

# Venous thromboembolism and coffee: critical review and meta-analysis

Giuseppe Lippi<sup>1</sup>, Camilla Mattiuzzi<sup>2</sup>, Massimo Franchini<sup>3</sup>

<sup>1</sup>Laboratory of Clinical Chemistry and Hematology, Academic Hospital of Parma, Parma, Italy; <sup>2</sup>Service of Clinical Governance, General Hospital of Trento, Trento, Italy; <sup>3</sup>Department of Hematology and Transfusion Medicine, C. Poma Hospital, Mantova, Italy

Correspondence to: Prof. Giuseppe Lippi. U.O. Diagnostica Ematochimica, Azienda Ospedaliero-Universitaria di Parma, Via Gramsci, 14, 43126 - Parma, Italy. Email: glippi@ao.pr.it; ulippi@tin.it.

**Background:** Among the various risk factors of venous thromboembolism (VTE), nutrients seem to play a significant role in the pathogenesis of this condition. This study aimed to clarify the relationship between coffee intake and venous thrombosis, and we performed a critical review of clinical studies that have been published so far.

**Methods:** An electronic search was carried out in Medline, Scopus and ISI Web of Science with the keywords “coffee” AND “venous thromboembolism” OR “deep vein thrombosis” OR “pulmonary embolism” in “Title/Abstract/Keywords”, with no language and date restriction.

**Results:** According to our criteria, three studies (two prospective and one case-control) were finally selected (inter-study heterogeneity: 78%;  $P < 0.001$ ). Cumulative data suggests that a modest intake of coffee (i.e., 1-4 cups/day) may be associated with an 11% increased risk of VTE compared to abstainers, whereas a larger intake (i.e.,  $\geq 5$  coffee/day) may be associated with a 25% decreased risk.

**Conclusions:** Our analysis of published data seemingly confirm the existence of a U-shape relationship between coffee intake and VTE, thus exhibiting a trend that overlaps with that previously reported for cardiovascular disease (CVD).

**Keywords:** Venous thromboembolism (VTE); thrombosis; coffee; risk

Submitted Jun 08, 2015. Accepted for publication Jun 12, 2015.

doi: 10.3978/j.issn.2305-5839.2015.06.14

View this article at: <http://dx.doi.org/10.3978/j.issn.2305-5839.2015.06.14>

## Introduction

Venous thromboembolism (VTE) is common and severe disorders, with an annual incidence that can be as high as 81.6 per 100,000 population (1). Among the various risk factors of VTE, nutrients seem to play a significant role in the pathogenesis of this condition (2). Several lines of evidence convincingly attest that a U-shaped relationship exists between coffee consumption and cardiovascular risk, wherein a lower risk is associated with low or high coffee intake, whereas a moderate consumption (i.e., 2-4 cups/day) is associated with a higher risk (3). Although several trials investigating the role of coffee in the pathogenesis of arterial thrombosis have been published so far, only few literature data exists on the association between coffee consumption and VTE. Therefore, to clarify the relationship between coffee intake and venous thrombosis,

we performed a critical review of clinical studies that have been published so far.

## Methods

An electronic search was carried out in Medline, Scopus and ISI Web of Science with the keywords “coffee” AND “venous thromboembolism” OR “deep vein thrombosis” OR “pulmonary embolism” in “Title/Abstract/Keywords”, with no language and date restriction. All articles identified according to the search criteria were systematically revised for quality by two authors (G.L. and M.F.). The references of the selected articles were also scrutinized in order to identify other pertinent items. Heterogeneity was evaluated by Chi-square based statistics and I-square test, wherein thresholds of 25%, 50% and 75% designate low, moderate,

**Table 1** Description of epidemiological studies investigating the association between coffee consumption and risk of VTE

Author	Study design	Population	Outcome	Results
Lutsey <i>et al.</i> , 2009 (4)	Prospective	37,393 women followed for 19 years	RR of incident VTE vs. coffee abstainers	<ul style="list-style-type: none"> <li>Any intake: 0.92 (95% CI, 0.80-1.06);</li> <li>1-4 cups/day: 0.94 (95% CI, 0.81-1.09);</li> <li>&gt;6 cups/day: 0.86 (95% CI, 0.70-1.06)</li> </ul>
Enga <i>et al.</i> , 2011 (5)	Prospective	26,755 subjects followed for 12.5 years	RR of incident VTE vs. coffee abstainers	<ul style="list-style-type: none"> <li>Any intake: 1.10 (95% CI, 0.75-1.62);</li> <li>1-4 cups/day: 1.06 (95% CI, 0.70-1.60);</li> <li>≥5 cups/day: 1.13 (95% CI, 0.76-1.67; P=0.544)</li> </ul>
Roach <i>et al.</i> , 2012 (6)	Case-control	3,606 subjects (50% with VTE)	RR of VTE vs. coffee abstainers	<ul style="list-style-type: none"> <li>Any intake: 0.85 (95% CI, 0.77-0.94);</li> <li>1-4 cups/day: 0.86 (95% CI, 0.78-0.96; P=0.006);</li> <li>≥5 cups/day: 0.82 (95% CI, 0.73-0.92)</li> </ul>
Cumulative data			RR of VTE vs. coffee abstainers	<ul style="list-style-type: none"> <li>Any intake: 0.97 (95% CI, 0.88-1.08);</li> <li>1-4 cups/day: 1.11 (95% CI, 1.00-1.22);</li> <li>≥5 cups/day: 0.75 (95% CI, 0.67-0.85)</li> </ul>

VTE, venous thromboembolism; RR, relative risk.

and high heterogeneity. The cumulative relative risk (RR) and 95% confidence interval (95% CI) were estimated from the original data reported in the articles, using MedCalc version 12.3.0 (MedCalc Software, Mariakerke, Belgium).

## Results

After elimination of duplicates across the scientific databases, a total number of 13 publications could be identified. Nine documents were excluded (one commentary, four review articles, and five publications with no data on the association between VTE and coffee intake). Therefore, three studies (two prospective and one case-control) were finally selected for our analysis (*Table 1*) (4-6). Inter-rater agreement was absolute ( $k=1.00$ ). The inter-study heterogeneity was high (I-squared, 78%;  $P<0.001$ ).

The first investigation was published by Lutsey *et al.*, who performed a prospective study including 37,393 women aged 55-69 years, who participated to the Iowa Women's Health Study, and were followed up for 19 years (4). The rate of incident VTE was 5.2% (1,950/37,393). Compared to abstainers, the RR of incident VTE was 0.92 (95% CI, 0.80-1.06;  $P=0.227$ ) in women consuming any amount of coffee, 0.94 (95% CI, 0.81-1.09;  $P=0.407$ ) in those consuming 1-4 cups/day, and 0.86 (95% CI, 0.70-1.06;  $P=0.151$ ) in those consuming >6 cups/day.

Enga *et al.* performed another prospective cohort study by means of a questionnaire which was administered to 26,755 participants of the fourth survey of the Tromsø study (age 25-97 years) (5). The mean follow-up period was

12.5 years, with a rate of incident VTE of 1.7% (462/26,755). Compared to abstainers, the RR of incident VTE was 1.10 (95% CI, 0.75-1.62;  $P=0.611$ ) in subjects consuming any amount of coffee, 1.06 (95% CI, 0.70-1.60;  $P=0.774$ ) in those consuming 1-4 cups/day, and 1.13 (95% CI, 0.76-1.67;  $P=0.544$ ) in those consuming ≥5 cups/day.

More recently, Roach *et al.* published a case-control study including 1,803 patients with VTE (50% males, age 18-70 years) and 1,803 matched partners (50% males, age 18-70 years) (6). Compared to abstainers, the RR of incident VTE was 0.85 (95% CI, 0.77-0.94;  $P=0.002$ ) in subjects consuming any amount of coffee, 0.86 (95% CI, 0.78-0.96;  $P=0.006$ ) in those consuming 1-4 cups/day, and 0.82 (95% CI, 0.73-0.92;  $P=0.001$ ) in those consuming ≥5 cups/day.

The pooled data available in these two prospective and one case-control investigations attest that no apparent relationship exist between VTE and any amount of coffee consumption (cumulative RR vs. abstainers, 0.97; 95% CI, 0.88-1.08;  $P=0.600$ ). On the other hand, a marginally significant relationship could be observed between VTE and modest coffee intake (cumulative RR of 1-4 cups/day vs. abstainers, 1.11; 95% CI, 1.00-1.22;  $P=0.047$ ), whereas subjects consuming ≥5 cups/day exhibited a lower risk compared to abstainers (cumulative RR, 0.75; 95% CI, 0.67-0.85;  $P<0.001$ ).

## Discussion

Coffee is one of the most widely consumed beverages around the world and thus the investigation on the clinical consequences of its chronic use is an important public health

issue. The relationship between coffee consumption and risk of coronary heart disease in Western countries has been recognized for more than 50 years (7), and several studies, systematic reviews and meta-analyses have been focused on this issue during the past decades. The most recent meta-analysis on the effect of long-term coffee consumption on cardiovascular disease (CVD) risk was published by Ding and colleagues, and included 36 prospective cohort studies totalling 1,279,804 participants and 36,352 CVD cases (8). Interestingly, a nonlinear association between coffee consumption and CVD risk was observed. Indeed, moderate coffee consumption was inversely associated with CVD risk, with the lowest risk at 3 to 5 cups per day, and heavy coffee intake was not associated with elevated CVD risk. Nevertheless, virtually all studies assessed the impact of coffee intake on arterial thrombotic risk (i.e., stroke and coronary heart disease), and limited information has been published so far on the association with VTE. The results of our meta-analysis of published data are, however, in keeping with those from Ding and colleagues (8) and seem to confirm the existence of a U-shape relationship between coffee intake and VTE, wherein a modest consumption (i.e., 1-4 cups/day) was associated with a 11% increased risk compared to abstainers, whereas a larger intake (i.e.,  $\geq 5$  coffee/day) was associated with a 25% decreased risk (*Table 1*), thus exhibiting a trend that overlaps with that previously reported for CVD (3). Although the biological mechanisms underlying this relationship can be hardly ascertained (coffee is a complex beverage, containing as many as 1,000 compounds) (9), these epidemiological findings may be at least in part explained by the high levels of polyphenols (especially flavonoids and phenolic acids) present in coffee, which have been inversely correlated with the risk of VTE (10).

## Conclusions

Although the results of our systematic review and meta-analysis seem to suggest an association between coffee consumption and VTE risk, the literature data are too limited to draw definitive conclusions. However, this topic is not trivial considering the great diffusion worldwide of coffee beverage and the morbidity and mortality burden of venous thrombosis. Therefore, additional studies are greatly awaited to confirm these limited and preliminary findings.

## Acknowledgements

*Authors' contributions:* Conception and design: G Lippi,

M Franchini; Development of methodology: G Lippi, C Mattiuzzi; Analysis and interpretation of data: G Lippi, M Franchini; Writing, review, and/or revision of the manuscript: G Lippi, C Mattiuzzi, M Franchini.

*Disclosure:* The authors declare no conflict of interest.

## References

1. Liao S, Woulfe T, Hyder S, et al. Incidence of venous thromboembolism in different ethnic groups: a regional direct comparison study. *J Thromb Haemost* 2014;12:214-9.
2. Phang M, Lazarus S, Wood LG, et al. Diet and thrombosis risk: nutrients for prevention of thrombotic disease. *Semin Thromb Hemost* 2011;37:199-208.
3. Montagnana M, Favaloro EJ, Lippi G. Coffee intake and cardiovascular disease: virtue does not take center stage. *Semin Thromb Hemost* 2012;38:164-77.
4. Lutsey PL, Steffen LM, Virnig BA, et al. Diet and incident venous thromboembolism: the Iowa Women's Health Study. *Am Heart J* 2009;157:1081-7.
5. Enga KF, Braekkan SK, Hansen-Krone IJ, et al. Coffee consumption and the risk of venous thromboembolism: the Tromsø study. *J Thromb Haemost* 2011;9:1334-9.
6. Roach RE, Siegerink B, le Cessie S, et al. Coffee consumption is associated with a reduced risk of venous thrombosis that is mediated through hemostatic factor levels. *J Thromb Haemost* 2012;10:2519-25.
7. Paul O, Lepper MH, Phelan WH, et al. A longitudinal study of coronary heart disease. *Circulation* 1963;28:20-31.
8. Ding M, Bhupathiraju SN, Satija A, et al. Long-term coffee consumption and risk of cardiovascular disease: a systematic review and a dose-response meta-analysis of prospective cohort studies. *Circulation* 2014;129:643-59.
9. O'Keefe JH, Bhatti SK, Patil HR, et al. Effects of habitual coffee consumption on cardiometabolic disease, cardiovascular health, and all-cause mortality. *J Am Coll Cardiol* 2013;62:1043-51.
10. Wang Y, Ho CT. Polyphenolic chemistry of tea and coffee: a century of progress. *J Agric Food Chem* 2009;57:8109-14.

**Cite this article as:** Lippi G, Mattiuzzi C, Franchini M. Venous thromboembolism and coffee: critical review and meta-analysis. *Ann Transl Med* 2015;3(11):152. doi: 10.3978/j.issn.2305-5839.2015.06.14