**Non-genetic and genetic risk factors for adult cerebral venous thrombosis**

Mackenzie Green1\*, Toby Styles1\*, Timothy Russell1\*, Charif Sada1, Ebrima Jallow1, Jack Stewart1, Otar Lazariashvili1, Irina Lubomirova2, Ioana Cotlarciuc1, Sapna Sharma1, Thang S Han1,3, Pankaj Sharma1

*\*These authors contributed equally to this work*

1Institute of Cardiovascular Research, Royal Holloway, University of London (ICR2UL), Egham, United Kingdom.

2Department of Medicine, Imperial College London, London, United Kingdom.

3Department of Endocrinology, Ashford and St Peter’s NHS Foundation Trust, Surrey, United Kingdom.

**Short title:** Non-genetic and genetic risk factors of CVT

**Text** = 3387 words, **Tables** = 2, **Figures** = 3

**Corresponding Authors**:

Dr TS Han and Professor P Sharma

Institute of Cardiovascular Research

Royal Holloway University of London (ICR2UL)

Egham, TW10 0EX, United Kingdom

Telephone: 01784443807, Email: pankaj.sharma@rhul.ac.uk

**ABSTRACT**

**Introduction**: A wide variety of non-genetic and genetic factors have been shown to associate with increased risk for cerebral venous thrombosis (CVT). However, there are a paucity of risk factor data and conclusions about their impact are often conflicting. Herein, we quantified the associations of non-genetic and genetic risk factors for CVT in adults.

**Materials and methods**: Electronic databases were searched up to January 2017. Meta-analyses were performed (RevMan v5.3) to determine pooled odds ratios (ORs and 95%CIs) for risk factors, interstudy heterogeneity and publication bias.

**Results**: Twenty non-genetic (n=2314) and 33 genetic (n=2117) studies up to January 2017 met the selection criteria. For non-genetic factors, CVT risk increased in the presence of glucocorticosteroid therapy by 18.3-fold (3.3-102.6), alcohol consumption 2.7-fold (1.8-3.9), infection 7.5-fold (2.6-21.6), surgery 9.6-fold (1.1-83.5), hypercholesterolaemia 2.4-fold (1.3-4.4), hyperhomocysteinaemia 3.1-fold (2.1-4.6), antiphospholipid antibodies 7.0-fold (2.1-23.6), autoimmune diseases 5.6-fold (2.3-13.6), anaemia 4.0-fold (2.1-7.9), malignancy 3.2-fold (1.4-7.1) and pregnancy/puerperium 11.4-fold (5.7-24.3). Smoking, hypertension and diabetes did not associate with CVT risk. For genetic factors, CVT risk increased in the presence of factor V Leiden (*G1691A*) by 2.5-fold (1.9-3.3), protein C deficiency 10.7-fold (3.1-37.7), protein S deficiency 5.7-fold (1.4-22.4), antithrombin deficiency 3.8-fold (1.0-13.8), prothrombin (*G20210A*) 5.5-fold (4.0-7.27) and TAFI gene variant (*C1040T*) 1.6-fold (1.0-2.4). Prothrombin *G20210A* and factor V Leiden polymorphisms tended to have higher ORs for CVT than for ischaemic stroke.

**Conclusions:** We provide quantitative data supporting astrong basis for genetic and non-genetic risk factors in CVT. Its genetic liability seems higher when compared with sporadic ischaemic stroke.

**Keywords:** Oral contraceptives, Glucocorticosteroid, Autoimmune disease, Factor V Leiden, Stroke

**INTRODUCTION**

Cerebral venous thrombosis (CVT) is a rare sub-type of stroke, accounting for <1% of all strokes [1] with an overall annual incidence estimated at 1.32 per 100,000 person-years [2]. CVT more commonly affects young adults with higher prevalence in women (childbearing age) than men (3: 1 ratio) [3]; this gender difference is thought to be related to oestrogen exposure and pregnancy/puerperium. The highest prevalence in the world is observed among South Asians [4] . CVT is caused by occlusion of dural venous sinuses resulting in a reduction of cerebral blood and cerebrospinal fluid outflow, and consequently venous infarct. Dural sinus occlusion is frequently accompanied with CVT [5]. Although CVT can lead to mortality or severe morbidity, it generally has a better prognosis than arterial stroke with about 79% of patients recovering completely [1].

A wide variety of non-genetic factors and genetic factors have been recognised as predisposing risk factors for CVT [5–19]. Among the non-genetic factors accounting for CVT are drugs, such as oral contraceptives with the proportion of cases associated with this risk factor reported to be 10-73% [8,9], glucocorticosteroids (5%) [10,11] and asparaginase (1-3%) while tamoxifen has also been implicated as a risk factor [10]. Other major non-genetic risk factors include pregnancy (reported proportion of cases: 5-20%) [10] and the first two days of the puerperium (15%) [10], metabolic disorders such as hyperhomocysteinemia (27-43%), hypertension and diabetes during gestation (10-26%) [12], autoimmune and inflammatory diseases (15%) of which inflammatory bowel disease accounted for about 3-10% of CVT cases [8,10,19], malignancy (6-9%) [9,10,13,14,15], head trauma (4-6%) [10,13], neurosurgical procedures or surgeries (19%) [13] and infections (6-14%) [10,16,17,18]. Genetic factors account for 20-30% of cases with CVT with factor V Leiden, proteins C and S deficiency being the leading genetic risk for CVT (10–25%) [8,12,16,17]. About 44% of CVT cases have more than one predisposing risk factor [12] while no cause can be found in about 20-35% of cases in previous reports [8,17] but more recently this figure has been revised to 15% [12,15]. Mostly within the first year, 2-5% of all patients with CVT have recurrent CVT [15,16,18] and 14% of affected patients will have recurrent venous thromboembolism (VTE) elsewhere [16].

Due to the rarity of this condition, there are a paucity of data on risk factors for CVT. Most of the available information has been published in small studies and the conclusions drawn are often conflicting. Two previous meta-analysis by Lauw et al (6) and Marjot et al (7) focused predominantly on genetic risk factors for CVT. In the present meta-analysis, we aimed to comprehensively quantify simultaneously the extent of all major known genetic and non-genetic risk factors of CVT.

**METHODS**

**Search strategy**

To identify all case-control studies published in all languages for genetic and non-genetic risk factors of CVT (also known as cerebral venous sinus thrombosis, CVST), MEDLINE (via PubMed), EMBASE (via Ovid) and the Cochrane Central Register of Controlled Trials (CENTRAL, the Cochrane Library) databases were searched up to January 2017 using terms listed in **Supplementary file**. Additional search for grey literature was performed using a number of other methods including Google Scholar, Web of Science, ClinicalTrials.gov, grey literature websites, Department of Health and National Institute for Health and Clinical Excellence *etc*. Our search strategy was conducted in accordance with meta-analysis of observational studies in epidemiology (MOOSE) guidelines [20].

**Study selection criteria**

Three authors independently selected studies for inclusion in this meta-analysis based on the following criteria: 1) case control design with numbers of patients and controls available, 2) objective diagnosis of CVT with magnetic resonance angiography and/or computed tomographic angiography and/or angiography and 3) analysis of CVT risk factors as dichotomous traits. Studies on children or neonates were excluded.

To ensure our work was comprehensive, all studies were included irrespective of the number of cases or controls. To avoid duplication, we closely examined studies on similar topics and those with similar authors or from the same centre. Findings from the three authors were mostly consistent with only minor discrepancies. Our protocol design was for discrepancies to be resolved by consensus and an additional co-investigator was involved when necessary.

**Statistical analysis**

Analysis was performed using RevMan *v*5.3. Data was extracted manually from the original articles for the total numbers of cases and controls and their respective events, odds ratios (ORs) and 95% confidence intervals (CI). Pooled ORs, 95% C), and heterogeneity were calculated for each gene polymorphism using the Cochran-Mantel-Haenszel statistical method and a random effects analysis model. Interstudy heterogeneity was examined by *I*2 index and studies were iteratively tested to reduce heterogeneity. An *I*2 value greater than 50% and *P* <0.05 were considered to indicate heterogeneity [21]. Publication bias was inspected visually by funnel plots [22]. Statistical significance threshold was accepted as *P* <0.05.

For clarity of presentation, we grouped non-genetic risk factors into four broad categories: 1) External risk factors (glucocorticosteroid therapy, alcohol consumption, smoking, infection and surgery), 2) Metabolic disorders (hypercholesterolaemia, hyperhomocysteinemia, hypertension and diabetes, 3) Autoimmune disorders (antiphospholipid antibodies and combination of autoimmune diseases) and 4) Others non-genetic risk factors (anaemia, malignancy and pregnancy/puerperium). In addition, interstudy heterogeneity and bias are described only when occurred.

For various conditions (*e.g.* antiphospholipid antibodies, hyperhomocysteinemia, and hypertension), variable definitions were used in the incorporated studies and some studies provided no definition. In all cases, the definition in the source publication was accepted.

**RESULTS**

Our initial search strategy found 10,248 studies. After considering our inclusion and exclusion criteria, 42 papers were included in our quantitative meta-analysis (**Fig 1**); nine of these examined non-genetic risk factors, while 22 examined genetic risk factors and 11 examined both types of risk factors. A summary of the studies examining risk factors associated with CVT, including distribution of cases and controls, as well as pooled ORs, is shown in **Table 1**.

**Non-genetic risk factors of CVT**

*External risk factors*

The risk of CVT was found to increase with glucocorticosteroid therapy by 18.26-fold (95% CI: 3.25-102.55, *P* <0.01) without significant interstudy heterogeneity (*I*2 = 0%, *P* = 0.76) [23-25]. The risk of CVT was also increased with alcohol consumption by 2.67-fold (95% CI: 1.84-3.88, *P* <0.001; *I*2 = 0%, *P* = 0.47) [24,26-28], infection (ear, nose and throat infection as well as meningitis and broader definitions such as any recent infection) by 7.49-fold (95% CI: 2.61-21.55, *P* <0.001; *I*2 = 30%, *P* = 0.22) [23,29-32], and surgical procedures by 9.55-fold (95% CI: 1.09-83.54, *P* = 0.040; *I*2 = 0%, *P* = 0.37) [29,30]. The risk of CVT was not associated with smoking (OR = 1.46, 95% CI: 0.82-2.59, *P* = 0.20; *I*2 = 46%, *P* = 0.12) [5,26-29,31,33,34]. There was no evidence of publication bias (symmetrical funnel plot) in all external risk factors for CVT studies.

*Metabolic disorders*

Metabolic disorders were variably defined by different studies, while some studies did not provide a definition [24]. Hypercholesterolemia was considered as fasting plasma cholesterol levels ≥5.2 mmol/l [31], hyperhomocysteinemia was defined by fasting total homocysteine levels [29, 31] or postmethionine load increments exceed the 90th percentile [36] or 95th percentile [29] of the values obtained in the control group. Hypertension was mostly considered for those with resting systolic ≥140 mmHg or diastolic blood pressure ≥90 mmHg [31].

The risk of CVT was found to increase among those with hypercholesterolaemia by 2.40-fold (95% CI: 1.31-4.39, *P* = 0.005; *I*2 = 0%, *P* = 0.45) [24,31] and hyperhomocysteinemia by 3.13-fold (95% CI: 2.12-4.61; *P* <0.001) [26,28,29,31-33,35,36]. Significant interstudy heterogeneity was observed (*I*2 = 60%, *P* = 0.010) which was eliminated (*I*2 = 42%, *P* = 0.11) after excluding the study by Tufano *et al* [31] while significant association between hyperhomocysteinemia and CVT persisted (OR = 3.53, 95% CI: 2.50-4.96, *P* <0.001). We found no association of the risk of CVT with hypertension (OR = 1.28, 95% CI: 0.87-1.89, *P* = 0.210; *I*2 = 0%, *P* = 0.87) [24,26,31,37] or with diabetes (OR = 1.01, 95% CI: 0.18-5.55, *P* = 0.990; *I*2 = 0%, *P* = 0.43) [24,37]. There was no evidence of publication bias (symmetrical funnel plot) in all metabolic risk factors for CVT studies.

*Autoimmune disorders*

The risk of CVT was found to increase in patients with antiphospholipid antibodies by 6.98-fold (95% CI: 2.06-23.64, *P* < 0.002; *I*2 = 52%, *P* = 0.06) [25,29-32,38] and with autoimmune disease by 5.56-fold (95% CI: 2.28-13.57, *P* <0.001; *I*2 = 41%, *P* = 0.10) [23-25,29-32,37,38]. Publication bias was not observed in all autoimmune disorders as risk factors for CVT studies.

*Other non-genetic risk factors*

The risk of CVT was also found to increase in patients with anaemia by 4.04-fold (95% CI: 2.07-7.89, *P* <0.001; *I*2 = 66%, *P* = 0.08) [24,39], malignancy by 3.19-fold (95% CI: 1.43-7.12; *P* = 0.005) [24,30,39] and pregnancy/puerperium by 17.34-fold (95% CI: 6.83-44.04, *P* <0.001) [23-26,29,30,32,39]. Heterogeneity between studies was detected (*I*2 = 56%, *P* = 0.03) which was eliminated after the removal of the outlier study by Cesarman-Maus (25) while the association between pregnancy/puerperium and CVT persisted (OR = 11.37, 95%CI = 5.66-24.32, P <0.001; *I*2 = 34%, *P* = 0.17). Funnel plots showed no evidence of publication bias in all other non-genetic risk factors for CVT studies.

*Risk factors in relation to CVT and non-cerebral venous thromboembolism*

Case-control studies were identified for eight of the nine non-genetic risk factors which allowed us to compare effect sizes between CVT and non-cerebral VTE [41-47]. We observed that anaemia, hyperhomocysteinemia, hypercholesterolemia and infection were more strongly associated with CVT while surgery, diabetes and malignancy were more strongly associated with VTE (**Table 2**).

**Genetic risk factors**

The risk of CVT was increased with factor V *G1691A* polymorphism by 2.51-fold (95% CI: 1.93-3.27, *P* <0.001; *I*2 = 0%, *P* = 0.58) [23,24-26,29,31,32,35,48-55]. There was no association between the risk of CVT with methylenetetrahydrofolate reductase (*MTHFR*) *C677T* polymorphism (OR = 1.59, 95% CI: 0.96-2.63, *P* = 0.070) [28,29,33,35,50,53,57,63-68] but significant interstudy heterogeneity was detected (*I*2 = 60%, *P* = 0.003) and after excluding two studies (Martinelli *et al* [29] and Ringelstein *et al* [64]), heterogeneity was eliminated (*I*2 = 22%, *P* = 0.24) while significant association emerged (OR = 2.11, 95% CI: 1.35-3.32, *P* = 0.001). There was no publication bias on examination of the funnel plot. The risk of CVT was also increased with prothrombin *G20210A* polymorphism by 5.53-fold (95% CI: 3.98-7.69, *P* <0.001; *I*2 = 12%, *P* = 0.30) [23,29-31,33,35,50,53-56,58-65,69-71] o. The symmetrical funnel plot also suggests no publication bias.

Two studies [72,73] comprising 131 cases and 243 controls were identified on the association of CVT with three thrombin activatable fibrinolysis inhibition factor (*TAFI*) polymorphisms (*C1040T*, *G438A* and *G505A*) and with plasminogen activator inhibitor-1 (*PAI-1*). Presence of the *TAFI* polymorphisms in both homozygous and heterozygous forms were pooled from each study. The risk of CVT was found to increase only with the *C1040T* variant (OR = 1.57, 95% CI: 1.02-2.42, *P* = 0.040) while no association was found with *TAFI G438A* (OR 0.87, 95% CI: 0.43-1.80, *P* = 0.72) or *TAFI G505A* (OR = 1.02, 95% CI: 0.56-1.84, *P* = 0.960) gene variants or with *PAI-1 4G/5G* (OR = 1.11, 95% CI: 0.84-1.45, *P* = 0.700). There was no evidence of interstudy heterogeneity (*I*2 = 0%, *P* = 0.48) or publication bias. Janus Kinase-2 *V617F* gene variants were also investigated in four studies but neither genotypes were identified in three of these studies thus meta-analysis could not be undertaken.

The risk of CVT was found to increase in the presence of protein C deficiency by 10.74-fold (95% CI: 3.07-37.65, *P* = 0.002), protein S deficiency by 5.68-fold (95% CI: 1.44-22.40, *P* = 0.020) and antithrombin by 3.75-fold (95% CI: 1.02-13.82, *P* = 0.050). There was no evidence of interstudy heterogeneity (*I*2 = 0%, P >0.40) or study bias [24,25,29,55,65].

**Comparison of all genetic and non-genetic risk factors**

The comprehensive meta-analysis of all risk factors revealed an additional twelve significant risk factors of CVT including antiphospholipid syndrome, L-Asparaginase therapy, trauma, autoimmune disease, obesity, protein C and protein S deficiency, and combined oral contraceptive pill treatment. In particular, alcohol consumption, exogenous glucocorticosteroid therapy, factor V Leiden *G1691A* and prothrombin *G20120A* were found to be strongly associated (*P* <0.005) with an increased risk of CVT (**Fig 2**).

**Comparison of genetic risk factors for CVT and ischaemic stroke**

A comparison of the risk of four candidate gene polymorphisms (*MTHFR* *C677T*, Prothrombin *G20210A*, Factor V Leiden *G1691A*, *PAI-1* *4G/5G*) on the presence of CVT and ischaemic stroke was conducted (**Fig 3**). Meta-analytic data for ischaemic stroke was extracted from equivalent papers that look at the same polymorphisms with similar inclusion criteria. The four gene polymorphisms were investigated in 21,110 ischaemic stroke cases and 39,599 controls [78-80]. Overall effect shows three of these genes were associated more strongly with CVT than with ischaemic stroke.

**DISCUSSION**

Our work has shown a wide range of non-genetic and genetic factors that are associated with increased risk of CVT. These findings provide further insights into the etiology of CVT, which could have clinical relevance with respect to screening of at-risk patients, modification of reversible risk factors and primary/secondary prevention of CV. The present study revealed a number of risk factors for CVT that are clearly preventable or reversible through lifestyle modification such as obesity and excessive alcohol consumption. We are not aware of any studies examining the reduction of risk of CVT in those who lost weight or abstain from alcohol. However, prevention of weight gain and excessive alcohol intake should be advocated to prevent the risk of CVT as well as other health complications.

Pregnancy/puerperium, a recognised risk factor of CVT, together with oestrogen containing drugs such as combined oral contraceptive pill, could account for some of the increased risk in females [1,3,74]. The elevated risk of CVT associated with combined oral contraceptive pill suggests that “at risk” females, *e.g.* those with strong family history of CVT, considering its use may benefit from further investigations for thrombophilic risk factors.

Although exogenous glucocorticosteroid therapy is associated with increased risk of CVT, the exact causative mechanism remains unclear since this risk may be exacerbated by other risk factors such as the patient’s underlying condition *per se* that is being treated by steroids, *e.g.* autoimmune disease or inflammatory bowel disease. Increasingly, many steroid-sparing drugs have been introduced for treating a number of diseases. Comparing CVT risk within a cohort of patients of the same disease who either receive steroids or steroid-sparing drugs may help quantify the relative contribution of steroids on CVT risk. This area of research is beyond the scope of our study.

**Comparison of CVT and non-cerebral VTE risk factors**

Anaemia, hyperhomocysteinemia and infection appear to more closely associate with CVT than non-cerebral VTE. We speculate that this disparity may be due to anatomical differences between central and peripheral vasculature and/or differences in prothrombotic factors released under these conditions. Conversely surgery, malignancy and diabetes appear associate more closely with non-cerebral VTE.

**Genetic risk factors**

Our investigation highlighted several gene polymorphisms that play a crucial role in the development of CVT and ischaemic stroke. Six genetic factors showed a significant risk association with CVT, namely factor V Leiden (*G1691A*), *MTHFR* (*C677T*), *TAFI* (*C1040T*) with protein C and S deficiency, and prothrombin mutation being amongst the strongest risk factors, genetic and non-genetic, of CVT. These genetic factors should thus be considered for first line screening, especially in those with additional prothrombotic conditions, *e.g.* hypertension. The remaining genetic factors did not significantly associate with CVT including antithrombin deficiency, *PAI-1*, and *TAFI* variants (*G438A & G505A*). Association with Janus Kinase-2 (*V617F*) could not be calculated due to the lack of gene variant presence in CVT and control subjects.

The comparison between four candidate gene variants and their risk associations in adult CVT and ischaemic stroke suggests that genetics play a greater role in the development of CVT than other forms of ischaemic stroke. ORs for factor V Leiden and prothrombin *G20210A* polymorphisms were significantly higher (2 and 3-fold respectively) in CVT than in ischaemic stroke. There were no significant differences between risk associations of *MTHFR* and *PAI-1* polymorphisms in adult CVT and in ischaemic stroke.

The *TAFI* (*C1040T*) *CT+TT* variant genotypes were associated with a 57% increase in risk of CVT. A meta-analysis conducted by [73] found that the *CT* genotype significantly increased the risk of all-type venous thrombosis but the increase was not significant in CVT alone. Additionally, no associations between the presence of *TAFI* polymorphisms and all-type ischemic stroke incidence have been observed [72]. Further investigations of this gene in future studies are necessary to establish a reliable risk association as bias is likely high considering only two studies were identified.

**Strengths and limitations**

This study is one of the most comprehensive for these specific non-genetic risk factors for CVT, evaluating 2314 subjects in 21 studies and 2117 subjects in 33 studies on genetic risk factors for CVT, spanning over 20 years of high quality publications.

Meta-analyses do however have limitations. There are drawbacks of case control studies, lack of systematic assessment of quality of evidence, heterogeneity between studies. There was no strict age and sex matching between CVT cases and controls in all of the individual studies. The wide CIs of the meta-analysis of some of the risk factors are attributable to low prevalence of the risk factors and small numbers. Differences in outcome definitions and analytic methods for parameters such as hyperhomocysteinemia and anaemia may confound disparity between individual studies.

Variability of definitions for common conditions such as hypertension and hypercholesterolaemia may affect the results. Case-control studies almost always over-estimate strength of association compared to well-designed prospective cohort studies but this may be tempered by studying very large numbers of subjects.

It would be of interest to assess the relative contributions towards CVT from genetic and non-genetic factors, and from within each of the risk factors such as different types of malignancy and autoimmune disease. A review of the literature suggests that up to 30% of CVT can be explained by genetic risk factors, while 15-20% are of unknown aetiology; suggesting that the majority of cases are the result of non-genetic risk factors. There is a substantial overlap between factors (44%) [12].

In order to obtain sufficient study data, we pooled all autoimmune disease into one group, however each autoimmune disease influences the development of CVT via different mechanism. Nevertheless, the forest plot provides a rounded overview of the association between autoimmune disease and CVT. Most studies were conducted in Europe as well some in India and Mexico; genetic factors and other environmental factors in different regions are likely to play a role in the heterogeneity of prevalence for CVT risk factors. Discrepancies can occur amongst studies due to co-existence of certain risk factors, this could potentially have introduced bias to the results.

The clinical use of *MTHFR* is debatable. Some recent clinical guidelines [81] do not recommend routine *MTHFR* polymorphism testing due to lack of evidence of its association with CVT. However, we feel that our findings are relevant in context of a research article and useful for future studies. It is of interest that some studies have observed that *MTHFR* alone is not a risk factor for VTE in the absence of hyperhomocysteinemia [82,83]. Caution should therefore be taken when interpreting the association between *MTHFR* and VTE. Our study was not designed to differentiate the relative contribution from these two factors towards the risk of VTE.

On comparison between CVT and VTE risk factors, some of the risk factors assessed in VTE did not have meta-analyses available for comparison with CVT; in these situations, case-control studies were used. Although a suitable meta-analysis or case-control study could not be identified for pregnancy/puerperium in VTE, a population-based cohort study by [75] showed the relative risk for VTE in pregnant/puerperal women to be 4.29 (3.49-5.22; *P* <0.001).

When analysing the non-genetic risk factors of this meta-analysis, the evidence was not sufficient to suggest that hypertension, smoking and diabetes are significant risk factors associated with CVT. However, while we have shown that smoking alone was not significantly associated with CVT, recent research has indicated that individuals who smoke and carry the *JAK*2 *617F* mutation have a 9.45-fold increase in the likelihood of developing CVT during their lifetime [76].

In conclusion, there is a strong basis for genetic and non-genetic risk factors in CVT. The risk association of these genes appears greater in CVT than in other forms of arterial ischaemic stroke.

**Contributorship:** TSH and PS reviewed the topic related literature. MG, TS, TR, CS and EJ performed literature search and meta-analysis, and co-wrote the first draft. JS, OL, SK, IL, IC, SS reviewed and commented on the manuscript. TSH and PS interpreted the data, edited and revised the manuscript. All authors checked, interpreted results and approved the final version. TSH and PS are the guarantors for the study.

**Funding:** None.

**Competing interests:** The authors declared no potential conflicts of interest with respect to the research, authorship, and publication of this paper.

**Provenance and peer review:** Not commissioned; externally peer reviewed.

**Data sharing statement:** No additional data are available.

**REFRENCES**

[1] Ferro JM. Prognosis of Cerebral Vein and Dural Sinus Thrombosis: Results of the International Study on Cerebral Vein and Dural Sinus Thrombosis (ISCVT). Stroke. 2004;35(3):664–670.

[2] Coutinho JM, de Bruijn SFTM, deVeber G, Stam J. Anticoagulation for cerebral venous sinus thrombosis. Stroke. 2012;43(4):e41–e42.

[3] Bushnell C, McCullough LD, Awad IA, Chireau MV, Fedder WN, Furie KL, Howard VJ, et al. Guidelines for the prevention of stroke in women: a statement for healthcare professionals from the American Heart Association/American Stroke Association. Stroke. 2014;45(5):1545-1588.

[4] Wasay M, Khatri IA, Kaul S. Stroke in south Asian countries. Nat Rev Neurol. 2014;10(3):135-143.

[5] Zuurbier SM. Cerebral venous thrombosis: Epidemiology, clinical course, and outcome. 2016.

[6] Lauw MN, Barco S, Coutinho JM, Middeldorp S. Cerebral venous thrombosis and thrombophilia: A systematic review and meta-analysis. Semin Thromb Hemost. 2013;39(8):913–927.

[7] Marjot T, Yadav S, Hasan N, Bentley P, Sharma P. Genes associated with adult cerebral venous thrombosis. Stroke. 2011;42(4):913–918.

[8] Bousser MG. Cerebral venous thrombosis: diagnosis and management. J Neurol. 2000;247(4):252-258.

[9] Zuurbier SM, Arnold M, Middeldorp S, Broeg-Morvay A, Silvis SM, Heldner MR, Meisterernst J, et al. Risk of cerebral venous thrombosis in obese women. JAMA Neurol. 2016;73(5):579-584.

[10] de Freitas GR, Bogousslavsky J. Risk factors of cerebral vein and sinus thrombosis. In Handbook on Cerebral Venous Thrombosis 2008 (Vol. 23, pp. 23-54). Karger Publishers.

[11] Stolz E, Klötzsch C, Schlachetzki F, Rahimi A. High-dose corticosteroid treatment is associated with an increased risk of developing cerebral venous thrombosis. Eur Neurol. 2003;49(4):247-248.

[12] Bousser MG, Ferro JM. Cerebral venous thrombosis: an update. Lancet Neurol. 2007;6(2):162-170.

[13] Park DS, Moon CT, Chun YI, Koh YC, Kim HY, Roh HG. Clinical characteristics of cerebral venous thrombosis in a single center in Korea. J Korean Neurosurg Soc. 2014;56(4):289-294.

[14] Silvis SM, Hiltunen S, Lindgren E, Jood K, Zuurbier SM, Middeldorp S, Putaala J, et al. Cancer and risk of cerebral venous thrombosis: a case–control study. J Thromb Haemost. 2018;16(1):90-95.

[15] Ferro JM, Bousser MG, Canhão P, Coutinho JM, Crassard I, Dentali F, di Minno M, et al. European Stroke Organization guideline for the diagnosis and treatment of cerebral venous thrombosis-endorsed by the European Academy of Neurology. Eur J Neurol. 2017;24(10):1203-1213.

[16] Saposnik G, Barinagarrementeria F, Brown RD, Bushnell CD, Cucchiara B, Cushman M, Ferro JM, Tsai FY. Diagnosis and management of cerebral venous thrombosis: a statement for healthcare professionals from the American Heart Association/American Stroke Association. Stroke. 2011 1:STR-0b013e31820a8364.

[17] Agnelli G, Verso M. Epidemiology of cerebral vein and sinus thrombosis. In Handbook on Cerebral Venous Thrombosis 2008 (Vol. 23, pp. 16-22). Karger Publishers.

[18] Stam J. Thrombosis of the cerebral veins and sinuses. N Engl J Med. 2005;352(17):1791-1798.

[19] Cognat E, Crassard I, Denier C, Vahedi K, Bousser MG. Cerebral venous thrombosis in inflammatory bowel diseases: eight cases and literature review. Int J Stroke. 2011 Dec 1;6(6):487-492.

[20] Stroup DF. Meta-analysis of Observational Studies in Epidemiology: A Proposal for Reporting. JAMA. 2000;283(15):2008-2012.

[21] Higgins JPT, Green S (editors). Cochrane Handbook for Systematic Reviews of Interventions | Cochrane Training. Cochrane . 2011.

[22] Higgins JPT, Thompson SG. Quantifying heterogeneity in a meta-analysis. Stat Med. 2002;21(11):1539–1558.

[23] Lichy C, Dong-Si T, Reuner K, Genius J, Rickmann H, Hampe T, Dolan T, et al. Risk of cerebral venous thrombosis and novel gene polymorphisms of the coagulation and fibrinolytic systems. J Neurol. 2006;253(3):316–320.

[24] Stolz E, Valdueza JM, Grebe M, Schlachetzki F, Schmitt E, Madlener K, Rahimi A, et al. Anemia as a risk factor for cerebral venous thrombosis? An old hypothesis revisited: Results of a prospective study. J Neurol. 2007;254(6):729–734.

[25] Cesarman-Maus G, Cantú-Brito C, Barinagarrementeria F, Villa R, Reyes E, Sanchez-Guerrero J, Hajjar KA, et al. Autoantibodies against the fibrinolytic receptor, annexin A2, in cerebral venous thrombosis. Stroke. 2011;42(2):501–503.

[26] De T, Prabhakar P, Nagaraja D, Christopher R. Janus kinase (JAK) 2 V617F mutation in Asian Indians with cerebral venous thrombosis and without overt myeloproliferative disorders. J Neurol Sci. 2012;323(1–2):178–182.

[27] Anadure RK, Nagaraja D, Christopher R. Plasma factor VIII in non-puerperal cerebral venous thrombosis: A prospective case-control study. J Neurol Sci. 2014;339(1–2):140–143.

[28] Bharatkumar VP, Nagaraja D, Christopher R. Hyperhomocysteinemia and Methylenetetrahydrofolate Reductase C677T Polymorphism in Cerebral Veno-sinus Thrombosis. Clin Appl Thromb. 2014;20(1):78–83.

[29] Martinelli I, Battaglioli T, Pedotti P, Cattaneo M, Mannucci PM. Hyperhomocysteinemia in cerebral vein thrombosis. Blood. 2003;102(4):1363–1366.

[30] Koopman K, Uyttenboogaart M, Hendriks HGD, Luijckx G-J, Cramwinckel IR, Vroomen PC, De Keyser J, et al. Thromboelastography in patients with cerebral venous thrombosis. Thromb Res. 2009;124(2):185–188.

[31] Tufano A, Guida A, Coppola A, Nardo A, Capua M Di, Quintavalle G, Di Minno MND, et al. Risk factors and recurrent thrombotic episodes in patients with cerebral venous thrombosis. Blood Transfus. 2014;12(SUPPL.1):s337-42.

[32] Maino A, Abbattista M, Bucciarelli P, Artoni A, Passamonti SM, Lanfranconi S, Martinelli I. Red cell distribution width and the risk of cerebral vein thrombosis: A case–control study. Eur J Intern Med. 2017;38:46–51.

[33] Ventura P, Cobelli M, Marietta M, Panini R, Rosa MC, Salvioli G. Hyperhomocysteinemia and other newly recognized inherited coagulation disorders (factor V Leiden and prothrombin gene mutation) in patients with idiopathic cerebral vein thrombosis. Cerebrovasc Dis. 2004;17(2–3):153–159.

[34] Gadelha T, André C, Jucá AA V, Nucci M. Prothrombin 20210A and Oral Contraceptive Use as Risk Factors for Cerebral Venous Thrombosis. Cerebrovasc Dis. 2005;19(1):49–52.

[35] Boncoraglio G, Carriero MR, Chiapparini L, Ciceri E, Ciusani E, Erbetta A, Parati EA. Hyperhomocysteinemia and other thrombophilic risk factors in 26 patients with cerebral venous thrombosis. Eur J Neurol. 2004;11(6):405–409.

[36] Cantu C, Alonso E, Jara A, Martínez L, Ríos C, De Los Angeles Fernández M, Garcia I, et al. Hyperhomocysteinemia, low folate and vitamin B12 concentrations, and methylene tetrahydrofolate reductase mutation in cerebral venous thrombosis. Stroke. 2004;35(8):1790–1794.

[37] Kruthika-Vinod TP, Nagaraja D, Christopher R. Coagulation factor VII R353Q polymorphism and the risk of puerperal cerebral venous thrombosis. J Clin Neurosci. 2012;19(1):190–191.

[38] Christopher R, Nagaraja D, Dixit NS, Narayanan CP. Anticardiolipin antibodies: a study in cerebral venous thrombosis. Acta Neurol Scand. 1999;99(2):121–4.

[39] Coutinho JM, Zuurbier SM, Gaartman AE, Dikstaal AA, Stam J, Middeldorp S, Cannegieter SC. Association between anemia and cerebral venous thrombosis: Case-control study. Stroke. 2015;46(10):2735–2740.

[40] Martinelli I, Sacchi E, Landi G, Taioli E, Duca F, Mannucci PM. High risk of cerebral-vein thrombosis in carriers of a prothrombin-gene mutation and in users of oral contraceptives. N Engl J Med. 1998;338(25):1793–1797.

[41] Schmidt M, Horvath-Puho E, Thomsen RW, Smeeth L, Sørensen HT. Acute infections and venous thromboembolism. J Intern Med. 2012;271(6):608–618.

[42] Hung S-H, Lin H-C, Chung S-D. Association between venous thromboembolism and iron-deficiency anemia. Blood Coagul Fibrinolysis. 2015;26(4):368–372.

[43] Den Heijer M, Lewington S, Clarke R. Homocysteine, MTHFR and risk of venous thrombosis: A meta-analysis of published epidemiological studies. J Thromb Haemost. 2005;3(2):292–299.

[44] Ageno W, Becattini C, Brighton T, Selby R, Kamphuisen PW. Cardiovascular Risk Factors and Venous Thromboembolism: A Meta-Analysis. Circulation. 2008;117(1):93–102.

[45] Heit JA, Silverstein MD, Mohr DN, Petterson TM, O’Fallon WM, Melton LJ. Risk factors for deep vein thrombosis and pulmonary embolism: a population-based case-control study. Arch Intern Med. 2000;160(6):809–15.

[46] Blom JW, Doggen CJM, Osanto S, Rosendaal FR. Malignancies, Prothrombotic Mutations, and the Risk of Venous Thrombosis. JAMA. 2005;293(6):715-722.

[47] Mi Y, Yan S, Lu Y, Liang Y, Li C. Venous thromboembolism has the same risk factors as atherosclerosis: A PRISMA-compliant systemic review and meta-analysis. Medicine (Baltimore). 2016;95(32):e4495.

[48] Martinelli I, Landi G, Merati G, Cella R, Tosetto A, Mannucci PM. Factor V gene mutation is a risk factor for cerebral venous thrombosis. Thromb Haemost. 1996;75(3):393–394.

[49] Zuber M, Toulon P, Marnet L, Mas JL. Factor V Leiden mutation in cerebral venous thrombosis. Stroke. 1996;27(10):1721–3.

[50] Hillier CE, Collins PW, Bowen DJ, Bowley S, Wiles CM. Inherited prothrombotic risk factors and cerebral venous thrombosis. Qjm. 1998;91(10):677–680.

[51] Lüdemann P, Nabavi DG, Junker R, Wolff E, Papke K, Buchner H, Assmann G, et al. Factor V Leiden mutation is a risk factor for cerebral venous thrombosis: a case-control study of 55 patients. Stroke. 1998;29(12):2507–2510.

[52] Weih M, Vetter B, Ziemer S, Mehraein S, Valdueza JM, Koscielny J, Kulozik AE, et al. Increased rate of factor V Leiden mutation in patients with cerebral venous thrombosis. J Neurol. 1998;245(3):149–152.

[53] Madonna P, De Stefano V, Coppola A, Albisinni R, Cerbone AM. G20210A PRTH Gene Mutation and Other Trombophilic Polymorphisms in Patients With Cerebral Vein Thrombosis. Stroke. 2000;31(7):1785–1790.

[54] Margaglione M, Brancaccio V, Ciampa A, Papa ML, Grandone E, Di Minno G. Inherited thrombophilic risk factors in a large cohort of individuals referred to italian thrombophilia centers: Distinct roles in different clinical settings. Haematologica. 2001;86(6):634–639.

[55] Bombeli T, Basic A, Fehr J. Prevalence of hereditary thrombophilia in patients with thrombosis in different venous systems. Am J Hematol. 2002;70(2):126–132.

[56] Rodrigues CA, Rocha LKA, Morelli VM, Franco RF, Lourenço DM. Prothrombin G20210A mutation, and not factor V Leiden mutation, is a risk factor for cerebral venous thrombosis in Brazilian patients. J Thromb Haemost. 2004;2(7):1211–1212.

[57] Tufano A, Coppola A, Varricchione N, De Simone C, Cirillo F, Palmieri NM, Cerbone AM. Predisposing factors in patients with early-onset cerebral vein thrombosis. Thromb Res. 2005;115(5):439–440.

[58] Colaizzo D, Amitrano L, Iannaccone L, Vergura P, Cappucci F, Grandone E, Guardascione MA, et al. Gain-of-function gene mutations and venous thromboembolism: distinct roles in different clinical settings. J Med Genet. 2007;44(6):412–416.

[59] Altinisik J, Ates O, Ulutin T, Cengiz M, Buyru N. Factor V Leiden, prothrombin G20210A and protein C mutation frequency in Turkish venous thrombosis patients. Clin Appl Thromb-Hemost. 2008;14(4):415–420.

[60] Le Cam-Duchez V, Bagan-Triquenot A, Barbay V, Mihout B, Borg JY. The G79A polymorphism of protein Z gene is an independent risk factor for cerebral venous thrombosis. J Neurol. 2008;255(10):1521–1525.

[61] Rahimi Z, Mozafari H, Amir Hossein Amiri Bigvand, Reza Mohammad Doulabi, Vaisi-Raygani A, Afshari D, Razazian N, et al. Cerebral Venous and Sinus Thrombosis and Thrombophilic Mutations in Western Iran: Association With Factor V Leiden. Clin Appl Thromb. 2010;16(4):430–434.

[62] Ashjazadeh N, Farjadian M, Shirin P. Factor V G1691A and prothrombin G20210A gene polymorphisms among Iranian patients with cerebral venous thrombosis. Neurol Asia. 2012;17(3):199 – 203.

[63] Ben Salem-Berrabah O, Fekih-Mrissa N, N’Siri B, Ben Hamida A, Benammar-Elgaaied A, Gritli N, Mrissa R. Thrombophilic polymorphisms - Factor v Leiden G1691A, prothrombin G20210A and MTHFR C677T - In Tunisian patients with cerebral venous thrombosis. J Clin Neurosci. 2012;19(9):1326–1327.

[64] Ringelstein M, Jung A, Berger K, Stoll M, Madlener K, Klötzsch C, Schlachetzki F, et al. Promotor polymorphisms of plasminogen activator inhibitor-1 and other thrombophilic genotypes in cerebral venous thrombosis: A case-control study in adults. J Neurol. 2012;259(11):2287–2292.

[65] Klai S, Fekih-Mrissa N, Mrissa R, Rachdi R, Gritli N. Maternal cerebral venous thrombosis, uncommon but serious disorder, pathologic predictors and contribution of prothrombotic abnormalities. Blood Coagul Fibrinolysis. 2013;24(3):269–272.

[66] Saadatnia M, Salehi M, Movahedian A, Samsam Shariat SZ, Salari M, Tajmirriahi M, Asadimobarakeh E, et al. Factor V Leiden, factor V Cambridge, factor II GA20210, and methylenetetrahydrofolate reductase in cerebral venous and sinus thrombosis: A case-control study. J Res Med Sci. 2015;20(6):554–562.

[67] Romero A, Marco P, Verdú J, Sánchez S, Castaño V. Trombofilia genética y trombosis de senos venosos cerebrales. Med Clin (Barc). 2007;128(17):655–656.

[68] Ghaznavi H, Soheili Z, Samiei S, Soltanpour MS. Association study of methylenetetrahydrofolate reductase C677T mutation with cerebral venous thrombosis in an Iranian population. Blood Coagul Fibrinolysis. 2015;26(8):869–873.

[69] Reuner KH, Ruf A, Grau A, Rickmann H, Stolz E, Jüttler E, Druschky K-F, et al. Prothrombin Gene G20210→A Transition Is a Risk Factor for Cerebral Venous Thrombosis. Stroke. 1998;29(9):1765–1769.

[70] Voetsch B, Damasceno BP, Camargo EC, Massaro a, Bacheschi L a, Scaff M, Annichino-Bizzacchi JM, et al. Inherited thrombophilia as a risk factor for the development of ischemic stroke in young adults. Thromb Haemost. 2000;83(2):229–33.

[71] Nagaraja D, Kruthika-Vinod TP, Christopher R. The prothrombin gene G20210A variant and puerperal cerebral venous and sinus thrombosis in South Indian women. J Clin Neurosci. 2007;14(7):635–638.

[72] Ladenvall C, Gils A, Jood K, Blomstrand C, Declerck PJ, Jern C. Thrombin activatable fibrinolysis inhibitor activation peptide shows association with all major subtypes of ischemic stroke and with TAFI gene variation. Arterioscler Thromb Vasc Biol. 2007;27(4):955–962.

[73] Qian K, Xu J, Wan H, Fu F, Lu J, Lin Z, Liu Z, et al. Impact of genetic polymorphisms in thrombin activatable fibrinolysis inhibitor (TAFI) on venous thrombosis disease: A meta-analysis. Gene. 2015;569(2):173–181.

[74] deVeber G, Andrew M, Adams C, Bjornson B, Booth F, Buckley DJ, Camfield CS, et al. Cerebral sinovenous thrombosis in children. N Engl J Med. 2001;345(6):417–423.

[75] Heit JA, Kobbervig CE, James AH, Petterson TM, Bailey KR, Melton LJ. Trends in the incidence of venous thromboembolism during pregnancy or postpartum: A 30-year population-based study. Ann Intern Med. 2005;143(10):697–706.

[76] Prabhakar P, De T, Nagaraja D, Christopher R. Association of factor XII gene C46T polymorphism with cerebral venous thrombosis in the south Indian population. J Thromb Haemost. 2012;10(7):1437–1439.

[77] Amoozegar F, Ronksley PE, Sauve R, Menon BK. Hormonal contraceptives and cerebral venous thrombosis risk: A systematic review and meta-analysis. Front Neurol. 2015;6(FEB):1-7.

[78] Bentley P, Peck G, Smeeth L, Whittaker J, Sharma P. Causal relationship of susceptibility genes to ischemic stroke: Comparison to ischemic heart disease and biochemical determinants. PLoS One. 2010;5(2):e9136.

[79] Song Y, Li B, Wang C, Wang P, Gao X, Liu G. Association between 5,10-Methylenetetrahydrofolate Reductase C677T Gene Polymorphism and Risk of Ischemic Stroke: A Meta-analysis. J Stroke Cerebrovasc Dis. 2016;25(3):679–687.

[80] Hu X, Zan X, Xie Z, Li Y, Lin S, Li H, You C. Association Between Plasminogen Activator Inhibitor-1 Genetic Polymorphisms and Stroke Susceptibility. Mol Neurobiol. 2017;54(1):328–341.

[81] Hickey SE, Curry CJ, Toriello HV. ACMG Practice Guideline: lack of evidence for MTHFR polymorphism testing. Genet Med. 2013;15(2):153.

[82] Bezemer ID, Doggen CJ, Vos HL, Rosendaal FR. No Association between the common MTHFR 677C→ T polymorphism and venous thrombosis. Arch Intern Med. 2007;167(5):497-501.

[83] Hsu TS, Hsu LA, Chang CJ, Sun CF, Ko YL, Kuo CT, Chiang CW, et al. Importance of hyperhomocysteinemia as a risk factor for venous thromboembolism in a Taiwanese population. A case-control study. Thrombosis research. 2001;102(5):387-95.

**LEGENDS**

**Fig 1.** Flow chart of literature search results and study selection.

**Fig 2.** Genetic and non-genetic risk factors of CVT. Pooled odds ratios of individual risk factors estimated from 42 papers selected in the present study (see supplemental material for further information). Squares represent combined estimate point value and confidence interval. \*OR was extracted from a recent meta-analysis conducted by Amoozegar et al [77]. \*\*Autoimmune disorders includes: “autoimmune disease”, diabetes, systemic lupus erythematosus and antiphospolipid syndrome.

**Fig 3.** Comparison of pooled effects of four candidate gene polymorphisms (MTHFR, Prothrombin, Factor V Leiden and PAI-1) on CVT (■) and ischaemic stroke (▲). Overall effect shows three of these genes were associated more strongly with CVT than with ischaemic stroke. Data published by Bentley et al [78], Song et al [79] and Hu et al [80].