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APPENDIX A6.1.4.10 APOLIPOPROTEIN A1(APO-A1) HEALTH EFFECTS OF SMOKING CESSATION

Short Term Health Effects

Apolipoprotein A1(Apo-A1)

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1. BACKGROUND

Apolipoprotein A1 (Apo-A1) is the major High Density Lipoprotein (HDL) apoprotein. It belongs to the group of reverse cholesterol transport proteins and has anti-atherogenic properties [1]. In addition, HDL and Apo-A1 exert innate protective effects in systemic inflammation [2] as well as anti-oxidative properties through its thiol groups [3].

Furthermore, redox proteomics showed Apo-A1 to be highly oxidatively modified and particularly susceptible to modification by 4-hydroxy-2-trans-nonenal (HNE) and malondialdehyde (MDA), which are lipid peroxidation products [4]. Site-specific oxidation of Apo-A1 impairs cholesterol export by ABCA1 (ATP-binding cassette transporter A1), a key cardioprotective function of HDL [5].

In the Apo-A1 amino acid sequence, tyrosine-192 is the predominant site of the myeloperoxidase (MPO)-mediated nitration and chlorination [6]. The latter modification leads to a significant impairment of the biological function or Apo-A1 and thus contributes to the development of inflammation and cardiovascular disease (CVD) [6, 7].

Lysine-226 of Apo-A1 is a target of acrolein resulting in the formation of Nε-(3-methylpyridinium) lysine, which is associated with a decrease of the normal reverse cholesterol transport of HDL [5]. Acrolein can also interfere with the Apo-A1-related anti-oxidative properties by reacting with the protein-bound thiol groups [3].

Recent evidence suggests that specific post-translational modifications of apoA-1 transform this genuine anti-inflammatory molecule into a proinflammatory one [8].

There is also emerging evidence that vitamin D plays an important role in the syntheses of Apo-A1 [9].

2. METHODS

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

(1) Monographs on biomarkers of effect and smoking:

- US Surgeon General Report 2010 [10]
- Life Sciences Research Office (LSRO) Report of 2007 [11]

(2) References extracted from the two monographs (Source 1) on Apo-A1

(3) Search 1 in the PubMed literature data base on 12.05.2015 for reviews on Apo-A1; search string: "(((apolipoprotein A-I[Title]) OR apolipoprotein A-1[Title]) OR apolipoprotein A1[Title]) OR apolipoprotein AI[Title] Filters: Review; published in the last 5 years"

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(4) Search 2 in the PubMed literature data base on 12.05.2015 for references on Apo-A1 and smoking; search string: "(((smoking[Title] OR smokers[Title] OR tobacco[Title] OR nicotine[Title] OR cigarettes[Title]))) AND ((((apolipoprotein A-I[Title]) OR apolipoprotein A-1[Title]) OR apolipoprotein A1[Title]) OR apolipoprotein AI[Title])"

(5) Search 3 in the PubMed literature data base on 12.05.2015 for references on Apo-A1 and CVD; search string: "(((((apolipoprotein A-I[Title]) OR apolipoprotein A-1[Title]) OR apolipoprotein A1[Title]) OR apolipoprotein AI[Title])) AND ((cardiovascular disease[Title] OR CVD[Title]))"

(6) Search 4 in the PubMed literature data base on 12.05.2015 for references on Apo-A1 and respiratory disease; search string: "(((((apolipoprotein A-I[Title]) OR apolipoprotein A-1[Title]) OR apolipoprotein A1[Title]) OR apolipoprotein AI[Title])) AND ((respiratory[Title] OR lung[Title] OR COPD[Title] OR emphysema[Title]))"

(7) Search 5 in the PubMed literature data base on 12.05.2015 for references on Apo-A1 and cancer; search string: "Search (((cancer[Title]))) AND ((((apolipoprotein A-I[Title]) OR apolipoprotein A-1[Title]) OR apolipoprotein A1[Title]) OR apolipoprotein AI[Title])"

(8) Relevant references extracted from articles retrieved from Sources 2 – 7 above

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 Apo-A1 and cardiovascular diseases (CVD) in a human cohort was investigated

B: Association between Apo-A1 and respiratory diseases in a human cohort was investigated

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C: Association between Apo-A1 and any other disease in a human cohort was investigated

D: Differences between in Apo-A1 levels between smokers and non-smokers were studied

E: The dose-response relationship between smoking intensity (determined for example by daily cigarette consumption, pack-year or cotinine) and Apo-A1 level was studied

F: The effect of smoking cessation on the Apo-A1 level was studied

G: The effect of switching from conventional cigarettes to modified risk tobacco products (MRTPs) or nicotine products on the Apo-A1 level was studied

R: Review article on Apo-A1

Reviews were used for generating Chapter 1 ('Background') and, if suitable, other parts of the text.

Studies not fulfilling any of the inclusion criteria A – G and R were excluded from the evaluation (assigned as '0' in Appendix 1).

3. FINDINGS

From Source 1 (Monographs) [10, 11], 16 articles [1, 3, 5, 6, 12-23] were extracted (all 16 originating from the Surgeon General Report 2010, the LSRO monograph did not mention Apo-A1).

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 criteria are compiled in Appendix 1.

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Table 1. Search results and distribution across the exclusion criteria.

Source (Description)	All	Relevant	Inclusion criteria[a]								Excluded
			A	B	C	D	E	F	G	R	
1 (Monographs)	2	2	2	0	0	2	2	2	0	2	0
2 (Articles extr. from 1)	16	12	2	0	0	10	2	1	0	2	4
3 (Search 1, reviews)	16	15	9	0	4	1	0	0	0	15	1
4 (Search 2, smoking)	9	9	0	0	0	9	1	3	0	0	0
5 (Search 3, CVD)	6	6	6	0	0	0	0	0	0	0	0
6 (Search 4, resp. dis.)	12	7	0	5	1	1	0	0	0	0	5
7 (Search 5, cancer other diseases)	11	8	0	0	8	0	0	0	0	0	3
8 (Cited articles)	8	6	0	0	0	6	2	1	0	0	2
Sum	80[b]	65	19	5	13	29	7	7	0	19	15

[a] Note that an article could fulfil several inclusion criteria

[b] Deviation from the 79 articles listed in Appendix 1 is caused by some overlap between the search results yielding identical articles

Of the 80 articles retrieved from the various sources, 65 appeared to be relevant to be considered for the generation of this document, 15 publications were of no or very limited relevance for this purpose. 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 Apo-A1 with other diseases was performed, since the category 'other diseases' was already represented in the other searches and, except for cancer, appears to be of minor importance. There were 43 articles which considered the relationship between Apo-A1 and smoking (D – G). The aspect of smoking cessation (F) was dealt with in 7 studies, whereas the dose-relationship between smoking and Apo-A1 levels was considered also in 5 articles. No articles were found dealing with the changes in Apo-A1 levels after switching to MRTPs or nicotine products (G).

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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

It is well established since about four decades that high-density lipoprotein (HDL), and thus also its protein component Apo-A1, are inversely associated with the risk of cardiovascular disease (CVD).This association is causal and primarily achieved by the Apo-A1 function of a reverse cholesterol transport protein [1].

Impairment of Apo-A1 functionality has been extensively studied. MPO-catalyzed nitration and chlorination [6, 24], reaction with acrolein and lipid peroxidation products such as malondialdehyde (MDA) and hydroxynonenal (HNE) [5, 25] as well oxidation of the thiol groups [3] have been reported to be key reactions in this process.

In most large epidemiological studies, HDL cholesterol was measured as a biomarker with good to excellent predicting power for the development of CVD [10, 11]. The determination of Apo-A1 can be regarded to be equivalent to HDL in terms of its suitability as a CVD risk biomarker. However, it has also been reported that serum Apo-A1 might be a better risk marker for CVD than other lipoproteins including HDL-C, at least for special populations [26].

More recently, it was proposed that the analysis of some Apo-A1 fractions might provide new disease-associated markers of cardiovascular disorder [27].

The role of Apo-A1 in preventing CVD is further underlined by recent findings that autoimmunity to this protein is associated with an increased risk to CVD and other diseases [28-30].

Furthermore, over the past few years, mimetics of Apo-A1 have been successfully used as therapeutics for CVD and other diseases, emphasizing the role of Apo-A1 as a protective protein against the development of CVD and other diseases in which inflammation and oxidative stress are involved [31-35].

4.2. Respiratory disease

The anti-inflammatory and anti–oxidative properties of Apo-A1 suggest that this protein can also have protective effects against lung injuries. Indeed, Apo-A1was found to be very effective against the development of experimental lung injury and fibrosis [36]. Similar findings with Apo-A1 mimetics were observed in rats [37] and mice [38]. Furthermore, it was observed that HDL and Apo-A1 exert innate protective effects in systemic inflammation including acute respiratory distress syndrome (ARDS), which was, for example, shown with Apo-A1 mimetics [2].

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On the other hand, in one study, Apo-A1 was found to be predictive of a significantly increased risk of developing an FEV1 (forced expired volume in 1 second) <LLN (lower limit of normal) [39].

4.3. Other diseases

As described above, the anti-inflammatory and anti-oxidative features of Apo-A1 make its involvement in other diseases more than likely. Using proteomic techniques decreased levels of Apo-A1 fragments were, for example, found in subjects with a variety of neurodegenerative disorders including Alzheimer's disease (AD), Parkinson's disease (PD), and Down's syndrome (DS) with gout subjects [4]. Data derived from recent studies suggest that Apo-A1 mimetics might also be used as a therapeutic intervention in the treatment of septicemia, transplantation rejection, diabetes and auto-immune diseases [31-35].

Furthermore, there is emerging evidence that Apo-A1 and mimetics, probably by their anti-oxidative and anti-inflammatory properties, are protective against varies types of cancer, including lung cancer [40, 41], ovarian cancer [42-45], breast cancer [46], and prostate cancer [47].

These observations suggest that decreased levels of Apo-A1 are to be expected to play a role in a number of diseases associated with oxidative stress and inflammatory processes. However, the predictive power of Apo-A1 levels for these diseases has not yet been systematically investigated.

5. SMOKING-BIOMARKER LINK

The inverse relationship between HDL and smoking has been extensively studied and can be regarded to be causal [10, 11]. Although much less investigated, the same can be assumed for the association between smoking and Apo-A1 levels. However, it was observed that a number of factors can lead to different changes in HDL and Apo-A1 [48].

There are a number of mechanisms by which smoking decreases the amount of functionally of intact Apo-A1 including:

- Nitration and chlorination of tyrosine-192 in Apo-A1 by MPO-mediated reactions. Smoking is known to promote this process.
- Reaction of lipid peroxidation products such as MDA, HNE and acrolein with lysine-226 of Apo-A1 [5, 24, 25]. Smoking is known to enhance lipid peroxidation. In addition, tobacco smoke contains appreciable amounts of acrolein.
- Oxidation and other chemical modifications of the thiol groups in Apo-A1 by reaction with acrolein and other smoke oxidants and toxicants [3].
- Inhibition of the APOA1 gene by the aryl hydrocarbon receptor (AhR) [49]. Smoking contains a number of AhR-binding compounds, for example benzo(a)pyrene. Nicotine, which does not bind to the AhR, had no effect on Apo-A1 synthesis [49].

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A single observation, not confirmed by other studies, is the finding that the tobacco-specific nitrosamine NNK (nicotine-derived nitrosamine ketone, also known as 4--1--1-butanone) can enhance the expression of Apo-A1 and Clara cell protein in the lung of rats after corn oil feeding [50]. The relevance of this finding is not yet clear and would require further research.

5.1. Smoking

In a comprehensive review and meta-analysis of serum lipid and lipoprotein concentrations in cigarette smokers, Craig et al. [14] investigated the influence of smoking on total cholesterol, triglycerides, HDL-C, LDL-C, VLDL-C, and Apo-A1 in blood of non-smokers and current smokers (categorized according to their daily cigarette consumption into 'light', 'moderate' and 'heavy' smokers). Altogether 54 studies were evaluated, most of them dealing with total cholesterol, triglycerides and HDL-C. There were 4 studies, which could be used for smoker (S) versus non-smoker (NS) differences in Apo-A1, 3 of them contained also information on the smoking dose. Average differences between S and NS were based on Z-scores and amounted to a 4.2 % decrease of Apo-A1 in smokers. Percent difference to NS for light and heavy smokers amounted to -3.7 and -5.7 %, respectively. Although small, these differences were statistically significant. Corresponding differences for the other lipids considered in this meta-analysis were in general larger.

In Table 2, available data for Apo-A1 of smokers, non-smokers and quitters are listed. Statistical significances for the difference in Apo-A1 levels between smokers and non-smokers are rather inconsistent (with about half of the comparison done being significant and the other half not). However, almost all studies show a trend for lower Apo-A1 levels in smokers.

Based on their results (Table 2), Kralova et al. [51] suggested that the impairment of the function of Apo-A1 as a reverse cholesterol transporter in smokers is probably due to a modification of this protein.

Additional information for the association between smoking and Apo-A1 levels came from some single observations. Mero et al. [19] reported that smokers exhibited significantly lower post-prandial levels of Apo-A1 compared to non-smokers. Saha et al. [52] found elevated Apo-A1 levels in non-smokers with a G to A substitution in the promotor region of the Apo-A1 gene compared to the wildtype, this difference was not observed in smokers.

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Table 2. Apo-A1 levels in smokers and non-smokers derived from various populations.

Author (reference)	Population	Smokers (S)	Non-smokers (NS)	p-Values and remarks
Berg et al. [53]	Healthy males (40 – 42 y old) from Northern Sweden	Apo-A1 in serum was determined by immunodiffusion, mean±SD[b], mg/dl: S (N=39): 109.4±17.4	Apo-A1 in serum was determined by immunodiffusion, mean±SD[b], mg/dl: NS (N=58): 124.3±30.4	S vs NS: p=0.007 Correlation between Apo-A1 and cig/d: r = 0.236 (p<0.05)
Dedonder-Decoopman et al. [54]	Healthy population (men and women from France	Apo-A1 in serum was analyzed immuno-nephelometry, , mean±SD[b], g/l: Males: S, <15 cig/d (N=45): 1.30±0.24 S, 15+ cig/d (N=50): 1.26±0.26 Females: S, <15 cig/d (N=29): 1.39±0.28 S, 15+ cig/d (N=11): 1.32±0.28	Apo-A1 in serum was analyzed immuno-nephelometry, , mean±SD[b], g/l: Males: NS (N=69): 1.39±0.26 Females: NS (N=226): 1.46±0.24	Males: S (15+ cig) vs NS: p<0.02 Other groups within one gender were not significantly different
Taylor et al. [55]	405 individuals randomly selected from the work force of a factory in the UK	Serum Apo-A1 was determined by immuno-diffusion, mean±SD[b], g/l: Males: S (N=113): 1.16±0.24 Females: S (N=116): 1.22±0.46	Serum Apo-A1 was determined by immuno-diffusion, mean±SD[b], g/l: Males: NS (N=68): 1.14±0.19 Females: NS (N=99): 1.25±0.29	S vs NS (males and females): Not significant

(table continues)

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Author (reference)	Population	Smokers (S)	Non-smokers (NS)	p-Values and remarks
Assmann et al. [56]	Company employees in Westphalia, Germany (4933 men, 2365 women)	Apo-A1 was analyzed by kinetic nephelometry, mean±SD[b], g/l: Males S (N=1592): 1.345±0.233 Females S (N=559): 1.425±0.256	Apo-A1 was analyzed by kinetic nephelometry, mean±SD[b], g/l: Males NS (N=1051): 1.370±0.216 Ex-S (N=866): 1.397±0.228 Females NS (N=960): 1.502±0.246 Ex-S (N=129): 1.494±0.217	Males: S vs NS: p<0.05 S vs Ex-S: p<0.001 Ex vs NS: Not sign. Females: S vs NS: p<0.001 S vs Ex-S: p<0.05 Ex vs NS: Not sign.
Haffner et al. [57]	2 % (randomly selected) of the Pacific Northwest Bell Telephone Company Health Survey (men and women, 38-64 y old)	Plasma Apo-A1 was analyzed by immuno-diffusion, , mean±SD[b], mg/dl: Males: S (N=11): 117.4±20.9 Females: S (N=3): 129.3±10.8	Plasma Apo-A1 was analyzed by immuno-diffusion, , mean±SD[b], mg/dl: Males: NS (N=22): 136.8±21.0 Females: S (N=14): 139.3±23.9	Males: S vs NS: p<0.02 Females: S vs NS: Not significant
Maeda et al. [48]	Healthy subjects (30 – 69 y, 349 men, 451 women) selected from the Nagoya (Japan) population	Apo-A1 determination by immunodiffusion, mean±SD[b], mg/dl: Male S (N=178): 141.9±18.0 Female S (N=30): 143.5±17.2	Apo-A1 determination by immunodiffusion, mean±SD[b], mg/dl: Male NS (N=70): 145.9±17.1 Female S (N=401): 147.8±18.5	S vs NS (males and females): Not significant No correlation with the number of cigarettes smoked was observed

(table continues)

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Author (reference)	Population	Smokers (S)	Non-smokers (NS)	p-Values and remarks
Masarei et al. [58]	Smokers (men and women, mean age 35-40 y) from a withdrawal program in Australia	Apo-A1 analyzed in serum by immunoturbimetry, mean±SEM[a], g/l: S, unsuccessful quitters (N=24): Baseline: 1.19±0.05 6 weeks later: 1.18±0.04	Apo-A1 analyzed in serum by immunoturbimetry, mean±SEM[a], g/l: S, successful quitters (all, N=26): Baseline: 1.20±0.03 6 weeks after quitting: 1.24±0.03 S, successful quitters, males (N=11): Baseline: 1.10±0.03 6 weeks after quitting: 1.19±0.04 S, successful quitters, females (N=11): Baseline: 1.28±0.04 6 weeks after quitting: 1.28±0.05	No significant difference between baseline and 6 weeks later (all subjects) Male quitters: p<0.05 Female quitters: Not significant
Takashima et al. [59]	Healthy male residents from two Japanese areas (40 – 49 y old, N=256)	No difference between S and NS observed. Also no difference between moderate (< 30 cig/d) and heavy S (30+ cig/d) was found.		S vs NS: Not significant

(table continues)

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Author (reference)	Population	Smokers (S)	Non-smokers (NS)	p-Values and remarks
Iscan et al. [18]	Smoking and non-smoking healthy mothers of full-term newborns in Turkey	Apo-A1 analyzed in serum by immunoturbimetry, mean±SD[b], mg/dl: S (N=38): 325±57	Apo-A1 analyzed in serum by immunoturbimetry, mean±SD[b], mg/dl: NS (N=42): 350±57	p<0.05
Kralova et al. [51]	Healthy, middle-aged women from Czechia	Serum Apo-A1 was measured by an immuno-turbidimetric assay, mean±SD[b], g/l: S (N=18): 1.59±0.29	Serum Apo-A1 was measured by an immuno-turbidimetric assay, mean±SD[b], g/l: NS (N=21): 1.71±0.27	S vs NS: Not significant The association between the cholesterol efflux (an indicator for the reverse cholesterol transport) and Apo-A1 is significantly lower in S compared to NS

[a] SEM: Standard error of the mean; [b] SD: Standard deviation

Studies on a dose-response relationship between smoking and Apo-A1 levels convey a similar picture to the studies on differences between smokers and non-smokers: There is a trend of decreasing Apo-A1 concentrations with increasing smoking dose although differences between various dose groups rarely reach statistical significance.

Berg et al. [53] (Table 2) reported a significant (inverse) correlation between Apo-A1 levels and the number of cigarettes smoked per day ($r=0.236$, $p<0.05$). Thus, about 6 % of the variability in the Apo-A1 levels could be explained by smoking.

Assmann et al. [56] (Table 2) reported decreasing Apo-A1 levels from non-smokers to smokers of 1 – 20 cigarettes/d to smokers of > 20cigarettes/d, for both men and women. The difference was significant between non-smokers and smokers of 1 – 20 cigarettes/d, for both men and women ($p<0.001$). The difference between non-smokers and smokers of > 20 cigarettes/d was significant only for males ($p<0.05$). No significant difference was observed between the low and high cigarette consumption groups.

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Dedonder-Decoopman et al. [54] found a decreasing trend for Apo-A1 with increasing amount of smoking (Table 2). Group differences, however, did not reach statistical significance.

Craig et al. [14] reported a significant dose response effect among non-smokers, light, and heavy smokers for Apo-A1 (0, -3.7 and -5.7% in non-smokers and light and heavy smokers, respectively).

Takashima et al. [59] (Table 2) found no difference in the Apo-A1 levels between moderate (< 30 cig/d) and heavy S (30+ cig/d).

Maeda et al. [48] (Table 2) observed no correlation between Apo-A1 levels and number of cigarettes smoked.

Hatsukami et al. [17] performed a smoking reduction study over 12 weeks in which they monitored a series of biomarkers of biological effect, including Apo-A1. In total, 65 of 151 smokers finished the study thereby decreasing their daily cigarette consumption from, on average of 24.2 (baseline) to 6.9 cigarettes/d (after12 weeks). Apo-A1 concentrations at baseline, weeks 4, 6 and 12 were 142.8, 141.7, 146.9 and 147.6 mg/dl, respectively, indicating a trend, but no significant increase in Apo-A1 levels upon smoking dose reduction.

Iwaoka et al. [60] reported that substantial reduction of the daily cigarette consumption by more than 50 % over 12 weeks did not significantly increase the Apo-A1 levels in smokers (145.9±33.4 versus 146.8±34.2 mg/dl, $p = 0.87$).

5.2. Smoking cessation

In three studies [58, 60, 61], smoking cessation was found to increase Apo-A1 concentrations within 2 – 6 weeks:

Stubbe et al. [61] reported a significant ($p<0.01$) increase in Apo-A1 two weeks after stopping smoking with the level remaining stable for the rest of the study (6 weeks total duration). Effects of quitting smoking were found to be more pronounced with HDL.

Masarei et al. [58] (Table 2) reported a significant increase in Apo-A1 6 weeks after quitting in males and but no difference in female quitters.

Iwaoka et al. [60] reported that successful smoking cessation following varenicline (7,8,9,10-Tetrahydro-6,10-methano-6H-pyrazino[2,3-h] [3]benzazepine) treatment increased the serum Apo-A1 level from 151.7±28.0 at baseline to 158.6±27.3 mg/dl after 12 weeks ($p<0.01$), whereas the Apo-A1 levels in the failure group (which reduced their cigarette consumption by more than 50 %) were 145.9±33.4 and 146.8±34.2 mg/dl, respectively ($p = 0.87$).

Long-term quitters (ex-smokers) achieve Apo-A1 concentrations of non-smokers, as reported by Assmann et al. [56] (Table 2), who found no significant difference in the serum Apo-A1 levels between non-smokers and ex-smokers for both men and women.

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5.3. Role in MRTP assessment

No published data are available for Apo-A1 levels of smokers who switched to MRTPs or other nicotine products.

6. CONCLUSION

Taken together, the evidence available for the link between smoking and Apo-A1 levels is consistent in terms of the observed (and also expected) trends: Smokers have lower levels than non-smokers, there is an inverse relationship with the smoking dose and smoking leads to an increase of the Apo-A1 level, achieving almost those of non-smokers. However, differences between groups and subgroups frequently do not reach statistical significance. HDL (of which Apo-A1 is a component), in general, shows similar, but more pronounced changes. Therefore, there is no obvious advantage for measuring Apo-A1 instead of HDL as a biomarker of effect in studies where smokers switch to MRTPs or other nicotine products.

The role of Apo-A1 in the development of diseases such as CVD, respiratory diseases and various types of cancer is well established. This is mainly due to its functionality as an endogenous, blood-bound molecule with reverse cholesterol transport, anti-oxidative and anti-inflammatory properties. Data on differences between smokers and non-smokers, dose-response relationships and smoking cessation suggest that the inverse association of the serum or plasma Apo-A1 levels with smoking is causal, but weak, thus frequently missing statistical significance. No data are available for Apo-A1 levels in smokers who switched to MRTPs or nicotine products.

Since the links between HDL and smoking are similar to that of Apo-A1 and smoking, but in general more pronounced and therefore more consistent in terms of statistical significance, HDL is rightly preferred as a biomarker of effect in epidemiological studies.

For future applications of Apo-A1 as a biomarker of effect, it should be considered that measurement of the modification and/or functionality of the protein be made instead of its mere concentration. In this document, several leverage points for this approach are mentioned.

Taken together, the information available does not justify to use Apo-A1 instead of HDL as a biomarker of effect for the assessment of MRTPs.

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Table 3. Strength of evidence for the suitability of Apo-A1 as a biomarker of effect for MRTP assessment.

Property	Evidence
Biological plausibility	Due to its biological properties, Apo-A1 can be regarded as a proven biomarker of risk for the development of CVD, respiratory diseases and various types of cancer.
Dose-response	Differences between smokers and non-smokers (zero dose) were reported for various groups of healthy subjects in several studies (Section 5.1, Table 2). However, findings were not consistent in terms of the statistical significance and groups were in part very small. There is consistent evidence that Apo-A1 tends to decrease with the smoking dose, results, however, are frequently not statistically significant.
Benchmark to cessation	There is some limited evidence that quitting smoking for weeks leads to a reduction in Apo-A1 levels which achieve almost non-smoker levels. Ex-smokers have been shown to exhibit similar A Apo-A1 levels as non-smokers.
Consistency[a]	Available data for Apo-A1 and smoking are limited but fairly consistent trends in terms of differences between smokers and non-smokers, dose-response and smoking cessation.
Coherence[b]	Epidemiological, animal and *in vitro* data proving the role of Apo-A1 as a risk factor for CVD, lung diseases and cancer are coherent. The available evidence for tobacco smoke as a modifier of Apo-A1 has been investigated with various approaches (human, animal, *in vitro*) to a limited extent. The available results are mostly coherent and suggest a decrease of amount of intact Apo-A1 in smokers.

[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 related to the included studies
7.2 Appendix 2 Included criteria A
7.3 Appendix 3 Included criteria B
7.4 Appendix 4 Included criteria C
7.5 Appendix 5 Included criteria D
7.6 Appendix 6 Included criteria E
7.7 Appendix 7 Included criteria F
7.8 Appendix 8 Included criteria G
7.9 Appendix 9 Review articles
7.10 Appendix 10 Excluded articles

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7.1. Appendix 1 References of included 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 The biomarker of interest is not considered in sufficient detail

02 Article deals with the biomarker of interest but does not contribute to any of the Chapters 1, 4 or 5

03 Articles deals with the biomarker of interest and a disease which is not relevant for healthy, adult smokers

04 Experimental study (with animals or in vitro) not directly relevant for smoking

05 Article deals with the biomarker of interest and a smoking-related disease, but smoking is only considered as confounding factor.

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

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

Source 2: Articles derived from monographs: 16 References [3-18]

Source 3: Articles from PubMed Search 1 (Reviews on APOA1): 16 References [19-34]

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Source 4: Articles derived from PubMed Search 2 (smoking-related studies on APOA1: 9 References [35-43]

Source 5: Articles derived from PubMed Search 3 (association between APOA1 and cardiovascular diseases): 6 References [44-49]

Source 6: Articles derived from PubMed Search 4 (association between APOA1 and respiratory diseases): 12 Reference [50-61]

Source 7: Articles derived from PubMed Search 4 (association between APOA1 and cancer): 11 References [51, 62-71]

Source 8: Articles derived from citations in publications from Sources 2 - 7: 8 References [72-79]

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7.2. Appendix 2 Inclusion criteria A

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7.3. Appendix 3 Inclusion criteria B

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7.4. Appendix 4 Inclusion criteria C

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

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7.5. Appendix 5 Inclusion criteria D

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

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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. **A, C, D, 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. **A, C, D, E, F, R**

Craig, W. Y., Palomaki, G. E., and Haddow, J. E. (1989) Cigarette smoking and serum lipid and lipoprotein concentrations: an analysis of published data. *BMJ.*, *298*, 784-788. **D, E**

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Iwaoka, M., Shimamura, H., Tsuji, T., and Kugiyama, K. (2014) Twelve weeks of smoking cessation therapy with varenicline increases the serum levels of apolipoprotein A-I only in the success group. *J Cardiol.*, *64*, 318-323. doi: 310.1016/j.jjcc.2014.1002.1009. Epub 2014 Mar 1024. **D, E, F**

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Dedonder-Decoopman, E., Fievet-Desreumaux, C., Campos, E., Moulin, S., Dewailly, P., Sezille, G., and Jaillard, J. (1980) Plasma levels of VLDL- + LDL-cholesterol, HDL-cholesterol, triglycerides and apoproteins B and A-I in a healthy population--influence of several risk factors. *Atherosclerosis.*, *37*, 559-568. **D, E**

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7.7. Appendix 7 Inclusion criteria F

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

Neese, R. A., Benowitz, N. L., Hoh, R., Faix, D., LaBua, A., Pun, K., and Hellerstein, M. K. (1994) Metabolic interactions between surplus dietary energy intake and cigarette smoking or its cessation. *Am J Physiol.*, *267*, E1023-1034. **D, F**

Assmann, G., Schulte, H., and Schriewer, H. (1984) The effects of cigarette smoking on serum levels of HDL cholesterol and HDL apolipoprotein A-I. Findings of a prospective epidemiological study on employees of several companies in Westphalia, West Germany. J Clin Chem Clin Biochem., 22, 397-402. **D, F**

Iwaoka, M., Shimamura, H., Tsuji, T., and Kugiyama, K. (2014) Twelve weeks of smoking cessation therapy with varenicline increases the serum levels of apolipoprotein A-I only in the success group. *J Cardiol.*, *64*, 318-323. doi: 310.1016/j.jjcc.2014.1002.1009. Epub 2014 Mar 1024. **D, E, F**

Masarei, J. R., Puddey, I. B., Vandongen, R., Beilin, L. J., and Lynch, W. J. (1991) Effect of smoking cessation on serum apolipoprotein A-I and A-II concentrations. *Pathology.*, *23*, 98-102. **D, F**

Stubbe, I., Eskilsson, J., and Nilsson-Ehle, P. (1982) High-density lipoprotein concentrations increase after stopping smoking. *Br Med J (Clin Res Ed). 284*, 1511-1513. **D, F**

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7.8. Appendix 8 Inclusion criteria G

No articles were identified with relevance to this inclusion criteria.

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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. **A, C, D, 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

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Tall, A. R. (1998) An overview of reverse cholesterol transport. *Eur Heart J.*, *19*, A31-35. **R**

Bashtovyy, D., Jones, M. K., Anantharamaiah, G. M., and Segrest, J. P. (2011) Sequence conservation of apolipoprotein A-I affords novel insights into HDL structure-function. J Lipid Res., 52, 435-450. doi: 410.1194/jlr.R012658. Epub 012010 Dec 012614. **R**

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7.10. Appendix 10 Excluded articles

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