Coffee Consumption and the Risk of Venous Thromboembolism – The Tromsø study

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SUMMARY

Background: Several studies have investigated the association between coffee consumption and cardiovascular disease, but little is known about coffee intake and risk of venous thromboembolism (VTE).

Objective: The aim of this prospective cohort study was to investigate the association between coffee consumption and risk of incident VTE in a general population.

Methods: Information about coffee consumption habits was obtained by a self-administered questionnaire in 26 755 subjects, aged 25-97 years, who participated in the fourth survey of the Tromsø study (1994-95). Incident VTE events were registered until the end of follow-up, 1 September 2007.

Results: There were 462 incident VTE events (1.60 per 1000 person-years, 95% CI: 1.46-1.75) during a median of 12.5 years of follow-up. A daily consumption of 3-4 cups was borderline associated (HR: 0.70; 95% CI: 0.48-1.02), while 5-6 cups (HR: 0.67; 95% CI: 0.45-0.97) of coffee was significantly associated with reduced risk of VTE compared to coffee abstainers in multivariable analysis adjusted for age, sex, BMI, smoking status, physical activity, diabetes, history of cardiovascular disease and cancer. Similar risk estimates were found for provoked and unprovoked VTE, and in sex-stratified analyses.

Conclusion: Our findings suggest a possible U-shaped relation between coffee consumption and VTE, and that moderate coffee consumption may be associated with reduced risk of VTE. However, more studies are needed to establish whether a moderate coffee consumption is inversely associated with the risk of VTE.

Key words: coffee consumption, risk factor, venous thromboembolism.

Venous thromboembolism (VTE), consisting of deep venous thrombosis (DVT) and pulmonary embolism (PE), is a disease with serious short- and long-term complications, such as post-thrombotic syndrome, pulmonary hypertension, and potential fatal outcome (1, 2). The annual incidence of VTE is 1-2 per 1000 person-years in developed countries (1, 3, 4), and it is the leading cause of preventable in-hospital deaths in the US (2). VTE is a multicausal disease of which the incidence increases markedly with age (1, 4, 5). Despite numerous known risk factors, still 25-50% of the events occur in the absence of predisposing factors (2, 6). In contrast to arterial cardiovascular disease (e.g. myocardial infarction), the incidence of VTE has not declined during the last decades (1). The relation between lifestyle factors and arterial cardiovascular disease has been extensively examined, while limited knowledge exists on the association between lifestyle factors and risk of VTE.

Coffee is one of the most widely consumed beverages in the world, and has been associated with both health benefits and health risks (7). Epidemiological studies have reported diverging results regarding the association between coffee consumption and risk of CVD (8-11), but more recent cohorts have shown an inverse association (8-11). Recently, a J-shaped curve was suggested for the association between coffee intake and acute coronary syndrome (ACS) (12), where a moderate coffee consumption was associated with reduced risk of ACS.

To our knowledge, only one prospective cohort study, including older women only, has investigated the association between coffee consumption and venous thrombosis (13). This study reported a weak inverse association between coffee consumption and VTE, but the association disappeared after adjustments for body mass index (BMI) and diabetes (13). Thus, our current knowledge of the impact of coffee consumption on risk of VTE is limited. The aim of the present study was to explore the association between coffee consumption and the

risk of future VTE, and to test whether this relation was linear, in a large prospective cohort recruited from a general population.

METHODS

Study population

Subjects were recruited from the fourth Tromsø study, a single-centered, prospective, population-based health study, which was carried out in 1994-95. All inhabitants of the municipality of Tromsø, aged 25 or older, were invited to participate, and 77% of the eligible population (n= 27 158) participated. The study was approved by the regional committee of research ethics, and all subjects gave their written consent to participate. Participants were excluded due to the following reasons; 300 did not give their consent to medical research, 43 were not officially registered as inhabitants of the municipality of Tromsø at the date of enrolment, 47 had a known history of VTE, and 13 had missing values on coffee consumption. Thus, a total of 26 755 participants were included in the study, and were followed from the date of enrolment in 1994-95 until the end of follow-up, 1 September 2007.

Baseline measurements

Baseline information was collected by physical examination, blood samples and self-administered questionnaires at a single time-point (date of inclusion). Height and weight were measured with subjects wearing light clothes and no shoes. BMI was calculated as weight in kilograms divided by the square of height in meters (kg m^{-2}). Non-fasting blood samples were collected from an antecubital vein, serum was prepared by centrifugation after 1 h respite at room temperature, and further analyzed at the Department of Clinical Chemistry, University Hospital of North Norway. Serum total cholesterol was analyzed by the CHOD-PAP method (Boeringer Mannheim, Mannheim, Germany). Baseline information on coffee consumption,

diabetes, smoking status, prior CVD (myocardial infarction, angina pectoris and stroke), daily caloric intake, physical activity, and current hormone therapy was collected by a self-administered questionnaire. The coffee consumption questions were: “How many cups of boiled coffee (coarsely ground coffee for brewing) do you usually drink daily?” and “How many cups of coffee, other than boiled, do you usually drink daily?” Physical activity was defined as exercise with sweat production and breathlessness ≥1 hour per week during leisure time. Current hormone therapy was defined as current use of oral contraceptives or current use of estrogen supplementation (tablets or patches). Information on cancer was obtained from the Norwegian Cancer Registry, and cancer exposure was defined as all diagnoses of cancer within the last 10 years prior to the baseline inclusion date. Data on daily caloric intake was available for a subpopulation of participants aged<70 years (n=17 141), and was calculated from information on dietary habits given in the questionnaire (14).

Identification and validation of venous thromboembolism

All incident VTE events during follow-up (from date of examination in 1994-95 until 1 September 2007) were identified by searching the hospital discharge diagnosis registry, the autopsy registry and the radiology procedure registry at the University hospital of North Norway as previously described (5). The University hospital of North Norway is the only hospital in the region, and all hospital care and diagnostic radiology is provided exclusively by this hospital.

The medical records for each potential VTE case were reviewed by trained personnel, who were blinded to all the baseline variables, including coffee consumption habits. Unclear cases or disputes were resolved by discussion with a senior consultant expert on VTE diagnosis (JBH). For subjects derived from the hospital discharge diagnosis registry and the radiology

procedure registry, an episode of VTE was verified and recorded as a validated outcome when all four of the following criteria were fulfilled; (i) objectively confirmed by diagnostic procedures (compression ultrasonography, venography, spiral computed tomography (spiral-CT), perfusion-ventilation scan (required moderate and high probability of PE), pulmonary angiography or autopsy); (ii) the medical record indicated that a physician had made a diagnosis of DVT or PE; (iii) signs and symptoms consistent with DVT or PE were present; (iv) the patient underwent therapy with anticoagulants (heparin, warfarin or a similar agent), thrombolytic therapy or surgery unless contraindications to anticoagulant treatment were specified in the medical record. Isolated calf vein DVT was diagnosed by compression ultrasonography alone or accompanied by venography if insecurity about the diagnosis and/or inadequate technical conditions (e.g. obesity). For subjects derived from the autopsy registry, a VTE event was recorded as an outcome when the autopsy registry indicated VTE as cause of death or as a significant condition contributing to death.

A VTE event was classified as provoked (≥1 provoking factors) or unprovoked (no provoking factors), by the presence of provoking factors at the time of diagnosis. Provoking factors were: recent surgery or trauma within the previous 8 weeks, acute medical conditions (acute MI, ischemic stroke or major infectious disease), active cancer, marked immobilization (bed rest >3 days, wheelchair, or long distant travels exceeding 4 hours within the last 14 days prior to event) or other provoking factors specifically described by a physician in the medical record (e.g. intravascular catheter).

Statistical analyses

For each participant, person-years were accrued from the date of enrolment in the Tromsø study (1994-95), to the date of the first VTE event, the date the participant died or moved

from the municipality of Tromsø, or to the end of follow-up, 1 September 2007. Subjects who moved from the municipality of Tromsø (n=3 716) or died (n=3 000) during the study period were censored.

Statistical analyses were performed using STATA version 11.0 (Stata corporation, College station, Texas, USA). The distribution of baseline characteristics was adjusted for age (with crude standard deviations), and tests for linear trends were carried out using logistic and linear regression. Age- and sex-adjusted incidence rates with 95% confidence intervals (CI) were calculated by direct standardization as number of events per 1000 person-years using the age distribution of the whole cohort as standard population. The association between daily coffee consumption and the risk of total, provoked and unprovoked VTE was assessed using Cox proportional hazard regression models to estimate age and sex-adjusted, and multivariable adjusted hazard ratios (HR) for VTE with 95% CI. The two questionnaire variables on coffee consumption (by type of coffee) were combined into a daily coffee consumption variable, which was used as our main exposure variable divided into 5 categories: 0 cups/day, 1-2 cups/day, 3-4 cups/day, 5-6 cups/day and more than 6 cups daily. The coffee abstainers (0 cups/day) served as the reference group. To correct for potential confounding, other risk factors and concomitant diseases possibly related to both coffee consumption and venous thrombosis were included in a multivariable model. Hence, in the multivariable analyses, the HRs were adjusted for age, sex, BMI, smoking status (current smoker yes/no), physical activity, prior history of CVD, cancer and self-reported diabetes. Adjustments for daily caloric intake in addition to the abovementioned factors were performed in a model including a subgroup of participants <70 years only. Further adjustments for estrogen use (as a 3-level variable; men, women not on estrogens, women on estrogens) were also conducted. Statistical interactions of coffee consumption with age or sex were tested by including cross product

terms in the proportional hazard models. There were no statistical interactions between coffee consumption and age or sex. The proportional hazard assumption was verified by evaluating the parallelism between the curves of the log-log survival function for categories of total coffee consumption. In addition, a test of the proportional hazard assumption using Schoenfeld residuals was performed for all of the relevant variables.

RESULTS

Table 1 shows the characteristics of VTE-patients at the time of the event. In total, there were 462 validated incident VTE events during 289 338 person-years of follow-up (median follow-up time 12.5 years). The overall crude incidence rate was 1.60 per 1000 person-years (95% CI: 1.46-1.75). Of the events, 64.3% (n=297) were DVT, while the remaining 35.7% (n=165) were pulmonary embolism with or without concurrent DVT (table 1). Moreover, 41.8% (n=193) of the events were classified as unprovoked. Active cancer was the most common provoking factor for VTE. The proportions of DVT and PE, provoked and unprovoked VTE, and the presence of clinical risk factors and provoking factors did not differ between sexes (data not shown).

Distribution of age-adjusted characteristics of subjects across categories of daily coffee consumption at baseline is shown in table 2. Age, BMI and total cholesterol levels increased significantly across categories of higher coffee consumption. The proportion of men and smokers increased, while the degree of physical activity and current use of hormone therapy (women only) decreased with increasing coffee consumption.

Incidence rates and hazard ratios for total, provoked and unprovoked VTE across categories of increasing coffee consumption are presented in table 3. The age- and sex-adjusted

incidence rate was highest among the coffee abstainers (IR=2.14 per 1000 person-years; 95% CI: 1.54-2.96). A moderate coffee consumption was inversely associated with risk of VTE (table 3). Drinking 3-4 cups (HR: 0.70, 95% CI: 0.48-1.02) was borderline associated, while 5-6 cups (HR: 0.67, 95% CI: 0.45-0.97) daily was significantly associated with reduced risk of VTE compared to coffee abstainers in analyses adjusted for age, sex, BMI, smoking status, physical activity, cancer, prior CVD and diabetes. The inverse association of coffee consumption was attenuated for subjects drinking more than 6 cups of coffee daily (multivariable HR: 0.85; 95% CI: 0.58-1.24). Similar risk estimates were found for provoked and unprovoked VTE in separate analyses (table 3). Including daily caloric intake in addition to the other adjustments among participants <70 years, did not significantly change the risk estimates (table 3). Further adjustments for current hormone therapy did neither significantly alter the risk of VTE (data not shown). The inverse association between moderate coffee intake and risk of VTE was similar in men and women in sex-stratified analysis (data not shown), and for boiled and non-boiled coffee intake (data not shown).

DISCUSSION

Our findings indicate that a moderate coffee consumption may be inversely associated with risk of VTE. A daily coffee consumption of 5-6 cups was significantly associated with 33% reduced risk of VTE compared to those who abstained from coffee. For heavy coffee drinkers (>6 cups daily) the inverse association of moderate coffee consumption was weakened. Similar risk estimates were found in separate analyses of unprovoked and provoked VTE, and in sex-stratified analyses. These findings suggest a possible U-shaped association between coffee intake and VTE.

To the best of our knowledge, only one previous observational study has investigated the association between coffee intake and VTE. In the Iowa Women's Health study, 37 393 women aged 55-69 years were included and followed for a median of 13 years (13). In agreement with our findings, this study reported a weak inverse association between coffee consumption and risk of VTE in a multivariable model adjusted for age, kilojoules, education level, smoking status and physical activity (13). However, the association vanished after further adjustments for BMI and diabetes (13). In our study, both men and women within a wide age-range were included, and the inverse association of moderate coffee consumption (5-6 cups daily) and VTE remained significant after multivariable adjustments.

In contrast to the limited number of studies on coffee and VTE, the relationship between coffee consumption and arterial CVD has been extensively examined. Several prospective cohort studies have shown an inverse association between CVD and coffee. The Stockholm Heart Epidemiology program (10), the Iowa Women's Health Study (8) and a pooled analysis of data from the Health Professionals Follow-up Study and the Nurses' Health Study (9) found a modest beneficial effect of coffee consumption on the risk of CVD mortality and overall mortality. Similar findings were reported in a Finnish cohort study (11). Contrary, early cohort studies did not find any association between coffee consumption and CVD (15-17), whereas some case-control studies even showed a positive association between coffee and risk of nonfatal myocardial infarction (18-20).

The high contents of polyphenols (especially flavanoids and phenolic acids) in coffee may explain the inverse association between coffee consumption and the risk of VTE (21). Platelet aggregation is vital for the formation of both arterial and venous thrombi (22, 23). Dietary polyphenols inhibit platelet aggregation (22, 24), and intake of 200 ml coffee has been shown

to inhibit platelet aggregation in humans *ex vivo* (24). The platelet inhibiting effect was independent of caffeine (24). In contrast, platelet reactivity was stimulated by caffeine administered in quantities corresponding to one cup of coffee (25). Thus, inhibition of platelet reactivity by coffee intake may reflect that the platelet inhibiting effect of polyphenols is superior to the platelet stimulating effect of caffeine, and thus may contribute to the protective effect of moderate coffee consumption on VTE risk.

Even though limited data are available, experimental studies suggest that coffee consumption increases the fibrinolytic activity without affecting the coagulation system. Coffee ingestion has been found to shorten whole blood fibrinolysis time, an effect ascribed to caffeine (26). Supportive results were found in another study where caffeine exposure in humans increased tissue plasminogen activator (t-PA) activity and decreased plasminogen activator inhibitor (PAI) levels in plasma (27). In contrast, a study comparing the intake of decaffeinated coffee with caffeinated coffee among 20 human subjects, found no differences in fibrinogen levels, platelet adhesiveness or clot lysis time (28). In addition, two randomized studies comparing filtered and boiled coffee with no coffee (29), reported no differences in hemostatic variables such as fibrinogen, factor VII activity, factor VIII antigen, protein C and protein S during the coffee intervention (29).

Confounding is a potential problem of cohort studies due to their non-randomized nature. Possible presence of personal characteristics that make the coffee abstainers different from the coffee consumers, may give rise to an observed inverse association between coffee consumption and risk of VTE that is actually a result of unrecognized confounders, rather than a true association. Coffee consumption is often perceived as part of an unhealthy lifestyle (30), and when confronted with health issues, some abstain from coffee for the benefit of

health (30). Thus, the high incidence of VTE among coffee abstainers in our study could possibly be explained by underlying disease(s). However, the incidence of self-reported diabetes mellitus, cardiovascular diseases, and cardiovascular risk factors such as smoking, and serum lipids were not increased in coffee abstainers in our study. This argument, along with our finding that moderate coffee consumption tended to reduce the risk of unprovoked VTE, attenuated the hypothesis that underlying diseases are confounders for the beneficial impact of coffee consumption on VTE risk.

The main strengths of our study are its prospective design, the large number of participants recruited from a general population with a high attendance rate, long follow-up time and validated VTE events. One single hospital serves the entire Tromsø population, which enhances the possibility of a complete VTE registry. The study also has limitations. Unfortunately, we did not have verified baseline information on previous history of VTE among the study-subjects. Hence, some of the subjects who were treated as healthy participants during follow-up could be prevalent VTE-cases who should have been excluded from the study population. However, this would lead to only a small change in the overall number of person-years at risk, and thus would presumably have a negligible influence on the risk estimates. Certain data points, such as the circumstances at the time of VTE diagnosis (e.g. provoking factors), were collected retrospectively, thus the potential of ascertainment bias in some cases cannot be completely ruled out. Lifestyle habits such as coffee consumption are highly modifiable. A possible change in risk profile during follow-up may lead to misclassification bias which attenuates the real association (31). Another possible study limitation is self-reported information. However, self-reported coffee consumption has been demonstrated to have high validity (32, 33) and reproducibility over time (34, 35). Information on daily caloric intake was not available for all subjects. However, adjustments

for daily caloric intake among a subgroup of participants aged 25-69 years did not alter the risk estimates. Finally, we were not able to investigate the contribution of caffeine independently because the questionnaire did not include questions about decaffeinated coffee.

In conclusion, our findings suggest a possible U-shaped relationship between coffee consumption and VTE, and that moderate coffee consumption may be associated with reduced risk of VTE in the general population. More studies from other general population cohorts are needed to ascertain whether dietary habits such as coffee consumption is associated with the risk of VTE.

Disclosure of Conflict of Interests

The authors reported no potential conflicts of interest.

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REFERENCES

1. Heit JA. Venous thromboembolism: disease burden, outcomes and risk factors. *J Thromb Haemost*. 2005;**3**:1611-7.
2. Beckman MG, Hooper WC, Critchley SE, Ortel TL. Venous thromboembolism: a public health concern. *Am J Prev Med*. 2010;**38**:S495-501.
3. Silverstein MD, Heit JA, Mohr DN, Petterson TM, O'Fallon WM, Melton LJ, 3rd. Trends in the incidence of deep vein thrombosis and pulmonary embolism: a 25-year population-based study. *Arch Intern Med*. 1998;**158**:585-93.
4. Rosendaal FR. Venous thrombosis: a multicausal disease. *Lancet*. 1999;**353**:1167-73.
5. Braekkan SK, Mathiesen EB, Njolstad I, Wilsgaard T, Stormer J, Hansen JB. Family history of myocardial infarction is an independent risk factor for venous thromboembolism: the Tromso study. *J Thromb Haemost*. 2008;**6**:1851-7.
6. White RH. The epidemiology of venous thromboembolism. *Circulation*. 2003;**107**:I4-8.
7. Higdon JV, Frei B. Coffee and health: a review of recent human research. *Crit Rev Food Sci Nutr*. 2006;**46**:101-23.
8. Andersen LF, Jacobs DR, Jr., Carlsen MH, Blomhoff R. Consumption of coffee is associated with reduced risk of death attributed to inflammatory and cardiovascular diseases in the Iowa Women's Health Study. *Am J Clin Nutr*. 2006;**83**:1039-46.
9. Lopez-Garcia E, van Dam RM, Li TY, Rodriguez-Artalejo F, Hu FB. The relationship of coffee consumption with mortality. *Ann Intern Med*. 2008;**148**:904-14.
10. Mukamal KJ, Hallqvist J, Hammar N, Ljung R, Gemes K, Ahlbom A, Ahnve S, Janszky I. Coffee consumption and mortality after acute myocardial infarction: the Stockholm Heart Epidemiology Program. *Am Heart J*. 2009;**157**:495-501.
11. Kleemola P, Jousilahti P, Pietinen P, Vartiainen E, Tuomilehto J. Coffee consumption and the risk of coronary heart disease and death. *Arch Intern Med*. 2000;**160**:3393-400.
12. 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. *J Nutr*. 2003;**133**:3228-32.
13. Lutsey PL, Steffen LM, Virnig BA, Folsom AR. Diet and incident venous thromboembolism: the Iowa Women's Health Study. *Am Heart J*. 2009;**157**:1081-7.
14. Jacobsen BK, Nilsen H. High education is associated with low fat and high fibre, beta-carotene and vitamin C - Computation of nutrient intake based on a short food frequency questionnaire in 71,265 men and women in the Tromsø study. *Norsk Epidemiologi*. 2000;**10**:57-62. Available at: http://www.ntnu.no/ojs/index.php/norepid/article/viewFile/515/485. Accessed 20 January, 2011.
15. Tverdal A, Stensvold I, Solvoll K, Foss OP, Lund-Larsen P, Bjartveit K. Coffee consumption and death from coronary heart disease in middle aged Norwegian men and women. *BMJ*. 1990;**300**:566-9.
16. Gyntelberg F, Hein HO, Suadicani P, Sorensen H. Coffee consumption and risk of ischaemic heart disease--a settled issue? *J Intern Med*. 1995;**237**:55-61.
17. Grobbee DE, Rimm EB, Giovannucci E, Colditz G, Stampfer M, Willett W. Coffee, caffeine, and cardiovascular disease in men. *N Engl J Med*. 1990;**323**:1026-32.
18. Rosenberg L, Palmer JR, Kelly JP, Kaufman DW, Shapiro S. Coffee drinking and nonfatal myocardial infarction in men under 55 years of age. *Am J Epidemiol*. 1988;**128**:570-8.
19. Tavani A, Bertuzzi M, Gallus S, Negri E, La Vecchia C. Risk factors for non-fatal acute myocardial infarction in Italian women. *Prev Med*. 2004;**39**:128-34.

20. Tavani A, Bertuzzi M, Negri E, Sorbara L, La Vecchia C. Alcohol, smoking, coffee and risk of non-fatal acute myocardial infarction in Italy. *Eur J Epidemiol*. 2001;**17**:1131-7.
21. Wang Y, Ho CT. Polyphenolic chemistry of tea and coffee: a century of progress. *J Agric Food Chem*. 2009;**57**:8109-14.
22. Nardini M, Natella F, Scaccini C. Role of dietary polyphenols in platelet aggregation. A review of the supplementation studies. *Platelets*. 2007;**18**:224-43.
23. Grossman ZD, Wistow BW, McAfee JG, Subramanian G, Thomas FD, Henderson RW, Rohner RF, Roskopf ML. Platelets labeled with oxine complexes of Tc-99m and In-111. Part 2. Localization of experimentally induced vascular lesions. *J Nucl Med*. 1978;**19**:488-91.
24. Natella F, Nardini M, Belelli F, Pignatelli P, Di Santo S, Ghiselli A, Violi F, Scaccini C. Effect of coffee drinking on platelets: inhibition of aggregation and phenols incorporation. *Br J Nutr*. 2008;**100**:1276-82.
25. Ammaturo V, Perricone C, Canazio A, Ripaldi M, Ruggiano A, Zuccarelli B, Monti M. Caffeine stimulates in vivo platelet reactivity. *Acta Med Scand*. 1988;**224**:245-7.
26. Samarrae WA, Truswell AS. Short-term effect of coffee on blood fibrinolytic activity in healthy adults. *Atherosclerosis*. 1977;**26**:255-60.
27. Wojta J, Kirchheimer JC, Peska MG, Binder BR. Effect of caffein ingestion on plasma fibrinolytic potential. *Thromb Haemost*. 1988;**59**:337-8.
28. Naismith DJ, Akinyanju PA, Szanto S, Yudkin J. The effect, in volunteers, of coffee and decaffeinated coffee on blood glucose, insulin, plasma lipids and some factors involved in blood clotting. *Nutr Metab*. 1970;**12**:144-51.
29. Bak AA, van Vliet HH, Grobbee DE. Coffee, caffeine and hemostasis: results from two randomized studies. *Atherosclerosis*. 1990;**83**:249-55.
30. van Dam RM. Coffee consumption and risk of type 2 diabetes, cardiovascular diseases, and cancer. *Appl Physiol Nutr Metab*. 2008;**33**:1269-83.
31. Clarke R, Shipley M, Lewington S, Youngman L, Collins R, Marmot M, Peto R. Underestimation of risk associations due to regression dilution in long-term follow-up of prospective studies. *Am J Epidemiol*. 1999;**150**:341-53.
32. van Dam RM, Hu FB. Coffee consumption and risk of type 2 diabetes: a systematic review. *JAMA*. 2005;**294**:97-104.
33. Jacobsen BK, Knutsen SF, Knutsen R. The Tromso Heart Study: comparison of information from a short food frequency questionnaire with a dietary history survey. *Scand J Soc Med*. 1987;**15**:41-7.
34. Saaksjarvi K, Knekt P, Mannisto S, Heliovaara M. Self-administered questionnaire is a reliable measure of coffee consumption. *J Epidemiol*. 2010;**20**:363-9.
35. Colditz GA, Willett WC, Stampfer MJ, Sampson L, Rosner B, Hennekens CH, Speizer FE. The influence of age, relative weight, smoking, and alcohol intake on the reproducibility of a dietary questionnaire. *Int J Epidemiol*. 1987;**16**:392-8.

Table 1. Characteristics of the incident VTE events (n=462) during follow-up. The Tromsø study 1994/95-2007.

	% (n)
Men	47.4 (219)
Deep vein thrombosis	64.3 (297)
Pulmonary embolism	35.7 (165)
Unprovoked	41.8 (193)
Clinical risk factors	-
Estrogen*	14.4 (35)
Pregnancy/puerperium*	1.2 (3)
Heredity†	2.8 (13)
Other medical conditions‡	21.6 (100)
Provoking factors	-
Surgery	17.1 (79)
Trauma	6.7 (31)
Acute medical conditions	15.1 (70)
Cancer	22.9 (106)
Immobility§	19.0 (88)
Other¶	4.1 (19)

* Only women included in analysis

† VTE in first degree relative before aged 60 years.

‡ Includes other diseases within the previous year (myocardial infarction, ischemic stroke, heart failure, inflammatory bowel disease, chronic infections, chronic obstructive pulmonary disease, or myeloproliferative disorders).

§ Immobility includes bed rest>3days, longtime travels with car, boat, train or by air >4 hours within last 14 days, or other type of immobilization.

¶ Other provoking factor described by a physician in the medical record (e.g. intravascular catheter).

Table 2. Baseline characteristics across categories of coffee consumption*. The Tromsø Study 1994/95-2007.

Characteristics	0 cups/day	1-2 cups/day	3-4 cups/day	5-6 cups/day	>6 cups/day	P for trend
Number of subjects	2671	2873	6581	7178	7452	-
Number of events	36	51	126	118	131	-
Men (%)	39.6 (1059)	39.4 (1133)	41.7 (2742)	47.0 (3372)	59.2 (4411)	<0.001
Age (years)	38.5±14.3	46.9±17.1	49.7±16.2	48.3±14.5	46.0±12.6	<0.001
BMI (kg/m^2)	25.2±4.1	24.9±3.8	25.0±3.8	25.2±3.8	25.4±3.8	<0.001
Total cholesterol (mmol/l)	5.75±1.20	5.85±1.30	5.99±1.35	6.09±1.29	6.25±1.27	<0.001
Self-reported diabetes (%)	1.1 (30)	1.3 (69)	1.0 (137)	1.2 (140)	1.0 (103)	0.50
Self-reported prior CVD† (%)	2.8 (103)	2.8 (223)	2.6 (535)	2.9 (509)	3.1 (404)	0.06
Current smoking (%)	15.6 (494)	16.0 (476)	24.2 (1560)	39.3 (2790)	58.0 (4341)	<0.001
Hormone therapy (%) ‡	23.7 (271)	23.9 (265)	20.8 (480)	18.3 (449)	14.9 (299)	<0.001
Physical activity (%)	30.0 (1005)	31.1 (937)	30.5 (1955)	28.9 (2077)	26.4 (2083)	<0.001
Cancer (%)	1.3 (37)	1.4 (74)	1.2 (160)	1.3 (163)	1.3 (129)	0.91
Daily caloric intake§	1775±513	1803±496	1843±512	1890±516	1997±553	<0.001

* Values are given as age-adjusted means ± crude standard deviations or as age-adjusted percentages with absolute numbers in brackets.

† Includes history of myocardial infarction, angina pectoris or stroke.

‡ The percentages are based on the female population.

§ Based on a subpopulation of participants <70 years (n=17 141).

Table 3. Incidence rates (IR) and hazard ratios (HR) for VTE by categories of daily coffee consumption. The Tromsø study 1994/95-2007.

	Person years	Events	IR[*†]	HR[†]	Multivariable HR[‡]	Multivariable HR[§]
Total VTE	-	-	-	-	-	-
0 cups/day	27298	36	2.14 (1.54-2.96)	Ref	Ref	-
1-2 cups/day	29808	51	1.59 (1.21-2.09)	0.77 (0.50-1.18)	0.78 (0.51-1.21)	-
3-4 cups/day	70435	126	1.51 (1.27-1.80)	0.70 (0.48-1.02)	0.70 (0.48-1.02)	-
5-6 cups/day	79014	118	1.40 (1.17-1.68)	0.68 (0.47-0.99)	0.67 (0.45-0.97)	-
>6 cups/day	82783	131	1.74 (1.46-2.06)	0.88 (0.61-0.99)	0.85 (0.58-1.24)	-
P for trend	-	-	-	0.96	0.71	-
Provoked VTE	-	-	-	-	-	-
0 cups/day	27199	21	1.21 (0.79-1.85)	Ref	Ref	-
1-2 cups/day	29646	25	0.78 (0.53-1.15)	0.62 (0.35-1.12)	0.61 (0.34-1.10)	-
3-4 cups/day	70102	76	0.88 (0.70-1.10)	0.70 (0.43-1.14)	0.67 (0.41-1.09)	-
5-6 cups/day	78635	68	0.81 (0.64-1.03)	0.66 (0.40-1.08)	0.62 (0.38-1.01)	-
>6 cups/day	82401	79	1.05 (0.84-1.31)	0.92 (0.57-1.49)	0.84 (0.51-1.38)	-
P for trend	-	-	-	0.50	0.84	-
Unprovoked VTE	-	-	-	-	-	-
0 cups/day	27190	15	0.95 (0.57-1.57)	Ref	Ref	-
1-2 cups/day	29622	26	0.86 (0.58-1.26)	0.98 (0.52-1.86)	1.06 (0.55-2.04)	-
3-4 cups/day	69936	50	0.65 (0.49-0.85)	0.70 (0.39-1.25)	0.75 (0.41-1.36)	-

5-6 cups/day	78539	50	0.61 (0.46-0.80)	0.71 (0.40-1.26)	0.74 (0.41-1.35)	-
>6 cups/day	82193	52	0.70 (0.53-0.92)	0.84 (0.47-1.49)	0.85 (0.46-1.56)	-
P for trend	-	-	-	0.49	0.42	-
Total VTE[¶]	-	-	-	-	-	-
0 cups/day	26155	29	2.03 (1.41-2.92)	Ref	Ref	Ref
1-2 cups/day	26548	27	1.30 (0.89-1.89)	0.60 (0.35-1.02)	0.64 (0.37-1.08)	0.57 (0.29-1.14)
3-4 cups/day	61766	77	1.35 (1.08-1.69)	0.61 (0.39-0.93)	0.65 (0.42-1.00)	0.50 (0.28-0.89)
5-6 cups/day	72912	78	1.18 (0.95-1.47)	0.53 (0.34-0.81)	0.56 (0.36-0.87)	0.60 (0.35-1.05)
>6 cups/day	79723	113	1.56 (1.29-1.87)	0.77 (0.51-1.16)	0.78 (0.51-1.20)	0.89 (0.52-1.52)
P for trend	-	-	-	0.88	0.74	0.33

[*] Incidence rate per 1000 person years.

[†] Adjusted for age and sex, with 95% confidence intervals

[‡] Adjusted for age, sex, BMI, smoking status, physical activity, diabetes, history of CVD and cancer, with 95% confidence intervals.

[§] Adjusted for age, sex, BMI, smoking status, physical activity, diabetes, history of CVD, cancer and daily caloric intake, with 95% confidence intervals. Includes only participants <70 years.

[¶] Includes a subpopulation of participants <70 years (n=17 141).