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

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**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.

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**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].