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# Review article: coffee consumption, the metabolic syndrome and non-alcoholic fatty liver disease

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## SUMMARY

### Background
Coffee consumption may modulate the risk of the metabolic syndrome (MetS) and non-alcoholic fatty liver disease (NAFLD).

### Aim
To review the experimental, epidemiological and clinical studies investigating the association between coffee consumption and the risk of MetS and NAFLD.

### Methods
A literature search was conducted with the aim of finding original experimental, epidemiological and clinical articles on the association between coffee consumption, MetS and NAFLD. The following databases were used: PubMed, Embase, Scopus and Science Direct. We included articles written in English and published up to July 2013.

### Results
Three experimental animal studies investigated the effects of coffee in the MetS, whereas five examined whether experimental coffee intake may modulate the risk of fatty liver infiltration. All of the animal studies showed a protective effect of coffee towards the development of MetS and NAFLD. Moreover, we identified eleven epidemiological and clinical studies that met the inclusion criteria. Of them, six were carried out on the risk of the MetS and five on the risk of NAFLD. Four of the six studies reported an inverse association between coffee consumption and the risk of MetS. The two studies showing negative results were from the same study cohort consisting of young persons with a low prevalence of the MetS. All of the epidemiological and clinical studies on NAFLD reported a protective effect of coffee intake.

### Conclusions
Coffee intake can reduce the risk of NAFLD. Whether this effect may be mediated by certain components of the MetS deserves further investigation.

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## INTRODUCTION

Because of its aromatic flavours and delicious taste, coffee is currently the second highest consumed beverage in the world after water, with approximately 500 billion cups drunk every year.[1–3] Moreover, coffee is a plant of enormous modern-day economic importance as it is the second largest traded commodity in the global market only second to oil.[4] Because coffee consumption is part of daily life of so many people around the world, several studies have explored its chemical composition along with its health effects in humans.[5–7] From a chemical standpoint, coffee is a complex mixture of potential physiologically active compounds.[1] According to the Institute for Coffee Studies, coffee contains over 1500 chemical components whose concentrations can be influenced by agricultural factors (e.g. species and variety of plant, cultivation methods) and preparation approaches (e.g. roasting, blending and brewing).[8] The main water-soluble constituents of coffee include phenolic polymers (8%), polysaccharides (6%), chlorogenic acids (4%), minerals (3%), water (2%), caffeine (1%), organic acids (0.5%), sugars (0.3%), lipids (0.2%) and aroma (0.1%).[8] Moreover, coffee has a lipid fraction, which is composed mainly of triacylglycerols, tocopherols, and esters of diterpene alcohols and fatty acids (mainly cafestol, kahweol and 16-O-methylcafestol).[9] Although caffeine is still considered the major active ingredient of coffee,[10] several other components (e.g. chlorogenic acid,[11] caffeic acid,[12] cafestol[13] and kahweol[14]) have a potent antioxidant activity, which can be maintained even after the roasting of coffee beans.[15]

For several years, the consumption of coffee has been considered an unhealthy practice and practitioners advised patients to avoid excess use because of the risks of caffeine dependence.[16] More recently, several studies have shown that coffee consumption may exert beneficial metabolic effects mainly because of its polyphenol compound content, which exhibit antioxidant and anti-inflammatory properties.[1–8] The complex nature of coffee and its multiple chemical components, including antioxidants, make its metabolic effects credible.

Emerging evidence from experimental, epidemiological and clinical studies supports the hypothesis that coffee consumption may modulate the risk of the metabolic syndrome (MetS) and also of its hepatic expression, non-alcoholic fatty liver disease (NAFLD). The purpose of this review was to evaluate all of the experimental, epidemiological and clinical studies reporting an association between coffee consumption and the risks of MetS and NAFLD. Given that the focus of this review was limited to the hepatic manifestations of the MetS, it was beyond the scope of the project to expand our search to other liver disorders, such as viral hepatitis or hepatocellular carcinoma.

## LITERATURE SEARCH AND SEARCH STRATEGY

A literature search was conducted with the aim of finding original experimental, epidemiological and clinical articles on the association between coffee consumption, MetS and NAFLD. The following databases were used: PubMed, Embase, Scopus and Science Direct. We included articles written in English and published up to July 2013. The terms used in the searches were as follows: coffee, coffee consumption, metabolic syndrome, insulin resistance syndrome, non-alcoholic fatty liver disease, non-alcoholic steatohepatitis and other terms related to experimental, epidemiological and clinical studies. The search strategy used in PubMed is shown in Table 1. Additional papers were identified in the reference lists of selected articles that met the inclusion criteria. All articles were read in full. Two independent investigators assessed papers for inclusion in a parallel manner. Three primary outcome measures were used for this review: (i) the experimental evidence linking coffee

**Table 1 |** Search strategy in PubMed

| | |
|---|---|
| Metabolic syndrome | Metabolic syndrome [MeSH] OR metabolic syndrome [All Fields] OR insulin resistance syndrome [All Fields] |
| Non-alcoholic fatty liver disease | Non-alcoholic fatty liver disease [MeSH] OR non-alcoholic fatty liver disease [All Fields] OR non-alcoholic steatohepatitis [All Fields] |
| Coffee | Coffee [All Fields] OR caffeine [All Fields] |
| Study type | Animal study [All Fields] OR in vitro study [All Fields] OR Case-control study [All Fields] OR epidemiological study [All Fields] OR retrospective study [All Fields] OR cohort study [All Fields] OR incidence study [All Fields] OR cross-sectional study [All Fields] OR longitudinal study [All Fields] OR prospective study [All Fields] |
| Language limits | English |

intake with MetS and fatty liver infiltration in animal models; (ii) the epidemiological and clinical evidence on the association between coffee consumption and the risk of MetS; (iii) the epidemiological and clinical evidence on the association between coffee consumption and the risk of NAFLD.

## RESULTS

### Experimental studies

Three experimental animal studies investigated the effects of coffee in the MetS,[17–19] whereas five examined whether experimental coffee intake may modulate the risk of fatty liver infiltration.[20–24]

*Coffee consumption and the risk of metabolic syndrome.* Fukushima *et al.*[17] have investigated the effect of coffee administration on liver and adipose tissue gene expression using an animal model of the MetS (mice fed a high-fat diet). The results indicated that the addition of both caffeine-containing instant coffee and 1.1% decaffeinated coffee to a high-fat diet significantly decreased body weights compared with the high-fat diet only. Interestingly, both serum aminotransferases and proinflammatory cytokine gene expression in the liver were significantly reduced by the addition of coffee to the diet. The authors concluded that the anti-inflammatory responses elicited by coffee consumption could play a role in reducing the risk of developing the MetS.[17] Another study assessed the effects of Colombian coffee extract in a rat model of human MetS (Wistar rats fed a high-carbohydrate, high-fat diet).[18] The results demonstrated that coffee supplementation attenuated the onset of common MetS features as well as and the development of NAFLD in experimental animals, without significant effects of abdominal obesity.[18] Similarly, a study conducted in diabetic Zucker rats affected by the MetS showed that daily doses of coffee drink given by gavage for 30 days resulted in significant hypoglycaemic and hypolipidaemic effects, ultimately protecting against the development of an adverse metabolic profile.[19]

*Coffee consumption and the risk of NAFLD.* Yamauchi and co-workers[20] showed that 2-fold-diluted coffee given for 5 weeks to spontaneously diabetic KK-Ay mice improved both insulin sensitivity and fatty liver. Similarly, Murase *et al.*[21] demonstrated that supplementation with coffee polyphenols significantly reduced diet-induced abdominal and liver fat accumulation in C57BL/6J mice. Coffee has been also shown to decrease liver fat and collagen content and reduce the hepatic concentrations of proinflammatory TNF-$\alpha$ and interferon-$\gamma$ as well as increase anti-inflammatory interleukin-4 and interleukin-10 in an animal model of steatohepatitis.[22] In keeping with previous findings, Matsuda *et al.*[23] demonstrated that 2.5-fold-diluted coffee or caffeine solution (200 mg/L) given for 17 weeks exerted an ameliorative effect on the expression of genes related to fatty acid synthesis in the liver of C57BL/6J mice fed a high-fat diet. Finally, it has been recently shown that the coffee interacts with training in influencing liver triglyceride levels in Sprague–Dawley rats.[24]

### Epidemiological and clinical studies

Eleven epidemiological and clinical studies met the inclusion criteria.[25–35] Six studies were carried out on the risk of the MetS[25–30] and five on the risk of NAFLD.[31–35] However, two of the studies on the risk of the MetS were conducted in the same cohort (the Amsterdam Growth and Health Longitudinal Study) at two different time points within the context of a longitudinal study.[26, 27]

*Coffee consumption and the risk of metabolic syndrome.* One population-based case–control study,[25] two population-based prospective studies[26, 27] and three population-based cross-sectional studies were identified.[28–30] Four of these studies originated from Japan[25, 28–30] and two from the Netherlands.[26, 27]

The population-based case–control study was conducted in a sample of 1902 Japanese aged over 40 years, who received population-based health check-up in 1999.[25] Participants were residents in a farming community located in Kyushu, a southwestern island of Japan. The results indicated that caffeine intake decreased stepwise according to the number of MetS Japanese criteria.[36] Moreover, the authors found a high frequency of the MetS in small coffee drinkers.[25]

The two population-based prospective studies were conducted in the same cohort from the Netherlands (the Amsterdam Growth and Health Longitudinal Study) at two different time points within the context of a longitudinal study.[26, 27] The Amsterdam Growth and Health Longitudinal Study is a multidisciplinary cohort study that was initially set up to examine growth and health among teenagers. Over the years, the investigators sought to address several research questions dealing with the relationships between the development of anthropometry, lifestyle, and health from adolescence into adulthood.[26, 27] The first study investigated the relationship of long-term coffee consumption between the age of 27 and

36 years with the prevalence of the MetS at the age of 36 years,[26] whereas the second investigation analysed the associations between coffee consumption between the age of 27 and 42 years and the components of MetS at the age of 42 years.[27] In both studies, the National Cholesterol Education Program Adult Treatment Panel III criteria were used for diagnosing the MetS.[37] The results of the two reports – which were conducted in a relatively healthy cohort with a low baseline prevalence of the MetS – showed no significant associations between long-term coffee consumption and MetS risk factors.[26, 27]

All of the three population-based cross-sectional studies were conducted in Japan.[28–30] In the study of Matsuura *et al.*[28], the odds ratios among men for the presence of metabolic syndrome were 0.79 (95% confidence interval: 0.56–1.03) and 0.61 (0.39–0.95), respectively, among moderate (≥4 cups of coffee per day) coffee drinkers as compared with noncoffee drinkers. However, no such association was seen in women. In line with these findings, Katami *et al.*[29] reported that greater coffee consumption was associated with a significantly lower prevalence of the MetS after adjustment for sex, age and other potential confounders. More recently, Mure *et al.*[30] demonstrated that habitual moderate coffee consumption has a significant inverse association with MetS-related biomarkers, including adiponectin. Therefore, these three studies concordantly found a significant inverse association between coffee consumption and the prevalence of MetS in the Japanese population.

*Coffee consumption and the risk of NAFLD.* We identified two cross-sectional studies[32, 33] and three case–control studies[31, 34, 35] investigating the association between coffee consumption and the risk of NAFLD. The first cross-sectional study was conducted in France in a sample of 195 severely obese patients.[32] All of the patients had liver biopsies and a specific questionnaire investigating different types of coffee (regular filtrated coffee and espresso) was used. The results demonstrated that the consumption of regular coffee was an independent protective factor for fibrosis (odds ratio: 0.752; 95% confidence interval: 0.578–0.980) after adjustment for potential confounders.[32] The second cross-sectional study was performed in the USA using a hospital-based sample.[33] Patients with ultrasound-diagnosed steatosis underwent liver biopsy and were asked to fill a validated caffeine questionnaire. The authors observed an inverse relationship between regular coffee consumption and hepatic fibrosis, with a statistically significant difference in caffeine and coffee intake observed between bland steatosis/not-non-alcoholic steatohepatitis (NASH) patients, NASH stage 0–1 fibrosis patients and NASH stage 2–4 fibrosis patients. All analyses were adjusted for age, sex, body mass index and race.[33]

Three case–control studies examined the association between NAFLD risk and coffee consumption.[31, 34, 35] The first study was conducted in an Italian out-patient clinic and day hospital.[31] A total of 137 patients with ultrasound-diagnosed NAFLD and 108 controls were enrolled. Coffee drinking was defined according to the absolute number of cups of coffee (only espresso coffee), and also graded as 1 (0 cups of coffee/day), 2 (1–2 cups of coffee/day), 3 (≥3 cups of coffee/day). Moreover, a multivariable model including the number of cups of coffee accounted for 37.1% of the variance in the bright liver scores.[31] The second study was conducted in Mexico in a cohort of 73 patients with ultrasound-diagnosed NAFLD and 57 controls.[34] All of the participants completed a dietary questionnaire to determine their coffee consumption. The results indicated that coffee and caffeine intake was lower in NAFLD cases than in controls, but no association was observed between the protective effect of coffee and oxidative stress markers.[34] Finally, Birerdinc *et al.*[35] performed a large case–control study (1782 patients with NAFLD and 16768 controls) using the National Health and Nutrition Examination Surveys (NHANES) cohort. Dietary intake data were collected as a part of the Dietary Recall Interview. The results indicated that caffeine consumption (in mg) was significantly associated with a reduced risk of NAFLD (odds ratio (95% confidence interval) 0.999319 (0.998955–0.999684).[35] Therefore, all of the available studies suggest a reduced risk of NAFLD associated with coffee drinking.

## DISCUSSION

The aim of this review was to examine whether a relationship exists between coffee intake and the risk of MetS and NAFLD in both animal and human studies.

The results of the three animal studies focusing on the effect of coffee consumption on the risk of MetS concordantly showed that coffee supplementation attenuated the expected onset of an adverse metabolic profile in animals fed high-fat diets.[17–19] Similarly, at least five experimental studies independently demonstrated that coffee consumption improved insulin sensitivity and fatty liver infiltration in animal models of NAFLD[20–24]

Concerning human clinical and epidemiological studies, eleven studies met the inclusion criteria.[25–35] Six studies were carried out on the risk of the MetS[25–30] and

five on the risk of NAFLD.[31–35] Four of the six studies reported an inverse association between coffee consumption and the risk of MetS.[25, 28–30] The two longitudinal studies showing statistically not significant result were both from the same study cohort (the Amsterdam Growth and Health Longitudinal Study) consisting of young persons with a low prevalence of the MetS.[26, 27] Therefore, the lack of the association between coffee consumption and the MetS in this case might have been due to the specific characteristics of the investigated cohort, which consisted of relatively healthy people. Strikingly, all of the studies on NAFLD reported a protective effect of coffee intake.[31–35] Collectively, these data indicate that coffee consumption may be considered a potential preventive agent for individuals at high risk of developing NAFLD. Whether this effect may be mediated at least in part by modulating certain components of the MetS deserves further investigation.

The biological mechanisms of the protective effect of coffee on the risk of NAFLD remain unclear. Although several coffee components have a scavenging effect on free radicals,[8] which may promote the development of NAFLD,[38, 39] one study found no association between the protective effect of coffee and oxidative stress markers.[34] However, coffee is currently considered the largest source of dietary antioxidants in industrialised countries[40] and we cannot exclude, at present, that its protective effects may be mediated at least in part by its scavenging effects on free radicals. In any case, it has been recently proposed that coffee may exert beneficial effects on the liver that may go beyond antioxidation. In this regard, caffeine has been shown to exert direct hepatoprotective effects.[3]As shown by experimental studies, caffeine attenuates the MetS in diet-induced obese rats, possibly via direct lipolytic effects.[18] Coffee has been also shown to decrease liver fat and collagen content and reduce the hepatic concentrations of proinflammatory TNF-$\alpha$ and interferon-$\gamma$ as well as increase anti-inflammatory interleukin-4 and interleukin-10 in an animal model of steatohepatitis.[22]

Furthermore, there is evidence suggesting that coffee can (i) attenuate the progression of liver fibrosis by inhibiting hepatic stellate cells[41]; (ii) inhibit the expression of connective tissue growth factor, alpha-smooth muscle actin and matrix metalloproteinases in the liver[42]; (iii) lower serum levels of aminotransferases[43, 44]; and (iv) improve insulin sensitivity and glucose tolerance in C57BL/6J mice fed a high-fat diet[23] as well as in spontaneously diabetic KK-A(y) mice.[20] All of these actions could be potential contributors to the inverse relationship observed between coffee intake and NAFLD.

We should acknowledge that the findings of the human clinical and epidemiological studies included in this review should be interpreted within the context of important limitations. First and foremost, the studies included in this review were quite heterogeneous in terms of methodology. However, all of the human studies on NAFLD reported a protective effect of coffee as also did the majority of those focusing on the MetS. Taken together with the results of animal studies, these data provide support for the contention that coffee itself may be protective towards the development of these metabolic disorders. Although all of the studies included in the review had a fairly large number of subjects, it is also possible that participants in each study could not be truly representative of the general population. Moreover, it is difficult to eliminate bias and confounding in observational diet-disease studies.[45] In this regard, future studies should provide a more in-depth analysis of the confounding effects of other beverages (e.g. alcohol and soft drinks), which may be detrimental for the liver and may promote the MetS. Furthermore, coffee consumption should be assessed in terms of the amount of active ingredient consumed in a given period. Future epidemiological investigations should take into account the method of preparation of coffee, its strength and temperature and whether the exposure to sugar associated with the intake of sugar-sweetened coffee may be detrimental. Moreover, further research is needed to investigate whether different coffee recipes and preparations may have a different effect on the risk of MetS and NAFLD, as preliminary data seem to suggest.[32] Finally, it is possible that our review may suffer from the effects of publication bias because studies where coffee appeared beneficial are more likely to be published than those in which it did not.

These caveats notwithstanding, the overall conclusion from this review of both animal and clinical studies is that an inverse association seems to exist between coffee consumption and the risk of NAFLD. Whether this effect may be mediated at least in part by modulating certain components of the MetS deserves further investigation.

## AUTHORSHIP

*Guarantor of the article*: Y. Yilmaz.

*Author contributions*: AY and YY conducted the literature review and extracted, synthesised and analysed data. AY originated the study. YY led the data interpretation and the writing of the article. Both authors

helped to conceptualise ideas and interpret findings and contributed to the writing and revision process. Both authors approved the final version of the article, including the authorship list.

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