

Coffee and disease: an overview with main emphasis on blood lipids and homocysteine

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Abstract

The issue of whether coffee is detrimental or beneficial to health has been studied in a large number of observational and clinical studies. Some observational studies have shown an association between coffee and coronary heart disease (CHD), while others have not. Both clinical trials and observational studies have shown that coffee consumption affects some CHD risk factors, e.g. plasma total homocysteine and serum total cholesterol. Studies on the association between coffee consumption and health have shown protective effects against type 2 diabetes, Parkinson's disease and Alzheimer's disease, whereas the protective effect against certain forms of cancer and possible hazards with regard to reproductive health are still debated. This review reports on the association between coffee intake and homocysteine and blood lipids in light of the results of studies by this group. A review of published papers on the relevant issues found that protective effects of coffee have been reported for type 2 diabetes, Parkinson's disease and Alzheimer's disease. These results are based on observational studies. More studies with adequate control of confounding variables are needed to confirm these findings. There are at present no relevant biological explanations for any protective effect. Studies by this group have confirmed that even filtered coffee has a total cholesterol-increasing effect. Whether this is due to changes in filter-paper quality or other unknown mechanisms is not clear. The homocysteine-raising effect of coffee is mainly seen among subjects with the methylenetetrahydrofolate reductase (MTHFR) 677TT polymorphism, demonstrating a nutrition–gene effect modification. In conclusion, the effects of coffee on blood lipids and plasma homocysteine are firmly based, but the studies reflect a certain heterogeneity, in part explained by genetic susceptibility. The coffee–health issue is still pending; there are certain firmly established biological effects of coffee intake, but the impact on future health is virtually unknown.

Keywords: *blood lipids; coffee; coronary heart disease; homocysteine; reproductive hazards*

Received: 17 January 2005; Revised: 21 March 2005; Accepted: 31 March 2005

Introduction

The issue of whether coffee is detrimental or beneficial to health is not new. King Gustav III of Sweden (1746–1792) decided that coffee was pure poison. To prove the truth of this theory he granted amnesty to a murderer who was condemned to death, and ordered him to drink coffee every day until he died. As a control he granted amnesty to another murderer, on condition that he should drink tea every day. Two doctors were designated to look after the experiment and assess the outcome. In this case, the doctors were the first to die. Then, the king was murdered in 1792. As time went by the first one of the two criminals died, 83 years old: it was the tea drinker. The consequence of the

experiment was not taken into account. Drinking coffee was forbidden in Sweden in 1794 and in 1822.

History of coffee

The coffee tree probably originated in the province of Kaffa, in the area known today as Ethiopia. It is not known exactly when, or how, it was first discovered that a rich and stimulating brew could be made from the coffee bean. Before coffee was consumed as a beverage, people may have chewed the cherries and beans. There is evidence to suggest that coffee trees were cultivated 1000 years ago. The first reports of commercial cultivation are from Yemen in the fifteenth century.

The first coffee houses were opened in Mecca, where coffee drinking was initially encouraged, and quickly spread throughout the Arab world. Venetian traders first brought coffee to Europe in 1615, and 30 years later a coffee house or “café” was opened in Venice. The growth of popular coffee houses, which became favourite meeting places for both social and business purposes, spread to other European countries. The Dutch became the first main suppliers of coffee to Europe, with Amsterdam as the trading centre.

In 1685 coffee was, according to the Customs of Göteborg, imported for the first time into Sweden. Two years later coffee was entered as a medicine on the chemists’ price list. King Karl XII increased coffee drinking in Sweden. On his return to Sweden from Turkey in 1716, he brought with him a Turkish coffee machine. During his 12 year exile in Turkey he had learned to appreciate the beverage.

Coffee is now one of the most valuable primary commodities in the world, often second in value only to oil as a source of foreign exchange to developing countries. Millions of people around the world earn their living from it.

The objectives of this paper are to assess, in particular, the association between coffee consumption and two important intermediary risk factors, both with relevance to cardiovascular and reproductive health: blood lipids and plasma homocysteine.

Coffee consumption

Estimates of coffee consumption are based on production, import, export and food surveys, calculated from the intake at individual or household level. Europe is the continent with the highest coffee consumption, 4.6 kg per person per year before roasting. The world average is estimated to be 1.2 kg per person per year. The Nordic countries are the highest coffee consumers in the world, with a figure of about 10 kg per person per year (1). The coffee commonly used in the Nordic countries is Arabica, with nearly 100% of the market.

Coffee chemistry

There are two main commercial varieties of raw coffee, Arabica coffee and Robusta coffee. They differ in composition, with Arabica containing more lipids and Robusta more caffeine and chlorogenic acids. Compounds typical of coffee have been

identified, the main ones being the diterpenes cafestol and kahweol.

More than 100 plant species are known to contain methylxanthine, particularly caffeine (1,3,7-trimethylxanthine). The most commonly used sources are coffee, tea and cocoa. The caffeine content of a cup of coffee can vary from 1–5 mg for decaffeinated coffee to 50–150 mg for a cup of regular coffee. Chlorogenic acid is a polyphenolic compound, which occurs in an amount of 70–200 mg per cup of Arabica coffee (2).

Coffee and disease

Epidemiological studies have led to the identification of a number of dietary components that are associated with an increased risk of a variety of chronic disorders. These studies are based on comparisons either between populations (international or cross-population ecological studies) or within populations (cross-sectional, case–control or longitudinal observational studies). Most of the evidence from diet–disease associations stems from studies of intermediary factors such as blood pressure, lipids and glucose. The level of these factors are related to dietary exposure and other lifestyle variables, as well as being influenced by genetic polymorphisms. Any causal analysis of the impact of dietary factors implies the assessment of a plausible aetiological model where both biological mechanism and consistent observational data can be included in a comprehensible manner. To some extent, the protective effect of fruit and vegetables with regard to cancer, the blood pressure-increasing effect of salt and the possible role of fatty acids on cognitive function fit into such models (3–6). Still, a considerable part of the disease variance is left unexplained in these models. This may seem surprising, but the major reasons are the incomplete knowledge of the causal models (i.e. there are other unknown factors aetiologically associated with the disorder) and non-differential misclassification of the exposure variables biasing the results towards null.

Coffee, being such a common beverage with obvious central stimulating effects but seemingly low nutritional value, has been studied in a number of epidemiological studies aiming at a broad array of health issues. Theoretically, coffee might be considered to have a direct positive protecting effect or a negative hazardous effect, or to be of no importance when it comes to health and disease.

Studies on the association between coffee consumption and health have given heterogeneous results. There are some seemingly consistent findings, such as the protective effects against type 2 diabetes (7–10), Parkinson's disease (11) and Alzheimer's disease (12), whereas the protective effect against certain forms of cancer (13) and possible hazards with regard to reproductive (14–16) and cardiovascular (17–21) health are still debated.

Numerous epidemiological studies have investigated the relationship between coffee consumption and cancer incidence at various sites. Overall, there is no evidence that moderate (2–5 cups per day) coffee drinking represents a significant risk for the development of cancer in humans. In contrast, many studies have revealed an inverse (protective) association between coffee consumption and the risk of certain gastrointestinal cancers (13).

The possible relationship between coffee consumption and reproductive problems has been studied in a number of papers, and there are indications that coffee or caffeine may carry a certain, albeit small, risk of reproductive complications (14–16).

Coffee and coronary heart disease

An increased risk of coronary heart disease (CHD) among coffee drinkers has been observed in some cohort studies (17–20), but the common attitude has been that coffee carried no substantial risk for CHD and that most of the observed associations could be explained by confounding factors such as smoking (22–24).

A report from northern Norway in 1983, however, brought coffee back onto the cardiovascular agenda (21). In this cross-sectional analysis from the Tromsø Heart Study, total cholesterol levels were shown to be 0.79 and 0.72 mmol l⁻¹ (14%) higher in men and women, respectively, in the highest coffee consumption category than in the lowest category.

Still, there are studies of cohorts with a low prevalence of smokers where a relation between coffee and CHD has been observed, such as the Johns Hopkins Precursor Study (17) and the Chicago Western Electric Study (18), where there was an increased risk of CHD associated with coffee consumption, independent of other risk factors. Several studies in different population groups have, however, shown no association between coffee intake and CHD (25–30).

There are theoretically two possible mechanisms associated with coffee, which may contribute to an increased CHD risk: the increasing effect of coffee on total homocysteine (tHcy) in plasma, and total cholesterol, in particular low-density lipoprotein (LDL) cholesterol, in serum. The association between coffee and plasma homocysteine levels was unexpectedly observed in an extensive Norwegian study (31). This association, if biologically real, may explain why coffee consumption was a predictor of coronary death in an earlier Norwegian study, even after adjusting for both smoking and serum cholesterol (19). As mentioned earlier, the John Hopkins Precursor Study, with a follow-up time of 28–44 years, also showed a strong dose–response association between coffee consumption and CHD among non-smokers (20). However, the three meta-analyses undertaken so far do not show much evidence of an association between coffee consumption and the development of CHD among habitual coffee drinkers (32–34).

These discrepant results, which emerged from the observational studies, may be explained by:

- the consumption of different coffee brands containing different amounts of the active substances
- differing preparation methods
- difficulties in dose comparisons (a cup is not always a cup)
- non-differential misclassification
- the heterogeneous distribution of so far unknown effect modifiers
- the possibility that there is no real causal association.

Added to these are differences in design of the studies and the problems in epidemiological research of controlling adequately for confounding factors, whereby coffee drinking may be a marker for a lifestyle characterized by atherogenic factors and not a causal factor in itself (35).

A summary of observational studies on the association between coffee consumption and CHD is given in Table 1.

Coffee and serum cholesterol

The cholesterol-raising effect of coffee was first described in the literature by Egede-Nissen in 1970 (46). The author, who was a well-known general practitioner in Oslo, did not tell how he arrived at the idea that coffee could have a serum cholesterol-

Table 1. Observational studies on coffee consumption and coronary heart disease (CHD)

Reference (year)	n	Years of follow-up	Results	Comments
25 (1973)	464	5	No association	No effect
26 (1974)	5 209	12	Positive association between coffee consumption and total mortality	No effect
27 (1977)	7 705	6	Positive association between coffee and CHD, not significant after adjustment for smoking	No effect
37 (1977)	834	12	No association	No effect
28 (1978)	2 530	4.5	No association	No effect
38 (1981)	16 911	11.5	No association	No effect
39 (1984)	851 M	17	Positive association between coffee and CHD, not significant after adjustment for smoking	No effect
17 (1986)	1 130 M	19–35	Coffee consumption >5 cups per day, RR 2.49 compared to 0 cups per day	Effect
35 (1987)	12 931	11.5	No association	No effect
18 (1987)	1 910	19	Coffee consumption >6 cups per day, RR 1.71 compared to <6 cups per day	Effect
40 (1989)	6 214	13–19	No association	No effect
36 (1990)	101 774	5	Slight association independent of s-cholesterol	Effect
41 (1990)	45 589	2	Positive association between decaffeinated coffee and CHD	Effect
19 (1990)	38 564	6.4	Strong association between coffee consumption and CHD	Effect
42 (1991)	6 765	7.1	Weak but not significant trend towards increasing incidence of CHD in heavy coffee consumers	No effect
43 (1992)	9 484	25	Small, significant association between coffee consumption and CHD mortality	Effect
20 (1994)	1 040	28–44	Strong association between coffee consumption and CHD	Effect
29 (1995)	2 975 M		No association	No effect
44 (1996)	85 747 F	10	No association	No effect
45 (1999)	>11 000	7.7	Negative association between coffee consumption and CHD	No effect
30 (2000)	20 179	10	No association	No effect

M: males; F: females; s-cholesterol: serum cholesterol; RR: relative risk.

raising effect: a pity! He put 15 patients with hypercholesterolaemia on 2 weeks of coffee abstinence while their diet was kept unchanged. The abstinence from coffee had a cholesterol-decreasing effect in all of these individuals.

The first cross-sectional study showing that the consumption of coffee was associated with total serum cholesterol was the Tromsø Heart Study (21). Since then this observation has been confirmed in several cross-sectional studies (19, 20, 42, 47–55), but not all. Thelle et al. concluded in their review that the incongruity of cross-sectional data points to a relationship between coffee and cholesterol in some populations, which needs to be further explored (56). This led to an increased interest in the possible effects of different brewing methods, first examined by Førde et al. (57) and later followed up by Dutch and Finnish groups (51, 58).

In a later meta-analysis Bak showed that total cholesterol increased by an average of $0.008 \text{ mmol l}^{-1}$ per cup of filtered coffee, compared with $0.038 \text{ mmol l}^{-1}$ per cup of unfiltered or boiled coffee (59). Further studies revealed that the cholesterol-raising effect was due to the natural

content of the diterpenes kahweol and cafestol in the green coffee beans (60–62). Cafestol is the most potent cholesterol-elevating compound known and is responsible for more than 80% of the effect on serum lipids (63). Each 10 mg of cafestol increases serum cholesterol by 0.13 mmol l^{-1} and serum triglycerides by 0.08 mmol l^{-1} after consumption for 4 weeks (62). Unfiltered coffee contains 3–6 mg of each diterpene per cup (63).

Several studies showed that a major part of the diterpenes is retained by a paper filter, which substantially reduces the cholesterol-raising effect of coffee (57, 59, 64, 65).

Recently, 14 clinical trials on the relation between coffee consumption and serum lipids were put together in a meta-analysis by Jee (66). This meta-analysis showed a dose-response relation between coffee consumption and both total cholesterol and LDL-cholesterol. Increases in serum lipids were greater in studies of patients with hyperlipaemia and in trials of caffeinated or boiled coffee. Intervention studies on the association between unfiltered and filtered coffee and serum cholesterol are shown in Tables 2 and 3, respectively.

Table 2. Intervention studies on the association between unfiltered coffee and serum cholesterol

Reference (year)	n	Duration (weeks)	Amount of coffee consumed	Results	Comments
57 (1985)	33	10	As usual	Coffee abstention resulted in a decrease in s-cholesterol by 1.16 mmol l ⁻¹ (10 weeks). Boiled coffee resulted in an increase in s-cholesterol by 0.52 mmol l ⁻¹ (after 5 weeks)	Effect
67 (1987)	42	6	8 cups of boiled coffee per day	s-cholesterol increased by 0.64 mmol l ⁻¹ in mild to moderate hyperlipaemic subjects	Effect
58 (1989)	107	12	4–6 cups of boiled coffee per day	s-cholesterol increased by 0.48 mmol l ⁻¹	Effect
68 (1996)	46	24	0.9 litre of café coffee per day	s-LDL-cholesterol increased by 0.24 mmol l ⁻¹	Effect
69 (2000)	64	10	1 litre of boiled coffee per day	Resulted in an increase in s-cholesterol by 0.5 mmol l ⁻¹	Effect

s-cholesterol: serum cholesterol; LDL: low-density lipoprotein.

A larger cholesterol-raising effect of filter-brewed coffee has been shown in three recent intervention studies (73, 77, 78). The effect of coffee in these three studies is remarkably consistent and of the same magnitude. However, nine of the 13 trials published so far on this issue have failed to show a cholesterol-enhancing effect of filtered coffee (Table 3). The mechanism behind the increase in serum cholesterol by filtered coffee is hard to explain. It may be due to an unknown compound

that passes through the filter and raises cholesterol, or diterpenes may have passed through the filters used in these studies.

Coffee and effect on total homocysteine

Elevated concentrations of homocysteine have been identified as an independent risk factor for CHD (79–82). It remains uncertain whether the relation between elevated concentrations of homocysteine and CHD is causal (83, 84). Randomized clinical

Table 3. Intervention studies on the association between filtered coffee and serum cholesterol

Reference (year)	n	Duration (weeks)	Amount of coffee consumed	Results	Comments
57 (1985)	33	10	As usual	Coffee abstention resulted in a decrease in s-cholesterol. No effect of filtered coffee	No effect
70 (1985)	12	3	8 cups of instant coffee per day	No effect	No effect
67 (1987)	42	6	8 cups of filtered coffee per day	No effect	No effect
58 (1989)	107	12	4–6 cups of filtered coffee per day	No effect	No effect
71 (1990)	21	4	3.6 cups of filtered coffee per day	No effect	No effect
72 (1990)	45	12	5 cups of filtered or decaffeinated filtered coffee per day	No effect	No effect
73 (1992)	100	16	7.2 dl of filtered coffee per day	s-cholesterol increased by 0.24 mmol l ⁻¹ . No effect of decaffeinated coffee	Effect
74 (1994)	119	2	7.5–10 dl of filtered or decaffeinated filtered coffee per day	No effect	No effect
75 (1995)	261	6	5 cups of instant coffee per day	s-cholesterol increased by 0.12 mmol l ⁻¹	Effect
76 (1995)	49	14	3 cups of filtered or decaffeinated filtered coffee per day	No effect	No effect
68 (1996)	46	24	0.9 litre of filtered coffee per day	No effect	No effect
77 (2001)	191	6	4 cups of filtered coffee per day	Abstention resulted in a decrease in s-cholesterol of 0.28 mmol l ⁻¹	Effect
78 (2003)	120	14	4 cups of filtered coffee per day or coffee abstention	Change in s-cholesterol by 0.15–0.36 mmol l ⁻¹	Effect

s-cholesterol: serum cholesterol.

trials are underway to study whether a reduction in homocysteine concentrations with B vitamins reduces the risk of cardiovascular disease (85).

The metabolism of homocysteine is dependent on the availability of the B vitamins folic acid, vitamin B₁₂ and pyridoxine (vitamin B₆). Although elevated levels of tHcy in plasma and serum are seen particularly in folate deficiency, elevated levels are also seen together with folate levels in the lower reference range (86).

These associations are reflected in population studies such as the Hordaland Homocysteine Study, where the major determinants for tHcy variation were age, gender, smoking, dietary folic acid intake, vitamin supplements and coffee consumption (31). The positive association between heavy coffee drinking and plasma concentrations of tHcy first reported by Nygård has since been observed in several cross-sectional surveys (55, 87–90). Nygård showed that in a population of 16 000 Norwegians, those who drank >9 cups coffee per day had tHcy concentrations that were >20% higher than those who refrained from drinking coffee (55). There was a significant positive relationship between coffee and tHcy in drinkers of filtered, boiled and instant coffee, but not decaffeinated coffee (91). In coffee consumers aged 40–42 years, the percentage increase in tHcy exceeded the percentage increase in total cholesterol in serum.

A summary of observational studies on the association between coffee consumption and tHcy is given in Table 4.

Five interventional studies examining the association between coffee and homocysteine had been

published up to 2003 (69, 77, 94–96) (Table 5). Three of the studies showed that consumption of about 1 litre of coffee per day resulted in an increase in tHcy of 1–1.5 $\mu\text{mol l}^{-1}$ (69, 77, 94). The study by Christensen et al. (77) showed that coffee abstention for 6 weeks resulted in a decrease in tHcy by 1.08 $\mu\text{mol l}^{-1}$, in participants who had been consuming on average 4 cups of coffee per day during the past year. Adjusting for different possible confounders did not alter the result. The study by Strandhagen et al. also showed that 4 cups of filtered coffee had an effect on plasma homocysteine, by 1 $\mu\text{mol l}^{-1}$ (96).

Until recently, no plausible mechanism was known to explain the homocysteine-raising effect of coffee, but a recent observational study showed a positive association between caffeine intake and homocysteine concentrations (90). This has been followed by a randomized cross-over trial by Verhoef et al., where caffeine capsules were compared with filtered coffee, which showed that caffeine is partly responsible for the tHcy-raising effect of coffee, since caffeine had only 25–50% of the tHcy-raising effect compared with paper-filtered coffee with a similar amount of caffeine (95). Thus, compounds in coffee other than caffeine may be additionally responsible for the tHcy-raising effect of coffee.

Another chemical substance, chlorogenic acid, has also been suggested as the biologically active substance responsible for the coffee–homocysteine association (97). The authors showed that chlorogenic acid raised tHcy levels, as the consumption of 2 g chlorogenic acid per day for 7 days, correspond-

Table 4. Observational studies on the association between coffee consumption and total homocysteine (tHcy)

Reference (year)	n	Results	Comments
55 (1997)	16 444	Women: >9 cups per day compared to no coffee: plasma tHcy 10.5 and 8.2 $\mu\text{mol l}^{-1}$, respectively. Men: >9 cups per day compared to no coffee: plasma tHcy 12.0 and 10.1 $\mu\text{mol l}^{-1}$, respectively. No association between decaffeinated coffee and tHcy	Effect
87 (1998)	310	No coffee compared to >1 litre coffee per day: a difference in plasma tHcy of about 1 $\mu\text{mol l}^{-1}$ (two different models)	Effect
88 (1999)	260	4 cups per day compared to 1 cup per day: difference in plasma tHcy 1.3 $\mu\text{mol l}^{-1}$	Effect
89 (2001)	3 025	Women: >6 cups per day compared to no coffee: difference in plasma tHcy 1.1 $\mu\text{mol l}^{-1}$. Men: >6 cups per day compared to no coffee: difference in plasma tHcy 1.6 $\mu\text{mol l}^{-1}$	Effect
90 (2001)	1 960	4 cups per day compared to 1 cup per day: difference in plasma tHcy 1.0 μmol (10.0 $\mu\text{mol}/9.0 \mu\text{mol l}^{-1}$). No association between decaffeinated coffee and tHcy	Effect
92 (2001)	486	Coffee drinkers compared to non-coffee drinkers: plasma tHcy 10.3 and 9.5 $\mu\text{mol l}^{-1}$, respectively. Not significant when adjusted for serum folate	No effect
93 (2001)	278	Weak positive correlation between coffee consumption and tHcy	Effect

Table 5. Intervention studies on the association between coffee consumption and total homocysteine (tHcy)

Reference (year)	n	Duration (weeks)	Type of coffee	Amount of coffee consumed	Result
69 (2000)	64	2	Boiled	1 litre per day	tHcy increased by $1.2 \mu\text{mol l}^{-1}$
94 (2000)	26	4	Filtered	5–8 cups per day	tHcy increased by $1.5 \mu\text{mol l}^{-1}$
77 (2001)	191	6	Filtered	Coffee abstention (4.9 cups before study)	tHcy decreased by $1.08 \mu\text{mol l}^{-1}$
95 (2002)	26	2	Caffeine capsules	870 mg caffeine per day	tHcy increased by $0.4 \mu\text{mol l}^{-1}$
		2	Filtered	0.9 litre per day	tHcy increased by $0.9 \mu\text{mol l}^{-1}$
96 (2002)	94	14	Filtered	4 cups per day or coffee abstention	tHcy increased by $0.8–0.9 \mu\text{mol l}^{-1}$ or decreased by $0.7–1.0 \mu\text{mol l}^{-1}$

ing to 1.5 litres of strong coffee per day, increased fasting homocysteine concentrations by 4% and non-fasting homocysteine concentrations (after a hot meal) by 12%. The conclusion so far is that chlorogenic acid and caffeine together probably account for most of the effect of coffee on total tHcy levels (95).

Gene–nutrition interaction

Any biological effects can be assessed as consequences of the interaction between external factors and genetic disposition. This implies that the absolute levels of intermediary risk factors are determined by both environmental factors and genes. The variation in environmental factors such as diet and the effect of genetically determined susceptibility may be a key to understand why populations differ with regard to risk-factor levels. These general considerations are relevant when discussing the effects of coffee on plasma homocysteine levels.

A recent study by the present group showed that the homocysteine-raising effect of coffee was mainly seen in subjects homozygous for the methylenetetrahydrofolate reductase (MTHFR) 677T genotype (98). This was confirmed by Shmeleva et al. (99) in a recent cross-sectional study. They showed that coffee drinking were more prevalent in patients with hyperhomocysteinaemia than in those with normal plasma tHcy levels, and that the effect of smoking and caffeine intake on plasma tHcy levels was increased in subjects with the MTHFR 677TT genotype.

Coffee, caffeine and reproductive hazards

Only a few observational studies have investigated the possible relationship between coffee consumption and reproductive problems. Two of them have shown a positive association with miscarriages (15) and low birth weight (14). A recent large Danish

prospective study of 18 478 pregnant women showed that drinking more than 8 cups of coffee per day during pregnancy was associated with a double risk of stillbirth, but not with infant death (16).

A much larger number of studies has addressed the possible association between reproductive hazards and the intake of caffeine, most of which have been put together in a meta-analysis by Fernandes et al. (100). This meta-analysis included 32 studies with a total of 64 268 pregnancies. The authors concluded that there is a small but statistically significant increase in the risks for spontaneous abortion and low birth-weight babies in pregnant women consuming >150 mg caffeine per day.

In 1987, Martin and Brackon suggested that high maternal caffeine intake may result in growth retardation in term newborns, and showed that the relative risk of low birth-weight was 4.6 for mothers consuming over 300 mg caffeine per day compared with no caffeine at all (101). A more recently published Swedish paper showed that caffeine consumption was directly associated with an increased risk of miscarriage in the first trimester of pregnancy (102).

However, Leviton and Cowan suggest in a review article that an association between caffeine consumption and a reproductive hazard is more likely to be seen in lower quality studies than in studies that come closer to approximating the ideal. This is especially evident for “lower” birth weight and congenital anomalies (103). The authors conclude that no convincing evidence has been presented to show that caffeine consumption increases the risk of any reproductive adversity. However, they do not describe the criteria for low- and high-quality studies, and in epidemiological terms low-quality studies are usually biased towards null.

Other methodological limitations in such studies are recording the number of tea or coffee servings

consumed per day, assessing the contribution of other sources of caffeine, interindividual variation in the metabolism of caffeine and assessing what is a low birth weight (104).

Elevated concentrations of tHcy have been identified as an independent risk factor for recurrent early spontaneous abortions (105–107), neural tube defects (108, 109), and other reproductive and foetal hazards (110, 111). The dose–response relationship between increasing risk of reproductive hazards such as pre-eclampsia, prematurity, low birth weight and stillbirths, and increasing concentrations of tHcy, was demonstrated retrospectively in the Hordaland Homocysteine Study (108). The same study recently demonstrated that high homocysteine concentrations were associated with risks of pre-eclampsia, premature delivery and low birth weight. This study, which includes 5883 women and the outcome of their 14 492 pregnancies (112), is the first large study to show these associations, but there was no association with coffee intake.

Conclusions and methodological considerations

Observational studies addressing trivial factors such as common dietary habits have a higher probability of being published if they show an association between the variable and the health outcome. Negative results are less likely to be published. One answer to this dilemma is the randomized controlled trial assessing the effect of certain nutritional habits on health outcome. Such trials are unrealistic when it comes to the majority of dietary issues, and we are therefore stuck with results from observational studies and the risk of publication bias. The protective effects of coffee for type 2 diabetes, Parkinson's disease and Alzheimer's disease are based on observational studies, and it is far too early to draw firm conclusions. A full discussion on aetiological associations would include issues such as dose–response, biological plausibility and mechanisms, as well as human and animal experiments using intermediary effects as outcome variables. The effects of coffee on blood lipids and plasma homocysteine are more firmly based, but the studies also reflect a certain heterogeneity, in part explained by genetic susceptibility. The coffee–health issue is still pending; there are certain firmly established biological effects of coffee intake, but the impact on future health is virtually unknown.

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