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DIABETES MELLITUS

# Relationship between long-term coffee consumption and components of the metabolic syndrome: the Amsterdam Growth and Health Longitudinal Study

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**Abstract** Cardiovascular diseases and diabetes mellitus type II (DM II) are both major health problems. A large risk factor for these diseases is the presence of the metabolic syndrome. It is known that the risk of DM II can be decreased by coffee consumption. Therefore, we examined the association between coffee consumption and the components of the metabolic syndrome. Prospective data from the Amsterdam Growth and Health Longitudinal Study (AGAHLS) is used to analyse the associations between coffee consumption (averaged over a period from 27 till 42 years) and the components of the metabolic syndrome (at the age of 42 years). This was done by linear regression analyses and associations were adjusted for physical activity, energy intake, alcohol consumption and smoking behaviour. The results showed that moderate and high (>3 cups/day) coffee consumption was significantly associated with lower HDL in women. For men, coffee consumption was not associated with any of the components of the metabolic syndrome.

**Keywords** Cardiovascular disease · Coffee consumption · Diabetes mellitus · Metabolic syndrome · Risk factors · Longitudinal study

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## Background

Cardiovascular diseases (CVD) and diabetes mellitus type II (DM II) are both major health problems and considerate research has been carried out to assess the determinants of these diseases [1–5]. A very important risk factor for these diseases is the 'metabolic syndrome' [6, 7]. This consists of five components; (1) elevated blood pressure, (2) low HDL cholesterol levels, (3) high triglyceride levels, (4) high fasting glucose levels and (5) abdominal obesity. When three or more of five of the components are present, metabolic syndrome is diagnosed [8, 9].

The presence of the metabolic syndrome is associated with an approximately two-fold elevation in the risk of fatal and non-fatal CVD in women [6]. A threefold increase in risk for coronary heart disease and stroke and a marked increase in cardiovascular mortality in subjects with the metabolic syndrome were also reported [7]. The main causes of the metabolic syndrome are overweight/obesity, genetic factors and lifestyle factors such as physical activity, nutrition, smoking behaviour and alcohol consumption [9–12]. However, one lifestyle aspect which has not been studied often in relation to the metabolic syndrome is coffee consumption, even though coffee is one of the most consumed beverages in the world [13].

The effects of coffee consumption on human health and in particular the components of the metabolic syndrome, are found to be inconsistent [3, 14–18]. Most of these studies however, focused on short term effects of coffee consumption. Therefore, in the present study the associations between long term coffee consumption and the components of the metabolic syndrome were investigated.

All analyses were performed with the use of data from the Amsterdam Growth and Health Longitudinal Study (AGAHLS).

## Methods

### Study design and subjects

The Amsterdam Growth and Health Longitudinal Study (AGAHLS) is an observational longitudinal study that began in 1976 with a group of 450 boys and girls. Its initial goals were to describe the natural development of growth, health and lifestyle of adolescents and to investigate longitudinal relationships between biological and lifestyle variables. The mean ± SD age of the subjects at the beginning of the study was 13.1 ± 0.8 years. Since then, a series of examinations have been performed during a 30-year follow-up period, collecting data on anthropometric (body height, body weight, and skin folds), biological (serum lipoprotein levels, blood pressure and physical fitness), lifestyle (nutritional habits, smoking behaviour, and daily physical activity), and psychological variables [19].

In the most recent measurement period (2006) at the age of 42 years, the five components of the metabolic syndrome, according to the current guidelines [8], were measured in 344 subjects. The coffee consumption of the subjects was measured at the ages of 27, 29, 32, 36 and 42 years. Subjects who missed data of two or more measurements on coffee consumption were excluded from the analyses.

The study was approved by the medical ethical committee of the VU University Medical Centre and all subjects gave their written informed consent.

### Metabolic syndrome and its components

Blood pressure was measured in a supine position with an automated device (Dinamap Procare 100), at 5-min intervals, for 60 min. For blood pressure as a continuous variable, the Mean Arterial Pressure (MAP) was calculated as (2*diastolic blood pressure + 1*systolic blood pressure)/3 [20]. High-density lipoprotein (and total) cholesterol, triglycerides and fasting blood glucose levels were measured by enzymatic techniques (Roche Diagnostics, Mannheim, Germany). Waist circumference was measured with a flexible steel tape (Martin circumeter; Franken & Itallie) at the level midway between the lowest rib margin and the iliac crest [21].

The identification of the metabolic syndrome and its components was based on a slightly modified version of the definition proposed by the National Cholesterol Education Program (NCEP) Adult Treatment Panel III [8, 9], i.e., when three or more of the following five risk factors were present: (1) a systolic blood pressure of 130 mmHg or higher and/or a diastolic blood pressure of 85 mmHg or higher; (2) a high-density lipoprotein cholesterol level of less than 1.03 mmol/l in men and less than 1.29 mmol/l in women; (3) a triglyceride level of 1.69 mmol/l or more; (4) a fasting plasma glucose levels of 6.1 mmol/l or more; and (5) a waist circumference of more than 94 cm in men and more than 80 cm in women, ie, more liberal cut off values then originally proposed (>102 cm in men and >88 cm in women), since they may be more appropriate in the identification of individuals at increased risk in young and apparently healthy populations [9, 21].

### Coffee consumption

Coffee consumption was measured with a questionnaire at the ages of 27, 29, 32, 36 and 42 years. In the questionnaires, it was asked for how many cups of coffee a subject drinks during weekdays and how many cups of coffee a subject drinks during weekend days. Furthermore a distinction was made between caffeinated and decaffeinated coffee consumption. The average coffee consumption over the total measurement period was calculated by taking the mean of the three, four or five coffee intake measurements and is expressed in cups/day. In the analyses, no distinction was made between the types of coffee (filtered, boiled, instant, pads) and between caffeinated and decaffeinated coffee.

### Covariates

The relationship between components of the metabolic syndrome and coffee consumption can be influenced by other lifestyle components [11, 22]. Consequently, possible confounding factors, such as physical activity, energy intake, alcohol consumption and smoking behaviour were taken into consideration.

Physical activity was assessed with a validated interview and is expressed in MET*min/week. For physical activity, year specific z-scores were calculated and the values were averaged over the period from the age of 27 till 36 years. Energy intake was measured with a cross-check dietary interview in which the subjects were asked to recall their usual dietary intake during the previous month. Frequency, amounts and methods of preparation of the foods and drinks consumed were reported and values are expressed in kcal/day. Year specific z-scores were calculated for energy intake and the values were averaged over the period from the age of 27 till 36 years. The dietary interview also provided information about alcohol consumption and the amount of alcohol consumed (in glasses/week) at the age of 42 years was obtained. Smoking was measured with a tobacco questionnaire and was divided into three groups (smokers, non-smokers and subjects who have smoked in the past, but not anymore).

More detailed information of the methods used in the AGAHLS can be found elsewhere [19].

### Statistical analysis

To examine the associations between coffee consumption (averaged over the period from the age of 27 to 42 years) and the five components of the metabolic syndrome at the age of 42 years, linear regression analyses were used. In men, the average coffee consumption between the ages of 27 and 42 years was categorized in four groups (≤2, >2 and ≤4, >4 and ≤6, >6 cups/day). Coffee consumption in women was categorized in three groups (≤2, >2 and ≤4, >4 cups/day) instead of four, as the highest category (>6 cups/day) was combined with the second highest category (>4 and ≤6), given that the group size of the highest category on its own was too small. The categorical variable was represented in the regression analyses by dummy variables, where the lowest category (≤2 cups/day) was used as the reference category. This (standard) approach results in regression coefficients indicating the difference in a particular outcome variable between the groups with a different amount of coffee consumption.

Of the outcome variables, triglyceride and fasting blood glucose were not normally distributed and these variables were logarithmically transformed to correspond with the assumptions of regression analysis. All analyses were performed separately for men and women. Besides the crude analyses, an adjustment for physical activity, energy intake, alcohol consumption and smoking was performed.

To evaluate main effects, a 5% significance level was assumed. All statistical analyses were performed with SPSS 14.0.

## Results

Table 1 shows the characteristics of the population, stratified by gender. Average coffee consumption for men was 4.5 cups/day, for women 3.1 cups/day.

Table 2 shows the prevalence of the metabolic syndrome and its components. The prevalence of the metabolic syndrome at the age of 42 years in the entire population was only 3.5% (around 8% for men and 0% for women).

Table 3 presents the results of the regression analyses, showing the effect of 15 years of coffee consumption on the five components of the metabolic syndrome at the age of 42 for men. The crude analyses show no significant effect for any of the variables. In the adjusted model (adjusted for physical activity, energy intake, smoking behaviour and alcohol consumption) no significant effects were found either.

Table 4 presents the results of the same analyses as Table 3, only for women. The crude analyses show some borderline significant effects for HDL. It seems that a moderate coffee consumption (>2 and ≤4 cups/day), as well as a high coffee consumption (>4 cups/day) decreases HDL levels. Although, these effects are just above the 5% significance level ($P = 0.06$). Adjustment for physical activity, energy intake, smoking behaviour and alcohol consumption, strengthened these associations. Furthermore, MAP appears to decrease with a moderate coffee consumption (>2 and ≤4 cups/day), although, this effect was only borderline significant. For all other components, no significant effects were found.

**Table 1** Mean and standard deviation (between brackets) of subject characteristics at the age of 42 years (measured in 2006)

| | Men ($N = 123$) | Women ($N = 160$) |
|---|---|---|
| Coffee total, cups/day | 4.5 (2.5) | 3.1 (1.9) |
| ≤2, no (%) | 19 (15.4) | 48 (30) |
| >2 and ≤4, no (%) | 32 (26.0) | 62 (38.1) |
| >4 and ≤6, no (%) | 47 (38.2) | 42 (26.3) |
| >6, no (%) | 25 (20.3) | 9 (5.6) |
| Systolic blood pressure | 122.2 (13.6) | 110.9 (12.6) |
| Diastolic blood pressure | 72.8 (7.7) | 67.8 (7.9) |
| Mean arterial pressure (mmHg)[a] | 89.3 (9.0) | 82.2 (9.0) |
| HDL (mmol/l) | 1.5 (0.3) | 1.9 (0.4) |
| Triglycerides (mmol/l) | 1.4 (1.1) | 1.0 (0.4) |
| Fasting glucose (mmol/l) | 5.2 (1.1) | 4.9 (0.5) |
| Waist circumference (cm) | 89.3 (8.1) | 77.6 (8.6) |
| Physical activity (Mets/week)[b] | 3604 (2190) | 3931 (1937) |
| Energy intake (Kcal/day)[b] | 2937 (636) | 2257 (419) |
| Alcohol consumption (glass/week)[c] | 6.3 (1.9–13.8) | 1.9 (0.6–6.3) |
| Smoking behaviour | | |
| Never, no (%) | 69 (56.1) | 98 (61.3) |
| Past, no (%) | 32 (26.0) | 43 (26.8) |
| Current, no (%) | 22 (17.9) | 19 (11.9) |

[a] Calculated as (2*diastolic blood pressure + systolic blood pressure)/3

[b] Averaged over period from 27 to 36 years

[c] Median (interquartile range)

**Table 2** Prevalence of the components metabolic syndrome

| Risk factor | Men ($N = 123$) | Women ($N = 160$) |
|---|---|---|
| Blood pressure (≥130/85 mmHg) | 26 (21.2%) | 16 (10.0%) |
| HDL (<1.03 mmol/l, men; <1.29 mmol/l, women) | 7 (5.7%) | 8 (5.0%) |
| Triglycerides (≥1.69 mmol/l) | 30 (24.4%) | 8 (5.0%) |
| Fasting blood glucose (≥6.1 mmol/l) | 8 (6.5%) | 3 (1.9%) |
| Waist circumference (>94 cm, men; >80 cm, women) | 33 (26.8%) | 48 (30%) |
| Metabolic syndrome[a] | 10 (8.1%) | 0 |

[a] 3 (or more) of 5 components

**Table 3** Effect (95% confidence interval) of coffee consumption on components of the metabolic syndrome for men

| | Coffee consumption (cups/day) | | | |
|---|---|---|---|---|
| | >2 and ≤4 | >4 and ≤6 | >6 | *P* for trend |
| Crude analysis | | | | |
| Mean arterial pressure (mmHG)[a] | −3.7 (−8.9 to 1.5) | −3.6 (−8.5 to 1.3) | −0.3 (−5.8 to 5.3) | 0.95 |
| | *P* = 0.16 | *P* = 0.15 | *P* = 0.93 | |
| HDL (mmol/l)[a] | 0.01 (−0.19 to 0.21) | 0.04 (−0.15 to 0.22) | −0.05 (−0.25 to 0.16) | 0.59 |
| | *P* = 0.90 | *P* = 0.68 | *P* = 0.66 | |
| Triglyceride (mmol/l)[b] | 1.07 (0.76 to 1.51) | 1.03 (0.75 to 1.40) | 1.19 (0.84 to 1.70) | 0.44 |
| | *P* = 0.68 | *P* = 0.87 | *P* = 0.34 | |
| Fasting glucose (mmol/l)[b] | 1.01 (0.92 to 1.09) | 1.03 (0.95 to 1.12) | 1.03 (0.94 to 1.12) | 0.36 |
| | *P* = 0.91 | *P* = 0.46 | *P* = 0.50 | |
| Waist circumference (cm)[a] | 0.7 (−4.0 to 5.3) | 0.4 (−4.0 to 4.8) | 2.5 (−2.4 to 7.4) | 0.37 |
| | *P* = 0.78 | *P* = 0.87 | *P* = 0.32 | |
| Adjusted analysis[c] | | | | |
| Mean arterial pressure (mmHG)[a] | −5.2 (−10.6 to 0.2) | −4.7 (−9.8 to 0.4) | −1.4 (−7.0 to 4.3) | 0.90 |
| | *P* = 0.06 | *P* = 0.07 | *P* = 0.06 | |
| HDL (mmol/l)[a] | 0.02 (−0.19 to 0.22) | 0.05 (−0.14 to 0.24) | −0.05 (−0.26 to 0.16) | 0.68 |
| | *P* = 0.87 | *P* = 0.62 | *P* = 0.61 | |
| Triglyceride (mmol/l)[b] | 1.03 (0.73 to 1.46) | 0.93 (0.67 to 1.30) | 1.12 (0.78 to 1.61) | 0.71 |
| | *P* = 0.85 | *P* = 0.68 | *P* = 0.53 | |
| Fasting glucose (mmol/l)[b] | 1.00 (0.92 to 1.09) | 1.01 (0.94 to 1.10) | 1.02 (0.93 to 1.11) | 0.59 |
| | *P* = 0.94 | *P* = 0.72 | *P* = 0.72 | |
| Waist circumference (cm)[a] | 0.6 (−4.4 to 5.5) | 0.2 (−4.5 to 4.8) | 2.3 (−2.8 to 7.4) | 0.42 |
| | *P* = 0.84 | *P* = 0.95 | *P* = 0.37 | |

[a] Effect is difference in average value with reference category ≤2 cups/day

[b] Effect is ratio in average value with reference category ≤2 cups/day

[c] Adjusted for energy intake, physical activity, smoking and alcohol consumption



The effect of coffee consumption on HDL appeared to be significant in women, but not in men. However, it should be noted that the difference in the relationship of HDL and coffee consumption between men and women was not statistically significant, given the overlapping confidence intervals.

To explore the relationship between coffee consumption and HDL in women a bit further, we first added body mass index (BMI) to the model to investigate whether the relationship between coffee consumption and HDL was mediated by BMI. This was not the case; the results of the analyses did not change (data not shown). In a second explorative analysis, a multiple regression analyses was performed in which coffee consumption was analysed in combination with BMI, waist circumference, physical activity, smoking behaviour and alcohol consumption. Table 5 shows the results of this multiple regression analysis. Also in this multiple regression model, coffee consumption remains (significantly) related to HDL, while also alcohol consumption (the more glasses/week, the higher HDL levels) and waist circumference (the higher waist circumference, the lower HDL levels) were significantly associated with HDL.

## Discussion

This study examined the association between coffee consumption and the components of the metabolic syndrome in a relatively healthy Dutch study population. It appeared that coffee consumption was inversely associated with HDL level in women. A significant, inverse relation between coffee consumption and HDL was found. Furthermore, an almost significant inverse association was found between average coffee consumption and MAP, and for men, waist circumference seems to be somewhat associated with a high coffee consumption.

In the present study, an inverse association was found between HDL level and average/high coffee consumption in women. A meta-analysis of randomized controlled trials (RCT) regarding associations between coffee consumption and cholesterol, showed that consuming 6 cups/day was

**Table 4** Effect (95% confidence interval) of coffee consumption on components of the metabolic syndrome for women

| | Coffee consumption (cups/day) | | |
|---|---|---|---|
| | >2 and ≤≤4 | >4 | *P* for trend |
| Crude analysis | | | |
| Mean arterial pressure (mmHG)[a] | −3.0 (−6.5 to 0.4) | 0.1 (−3.5 to 3.7) | 0.94 |
| | *P* = 0.08 | *P* = 0.96 | |
| HDL (mmol/l)[a] | −0.15 (−0.30 to 0.01) | −0.15 (−0.31 to 0.01) | 0.06 |
| | *P* = 0.06 | *P* = 0.06 | |
| Triglyceride (mmol/l)[b] | 1.01 (0.87 to 1.17) | 1.04 (0.89 to 1.22) | 0.58 |
| | *P* = 0.90 | *P* = 0.59 | |
| Fasting glucose (mmol/l)[b] | 1.03 (0.99 to 1.07) | 1.01 (0.97 to 1.05) | 0.58 |
| | *P* = 0.16 | *P* = 0.54 | |
| Waist circumference (cm)[a] | 1.4 (−1.9 to 4.7) | 2.5 (−1.0 to 5.9) | 0.16 |
| | *P* = 0.41 | *P* = 0.16 | |
| Adjusted analysis[c] | | | |
| Mean arterial pressure (mmHG)[a] | −3.1 (−6.7 to 0.5) | −0.1 (−3.8 to 3.7) | 0.95 |
| | *P* = 0.09 | *P* = 0.97 | |
| HDL (mmol/l)[a] | −0.18 (−0.34 to −0.02) | −0.20 (−0.36 to −0.03) | 0.03 |
| | *P* = 0.03 | *P* = 0.02 | |
| Triglyceride (mmol/l)[b] | 0.98 (0.83 to 1.14) | 1.05 (0.90 to 1.24) | 0.59 |
| | *P* = 0.75 | *P* = 0.53 | |
| Fasting glucose (mmol/l)[b] | 1.02 (0.99 to 1.07) | 1.01 (0.97 to 1.05) | 0.75 |
| | *P* = 0.20 | *P* = 0.61 | |
| Waist circumference (cm)[a] | 1.36 (−2.4 to 4.9) | 2.6 (−1.1 to 6.3) | 0.17 |
| | *P* = 0.44 | *P* = 0.17 | |

[a] Effect is difference in average value with reference category ≤2 cups/day

[b] Effect is ratio in average value with reference category ≤2 cups/day

[c] Adjusted for energy intake, physical activity, smoking and alcohol consumption

**Table 5** Results of a multiple regression analysis to explore the effect of coffee consumption and other risk factors on HDL in women

| | Effect (95% CI) | *P*-value |
|---|---|---|
| Coffee consumption[a] | | |
| >2 and ≤4 cups/day | −0.17 (−0.32 to −.02) | 0.03 |
| >4 cups/day | −0.15 (−0.31 to 0.00) | 0.06 |
| Alcohol consumption (glasses/week) | 0.02 (0.01 to 0.03) | 0.01 |
| Physical activity | 0.02 (−0.06 to 0.09) | 0.70 |
| Waist circumferenace | −0.02 (−0.04 to −0.01) | 0.02 |
| Body mass index | 0.01 (−0.03 to 0.04) | 0.61 |
| Smoking behaviour[b] | | |
| Past | 0.01 (−0.14 to 0.15) | 0.91 |
| Current | −0.08 (−0.27 to 0.12) | 0.45 |

[a] ≤2 Cups/day is used as reference category

[b] Never smokers is used as reference category

associated with increased LDL cholesterol, but not with HDL. A distinct difference in outcome in blood cholesterol levels appeared between boiled coffee and filtered coffee. Increases in serum lipids (except for HDL) were greater in studies where people drank boiled coffee [16]. These differences in effect on blood cholesterol between filtered and unfiltered/boiled coffee were found in several other studies as well [23–25]. However, at least one trial using filtered coffee, has shown that coffee consumption was associated with an increase in total serum cholesterol [26]. The cholesterol raising factors in boiled coffee are cafestol and kahweol. Two fat-soluble matters, which are originally present in coffee oil. In particular cafestol is found to raise blood cholesterol [27]. The population in the present study drank mostly drip-filtered caffeinated coffee, which does not contain cafestol and kahweol.

Regarding waist circumference, positive associations were found in both male and female subjects with a high coffee consumption. However, these associations were not statistically significant. To our knowledge there are almost no studies reporting a relationship between coffee consumption and waist circumference. However, many studies investigate the relationship between coffee consumption and body mass index as indicator for body fatness. Positive

associations between coffee consumption and body mass index (BMI) were found in several studies [13, 28, 29]. However, also contrary effects were found. In a prospective study over a period of 12 years, it appeared that an increase in caffeine intake, mainly due to coffee consumption, led to a small reduction in long-term weight gain [30].

In the present study, triglycerides were not associated with coffee consumption in either men or women. Contradictory to this outcome, a meta-analysis of RCT's reported a dose-response relation between coffee consumption and triglycerides [16]. On the other hand, a longitudinal study in Japan showed that triglyceride levels were significantly and inversely associated with coffee consumption [18].

In the present study, blood pressure was to some extent inversely associated with moderate coffee consumption. Comparable to this outcome, an inverse association between coffee and blood pressure was found in a study in a general Norwegian population [14]. However, in previous studies it has been suggested that coffee raises blood pressure. A meta-analysis of RCT's revealed a significant association between coffee consumption and both systolic and diastolic blood pressure [33]. In a more recent meta-analysis it was suggested that caffeine, when ingested through coffee, either has a very small, or no effect on blood pressure [31]. This finding is supported by many single studies as well [32–35].

For fasting blood glucose, no associations with coffee consumption were found in the present study. There are numerous studies, which claim positive health effects of coffee consumption on diabetes mellitus type II or insulin resistance. Several studies conclude that caffeine intake, mainly due to coffee consumption, can reduce risk of DM II and reduce insulin resistance [5, 11, 30, 36, 37]. The present study does not support these outcomes. However, also in a study in which a reduced risk of DM II was found due to high coffee consumption, no association between high coffee consumption and fasting plasma glucose levels was found [38]. On the other hand, Keyzers found an inverse relationship between insulin sensitivity and caffeine in healthy humans [39]. This effect however, was a short-term effect and was as a result of just (intravenous) caffeine intake instead of coffee intake.

### Limitations

Although this study is probably one of the first in which long term coffee consumption is related to health outcomes, a few limitations should be mentioned. This study was supposed to examine the association between long term coffee consumption and the metabolic syndrome. However, the prevalence of the metabolic syndrome in our study population was only 3.5% (around 8% for men and 0% for women) so it was not possible to analyze this relationship. This prevalence of the metabolic syndrome in our study population was extremely low, compared to the prevalence of the metabolic syndrome for adults in the Netherlands (15–22% for men and 9–15% for women) [40].

There are several reasons for not finding strong effects of coffee consumption on the components of the metabolic syndrome. First, as mentioned before, the study population was relatively healthy. Besides the low prevalence for the metabolic syndrome, the population seemed to be healthy for the separate components as well (see Table 2). Furthermore, it was not possible to take coffee additives as milk, cream and sugar into consideration. Although these variables were not included in our analyses, adjustments were made for energy intake (kcal/day). Besides this, the average coffee consumption in the population was 4.5 cups/day for men and 3.1 cups/day for women. These averages are relatively low compared to existing literature, while it is known that especially the higher coffee consumption (>6 or >7 cups/day) shows the largest effects [3]. Especially in women, the highest coffee category was extremely small and had to be combined with the second highest category.

In conclusion, 15 years of coffee consumption was inversely associated with HDL and with MAP (the latter only for moderate coffee consumption) for women. For men, no significant associations were found between long term coffee consumption and metabolic syndrome risk factors.





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Panagiotakos DB, Pitsavos C, Chrysohoou C, Kokkinos P, Toutouzas P, Stefanadis C.
**The J-Shaped Effect of Coffee Consumption on the Risk of Developing Acute Coronary Syndromes: The CARDIO2000 Case-Control Study.**
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**abstract**

The effect of coffee consumption on cardiovascular disease has been debated for many years. In this work, we evaluated the association between coffee consumption and the risk of developing acute coronary syndromes, based on a random sample of 848 patients with their first coronary heart disease event and 1078 frequency-matched controls with no cardiovascular disease in their medical history, from the entire country. The multivariate analysis raises a J-shaped association between the risk of developing acute coronary syndromes and the quantity of coffee consumed per day. In particular, the odds ratios for moderate (<300 mL/d), heavy (300–600 mL/d), and very heavy (>600 mL/d), consumption, relative to no consumption, were 0.69 (95% CI, 0.50–0.86), 1.56 (95% CI, 1.10–2.34) and 3.10 (95% CI, 1.82–5.26), respectively, after controlling for the presence of hypertension, hypercholesterolemia, diabetes mellitus, family history of premature coronary heart disease, physical activity status, smoking habits, BMI, alcohol consumption, triglycerides, consumption of several food items, depression scale score and education status. The suggested J-shaped association between coffee consumption and the risk of developing acute coronary syndromes may partially explain the conflicting results from other studies in the past.

***Study population.***

The CARDIO2000 is a multicenter case-control study that explores the association between several demographic, nutritional, psychological, lifestyle and clinical factors with the risk of developing nonfatal acute coronary syndromes. According to the population distribution provided by the National Statistical Services we stratified our sampling into all regions of Greece. For each region, we randomly selected a specific number of patients from the prefectorial or the major private hospitals of each county. The patients were from approximately half of the clinics in Athens and Thessalonica (the two major cities in Greece, covering ~55% of the total population), and from almost all of the clinics of the other counties. The number of participants was determined through power analysis to evaluate a minimum difference of 7% in relative risk between those who do and do not drink coffee with statistical power of 0.80 and $P < 0.05$. Thus, from January 2000 to August 2001, 848 of 956 patients (89% response rate) who had been randomly preselected from the hospitals with a first symptom of coronary heart disease (stable angina was excluded from the analysis) in their life agreed to participate in the study (cases). The inclusion criteria for cardiac cases were as follows: *1*) diagnosis of first acute myocardial infarction that was defined by two of three features, i.e., electrocardiographic changes, or compatible clinical symptoms or/and specific diagnostic enzyme elevations (49% of the patients had myocardial infarction); or *2*) diagnosis of unstable angina (i.e., one or more angina episodes at rest within the preceding 48 h with no abnormal enzyme rise) corresponding to class III of the Braunwald classification (51% of the patients had unstable angina). Patients with a previous history of cardiovascular disease, including aortic aneurysm, stroke and peripheral vascular disease, were excluded from this study.

After the selection of the cardiac patients, we randomly selected 1300 controls who were free of cardiovascular disease; 1078 of these (83% response rate) agreed to participate. The controls were frequency matched to the patients according to their age distribution (within classes of ± 3 y), their gender and the region of Greece (we matched the controls with the patients by region to reduce the potential confounding effect of culture differences among Greek citizens). Controls were mainly individuals (91% of the total number of controls) who

visited the outpatient departments of the same hospital during the same time period as the coronary patients for minor surgical operations (e.g., bone fracture) or for routine examinations (e.g., medical examinations for the driving license or other official certificates such as validation of the social security handbooks). We used these types of controls to have more accurate medical information, to eliminate the potential adverse effect of several, unknown, confounders and to increase the likelihood that cases and controls shared the same study base (18). However, in a few country hospitals in which the available number of "hospitalized" controls was not sufficient for the matching procedure, we randomly selected a small proportion of people (9% of the total number of controls) from the municipality rolls. An indicator variable was used for the sensitivity analysis that was applied to explore whether the different "sources" of controls might influence our findings. All controls were people without any clinical symptoms, signs or suspicion of cardiovascular disease in their medical history, including stroke, aortic aneurysm and peripheral vascular disease, as evaluated by a cardiologist.

***Investigated measurements.***

All participants were asked to describe their usual frequency of consumption of coffee over the last year. Based on the distribution of coffee consumption, we categorized usual coffee consumption as none, up to 300 mL/d (moderate use), or up to 600 mL/d (heavy use) and >600 mL/d (very heavy use). All reported types of coffee (instant coffee, "Greek" type, filtered or "cappuccino") were adjusted for one cup (150 mL) of coffee and a caffeine concentration of 27.5% (19). We did not include the consumption of decaffeinated coffee, tea and caffeine-containing drinks (Coca-Cola) or chocolate. Ceasing to drink coffee during the last year (in months of abstinence) was recorded and taken into account as a covariate for the analysis.

TABLE 1 *Clinical, demographic and lifestyle characteristics of the study population*[1,2]

| | Patients | | Controls | | |
|---|---|---|---|---|---|
| | Men | Women | Men | Women | *P*-value |
| *n* | 700 | 148 | 682 | 216 | |
| Age, *y* | 59.1 ± 10 | 65.3 ± 9 | 58.8 ± 10 | 64.8 ± 10 | |
| Education status | | | | | 0.012 |
| 0–9 y of schooling, *n (%)* | 406 (58) | 114 (77) | 474 (55) | 147 (68) | |
| 10–14 y of schooling, *n (%)* | 182 (26) | 31 (21) | 198 (23) | 41 (19) | |
| >14 y of schooling, *n (%)* | 112 (16) | 3 (2) | 190 (22) | 28 (13) | |
| Current smoker, *n (%)* | 525 (75) | 44 (30) | 500 (58) | 54 (25) | <0.001 |
| Pack years, *y* | 39.9 ± 14 | 13.1 ± 9 | 21.5 ± 13 | 5.2 ± 6 | <0.001 |
| Hypertensive, *n (%)* | 308 (44) | 102 (69) | 216 (25) | 69 (32) | <0.001 |
| Hypercholesterolemic, *n (%)* | 413 (59) | 100 (68) | 203 (24) | 67 (31) | <0.001 |
| Diabetic, *n (%)* | 168 (24) | 44 (30) | 86 (10) | 17 (8) | <0.001 |
| Family history of heart disease, *n (%)* | 308 (44) | 77 (52) | 129 (15) | 39 (18) | <0.001 |
| BMI, $kg/m^2$ | 27.4 ± 4 | 27.1 ± 4 | 27.1 ± 3 | 26.7 ± 2 | 0.120 |
| Physically inactive, *n (%)* | 448 (64) | 111 (75) | 491 (57) | 132 (61) | <0.01 |
| Adopted the Mediterranean diet, *n (%)* | 119 (17) | 34 (23) | 198 (23) | 69 (32) | 0.045 |

| | | | | | |
|---|---|---|---|---|---|
| Alcohol consumer (>100 mL/d), *n (%)* | 336 (48) | 25 (17) | 379 (44) | 30 (14) | <0.05 |
| Experienced depressive episodes, *n (%)* | 161 (23) | 46 (31)1 | 29 (15) | 41 (19) | <0.05 |

[1] Values are means ± SD.
[2] *P*-values are for the differences between patients and controls.

**TABLE 2** *Results from the multivariate logistic model for the effect of coffee consumption on the risk of developing acute coronary syndromes in a random sample of patients with their first coronary heart disease event and frequency-matched controls with no cardiovascular disease in their medical history after controlling for several potential confounders*[1]

| | Patients | Controls | Odds ratio | 95% CI |
|---|---|---|---|---|
| Total number of subjects | 848 | 1078 | | |
| Subjects with no coffee consumption (reference group) | 171 | 158 | 1.00 | — |
| Subjects with moderate (<300 mL/d) coffee consumption | 484 | 773 | 0.69 | 0.50–0.86 |
| Subjects with heavy (300–600 mL/d) coffee consumption | 136 | 97 | 1.56 | 1.10–2.34 |
| Subjects with very heavy (>600 mL/d) coffee consumption | 47 | 20 | 3.10 | 1.82–5.26 |

[1] Confounders included age, gender, as well as the effect of hypertension, hypercholesterolemia, diabetes mellitus, family history of premature coronary heart disease, physical activity status, smoking habits, BMI, alcohol consumption, triglyceride levels, adoption of Mediterranean diet, education status and depression scale score of the participants.