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APPENDIX A6.1.4.4 FIBRINOGEN HEALTH EFFECTS OF SMOKING CESSATION

Short Term Health Effects

Fibrinogen

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1 BACKGROUND

Fibrinogen (FIB) is a soluble plasma glycoprotein (molecular weight 340 kDa), which belongs to the acute phase proteins. FIB is converted by thrombin to fibrin during blood clot formation. FIB is synthesized in the liver, normal plasma concentrations in humans amount to 200–400 mg/dl [1].

Together with C-reactive protein (CRP), FIB is an inflammatory marker and plays a particular role in the generation of atherosclerosis [2, 3]. FIB concentrations in blood are about similar or somewhat lower in men compared to women and increase with age [4-9] and FIB plasma levels are reported to be higher in black than in white people [4, 10, 11].

Stress, social isolation and lower social class are associated with elevated FIB concentrations in blood [4].

Genetic polymorphism, in particular at the G/A-455 position (located in the promoter region) are associated with lower FIB levels in non-smokers [12]. However, no influence of genetic polymorphisms at this FIB locus was found in another study [13].

FIB has been intensively investigated in large prospective epidemiological studies, frequently together with smoking as a risk factor [14, 15]. FIB was found to be involved in the major smoking-related diseases such as cardiovascular disease (CVD), respiratory diseases and cancer.

More recently, FIB concentrate has been applied for clinical treatments (e.g. in bleeding conditions) [16-23].

2 METHODS

The published information for generating the present document was collected from the following sources:

- Monographs on biomarkers of effect and smoking:
  - US Surgeon General Report 2010 [15]
  - Life Sciences Research Office (LSRO) Report of 2007 [24]
- References related to FIB extracted from the two monographs (Source 1)
- Search 1 in the PubMed literature data base on 19.05.2015 for reviews on FIB; search string: “fibrinogen[Title] Filters: Review; Full text; published in the last 5 years; Humans”
- Search 2 in the PubMed literature data base on 19.05.2015 for references on FIB and smoking or nicotine; search string: (fibrinogen[Title]) AND (smoking[Title] OR smoker[Title] OR smokers[Title] OR tobacco[Title] OR nicotine[Title]) Filters: published in the last 10 years; Humans”
- Search 3 in the PubMed literature data base on 19.05.2015 for references on FIB and CVD; search string: Search (fibrinogen[Title]) AND cardiovascular disease[Title] Filters: published in the last 5 years”
- Search 4 in the PubMed literature data base on 19.05.2015 for references on FIB and respiratory disease; search string: “(fibrinogen[Title]) AND (respiratory[Title] OR lung[Title]) Filters: published in the last 5 years”

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- Search 5 in the PubMed literature data base on 19.05.2015 for references on FIB and cancer; search string: "(fibrinogen[Title]) AND cancer[Title] Filters: published in the last 5 years; Humans"
- Cited articles from Sources 2 – 7 with relevance for the topic of interest.

Studies were selected for evaluations in Chapter 4 ('Biomarker-disease link') and Chapter 5 ('Smoking-biomarker link') according to the following inclusion criteria:

A:	Association between FIB and cardiovascular diseases (CVD) in a human cohort was investigated
B:	Association between FIB and respiratory diseases in a human cohort was investigated
C:	Association between FIB and any other disease in a human cohort was investigated
D:	Differences between in FIB levels between smokers and non-smokers were investigated and suitable data presented
E:	The dose-response relationship between smoking intensity (determined for example by daily cigarette consumption, pack-year or cotinine) and FIB level was studied and suitable data presented
F:	The effect of smoking cessation on the FIB level was studied and accordingly and suitable data presented
G:	The effect of switching from conventional cigarettes to modified risk tobacco products (MRTPs) or nicotine products on the FIB level was investigated
R:	Review article on FIB

Reviews were used for generating Chapter 1 ('Background') and, if suitable, also for Chapters 4 and 5.

Studies not fulfilling any of the inclusion criteria A – G and R were excluded from the evaluation (assigned as '01 to 05' in Appendix 1 together with the reason for exclusion).

3 FINDINGS

From Source 1 (Monographs) [15, 24], 34 articles [2-7, 12, 14, 25-50] were extracted (25 originating from the Surgeon General Report 2010, 9 from the LSRO monograph).

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The distribution of articles according to the Sources 1 – 8 described in Chapter 2 ('Methods') and according the inclusion criteria A – G and R are summarized in Table 1. The individual articles according to sources and assignment to inclusion and exclusion criteria are compiled in Appendix 1.

Table 1. Number of articles according to source and inclusion criteria.

Source (Description)	All	Relevant	Inclusion criteria[a]								Ex-cluded
			A	B	C	D	E	F	G	R	
1 (Monographs)	2	2	2	1	1	2	2	2	0	2	0
2 (Articles extr. from 1)	34	33	12	3	0	22	5	12	6	3	1
3 (Search 1, reviews)	42	15	3	2	1	0	0	0	0	14	27
4 (Search 2, smoking)	6	5	0	0	2	5	1	1	0	0	1
5 (Search 3, CVD)	10	10	10	0	0	0	0	0	0	0	0
6 (Search 4, resp. dis.)	13	8	0	3	6	0	0	0	0	1	5
7 (Search 5, cancer other diseases)	23	16	0	0	16	0	0	0	0	0	7
8 (Cited articles in 2 - 7)	20	18	1	1	0	5	9	5	3	2	2
Sum	150[b]	107	28	10	26	34	17	20	9	22	43

[a] Note that an article could fulfil several inclusion criteria
[b] Deviation from the 144 articles listed in Appendix 1 is caused by some overlap between the search results yielding identical articles

Of the 150 articles retrieved from the various sources, 107 were considered to be relevant for the generation of this document, 43 publications were of no or very limited relevance for this purpose and therefore excluded. Five reasons for exclusion are given in Appendix 1.

Most articles retrieved deal with the criteria CVD (A), other diseases, in particular cancer (C) and smoking (D – G) or were reviews (R). No separate search for the association of FIB with other diseases was performed, since the category 'other diseases' was already represented in the other searches. The importance of FIB for respiratory diseases (B) is reflected by the fact that 10 articles deal with this topic. There were 78 articles which considered the relationship between FIB and smoking (D – G). The aspect of smoking cessation (F) was dealt with in 20 studies, whereas the dose-relationship between

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smoking and FIB levels was considered in 17 articles. It bears mentioning that 9 articles were found, which deal with the changes in FIB levels after switching to MRTPs or nicotine products (G).

It should be noted that the classification of the retrieved articles was done after a first inspection (usually by reading the abstract). The final classification can somewhat deviate from this assignment. However, the distribution of the articles according the defined criteria was very similar to that shown in Table 1, thus, these numbers reflect rather well the knowledge and the load of evidence available for the various categories.

4 BIOMARKER-DISEASE LINK

4.1 Cardiovascular disease

There is a strong association between plasma levels of FIB and cardiovascular diseases (CVD), including coronary heart disease (CHD), stroke, myocardial infarction (MI) and atherosclerosis [6, 14, 15, 24, 26, 29, 31, 46] thus FIB can be regarded as a strong predictor for these diseases.

The potential pathophysiological mechanisms of the involvement of FIB in the generation of CVD includes atherogenesis, thrombogenesis, ischaemia due to increased blood viscosity, modulation of endothelial function, promotion of smooth muscle cell proliferation and finally its response to inflammatory conditions as an acute phase protein [25, 34, 46].

The evidence available suggests that a causal relationship between plasma FIB concentrations and CVD is most likely [14, 25, 29]. However, the findings that specific genotypes lead to differences in fibrinogen levels, but not to corresponding differences in cardiovascular risks, raises questions related to the hypothesis of causality between FIB and CVD [51].

4.2 Respiratory disease

An association between plasma FIB levels and respiratory diseases and lung function impairments was observed in a number of studies. Elevated FIB concentrations were found in COPD patients [32, 52, 53] and increased fibrin deposits and nitration of FIB-bound tyrosine was reported in acute respiratory distress syndrome (ARDS) patients [43]. FIB was found to be inversely associated with FEV1 (forced expired volume in 1 second) in healthy adults [54] and FIB was also shown to be significantly elevated in subjects with symptoms of chronic bronchitis, irrespective of smoking [55].

The most likely explanation for the observed associations of FIB with the various respiratory diseases is its role as an acute phase protein, responding to inflammatory stress.

FIB might have some value as a predictor for respiratory diseases given the associations described above. The evidence in the published literature, however, is as yet very limited.

4.3 Other diseases

Everett et al. [10] reported an association between elevated FIB levels and increased risk of respiratory/intrathoracic organ cancer mortality in black and non-black smokers.

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Fibrinogen was also found to be a predictor of other types of cancer mortality among black subjects, but not among non-black subjects [10].

Elevated FIB levels were reported to be predictive of a bad prognosis in a number of cancer types, including lung cancer [10, 56-62], endometrial cancer [63], breast cancer [64], rectal cancer [65, 66], kidney cancer [67], ovarian cancer [68], vulvar cancer [69], colon cancer [57, 70] and pancreatic cancer [70-72].

The pathophysiological mechanism of the involvement of FIB in cancer development is most probably not causal but a response to inflammatory processes. On the other hand, FIB has been linked to angiogenesis and metastases of tumors [10].

5 SMOKING-BIOMARKER LINK

The association between smoking and elevated plasma FIB concentrations is well established by numerous studies on the difference in FIB levels between smokers and non-smokers (Section 5.1), dose-response relationship, decrease of FIB levels upon quitting smoking and switching to MRTPs or other nicotine products. These associations could be secondary (non-causal) and due to the fact that smoking is related to a number of diseases which are accompanied by elevated FIB levels (see Biomarker-disease link). However, there are a number of mechanisms which suggest that smoking may be causally related to increased FIB concentrations and/or increased detrimental effects of FIB in the development of diseases. Potential mechanisms include:

- Cigarette smoking results in a chronic inflammatory state, as evidenced by increased levels of circulating leukocytes and C-reactive protein (CRP) in turn leading to increased levels of acute phase reactants such as FIB [34].
- Elevation in plasma fibrinogen due to smoking-induced disturbance of vascular endothelium or pulmonary epithelium may induce the release of cytokines such as interleukin-6 which increase hepatic synthesis of FIB [46].
- There is evidence that smoking interacts with the G-455A-fibrinogen gene promoter and may thus increase the plasma FIB level [34].
- Increased nitration of tyrosine in FIB in smokers, for which there is ample evidence [33, 38, 41, 43, 44, 47] may lead to a pro-thrombotic state accompanied by a more rapid formation of fibrin clots [33].
- The same is true for the smoking-related protein carbonylation of FIB [41].
- Smoking induces FIB synthesis [40], the increase in synthesis rate is about 33-34 % and thus higher than the difference in FIB levels between S and NS (10-20 %), suggesting that also degradation and deposition of FIB is higher in smokers than in non-smokers.
- Reduction in leukocyte count suggests that smoking may increase fibrinogen, at least in part, through leucocytosis [4].

Therefore, it is highly likely that smoking is causally related to increased plasma FIB levels and its detrimental effects. Experimental studies also show that the effect of smoking on the FIB concentration takes places very rapidly (within < 1 h) [53] (see Table 2, last study).

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5.1 Smoking

In Table 2, FIB results of 14 different studies published over the last 3 decades are presented. The data consistently show that smokers have increased FIB levels compared to non-smokers. The relative differences between these two groups are in the range of 10 – 20%. Most of the analyzed differences between smokers and non-smokers were statistically significant.

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Table 2. Fibrinogen (FIB) levels in smokers and non-smokers or ex-smokers derived from various populations.

Author (reference)	Population	Smokers (S)	Non-smokers (NS)	p-Values and remarks
Wilhelmsen et al. [29]	Men living in Göteborg, Sweden, born 1913. Investigations in 1963 and 1967	Significant correlation between FIB and smoking		P<0.001
Meade et al. [73]	White men aged 40-65 years from the Northwick Park Heart Study (NPHS), UK	Plasma FIB, mean, g/L: Cigarette S (N=525): 3.1 Pipe/cigar S (N=139): 2.9	Plasma FIB, mean, g/L: Ex-S (N=407): 2.9 Never S (N=257): 2.8	(not reported)
Lee et al. [9]	Subjects from the Scottish Heart Study (40-59 years old)	Plasma fibrinogen, mean±SD[c], gL: Male current S (N=1741): 2.5±0.7 Female current S (N=1627): 2.5±0.7	Plasma fibrinogen, mean±SD[c], g/l: Male ex-S (N=1576): 2.2±0.7 Male never S (N=1190): 2.2±0.6 Female ex-S (N=880): 2.3±0.7 Female never S (N=1794): 2.3±0.7	Current S vs ex-S or NS (both sexes): P<0.001 Ex-S vs NS: Males: P<0.01 Females: P=0.18 Dose-response relationship to CPD

(table continues)

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Author (reference)	Population	Smokers (S)	Non-smokers (NS)	p-Values and remarks
Folsom et al. [4]	Subjects from the ARIC (Atherosclerosis in Communities) Study (USA), 45-64 years old.	Plasma FIB, mean±SEM[a], mg/dL: Male S (N=1380): 326±2 Female S (N=1605): 330±1	Plasma FIB, mean±SEM[a], mg/dL: Male NS (N=1494): 285±2 Male Ex-S (N=2241): 292±1 Female NS (N=3405): 308±2 Female Ex-S (N=1484): 310±2	ANOVA for each sex: p<0.01 FIB was higher in blacks than whites and in women than men.
Thomas et al. [12]	Men from general practices in the UK (mean age 55 years)	Plasma FIB, mean (95 % CI[b]), g/L: Male S (N=120): 2.9 (2.8-3.1)	Plasma FIB, mean (95 % CI[b]), g/L: Male NS (N=172): 2.6 (2.5-2.7)	S vs NS: P<0.0001 In NS, the 455-G/A polymorphisms plays an important role of FIB variation. In S, smoking is more important than the polymorphism

(table continues)

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Author (reference)	Population	Smokers (S)	Non-smokers (NS)	p-Values and remarks
Eliasson et al. [50]	Subjects from the Northern Sweden MONICA Study (healthy, 25-64 y old)	Plasma FIB, geom. mean (95 % CI[b]), g/L: Male S (N=162): 3.6 (3. 5-3.7) Female S (N=194): 3.7 (3.5-3. 8)	Plasma FIB, geom. mean (95 % CI[b]), g/L: Male NS (N=216): 3.2 (3.1-3.3) Female NS (N=353): 3.6 (3.5-3.7) Male snuff users (N=90): 3.2 (3.0-3.3)	Males: S vs NS: P<0.001 Snuff vs S: P<0.001 Females: S vs NS: P<0.01 No sign. correlation between smoking dose or duration and FIB
Cullen et al. [74]	Subjects from the Muenster Heart Study (PROCAM), mean age 35-40 years	Plasma FIB, mean±SD[c], g/L: Male S (N=2,646): 2.8±0.6 Female S (N=1,009): 2.7±0.6	Plasma FIB, mean±SD[c], g/L: Male NS (N=5,589): 2.5±0.5 Male ex-S (N=2,641): 2.5±0.5 Female NS (N=2,096): 2.6±0.5 Female ex-S (N=350): 2. 6±0.5	S vs NS: P<0.001 Ex-S vs NS: Not significant Significant dose-response relationship with CPD
Jousilahti et al. [55]	Subjects from the Finish MONICA Study (45-64 years old)	Plasma FIB, mean, g/L: Male S without symptoms of chronic bronchitis (N=182): 3.7 Female S without symptoms of chronic bronchitis (N=110): 3.8	Plasma FIB, mean, g/L: Male NS without symptoms of chronic bronchitis (N=608): 3.3 Female NS without symptoms of chronic bronchitis (N=792): 3.4	S vs NS: Not analyzed. Authors stated “markedly higher in S” (both genders)

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Author (reference)	Population	Smokers (S)	Non-smokers (NS)	p-Values and remarks
Hunter et al. [40]	Healthy male subjects from the UK (mean age 37 y, S and NS were age-matched)	Plasma FIB, mean±SEM[a], g/L: Male S (N=8): 2.9±0.2	Plasma FIB, mean±SEM[a], g/L: Male NS (N=8): 2.6±0.2	S vs NS: Not sign. Synthesis rate of FIB was significantly higher in S compared to NS
Tuut and Hense [39]	Subjects from the MONICA Study in Augsburg, Germany (25-74 years old)	Plasma FIB, mean±SD[c], mg/dL: Male S (N=620): 394.5±95.3 Female S (N=441): 383.9±78.5	Plasma FIB, mean±SD[c], mg/dL: Male NS (N=1,220): 359.1±78.1 Female NS (N=1,343): 383.9±78.5	S vs NS: Males: P<0.001 Females: Not sign.
Bazzano et al. [35]	Participants in the Third National Health and Nutrition Exami-nation Survey (NHANES) in the USA (40+ years old)	FIB in serum, mean±SEM[a], µmol/L: Current S (N=4945): 8.91±0.10	FIB in serum, mean±SEM[a], µmol/L: Former S (N=4791): 8.32±0.11 Never S (N=9864): 8.11±0.10	P<0.001 Odds ratios for FIB smoking 0, 1-9, 10-19 and 20+ cig/d were 1.00, 1.01, .172, 2.15, respectively (P<0.001)

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Author (reference)	Population	Smokers (S)	Non-smokers (NS)	p-Values and remarks
Everett et al. [10]	Subjects from the ARIC Study (Atherosclerosis in Communities) Study (USA), 45-64 years old.	Plasma FIB, mean, mg/dL: Non-black: Heavy S (N=2045): 322 Light S (N=487): 300 Black: Heavy S (N=593): 338 Light S (N=541): 328 Light: < 15, heavy: 15+ cig/d	Plasma FIB, mean, mg/dL: Non-black: Ex heavy S (N=2647): 291 Ex light S (N=1083): 287 Never S (N=4242): 289 Black: Ex heavy S (N=430): 319 Ex light S (N=468): 311 Never S (N=1784): 313	Black and non-black): Heavy vs light S: P<0.05 Ex vs never S: Not significant, except: black ex heavy vs never S: P<0.05
Pineda-Frost et al. [75]	Total Exposure Study (TES) in the USA, comprising healthy adults, 21+ years old	Plasma FIB, mean±SD[c], mg/dl: S (N=3459): 326±78.9	Plasma FIB, mean±SD[c], mg/dl: NS (N=1042): 309±68.0	S vs NS: P<0.0001
Van Dijk et al. [53]	COPD patients (smokers)	Changes in plasma FIB from baseline (8 h smoking abstinent) after smoking 2 cigarettes, mean (95 % CI), mg/dl: S with COPD (N=35): 15 min after smoking: 9.4 (4.2- 14.5) 35 min after smoking: 5.3 (0-10.7) Results are irrespective of treatment (bronchodilator or placebo)		15 min vs baseline: P<0.001 35 min vs baseline: P=0.052

[a] SEM: Standard error of the mean; [b] SD: Standard deviation; [c] CI: Confidence interval

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An increase of FIB with the smoking dose was observed in a study performed 30 years ago [76]. A very weak (not significant) association between FIB and smoking dose (cig/d) was found by Yarnell et al. [77].

In a study with 5614 men, aged 45 – 64 years, Wilkes et al. [78] observed FIB plasma levels of 3.6, 3.9, 4.0, 4.0, 4.2 g/L in non-smokers and smokers of 1-10, 11-20, 21-30 and >30 cigarettes/d, respectively, indicating a clear dose-response relationship.

Folsom et al. [4] (Table 2) reported a significant dose-response relationship between daily cigarette consumption (CPD) and FIB plasma levels for both sexes.

Eliasson et al. [50] found no significant correlation between the smoking dose (determined by CPD, plasma nicotine or cotinine) or smoking duration and plasma FIB.

Lee et al. [9] and Cullen et al. [74] reported a dose-response relationship between CPD and plasma FIB concentrations.

Green et al. [11] found a significant correlation between CPD and FIB levels in white but not black subjects.

Krobot et al. [8] reported a significant association between CPD and FIB in men but not in women.

Results by Bazzano et al. [35] show a positive and significant dose-response relationship between measures of cigarette smoking (cigarettes per day, pack-years, and serum cotinine levels) and elevated levels of FIB (Table 2).

In a smoking reduction study, Eliasson et al. [7] reported a decrease of CPD from 21.5 (baseline) to 10.8 (after 9 weeks) to abstinence (after 17 weeks). Corresponding FIB levels were 2.9, 2.7 and 2.7 g/L, respectively.

The results described above rather consistently show that there is a dose-response relationship between smoking dose and plasma FIB levels.

5.2 Smoking cessation

When the effects of smoking cessation on the FIB levels are evaluated, acute (days to several weeks of quitting) and chronic effects (years, mostly data from ex-smokers) have to be differentiated.

As shown by von Dijk et al. [53] (Table 2), smoking very rapidly leads to an increase in FIB levels (15 min after smoking). After 35 min, FIB levels already show a decreasing trend. Most acute cessation studies were performed over several days and up to several weeks. Feher et al. [79] reported significantly lower FIB concentrations 2 weeks after quitting smoking (3.0 vs 3.5, $P<0.01$). Rothwell et al. [5] found a decrease in FIB blood concentrations (as in other hemorheological parameters) of 13% 2 days after smoking cessation. FIB levels remained constant thereafter until 12 days (end of the study). Hunter et al. [40] reported a mean value for plasma FIB of 3.1±0.1 g/L while smoking and an FIB value of 2.5±0.1 g/L after 2 weeks abstinence ($P<0.001$). In a smoking reduction and cessation study, Eliasson et al. [7] reported a decrease of FIB from 2.9 (baseline) to 2.7 g/L (after 17 weeks).

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Chronic effects of smoking cessation were derived mostly from ex-smokers and therefore cover years or even decades of quitting smoking. Meade et al. [73] reported that FIB levels of ex-smokers were intermediate between current and never smokers (Table 2). In a prospective study with FIB determinations at baseline and at 6 years follow up, the same authors [28] observed a significant ($p<0.05$) increase of plasma FIB of 2.4 % in continuing smokers (N=531), whereas FIB levels dropped by 3.4-4.2 % in those who stopped smoking (N=156, $P<0.03$).

Yarnell et al. [77] reported that among the ex-smokers there was a significant (P<0 01) trend for fibrinogen to decline with the increase in the number of years after giving up. Men who gave up in the past year had FIB levels that were nearly as high as those of the current smokers whilst men who gave up smoking 10 years or more before had levels that had nearly, but not quite, returned to those of the men who had never smoked. Lee et al. [9] (Table 2) found that ex-smokers were not significantly different in their FIB levels compared to non-smokers in females, but still significantly elevated in males. Krobot et al. [8] also observed lower FIB levels in ex-smokers, however still somewhat elevated compared to never smokers.

Eliasson et al. [50] reported that female smokers had significantly higher fibrinogen levels than ex-smokers but the difference compared with non-smokers was not significant. The use of moist snuff did not affect fibrinogen levels.

FIB data for ex-smokers derived from studies by Folsom et al. [4], Cullen et al. [74], Bazzano et al. [35] and Everett et al. [10] are shown in Table 2. The results confirm essentially those described above.

In summary, the published data provide strong evidence that plasma FIB concentrations decrease within days to weeks after quitting smoking but ex-smokers who had quit smoking for years or even decades still show somewhat elevated FIB levels compared to never smokers.

5.3 Role in MRTP assessment

In a number of studies, plasma FIB concentrations were analyzed after switching from smoking cigarettes to an NRT (nicotine replacement therapy) product as a quitting aid.

Benowitz et al. [80] reported that nicotine patches had no effect on plasma FIB concentrations. In a smoking reduction and abstinence study by Eliasson et al. [7] (see Section 5.2), more than half of the abstinent smokers used nicotine nasal spray, which had no detrimental effect on the FIB level in blood. The same authors [49] observed no significant difference in FIB levels between long-term nicotine gum users (previous smokers, who used the gum for at least 11 months) and non-smokers. Haustein el al. [37] reported that after stopping smoking with the aid of nicotine gum or patches supplied until week 12, there was a significant decrease in mean plasma FIB from 9.94 µmol/l at baseline to 9.1 µmol/l at week 8, 8.6 µmol/L at week 12 and 8.2 µmol/L at week 26 ($p< 0.003$). FIB levels in continuing smokers were almost stable over the study period.

In a clinical study with ulcerative colitis (UC) patients, Ingram et al. [81] found that nicotine enemas applied to patients (all non-smokers) had no effect in either direction on

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plasma FIB levels. Thomas et al. [82] reported that nicotine patches applied to UC patients (non-smokers) significantly lowered the plasma FIB levels.

Two published studies were retrieved that can be classified as MRTP switching studies:

Eliasson et al. [50] measured FIB concentrations in snuff users and found no significant difference to that in non-tobacco users.

Roethig et al. [83] reported that the FIB levels in smokers who switched from conventional cigarettes (CC) to electrically heated cigarettes (EHC) decreased from 318 to 306 mg/dl after 12 months, whereas in smokers who continued to smoke CC, the FIB concentration remained stable (320 vs 319 mg/dl).

6 CONCLUSION

The role of FIB in the development of pathologies such as CVD, respiratory diseases and various types of cancer is well established. This is mainly due to the functionality of FIB in atherogenesis, thrombogenesis, increased blood viscosity, and its role as an acute phase protein responding to inflammation. Data on differences between smokers and non-smokers, dose-response relationship and smoking cessation suggest that the positive association of plasma FIB levels with smoking is likely to be causal. There are a number of mechanisms (see: Smoking-biomarker link), which support a causal relationship between smoking and elevation in FIB plasma levels. There are a number of studies available, which show that FIB levels in smokers who used nicotine as NRT product or switched to MRTPs decreased to almost non-smokers levels. This provides evidence that tobacco combustion products released from conventional cigarettes are responsible for the observed increase in FIB levels in smokers. In addition, these results strongly suggest that nicotine alone does not influence the FIB level in acute and long-term tobacco users.

A severe limitation of FIB as a biomarker of effect for smoking-related diseases is the weakness of the association, which leads to rather small differences in FIB levels between smokers and non-smokers, sometimes missing statistical significance and preventing the finding of strong dose-response relationships. Furthermore, many studies have shown that the functionality of FIB as an acute phase protein in response to inflammatory conditions is better reflected in changes of C-reactive protein (CRP) than in corresponding changes of FIB levels.

Taken together, the information available does not strongly support the use FIB as a biomarker of effect for the assessment of MRTPs. However, FIB's role in the pathophysiology of major smoking-related diseases should lead to considering its use in large epidemiological studies.

The evidence for suitability of FIB as a biomarker of effect in the assessment of MRTPs is summarized in Table 3.

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Table 3. Strength of evidence for the suitability of FIB as a biomarker of effect for MRTP assessment.

Property	Evidence
Biological plausibility	Due to its biological properties, FIB can be regarded as a proven biomarker of risk for the development of CVD, respiratory diseases and various types of cancer. FIB has a number of detrimental effects in the development of CVD such as its involvement in atherogenesis, thrombogenesis and increase of blood viscosity. The increasing effect of smoking can be explained by a number of potential mechanisms (Chapter 5)
Dose-response	Differences between smokers and non-smokers (zero dose) were reported for various groups of healthy subjects in many studies (Section 5.1, Table 2). Findings are consistent, despite the fact that some studies miss statistical significance. There is consistent evidence that FIB tends to increase with the smoking dose. Results, however, are frequently not statistically significant, probably due to the weakness of the association between smoking and FIB level.
Benchmark to cessation	There is consistent evidence that quitting smoking rapidly (within hours or days) leads to a reduction in FIB levels. FIB concentrations in ex-smokers are still somewhat elevated compared to non-smokers, even after years of quitting.
Consistency[a]	Available data for FIB and smoking are very consistent in terms of differences between smokers and non-smokers, dose-response and smoking cessation.
Coherence[b]	In this document, almost exclusively human data from clinical and epidemiological studies were evaluated. Also not in the focus of this review, no evidence was found that results from animal and *in vitro* studies would deviate from the human data.

[a] Consistent findings in various studies strengthens the likelihood that the finding is true
[b] Coherence of findings from epidemiological, laboratory, animal and *in vitro* studies increases the likelihood that the result is true

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7 APPENDICES

7.1 Appendix 1 References of included studies
7.2 Appendix 2 Inclusion criteria A
7.3 Appendix 3 Inclusion criteria B
7.4 Appendix 4 Inclusion criteria C
7.5 Appendix 5 Inclusion criteria D
7.6 Appendix 6 Inclusion criteria E
7.7 Appendix 7 Inclusion criteria F
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7.9 Appendix 9 Review articles
7.10 Appendix 10 Excluded articles

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7.1 Appendix 1 References of included and excluded studies

Articles were assigned (included, excluded) according the following criteria

0x	Excluded (not belonging to at least one category A - G or R)
A	Association to CVD
B	Association to respiratory diseases
C	Association to other diseases
D	Levels in smokers and non-smokers
E	Dose-response relationship to smoking intensity
F	Effect of smoking cessation
G	Effect of switching to MRTPs or other products
R	Review article

Articles were included, if they provide relevant information on the criteria A – G or were assigned as relevant review for the biomarker of interest. All other articles are excluded from the evaluation (assigned as 0x, x (reason for exclusion) = 1 to 5).

01	No usable data for FIB were presented
02	FIB (or FIB concentrates) investigated for clinical or treatment purposes
03	No relation to smoking or a smoking-related disease
04	No relevant population investigated (e.g. pregnant women, newborns and children)
05	Animal or *in vitro* studies with no obvious relation to humans

Sources for published articles to be used for generation of the document

Source 1: Two monographs on biomarkers of effect and smoking [1, 2]

Source 2: Articles derived from monographs: 34 References [3-36]

Source 3: Articles from PubMed Search 1 (Reviews on FIB): 42 References [37-78]

Source 4: Articles derived from PubMed Search 2 (smoking-related studies on FIB: 6 References [79-84]

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Source 5: Articles derived from PubMed Search 3 (association between FIB and cardiovascular diseases): 10 References [74, 85-93]

Source 6: Articles derived from PubMed Search 4 (association between FIB and respiratory diseases): 13 Reference [94-106]

Source 7: Articles derived from PubMed Search 4 (association between FIB and cancer): 23 References [99, 101, 103, 105-124]

Source 8: Articles derived from citations in publications from Sources 2 - 7: 20 References [125-144]

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Slodczyk, E., Szoltysek-Boldys, I., Kozar-Konieczna, A., Goniewicz, J., Ptak, M., Olszowy, Z., Kosmider, L., Goniewicz, M. L., and Sobczak, A. (2012) [Plasma fibrinogen concentration in smoking and nonsmoking patients treated from alcohol addiction]. *Przegl Lek*, *69*, 812-815. **D, A**

van Dijk, W. D., Akkermans, R., Heijdra, Y., Weel, C., Schermer, T. R., Scheepers, P. T., and Lenders, J. W. (2013) The acute effect of cigarette smoking on the high-sensitivity CRP and fibrinogen biomarkers in chronic obstructive pulmonary disease patients. Biomark Med., 7, 211-219. doi: 210.2217/bmm.2212.2112. **D**

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Cullen, P., Schulte, H., and Assmann, G. (1998) Smoking, lipoproteins and coronary heart disease risk. Data from the Munster Heart Study (PROCAM). *European heart journal*, *19*, 1632-1641. **D, E**

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Jousilahti, P., Salomaa, V., Rasi, V., and Vahtera, E. (1999) Symptoms of chronic bronchitis, haemostatic factors, and coronary heart disease risk. Atherosclerosis, 142, 403-407. **D, B**

Lee, A. J., Smith, W. C., Lowe, G. D., and Tunstall-Pedoe, H. (1990) Plasma fibrinogen and coronary risk factors: the Scottish Heart Health Study. *Journal of clinical epidemiology*, *43*, 913-919. **D, E, F**

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Roethig, H. J., Feng, S., Liang, Q., Liu, J., Rees, W. A., and Zedler, B. K. (2008) 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.*, *48*, 580-591. **D, G**

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7.6 Appendix 6 Inclusion criteria E

Life Sciences Research Office (LSRO). (2007) *Biological effects assessment in the evaluation of potential reduced-risk tobacco products*. Bethesda, Maryland, USA. **D, A, E, F, R**

US Department of Health and Human Services. (2010) How Tobacco Smoke Causes Disease: The Biology and Behavioral Basis for Smoking-Attributable Disease A Report of the Surgeon General. **D, A, E, F, R**

Bazzano, L. A., He, J., Muntner, P., Vupputuri, S., and Whelton, P. K. (2003) Relationship between cigarette smoking and novel risk factors for cardiovascular disease in the United States. *Ann Intern Med.*, *138*, 891-897. **D, E**

Eliasson, B., Hjalmarson, A., Kruse, E., Landfeldt, B., and Westin, A. (2001) Effect of smoking reduction and cessation on cardiovascular risk factors. *Nicotine Tob Res.*, *3*, 249-255. **D, E, F, G**

Godtfredsen, N. S., Osler, M., Vestbo, J., Andersen, I., and Prescott, E. (2003) Smoking reduction, smoking cessation, and incidence of fatal and non-fatal myocardial infarction in Denmark 1976-1998: a pooled cohort study. *J Epidemiol Community Health.*, *57*, 412-416. **D, E, F, A**

Hurt, R. D., Croghan, G. A., Wolter, T. D., Croghan, I. T., Offord, K. P., Williams, G. M., Djordjevic, M. V., Richie, J. P., Jr., and Jeffrey, A. M. (2000) Does smoking reduction result in reduction of biomarkers associated with harm? A pilot study using a nicotine inhaler. *Nicotine Tob Res.*, *2*, 327-336. **D, E, F, G**

Jensen, E. J., Pedersen, B., Frederiksen, R., and Dahl, R. (1998) Prospective study on the effect of smoking and nicotine substitution on leucocyte blood counts and relation between blood leucocytes and lung function. *Thorax.*, *53*, 784-789. **D, E, F, B**

Tracy, R. P., Psaty, B. M., Macy, E., Bovill, E. G., Cushman, M., Cornell, E. S., and Kuller, L. H. (1997) Lifetime smoking exposure affects the association of C-reactive protein with cardiovascular disease risk factors and subclinical disease in healthy elderly subjects. *Arterioscler Thromb Vasc Biol.*, *17*, 2167-2176. **D, E, F, A**

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Balleisen, L., Bailey, J., Epping, P. H., Schulte, H., and van de Loo, J. (1985) Epidemiological study on factor VII, factor VIII and fibrinogen in an industrial population: I. Baseline data on the relation to age, gender, body-weight, smoking, alcohol, pill-using, and menopause. *Thrombosis and haemostasis*, *54*, 475-479. **D, E, A**

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Krobot, K., Hense, H. W., Cremer, P., Eberle, E., and Keil, U. (1992) Determinants of plasma fibrinogen: relation to body weight, waist-to-hip ratio, smoking, alcohol, age, and sex. Results from the second MONICA Augsburg survey 1989-1990. *Arteriosclerosis and thrombosis : a journal of vascular biology / American Heart Association*, *12*, 780-788. **E, F**

Lee, A. J., Smith, W. C., Lowe, G. D., and Tunstall-Pedoe, H. (1990) Plasma fibrinogen and coronary risk factors: the Scottish Heart Health Study. *Journal of clinical epidemiology*, *43*, 913-919. **D, E, F**

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Wilkes, H. C., Kelleher, C., and Meade, T. W. (1988) Smoking and plasma fibrinogen. *Lancet*, *1*, 307-308. **E**

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7.7 Appendix 7 Inclusion criteria F

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Eliasson, B., Hjalmarson, A., Kruse, E., Landfeldt, B., and Westin, A. (2001) Effect of smoking reduction and cessation on cardiovascular risk factors. *Nicotine Tob Res.*, *3*, 249-255. **D, E, F, G**

Eliasson, B., Taskinen, M. R., and Smith, U. (1996) Long-term use of nicotine gum is associated with hyperinsulinemia and insulin resistance. *Circulation.*, *94*, 878-881. **F, G**

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Godtfredsen, N. S., Osler, M., Vestbo, J., Andersen, I., and Prescott, E. (2003) Smoking reduction, smoking cessation, and incidence of fatal and non-fatal myocardial infarction in Denmark 1976-1998: a pooled cohort study. *J Epidemiol Community Health.*, *57*, 412-416. **D, E, F, A**

Haustein, K. O., Krause, J., Haustein, H., Rasmussen, T., and Cort, N. (2002) Effects of cigarette smoking or nicotine replacement on cardiovascular risk factors and parameters of haemorheology. *J Intern Med.*, *252*, 130-139. **D, F, G**

Hunter, K. A., Garlick, P. J., Broom, I., Anderson, S. E., and McNurlan, M. A. (2001) Effects of smoking and abstention from smoking on fibrinogen synthesis in humans. *Clin Sci (Lond). 100*, 459-465. **D, F**

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Jensen, E. J., Pedersen, B., Frederiksen, R., and Dahl, R. (1998) Prospective study on the effect of smoking and nicotine substitution on leucocyte blood counts and relation between blood leucocytes and lung function. *Thorax.*, *53*, 784-789. **D, E, F, B**

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Feher, M. D., Rampling, M. W., Brown, J., Robinson, R., Richmond, W., Cholerton, S., Bain, B. J., and Sever, P. S. (1990) Acute changes in atherogenic and thrombogenic factors with cessation of smoking. *Journal of the Royal Society of Medicine*, *83*, 146-148. **F**

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Meade, T. W., Mellows, S., Brozovic, M., Miller, G. J., Chakrabarti, R. R., North, W. R., Haines, A. P., Stirling, Y., Imeson, J. D., and Thompson, S. G. (1986) Haemostatic function and ischaemic heart disease: principal results of the Northwick Park Heart Study. *Lancet*, *2*, 533-537. **F**

Yarnell, J. W., Sweetnam, P. M., Rogers, S., Elwood, P. C., Bainton, D., Baker, I. A., Eastham, R., O'Brien, J. R., and Etherington, M. D. (1987) Some long term effects of smoking on the haemostatic system: a report from the Caerphilly and Speedwell Collaborative Surveys. *Journal of clinical pathology*, *40*, 909-913. **E, F**

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7.8 Appendix 8 Inclusion criteria G

Eliasson, B., Hjalmarson, A., Kruse, E., Landfeldt, B., and Westin, A. (2001) Effect of smoking reduction and cessation on cardiovascular risk factors. Nicotine Tob Res., 3, 249-255. **D, E, F, G**

Eliasson, B., Taskinen, M. R., and Smith, U. (1996) Long-term use of nicotine gum is associated with hyperinsulinemia and insulin resistance. *Circulation., 94*, 878-881. **F, G**

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Hurt, R. D., Croghan, G. A., Wolter, T. D., Croghan, I. T., Offord, K. P., Williams, G. M., Djordjevic, M. V., Richie, J. P., Jr., and Jeffrey, A. M. (2000) Does smoking reduction result in reduction of biomarkers associated with harm? A pilot study using a nicotine inhaler. *Nicotine Tob Res., 2*, 327-336. **D, E, F, G**

Ingram, J. R., Rhodes, J., Collins, P. W., Williams, G. T., Newcombe, R. G., and Thomas, G. A. (2005) Plasma fibrinogen in ulcerative colitis: the effect of disease activity and nicotine therapy in a randomised controlled trial. *Dig Liver Dis., 37*, 832-837. Epub 2005 Sep 2015. **D, G, C**

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Thomas, G. A., Davies, S. V., Rhodes, J., Russell, M. A., Feyerabend, C., and Sawe, U. (1995) Is transdermal nicotine associated with cardiovascular risk? *Journal of the Royal College of Physicians of London, 29*, 392-396. **G**

Thomas, G. A., Davies, S. V., Rhodes, J., Russell, M. A., Feyerabend, C., and Sawe, U. (1995) Is transdermal nicotine associated with cardiovascular risk? *Journal of the Royal College of Physicians of London, 29*, 392-396. **G**

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7.9 Appendix 9 Review articles

Life Sciences Research Office (LSRO). (2007) *Biological effects assessment in the evaluation of potential reduced-risk tobacco products*. Bethesda, Maryland, USA. **D, A, E, F, R**

US Department of Health and Human Services. (2010) How Tobacco Smoke Causes Disease: The Biology and Behavioral Basis for Smoking-Attributable Disease A Report of the Surgeon General. **D, A, E, F, R**

Ernst, E., and Resch, K. L. (1993) Fibrinogen as a cardiovascular risk factor: a meta-analysis and review of the literature. *Ann Intern Med.*, *118*, 956-963. **A, R**

Koenig, W. (2003) Fibrin(ogen) in cardiovascular disease: an update. *Thromb Haemost.*, *89*, 601-609. **R, A**

Libby, P., Ridker, P. M., and Maseri, A. (2002) Inflammation and atherosclerosis. *Circulation.*, *105*, 1135-1143. **R**

Aleman, M. M., Walton, B. L., Byrnes, J. R., and Wolberg, A. S. (2014) Fibrinogen and red blood cells in venous thrombosis. *Thromb Res.*, *133*, S38-40. doi: 10.1016/j.thromres.2014.1003.1017. **R, A**

Cortes-Canteli, M., Zamolodchikov, D., Ahn, H. J., Strickland, S., and Norris, E. H. (2012) Fibrinogen and altered hemostasis in Alzheimer's disease. *J Alzheimers Dis*, *32*, 599-608. doi: 510.3233/JAD-2012-120820. **R, C**

Davalos, D., and Akassoglou, K. (2012) Fibrinogen as a key regulator of inflammation in disease. *Semin Immunopathol.*, *34*, 43-62. doi: 10.1007/s00281-00011-00290-00288. Epub 02011 Oct 00231. **R, C**

de Moerloose, P., Casini, A., and Neerman-Arbez, M. (2013) Congenital fibrinogen disorders: an update. *Semin Thromb Hemost.*, *39*, 585-595. doi: 510.1055/s-0033-1349222. Epub 1342013 Jul 1349212. **R**

Duvoix, A., Dickens, J., Haq, I., Mannino, D., Miller, B., Tal-Singer, R., and Lomas, D. A. (2013) Blood fibrinogen as a biomarker of chronic obstructive pulmonary disease. *Thorax.*, *68*, 670-676. doi: 610.1136/thoraxjnl-2012-201871. Epub 202012 Jun 201828. **R, B**

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Farrell, D. H. (2012) gamma' Fibrinogen as a novel marker of thrombotic disease. *Clin Chem Lab Med.*, *50*, 1903-1909. doi: 1910.1515/cclm-2012-0005. **R, A**

Fish, R. J., and Neerman-Arbez, M. (2012) Fibrinogen gene regulation. *Thromb Haemost.*, *108*, 419-426. doi: 410.1160/TH1112-1104-0273. Epub 2012 Jul 1126. **R**

Franchini, M., and Lippi, G. (2012) Fibrinogen replacement therapy: a critical review of the literature. *Blood Transfus.*, *10*, 23-27. doi: 10.2450/2011.0015-2411. Epub 2011 Nov 2415. **R**

Gu, L., Wu, G., Su, L., Yan, Y., Long, J., Tan, J., Liang, B., Guo, X., and Huang, G. (2014) Genetic polymorphism of beta-fibrinogen gene-455G/A can contribute to the risk of ischemic stroke. *Neurol Sci.*, *35*, 151-161. doi: 110.1007/s10072-10013-11608-10071. Epub 12013 Dec 10024. **R, A**

Iwaki, T. (2010) [Important role of fibrinogen beyond hemostasis]. *Rinsho Ketsueki.*, *51*, 612-619. **R, C**

Ou, N. J., and Tang, M. Z. (2014) [Research progress on hereditary fibrinogen abnormalities]. *Zhongguo Shi Yan Xue Ye Xue Za Zhi.*, *22*, 1188-1192. doi: 1110.7534/j.issn.1009-2137.2014.1104.1058. **R**

Saldanha, C. (2013) Fibrinogen interaction with the red blood cell membrane. *Clin Hemorheol Microcirc*, *53*, 39-44. doi: 10.3233/CH-2012-1574. **R**

Tousoulis, D., Papageorgiou, N., Androulakis, E., Briasoulis, A., Antoniades, C., and Stefanadis, C. (2011) Fibrinogen and cardiovascular disease: genetics and biomarkers. *Blood Rev.*, *25*, 239-245. doi: 210.1016/j.blre.2011.1005.1001. Epub 2011 Jun 1018. **R, A**

Lock-Johansson, S., Vestbo, J., and Sorensen, G. L. (2014) Surfactant protein D, Club cell protein 16, Pulmonary and activation-regulated chemokine, C-reactive protein, and Fibrinogen biomarker variation in chronic obstructive lung disease. *Respir Res.*, *15*, 147. doi: 110.1186/s12931-12014-10147-12935. **R, B**

Berg, K., and Kierulf, P. (1989) DNA polymorphisms at fibrinogen loci and plasma fibrinogen concentration. *Clinical genetics*, *36*, 229-235. **R**

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Schultz, D. R., and Arnold, P. I. (1990) Properties of four acute phase proteins: C-reactive protein, serum amyloid A protein, alpha 1-acid glycoprotein, and fibrinogen. *Seminars in arthritis and rheumatism*, *20*, 129-147. **R**

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7.10 Appendix 10 Excluded articles

Hatsukami, D. K., Kotlyar, M., Allen, S., Jensen, J., Li, S., Le, C., and Murphy, S. (2005) Effects of cigarette reduction on cardiovascular risk factors and subjective measures. *Chest.*, *128*, 2528-2537. **01**

Oksala, N. K., Heikkinen, M., Mikkelsson, J., Pohjasvaara, T., Kaste, M., Erkinjuntti, T., and Karhunen, P. J. (2007) Smoking and the platelet fibrinogen receptor glycoprotein IIb/IIIA PlA1/A2 polymorphism interact in the risk of lacunar stroke and midterm survival. *Stroke.*, *38*, 50-55. Epub 2006 Nov 2030. **01**

de Bree, A., Verschuren, W. M., Blom, H. J., and Kromhout, D. (2001) Lifestyle factors and plasma homocysteine concentrations in a general population sample. *American journal of epidemiology*, *154*, 150-154. **01**

Jacques, P. F., Bostom, A. G., Wilson, P. W., Rich, S., Rosenberg, I. H., and Selhub, J. (2001) Determinants of plasma total homocysteine concentration in the Framingham Offspring cohort. *The American journal of clinical nutrition*, *73*, 613-621. **01**

Aubron, C., Reade, M. C., Fraser, J. F., and Cooper, D. J. (2014) Efficacy and safety of fibrinogen concentrate in trauma patients--a systematic review. *J Crit Care.*, *29*, 471.e411-477. doi: 410.1016/j.jcrc.2013.1012.1011. Epub 2013 Dec 1030. **02**

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