean age 54.2±7.1 years	23,984 women at baseline	Mean follow-up of 10 years	Apparently healthy women
Lopez-Camp os et al. [22]							
Vaidya et al. [9]	N/A	Population-based study	MESA subjects	997; M + F; aged 45–84 years	997 individuals	Baseline values	Selected for no CVD baseline
Gross et al. [1]	1985 onwards	Population-based	YALTA/CARD IA subjects	7050; M + F; aged 18–30 years	2378 CAC 2432 CAS 2240 IMT	Values at 15 and 20 years	Apparently healthy young adults at baseline
Emeny et al. [5]	1984–1995	Case-cohort study	MONICA/KOR A study subjects	1027; M + F; aged 35–64 years	1027 employed participants	Mean follow-up of 12 years	Employees

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Author	Study Period	Study Design	Study Population	Study Size; Sex, Age Distrib.	Experimental Group(s) (or Case Definition or At Risk Population)	Control Group(s) (or Controls or Median Follow-up Period)	Selection, Matching Factors
Hsu et al. [2]	N/A	Population-based study	Taiwanese population	609; M + F; mean age 45.9±10.3 years	609 study subjects	Baseline values	Selected for no known history of major systemic and CVD
Jacobs et al. [28]	N/O*	Population-based study	CODAM subjects	560; M + F; 59.5±7.0 years	560 subjects with increased risk of type 2 diabetes	Baseline values	Selected for increased risk of type 2 diabetes
Chen et al. [7]	N/A	Cohort study	Healthy adolescents	257; M + F; mean age 14.5±1.0 years	257 adolescents	Baseline values	Apparently healthy adolescents
Choi et al. [8]	N/A	Cross-sectional study	Stable PD patients	137; M + F	105 stable PD patients	32 healthy controls	Age- and sex-matched healthy controls
Nguyen et al. [6]	2000-2001	Cohort study	Bogalusa Heart Study	1184; M + F; aged 24–44 years	1184 young adults	Baseline values	Asymptomatic young adults
Wang et al. [14]	N/A	Cross-sectional study	Mongolian subjects	2589; M + F; aged >20 years	2589 Mongolian subjects	Baseline values	

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Author	Study Period	Study Design	Study Population	Study Size; Sex, Age Distrib.	Experimental Group(s) (or Case Definition or At Risk Population)	Control Group(s) (or Controls or Median Follow-up Period)	Selection, Matching Factors
El-Deek et al. [29]	N/A	Cross-sectional study	COPD patients, smokers, non-smokers	90 male, 54-64 years	COPD patients (64), smokers (12), non-smokers (14)	No follow up	COPD subjects were Grade I (10), Grade II (17), Grade III (17),Grade IV (20)
Blidberg, K. et al. [15]	N/A	Cross-sectional study	COPD patients, healthy smokers and healthy non-smokers	30 male, 31 female 55-62 years	Control(22), smokers (21), smokers with COPD (18)	No follow up	COPD smokers had FEV_1 >40% pred and FEV_1/FVC <70% post bronchodilator
Aaron et al. [19]	2000-2012	Longitudinal	Emphysema patients	MESA study	Participants were stratified by quintile of sICAM-1		

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A study that compared non-smokers with smokers and smokers with COPD found that not only were the levels of sICAM increased in healthy smokers (103.4±1.7ng/mL) compared to non-smokers (99.7±2.4 ng/mL) but that they were inceased still further in subjects with COPD with the levels rising with respect to disease grade (Grade I 116.6±16.6; Grade II 122.4±9.1; Grade III 163.7±46.3 and Grade 4 173.4±34.9 mg/mL) [29].

In a smaller but similar sudy, Blidberg et al. [15] also showed that sICAM levels were higher (P=0.02) in COPD patients than healthy never smokers and healthy smokers.

When data from the MESA lung study was anaysed it showed that sICAM-1 levels were associated with

accelerated progression of percent emphysema on computerized tomography (CT) scan over ten years (general population sample) suggesting that ICAM-1 may be important in the pathogenesis of emphysema [19]. Peripheral arterial disease patients (97% smokers) also had significantly increased levels of sICAM-1 (257.8 ng/mL) compared to healthy (47% current of former smokers) subjects (195.4 ng/mL, P<0.0001) [30].

In an early study, smoking was associated with increased levels of sICAM-1 with median sICAM-1 levels approximately 20% lower among non-smokers (past and never smokers, 337.5 ng/mL) compared to smokers (422.3 ng/mL) with no significant difference in the median sICAM-1 levels of past smokers and never smokers. Among smokers, baseline sICAM-1 levels were significantly associated with incident CVD events, a finding consistent with the "generalized" proinflammatory state of smoking and tendency to promote plaque instability [4].

One recent study showed that sICAM was increased in male users of both conventional cigarettes (average over all age groups =145.1 ng/mL) compared to users of moist snuff (119.8 ng/mL) and non-smokers (110.3 ng/mL) [31]. The principal component analysis in this study clearly identifies a separation between smoking and both moist snuff users and non-smokers, suggesting that, sICAM-1 (and IL-12(p70) & IL-8), representing inflammation and immunity, are elevated in smokers compared to the other two groups.

A small study in 30 18-40 year old male and female subjects showed that after one week of smoking cessation sICAM levels were much the same as before cessation (9.4±03 compared to 9.6±0.4, respectively) [32].

A very small study with 27 male subjects (all of whom had mild but exacerbation-free COPD), of which 20 had quit smoking for 2 years and 7 continued to smoke, found that there was no significant differences in sICAM levels (in plasma and in sputm) between the two groups [33].

4.1 Smoking cessation

Very few studies in the last six years have examined the direct effects of smoking cessation on sICAM levels.

One study measured sICAM levels in subjects who participated in a 2-month smoking cessation program. Of 166 eligible smokers, 41 completed the program and 33 had quit and 8 did not [34]. sICAM levels decreased gradually and significantly (P<0.0001) over

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time in those who quit smoking, with mean values of 436.8, 392.8, 381.1, and 337.7 ng/mL at baseline, day 7, day 30, and day 60, respectively. sICAM levels did not significantly decline in non-quitters (P=0.0711), with mean values of 327.1, 326.6, 328.9, and 280.3 ng/mL, respectively.

In another study, 52 smokers with CVD or additional risk factors participating in a smoking cessation program and were followed up for 1 year, with 41 subjects completing the study (17 quitters and 24 non-quitters). sICAM levels decreased from 184.7 ± 66.2 ng/mL to 148.9 ± 61.1 ng/ml in quitters but increased in current smokers from 179.6 ± 73.1 mg/mL to 185.9 ± 58.4 ng/mL (P=0.04) [35]. By contrast, the changes in other markers of inflammation and endothelial cell activation, including E-selectin, tumor necrosis factor-α, interleukin-6 and -8, von Willebrand factor, and CRP were not significantly different between the smokers and quitters (Table 2 and Table 4).

Both of these studies indicate that smoking cessation is associated with a decline in plasma sICAM levels that occurs rapidly after smoking cessation, and may be maintained for a long period of time. However, further evidence is needed to confirm these findings, especially considering the apparently inconsistent changes in sICAM levels in non-smokers in these studies.

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Table 3. Evidence for association between sICAM, smoking and smoking cessation.

Author	Study Period	Study Design	Study Population	Study Size; Sex, Age Distrib.	Experimental Group(s) (or Case Definition or At Risk Population)	Control Group(s) (or Controls or Median Follow-up Period)	Selection, Matching Factors
Lopez-Campos et al. [22]	May 2007-September 2010	Cross-sectional study	COPD patients	142; M + F; mean age 64.5 (SD 10.1)	48 active smokers)	55 controls (41 active smokers)	Selected for the GOLD criteria of COPD
Nagayasu et al. [26]	April 2009-Septemeber 2010	Cross-sectional study	Japanese males	360; M; mean age 51.9–56.3 years	23 obese smokers 70 non-obese smokers	88 obese non-smokers 179 non-obese non-smokers	Stratified by smoking status and obesity
Halvorsen et al. [35]	N/A	Prospective study	Smokers	52; M + F; 32–64 years	24 smokers	17 quitters	Selected for history of CVD or at least one cardiovascular risk factor
Tsai et al. [34]	September 2003–December 2007	N/A	Smokers	166; M + F; mean age 48.07 (SE 2.18) years	8 smokers and 33 quitters	Followed up at 1st, 5th, and 9th weeks after smoking cessation	Smokers attending a smoking cessation clinic

table continues

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Author	Study Period	Study Design	Study Population	Study Size; Sex, Age Distrib.	Experimental Group(s) (or Case Definition or At Risk Population)	Control Group(s) (or Controls or Median Follow-up Period)	Selection, Matching Factors
Conen et al. [27]	N/A	Prospective study	Smokers	39,825; F; mean age between 53.8-55 years	20,336 never smokers, 14,263 ex-smokers, 1967 current smokers (<15 cigarettes/day), 3259 current smokers (≥15 cigarettes/day)	Follow-up of 12.7 (median 12.4–13.8) years	Selected free of CVD
Nordskog et al. [31]	2008-2009	Cross-sectional	Smokers, non-smokers, snuff users	Healthy males 26-49 years	60 smokers; 48 snuff users; 60 non-smokers		Smokers had smoked at least 15 cpd for 3 years

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5 CONCLUSION

The studies retrieved suggest that sICAM is a reliable biomarker for CVD risk. Smoking cessation was associated with a decline in plasma sICAM levels that occurred rapidly after cessation, and this decline was maintained for up to 1 year. However, further evidence is needed to confirm these findings, especially considering the apparently inconsistent changes in sICAM levels in ex-smokers in these studies. Strengths and association of sICAM and disease are presented in Table 4.

Table 4. Strength of association of sICAM with disease

Sufficient evidence of a causal relationship	sICAM is abundant in atherosclerotic plaques, and plays a pathogenic role in the promotion of leukocyte infiltration into vascular lesions. Therefore, sICAM is a critical factor in the etiology of atherosclerosis-related disorders.
Sufficient evidence of a relationship	A significant association between the severity of inflammation and serum levels of sICAM has been reported.

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6 APPENDICES

6.1 Appendix 1 All references obtained
6.2 Appendix 2 References used in Report
6.3 Appendix 3 Articles excluded from Search 1
6.4 Appendix 4 Articles excluded from Search 2
6.5 Appendix 5 Articles excluded from Search 2

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6.1 Appendix 1 All references obtained

Search 1 *(sICAM OR (soluble intracellular adhesion molecule)) AND (smokers OR smoking OR nicotine replacement OR cessation) AND ("2008"[Date - Publication]: "2015"[Date - Publication]) AND English[Language]*

1.1: Nordskog BK, Brown BG, Marano KM, Campell LR, Jones BA, Borgerding MF. Study of cardiovascular disease biomarkers among tobacco consumers, part 2: biomarkers of biological effect. Inhal Toxicol. 2015 Feb;27(3):157-66. doi: 10.3109/08958378.2015.1013227. Epub 2015 Mar 19. PubMed PMID: 25787701; PubMed Central PMCID: PMC4496813.

1.2: van Bussel BC, Henry RM, Ferreira I, van Greevenbroek MM, van der Kallen CJ, Twisk JW, Feskens EJ, Schalkwijk CG, Stehouwer CD. A healthy diet is associated with less endothelial dysfunction and less low-grade inflammation over a 7-year period in adults at risk of cardiovascular disease. J Nutr. 2015 Mar;145(3):532-40. doi: 10.3945/jn.114.201236. Epub 2014 Dec 31. PubMed PMID: 25733469.

1.3: Wan Ahmad WN, Sakri F, Mokhsin A, Rahman T, Mohd Nasir N, Abdul-Razak S, Md Yasin M, Mohd Ismail A, Ismail Z, Nawawi H. Low serum high density lipoprotein cholesterol concentration is an independent predictor for enhanced inflammation and endothelial activation. PLoS One. 2015 Jan 23;10(1):e0116867. doi: 10.1371/journal.pone.0116867. eCollection 2015. PubMed PMID: 25614985; PubMed Central PMCID: PMC4304817.

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Search 2 *(sICAM OR soluble intracellular adhesion molecule) AND ((cardiovascular disease) AND (association)) AND ("2008"[Date - Publication]: "2015"[Date - Publication]))) AND English[Language])*

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35. Halvorsen B, Lund Sagen E, Ueland T, Aukrust P, Tonstad S. Effect of smoking cessation on markers of inflammation and endothelial cell activation among individuals with high risk for cardiovascular disease. Scand J Clin Lab Invest. 2007;67(6):604-11.

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6.3 Appendix 3 Articles excluded from Search 1

Exclusion criteria E1 sICAM used only as control/biomarker of exposure

1.28: Liesker JJ, Bathoorn E, Postma DS, Vonk JM, Timens W, Kerstjens HA. Sputum inflammation predicts exacerbations after cessation of inhaled corticosteroids in COPD. Respir Med. 2011 Dec;105(12):1853-60. doi: 10.1016/j.rmed.2011.07.002. Epub 2011 Jul 29. PubMed PMID: 21802933.

Exclusion criteria E2 sICAM lacked link to disease or smoking

1.3: Wan Ahmad WN, Sakri F, Mokhsin A, Rahman T, Mohd Nasir N, Abdul-Razak S, Md Yasin M, Mohd Ismail A, Ismail Z, Nawawi H. Low serum high density lipoprotein cholesterol concentration is an independent predictor for enhanced inflammation and endothelial activation. PLoS One. 2015 Jan 23;10(1):e0116867. doi: 10.1371/journal.pone.0116867. eCollection 2015. PubMed PMID: 25614985; PubMed Central PMCID: PMC4304817.

1.16: van Bussel BC, Ferreira I, van de Waarenburg MP, van Greevenbroek MM, van der Kallen CJ, Henry RM, Feskens EJ, Stehouwer CD, Schalkwijk CG. Multiple inflammatory biomarker detection in a prospective cohort study: a cross-validation between well-established single-biomarker techniques and an electrochemiluminescense-based multi-array platform. PLoS One. 2013;8(3):e58576. doi: 10.1371/journal.pone.0058576. Epub 2013 Mar 5. PubMed PMID: 23472208; PubMed Central PMCID: PMC3589355.

1.34: Wijnstok NJ, Twisk JW, Young IS, Woodside JV, McFarlane C, McEneny J, Hoekstra T, Murray L, Boreham CA. Inflammation markers are associated with cardiovascular diseases risk in adolescents: the Young Hearts project 2000. J Adolesc Health. 2010 Oct;47(4):346-51. doi: 10.1016/j.jadohealth.2010.04.008. Epub 2010 May 20. PubMed PMID: 20864003; PubMed Central PMCID: PMC2958312.

1.42: Valappil NI, Jacobs DR, Duprez DA, Gross MD, Arnett DK, Glasser S. Association between Endothelial Biomarkers and Arterial Elasticity in Young Adults - The CARDIA Study. J Am Soc Hypertens. 2008 Mar-Apr;2(2):70-9. doi: 10.1016/j.jash.2007.10.002. PubMed PMID: 19343081; PubMed Central PMCID: PMC2390876.

Exclusion criteria E3 Disease not covered by search categories

1.5: Herder C, Bongaerts BW, Rathmann W, Heier M, Kowall B, Koenig W, Thorand B, Roden M, Meisinger C, Ziegler D. Differential association between biomarkers of subclinical inflammation and painful polyneuropathy: results from the KORA F4 study.

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Diabetes Care. 2015 Jan;38(1):91-6. doi: 10.2337/dc14-1403. Epub 2014 Oct 16. PubMed PMID: 25325880.

1.9: Roed T, Kristoffersen US, Knudsen A, Wiinberg N, Lebech AM, Almdal T, Thomsen RW, Kjær A, Weis N. Increased prevalence of coronary artery disease risk markers in patients with chronic hepatitis C--a cross-sectional study. Vasc Health Risk Manag. 2014 Jan 21;10:55-62. doi: 10.2147/VHRM.S53557. eCollection 2014. PubMed PMID: 24482574; PubMed Central PMCID: PMC3905100.

1.11: Sypniewska G, Pollak J, Strozecki P, Camil F, Kretowicz M, Janikowski G, Mankowska-Cyl A, Pater A, Manitius J. 25-hydroxyvitamin D, biomarkers of endothelial dysfunction and subclinical organ damage in adults with hypertension. Am J Hypertens. 2014 Jan;27(1):114-21. doi: 10.1093/ajh/hpt174. Epub 2013 Sep 16. PubMed PMID: 24042165.

1.12: de Jager J, Kooy A, Schalkwijk C, van der Kolk J, Lehert P, Bets D, Wulffelé MG, Donker AJ, Stehouwer CD. Long-term effects of metformin on endothelial function in type 2 diabetes: a randomized controlled trial. J Intern Med. 2014 Jan;275(1):59-70. doi: 10.1111/joim.12128. Epub 2013 Sep 16. PubMed PMID: 23981104.

1.18: Miller AM, Purves D, McConnachie A, Asquith DL, Batty GD, Burns H, Cavanagh J, Ford I, McLean JS, Packard CJ, Shiels PG, Turner H, Velupillai YN, Deans KA, Welsh P, McInnes IB, Sattar N. Soluble ST2 associates with diabetes but not established cardiovascular risk factors: a new inflammatory pathway of relevance to diabetes? PLoS One. 2012;7(10):e47830. doi: 10.1371/journal.pone.0047830. Epub 2012 Oct 24. PubMed PMID: 23112853; PubMed Central PMCID: PMC3480428.

1.20: Qian Q, Zhan P, Sun WK, Zhang Y, Song Y, Yu LK. Vascular endothelial growth factor and soluble intercellular adhesion molecule-1 in lung adenocarcinoma with malignant pleural effusion: correlations with patient survival and pleural effusion control. Neoplasma. 2012;59(4):433-9. doi: 10.4149/neo_2012_056. PubMed PMID: 22489699.

1.22: Seed M, Betteridge DJ, Cooper J, Caslake M, Durrington PN, Thompson GR, Sattar N, Humphries SE, Neil HA. Normal levels of inflammatory markers in treated patients with familial hypercholesterolaemia: a cross-sectional study. JRSM Cardiovasc Dis. 2012 Jun 30;1(3). pii: cvd.2012.012011. doi: 10.1258/cvd.2012.012011. eCollection 2012. PubMed PMID: 24175066; PubMed Central PMCID: PMC3738326.

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1.26: Thompson AM, Zhang Y, Tong W, Xu T, Chen J, Zhao L, Kelly TN, Chen CS, Bazzano LA, He J. Association of inflammation and endothelial dysfunction with metabolic syndrome, prediabetes and diabetes in adults from Inner Mongolia, China. BMC Endocr Disord. 2011 Oct 11;11:16. doi: 10.1186/1472-6823-11-16. PubMed PMID: 21989115; PubMed Central PMCID: PMC3204247.

1.29: Landt S, Wehling M, Heidecke H, Jeschke S, Korlach S, Stöblen F, Schmid P, Blohmer JU, Lichtenegger W, Sehouli J, Kümmel S. Prognostic significance of angiogenic factors in uterine cervical cancer. Anticancer Res. 2011 Aug;31(8):2589-95. PubMed PMID: 21778309.

1.31: Herder C, Baumert J, Zierer A, Roden M, Meisinger C, Karakas M, Chambless L, Rathmann W, Peters A, Koenig W, Thorand B. Immunological and cardiometabolic risk factors in the prediction of type 2 diabetes and coronary events: MONICA/KORA Augsburg case-cohort study. PLoS One. 2011;6(6):e19852. doi: 10.1371/journal.pone.0019852. Epub 2011 Jun 6. PubMed PMID: 21674000; PubMed Central PMCID: PMC3108947.

1.33: Sáez CG, Olivares P, Pallavicini J, Panes O, Moreno N, Massardo T, Mezzano D, Pereira J. Increased number of circulating endothelial cells and plasma markers of endothelial damage in chronic cocaine users. Thromb Res. 2011 Oct;128(4):e18-23. doi: 10.1016/j.thromres.2011.04.019. Epub 2011 May 23. PubMed PMID: 21601240.

1.36: Baker J, Ayenew W, Quick H, Hullsiek KH, Tracy R, Henry K, Duprez D, Neaton JD. High-density lipoprotein particles and markers of inflammation and thrombotic activity in patients with untreated HIV infection. J Infect Dis. 2010 Jan 15;201(2):285-92. doi: 10.1086/649560. PubMed PMID: 19954384; PubMed Central PMCID: PMC2798007.

1.38: Han JH, Wong KS, Wang YY, Fu JH, Ding D, Hong Z. Plasma level of sICAM-1 is associated with the extent of white matter lesion among asymptomatic elderly subjects. Clin Neurol Neurosurg. 2009 Dec;111(10):847-51. doi: 10.1016/j.clineuro.2009.08.018. Epub 2009 Oct 12. PubMed PMID: 19825506.

1.40: Al Lawati N, Mulgrew A, Cheema R, vanEeden S, Butt A, Fleetham J, Ryan F, Ayas N. Pro-atherogenic cytokine profile of patients with suspected obstructive sleep apnea. Sleep Breath. 2009 Nov;13(4):391-5. doi: 10.1007/s11325-009-0259-1. Epub 2009 May 5. PubMed PMID: 19415358.

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1.41: Hsu LA, Ko YL, Wu S, Teng MS, Chou HH, Chang CJ, Chang PY. Association of soluble intercellular adhesion molecule-1 with insulin resistance and metabolic syndrome in Taiwanese. Metabolism. 2009 Jul;58(7):983-8. doi: 10.1016/j.metabol.2009.02.021. PubMed PMID: 19394054.

1.44: Siasos G, Tousoulis D, Vlachopoulos C, Antoniades C, Stefanadi E, Ioakeimidis N, Zisimos K, Siasou Z, Papavassiliou AG, Stefanadis C. The impact of oral L-arginine supplementation on acute smoking-induced endothelial injury and arterial performance. Am J Hypertens. 2009 Jun;22(6):586-92. doi: 10.1038/ajh.2009.57. Epub 2009 Mar 19. PubMed PMID: 19300425.

1.45: Davidson KW, Schwartz JE, Kirkland SA, Mostofsky E, Fink D, Guernsey D, Shimbo D. Relation of inflammation to depression and incident coronary heart disease (from the Canadian Nova Scotia Health Survey [NSHS95] Prospective Population Study). Am J Cardiol. 2009 Mar 15;103(6):755-61. doi: 10.1016/j.amjcard.2008.11.035. Epub 2009 Jan 24. PubMed PMID: 19268727; PubMed Central PMCID: PMC2905847.

1.48: Ao C, Qi L, Xiong Z, Kang A, Guo H, Xue L, Huo Y. Circulating secretory type IIA phospholipase A2, lipoprotein (a) and soluble cellular adhesion molecule levels in patients with angina pectoris. Clin Biochem. 2008 Dec;41(18):1423-8. doi: 10.1016/j.clinbiochem.2008.09.101. Epub 2008 Sep 30. PubMed PMID: 18848929.

1.49: Shavelle DM, Katz R, Takasu J, Lima JA, Jenny NS, Budoff MJ, O'Brien KD. Soluble intercellular adhesion molecule-1 (sICAM-1) and aortic valve calcification in the multi-ethnic study of atherosclerosis (MESA). J Heart Valve Dis. 2008 Jul;17(4):388-95. PubMed PMID: 18751468.

1.50: Lopes-Virella MF, Carter RE, Gilbert GE, Klein RL, Jaffa M, Jenkins AJ, Lyons TJ, Garvey WT, Virella G; Diabetes Control and Complications Trial/Epidemiology of Diabetes Intervention and Complications Cohort Study Group. Risk factors related to inflammation and endothelial dysfunction in the DCCT/EDIC cohort and their relationship with nephropathy and macrovascular complications. Diabetes Care. 2008 Oct;31(10):2006-12. doi: 10.2337/dc08-0659. Epub 2008 Jul 15. PubMed PMID: 18628568; PubMed Central PMCID: PMC2551645.

1.51: Pischon T, Hu FB, Rexrode KM, Girman CJ, Manson JE, Rimm EB. Inflammation, the metabolic syndrome, and risk of coronary heart disease in women and men. Atherosclerosis. 2008 Mar;197(1):392-9. Epub 2007 Aug 2. PubMed PMID: 17681508; PubMed Central PMCID: PMC2375142.

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1.52: Wang JJ, Ross RJ, Tuo J, Burlutsky G, Tan AG, Chan CC, Favaloro EJ, Williams A, Mitchell P. The LOC387715 polymorphism, inflammatory markers, smoking, and age-related macular degeneration. A population-based case-control study. Ophthalmology. 2008 Apr;115(4):693-9. Epub 2007 Aug 2. PubMed PMID: 17675241; PubMed Central PMCID: PMC2561271.

Exclusion criteria E4 Studies of passive or parental smoking

1.8: Matsunaga Y, Vardavas CI, Plada M, Wärnberg J, Gómez-Martinez S, Tzatzarakis MN, Tsatsakis AM, Díaz EL, Marcos A, Kafatos AG. The relationship between cotinine concentrations and inflammatory markers among highly secondhand smoke exposed non-smoking adolescents. Cytokine. 2014 Mar;66(1):17-22. doi: 10.1016/j.cyto.2013.12.007. Epub 2013 Dec 31. PubMed PMID: 24548420.

1.32: Chiu YH, Spiegelman D, Dockery DW, Garshick E, Hammond SK, Smith TJ, Hart JE, Laden F. Secondhand smoke exposure and inflammatory markers in nonsmokers in the trucking industry. Environ Health Perspect. 2011 Sep;119(9):1294-300. doi: 10.1289/ehp.1003199. Epub 2011 May 31. PubMed PMID: 21628108; PubMed Central PMCID: PMC3230397.

Exclusion criteria E5 Studies in a narrow population (e.g. pregnant women)

1.21: Bartha JL, Fernández-Deudero A, Bugatto F, Fajardo-Exposito MA, González-González N, Hervías-Vivancos B. Inflammation and cardiovascular risk in women with preterm labor. J Womens Health (Larchmt). 2012 Jun;21(6):643-8. doi: 10.1089/jwh.2011.3013. Epub 2012 Mar 8. PubMed PMID: 22401498.

1.37: Chacko SA, Song Y, Nathan L, Tinker L, de Boer IH, Tylavsky F, Wallace R, Liu S. Relations of dietary magnesium intake to biomarkers of inflammation and endothelial dysfunction in an ethnically diverse cohort of postmenopausal women. Diabetes Care. 2010 Feb;33(2):304-10. doi: 10.2337/dc09-1402. Epub 2009 Nov 10. PubMed PMID: 19903755; PubMed Central PMCID: PMC2809271.

1.46: Robb AO, Mills NL, Smith IB, Short A, Tura-Ceide O, Barclay GR, Blomberg A, Critchley HO, Newby DE, Denison FC. Influence of menstrual cycle on circulating endothelial progenitor cells. Hum Reprod. 2009 Mar;24(3):619-25. doi: 10.1093/humrep/den411. Epub 2008 Dec 16. PubMed PMID: 19088108.

Exclusion criteria E6 *In vitro* studies or studies using *in vivo* animal models

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1.15: Kratzer A, Chu HW, Salys J, Moumen Z, Leberl M, Bowler R, Cool C, Zamora M, Taraseviciene-Stewart L. Endothelial cell adhesion molecule CD146: implications for its role in the pathogenesis of COPD. J Pathol. 2013 Aug;230(4):388-98. doi: 10.1002/path.4197. PubMed PMID: 23649916.

1.27: Amsellem V, Gary-Bobo G, Marcos E, Maitre B, Chaar V, Validire P, Stern JB, Noureddine H, Sapin E, Rideau D, Hue S, Le Corvoisier P, Le Gouvello S, Dubois-Randé JL, Boczkowski J, Adnot S. Telomere dysfunction causes sustained inflammation in chronic obstructive pulmonary disease. Am J Respir Crit Care Med. 2011 Dec 15;184(12):1358-66. doi: 10.1164/rccm.201105-0802OC. Epub 2011 Sep 1. PubMed PMID: 21885626.

Exclusion criteria E7 Studies in which sICAM was measured for toxicological or forensic purposes

None

Exclusion criteria E8 Studies with no comparison to smoking and cessation/switching

1.2: van Bussel BC, Henry RM, Ferreira I, van Greevenbroek MM, van der Kallen CJ, Twisk JW, Feskens EJ, Schalkwijk CG, Stehouwer CD. A healthy diet is associated with less endothelial dysfunction and less low-grade inflammation over a 7-year period in adults at risk of cardiovascular disease. J Nutr. 2015 Mar;145(3):532-40. doi: 10.3945/jn.114.201236. Epub 2014 Dec 31. PubMed PMID: 25733469.

1.6: Ridker PM, Chasman DI, Rose L, Loscalzo J, Elias JA. Plasma levels of the proinflammatory chitin-binding glycoprotein YKL-40, variation in the chitinase 3-like 1 gene (CHI3L1), and incident cardiovascular events. J Am Heart Assoc. 2014 Jun 23;3(3):e000897. doi: 10.1161/JAHA.114.000897. PubMed PMID: 24958781; PubMed Central PMCID: PMC4309091.

1.7: Jensen A, Karottki DG, Christensen JM, Bønløkke JH, Sigsgaard T, Glasius M, Loft S, Møller P. Biomarkers of oxidative stress and inflammation after wood smoke exposure in a reconstructed Viking Age house. Environ Mol Mutagen. 2014 Oct;55(8):652-61. doi: 10.1002/em.21877. Epub 2014 Jun 3. PubMed PMID: 24889798.

1.14: Strohacker K, Wing RR, McCaffery JM. Contributions of body mass index and exercise habits on inflammatory markers: a cohort study of middle-aged adults living in the USA. BMJ Open. 2013 May 28;3(5). pii: e002623. doi: 10.1136/bmjopen-2013-002623. PubMed PMID: 23793684; PubMed Central PMCID: PMC3657650.

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1.30: van Bussel BC, Henry RM, Schalkwijk CG, Ferreira I, Feskens EJ, Streppel MT, Smulders YM, Twisk JW, Stehouwer CD. Fish consumption in healthy adults is associated with decreased circulating biomarkers of endothelial dysfunction and inflammation during a 6-year follow-up. J Nutr. 2011 Sep;141(9):1719-25. doi: 10.3945/jn.111.139733. Epub 2011 Jul 13. Erratum in: J Nutr. 2011 Dec;141(12):2258. PubMed PMID: 21753064.

1.39: Fang SC, Eisen EA, Cavallari JM, Mittleman MA, Christiani DC. Circulating adhesion molecules after short-term exposure to particulate matter among welders. Occup Environ Med. 2010 Jan;67(1):11-6. doi: 10.1136/oem.2008.043794. Epub 2009 Sep 6. PubMed PMID: 19736177; PubMed Central PMCID: PMC3071151.

1.43: Marcaccini AM, Meschiari CA, Sorgi CA, Saraiva MC, de Souza AM, Faccioli LH, Tanus-Santos JE, Novaes AB, Gerlach RF. Circulating interleukin-6 and high-sensitivity C-reactive protein decrease after periodontal therapy in otherwise healthy subjects. J Periodontol. 2009 Apr;80(4):594-602. doi: 10.1902/jop.2009.080561. PubMed PMID: 19335079.

1.47: Craft LL, Guralnik JM, Ferrucci L, Liu K, Tian L, Criqui MH, Tan J, McDermott MM. Physical activity during daily life and circulating biomarker levels in patients with peripheral arterial disease. Am J Cardiol. 2008 Nov1;102(9):1263-8. doi: 10.1016/j.amjcard.2008.06.051. Epub 2008 Sep 5. PubMed PMID: 18940304; PubMed Central PMCID: PMC3404486.

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6.4 Appendix 4 Articles excluded from Search 2

Exclusion criteria E1 sICAM used only as control/biomarker of exposure

2.2: Rizza S, Copetti M, Cardellini M, Menghini R, Pecchioli C, Luzi A, Di Cola G, Porzio O, Ippoliti A, Romeo F, Pellegrini F, Federici M. A score including ADAM17 substrates correlates to recurring cardiovascular event in subjects with atherosclerosis. Atherosclerosis. 2015 Apr;239(2):459-64. doi: 10.1016/j.atherosclerosis.2015.01.029. Epub 2015 Jan 29. PubMed PMID: 25687272.

Exclusion criteria E2 sICAM lacked link to disease or smoking

2.14: Ridker PM, Chasman DI, Rose L, Loscalzo J, Elias JA. Plasma levels of the proinflammatory chitin-binding glycoprotein YKL-40, variation in the chitinase 3-like 1 gene (CHI3L1), and incident cardiovascular events. J Am Heart Assoc. 2014 Jun 23;3(3):e000897. doi: 10.1161/JAHA.114.000897. PubMed PMID: 24958781; PubMed Central PMCID: PMC4309091.

2.19: Chae JS, Kwak JH, Kim M, Shin KH, Lee SH, Jeong TS, Lee JH. Effects of A379V variant of the Lp-PLA 2 gene on Lp-PLA 2 activity and markers of oxidative stress and endothelial function in Koreans. J Thromb Thrombolysis. 2014 Nov;38(4):477-84. doi: 10.1007/s11239-014-1074-5. PubMed PMID: 24682749.

2.22: Heringa SM, van den Berg E, Reijmer YD, Nijpels G, Stehouwer CD, Schalkwijk CG, Teerlink T, Scheffer PG, van den Hurk K, Kappelle LJ, Dekker JM, Biessels GJ. Markers of low-grade inflammation and endothelial dysfunction are related to reduced information processing speed and executive functioning in an older population - the Hoorn Study. Psychoneuroendocrinology. 2014 Feb;40:108-18. doi: 10.1016/j.psyneuen.2013.11.011. Epub 2013 Nov 22. PubMed PMID: 24485482.

2.35: Santos S, Oliveira A, Lopes C. Systematic review of saturated fatty acids on inflammation and circulating levels of adipokines. Nutr Res. 2013 Sep;33(9):687-95. doi: 10.1016/j.nutres.2013.07.002. Epub 2013 Aug 6. Review. PubMed PMID: 24034567.

2.36: Koenig W. High-sensitivity C-reactive protein and atherosclerotic disease: from improved risk prediction to risk-guided therapy. Int J Cardiol. 2013 Oct 15;168(6):5126-34. doi: 10.1016/j.ijcard.2013.07.113. Epub 2013 Aug 24. Review. PubMed PMID: 23978367.

2.49: Duprez DA, Hearst MO, Lutsey PL, Herrington DM, Ouyang P, Barr RG, Bluemke DA, McAllister D, Carr JJ, Jacobs DR Jr. Associations among lung function, arterial elasticity, and circulating endothelial and inflammation markers: the multiethnic study of

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atherosclerosis. Hypertension. 2013 Feb;61(2):542-8. doi: 10.1161/HYPERTENSIONAHA.111.00272. Epub 2013 Jan 2. PubMed PMID: 23283358; PubMed Central PMCID: PMC3586233.

2.64: Guan X, Yang W, Sun X, Wang L, Ma B, Li H, Zhou J. Association of influenza virus infection and inflammatory cytokines with acute myocardial infarction. Inflamm Res. 2012 Jun;61(6):591-8. doi: 10.1007/s00011-012-0449-3. Epub 2012 Feb 29. PubMed PMID: 22373653.

2.65: Sesso HD, Wang L, Ridker PM, Buring JE. Tomato-based food products are related to clinically modest improvements in selected coronary biomarkers in women. J Nutr. 2012 Feb;142(2):326-33. doi: 10.3945/jn.111.150631. Epub 2012 Jan 5. PubMed PMID: 22223578; PubMed Central PMCID: PMC3260061.

2.66: Arnett DK, McClelland RL, Bank A, Bluemke DA, Cushman M, Szalai AJ, Jain N, Gomes AS, Heckbert SR, Hundley WG, Lima JA. Biomarkers of inflammation and hemostasis associated with left ventricular mass: The Multiethnic Study of Atherosclerosis (MESA). Int J Mol Epidemiol Genet. 2011;2(4):391-400. Epub 2011 Nov 28. PubMed PMID: 22200000; PubMed Central PMCID: PMC3243453.

2.68: Tomaschitz A, Pilz S, Ritz E, Grammer T, Amrein K, Merger S, Meinitzer A, Winkelmann BR, Boehm BO, März W. Relationship between plasma aldosterone concentration and soluble cellular adhesion molecules in patients referred to coronary angiography. Exp Clin Endocrinol Diabetes. 2011 Nov;119(10):649-55. doi: 10.1055/s-0031-1287791. Epub 2011 Nov 8. PubMed PMID: 22068558.

2.72: van Bussel BC, Henry RM, Schalkwijk CG, Ferreira I, Feskens EJ, Streppel MT, Smulders YM, Twisk JW, Stehouwer CD. Fish consumption in healthy adults is associated with decreased circulating biomarkers of endothelial dysfunction and inflammation during a 6-year follow-up. J Nutr. 2011 Sep;141(9):1719-25. doi: 10.3945/jn.111.139733. Epub 2011 Jul 13. Erratum in: J Nutr. 2011 Dec;141(12):2258. PubMed PMID: 21753064.

2.77: Paré G, Ridker PM, Rose L, Barbalic M, Dupuis J, Dehghan A, Bis JC, Benjamin EJ, Shiffman D, Parker AN, Chasman DI. Genome-wide association analysis of soluble ICAM-1 concentration reveals novel associations at the NFKBIK, PNPLA3, RELA, and SH2B3 loci. PLoS Genet. 2011 Apr;7(4):e1001374. doi: 10.1371/journal.pgen.1001374. Epub 2011 Apr 21. PubMed PMID: 21533024; PubMed Central PMCID: PMC3080865.

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2.83: Mohamed AA, Rashed L, Amin H, Abu-Farha M, El Fadl SA, Pakhoum S. K469E polymorphism of the intercellular adhesion molecule-1 gene in Egyptians with coronary heart disease. Ann Saudi Med. 2010 Nov-Dec;30(6):432-6. doi: 10.4103/0256-4947.71061. PubMed PMID: 20940515; PubMed Central PMCID: PMC2994157.

2.86: Luttmann-Gibson H, Suh HH, Coull BA, Dockery DW, Sarnat SE, Schwartz J, Stone PH, Gold DR. Systemic inflammation, heart rate variability and air pollution in a cohort of senior adults. Occup Environ Med. 2010 Sep;67(9):625-30. doi: 10.1136/oem.2009.050625. Epub 2010 Jun 2. PubMed PMID: 20519749; PubMed Central PMCID: PMC4472481.

2.96: Vaverkova H, Karasek D, Novotny D, Jackuliakova D, Lukes J, Halenka M, Frohlich J. Apolipoprotein B versus LDL-cholesterol: Association with other risk factors for atherosclerosis. Clin Biochem. 2009 Aug;42(12):1246-51. doi: 10.1016/j.clinbiochem.2009.05.004. Epub 2009 May 18. PubMed PMID: 19450572.

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2.111: Umemura T, Kawamura T, Sakakibara T, Kanai A, Sano T, Hotta N, Sobue G. Association of soluble adhesion molecule and C-reactive protein levels with silent brain infarction in patients with and without type 2 diabetes. Curr Neurovasc Res. 2008 May;5(2):106-11. PubMed PMID: 18473826.

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2.115: Astrup AS, Tarnow L, Pietraszek L, Schalkwijk CG, Stehouwer CD, Parving HH, Rossing P. Markers of endothelial dysfunction and inflammation in type 1 diabetic patients with or without diabetic nephropathy followed for 10 years: association with mortality and decline of glomerular filtration rate. Diabetes Care. 2008 Jun;31(6):1170-6. doi: 10.2337/dc07-1960. Epub 2008 Mar 10. PubMed PMID: 18332153.

2.116: Orion D, Schwammenthal Y, Reshef T, Schwartz R, Tsabari R, Merzeliak O, Chapman J, Mekori YA, Tanne D. Interleukin-6 and soluble intercellular adhesion molecule-1 in acute brain ischaemia. Eur J Neurol. 2008 Apr;15(4):323-8. doi: 10.1111/j.1468-1331.2008.02066.x. Epub 2008 Feb 26. PubMed PMID: 18312408.

2.119: Pischon T, Hu FB, Rexrode KM, Girman CJ, Manson JE, Rimm EB. Inflammation, the metabolic syndrome, and risk of coronary heart disease in women and men. Atherosclerosis. 2008 Mar;197(1):392-9. Epub 2007 Aug 2. PubMed PMID: 17681508; PubMed Central PMCID: PMC2375142.

2.121: Parissis JT, Karavidas A, Bistola V, Arapi S, Paraskevaidis IA, Farmakis D, Korres D, Filippatos G, Matsakas E, Kremastinos DT. Effects of levosimendan on flow-mediated vasodilation and soluble adhesion molecules in patients with advanced chronic heart failure. Atherosclerosis. 2008 Mar;197(1):278-82. Epub 2007 Jun 12. PubMed PMID: 17568589.

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Exclusion criteria E4 Studies of passive or parental smoking

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Exclusion criteria E5 Studies in a narrow population (e.g. pregnant women)

2.9: Drost JT, Maas AH, Holewijn S, Joosten LA, van Eyck J, van der Schouw YT, de Graaf J. Novel cardiovascular biomarkers in women with a history of early preeclampsia. Atherosclerosis. 2014 Nov;237(1):117-22. doi: 10.1016/j.atherosclerosis.2014.09.009. Epub 2014 Sep 16. PubMed PMID: 25238218.

2.10: Valle M, Martos R, Cañete MD, Valle R, van Donkelaar EL, Bermudo F, Cañete R.Association of serum uric acid levels to inflammation biomarkers and endothelial dysfunction in obese prepubertal children. Pediatr Diabetes. 2014 Aug 18. doi: 10.1111/pedi.12199. [Epub ahead of print] PubMed PMID: 25131560.

2.17: Fadel FI, Elshamaa MF, Nabhan MM, Essam RG, Kantoush N, El Sonbaty MM, Raafat M, Abd-El Haleem DA. Soluble adhesion molecules as markers of native arteriovenous fistula thrombosis in children on uremia. Blood Coagul Fibrinolysis. 2014 Oct;25(7):675-82. doi: 10.1097/MBC.0000000000000125. PubMed PMID: 24806324.

2.18: Sokup A, Ruszkowska-Ciastek B, Walentowicz-Sadłecka M. Heterogeneity of cardiovascular risk factors profile in non-diabetic women 2-24 months post gestational diabetes mellitus. Gynecol Endocrinol. 2014 May;30(5):350-4. doi: 10.3109/09513590.2013.831830. PubMed PMID: 24734889.

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Jan;47(1-2):44-8. doi: 10.1016/j.clinbiochem.2013.10.021. Epub 2013 Oct 29. PubMed PMID: 24183883.

2.32: Duivenvoorden R, Mani V, Woodward M, Kallend D, Suchankova G, Fuster V, Rudd JH, Tawakol A, Farkouh ME, Fayad ZA. Relationship of serum inflammatory biomarkers with plaque inflammation assessed by FDG PET/CT: the dal-PLAQUE study. JACC Cardiovasc Imaging. 2013 Oct;6(10):1087-94. doi: 10.1016/j.jcmg.2013.03.009. PubMed PMID: 24135322; PubMed Central PMCID: PMC3831277.

2.42: Olza J, Gil-Campos M, Leis R, Rupérez AI, Tojo R, Cañete R, Gil A, Aguilera CM. Influence of variants in the NPY gene on obesity and metabolic syndrome features in Spanish children. Peptides. 2013 Jul;45:22-7. doi: 10.1016/j.peptides.2013.04.007. Epub 2013 Apr 25. PubMed PMID: 23624317.

2.44: Lamotte C, Iliescu C, Beghin L, Salleron J, Gonzalez-Gross M, Marcos A, De Henauw S, Moreno LA, Libersa C, Gottrand F. Association of socioeconomic status, truncal fat and sICAM-1 with carotid intima-media thickness in adolescents: the HELENA study. Atherosclerosis. 2013 Jun;228(2):460-5. doi: 10.1016/j.atherosclerosis.2013.03.007. Epub 2013 Mar 19. PubMed PMID: 23561648.

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2.79: Wang L, Manson JE, Gaziano JM, Liu S, Cochrane B, Cook NR, Ridker PM, Rifai N, Sesso HD. Circulating inflammatory and endothelial markers and risk of hypertension in white and black postmenopausal women. Clin Chem. 2011 May;57(5):729-36. doi: 10.1373/clinchem.2010.156794. Epub 2011 Mar 11. PubMed PMID: 21398601; PubMed Central PMCID: PMC3084895.

2.80: Wang G, Wang A, Tong W, Liu Y, Zhang Y. Association of elevated inflammatory and endothelial biomarkers with prehypertension among Mongolians in China. Hypertens Res. 2011 Apr;34(4):516-20. doi: 10.1038/hr.2010.255. Epub 2010 Dec 23. PubMed PMID: 21179100.

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2.106: Khaleghi M, Ali Z, Mosley TH Jr, Turner ST, Kullo IJ. Association of soluble cell adhesion molecules with ankle-brachial index in a biethnic cohort of predominantly hypertensive individuals. Clin Chem. 2008 Nov;54(11):1788-95. doi: 10.1373/clinchem.2008.107003. Epub 2008 Sep 11. PubMed PMID: 18787016; PubMed Central PMCID: PMC2752683.

Exclusion criteria E6 *In vitro* studies or studies using *in vivo* animal models

2.13: Malek HA, Shata A. Effect of a high dose of vitamin D on a rabbit model of atherosclerosis. Int J Immunopathol Pharmacol. 2014 Apr-Jun;27(2):195-201. PubMed PMID: 25004831.

Exclusion criteria E7 Studies in which sICAM was measured for toxicological or forensic purposes

None

Exclusion criteria E8 Studies with no comparison to smoking and cessation/switching

2.12: Schneider JG, Isermann B, Kleber ME, Wang H, Boehm BO, Grammer TB, Prueller F, Nawroth PP, Maerz W. Inverse association of the endogenous thrombin potential (ETP) with cardiovascular death: the Ludwigshafen Risk and Cardiovascular Health (LURIC) study. Int J Cardiol. 2014 Sep;176(1):139-44. doi: 10.1016/j.ijcard.2014.07.026. Epub 2014 Jul 15. PubMed PMID: 25085378.

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2.58: Widmer RJ, Freund MA, Flammer AJ, Sexton J, Lennon R, Romani A, Mulinacci N, Vinceri FF, Lerman LO, Lerman A. Beneficial effects of polyphenol-rich olive oil in patients with early atherosclerosis. Eur J Nutr. 2013 Apr;52(3):1223-31. doi: 10.1007/s00394-012-0433-2. Epub 2012 Aug 8. PubMed PMID: 22872323; PubMed Central PMCID: PMC3915409.

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2.60: Wlazlo N, van Greevenbroek MM, Ferreira I, Jansen EJ, Feskens EJ, van der Kallen CJ, Schalkwijk CG, Bravenboer B, Stehouwer CD. Low-grade inflammation and insulin resistance independently explain substantial parts of the association between body fat and serum C3: the CODAM study. Metabolism. 2012 Dec;61(12):1787-96. doi: 10.1016/j.metabol.2012.05.015. Epub 2012 Jul 2. PubMed PMID: 22762725.

2.69: Masiá M, Padilla S, Robledano C, Ramos JM, Gutiérrez F. Evaluation of endothelial function and subclinical atherosclerosis in association with hepatitis C virus in HIV-infected patients: a cross-sectional study. BMC Infect Dis. 2011 Oct 3;11:265. doi: 10.1186/1471-2334-11-265. PubMed PMID: 21967471; PubMed Central PMCID: PMC3198698.

2.74: Wilker EH, Alexeeff SE, Suh H, Vokonas PS, Baccarelli A, Schwartz J. Ambient pollutants, polymorphisms associated with microRNA processing and adhesion molecules: the Normative Aging Study. Environ Health. 2011 May 21;10:45. doi: 10.1186/1476-069X-10-45. PubMed PMID: 21600003; PubMed Central PMCID: PMC3124411.

2.81: Frisbee SJ, Chambers CB, Frisbee JC, Goodwill AG, Crout RJ. Association between dental hygiene, cardiovascular disease risk factors and systemic inflammation in rural adults. J Dent Hyg. 2010 Fall;84(4):177-84. Epub 2010 Nov 1. PubMed PMID: 21047463.

2.87: Thompson AM, Zhang Y, Tong W, Xu T, Chen J, Zhao L, Kelly TN, Chen CS, Bazzano LA, He J. Association of obesity and biomarkers of inflammation and endothelial dysfunction in adults in Inner Mongolia, China. Int J Cardiol. 2011 Aug 4;150(3):247-52. doi: 10.1016/j.ijcard.2010.04.011. Epub 2010 May 1. PubMed PMID: 20439121; PubMed Central PMCID: PMC4364655.

2.114: Sacristán D, López-Farré AJ, Zamorano-León JJ, Azcona L, Fernández-Ortiz A, Romero J, Farré J, Macaya C. Effects of coronary prestenting platelet inhibition on coronary poststenting inflammation. J Cardiovasc Pharmacol. 2008 Mar;51(3):286-92. doi: 10.1097/FJC.0b013e318163a90f. PubMed PMID: 18356694.

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6.5 Appendix 5 Articles excluded from Search 2

Exclusion criteria E1 sICAM used only as control/biomarker of exposure

None

Exclusion criteria E2 sICAM lacked link to disease or smoking

None

Exclusion criteria E3 Disease not covered by search categories

3.1: Yoshikawa M, Yamauchi M, Fujita Y, Koyama N, Fukuoka A, Tamaki S, Yamamoto Y, Tomoda K, Kimura H. The impact of obstructive sleep apnea and nasal CPAP on circulating adiponectin levels. Lung. 2014 Apr;192(2):289-95. doi: 10.1007/s00408-013-9550-9. Epub 2014 Jan 7. PubMed PMID: 24395128.

3.2: Davey RT Jr, Lynfield R, Dwyer DE, Losso MH, Cozzi-Lepri A, Wentworth D, Lane HC, Dewar R, Rupert A, Metcalf JA, Pett SL, Uyeki TM, Bruguera JM, Angus B, Cummins N, Lundgren J, Neaton JD; INSIGHT FLU 002 & 003 Study Groups. The association between serum biomarkers and disease outcome in influenza A(H1N1)pdm09 virus infection: results of two international observational cohort studies. PLoS One. 2013;8(2):e57121. doi: 10.1371/journal.pone.0057121. Epub 2013 Feb 27. PubMed PMID: 23468921; PubMed Central PMCID: PMC3584122.

3.5: Guan X, Yang W, Sun X, Wang L, Ma B, Li H, Zhou J. Association of influenza virus infection and inflammatory cytokines with acute myocardial infarction. Inflamm Res. 2012 Jun;61(6):591-8. doi: 10.1007/s00011-012-0449-3. Epub 2012 Feb 29. PubMed PMID: 22373653.

3.6: Gu X, Ma C, Yuan D, Song Y. Circulating soluble intercellular adhesion molecule-1 in lung cancer: a systematic review. Transl Lung Cancer Res. 2012 Mar;1(1):36-44. doi: 10.3978/j.issn.2218-6751.08.01. Review. PubMed PMID: 25806153; PubMed Central PMCID: PMC4367581.

3.8: Stapleton RD, Dixon AE, Parsons PE, Ware LB, Suratt BT; NHLBI Acute Respiratory Distress Syndrome Network. The association between BMI and plasma cytokine levels in patients with acute lung injury. Chest. 2010 Sep;138(3):568-77. doi: 10.1378/chest.10-0014. Epub 2010 Apr 30. PubMed PMID: 20435656; PubMed Central PMCID: PMC2940070.

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Exclusion criteria E4 Studies of passive or parental smoking

None

Exclusion criteria E5 Studies in a narrow population (e.g. pregnant women)

3.9: Huang F, del-Río-Navarro BE, Monge JJ, Torres Alcántara S, Ontiveros JA, Olivos EN, Martínez de Castro NG, Zhao L, Hong E. Endothelial activation and systemic inflammation in obese asthmatic children. Allergy Asthma Proc. 2008 Sep-Oct;29(5):453-60. doi: 10.2500/aap.2008.29.3149. PubMed PMID: 18926053.

Exclusion criteria E6 *In vitro* studies or studies using *in vivo* animal models

None

Exclusion criteria E7 Studies in which sICAM was measured for toxicological or forensic purposes

None

Exclusion criteria E8 Studies with no comparison to smoking and cessation/switching

3.2: Davey RT Jr, Lynfield R, Dwyer DE, Losso MH, Cozzi-Lepri A, Wentworth D, Lane HC, Dewar R, Rupert A, Metcalf JA, Pett SL, Uyeki TM, Bruguera JM, Angus B, Cummins N, Lundgren J, Neaton JD; INSIGHT FLU 002 & 003 Study Groups. The association between serum biomarkers and disease outcome in influenza A(H1N1)pdm09 virus infection: results of two international observational cohort studies. PLoS One. 2013;8(2):e57121. doi: 10.1371/journal.pone.0057121. Epub 2013 Feb 27. PubMed PMID: 23468921; PubMed Central PMCID: PMC3584122.

3.7: Buckley ST, Medina C, Kasper M, Ehrhardt C. Interplay between RAGE, CD44, and focal adhesion molecules in epithelial-mesenchymal transition of alveolar epithelial cells. Am J Physiol Lung Cell Mol Physiol. 2011 Apr;300(4):L548-59. doi: 10.1152/ajplung.00230.2010. Epub 2011 Jan 28. PubMed PMID: 21278261.

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