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BMJ Open

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

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lupus-2023-000902.R1 (transferred from Lupus Science & Medicine to BMJ Open)

The incidence and prevalence of antiphospholipid syndrome (APS) in the United States (2016–2019) Short title: Antiphospholipid syndrome incidence and prevalence Author list, affiliations and degree information: Meheni Khellaf^{1,2}, Paul Meisner³, Maria Sarno⁴, Piotr Zaremba⁵, Adam Jedrzejczyk⁶, Anna Scowcroft⁷ ¹Global Real World Evidence, UCB Pharma, Brussels, Belgium; ²Life Sciences, Planet Pharma, London, United Kingdom; ³Global Clinical & Regulatory Strategy Rare Disease, UCB Pharma, Raleigh, United States; ⁴Translational Medicine Immunology and Oncology, UCB Pharma, Slough, United Kingdom; ⁵Real World Data Analytics Team, UCB Pharma, Katowice, Poland; ⁶Real World Data Analytics Team, UCB Pharma, Warsaw, Poland; ⁷Global Real World Evidence, UCB Pharma, Slough, United Kingdom. **Corresponding author:** Anna Scowcroft Address: 208 Bath Road, Slough, SL1 3WE, United Kingdom Tel: +44 1753 534655 Email: anna.scowcroft@ucb.com

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1 2		lupus-2023-000902.R1 (transferred from Lupus Science & Medicine to BMJ Open)		
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57 58 59		Page 2 of 25		
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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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2 3 4	48	Conclusions: These data add to the estimates of prevalence and incidence of APS in the
5 6 7	49	literature, all of which have different strengths and limitations of the different data sources and
8 9	50	case ascertainment methods.
10 11 12	51	Keywords: Antibodies, antiphospholipid; antiphospholipid syndrome; autoimmune diseases;
13 14 15	52	epidemiology
$\begin{array}{c} 15\\ 16\\ 17\\ 18\\ 19\\ 20\\ 21\\ 22\\ 23\\ 24\\ 25\\ 26\\ 27\\ 28\\ 29\\ 30\\ 31\\ 32\\ 33\\ 34\\ 35\\ 36\\ 37\\ 38\\ 39\\ 40\\ 41\\ 42\\ 43\\ 44\\ 45\\ 46\\ 47\\ 48\\ 49\\ 50\\ 51\\ \end{array}$	53	epidemiology
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Strengths and limitations of this study

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

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2		
3 4 5	72	INTRODUCTION
5 6 7	73	Antiphospholipid syndrome (APS) is an autoimmune disease caused by anti-phospholipid
8 9	74	antibodies (aPLs) that results in a wide spectrum of clinical manifestations, involving the
10 11 12	75	hematological, obstetrical, neurological, cardiovascular, renal, and orthopedic systems, among
13 14	76	others.(1) aPLs include lupus anticoagulant (LAC), anti-cardiolipin (aCL), and
15 16 17	77	anti-β2-glycoprotein I (anti-β2GPI) immunoglobulin (Ig) G and IgM antibodies.
18 19 20	78	According to the Sydney 2006 International Classification Criteria Consensus, clinical diagnosis
21 22	79	of APS requires the presence of clinical symptoms associated with APS (vascular thrombosis or
23 24 25	80	pregnancy morbidity) and two positive test results for aPL, 12 weeks apart.(2) However, there is
26 27	81	no standardized use of confirmatory aPL tests or titer cut-off points in epidemiological studies.
28 29 30	82	Low-titer, transient aPL that is not associated with disease can be detected in 5–10% of
30 31 32	83	asymptomatic persons.(3) It is this background presence of asymptomatic aPL in the general
33 34 35 36 37 38 39 40 41 42	84	population which complicates attempts to assess the incidence and prevalence of APS.
	85	Furthermore, older epidemiology studies were undertaken before LAC, aCL, and anti- β 2GPI
	86	antibodies were recognized as aPLs in the 2006 update of the classification criteria.(2) As a
	87	result, few studies have been carried out to assess the epidemiology of APS, while the few data
43 44	88	that have been published are inconsistent.(4)
45 46 47	89	Since completion of this study, a manuscript supported by the American College of
48 49 50	90	Rheumatology (ACR) Board of Directors and the European Alliance of Associations for
51 52	91	Rheumatology (EULAR) has been published, in which a new classification criterion of APS has
53 54 55 56	92	been proposed.(5)

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3 4	93	In the United States (US), Duarte-Garcia et al. (2019) estimated the overall a
5 6 7	94	and prevalence rates of APS for patients aged \geq 18 years at 2.1 per 100,000
7 8 9	95	and 50 per 100,000 persons, respectively.(6) Studies worldwide have estimation
10 11	96	prevalence ranging from 7.5 per 100,000 PY in Korea (7) to 40 per 100,000 F
12 13 14	97	from 16.8 per 100,000 people in the Piedmont and Aosta Valley regions (9)
15 16	98	people in Korea,(7) respectively. Previous studies have also shown that the
17 18 10	99	APS differs for men and women. In the UK, Rodziewicz et al. (2019) used da
19 20 21	100	Clinical Practice Research Datalink to estimate the peak APS incidence of 7.
22 23	101	women occurring between the ages of 35 and 39 years, while the peak APS
24 25 26 27 28 29 30 31 32 33 34	102	was 2.2 per 100,000 PY and occurred later in life, between the ages of 55 ar
	103	Prevalence of APS in the UK was also higher in women compared with men
	104	100,000 persons, respectively.(10)
	105	The Merative MarketScan Commercial Claims and Encounters (CCAE) and M
35 36	106	Supplemental and Coordination of Benefits (MDCR) databases represent ins
37 38 39	107	US employees and their dependents, from all US census regions, covering a
39 40 41 42 43 44 45 46	108	million persons in the US annually. Using this large, real-world database, we
	109	retrospectively and cross-sectionally estimate the incidence and prevalence
	110	population during 2016 and 2019. We have used the Sydney 2006 classifica
47 48	111	because the variables required to apply the criterion or create proxy variabl
49 50 51	112	criterion are part of the MarketScan database. This study was already comp

arcia et al. (2019) estimated the overall annual incidence ients aged ≥18 years at 2.1 per 100,000 person-years (PY) tively.(6) Studies worldwide have estimated incidence and 0,000 PY in Korea (7) to 40 per 100,000 PY in Spain,(8) and e Piedmont and Aosta Valley regions (9) to 61.9 per 100,000 evious studies have also shown that the peak incidence of the UK, Rodziewicz et al. (2019) used data from the UK o estimate the peak APS incidence of 7.5 per 100,000 PY for s of 35 and 39 years, while the peak APS incidence for men ed later in life, between the ages of 55 and 59 years.(10) o higher in women compared with men: 50 and 9.8 per cial Claims and Encounters (CCAE) and Medicare Benefits (MDCR) databases represent insurance claims from s, from all US census regions, covering approximately 50 Using this large, real-world database, we aimed to ly estimate the incidence and prevalence of APS in the US We have used the Sydney 2006 classification criterion, pply the criterion or create proxy variables to define the n 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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114	METHODS
115	Study design and data source
116	This was a retrospective, cross-sectional analysis of APS incidence and prevalence, using the
117	CCAE and MDCR databases during the study period of January 1, 2015, to December 31, 2019.
118	The database is Health Insurance Portability and Accountability Act compliant, and all patient
119	data were de-identified before delivery to the study team. No ethics committee approval was
120	required.
121	Patient involvement
122	Patients and their families were not involved in the design, implementation, or setting the research
123	question or the outcome measures.
124	Case definition and identification
125	APS cases were defined as claims for at least two aPL tests undertaken at least 12 weeks apart,
126	and a diagnosis claim for APS as a primary or secondary diagnosis on or after the second
127	antibody test, identified from International Classification of Diseases, tenth revision (ICD-10)
128	codes. In October 2015, APS was given a unique ICD code (D68.61) with the introduction of the
129	Clinical Modification (CM). Prior to ICD-10-CM, APS was coded together with multiple other
130	hypercoagulation defects into 289.81 (Primary Hypercoagulable State). Thus, cases of APS can
131	only be ascertained from October 2015 onwards.
132	The Sydney International Classification Criteria Consensus case definition requires laboratory
133	criteria (at least 12 weeks between the initial and repeated positive aPL test) and at least one of
134	the clinical criteria (vascular thrombosis or pregnancy morbidity). An aPL test is confirmed
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2 3 4	135	positive if one or more of the following aPLs are detected on two or more occasions at least 12
5 6 7	136	weeks apart: (i) LAC present in plasma detected according to the International Society on
7 8 9	137	Thrombosis and Haemostasis guidelines (2, 11, 12); (ii) aCL of IgG and/or IgM isotype in serum
10 11	138	or plasma at medium or high titer (>40 IgG or IgM phospholipid units, or >99th percentile)
12 13 14	139	measured by a standardized ELISA; or (iii) anti- β 2GPI of IgG and/or IgM isotype in serum or
15 16 17	140	plasma (>99th percentile) measured by a standardized ELISA.(2)
18 19	141	As aPL test results are not available from the CCAE and MDCR databases, a proxy was used for a
20 21 22	142	positive result. If a second, repeated aPL test was carried out 12 weeks later than the first test,
23 24	143	it was assumed at least one of the tests was positive. aPL test codes were 86148, 86146, and
25 26 27	144	86147, corresponding to aPL, anti- β 2GPI, and aCL, respectively. At least one clinical criterion
28 29	145	(vascular thrombosis or pregnancy morbidity) was added to the case definition as a sensitivity
30 31 32	146	analysis. The index date was defined as the date of the first APS diagnosis which could be
33 34	147	before, on or after the second aPL test.
35 36 37	148	Study populations and APS subtypes
38 39 40	149	The study population comprised all patients identified as having APS according to the criteria
40 41 42	150	described above. Patients were also required to have at least 12 months of continued medical
43 44	151	and pharmacy benefits memberships prior to index date (not required for children aged
45 46 47	152	<1 year) from January 1, 2016, to December 31, 2019 and, for incident patients, no diagnosis
48 49	153	record of APS (ICD-9 or ICD-10) at any time prior to the index date. APS was classified as
50 51 52	154	primary APS in the absence of systemic autoimmune disease (per the Sydney 2006 International
53 54	155	Classification Criteria Consensus (2)), however primary and secondary APS were not analyzed
55 56 57	156	separately. APS subtypes were classified into five mutually exclusive categories as thrombotic
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2 3 4 5 6 7 8 9 10 11 12	157	APS only, obstetric APS only (women aged \geq 14 years only), mixed APS (both thrombotic APS
	158	and obstetric APS events; women aged ≥14 years only), other APS manifestations not included
	159	in the Sydney criteria (Supplementary Tables 1 and 2), and APS type unknown. In addition,
	160	catastrophic APS (CAPS) was analyzed as a subtype of thrombotic and mixed APS, defined as
13 14	161	thrombosis in three or more organs developing in less than a week. This definition was as close
15 16 17	162	as possible to the 10 th and 14 th International Congress on Antiphospholipid Antibodies
18 19	163	definitions,(13-15) without the required information on aPL status and biopsy, which was not
20 21 22	164	available in this database.
23 24	165	Study outcomes and statistical analyses
25 26 27	166	Distribution of APS subtypes by age and sex during 2016–2019, and by specialty involved in the
27 28 29 30 31 32 33 34 35 36 37 38 39 40 41 42	167	first APS diagnosis for the period 2018–2019, were assessed. Overall distribution of CAPS was
	168	calculated and presented as one result for the aggregated incident cohort. The annual incidence
	169	and prevalence of APS and APS subtypes were calculated by age and sex in each calendar year
	170	from 2016 to 2019. Incidence of APS was age- and sex-standardized indirectly to the US 2020
	171	population by using age- and sex-specific population census data as weights and applying them
	172	to the age- and sex-specific incidence rates.(16)
43 44	173	Incidence, the number of new APS cases during a specific time period,(17) was reported as a
45 46 47	174	rate per 100,000 PY. Person-time was defined as the sum of each patient's duration of follow-
48 49	175	up from January 1 to December 31 of each year, to the end of the patient record, to the end of
50 51 52	176	the first insurance claim if there was a gap greater than 60 days, or to the APS diagnosis –
53 54	177	whichever came first. Incidence was calculated as the number of incident cases divided by the
55 56 57	178	person-time of observation per year. The annual incidence rate was calculated as the number
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3 	179	of incident cases in a year divided by the person-time corresponding to that year. Prevalence,
5	180	the proportion of the population with APS in a given time period,(17) was expressed as
3	181	prevalence per 100,000 persons. The denominator was all patients in the CCAE and MDCR
0 1	182	database on July 1 of each year. The annual prevalence rate was calculated as prevalent cases
2 3 4	183	in a year divided by the overall population corresponding to that year. The 95% confidence
5 6	184	interval (CI) of the prevalence and incidence rates were estimated by the Poisson
7 8 9	185	distribution.(18)
20 21 22	186	Sensitivity analysis
23 24	187	To assess the robustness of the case definition in this study, a number of alternative case
25 26 27	188	definitions were considered for the incidence and prevalence calculation. Patients could have
28 29	189	one of the following: (A) at least one APS diagnosis (primary or secondary) with no requirement
80 81 82	190	of an aPL test; (B) at least one APS diagnosis (primary or secondary) with at least one aPL test;
83 84	191	(C) at least one APS diagnosis with two aPL tests undertaken 12–26 weeks apart and 2–13
85 86	192	weeks before an APS diagnosis code; (D) for a patient with a membership gap during follow-up,
87 88 89	193	the follow-up included all time at risk including during and after the gap (i.e., they were treated
40 41	194	as if there was no gap); (E) at least one diagnosis record of LAC syndrome (ICD-10 code 68.62)
2 3 4	195	with two aPL tests at least 12 weeks apart and ≥1 diagnostic record of thrombotic or obstetric
15 16	196	events according to the Sydney criteria; or (F) at least one of the clinical criteria (vascular
17 18 19	197	thrombosis or pregnancy morbidity per the definitions in Supplementary Table 1) with at least
50 51	198	two aPL tests undertaken at least 12 weeks apart, and a diagnosis claim for APS as a primary or
52 53	199	secondary diagnosis on or after the second antibody test. All statistical analyses were
54 55 56	200	performed using SAS Version 9.4.
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2 3 4	201	RESULTS
5 6 7	202	Baseline characteristics
8 9 10	203	A total of 1708 cases of APS that met our case definition during 2016–2019 were identified,
10 11 12	204	with the majority being women (n=1411, 83%; Table 1). For women, the number of incident
13 14 15	205	APS cases was highest among the 25–44 years age category (n=706, 50.0%), and 376 (26.6%)
16 17	206	patients had obstetric APS. For men, the number of incident APS cases was highest among
18 19 20	207	patients aged 45–64 years (n=201, 67.7%). The overall number of pediatric APS cases was small
20 21 22	208	(n=23), with most cases identified within the 15–17 years age category (n=16) for both female
23 24	209	and male patients. Thrombotic APS was the most frequent subtype identified (n=728, 42.6%),
25 26 27	210	followed by APS of unknown subtype (n=404, 23.7%), obstetric APS (n=376, 22.0%), other APS
28 29	211	(n=138, 8.1%), and mixed APS (n=62, 3.6%). Seventy-five cases of CAPS were identified,
30 31 32	212	representing 4.4% of all APS cases. The acute care hospital was the most frequently visited
33 34	213	healthcare specialty site for diagnosis (n=227, 26.9%), followed by laboratory (n=161, 19.1%),
35 36 37	214	rheumatology (n=89, 10.5%), internal medicine (n=87, 10.3%), obstetrics and gynecology (n=72,
38 39	215	8.5%) and hematology (n=70, 8.3%). Other categories for APS diagnoses included oncology,
40 41 42	216	family practice, pathology, neurology, multispecialty, and medical doctors.
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18	Table 1. Incident APS cases b	by baseline gender an	d age distribution, and APS su	ubtype.
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	Male	Female	Male	Female	Male	Female	Male	feemate	Male	Female
		458		406		459		385 ° D		.708
n (%)	77 (16.8)	381 (83.2)	76 (18.7)	330 (81.2)	82 (17.9)	377 (82.1)	62 (16.1)	32% (188.9)	297 (17.4)	1411 (82
Age, years, n (%)								nbe sei(s re		
Adults								r 20 ynei late		
18–24	4 (5.2)	17 (4.5)	1 (1.3)	14 (4.2)	2 (2.4)	15 (4.0)	3 (4.8)	himber 2024. [hiseignement srelated20	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)		49 (16.5)	706 (50.
45–64	53 (68.8)	161 (42.3)	<mark>5</mark> 3 (69.7)	143 (43.3)	56 (68.3)	155 (41.1)	39 (62.9)	124 687.5)	201 (67.7)	580 (41.
65+	8 (10.3)	15 (3.9)	5 (6.6)	6 (1.8)	11 (13.4)	12 (3.2)	4 (6.5)		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 mini	288 (97.0)	1397 (99
Pediatric		1						mini		
0–4	0	1 (0.3)	0	0	1 (1.2)	0	0	Ģ 0 <mark>t</mark>	1 (0.3)	1 (0.1)
5–9	1 (1.3)	0	0	0	0	0	0	Al traini	1 (0.3)	0
10–14	1 (1.3)	1 (0.3)	0	2 (0.6)	0	0	0	ain 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)	ų (1. <mark>≱</mark>)	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)	a (1.2)	9 (3.0)	14 (1.0
Catastrophic APS, n (%)	_	-	-	-	_		_		27 (9.1)	48 (3.4
APS subtype, n (%)	I	1					6,	similar		1
Thrombotic	65 (84.4)	113 (29.6)	68 (89.5)	112 (33.9)	65 (79.3)	131 (34.7)	53 (85.5)	12∰ (3≝5)	251 (84.5)	477 (33.
Obstetric	0	95 (24.9)	0	82 (24.8)	0	109 (28.9)	0	9 8 (2799)	0	376 (26.
Mixed	0	17 (4.5)	0	16 (4.8)	0	16 (4.2)	0	1000 (4100)	0	62 (4.4
Other	3 (3.9)	34 (8.9)	2 (2.6)	25 (7.6)	5 (6)	34 (9)	6 (9.7)	249 (9.9)	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	30 (10.1)	374 (26.

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2 3 4	221	Incidence of APS
5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34 35 36 37 38 39 40 41 42 43	222	The overall annual incidence rate of APS per 100,000 PY (95% confidence interval [CI])
	223	standardized to the US 2020 population census increased slightly over the study period, from
	224	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,
	225	respectively (Figure 1). Over the whole study period, the APS incidence rates were higher in
	226	women, potentially due to certain subtypes being applicable to women only. In 2019, the
	227	annual incidence rate (standardized to the US 2020 population census) was 4.45 (3.99–4.96)
	228	per 100,000 PY for women, and 0.91 (0.71–1.17) per 100,000 PY for men. The incidence rate of
	229	APS in women was always highest in patients aged 30–39 years old, ranging from 10.09 per
	230	100,000 PY in 2016 to 11.80 and 11.22 per 100,000 PY in 2018 and 2019 (Supplementary Table
	231	3). However, in men, the age categories with the highest incidence rates varied each year
	232	(Supplementary Table 3).
	233	Prevalence of APS
	234	The estimated annual prevalence of APS per 100,000 persons (95% CI) was 10.42 per 100,000
	235	persons (9.96–10.90) in 2019 (Figure 1). In 2019, APS prevalence among women was four times
	236	higher than in men: 16.59 (15.78–17.45) and 4.00 (3.60–4.44) per 100,000 persons,
	237	respectively. Based on this and US census data, we have estimated that slightly more than
44 45 46	238	34,000 persons in the US were affected by APS in 2019. Among women, the prevalence rate of
47 48	239	APS was highest in the 40–49 years age group, ranging from 14.71 in 2016 to 30.61 per 100,000
49 50 51	240	persons in 2019. Among men, APS prevalence was highest in patients aged 60–69 years old
52 53	241	between 2016 (6.27 per 100,000 persons) and 2018(10.85 per 100,000 persons), and in patients
54 55 56	242	aged 80+ years in 2019 (13.57 per 100,000 persons) (Supplementary Table 4).
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243	Incidence rates of APS subtypes
244	Incidence rates of APS subtype were standardized to the US 2020 population census. In 2019,
245	the overall annual incidence (95% CI) of thrombotic APS was 1.28 (1.10–1.49) per 100,000 PY,
246	which was the highest incidence over the study period. The 2019 annual incidence rate of
247	thrombotic APS patients was higher in women (1.76 per 100,000 PY) than in men (0.79 per
248	100,000 PY) (Supplementary Figure 1a). In 2019, among women only, the incidence rate of
249	obstetric APS was 1.24 (1.01–1.53) per 100,000 PY (Supplementary Figure 1b), and the
250	incidence rate of mixed APS was 0.17 (0.10–0.30) per 100,000 PY. The other APS cases
251	represent 8.1% of the total APS population, with an overall annual incidence rate in 2019 of
252	0.23 (0.16–0.32) per 100,000 PY. The unknown APS cases represent almost a quarter (23.65%)
253	of the total APS population, with an overall incidence rate in 2019 of 0.48 (0.38–0.60) per
254	100,000 PY (Supplementary Table 5).
254 255	100,000 PY (Supplementary Table 5). Prevalence rates of APS subtypes
255	Prevalence rates of APS subtypes
255 256	Prevalence rates of APS subtypes The overall annual prevalence (95% CI) of thrombotic APS was 5.38 (5.05–5.73) per 100,000
255 256 257	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
255 256 257 258	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
255 256 257 258 259	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
255 256 257 258 259 260	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
255 256 257 258 259 260 261	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
255 256 257 258 259 260 261 262	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

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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

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1 2		
3 4	286	between them was the method used for identification of APS cases. A study of the incidence
5 6 7 8 9 10 11 12 13 14 15 16 17 18 19	287	and prevalence of APS cases in Korea, identified from the Korean Health Insurance and Review
	288	Agency, used the Korean Classification of Disease, 7th edition code D68.6 (other
	289	thrombophilia), which corresponds to ICD-10: D68.6 and includes anticardiolipin syndrome,
	290	APS, and the presence of lupus anticoagulant, and V253 code of rare intractable disease to
	291	confirm APS cases.(7) Therefore, the identification and retrieval of APS cases was not
	292	exhaustive, which might affect the accuracy of identification. Radin et al. (2020) estimated the
20 21	293	incidence and prevalence from the Piedmont and Aosta Valley regional registry, a part of the
22 23 24	294	Italian National Registry of Rare Diseases, but data from the National Registry are not
25 26	295	reported.(9) The study was carried out between 2010 and 2019, but the authors do not report
27 28 29	296	on how the cases were ascertained or coded, or whether the Sydney criteria were used, and
30 31 32 33 34 35 36 37 38 39 40 41 42 43	297	the potential completeness of the registry has not been described.(9) Duarte-Garcia et al.
	298	(2019) included data from a population-based study run in the Mayo Clinic, Olmsted County,
	299	between 2000 and 2015.(6) While this study provided a rich clinical and epidemiological
	300	knowledge of APS, the authors acknowledged that outcomes could only be generalized to
	301	populations with the same demographic profile.(6) In addition, the study sample size of only 33
	302	patients after applying the Sydney criteria does not allow extrapolation of outcomes to the
44 45 46	303	country level.(6) In the present study, the specific APS code, D68.61, was used to identify
47 48	304	patients since the switch from ICD-9-CM to ICD-10-CM in October 2015, and the prior period
49 50 51	305	was excluded to avoid any misclassification or underestimation of APS cases.
52 53 54	306	Our standardized estimate of APS incidence (2.31 per 100,000 PY in 2016 to a high of 2.71 per
55 56	307	100,000 PY in 2019) is higher than the incidence reported from the Piedmont and Aosta Valley
57 58		Page 17 of 25
59 60		For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

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3 4	308	regions in Italy,(9) and also higher than that reported in the previous US (2.1 per 100,000 PY)
5 6 7 8 9 10 11 12 13 14 15 16	309	and UK (7.5 per 100,000 PY for women aged 35–39 years and 2.2 per 100,000 PY for men aged
	310	55–59 years) studies.(6, 10) The study in South Korea reported a higher incidence rate (7.5 per
	311	100,000 PY) than found in any of the other studies.(7) Our estimation of prevalence rate (10.42
	312	per 100,000 persons in 2019) was close to that estimated for the Piedmont and Aosta Valley
	313	region (16.8 per 100,000 persons).(9) In other studies, prevalence rates ranged from 40 per
17 18	314	100,000 persons in Spain,(8) to 61.9 per 100,000 persons in South Korea.(7) The UK study
19 20 21	315	estimated that prevalence rates were 43 per 100,000 persons,(10) while the Olmsted County
22 23	316	study in the US had an estimated prevalence of 50 per 100,000 persons.(6) The difference in
24 25 26	317	the population inclusion and the design of the study might explain the heterogeneity of
26 27 28 29 30 31 32 33 34 35 36 37 38	318	prevalence rates estimation. When assessing APS subtype, the overall annual standardized
	319	incidences of thrombotic APS and obstetric APS in 2019 were 1.28 per 100,000 PY, and 1.24 per
	320	100,000 PY, respectively. These incidences are close to those reported by Duarte-Garcia et al.
	321	(2019), but far from those reported by Andreoli et al. (2013), who estimated the overall annual
	322	incidence of thrombotic APS by the indirect method as 1.8 and 65 per 100,000 PY, respectively,
39 40	323	and 0.2 and 15 per 100,000 PY, respectively, for obstetric APS.(6, 19)
41		
42 43 44	324	It has been previously estimated that CAPS patients represent less than 1% of all patients with
45 46	325	APS, owing to the life-threatening nature of CAPS that requires high clinical awareness.(13)
47 48 49	326	However, the proportion of CAPS cases in the present study was substantially higher (4.4%),
50 51	327	and more in line with the proportion (3.0%) reported by Hwang et al. (2020) in Korea.(7) This
52 53	328	discrepancy could be attributed to the classification criteria for CAPS, which require the
54 55 56	329	knowledge of aPL test result and a biopsy, neither of which were available in the present study
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59 60		For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

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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 Page 19 of 25

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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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DATA AVAILABILITY STATEMENT

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

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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

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37 38 39	405	UCB Pharma.
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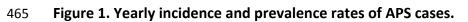
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1 2 3 4 5	408	REFERENCES					
6 7	409	1. Uthman I, Noureldine MHA, Ruiz-Irastorza G, Khamashta M. Management of					
8	410	antiphospholipid syndrome. Ann Rheum Dis. 2019;78(2):155-61.					
9 10	411	2. Miyakis S, Lockshin MD, Atsumi T, Branch DW, Brey RL, Cervera R, et al. International					
11 12	412	consensus statement on an update of the classification criteria for definite antiphospholipid					
13 14	413	syndrome (APS). J Thromb Haemost. 2006;4(2):295-306.					
15 16	414	3. Vila P, Hernández MC, López-Fernández MF, Batlle J. Prevalence, follow-up and clinical					
17 18	415	significance of the anticardiolipin antibodies in normal subjects. Thromb Haemost.					
19	416	1994;72(2):209-13.					
20 21	417	4. Dabit JY, Valenzuela-Almada MO, Vallejo-Ramos S, Duarte-García A. Epidemiology of					
22 23	418	Antiphospholipid Syndrome in the General Population. Curr Rheumatol Rep. 2022;23(12):85					
24 25	419	5. Barbhaiya M, Zuily S, Naden R, Hendry A, Manneville F, Amigo MC, et al. The 2023					
26 27	420	ACR/EULAR Antiphospholipid Syndrome Classification Criteria. Arthritis Rheumatol.					
28 29	421	2023;75(10):1687-702.					
30 31	422	6. Duarte-García A, Pham MM, Crowson CS, Amin S, Moder KG, Pruthi RK, et al. The					
32	423	Epidemiology of Antiphospholipid Syndrome: A Population-Based Study. Arthritis Rheumatol.					
33 34 35 36 37 38	424	2019;71(9):1545-52.					
	425	7. Hwang JJ, Shin SH, Kim YJ, Oh YM, Lee SD, Kim YH, et al. Epidemiology of					
	426	Antiphospholipid Syndrome in Korea: a Nationwide Population-based Study. J Korean Med Sci.					
39 40	427	2020;35(5):e35-e.					
41	428	8. Sisó-Almirall A, Kostov B, Martínez-Carbonell E, Brito-Zerón P, Ramirez PB, Acar-Denizli					
42 43	429	N, et al. The prevalence of 78 autoimmune diseases in Catalonia (MASCAT-PADRIS Big Data					
44 45	430	Project). Autoimmun Rev. 2020;19(2):102448.					
46 47	431	9. Radin M, Sciascia S, Bazzan M, Bertero T, Carignola R, Montabone E, et al.					
48 49	432	Antiphospholipid Syndrome Is Still a Rare Disease-Estimated Prevalence in the Piedmont and					
50 51	433	Aosta Valley Regions of Northwest Italy: Comment on the Article by Duarte-García et al.					
52	434	Arthritis Rheumatol. 2020;72(10):1774-6.					
53 54	435	10. Rodziewicz M, D'Cruz DP, Gulliford M. The epidemiology of antiphospholipid syndrome					
55 56	436	in the UK, 1990-2016. Arthritis Rheumatol. 2019; 71					
57 58		Page 23 of 25					
59							

59 60

1		lupus-2023-000902.R1 (transferred from Lupus Science & Medicine to BMJ Open)					
2 3	437	11. Pengo V, Tripodi A, Reber G, Rand JH, Ortel TL, Galli M, et al. Update of the guidelines					
4 5 6 7 8 9	438	for lupus anticoagulant detection. Subcommittee on Lupus Anticoagulant/Antiphospholipid					
	439	Antibody of the Scientific and Standardisation Committee of the International Society on					
	440	Thrombosis and Haemostasis. J Thromb Haemost. 2009;7(10):1737-40.					
10 11	441	12. Brandt JT, Triplett DA, Alving B, Scharrer I. Criteria for the diagnosis of lupus					
12 13	442	anticoagulants: an update. On behalf of the Subcommittee on Lupus					
14	443	Anticoagulant/Antiphospholipid Antibody of the Scientific and Standardisation Committee of					
15 16 17 18 19 20	444	the ISTH. Thromb Haemost. 1995;74(4):1185-90.					
	445	13. Asherson RA, Cervera R, de Groot PG, Erkan D, Boffa MC, Piette JC, et al. Catastrophic					
	446	antiphospholipid syndrome: international consensus statement on classification criteria and					
21 22	447	treatment guidelines. Lupus. 2003;12(7):530-4.					
22 23 24	448	14. Cervera R, Font J, Gómez-Puerta JA, Espinosa G, Cucho M, Bucciarelli S, et al. Validation					
25 26	449	of the preliminary criteria for the classification of catastrophic antiphospholipid syndrome. Ann					
27	450	Rheum Dis. 2005;64(8):1205-9.					
28 29 30 31	451	15. Cervera R, Rodríguez-Pintó I, Colafrancesco S, Conti F, Valesini G, Rosário C, et al. 14th					
	452	International Congress on Antiphospholipid Antibodies Task Force Report on Catastrophic					
32 33	453	Antiphospholipid Syndrome. Autoimmun Rev. 2014;13(7):699-707.					
33 34 35	454	16. CDC. United States Cancer Statistics (USCS): Incidence and Death Rates 2021 [Available					
36	455	from: https://www.cdc.gov/cancer/uscs/technical_notes/stat_methods/rates.htm .					
37 38	456	17. National Institute of Mental Health. What is Prevalence? [Available from:					
39 40	457	https://www.nimh.nih.gov/health/statistics/what-is-prevalence#part_2626.					
41 42	458	18. Haight F. Handbook of the Poisson Distribution. New York, NY, USA: John Wiley & Sons;					
43 44	459	1967.					
45 46	460	19. Andreoli L, Chighizola CB, Banzato A, Pons-Estel GJ, Ramire de Jesus G, Erkan D.					
47 48	461	Estimated frequency of antiphospholipid antibodies in patients with pregnancy morbidity,					
49	462	stroke, myocardial infarction, and deep vein thrombosis: a critical review of the literature.					
50 51	463	Arthritis Care Res (Hoboken). 2013;65(11):1869-73.					
52 53	464						
54 55	-0-						
56 57							
58 59		Page 24 of 25					
60		For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml					

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

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468 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 Author list, affiliations and degree information: Meheni Khellaf^{1,2}, Paul Meisner³, Maria Sarno⁴, Piotr Zaremba⁵, Adam Jedrzejczyk⁶, Anna Scowcroft⁷ ¹Global Real World Evidence, UCB Pharma, Brussels, Belgium; ²Life Sciences, Planet Pharma, London, United Kingdom; ³Global Clinical & Regulatory Strategy Rare Disease, UCB Pharma, Raleigh, United States; ⁴Translational Medicine Immunology and Oncology, UCB Pharma, Slough, United Kingdom; ⁵Real World Data Analytics Team, UCB Pharma, Katowice, Poland; ⁶Real World Data Analytics Team, UCB Pharma, Warsaw, Poland; ⁷Global Real World Evidence, UCB Pharma, Slough, United Kingdom. **Corresponding author:** Anna Scowcroft Address: 208 Bath Road, Slough, SL1 3WE, United Kingdom Tel: +44 1753 534655 Email: anna.scowcroft@ucb.com For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

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29	ABSTRACT
30	Objective: Few epidemiological studies are reported in the published literature on the
31	incidence or prevalence of antiphospholipid syndrome (APS), and available results are
32	heterogeneous. This study aimed to estimate the incidence and prevalence of APS in the United
33	States (US), overall and by APS subtype.
34 35	Design : A retrospective analysis of APS disease incidence and a cross-sectional analysis of disease prevalence.
36	Setting: Merative MarketScan Commercial Claims and Encounters Database, and the Medicare
37	Supplemental and Coordination of Benefits Database.
38	Participants: All individuals with claims for at least two aPL tests undertaken at least 12 weeks
39	apart, and a diagnosis claim for APS as a primary or secondary diagnosis on or after the second
40	antibody test, during the period January 1, 2016, to December 31, 2019.
41	Main outcome measures: Annual incidence and prevalence of APS and APS subtypes.
42	Results: In total, 1708 cases of APS were identified during the study period (2016–2019), of
43	which 83% were women. The overall annual standardized incidence rate of APS per 100,000
44	person-years increased slightly over the study period, from 2.31 in 2016 to 2.71 in 2019. In
45	2019, the estimated annual prevalence of APS per 100,000 persons was 10.42 per 100,000
46	persons (95% confidence interval: 9.96–10.90). Based on this and US census data, we have
47	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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54	Strer	ngths and limitations of this study
55	•	The Merative MarketScan CCAE and MDCR used in this study is a large database
56	•	The identification of the APS claims were realized by using a unique APS-specific ICD
57		code (D68.61) which was made available during the study period, whereas previous
58		studies use a non-specific code
59	•	Instead of the full Sydney criteria, a case definition proxy was applied to identify APS
60		cases
61	•	Given our estimate of incidence is calculated using claims from only a subset of the total
62		US population, which is not a representative sample, it cannot be extrapolated to the
63		full US population or populations in other countries

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1 2		
3 4	64	INTRODUCTION
5 6 7 8 9 10 11 12	65	Antiphospholipid syndrome (APS) is an autoimmune disease caused by anti-phospholipid
	66	antibodies (aPLs) that results in a wide spectrum of clinical manifestations, involving the
	67	hematological, obstetrical, neurological, cardiovascular, renal, and orthopedic systems, among
13 14 15	68	others.(1) aPLs include lupus anticoagulant (LAC), anti-cardiolipin (aCL), and
15 16 17	69	anti- β 2-glycoprotein I (anti- β 2GPI) immunoglobulin (Ig) G and IgM antibodies.
18 19 20	70	According to the Sydney 2006 International Classification Criteria Consensus, clinical diagnosis
21 22	71	of APS requires the presence of clinical symptoms associated with APS (vascular thrombosis or
23 24 25	72	pregnancy morbidity) and two positive test results for aPL, 12 weeks apart.(2) Furthermore,
26 27	73	older epidemiology studies were undertaken before LAC, aCL, and anti-β2GPI antibodies were
28 29 30	74	recognized as aPLs in the 2006 update of the classification criteria.(2) As a result, few studies
31 32	75	have been carried out to assess the epidemiology of APS, while the few data that have been
33 34 35	76	published are inconsistent.(3)
36 37 38	77	Since completion of this study, a manuscript supported by the American College of
39 40	78	Rheumatology (ACR) Board of Directors and the European Alliance of Associations for
41 42 43	79	Rheumatology (EULAR) has been published, in which a new classification criterion of APS has
43 44 45 46	80	been proposed.(4)
47 48	81	In the United States (US), Duarte-Garcia et al. (2019) estimated the overall annual incidence
49 50 51	82	and prevalence rates of APS for patients aged \geq 18 years at 2.1 per 100,000 person-years (PY)
52 53	83	and 50 per 100,000 persons, respectively.(5) Studies worldwide have estimated incidence and
54 55 56	84	prevalence ranging from 7.5 per 100,000 PY in Korea (6) to 40 per 100,000 PY in Spain,(7) and
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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

105 CCAE and MDCR databases during the study period of January 1, 2015, to December 31, 2019

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approval was required.

Patient and public involvement

Case definition and identification

research question or the outcome measures.

only be ascertained from October 2015 onwards.

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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

Patients and their families were not involved in the design, implementation, or setting the

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)

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

codes. In October 2015, APS was given a unique ICD code (D68.61) with the introduction of the

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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) Page **8** of **26**

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measured by a standardized ELISA; or (iii) anti- β 2GPI 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- β 2GPI, 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 \geq 14 years only), mixed APS (both thrombotic APS and obstetric APS events; women aged \geq 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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bmjopen-2024-084563.R1 149 thrombosis in three or more organs developing in less than a week. This definition was as close 150 as possible to the 10th and 14th International Congress on Antiphospholipid Antibodies 151 definitions, (13-15) without the required information on aPL status and biopsy, which was not 152 available in this database. Study outcomes and statistical analyses 153 Distribution of APS subtypes by age and sex during 2016–2019, and by specialty involved in the 154 first APS diagnosis for the period 2018–2019, were assessed. Overall distribution of CAPS was 155 calculated and presented as one result for the aggregated incident cohort. The annual incidence 156 157 and prevalence of APS and APS subtypes were calculated by age and sex in each calendar year 158 from 2016 to 2019. Incidence of APS was age- and sex-standardized indirectly to the US 2020 159 population by using age- and sex-specific population census data as weights and applying them to the age- and sex-specific incidence rates.(16) 160 Incidence, the number of new APS cases during a specific time period, (17) was reported as a 161 rate per 100,000 PY. Person-time was defined as the sum of each patient's duration of follow-162 163 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 – 164 whichever came first. Incidence was calculated as the number of incident cases divided by the 165 person-time of observation per year. The annual incidence rate was calculated as the number 166 of incident cases in a year divided by the person-time corresponding to that year. Prevalence, 167 168 the proportion of the population with APS in a given time period, (17) was expressed as

169 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

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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)

174 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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2 3 4 5	189	RESULTS
6 7	190	Baseline characteristics
8 9 10	191	A total of 1708 cases of APS that met our case definition during 2016–2019 were identified,
11 12	192	with the majority being women (n=1411, 83%; Table 1, Supplementary Table 4). For women,
13 14 15	193	the number of incident APS cases was highest among the 25–44 years age category (n=706,
16 17	194	50.0%), and 376 (26.6%) patients had obstetric APS. For men, the number of incident APS cases
18 19 20	195	was highest among patients aged 45–64 years (n=201, 67.7%). The overall number of pediatric
21 22	196	APS cases was small (n=23), with most cases identified within the 15–17 years age category
23 24 25	197	(n=16) for both female and male patients. Thrombotic APS was the most frequent subtype
26 27	198	identified (n=728, 42.6%), followed by APS of unknown subtype (n=404, 23.7%), obstetric APS
28 29 30	199	(n=376, 22.0%), other APS (n=138, 8.1%), and mixed APS (n=62, 3.6%). Seventy-five cases of
31 32	200	CAPS were identified, representing 4.4% of all APS cases. The acute care hospital was the most
33 34 35	201	frequently visited healthcare specialty site for diagnosis (n=227, 26.9%), followed by laboratory
36 37	202	(n=161, 19.1%), rheumatology (n=89, 10.5%), internal medicine (n=87, 10.3%), obstetrics and
38 39 40	203	gynecology (n=72, 8.5%) and hematology (n=70, 8.3%). Other categories for APS diagnoses
40 41 42	204	included oncology, family practice, pathology, neurology, multispecialty, and medical doctors.
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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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208 Incidence of APS

3 4	208	Incidence of APS
5 6 7	209	The overall annual incidence rate of APS per 100,000 PY (95% confidence interval [CI])
8 9	210	standardized to the US 2020 population census increased slightly over the study period, from
10 11	211	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,
12 13 14	212	respectively (Figure 3). Over the whole study period, the APS incidence rates were higher in
15 16	213	women, potentially due to certain subtypes being applicable to women only. In 2019, the
17 18 19	214	annual incidence rate (standardized to the US 2020 population census) was 4.45 (3.99–4.96)
20 21	215	per 100,000 PY for women, and 0.91 (0.71–1.17) per 100,000 PY for men. The incidence rate of
22 23	216	APS in women was always highest in patients aged 30–39 years old, ranging from 10.09 per
24 25 26	217	100,000 PY in 2016 to 11.80 and 11.22 per 100,000 PY in 2018 and 2019 (Supplementary Table
27 28	218	5). However, in men, the age categories with the highest incidence rates varied each year
29 30 31	219	(Supplementary Table 5).
32 33 34	220	Prevalence of APS
35 36	221	The estimated annual prevalence of APS per 100,000 persons (95% CI) was 10.42 per 100,000
37 38 39	222	persons (9.96–10.90) in 2019 (Figure 3). In 2019, APS prevalence among women was four times
40 41	223	higher than in men: 16.59 (15.78–17.45) and 4.00 (3.60–4.44) per 100,000 persons,
42 43 44	224	respectively. Based on this and US census data, we have estimated that slightly more than
44 45 46	225	34,000 persons in the US were affected by APS in 2019. Among women, the prevalence rate of
47 48	226	APS was highest in the 40–49 years age group, ranging from 14.71 in 2016 to 30.61 per 100,000
49 50 51	227	persons in 2019. Among men, APS prevalence was highest in patients aged 60–69 years old
52 53	228	between 2016 (6.27 per 100,000 persons) and 2018 (10.85 per 100,000 persons), and in
54 55 56	229	patients aged 80+ years in 2019 (13.57 per 100,000 persons) (Supplementary Table 6).
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3 4 5	230	Incidence rates of APS subtypes
5 6 7	231	Incidence rates of APS subtype were standardized to the US 2020 population census. In 2019,
8 9	232	the overall annual incidence (95% CI) of thrombotic APS was 1.28 (1.10–1.49) per 100,000 PY,
10 11 12	233	which was the highest incidence over the study period. The 2019 annual incidence rate of
12 13 14	234	thrombotic APS patients was higher in women (1.76 per 100,000 PY) than in men (0.79 per
15 16	235	100,000 PY) (Supplementary Figure 1a). In 2019, among women only, the incidence rate of
17 18 19	236	obstetric APS was 1.24 (1.01–1.53) per 100,000 PY (Supplementary Figure 1b), and the
20 21	237	incidence rate of mixed APS was 0.17 (0.10–0.30) per 100,000 PY. The other APS cases
22 23 24	238	represent 8.1% of the total APS population, with an overall annual incidence rate in 2019 of
25 26	239	0.23 (0.16–0.32) per 100,000 PY. The unknown APS cases represent almost a quarter (23.65%)
27 28	240	of the total APS population, with an overall incidence rate in 2019 of 0.48 (0.38–0.60) per
29 30 31	241	100,000 PY (Supplementary Table 7).
32		
33 34	242	Prevalence rates of APS subtypes
33 34 35 36	242 243	Prevalence rates of APS subtypes The overall annual prevalence (95% CI) of thrombotic APS was 5.38 (5.05–5.73) per 100,000
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33 34 35 36 37 38 39 40 41	243	The overall annual prevalence (95% CI) of thrombotic APS was 5.38 (5.05–5.73) per 100,000
33 34 35 36 37 38 39 40	243 244	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
 33 34 35 36 37 38 39 40 41 42 43 44 45 46 	243 244 245	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
 33 34 35 36 37 38 39 40 41 42 43 44 45 46 47 48 	243 244 245 246	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
 33 34 35 36 37 38 39 40 41 42 43 44 45 46 47 48 49 50 51 	243 244 245 246 247	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
 33 34 35 36 37 38 39 40 41 42 43 44 45 46 47 48 49 50 51 52 53 	243 244 245 246 247 248	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
 33 34 35 36 37 38 39 40 41 42 43 44 45 46 47 48 49 50 51 52 	243 244 245 246 247 248 249	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

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252 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

266 epidemiological information on APS in their respective regions (Supplementary Table 8).

267 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

269 in variation in socioeconomic demographics among the populations included.(3)

270 In particular, our sensitivity analysis shows that differences in incidence rates are apparent
271 when using different diagnostic scenarios, thus results may be sensitive to the case definition

54
55 272 used. This is evident when evaluating studies in the literature, as one pertinent difference
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273	between them was the method used for identification of APS cases. A study of the incidence
274	and prevalence of APS cases in Korea, identified from the Korean Health Insurance and Review
275	Agency, used the Korean Classification of Disease, 7th edition code D68.6 (other
276	thrombophilia), which corresponds to ICD-10: D68.6 and includes anticardiolipin syndrome,
277	APS, and the presence of lupus anticoagulant, and V253 code of rare intractable disease to
278	confirm APS cases.(6) Therefore, the identification and retrieval of APS cases was not
279	exhaustive, which might affect the accuracy of identification. Radin et al. (2020) estimated the
280	incidence and prevalence from the Piedmont and Aosta Valley regional registry, a part of the
281	Italian National Registry of Rare Diseases, but data from the National Registry are not
282	reported.(8) The study was carried out between 2010 and 2019, but the authors do not report
283	on how the cases were ascertained or coded, or whether the Sydney criteria were used, and
284	the potential completeness of the registry has not been described.(8) Duarte-Garcia et al.
285	(2019) included data from a population-based study run in the Mayo Clinic, Olmsted County,
286	between 2000 and 2015.(5) While this study provided a rich clinical and epidemiological
287	knowledge of APS, the authors acknowledged that outcomes could only be generalized to
288	populations with the same demographic profile.(5) In addition, the study sample size of only 33
289	patients after applying the Sydney criteria does not allow extrapolation of outcomes to the
290	country level.(5) In the present study, the specific APS code, D68.61, was used to identify
291	patients since the switch from ICD-9-CM to ICD-10-CM in October 2015, and the prior period
292	was excluded to avoid any misclassification or underestimation of APS cases.
293	Our standardized estimate of APS incidence (2.31 per 100,000 PY in 2016 to a high of 2.71 per
294	100,000 PY in 2019) is higher than the incidence reported from the Piedmont and Aosta Valley

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2		
3 4	295	regions in Italy,(8) and also higher than that reported in the previous US (2.1 per 100,000 PY)
5 6 7	296	and UK (1.8 per 100,000 PY) studies.(5, 9) The study in South Korea reported a higher incidence
, 8 9	297	rate (7.5 per 100,000 PY) than found in any of the other studies (6). Our estimation of
10 11	298	prevalence rate (10.42 per 100,000 persons in 2019) was close to that estimated for the
12 13 14	299	Piedmont and Aosta Valley region (16.8 per 100,000 persons).(8) In other studies, prevalence
15 16	300	rates ranged from 40 per 100,000 persons in Spain,(7) to 61.9 per 100,000 persons in South
17 18 19	301	Korea.(6) The UK study estimated that prevalence rates were 43 per 100,000 persons,(9) while
20 21	302	the Olmsted County study in the US had an estimated prevalence of 50 per 100,000 persons.(5)
22 23 24	303	The difference in the population inclusion and the design of the study might explain the
24 25 26	304	heterogeneity of prevalence rates estimation. When assessing APS subtype, the overall annual
27 28 29	305	standardized incidences of thrombotic APS and obstetric APS in 2019 were 1.28 per 100,000 PY,
29 30 31	306	and 1.24 per 100,000 PY, respectively. These incidences are close to those reported by Duarte-
32 33	307	Garcia et al. (2019), but far from those reported by Andreoli et al. (2013), who estimated the
34 35 36	308	overall annual incidence of thrombotic APS by the indirect method as 1.8 and 65 per 100,000
37 38 39	309	PY, respectively, and 0.2 and 15 per 100,000 PY, respectively, for obstetric APS.(5, 20)
40 41 42	310	It has been previously estimated that CAPS patients represent less than 1% of all patients with
42 43 44	311	APS, owing to the life-threatening nature of CAPS that requires high clinical awareness.(13)
45 46	312	However, the proportion of CAPS cases in the present study was substantially higher (4.4%),
47 48 49	313	and more in line with the proportion (3.0%) reported by Hwang et al. (2020) in Korea.(6) This
50 51	314	discrepancy could be attributed to the classification criteria for CAPS, which require the
52 53 54 55	315	knowledge of aPL test result and a biopsy, neither of which were available in the present study

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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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1 2		
3 4	338	populational studies in the literature on the prevalence of aPL and a lack of standardization
5 6 7	339	between aPL tests. Relatedly, to ensure that we captured every possible APS case, we did not
8 9	340	limit APS claims to include only those with a clinical manifestation. Nevertheless, a sensitivity
10 11 12	341	analysis (Scenario F) has been considered including the condition of clinical criteria (per the
13 14	342	Sydney classification) linked to APS claims. These patients, classified as 'Unknown' in our study,
15 16 17	343	may have therefore had a specific clinical manifestation or APS subtype that was not captured.
17 18 19	344	For example, data may have been incomplete for obstetric APS if patients were misclassified as
20 21	345	'Unknown' but were pregnant at the time or even after the period of identification. Indeed, a
22 23 24	346	peak in incidence and prevalence of APS, irrespective of subtype, is observed in women of
25 26	347	child-bearing age that is not observed in men (Supplementary Tables 5 and 6). Additionally,
27 28 29	348	some of the confidence intervals were wide ranging, owing to variability in the number of
30 31	349	events per category, and should be interpreted with caution. A further limitation of the case
32 33 34	350	definition is that primary and secondary APS were not separated. Finally, absence of a unique
35 36	351	ICD code for APS prior to introduction of ICD-10-CM in October 2015 limits the ability to
37 38	352	estimate APS incidence and prevalence prior to 2016. Our estimation of prevalence from 2016
39 40 41	353	to 2019 is likely to under-ascertain prevalent cases diagnosed prior to October 2015. The
42 43	354	impact of this underestimation of prevalence will be most pronounced in the years immediately
44 45 46	355	after the change in ICD coding.
47 48 49	356	Very few epidemiological studies are reported in the published literature on the incidence or
50 51	357	prevalence of APS, and estimates reported in these studies are heterogeneous. A careful
52 53 54	358	interpretation should be considered when comparing these results to other countries that may

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3 4	359	have a different healthcare system with variations in APS management, including treatment
5 6 7	360	administration, as well as possible socioeconomic differences.
8 9 10	361	This study identified a trend towards a yearly increase in incidence and prevalence of APS in the
11 12	362	US over the study period. The results of this study add to existing estimates published in the
13 14 15	363	literature, but further studies are needed to fully elucidate the global epidemiology of APS
16 17 18	364	using the 2023 classification criteria of APS by Barbhaiya et al.(4)
19 20 21	365	DATA AVAILABILITY STATEMENT
22 23	366	Data from non-interventional studies is outside of UCB's data sharing policy and is unavailable for
24 25 26 27	367	sharing.
28 29	368	ETHICS STATEMENTS
30 31 32	369	Patient consent for publication
33 34 35	370	Not applicable.
36 37 38 39	371	Ethics approval
40 41	372	The CCAE and MDCR databases are Health Insurance Portability and Accountability Act
42 43 44	373	compliant, and all patient data were de-identified before delivery to the study team. No ethics
45 46 47	374	committee approval was required.
48 49 50	375	ACKNOWLEDGMENTS
51 52	376	The authors thank Margarita Lens, MSci, CMPP of UCB Pharma for publication and editorial
53 54 55 56 57	377	support.
58 59 60		Page 21 of 26 For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

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4 5		
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10 11 12	381	data. A. Scowcroft is responsible for the overall content as guarantor. All authors revised the
13 14 15	382	work for important intellectual content and provided approval of the final version to be
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45 46 47	394	Pharma. Paul Meisner, Maria Sarno and Anna Scowcroft are employees and stockholders of
48 49	395	UCB Pharma.
50 51 52 53 54 55 56 57 58	396	
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		BMJ Open
1		bmjopen-2024-084563.R1
2 3 4 5	398	REFERENCES
6 7	399	1. Uthman I, Noureldine MHA, Ruiz-Irastorza G, Khamashta M. Management of
8	400	antiphospholipid syndrome. Ann Rheum Dis. 2019;78(2):155-61.
9 10	401	2. Miyakis S, Lockshin MD, Atsumi T, Branch DW, Brey RL, Cervera R, et al. International
11 12	402	consensus statement on an update of the classification criteria for definite antiphospholipid
13 14	403	syndrome (APS). J Thromb Haemost. 2006;4(2):295-306.
15 16	404	3. Dabit JY, Valenzuela-Almada MO, Vallejo-Ramos S, Duarte-García A. Epidemiology of
17 18	405	Antiphospholipid Syndrome in the General Population. Curr Rheumatol Rep. 2022;23(12):85
19	406	4. Barbhaiya M, Zuily S, Naden R, Hendry A, Manneville F, Amigo MC, et al. The 2023
20 21	407	ACR/EULAR Antiphospholipid Syndrome Classification Criteria. Arthritis Rheumatol.
22 23	408	2023;75(10):1687-702.
24 25	409	5. Duarte-García A, Pham MM, Crowson CS, Amin S, Moder KG, Pruthi RK, et al. The
26 27	410	Epidemiology of Antiphospholipid Syndrome: A Population-Based Study. Arthritis Rheumatol.
28 29	411	2019;71(9):1545-52.
30	412	6. Hwang JJ, Shin SH, Kim YJ, Oh YM, Lee SD, Kim YH, et al. Epidemiology of
31 32	413	Antiphospholipid Syndrome in Korea: a Nationwide Population-based Study. J Korean Med Sci.
33 34	414	2020;35(5):e35-e.
35 36	415	7. Sisó-Almirall A, Kostov B, Martínez-Carbonell E, Brito-Zerón P, Ramirez PB, Acar-Denizli
37 38	416	N, et al. The prevalence of 78 autoimmune diseases in Catalonia (MASCAT-PADRIS Big Data
39 40	417	Project). Autoimmun Rev. 2020;19(2):102448.
41	418	8. Radin M, Sciascia S, Bazzan M, Bertero T, Carignola R, Montabone E, et al.
42 43	419	Antiphospholipid Syndrome Is Still a Rare Disease-Estimated Prevalence in the Piedmont and
44 45	420	Aosta Valley Regions of Northwest Italy: Comment on the Article by Duarte-García et al.
46 47	421	Arthritis Rheumatol. 2020;72(10):1774-6.

- 9. Rodziewicz M, D'Cruz DP, Gulliford M. The epidemiology of antiphospholipid syndrome in the UK, 1990-2016. Arthritis Rheumatol. 2019; 71
- 10. Merative MarketScan Research Databases for life sciences researchers: Merative; [Available from:

 Page 25 of 41

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2		
3 4	426	https://www.merative.com/content/dam/merative/documents/brief/marketscan-research-
5 6	427	databases-for-life-sciences-researchers.pdf.
7	428	11. Pengo V, Tripodi A, Reber G, Rand JH, Ortel TL, Galli M, et al. Update of the guidelines
6	429	for lupus anticoagulant detection. Subcommittee on Lupus Anticoagulant/Antiphospholipid
	430	Antibody of the Scientific and Standardisation Committee of the International Society on
	431	Thrombosis and Haemostasis. J Thromb Haemost. 2009;7(10):1737-40.
14	432	12. Brandt JT, Triplett DA, Alving B, Scharrer I. Criteria for the diagnosis of lupus
16 17 18 19 20 21	433	anticoagulants: an update. On behalf of the Subcommittee on Lupus
	434	Anticoagulant/Antiphospholipid Antibody of the Scientific and Standardisation Committee of
	435	the ISTH. Thromb Haemost. 1995;74(4):1185-90.
	436	13. Asherson RA, Cervera R, de Groot PG, Erkan D, Boffa MC, Piette JC, et al. Catastrophic
23 24	437	antiphospholipid syndrome: international consensus statement on classification criteria and
25 26	438	treatment guidelines. Lupus. 2003;12(7):530-4.
27	439	14. Cervera R, Font J, Gómez-Puerta JA, Espinosa G, Cucho M, Bucciarelli S, et al. Validation
28 29	440	of the preliminary criteria for the classification of catastrophic antiphospholipid syndrome. Ann
30 31	441	Rheum Dis. 2005;64(8):1205-9.
32 33	442	15. Cervera R, Rodríguez-Pintó I, Colafrancesco S, Conti F, Valesini G, Rosário C, et al. 14th
34	443	International Congress on Antiphospholipid Antibodies Task Force Report on Catastrophic
35 36 37	444	Antiphospholipid Syndrome. Autoimmun Rev. 2014;13(7):699-707.
38	445	16. CDC. United States Cancer Statistics (USCS): Incidence and Death Rates 2021 [Available
39 40	446	from: https://www.cdc.gov/cancer/uscs/technical_notes/stat_methods/rates.htm.
41 42	447	17. National Institute of Mental Health. What is Prevalence? [Available from:
43 44	448	https://www.nimh.nih.gov/health/statistics/what-is-prevalence#part 2626.
45 46	449	18. Haight F. Handbook of the Poisson Distribution. New York, NY, USA: John Wiley & Sons;
47	450	1967.
48 49	451	19. Andreoli L, Nalli C, Raffetti E, Angeli F, Pascariello G, Zentilin A, et al. The prevalence and
50 51	452	incidence of thrombotic primary antiphospholipid syndrome in adults aged 18-49 years: A
52 53	453	population-based study in a mountain community in northern Italy. Clin Immunol.
54 55	454	2024;260:109905.
56		
57 58		

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2		
- 3 4	455	20. Andreoli L, Chighizola CB, Banzato A, Pons-Estel GJ, Ramire de Jesus G, Erkan D.
5 6	456	Estimated frequency of antiphospholipid antibodies in patients with pregnancy morbidity
7	457	stroke, myocardial infarction, and deep vein thrombosis: a critical review of the literature
8 9	458	Arthritis Care Res (Hoboken). 2013;65(11):1869-73.
10 11		
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3 4	460	FIGURE LEGENDS
5 6 7	461	Figure 1. MarketScan research databases (10)
8 9 10	462	Figure 2. Study design
11 12	463	aPL, antiphospholipid antibody; APS, antiphospholipid syndrome; ICD, International Classification of
13 14 15	464	Diseases.
16 17	465	Figure 3. Yearly incidence and prevalence rates of APS cases
18 19 20	466	Lines represent incidence rates per 100,000 PY, bars represent prevalence rates per 100,000 persons.
21 22 23	467	APS, antiphospholipid syndrome; PY, person-years.
23 24 25		APS, antiphospholipid syndrome; PY, person-years.
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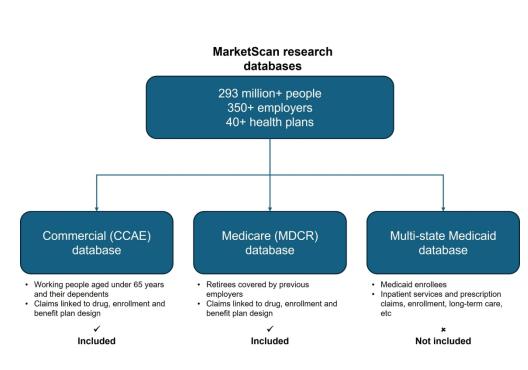
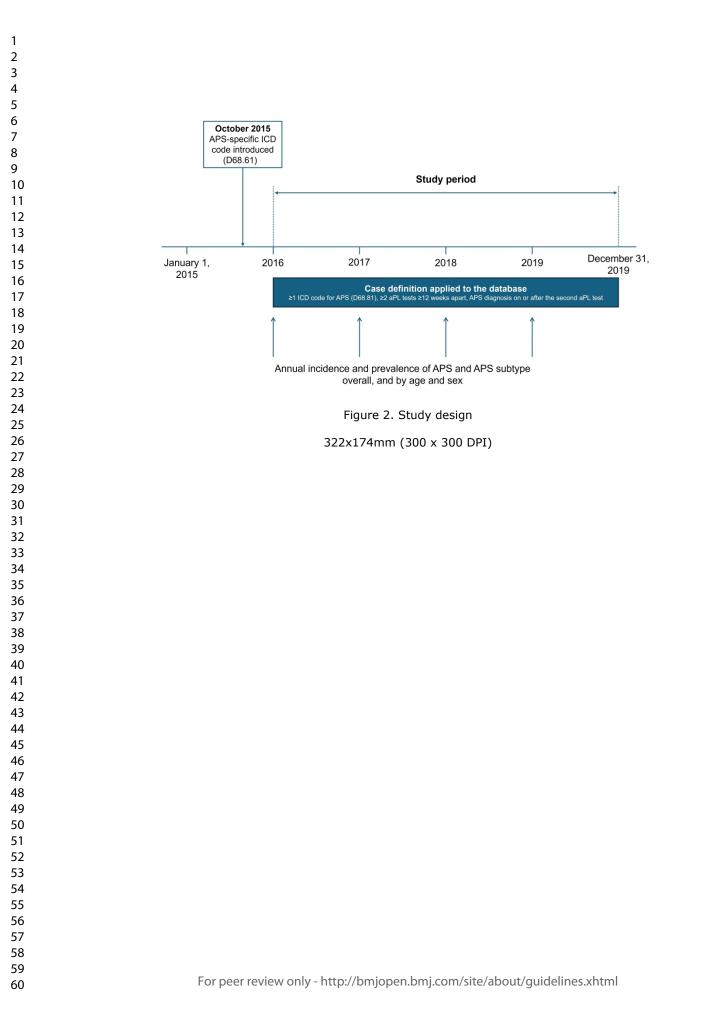


Figure 1. MarketScan research databases (10)

265x165mm (300 x 300 DPI)

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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	174
Cavernous sinus thrombosis	437.6	167.6
Cerebral infarction (including ischemic stroke)	434	163, 169.3
Cerebral venous sinus thrombosis,	437.6	167.6
Coronary thrombosis (without infarct)	-	124.0
Myocardial infarction	410, 411.0, 412, 429.7	121-123, 124.1, 125.2 Baseline variable
Personal history of venous thrombosis	Baseline variable only	only
	V12.51, V12.54, V12.55	Z68.711, Z68.718 Z68.73
Pulmonary embolism (acute or chronic)	415.1, 416.2	126
Pulmonary hypertension (thromboembolic)	416.8	127.2
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 (acute) Deep veins of lower extremity (acute) Veins of upper extremity (acute) 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	181, 182
Thrombotic events during pregnancy or po	-	
Cerebral venous sinus thrombosis	671.5	022.5, 087.3
Deep vein thrombosis	671.3	087.1, 022.3
	671.4	

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Obstetric events		
Eclampsia	642.6	015
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	003
Poor fetal growth, including placental insufficiency	656.5, V28.4	O36.5, Z36.4
Pre-eclampsia	642.4-642.7	011, 014
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	060.0, 060.2, 047.0

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.

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	134, 135
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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2 3 4 5 6	Supplementa	ry Table 3. Ca	ase definition	is used in ma	in analysis an	d sensitivity	ight, includir	6/bmjopen-2024-084563 on 1 .cted by copyright, including			
7 8 9 10 11 12 13		≥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 test 12–26 weeks apart ent	APS Caliagnosis on Second aPL Second aPL Second aPL Caliagnosis on Second aPL Caliagnosis on Second aPL	APS diagnosis 2– 13 weeks after the second aPL test [‡]	
14 15 16	Case definition used			6				text and	Downloaded fro		
17 18	Sensitivity scenario A	~			0.			data r	ded fro		
19 20 21	Sensitivity scenario B	✓				~		nining			
21 22 23	Sensitivity scenario C	✓			16				p://bm	✓	
23 24 25	Sensitivity scenario D [§]	✓				0	1	Al training	ijopen		
26 27	Sensitivity scenario E		✓	1				, and	.bmj.e		
28 29	Sensitivity scenario F	✓			✓			simila	som/ ₀		
30 31 32 33 34 35 36 37 38 39 40 41 42 43 44 45	*Primary or se	condary. [†] Acco					o case definition	nologies.	ה ר		

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

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Supplementary Table 4.	Incident Af	PS cases by	baseline g	ender and	age distrib	oution, and	APS subty	ar 6/bmjopen-2024-094563 on 11 cted by copyright,9ncluding f pe 19
	20)16	20)17	20)18	20	19 ⁶ 1
	Male	Female	Male	Female	Male	Female	Male	Fema
(6()		458		406		459		385 8 En
n (%)	77 (16.8)	381 (83.2)	76 (18.7)	330 (81.2)	82 (17.9)	377 (82.1)	62 (16.1)	32 elated to
Age, years, n (%)								nem ated
Adults					a (a . i)		- (+ -)	
18–24	4 (5.2)	17 (4.5)	1 (1.3)	14 (4.2)	2 (2.4)	15 (4.0)	3 (4.8)	to 24:50) 24:50 (100) 16:50 (100) 16:50 (100) 16:50 (100)
25–44	9 (11.6)	185 (48.6)	16 (21.1)	164 (49.7)	11 (13.4)	191 (50.7)	13 (21.0)	
45–64	53 (68.8)	161 (42.3)	53 (69.7)	143 (43.3)	56 (68.3)	155 (41.1)	39 (62.9)	12(1) 12(1)(1)(1)(1)(1)(1)(1)(1)(1)(1)(1)(1)(1)(
65+	8 (10.3)	15 (3.9)	5 (6.6)	6 (1.8)	11 (13.4)	12 (3.2)	4 (6.5)	
Subtotal	74 (96.1)	378 (99.2)	75 (96.7)	327 (99.1)	80 (97.6)	373 (98.9)	59 (95.2)	1 mBning,
Pediatric) . ng,
0–4	0	1 (0.3)	0	0	1 (1.2)	0	0) . 0 0 0 1) Al training,
5–9	1 (1.3)	0	0	0	0	0	0	njo rain
10–14	1 (1.3)	1 (0.3)	0	2 (0.6)	0	0	0	oen 0 ing
15–17	1 (1.3)	1 (0.3)	1 (1.3)	1 (0.3)	1 (1.2)	4 (1.1)	3 (4.8)	83 (1.23)
Subtotal	3 (3.9)	3 (0.8)	1 (1.3)	3 (0.9)	2 (2.4)	4 (1.1)	3 (4.8)	<u>a</u> .(1.2)
Catastrophic APS, n (%)	_	_	_	_	_		6	eimilar tecl
APS subtype, n (%)								ir b te
Thrombotic	65 (84.4)	113 (29.6)	68 (89.5)	112 (33.9)	65 (79.3)	131 (34.7)	53 (85.5)	12 (3 .5)
Obstetric	0	95 (24.9)	0	82 (24.8)	0	109 (28.9)	0	9 8 (27,9)
Mixed	0	17 (4.5)	0	16 (4.8)	0	16 (4.2)	0	1, (4)
Other	3 (3.9)	34 (8.9)	2 (2.6)	25 (7.6)	5 (6)	34 (9)	6 (9.7)	29 (9 2)
Unknown	9 (11.7)	122 (32)	6 (7.9)	95 (28.8)	12 (14.6)	87 (23)	3 (4.8)	70 (2 1 6 7)
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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– <mark>2</mark> .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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•	2016	2017	2010	2010
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)

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

APS, antiphospholipid syndrome; CI, confidence interval.

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

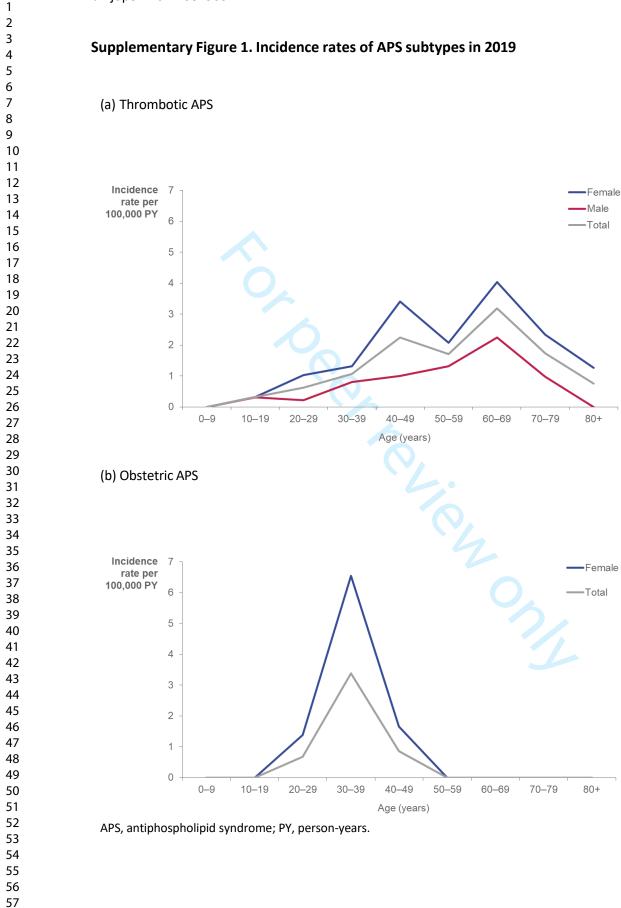
Age, years	2016	2017	2018	2019
Incidence rates (95% CI)			
Female				
Thrombotic	1.07 (0.89–1.28)	1.17 (0.97–1.41)	1.48 (1.25–1.76)	1.76 (1.47–2.10)
Obstetric	1.00 (0.82–1.22)	0.98 (0.79–1.22)	1.33 (1.10–1.60)	1.24 (1.01–1.53)
Mixed	0.18 (0.11–0.29)	0.19 (0.12–0.32)	0.19 (0.12–0.31)	0.17 (0.10-0.30)
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– <mark>0</mark> .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)	(0.03–0.16) 0.15 (0.09–0.27)	
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.

Study	Country	Study period	Data source	APS type	Estimated incidence per 100,000 PY (95%	ected by copyright, includine ເອງ	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)	Enseignement ses related to t	3 10.42 (9.96–10.90)
Radin et al., 2020 (8)	Italy	2010–2019	Registry	Primary	1.1 (not provided)	Superieur (text and dat	16.8 (not provided)
Huang et al., 2019 (6)	Korea	2008–2017	Claims database	Primary, secondary, obstetric, CAPS	7.5 (7.3–7.8)	ABES) . a mining,	61.9 (59.8–64.1)
Duarte-Garcia et al., 2019 (5)	United States	2000–2015	EHRs	Primary	2.1 (1.4–2.8)	Al training,	50 (42–58)
Rodziewicz et al., 2019 (9)	United Kingdom	1990–2016	EHRs	Primary, SLE- related	1.8* (not provided)	, and simi	43 (not provided)
Sisó-Almirall et al., 2020 (7)	Spain	2012–2017	EHRs	Not stated	Not provided	and similar technologies.	40 (not provided)
Andreoli et al., 2024 (18)	Italy	2011–2015	EHRs	Thrombotic primary; aged 18–49 years	5.0 (2.6–8.7)	o, zuzo at Agenice bibliographilque de l ologies.	22.9 (11.4–41.0)

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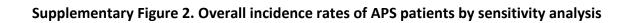
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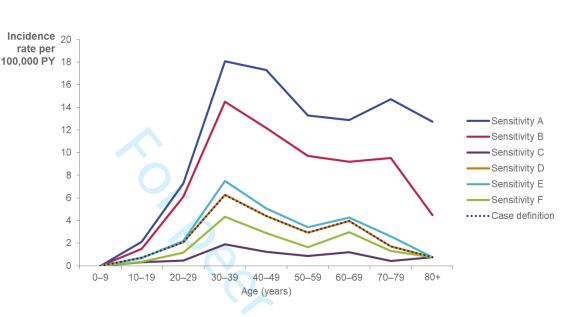


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scenarios in 2019

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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 Author list, affiliations and degree information: Meheni Khellaf^{1,2}, Paul Meisner³, Maria Sarno⁴, Piotr Zaremba⁵, Adam Jedrzejczyk⁶, Anna Scowcroft⁷ ¹Global Real World Evidence, UCB, Brussels, Belgium; ²Life Sciences, Planet Pharma, London, United Kingdom; ³Global Clinical & Regulatory Strategy Rare Disease, UCB, Raleigh, United States; ⁴Translational Medicine Immunology and Oncology, UCB, Slough, United Kingdom; ⁵Real World Data Analytics Team, UCB, Katowice, Poland; ⁶Real World Data Analytics Team, UCB, Warsaw, Poland; ⁷Global Real World Evidence, UCB, Slough, United Kingdom. **Corresponding author:** Anna Scowcroft Address: 208 Bath Road, Slough, SL1 3WE, United Kingdom Tel: +44 1753 534655 Email: anna.scowcroft@ucb.com

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28	ABSTRACT
29	Objective: Few epidemiological studies are reported in the published literature on the
30	incidence or prevalence of antiphospholipid syndrome (APS), and available results are
31	heterogeneous. This study aimed to estimate the incidence and prevalence of APS in the United
32	States (US), overall and by APS subtype.
33	Design: A retrospective analysis of APS disease incidence and a cross-sectional analysis of
34	disease prevalence.
35	Setting: Merative MarketScan Commercial Claims and Encounters Database, and the Medicare
36	Supplemental and Coordination of Benefits Database.
37	Participants: All individuals with claims for at least two aPL tests undertaken at least 12 weeks
38	apart, and a diagnosis claim for APS as a primary or secondary diagnosis on or after the second
39	antibody test, during the period January 1, 2016, to December 31, 2019.
40	Main outcome measures: Annual incidence and prevalence of APS and APS subtypes.
41	Results: In total, 1708 cases of APS were identified during the study period (2016–2019), of
42	which 83% were women. The overall annual standardized incidence rate of APS per 100,000
43	person-years increased slightly over the study period, from 2.31 in 2016 to 2.71 in 2019. In
44	2019, the estimated annual prevalence of APS per 100,000 persons was 10.42 per 100,000
45	persons (95% confidence interval: 9.96–10.90). Based on this and US census data, we have
46	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. .iphospholip. Keywords: Antibodies, antiphospholipid; antiphospholipid syndrome; autoimmune diseases; epidemiology

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

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3 4	63	INTRODUCTION
5 6 7	64	Antiphospholipid syndrome (APS) is an autoimmune disease caused by anti-phospholipid
8 9	65	antibodies (aPLs) that results in a wide spectrum of clinical manifestations, involving the
10 11 12	66	hematological, obstetrical, neurological, cardiovascular, renal, and orthopedic systems, among
13 14	67	others.[1] Criteria aPLs include lupus anticoagulant (LAC), anti-cardiolipin (aCL), and
15 16 17	68	anti- β 2-glycoprotein I (anti- β 2GPI) immunoglobulin (Ig) G and IgM antibodies.
18 19 20	69	According to the Sydney 2006 International Classification Criteria Consensus, clinical diagnosis
21 22	70	of APS requires the presence of clinical symptoms associated with APS (vascular thrombosis or
23 24 25	71	pregnancy morbidity) and two positive test results for aPL, 12 weeks apart.[2] Furthermore,
26 27	72	older epidemiology studies were undertaken before LAC, aCL, and anti-β2GPI antibodies were
28 29 30	73	recognized as aPLs in the 2006 update of the classification criteria.[2] As a result, few studies
31 32	74	have been carried out to assess the epidemiology of APS, while the few data that have been
33 34 35	75	published are inconsistent.[3]
36 37 38	76	Since completion of this study, a manuscript supported by the American College of
39 40	77	Rheumatology (ACR) Board of Directors and the European Alliance of Associations for
41 42	78	Rheumatology (EULAR) has been published, in which a new classification criterion of APS has
43 44 45 46	79	been proposed.[4]
40 47 48	80	In the United States (US), Duarte-Garcia et al. (2019) estimated the overall annual incidence
49 50	81	and prevalence rates of APS for patients aged ≥18 years at 2.1 per 100,000 person-years (PY)
51 52 53	82	and 50 per 100,000 persons, respectively.[5] Studies worldwide have estimated incidence and
54 55 56	83	prevalence ranging from 7.5 per 100,000 PY in Korea [6] to 40 per 100,000 PY in Spain,[7] and
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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

103 This was a retrospective, cross-sectional analysis of APS incidence and prevalence, using the 104 CCAE and MDCR databases during the study period of January 1, 2015, to December 31, 2019

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105	(Figure 2). The database is Health Insurance Portability and Accountability Act compliant, and
106	all patient data were de-identified before delivery to the study team. No ethics committee
107	approval was required.
108	Patient and public involvement
109	Patients and their families were not involved in the design, implementation, or setting the
110	research question or the outcome measures.
111	Case definition and identification
112	APS cases were defined as claims for at least two aPL tests undertaken at least 12 weeks apart,
113	and a diagnosis claim for APS as a primary or secondary diagnosis on or after the second
114	antibody test, identified from International Classification of Diseases, tenth revision (ICD-10)
115	codes. In October 2015, APS was given a unique ICD code (D68.61) with the introduction of the
116	Clinical Modification (CM). Prior to ICD-10-CM, APS was coded together with multiple other
117	hypercoagulation defects into 289.81 (Primary Hypercoagulable State). Thus, cases of APS can
118	only be ascertained from October 2015 onwards.
119	The Sydney International Classification Criteria Consensus case definition requires laboratory
120	criteria (at least 12 weeks between the initial and repeated positive aPL test) and at least one of
121	the clinical criteria (vascular thrombosis or pregnancy morbidity). An aPL test is confirmed
122	positive if one or more of the following aPLs are detected on two or more occasions at least 12
123	weeks apart: (i) LAC present in plasma detected according to the International Society on
124	Thrombosis and Haemostasis guidelines [2, 11, 12]; (ii) aCL of IgG and/or IgM isotype in serum
125	or plasma at medium or high titer (>40 IgG or IgM phospholipid units, or >99th percentile)

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measured by a standardized ELISA; or (iii) anti- β 2GPI 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- β 2GPI, 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 Page 9 of 26

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type unknown (APS cases that were not linked to any clinical criteria relating to the listed 148 149 subtypes). In addition, catastrophic APS (CAPS) was analyzed as a subtype of thrombotic and 150 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 151 152 Antiphospholipid Antibodies definitions, [13-15] without the required information on aPL status 153 and biopsy, which was not available in this database. Study outcomes and statistical analyses 154 155 Distribution of APS subtypes by age and sex during 2016–2019, and by specialty involved in the 156 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 157 158 and prevalence of APS and APS subtypes were calculated by age and sex in each calendar year 159 from 2016 to 2019. Incidence of APS was age- and sex-standardized indirectly to the US 2020

160 population by using age- and sex-specific population census data as weights and applying them

to the age- and sex-specific incidence rates.[16] 161

Incidence, the number of new APS cases during a specific time period, [17] was reported as a 162 163 rate per 100,000 PY. Person-time was defined as the sum of each patient's duration of followup from January 1 to December 31 of each year, to the end of the patient record, to the end of 164 165 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 166 167 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, 168 the proportion of the population with APS in a given time period, [17] was expressed as 169

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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]

175 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 \geq 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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190	RESULTS
191	Baseline characteristics
192	A total of 1708 cases of APS that met our case definition during 2016–2019 were identified,
193	with the majority being women (n=1411, 83%; Table 1, Supplementary Table 4). For women,
194	the number of incident APS cases was highest among the 25–44 years age category (n=706,
195	50.0%), and 376 (26.6%) patients had obstetric APS. For men, the number of incident APS cases
196	was highest among patients aged 45–64 years (n=201, 67.7%). The overall number of pediatric
197	APS cases was small (n=23), with most cases identified within the 15–17 years age category
198	(n=16) for both female and male patients. Thrombotic APS was the most frequent subtype
199	identified (n=728, 42.6%), followed by APS of unknown subtype (n=404, 23.7%), obstetric APS
200	(n=376, 22.0%), other APS (n=138, 8.1%), and mixed APS (n=62, 3.6%). Seventy-five cases of
201	CAPS were identified, representing 4.4% of all APS cases. The acute care hospital was the most
202	frequently visited healthcare specialty site for diagnosis (n=227, 26.9%), followed by laboratory
203	(n=161, 19.1%), rheumatology (n=89, 10.5%), internal medicine (n=87, 10.3%), obstetrics and
204	gynecology (n=72, 8.5%) and hematology (n=70, 8.3%). Other categories for APS diagnoses
205	included oncology, family practice, pathology, neurology, multispecialty, and medical doctors.
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Total (2016–2019)

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

	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)

1 2		
3 4 5 6 7 8 9 10 11 12 13 14 15 16	209	Incidence of APS
	210	The overall annual incidence rate of APS per 100,000 PY (95% confidence interval [CI])
	211	standardized to the US 2020 population census increased slightly over the study period, from
	212	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,
	213	respectively (Figure 3). Over the whole study period, the APS incidence rates were higher in
	214	women, potentially due to certain subtypes being applicable to women only. In 2019, the
17 18 19	215	annual incidence rate (standardized to the US 2020 population census) was 4.45 (3.99–4.96)
20 21	216	per 100,000 PY for women, and 0.91 (0.71–1.17) per 100,000 PY for men. The incidence rate of
22 23 24	217	APS in women was always highest in patients aged 30–39 years old, ranging from 10.09 per
24 25 26 27 28 29	218	100,000 PY in 2016 to 11.80 and 11.22 per 100,000 PY in 2018 and 2019 (Supplementary Table
	219	5). However, in men, the age categories with the highest incidence rates varied each year
29 30 31	220	(Supplementary Table 5).
32 33 34	221	Prevalence of APS
35 36	222	The estimated annual prevalence of APS per 100,000 persons (95% CI) was 10.42 per 100,000
37 38 39	223	persons (9.96–10.90) in 2019 (Figure 3). In 2019, APS prevalence among women was four times
40 41	224	higher than in men: 16.59 (15.78–17.45) and 4.00 (3.60–4.44) per 100,000 persons,
42 43 44	225	respectively. Based on this and US census data, we have estimated that slightly more than
45 46	226	34,000 persons in the US were affected by APS in 2019. Among women, the prevalence rate of
47 48 49	227	APS was highest in the 40–49 years age group, ranging from 14.71 in 2016 to 30.61 per 100,000
50 51	228	persons in 2019. Among men, APS prevalence was highest in patients aged 60–69 years old
52 53 54	229	between 2016 (6.27 per 100,000 persons) and 2018 (10.85 per 100,000 persons), and in
55 56	230	patients aged 80+ years in 2019 (13.57 per 100,000 persons) (Supplementary Table 6).
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Incidence rates of APS subtypes 231

)) ,	232	Incidence rates of APS subtype were standardized to the US 2020 population census. In 2019,
}	233	the overall annual incidence (95% CI) of thrombotic APS was 1.28 (1.10–1.49) per 100,000 PY,
0 1	234	which was the highest incidence over the study period. The 2019 annual incidence rate of
2 3 4	235	thrombotic APS patients was higher in women (1.76 per 100,000 PY) than in men (0.79 per
5 6	236	100,000 PY) (Supplementary Figure 1a). In 2019, among women only, the incidence rate of
7 8 9	237	obstetric APS was 1.24 (1.01–1.53) per 100,000 PY (Supplementary Figure 1b), and the
20 21	238	incidence rate of mixed APS was 0.17 (0.10–0.30) per 100,000 PY. The other APS cases
22 23	239	represent 8.1% of the total APS population, with an overall annual incidence rate in 2019 of
24 25 26	240	0.23 (0.16–0.32) per 100,000 PY. The unknown APS cases represent almost a quarter (23.65%)
27 28	241	of the total APS population, with an overall incidence rate in 2019 of 0.48 (0.38–0.60) per
9 0 1	242	100,000 PY (Supplementary Table 7).
2 3 4	243	Prevalence rates of APS subtypes
5	244	The overall annual prevalence (95% CI) of thrombotic APS was 5.38 (5.05–5.73) per 100,000
6		
57 18	245	persons in 2019, and the annual prevalence rate of thrombotic APS was higher in women
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57 58 59 50 51 52 53	245	persons in 2019, and the annual prevalence rate of thrombotic APS was higher in women
87 88 99 10 11 12	245 246	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
57 58 59 50 51 52 54 55 56 57 58	245 246 247	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
67 68 69 60 61 62 63 64 65 66 7	245 246 247 248	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
77 88 99 00 11 22 33 44 55 66 77 88 99 01 12 23	245 246 247 248 249	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
77 88 99 00 11 22 33 44 55 66 77 88 99 00 11 22	245 246 247 248 249 250	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

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2		
3 4	253	Sensitivity analysis
5 6 7 8 9 10 11 12 13 14	254	Outcomes from a sensitivity analysis for different predefined scenarios for the last year of the
	255	study period, 2019, are shown in Supplementary Figure 2. The outcomes obtained from the rest
	256	of the study years were similar to those for 2019, and the subtypes of APS showed the same
	257	behaviors for the sensitivity analysis as for the overall APS cases.
15 16 17 18	258	DISCUSSION
19 20	259	The incidence and prevalence of APS in the US have been assessed using the large CCAE and
21 22 23	260	MDCR databases, which includes claims data on more than 60 million insured US employees
24 25	261	and their dependents. Our data suggest there is a trend towards a yearly increase in incidence
26 27 28	262	and prevalence of APS over time, which may be a product of generally increased awareness of
28 29 30	263	the disease.[3] Additionally, adoption of the ICD-10 code in 2015 may have also contributed to
31 32 33	264	the observed increase in prevalence.
34 35 36	265	There are a number of published studies that aimed to assess the incidence and prevalence of
37 38	266	APS in different countries around the world, [5-9, 19] which revealed important clinical and
39 40	267	epidemiological information on APS in their respective regions (Supplementary Table 8).
41 42 43	268	However, the incidence and prevalence estimates reported vary, likely due to the variation in
44 45	269	APS case definitions, design across studies, and the type of database analyzed, which may result
46 47 48 49 50 51	270	in variation in socioeconomic demographics among the populations included.[3]
	271	In particular, our sensitivity analysis shows that differences in incidence rates are apparent
52 53	272	when using different diagnostic scenarios, thus results may be sensitive to the case definition
54 55 56 57	273	used. This is evident when evaluating studies in the literature, as one pertinent difference
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> 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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$\begin{array}{c} 3\\ 4\\ 5\\ 6\\ 7\\ 8\\ 9\\ 10\\ 11\\ 12\\ 13\\ 14\\ 15\\ 16\\ 17\\ 18\\ 19\\ 20\\ 21\\ 22\\ 23\\ 24\\ 25\\ 26\\ 27\\ 28\\ 29\\ 30\\ 31\\ 32\\ 33\\ 45\\ 36\\ 37\\ 38\\ 39\\ 40\\ 41\\ 42\\ 43\\ 44\\ 5\\ 46\end{array}$	296	regions in Italy,[8] and also higher than that reported in the previous US (2.1 per 100,000 PY)
	297	and UK (1.8 per 100,000 PY) studies.[5, 9] The study in South Korea reported a higher incidence
	298	rate (7.5 per 100,000 PY) than found in any of the other studies [6]. Our estimation of
	299	prevalence rate (10.42 per 100,000 persons in 2019) was close to that estimated for the
	300	Piedmont and Aosta Valley region (16.8 per 100,000 persons).[8] In other studies, prevalence
	301	rates ranged from 40 per 100,000 persons in Spain,[7] to 61.9 per 100,000 persons in South
	302	Korea.[6] The UK study estimated that prevalence rates were 43 per 100,000 persons,[9] while
	303	the Olmsted County study in the US had an estimated prevalence of 50 per 100,000 persons.[5]
	304	The difference in the population inclusion and the design of the study might explain the
	305	heterogeneity of prevalence rates estimation. When assessing APS subtype, the overall annual
	306	standardized incidences of thrombotic APS and obstetric APS in 2019 were 1.28 per 100,000 PY,
	307	and 1.24 per 100,000 PY, respectively. These incidences are close to those reported by Duarte-
	308	Garcia et al. (2019), but far from those reported by Andreoli et al. (2013), who estimated the
	309	overall annual incidence of thrombotic APS by the indirect method as 1.8 and 65 per 100,000
	310	PY, respectively, and 0.2 and 15 per 100,000 PY, respectively, for obstetric APS.[5, 20]
	311	It has been previously estimated that CAPS patients represent less than 1% of all patients with
	312	APS, owing to the life-threatening nature of CAPS that requires high clinical awareness.[13]
	313	However, the proportion of CAPS cases in the present study was substantially higher (4.4%),
47 48	314	and more in line with the proportion (3.0%) reported by Hwang et al. (2020) in Korea.[6] This
49 50 51	315	discrepancy could be attributed to the classification criteria for CAPS, which require the
52 53	316	knowledge of aPL test result and a biopsy, neither of which were available in the present study
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> 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 Page 21 of 41

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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.

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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

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361	have a different healthcare system with variations in APS management, including treatment
362	administration, as well as possible socioeconomic differences.
363	This study identified a trend towards a yearly increase in incidence and prevalence of APS in the
364	US over the study period. The results of this study add to existing estimates published in the
365	literature, but further studies are needed to fully elucidate the global epidemiology of APS
366	using the 2023 classification criteria of APS by Barbhaiya et al.[4]
367	DATA AVAILABILITY STATEMENT
368	Data from non-interventional studies is outside of UCB's data sharing policy and is unavailable for
369	sharing.
370	ETHICS STATEMENTS
371	Patient consent for publication
372	ETHICS STATEMENTS Patient consent for publication Not applicable.
373	Ethics approval
374	The CCAE and MDCR databases are Health Insurance Portability and Accountability Act
375	compliant, and all patient data were de-identified before delivery to the study team. No ethics
376	committee approval was required.
377	ACKNOWLEDGMENTS
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393	Meheni Khellaf, Piotr Zaremba and Adam Jedrzejczyk are contractors employed by UCB. Paul
394	Meisner, Maria Sarno and Anna Scowcroft are employees and stockholders of UCB.
395	

1 2 3	207	DEEEDENCES
4 5	397	REFERENCES
6 7	398	1. Uthman I, Noureldine MHA, Ruiz-Irastorza G, Khamashta M. Management of
8	399	antiphospholipid syndrome. Ann Rheum Dis. 2019;78(2):155-61.
9 10	400	2. Miyakis S, Lockshin MD, Atsumi T, Branch DW, Brey RL, Cervera R, et al. International
11 12	401	consensus statement on an update of the classification criteria for definite antiphospholipid
13 14	402	syndrome (APS). J Thromb Haemost. 2006;4(2):295-306.
15 16	403	3. Dabit JY, Valenzuela-Almada MO, Vallejo-Ramos S, Duarte-García A. Epidemiology of
17	404	Antiphospholipid Syndrome in the General Population. Curr Rheumatol Rep. 2022;23(12):85
18 19	405	4. Barbhaiya M, Zuily S, Naden R, Hendry A, Manneville F, Amigo MC, et al. The 2023
20 21	406	ACR/EULAR Antiphospholipid Syndrome Classification Criteria. Arthritis Rheumatol.
22 23	407	2023;75(10):1687-702.
24 25	408	5. Duarte-García A, Pham MM, Crowson CS, Amin S, Moder KG, Pruthi RK, et al. The
26 27	409	Epidemiology of Antiphospholipid Syndrome: A Population-Based Study. Arthritis Rheumatol.
28	410	2019;71(9):1545-52.
29 30	411	6. Hwang JJ, Shin SH, Kim YJ, Oh YM, Lee SD, Kim YH, et al. Epidemiology of
31 32	412	Antiphospholipid Syndrome in Korea: a Nationwide Population-based Study. J Korean Med Sci.
33 34	413	2020;35(5):е35-е.
35 36	414	7. Sisó-Almirall A, Kostov B, Martínez-Carbonell E, Brito-Zerón P, Ramirez PB, Acar-Denizli
37 38	415	N, et al. The prevalence of 78 autoimmune diseases in Catalonia (MASCAT-PADRIS Big Data
39	416	Project). Autoimmun Rev. 2020;19(2):102448.
40 41	417	8. Radin M, Sciascia S, Bazzan M, Bertero T, Carignola R, Montabone E, et al.
42 43	418	Antiphospholipid Syndrome Is Still a Rare Disease-Estimated Prevalence in the Piedmont and
44 45	419	Aosta Valley Regions of Northwest Italy: Comment on the Article by Duarte-García et al.
46 47	420	Arthritis Rheumatol. 2020;72(10):1774-6.
48 49	421	9. Rodziewicz M, D'Cruz DP, Gulliford M. The epidemiology of antiphospholipid syndrome
50	422	in the UK, 1990-2016. Arthritis Rheumatol. 2019; 71
51 52	423	10. Merative MarketScan Research Databases for life sciences researchers: Merative;
53 54 55 56	424	[Available from:
57 58 50		

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Page 25 of 41

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1 2		
3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18	425	https://www.merative.com/content/dam/merative/documents/brief/marketscan-research-
	426	databases-for-life-sciences-researchers.pdf.
	427	11. Pengo V, Tripodi A, Reber G, Rand JH, Ortel TL, Galli M, et al. Update of the guidelines
	428	for lupus anticoagulant detection. Subcommittee on Lupus Anticoagulant/Antiphospholipid
	429	Antibody of the Scientific and Standardisation Committee of the International Society on
	430	Thrombosis and Haemostasis. J Thromb Haemost. 2009;7(10):1737-40.
	431	12. Brandt JT, Triplett DA, Alving B, Scharrer I. Criteria for the diagnosis of lupus
	432	anticoagulants: an update. On behalf of the Subcommittee on Lupus
	433	Anticoagulant/Antiphospholipid Antibody of the Scientific and Standardisation Committee of
19 20	434	the ISTH. Thromb Haemost. 1995;74(4):1185-90.
21 22	435	13. Asherson RA, Cervera R, de Groot PG, Erkan D, Boffa MC, Piette JC, et al. Catastrophic
23 24	436	antiphospholipid syndrome: international consensus statement on classification criteria and
25 26	437	treatment guidelines. Lupus. 2003;12(7):530-4.
20 27 28	438	14. Cervera R, Font J, Gómez-Puerta JA, Espinosa G, Cucho M, Bucciarelli S, et al. Validation
29	439	of the preliminary criteria for the classification of catastrophic antiphospholipid syndrome. Ann
30 31 32 33	440	Rheum Dis. 2005;64(8):1205-9.
	441	15. Cervera R, Rodríguez-Pintó I, Colafrancesco S, Conti F, Valesini G, Rosário C, et al. 14th
34 35	442	International Congress on Antiphospholipid Antibodies Task Force Report on Catastrophic
36 37 38 39	443	Antiphospholipid Syndrome. Autoimmun Rev. 2014;13(7):699-707.
	444	16. CDC. United States Cancer Statistics (USCS): Incidence and Death Rates 2021 [Available
40	445	from: https://www.cdc.gov/cancer/uscs/technical_notes/stat_methods/rates.htm.
41 42 43 44 45 46 47 48 49 50 51 52 53 54 55 56 57 58	446	17. National Institute of Mental Health. What is Prevalence? [Available from:
	447	https://www.nimh.nih.gov/health/statistics/what-is-prevalence#part_2626.
	448	18. Haight F. Handbook of the Poisson Distribution. New York, NY, USA: John Wiley & Sons;
	449	1967.
	450	19. Andreoli L, Nalli C, Raffetti E, Angeli F, Pascariello G, Zentilin A, et al. The prevalence and
	451	incidence of thrombotic primary antiphospholipid syndrome in adults aged 18-49 years: A
	452	population-based study in a mountain community in northern Italy. Clin Immunol.
	453	2024;260:109905.
59		Page 24 of 26

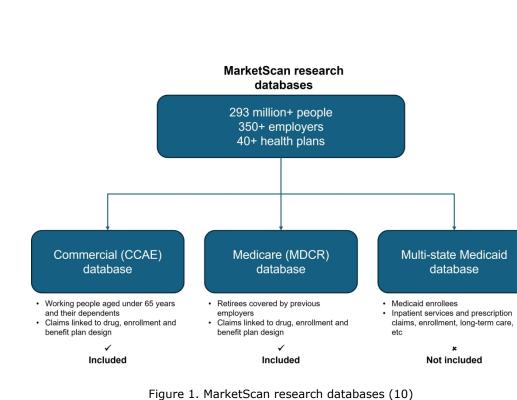
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454	20.	Andreoli L, Chighizola CB, Banzato A, Pons-Estel GJ, Ramire de Jesus G, Erkan D.
455	Estima	ated frequency of antiphospholipid antibodies in patients with pregnancy morbidity,
456	stroke	, myocardial infarction, and deep vein thrombosis: a critical review of the literature.
457	Arthri	tis Care Res (Hoboken). 2013;65(11):1869-73.
458		
459		

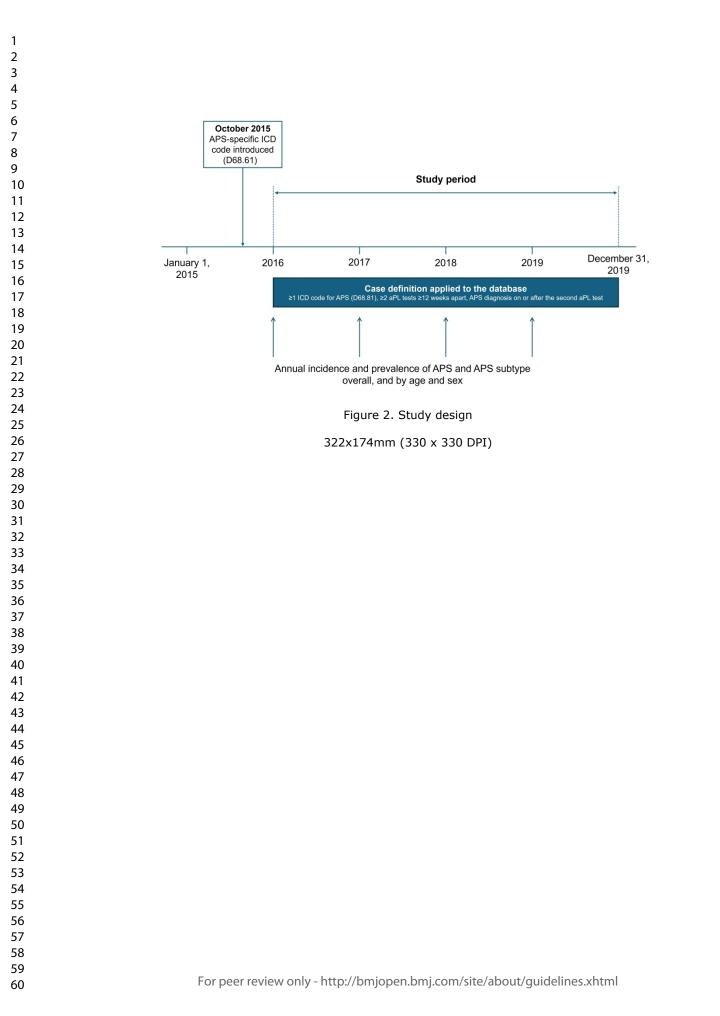
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3 4	460	FIGURE LEGENDS
5 6 7	461	Figure 1. MarketScan research databases [10]
8 9 10	462	Figure 2. Study design
11 12	463	aPL, antiphospholipid antibody; APS, antiphospholipid syndrome; ICD, International Classification of
13 14 15	464	Diseases.
16 17	465	Figure 3. Yearly incidence and prevalence rates of APS cases
18 19 20	466	Lines represent incidence rates per 100,000 PY, bars represent prevalence rates per 100,000 persons.
21 22 23	467	APS, antiphospholipid syndrome; PY, person-years.
23 24 25		APS, antiphospholipid syndrome; PY, person-years.
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Figure 3. Yearly incidence and prevalence rates of APS cases

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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	174
Cavernous sinus thrombosis	437.6	167.6
Cerebral infarction (including ischemic stroke)	434	163, 169.3
Cerebral venous sinus thrombosis,	437.6	167.6
Coronary thrombosis (without infarct)	-	124.0
Myocardial infarction	410, 411.0, 412, 429.7	I21-I23, I24.1, I25.2 Baseline variable
Personal history of venous thrombosis	Baseline variable only	only
Personal history of venous thrombosis	V12.51, V12.54, V12.55	Z68.711, Z68.718 Z68.73
Pulmonary embolism (acute or chronic)	415.1, 416.2	126
Pulmonary hypertension (thromboembolic)	416.8	127.2
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 (acute) Veins of upper extremity (acute) 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	181, 182
Thrombotic events during pregnancy or po	-	
Cerebral venous sinus thrombosis	671.5	022.5, 087.3
Deep vein thrombosis	671.3	087.1, 022.3
Obstetric thromboembolism	671.4 673.2	088.2

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Obstetric events		
Eclampsia	642.6	015
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	011, 014
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	002.1, 036.4, P95, Z37.1, Z37.4, Z37.7
Threatened preterm labor (before week 37)	644.0	060.0, 060.2, 047.0

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.

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	134, 135
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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7 8 9 10 11 12 13		≥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 test 12–26 weeks apart apart apart	APS Contracting Co	APS diagnosis 2– 13 weeks after the second aPL test [‡]
14 15 16	Case definition used	✓		6			~	b text and data mining, Al training	Download Gumprin	
17 18	Sensitivity scenario A	1		0	0.			data r	ded fro	
19 20	Sensitivity scenario B	✓				✓		nining	om htt	
21 22 23	Sensitivity scenario C	✓			16			, Al tr	p://bm	✓
23 24 25	Sensitivity scenario D§	✓				R	✓	aining	ijopen ✓	
26 27	Sensitivity scenario E		✓	✓			11	, and	.bmj.com/ on	
28 29	Sensitivity scenario F	✓			✓			simila	om/ √	
30 31 32 33 34 35 36 37 38 39 40 41 42 43 44 45 46 47	Sensitivity scenario F *Primary or seco	ondary. [†] Accordi			us unavailable. [§] l http://bmjopen			<u>,</u>	n June 8, 2025 at Agence Bibliographique de l	

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

	20)16	20)17	20	18	20	6/bmjopen-2024-084563 on 11 cted by copyright, including f	То	tal
	Male	Female	Male	Female	Male	Female	Male	Fema	Male	Female
		458		406		459		385 e 185 e		708
n (%)	77 (16.8)	381 (83.2)	76 (18.7)	330 (81.2)	82 (17.9)	377 (82.1)	62 (16.1)	327elated to	297 (17.4)	1411 (82.6
Age, years, n (%)								nem ated		
Adults	4 (5.2)		1 (1 2)	11(12)	2 (2 4)	45 (4.0)	2 (4 0)		10 (2.4)	(7 (4 7)
18-24	4 (5.2)	17 (4.5)	1 (1.3)	14 (4.2)	2 (2.4)	15 (4.0)	3 (4.8)		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)		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)	12data (Alta)	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)		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)	3111) (B) 3111) (B) 3111) (B) (B) (B) (B) (B) (B) (B) (B) (B) (B) (B	288 (97.0)	1397 (99.0
Pediatric		1						G · <mark>†</mark>		
0–4	0	1 (0.3)	0	0	1 (1.2)	0	0		1 (0.3)	1 (0.1)
5–9	1 (1.3)	0	0	0	0	0	0	trainii	1 (0.3)	0
10–14	1 (1.3)	1 (0.3)	0	2 (0.6)	0	0	0	ning,	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)	₽ <u>3</u> (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)	<u>4</u> .(1.3)	9 (3.0)	14 (1.0)
Catastrophic APS, n (%)	-	-	_	-	_		<u>h-</u>	nilar t	27 (9.1)	48 (3.4)
APS subtype, n (%)	1	1				-			1	1
Thrombotic	65 (84.4)	113 (29.6)	68 (89.5)	112 (33.9)	65 (79.3)	131 (34.7)	53 (85.5)	12 (3 a .5)	251 (84.5)	477 (33.8
Obstetric	0	95 (24.9)	0	82 (24.8)	0	109 (28.9)	0	9 8 (27,9)	0	376 (26.6
Mixed	0	17 (4.5)	0	16 (4.8)	0	16 (4.2)	0	126 (426)	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 2)	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 (2 ឆ្ន ំ7)	30 (10.1)	374 (26.5

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 (12.98–15.8	
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

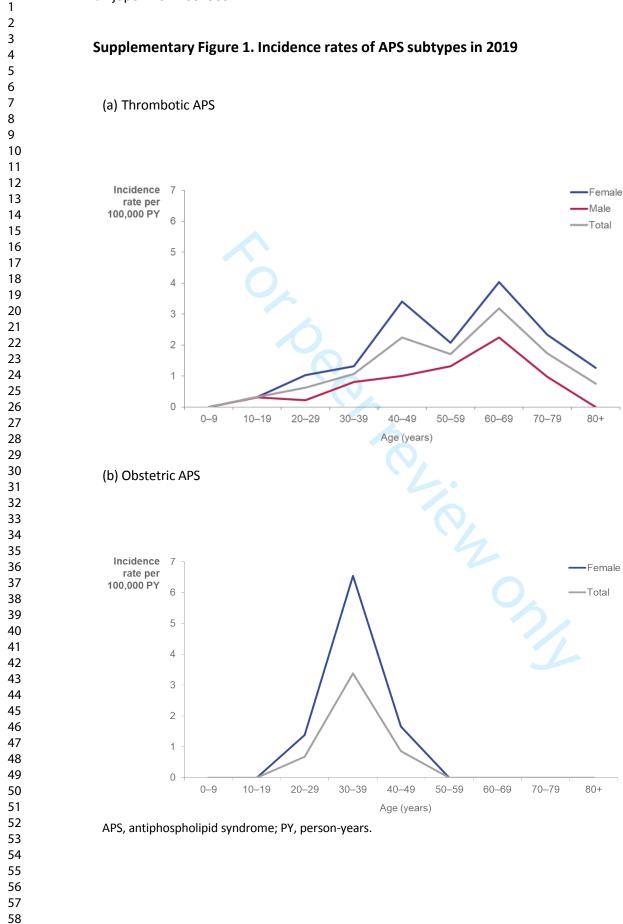
Age, years	2016	2017	2018	2019
Incidence rates (95% CI)			
Female				
Thrombotic	1.07 (0.89–1.28)	1.17 (0.97–1.41)	1.48 (1.25–1.76)	1.76 (1.47–2.10)
Obstetric	1.00 (0.82–1.22)	0.98 (0.79–1.22)	1.33 (1.10–1.60)	1.24 (1.01–1.53)
Mixed	0.18 (0.11–0.29)	0.19 (0.12–0.32)	0.19 (0.12–0.31)	0.17 (0.10-0.30)
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. <mark>53–</mark> 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.

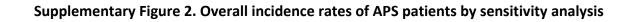
Study	Country	Study period	Data source	APS type	studies of APS Estimated incidence r per 100,000 PY (95%	C4) (rate per 100,000
Khellaf et al., 2024	United States	2015–2019	Claims database	Primary, secondary, thrombotic, obstetric, mixed, CAPS	2.71 (2.45–2.99)	Enseignement Su Uses related to tex	3 10.42 (9.96–10.90)
Radin et al., 2020 (8)	Italy	2010–2019	Registry	Primary	1.1 (not provided)	text and data	16.8 (not provided)
Huang et al., 2019 (6)	Korea	2008–2017	Claims database	Primary, secondary, obstetric, CAPS	7.5 (7.3–7.8)	ABES) . a mining,	
Duarte-Garcia et al., 2019 (5)	United States	2000–2015	EHRs	Primary	2.1 (1.4–2.8)	Al training,	50 (42–58)
Rodziewicz et al., 2019 (9)	United Kingdom	1990–2016	EHRs	Primary, SLE- related	1.8* (not provided)	, and simi	43 (not provided)
Sisó-Almirall et al., 2020 (7)	Spain	2012–2017	EHRs	Not stated	Not provided	and similar technologies.	
Andreoli et al., 2024 (18)	Italy	2011–2015	EHRs	Thrombotic primary; aged 18–49 years	5.0 (2.6–8.7)	o, 2023 at Agenice bibliographilque de l ologies.	22.9 (11.4–41.0)

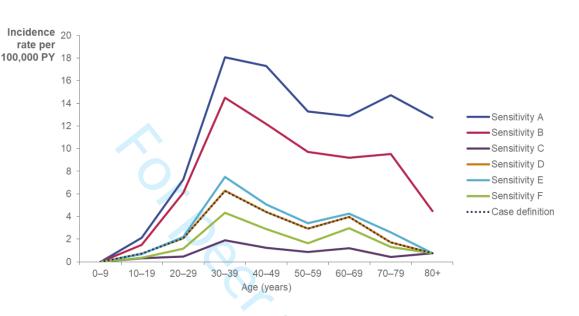
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scenarios in 2019





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.