

Quantification of the Effect of Smoking and Smoking Cessation on Lipid Parameters: A Meta-Analysis

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Introduction and Objectives

In the last 40 years, smoking has been identified as a risk factor for cardiovascular disease (CVD) including coronary artery disease, peripheral arterial disease and stroke (Pipe et al 2010). The mechanisms by which smoking influences CVD risk have not been fully elucidated, however, there is consistent evidence that smoking alters lipid metabolism and this could be one of the underlying factors by which smoking increased CVD risk (Frei et al 1991). Furthermore, some studies have shown reversal of smoking deleterious effect on lipids after smoking cessation (Maeda et al 2003).

It has been known since the 1950's that High-Density Lipoprotein Cholesterol (HDL-C) is associated with a decreased risk of CVD. The two sub fractions of HDL-C (HDL-C₂ and HDL-C₃) have also been associated to decreased CVD risk separately (Robinson et al 1987). The opposite association is seen for triglyceride levels (TG) and CVD risk as high levels of TG are associated to increased risk of myocardial infarction and stroke (Alagona 2009). Other lipid-carrying proteins associated with a decreased risk are apolipoproteins A-I (Apo A-I) and A-II (Apo A-II) (Faergman 2006) while apolipoprotein B (Apo B) and the ratio of Apo B/Apo A-I are associated with increased risk for CVD morbidity and mortality (Holewijn et al 2010). Finally, Lipoprotein (a) [Lp(a)] levels have also been associated to increased risk of CVD risk (Emerging Risk Factors Collaboration, 2009).

The aim of this study is to assess the difference in lipid levels between smokers and non-smokers and the effect of smoking cessation on the same parameters.

Materials and Methods

The Medline database (Pubmed) was searched for studies that evaluated the relationship between smoking or smoking cessation and lipid parameters which included: HDL-C (including its sub fractions HDL-C₂ and HDL-C₃), apolipoproteins (Apo A-I, Apo A-II, Apo B), Lip (a) and TG. The search was performed between September 28th and April 10th 2013 using the following key words: "smoking", "smoking cessation", "quitting", "apolipoprotein", "Lip (a)", "High Density Lipoprotein", "triglyceride". Selection of articles was further limited to those written in English and considering human populations. To identify other available studies, the reference lists of the publications obtained through the original search were checked for any additional articles.

Inclusion Criteria

- Case control or cohort studies (observational and experimental studies)
- Adult human populations were studied
- Measurements of HDL-C, TG or Apolipoproteins by exposure with the following measures available: mean lipid levels by group, SD or SE (of the mean), sample size per group or with enough information to allow for the calculation of mean and SD.
- Studies published after 1970 (inclusive)

Exclusion Criteria

- Review articles, case reports, articles or editorials
- Reports with incomplete data which could not be incorporated into Revman 5.1.
- Duplicate publication of the same study
- Studies performed in diseased populations
- Unknown time of quitting for cessation studies

Statistical Analysis

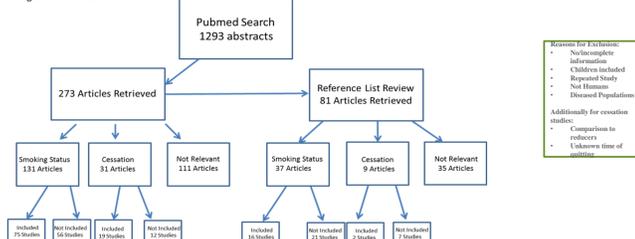
To quantify the effects of smoking and smoking cessation on lipid levels, pooled mean differences between smokers and non-smokers (when assessing effects of smoking on lipids) or between quitters and their baseline measurements (when assessing the effects of quitting smoking on lipid parameters) and 95% confidence intervals (95%CI) were calculated using the fixed-effects model in Review Manager version 5.0 (Cochrane Collaboration, Oxford, UK). The degree of heterogeneity between the study results was tested by the inconsistency statistic (I²) (Higgins et al 2003), when the between study heterogeneity was high (I²>75%) the random effects model was used to correct for heterogeneity and the results compared to the fixed effects model. Funnel plots were used to evaluate publication bias (Macaskill et al 2001).

Results

Search Results

A total of 1293 studies were identified through the Pubmed search and the reference list check yielded 81 studies. A detailed description of the data extraction is shown on Figure 1.

Figure 1 Data Extraction Details



Smoking Influence on Lipid Levels

Seventy-eight studies presented data on smoking status and HDL-C levels. The results of the meta-analysis for the effect of smoking on HDL-C showed that smokers have lower levels of HDL-C than non-smokers (mean difference = -0.09, mmol/L, 95%CI: -0.10, -0.08, p<0.00001) (Table 1). Since the heterogeneity among studies was high (I² = 91%) subgroup analyses were performed by geographic area. Applying a random effects model to the meta-analysis yielded similar results (mean difference = -0.09 mmol/L, 95%CI: -0.11, -0.08, p<0.00001). Further subgroup analyses by year of publication did not yield different results. Analyses limiting the number of studies to papers defining smoking as 20 cigarettes a day or more, saw a decrease in heterogeneity to 79% and it was also lower in geographical region subgroup analyses (Table 1).

The comparison of TG levels in smokers to non-smokers was reported by 58 studies. The overall meta-analysis results showed increased mean TG levels in smokers compared to non-smokers (mean difference = 0.14 mmol/L, 95%CI: 0.13, 0.14, p<0.00001) (Table 2). The results did not significantly change after applying the random effects model (mean difference = 0.20 mmol/L, 95%CI: 0.15, 0.24, p<0.00001). To explain the heterogeneity subgroup analyses were performed by geographic region. When limiting by definition of smoking the overall results remained.

The results of the meta-analyses of the other lipid carrying proteins and the effect of smoking can be seen on Table 3. Statistically significant associations were found for HDL-C₂ (mean difference = -0.09, mmol/L, 95%CI: -0.14, -0.05, p<0.0001, I²=29%), HDL-C₃ (mean difference = -0.06 mmol/L, 95%CI: -0.10, -0.03, p<0.0001, I² = 88%), Apo A-I (mean difference = -0.05 g/L, 95%CI: -0.05, -0.04, p<0.00001, I² = 89%), Apo A-II (mean difference = -0.02, g/L, 95%CI: -0.02, -0.01, p<0.0001, I² = 52%), Apo B (mean difference = 0.07 g/L, 95%CI: 0.06, 0.07, p<0.00001, I² = 87%), Apo B/Apo A-I ratio (mean difference = 0.01, 95%CI: 0.03, 0.05, p<0.00001, I² = 99%). No difference in Lp(a) levels was found (mean difference = 1.46, g/L, 95%CI: -0.56, 3.49, p = 0.16, I² = 0%).

The analyses were performed in a subsample of articles restricted by the definition of smoking whenever possible, this did not affect the results.

Table 1 Smoking & HDL-C Levels - Fixed Effects Model

Type	Lipid	Countries	Studies	Comparisons	Mean Difference	95%CI	p-value	I squared
All	HDL-C	US & Canada	16	18	-0.06(-0.06, -0.05)	mmol/L	<0.00001	87%
All	HDL-C	Europe	41	61	-0.07(-0.07, -0.06)	mmol/L	<0.00001	72%
All	HDL-C	Asia	15	32	-0.10(-0.11, -0.10)	mmol/L	<0.00001	87%
All	HDL-C	India	4	4	-0.17(-0.20, 0.15)	mmol/L	<0.00001	98%
All	HDL-C	Other	7	9	-0.05(-0.06, -0.04)	mmol/L	<0.00001	46%
All	HDL-C	Total	83	124	-0.08(-0.09, -0.08)	mmol/L	<0.00001	87%
>20 cigs	HDL-C	US	6	7	-0.12(-0.15, -0.09)	mmol/L	<0.00001	86%
>20 cigs	HDL-C	Europe	9	22	-0.08(-0.09, -0.06)	mmol/L	<0.00001	64%
>20 cigs	HDL-C	Asia	8	8	-0.09(-0.10, -0.08)	mmol/L	<0.00001	85%
>20 cigs	HDL-C	Other	4	5	-0.05(-0.06, -0.04)	mmol/L	<0.00001	10%
>20 cigs	HDL-C	Total	27	42	-0.08(-0.08, -0.07)	mmol/L	<0.00001	79%

Table 2 Smoking and TG Levels - Fixed Effects Model

Type	Lipid	Countries	Studies	Comparisons	Mean Difference	95%CI	p-value	I squared
All	TG	US & Canada	14	15	0.11(0.08, 0.14)	mmol/L	<0.00001	59%
All	TG	Europe	25	30	0.07(0.06, 0.09)	mmol/L	<0.00001	91%
All	TG	Asia	14	27	0.18(0.17, 0.19)	mmol/L	<0.00001	97%
All	TG	Other	5	7	0.11(0.07, 0.16)	mmol/L	<0.00001	74%
All	TG	Total	58	79	0.14(0.13, 0.14)	mmol/L	<0.00001	94%
>20 cigs	TG	US & Canada	3	3	0.08(0.01, 0.15)	mmol/L	<0.00001	54%
>20 cigs	TG	Europe	5	8	0.23(0.20, 0.27)	mmol/L	<0.00001	83%
>20 cigs	TG	Asia	7	8	0.38(0.28, 0.47)	mmol/L	<0.00001	54%
>20 cigs	TG	Turkey	2	3	0.00(-0.07, 0.08)	mmol/L	0.91	0%
>20 cigs	TG	Total	17	22	0.18(0.15, 0.21)	mmol/L	<0.00001	83%

Table 3 Smoking & Other lipid carrying proteins - Fixed Effects Model

Studies	Lipid	Studies	Comparisons	Mean Difference	95%CI	p-value	I squared
All	HDL-C ₂	6	7	-0.09(-0.14, -0.05)	mmol/L	<0.0001	29%
All	HDL-C ₃	6	7	-0.06(-0.10, -0.03)	mmol/L	<0.0001	88%
All	Apo A-I	21	26	-0.05(-0.05, -0.04)	g/L	<0.00001	92%
>20 cigs	Apo A-I	4	7	-0.10(-0.15, -0.05)	g/L	0.0001	0%
All	Apo A-II	6	8	-0.02(-0.02, -0.01)	g/L	<0.0001	52%
All	Apo B	16	16	0.07(0.06, 0.08)	g/L	<0.00001	84%
>20 cigs	Apo B	4	6	0.07(0.03, 0.11)	g/L	0.002	80%
All	Apo B/Apo A-I	12	14	0.01(0.00, 0.01)		<0.00001	99%
>20 cigs	Apo B/Apo A-I	4	6	0.04(0.03, 0.05)		<0.00001	99%
All	Lp(a)	5	5	1.46(-0.56, 3.49)	g/L	0.16	0%

Smoking Cessation & Lipid Levels

For the analyses of the effect of smoking cessation, 40 studies were retrieved that compared lipid levels collected at baseline with those after 1 week to 1 year after cessation. The study by Maeda et al (2003) which was a meta-analysis, was used to identify additional studies. Only 20 studies were included in the analyses. Articles comparing HDL-C levels at baseline with those at 1 month, 6 weeks, 2 months, 3 months and 1 year after quitting. Information on TG was found for observations after 6 weeks, 3 months and 1 year after cessation.

The results are seen on Figure 2 for HDL-C and Figure 3 for TG. Changes in HDL-C were seen as early as 2 weeks after cessation (mean difference= 0.18 mmol/L, 95%CI: 0.04, 0.31, p=0.009, I²=32%) although the impact of cessation on HDL-C diminished over time (mean difference=0.06 mmol/L, 95%CI: 0.01, 0.11, p=0.02, I²=0%). There was no influence of smoking cessation on TG levels.

Figure 2 Smoking Cessation and HDL-C levels

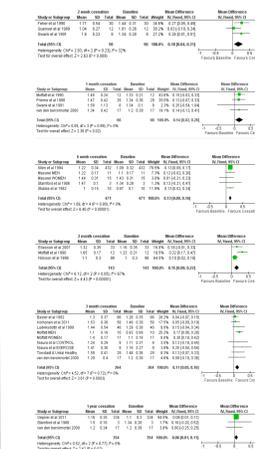
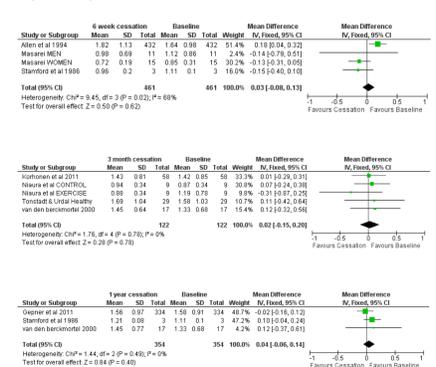


Figure 3 Smoking Cessation and TG Levels



Summary and Conclusions

The meta-analyses show that smokers have a worse lipid profile characterized by lower HDL-C (including HDL-C₂ and HDL-C₃), Apo A-I and A-II and higher TG, Apo B and Apo B/Apo A-I ratio, all of which have been associated to cardiovascular disease risk.

The meta-analysis of smoking cessation demonstrates an improvement of the lipid profile of those who quit smoking. Levels of HDL-C increase as early as 2 weeks after quitting and remain higher 1 year after, although the increase is not as steep as in early cessation. We did not find a decrease in TG levels after smoking cessation and there were not enough publications to perform analyses for the other lipid measurements included in the first part of our analyses. Smoking cessation has been proven to improve lipid profiles in healthy individuals taking no medication or short-term nicotine replacement therapy (Botella-Carretero et al 2004), although there is consistent evidence that smoking cessation is followed by a variable degree of weight gain that could be the reason behind the lack of change in TG levels (Botella-Carretero et al 2004).

In conclusion, smoking cessation improves levels of HDL-C while no effect on TG levels was seen in this meta analysis, possibly due to the weight gain that is observed in those who stop smoking.

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