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The incidence and prevalence of antiphospholipid syndrome (APS) in the United States (2016–2019)

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The incidence and prevalence of antiphospholipid syndrome (APS) in the United States (2016–2019)

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ABSTRACT

Objective: Few epidemiological studies are reported in the published literature on the incidence or prevalence of antiphospholipid syndrome (APS), and available results are heterogeneous. This study aimed to estimate the incidence and prevalence of APS in the United States (US), overall and by APS subtype.

Design: A retrospective analysis of APS disease incidence and a cross-sectional analysis of disease prevalence.

Setting: Merative MarketScan Commercial Claims and Encounters Database, and the Medicare Supplemental and Coordination of Benefits Database.

Participants: All individuals with claims for at least two aPL tests undertaken at least 12 weeks apart, and a diagnosis claim for APS as a primary or secondary diagnosis on or after the second antibody test, during the period January 1, 2016, to December 31, 2019.

Main outcome measures: Annual incidence and prevalence of APS and APS subtypes.

Results: In total, 1708 cases of APS were identified during the study period (2016–2019), of which 83% were women. The overall annual standardized incidence rate of APS per 100,000 person-years increased slightly over the study period, from 2.31 in 2016 to 2.71 in 2019. In 2019, the estimated annual prevalence of APS per 100,000 persons was 10.42 per 100,000 persons (95% confidence interval: 9.96–10.90). Based on this and US census data, we have estimated that 34,000 persons in the US were affected by APS in 2019.

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Conclusions: These data add to the estimates of prevalence and incidence of APS in the literature, all of which have different strengths and limitations of the different data sources and case ascertainment methods.

Keywords: Antibodies, antiphospholipid; antiphospholipid syndrome; autoimmune diseases; epidemiology

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Strengths and limitations of this study

- The Merative MarketScan CCAE and MDCR used in this study is a large database, ensuring sufficient patients were identified with this rare disease to estimate prevalence and incidence in the population
- The identification of the APS claims were realized by using a unique APS-specific ICD code (D68.61) during the study period, whereas previous studies use a non-specific code
- The few published epidemiological studies which have assessed the incidence and prevalence of APS have either been carried out in small populations or used an unclear or biased identification of the APS cases. This study was more exhaustive in the ascertainment of APS cases by using the Sydney definition criteria
- As the MarketScan database lacks some information needed for case ascertainment, especially for the laboratory test status and the clinical manifestation liked to the APS claim, we were not able to use the full Sydney criteria. Instead, a case definition proxy was applied
- The prevalence and incidence estimated in this study are close to those reported in other studies. However, given our estimate of incidence is calculated using claims from only a subset of the total US population, which is not a representative sample, it cannot be extrapolated to the full US population or populations in other countries

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INTRODUCTION

Antiphospholipid syndrome (APS) is an autoimmune disease caused by anti-phospholipid antibodies (aPLs) that results in a wide spectrum of clinical manifestations, involving the hematological, obstetrical, neurological, cardiovascular, renal, and orthopedic systems, among others.(1) aPLs include lupus anticoagulant (LAC), anti-cardiolipin (aCL), and anti-β2-glycoprotein I (anti-β2GPI) immunoglobulin (Ig) G and IgM antibodies.

According to the Sydney 2006 International Classification Criteria Consensus, clinical diagnosis of APS requires the presence of clinical symptoms associated with APS (vascular thrombosis or pregnancy morbidity) and two positive test results for aPL, 12 weeks apart.(2) However, there is no standardized use of confirmatory aPL tests or titer cut-off points in epidemiological studies. Low-titer, transient aPL that is not associated with disease can be detected in 5–10% of asymptomatic persons.(3) It is this background presence of asymptomatic aPL in the general population which complicates attempts to assess the incidence and prevalence of APS. Furthermore, older epidemiology studies were undertaken before LAC, aCL, and anti-β2GPI antibodies were recognized as aPLs in the 2006 update of the classification criteria.(2) As a result, few studies have been carried out to assess the epidemiology of APS, while the few data that have been published are inconsistent.(4)

Since completion of this study, a manuscript supported by the American College of Rheumatology (ACR) Board of Directors and the European Alliance of Associations for Rheumatology (EULAR) has been published, in which a new classification criterion of APS has been proposed.(5)

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In the United States (US), Duarte-Garcia et al. (2019) estimated the overall annual incidence and prevalence rates of APS for patients aged ≥18 years at 2.1 per 100,000 person-years (PY) and 50 per 100,000 persons, respectively.(6) Studies worldwide have estimated incidence and prevalence ranging from 7.5 per 100,000 PY in Korea (7) to 40 per 100,000 PY in Spain,(8) and from 16.8 per 100,000 people in the Piedmont and Aosta Valley regions (9) to 61.9 per 100,000 people in Korea,(7) respectively. Previous studies have also shown that the peak incidence of APS differs for men and women. In the UK, Rodziewicz et al. (2019) used data from the UK Clinical Practice Research Datalink to estimate the peak APS incidence of 7.5 per 100,000 PY for women occurring between the ages of 35 and 39 years, while the peak APS incidence for men was 2.2 per 100,000 PY and occurred later in life, between the ages of 55 and 59 years.(10) Prevalence of APS in the UK was also higher in women compared with men: 50 and 9.8 per 100,000 persons, respectively.(10)

The Merative MarketScan Commercial Claims and Encounters (CCAE) and Medicare Supplemental and Coordination of Benefits (MDCR) databases represent insurance claims from US employees and their dependents, from all US census regions, covering approximately 50 million persons in the US annually. Using this large, real-world database, we aimed to retrospectively and cross-sectionally estimate the incidence and prevalence of APS in the US population during 2016 and 2019. We have used the Sydney 2006 classification criterion, because the variables required to apply the criterion or create proxy variables to define the criterion are part of the MarketScan database. This study was already complete prior to the 2023 publication of the new APS classification by Barbhaiya et al.(5)

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METHODS

Study design and data source

This was a retrospective, cross-sectional analysis of APS incidence and prevalence, using the CCAE and MDCR databases during the study period of January 1, 2015, to December 31, 2019. The database is Health Insurance Portability and Accountability Act compliant, and all patient data were de-identified before delivery to the study team. No ethics committee approval was required.

Patient involvement

Patients and their families were not involved in the design, implementation, or setting the research question or the outcome measures.

Case definition and identification

APS cases were defined as claims for at least two aPL tests undertaken at least 12 weeks apart, and a diagnosis claim for APS as a primary or secondary diagnosis on or after the second antibody test, identified from International Classification of Diseases, tenth revision (ICD-10) codes. In October 2015, APS was given a unique ICD code (D68.61) with the introduction of the Clinical Modification (CM). Prior to ICD-10-CM, APS was coded together with multiple other hypercoagulation defects into 289.81 (Primary Hypercoagulable State). Thus, cases of APS can only be ascertained from October 2015 onwards.

The Sydney International Classification Criteria Consensus case definition requires laboratory criteria (at least 12 weeks between the initial and repeated positive aPL test) and at least one of the clinical criteria (vascular thrombosis or pregnancy morbidity). An aPL test is confirmed

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positive if one or more of the following aPLs are detected on two or more occasions at least 12 weeks apart: (i) LAC present in plasma detected according to the International Society on Thrombosis and Haemostasis guidelines (2, 11, 12); (ii) aCL of IgG and/or IgM isotype in serum or plasma at medium or high titer (>40 IgG or IgM phospholipid units, or >99th percentile) measured by a standardized ELISA; or (iii) anti-β2GPI of IgG and/or IgM isotype in serum or plasma (>99th percentile) measured by a standardized ELISA.(2)

As aPL test results are not available from the CCAE and MDCR databases, a proxy was used for a positive result. If a second, repeated aPL test was carried out 12 weeks later than the first test, it was assumed at least one of the tests was positive. aPL test codes were 86148, 86146, and 86147, corresponding to aPL, anti-β2GPI, and aCL, respectively. At least one clinical criterion (vascular thrombosis or pregnancy morbidity) was added to the case definition as a sensitivity analysis. The index date was defined as the date of the first APS diagnosis which could be before, on or after the second aPL test.

Study populations and APS subtypes

The study population comprised all patients identified as having APS according to the criteria described above. Patients were also required to have at least 12 months of continued medical and pharmacy benefits memberships prior to index date (not required for children aged <1 year) from January 1, 2016, to December 31, 2019 and, for incident patients, no diagnosis record of APS (ICD-9 or ICD-10) at any time prior to the index date. APS was classified as primary APS in the absence of systemic autoimmune disease (per the Sydney 2006 International Classification Criteria Consensus (2)), however primary and secondary APS were not analyzed separately. APS subtypes were classified into five mutually exclusive categories as thrombotic

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APS only, obstetric APS only (women aged ≥14 years only), mixed APS (both thrombotic APS and obstetric APS events; women aged ≥14 years only), other APS manifestations not included in the Sydney criteria (Supplementary Tables 1 and 2), and APS type unknown. In addition, catastrophic APS (CAPS) was analyzed as a subtype of thrombotic and mixed APS, defined as thrombosis in three or more organs developing in less than a week. This definition was as close as possible to the 10th and 14th International Congress on Antiphospholipid Antibodies definitions,(13-15) without the required information on aPL status and biopsy, which was not available in this database.

Study outcomes and statistical analyses

Distribution of APS subtypes by age and sex during 2016–2019, and by specialty involved in the first APS diagnosis for the period 2018–2019, were assessed. Overall distribution of CAPS was calculated and presented as one result for the aggregated incident cohort. The annual incidence and prevalence of APS and APS subtypes were calculated by age and sex in each calendar year from 2016 to 2019. Incidence of APS was age- and sex-standardized indirectly to the US 2020 population by using age- and sex-specific population census data as weights and applying them to the age- and sex-specific incidence rates.(16)

Incidence, the number of new APS cases during a specific time period,(17) was reported as a rate per 100,000 PY. Person-time was defined as the sum of each patient's duration of follow-up from January 1 to December 31 of each year, to the end of the patient record, to the end of the first insurance claim if there was a gap greater than 60 days, or to the APS diagnosis – whichever came first. Incidence was calculated as the number of incident cases divided by the person-time of observation per year. The annual incidence rate was calculated as the number

of incident cases in a year divided by the person-time corresponding to that year. Prevalence, the proportion of the population with APS in a given time period,(17) was expressed as prevalence per 100,000 persons. The denominator was all patients in the CCAE and MDCR database on July 1 of each year. The annual prevalence rate was calculated as prevalent cases in a year divided by the overall population corresponding to that year. The 95% confidence interval (CI) of the prevalence and incidence rates were estimated by the Poisson distribution.(18)

Sensitivity analysis

To assess the robustness of the case definition in this study, a number of alternative case definitions were considered for the incidence and prevalence calculation. Patients could have one of the following: (A) at least one APS diagnosis (primary or secondary) with no requirement of an aPL test; (B) at least one APS diagnosis (primary or secondary) with at least one aPL test; (C) at least one APS diagnosis with two aPL tests undertaken 12–26 weeks apart and 2–13 weeks before an APS diagnosis code; (D) for a patient with a membership gap during follow-up, the follow-up included all time at risk including during and after the gap (i.e., they were treated as if there was no gap); (E) at least one diagnosis record of LAC syndrome (ICD-10 code 68.62) with two aPL tests at least 12 weeks apart and ≥1 diagnostic record of thrombotic or obstetric events according to the Sydney criteria; or (F) at least one of the clinical criteria (vascular thrombosis or pregnancy morbidity per the definitions in Supplementary Table 1) with at least two aPL tests undertaken at least 12 weeks apart, and a diagnosis claim for APS as a primary or secondary diagnosis on or after the second antibody test. All statistical analyses were performed using SAS Version 9.4.

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RESULTS

Baseline characteristics

A total of 1708 cases of APS that met our case definition during 2016–2019 were identified, with the majority being women (n=1411, 83%; Table 1). For women, the number of incident APS cases was highest among the 25–44 years age category (n=706, 50.0%), and 376 (26.6%) patients had obstetric APS. For men, the number of incident APS cases was highest among patients aged 45–64 years (n=201, 67.7%). The overall number of pediatric APS cases was small (n=23), with most cases identified within the 15–17 years age category (n=16) for both female and male patients. Thrombotic APS was the most frequent subtype identified (n=728, 42.6%), followed by APS of unknown subtype (n=404, 23.7%), obstetric APS (n=376, 22.0%), other APS (n=138, 8.1%), and mixed APS (n=62, 3.6%). Seventy-five cases of CAPS were identified, representing 4.4% of all APS cases. The acute care hospital was the most frequently visited healthcare specialty site for diagnosis (n=227, 26.9%), followed by laboratory (n=161, 19.1%), rheumatology (n=89, 10.5%), internal medicine (n=87, 10.3%), obstetrics and gynecology (n=72, 8.5%) and hematology (n=70, 8.3%). Other categories for APS diagnoses included oncology, family practice, pathology, neurology, multispecialty, and medical doctors.

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Table 1. Incident APS cases by baseline gender and age distribution, and APS subtype.

	2016		2017		2018		2019		Total	
	Male	Female	Male	Female	Male	Female	Male	Female	Male	Female
	N=458		N=406		N=459		N=385		N=1708	
n (%)	77 (16.8)	381 (83.2)	76 (18.7)	330 (81.2)	82 (17.9)	377 (82.1)	62 (16.1)	323 (83.9)	297 (17.4)	1411 (82.6)
Age, years, n (%)										
Adults										
18–24	4 (5.2)	17 (4.5)	1 (1.3)	14 (4.2)	2 (2.4)	15 (4.0)	3 (4.8)	21 (6.5)	10 (3.4)	67 (4.7)
25–44	9 (11.6)	185 (48.6)	16 (21.1)	164 (49.7)	11 (13.4)	191 (50.7)	13 (21.0)	166 (51.4)	49 (16.5)	706 (50.0)
45–64	53 (68.8)	161 (42.3)	53 (69.7)	143 (43.3)	56 (68.3)	155 (41.1)	39 (62.9)	128 (39.5)	201 (67.7)	580 (41.1)
65+	8 (10.3)	15 (3.9)	5 (6.6)	6 (1.8)	11 (13.4)	12 (3.2)	4 (6.5)	11 (3.4)	28 (9.4)	44 (3.1)
Subtotal	74 (96.1)	378 (99.2)	75 (96.7)	327 (99.1)	80 (97.6)	373 (98.9)	59 (95.2)	312 (96.8)	288 (97.0)	1397 (99.0)
Pediatric										
0–4	0	1 (0.3)	0	0	1 (1.2)	0	0	0	1 (0.3)	1 (0.1)
5–9	1 (1.3)	0	0	0	0	0	0	0	1 (0.3)	0
10–14	1 (1.3)	1 (0.3)	0	2 (0.6)	0	0	0	0	1 (0.3)	3 (0.2)
15–17	1 (1.3)	1 (0.3)	1 (1.3)	1 (0.3)	1 (1.2)	4 (1.1)	3 (4.8)	4 (1.2)	6 (2.0)	10 (0.7)
Subtotal	3 (3.9)	3 (0.8)	1 (1.3)	3 (0.9)	2 (2.4)	4 (1.1)	3 (4.8)	4 (1.2)	9 (3.0)	14 (1.0)
Catastrophic APS, n (%)	–	–	–	–	–	–	–	–	27 (9.1)	48 (3.4)
APS subtype, n (%)										
Thrombotic	65 (84.4)	113 (29.6)	68 (89.5)	112 (33.9)	65 (79.3)	131 (34.7)	53 (85.5)	121 (37.5)	251 (84.5)	477 (33.8)
Obstetric	0	95 (24.9)	0	82 (24.8)	0	109 (28.9)	0	90 (27.9)	0	376 (26.6)
Mixed	0	17 (4.5)	0	16 (4.8)	0	16 (4.2)	0	13 (4.0)	0	62 (4.4)
Other	3 (3.9)	34 (8.9)	2 (2.6)	25 (7.6)	5 (6)	34 (9)	6 (9.7)	29 (9.0)	16 (5.4)	122 (8.6)
Unknown	9 (11.7)	122 (32)	6 (7.9)	95 (28.8)	12 (14.6)	87 (23)	3 (4.8)	70 (21.7)	30 (10.1)	374 (26.5)

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Incidence of APS

The overall annual incidence rate of APS per 100,000 PY (95% confidence interval [CI]) standardized to the US 2020 population census increased slightly over the study period, from 2.31 (2.11–2.53) in 2016 to 2.84 (2.59–3.11) and 2.71 (2.45–2.99) in 2018 and 2019, respectively (Figure 1). Over the whole study period, the APS incidence rates were higher in women, potentially due to certain subtypes being applicable to women only. In 2019, the annual incidence rate (standardized to the US 2020 population census) was 4.45 (3.99–4.96) per 100,000 PY for women, and 0.91 (0.71–1.17) per 100,000 PY for men. The incidence rate of APS in women was always highest in patients aged 30–39 years old, ranging from 10.09 per 100,000 PY in 2016 to 11.80 and 11.22 per 100,000 PY in 2018 and 2019 (Supplementary Table 3). However, in men, the age categories with the highest incidence rates varied each year (Supplementary Table 3).

Prevalence of APS

The estimated annual prevalence of APS per 100,000 persons (95% CI) was 10.42 per 100,000 persons (9.96–10.90) in 2019 (Figure 1). In 2019, APS prevalence among women was four times higher than in men: 16.59 (15.78–17.45) and 4.00 (3.60–4.44) per 100,000 persons, respectively. Based on this and US census data, we have estimated that slightly more than 34,000 persons in the US were affected by APS in 2019. Among women, the prevalence rate of APS was highest in the 40–49 years age group, ranging from 14.71 in 2016 to 30.61 per 100,000 persons in 2019. Among men, APS prevalence was highest in patients aged 60–69 years old between 2016 (6.27 per 100,000 persons) and 2018(10.85 per 100,000 persons), and in patients aged 80+ years in 2019 (13.57 per 100,000 persons) (Supplementary Table 4).

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Incidence rates of APS subtypes

Incidence rates of APS subtype were standardized to the US 2020 population census. In 2019, the overall annual incidence (95% CI) of thrombotic APS was 1.28 (1.10–1.49) per 100,000 PY, which was the highest incidence over the study period. The 2019 annual incidence rate of thrombotic APS patients was higher in women (1.76 per 100,000 PY) than in men (0.79 per 100,000 PY) (Supplementary Figure 1a). In 2019, among women only, the incidence rate of obstetric APS was 1.24 (1.01–1.53) per 100,000 PY (Supplementary Figure 1b), and the incidence rate of mixed APS was 0.17 (0.10–0.30) per 100,000 PY. The other APS cases represent 8.1% of the total APS population, with an overall annual incidence rate in 2019 of 0.23 (0.16–0.32) per 100,000 PY. The unknown APS cases represent almost a quarter (23.65%) of the total APS population, with an overall incidence rate in 2019 of 0.48 (0.38–0.60) per 100,000 PY (Supplementary Table 5).

Prevalence rates of APS subtypes

The overall annual prevalence (95% CI) of thrombotic APS was 5.38 (5.05–5.73) per 100,000 persons in 2019, and the annual prevalence rate of thrombotic APS was higher in women compared to men over the whole study period. The annual prevalence of obstetric APS subtype among women only was 3.70 (3.33–4.12) per 100,000 persons in 2019, and the highest prevalence rate of obstetric APS was in those aged 30–39 years old (12.98 [11.24–15.00] per 100,000 persons). The annual prevalence of mixed APS was 1.19 (0.99–1.44) per 100,000 persons in 2019, among women only. The overall annual prevalence rates of other APS and unknown APS in 2019 were 0.90 (0.77–1.05) per 100,000 persons and 2.19 (1.99–2.42) per 100,000 persons, respectively (Supplementary Table 5).

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Sensitivity analysis

Outcomes from a sensitivity analysis for different predefined scenarios for the last year of the study period, 2019, are shown in Supplementary Figure 2. The outcomes obtained from the rest of the study years were similar to those for 2019, and the subtypes of APS showed the same behaviors for the sensitivity analysis as for the overall APS cases.

DISCUSSION

The incidence and prevalence of APS in the US have been assessed using the large CCAE and MDCR databases, which includes claims data on more than 60 million insured US employees and their dependents. Our data suggest there is a trend towards a yearly increase in incidence and prevalence of APS over time, which may be a product of the discovery of new autoantibodies and generally increased awareness of the disease.(4) Additionally, adoption of the ICD-10 code in 2015 may have also contributed to the observed increase in prevalence.

There are a number of published studies that aimed to assess the incidence and prevalence of APS in different countries around the world,(6-10) which revealed important clinical and epidemiological information on APS in their respective regions (Supplementary Table 6). However, the incidence and prevalence estimates reported vary, likely due to the variation in APS case definitions, design across studies, and the type of database analyzed, which may result in variation in socioeconomic demographics among the populations included.(4)

In particular, our sensitivity analysis shows that differences in incidence rates are apparent when using different diagnostic scenarios, thus results may be sensitive to the case definition used. This is evident when evaluating studies in the literature, as one pertinent difference

between them was the method used for identification of APS cases. A study of the incidence and prevalence of APS cases in Korea, identified from the Korean Health Insurance and Review Agency, used the Korean Classification of Disease, 7th edition code D68.6 (other thrombophilia), which corresponds to ICD-10: D68.6 and includes anticardiolipin syndrome, APS, and the presence of lupus anticoagulant, and V253 code of rare intractable disease to confirm APS cases.(7) Therefore, the identification and retrieval of APS cases was not exhaustive, which might affect the accuracy of identification. Radin et al. (2020) estimated the incidence and prevalence from the Piedmont and Aosta Valley regional registry, a part of the Italian National Registry of Rare Diseases, but data from the National Registry are not reported.(9) The study was carried out between 2010 and 2019, but the authors do not report on how the cases were ascertained or coded, or whether the Sydney criteria were used, and the potential completeness of the registry has not been described.(9) Duarte-Garcia et al. (2019) included data from a population-based study run in the Mayo Clinic, Olmsted County, between 2000 and 2015.(6) While this study provided a rich clinical and epidemiological knowledge of APS, the authors acknowledged that outcomes could only be generalized to populations with the same demographic profile.(6) In addition, the study sample size of only 33 patients after applying the Sydney criteria does not allow extrapolation of outcomes to the country level.(6) In the present study, the specific APS code, D68.61, was used to identify patients since the switch from ICD-9-CM to ICD-10-CM in October 2015, and the prior period was excluded to avoid any misclassification or underestimation of APS cases.

Our standardized estimate of APS incidence (2.31 per 100,000 PY in 2016 to a high of 2.71 per 100,000 PY in 2019) is higher than the incidence reported from the Piedmont and Aosta Valley

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regions in Italy,(9) and also higher than that reported in the previous US (2.1 per 100,000 PY) and UK (7.5 per 100,000 PY for women aged 35–39 years and 2.2 per 100,000 PY for men aged 55–59 years) studies.(6, 10) The study in South Korea reported a higher incidence rate (7.5 per 100,000 PY) than found in any of the other studies.(7) Our estimation of prevalence rate (10.42 per 100,000 persons in 2019) was close to that estimated for the Piedmont and Aosta Valley region (16.8 per 100,000 persons).(9) In other studies, prevalence rates ranged from 40 per 100,000 persons in Spain,(8) to 61.9 per 100,000 persons in South Korea.(7) The UK study estimated that prevalence rates were 43 per 100,000 persons,(10) while the Olmsted County study in the US had an estimated prevalence of 50 per 100,000 persons.(6) The difference in the population inclusion and the design of the study might explain the heterogeneity of prevalence rates estimation. When assessing APS subtype, the overall annual standardized incidences of thrombotic APS and obstetric APS in 2019 were 1.28 per 100,000 PY, and 1.24 per 100,000 PY, respectively. These incidences are close to those reported by Duarte-Garcia et al. (2019), but far from those reported by Andreoli et al. (2013), who estimated the overall annual incidence of thrombotic APS by the indirect method as 1.8 and 65 per 100,000 PY, respectively, and 0.2 and 15 per 100,000 PY, respectively, for obstetric APS.(6, 19)

It has been previously estimated that CAPS patients represent less than 1% of all patients with APS, owing to the life-threatening nature of CAPS that requires high clinical awareness.(13) However, the proportion of CAPS cases in the present study was substantially higher (4.4%), and more in line with the proportion (3.0%) reported by Hwang et al. (2020) in Korea.(7) This discrepancy could be attributed to the classification criteria for CAPS, which require the knowledge of aPL test result and a biopsy, neither of which were available in the present study

and in the study conducted in Korea. As a result, it is possible that the number of CAPS cases were overestimated in both studies.

This study has several limitations, inherent to retrospective epidemiological studies, and the use of insurance claims databases. Firstly, the Merative MarketScan CCAE and MDCR are commercial insurance databases and under-represent smaller employers, and persons aged under 65 with no occupational health insurance. The CCAE also excludes those with state-funded insurance. Additionally, any medical history prior to membership of an insurance plan will also be excluded, and it is possible that some patients were diagnosed with APS prior to entering the MarketScan database. Similarly, the MDCR captures information only for the subset of Medicare patients who have supplemental insurance paid by their employers. As a result, our estimate of incidence is calculated using claims from only a subset of the total US population, and therefore may not be fully accurate or generalizable and extrapolated. Secondly, the data is collected for billing of insurance claims, and the validity of the claims is reliant upon the accuracy of the data in the claims, therefore may not truly reflect medical diagnosis. Thirdly, antibody titers were not available, and not all APS claims were linked to the clinical criteria as required per the Sydney classification.(2) Thus, the case definition used in this study, although based on the Sydney classification criteria,(2) is not complete. We have minimized this limitation by using a case definition that requires two aPL test claims at least 12 weeks apart, plus an APS diagnosis claim on or after the second laboratory diagnosis. However, this missing information could result in cases being classified as APS which do not meet the Sydney criteria, thus overestimating the incidence and prevalence of APS in the US. Relatedly, to ensure that we captured every possible APS case, we did not limit APS claims to include only

those with a clinical manifestation. Nevertheless, a sensitivity analysis (Scenario F) has been considered including the condition of clinical criteria (per the Sydney classification) linked to APS claims. These patients, classified as 'Unknown' in our study, may have therefore had a specific clinical manifestation or APS subtype that was not captured. For example, data may have been incomplete for obstetric APS if patients were misclassified as 'Unknown' but were pregnant at the time or even after the period of identification. Indeed, a peak in incidence and prevalence of APS, irrespective of subtype, is observed in women of child-bearing age that is not observed in men (Supplementary Tables 3 and 4). Additionally, some of the confidence intervals were wide ranging, owing to variability in the number of events per category, and should be interpreted with caution. A further limitation of the case definition is that primary and secondary APS were not separated. Finally, absence of a unique ICD code for APS prior to introduction of ICD-10-CM in October 2015 limits the ability to estimate APS incidence and prevalence prior to 2016. Our estimation of prevalence from 2016 to 2019 is likely to under-ascertain prevalent cases diagnosed prior to October 2015. The impact of this underestimation of prevalence will be most pronounced in the years immediately after the change in ICD coding.

Very few epidemiological studies are reported in the published literature on the incidence or prevalence of APS, and estimates reported in these studies are heterogeneous. A careful interpretation should be considered when comparing these results to other countries that may have a different healthcare system with variations in APS management, including treatment administration, as well as possible socioeconomic differences.

This study identified a trend towards a yearly increase in incidence and prevalence of APS in the US over the study period. The results of this study add to existing estimates published in the

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literature, but further studies are needed to fully elucidate the global epidemiology of APS using the 2023 classification criteria of APS by Barbhaiya et al.(5)

DATA AVAILABILITY STATEMENT

Data from non-interventional studies is outside of UCB's data sharing policy and is unavailable for sharing.

ETHICS STATEMENTS

Patient consent for publication

Not applicable.

Ethics approval

The CCAE and MDCR databases are Health Insurance Portability and Accountability Act compliant, and all patient data were de-identified before delivery to the study team. No ethics committee approval was required.

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CONTRIBUTORS

M. Khellaf, P. Meisner, M. Sarno, P. Zaremba, A. Jedrzejczyk, and A. Scowcroft provided substantial contributions to the conception or design of the work, analysis, or interpretation of

data. All authors revised the work for important intellectual content and provided approval of the final version to be published.

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COMPETING INTERESTS

Meheni Khellaf, Piotr Zaremba and Adam Jedrzejczyk are contractors employed by UCB Pharma. Paul Meisner, Maria Sarno and Anna Scowcroft are employees and stockholders of UCB Pharma.

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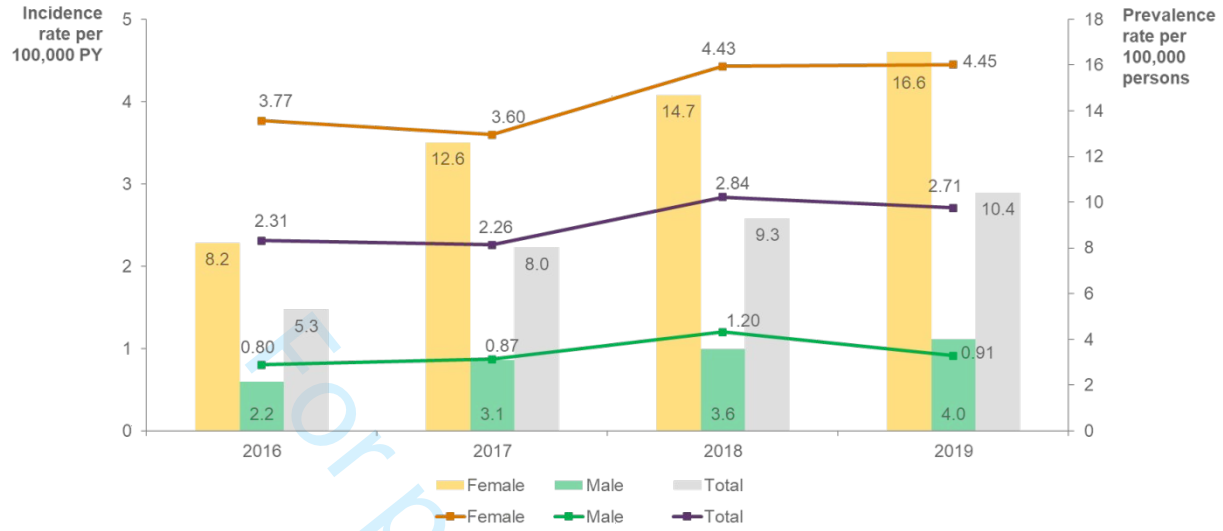
Figure 1. Yearly incidence and prevalence rates of APS cases.



Lines represent incidence rates per 100,000 PY, bars represent prevalence rates per 100,000 persons.

APS, antiphospholipid syndrome; PY, person-years.

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The incidence and prevalence of antiphospholipid syndrome (APS) in the United States (2016–2019): A retrospective database study

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The incidence and prevalence of antiphospholipid syndrome (APS) in the United States (2016–2019): A retrospective database study

Short title: Antiphospholipid syndrome incidence and prevalence

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ABSTRACT

Objective: Few epidemiological studies are reported in the published literature on the incidence or prevalence of antiphospholipid syndrome (APS), and available results are heterogeneous. This study aimed to estimate the incidence and prevalence of APS in the United States (US), overall and by APS subtype.

Design: A retrospective analysis of APS disease incidence and a cross-sectional analysis of disease prevalence.

Setting: Merative MarketScan Commercial Claims and Encounters Database, and the Medicare Supplemental and Coordination of Benefits Database.

Participants: All individuals with claims for at least two aPL tests undertaken at least 12 weeks apart, and a diagnosis claim for APS as a primary or secondary diagnosis on or after the second antibody test, during the period January 1, 2016, to December 31, 2019.

Main outcome measures: Annual incidence and prevalence of APS and APS subtypes.

Results: In total, 1708 cases of APS were identified during the study period (2016–2019), of which 83% were women. The overall annual standardized incidence rate of APS per 100,000 person-years increased slightly over the study period, from 2.31 in 2016 to 2.71 in 2019. In 2019, the estimated annual prevalence of APS per 100,000 persons was 10.42 per 100,000 persons (95% confidence interval: 9.96–10.90). Based on this and US census data, we have estimated that 34,000 persons in the US were affected by APS in 2019.

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Conclusions: These data add to the estimates of prevalence and incidence of APS in the literature, all of which have different strengths and limitations of the different data sources and case ascertainment methods.

Keywords: Antibodies, antiphospholipid; antiphospholipid syndrome; autoimmune diseases; epidemiology

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Strengths and limitations of this study

- The Merative MarketScan CCAE and MDCR used in this study is a large database
- The identification of the APS claims were realized by using a unique APS-specific ICD code (D68.61) which was made available during the study period, whereas previous studies use a non-specific code
- Instead of the full Sydney criteria, a case definition proxy was applied to identify APS cases
- Given our estimate of incidence is calculated using claims from only a subset of the total US population, which is not a representative sample, it cannot be extrapolated to the full US population or populations in other countries

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INTRODUCTION

Antiphospholipid syndrome (APS) is an autoimmune disease caused by anti-phospholipid antibodies (aPLs) that results in a wide spectrum of clinical manifestations, involving the hematological, obstetrical, neurological, cardiovascular, renal, and orthopedic systems, among others.(1) aPLs include lupus anticoagulant (LAC), anti-cardiolipin (aCL), and anti-β2-glycoprotein I (anti-β2GPI) immunoglobulin (Ig) G and IgM antibodies.

According to the Sydney 2006 International Classification Criteria Consensus, clinical diagnosis of APS requires the presence of clinical symptoms associated with APS (vascular thrombosis or pregnancy morbidity) and two positive test results for aPL, 12 weeks apart.(2) Furthermore, older epidemiology studies were undertaken before LAC, aCL, and anti-β2GPI antibodies were recognized as aPLs in the 2006 update of the classification criteria.(2) As a result, few studies have been carried out to assess the epidemiology of APS, while the few data that have been published are inconsistent.(3)

Since completion of this study, a manuscript supported by the American College of Rheumatology (ACR) Board of Directors and the European Alliance of Associations for Rheumatology (EULAR) has been published, in which a new classification criterion of APS has been proposed.(4)

In the United States (US), Duarte-Garcia et al. (2019) estimated the overall annual incidence and prevalence rates of APS for patients aged ≥18 years at 2.1 per 100,000 person-years (PY) and 50 per 100,000 persons, respectively.(5) Studies worldwide have estimated incidence and prevalence ranging from 7.5 per 100,000 PY in Korea (6) to 40 per 100,000 PY in Spain,(7) and

from 16.8 per 100,000 people in the Piedmont and Aosta Valley regions (8) to 61.9 per 100,000 people in Korea,(6) respectively. Previous studies have also shown that the peak incidence of APS differs for men and women. In the UK, Rodziewicz et al. (2019) used data from the UK Clinical Practice Research Datalink to estimate the peak APS incidence of 7.5 per 100,000 PY for women occurring between the ages of 35 and 39 years, while the peak APS incidence for men was 2.2 per 100,000 PY and occurred later in life, between the ages of 55 and 59 years.(9) Prevalence of APS in the UK was also higher in women compared with men: 50 and 9.8 per 100,000 persons, respectively.(9)

The Merative MarketScan Commercial Claims and Encounters (CCAE) and Medicare Supplemental and Coordination of Benefits (MDCR) databases represent insurance claims from US employees and their dependents, from all US census regions, covering approximately 40 million persons in the US annually (Figure 1).(10) Using this large, real-world database, we aimed to retrospectively and cross-sectionally estimate the incidence and prevalence of APS in the US population during 2016 and 2019. A proxy definition for APS cases was developed using clinical variables available in the Marketscan database, with the aim to be as close as possible to the Syndey 2006 classification criteria. This study was already complete prior to the 2023 publication of the new APS classification by Barbhaiya et al.(4)

METHODS

Study design and data source

This was a retrospective, cross-sectional analysis of APS incidence and prevalence, using the CCAE and MDCR databases during the study period of January 1, 2015, to December 31, 2019

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(Figure 2). The database is Health Insurance Portability and Accountability Act compliant, and all patient data were de-identified before delivery to the study team. No ethics committee approval was required.

Patient and public involvement

Patients and their families were not involved in the design, implementation, or setting the research question or the outcome measures.

Case definition and identification

APS cases were defined as claims for at least two aPL tests undertaken at least 12 weeks apart, and a diagnosis claim for APS as a primary or secondary diagnosis on or after the second antibody test, identified from International Classification of Diseases, tenth revision (ICD-10) codes. In October 2015, APS was given a unique ICD code (D68.61) with the introduction of the Clinical Modification (CM). Prior to ICD-10-CM, APS was coded together with multiple other hypercoagulation defects into 289.81 (Primary Hypercoagulable State). Thus, cases of APS can only be ascertained from October 2015 onwards.

The Sydney International Classification Criteria Consensus case definition requires laboratory criteria (at least 12 weeks between the initial and repeated positive aPL test) and at least one of the clinical criteria (vascular thrombosis or pregnancy morbidity). An aPL test is confirmed positive if one or more of the following aPLs are detected on two or more occasions at least 12 weeks apart: (i) LAC present in plasma detected according to the International Society on Thrombosis and Haemostasis guidelines (2, 11, 12); (ii) aCL of IgG and/or IgM isotype in serum or plasma at medium or high titer (>40 IgG or IgM phospholipid units, or >99th percentile)

measured by a standardized ELISA; or (iii) anti-β2GPI of IgG and/or IgM isotype in serum or plasma (>99th percentile) measured by a standardized ELISA.(2)

As aPL test results are not available from the CCAE and MDCR databases, a proxy was used for a positive result. If a second, repeated aPL test was carried out 12 weeks later than the first test, it was assumed at least one of the tests was positive. aPL test codes were 86148, 86146, and 86147, corresponding to aPL, anti-β2GPI, and aCL, respectively. At least one clinical criterion (vascular thrombosis or pregnancy morbidity) was added to the case definition as a sensitivity analysis. The index date was defined as the date of the first APS diagnosis which could be before, on or after the second aPL test.

Study populations and APS subtypes

The study population comprised all patients identified as having APS according to the criteria described above. Patients were also required to have at least 12 months of continued medical and pharmacy benefits memberships prior to index date (not required for children aged <1 year) from January 1, 2016, to December 31, 2019 and, for incident patients, no diagnosis record of APS (ICD-9 or ICD-10) at any time prior to the index date. APS was classified as primary APS in the absence of systemic autoimmune disease (per the Sydney 2006 International Classification Criteria Consensus (2)), however primary and secondary APS were not analyzed separately. APS subtypes were classified into five mutually exclusive categories as thrombotic APS only, obstetric APS only (women aged ≥14 years only), mixed APS (both thrombotic APS and obstetric APS events; women aged ≥14 years only), other APS manifestations not included in the Sydney criteria (Supplementary Tables 1 and 2), and APS type unknown. In addition, catastrophic APS (CAPS) was analyzed as a subtype of thrombotic and mixed APS, defined as

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thrombosis in three or more organs developing in less than a week. This definition was as close as possible to the 10th and 14th International Congress on Antiphospholipid Antibodies definitions,(13-15) without the required information on aPL status and biopsy, which was not available in this database.

Study outcomes and statistical analyses

Distribution of APS subtypes by age and sex during 2016–2019, and by specialty involved in the first APS diagnosis for the period 2018–2019, were assessed. Overall distribution of CAPS was calculated and presented as one result for the aggregated incident cohort. The annual incidence and prevalence of APS and APS subtypes were calculated by age and sex in each calendar year from 2016 to 2019. Incidence of APS was age- and sex-standardized indirectly to the US 2020 population by using age- and sex-specific population census data as weights and applying them to the age- and sex-specific incidence rates.(16)

Incidence, the number of new APS cases during a specific time period,(17) was reported as a rate per 100,000 PY. Person-time was defined as the sum of each patient's duration of follow-up from January 1 to December 31 of each year, to the end of the patient record, to the end of the first insurance claim if there was a gap greater than 60 days, or to the APS diagnosis – whichever came first. Incidence was calculated as the number of incident cases divided by the person-time of observation per year. The annual incidence rate was calculated as the number of incident cases in a year divided by the person-time corresponding to that year. Prevalence, the proportion of the population with APS in a given time period,(17) was expressed as prevalence per 100,000 persons. The denominator was all patients in the CCAE and MDCR database on July 1 of each year. The annual prevalence rate was calculated as prevalent cases

in a year divided by the overall population corresponding to that year. The 95% confidence interval (CI) of the prevalence and incidence rates were estimated by the Poisson distribution.(18)

Sensitivity analysis

To assess the robustness of the case definition in this study, a number of alternative case definitions were considered for the incidence and prevalence calculation. Patients could have one of the following: (A) at least one APS diagnosis (primary or secondary) with no requirement of an aPL test; (B) at least one APS diagnosis (primary or secondary) with at least one aPL test; (C) at least one APS diagnosis with two aPL tests undertaken 12–26 weeks apart and 2–13 weeks before an APS diagnosis code; (D) for a patient with a membership gap during follow-up, the follow-up included all time at risk including during and after the gap (i.e., they were treated as if there was no gap); (E) at least one diagnosis record of LAC syndrome (ICD-10 code 68.62) with two aPL tests at least 12 weeks apart and ≥1 diagnostic record of thrombotic or obstetric events according to the Sydney criteria; or (F) at least one of the clinical criteria (vascular thrombosis or pregnancy morbidity per the definitions in Supplementary Table 1) with at least two aPL tests undertaken at least 12 weeks apart, and a diagnosis claim for APS as a primary or secondary diagnosis on or after the second antibody test (Supplementary Table 3). All statistical analyses were performed using SAS Version 9.4

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RESULTS

Baseline characteristics

A total of 1708 cases of APS that met our case definition during 2016–2019 were identified, with the majority being women (n=1411, 83%; Table 1, Supplementary Table 4). For women, the number of incident APS cases was highest among the 25–44 years age category (n=706, 50.0%), and 376 (26.6%) patients had obstetric APS. For men, the number of incident APS cases was highest among patients aged 45–64 years (n=201, 67.7%). The overall number of pediatric APS cases was small (n=23), with most cases identified within the 15–17 years age category (n=16) for both female and male patients. Thrombotic APS was the most frequent subtype identified (n=728, 42.6%), followed by APS of unknown subtype (n=404, 23.7%), obstetric APS (n=376, 22.0%), other APS (n=138, 8.1%), and mixed APS (n=62, 3.6%). Seventy-five cases of CAPS were identified, representing 4.4% of all APS cases. The acute care hospital was the most frequently visited healthcare specialty site for diagnosis (n=227, 26.9%), followed by laboratory (n=161, 19.1%), rheumatology (n=89, 10.5%), internal medicine (n=87, 10.3%), obstetrics and gynecology (n=72, 8.5%) and hematology (n=70, 8.3%). Other categories for APS diagnoses included oncology, family practice, pathology, neurology, multispecialty, and medical doctors.

Table 1. Overall incident APS cases by baseline gender and age distribution, and APS subtype

	Total (2016–2019) N=1708	
	Male	**Female**
n (%)	297 (17.4)	1411 (82.6)
Age, years, n (%)		
Adults		
18–24	10 (3.4)	67 (4.7)
25–44	49 (16.5)	706 (50.0)
45–64	201 (67.7)	580 (41.1)
65+	28 (9.4)	44 (3.1)
Subtotal	288 (97.0)	1397 (99.0)
Pediatric		
0–4	1 (0.3)	1 (0.1)
5–9	1 (0.3)	0
10–14	1 (0.3)	3 (0.2)
15–17	6 (2.0)	10 (0.7)
Subtotal	9 (3.0)	14 (1.0)
Catastrophic APS, n (%)	27 (9.1)	48 (3.4)
APS subtype, n (%)		
Thrombotic	251 (84.5)	477 (33.8)
Obstetric	0	376 (26.6)
Mixed	0	62 (4.4)
Other	16 (5.4)	122 (8.6)
Unknown	30 (10.1)	374 (26.5)

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Incidence of APS

The overall annual incidence rate of APS per 100,000 PY (95% confidence interval [CI]) standardized to the US 2020 population census increased slightly over the study period, from 2.31 (2.11–2.53) in 2016 to 2.84 (2.59–3.11) and 2.71 (2.45–2.99) in 2018 and 2019, respectively (Figure 3). Over the whole study period, the APS incidence rates were higher in women, potentially due to certain subtypes being applicable to women only. In 2019, the annual incidence rate (standardized to the US 2020 population census) was 4.45 (3.99–4.96) per 100,000 PY for women, and 0.91 (0.71–1.17) per 100,000 PY for men. The incidence rate of APS in women was always highest in patients aged 30–39 years old, ranging from 10.09 per 100,000 PY in 2016 to 11.80 and 11.22 per 100,000 PY in 2018 and 2019 (Supplementary Table 5). However, in men, the age categories with the highest incidence rates varied each year (Supplementary Table 5).

Prevalence of APS

The estimated annual prevalence of APS per 100,000 persons (95% CI) was 10.42 per 100,000 persons (9.96–10.90) in 2019 (Figure 3). In 2019, APS prevalence among women was four times higher than in men: 16.59 (15.78–17.45) and 4.00 (3.60–4.44) per 100,000 persons, respectively. Based on this and US census data, we have estimated that slightly more than 34,000 persons in the US were affected by APS in 2019. Among women, the prevalence rate of APS was highest in the 40–49 years age group, ranging from 14.71 in 2016 to 30.61 per 100,000 persons in 2019. Among men, APS prevalence was highest in patients aged 60–69 years old between 2016 (6.27 per 100,000 persons) and 2018 (10.85 per 100,000 persons), and in patients aged 80+ years in 2019 (13.57 per 100,000 persons) (Supplementary Table 6).

Incidence rates of APS subtypes

Incidence rates of APS subtype were standardized to the US 2020 population census. In 2019, the overall annual incidence (95% CI) of thrombotic APS was 1.28 (1.10–1.49) per 100,000 PY, which was the highest incidence over the study period. The 2019 annual incidence rate of thrombotic APS patients was higher in women (1.76 per 100,000 PY) than in men (0.79 per 100,000 PY) (Supplementary Figure 1a). In 2019, among women only, the incidence rate of obstetric APS was 1.24 (1.01–1.53) per 100,000 PY (Supplementary Figure 1b), and the incidence rate of mixed APS was 0.17 (0.10–0.30) per 100,000 PY. The other APS cases represent 8.1% of the total APS population, with an overall annual incidence rate in 2019 of 0.23 (0.16–0.32) per 100,000 PY. The unknown APS cases represent almost a quarter (23.65%) of the total APS population, with an overall incidence rate in 2019 of 0.48 (0.38–0.60) per 100,000 PY (Supplementary Table 7).

Prevalence rates of APS subtypes

The overall annual prevalence (95% CI) of thrombotic APS was 5.38 (5.05–5.73) per 100,000 persons in 2019, and the annual prevalence rate of thrombotic APS was higher in women compared to men over the whole study period. The annual prevalence of obstetric APS subtype among women only was 3.70 (3.33–4.12) per 100,000 persons in 2019, and the highest prevalence rate of obstetric APS was in those aged 30–39 years old (12.98 [11.24–15.00] per 100,000 persons). The annual prevalence of mixed APS was 1.19 (0.99–1.44) per 100,000 persons in 2019, among women only. The overall annual prevalence rates of other APS and unknown APS in 2019 were 0.90 (0.77–1.05) per 100,000 persons and 2.19 (1.99–2.42) per 100,000 persons, respectively (Supplementary Table 7).

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Sensitivity analysis

Outcomes from a sensitivity analysis for different predefined scenarios for the last year of the study period, 2019, are shown in Supplementary Figure 2. The outcomes obtained from the rest of the study years were similar to those for 2019, and the subtypes of APS showed the same behaviors for the sensitivity analysis as for the overall APS cases.

DISCUSSION

The incidence and prevalence of APS in the US have been assessed using the large CCAE and MDCR databases, which includes claims data on more than 60 million insured US employees and their dependents. Our data suggest there is a trend towards a yearly increase in incidence and prevalence of APS over time, which may be a product of generally increased awareness of the disease.(3) Additionally, adoption of the ICD-10 code in 2015 may have also contributed to the observed increase in prevalence.

There are a number of published studies that aimed to assess the incidence and prevalence of APS in different countries around the world,(5-9, 19) which revealed important clinical and epidemiological information on APS in their respective regions (Supplementary Table 8). However, the incidence and prevalence estimates reported vary, likely due to the variation in APS case definitions, design across studies, and the type of database analyzed, which may result in variation in socioeconomic demographics among the populations included.(3)

In particular, our sensitivity analysis shows that differences in incidence rates are apparent when using different diagnostic scenarios, thus results may be sensitive to the case definition used. This is evident when evaluating studies in the literature, as one pertinent difference

between them was the method used for identification of APS cases. A study of the incidence and prevalence of APS cases in Korea, identified from the Korean Health Insurance and Review Agency, used the Korean Classification of Disease, 7th edition code D68.6 (other thrombophilia), which corresponds to ICD-10: D68.6 and includes anticardiolipin syndrome, APS, and the presence of lupus anticoagulant, and V253 code of rare intractable disease to confirm APS cases.(6) Therefore, the identification and retrieval of APS cases was not exhaustive, which might affect the accuracy of identification. Radin et al. (2020) estimated the incidence and prevalence from the Piedmont and Aosta Valley regional registry, a part of the Italian National Registry of Rare Diseases, but data from the National Registry are not reported.(8) The study was carried out between 2010 and 2019, but the authors do not report on how the cases were ascertained or coded, or whether the Sydney criteria were used, and the potential completeness of the registry has not been described.(8) Duarte-Garcia et al. (2019) included data from a population-based study run in the Mayo Clinic, Olmsted County, between 2000 and 2015.(5) While this study provided a rich clinical and epidemiological knowledge of APS, the authors acknowledged that outcomes could only be generalized to populations with the same demographic profile.(5) In addition, the study sample size of only 33 patients after applying the Sydney criteria does not allow extrapolation of outcomes to the country level.(5) In the present study, the specific APS code, D68.61, was used to identify patients since the switch from ICD-9-CM to ICD-10-CM in October 2015, and the prior period was excluded to avoid any misclassification or underestimation of APS cases.

Our standardized estimate of APS incidence (2.31 per 100,000 PY in 2016 to a high of 2.71 per 100,000 PY in 2019) is higher than the incidence reported from the Piedmont and Aosta Valley

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regions in Italy,(8) and also higher than that reported in the previous US (2.1 per 100,000 PY) and UK (1.8 per 100,000 PY) studies.(5, 9) The study in South Korea reported a higher incidence rate (7.5 per 100,000 PY) than found in any of the other studies (6). Our estimation of prevalence rate (10.42 per 100,000 persons in 2019) was close to that estimated for the Piedmont and Aosta Valley region (16.8 per 100,000 persons).(8) In other studies, prevalence rates ranged from 40 per 100,000 persons in Spain,(7) to 61.9 per 100,000 persons in South Korea.(6) The UK study estimated that prevalence rates were 43 per 100,000 persons,(9) while the Olmsted County study in the US had an estimated prevalence of 50 per 100,000 persons.(5) The difference in the population inclusion and the design of the study might explain the heterogeneity of prevalence rates estimation. When assessing APS subtype, the overall annual standardized incidences of thrombotic APS and obstetric APS in 2019 were 1.28 per 100,000 PY, and 1.24 per 100,000 PY, respectively. These incidences are close to those reported by Duarte-Garcia et al. (2019), but far from those reported by Andreoli et al. (2013), who estimated the overall annual incidence of thrombotic APS by the indirect method as 1.8 and 65 per 100,000 PY, respectively, and 0.2 and 15 per 100,000 PY, respectively, for obstetric APS.(5, 20)

It has been previously estimated that CAPS patients represent less than 1% of all patients with APS, owing to the life-threatening nature of CAPS that requires high clinical awareness.(13) However, the proportion of CAPS cases in the present study was substantially higher (4.4%), and more in line with the proportion (3.0%) reported by Hwang et al. (2020) in Korea.(6) This discrepancy could be attributed to the classification criteria for CAPS, which require the knowledge of aPL test result and a biopsy, neither of which were available in the present study

and in the study conducted in Korea. As a result, it is possible that the number of CAPS cases were overestimated in both studies.

This study has several limitations, inherent to retrospective epidemiological studies, and the use of insurance claims databases. Firstly, the Merative MarketScan CCAE and MDCR are commercial insurance databases and under-represent smaller employers, and persons aged under 65 years with no occupational health insurance. The CCAE also excludes those with state-funded insurance. Additionally, any medical history prior to membership of an insurance plan will also be excluded, and it is possible that some patients were diagnosed with APS prior to entering the MarketScan database. Similarly, the MDCR captures information only for the subset of Medicare patients who have supplemental insurance paid by their employers. As a result, our estimate of incidence is calculated using claims from only a subset of the total US population, and therefore may not be fully accurate or generalizable and extrapolated. Secondly, the data is collected for billing of insurance claims, and the validity of the claims is reliant upon the accuracy of the data in the claims, therefore may not truly reflect medical diagnosis. Thirdly, antibody titers were not available, and not all APS claims were linked to the clinical criteria as required per the Sydney classification.(2) Thus, the case definition used in this study, although based on the Sydney classification criteria,(2) is not complete. We have minimized this limitation by using a case definition that requires two aPL test claims at least 12 weeks apart, plus an APS diagnosis claim on or after the second laboratory diagnosis. However, this missing information could result in cases being classified as APS which do not meet the Sydney criteria, thus overestimating the incidence and prevalence of APS in the US. The lack of aPL data is a limitation inherent to the database, which may have contributed to very few

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populational studies in the literature on the prevalence of aPL and a lack of standardization between aPL tests. Relatedly, to ensure that we captured every possible APS case, we did not limit APS claims to include only those with a clinical manifestation. Nevertheless, a sensitivity analysis (Scenario F) has been considered including the condition of clinical criteria (per the Sydney classification) linked to APS claims. These patients, classified as 'Unknown' in our study, may have therefore had a specific clinical manifestation or APS subtype that was not captured. For example, data may have been incomplete for obstetric APS if patients were misclassified as 'Unknown' but were pregnant at the time or even after the period of identification. Indeed, a peak in incidence and prevalence of APS, irrespective of subtype, is observed in women of child-bearing age that is not observed in men (Supplementary Tables 5 and 6). Additionally, some of the confidence intervals were wide ranging, owing to variability in the number of events per category, and should be interpreted with caution. A further limitation of the case definition is that primary and secondary APS were not separated. Finally, absence of a unique ICD code for APS prior to introduction of ICD-10-CM in October 2015 limits the ability to estimate APS incidence and prevalence prior to 2016. Our estimation of prevalence from 2016 to 2019 is likely to under-ascertain prevalent cases diagnosed prior to October 2015. The impact of this underestimation of prevalence will be most pronounced in the years immediately after the change in ICD coding.

Very few epidemiological studies are reported in the published literature on the incidence or prevalence of APS, and estimates reported in these studies are heterogeneous. A careful interpretation should be considered when comparing these results to other countries that may

have a different healthcare system with variations in APS management, including treatment administration, as well as possible socioeconomic differences.

This study identified a trend towards a yearly increase in incidence and prevalence of APS in the US over the study period. The results of this study add to existing estimates published in the literature, but further studies are needed to fully elucidate the global epidemiology of APS using the 2023 classification criteria of APS by Barbhaiya et al.(4)

DATA AVAILABILITY STATEMENT

Data from non-interventional studies is outside of UCB's data sharing policy and is unavailable for sharing.

ETHICS STATEMENTS

Patient consent for publication

Not applicable.

Ethics approval

The CCAE and MDCR databases are Health Insurance Portability and Accountability Act compliant, and all patient data were de-identified before delivery to the study team. No ethics committee approval was required.

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CONTRIBUTORS

M. Khellaf, P. Meisner, M. Sarno, P. Zaremba, A. Jedrzejczyk, and A. Scowcroft provided substantial contributions to the conception or design of the work, analysis, or interpretation of data. A. Scowcroft is responsible for the overall content as guarantor. All authors revised the work for important intellectual content and provided approval of the final version to be published.

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COMPETING INTERESTS

Meheni Khellaf, Piotr Zaremba and Adam Jedrzejczyk are contractors employed by UCB Pharma. Paul Meisner, Maria Sarno and Anna Scowcroft are employees and stockholders of UCB Pharma.

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FIGURE LEGENDS

Figure 1. MarketScan research databases (10)

Figure 2. Study design

aPL, antiphospholipid antibody; APS, antiphospholipid syndrome; ICD, International Classification of Diseases.

Figure 3. Yearly incidence and prevalence rates of APS cases

Lines represent incidence rates per 100,000 PY, bars represent prevalence rates per 100,000 persons.

APS, antiphospholipid syndrome; PY, person-years.

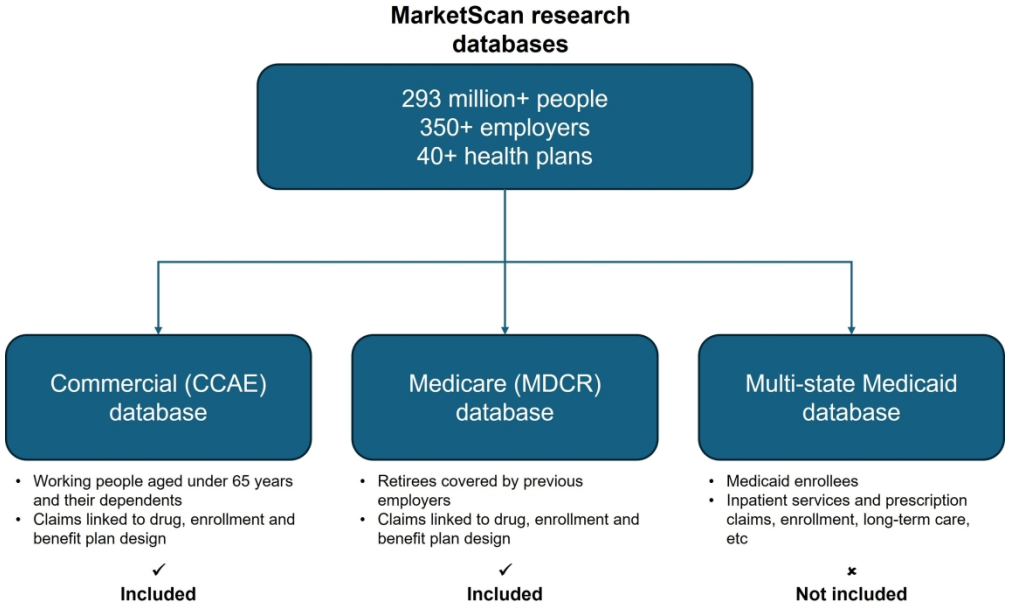

Figure 1. MarketScan research databases (10)

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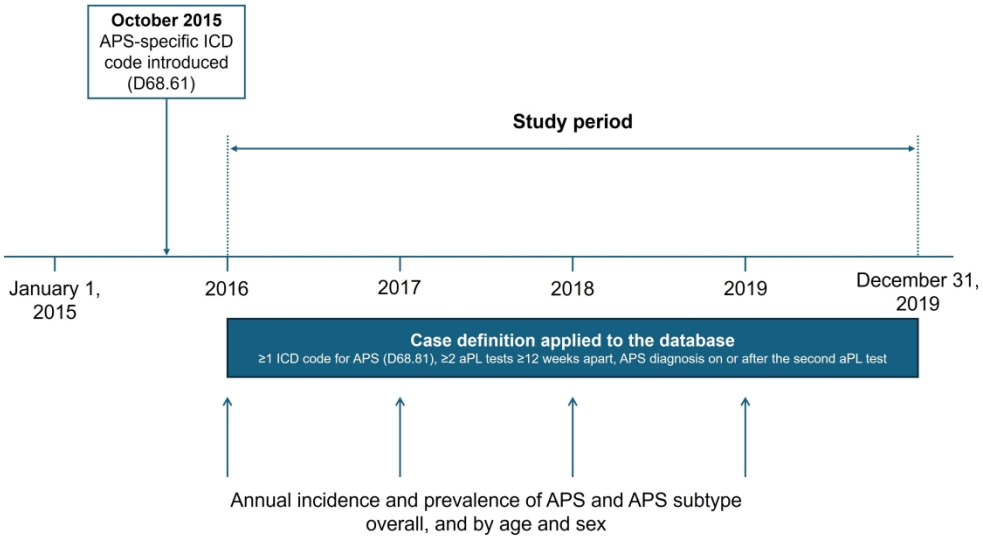

Figure 2. Study design

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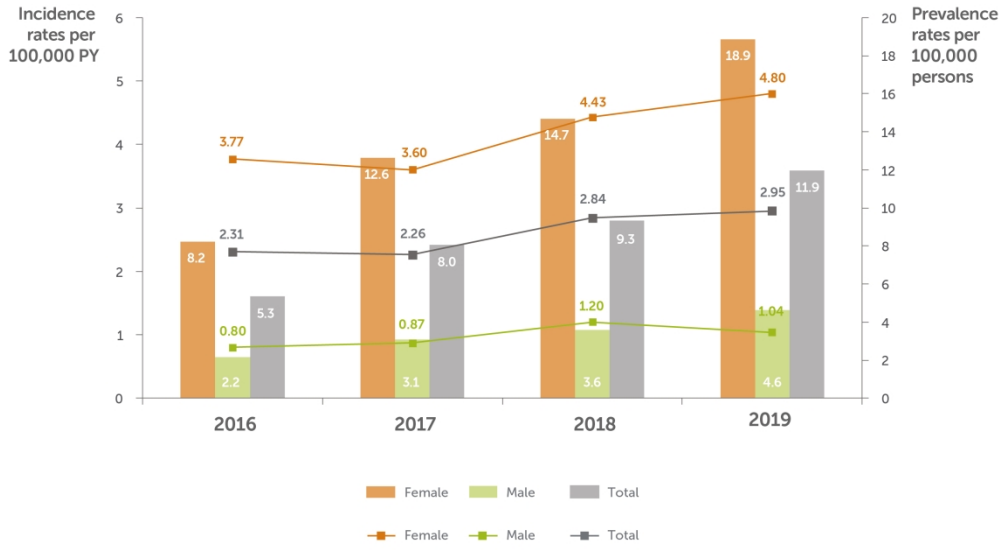

Figure 3. Yearly incidence and prevalence rates of APS cases

240x151mm (300 x 300 DPI)

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The incidence and prevalence of antiphospholipid syndrome (APS) in the United States (2016–2019): A retrospective database study

Supporting information

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Supplementary Table 1. Thrombotic and obstetric events included in the Sydney criteria

Thrombotic events	ICD-9-CM	ICD-10-CM
Arterial thromboembolism	444	I74
Cavernous sinus thrombosis	437.6	I67.6
Cerebral infarction (including ischemic stroke)	434	I63, I69.3
Cerebral venous sinus thrombosis,	437.6	I67.6
Coronary thrombosis (without infarct)	-	I24.0
Myocardial infarction	410, 411.0, 412, 429.7	I21-I23, I24.1, I25.2
Personal history of venous thrombosis	Baseline variable only V12.51, V12.54, V12.55	Baseline variable only Z68.711, Z68.718 Z68.73
Pulmonary embolism (acute or chronic)	415.1, 416.2	I26
Pulmonary hypertension (thromboembolic)	416.8	I27.2
Retinal vein occlusion, including amaurosis fugax	362.3	H34, G45.3
Thrombotic microangiopathy (acute)	446.6	M31.1
Transient ischemic attack	435	G45
Venous thromboembolism, including thrombosis or embolism of: Portal vein Hepatic vein (Budd-Chiari Syndrome) Renal vein thrombosis Vena cava & thoracic veins Deep veins of lower extremity (acute) Deep veins of lower extremity (chronic) Veins of upper extremity (acute) Veins of upper extremity (chronic) Axillary vein Subclavian vein Internal jugular vein Other specified vein Unspecified vein Thrombophlebitis migraines	452, 453	I81, I82
Thrombotic events during pregnancy or postpartum		
Cerebral venous sinus thrombosis	671.5	O22.5, O87.3
Deep vein thrombosis	671.3 671.4	O87.1, O22.3
Obstetric thromboembolism	673.2	O88.2

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Obstetric events		
Eclampsia	642.6	O15
History of recurrent pregnancy loss	Baseline variable only 629.81,646.3	Baseline variable only N96, O26.2
Low birth weight infant	764 V21.3	P05.0, P05.1 P05.9, P07.0, P07.1
Miscarriage or spontaneous abortion (due to natural causes before week 20)*	634,761.8	O03
Poor fetal growth, including placental insufficiency	656.5, V28.4	O36.5, Z36.4
Pre-eclampsia	642.4-642.7	O11, O14
Short-gestation birth (before week 37)	644.2, 765.0-765.2	O60.1, P07.2, P07.3
Stillbirth or late pregnancy loss (due to natural causes, week 20+)	632, 656.4, 779.9, V27.1, V27.4, V27.7	O02.1, O36.4, P95, Z37.1, Z37.4, Z37.7
Threatened preterm labor (before week 37)	644.0	O60.0, O60.2, O47.0

Diagnosis codes were selected to be compatible with the manifestations included in the Sydney 2006 International Classification Criteria and with those extra-criteria manifestations which are likely to be linked to the presence of anti-phospholipid antibodies.

*Multiple miscarriages or spontaneous abortions is defined using ICD code in table 7 and requires at least 3 miscarriages or 3 spontaneous abortions in the patients record. Events should be at least 4 months apart.

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Supplementary Table 2. APS manifestations not in the Sydney criteria

Events	ICD-9-CM	ICD-10-CM
Chorea	333.5	G25.5
Epilepsy	345	G40
Gangrene with peripheral vascular disease (excluding atherosclerosis)	249.7, 250.7, 785.4	E08.52, E09.52, E10.52, E11.52, E12.52, E13.52 I73.01, I96
Hemolytic anemia (acquired)	283	D58
Ulcers (excluding pressure ulcers)	707.1, 707.8, 707.9	L97, L98.4
Livedo reticularis/ Livedo vasculitis	782.61, 709.1	R23.1/ L95.0
Mitral and aortic valve diseases (non-rheumatic)	424.0, 424.1	I34, I35
Osteonecrosis (idiopathic)	No specific code	M87.1
Thrombocytopenia (idiopathic or primary)	287.3, 287.5	D69.3, D69.4, D69.6
Vascular dementia	290.4	F01

Diagnosis codes were selected to be compatible with the manifestations included in the Sydney 2006 International Classification Criteria and with those extra-criteria manifestations which are likely to be linked to the presence of anti-phospholipid antibodies.

APS, antiphospholipid syndrome.

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Supplementary Table 3. Case definitions used in main analysis and sensitivity analysis

	≥1 APS diagnosis claim*	≥1 LAC syndrome diagnosis claim	≥1 diagnostic record of thrombotic or obstetric events†	≥1 clinical criteria (vascular thrombosis or pregnancy morbidity)	≥1 aPL test‡	≥2 aPL tests‡ ≥12 weeks apart	≥2 aPL tests‡ 12–26 weeks apart	APS diagnosis on or after the second aPL test‡	APS diagnosis 2–13 weeks after the second aPL test‡
Case definition used									
Sensitivity scenario A	✓								
Sensitivity scenario B	✓				✓				
Sensitivity scenario C	✓						✓		✓
Sensitivity scenario D§	✓					✓		✓	
Sensitivity scenario E		✓	✓			✓			
Sensitivity scenario F	✓			✓		✓		✓	

*Primary or secondary. †According to Sydney criteria. ‡Test status unavailable. §Identical to case definition without follow-up gap.

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Supplementary Table 4. Incident APS cases by baseline gender and age distribution, and APS subtype by year

	2016		2017		2018		2019	
	Male	Female	Male	Female	Male	Female	Male	Female
	N=458		N=406		N=459		N=385	
n (%)	77 (16.8)	381 (83.2)	76 (18.7)	330 (81.2)	82 (17.9)	377 (82.1)	62 (16.1)	323 (83.9)
Age, years, n (%)								
Adults								
18–24	4 (5.2)	17 (4.5)	1 (1.3)	14 (4.2)	2 (2.4)	15 (4.0)	3 (4.8)	21 (6.5)
25–44	9 (11.6)	185 (48.6)	16 (21.1)	164 (49.7)	11 (13.4)	191 (50.7)	13 (21.0)	163 (50.4)
45–64	53 (68.8)	161 (42.3)	53 (69.7)	143 (43.3)	56 (68.3)	155 (41.1)	39 (62.9)	121 (37.5)
65+	8 (10.3)	15 (3.9)	5 (6.6)	6 (1.8)	11 (13.4)	12 (3.2)	4 (6.5)	11 (3.4)
Subtotal	74 (96.1)	378 (99.2)	75 (96.7)	327 (99.1)	80 (97.6)	373 (98.9)	59 (95.2)	316 (97.8)
Pediatric								
0–4	0	1 (0.3)	0	0	1 (1.2)	0	0	0
5–9	1 (1.3)	0	0	0	0	0	0	0
10–14	1 (1.3)	1 (0.3)	0	2 (0.6)	0	0	0	0
15–17	1 (1.3)	1 (0.3)	1 (1.3)	1 (0.3)	1 (1.2)	4 (1.1)	3 (4.8)	4 (1.2)
Subtotal	3 (3.9)	3 (0.8)	1 (1.3)	3 (0.9)	2 (2.4)	4 (1.1)	3 (4.8)	4 (1.2)
Catastrophic APS, n (%)	–	–	–	–	–	–	–	–
APS subtype, n (%)								
Thrombotic	65 (84.4)	113 (29.6)	68 (89.5)	112 (33.9)	65 (79.3)	131 (34.7)	53 (85.5)	121 (36.5)
Obstetric	0	95 (24.9)	0	82 (24.8)	0	109 (28.9)	0	90 (27.9)
Mixed	0	17 (4.5)	0	16 (4.8)	0	16 (4.2)	0	13 (4.0)
Other	3 (3.9)	34 (8.9)	2 (2.6)	25 (7.6)	5 (6)	34 (9)	6 (9.7)	29 (9.0)
Unknown	9 (11.7)	122 (32)	6 (7.9)	95 (28.8)	12 (14.6)	87 (23)	3 (4.8)	70 (21.7)

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Supplementary Table 5. Yearly incidence rates of APS cases per 100,000 person years (95% CI) by age category

Age, years	2016	2017	2018	2019
Female				
0–9	0.12 (0.02–0.85)	0	0	0
10–19	0.41 (0.17–0.99)	0.64 (0.30–1.34)	0.57 (0.25–1.26)	1.08 (0.58–2.01)
20–29	2.61 (1.82–3.76)	2.46 (1.66–3.64)	3.64 (2.62–5.04)	3.90 (2.78–5.45)
30–39	10.09 (8.42–12.09)	9.87 (8.15–11.96)	11.80 (9.88–14.09)	11.22 (9.25–13.61)
40–49	7.06 (5.81–8.57)	6.75 (5.48–8.32)	7.19 (5.85–8.84)	7.44 (5.98–9.24)
50–59	4.58 (3.68–5.71)	4.44 (3.50–5.62)	5.14 (4.10–6.44)	4.07 (3.09–5.35)
60–69	3.59 (2.65–4.85)	3.41 (2.44–4.78)	4.88 (3.62–6.58)	5.38 (3.95–7.34)
70–79	1.61 (0.72–3.57)	1.12 (0.36–3.46)	1.11 (0.28–4.43)	2.34 (0.75–7.25)
80+	0.33 (0.05–2.34)	0	2.45 (0.79–7.59)	1.26 (0.18–8.97)
Overall	3.77 (3.41–4.17)	3.60 (3.23–4.01)	4.43 (4.01–4.91)	4.45 (3.99–4.96)
Male				
0–9	0.11 (0.02–0.81)	0	0.13 (0.02–0.92)	0
10–19	0.32 (0.12–0.85)	0.18 (0.04–0.70)	0.09 (0.01–0.64)	0.41 (0.16–1.10)
20–29	0.18 (0.05–0.72)	0.10 (0.01–0.70)	0.50 (0.21–1.21)	0.33 (0.11–1.02)
30–39	0.49 (0.21–1.18)	0.75 (0.36–1.58)	0.65 (0.29–1.45)	0.93 (0.47–1.86)
40–49	1.34 (0.83–2.15)	1.73 (1.11–2.68)	1.34 (0.81–2.22)	1.09 (0.61– 1.98)
50–59	1.80 (1.23–2.63)	2.04 (1.41–2.96)	1.75 (1.17–2.64)	1.66 (1.06–2.60)
60–69	1.88 (1.20–2.95)	1.83 (1.12–2.98)	3.01 (2.02–4.49)	2.39 (1.47–3.90)
70–79	0.62 (0.15–2.47)	0	3.23 (1.34–7.75)	0.98 (0.14–6.94)
80+	0	1.46 (0.37–5.85)	2.35 (0.59–9.40)	0
Overall	0.80 (0.64–1.00)	0.87 (0.69–1.09)	1.20 (0.96–1.48)	0.91 (0.71–1.17)
Total				
0–9	0.12 (0.03–0.47)	0	0.07 (0.01–0.47)	0
10–19	0.36 (0.19–0.70)	0.40 (0.21–0.77)	0.32 (0.15–0.68)	0.74 (0.44–1.25)
20–29	1.40 (0.98–1.98)	1.28 (0.87–1.88)	2.07 (1.52–2.81)	2.08 (1.50–2.86)
30–39	5.61 (4.70–6.70)	5.60 (4.65–6.74)	6.54 (5.50–7.78)	6.25 (5.19–7.52)
40–49	4.37 (3.65–5.23)	4.39 (3.63–5.30)	4.43 (3.66–5.36)	4.39 (3.58–5.39)
50–59	3.29 (2.72–3.98)	3.31 (2.72–4.04)	3.54 (2.90–4.31)	2.92 (2.31–3.69)
60–69	2.80 (2.18–3.60)	2.67 (2.03–3.53)	3.99 (3.14–5.07)	3.97 (3.05–5.15)
70–79	1.15 (0.57–2.29)	0.59 (0.19–1.84)	2.09 (1.00–4.38)	1.73 (0.65–4.62)
80+	0.20 (0.03–1.41)	0.59 (0.15–2.37)	2.41 (1.00–5.78)	0.75 (0.11–5.32)
Overall	2.31 (2.11–2.53)	2.26 (2.05–2.49)	2.84 (2.59–3.11)	2.71 (2.45–2.99)

APS, antiphospholipid syndrome; CI, confidence interval.

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Supplementary Table 6. Yearly prevalence rates of APS cases per persons (95% CI) by age category

Age, years	2016	2017	2018	2019
Female				
0–9	0.08 (0.01–0.59)	0.09 (0.01–0.62)	0.09 (0.01–0.62)	0
10–19	0.56 (0.29–1.07)	0.98 (0.59–1.62)	0.98 (0.59–1.62)	1.38 (0.86–2.22)
20–29	3.98 (3.16–5.02)	5.32 (4.33–6.54)	7.37 (6.19–8.77)	7.86 (6.52–9.48)
30–39	14.59 (12.92–16.48)	21.20 (19.12–23.51)	23.65 (21.48–26.04)	26.18 (23.64–28.98)
40–49	14.71 (13.10–16.52)	22.84 (20.76–25.13)	26.51 (24.27–28.95)	30.61 (27.91–33.56)
50–59	10.87 (9.58–12.34)	17.47 (15.75–19.37)	19.76 (17.92–21.79)	21.60 (19.44–24.00)
60–69	10.23 (8.68–12.05)	17.00 (14.84–19.46)	18.97 (16.64–21.63)	21.29 (18.48–24.52)
70–79	6.20 (4.19–9.18)	7.13 (4.65–10.94)	11.85 (8.24–17.06)	20.42 (14.19–29.38)
80+	2.17 (1.03–4.55)	0.92 (0.23–3.68)	3.07 (1.28–7.36)	3.43 (1.11–10.64)
Overall	8.22 (7.74–8.74)	12.62 (11.99–13.28)	14.69 (14.01–15.40)	16.59 (15.78–17.45)
Male				
0–9	0.08 (0.01–0.56)	0.08 (0.01–0.59)	0.08 (0.01–0.59)	0.11 (0.01–0.75)
10–19	0.42 (0.20–0.87)	0.81 (0.47–1.40)	0.63 (0.34–1.17)	0.62 (0.31–1.24)
20–29	0.69 (0.39–1.22)	0.91 (0.55–1.51)	0.71 (0.40–1.25)	1.20 (0.74–1.93)
30–39	1.54 (1.03–2.30)	1.46 (0.96–2.22)	1.89 (1.32–2.70)	1.72 (1.15–2.60)
40–49	2.26 (1.65–3.09)	3.27 (2.51–4.27)	3.56 (2.76–4.58)	4.23 (3.27–5.47)
50–59	4.04 (3.23–5.04)	7.03 (5.91–8.36)	7.63 (6.47–9.00)	8.73 (7.34–10.38)
60–69	6.27 (5.00–7.85)	8.18 (6.65–10.07)	10.85 (9.04–13.02)	11.90 (9.75–14.52)
70–79	3.75 (2.18–6.47)	4.27 (2.36–7.71)	7.38 (4.45–12.24)	10.53 (5.98–18.54)
80+	0.48 (0.07–3.39)	3.45 (1.44–8.30)	7.34 (3.67–14.68)	13.57 (6.79–27.13)
Overall	2.15 (1.90–2.43)	3.10 (2.79–3.45)	3.57 (3.23–3.94)	4.00 (3.60–4.44)
Total				
0–9	0.08 (0.02–0.32)	0.09 (0.02–0.34)	0.09 (0.02–0.34)	0.05 (0.01–0.38)
10–19	0.48 (0.30–0.79)	0.89 (0.62–1.29)	0.80 (0.54–1.18)	0.99 (0.67–1.47)
20–29	2.36 (1.91–2.93)	3.15 (2.60–3.81)	4.07 (3.45–4.81)	4.50 (3.79–5.36)
30–39	8.49 (7.55–9.54)	11.92 (10.78–13.18)	13.30 (12.12–14.59)	14.32 (12.98–15.81)
40–49	8.85 (7.94–9.87)	13.60 (12.43–14.88)	15.58 (14.33–16.93)	17.92 (16.44–19.55)
50–59	7.68 (6.88–8.57)	12.56 (11.50–13.73)	13.99 (12.86–15.21)	15.44 (14.11–16.89)
60–69	8.39 (7.35–9.57)	12.86 (11.48–14.41)	15.12 (13.59–16.82)	16.83 (15.00–18.89)
70–79	5.07 (3.69–6.97)	5.80 (4.10–8.20)	9.82 (7.31–13.20)	16.01 (11.79–21.75)
80+	1.50 (0.75–3.00)	1.93 (0.92–4.05)	4.78 (2.77–8.23)	7.51 (4.16–13.57)
Overall	5.31 (5.03–5.61)	8.03 (7.67–8.40)	9.29 (8.90–9.70)	10.42 (9.96–10.90)

APS, antiphospholipid syndrome; CI, confidence interval.

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Supplementary Table 7. Yearly incidence and prevalence rates of APS subtype cases

Age, years	2016	2017	2018	2019
Incidence rates (95% CI)				
Female				
Thrombotic	1.07 (0.89–1.28)	1.17 (0.97–1.41)	1.48 (1.25–1.76)	1.76 (1.47–2.10)
Obstetric	1.00 (0.82–1.22)	0.98 (0.79–1.22)	1.33 (1.10–1.60)	1.24 (1.01–1.53)
Mixed	0.18 (0.11–0.29)	0.19 (0.12–0.32)	0.19 (0.12–0.31)	0.17 (0.10–0.30)
Other	0.34 (0.24–0.47)	0.26 (0.17–0.38)	0.41 (0.30–0.58)	0.37 (0.26–0.53)
Unknown	1.19 (0.99–1.42)	1.01 (0.82–1.23)	1.02 (0.83–1.26)	0.91 (0.72–1.15)
Male				
Thrombotic	0.68 (0.53–0.87)	0.78 (0.61–0.98)	0.99 (0.78–1.26)	0.79 (0.60–1.04)
Other	0.03 (0.01–0.09)	0.02 (0.01–0.09)	0.05 (0.02–0.13)	0.08 (0.04–0.18)
Unknown	0.09 (0.05–0.18)	0.07 (0.03–0.16)	0.15 (0.09–0.27)	0.04 (0.01–0.12)
Total				
Thrombotic	0.88 (0.76–1.02)	0.97 (0.84–1.13)	1.24 (1.08–1.43)	1.28 (1.10–1.49)
Obstetric	0.51 (0.42–0.62)	0.50 (0.40–0.62)	0.67 (0.56–0.81)	0.63 (0.51–0.78)
Mixed	0.09 (0.06–0.15)	0.10 (0.06–0.16)	0.10 (0.06–0.16)	0.09 (0.05–0.15)
Other	0.19 (0.13–0.26)	0.14 (0.10–0.21)	0.24 (0.17–0.32)	0.23 (0.16–0.32)
Unknown	0.65 (0.55–0.77)	0.55 (0.45–0.66)	0.59 (0.49–0.72)	0.48 (0.38–0.60)
Prevalence rates (95% CI)				
Female				
Thrombotic	4.06 (3.72–4.43)	5.86 (5.44–6.32)	6.61 (6.15–7.09)	7.22 (6.69–7.79)
Obstetric	1.37 (1.18–1.59)	2.38 (2.12–2.68)	3.13 (2.83–3.47)	3.70 (3.33–4.12)
Mixed	0.77 (0.63–0.94)	1.09 (0.92–1.30)	1.27 (1.08–1.50)	1.19 (0.99–1.44)
Other	0.73 (0.60–0.90)	1.14 (0.96–1.35)	1.26 (1.08–1.49)	1.51 (1.27–1.78)
Unknown	1.56 (1.36–1.80)	2.73 (2.44–3.04)	3.27 (2.96–3.61)	3.92 (3.53–4.35)
Male				
Thrombotic	1.97 (1.73–2.24)	2.74 (2.45–3.07)	3.15 (2.84–3.50)	3.46 (3.09–3.87)
Other	0.06 (0.03–0.13)	0.15 (0.09–0.24)	0.16 (0.10–0.26)	0.26 (0.17–0.39)
Unknown	0.15 (0.09–0.23)	0.28 (0.20–0.40)	0.36 (0.27–0.50)	0.40 (0.29–0.55)
Total				
Thrombotic	3.06 (2.85–3.29)	4.36 (4.09–4.64)	4.93 (4.65–5.23)	5.38 (5.05–5.73)
Obstetric	0.71 (0.61–0.83)	1.23 (1.10–1.39)	1.61 (1.45–1.78)	1.89 (1.70–2.10)
Mixed	0.40 (0.33–0.49)	0.57 (0.48–0.67)	0.65 (0.56–0.77)	0.61 (0.50–0.73)
Other	0.41 (0.34–0.50)	0.66 (0.56–0.77)	0.73 (0.63–0.85)	0.90 (0.77–1.05)
Unknown	0.88 (0.77–1.01)	1.55 (1.39–1.72)	1.86 (1.69–2.04)	2.19 (1.99–2.42)

APS, antiphospholipid syndrome; CI, confidence interval.

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Supplementary Table 8. Estimated incidence and prevalence rates from different studies of APS

Study	Country	Study period	Data source	APS type	Estimated incidence rate per 100,000 PY (95% CI)	Estimated prevalence rate per 100,000 persons (95% CI)
Khellaf et al., 2024	United States	2015–2019	Claims database	Primary, secondary, thrombotic, obstetric, mixed, CAPS	2.71 (2.45–2.99)	10.42 (9.96–10.90)
Radin et al., 2020 (8)	Italy	2010–2019	Registry	Primary	1.1 (not provided)	16.8 (not provided)
Huang et al., 2019 (6)	Korea	2008–2017	Claims database	Primary, secondary, obstetric, CAPS	7.5 (7.3–7.8)	61.9 (59.8–64.1)
Duarte-Garcia et al., 2019 (5)	United States	2000–2015	EHRs	Primary	2.1 (1.4–2.8)	50 (42–58)
Rodziewicz et al., 2019 (9)	United Kingdom	1990–2016	EHRs	Primary, SLE-related	1.8* (not provided)	43 (not provided)
Sisó-Almirall et al., 2020 (7)	Spain	2012–2017	EHRs	Not stated	Not provided	40 (not provided)
Andreoli et al., 2024 (18)	Italy	2011–2015	EHRs	Thrombotic primary; aged 18–49 years	5.0 (2.6–8.7)	22.9 (11.4–41.0)

*Peak incidence and prevalence estimates.

APS, antiphospholipid syndrome; EHR, electronic health record; CI, confidence interval; PY, person-years.

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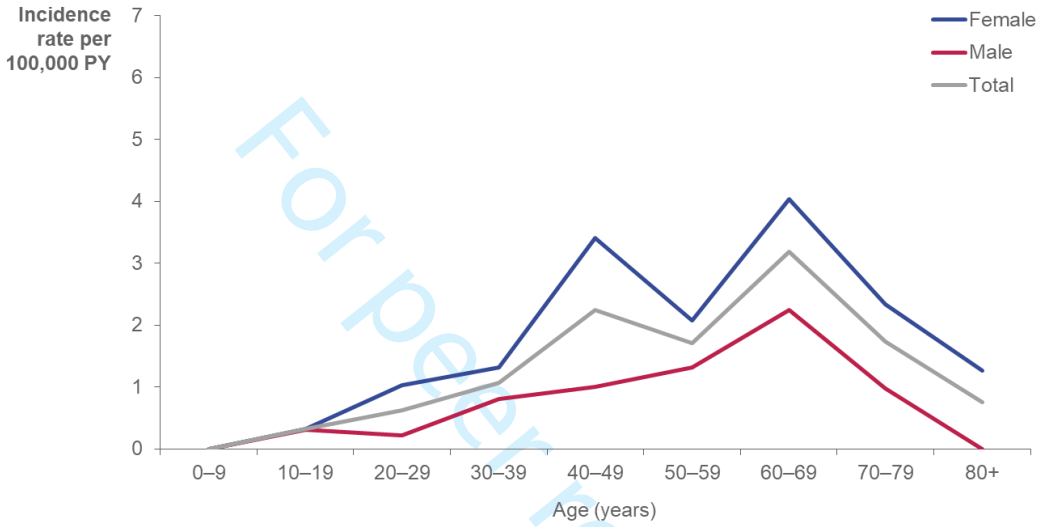
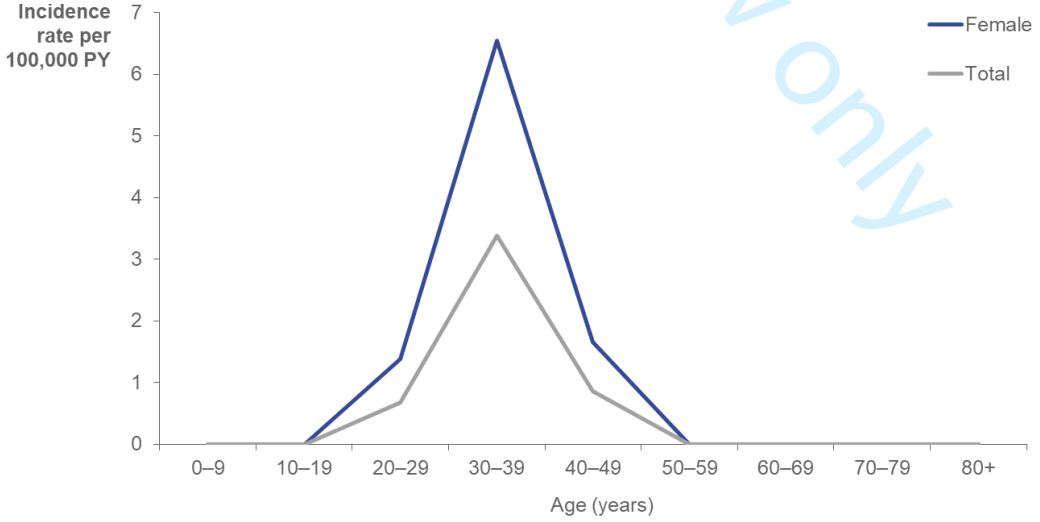
Supplementary Figure 1. Incidence rates of APS subtypes in 2019

(a) Thrombotic APS



(b) Obstetric APS



APS, antiphospholipid syndrome; PY, person-years.

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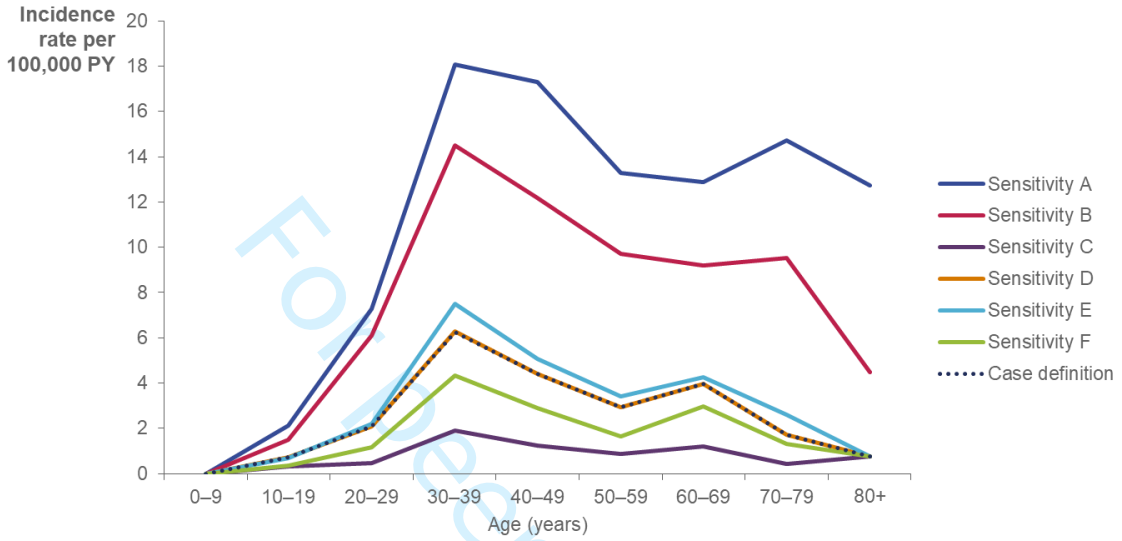
Supplementary Figure 2. Overall incidence rates of APS patients by sensitivity analysis scenarios in 2019



Case definition and scenario D yielded very similar results but are not identical. Scenario A: at least one APS diagnosis (primary or secondary) with no requirement of an aPL test. Scenario B: at least one APS diagnosis (primary or secondary) with at least one aPL test. Scenario C: at least one APS diagnosis with two aPL tests undertaken 12–26 weeks apart and 2–13 weeks before an APS diagnosis code. Scenario D: membership gap during follow-up in which the follow-up included all time at risk including during and after the gap. Scenario E: at least one diagnosis record of LAC syndrome (ICD-10 code 68.62) with two aPL tests at least 12 weeks apart and ≥1 diagnostic record of thrombotic or obstetric events according to the Sydney criteria. Scenario F: at least one of the clinical criteria (vascular thrombosis or pregnancy morbidity per the definitions in Supplementary Table 1) with at least two aPL tests undertaken at least 12 weeks apart, and a diagnosis claim for APS as a primary or secondary diagnosis on or after the second antibody test.

aPL, antiphospholipid antibody; APS, antiphospholipid syndrome; LAC, lupus anticoagulant; PY, person years.

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The incidence and prevalence of antiphospholipid syndrome (APS) in the United States (2016–2019): A retrospective database study

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The incidence and prevalence of antiphospholipid syndrome (APS) in the United States (2016–2019): A retrospective database study

Short title: Antiphospholipid syndrome incidence and prevalence

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ABSTRACT

Objective: Few epidemiological studies are reported in the published literature on the incidence or prevalence of antiphospholipid syndrome (APS), and available results are heterogeneous. This study aimed to estimate the incidence and prevalence of APS in the United States (US), overall and by APS subtype.

Design: A retrospective analysis of APS disease incidence and a cross-sectional analysis of disease prevalence.

Setting: Merative MarketScan Commercial Claims and Encounters Database, and the Medicare Supplemental and Coordination of Benefits Database.

Participants: All individuals with claims for at least two aPL tests undertaken at least 12 weeks apart, and a diagnosis claim for APS as a primary or secondary diagnosis on or after the second antibody test, during the period January 1, 2016, to December 31, 2019.

Main outcome measures: Annual incidence and prevalence of APS and APS subtypes.

Results: In total, 1708 cases of APS were identified during the study period (2016–2019), of which 83% were women. The overall annual standardized incidence rate of APS per 100,000 person-years increased slightly over the study period, from 2.31 in 2016 to 2.71 in 2019. In 2019, the estimated annual prevalence of APS per 100,000 persons was 10.42 per 100,000 persons (95% confidence interval: 9.96–10.90). Based on this and US census data, we have estimated that 34,000 persons in the US were affected by APS in 2019.

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Conclusions: These data add to the estimates of prevalence and incidence of APS in the literature, all of which have different strengths and limitations of the different data sources and case ascertainment methods.

Keywords: Antibodies, antiphospholipid; antiphospholipid syndrome; autoimmune diseases; epidemiology

Strengths and limitations of this study

- The Merative MarketScan CCAE and MDCR used in this study is a large database
- The identification of the APS claims were realized by using a unique APS-specific ICD code (D68.61) which was made available during the study period, whereas previous studies use a non-specific code
- Instead of the full Sydney criteria, a case definition proxy was applied to identify APS cases
- Given our estimate of incidence is calculated using claims from only a subset of the total US population, which is not a representative sample, it cannot be extrapolated to the full US population or populations in other countries

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INTRODUCTION

Antiphospholipid syndrome (APS) is an autoimmune disease caused by anti-phospholipid antibodies (aPLs) that results in a wide spectrum of clinical manifestations, involving the hematological, obstetrical, neurological, cardiovascular, renal, and orthopedic systems, among others.[1] Criteria aPLs include lupus anticoagulant (LAC), anti-cardiolipin (aCL), and anti-β2-glycoprotein I (anti-β2GPI) immunoglobulin (Ig) G and IgM antibodies.

According to the Sydney 2006 International Classification Criteria Consensus, clinical diagnosis of APS requires the presence of clinical symptoms associated with APS (vascular thrombosis or pregnancy morbidity) and two positive test results for aPL, 12 weeks apart.[2] Furthermore, older epidemiology studies were undertaken before LAC, aCL, and anti-β2GPI antibodies were recognized as aPLs in the 2006 update of the classification criteria.[2] As a result, few studies have been carried out to assess the epidemiology of APS, while the few data that have been published are inconsistent.[3]

Since completion of this study, a manuscript supported by the American College of Rheumatology (ACR) Board of Directors and the European Alliance of Associations for Rheumatology (EULAR) has been published, in which a new classification criterion of APS has been proposed.[4]

In the United States (US), Duarte-Garcia et al. (2019) estimated the overall annual incidence and prevalence rates of APS for patients aged ≥18 years at 2.1 per 100,000 person-years (PY) and 50 per 100,000 persons, respectively.[5] Studies worldwide have estimated incidence and prevalence ranging from 7.5 per 100,000 PY in Korea [6] to 40 per 100,000 PY in Spain,[7] and

from 16.8 per 100,000 people in the Piedmont and Aosta Valley regions [8] to 61.9 per 100,000 people in Korea,[6] respectively. Previous studies have also shown that the peak incidence of APS differs for men and women. In the UK, Rodziewicz et al. (2019) used data from the UK Clinical Practice Research Datalink to estimate the peak APS incidence of 7.5 per 100,000 PY for women occurring between the ages of 35 and 39 years, while the peak APS incidence for men was 2.2 per 100,000 PY and occurred later in life, between the ages of 55 and 59 years.[9] Prevalence of APS in the UK was also higher in women compared with men: 50 and 9.8 per 100,000 persons, respectively.[9]

The Merative MarketScan Commercial Claims and Encounters (CCAE) and Medicare Supplemental and Coordination of Benefits (MDCR) databases represent insurance claims from US employees and their dependents, from all US census regions, covering approximately 40 million persons in the US annually (Figure 1).[10] Using this large, real-world database, we aimed to retrospectively and cross-sectionally estimate the incidence and prevalence of APS in the US population during 2016 and 2019. A proxy definition for APS cases was developed using clinical variables available in the Marketscan database, with the aim to be as close as possible to the Syndey 2006 classification criteria. This study was already complete prior to the 2023 publication of the new APS classification by Barbhaiya et al.[4]

METHODS

Study design and data source

This was a retrospective, cross-sectional analysis of APS incidence and prevalence, using the CCAE and MDCR databases during the study period of January 1, 2015, to December 31, 2019

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(Figure 2). The database is Health Insurance Portability and Accountability Act compliant, and all patient data were de-identified before delivery to the study team. No ethics committee approval was required.

Patient and public involvement

Patients and their families were not involved in the design, implementation, or setting the research question or the outcome measures.

Case definition and identification

APS cases were defined as claims for at least two aPL tests undertaken at least 12 weeks apart, and a diagnosis claim for APS as a primary or secondary diagnosis on or after the second antibody test, identified from International Classification of Diseases, tenth revision (ICD-10) codes. In October 2015, APS was given a unique ICD code (D68.61) with the introduction of the Clinical Modification (CM). Prior to ICD-10-CM, APS was coded together with multiple other hypercoagulation defects into 289.81 (Primary Hypercoagulable State). Thus, cases of APS can only be ascertained from October 2015 onwards.

The Sydney International Classification Criteria Consensus case definition requires laboratory criteria (at least 12 weeks between the initial and repeated positive aPL test) and at least one of the clinical criteria (vascular thrombosis or pregnancy morbidity). An aPL test is confirmed positive if one or more of the following aPLs are detected on two or more occasions at least 12 weeks apart: (i) LAC present in plasma detected according to the International Society on Thrombosis and Haemostasis guidelines [2, 11, 12]; (ii) aCL of IgG and/or IgM isotype in serum or plasma at medium or high titer (>40 IgG or IgM phospholipid units, or >99th percentile)

measured by a standardized ELISA; or (iii) anti-β2GPI of IgG and/or IgM isotype in serum or plasma (>99th percentile) measured by a standardized ELISA.[2]

As aPL test results are not available from the CCAE and MDCR databases, a proxy was used for a positive result. If a second, repeated aPL test was carried out 12 weeks later than the first test, it was assumed at least one of the tests was positive. aPL test codes were 86148, 86146, and 86147, corresponding to aPL, anti-β2GPI, and aCL, respectively. At least one clinical criterion (vascular thrombosis or pregnancy morbidity) was added to the case definition as a sensitivity analysis. The index date was defined as the date of the first APS diagnosis which could be before, on or after the second aPL test.

Study populations and APS subtypes

The study population comprised all patients identified as having APS according to the criteria described above. Patients were also required to have at least 12 months of continued medical and pharmacy benefits memberships prior to index date (not required for children aged <1 year) from January 1, 2016, to December 31, 2019 and, for incident patients, no diagnosis record of APS (ICD-9 or ICD-10) at any time prior to the index date. APS was classified as primary APS in the absence of systemic autoimmune disease (per the Sydney 2006 International Classification Criteria Consensus [2]), however primary and secondary APS were not analyzed separately. APS subtypes were classified into five mutually exclusive categories as thrombotic APS only (with ≥1 clinical criteria as described in Supplementary Table 1), obstetric APS only (women aged ≥14 years only with ≥1 clinical criteria as described in Supplementary Table 1), mixed APS (both thrombotic APS and obstetric APS events; women aged ≥14 years only), other APS manifestations not included in the Sydney criteria (Supplementary Tables 1 and 2), and APS

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type unknown (APS cases that were not linked to any clinical criteria relating to the listed subtypes). In addition, catastrophic APS (CAPS) was analyzed as a subtype of thrombotic and mixed APS, defined as thrombosis in three or more organs developing in less than a week. This definition was as close as possible to the 10th and 14th International Congress on Antiphospholipid Antibodies definitions,[13-15] without the required information on aPL status and biopsy, which was not available in this database.

Study outcomes and statistical analyses

Distribution of APS subtypes by age and sex during 2016–2019, and by specialty involved in the first APS diagnosis for the period 2018–2019, were assessed. Overall distribution of CAPS was calculated and presented as one result for the aggregated incident cohort. The annual incidence and prevalence of APS and APS subtypes were calculated by age and sex in each calendar year from 2016 to 2019. Incidence of APS was age- and sex-standardized indirectly to the US 2020 population by using age- and sex-specific population census data as weights and applying them to the age- and sex-specific incidence rates.[16]

Incidence, the number of new APS cases during a specific time period,[17] was reported as a rate per 100,000 PY. Person-time was defined as the sum of each patient's duration of follow-up from January 1 to December 31 of each year, to the end of the patient record, to the end of the first insurance claim if there was a gap greater than 60 days, or to the APS diagnosis – whichever came first. Incidence was calculated as the number of incident cases divided by the person-time of observation per year. The annual incidence rate was calculated as the number of incident cases in a year divided by the person-time corresponding to that year. Prevalence, the proportion of the population with APS in a given time period,[17] was expressed as

prevalence per 100,000 persons. The denominator was all patients in the CCAE and MDCR database on July 1 of each year. The annual prevalence rate was calculated as prevalent cases in a year divided by the overall population corresponding to that year. The 95% confidence interval (CI) of the prevalence and incidence rates were estimated by the Poisson distribution.[18]

Sensitivity analysis

To assess the robustness of the case definition in this study, a number of alternative case definitions were considered for the incidence and prevalence calculation. Patients could have one of the following: (A) at least one APS diagnosis (primary or secondary) with no requirement of an aPL test; (B) at least one APS diagnosis (primary or secondary) with at least one aPL test; (C) at least one APS diagnosis with two aPL tests undertaken 12–26 weeks apart and 2–13 weeks before an APS diagnosis code; (D) for a patient with a membership gap during follow-up, the follow-up included all time at risk including during and after the gap (i.e., they were analyzed as if there was no gap); (E) at least one diagnosis record of LAC syndrome (ICD-10 code 68.62) with two aPL tests at least 12 weeks apart and ≥1 diagnostic record of thrombotic or obstetric events according to the Sydney criteria; or (F) at least one of the clinical criteria (vascular thrombosis or pregnancy morbidity per the definitions in Supplementary Table 1) with at least two aPL tests undertaken at least 12 weeks apart, and a diagnosis claim for APS as a primary or secondary diagnosis on or after the second antibody test (Supplementary Table 3).

All statistical analyses were performed using SAS Version 9.4

RESULTS

Baseline characteristics

A total of 1708 cases of APS that met our case definition during 2016–2019 were identified, with the majority being women (n=1411, 83%; Table 1, Supplementary Table 4). For women, the number of incident APS cases was highest among the 25–44 years age category (n=706, 50.0%), and 376 (26.6%) patients had obstetric APS. For men, the number of incident APS cases was highest among patients aged 45–64 years (n=201, 67.7%). The overall number of pediatric APS cases was small (n=23), with most cases identified within the 15–17 years age category (n=16) for both female and male patients. Thrombotic APS was the most frequent subtype identified (n=728, 42.6%), followed by APS of unknown subtype (n=404, 23.7%), obstetric APS (n=376, 22.0%), other APS (n=138, 8.1%), and mixed APS (n=62, 3.6%). Seventy-five cases of CAPS were identified, representing 4.4% of all APS cases. The acute care hospital was the most frequently visited healthcare specialty site for diagnosis (n=227, 26.9%), followed by laboratory (n=161, 19.1%), rheumatology (n=89, 10.5%), internal medicine (n=87, 10.3%), obstetrics and gynecology (n=72, 8.5%) and hematology (n=70, 8.3%). Other categories for APS diagnoses included oncology, family practice, pathology, neurology, multispecialty, and medical doctors.

Table 1. Overall incident APS cases by baseline gender and age distribution, and APS subtype

	Total (2016–2019) N=1708	
	Male	**Female**
n (%)	297 (17.4)	1411 (82.6)
Age, years, n (%)		
Adults		
18–24	10 (3.4)	67 (4.7)
25–44	49 (16.5)	706 (50.0)
45–64	201 (67.7)	580 (41.1)
65+	28 (9.4)	44 (3.1)
Subtotal	288 (97.0)	1397 (99.0)
Pediatric		
0–4	1 (0.3)	1 (0.1)
5–9	1 (0.3)	0
10–14	1 (0.3)	3 (0.2)
15–17	6 (2.0)	10 (0.7)
Subtotal	9 (3.0)	14 (1.0)
Catastrophic APS, n (%)	27 (9.1)	48 (3.4)
APS subtype, n (%)		
Thrombotic	251 (84.5)	477 (33.8)
Obstetric	0	376 (26.6)
Mixed	0	62 (4.4)
Other	16 (5.4)	122 (8.6)
Unknown	30 (10.1)	374 (26.5)

Incidence of APS

The overall annual incidence rate of APS per 100,000 PY (95% confidence interval [CI]) standardized to the US 2020 population census increased slightly over the study period, from 2.31 (2.11–2.53) in 2016 to 2.84 (2.59–3.11) and 2.71 (2.45–2.99) in 2018 and 2019, respectively (Figure 3). Over the whole study period, the APS incidence rates were higher in women, potentially due to certain subtypes being applicable to women only. In 2019, the annual incidence rate (standardized to the US 2020 population census) was 4.45 (3.99–4.96) per 100,000 PY for women, and 0.91 (0.71–1.17) per 100,000 PY for men. The incidence rate of APS in women was always highest in patients aged 30–39 years old, ranging from 10.09 per 100,000 PY in 2016 to 11.80 and 11.22 per 100,000 PY in 2018 and 2019 (Supplementary Table 5). However, in men, the age categories with the highest incidence rates varied each year (Supplementary Table 5).

Prevalence of APS

The estimated annual prevalence of APS per 100,000 persons (95% CI) was 10.42 per 100,000 persons (9.96–10.90) in 2019 (Figure 3). In 2019, APS prevalence among women was four times higher than in men: 16.59 (15.78–17.45) and 4.00 (3.60–4.44) per 100,000 persons, respectively. Based on this and US census data, we have estimated that slightly more than 34,000 persons in the US were affected by APS in 2019. Among women, the prevalence rate of APS was highest in the 40–49 years age group, ranging from 14.71 in 2016 to 30.61 per 100,000 persons in 2019. Among men, APS prevalence was highest in patients aged 60–69 years old between 2016 (6.27 per 100,000 persons) and 2018 (10.85 per 100,000 persons), and in patients aged 80+ years in 2019 (13.57 per 100,000 persons) (Supplementary Table 6).

Incidence rates of APS subtypes

Incidence rates of APS subtype were standardized to the US 2020 population census. In 2019, the overall annual incidence (95% CI) of thrombotic APS was 1.28 (1.10–1.49) per 100,000 PY, which was the highest incidence over the study period. The 2019 annual incidence rate of thrombotic APS patients was higher in women (1.76 per 100,000 PY) than in men (0.79 per 100,000 PY) (Supplementary Figure 1a). In 2019, among women only, the incidence rate of obstetric APS was 1.24 (1.01–1.53) per 100,000 PY (Supplementary Figure 1b), and the incidence rate of mixed APS was 0.17 (0.10–0.30) per 100,000 PY. The other APS cases represent 8.1% of the total APS population, with an overall annual incidence rate in 2019 of 0.23 (0.16–0.32) per 100,000 PY. The unknown APS cases represent almost a quarter (23.65%) of the total APS population, with an overall incidence rate in 2019 of 0.48 (0.38–0.60) per 100,000 PY (Supplementary Table 7).

Prevalence rates of APS subtypes

The overall annual prevalence (95% CI) of thrombotic APS was 5.38 (5.05–5.73) per 100,000 persons in 2019, and the annual prevalence rate of thrombotic APS was higher in women compared to men over the whole study period. The annual prevalence of obstetric APS subtype among women only was 3.70 (3.33–4.12) per 100,000 persons in 2019, and the highest prevalence rate of obstetric APS was in those aged 30–39 years old (12.98 [11.24–15.00] per 100,000 persons). The annual prevalence of mixed APS was 1.19 (0.99–1.44) per 100,000 persons in 2019, among women only. The overall annual prevalence rates of other APS and unknown APS in 2019 were 0.90 (0.77–1.05) per 100,000 persons and 2.19 (1.99–2.42) per 100,000 persons, respectively (Supplementary Table 7).

Sensitivity analysis

Outcomes from a sensitivity analysis for different predefined scenarios for the last year of the study period, 2019, are shown in Supplementary Figure 2. The outcomes obtained from the rest of the study years were similar to those for 2019, and the subtypes of APS showed the same behaviors for the sensitivity analysis as for the overall APS cases.

DISCUSSION

The incidence and prevalence of APS in the US have been assessed using the large CCAE and MDCR databases, which includes claims data on more than 60 million insured US employees and their dependents. Our data suggest there is a trend towards a yearly increase in incidence and prevalence of APS over time, which may be a product of generally increased awareness of the disease.[3] Additionally, adoption of the ICD-10 code in 2015 may have also contributed to the observed increase in prevalence.

There are a number of published studies that aimed to assess the incidence and prevalence of APS in different countries around the world,[5-9, 19] which revealed important clinical and epidemiological information on APS in their respective regions (Supplementary Table 8). However, the incidence and prevalence estimates reported vary, likely due to the variation in APS case definitions, design across studies, and the type of database analyzed, which may result in variation in socioeconomic demographics among the populations included.[3]

In particular, our sensitivity analysis shows that differences in incidence rates are apparent when using different diagnostic scenarios, thus results may be sensitive to the case definition used. This is evident when evaluating studies in the literature, as one pertinent difference

between them was the method used for identification of APS cases. A study of the incidence and prevalence of APS cases in Korea, identified from the Korean Health Insurance and Review Agency, used the Korean Classification of Disease, 7th edition code D68.6 (other thrombophilia), which corresponds to ICD-10: D68.6 and includes anticardiolipin syndrome, APS, and the presence of lupus anticoagulant, and V253 code of rare intractable disease to confirm APS cases.[6] Therefore, the identification and retrieval of APS cases was not exhaustive, which might affect the accuracy of identification. Radin et al. (2020) estimated the incidence and prevalence from the Piedmont and Aosta Valley regional registry, a part of the Italian National Registry of Rare Diseases, but data from the National Registry are not reported.[8] The study was carried out between 2010 and 2019, but the authors do not report on how the cases were ascertained or coded, or whether the Sydney criteria were used, and the potential completeness of the registry has not been described.[8] Duarte-Garcia et al. (2019) included data from a population-based study run in the Mayo Clinic, Olmsted County, between 2000 and 2015.[5] While this study provided a rich clinical and epidemiological knowledge of APS, the authors acknowledged that outcomes could only be generalized to populations with the same demographic profile.[5] In addition, the study sample size of only 33 patients after applying the Sydney criteria does not allow extrapolation of outcomes to the country level.[5] In the present study, the specific APS code, D68.61, was used to identify patients since the switch from ICD-9-CM to ICD-10-CM in October 2015, and the prior period was excluded to avoid any misclassification or underestimation of APS cases.

Our standardized estimate of APS incidence (2.31 per 100,000 PY in 2016 to a high of 2.71 per 100,000 PY in 2019) is higher than the incidence reported from the Piedmont and Aosta Valley

regions in Italy,[8] and also higher than that reported in the previous US (2.1 per 100,000 PY) and UK (1.8 per 100,000 PY) studies.[5, 9] The study in South Korea reported a higher incidence rate (7.5 per 100,000 PY) than found in any of the other studies [6]. Our estimation of prevalence rate (10.42 per 100,000 persons in 2019) was close to that estimated for the Piedmont and Aosta Valley region (16.8 per 100,000 persons).[8] In other studies, prevalence rates ranged from 40 per 100,000 persons in Spain,[7] to 61.9 per 100,000 persons in South Korea.[6] The UK study estimated that prevalence rates were 43 per 100,000 persons,[9] while the Olmsted County study in the US had an estimated prevalence of 50 per 100,000 persons.[5] The difference in the population inclusion and the design of the study might explain the heterogeneity of prevalence rates estimation. When assessing APS subtype, the overall annual standardized incidences of thrombotic APS and obstetric APS in 2019 were 1.28 per 100,000 PY, and 1.24 per 100,000 PY, respectively. These incidences are close to those reported by Duarte-Garcia et al. (2019), but far from those reported by Andreoli et al. (2013), who estimated the overall annual incidence of thrombotic APS by the indirect method as 1.8 and 65 per 100,000 PY, respectively, and 0.2 and 15 per 100,000 PY, respectively, for obstetric APS.[5, 20]

It has been previously estimated that CAPS patients represent less than 1% of all patients with APS, owing to the life-threatening nature of CAPS that requires high clinical awareness.[13] However, the proportion of CAPS cases in the present study was substantially higher (4.4%), and more in line with the proportion (3.0%) reported by Hwang et al. (2020) in Korea.[6] This discrepancy could be attributed to the classification criteria for CAPS, which require the knowledge of aPL test result and a biopsy, neither of which were available in the present study

and in the study conducted in Korea. As a result, it is possible that the number of CAPS cases were overestimated in both studies.

This study has several limitations, inherent to retrospective epidemiological studies, and the use of insurance claims databases. Firstly, the Merative MarketScan CCAE and MDCR are commercial insurance databases and under-represent smaller employers, and persons aged under 65 years with no occupational health insurance. The CCAE also excludes those with state-funded insurance. Additionally, any medical history prior to membership of an insurance plan will also be excluded, and it is possible that some patients were diagnosed with APS prior to entering the MarketScan database. Similarly, the MDCR captures information only for the subset of Medicare patients who have supplemental insurance paid by their employers. As a result, our estimate of incidence is calculated using claims from only a subset of the total US population, and therefore may not be fully accurate or generalizable and extrapolated. Secondly, the data is collected for billing of insurance claims, and the validity of the claims is reliant upon the accuracy of the data in the claims, therefore may not truly reflect medical diagnosis. Thirdly, antibody titers were not available, and not all APS claims were linked to the clinical criteria as required per the Sydney classification.[2] Thus, the case definition used in this study, although based on the Sydney classification criteria,[2] is not complete. We have minimized this limitation by using a case definition that requires two aPL test claims at least 12 weeks apart, plus an APS diagnosis claim on or after the second laboratory diagnosis. However, there are no data to confirm that these tests yielded positive and persistent results. This missing information could result in cases being classified as APS which do not meet the Sydney criteria, thus overestimating the incidence and prevalence of APS in the US. The lack of aPL data

is a limitation inherent to the database, which may have contributed to very few populational studies in the literature on the prevalence of aPL and a lack of standardization between aPL tests. Relatedly, to ensure that we captured every possible APS case, we did not limit APS claims to include only those with a clinical manifestation. Nevertheless, a sensitivity analysis (Scenario F) has been considered including the condition of clinical criteria (per the Sydney classification) linked to APS claims. These patients, classified as 'Unknown' in our study, may have therefore had a specific clinical manifestation or APS subtype that was not captured. For example, data may have been incomplete for obstetric APS if patients were misclassified as 'Unknown' but were pregnant at the time or even after the period of identification. Indeed, a peak in incidence and prevalence of APS, irrespective of subtype, is observed in women of child-bearing age that is not observed in men (Supplementary Tables 5 and 6). Additionally, some of the confidence intervals were wide ranging, owing to variability in the number of events per category, and should be interpreted with caution. A further limitation of the case definition is that primary and secondary APS were not separated. Finally, absence of a unique ICD code for APS prior to introduction of ICD-10-CM in October 2015 limits the ability to estimate APS incidence and prevalence prior to 2016. Our estimation of prevalence from 2016 to 2019 is likely to under-ascertain prevalent cases diagnosed prior to October 2015. The impact of this underestimation of prevalence will be most pronounced in the years immediately after the change in ICD coding.

Very few epidemiological studies are reported in the published literature on the incidence or prevalence of APS, and estimates reported in these studies are heterogeneous. A careful interpretation should be considered when comparing these results to other countries that may

have a different healthcare system with variations in APS management, including treatment administration, as well as possible socioeconomic differences.

This study identified a trend towards a yearly increase in incidence and prevalence of APS in the US over the study period. The results of this study add to existing estimates published in the literature, but further studies are needed to fully elucidate the global epidemiology of APS using the 2023 classification criteria of APS by Barbhaiya et al.[4]

DATA AVAILABILITY STATEMENT

Data from non-interventional studies is outside of UCB's data sharing policy and is unavailable for sharing.

ETHICS STATEMENTS

Patient consent for publication

Not applicable.

Ethics approval

The CCAE and MDCR databases are Health Insurance Portability and Accountability Act compliant, and all patient data were de-identified before delivery to the study team. No ethics committee approval was required.

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CONTRIBUTORS

M. Khellaf, P. Meisner, M. Sarno, P. Zaremba, A. Jedrzejczyk, and A. Scowcroft provided substantial contributions to the conception or design of the work, analysis, or interpretation of data. A. Scowcroft is responsible for the overall content as guarantor. All authors revised the work for important intellectual content and provided approval of the final version to be published.

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COMPETING INTERESTS

Meheni Khellaf, Piotr Zaremba and Adam Jedrzejczyk are contractors employed by UCB. Paul Meisner, Maria Sarno and Anna Scowcroft are employees and stockholders of UCB.

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FIGURE LEGENDS

Figure 1. MarketScan research databases [10]

Figure 2. Study design

aPL, antiphospholipid antibody; APS, antiphospholipid syndrome; ICD, International Classification of Diseases.

Figure 3. Yearly incidence and prevalence rates of APS cases

Lines represent incidence rates per 100,000 PY, bars represent prevalence rates per 100,000 persons.

APS, antiphospholipid syndrome; PY, person-years.

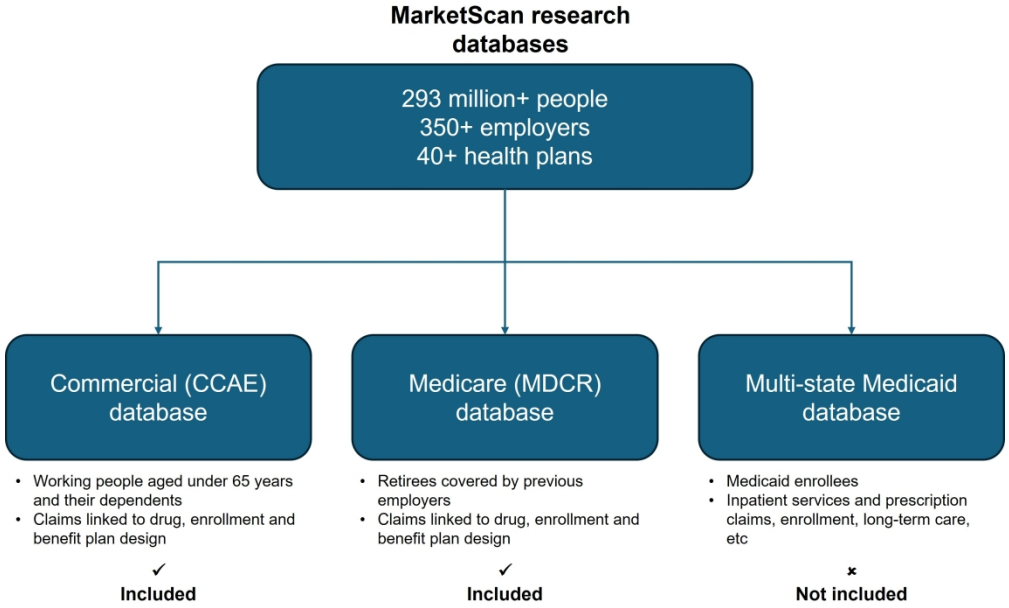

Figure 1. MarketScan research databases (10)

265x165mm (330 x 330 DPI)

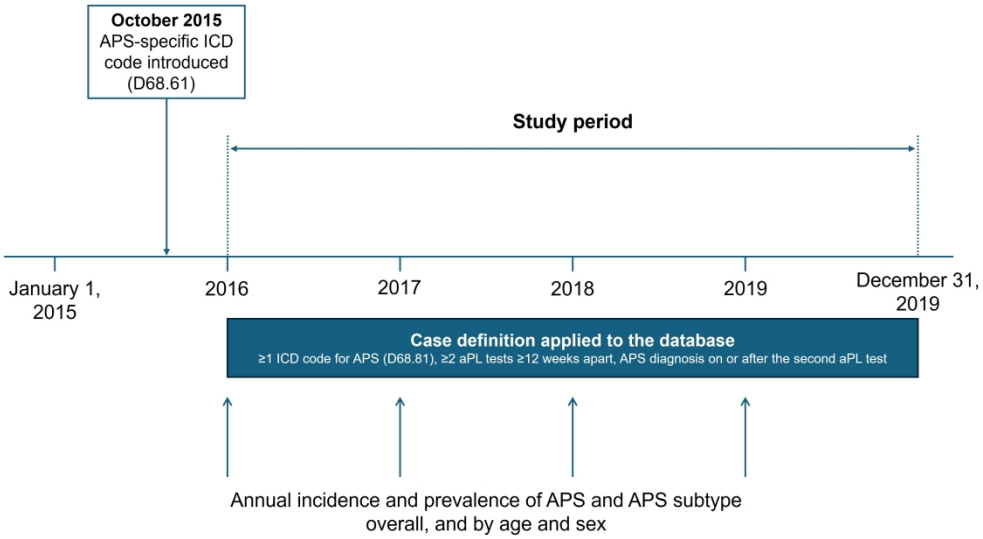

Figure 2. Study design

322x174mm (330 x 330 DPI)

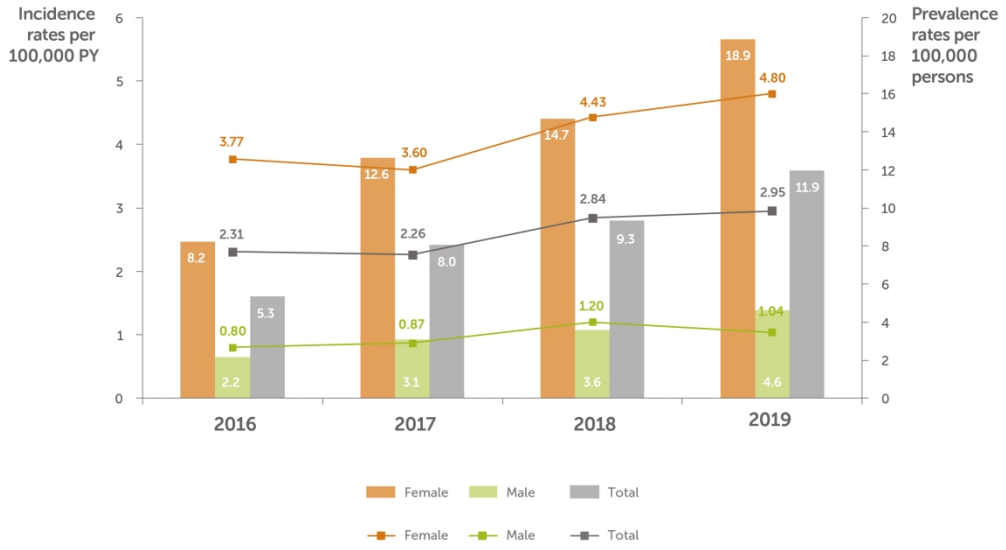

Figure 3. Yearly incidence and prevalence rates of APS cases

240x151mm (300 x 300 DPI)

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The incidence and prevalence of antiphospholipid syndrome (APS) in the United States (2016–2019): A retrospective database study

Supporting information

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Supplementary Table 1. Thrombotic and obstetric events included in the Sydney criteria

Thrombotic events	ICD-9-CM	ICD-10-CM
Arterial thromboembolism	444	I74
Cavernous sinus thrombosis	437.6	I67.6
Cerebral infarction (including ischemic stroke)	434	I63, I69.3
Cerebral venous sinus thrombosis,	437.6	I67.6
Coronary thrombosis (without infarct)	-	I24.0
Myocardial infarction	410, 411.0, 412, 429.7	I21-I23, I24.1, I25.2
Personal history of venous thrombosis	Baseline variable only V12.51, V12.54, V12.55	Baseline variable only Z68.711, Z68.718 Z68.73
Pulmonary embolism (acute or chronic)	415.1, 416.2	I26
Pulmonary hypertension (thromboembolic)	416.8	I27.2
Retinal vein occlusion, including amaurosis fugax	362.3	H34, G45.3
Thrombotic microangiopathy (acute)	446.6	M31.1
Transient ischemic attack	435	G45
Venous thromboembolism, including thrombosis or embolism of: Portal vein Hepatic vein (Budd-Chiari Syndrome) Renal vein thrombosis Vena cava & thoracic veins Deep veins of lower extremity (acute) Deep veins of lower extremity (chronic) Veins of upper extremity (acute) Veins of upper extremity (chronic) Axillary vein Subclavian vein Internal jugular vein Other specified vein Unspecified vein Thrombophlebitis migraines	452, 453	I81, I82
Thrombotic events during pregnancy or postpartum		
Cerebral venous sinus thrombosis	671.5	O22.5, O87.3
Deep vein thrombosis	671.3 671.4	O87.1, O22.3
Obstetric thromboembolism	673.2	O88.2

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Obstetric events		
Eclampsia	642.6	O15
History of recurrent pregnancy loss	Baseline variable only 629.81,646.3	Baseline variable only N96, O26.2
Low birth weight infant	764 V21.3	P05.0, P05.1 P05.9, P07.0, P07.1
Miscarriage or spontaneous abortion (due to natural causes before week 20)*	634,761.8	O03
Poor fetal growth, including placental insufficiency	656.5, V28.4	O36.5, Z36.4
Pre-eclampsia	642.4-642.7	O11, O14
Short-gestation birth (before week 37)	644.2, 765.0-765.2	O60.1, P07.2, P07.3
Stillbirth or late pregnancy loss (due to natural causes, week 20+)	632, 656.4, 779.9, V27.1, V27.4, V27.7	O02.1, O36.4, P95, Z37.1, Z37.4, Z37.7
Threatened preterm labor (before week 37)	644.0	O60.0, O60.2, O47.0

Diagnosis codes were selected to be compatible with the manifestations included in the Sydney 2006 International Classification Criteria and with those extra-criteria manifestations which are likely to be linked to the presence of anti-phospholipid antibodies.

*Multiple miscarriages or spontaneous abortions is defined using ICD code in table 7 and requires at least 3 miscarriages or 3 spontaneous abortions in the patients record. Events should be at least 4 months apart.

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Supplementary Table 2. APS manifestations not in the Sydney criteria

Events	ICD-9-CM	ICD-10-CM
Chorea	333.5	G25.5
Epilepsy	345	G40
Gangrene with peripheral vascular disease (excluding atherosclerosis)	249.7, 250.7, 785.4	E08.52, E09.52, E10.52, E11.52, E12.52, E13.52 I73.01, I96
Hemolytic anemia (acquired)	283	D58
Ulcers (excluding pressure ulcers)	707.1, 707.8, 707.9	L97, L98.4
Livedo reticularis/ Livedo vasculitis	782.61, 709.1	R23.1/ L95.0
Mitral and aortic valve diseases (non-rheumatic)	424.0, 424.1	I34, I35
Osteonecrosis (idiopathic)	No specific code	M87.1
Thrombocytopenia (idiopathic or primary)	287.3, 287.5	D69.3, D69.4, D69.6
Vascular dementia	290.4	F01

Diagnosis codes were selected to be compatible with the manifestations included in the Sydney 2006 International Classification Criteria and with those extra-criteria manifestations which are likely to be linked to the presence of anti-phospholipid antibodies.

APS, antiphospholipid syndrome.

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Supplementary Table 3. Case definitions used in main analysis and sensitivity analysis

	≥1 APS diagnosis claim*	≥1 LAC syndrome diagnosis claim	≥1 diagnostic record of thrombotic or obstetric events†	≥1 clinical criteria (vascular thrombosis or pregnancy morbidity)	≥1 aPL test‡	≥2 aPL tests‡ ≥12 weeks apart	≥2 aPL tests‡ 12–26 weeks apart	APS diagnosis on or after the second aPL test‡	APS diagnosis 2–13 weeks after the second aPL test‡
Case definition used	✓					✓		✓	
Sensitivity scenario A	✓								
Sensitivity scenario B	✓				✓				
Sensitivity scenario C	✓						✓		✓
Sensitivity scenario D§	✓					✓		✓	
Sensitivity scenario E		✓	✓			✓			
Sensitivity scenario F	✓			✓		✓		✓	

*Primary or secondary. †According to Sydney criteria. ‡Test status unavailable. §Identical to case definition without follow-up ap

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Supplementary Table 4. Incident APS cases by baseline gender and age distribution, and APS subtype

	2016		2017		2018		2019		Total	
	Male	Female	Male	Female	Male	Female	Male	Female	Male	Female
	N=458		N=406		N=459		N=385		N=1708	
n (%)	77 (16.8)	381 (83.2)	76 (18.7)	330 (81.2)	82 (17.9)	377 (82.1)	62 (16.1)	323 (83.9)	297 (17.4)	1411 (82.6)
Age, years, n (%)										
Adults										
18–24	4 (5.2)	17 (4.5)	1 (1.3)	14 (4.2)	2 (2.4)	15 (4.0)	3 (4.8)	21 (6.5)	10 (3.4)	67 (4.7)
25–44	9 (11.6)	185 (48.6)	16 (21.1)	164 (49.7)	11 (13.4)	191 (50.7)	13 (21.0)	166 (51.4)	49 (16.5)	706 (50.0)
45–64	53 (68.8)	161 (42.3)	53 (69.7)	143 (43.3)	56 (68.3)	155 (41.1)	39 (62.9)	121 (37.5)	201 (67.7)	580 (41.1)
65+	8 (10.3)	15 (3.9)	5 (6.6)	6 (1.8)	11 (13.4)	12 (3.2)	4 (6.5)	11 (3.4)	28 (9.4)	44 (3.1)
Subtotal	74 (96.1)	378 (99.2)	75 (96.7)	327 (99.1)	80 (97.6)	373 (98.9)	59 (95.2)	319 (98.8)	288 (97.0)	1397 (99.0)
Pediatric										
0–4	0	1 (0.3)	0	0	1 (1.2)	0	0	0	1 (0.3)	1 (0.1)
5–9	1 (1.3)	0	0	0	0	0	0	0	1 (0.3)	0
10–14	1 (1.3)	1 (0.3)	0	2 (0.6)	0	0	0	0	1 (0.3)	3 (0.2)
15–17	1 (1.3)	1 (0.3)	1 (1.3)	1 (0.3)	1 (1.2)	4 (1.1)	3 (4.8)	1 (0.3)	6 (2.0)	10 (0.7)
Subtotal	3 (3.9)	3 (0.8)	1 (1.3)	3 (0.9)	2 (2.4)	4 (1.1)	3 (4.8)	1 (0.3)	9 (3.0)	14 (1.0)
Catastrophic APS, n (%)	–	–	–	–	–	–	–	–	27 (9.1)	48 (3.4)
APS subtype, n (%)										
Thrombotic	65 (84.4)	113 (29.6)	68 (89.5)	112 (33.9)	65 (79.3)	131 (34.7)	53 (85.5)	121 (37.5)	251 (84.5)	477 (33.8)
Obstetric	0	95 (24.9)	0	82 (24.8)	0	109 (28.9)	0	90 (27.9)	0	376 (26.6)
Mixed	0	17 (4.5)	0	16 (4.8)	0	16 (4.2)	0	13 (4.0)	0	62 (4.4)
Other	3 (3.9)	34 (8.9)	2 (2.6)	25 (7.6)	5 (6)	34 (9)	6 (9.7)	29 (9.0)	16 (5.4)	122 (8.6)
Unknown	9 (11.7)	122 (32)	6 (7.9)	95 (28.8)	12 (14.6)	87 (23)	3 (4.8)	70 (21.7)	30 (10.1)	374 (26.5)

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Supplementary Table 5. Yearly incidence rates of APS cases per 100,000 person years (95% CI) by age category

Age, years	2016	2017	2018	2019
Female				
0–9	0.12 (0.02–0.85)	0	0	0
10–19	0.41 (0.17–0.99)	0.64 (0.30–1.34)	0.57 (0.25–1.26)	1.08 (0.58–2.01)
20–29	2.61 (1.82–3.76)	2.46 (1.66–3.64)	3.64 (2.62–5.04)	3.90 (2.78–5.45)
30–39	10.09 (8.42–12.09)	9.87 (8.15–11.96)	11.80 (9.88–14.09)	11.22 (9.25–13.61)
40–49	7.06 (5.81–8.57)	6.75 (5.48–8.32)	7.19 (5.85–8.84)	7.44 (5.98–9.24)
50–59	4.58 (3.68–5.71)	4.44 (3.50–5.62)	5.14 (4.10–6.44)	4.07 (3.09–5.35)
60–69	3.59 (2.65–4.85)	3.41 (2.44–4.78)	4.88 (3.62–6.58)	5.38 (3.95–7.34)
70–79	1.61 (0.72–3.57)	1.12 (0.36–3.46)	1.11 (0.28–4.43)	2.34 (0.75–7.25)
80+	0.33 (0.05–2.34)	0	2.45 (0.79–7.59)	1.26 (0.18–8.97)
Overall	3.77 (3.41–4.17)	3.60 (3.23–4.01)	4.43 (4.01–4.91)	4.45 (3.99–4.96)
Male				
0–9	0.11 (0.02–0.81)	0	0.13 (0.02–0.92)	0
10–19	0.32 (0.12–0.85)	0.18 (0.04–0.70)	0.09 (0.01–0.64)	0.41 (0.16–1.10)
20–29	0.18 (0.05–0.72)	0.10 (0.01–0.70)	0.50 (0.21–1.21)	0.33 (0.11–1.02)
30–39	0.49 (0.21–1.18)	0.75 (0.36–1.58)	0.65 (0.29–1.45)	0.93 (0.47–1.86)
40–49	1.34 (0.83–2.15)	1.73 (1.11–2.68)	1.34 (0.81–2.22)	1.09 (0.61– 1.98)
50–59	1.80 (1.23–2.63)	2.04 (1.41–2.96)	1.75 (1.17–2.64)	1.66 (1.06–2.60)
60–69	1.88 (1.20–2.95)	1.83 (1.12–2.98)	3.01 (2.02–4.49)	2.39 (1.47–3.90)
70–79	0.62 (0.15–2.47)	0	3.23 (1.34–7.75)	0.98 (0.14–6.94)
80+	0	1.46 (0.37–5.85)	2.35 (0.59–9.40)	0
Overall	0.80 (0.64–1.00)	0.87 (0.69–1.09)	1.20 (0.96–1.48)	0.91 (0.71–1.17)
Total				
0–9	0.12 (0.03–0.47)	0	0.07 (0.01–0.47)	0
10–19	0.36 (0.19–0.70)	0.40 (0.21–0.77)	0.32 (0.15–0.68)	0.74 (0.44–1.25)
20–29	1.40 (0.98–1.98)	1.28 (0.87–1.88)	2.07 (1.52–2.81)	2.08 (1.50–2.86)
30–39	5.61 (4.70–6.70)	5.60 (4.65–6.74)	6.54 (5.50–7.78)	6.25 (5.19–7.52)
40–49	4.37 (3.65–5.23)	4.39 (3.63–5.30)	4.43 (3.66–5.36)	4.39 (3.58–5.39)
50–59	3.29 (2.72–3.98)	3.31 (2.72–4.04)	3.54 (2.90–4.31)	2.92 (2.31–3.69)
60–69	2.80 (2.18–3.60)	2.67 (2.03–3.53)	3.99 (3.14–5.07)	3.97 (3.05–5.15)
70–79	1.15 (0.57–2.29)	0.59 (0.19–1.84)	2.09 (1.00–4.38)	1.73 (0.65–4.62)
80+	0.20 (0.03–1.41)	0.59 (0.15–2.37)	2.41 (1.00–5.78)	0.75 (0.11–5.32)
Overall	2.31 (2.11–2.53)	2.26 (2.05–2.49)	2.84 (2.59–3.11)	2.71 (2.45–2.99)

APS, antiphospholipid syndrome; CI, confidence interval.

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Supplementary Table 6. Yearly prevalence rates of APS cases per persons (95% CI) by age category

Age, years	2016	2017	2018	2019
Female				
0–9	0.08 (0.01–0.59)	0.09 (0.01–0.62)	0.09 (0.01–0.62)	0
10–19	0.56 (0.29–1.07)	0.98 (0.59–1.62)	0.98 (0.59–1.62)	1.38 (0.86–2.22)
20–29	3.98 (3.16–5.02)	5.32 (4.33–6.54)	7.37 (6.19–8.77)	7.86 (6.52–9.48)
30–39	14.59 (12.92–16.48)	21.20 (19.12–23.51)	23.65 (21.48–26.04)	26.18 (23.64–28.98)
40–49	14.71 (13.10–16.52)	22.84 (20.76–25.13)	26.51 (24.27–28.95)	30.61 (27.91–33.56)
50–59	10.87 (9.58–12.34)	17.47 (15.75–19.37)	19.76 (17.92–21.79)	21.60 (19.44–24.00)
60–69	10.23 (8.68–12.05)	17.00 (14.84–19.46)	18.97 (16.64–21.63)	21.29 (18.48–24.52)
70–79	6.20 (4.19–9.18)	7.13 (4.65–10.94)	11.85 (8.24–17.06)	20.42 (14.19–29.38)
80+	2.17 (1.03–4.55)	0.92 (0.23–3.68)	3.07 (1.28–7.36)	3.43 (1.11–10.64)
Overall	8.22 (7.74–8.74)	12.62 (11.99–13.28)	14.69 (14.01–15.40)	16.59 (15.78–17.45)
Male				
0–9	0.08 (0.01–0.56)	0.08 (0.01–0.59)	0.08 (0.01–0.59)	0.11 (0.01–0.75)
10–19	0.42 (0.20–0.87)	0.81 (0.47–1.40)	0.63 (0.34–1.17)	0.62 (0.31–1.24)
20–29	0.69 (0.39–1.22)	0.91 (0.55–1.51)	0.71 (0.40–1.25)	1.20 (0.74–1.93)
30–39	1.54 (1.03–2.30)	1.46 (0.96–2.22)	1.89 (1.32–2.70)	1.72 (1.15–2.60)
40–49	2.26 (1.65–3.09)	3.27 (2.51–4.27)	3.56 (2.76–4.58)	4.23 (3.27–5.47)
50–59	4.04 (3.23–5.04)	7.03 (5.91–8.36)	7.63 (6.47–9.00)	8.73 (7.34–10.38)
60–69	6.27 (5.00–7.85)	8.18 (6.65–10.07)	10.85 (9.04–13.02)	11.90 (9.75–14.52)
70–79	3.75 (2.18–6.47)	4.27 (2.36–7.71)	7.38 (4.45–12.24)	10.53 (5.98–18.54)
80+	0.48 (0.07–3.39)	3.45 (1.44–8.30)	7.34 (3.67–14.68)	13.57 (6.79–27.13)
Overall	2.15 (1.90–2.43)	3.10 (2.79–3.45)	3.57 (3.23–3.94)	4.00 (3.60–4.44)
Total				
0–9	0.08 (0.02–0.32)	0.09 (0.02–0.34)	0.09 (0.02–0.34)	0.05 (0.01–0.38)
10–19	0.48 (0.30–0.79)	0.89 (0.62–1.29)	0.80 (0.54–1.18)	0.99 (0.67–1.47)
20–29	2.36 (1.91–2.93)	3.15 (2.60–3.81)	4.07 (3.45–4.81)	4.50 (3.79–5.36)
30–39	8.49 (7.55–9.54)	11.92 (10.78–13.18)	13.30 (12.12–14.59)	14.32 (12.98–15.81)
40–49	8.85 (7.94–9.87)	13.60 (12.43–14.88)	15.58 (14.33–16.93)	17.92 (16.44–19.55)
50–59	7.68 (6.88–8.57)	12.56 (11.50–13.73)	13.99 (12.86–15.21)	15.44 (14.11–16.89)
60–69	8.39 (7.35–9.57)	12.86 (11.48–14.41)	15.12 (13.59–16.82)	16.83 (15.00–18.89)
70–79	5.07 (3.69–6.97)	5.80 (4.10–8.20)	9.82 (7.31–13.20)	16.01 (11.79–21.75)
80+	1.50 (0.75–3.00)	1.93 (0.92–4.05)	4.78 (2.77–8.23)	7.51 (4.16–13.57)
Overall	5.31 (5.03–5.61)	8.03 (7.67–8.40)	9.29 (8.90–9.70)	10.42 (9.96–10.90)

APS, antiphospholipid syndrome; CI, confidence interval.

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Supplementary Table 7. Yearly incidence and prevalence rates of APS subtype cases

Age, years	2016	2017	2018	2019
Incidence rates (95% CI)				
Female				
Thrombotic	1.07 (0.89–1.28)	1.17 (0.97–1.41)	1.48 (1.25–1.76)	1.76 (1.47–2.10)
Obstetric	1.00 (0.82–1.22)	0.98 (0.79–1.22)	1.33 (1.10–1.60)	1.24 (1.01–1.53)
Mixed	0.18 (0.11–0.29)	0.19 (0.12–0.32)	0.19 (0.12–0.31)	0.17 (0.10–0.30)
Other	0.34 (0.24–0.47)	0.26 (0.17–0.38)	0.41 (0.30–0.58)	0.37 (0.26–0.53)
Unknown	1.19 (0.99–1.42)	1.01 (0.82–1.23)	1.02 (0.83–1.26)	0.91 (0.72–1.15)
Male				
Thrombotic	0.68 (0.53–0.87)	0.78 (0.61–0.98)	0.99 (0.78–1.26)	0.79 (0.60–1.04)
Other	0.03 (0.01–0.09)	0.02 (0.01–0.09)	0.05 (0.02–0.13)	0.08 (0.04–0.18)
Unknown	0.09 (0.05–0.18)	0.07 (0.03–0.16)	0.15 (0.09–0.27)	0.04 (0.01–0.12)
Total				
Thrombotic	0.88 (0.76–1.02)	0.97 (0.84–1.13)	1.24 (1.08–1.43)	1.28 (1.10–1.49)
Obstetric	0.51 (0.42–0.62)	0.50 (0.40–0.62)	0.67 (0.56–0.81)	0.63 (0.51–0.78)
Mixed	0.09 (0.06–0.15)	0.10 (0.06–0.16)	0.10 (0.06–0.16)	0.09 (0.05–0.15)
Other	0.19 (0.13–0.26)	0.14 (0.10–0.21)	0.24 (0.17–0.32)	0.23 (0.16–0.32)
Unknown	0.65 (0.55–0.77)	0.55 (0.45–0.66)	0.59 (0.49–0.72)	0.48 (0.38–0.60)
Prevalence rates (95% CI)				
Female				
Thrombotic	4.06 (3.72–4.43)	5.86 (5.44–6.32)	6.61 (6.15–7.09)	7.22 (6.69–7.79)
Obstetric	1.37 (1.18–1.59)	2.38 (2.12–2.68)	3.13 (2.83–3.47)	3.70 (3.33–4.12)
Mixed	0.77 (0.63–0.94)	1.09 (0.92–1.30)	1.27 (1.08–1.50)	1.19 (0.99–1.44)
Other	0.73 (0.60–0.90)	1.14 (0.96–1.35)	1.26 (1.08–1.49)	1.51 (1.27–1.78)
Unknown	1.56 (1.36–1.80)	2.73 (2.44–3.04)	3.27 (2.96–3.61)	3.92 (3.53–4.35)
Male				
Thrombotic	1.97 (1.73–2.24)	2.74 (2.45–3.07)	3.15 (2.84–3.50)	3.46 (3.09–3.87)
Other	0.06 (0.03–0.13)	0.15 (0.09–0.24)	0.16 (0.10–0.26)	0.26 (0.17–0.39)
Unknown	0.15 (0.09–0.23)	0.28 (0.20–0.40)	0.36 (0.27–0.50)	0.40 (0.29–0.55)
Total				
Thrombotic	3.06 (2.85–3.29)	4.36 (4.09–4.64)	4.93 (4.65–5.23)	5.38 (5.05–5.73)
Obstetric	0.71 (0.61–0.83)	1.23 (1.10–1.39)	1.61 (1.45–1.78)	1.89 (1.70–2.10)
Mixed	0.40 (0.33–0.49)	0.57 (0.48–0.67)	0.65 (0.56–0.77)	0.61 (0.50–0.73)
Other	0.41 (0.34–0.50)	0.66 (0.56–0.77)	0.73 (0.63–0.85)	0.90 (0.77–1.05)
Unknown	0.88 (0.77–1.01)	1.55 (1.39–1.72)	1.86 (1.69–2.04)	2.19 (1.99–2.42)

APS, antiphospholipid syndrome; CI, confidence interval.

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Supplementary Table 8. Estimated incidence and prevalence rates from different studies of APS

Study	Country	Study period	Data source	APS type	Estimated incidence rate per 100,000 PY (95% CI)	Estimated prevalence rate per 100,000 persons (95% CI)
Khellaf et al., 2024	United States	2015–2019	Claims database	Primary, secondary, thrombotic, obstetric, mixed, CAPS	2.71 (2.45–2.99)	10.42 (9.96–10.90)
Radin et al., 2020 (8)	Italy	2010–2019	Registry	Primary	1.1 (not provided)	16.8 (not provided)
Huang et al., 2019 (6)	Korea	2008–2017	Claims database	Primary, secondary, obstetric, CAPS	7.5 (7.3–7.8)	61.9 (59.8–64.1)
Duarte-Garcia et al., 2019 (5)	United States	2000–2015	EHRs	Primary	2.1 (1.4–2.8)	50 (42–58)
Rodziewicz et al., 2019 (9)	United Kingdom	1990–2016	EHRs	Primary, SLE-related	1.8* (not provided)	43 (not provided)
Sisó-Almirall et al., 2020 (7)	Spain	2012–2017	EHRs	Not stated	Not provided	40 (not provided)
Andreoli et al., 2024 (18)	Italy	2011–2015	EHRs	Thrombotic primary; aged 18–49 years	5.0 (2.6–8.7)	22.9 (11.4–41.0)

*Peak incidence and prevalence estimates.

APS, antiphospholipid syndrome; EHR, electronic health record; CI, confidence interval; PY, person-years.

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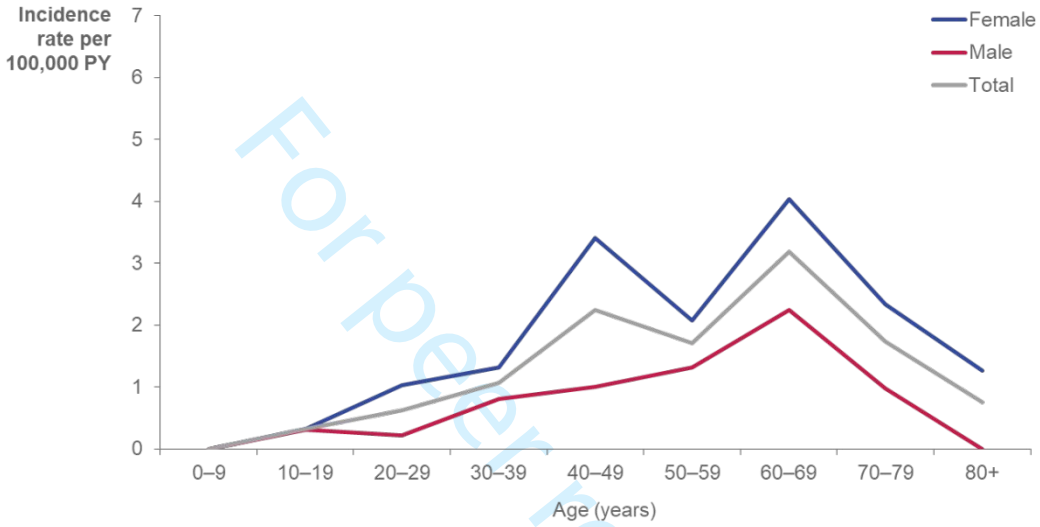
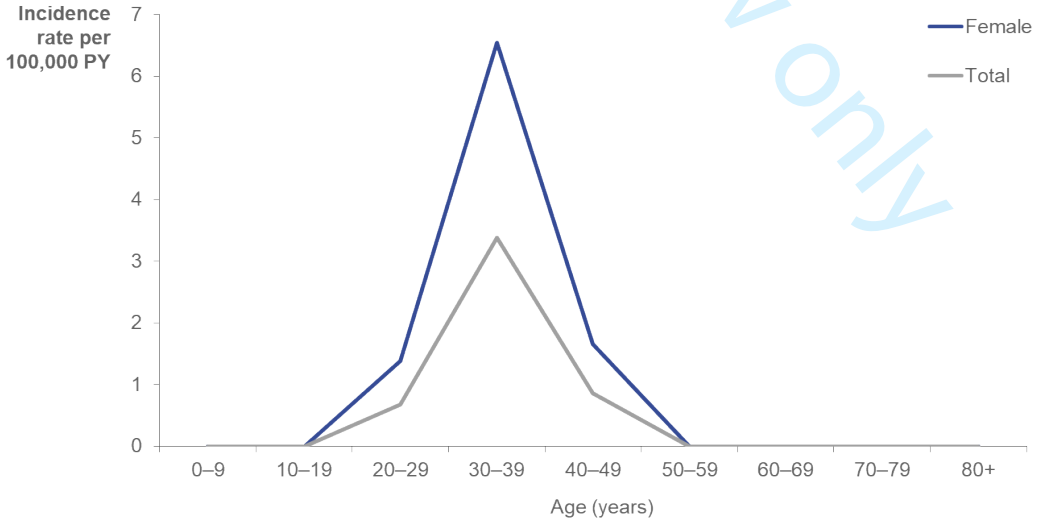
Supplementary Figure 1. Incidence rates of APS subtypes in 2019

(a) Thrombotic APS



(b) Obstetric APS



APS, antiphospholipid syndrome; PY, person-years.

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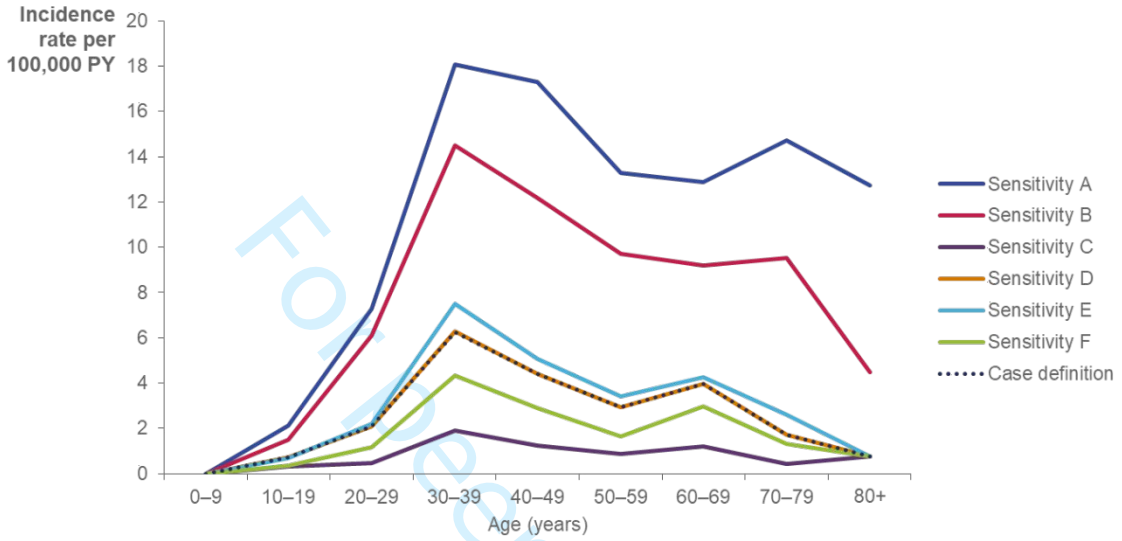
Supplementary Figure 2. Overall incidence rates of APS patients by sensitivity analysis scenarios in 2019



Case definition and scenario D yielded very similar results but are not identical. Scenario A: at least one APS diagnosis (primary or secondary) with no requirement of an aPL test. Scenario B: at least one APS diagnosis (primary or secondary) with at least one aPL test. Scenario C: at least one APS diagnosis with two aPL tests undertaken 12–26 weeks apart and 2–13 weeks before an APS diagnosis code. Scenario D: membership gap during follow-up in which the follow-up included all time at risk including during and after the gap. Scenario E: at least one diagnosis record of LAC syndrome (ICD-10 code 68.62) with two aPL tests at least 12 weeks apart and ≥1 diagnostic record of thrombotic or obstetric events according to the Sydney criteria. Scenario F: at least one of the clinical criteria (vascular thrombosis or pregnancy morbidity per the definitions in Supplementary Table 1) with at least two aPL tests undertaken at least 12 weeks apart, and a diagnosis claim for APS as a primary or secondary diagnosis on or after the second antibody test.

aPL, antiphospholipid antibody; APS, antiphospholipid syndrome; LAC, lupus anticoagulant; PY, person years.