

# A prospective cohort study on the association between coffee drinking and risk of non-gallstone-related acute pancreatitis

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## Abstract

Only one previous study has examined the association between coffee consumption and risk of acute pancreatitis, and it found a reduced risk for alcohol-related episodes among high consumers of coffee. Therefore, we examined (1) the association between coffee consumption and risk of non-gallstone-related acute pancreatitis and (2) whether this association was modified by alcohol intake. Data were obtained from two prospective cohorts, the Cohort of Swedish Men and the Swedish Mammography Cohort, including 76 731 men and women (born 1914–1952). Coffee consumption was assessed at baseline with a FFQ, and the cohorts were followed up between 1998 and 2012 via linkage to national health registries. Hazard ratios were estimated using Cox models, with adjustment for potential confounding factors. During 1 035 881 person-years of total follow-up, 383 cases (246 in men and 137 in women) of incident non-gallstone-related acute pancreatitis were identified. Overall, and irrespective of whether a categorical or a continuous exposure model was used, we observed no association between coffee consumption and risk of non-gallstone-related acute pancreatitis (e.g. the multivariable-adjusted hazard ratio for each 1 cup/d increase in coffee consumption was 0.97; 95% CI 0.92, 1.03). There was no evidence of effect modification by alcohol intake ( $P_{\text{interaction}} = 0.77$ ). In conclusion, coffee consumption was not associated with risk of non-gallstone-related acute pancreatitis in this large prospective cohort study. Because of the limited number of epidemiological studies and their conflicting results, further research is needed to elucidate this potential association.

**Key words:** Pancreatitis: Coffee consumption: Risks: Prospective studies: Cohort studies

Acute pancreatitis is a common reason for hospitalisation in the Western world<sup>(1)</sup>, and the annual healthcare costs for acute pancreatitis and its related care are substantial. For example, in 2009, the costs were estimated to be \$2.6 billion in the USA<sup>(2)</sup> and €38.5 million in Sweden<sup>(3)</sup>.

Increasing evidence indicates that coffee is part of a healthy lifestyle. A reduced risk of several diseases, from diabetes<sup>(4)</sup> and stroke<sup>(5)</sup> to depression<sup>(6)</sup> and Alzheimer's dementia<sup>(7)</sup>, as well as a reduced total mortality<sup>(8)</sup>, has been associated with coffee consumption in previous studies. What has been less studied is whether coffee consumption reduces the risk for acute pancreatitis. In the only published study, Morton *et al.*<sup>(9)</sup> observed an inverse association between coffee consumption and risk of alcohol-related acute pancreatitis in a prospective cohort of US men and women. An inverse association between coffee consumption and risk of acute pancreatitis is biologically plausible because coffee consumption may reduce the incidence of diabetes and adiposity<sup>(10,11)</sup> – that is, potential risk factors for acute pancreatitis<sup>(12,13)</sup>. Also, given that increased concentrations of oxidative stress markers, inflammatory markers and Ca have

been implicated in the pathogenesis of acute pancreatitis<sup>(14,15)</sup>, an inverse association is biologically plausible because of the antioxidant and anti-inflammatory properties of coffee and because of its potential to promote a negative Ca balance<sup>(10,11)</sup>.

The aims of this prospective cohort study were to examine (1) the association between coffee consumption and risk of non-gallstone-related acute pancreatitis and (2) whether this association was modified by alcohol intake.

## Methods

### Participants and covariates

We used data from 48 850 men (born 1918–1952) and 39 227 women (born 1914–1948), residing in central Sweden and enrolled in two population-based prospective studies, the Cohort of Swedish Men and the Swedish Mammography Cohort, who responded to a questionnaire on diet and lifestyle factors in the late fall of 1997. The response rate for those

**Abbreviation:** HR, hazard ratio.

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eligible to participate was 49% in men and 70% in women. Further details of the cohorts, as well as a full version of the questionnaire, are available at [www.ki.se/en/imm/unit-of-nutritional-epidemiology](http://www.ki.se/en/imm/unit-of-nutritional-epidemiology). Ethical approval was granted by the Regional Ethical Board at Karolinska Institutet and return of a completed questionnaire was taken as informed consent to participate.

At baseline, the participants reported their average coffee consumption over the past year in cups/d or cups/week using a ninety-six-item FFQ (one cup approximately 1.5 dl); the Spearman's correlation with fourteen 24-h dietary recall interviews was 0.71 (A. Wolk, unpublished results). The FFQ was used to retrieve information on all covariates related to food and beverage intake. A total score of glycaemic load was calculated by (1) multiplying a food item's carbohydrate content (g) (based on age- and sex-specific portion sizes) by its glycaemic index score (according to an international table), (2) multiplying that product by the number of servings per d and (3) summing the glycaemic loads from all individual food items (Spearman's correlation with two 1-week dietary records = 0.77)<sup>(16)</sup>. Information on non-dietary covariates was obtained solely from the questionnaire, with the exception of hyperlipidaemia and diabetes for which we obtained additional information from the Swedish National Patient Register and the Swedish National Diabetes Register. BMI was calculated as self-reported weight (kg) divided by self-reported height squared (m<sup>2</sup>). Although no direct validity assessment has been made in these specific cohorts, it is known that people tend to overestimate their height and underestimate their weight<sup>(17)</sup>. In a previous study based on a sample of the adult population in central Sweden, the validity of self-reported BMI was reported to be 0.89 (as measured by the slope of a linear regression)<sup>(18)</sup>.

#### Case ascertainment and follow-up

Follow-up was conducted from 1 January 1998 to 31 December 2012. We obtained data on acute pancreatitis (code K85 in International Classification of Diseases-10) from the Swedish National Patient Register. This register has a high validity of records of acute pancreatitis (positive predictive value ranging from 83 (definitive disease) to 98% (probable disease))<sup>(19)</sup>, and the agreement between the incidence rates in our cohorts<sup>(16)</sup> and those in Sweden<sup>(20)</sup> has been shown to be good. Data on other exocrine pancreatic diseases (codes K86 and K87 in International Classification of Diseases-10), cancer and death were obtained from the Swedish National Patient Register, the Swedish National Cancer Registry and the Swedish National Cause of Death Register, respectively.

Previous studies have observed an inverse association between coffee consumption and risk of cholecystectomy (used as a proxy for symptomatic gallstone disease)<sup>(21–23)</sup> – that is, the surgical intervention recommended by national and international guidelines as the definitive treatment for patients with gallstone-related acute pancreatitis<sup>(24,25)</sup>. Therefore, to avoid analyses of acute pancreatitis as yet another proxy for symptomatic gallstone disease, the outcome of interest in this study was non-gallstone-related acute pancreatitis. This was defined as an episode of acute pancreatitis (except K85.1 (biliary

pancreatitis)) in which no diagnosis of cholelithiasis (code K80 in International Classification of Diseases-10) or surgery to the gallbladder and bile duct (codes JKA20, JKA21, JKE00, JKE02, JKE12, JKE18 or JKB30 in NOMESCO Classification of Surgical Procedures) was recorded within 3 months after the index episode. The percentage of all episodes of acute pancreatitis that were classified as non-gallstone-related according to this definition was 55%, which was similar to that in Swedish studies with access to medical charts (58–61%)<sup>(19,26)</sup>.

Of the 88 077 participants who were followed up, we excluded 6717 who, at baseline, had incorrect personal identity numbers, prevalent cancer or exocrine pancreatic diseases or extreme energy intakes (>3 sd of the sex-specific log-transformed mean) as well as 4329 who, at baseline, had missing or extremely high coffee consumption (>10 cups/d). We also excluded 300 participants who developed pancreatic cancer during follow-up, leaving 76 731 participants for analysis.

#### Statistical analysis

Hazard ratios (HR) were estimated using Cox models, with time since baseline (1 January 1998) as timescale, and with acute pancreatitis, other exocrine pancreatic diseases, death or study end (31 December 2012) as censoring events. Use of attained age as timescale, instead of time-on-study, had negligible influence on the results. Coffee consumption was analysed continuously and categorically (<2, 2, 3–4, ≥5 cups/d) in separate exposure models. In the continuous model, we used three-knot restricted cubic splines to allow for potential non-linear associations<sup>(27)</sup>. There was no evidence of departure from the proportional hazards assumption in any of the models. A power calculation was conducted using the Episheet software developed by Rothman<sup>(28)</sup>, and it revealed that the study had a power of 80% to detect an HR of 0.58 for the highest compared with the lowest category of coffee consumption. To detect an HR of 0.50, which was observed in the previous study by Morton *et al.*<sup>(9)</sup>, the power was 93%.

Cox models were stratified by age and sex and adjusted for education, smoking status, alcohol intake and physical activity (measured as time spent walking or cycling). Adjusting for other aspects of physical activity (e.g. exercise and work occupation) did not change the results. Further adjustment for diet (tea, vegetables, fish, glycaemic load and energy) was made in a separate model. As diabetes, hyperlipidaemia and BMI could be intermediate factors<sup>(10,11)</sup>, as well as confounding factors, we also made adjustment for them in a separate model. (See Table 2, footnotes, for categorisation of each potential confounding factor.) The missing-indicator method was used to handle missing data on covariates; however, results based on complete case data and on multiple imputed data were similar.

We tested for effect modification by alcohol intake (using the Wald's test) and also performed subgroup analyses by alcohol intake as a sensitivity analysis. In another sensitivity analysis, we performed separate analyses of men and women (with further adjustment for menopausal status and use of post-menopausal hormones (premenopausal, never use, ever use)). In these interaction and subgroup analyses, coffee consumption was analysed as a continuous variable.

Analyses were run in Stata version 12.0 (StataCorp LP), with statistical significance set at the two-sided 0.05 level.

**Results**

At baseline, the mean coffee consumption was 3.4 (SD 2.0) cups/d in men and 3.1 (SD 1.7) cups/d in women. Participants in the highest category of coffee consumption differed from those in the lowest category as they were more likely to be smokers and less likely to be well educated, to drink tea and to have used postmenopausal hormones (Table 1).

During 1 035 881 person-years of total follow-up, 383 cases (246 in men and 137 in women) of incident non-gallstone-related acute pancreatitis were identified. Overall, and irrespective of whether a categorical or a continuous exposure model was used, we observed no association between coffee consumption and risk of non-gallstone-related acute pancreatitis. There was no evidence of non-linearity in a restricted cubic spline analysis (Table 2, model 1). In sex-specific analyses, the multivariable-adjusted HR for each 1 cup/d increase in coffee consumption was 0.99 (95% CI 0.93, 1.06) in men and 0.92 (95% CI 0.83, 1.03) in women (results not shown in Table 2). Further adjustment for diet (Table 2, model 2), as well as for potential intermediate factors (Table 2, model 3), did not change the association between coffee consumption and risk for non-gallstone-related acute pancreatitis. Finally, there was no evidence of effect modification by alcohol intake (low, high; high defined as  $\geq 12$  g/d in women and  $\geq 24$  g/d in men) ( $P_{\text{interaction}} = 0.77$ ). In subgroup analyses, the multivariable-adjusted HR for each 1 cup/d increase in coffee consumption was 0.96 (95% CI 0.90, 1.03) in participants with a low alcohol intake ( $n$  64 380, including 302 cases) and 0.97 (95% CI 0.85,

1.11) in those with a high alcohol intake ( $n$  10 492, including sixty-six cases).

**Discussion**

In this large prospective cohort study of men and women, we observed neither an overall association between coffee consumption and risk of non-gallstone-related acute pancreatitis nor an effect modification by alcohol intake.

Among the strengths of our study were the prospective study design, the fairly large sample size, the inclusion of both men and women and the availability of potential risk factors for acute pancreatitis. The study also had limitations. First, a certain level of misclassification is to be expected with self-reported exposure data, despite the fact that there was a good agreement between coffee consumption from the FFQ and that from dietary recall interviews. Moreover, as the exposure was measured only once at baseline, further misclassification may have occurred because of potential changes in coffee consumption during follow-up. However, these types of exposure misclassification are in general non-differential in prospective cohort studies – that is, similar between cases and non-cases. Second, we had to rely solely on register-based data for the ascertainment of cases, which may not have been entirely correct. However, the Swedish National Patient Register has been shown to have a high validity of records of acute pancreatitis<sup>(19)</sup>, and, as previously reported by our research group, the studied population was representative for Sweden with respect to the incidence of the disease<sup>(16)</sup>. Importantly, the percentage of all episodes of acute pancreatitis that were classified as non-gallstone-related was highly similar to that in Swedish studies with access to medical charts<sup>(19,26)</sup>. Finally, because of the observational

**Table 1.** Baseline characteristics of study participants ( $n$  76 731) by sex and category of coffee consumption in 1998 (Mean values; percentages)

Characteristics*†	Category of coffee consumption (cups/d)							
	Men ( $n$ 42 215)				Women ( $n$ 34 516)			
	<2	2	3–4	$\geq 5$	<2	2	3–4	$\geq 5$
Number of participants	6745	10 219	15 348	9903	5762	9608	13 656	5490
Age (years) (mean)	61	62	60	58	62	63	62	59
University education (%)	19	18	16	12	25	21	18	15
Current smoker (%)	17	20	23	36	12	14	20	35
BMI $\geq 30$ kg/m <sup>2</sup> (%)	11	10	9	11	11	10	10	12
Ever use of postmenopausal hormones (%)‡	–	–	–	–	59	56	53	50
History of diabetes (%)	11	10	9	10	5	5	4	4
History of hyperlipidaemia (%)	17	17	16	17	9	8	9	9
Physical activity >40 min of walking or cycling/d (%)	32	33	33	33	36	35	36	35
Dietary intakes (mean)								
Alcohol (g/d)	15	14	13	13	6	6	5	5
Tea (cups/week)	8	5	3	2	8	5	3	2
Vegetables (servings/d)	2	2	2	2	3	3	3	3
Fish (servings/week)	2	2	2	2	2	2	2	2
Glycaemic load (score/d)§	197	195	195	195	185	184	184	183
Energy (kJ/d)	10 298	10 636	11 251	12 055	6903	7090	7436	7762

\* Standardised (except age) to the sex-specific age distribution of men and women.

† Calculated for participants with known data. The percentage of missing data was 0.4% for education, 1.5% for smoking, 3.5% for BMI, 5.8% for postmenopausal hormones, 8.5% for physical activity, 2.4% for alcohol, 0.5% for vegetables and 1.6% for fish.

‡ Among postmenopausal women only.

§ Energy adjusted (to 8368 kJ/d).

**Table 2.** Cox analysis of the association between coffee consumption and risk of non-gallstone-related acute pancreatitis (1998–2012) (Hazard ratios (HR) and 95% confidence intervals)

Coffee consumption	Number of participants	Number of cases/person-years	Model 1*		Model 2†		Model 3‡	
			HR	95% CI	HR	95% CI	HR	95% CI
<b>Categorical model</b>								
<2 cups/d (median, 1 cup/d)	12 507	61/166 328	1.00	Ref.	1.00	Ref.	1.00	Ref.
2 cups/d	19 827	110/265 150	1.12	0.82, 1.53	1.12	0.81, 1.53	1.12	0.81, 1.53
3–4 cups/d	29 004	141/392 421	0.96	0.71, 1.30	0.95	0.69, 1.29	0.95	0.70, 1.30
≥5 cups/d (median, 6 cups/d)	15 393	71/211 982	0.84	0.59, 1.20	0.81	0.56, 1.17	0.81	0.56, 1.17
<i>P</i> <sub>overall association</sub> §	–	–		0.34		0.25		0.25
<b>Continuous model</b>								
For each 1 cup/d increase	76 731	383/1 035 881	0.97	0.92, 1.03	0.96	0.91, 1.02	0.96	0.91, 1.02
<i>P</i> <sub>non-linearity</sub>	–	–		0.28		0.30		0.31

Ref., referent values.

\* Derived from a Cox model that was stratified by age (5-year categories) and sex and adjusted for education (primary school, high school, university), smoking status (never smoker, past smoker with <10 or ≥10 pack-years, current smoker with <20 or ≥20 pack-years), alcohol intake (sex-specific quartiles of g/d) and physical activity (<20, 20–40, >40 min of walking or cycling/d).

† Adjusted for the same covariates as in model 1 and further adjusted for tea consumption (never, <2, ≥2 cups/d), vegetable consumption (quartiles of servings/d), fish consumption (<1.0, 1.0–1.9, 2.0–3.0, >3.0 servings/week), glycaemic load (quartiles of score/d) and energy intake (sex-specific quartiles of kJ/d).

‡ Adjusted for the same covariates as in model 2 and further adjusted for diabetes (no, yes), hyperlipidaemia (no, yes) and BMI (<25, 25–29, ≥30 kg/m<sup>2</sup>).

§ Test for overall association was calculated by using the Wald's test, testing the coefficients of the categorical variable jointly equal to 0.

|| Test for non-linearity was calculated by using the Wald's test in a restricted cubic spline model (knots at 1, 3 and 6 cups/d), testing the coefficient of the second spline transformation equal to 0.

study design, we cannot rule out the possibility that residual and/or unmeasured confounding may have been present.

Coffee consumption has been associated with several health effects, as reviewed by Rebello & van Dam<sup>(10)</sup> and by O'Keefe *et al.*<sup>(11)</sup>, of which some could theoretically reduce the risk for acute pancreatitis, including reduced concentrations of oxidative stress markers, inflammatory markers and Ca<sup>(14,15)</sup> as well as reduced incidences of diabetes and adiposity<sup>(12,13)</sup>. In contrast, coffee consumption has been shown to stimulate intestinal release of cholecystokinin<sup>(29)</sup>. Infusion with cholecystokinin is the most common way to induce experimental acute pancreatitis<sup>(30)</sup>, although the required concentrations are at least 10-fold greater than those observed in response to any type of meal. Moreover, coffee consumption, especially of boiled coffee, may increase TAG concentrations<sup>(10)</sup>, which in turn have been associated with acute pancreatitis<sup>(26)</sup>.

As far as we know, only one previous study has examined the association between coffee consumption and risk of acute pancreatitis<sup>(9)</sup>, although its focus was on acute and chronic pancreatitis combined rather than on acute pancreatitis alone. Among 128 934 US men and women recruited between 1978 and 1985 and followed up through 1998, Morton *et al.* observed that coffee consumption was inversely associated with risk of alcohol-related pancreatitis (either acute or chronic; *n* 125) (HR 0.5; 95% CI 0.3, 0.9 for ≥4 *v.* 0 cups/d; *P*<sub>continuous</sub> < 0.001) but not with risk of other subtypes of pancreatitis (gallstone-related (*n* 168) (HR 0.9; 95% CI 0.6, 1.5) and idiopathic (*n* 110) (HR 0.9; 95% CI 0.5, 1.6)). This association remained when the analysis was restricted to alcohol-related acute pancreatitis (*n* 82) (HR 0.5; 95% CI 0.2, 0.99).

In view of the conflicting results, and because any underlying biological mechanism would be the same, a thorough comparison between our study and that of Morton *et al.* is required. The studies had shared strengths, such as a fairly large sample size and a prospective study design, as well as shared limitations, such as a self-reported exposure assessment and

the possibility of unmeasured and residual confounding. With respect to differences, the distribution of coffee consumption was dissimilar. As an example, 41% of the US participants, but only 5% of the Swedish participants, consumed <1 cup/d. Moreover, although neither study had data on type (caffeinated, decaffeinated) or preparation method (filtered, boiled), decaffeinated coffee is more common in the USA than in Sweden and vice versa, with respect to boiled coffee. An additional difference was that the incidence of non-gallstone-related pancreatitis was higher in our study (37 *v.* 15 cases/100 000 person-years), despite the fact that it focused only on acute episodes (and not on a combination of acute and chronic episodes). We also lacked access to medical charts, as previously mentioned, and could therefore not determine the specific clinical classification of non-gallstone-related acute pancreatitis, leading to a mixture of alcohol-related and idiopathic episodes. Given that Morton *et al.* observed only an inverse association with risk of alcohol-related pancreatitis (classified on the basis of medical charts), this may explain the conflicting results. However, we observed no evidence of effect modification by alcohol intake (low, high; high defined as ≥12 g/d (≥1 drink/d) in women and ≥24 g/d (≥2 drinks/d) in men). Moreover, disregarding the statistical significance, there was not even a suggestion of a stronger association in participants with a high alcohol intake. Cases in this subgroup should have had the highest likelihood of being clinically classified as having alcohol-related acute pancreatitis, as it is highly dependent on patients' self-reported alcohol intake. As an example, in the study by Morton *et al.*, 67% of the alcohol-related cases reported that they consumed >1 drink of alcohol/d at baseline, compared with 14% of the idiopathic cases. Finally, the studies differed in ethnic distribution. The Swedish participants were non-Hispanic whites, whereas the US participants were ethnically diverse (black, white (including Hispanic white), Asian and mixed/other ethnicities). Of note, in that study, the inverse association between coffee consumption and risk of

alcohol-related pancreatitis appeared to be stronger in blacks (HR 0.5; 95% CI 0.2, 1.3) than in whites (HR 0.9; 95% CI 0.3, 2.5).

In summary, in this large prospective cohort study, we observed no overall association between coffee consumption and risk of non-gallstone-related acute pancreatitis, without evidence of effect modification by alcohol intake. Because of the limited number of epidemiological studies and their conflicting results, further research is needed to elucidate this potential association.

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There are no conflicts of interest to declare.

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