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Review article

Epidemiology of thromboembolic events in children and adolescents with antiphospholipid syndrome: A systematic review with meta-analysis



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ABSTRACT

Background and aim: This was a systematic review and meta-analysis of the prevalence of thromboembolic events in children and adolescents with antiphospholipid syndrome (APS).

Methods: We searched PubMed, EMBASE and Web of Science to select relevant articles published between 1 January 2000 and 27 February 2022. We used the random-effects meta-analysis to estimate pooled point prevalence rates of thromboembolic events in studies with a minimum sample size of 30.

Results: We included five studies reporting data of 336 children and adolescents with primary APS and secondary APS (SAPS). Pooled point prevalence rates of initial general thrombosis, arterial thrombosis, venous thrombosis and stroke in individuals with seropositive APS were 98.2% (95% confidence interval [CI] 87.5–100), 27.6% (95% CI 21.4–34.2), 51.1% (95% CI 38.2–63.9) and 13.4% 95% CI (6.3–22.7), respectively. Pooled point prevalence rates of initial arterial and venous thromboses in children and adolescents with SAPS were 45.7% (95% CI 21.1–71.6) and 29.2% (95% CI 14.8–46), respectively.

Conclusion: Arterio-venous thromboembolism is highly frequent in children and adolescents with SAPS. More studies using thrombotic and non-thrombotic APS classification criteria are warranted to better assess the frequency and predictors of thromboembolism in age- and ancestry-diverse pediatric populations affected by different types of APS.

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Epidemiología de los acontecimientos tromboembólicos en niños y adolescentes con síndrome antifosfolípido: una revisión sistemática con metaanálisis

RESUMEN

Antecedentes y objetivo: Se trata de una revisión sistemática y un metaanálisis de la prevalencia de acontecimientos tromboembólicos en niños y adolescentes con síndrome antifosfolípido (SAF).

Métodos: Se realizaron búsquedas en PubMed, EMBASE y Web of Science para seleccionar los artículos pertinentes publicados entre el 1 de enero de 2000 y el 27 de febrero de 2022. Se utilizó el metaanálisis de efectos aleatorios para estimar las tasas de prevalencia puntual agrupadas de eventos tromboembólicos en estudios con un tamaño muestral mínimo de 30.

Palabras clave:

Síndrome antifosfolípido

Eventos tromboembólicos

Epidemiología

Prevalencia

Niños

Adolescentes

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Resultados: Se incluyeron cinco estudios con datos de 336 niños y adolescentes con APS primario y APS secundario (SAPS). Las tasas de prevalencia puntual agrupadas de trombosis general inicial, trombosis arterial, trombosis venosa e ictus en individuos con SAF seropositivo fueron de 98,2% (intervalo de confianza [IC] 95%: 87,5–100), 27,6% (IC 95%: 21,4–34,2), 51,1% (IC 95%: 38,2–63,9) y 13,4% (IC 95%: 6,3–22,7), respectivamente. Las tasas de prevalencia puntual agrupadas de trombosis arteriales y venosas iniciales en niños y adolescentes con SAF secundario fueron de 45,7% (IC 95%: 21,1–71,6) y de 29,2% (IC 95%: 14,8–46), respectivamente.

Conclusión: La tromboembolia arteriovenosa es muy frecuente en niños y adolescentes con SAF. Se justifica la realización de más estudios que utilicen criterios de clasificación del SCA trombótico y no trombótico para evaluar mejor la frecuencia y los factores predictivos de la tromboembolia en poblaciones pediátricas de edad y ascendencia diversas afectadas por distintos tipos de SCA.

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Introduction

The antiphospholipid syndrome (APS) is an acquired autoimmune thrombophilia mainly defined by a combined presentation of seropositivity for at least one antiphospholipid antibody (aPL) and either thromboembolism or pregnancy morbidity or both. Diagnostic antiphospholipid antibodies are lupus anticoagulant (LA), anticardiolipin (aCL) IgG/IgM, and anti-beta-2-glycoprotein I (aβ2GPI) IgG/IgM antibodies. The pregnancy morbidity includes three or more miscarriages before the 10th week of gestation, one fetal demise or more at or beyond the 10th week of gestation and one delivery or more before the 34th week of gestation due to eclampsia, severe pre-eclampsia or placental insufficiency.^{1,2} APS can occur at any age,³ but unlike adults, pediatric subjects with APS have a high frequency of non-criteria hematological and neurological manifestations and a low rate of pregnancy morbidity.^{3–6}

Considering the phenotypic differences between juvenile-onset and adult onset APS, the lack of pediatric-specific APS classification criteria is a major limitation in assessing the epidemiology of APS in the pediatric population.^{5–7} A registry-based study conducted in the Italian Piedmont and Aosta Valley between 2011 and 2022 found an APS point prevalence rate of 2.5. per 100,000 population among children and adolescents.⁶ Secondary APS (SAPS) is the most frequent type of APS in children and adolescents, and systemic lupus erythematosus (SLE) the most common autoimmune disease associated with APS.^{6,7}

The fact that little is known about the epidemiology of APS in the pediatric population means that the frequency of thromboembolism in pediatric patients with APS is also poorly understood. Notably, the few available data on the frequency of thromboembolism in pediatric patients have not been meta-analyzed so far, leaving an uncertainty about the overall frequency of thromboembolism in the pediatric population with APS.⁶ The goal of this work was to assess the pooled prevalence of initial and recurrent thromboembolic events in the pediatric population with APS through a systematic review and meta-analysis.

Methods

Design

This article reports only data from the pediatric population included in the ETEAPS (Epidemiology of Thromboembolic Events in APS) systematic review and meta-analysis. The overarching goal of the ETEAPS systematic review and meta-analysis was to determine the cumulative incidence, point prevalence and predictors of thromboembolic events in individuals with APS of all age groups. The ETEAPS protocol is registered with PROSPERO (CRD42022312340). ETEAPS and this report were based on the

2020 PRISMA (Preferred Reporting Items for Systematic Review and Meta-analyses) guidelines.⁸

Literature search

We performed electronic searches for relevant articles published between 1 January 2000 and 27 February 2022 in the following databases: PubMed, EMBASE and Web of Science. The electronic search was supplemented by a manual screening of references of relevant articles retrieved by electronic searches. The search strategy was comprised of terms referring to the two concepts “antiphospholipid syndrome” and “thromboembolism”. The full search strategy is displayed in [Supplementary Table 1](#).

Study selection

We only included cross-sectional/prevalence studies reporting point prevalence rates of thromboembolic events among children and adolescents. Studies reporting thromboembolic events in adults with APS are considered in a separate manuscript. The classification for APS in studies herein included was based on Sapporo and revised Sapporo/Sydney criteria,^{1,2} except for one study in which authors established their own classification criteria based on knowledge about common signs of APS in children and adolescents. Those criteria were subdivided into an entry criterion (presence of aPLs), major and minor criteria. Major criteria included arterial or venous thrombosis, pulmonary hypertension, peripheral arterial gangrene, cutaneous necrosis, and isolated chronic thrombocytopenia. Isolated chronic thrombocytopenia was defined as an unexplained low platelet count with value less than 100,000/mm³ in the case of SLE/SLE-like disease-APS, or the combination of a platelet count lower than 100,000/mm³ with anti-platelet antibodies/bone marrow biopsy findings compatible with idiopathic thrombocytopenia in the case of PAPS. Minor criteria were: livedo reticularis, migraine, headache, chorea, Bell's palsy, psychosis and severe Raynaud's phenomenon. The classification for APS was therefore based on the combination of a positive aPL test result with at least one major criterion, or the combination of at least two minor criteria.⁹ We considered all the thromboembolic events recorded in records of included studies. The age range of included participants complies with the pediatric age range set by the National Institute of Child Health and Human Development in the United States: birth before the 37th week of gestation–21 years old.¹⁰

To increase the precision and reliability of pooled estimates, we excluded studies with fewer than 30 APS participants and salami-sliced articles (multiple articles based on the same dataset).^{11,12}

ME and JRN independently screened the titles and abstracts of studies retrieved electronically, and the full-texts of articles deemed potentially eligible were further assessed for final inclu-

Table 1
Risk of bias in included studies assessed.

| Cross-sectional studies | | | | | | | | | | |
|-------------------------|---------------------|---------|---------|--------|---------|--------|---------|---------|--------|----------------|
| Author | Year of publication | Item 1 | Item 2 | Item 3 | Item 4 | Item 5 | Item 6 | Item 7 | Item 8 | |
| Islabao | 2020 | Yes | No | Yes | Yes | No | No | Unclear | No | |
| Ma | 2018 | Yes | No | Yes | Yes | No | No | Unclear | No | |
| Von Scheven | 2002 | Yes | Yes | Yes | No | No | No | Yes | No | |
| Prevalence studies | | | | | | | | | | |
| Author | Year of publication | Item 1 | Item 2 | Item 3 | Item 4 | Item 5 | Item 6 | Item 7 | Item 8 | Item 9 |
| Avcin | 2008 | Yes | No | Yes | Yes | Yes | Unclear | Yes | Yes | Not applicable |
| Zamora-Ustaran | 2012 | Unclear | Unclear | Yes | Unclear | Yes | Yes | Yes | Yes | Not applicable |

The risk of bias assessment tool of the Joanna Briggs Institute used is downloadable at <https://jbi-global-wiki.refined.site/space/MANUAL>.

sion. They resolved their discrepancies regarding study selection through consensual discussions involving JJN.

Data extraction and management

Data were extracted by ME and JRN, and cross-checked by ME. We used a standard data abstraction form including variables related to characteristics of included studies, patients’ characteristics, as well as the types and prevalence rates of thromboembolic events.

The methodological quality of each included study was assessed using the Joanna Briggs Institute appraisal tool (Table 1).¹³

Statistical analysis

We synthesized data quantitatively and qualitatively. For the quantitative analysis, we pooled prevalence rates using the inverse variance method of the random-effects meta-analysis model on R (version 3.6.2, The R Foundation for statistical computing). We compared low estimates using the Freeman and Tukey double-arcsine transformation. The degree of between-study heterogeneity was assessed using the Cochran’s $Q \chi^2$ test statistics. Low, moderate, substantial and considerable heterogeneity correspond to the following I^2 values: below 30%, 30–49%, 50–70%, and over 70%, respectively.¹⁴ We could not assess sources of between-study heterogeneity because the number of included studies did not reach 10, an ideal minimum number of required studies for this type of analysis.¹⁵ The publication bias analysis was also not possible given the high heterogeneity of included studies, with all I^2 values being above 50%.¹⁶ When the prevalence of a thromboembolic event could not be meta-analyzed because it was reported in one study or in two studies with many methodological differences,¹⁷ data were synthesized narratively.

Results

Study selection and characteristics of included studies

Of 15,462 articles identified for the whole ETEAPS systematic review and meta-analysis, we finally included five studies that reported thromboembolic events in 336 individuals of the pediatric population with APS between 1996 and 2016 (Fig. 1). Among those studies, one came from the United States, one from China, one from Mexico, one from Brazil, and the last one was the Ped-APS study. The Ped-APS study is the largest hospital-based registry study. Through a prospective data collection, the Ped-APS study assesses APS in the pediatric population since 2004.¹⁸ The proportion of female individuals and the mean/median age of patients at diagnosis of APS ranged from 44% to 88%, and from 10.7 to 14 years, respectively. SAPS was the commonest type of APS and

was reported in 49.6–100% of patients. SLE was the predominant autoimmune disease and was reported in 24.1–100% of individuals with SAPS. No case of neonatal or ‘non-criteria’ APS¹⁹ was recorded. Further details on characteristics of included studies are available in Supplementary Tables S2 and S3.

Point prevalence of initial thromboembolic events

General thrombosis

The point prevalence of general thrombosis was reported in four studies.^{18,20–22} The pooled point prevalence of general thrombosis among individuals with APS was 98.2% (95% CI 87.5–100) (Fig. 2). The point prevalence of general thrombosis among individuals with primary APS (PAPS) was 100% in the Ped-APS study,¹⁸ and 86% in the cross-sectional study from China that involved 58 individuals with APS.²¹ The point prevalence of general thrombosis among individuals with SAPS was 100% in the Ped-APS study,¹⁸ and 45% in the study from China.²¹ The point prevalence of general thrombosis among individuals with SLE-APS was 70% in the study from China.²¹

Arterial thrombosis

The point prevalence of arterial thrombosis was reported in four studies.^{18,20–22} Pooled point prevalence rates of arterial thrombosis among individuals with APS in general and those with SAPS specifically were 27.6% (95% CI 21.4–34.2; Fig. 3) and 29.2% (95% CI 14.8–46; Supplementary Fig. S1), respectively. The point prevalence of arterial thrombosis among individuals with PAPS was 45% in the Ped-APS study,¹⁸ and 7% in the study from China.²¹ The point prevalence of arterial thrombosis in individuals with SLE-APS was 52.2% in the study from Brazil which was a nationwide study on APS in childhood-onset SLE (cSLE) involving 1519 cases of cSLE, among which 67 had APS.²²

Stratifying by the site of arteries involved, the point prevalence of peripheral arterial thrombosis was 2.5% in the Ped-APS study.¹⁸ The point prevalence of retinal artery thrombosis and renal artery thrombosis in the Ped-APS study was 1.7% for each. The point prevalence of myocardial infarction and mesenteric artery thrombosis in the Ped-APS study was 0.8% for each.¹⁸ The point prevalence of mesenteric artery thrombosis was 3.1% in the cross-sectional study from Mexico which included 32 individuals with APS.²⁰ We did not find data on site-specific arterial thromboembolism for PAPS and for SAPS.^{18,20–22}

Stroke

The point prevalence of stroke (ischemic stroke and cerebral vein sinus thrombosis),²³ was reported in four studies.^{9,18,20,22} The pooled point prevalence of stroke among individuals with APS was 13.4% (95% CI 6.3–22.7); see Fig. 4. The point prevalence of stroke among individuals with PAPS was 38.3% in the Ped-APS study.¹⁸ The point prevalence of stroke among individuals with SAPS was 11.7% in the Ped-APS study,¹⁸ and 44.8% in the study from Brazil.²¹

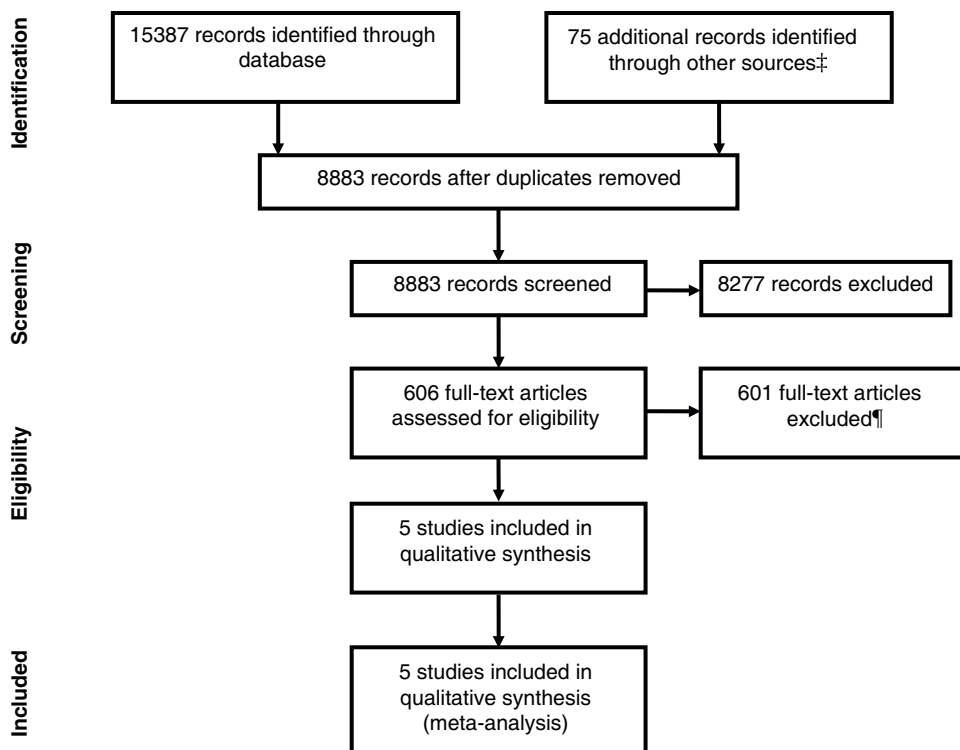


Fig. 1. PRISMA flow chart of the selection of studies involving individuals of the pediatric age group in the ETEAPS systematic review and meta-analysis. ‡Other sources included websites, organizations and citation searching. ¶Reasons for exclusion of articles were: wrong outcome ($n=237$), antiphospholipid syndrome (APS) in adults ($n=138$), lack of consensus APS classification criteria ($n=98$), fewer than 30 participants with APS ($n=59$), data duplication and salami-sliced articles ($n=42$), impossibility to disaggregate data on APS from data related to other diseases, unclear type of APS ($n=7$), review articles ($n=4$), case reports ($n=2$), image type of article ($n=1$), unclear age group ($n=1$), participant selection based on the presence of a specific type of thromboembolic event.

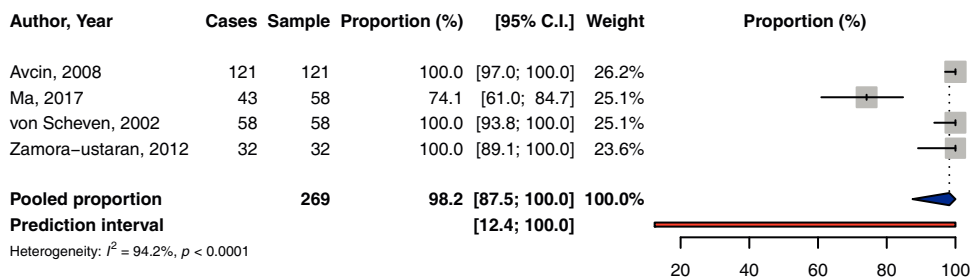


Fig. 2. Forest plot of the prevalence of general thrombosis in subjects with primary antiphospholipid syndrome and subjects with secondary antiphospholipid syndrome.

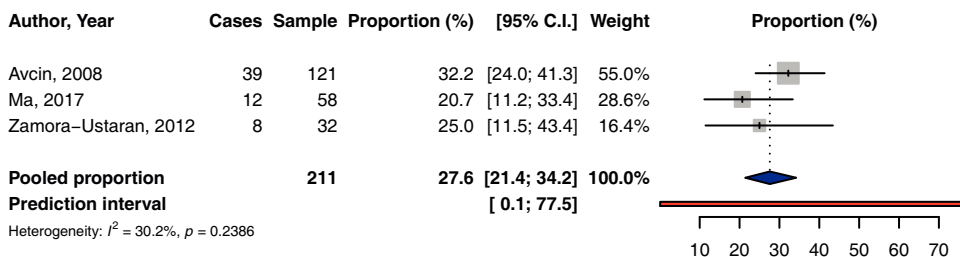


Fig. 3. Forest plot of the prevalence of arterial thrombosis in subjects with primary antiphospholipid syndrome and secondary antiphospholipid syndrome.

Accordingly, the point prevalence of stroke among individuals with SLE-APS was 44.8% in the study from Brazil.²¹

Venous thrombosis

The point prevalence of venous thrombosis was reported in five studies.^{9,18,20–22} Pooled point prevalence rates of venous thrombosis among individuals with APS in general and those with SAPS specifically were respectively 51.1% (95% CI 38.2–63.9; Fig. 5) and

45.7% (95% CI 21.1–71.6; Supplementary Fig. S2). The point prevalence of venous thrombosis among individuals with PAPS was 51.7% in the Ped-APS study,¹⁸ and 71% in the study from China.²¹ Point prevalence rates of venous thrombosis among individuals with SLE-APS were 59.7% and 47.5% in studies from China²¹ and Brazil,²² respectively.

Stratifying by the site of venous thrombosis, the point prevalence of deep vein thrombosis was 12.1% in the study from the

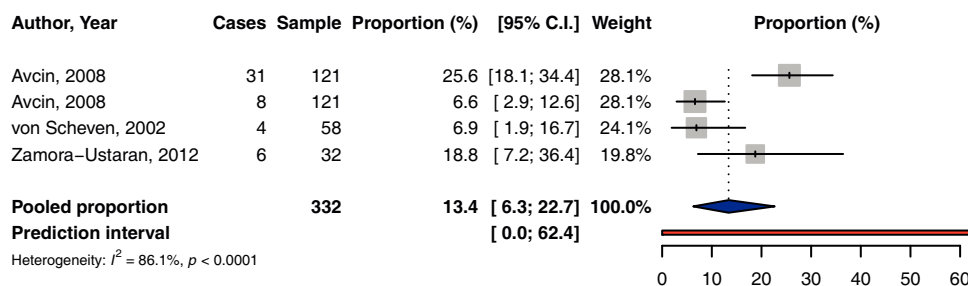


Fig. 4. Forest plot of the prevalence of stroke in subjects with primary antiphospholipid syndrome and secondary antiphospholipid syndrome.

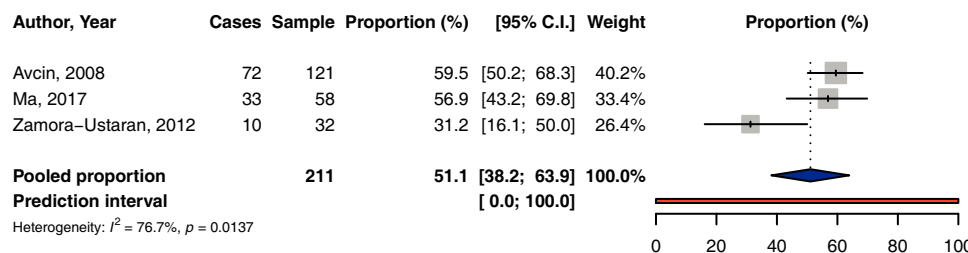


Fig. 5. Forest plot of the prevalence of venous thrombosis in subjects with primary antiphospholipid syndrome and secondary antiphospholipid syndrome.

United States that included 58 individuals with APS classified using authors’ criteria as mentioned above,⁹ and 31.2% in the study from Mexico.²⁰ The point prevalence of portal vein thrombosis was 3.3% in the Ped-APS study. The point prevalence of superficial vein thrombosis and renal vein thrombosis in the Ped-APS study was 1.6% for each.¹⁸ The point prevalence of inferior vena cava thrombosis, jugular vein thrombosis and retinal vein thrombosis in the Ped-APS study was 0.8% for each.¹⁸ We did not find data on site-specific venous thromboembolism for PAPS and SAPS.^{9,21,22}

Pulmonary thromboembolism

The point prevalence of pulmonary embolism and pulmonary artery thrombosis was reported in three studies.^{9,20,21} The point prevalence of pulmonary embolism among individuals with APS was 3.4% in the study from the United States,⁹ and 24.1% in the study from China.²¹ The point prevalence of pulmonary arterial thrombosis was 3.1% in the study from Mexico.²⁰ We did not find data on pulmonary embolism and pulmonary artery thrombosis for PAPS and SAPS.^{9,20,21}

Mixed arterial–venous thrombosis

The point prevalence of mixed arterial–venous thrombosis was reported in two studies.^{18,21} The point prevalence of mixed arterial–venous thrombosis among individuals with APS was 2.5% in the Ped-APS study.¹⁸ In the study from China,²¹ point prevalence rates of mixed arterial–venous thrombosis among individuals with APS, PAPS, SAPS and SLE-APS were and 20.7%, 7%, 2.2% and 2.5%, respectively.²¹

Small vessel thrombosis

The point prevalence of small vessel thrombosis was reported in four studies.^{18,20–22} Point prevalence rates of small-vessel thrombosis among individuals with APS in the Ped-APS study¹⁸ and the study from Mexico²¹ were 5.8% and 43.7%, respectively. Point prevalence rates of digital ischemia among individuals with APS in the Ped-APS study and the study from Mexico were 3.3% and 43.8%, respectively. Point prevalence rates of splenic infarction and renal thrombotic microangiopathy among individuals with APS in the Ped-APS study were 2.5%, and 0.8%, respectively.¹⁸ Point prevalence rates of small vessel thrombosis and catastrophic APS among individuals with SLE-APS in the study from Brazil were 13.4% and

0, respectively.²² We did not find reports on the point prevalence of small vessel thrombosis among individuals with PAPS.

Point prevalence of recurrent events

General thrombosis

The point prevalence of recurrent general thrombosis was reported in two studies.^{18,22} The point prevalence of recurrent general thrombosis among individuals with APS, PAPS and SAPS in the Ped-APS study were 19%, 23.3%, and 15%, respectively.¹⁸ The point prevalence of recurrent general thrombosis among individuals with SLE-APS was 26.9% in the study from Brazil.²²

Different types of thromboembolic events

Prevalence rates of the different types of recurrent thromboembolic events were not available in articles of included studies.

Heterogeneity

We detected a high heterogeneity in the meta-analysis of all prevalence rates, except for that of arterial thrombosis in the whole APS population.

Discussion

In this first meta-analysis of the prevalence of thromboembolism in children and adolescents with APS, we found the following pooled point prevalence rates for initial general thrombosis, venous thrombosis, arterial thrombosis and stroke: 98.2% (95% CI 87.5–100), 51.1% (95% CI 38.2–63.9), 27.6% (95% CI 21.4–34.2) and 13.4% (95% CI 6.3–22.7), respectively. Pooled point prevalence rates of initial arterial thrombosis and venous thrombosis in children and adolescents with SAPS were respectively 45.7% (95% CI 21.1–71.6) and 29.2% (95% CI 14.8–46). Our findings confirm the major importance of thromboembolism in children and adolescents with APS.^{3–7} They also corroborate data highlighting a higher prevalence of venous than arterial thrombosis in adults with APS and the general young population.^{5,6,23} However, the pooled point prevalence rate of arterial thrombosis in individuals with SLE-SAPS was higher than that of venous thrombosis. This is consistent with data from the prospective Childhood arthritis and Rheumatology

Research Alliance (CARRA) registry which showed a 2.5% point prevalence rate of arterial thrombosis and a 3.6% point prevalence rate of venous thrombosis among 979 individuals with cSLE, along with an independent association between aPL positivity and general thrombosis (odds ratio 2.95, 95% CI: (1.38, 6.28)).²⁴

The reasons why venous thromboembolism is the most frequent type of thromboembolism in individuals with APS of all age groups remain incompletely elucidated. Functional differences between arteries and veins which mainly account for these differences in the general population potentially contribute in individuals with APS as well. Those functional differences include, but are not limited to: a higher propensity for blood coagulation in veins than arteries due to reduced blood flow, a lower shear stress in arteries than veins, and a stronger resistance of venous thrombi than arterial thrombi.²³ Differences in thrombi structure and composition between arteries and veins as well as non-thrombotic manifestations of APS may be additional underlying factors of this prevalence gradient in individuals with APS. For example, thrombocytopenia is an APS manifestation that may limit the capacity of individuals with APS to generate arterial thrombi since arterial thrombi are essentially made up of platelets.^{3,25} Further studies are needed to deeply assess the factors driving a prevalence gradient between venous thrombosis and arterial thrombosis in individuals with APS in all age groups.

Another striking observation is the high prevalence of stroke, which suggests that more than one in 10 children and adolescents with APS have stroke. Stroke is a public health issue in children and adolescents with APS, similarly as in adults with APS and the general population.^{26,27} Besides ischemic stroke which is the commonest stroke presentation in young individuals of the general population²⁶ and in adults with APS,²⁷ cerebral vein sinus thrombosis was also recorded in 8 of the 121 individuals included in the Ped-APS study until 1 December 2007.¹⁸ This frequency is higher than 7 per 1000 persons which is the 1999–2001 point prevalence of cerebral vein sinus thrombosis in the Euro-phospholipid study, a study that mainly involved adult participants.²⁸ Future studies will need to thoroughly assess distinct and overlapping epidemiological characteristics (aPL and non-aPL risk factors, manifestations, effective management strategies and recurrence rates) of cerebral vein sinus thrombosis across age groups in individuals with APS.^{10,18,26,27}

Besides the urge for further assessments on cerebral vein sinus thrombosis, findings from this systematic review and meta-analysis have many implications for future research on APS in the pediatric population. The current limited amount of data calls for additional high-quality studies not only to estimate the frequency of thromboembolic events in the pediatric population with APS, but also to evaluate suitable prediction models tailored to this age group. Greater efforts need to be made to recruit neonates and infants in future studies.¹⁸ Methods of data collection and reporting also need to be harmonized and standardized for proper interpretation. Interestingly, a set of APS classification criteria that gives an equally important weight to non-thrombotic manifestations of APS has recently been published, and will also contribute to polish future prevalence and prediction studies of thromboembolism in the pediatric APS population.²⁹

This research has noticeable limitations. For instance, the common selection bias of meta-analyses of observational studies³⁰ is likely, especially since the minimum study sample size for inclusion was set at 30 to increase the precision of pooled rates. It may be considered that this selection criterion impeded the inclusion of studies from Africa and therefore hinders the generalization of our results at the global level. However, a previous systematic review on APS in Africa also did not identify local studies.³¹

The non-representativeness of Africa is more likely due to the underdiagnosis and underreporting of APS in Africa. This situation needs to be reversed through combined efforts from the local and global APS community.³² Prevalence rates of thromboembolic events may also have been overestimated as a result of the selection bias, given that the classification for APS was mainly based on thrombotic criteria in four of the five included studies.^{9,18,20–22} As mentioned earlier, the use^{18,10,22} of new APS classification criteria²⁹ and future pediatric-specific APS classification criteria will enable the determination of more reliable prevalence estimates in subsequent meta-analyses. The precision of estimates that were not meta-analysed is also not well known, as their 95% CIs were missing in included articles.^{9,18,20–22} Moreover, the retrospective timeline of data collection in all included studies apart from the Ped-APS, is a potential source of recall bias in this research.³⁰ Finally, it is worth reminding that we did not perform heterogeneity and publication analyses.

Overall, ETEAPS provides a snapshot of the epidemiological frequency and body distribution of thromboembolism in the pediatric population with APS based on Sapporo and Sydney classification criteria.

Conclusion

The epidemiology of thromboembolism in the pediatric population with APS is poorly characterized. Based on available data, the vast majority of patients of the pediatric age group with APS present with thromboembolic events mainly in veins, arteries and intracranial vessels. Additional studies using thrombotic and non-thrombotic APS classification criteria are needed to better assess the frequency and predictors of thromboembolism in age- and ancestry-diverse pediatric populations affected by different types of APS.

Authors' contributions

Conception and design: ME, JJN. Search strategy: ME, JJN. Study selection: ME, JRN. Data extraction: ME, JRN. Data synthesis and interpretation: ME, JJN. Manuscript drafting: ME. Manuscript revision: all authors. Approval of the final manuscript: All authors. Supervision: JJN.

Availability of data and materials

The datasets analyzed during the current study are available from the corresponding author upon reasonable request.

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Conflicts of interests

The authors declare no conflicts of interests.

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None.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at [doi:10.1016/j.reuma.2023.10.001](https://doi.org/10.1016/j.reuma.2023.10.001).

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