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APPENDIX A6.1.4.9 LDL-C (LOW DENSITY LIPOPROTEIN CHOLESTEROL)

HEALTH EFFECTS OF SMOKING CESSATION

LDL-C (Low density lipoprotein cholesterol)

Dr. Gerhard Scherer

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1 BACKGROUND

Low density lipoprotein (LDL) belongs to the plasma lipoproteins which are classified according to their density. LDL particles have a density of 1.019 – 1.063 g/ml, a particle size of 18 – 28 nm and an average cholesterol content of 50 %. Other plasma lipoproteins are high density lipoprotein (HDL, >1.063 g/ml, 5 – 15 nm, 30 % cholesterol), intermediate density lipoprotein (IDL, 1.006 – 1.063 g/ml, 25 – 50 nm, 29 %), very low density lipoprotein (VLDL, 0.95 – 1.006 g/ml, 30 – 80 nm, 22 % cholesterol) and chylomicrons (<0.95 g/ml, 100 – 1000 nm, 8 % cholesterol). LDL is, therefore, the major carrier of cholesterol between organs and cells. LDL receptor proteins (LDLR) have been identified on various cell types [1]. The apoprotein of LDL is apoprotein B. LDL cholesterol (LDL-C) is atherogenic and a well-established risk factor for coronary vascular diseases (CVD) and a therapeutic biomarker for monitoring the statin treatment success in patients [2, 3]. LDL-C is, therefore, also termed the 'bad cholesterol'. HDL-C (the 'good cholesterol') is inversely correlated with CVD.

LDL-C in fasted blood samples is frequently indirectly determined by using the Friedewald formula:

LDL-C = Total C minus HDL-C minus triglycerides (TG)/5

In the majority of healthy subjects and patients, this approach for LDL-C determination is sufficient [4, 5]. In samples from not fasting subjects, LDL-C determination by direct assays is necessary [4, 6, 7]. As a target value, the LDL-C level should not exceed 70 mg/dL [8]. It has been found that dietary supplements such as plant sterols, isoflavones, panthetine or mediterranean diet can lower LDL-C levels [9-13].

Various genetic polymorphisms have been identified, which directly influence LDL-C levels [14, 15]. More recent research has shown that measurement of LDL particles (LDL-P) either by apoprotein B-specific assays or a nuclear magnetic resonance (NMR) methodology is a better predictor of cardiovascular risk than the classic measurement of the LDL-C concentration [16-18].

A number of recent studies have shown that non-HDL cholesterol (non-HDL-C) might be a better risk marker for CVD than LDL-C [19-28]. Non-HDL-C is defined as total C minus HDL-C and mainly consists of LDL-C + VLDL-C.

Furthermore, some studies have shown that small and dense LDL-C particles (sdLDL-C) might be more strongly associated with CVD than the LDL-C values [17, 19, 29-33].

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 [34]
- Life Sciences Research Office (LSRO) Report of 2007 [35]

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(2) References extracted from the two Monographs (Source 1) on LDL-C: 17 Articles

(3) Search 1 in the PubMed literature data base on 24.04.2015 for reviews on LDL-C; search string: "((low density lipoprotein[Title] AND cholesterol[Title])) OR (LDL[Title] AND cholesterol[Title]) Filters: Review; published in the last 5 years; Humans"

(4) Search 2 in the PubMed literature data base on 24.04.2015 for references on LDL-C and smoking; search string: "Search ((((low density lipoprotein[Title] AND cholesterol[Title])) OR (LDL[Title] AND cholesterol[Title]))) AND (smoking[Title] OR smokers[Title] OR tobacco[Title] OR nicotine[Title] OR cigarettes[Title])"

(5) Search 3 in the PubMed literature data base on 24.04.2015 for references on LDL-C and CVD; search string: "((((low density lipoprotein[Title] AND cholesterol[Title])) OR (LDL[Title] AND cholesterol[Title]))) AND (cardiovascular[Title] OR coronary heart[Title])" Filters: published in the last 5 years

(6) Search 4 in the PubMed literature data base on 24.04.2015 for references on LDL-C and respiratory disease; search string: "((((low density lipoprotein[Title] AND cholesterol[Title])) OR (LDL[Title] AND cholesterol[Title]))) AND (respiratory disease[Title/Abstract] OR lung disease[Title/Abstract])"

(7) Search 5 in the PubMed literature data base on 24.04.2015 for references on LDL-C and cancer ; search string: "((((low density lipoprotein[Title] AND cholesterol[Title])) OR (LDL[Title] AND cholesterol[Title]))) AND cancer[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 LDL-C and CVD in a human cohort was investigated
B:	Association between LDL-C and respiratory diseases in a human cohort was investigated
C:	Association between LDL-C and any other disease in a human cohort was investigated
D:	Differences between in LDL-C levels between smokers and non-smokers were studied

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E:	The dose-response relationship between smoking intensity (determined for example by daily cigarette consumption, pack-year or cotinine) and LDL-C level was studied
F:	The effect of smoking cessation on the LDL-C level was studied
G:	The effect of switching from conventional cigarettes to a modified risk tobacco product (MRTP) or a nicotine products on the LDL-C level was studied
R:	Review article on LDL-C

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 0x, x (reason for exclusion) = 1 to 5).

01	No usable data or information on LDL-C were presented
02	Clinical study with patients, focus on diagnosis, therapy and prognosis
03	Population investigated is not relevant for the purpose of this document
	(e.g. children, pregnant women, ill persons)
04	The topic investigated is not relevant for smoking or a smoking-related disease
05	Animal or in vitro studies with no obvious relation to humans

3 FINDINGS

From Source 1 (Monographs [34, 35]), 17 articles [17, 18, 31, 36-49] were extracted (12 originating from the Surgeon General Report 2010, 6 extracted from the LSRO monograph, 1 relevant article [39] was cited in both monographs).

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. Number of articles according to source and inclusion 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)	17	16	3	0	0	10	5	3	0	2	1
3 (Search 1, reviews)	63	22	9	0	2	0	0	0	0	22	41
4 (Search 2, smoking)	11	11	4	0	1	11	3	0	3	0	0
5 (Search 3, CVD)	83	50	50	0	3	0	0	0	0	0	33
6 (Search 4, resp. dis.)	1	0	0	0	0	0	0	0	0	0	1
7 (Search 5, cancer)	21	17	0	0	17	0	1	0	0	0	4
8 (Cited articles)	5	2	0	0	0	1	1	1	1	0	3
Sum	203[b]	120	68	0	23	24	12	6	4	26	83

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

[b] Deviation from the 197 articles listed in Appendix 1 is caused by some overlap between the search results yielding identical articles

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Of the 197 articles retrieved from the various sources, 120 appeared to be relevant to be considered for the generation of this document, 83 publications were of no or very limited relevance for this purpose. Most articles retrieved dealt 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 LDL-C with other diseases was performed, since the category 'other diseases' was already well represented in the other searches. There were 46 articles which considered the relationship between LDL-C and smoking (D – G). The aspect of smoking cessation (F) was dealt with in 6 studies, whereas the dose-relationship between smoking and LDL-C levels was considered in 6 articles. No relevant studies were found which looked at the association between LDL-C and respiratory diseases (B). Changes in LDL-C levels after switching to nicotine products or MRTPs (G) were described in 4 studies.

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 to 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

The association between LDL-C and CVD, in particular atherosclerotic CVD, was consistently found in numerous studies, including large prospective epidemiological studies indicating that the relationship might be regarded to be causal [2, 7, 50-52].

Genetic polymorphisms of LDL-C are assumed to play a significant role in coronary heart disease (CHD) and CVD [14, 53]. Particle diameter and density of LDL has been found to be of importance for CVD risk [17, 30, 32, 33].

In some studies, non-HDL-C instead of LDL-C was found to be a superior risk marker for CVD [20, 22, 23].

Lowering the LDL-C concentrations in hyperchlosterolemic patients as well as in healthy subjects, for example by statin treatment, was found to be beneficial in all, including low LDL-C levels [8, 54]. Exposure to lower LDL-C beginning early in life is associated with a substantially greater reduction in the risk of CHD and CVD than the current practice of lowering LDL-C beginning later in life [50].

These properties would qualify LDL-C as a suitable early biomarker of effect for CVD, if the third factor of interest (smoking) is independently and causally linked to LDL-C. The available evidence for this link is summarized later.

4.2 Respiratory diseases

A search for the association between LDL-C and respiratory diseases (Source 6, Search 4) revealed no relevant publications.

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4.3 Other diseases

In numerous studies, an inverse association between LDL-C and all types of cancer was observed [55-59]. It is highly likely that this correlation is not causal, but probably a consequence of the tumor. One possible reason might be the fact that tumor cells express more LDLRs than normal cells in order to take up more cholesterol required for tumor growth (used for construction of cell membranes) [60, 61]. On the other hand, genetic polymorphisms which are related with life-long lowered LDL-C levels or statin treatment for lowering LDL-C are not associated with a higher cancer risk [58, 59, 62-64]. This provides further evidence for a non-causal relationship between low LDL-C and elevated cancer risk.

In one study [65], no statistically significant differences of LDL-C concentrations between lung cancer patients and controls, and between the clinical stages of small cell lung cancer was observed. In another study with hypercholesterolemic mice [66], mechanistic evidence was provided that high LDL-C levels promote breast cancer progression.

Taken together, no evidence exists that LDL-C could be used as biomarker of effect, which predicts a future risk for other diseases and for any particular type of cancer.

5 SMOKING-BIOMARKER LINK

There is ample evidence in the literature that smoking is strongly associated with CVD [34, 40, 44]. The US Surgeon General [34] has estimated that smoking increases the risk for CVD by about 70 %. There are several mechanisms and pathways by which the exposure to tobacco smoke is assumed to be involved in the generation of detrimental effects on the cardiovascular system, these include altered blood coagulation, lesions of the arterial wall and changes in blood lipid and lipoprotein concentrations [34, 67]. Furthermore, smoking increases the formation of oxidized LDL (ox-LDL), which is known to have a high atherogenic potency [68].

A possible mechanism by which smoking might increase LDL-C concentrations in blood is the well-established observation from many studies that smoking increases the level of free fatty acids (FFA) in blood, which in turn stimulates the hepatic synthesis and excretion of cholesterol.

Czerwinski et al. [69] found that smoking may alter the expression of genes influencing the LDL particle diameter, which is supposed to increase the atherogenic potency of LDL-C.

A general important confounding factor to be considered when investigating the association between smoking and LDL-C is the known difference in dietary habits between smokers and non-smokers. However, adjustment for these factors as well as observed dose-response relationships (see Section 5.1), decrease to almost non-smoker levels after quitting (see Section 5.2) and evidence form animal experiments [38] suggest that a causal relationship between smoking and increase in LDL-C is likely to exists [48, 67].

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In a comprehensive review and meta-analysis of serum lipid and lipoprotein concentrations in cigarette smokers, Craig et al. [67] investigated the influence of smoking on total cholesterol, triglycerides, HDL-C, LDL-C, VLDL-C, and apoprotein 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 6 studies, which could be used for smoker (S) *versus* non-smoker (NS) differences in LDL-C, 4 studies also contained information on the smoking dose. Average differences between S and NS were based on Z-scores and amounted to a 1.7% increase in LDL-C in smokers. Percent difference to NS for light, moderate and heavy smokers amounted to – 1.1, 1.4 and 11.0%, respectively. Although very small, these differences were statistically significant. Corresponding differences for the other lipids considered in this meta-analysis were in general larger.

Wilson et al. [47] found positive but very weak associations between smoking and LDL-C in men and women of the Framingham Study. The associations appear to be somewhat stronger in younger people. Table 2 summarizes the results for LDL-C levels in smokers, non-smokers and ex-smokers reported in some additional, more recent studies. A remarkable result from an older study was also included [68], showing that smoking in combination with coffee drinking led to the highest increase in LDL-C, whereas the effects of each factor alone were not significant.

In 4 of the 5 other studies, significantly higher LDL-C concentrations in smokers compared to non-smokers were found. It is notable that in the by far largest study of this compilation (the Atherosclerosis Risk in Communities (ARIC) Study) [69], levels in current, former and never smokers were not significantly different. Relative differences in LDL-C levels between smokers and non-smokers are in the range of 5 – 15% with one study [70] showing S/NS differences of 40% and thus larger than the relative increase in smokers of 1.7 % found in the meta-analysis of Craig et al. [67].

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Table 2. LDL-C levels in smokers and non-smokers derived from various populations.

Author (reference)	Population	Smokers (S)	Non-smokers (NS)	p-Values and remarks
Heyden et al. [68]	Evans county, USA subjects (healthy, biracial)	Means, mg/dL Non-coffee drinkers: S (N=61): 136 Coffee-drinkers: S (N=14): 158	Means, mg/dL Non-coffee drinkers: NS (N=69): 139 Coffee-drinkers: NS (N=31): 135	P for overall interaction: 0.003
Freeman et al. [71]	Healthy volunteers from Glasgow, UK, males and females, age: ~ 40 years	Mean±SD, mmol/L S (N=66): 3.68±0.97	Mean±SD, mmol/L Ex-S (N=41): 3.78±0.97 NS (N=90): 3.34±0.94	S vs NS: P<0.05 Ex-S vs NS: P<0.05
Vincelj et al. [72]	Patients with AMI[a] (N=190, aged 34-87y), healthy controls (N=103, aged 29-90y) from Croatia	Means from a graph, mmol/L Controls S (<10 cig/d): 3.0 S (10-20 cig/d): 3.0 S (>20 cig/d): 3.5 AMI patients S (<10 cig/d): 4.1	Means from a graph, mmol/L Controls Never S: 3.0 AMI patients Never S: 4.1	S (>20 cig/d) vs Never S: P<0.05

(table continues)

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Author (reference)	Population	Smokers (S)	Non-smokers (NS)	p-Values and remarks
		S (10-20 cig/d): 4.1 S (>20 cig/d): 4.4		
Schuitemaker et al. [73]	Healthy adults from a Dutch village, 26-66 y old	Mean±SD, mmol/L S (N=178): 5.00±0.89	Mean±SD, mmol/L NS (N=290): 4.74±0.80	p<0.001 (for all and for males, females: not significant)
Hozawa et al. [69]	ARIC Study (general population from 4 US communities)	Mean, mg/dL Current S (N=3392): 138.1	Mean, mg/dL Former S (N=4257): 136.9 Never S (N=5761): 136.4	P=0.11 (ANOVA[b])
Calapai et al. [74]	Healthy smoker (10 years of smoking) and non-smokers from Italy	Geometric mean (95% CI), mmol/L Moderate S (N=20): 2.82 (2.52-3.14) S (N=20): 3.05 (2.70-3.46)	Geometric mean (95% CI), mmol/L Never S (N=20): 2.91 (2.62-3.24)	No significant difference between moderate S or S and never S

(table continues)

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Author (reference)	Population	Smokers (S)	Non-smokers (NS)	p-Values and remarks
Frost-Pineda et al. [75]	Healthy US adults (21 years or older)	Mean±SD, median (range), mg/dL S (N=3404): 115±36.3, 112 (0.00-297)	Mean±SD, median (range), mg/dL NS (N=1025): 113±34.1, 109 (20.0-317)	P<0.05
Ebesunun et al. [70]	Healthy males from Nigeria, mean age ~40 y	Mean±SE, mg/dL S (N=80): 143.7±2.8 S (N=35, <13y smoking): 132.7±1.8 S (N=49, 14-22y smoking): 137.2±2.8	Mean±SE, mg/dL NS (N=80): 102.6±2.8	S vs NS: P<0.001 S (<13y) vs S (14-22y): P<0.001

[a] AMI: Acute myocardial infarction; [b] ANOVA: Analysis of variance

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5.1 Smoking

Eliasson et al. [39] conducted a smoking reduction study with 33 smokers, who were allowed to use nicotine nasal spray *ad libitum* during the course of the study. At week 9, the cigarette consumption was halved from about 20 to 10 cigarettes per day. At week 17, all smokers had quit smoking. LDL-C concentrations (mmol/l) were found to be 3.78 (baseline), 3.72 (week 9, not significant) and 3.52 (week 17, $p = 0.015$), indicating a dose-response relationship between smoking and LDL-C levels.

Hatsukami et al. [36] performed a smoking reduction study over 12 weeks in which they monitored a series of biomarkers of biological effect, including LDL-C. In total, 65 of 151 smokers finished the study thereby decreasing their daily cigarette consumption from, on average, 24.2 (baseline) to 6.9 cigarettes/d (after 12 weeks). LDL-C concentrations at baseline, weeks 4, 6 and 12 were 122.1, 122.3, 125.8 and 124.4 mg/dl, respectively, indicating no significant decline in LDL-C levels upon smoking dose reduction.

The study of Vincelji et al. [72] (Table 2) and two older studies [48, 49] provide evidence that LDL-C is positively associated with the number of cigarettes smoked per day.

The results reported by Ebesunun et al. [70] (Table 2) suggest that LDL-C might also increase with years of smoking. However, it has to be established that this is not caused by an age-effect.

5.2 Smoking cessation

The studies by Freeman et al. [71] and Hozawa et al. [69] listed in Table 2 found similar LDL-C levels in current and former smokers. Results reported by Hatsukami et al. [36] (see Section 5.2) also provide no evidence that quitting smoking would reduce the LDL-C concentrations to that of non-smokers. In contrast to this, Ludviksdottir et al. [42] reported that stopping smoking resulted in lower LDL-C levels, which decreased from 4.00 (baseline) to 3.54 mmol/L after 3 months. Allen et al. [45] observed that abstinent patients showed a positive effect of smoking cessation on cardiovascular risk factors including LDL-C.

In the study of Ludviksdottir et al. [42], nicotine treatment (provided via a nicotine nasal spray) for as long as 3 months had no significant effects on the LDL-C level when compared to a placebo group which stopped smoking without a pharmaceutical aid. A similar observation was made by Allen et al. [45].

The study by Eliasson et al. [39], in which subjects used nicotine nasal spray as a quitting aid also provides evidence that pure nicotine does not negatively influence the blood LDL-C level.

Roethig et al. [76] investigated the changes of some biomarkers of harm including LDL-C after switching from conventional cigarettes (CCs) to an electrically heated cigarette smoking system (EHCSS). Twelve months after switching, LDL-C decreased by 2 mg/dl in the EHC group, whereas it increased by 4 mg/dl in the CC group. Differences from baseline were not statistically significant, but showed a trend in the expected direction.

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6 CONCLUSION

6.1 Role in MRTP assessment

The role of LDL-C as a risk marker for CVD and clinical biomarker for diagnosis, prognosis and therapeutic control (statin treatment) for this disease group is well established. There is some evidence that smoking leads to a dose-dependent increase in LDL-C. No clear evidence exists that smoking cessation for weeks, months or years (former smokers) leads to a reduction in LDL-C concentrations achieving levels of never smokers.

Despite the somewhat inconsistent findings, there is largely agreement in the scientific community that the association between smoking and LDL-C is causal. Switching to nicotine nasal spray (as a nicotine replacement therapy in quitting) does not show detrimental nicotine effects on LDL-C levels.

The strength of the evidence for the suitability of LDL-C as a biomarker of effect is summarized in Table 3.

Taken together, the information available does not provide strong evidence for the suitability of LDL-C as a biomarker of effect for the assessment of MRTPs.

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

Property	Evidence
Biological plausibility	LDL-C is a biomarker of risk for the development of CVD. LDL-C is directly involved in the atherosclerotic process ('bad cholesterol').
Dose-response	Differences between smokers and non-smokers (zero dose) were reported for CVD patients and healthy subjects in several studies (Section 5.1, Table 2). Reported relative increases in smokers compared to non-smokers are somewhat inconsistent and range from 1 to 40 %. There is some inconsistent evidence that LDL-C increases with the smoking dose as determined by daily cigarette consumption.
Benchmark to cessation	There is as well some inconsistent evidence that quitting smoking for years, months or years (former smokers) leads to a reduction in LDL-C levels which achieve almost non-smoker levels.
Consistency[a]	Available data for LDL-C and smoking are fairly inconsistent, particularly in terms of dose-response and smoking cessation.
Coherence[b]	Epidemiological, animal and *in vitro* data on the role of LDL-C as a risk factor for CVD are coherent. The available evidence for tobacco smoke as an elevator of LDL-C has been investigated with various approaches only to a limited extent. The available results, however, are mostly coherent.

[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 Complete list of retrieved studies
7.2 Appendix 2 Inclusion criteria A
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7.1 Appendix 1 References of included studies

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7.3 Appendix 3 Inclusion criteria B

No articles were identified with relevance to this inclusion criteria.

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7.6 Appendix 6 Inclusion criteria E

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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

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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, D, E, R**

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Martin, S. S., Blumenthal, R. S., and Miller, M. (2012) LDL cholesterol: the lower the better. *Med Clin North Am.*, *96*, 13-26. doi: 10.1016/j.mcna.2012.1001.1009. **R, A**

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Ference, B. A., Yoo, W., Alesh, I., Mahajan, N., Mirowska, K. K., Mewada, A., Kahn, J., Afonso, L., Williams, K. A., Sr., and Flack, J. M. (2012) Effect of long-term exposure to lower low-density lipoprotein cholesterol beginning early in life on the risk of coronary heart disease: a Mendelian randomization analysis. *J Am Coll Cardiol.*, *60*, 2631-2639. doi: 2610.1016/j.jacc.2012.2609.2017. Epub 2012 Oct 2617. **R, A**

Contois, J. H., Warnick, G. R., and Sniderman, A. D. (2011) Reliability of low-density lipoprotein cholesterol, non-high-density lipoprotein cholesterol, and apolipoprotein B measurement. *J Clin Lipidol.*, *5*, 264-272. doi: 210.1016/j.jacl.2011.1005.1004. Epub 2011 May 1027. **R**

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Sniderman, A. D., and Thanassoulis, G. (2013) Among statin-treated patients, LDL, non-HDL and apoB cholesterol biomarkers were associated with increased risks of cardiovascular events. *Evid Based Med.*, *18*, 73-74. doi: 10.1136/eb-2012-100787. Epub 102012 Aug 100714. **R**

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Nauck, M., Warnick, G. R., and Rifai, N. (2002) Methods for measurement of LDL-cholesterol: a critical assessment of direct measurement by homogeneous assays versus calculation. *Clin Chem.*, *48*, 236-254. **R**

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7.10 Appendix 10 Excluded literature

01 No usable data or information on LDL-C were presented

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Bayturan, O., Utuk, O., and Tuzcu, E. M. (2011) [Beyond lowering LDL cholesterol]. *Anadolu Kardiyol Derg.*, *11*, 163-167. doi: 110.5152/akd.2011.5039. Epub 2011 Feb 5123. **01**

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Gal, D., MacDonald, P. C., and Simpson, E. R. (1981) Cholesterol metabolism in human cancer cells in monolayer culture. V. The effect of progesterone on the regulation of 3-hydroxy-3-methylglutaryl coenzyme A reductase activity by low density lipoprotein. *J Clin Endocrinol Metab.*, *53*, 29-33. **01**

Grundy, S. M., Pasternak, R., Greenland, P., Smith, S., Jr., and Fuster, V. (1999) AHA/ACC scientific statement: Assessment of cardiovascular risk by use of multiple-risk-factor assessment equations: a statement for healthcare professionals from the American Heart Association and the American College of Cardiology. *J Am Coll Cardiol.*, *34*, 1348-1359. **01**

Jacobson, T. A., Glickstein, S. B., Rowe, J. D., and Soni, P. N. (2012) Effects of eicosapentaenoic acid and docosahexaenoic acid on low-density lipoprotein cholesterol and other lipids: a review. J Clin Lipidol., 6, 5-18. doi: 10.1016/j.jacl.2011.1010.1018. Epub 2011 Nov 1013. **01**

Khan, N., Monagas, M., Andres-Lacueva, C., Casas, R., Urpi-Sarda, M., Lamuela-Raventos, R. M., and Estruch, R. (2012) Regular consumption of cocoa powder with milk increases HDL cholesterol and reduces oxidized LDL levels in subjects at high-risk of cardiovascular disease. Nutr Metab Cardiovasc Dis., 22, 1046-1053. doi: 1010.1016/j.numecd.2011.1002.1001. Epub 2011 May 1046. **01**

Kim, A., Chiu, A., Barone, M. K., Avino, D., Wang, F., Coleman, C. I., and Phung, O. J. (2011) Green tea catechins decrease total and low-density lipoprotein cholesterol: a systematic review and meta-analysis. *J Am Diet Assoc.*, *111*, 1720-1729. doi: 1710.1016/j.jada.2011.1708.1009. **01**

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Nakamura, T., Obata, J. E., Hirano, M., Kitta, Y., Fujioka, D., Saito, Y., Kawabata, K., Watanabe, K., Watanabe, Y., Mishina, H., and Kugiyama, K. (2011) Predictive value of remnant lipoprotein for cardiovascular events in patients with coronary artery disease after achievement of LDL-cholesterol goals. Atherosclerosis., 218, 163-167. doi: 110.1016/j.atherosclerosis.2011.1004.1040. Epub 2011 May 1016. **01**

Olsson, A. G. (2011) [Target levels for LDL cholesterol are put out of the running. Cholesterol should be lowered maximally in high cardiovascular risk]. *Lakartidningen.*, *108*, 1240-1243. **01**

Paavola, T., Kangas-Kontio, T., Salonurmi, T., Kuusisto, S., Huusko, T., Savolainen, M. J., and Kakko, S. (2012) Plasma levels of antibodies against oxidized LDL are inherited but not associated with HDL-cholesterol level in families with early coronary heart disease. Atherosclerosis., 224, 123-128. doi: 110.1016/j.atherosclerosis.2012.1006.1056. Epub 2012 Jun 1028. **01**

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Sharrett, A. R., Coady, S. A., Folsom, A. R., Couper, D. J., and Heiss, G. (2004) Smoking and diabetes differ in their associations with subclinical atherosclerosis and coronary heart disease-the ARIC Study. *Atherosclerosis.*, *172*, 143-149. **01**

Sherbet, D. P., Garg, P., Brilakis, E. S., and Banerjee, S. (2013) Low-density lipoprotein cholesterol: how low can we go? Am J Cardiovasc Drugs., 13, 225-232. doi: 210.1007/s40256-40013-40013-40258. **01**

Strandberg, T. E. (2008) Low low-density lipoprotein cholesterol and cancer risk. *J Am Coll Cardiol.*, *51*, 91-92; author reply 92. doi: 10.1016/j.jacc.2007.1008.1053. **01**

Zhang, Y. H., An, T., Zhang, R. C., Zhou, Q., Huang, Y., and Zhang, J. (2013) Very high fructose intake increases serum LDL-cholesterol and total cholesterol: a meta-analysis of controlled feeding trials. *J Nutr.*, *143*, 1391-1398. doi: 1310.3945/jn.1113.175323. Epub 172013 Jul 175323. **01**

02 Clinical study with patients, focus on diagnosis, therapy and prognosis

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Kizer, J. R., Madias, C., Wilner, B., Vaughan, C. J., Mushlin, A. I., Trushin, P., Gotto, A. M., Jr., and Pasternak, R. C. (2010) Relation of different measures of low-density lipoprotein cholesterol to risk of coronary artery disease and death in a meta-regression analysis of large-scale trials of statin therapy. *Am J Cardiol.*, *105*, 1289-1296. doi: 1210.1016/j.amjcard.2009.1212.1051. Epub 2010 Mar 1220. **02**

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