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Inherited and Acquired Thrombophilia in Adults with Retinal Vascular Occlusion: A Systematic Review and Meta-Analysis.

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ESSENTIALS:

- The prevalence of thrombophilias in patients with retinal vascular occlusion is unclear.
- Systematic Reviews and Meta-Analysis of 95 studies were performed.
- Similar prevalences were observed in retinal vascular occlusion and the general population.
- Routine thrombophilia screening may not be useful in patients with retinal vascular occlusion.

ABSTRACT

Background: Retinal vascular occlusion is a leading cause of sight loss. Both retinal artery occlusion (RAO) and retinal vein occlusion (RVO) have been associated with hypercoagulable states; however, the burden of thrombophilia in these patients is unclear.

Objectives: This study aims at estimating the prevalence of inherited and acquired thrombophilias in adults with RAO or RVO, through a systematic review and meta-analysis of the literature.

Patients/Methods: Pubmed and EMBASE were systematically searched from inception to 29th February 2020. All studies reporting prevalences of Factor V Leiden (FVL) and Prothrombin (F-II) G20210A mutations, MTHFR C677T and PAI 4G polymorphisms, Antithrombin III (AT-III), Protein C (PC) and Protein S (PS) activity deficiencies, hyperhomocysteinemia and antiphospholipid (APL) antibodies in adults with RAO or RVO were included. Pooled prevalences and 95% Confidence Intervals (CI) were calculated.

Results: Ninety-five studies were included; FVL and F-II mutations were found in 6% (95%CI: 5-8%) and 3% (95%CI: 2-4%) of individuals with RVO, respectively, while AT-III, PC and PS activity deficiencies were found in less than 2%. The MTHFR C677T and PAI 4G homozygous polymorphism were observed in 13% (95%CI: 10-17%) and 23% (95%CI: 16-31%) of RVO, respectively; 8% presented APL antibodies. Similar findings were observed in individuals with RAO.

Conclusions: Compared to healthy subjects, patients with retinal vascular occlusion showed similar prevalences of inherited and acquired thrombophilias. These findings do not support routine thrombophilia screening in individuals with RAO or RVO.

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Key Words: Retinal Vein Occlusion, Retinal Artery Occlusion, Thrombophilia, Systematic Review, Meta-Analysis.

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INTRODUCTION

Vascular occlusion of the retina is one of the major causes of vision loss throughout the world.[1] Vascular occlusion may occur as Retinal Artery Occlusion (RAO) or Retinal Vein Occlusion (RVO); both conditions are also categorized based on the anatomic site of the obstruction as central RAO (CRAO), branch RAO (BRAO), central RVO (CRVO) and branch RVO (BRVO).

The pathophysiology of retinal vascular occlusion is multifactorial, with a wide range of modifiable and non-modifiable risk factors[2] including aging, hypertension, diabetes and dyslipidemia.[3,4] Even hypercoagulable states - which may predispose subjects to a higher risk of blood clot formation - has been associated with a higher incidence of both RAO and RVO in several population-based cohorts. Several gene variants have been already identified and linked to an increased risk of thrombosis (especially venous thromboembolism [VTE]), including mutations in genes encoding coagulation factors (e.g. Factor V and Factor II) or natural anticoagulants (Antithrombin III, Protein C, Protein S).[5,6] Unusual form of VTE, i.e. thrombosis occurring at different sites than lower limbs, have been linked to genetic variants of hemostasis traits;[7] however, clinical studies have provided conflicting findings on the clinical significance of both inherited (e.g. Factor V Leiden (FVL) Mutation, Prothrombin (F-II) G20210A mutation) and acquired (i.e. Antiphospholipid (APL) antibodies syndrome) thrombophilias in the pathogenesis of retinal vascular occlusions.[8,9] Beyond well-known acquired and inherited thrombophilia, casual VTE risk factors, other conditions including PAI-1 and MTHFR variants, as well as hyperhomocysteinemia, failed in explaining a higher risk of VTE;[10,11] nevertheless, they have been linked to a higher incidence of retinal vascular occlusion with conflicting results, and their assessment is sometimes part of the diagnostic work-up of these patients. A better understanding of the strength of the association between hypercoagulability and retinal vascular occlusion may inform on the management of patients with both RAO and RVO, with important consequences on diagnostic work-up and treatment.

This study aims to provide a systematic review and meta-analysis of studies reporting the prevalence of several inherited and acquired thrombophilias in adults with RAO or RVO.

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METHODS

This systematic review was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines and recommendations (http://www.prisma-statement.org).

Search Strategy

A systematic and comprehensive literature search was performed on Pubmed and EMBASE databases, from inception to 29th of February 2020. Keywords used and combined in the search strategy comprised a combination of terms relevant to the research question, including 'Retinal Vein Occlusion', 'Retinal Artery Occlusion', 'Thrombophilia', and terms related to the hypercoagulable states investigated. The full search strategy is listed in the supplementary materials.

Studies Selection

According to PRISMA guidance, all records retrieved from the search were systematically screened in parallel and independently by two authors (BC and MB), according to their titles and abstracts. Each record included after the first phase was then independently evaluated for full-text eligibility by two authors (BC and MB); conflicts were resolved by collegial discussion, with a third author when necessary (GFR). Inclusion criteria were: i) studies on adults with RAO, RVO or their specific forms (CRAO, BRAO, CRVO, BRVO); ii) studies reporting the prevalence of following thrombophilias: F-V Leiden mutation (rs6025); F-II G20210A mutation (rs1799963); Antithrombin III (AT-III) deficiency; Protein C (PC) deficiency; Protein S (PS) deficiency, hyperhomocysteinemia, methylenetetrahydrofolate reductase (MTHFR) C677T mutation (rs1801133), plasminogen activator inhibitor-1 (PAI) 4G mutation (rs1799889), and antiphospholipid antibodies (APL). Exclusion criteria were: i) studies with less than <20 patients for each disease (RAO or RVO); ii) studies that did not report data on the aforementioned thrombophilic conditions; iii) studies that investigated highly selected cohorts, i.e. only adults presenting with retinal vascular occlusion and no existing comorbidities or predisposing conditions, or cohort composed of only very young patients (<40 years old); iv) conference abstracts, comments, editorials, case reports, systematic reviews and meta-analysis; v) article written in languages other than English. In the case of two or

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more studies based on the same cohort of subjects and exploring the same outcome(s), only the most recently published was selected and included in the systematic review and meta-analysis.

Data Extraction and Quality Assessment

Data from the studies included were extracted independently by two co-authors (BC and MB), under the supervision of a third author (GFR). Data on sample size, type of retinal vascular occlusion, mean or median age, and percentage of males adults were collected, along with the number of patients presenting with each thrombophilia.

All studies included were independently evaluated by two co-authors (GFR and BC) to assess the risk of bias, according to recommendations of the Agency for Healthcare Research and Quality.[12] The screening was performed for five main bias domains (selection bias, performance bias, attrition bias, detection bias and reporting bias). An overall, synthetic grade was produced for each study.

Outcomes Definition

Primary outcomes were the prevalence of the inherited and acquired thrombophilias, i.e. F-V Leiden, F-II G20210A, MTHFR C677T, and PAI 4G mutations, AT-III, PC and PS activity deficiency, hyperhomocysteinemia and APL antibodies. For F-V and F-II mutations, only a small proportion of patients were described as homozygous; also, in several studies, no clear distinction between heterozygous and homozygous mutations was made, so that we computed homozygous patients together with heterozygous carriers. AT-III, PC, and PS activity deficiencies, as well as hyperhomocysteinemia, were defined according to the definition used in the original studies. Patients with heterozygous (CT) or homozygous (TT) MTHFR C677T and PAI 4G polymorphisms were analyzed separately. APL antibodies were defined as positivity for both anticardiolipin (ACA) and anti-β2 glycoprotein-I antibodies, where available, or the positivity of the only one reported; several studies reported data only on ACA antibodies and were included as well in the analysis.

Statistical Analysis

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Prevalences from original studies were pooled and compared using a random-effects model as for primary analysis; as a secondary analysis, fixed-effect models were also computed.

When pooling prevalences which tend to extreme ranges (i.e. 0% or 100%), the variance of the study may be overestimated, so we conducted our analysis transforming prevalence estimated with the Freeman-Tukey double arcsine method, as previously reported.[13,14] Pooled estimates were reported as pooled prevalence and 95% confidence intervals (CI).

The inconsistency index (I^2) was calculated to measure heterogeneity. According to pre-specified cut-offs, low heterogeneity was defined as an I^2 of <25%, moderate heterogeneity when I^2 falls between 25 and 75%, and high heterogeneity when I^2 was >75%.

In patients with RVO, we also performed two additional secondary analyses: i) we stratified studies according to the localization of the occlusion (CRVO vs. BRVO); ii) we stratified studies according to the risk of bias (low vs. medium/high overall risk of bias). Statistical analysis was performed using Stata 16 (StataCorp, USA).

RESULTS

A total of 2,856 articles were retrieved (2,042 from Pubmed and 814 from EMBASE). After the titles and abstracts screening, a total of 161 full-texts were assessed, of which 66 were subsequently excluded. A total of 95 articles were included in the analysis (Figure S1). Table 1 summarizes the main characteristics and findings of the studies included: 89 reported data on RVO and 11 on RAO. Most of the studies (n=54, 57%) were conducted in Europe; 22 in Middle East or North Africa, 9 in North America, 6 in Asia, and 2 in South America and Oceania. According to the type of thrombophilia, 50 studies explored FVL mutation; 38 reported about F-II G20210A mutation, 35 on hyperhomocysteinemia, 31 on MTHFR C677T mutation, 28 on APL antibodies presence, 24 on PC activity deficit, 22 on AT-III activity deficit and 20 on PS activity deficit, while only six reported about PAI 4G mutation.

The risk of bias was assessed for each study as reported in Table S1: 63 studies were rated at low risk, 24 at medium risk, and 8 at high risk of bias.

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Factor V Leiden mutation

Among 3,981 patients with RVO, the pooled prevalence of FVL mutation was 6% (95% CI: 5-8%; I^2=80%; figure 1A). Significant heterogeneity was found between geographical groups (p=0.016), with the higher prevalence reported in middle east/north African studies (pooled prevalence: 13%, 95% CI: 6-22%). The pooled prevalence of FVL mutation was lower in European (6% [95% CI 4-7%]) and north-American cohorts (5% [95% CI 3-8%]). Similar results were obtained with the fixed-effect model (figure S2A). Only six studies explored the association between FVL mutation and RAO, with a similar pooled prevalence to that of RVO (7%, 95% CI: 2-13%, I^2=62%, figure 1, panel B), regardless of the model applied (figure S2B).

F-II G20210A mutation

Across 34 studies, a pooled prevalence of 3% (95% CI: 2-4%; I^2=54%; figure 2A) was computed with no significant heterogeneity across geographical groups. Five studies reported on the association between RAO and F-II G20210A mutation, with a pooled prevalence of 3% (95% CI: 1-6%, I^2=13%; figure 2B). Similar results were shown using a fixed-effect model (Figure S3A-B).

AT-III, PC and PS activity deficiencies

Among the twenty studies reporting on the AT-III deficit in patients with RVO had large heterogeneity in the thrombophilia definition (i.e. cut-off AT-III activity): <100% of normal reference activity (n=1); [Supplementary Reference 7, S7] <81-89% (n=3),[S51,S55,S67] <80% (n=7).[S15,S34,S44,S49,S65,S73,S86] An even lower cut-off was used (n=2),[S74,S75] and in eight studies no clear definition was provided.[S1,S3,S6,S10,S57,S58,S60,S85]

Pooled estimates showed a low prevalence of AT-III deficiency (1%; 95% CI: 0-2%; I^2= 68%, Figure 3A), with significant heterogeneity across geographical group (p=0.023) and the higher prevalence in middle-east/north-Africans (5%, 95% CI: 1-10%).

Twenty-two studies looked at PC activity deficiency, with a total of 1,738 RVO patients. Nine studies used a definition of <70% of normal reference activity;[S7,S15,S20,S44,S49,S51,S74,S75,S86] two studies included patients with higher cut-offs (<73%[S34] and <85%[S67]) and only one study adopted lower level

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(<60%[S40]). For 10 studies, a clear definition was not identifiable.[S1,S3,S6,S10,S57,S58,S60,S78,S81,S85] Pooled estimates showed a prevalence of 2% (95% CI 0-3%, I^2=75%, figure 3B), with significant heterogeneity (p<0.001) between geographical groups: European-based cohorts showed a lower prevalence (0%, 95% CI: 0-1%, I^2=15%) than middle-east and north-African studies, (pooled prevalence: 13%, 95% CI: 6-22%, I^2=13%).

Seventeen studies reported data about PS activity deficiency in RVO adults, for a total of 1276 patients. As for the definitions used, five studies adopted a cut-off of <70% of normal reference activity,[S7,S15,S20,S67,S75] and 4 studies used a lower-cut-off (ranging from <65% to <60%).[S40,S44,S49,S86] For eight studies a clear definition of PS activity deficit was not found.[S1,S3,S10,S57,S58,S60,S78,S85] A pooled prevalence of 2% (95% CI:0-4%; I^2=74%, figure 3C) was calculated with no significant heterogeneity was across geographical groups and a higher prevalence in middle-east and north-Africans. Similar findings were observed in the fixed-effect models (Figure S4A-C respectively).

Only 4 studies investigated RAO patients.[S34,S48,S59,S65] Pooled prevalence for AT-III activity deficit in adults with RAO was 3% (95% CI: 0-9%, I^2=57%, figure S5-A), higher as compared with that observed in RVO; PC and PS activity deficiencies were similarly prevalent in RAO to those in RVO (2%, 95% CI 0-10%, I^2=61% and 1%, 95% CI: 0-4, I^2=24%, respectively, figure S5B-C). Fixed-effect models for AT-III, PC, and PS activity deficits in RAO are reported in figure S6A-C respectively.

Hyperhomocysteinemia and MTHFR C677T polymorphism

Thirty studies reported data about hyperhomocysteinemia in patients with RVO, for a total of 2,656 patients. High grade of heterogeneity was found according to the definition of hyperhomocysteinemia, based on different cut-offs of homocysteine level: between 15 and 16 µmol/L;[S20,S28,S30,S56,S62,S73,S87,S93] above 16 µmol/L;[S3,S16,S60,S85] and above 15 µmol/L.[S2,S12,S15,S46,S49 S67,S70,S72,S88,S94] Furthermore, five studies reported data based on sex-specific cut-off [S13,S25,S53,S61,S82] and one study according to different cut-offs by sex and age.[S40] Finally, the definition was unclear in 2 studies.[S78,S79] Pooled prevalence of 24% (95% CI: 19-30%, I^2=89%, figure 4A) was found across studies included. Non-significant heterogeneity was

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observed across different geographical areas, but higher pooled prevalences were found in middle-east/north-African and North-American studies, as compared with European and Asian cohorts. The fixed-effect model showed a slightly lower prevalence (22%, 95% CI: 20-24%, figure S7A).

Overall, 30 studies reported about MTHFR C677T mutations, although several explored only CT or TT mutations. As for heterozygous mutation, a pooled prevalence of 44% (95% CI: 39-48%, I^2=77%, Figure 4B) was computed, without significant heterogeneity between geographical groups; middle east and north-African cohorts contributes for the most of the heterogeneity. As for the homozygous C677T mutation, a pooled prevalence of 13% (95% CI: 10-17%, I^2=79%, figure 4C) was found, with non-significant heterogeneity between geographical locations (p=0.124): European and Asian-based cohorts showed slightly higher pooled prevalences (15% and 13%, respectively), while south-American and middle-east/North African studies yielded lower estimates (9% and 10%, respectively). Fixed-effect models showed similar results for both CT and TT mutation (Figure S7B-C, respectively).

In patients with RAO, a pooled prevalence of 27% (95% CI: 14-42%, I^2=93%, figure 5A) was found for hyperhomocysteinemia across 6 studies. However, when performing a fixed-effect model, pooled prevalence drops to 17% (95% CI: 16-18%, figure S8A) due to the higher weight of an Australian-based population study.[S17]

As for the MTHFR C677T mutation, the prevalence of the heterozygous and homozygous mutation in patients with RAO was respectively 48% (95% CI: 39-56%) and 23% (95% CI 7-43%) across 2 studies (figure 5B-C respectively). Fixed-effect models for both MTHFR C677T heterozygous and homozygous mutation in patients with RAO are reported in figure S8B-C respectively.

PAI 4G mutation

Overall, six studies report about the association between RVO and PAI 4G mutation. As for the heterozygous 4G mutation, a pooled prevalence of 50% (95% CI: 43-57%, I^2=58%, Figure 6A) was found across the study included, five of which were from Europe; a pooled prevalence of 25% (95% CI: 16-31%, I^2=74%, Figure 6B) was calculated for homozygous 4G mutation. Fixed-effect models produced comparable results (Figure S9A-B).

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Since only one study reported data on the prevalence of PAI 4G mutation in patients with RAO, pooled prevalence estimate for this thrombophilia was not computed.

APL Antibodies

Across 24 studies and a total of 2130 patients, a pooled prevalence of 8% (95% CI 5-12%, I^2=86%; Figure 6C) was found for the presence of APL antibodies. Non-significant heterogeneity was found between geographical groups (p=0.051), with Asian and European-based cohorts showing lower prevalence (2% and 7%, respectively). Similar results were observed with fixed-effect models (Figure S9C).

In patients with RAO, across 4 studies, the pooled prevalence of APL antibodies was equal to 13% (95% CI: 4-26%, I^2=77%, figure S10A) when using a random-effect model, and resulted higher with a fixed-effect model (17%, 95% CI: 12-23%, figure S10B).

Comparison in the Prevalence of Thrombophilias between RAO and RVO

Overall, similar prevalences for all thrombophilias were shown with random-effect models (Table S2). However, such findings were not confirmed by the fixed-effect models, for hyperhomocystenemia more prevalent in RVO patients (22% [95% CI: 20-24%] vs. 17% [95% CI: 16-18%], p for heterogeneity: <0.001), while APL antibodies resulted more associated with RAO (pooled prevalence 17% [95% CI: 12-23%] vs. 7% [95% CI: 6-8%], p for heterogeneity: <0.001).

Sensitivity Analysis

In a first sensitivity analysis, we compared pooled estimates in patients with CRVO and BRVO using a random-effect model (Figure 7A). No significant heterogeneity was observed between the two groups in terms of pooled prevalence for each thrombophilia explored. BRVO patients showed a non-significant trend of higher FVL mutation and PS deficiency prevalences, while in CRVO a non-significantly higher prevalence of APL antibodies was observed.

In a second sensitivity analysis, we analyzed pooled prevalences according to the overall risk of bias of the studies (low vs. medium or high risk of bias; Figure 7B). Pooled prevalences of APL antibodies resulted lower in studies with low risk of bias (5%, 95% CI: 3-8% vs. 14%, 95% CI: 7-23% of studies with a medium-high risk of bias, p for

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heterogeneity=0.018); on the other side, pooled estimate for hyperhomocysteinemia was higher in low-risk of bias studies (29% 95% CI: 23-35% vs. 17%, 95% CI: 10-25%, p for heterogeneity=0.016). Non-significant trends were also observed for MTHFR C677 homozygous mutation and PC activity deficiency.

DISCUSSION

In this systematic review and meta-analysis, we reported the pooled prevalence of inherited and acquired thrombophilia in over 10.000 patients with retinal vascular occlusion, across 95 studies. Overall, congenital AT-III, PC, and PS activity deficiencies were the least represented inherited thrombophilia in patients with RAO or RVO, while FVL and APL antibodies were the most represented. Moreover, hyperhomocysteinemia, MTHFR C677T, and PAI 4G polymorphism were also highly prevalent. Of note, the distribution of thrombophilias is very similar to that observed in generally healthy populations (Table S3). The only significant differences were observed for AT-III, PC, and PS deficiencies, which were found more prevalent in subjects with RAO and RVO, and also the prevalence of APL antibodies, slightly higher in patients with RAO. Nevertheless, such differences observed might be due to heterogeneity in the definition of these thrombophilic conditions in the original studies, both for the anticoagulant deficiencies and for the presence of APL antibodies.

The total prevalence of inherited thrombophilia in patients with retinal vascular occlusion varies according to the site of the obstruction and geographical setting. When stratifying our results according to geographical locations of the original studies, we found a higher prevalence of FVL mutation in middle-east and north-African cohorts as compared with both European and north-American studies as well as compared with healthy populations from the same regions (13% vs. 0-2%,[15,16] respectively). Similar findings were observed for F-II G20210A mutation, with higher prevalence in patients with RVO from middle-east and north African countries compared to similar general populations (4% vs. approximately 0.5%[17,18] for F-II G20210A, respectively). While our findings may suggest a different degree of association between retinal vascular occlusion and thrombophilic conditions across different ethnicities, we cannot exclude that these results may be driven by few studies, which may have inflated the pooled prevalence in some groups. These findings, however, should be taken carefully into account by treating

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physicians, since they might have implications in the management of those ethnicities at higher risk of presenting with thrombophilic conditions.

To our knowledge, our study is the first to comprehensively evaluate the burden of a broad spectrum of thrombophilic conditions in patients with retinal vascular occlusion. The Association between thrombophilia and risk of both RAO and RVO has long been speculated,[19] but with great uncertainty according to existing evidence. Our findings showed that the overall prevalences of inherited and acquired hemostatic disorder in patients with retinal vascular occlusion are broadly similar to those observed in general, unaffected populations. Although younger patients may present a higher prevalence of these thrombophilic conditions,[S48,S51,S87] our study does not demonstrate a higher prevalence of thrombophilia in the overall cohort of patients with RAO and RVO. The vast majority of retinal vascular occlusion, in fact, affects elderly patients, in which traditional cardiovascular risk factors may have a more important underlying role in the onset of the disease. Most of the cohorts included in this analysis, indeed, were mainly composed of elderly, and this may contribute to the overall prevalence of the thrombophilias tested. A potential bias in the pooled prevalence observed, and limited generalizability of the findings to younger patients cannot be excluded. In fact, a greater prevalence of inherited or acquired thrombophilias could be present among young adults with retinal vascular occlusion, since in this subgroup of patients the contribution of other cardiovascular risk factors may be less important. Therefore, the results of this meta-analysis may not apply to all patients with retinal vascular occlusion, especially those with a younger age.

These results are also consistent with previously published studies, that reported no association between retinal vascular occlusion and familiar history of VTE.[20] suggesting that inherited thrombophilias, which are strong and well-known causative factors for familiar susceptibility to VTE, are unlikely of primary importance in the pathogenesis of retinal vascular occlusion.

As for the comparison between RAO and RVO, according to our primary analysis, we did not find any significant differences in terms of prevalence of any of the explored thrombophilic conditions. This may reinforce the hypothesis that RAO and RVO share similar risk factors, including cardiovascular and metabolic comorbidities (hypertension, dyslipidemia, diabetes) and hemostatic disorders. Also, retinal artery and retinal vein present close anatomical relation, since they share a common adventitia sheat, and this

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may influence the pathogenesis of vascular occlusions. Particularly, CRVO was associated with compression from the central retinal artery at the lamina cribrosa, where the two vessels are strongly bond. [21–23] However, most of the studies investigated RVO, and evidence regarding RAO is scarce and limited. Actual differences may exist, and further studies may be required to draw definitive conclusions. Similarly, our analysis did not show any significant differences between BRVO and CRVO, supporting the hypothesis that potential pathogenesis differences between these forms of RVO may be sustained by other factors.

The key message and implication of our study may affect the diagnostic work-up of patients presenting with RAO or RVO. Based on our findings, there is no clear evidence to support a mass screening for thrombophilia in the overall cohort of patients with retinal vascular occlusion. Some patients may benefit from a thorough and comprehensive haematological investigation: i) young patients at higher risk of being carriers of thrombophilic conditions, especially in the absence of other risk factors for retinal vascular occlusion; ii) individuals of selected geographical areas, with a higher prevalence of certain thrombophilia; iii) individuals with a family or personal history of venous or arterial thrombotic events, mainly when recurrent or occurring at a younger age; iv) the presence of autoimmune diseases, know to be associated with higher thrombotic risk. Although the identification of specific categories at higher risk of thrombophilia was beyond the scope of this analysis, we do support a careful screening on a case-by-case basis, considering the pre-test probability, the cost-benefit ratio and the potential psychological implication for patients. This approach is consistent with the actual guidance on the management of patients with retinal vascular occlusion.[24]

Limitations

Our analysis has several limitations. First, our review protocol did not include a screening of gray literature; however, given the research question, this is unlikely to have significantly limited the comprehensiveness of our analysis. Second high heterogeneity between studies (both in terms of the definition of thrombophilic conditions and methods used for their assessment) may have influenced our results. Particularly, a high grade of heterogeneity was found for the definition of AT-III, PC and PS deficiencies, and the presence of APL antibodies, and this might have been responsible for the higher

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prevalence observed. This definition bias has to be considered in the careful interpretation of our findings. Also, studies exploring the association of F-V and F-II mutations with retinal vascular occlusion barely reported data disaggregated according to the heterozygosity or homozygosity of the genetic variants. A relatively low number of patients with homozygous mutations were computed along with heterozygous carriers. Given that not all studies reported clearly about homozygous individuals, we were not able to produce reliable estimates for these prevalences. Nevertheless, we did not exclude these subjects from the analysis, since this would have led to an underestimation of the actual prevalence of the conditions. Second, most of the studies were based on small cohorts, with a potentially high risk of selection bias, especially for those studies which include only relatively young patients or adults referred for thrombophilia screening by their ophthalmologists. Moreover, a substantial grade of heterogeneity was also found across the studies included, for several thrombophilic conditions. However, we performed our primary analysis with the use of random-effect models, to mitigate heterogeneity and the potential impact of a single study on the overall estimates. We also provide a sensitivity analysis according to the overall risk of bias, to exclude the contribution of studies with a medium or high risk of bias. Finally, relatively few studies investigated the association between thrombophilia and RAO, thus limiting our ability to explore this association.

CONCLUSIONS

In patients with retinal vascular occlusion, pooled prevalences of inherited and acquired thrombophilias were estimated and resulted similar to what observed in the general population. No significant differences were observed in the primary analysis between RAO and RVO patients, nor according to the localization of RVO (i.e. CRVO vs. BRVO). Our findings are consistent with current recommendations, which do not support thrombophilia screening in the diagnostic workup of all patients presenting with retinal vascular occlusion.

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Addendum: GFR conceived and designed the study, performed the search, performed the statistical analysis, interpreted data and produced the first draft of the manuscript; BC and MB performed studies selection, extracted the data, performed the bias assessment, contributed to data interpretation and critically revised the manuscript; GV contributed to data interpretation and to the drafting of the manuscript; EP, RC, MP, SB and VR contributed to conception and design of the study and critically revised the manuscript for important intellectual content. All gave final approval and agree to the submission of the manuscript.

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FIGURE LEGENDS

Figure 1: Pooled Prevalence for Factor V Leiden mutation in RVO and RAO
Legend: Panel A: RVO, Random-Effects model; Panel B: RAO, Random-Effects model

Figure 2: Pooled Prevalence for Factor II G20210A mutation in RVO and RAO
Legend: Panel A: RVO, Random-Effects model; Panel B: RAO: Random-Effects model

Figure 3: Pooled Prevalence for Antithrombin III, Protein C and Protein S Activity Deficit in patients with RVO
Legend: Panel A: Antithrombin III deficit, Random-Effects model; Panel B: Protein C deficit, Random-Effects model; Panel C: Protein S deficit, Random-Effects model

Figure 4: Pooled Prevalence for Hyperhomocysteinemia, MTHFR C677T Heterozygous mutation and MTHFR C677T Homozygous mutation in patients with RVO
Legend: Panel A: Hyperhomocysteinemia, Random-Effects model; Panel B: MTHFR C677T Heterozygous, Random-Effects model; Panel C: MTHFR C677T Homozygous, Random-Effects model

Figure 5: Pooled Prevalence for Hyperhomocysteinemia, MTHFR C677T Heterozygous mutation and MTHFR C677T Homozygous mutation in patients with RAO
Legend: Panel A: Hyperhomocysteinemia, Random-Effects model; Panel B: MTHFR C677T Heterozygous, Random-Effects model; Panel C: MTHFR C677T Homozygous, Random-Effects model

Figure 6: Pooled Prevalence for PAI 4G Heterozygous mutation, PAI 4G Homozygous mutation and Antiphospholipid antibodies in patients with RVO
Legend: Panel A: PAI 4G Heterozygous, Random-Effects model; Panel B: PAI 4G Homozygous, Random-Effects model; Panel C: Antiphospholipid antibodies, Random-Effects model

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Figure 7: Sensitivity analysis according to RVO localization and overall risk of bias

Legend: Panel A: CRVO vs. BRVO; Panel B: Low vs. High Risk of Bias

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Table 1: Main Characteristics of the Studies Included in the Systematic Review21]

AUTHOR	Year	Type of Study	Geographical Location	N of pts	Type of RVO/RAO	Age (Mean ± SD)	Males (n, %)	Thrombophilic conditions Reported
El-Asrar et al.[S1]	1998	Single Center Cohort	Middle East/North Africa	57	CRVO: 35 BRVO: 22	48 ± 11.5	44 (77%)	APL antibodies, AT-III, PC, PS deficit
El-Asrar et al.[S2]	2002	Single Center Cohort	Middle East/North Africa	56	CRVO: 36 BRVO: 12	43.9 ± 11.4 49.5 ± 7.7	44 (79%)	HyperHcys
Adamczuk et al.[S3]	2002	Single Center Cohort	South America	37	CRVO: 37	49[a]	17 (46%)	APL antibodies, F-V, F-II, AT-III, PC, PS, HyperHcys, MTHFR, PAI
Albisinni et al.[S4]	1998	Single Center Cohort	Europe	36	RVO: 36	53	16 (44%)	F-V, F-II
Aras et al.[S5]	2001	Single Center Cohort	Middle East/North Africa	40	CRVO: 19 BRVO: 21	59 ± 10	21 (53%)	F-V, F-II
Arsène et al.[S6]	2005	Single Center Cohort	Europe	234	CRVO: 153 BRVO: 81	62 ± 14	149 (64%)	F-V, F-II, AT-III, PC
Ates et al.[S7]	2006	Single Center Cohort	Middle East/North Africa	54	CRVO: 27 BRVO: 27	22-86	-	AT-III, PC, PS
Biancardi et al.[S8]	2007	Single Center Cohort	South America	55	RVO: 55	17-83	23 (42%)	F-V, F-II, MTHFR
Birinci et al.[S9]	2003	Single Center Cohort	Middle East/North Africa	24	CRVO: 24	59.0 ± 3.5	-	APL Antibodies
Bombeli et al.[S10]	2002	Single Center Cohort	Europe	68	RVO: 68	51.6	39 (57%)	F-V, F-II, AT-III, PC, PS
Boyd et al.[S11]	2001	Single Center Cohort	Europe	66	CRVO: 66	60.3 ± 16.2	-	F-II, MTHFR
Brown et al.[S12]	2002	Single Center Cohort	North America	20	RVO: 20	69.1 ± 10.7	12 (60%)	HyperHcys

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Bucciarelli et al.[S13]	2017	Single Center Cohort	Europe	313	RVO: 313	54 [41-63]	147 (47%)	F-V, F-II, HyperHcys
Cahill et al.[S14]	2001	Single Center Cohort	Europe	61	RVO: 61	-	-	MTHFR
					RAO: 26			
Chapin et al.[S15]	2015	Two Centers Cohort	South America	37	RVO: 20	51	7 (35%)	APL antibodies, F-V, F-II, AT-III, PC, PS, HyperHcys
Cho et al.[S16]	2019	Single Center Cohort	Asia	1928	CRVO: 417	61.2 ± 16.7	217 (52%)	HyperHcys
					BRVO: 1511	62.0 ± 13.1	680 (45%)	
Chua et al.[S17]	2006	Population-based Cohort	Oceania	3409	RAO: 3409	66.7	1463 (43%)	HyperHcys
Ciardella et al.[S18]	1998	Single Center Cohort	North America	30	RVO: 30	66 ± 13	-	F-V
Coniglio et al.[S19]	1996	Single Center Cohort	Europe	48	RVO: 48	46.5	26 (54%)	APL antibodies
Cruciani et al.[S20]	2003	Single Center Cohort	Europe	29	RVO: 29	39.3	15 (52%)	APL Antibodies, F-V, F-II, PC, PS, HyperHcys, MTHFR
De Polo et al.[S21]	2015	Single Center Cohort	Europe	37	RVO: 37	74.5 ± 8.8	17 (46%)	F-V, F-II, MTHFR
Demirci et al.[S22]	1999	Single Center Cohort	Middle East/North Africa	50	CRVO: 25	46.7	8 (32%)	F-V
					BRVO: 25	53.0	9 (36%)	
Di Capua et al.[S23]	2010	Single Center Cohort	Europe	110	CRVO: 62	47 ± 15	29 (47%)	APL Antibodies, F-V, F-II, MTHFR.
					BRVO: 48	55 ± 9	22 (54%)	
Dodson et al.[S24]	2003	Single Center Cohort	North America	40	RVO: 40	66.1	21 (52%)	F-V, F-II, MTHFR
Dong et al.[S25]	2014	Single Center Cohort	Asia	36	CRVO: 36	60.6 ± 6.3	17 (47%)	HyperHcys, MTHFR.
Fernandez-Vega et	2019	Single Center Cohort	Europe	172	CRVO: 38	62.7 ± 13.2	19 (50%)	MTHFR

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al.[S26]					BRVO: 134	63.0 ± 10.1	63 (47%)	
Ferrazzi et al.[S27]	2005	Single Center Cohort	Europe	69	RVO: 69	64.1 ± 14.6	40 (58%)	MTHFR
Gao et al.[S28]	2006	Single Center Cohort	Asia	64	CRVO: 64	59.5 ± 3.8	33 (52%)	HyperHcys
Gao et al.[S29]	2008	Single Center Cohort	Asia	64	CRVO: 64	59.5 ± 3.8	33 (52%)	MTHFR
Ghaznavi et al.[S30]	2016	Single Center Cohort	Middle East/North Africa	73	RVO: 73	52.7 ± 16.2	35 (48%)	HyperHcys
Giannaki et al.[S31]	2013	Single Center Cohort	Europe	51	RVO: 51	70	22 (43%)	F-V, F-II, MTHFR, PAI.
Giordano et al.[S32]	1998	Single Center Cohort	Europe	30	CRVO: 18	48 ± 4.3	14 (47%)	APL Antibodies
					BRVO: 10	53 ± 2.1		
Glacet-Bernard et al.[S33]	1994	Single Center Cohort	Europe	75	CRVO: 44	57	28 (64%)	APL Antibodies
					BRVO: 24	67	12 (50%)	
Glueck et al.[S34]	2012	Single Center Cohort	North America	164	CRVO: 132	57 ± 14	55 (42%)	APL Antibodies, F-V, F-II, AT-III, PC, PS, HyperHcys, MTHFR, PAI
					CRAO: 32	52 ± 16	13 (41%)	
Gori et al.[S35]	2004	Single Center Cohort	Europe	112	RVO: 112	60[a]	52 (46%)	PAI
Gottlieb et al.[S36]	1998	Single Center Cohort	North America	21	CRVO: 21	42.1	15 (71%)	F-V
Graham et al.[S37]	1996	Single Center Cohort	Oceania	23	CRVO: 23	60.2 ± 16.2	-	F-V
Greiner et al.[S38]	1999	Single Center Cohort	Europe	116	CRVO: 48	24-91	65 (56%)	F-V
					BRVO: 33			
					CRAO: 21			
					BRAO: 14			
Gumus et al.[S39]	2006	Single Center Cohort	Middle East/North Africa	82	CRVO: 26	57.7 ± 9.4	36 (44%)	F-V, F-II.
					BRVO: 56			

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Hansen et al.[S40]	2000	Single Center Cohort	Europe	54	RVO: 54	56[a]	32 (57%)	APL Antibodies, F-V, PC, PS, HyperHcys
Hvarfner et al.[S41]	2003	Single Center Cohort	Europe	166	CRVO: 166	64 ± 15	86 (52%)	F-V
Incorvaia et al.[S42]	2001	Single Center Cohort	Europe	100	CRVO: 50	70.5 ± 8.7	27 (54%)	F-II
					BRVO: 50	68.7 ± 7.8	23 (46%)	
Johnson et al.[S43]	2001	Single Center Cohort	North America	44	CRVO: 44	66.6	30 (68%)	F-V
Kadayifcilar et al.[S44]	2001	Single Center Cohort	Middle East/North Africa	54	CRVO: 22	59.7 ± 12	30 (55%)	APL Antibodies, AT-III, PC
					BRVO: 32			
Kalayci et al.[S45]	1999	Single Center Cohort	Middle East/North Africa	52	CRVO: 25	64 ± 15	15 (60%)	F-V, F-II
					BRVO: 27	57 ± 13	16 (59%)	
Koylu et al.[S46]	2017	Single Center Cohort	Middle East/North Africa	49	RVO: 49	52.1 ± 17.4	39 (80%)	F-V; F-II, HyperHcys, MTHFR
Kuhli et al.[S47]	2002	Single Center Cohort	Europe	142	RVO: 142	52.1	74 (52%)	F-V
Kuhli-Hattenbach et al.[S48]	2016	Two centers Cohort	Europe	25	RAO: 25	42.8 ± 10.8	7 (28%)	APL Antibodies, F-V, F-II, AT-III, PC, PS, HyperHcys
Lahey et al.[S49]	2002	Single Center Cohort	North America	55	CRVO: 55	44	25 (45%)	APL Antibodies, F-V, AT-III, PC, PS, HyperHcys
Larsson et al.[S50]	1999	Single Center Cohort	Europe	129	CRVO: 129	59	74 (57%)	F-II
Larsson et al.[S51]	1999	Single Center Cohort	Europe	37	CRVO: 37	40.5	21 (57%)	AT-III, PC
Larsson et al.[S52]	2000	Single Center Cohort	Europe	116	CRVO: 116	60.1	67 (58%)	MTHFR
Lattanzio et al.[S53]	2006	Single Center Cohort	Europe	58	CRVO: 58	39.8 ± 9.6	38 (66%)	HyperHcys
Linna et al.[S54]	1996	Single Center Cohort	Europe	46	CRVO: 28	40.5	24 (52%)	F-V
					BRVO: 18			

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Loewenstein et al.[S55]	1999	Single Center Cohort	Middle East/North Africa	59	RVO: 59	61.4 ± 12.9	29 (49%)	F-V, AT-III
Manaviat et al.[S56]	2006	Single Center Cohort	Middle East/North Africa	21	RVO: 21	52.5 ± 12.7	14 (67%)	HyperHcys
Marcucci et al.[S57]	2001	Single Center Cohort	Europe	100	RVO: 100	59[a]	54 (54%)	AT-III, PC, PS
Marcucci et al.[S58]	2003	Single Center Cohort	Europe	55	CRVO: 26	57[a]	24 (44%)	AT-III, PC, PS
					BRVO: 29			
Marcucci et al.[S59]	2007	Single Center Cohort	Europe	41	CRAO: 25	69.6 ± 12.8	20 (49%)	APL, F-V, F-II, AT-III, PC, PS, HyperHcys
					BRAO: 16			
Martinez et al.[S60]	2014	Single Center Cohort	Europe	100	CRVO: 26	60.0 ± 13.5	18 (69%)	F-V, F-II, AT-III, PC, PS, HyperHcys
					BRVO: 74	59.0 ± 12.4	40 (54%)	
Minniti et al.[S61]	2014	Single Center Cohort	Europe	91	RVO: 91	57 ± 12	51 (56%)	HyperHcys, MTHFR
Moghimi et al.[S62]	2008	Single Center Cohort	Middle East/North Africa	54	CRVO: 54	59.8 ± 12.7	32 (59%)	HyperHcys
Mrad et al.[S63]	2014	Single Center Cohort	Middle East/North Africa	88	CRVO: 20	51.5 ± 18.5	62 (70%)	F-V, F-II
					BRVO: 68	49.5 ± 17.7		
Mrad et al.[S64]	2014	Single Center Cohort	Middle East/North Africa	72	RVO: 72	48.5 ± 17.4	50 (69%)	MTHFR
Nagy et al.[S65]	2008	Single Center Cohort	Europe	28	RAO: 28	61.1 ± 12.3	16 (57%)	F-V, F-II, AT-III, PC, PS
Nalcaci et al.[S66]	2019	Single Center Cohort	Middle East/North Africa	40	CRVO: 18	41.6 ± 10.0	22 (55%)	F-V, F-II, MTHFR
					BRVO: 22			
Napal et al.[S67]	2016	Single Center Cohort	Europe	170	RVO: 170	68 ± 11	93 (55%)	APL Antibodies, F-V, F-II, AT-III, PC, PS, HyperHcys

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Nema et al.[S68]	2018	Single Center Cohort	Asia	50	RVO: 50	54.6 ± 13.9	18 (36%)	F-V, MTHFR
Paccalin et al.[S69]	2006	Single Center Cohort	Europe	68	RVO: 68	32-90	30 (44%)	APL Antibodies
Palmowski-Wolfe et al.[S70]	2005	Single Center Cohort	Europe	253	CRVO: 93 BRVO: 70 CRAO: 41 BRAO: 49	-	-	HyperHcys
Palmowski-Wolfe et al.[S71]	2007	Single Center Cohort	Europe	254	CRVO: 93 BRVO: 67 CRAO: 41 BRAO: 53	66.5 ± 11.2	-	APL Antibodies
Pianka et al.[S72]	2000	Single Center Cohort	Middle East/North Africa	21	CRVO: 21	58.6 ± 2.7	-	HyperHcys
Ponto et al.[S73]	2019	Single Center Cohort	Europe	92	CRVO: 61 BRVO: 31	64 63	34 (56%) 17 (55%)	APL Antibodies, F-V, F-II, AT-III, HyperHcys
Rehak et al.[S74]	2010	Single Center Cohort	Europe	121	CRVO: 79 BRVO: 42	63.5	57 (47%)	F-V, AT-III, PC
Risse et al.[S75]	2014	Single Center Cohort	Europe	139	CRVO: 88 BRVO: 51	67.3 ± 12.9 65.9 ± 11.7	50 (57%) 26 (51%)	APL Antibodies, F-V, F-II, AT-III, PC, PS, MTHFR
Russo et al.[S76]	2015	Single Center Cohort	Europe	113	RVO: 113	18-77	57 (50%)	F-V, F-II, MTHFR, PAI
Salomon et al.[S77]	1998	Single Center Cohort	Middle East/North Africa	102	RVO: 102	59.9 ± 16.1 64.0 ± 12.9	58 (57%)	F-V, F-II, MTHFR
Sartori et al.[S78]	2013	Single Center Cohort	Europe	132	RVO: 132	53.6 ± 16.7	77 (58%)	APL Antibodies, F-V, F-II, PC, PS, HyperHcys.

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Schockman et al.[S79]	2015	Single Center Cohort	North America	191	CRVO: 172 BRVO: 19	57 ± 15	75 (39%)	APL Antibodies, F-V, F-II, HyperHcys
Scott et al.[S80]	2001	Single Center Cohort	Europe	45	CRVO: 24 BRVO: 21	38.7[a] 46.8[a]	11 (46%) 8 (38%)	APL Antibodies, F-V
Sinawat et al.[S81]	2017	Single Center Cohort	Asia	100	CRVO: 70 BRVO: 30	36.5 ± 8.7 43 ± 8.2	32 (46%) 17 (57%)	APL Antibodies, PC, PS.
Sodi et al.[S82]	2011	Single Center Cohort	Europe	103	CRVO: 103	67.4 ± 7.7	54 (52%)	APL Antibodies, F-V, F-II, HyperHcys, MTHFR
Sofi et al.[S83]	2008	Single Center Cohort	Europe	127	BRVO: 127	65[a]	53 (42%)	MTHFR
Soltanpour et al.[S84]	2013	Single Center Cohort	Middle East/North Africa	73	RVO: 73	52.7 ± 16.2	35 (48%)	MTHFR
Sottilotta et al.[S85]	2010	Single Center Cohort	Europe	105	RVO: 105	-	46 (43%)	F-V, F-II, AT-III, PC, PS, HyperHcys, MTHFR
Tekeli et al.[S86]	1999	Single Center Cohort	Middle East/North Africa	45	CRVO: 31 BRVO: 14	56 ± 2	25 (56%)	AT-III, PC, PS
Vieira et al.[S87]	2019	Single Center Cohort	Europe	60	CRVO: 35 BRVO: 25	64.0 ± 13.5	35 (58%)	APL, F-V, F-II, HyperHcys, MTHFR, PAI
Vine et al.[S88]	2000	Single Center Cohort	North America	74	CRVO: 74	69.8	29 (39%)	HyperHcys
Weger et al.[S89]	2003	Single Center Cohort	Europe	136	RAO: 136	69.8 ± 10.1	78 (57%)	F-V, F-II
Weger et al.[S90]	2005	Single Center Cohort	Europe	294	BRVO: 294	67.0 ± 11.4	128 (44%)	F-V, F-II
Weger et al.[S91]	2002	Single Center Cohort	Europe	105	RAO: 105	69.1 ± 10.6	59 (56%)	HyperHcys, MTHFR
Weger et al.[S92]	2002	Single Center Cohort	Europe	84	BRVO: 84	68.1 ± 11.1	37 (44%)	MTHFR
Weger et al.[S93]	2002	Single Center Cohort	Europe	78	CRVO: 78	68.7 ± 11.4	33 (42%)	HyperHcys, MTHFR.

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Yildirim et al.[S94]	2004	Single Center Cohort	Middle East/North Africa	33	RVO: 33	61	15 (45%)	HyperHcys
Yioti et al.[S95]	2013	Single Center Cohort	Europe	48	RVO: 48	64 [53-70]	34 (71%)	F-V, F-II

Legend: AT-III: Antithrombin-III Activity Deficiency, F-V: Factor V Leiden Mutation; F-II: Factor II G20210A Mutation, HyperHcys: Hyperhomocysteinemia; MTHFR: MTHFR C677T Mutation; PAI: PAI 4G Mutation; PC: Protein C Activity Deficiency; PS: Protein S Activity Deficiency

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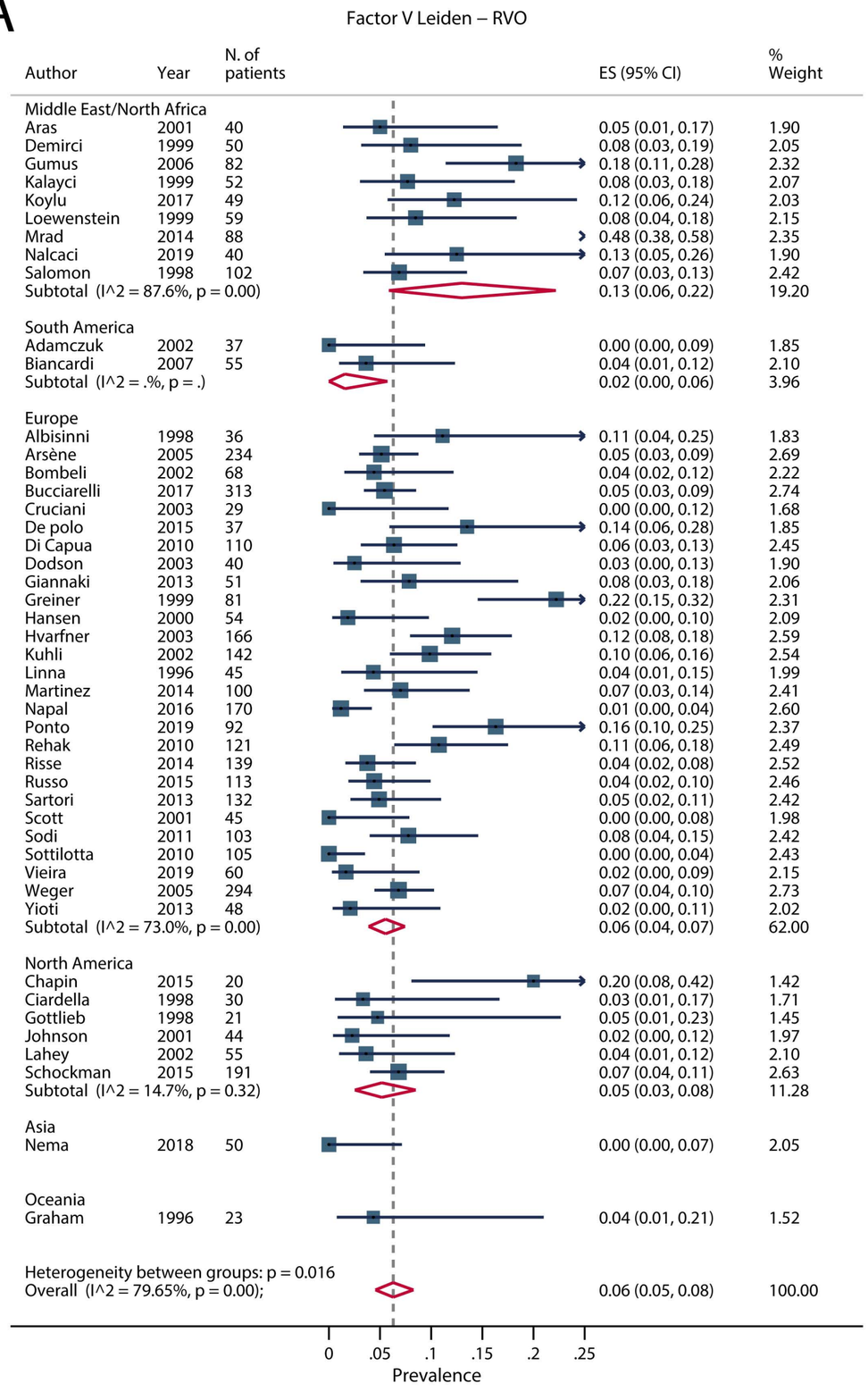
Figure 1


A
Factor V Leiden – RVO
Author
Year
N. of patients
ES (95% CI)
% Weight
Middle East/North Africa
Aras 2001 40 0.05 (0.01, 0.17) 1.90
Demirci 1999 50 0.08 (0.03, 0.19) 2.05
Gumus 2006 82 0.18 (0.11, 0.28) 2.32
Kalayci 1999 52 0.08 (0.03, 0.18) 2.07
Koylu 2017 49 0.12 (0.06, 0.24) 2.03
Loewenstein 1999 59 0.08 (0.04, 0.18) 2.15
Mrad 2014 88 0.48 (0.38, 0.58) 2.35
Nalcaci 2019 40 0.13 (0.05, 0.26) 1.90
Salomon 1998 102 0.07 (0.03, 0.13) 2.42
Subtotal (I^2 = 87.6%, p = 0.00) 0.13 (0.06, 0.22) 19.20
South America
Adamczuk 2002 37 0.00 (0.00, 0.09) 1.85
Biancardi 2007 55 0.04 (0.01, 0.12) 2.10
Subtotal (I^2 = .%, p = .) 0.02 (0.00, 0.06) 3.96
Europe
Albisinni 1998 36 0.11 (0.04, 0.25) 1.83
Arsène 2005 234 0.05 (0.03, 0.09) 2.69
Bombeli 2002 68 0.04 (0.02, 0.12) 2.22
Bucciarelli 2017 313 0.05 (0.03, 0.09) 2.74
Cruciani 2003 29 0.00 (0.00, 0.12) 1.68
De polo 2015 37 0.14 (0.06, 0.28) 1.85
Di Capua 2010 110 0.06 (0.03, 0.13) 2.45
Dodson 2003 40 0.03 (0.00, 0.13) 1.90
Giannaki 2013 51 0.08 (0.03, 0.18) 2.06
Greiner 1999 81 0.22 (0.15, 0.32) 2.31
Hansen 2000 54 0.02 (0.00, 0.10) 2.09
Hvarfner 2003 166 0.12 (0.08, 0.18) 2.59
Kuhli 2002 142 0.10 (0.06, 0.16) 2.54
Linna 1996 45 0.04 (0.01, 0.15) 1.99
Martinez 2014 100 0.07 (0.03, 0.14) 2.41
Napal 2016 170 0.01 (0.00, 0.04) 2.60
Ponto 2019 92 0.16 (0.10, 0.25) 2.37
Rehak 2010 121 0.11 (0.06, 0.18) 2.49
Risse 2014 139 0.04 (0.02, 0.08) 2.52
Russo 2015 113 0.04 (0.02, 0.10) 2.46
Sartori 2013 132 0.05 (0.02, 0.11) 2.42
Scott 2001 45 0.00 (0.00, 0.08) 1.98
Sodi 2011 103 0.08 (0.04, 0.15) 2.42
Sottilotta 2010 105 0.00 (0.00, 0.04) 2.43
Vieira 2019 60 0.02 (0.00, 0.09) 2.15
Weger 2005 294 0.07 (0.04, 0.10) 2.73
Yioti 2013 48 0.02 (0.00, 0.11) 2.02
Subtotal (I^2 = 73.0%, p = 0.00) 0.06 (0.04, 0.07) 62.00
North America
Chapin 2015 20 0.20 (0.08, 0.42) 1.42
Ciardella 1998 30 0.03 (0.01, 0.17) 1.71
Gottlieb 1998 21 0.05 (0.01, 0.23) 1.45
Johnson 2001 44 0.02 (0.00, 0.12) 1.97
Lahey 2002 55 0.04 (0.01, 0.12) 2.10
Schockman 2015 191 0.07 (0.04, 0.11) 2.63
Subtotal (I^2 = 14.7%, p = 0.32) 0.05 (0.03, 0.08) 11.28
Asia
Nema 2018 50 0.00 (0.00, 0.07) 2.05
Oceania
Graham 1996 23 0.04 (0.01, 0.21) 1.52
Heterogeneity between groups: p = 0.016
Overall (I^2 = 79.65%, p = 0.00); 0.06 (0.05, 0.08) 100.00
0
.05
.1
.15
.2
.25
Prevalence

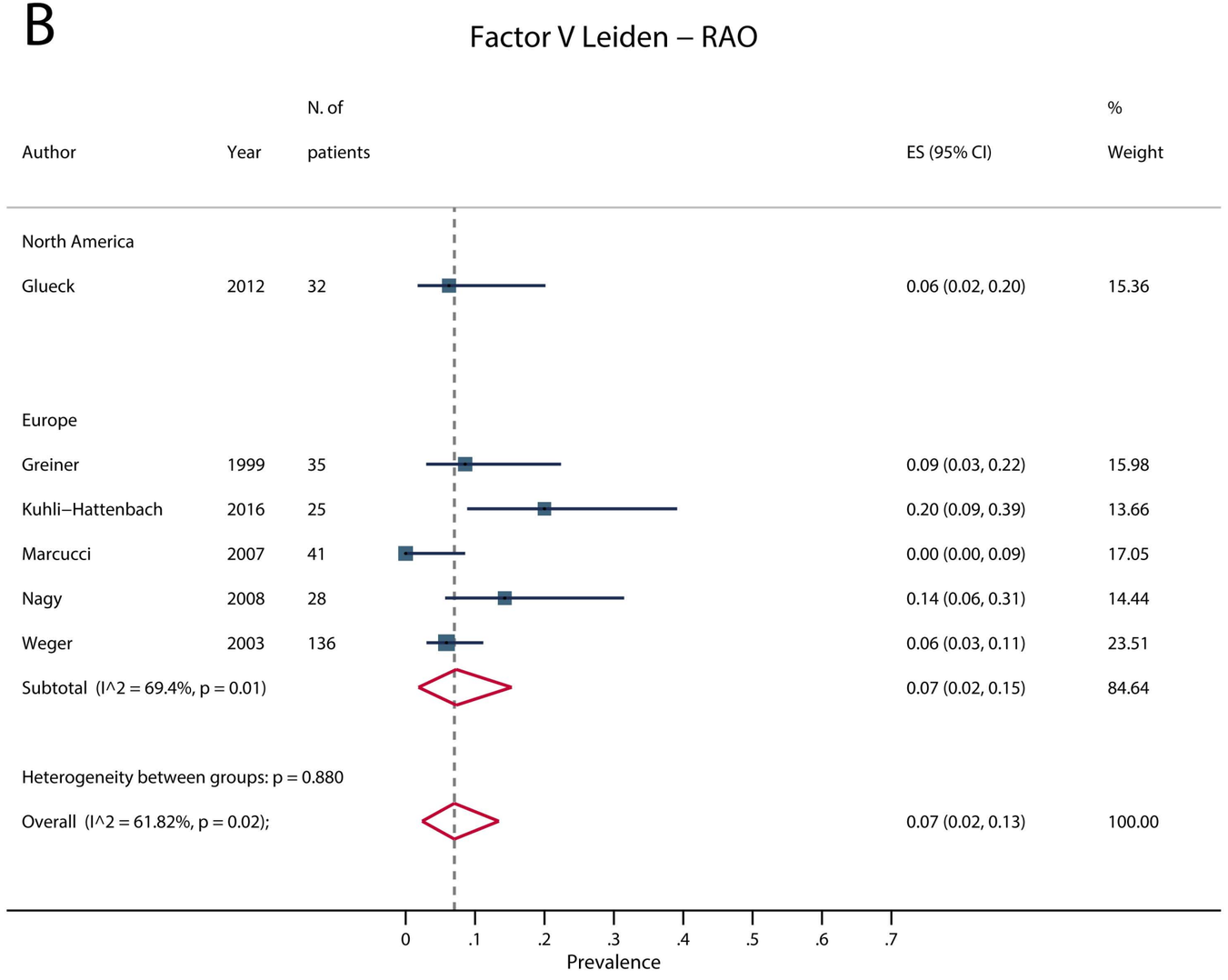
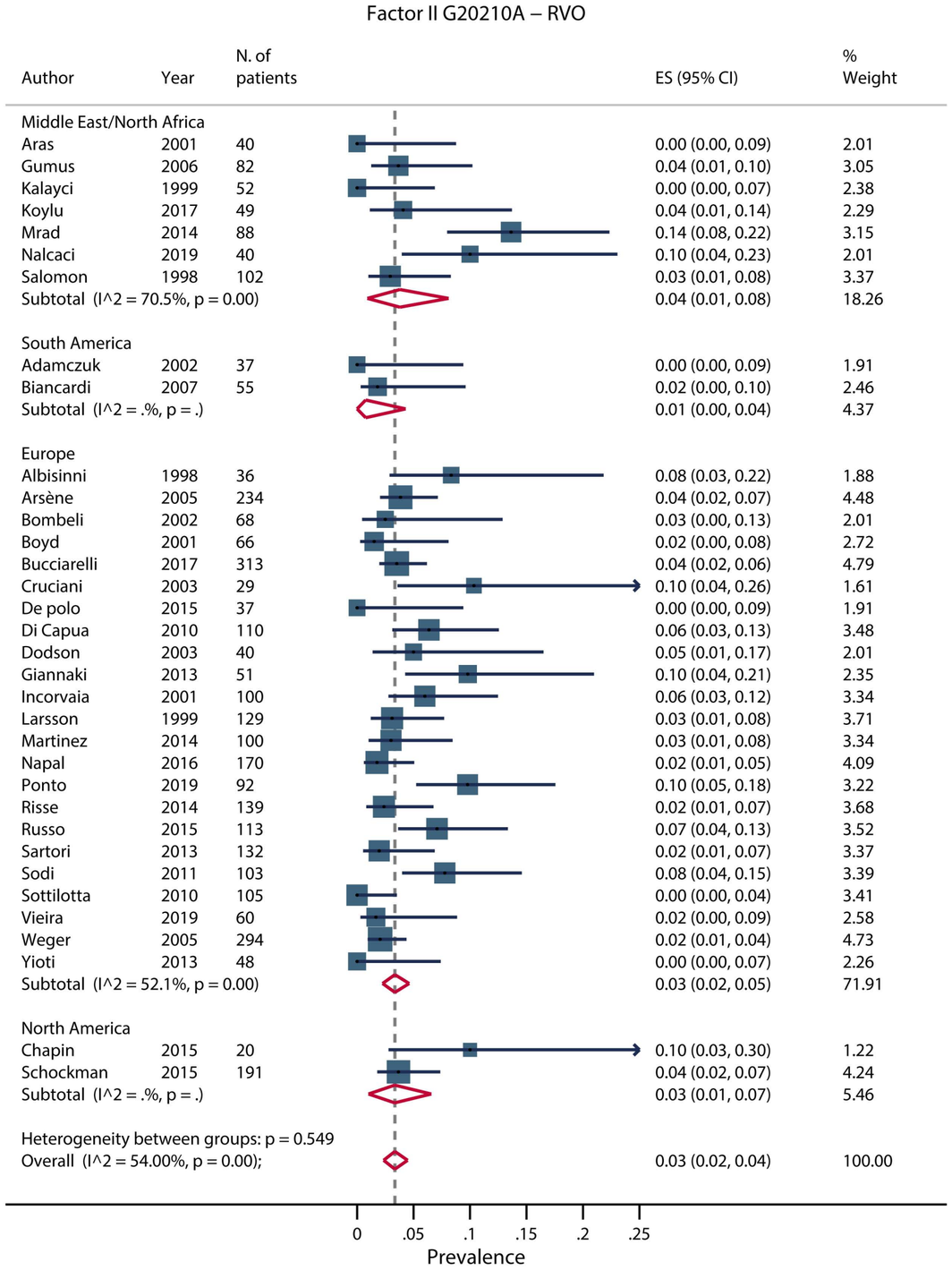

B
Factor V Leiden – RAO
Author
Year
N. of patients
ES (95% CI)
% Weight
North America
Glueck 2012 32 0.06 (0.02, 0.20) 15.36
Europe
Greiner 1999 35 0.09 (0.03, 0.22) 15.98
Kuhli–Hattenbach 2016 25 0.20 (0.09, 0.39) 13.66
Marcucci 2007 41 0.00 (0.00, 0.09) 17.05
Nagy 2008 28 0.14 (0.06, 0.31) 14.44
Weger 2003 136 0.06 (0.03, 0.11) 23.51
Subtotal (I^2 = 69.4%, p = 0.01) 0.07 (0.02, 0.15) 84.64
Heterogeneity between groups: p = 0.880
Overall (I^2 = 61.82%, p = 0.02); 0.07 (0.02, 0.13) 100.00
0
.1
.2
.3
.4
.5
.6
.7
Prevalence

Figure 2

A


Factor II G20210A – RVO
Author
Year
N. of patients
ES (95% CI)
% Weight
Middle East/North Africa
Aras 2001 40 0.00 (0.00, 0.09) 2.01
Gumus 2006 82 0.04 (0.01, 0.10) 3.05
Kalayci 1999 52 0.00 (0.00, 0.07) 2.38
Koylu 2017 49 0.04 (0.01, 0.14) 2.29
Mrad 2014 88 0.14 (0.08, 0.22) 3.15
Nalcaci 2019 40 0.10 (0.04, 0.23) 2.01
Salomon 1998 102 0.03 (0.01, 0.08) 3.37
Subtotal (I^2 = 70.5%, p = 0.00) 0.04 (0.01, 0.08) 18.26
South America
Adamczuk 2002 37 0.00 (0.00, 0.09) 1.91
Biancardi 2007 55 0.02 (0.00, 0.10) 2.46
Subtotal (I^2 = .%, p = .) 0.01 (0.00, 0.04) 4.37
Europe
Albisinni 1998 36 0.08 (0.03, 0.22) 1.88
Arsène 2005 234 0.04 (0.02, 0.07) 4.48
Bombeli 2002 68 0.03 (0.00, 0.13) 2.01
Boyd 2001 66 0.02 (0.00, 0.08) 2.72
Bucciarelli 2017 313 0.04 (0.02, 0.06) 4.79
Cruciani 2003 29 0.10 (0.04, 0.26) 1.61
De polo 2015 37 0.00 (0.00, 0.09) 1.91
Di Capua 2010 110 0.06 (0.03, 0.13) 3.48
Dodson 2003 40 0.05 (0.01, 0.17) 2.01
Giannaki 2013 51 0.10 (0.04, 0.21) 2.35
Incorvaia 2001 100 0.06 (0.03, 0.12) 3.34
Larsson 1999 129 0.03 (0.01, 0.08) 3.71
Martinez 2014 100 0.03 (0.01, 0.08) 3.34
Napal 2016 170 0.02 (0.01, 0.05) 4.09
Ponto 2019 92 0.10 (0.05, 0.18) 3.22
Risse 2014 139 0.02 (0.01, 0.07) 3.68
Russo 2015 113 0.07 (0.04, 0.13) 3.52
Sartori 2013 132 0.02 (0.01, 0.07) 3.37
Sodi 2011 103 0.08 (0.04, 0.15) 3.39
Sottilotta 2010 105 0.00 (0.00, 0.04) 3.41
Vieira 2019 60 0.02 (0.00, 0.09) 2.58
Weger 2005 294 0.02 (0.01, 0.04) 4.73
Yioti 2013 48 0.00 (0.00, 0.07) 2.26
Subtotal (I^2 = 52.1%, p = 0.00) 0.03 (0.02, 0.05) 71.91
North America
Chapin 2015 20 0.10 (0.03, 0.30) 1.22
Schockman 2015 191 0.04 (0.02, 0.07) 4.24
Subtotal (I^2 = .%, p = .) 0.03 (0.01, 0.07) 5.46
Heterogeneity between groups: p = 0.549
Overall (I^2 = 54.00%, p = 0.00); 0.03 (0.02, 0.04) 100.00
0
.05
.1
.15
.2
.25
Prevalence

B

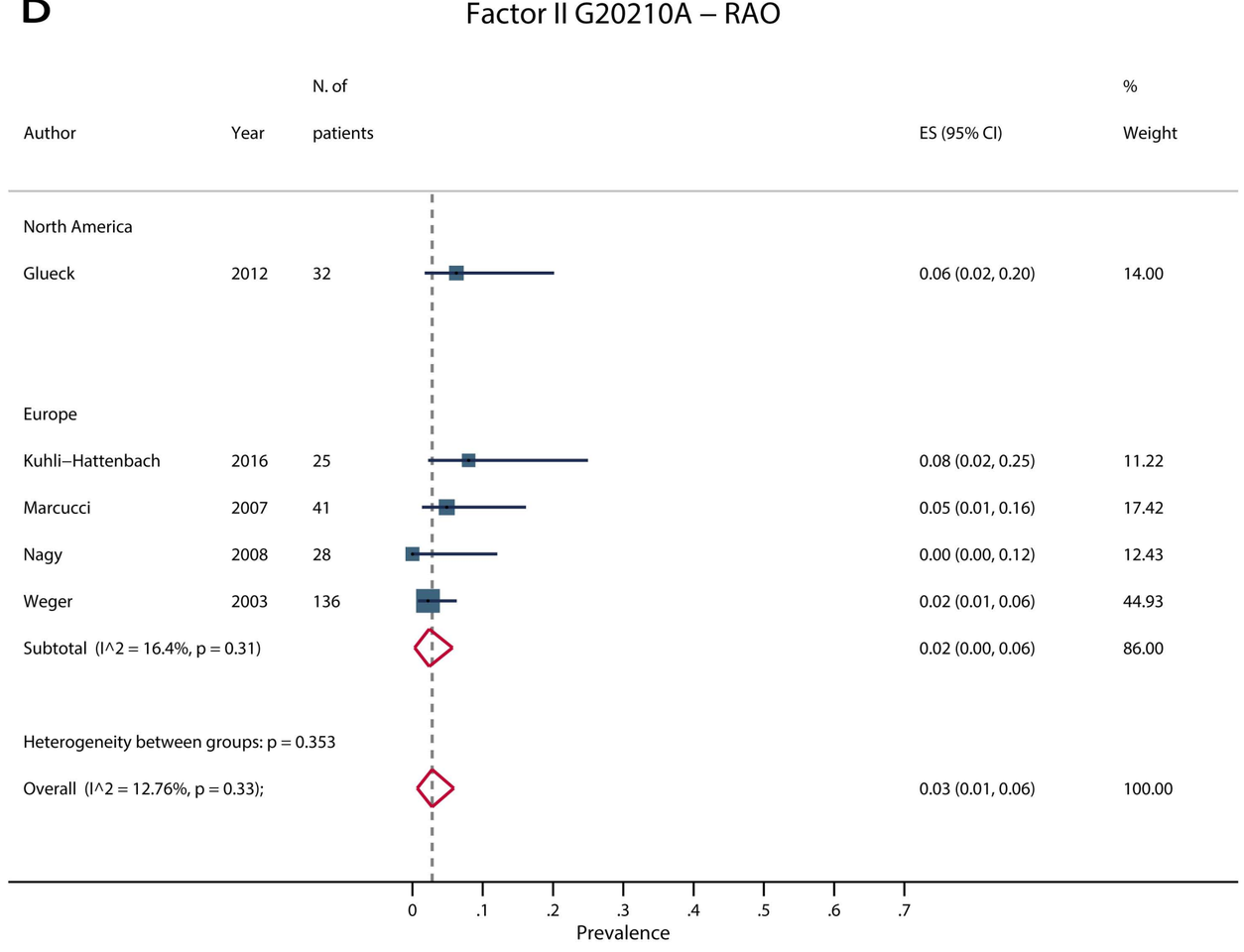

Factor II G20210A – RAO
Author
Year
N. of patients
ES (95% CI)
% Weight
North America
Glueck 2012 32 0.06 (0.02, 0.20) 14.00
Europe
Kuhli–Hattenbach 2016 25 0.08 (0.02, 0.25) 11.22
Marcucci 2007 41 0.05 (0.01, 0.16) 17.42
Nagy 2008 28 0.00 (0.00, 0.12) 12.43
Weger 2003 136 0.02 (0.01, 0.06) 44.93
Subtotal (I^2 = 16.4%, p = 0.31) 0.02 (0.00, 0.06) 86.00
Heterogeneity between groups: p = 0.353
Overall (I^2 = 12.76%, p = 0.33); 0.03 (0.01, 0.06) 100.00
0
.1
.2
.3
.4
.5
.6
.7
Prevalence

Figure 3

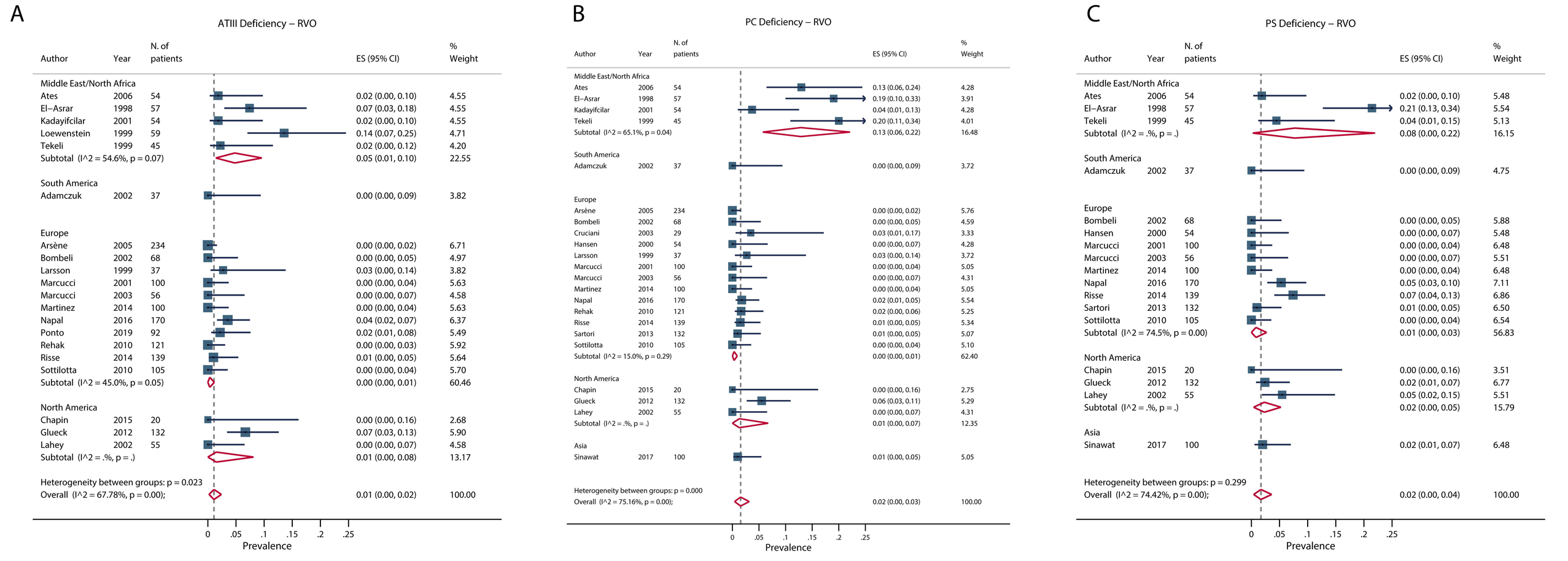
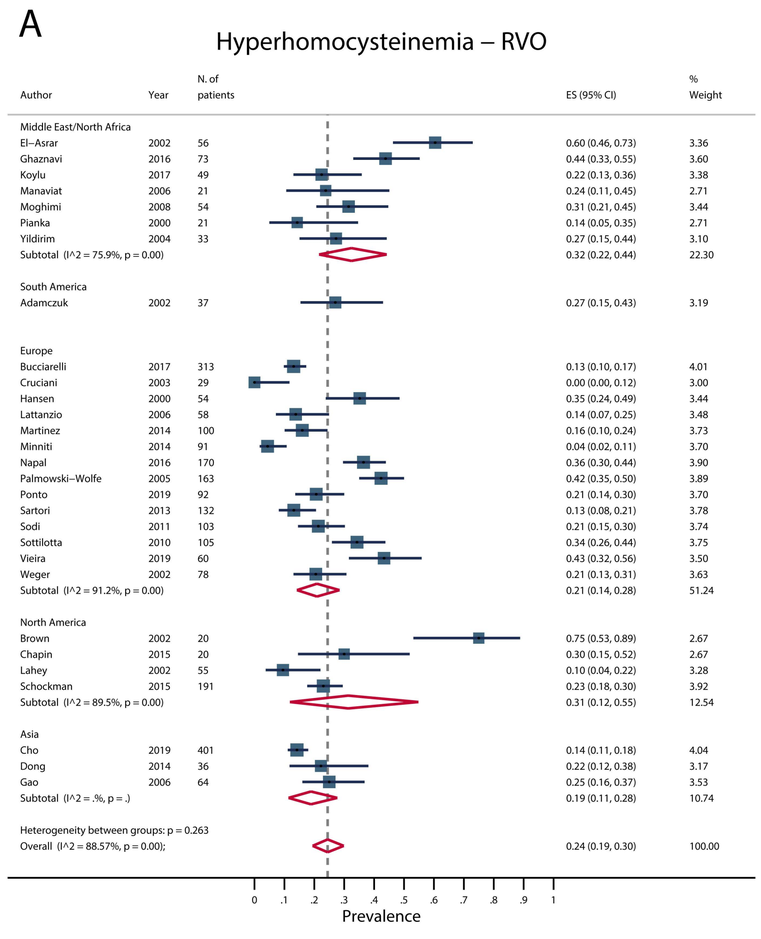
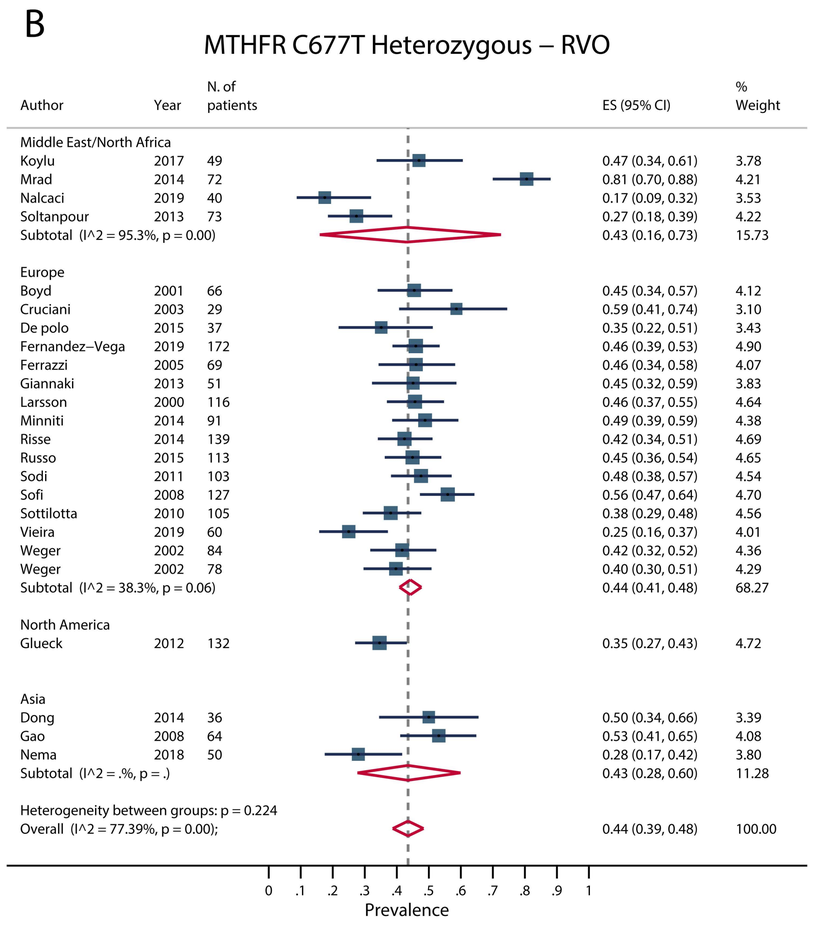

A
ATIII Deficiency – RVO
Author
Year
N. of patients
ES (95% CI)
% Weight
Middle East/North Africa
Ates 2006 54 0.02 (0.00, 0.10) 4.55
El–Asrar 1998 57 0.07 (0.03, 0.18) 4.55
Kadayifcilar 2001 54 0.02 (0.00, 0.10) 4.55
Loewenstein 1999 59 0.14 (0.07, 0.25) 4.71
Tekeli 1999 45 0.02 (0.00, 0.12) 4.20
Subtotal (I^2 = 54.6%, p = 0.07) 0.05 (0.01, 0.10) 22.55
South America
Adamczuk 2002 37 0.00 (0.00, 0.09) 3.82
Europe
Arsène 2005 234 0.00 (0.00, 0.02) 6.71
Bombeli 2002 68 0.00 (0.00, 0.05) 4.97
Larsson 1999 37 0.03 (0.00, 0.14) 3.82
Marcucci 2001 100 0.00 (0.00, 0.04) 5.63
Marcucci 2003 56 0.00 (0.00, 0.07) 4.58
Martinez 2014 100 0.00 (0.00, 0.04) 5.63
Napal 2016 170 0.04 (0.02, 0.07) 6.37
Ponto 2019 92 0.02 (0.01, 0.08) 5.49
Rehak 2010 121 0.00 (0.00, 0.03) 5.92
Risse 2014 139 0.01 (0.00, 0.05) 5.64
Sottilotta 2010 105 0.00 (0.00, 0.04) 5.70
Subtotal (I^2 = 45.0%, p = 0.05) 0.00 (0.00, 0.01) 60.46
North America
Chapin 2015 20 0.00 (0.00, 0.16) 2.68
Glueck 2012 132 0.07 (0.03, 0.13) 5.90
Lahey 2002 55 0.00 (0.00, 0.07) 4.58
Subtotal (I^2 = .%, p = .) 0.01 (0.00, 0.08) 13.17
Heterogeneity between groups: p = 0.023
Overall (I^2 = 67.78%, p = 0.00); 0.01 (0.00, 0.02) 100.00
0 .05 .1 .15 .2 .25
Prevalence
B
PC Deficiency – RVO
Author
Year
N. of patients
ES (95% CI)
% Weight
Middle East/North Africa
Ates 2006 54 0.13 (0.06, 0.24) 4.28
El–Asrar 1998 57 0.19 (0.10, 0.33) 3.91
Kadayifcilar 2001 54 0.04 (0.01, 0.13) 4.28
Tekeli 1999 45 0.20 (0.11, 0.34) 4.01
Subtotal (I^2 = 65.1%, p = 0.04) 0.13 (0.06, 0.22) 16.48
South America
Adamczuk 2002 37 0.00 (0.00, 0.09) 3.72
Europe
Arsène 2005 234 0.00 (0.00, 0.02) 5.76
Bombeli 2002 68 0.00 (0.00, 0.05) 4.59
Cruciani 2003 29 0.03 (0.01, 0.17) 3.33
Hansen 2000 54 0.00 (0.00, 0.07) 4.28
Larsson 1999 37 0.03 (0.00, 0.14) 3.72
Marcucci 2001 100 0.00 (0.00, 0.04) 5.05
Marcucci 2003 56 0.00 (0.00, 0.07) 4.31
Martinez 2014 100 0.00 (0.00, 0.04) 5.05
Napal 2016 170 0.02 (0.01, 0.05) 5.54
Rehak 2010 121 0.02 (0.00, 0.06) 5.25
Risse 2014 139 0.01 (0.00, 0.05) 5.34
Sartori 2013 132 0.01 (0.00, 0.05) 5.07
Sottilotta 2010 105 0.00 (0.00, 0.04) 5.10
Subtotal (I^2 = 15.0%, p = 0.29) 0.00 (0.00, 0.01) 62.40
North America
Chapin 2015 20 0.00 (0.00, 0.16) 2.75
Glueck 2012 132 0.06 (0.03, 0.11) 5.29
Lahey 2002 55 0.00 (0.00, 0.07) 4.31
Subtotal (I^2 = .%, p = .) 0.01 (0.00, 0.07) 12.35
Asia
Sinawat 2017 100 0.01 (0.00, 0.05) 5.05
Heterogeneity between groups: p = 0.000
Overall (I^2 = 75.16%, p = 0.00); 0.02 (0.00, 0.03) 100.00
0 .05 .1 .15 .2 .25
Prevalence
C
PS Deficiency – RVO
Author
Year
N. of patients
ES (95% CI)
% Weight
Middle East/North Africa
Ates 2006 54 0.02 (0.00, 0.10) 5.48
El–Asrar 1998 57 0.21 (0.13, 0.34) 5.54
Tekeli 1999 45 0.04 (0.01, 0.15) 5.13
Subtotal (I^2 = .%, p = .) 0.08 (0.00, 0.22) 16.15
South America
Adamczuk 2002 37 0.00 (0.00, 0.09) 4.75
Europe
Bombeli 2002 68 0.00 (0.00, 0.05) 5.88
Hansen 2000 54 0.00 (0.00, 0.07) 5.48
Marcucci 2001 100 0.00 (0.00, 0.04) 6.48
Marcucci 2003 56 0.00 (0.00, 0.07) 5.51
Martinez 2014 100 0.00 (0.00, 0.04) 6.48
Napal 2016 170 0.05 (0.03, 0.10) 7.11
Risse 2014 139 0.07 (0.04, 0.13) 6.86
Sartori 2013 132 0.01 (0.00, 0.05) 6.50
Sottilotta 2010 105 0.00 (0.00, 0.04) 6.54
Subtotal (I^2 = 74.5%, p = 0.00) 0.01 (0.00, 0.03) 56.83
North America
Chapin 2015 20 0.00 (0.00, 0.16) 3.51
Glueck 2012 132 0.02 (0.01, 0.07) 6.77
Lahey 2002 55 0.05 (0.02, 0.15) 5.51
Subtotal (I^2 = .%, p = .) 0.02 (0.00, 0.05) 15.79
Asia
Sinawat 2017 100 0.02 (0.01, 0.07) 6.48
Heterogeneity between groups: p = 0.299
Overall (I^2 = 74.42%, p = 0.00); 0.02 (0.00, 0.04) 100.00
0 .05 .1 .15 .2 .25
Prevalence

Figure 4


A
Hyperhomocysteinemia – RVO
Author
Year
N. of patients
ES (95% CI)
% Weight
Middle East/North Africa
El–Asrar 2002 56 0.60 (0.46, 0.73) 3.36
Ghaznavi 2016 73 0.44 (0.33, 0.55) 3.60
Koylu 2017 49 0.22 (0.13, 0.36) 3.38
Manaviat 2006 21 0.24 (0.11, 0.45) 2.71
Moghimi 2008 54 0.31 (0.21, 0.45) 3.44
Pianka 2000 21 0.14 (0.05, 0.35) 2.71
Yildirim 2004 33 0.27 (0.15, 0.44) 3.10
Subtotal (I^2 = 75.9%, p = 0.00) 0.32 (0.22, 0.44) 22.30
South America
Adamczuk 2002 37 0.27 (0.15, 0.43) 3.19
Europe
Bucciarelli 2017 313 0.13 (0.10, 0.17) 4.01
Cruciani 2003 29 0.00 (0.00, 0.12) 3.00
Hansen 2000 54 0.35 (0.24, 0.49) 3.44
Lattanzio 2006 58 0.14 (0.07, 0.25) 3.48
Martinez 2014 100 0.16 (0.10, 0.24) 3.73
Minniti 2014 91 0.04 (0.02, 0.11) 3.70
Napal 2016 170 0.36 (0.30, 0.44) 3.90
Palmowski–Wolfe 2005 163 0.42 (0.35, 0.50) 3.89
Ponto 2019 92 0.21 (0.14, 0.30) 3.70
Sartori 2013 132 0.13 (0.08, 0.21) 3.78
Sodi 2011 103 0.21 (0.15, 0.30) 3.74
Sottilotta 2010 105 0.34 (0.26, 0.44) 3.75
Vieira 2019 60 0.43 (0.32, 0.56) 3.50
Weger 2002 78 0.21 (0.13, 0.31) 3.63
Subtotal (I^2 = 91.2%, p = 0.00) 0.21 (0.14, 0.28) 51.24
North America
Brown 2002 20 0.75 (0.53, 0.89) 2.67
Chapin 2015 20 0.30 (0.15, 0.52) 2.67
Lahey 2002 55 0.10 (0.04, 0.22) 3.28
Schockman 2015 191 0.23 (0.18, 0.30) 3.92
Subtotal (I^2 = 89.5%, p = 0.00) 0.31 (0.12, 0.55) 12.54
Asia
Cho 2019 401 0.14 (0.11, 0.18) 4.04
Dong 2014 36 0.22 (0.12, 0.38) 3.17
Gao 2006 64 0.25 (0.16, 0.37) 3.53
Subtotal (I^2 = .%, p = .) 0.19 (0.11, 0.28) 10.74
Heterogeneity between groups: p = 0.263
Overall (I^2 = 88.57%, p = 0.00); 0.24 (0.19, 0.30) 100.00
0 .1 .2 .3 .4 .5 .6 .7 .8 .9 1
Prevalence


B
MTHFR C677T Heterozygous – RVO
Author
Year
N. of patients
ES (95% CI)
% Weight
Middle East/North Africa
Koylu 2017 49 0.47 (0.34, 0.61) 3.78
Mrad 2014 72 0.81 (0.70, 0.88) 4.21
Nalcaci 2019 40 0.17 (0.09, 0.32) 3.53
Soltanpour 2013 73 0.27 (0.18, 0.39) 4.22
Subtotal (I^2 = 95.3%, p = 0.00) 0.43 (0.16, 0.73) 15.73
Europe
Boyd 2001 66 0.45 (0.34, 0.57) 4.12
Cruciani 2003 29 0.59 (0.41, 0.74) 3.10
De polo 2015 37 0.35 (0.22, 0.51) 3.43
Fernandez–Vega 2019 172 0.46 (0.39, 0.53) 4.90
Ferrazzi 2005 69 0.46 (0.34, 0.58) 4.07
Giannaki 2013 51 0.45 (0.32, 0.59) 3.83
Larsson 2000 116 0.46 (0.37, 0.55) 4.64
Minniti 2014 91 0.49 (0.39, 0.59) 4.38
Risse 2014 139 0.42 (0.34, 0.51) 4.69
Russo 2015 113 0.45 (0.36, 0.54) 4.65
Sodi 2011 103 0.48 (0.38, 0.57) 4.54
Sofi 2008 127 0.56 (0.47, 0.64) 4.70
Sottilotta 2010 105 0.38 (0.29, 0.48) 4.56
Vieira 2019 60 0.25 (0.16, 0.37) 4.01
Weger 2002 84 0.42 (0.32, 0.52) 4.36
Weger 2002 78 0.40 (0.30, 0.51) 4.29
Subtotal (I^2 = 38.3%, p = 0.06) 0.44 (0.41, 0.48) 68.27
North America
Glueck 2012 132 0.35 (0.27, 0.43) 4.72
Asia
Dong 2014 36 0.50 (0.34, 0.66) 3.39
Gao 2008 64 0.53 (0.41, 0.65) 4.08
Nema 2018 50 0.28 (0.17, 0.42) 3.80
Subtotal (I^2 = .%, p = .) 0.43 (0.28, 0.60) 11.28
Heterogeneity between groups: p = 0.224
Overall (I^2 = 77.39%, p = 0.00); 0.44 (0.39, 0.48) 100.00
0 .1 .2 .3 .4 .5 .6 .7 .8 .9 1
Prevalence

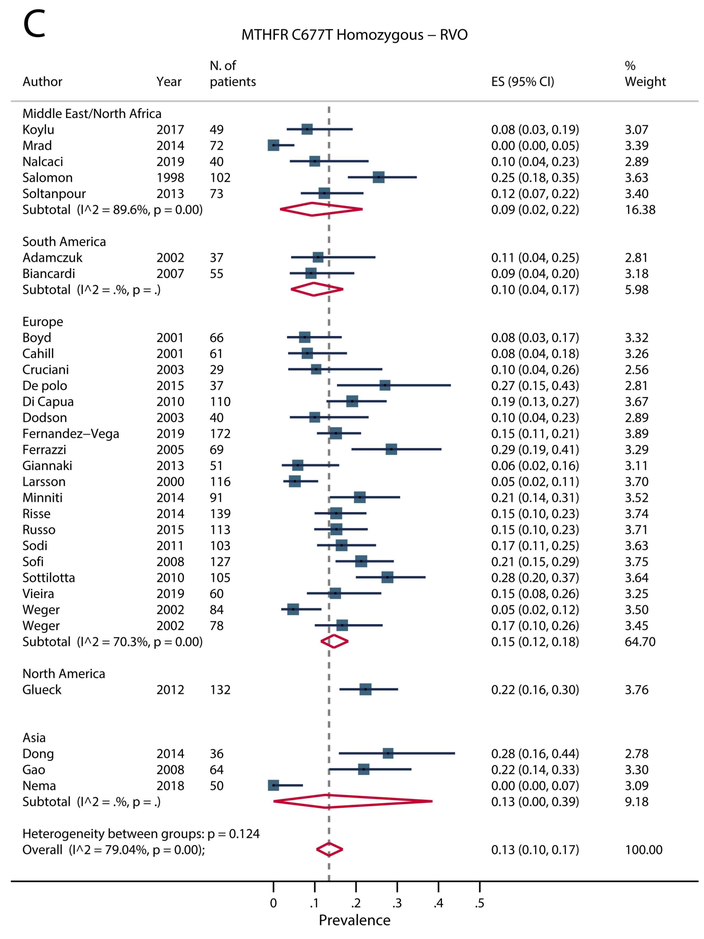
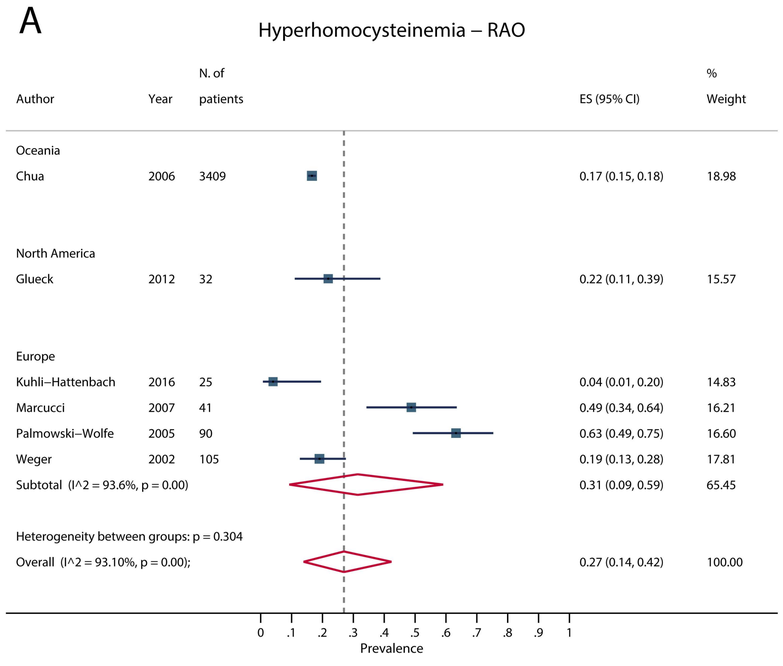
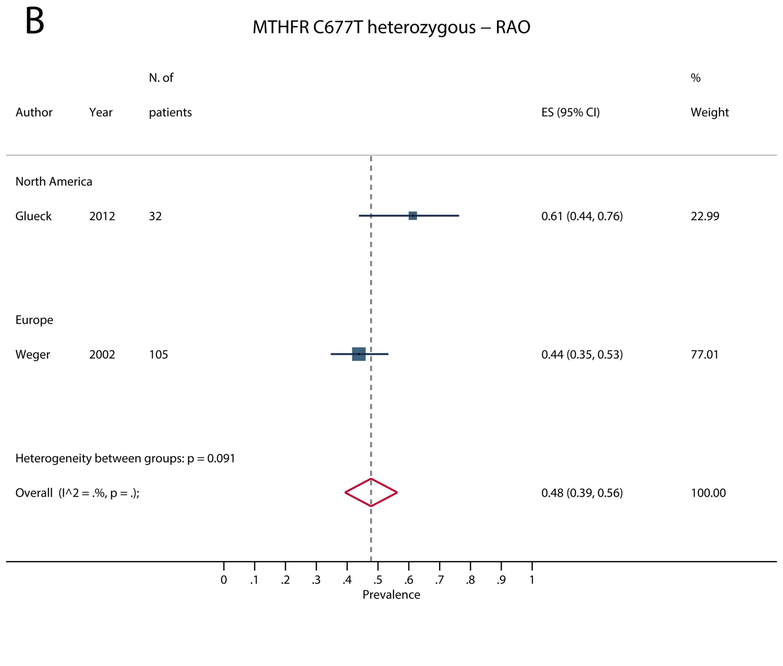

C
MTHFR C677T Homozygous – RVO
Author
Year
N. of patients
ES (95% CI)
% Weight
Middle East/North Africa
Koylu 2017 49 0.08 (0.03, 0.19) 3.07
Mrad 2014 72 0.00 (0.00, 0.05) 3.39
Nalcaci 2019 40 0.10 (0.04, 0.23) 2.89
Salomon 1998 102 0.25 (0.18, 0.35) 3.63
Soltanpour 2013 73 0.12 (0.07, 0.22) 3.40
Subtotal (I^2 = 89.6%, p = 0.00) 0.09 (0.02, 0.22) 16.38
South America
Adamczuk 2002 37 0.11 (0.04, 0.25) 2.81
Biancardi 2007 55 0.09 (0.04, 0.20) 3.18
Subtotal (I^2 = .%, p = .) 0.10 (0.04, 0.17) 5.98
Europe
Boyd 2001 66 0.08 (0.03, 0.17) 3.32
Cahill 2001 61 0.08 (0.04, 0.18) 3.26
Cruciani 2003 29 0.10 (0.04, 0.26) 2.56
De polo 2015 37 0.27 (0.15, 0.43) 2.81
Di Capua 2010 110 0.19 (0.13, 0.27) 3.67
Dodson 2003 40 0.10 (0.04, 0.23) 2.89
Fernandez–Vega 2019 172 0.15 (0.11, 0.21) 3.89
Ferrazzi 2005 69 0.29 (0.19, 0.41) 3.29
Giannaki 2013 51 0.06 (0.02, 0.16) 3.11
Larsson 2000 116 0.05 (0.02, 0.11) 3.70
Minniti 2014 91 0.21 (0.14, 0.31) 3.52
Risse 2014 139 0.15 (0.10, 0.23) 3.74
Russo 2015 113 0.15 (0.10, 0.23) 3.71
Sodi 2011 103 0.17 (0.11, 0.25) 3.63
Sofi 2008 127 0.21 (0.15, 0.29) 3.75
Sottilotta 2010 105 0.28 (0.20, 0.37) 3.64
Vieira 2019 60 0.15 (0.08, 0.26) 3.25
Weger 2002 84 0.05 (0.02, 0.12) 3.50
Weger 2002 78 0.17 (0.10, 0.26) 3.45
Subtotal (I^2 = 70.3%, p = 0.00) 0.15 (0.12, 0.18) 64.70
North America
Glueck 2012 132 0.22 (0.16, 0.30) 3.76
Asia
Dong 2014 36 0.28 (0.16, 0.44) 2.78
Gao 2008 64 0.22 (0.14, 0.33) 3.30
Nema 2018 50 0.00 (0.00, 0.07) 3.09
Subtotal (I^2 = .%, p = .) 0.13 (0.00, 0.39) 9.18
Heterogeneity between groups: p = 0.124
Overall (I^2 = 79.04%, p = 0.00); 0.13 (0.10, 0.17) 100.00
0 .1 .2 .3 .4 .5
Prevalence

Figure 5


A
Hyperhomocysteinemia – RAO
Author
Year
N. of patients
ES (95% CI)
% Weight
Oceania
Chua 2006 3409 0.17 (0.15, 0.18) 18.98
North America
Glueck 2012 32 0.22 (0.11, 0.39) 15.57
Europe
Kuhli–Hattenbach 2016 25 0.04 (0.01, 0.20) 14.83
Marcucci 2007 41 0.49 (0.34, 0.64) 16.21
Palmowski–Wolfe 2005 90 0.63 (0.49, 0.75) 16.60
Weger 2002 105 0.19 (0.13, 0.28) 17.81
Subtotal (I^2 = 93.6%, p = 0.00) 0.31 (0.09, 0.59) 65.45
Heterogeneity between groups: p = 0.304
Overall (I^2 = 93.10%, p = 0.00); 0.27 (0.14, 0.42) 100.00
0 .1 .2 .3 .4 .5 .6 .7 .8 .9 1
Prevalence


B
MTHFR C677T heterozygous – RAO
Author
Year
N. of patients
ES (95% CI)
% Weight
North America
Glueck 2012 32 0.61 (0.44, 0.76) 22.99
Europe
Weger 2002 105 0.44 (0.35, 0.53) 77.01
Heterogeneity between groups: p = 0.091
Overall (I^2 = .%, p = .); 0.48 (0.39, 0.56) 100.00
0 .1 .2 .3 .4 .5 .6 .7 .8 .9 1
Prevalence

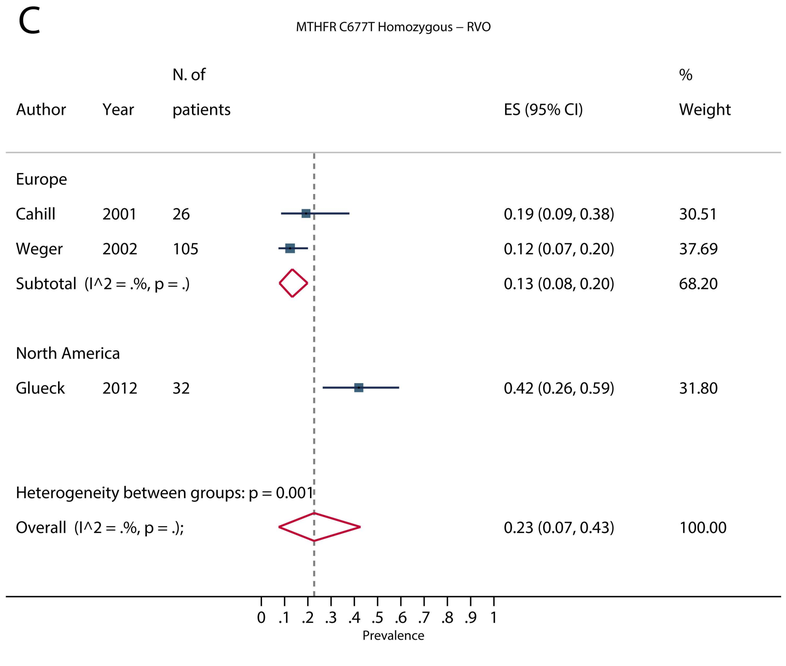

C
MTHFR C677T Homozygous – RVO
Author
Year
N. of patients
ES (95% CI)
% Weight
Europe
Cahill 2001 26 0.19 (0.09, 0.38) 30.51
Weger 2002 105 0.12 (0.07, 0.20) 37.69
Subtotal (I^2 = .%, p = .) 0.13 (0.08, 0.20) 68.20
North America
Glueck 2012 32 0.42 (0.26, 0.59) 31.80
Heterogeneity between groups: p = 0.001
Overall (I^2 = .%, p = .); 0.23 (0.07, 0.43) 100.00
0 .1 .2 .3 .4 .5 .6 .7 .8 .9 1
Prevalence

Figure 6

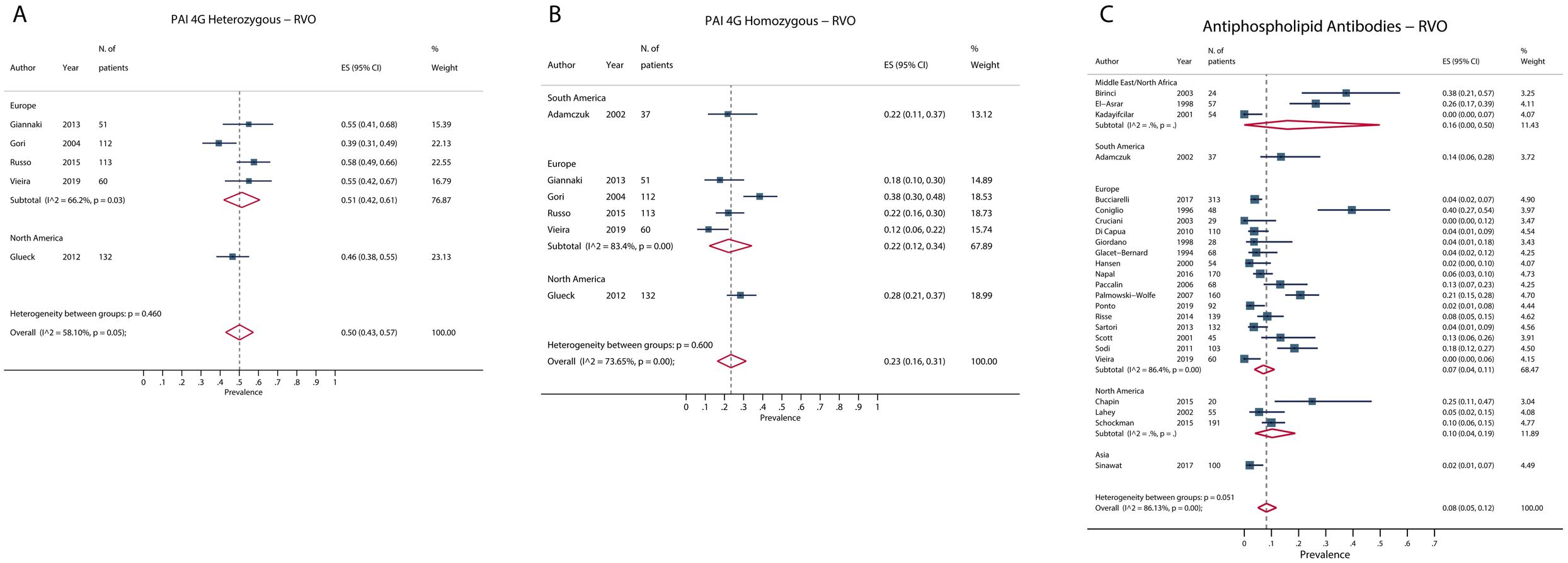
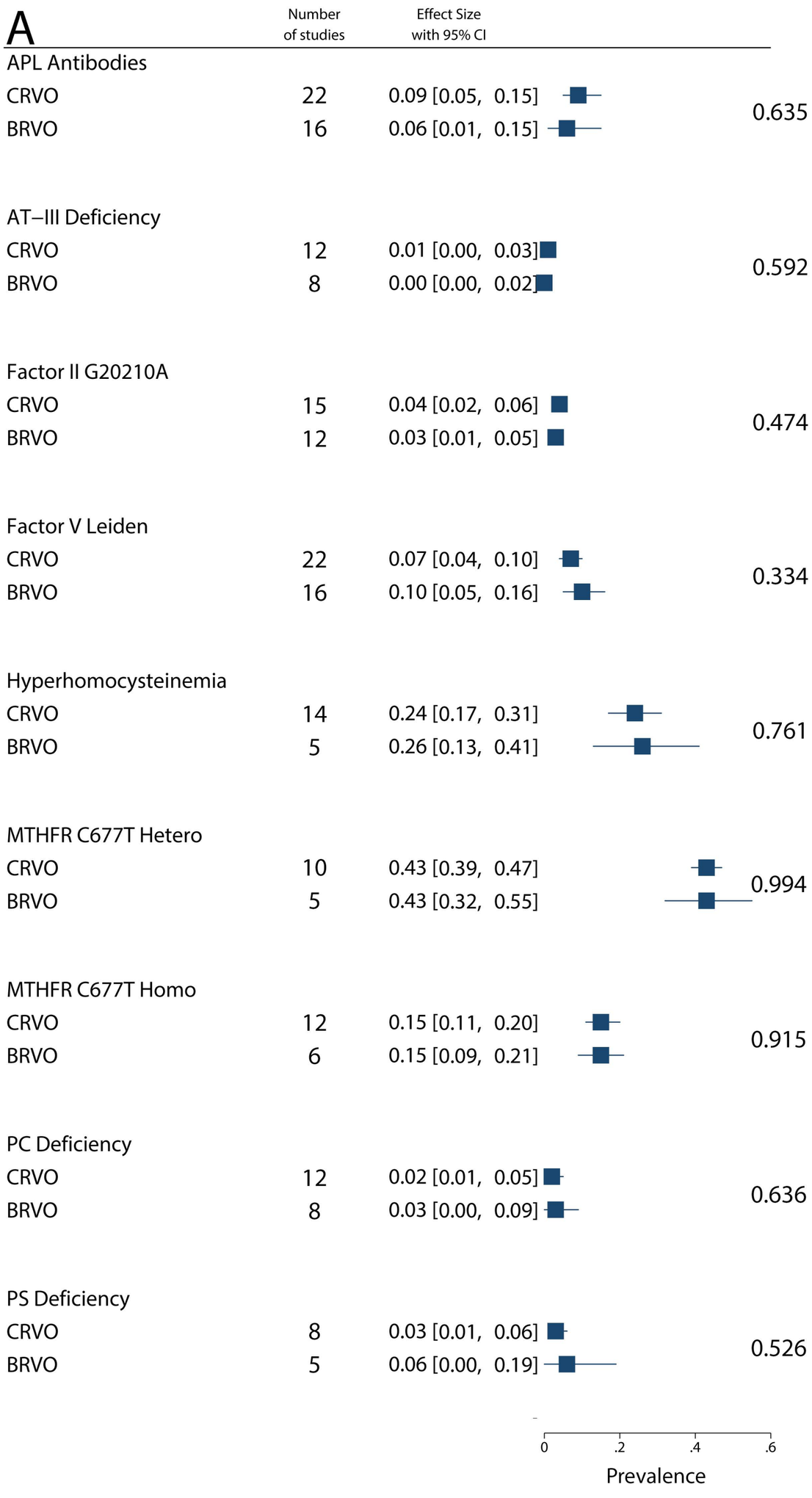
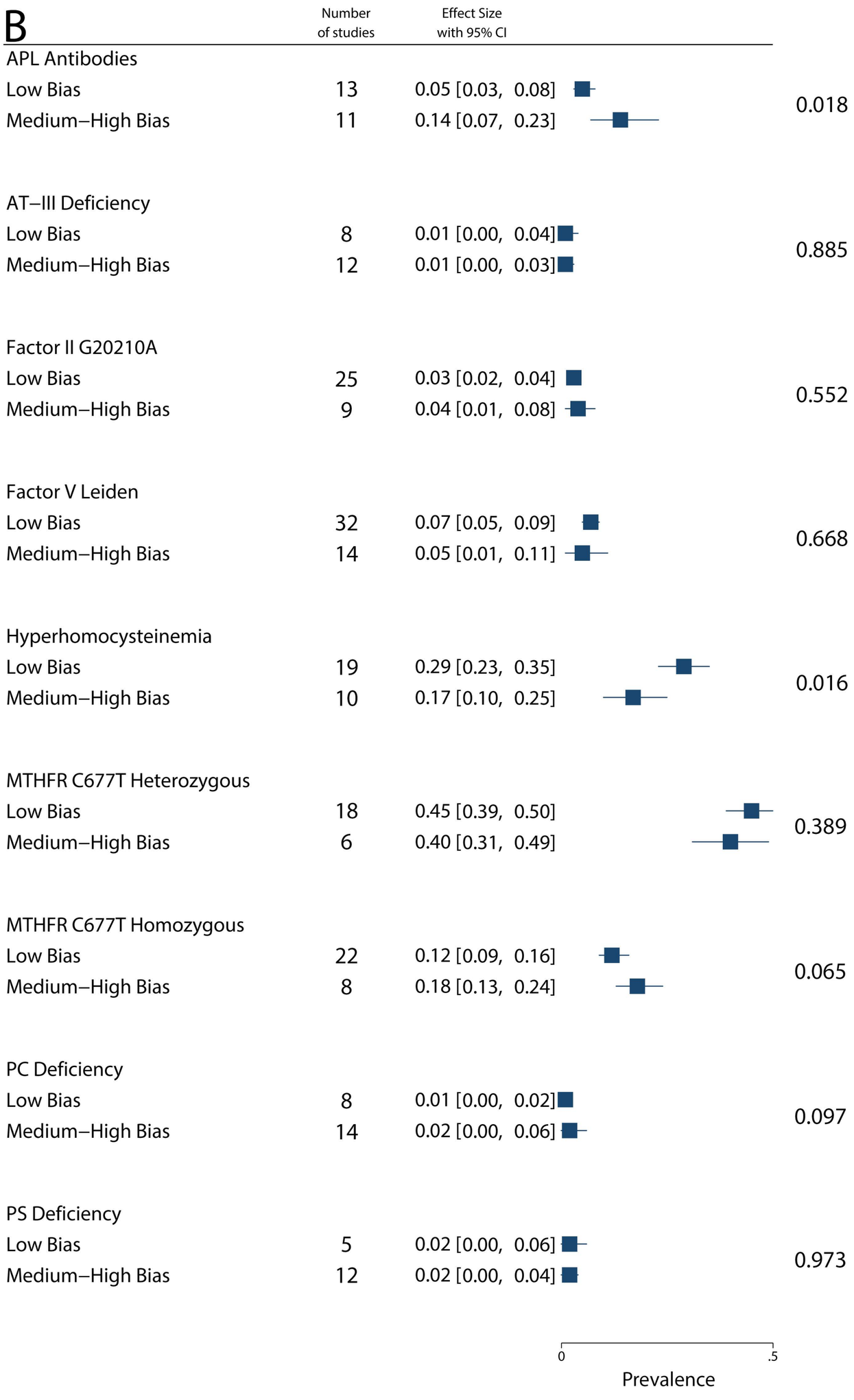

A
PAI 4G Heterozygous – RVO
Author
Year
N. of patients
ES (95% CI)
% Weight
Europe
Giannaki 2013 51 0.55 (0.41, 0.68) 15.39
Gori 2004 112 0.39 (0.31, 0.49) 22.13
Russo 2015 113 0.58 (0.49, 0.66) 22.55
Vieira 2019 60 0.55 (0.42, 0.67) 16.79
Subtotal (I^2 = 66.2%, p = 0.03) 0.51 (0.42, 0.61) 76.87
North America
Glueck 2012 132 0.46 (0.38, 0.55) 23.13
Heterogeneity between groups: p = 0.460
Overall (I^2 = 58.10%, p = 0.05); 0.50 (0.43, 0.57) 100.00
0 .1 .2 .3 .4 .5 .6 .7 .8 .9 1
Prevalence
B
PAI 4G Homozygous – RVO
Author
Year
N. of patients
ES (95% CI)
% Weight
South America
Adamczuk 2002 37 0.22 (0.11, 0.37) 13.12
Europe
Giannaki 2013 51 0.18 (0.10, 0.30) 14.89
Gori 2004 112 0.38 (0.30, 0.48) 18.53
Russo 2015 113 0.22 (0.16, 0.30) 18.73
Vieira 2019 60 0.12 (0.06, 0.22) 15.74
Subtotal (I^2 = 83.4%, p = 0.00) 0.22 (0.12, 0.34) 67.89
North America
Glueck 2012 132 0.28 (0.21, 0.37) 18.99
Heterogeneity between groups: p = 0.600
Overall (I^2 = 73.65%, p = 0.00); 0.23 (0.16, 0.31) 100.00
0 .1 .2 .3 .4 .5 .6 .7 .8 .9 1
Prevalence
C
Antiphospholipid Antibodies – RVO
Author
Year
N. of patients
ES (95% CI)
% Weight
Middle East/North Africa
Birinci 2003 24 0.38 (0.21, 0.57) 3.25
El–Asrar 1998 57 0.26 (0.17, 0.39) 4.11
Kadayifcilar 2001 54 0.00 (0.00, 0.07) 4.07
Subtotal (I^2 = .%, p = .) 0.16 (0.00, 0.50) 11.43
South America
Adamczuk 2002 37 0.14 (0.06, 0.28) 3.72
Europe
Bucciarelli 2017 313 0.04 (0.02, 0.07) 4.90
Coniglio 1996 48 0.40 (0.27, 0.54) 3.97
Cruciani 2003 29 0.00 (0.00, 0.12) 3.47
Di Capua 2010 110 0.04 (0.01, 0.09) 4.54
Giordano 1998 28 0.04 (0.01, 0.18) 3.43
Glacet–Bernard 1994 68 0.04 (0.02, 0.12) 4.25
Hansen 2000 54 0.02 (0.00, 0.10) 4.07
Napal 2016 170 0.06 (0.03, 0.10) 4.73
Paccalin 2006 68 0.13 (0.07, 0.23) 4.25
Palmowski–Wolfe 2007 160 0.21 (0.15, 0.28) 4.70
Ponto 2019 92 0.02 (0.01, 0.08) 4.44
Risse 2014 139 0.08 (0.05, 0.15) 4.62
Sartori 2013 132 0.04 (0.01, 0.09) 4.56
Scott 2001 45 0.13 (0.06, 0.26) 3.91
Sodi 2011 103 0.18 (0.12, 0.27) 4.50
Vieira 2019 60 0.00 (0.00, 0.06) 4.15
Subtotal (I^2 = 86.4%, p = 0.00) 0.07 (0.04, 0.11) 68.47
North America
Chapin 2015 20 0.25 (0.11, 0.47) 3.04
Lahey 2002 55 0.05 (0.02, 0.15) 4.08
Schockman 2015 191 0.10 (0.06, 0.15) 4.77
Subtotal (I^2 = .%, p = .) 0.10 (0.04, 0.19) 11.89
Asia
Sinawat 2017 100 0.02 (0.01, 0.07) 4.49
Heterogeneity between groups: p = 0.051
Overall (I^2 = 86.13%, p = 0.00); 0.08 (0.05, 0.12) 100.00
0 .1 .2 .3 .4 .5 .6 .7
Prevalence

Figure 7


A
Number of studies
Effect Size with 95% CI
APL Antibodies
CRVO 22 0.09 [0.05, 0.15]
BRVO 16 0.06 [0.01, 0.15]
0.635
AT–III Deficiency
CRVO 12 0.01 [0.00, 0.03]
BRVO 8 0.00 [0.00, 0.02]
0.592
Factor II G20210A
CRVO 15 0.04 [0.02, 0.06]
BRVO 12 0.03 [0.01, 0.05]
0.474
Factor V Leiden
CRVO 22 0.07 [0.04, 0.10]
BRVO 16 0.10 [0.05, 0.16]
0.334
Hyperhomocysteinemia
CRVO 14 0.24 [0.17, 0.31]
BRVO 5 0.26 [0.13, 0.41]
0.761
MTHFR C677T Hetero
CRVO 10 0.43 [0.39, 0.47]
BRVO 5 0.43 [0.32, 0.55]
0.994
MTHFR C677T Homo
CRVO 12 0.15 [0.11, 0.20]
BRVO 6 0.15 [0.09, 0.21]
0.915
PC Deficiency
CRVO 12 0.02 [0.01, 0.05]
BRVO 8 0.03 [0.00, 0.09]
0.636
PS Deficiency
CRVO 8 0.03 [0.01, 0.06]
BRVO 5 0.06 [0.00, 0.19]
0.526
0
.2
.4
.6
Prevalence


B
Number of studies
Effect Size with 95% CI
APL Antibodies
Low Bias 13 0.05 [0.03, 0.08]
Medium–High Bias 11 0.14 [0.07, 0.23]
0.018
AT–III Deficiency
Low Bias 8 0.01 [0.00, 0.04]
Medium–High Bias 12 0.01 [0.00, 0.03]
0.885
Factor II G20210A
Low Bias 25 0.03 [0.02, 0.04]
Medium–High Bias 9 0.04 [0.01, 0.08]
0.552
Factor V Leiden
Low Bias 32 0.07 [0.05, 0.09]
Medium–High Bias 14 0.05 [0.01, 0.11]
0.668
Hyperhomocysteinemia
Low Bias 19 0.29 [0.23, 0.35]
Medium–High Bias 10 0.17 [0.10, 0.25]
0.016
MTHFR C677T Heterozygous
Low Bias 18 0.45 [0.39, 0.50]
Medium–High Bias 6 0.40 [0.31, 0.49]
0.389
MTHFR C677T Homozygous
Low Bias 22 0.12 [0.09, 0.16]
Medium–High Bias 8 0.18 [0.13, 0.24]
0.065
PC Deficiency
Low Bias 8 0.01 [0.00, 0.02]
Medium–High Bias 14 0.02 [0.00, 0.06]
0.097
PS Deficiency
Low Bias 5 0.02 [0.00, 0.06]
Medium–High Bias 12 0.02 [0.00, 0.04]
0.973
0
.5
Prevalence