DOES COFFEE CONSUMPTION ALTER PLASMA LIPOPROTEIN(A) CONCENTRATIONS? A SYSTEMATIC REVIEW.

Peter Penson[1], Maria-Corina Serban[2,], Sorin Ursoniu[3], Maciej Banach[4-6]

for *the Lipid and Blood Pressure Meta-analysis Collaboration (LBPMC) Group*

[1]School of Pharmacy and Biomolecular Sciences, Liverpool John Moores University, Liverpool, UK; [2]Department of Functional Sciences, Discipline of Pathophysiology, "Victor Babes" University of Medicine and Pharmacy, Timisoara, Romania; [3]Department of Functional Sciences, Discipline of Public Health, "Victor Babes" University of Medicine and Pharmacy, Timisoara, Romania; [4]Department of Hypertension, Chair of Nephrology and Hypertension, Medical University of Lodz, Lodz, Poland; [5]Healthy Aging Research Centre (HARC), Medical University of Lodz, Lodz, Poland; [6]Polish Mother's Memorial Hospital Research Institute, Lodz, Poland.

***Correspondence to:** Prof. Maciej Banach, MD, PhD, FNLA, FAHA, FESC; FASA, Head, Department of Hypertension, WAM University Hospital in Lodz, Medical University of Lodz, Zeromskiego 113; 90-549 Lodz, Poland. **Phone:** +48 42 639 37 71; **Fax:** +48 42 639 37 71; **E-mail:** maciejbanach77@gmail.com

Conflict of Interest Disclosures: None

ABSTRACT:

Coffee consumption alters plasma lipid and cholesterol concentrations, however, its effects on lipoprotein(a) (Lp(a)) have received little study. The aim of this PRISMA compliant systematic review was to examine the role of coffee on serum Lp(a).

This study was prospectively registered (PROSPERO 2015:CRD42015032335). PubMed, Scopus, Web of Science and Cochrane Central were searched from inception until 9th January 2016 to detect trials and epidemiological studies investigating the impact of coffee on serum Lp(a) concentrations in humans.

We identified six relevant publications describing nine experimental trials of various designs. There were a total of 640 participants across all studies and experimental groups. In short-term controlled studies, consumption of coffee, or coffee diterpenes was associated with either a reduction in serum Lp(a) of ≤11 mg/dl (6 trials, 275 participants), or no effect (2 trials, 56 participants). Conversely, one cross-sectional study with 309 participants showed serum Lp(a) was elevated in chronic consumers of boiled coffee who had a median Lp(a) of 13.0 mg/dl (range 0-130) compared with consumers of filtered coffee who had median Lp(a) 7.9 mg/dl (range 0-144)

The effect of coffee on Lp(a) is complex and may follow a biphasic time-course. The type of coffee and the method of preparation appear to be important to determining the effect on Lp(a)

Keywords: cafestol, coffee, diterpenes, kahweol, lipoprotein(a).

No. of words: 209

INTRODUCTION

Coffee is a caffeine-containing beverage prepared as an aqueous extract of the beans of the *Coffea* plant. It is commonly consumed in Western society (Doepker et al. 2016). Previous meta-analyses have demonstrated associations between coffee consumption (particularly unfiltered coffee) and serum lipid concentrations (Jee et al. 2001). In particular, plasma concentrations of LDL-cholesterol and total cholesterol increase in a dose-dependent manner with exposure to coffee (Jee et al. 2001, Cai et al. 2012). Two diterpenes: kahweol and cafestol have been shown to be implicated in the lipid-modulating effects of coffee (Heckers et al. 1994, Weustenvanderwouw et al. 1994). These diterpenes are sometimes trapped by the paper filter used in some methods of coffee preparation. Scandinavian boiled coffee was shown to contain 3-4 mg of each diterpene per cup, compared with less than 0.1mg of each diterpene when the coffee was filtered (Urgert et al. 1995, Urgert et al. 1997). This helps to explain the observation that different methods for brewing coffee result in different effects on serum lipids (Dusseldorp et al. 1991).

Lipoprotein(a) (Lp(a)) particles consist of low-density-lipoprotein-like particles which are covalently bound to apolipoprotein(a) (Bos et al. 2014). Serum concentrations of lipoprotein(a) are positively correlated with cardiovascular risk (Kamstrup et al. 2009). Evidence from a study employing Mendelian randomization suggests that the link is causal (Kamstrup et al. 2009). A recent meta-analysis has demonstrated that elevated Lp(a) is an independent risk-factor for stroke (Nave et al. 2015). Low-fat diets that result in weight loss do not appear to result in alterations in plasma Lp(a) and two comprehensive reviews have concluded that the effects of diet on plasma Lp(a) concentrations are negligible (Puckey et al. 1999, Bos et al. 2014). Nevertheless, the well documented lipid-modulating effects of coffee, and the increasing recognition of Lp(a) as a risk factor for cardiovascular disease warrant investigation as to whether coffee can modulate plasma concentrations of Lp(a). It was our intention to carry out a systematic review and meta-analysis of studies of randomized controlled trials investigating the effect of coffee consumption on plasma Lp(a) concentrations in humans.

Our extensive and systematic literature search uncovered a limited, but interesting body of knowledge on this topic. There were insufficient randomised-controlled trials to perform a meta-analysis, so, instead we summarised in narrative format all the available evidence from studies in humans.

METHODS

Registration and search strategy

This PRISMA compliant study was prospectively registered (PROSPERO 2015: CRD42015032335). PubMed, Scopus, Web of Science and Cochrane Central were searched from inception until 9th January 2016. All fields were searched for the terms: (coffee OR "coffee" OR coffee* OR caffeine OR caffeine* OR "caffeine") AND (lipoprotein a OR LPa OR LP(a) OR lipoprotein(a) OR lipoprotein(a). Additionally, in the PubMed database, the terms were searched as MESH headers and all subheadings were included in the searches.

Inclusion and Exclusion Criteria

Inclusion Criteria

This systematic review included all studies in humans that examined the relationship between the consumption of coffee (or extracts of coffee) upon plasma concentrations of Lp(a). The PICOS strategy is outlined in **Table 1**. When results of a study were reported more than once, the most recent or complete article, or the one with the largest sample size, was included.

The following criteria were applied for inclusion:

- Controlled trials or crossover trials which reported serum Lp(a) concentration at the baseline and completion and included coffee consumption (or abstinence) as an intervention (and studies from which these data were not reported but could be obtained from the study authors)
- Prospective cohort studies or other epidemiological studies which reported serum lipoprotein(a) concentrations and coffee consumption (and studies from which these data were not reported but could be obtained from the study authors)

Exclusion Criteria

Studies which were not conducted in humans were excluded. Studies which did not enable us to obtain sufficient information regarding Lp(a) were also excluded, except when that information could be obtained from study investigators.

Study Selection

All relevant articles were independently reviewed by two investigators (PP & MCS). The above inclusion and exclusion criteria were used to evaluate each article for selection into the systematic review. A third investigator (SU) was consulted to resolve study inclusion and exclusion discrepancies.

Data extraction

Eligible studies were reviewed and the following data were abstracted: first author's name; year of publication; country were the study was performed; study design; number of participants (divided into experimental groups where appropriate); details of coffee intervention; age, gender and body mass index (BMI) of the participants; baseline systolic and diastolic blood pressures; baseline TC, HDL-C, LDL-C and TG; baseline and (where appropriate) follow-up values of plasma concentrations of Lp(a). Studies reported their results in a variety of units. Where the units for lipids given in the units mmol/l they were converted to mg/dL by multiplying by the following conversion factors (HDL-C, 38.61; LDL-C, 38.61; TC, 38.61; Triglycerides, 88.50). Data extraction was carried out by two investigators (PP & CS)

Quality Assessment

In order to assess the risk of bias in trials included in this review, the Cochrane Collaboration's tool for assessing risk of bias in randomized studies was used (Higgins et al. 2011, Higgins et al. 2011). Appropriate sections of this tool were completed for the one cross-sectional study. No trials, which met the inclusion criteria, were excluded from the systematic review on quality grounds.

RESULTS

Search results and trial flow

The flow of papers through the process is shown in **Figure 1**. Our searches found 945 papers. An initial screen of titles and abstracts was performed in order to remove articles, which were clearly irrelevant. After reading the full-texts of the remaining 121 papers, we identified 6 relevant papers (Urgert et al. 1996, Urgert et al. 1997, Strandhagen et al. 2003, Yukawa et al. 2004, Bukowska et al. 2006, Correa et al. 2013).

Description of studies

The characteristics of the studies and their participants and methods of the relevant papers we found are summarized in **Table 2.** The methods employed in the studies were extremely diverse The Quality assessment is shown in **Table 3**. The papers were published between 1996 and 2013 and included one relevant epidemiological study and five experimental papers describing nine trials of various designs. There were a total of 640 participants across all studies and experimental groups. Included in these figures are studies, which did not report the effect of coffee on Lp(a) quantitatively, but where that data was kindly provided by the authors. The studies included crossover and parallel group designs as well as trials in which participants were followed through a time course of coffee consumption and coffee abstinence. Interventions included boiled and filtered coffee and coffee diterpenes dissolved in oil. Comparators included abstinence from coffee, alternative methods of coffee consumption and placebo oil, or oil stripped of diterpenes. The effects of coffee consumption upon plasma Lp(a) are summarized in **Table 4.**

DISCUSSION

With respects to the methods employed, the studies were very heterogeneous. In studies where two blends of coffee were prepared, masking of participants to the blend was possible; in other circumstances masking the coffee intervention would have been extremely difficult and was not attempted. Nevertheless, it is unlikely that a participant's knowledge of their intervention would affect their plasma Lp(a) in a manner that would introduce bias. The difficulty of producing a placebo alternative to coffee may explain the paucity of randomized placebo controlled parallel group studies.

Urgert *et al.* published a paper that reported the results of four clinical trials(Urgert et al. 1997). They called these: Trial A, Trial B, Trial C and Trial D (Urgert et al. 1997). All were of relevance to this systematic review, and together provide information about the magnitude and direction of the effect of coffee on Lp(a), and also the components within coffee responsible for these effects. Trial B and Trial C were randomised placebo-controlled trials, Trials A and D had alternative study designs.

'Trial A' which was designed to compare the effects on Lp(a) of diterpene-rich unfiltered coffee with filtered coffee (Urgert et al. 1997). After a run-in period of four weeks in which the participants drank filtered, coffee, they were randomised to receive 0.9 l/day (5 cups) of either filtered coffee or cafetiere coffee (Urgert et al. 1997). The concentrations of the diterpenes in the coffee were measured and translated in to daily doses (Urgert et al. 1997). Filtered coffee provided less than 1mg/day of each diterpene. Cafetiere coffee provided 38 mg/day cafestol and 33mg/day kahweol. Repeated measurements of Lp(a) were taken over time. Cafetiere coffee produced a fall in Lp(a) which was maximal at 8 weeks (1.5 mg/dL) and which stabilized at around 0.5 mg/dL between weeks 12 and 24 (Urgert et al. 1997). This time course may be of interest in explaining the results of an epidemiological study, described later, in which coffee consumption was associated with elevated Lp(a).

In Trial B, Urgert *et al.* performed a double-masked randomised-controlled trial in which 32 participants were randomised to receive 3g/day of either placebo oil (a 3:2 w/w mixture of sunflower oil and palm oil) or coffee oil which gave a daily dose of 85 mg of cafestol and 103 mg of kahweol(Urgert et al. 1997). The intervention was administered for four weeks, after which a statistically significant difference was found between the two groups, with respect to Lp(a) concentrations which were lower by a median of 5.3 mg/dL in the coffee oil group than in the placebo oil group (Urgert et al. 1997). Whilst these results seem to demonstrate a clear effect of coffee diterpenes on Lp(a), it should be noted that the daily doses of diterpenes are rather high, compared to that which might be expected from dietary coffee consumption. Another study reported in the same paper the authors found that 0.9 l of cafetiere coffee provided a dose of 38 mg cafestol and 33 mg kahweol (Urgert et al. 1997).

Also reported in the same paper was ‘Trial C’ which used very similar methods to ‘Trial B’ and was also conducted over four weeks (Urgert et al. 1997). The 36 participants were randomised to receive 2g/day of placebo oil, coffee oil (equivalent to a daily dose of 57 mg cafestol and 69 mg kahweol), or coffee oil that had been stripped of cafestol and kahweol (Urgert et al. 1997). Coffee oil reduced LP(a) concentrations by 3.1 mg/dL, an effect that was not seen with placebo oil or stripped oil (Urgert et al. 1997). These trials, although small, provide evidence that diterpenes are responsible for the acute effects of coffee consumption upon Lp(a) (Urgert et al. 1997).

Further insight into the agent responsible for the acute Lp(a)-lowering effects of coffee was provided by Trial D (Urgert et al. 1997). Participants received either a mixture of cafestol (60 mg/day) and kahweol (48-54 mg/day) dissolved in placebo oil, or cafestol alone (61-64 mg cafestol/day and ≤ 1mg/day kahweol). After a seven-week washout period, during which they took placebo oil, they were crossed-over to the other treatment group (Urgert et al. 1997). Cafestol alone produced a reduction in Lp(a) of 3.5 ±0.8 mg/dL (mean ±S.D.) compared with 3.9 ± 1.0 for the mixture. The changes from baseline were statistically significant, but the differences between the groups were not. This suggests that cafestol is the major diterpene involved in Lp(a) reduction observed with acute consumption of coffee (Urgert et al. 1997). The results of this trial are interesting, but should be treated with caution, because of the small number of participants (5 in each group), and because two participants in treatment groups were switched to placebo after having elevated alanine amino transferase which exceeded the safety limits defined by the investigators.

By combining data from all four of their randomised controlled trials. Urgert *et al.* made the interesting observation that the initial concentration of Lp(a) in an individual appears to influence the responsiveness of Lp(a) to coffee (or diterpene) treatment. After pooling the data, the investigators stratified participants into tertiles according to baseline Lp(a). Those with the highest initial values of Lp(a) saw the largest absolute reductions after treatment. Coffee or diterpenes treated participants in the highest baseline Lp(a) saw a median change in Lp(a) of -6.5 mg/dL, compared with control participants in the same Lp(a) tertile. For the middle Lp(a) tertile, the median difference was -3.3 mg/dL, and for the lowest tertile, -0.3 mg/dL (Urgert et al. 1997).

Whilst Urgert *et al.* had found no effect of filter coffee upon Lp(a) (Urgert et al. 1997), a later study by Strandhagen and Thelle demonstrated an increase in Lp(a) after four weeks of consumption of 600 mml filter coffee per day (Strandhagen et al. 2003). The study consisted of two four-week periods of coffee consumption and two three-week periods of coffee abstention (Strandhagen et al. 2003). During both coffee consumption periods, Lp(a) values were reduced In the first period, the median difference was -11 mg/dl, in the second period it was -4 mg/dl (Strandhagen et al. 2003).The authors described the results as inconsistent, because there was no change in Lp(a) during the first abstention period, but a median increase of 15 mg/dl during the second abstention period. By comparison, total cholesterol increased during both the consumption periods and decreased during both the abstention periods (Strandhagen et al. 2003). Nevertheless, given the relatively small number of participants, the large variation in baseline Lp(a) levels between individuals, this would appear to be interesting evidence of a Lp(a)-lowering effect of filtered coffee (Strandhagen et al. 2003).

Also employing filtered coffee, Correa *et al.* conducted a randomised crossover trial designed to compare the effects of medium roast coffee and medium light roast coffee on lipids and other biomarkers (Correa et al. 2013). The twenty participants drank three or four cups daily of the first roast, before switching over to the other type. The diterpene concentrations of the coffee were measured and, concentrations of cafestol were substantially higher than those seen in other studies employing filtered coffee (Correa et al. 2013). Medium light roast provided 5.36 mg cafestol and 0.79 mg kahweol per 150 mg cup; medium roast provided 6.3 mg cafestol and 0.51mg kahweol per 150 mg cup. Mean coffee consumption was 462 ml/day, equivalent to a daily dose of cafestol of approximately 20mg (Correa et al. 2013). There were no statistically significant changes in plasma Lp(a) throughout the trial. However the small sample size of the trial may have rendered it underpowered to detect differences in Lp(a). It is also possible that the relatively low cafestol dose in this trial may have been insufficient to have an effect on Lp(a), although the trial did show interesting differences in cholesterol and biomarkers of inflammation. Importantly this study demonstrates that diterpenes are not always retained by a paper filter (Correa et al. 2013).

In a randomised double-masked crossover trial, Bukowska *et al.* compared “natural unfiltered” coffee and coffee “modified by water and pressure extraction” with intervention periods of 28 days (Correa et al. 2013). The study included 36 healthy volunteers and compared Lp(a) before and after the intervention. The authors found no statistically significant differences in mean Lp(a) for either form of coffee (Lp(a) before ‘modified form’ coffee 32 ± 24 mg/dL, after 38 ± 26 mg/dL; before ‘natural coffee 31 ± 27 mg/dL, after 32 ± 28 mg/dL). The study did, however show an increase in homocysteine in participants drinking the “natural unfiltered coffee”, however the variance in baseline homocysteine was much smaller that for Lp(a), thus the trial may have been underpowered to detect changes in Lp(a) (Bukowska et al. 2006).

Yukawa conducted a study in 11 healthy male students in which participants drank 150 ml coffee three times per day for a week, preceded and followed by abstinence periods in which they drank only mineral water (Yukawa et al. 2004). The study aimed to investigate the effects of coffee on lipid metabolism and the oxidative modification of LDL-C. There were no differences between serum Lp(a) concentrations at the end of the baseline period (25.1± 16.2 mg/dL), the end of the coffee consumption period (23.2 ± 11.4 mg/dL), and the washout period (23.7 ± 13.9 mg mg/dL) (Yukawa et al. 2004). It is likely that this trial was underpowered to detect differences in Lp(a) over the time period employed, however, statistically significant decreases in TC and LDL-C were observed (Yukawa et al. 2004). The authors suggested that the relatively high dose of coffee used in this study (150 ml three times a day) may explain the fact that opposite effects of coffee on TC and LDL-C were seen here, compared to other studies (Yukawa et al. 2004).

Urgert *et al.* conducted a cross-sectional study comparing serum concentrations of Lp(a) in 150 habitual consumers of boiled coffee and 159 consumers of filter coffee (Urgert et al. 1996). Participants aged 40-42 years who reported drinking five or more cups of coffee per day were included in the analysis. Higher plasma concentrations of Lp(a) were found in consumers of boiled coffee (median 13.0 mg/dL; range 0-130 mg/dL) than in those who drank filter coffee (median 7.9 mg/dL; range 0-144 mg/dL). There was evidence of a dose-response relationship between boiled coffee consumption and Lp(a). The subset of boiled coffee drinkers who reported consuming nine or more cups of coffee per day had a median Lp(a) concentration of 13.6 mg/dL compared with 11.7 mg/dL for those who drank fewer than nine cups. For filter coffee the values were 8.0 mg/dL; and mg/dL (Urgert et al. 1996). Despite the fact that these results seem to be in opposition to those reported in experimental studies, they are convincing because of the relatively large number of participants and because the results appear to show a dose-response relationship between coffee and Lp(a). These results cannot demonstrate causality, nor can they tell us whether the same chemical components of coffee are responsible for the short term reduction, and the long term elevation of Lp(a), however the fact that consumers of filtered coffee had lower Lp(a) than consumers of boiled coffee, suggests the responsible component may be trapped in a filter in the same way as the diterpenes have been in some studies.

In seeking to explain this result, the authors referred to previous observations that coffee increases serum alanine aminotransferase acutely. This marker is also elevated in liver disease (Weustenvanderwouw et al. 1994, Vanrooij et al. 1995). The investigators suggested, therefore, that in the short term diterpenes may disturb hepatocyte integrity, an effect which would be expected to result in reduced circulating Lp(a) (Gregory et al. 1994, Vanwersch

1994). Because normal serum concentrations of alanine aminotransferase were seen in this study, it was proposed that adaption occurs when coffee is consumed chronically. How and when this adaption occurs is unclear. This result is interesting in light of 'Trial A' described above, Urgert *et al.* reported maximal Lp(a) reduction after 8 weeks of consumption of boiled coffee, with a much smaller reduction from baseline seen thereafter (Urgert et al. 1997). The time-course demonstrated in that experiments supports the hypothesis that acute and chronic exposure to coffee may have different effects on Lp(a).

Clinical implications

No clinical recommendations can be made based upon the current evidence. The possible biphasic effect of coffee on Lp(a) mean that whilst coffee may have a short term beneficial effect in reducing Lp(a), in the longer term it may prove to be detrimental. Furthermore, seemingly beneficial effects of coffee in reducing plasma Lp(a) are likely to be counteracted by the effects of coffee consumption at increasing plasma total cholesterol and low-density-lipoprotein cholesterol which have been observed in most trials. Additionally, whilst elevated serum concentrations of Lp(a) are correlated with increased incidence of cardiovascular and cerebrovascular disease, the therapeutic benefit of Lp(a)-lowering is less well understood. Lp(a) should be more frequently measured and reported in clinical trials to enable us better to understand its prognostic importance, and to learn how it is affected by dietary and pharmacological interventions. Of the 106 papers selected for full-text screening but rejected for not reporting Lp(a), almost all reported numerous other lipid parameters.

Limitations

A limitation of this systematic review is the heterogeneity of study designs and interventions we included. Because of the small number of trials investigating the effects of coffee consumption on Lp(a), we included all types of study design which included humans. The number of participants in trials was generally very small. With respect to the intervention, coffee came from a variety of sources and multiple methods of preparation were employed. Therefore the results are hard to assimilate, and it was not possible to perform a meta-analysis. Despite the heterogeneity in reported methods of coffee preparations examined, there is a lack of data regarding decaffeinated coffee and coffee produced by automated coffee machines.

Heterogeneity of baseline serum concentrations of Lp(a) was noted within and between trials. The variability in this parameter is likely to increase the sample size required to demonstrate statistically significant changes with treatment. Additionally dietary interventions are harder to control than pharmaceutical intervention, adding another source of variability between participants. Thus trials which showed no effect of coffee on Lp(a) (Yukawa et al. 2004, Bukowska et al. 2006, Correa et al. 2013) or which showed an equivocal effect (Strandhagen et al. 2003) may have been underpowered with respect to Lp(a), despite being able to demonstrate changes in other parameters with baseline values which displayed less variance.

All the studies included in this systematic review relied on participants accurately reporting their dietary habits, or carefully following instructions regarding coffee preparation and consumption. This is a methodological weakness of any research investigating diet, however there is no reason to suppose that incorrect reporting by participants would systematically bias the study, rather than increasing variance in all groups.

The majority of the trials were not placebo controlled. Clearly it is clearly difficult to provide a placebo for coffee, without prior knowledge of the active Lp(a)-modifying agent. Even with this knowledge, it would be hard to produce a placebo whilst being certain that the difference could not be detected by taste. Several of the trials could have been made more rigorous by parallel comparison of coffee-consuming groups and abstaining groups.

CONCLUSIONS

The effects of coffee consumption on plasma Lp(a) are complex and are likely to be affected by the baseline Lp(a) concentration, the source of the coffee, the method of preparation, the dose and the duration of consumption. There is a trend towards Lp(a)-lowering effects of short-term consumption, with increased Lp(a) seen in chronic coffee drinkers. There is a need for more widespread reporting of Lp(a) in clinical trials.

ADDITIONAL INFORMATION:

This systematic review has been prepared within Lipid and Blood Pressure Meta-analysis Collaboration (LBPMC) Group (www.lbpmcgroup.umed.pl). The authors declare no competing financial interests.

ACKNOWLEDGEMENTS

We are grateful to the following individuals who kindly provided quantitative information on Lp(a) or other additional details which was not reported in their papers. Dr Telma Faraldo Correa provided information on (Correa et al. 2013) and Dr Elisabeth Strandhagen provided information on (Strandhagen et al. 2003).

DECLARATION OF INTERESTS

The authors declare no competing financial interests.

FUNDING

This article was prepared without the aid of any specific funding.

REFERENCES:

Bos, S., R. Yayha and J. E. van Lennep (2014). Latest developments in the treatment of lipoprotein (a). *Curr Opin Lipidol* **25**(6): 452-460.

Bukowska, H., I. Goracy, K. Chelstowski and M. Naruszewicz (2006). The assessment of the influence of natural coffee and its modified form on the level of homocysteine, vitamin B6 and folic acid in healthy volunteers. *Polski merkuriusz lekarski : organ Polskiego Towarzystwa Lekarskiego* **20**(116): 176-179.

Cai, L., D. Ma, Y. Zhang, Z. Liu and P. Wang (2012). The effect of coffee consumption on serum lipids: a meta-analysis of randomized controlled trials. *Eur J Clin Nutr* **66**(8): 872-877.

Correa, T. A., M. M. Rogero, B. M. Mioto, D. Tarasoutchi, V. L. Tuda, L. A. Cesar and E. A. Torres (2013). Paper-filtered coffee increases cholesterol and inflammation biomarkers independent of roasting degree: a clinical trial. *Nutrition* **29**(7-8): 977-981.

Doepker, C., H. R. Lieberman, A. P. Smith, J. D. Peck, A. El-Sohemy and B. T. Welsh (2016). Caffeine: Friend or Foe? *Food Science and Technology* **7**.

Dusseldorp, M., M. B. Katan, T. Vliet, P. N. Demacker and A. F. Stalenhoef (1991). Cholesterol-raising factor from boiled coffee does not pass a paper filter. *Arteriosclerosis and thrombosis* **11**(3): 586-593.

Gregory, W. L., F. L. Game, M. Farrer, J. R. Idle, M. F. Laker and O. F. W. James (1994). Reduced serum lipoprotein(a) levels in patients with primary biliary-cirrhosis. *Atherosclerosis* **105**(1): 43-50.

Heckers, H., U. Gobel and U. Kleppel (1994). End of the coffee mystery: diterpene alcohols raise serum low-density lipoprotein cholesterol and triglyceride levels. *J Intern Med* **235**(2): 192-193.

Higgins, J. P. T., D. G. Altman, P. C. Gøtzsche, P. Jüni, D. Moher, A. D. Oxman, J. Savović, K. F. Schulz, L. Weeks and J. A. C. Sterne (2011). The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ* **343**.

Higgins, J. P. T. and S. Green (2011). Cochrane Handbook for Systematic Reviews of Interventions, The Cochrane Collaboration.

Jee, S. H., J. He, L. J. Appel, P. K. Whelton, I. Suh and M. J. Klag (2001). Coffee consumption and serum lipids: a meta-analysis of randomized controlled clinical trials. *American journal of epidemiology* **153**(4): 353-362.

Kamstrup, P. R., A. Tybjaerg-Hansen, R. Steffensen and B. G. Nordestgaard (2009). Genetically elevated lipoprotein(a) and increased risk of myocardial infarction. *JAMA* **301**(22): 2331-2339.

Nave, A. H., K. S. Lange, C. O. Leonards, B. Siegerink, W. Doehner, U. Landmesser, E. Steinhagen-Thiessen, M. Endres and M. Ebinger (2015). Lipoprotein (a) as a risk factor for ischemic stroke: A meta-analysis. *Atherosclerosis* **242**(2): 496-503.

Puckey, L. and B. Knight (1999). Dietary and genetic interactions in the regulation of plasma lipoprotein(a). *Current Opinion in Lipidology* **10**(1): 35-40.

Strandhagen, E. and D. S. Thelle (2003). Filtered coffee raises serum cholesterol: Results from a controlled study. *European Journal of Clinical Nutrition* **57**(9): 1164-1168.

Urgert, R. and M. B. Katan (1997). The cholesterol-raising factor from coffee beans. *Annu Rev Nutr* **17**: 305-324.

Urgert, R., G. Vanderweg, T. G. Kosmeijerschuil, P. Vandebovenkamp, R. Hovenier and M. B. Katan (1995). Levels of the cholesterol-elevating diterpenes cafestol and kahweol in various coffee brews. *Journal of Agricultural and Food Chemistry* **43**(8): 2167-2172.

Urgert, R., M. P. Weusten-van der Wouw, R. Hovenier, P. G. Lund-Larsen and M. B. Katan (1996). Chronic consumers of boiled coffee have elevated serum levels of lipoprotein(a). *J Intern Med* **240**(6): 367-371.

Urgert, R., M. P. Weusten-van der Wouw, R. Hovenier, S. Meyboom, A. C. Beynen and M. B. Katan (1997). Diterpenes from coffee beans decrease serum levels of lipoprotein(a) in humans: results from four randomised controlled trials. *Eur J Clin Nutr* **51**(7): 431-436.

Vanrooij, J., G. H. D. Vanderstegen, R. C. Schoemaker, C. Kroon, J. Burggraaf, L. Hollaar, T. Vroon, A. H. M. Smelt and A. F. Cohen (1995). A placebo-controlled parallel study of the effect of 2 types of coffee oil on serum-lipids and transaminases - identification of chemical-substances involved in the cholesterol-raising effect of coffee. *American Journal of Clinical Nutrition* **61**(6): 1277-1283.

Vanwersch, J. W. J. (1994). The behavior of lipoprotein(a) in patients with various diseases. *Scandinavian Journal of Clinical & Laboratory Investigation* **54**(7): 559-562.

Weustenvanderwouw, M., M. B. Katan, R. Viani, A. C. Huggett, R. Liardon, P. G. Lundlarsen, D. S. Thelle, I. Ahola, A. Aro, S. Meyboom and A. C. Beynen (1994). Identity of the cholesterol-raising factor from boiled coffee and its effects on liver-function enzymes. *Journal of Lipid Research* **35**(4): 721-733.

Yukawa, G. S., M. Mune, H. Otani, Y. Tone, X. M. Liang, H. Iwahashi and W. Sakamoto (2004). Effects of coffee consumption on oxidative susceptibility of low-density lipoproteins and serum lipid levels in humans. *Biochemistry (Mosc)* **69**(1): 70-74.

Table 1. Description of the PICOS criteria used to define the research question

Parameter	**Description**
Population	Humans, without any restrictions.
Intervention	Coffee consumption, ingestion of coffee-derived products, abstinence from coffee in habitual consumers
Comparator	Placebo or abstinence from coffee consumption.
Outcome	Change in plasma concentration of lipoprotein(a) after intervention
Study Design	All study designs in humans.

Table 2. Design of the studies selected for analysis and demographic characteristics and baseline parameters of participants.

Study	Bukowska *et al.*	Correa *et al.*	Strandhagen *et al.*	Urgert *et al.*	Urgert *et al.* Trial A	Urgert *et al.* Trial B	Urgert *et al.* Trial C	Urgert *et al.* Trial D	Yukawa *et al.* (Yukawa et al. 2004)
Publication Year	2006	2013	2003	1996	1997	1997	1997	1997	2004
Location	Poland	Brazil	Sweden	Norway	The Netherlands	The Netherlands	The Netherlands	The Netherlands	Japan
Design	Randomised placebo controlled crossover trial	Crossover Clinical Trial	Controlled Study	Cross-Sectional Study	Randomised Controlled Trial	Randomised Controlled Trial	Randomised Controlled Trial	Randomised Controlled Crossover Trial	Controlled Study
Comparison	Natural coffee *vs* pressure extracted modified coffee	Medium roast coffee *vs* medium light roast	Filtered coffee *vs* abstinence	Boiled coffee drinkers *vs* filter coffee drinkers	Filtered coffee *vs* Cafetiere coffee	Placebo oil *vs* coffee oil	Placebo oil *vs* coffee oil v ‘stripped oil.	Cafestol *vs* cafestol & kahweol	Coffee *vs* abstinence

Trial Protocol	4 weeks of first intervention; 28 day break; 4 weeks second intervention	1 week run-in; 4 weeks first intervention; 4 weeks second intervention	2 x (3 weeks abstinence, 4 weeks consumption)	NA	4 weeks filter coffee; 24 weeks randomised intervention; 12 weeks follow up	2 weeks placebo oil; 4 weeks randomised intervention; 4 weeks follow up	1 week placebo oil; 4 weeks randomised intervention; 4 weeks follow up.	2 x (2 week placebo oil; 4 weeks randomised intervention, 7 weeks follow up)	1 week baseline, 1 week coffee, 1 week washout
Inclusion criteria	Healthy participants at age 28-55 years (50% smokers). The study was conducted in the summer months to avoid vitamin deficiencies.	Age 20 y to 65 y, plasma cholesterol <240 mg/dl∞, blood glucose <5.56 mmol/L, nonsmoker or former smoker (>2 y), alcohol consumption less than one drink	Inclusion criteria were age range 30–65 y, free of clinically recognized chronic diseases such as cardiovascular diseases,	Recruited as part of the Norwegian National Health Screening in 1992, a population. Aged 40–42 years Subjects were considered	N/A	N/A	N/A	N/A	N/A

		per day, absence of chronic diseases, and no use of regular medication	cancer, renal disorders, liver disease and diabetes mellitus. They were not on antiepileptic or cholesterol-lowering drugs, had been using coffee on a regular basis for at least 5y and were currently nonsmokers (at least for the last 6 months)	eligible if they were healthy, did not take any medication known to affect liver enzymes or serum lipids, and did not consume more than three alcohol-containing beverages per day					

Source and type of coffee	Two commercially available blends: natural coffee (MK Cafe – 100% Arabica) *vs.* modified coffee with 60% less quantity of 2-methylisoborneol (MK Cafe Feelings; both: MK Cafe, Poland)	Two commercially available blends (80% Coffee Arabica L. cv. Bourbon and 20% C. canephora cv. Robusta) of caffeinated, roasted, ground coffee	Not stated, but provided by investigators to ensure consistency	N/A	Roodmerk (Douwe Egberts) a blend of Arabica and Robusta beans	N/A	N/A	N/A	Arabica coffee (Ajinomoto General Foods, Inc., Japan)
Methods of coffee preparation	Natural coffee *vs* pressure extracted	Filtered	Filtered	N/A	Filtered or Cafetiere	Oil	Oil	Oil	Coffee dissolved in boiling

	coffee								water
Dose of coffee	3 x 180 ml daily. Each serving prepared with 13g ground coffee	3-4 x 150 ml cups of coffee per day: mean 482 ± 61 ml/day	600ml/day	NA. Participants who habitually consumed five or more cups of boiled coffee per day were compared with matched filter coffee consumers	Filtered coffee (0.9 L/day) Cafetiere coffee (0.9 L/day)	Placebo oil (3g/day) Coffee oil (3g/day)	Placebo oil (2g/day) Coffee oil (2g/day) Stripped oil (2g/day)	Cafestol Cafestol + kahweol	150 ml three times per day Each serving prepared with 8g coffee.
Daily Cafestol dose (mg)	N/A	Approx 20	Not reported	N/A	<1 (filtered) 38 (Cafetiere)	0 (placebo oil) 85 (coffee oil	0 (placebo) 57 (coffee oil) Not reported (stripped oil)	61-64 (Cafestol) 60 (cafestol plus kahweol)	N/A

Daily Kahwol dose (mg)	N/A	Approx 2.5	Not reported	N/A	<1 (filtered) 33 (cafetiere	0 (placebo oil 103 (coffee oil)	0 69 Not reported (stripped oil)	0-1 (Cafestol) 48-56 (cafestol plus kahweol)	N/A
Participants	36	20	120 (first trial period); 116 (second trial period)	150 (boiled) 159 (filtered)	24 (filtered) 22 (cafetiere)	16 (placebo oil) 16 (coffee oil)	15 (placebo oil) 15 (coffee oil) 16 (stripped oil)	10 (cafestol) 10 (cafestol plus kahweol)	11
Age (years)	42.7±5.8	49±9	48.6 (29-65)	41 ± 1 (boiled) 41 ± 1 (filtered)	29 ± 10	22 ± 2	22 ± 2	24 ± 4	Range 21-31
Male (%)	44	30	22	52.7 (boiled) 55.3 (filtered)	48.9	46.9	58.3	100	100
BMI ((kg/m2)	24.3±2.5	27.0±3.8	25.7 ± 3.4	25 ± 4 (boiled)	22 ± 3	22 ± 2	22 ±2	21 ±2	NS

				25 ± 3 (filtered)					
SBP (mmHg)	N/A	110.2 ± 9.2	125.6 ± 17.3	N/A N/A	N/A	N/A	N/A	N/A	N/A
DBP (mmHg)	N/A	70.5 ± 6.9	78.8 ± 11	N/A N/A	N/A	N/A	N/A	N/A	N/A
TC (mg/dL)	226 ± 35 (Modified) ∞ 221 ± 37 (Natural) ∞	186 ± 23 ∞	201 ± 36 ∞	231 ± 42 ∞ (boiled) 219 ± 41 ∞ (filtered)	189 ± 27 ∞	174 ± 19 ∞	174 ± 28 ∞	186 ± 35 ∞	185 ± 18
HDL-C (mg/dL)	57 ± 11 (Modified) ∞ 53 ± 11 (Natural) ∞	46 ± 12 ∞	56 ± 15 ∞	N/A N/A	58 ± 12 ∞	58 ± 12 ∞	54 ± 12 ∞	58 ±15 ∞	57 ± 13
LDL-C (mg/dL)	125 ± 34 (Modified) ∞	120 ± 19 ∞	N/A	N/A	116 ± 31 ∞	97 ± 19 ∞	104 ± 23 ∞	116 ± 27 ∞	122 ± 25

	127 ± 38 (Natural) ∞			N/A					
TG (mg/dL)	123 ± 62 (Modified) ∞	97 ± 35	110 ± 67 ∞	190 ± 137 ∞ (boiled)	97 ± 35∞	89 ± 27 ∞	79 ± 27 ∞	71 ± 18 ∞	93 ± 31
	129 ± 64 (Natural) ∞			170 ±110 ∞ (filtered)					
Lp(a) (mg/dl)	32 ± 24 (Modified)	22 ± 26 (median = 11.5)	NS	NA	20.8 ± 22.3 (median = 9.2) (filtered coffee)	25.9 ± 23.8 (median = 17.2) (placebo oil)	24.4 ± 23.4 (median =17.7) (placebo oil)	13.9 ± 7.5 (median =11.5) (cafestol)	25.1 ± 16.2
	31±27 (Natural)				15.2 ± 19.9 (median=9.8) (cafetiere coffee)	29.1 ± 32.7 (median =14.9) (coffee oil)	16.6 ± 16.6 (median =9.2) (coffee oil)	13.9 ± 7.5 11.5 (median) (cafestol + kahweol)	
							22.1 ± 25.5 (median =12.8) (stripped oil)		

Values are expressed as mean±SD unless otherwise stated ; ∞ values converted to units expressed here using http://www.endmemo.com/medical/unitconvert/

Abbreviations: SD: standard deviation; SEM: standard error of the mean; BMI: body mass index; NA: not available; SBP: systolic blood pressure, DBP: diastolic blood pressure; TC: Total Cholesterol; LDL-C: low-density lipoprotein cholesterol; HDL-C: high-density lipoprotein cholesterol; TG, triglycerides.

Table 3: Assessment of risk of bias in the included studies using a checklist based on the Cochrane Risk of Bias Assessment for Randomised Trials (with appropriate sections completed for the one cross-sectional study).

Author and date	Sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective outcome reporting	Other potential threats to validity
Bukowska *et al.* (2006)	U	U	L	L	L	U	L
Correa *et al.* (2013)	U	U	L	L	L	U	L
Strandhagen *et al.* (2003)	NA	NA	L	L	L	U	L
Urgert *et al.* (1996)	NA	NA	NA	L	L	U	L
Urgert *et al.* (1997) Trial A	U	U	L	L	L	U	L

Urgert *et al.* (1997) Trial B	U	U	L	L	L	U	L
Urgert *et al.* (1997) Trial C	U	U	L	L	L	U	L
Urgert *et al.* (1997) Trial D	U	U	L	L	H	U	L
Yukawa *et al.* (2004)	NA	NA	L	L	L	U	L

L: low risk of bias; H: high risk of bias; NA: Not applicable; U: unclear risk of bias.

Table 4: Summary of the results of studies included in the systematic review

Study	Design	Intervention / Exposure	Lp(a) at baseline mg/dL Mean ± S.D. unless otherwise stated	Lp(a) at endpoint mg/dL Mean ± S.D. unless otherwise stated	Summary
Bukowska *et al.* (Bukowska et al. 2006)	Randomised crossover trial	Natural coffee	31 ± 27	32 ± 28	No effect of coffee on Lp(a) No difference between groups
		Pressure extracted coffee	32 ± 24	38 ± 26	
Correa *et al.* (Correa et al. 2013)	Crossover Clinical Trial	Medium roast coffee	22 ± 26 11.5 (median)	22 ± 26 14.0 (median)	No effect of coffee on Lp(a) No difference between groups
		Medium light roast coffee	22 ± 26 11.5 (median)	23 ± 29 13.9 (median)	
Strandhagen *et al.* (Strandhagen et al. 2003)	Controlled Study	Filtered coffee	NS	-11 (median, 1st consumption)*	Lp(a) reduction during first period of coffee

					-4 (median, 2nd consumption)	consumption. Lp(a) increase during second abstention period. (*P<0.05)
			Abstinence from coffee	NS	+2 (median, 1st abstention) +15 (median, 2nd abstention)*	
Urgert *et al.* (Urgert et al. 1996)		Cross-Sectional Study	Boiled coffee drinkers	N/A	13 (0-130) Median(range)	Higher Lp(a) in boiled coffee drinkers (P = 0.048)
			Filter coffee drinkers	N/A	7.9 (0-144) Median(range)	
Urgert *et al.* (Urgert et al. 1997)	Trial A	Randomised Controlled Trial	Filtered coffee	20.8 ± 22.3 9.2 (Median)	Change from baseline: +0.2 ± 0.8* +0.3 (median)	Lower Lp(a) in cafetiere coffee drinkers than filtered coffee drinkers (*P<0.05)
			Cafetiere coffee	15.2 ± 19.9 9.8 (median)	Change from baseline: -2.0 ± 0.8	

					-0.9 (median)	
Urgert *et al.* (Urgert et al. 1997)	Trial B	Randomised Controlled Trial	Placebo oil	25.9 ± 23.8 17.2 (median)	Change from baseline: +1.1 ± 0.9 +0.5	Lower mean and median Lp(a) in consumers of coffee oil than consumers of placebo oil (**P<0.01)
			Coffee oil	29.1 ± 32.7 14.9 (median)	Change from baseline: -5.5 ± 1.4** -4.8 (median)**	
Urgert *et al.* (Urgert et al. 1997)	Trial C	Randomised Controlled Trial	Placebo oil	24.4 ± 23.4 17.7 (median)	Change from baseline: -1.0 ± 1.6 +0.8 (median)	Lp(a) lowest in coffee oil consuming group.(*P<0.05)
			Coffee oil	16.6 ± 16.6 9.2 (median)	Change from baseline: -4.5 ± 1.3 -2.3 (median)*	

			Stripped oil	22.1 ± 25.5 12.8 (median)	Change from baseline: -1.1 ± 1.3 -0.3 (median)	
Urgert *et al.* (Urgert et al. 1997)	Trial D	Randomised Controlled Crossover Trial	Cafestol	13.9 ± 7.5 11.5 (median)	Change from baseline: -3.5 ± 0.8** -3.1 (median)**	Reduction in both groups compared to baseline (**P<0.01)
			Cafestol & kahweol	13.9 ± 7.5 11.5 (median)	Change from baseline: -3.9 ± 1.0** -3.5 (median)**	
Yukawa *et al.* (Yukawa et al. 2004)		Controlled Study	Coffee	25.1 ± 16.2	23.2 ± 11.4	No effect of coffee on Lp(a)

FIGURE LEGENDS

Figure 1. Flow chart showing the number of studies identified, screened and included in the systematic review.