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MAJOR ARTICLE

Risk of Incident Tuberculosis Disease in a Large Integrated Health Care System in California, 2004–2022

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Background. Few studies have assessed tuberculosis (TB) disease incidence and risk in a large US-based cohort with long-term longitudinal follow-up.

Methods. In a retrospective cohort study from 2004 to 2022, we assessed risk of incident microbiologically confirmed TB disease using Cox proportional hazards models. Primary exposures were (1) nativity and (2) high-risk medical conditions for progression to TB disease.

Results. Among 4 761 427 adults with 35 591 565 person-years (PY) of follow-up, 12.3% were born in TB-endemic countries and 5.5% had a high-risk medical condition. In all, 1463 had incident TB disease (incidence rate, 4.11/100 000PY), with persons born in TB-endemic countries (incidence rate [IR], 17.6/100 000PY; 95% CI, 16.4–18.7/100 000PY) having higher TB disease rates than US-born persons (IR, 1.27/100 000PY; 95% CI, 1.09–1.44/100 000PY), with an adjusted hazard ratio (aHR) of 15.3 (95% CI, 13.2–17.9). Persons with high-risk conditions (IR, 11.3/100 000PY; 95% CI, 10.0–12.6/100 000PY) had higher TB disease rates than persons without any conditions (IR, 2.63/100 000PY; 95% CI, 2.43–2.82/100 000PY). Persons with HIV infection (aHR, 3.77; 95% CI, 2.7–3.89), hematologic malignancy (aHR, 1.62; 95% CI, 1.17–2.22), diabetes mellitus (aHR, 2.85; 95% CI, 2.53–3.20), end-stage renal disease (aHR, 2.84; 95% CI, 2.07–3.20), and those who had received corticosteroids (aHR, 1.39; 95% CI, 1.10–1.77) or other immunosuppressants (aHR, 2.37; 95% CI, 1.73–3.24) had significantly increased TB disease risk compared with persons without those conditions. Persons born in TB-endemic countries accounted for 79.1% all TB cases among persons with high-risk conditions.

Conclusions. Persons born in TB-endemic countries are the largest group and have the highest risk for developing TB disease in the United States, and thus should be prioritized for LTBI screening and treatment.

Keywords. California; tuberculosis; risk; epidemiology; immunosuppression.

Tuberculosis (TB) elimination, defined as TB disease incidence of <1/1 000 000 person-years, is a goal for both the state of California and the United States [1–3]. Over 85% of TB disease cases are due to reactivation among persons with latent tuberculosis infection (LTBI), and thus LTBI screening and treatment are key strategies to reduce TB incidence in the United States [4–6]. However, although LTBI screening and treatment for TB prevention are supported by >40 years of good quality evidence for both efficacy and effectiveness, are endorsed by both national and California-specific guidelines, and rely on readily available tests (eg, the tuberculin skin test, developed in 1907, and interferon-gamma release assay, approved in 2001) and treatments (eg, rifampin, introduced in 1968), implementation in most health systems has been poor [4–11].

LTBI screening and treatment are commonly incorporated into primary care settings, which deliver most recommended health prevention interventions (eg, cervical, colon, and breast cancer screening, diabetes and hypertension screening) [4]. However, most of our understanding of TB disease risk is from national and local public health surveillance systems, local tuberculosis control units, and special studies of immigrant populations; these data sources do not rely on longitudinal follow-up of well-defined populations and do not account for prior LTBI treatment [12, 13]. Few studies to date have defined the absolute risk of and risk factors for TB disease in a general population using a cohort design with longitudinal follow-up in a health care setting. These data are critical for primary care providers and health systems to understand TB disease

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risk for patients in primary care settings. Second, current guidelines define 2 main risk groups for LTBI screening: (1) persons born in TB-endemic countries (any country other than the United States, Canada, Australia, New Zealand, or a country in Western or Northern Europe) who have increased risk of TB infection due to exposure before immigrating to the United States; and (2) persons with medical conditions that increase risk of progression to TB disease (eg, current or planned immunosuppression). However, few studies have comprehensively assessed the potential overlap between these 2 non–mutually exclusive risk categories. Third, few longitudinal studies of TB disease risk have complete records of LTBI treatment and thus estimate the risk of incident TB disease in persons who have not been treated for LTBI.

To address these data gaps, we conducted a retrospective cohort study in a large integrated health care system with over 4.7 million persons and 35 million person-years of follow-up to (1) estimate the absolute incidence of TB disease among persons born in TB-endemic countries or with medical conditions that increase TB disease risk; (2) estimate the relative risk of TB disease among persons born in TB-endemic countries or with medical conditions; (3) define the overlap in TB disease risk among persons born in TB-endemic countries and those with medical conditions.

METHODS

Setting

Kaiser Permanente Northern California (KPNC) is an integrated health system that serves >4.7 million members in Northern and Central California and provides comprehensive preventive and curative care in inpatient and outpatient settings across 266 medical offices and 21 hospitals. Members receive all primary care services and most other clinical services, including laboratory testing, outpatient, and inpatient care in KPNC facilities. Members have similar sociodemographic characteristics to the diverse population of Northern and Central California [14].

Study Design

We conducted a retrospective cohort study of all KPNC members aged ≥18 years with at least 2 years of continuous membership between January 1, 2003, and September 30, 2022. We defined the start of follow-up (index date) as 1 year after date of first enrolling as a KPNC member during the study period. We excluded persons with any history of TB disease (microbiologically confirmed TB disease based on culture result or nucleic acid amplification test positive for *Mycobacterium tuberculosis* or International Classification of Diseases, 9th Revision [ICD-9], codes 010–018 before the index date or any treatment for LTBI or TB disease, defined as prescription fill for rifampin, isoniazid or rifapentine before the index date). The primary outcome was microbiologically confirmed TB disease based on a positive mycobacterial culture or nucleic acid amplification test for *Mycobacterium tuberculosis*. Persons were followed from index date until date of (1) diagnosis of TB disease (primary outcome); (2) any prescription fill for rifampin, isoniazid, or rifapentine as these medications are used for LTBI treatment and prevent progression to TB disease; (3) disenrollment from KPNC; (4) death; (5) end of study period on September 30, 2022. Data were obtained from the KPNC Virtual Data Warehouse, a common data model into which standardized data are extracted from clinical and administrative databases including an integrated electronic health record (EHR) database (Epic, Verona, WI, USA). The study was approved by the Kaiser Permanente Southern California and KPNC Institutional Review Boards with waivers of the requirement for informed consent.

Exposures and Covariates

As our primary exposure, we defined 5 nativity categories. Data on place of birth, including country, are collected during registration events at KPNC, and data on preferred language are collected as part of clinical encounters. We used EHR data on country of birth and preferred language to define the following nativity categories (detailed mapping in Supplementary Table 1): (1) "born in TB-endemic country" was defined as EHR documentation of birth in any country other than the United States, Canada, Australia, New Zealand, or Northern and Western Europe; (2) "non-US-born by language only" was used if there was no EHR documentation of country of birth, but there was documentation of preferred language predominantly spoken in TB-endemic countries (eg, Arabic, Quechua, Swahili); (3) "non-US-born in non-TB-endemic country" was based on EHR documentation of birth in Canada, Australia, New Zealand, or Western or Northern Europe; (4) "US-born" was based on EHR documentation of birth in the United States; (5) "unknown" was defined as no EHR documentation of country of birth and preferred language unknown or English. Persons born in TB-endemic countries were grouped into geographic regions (Caribbean, Central America, South America, Africa, Eastern Europe, Eastern Asia, South Asia, Southeast Asia, Central and Western Asia, Oceania).

As our secondary exposure of interest, we defined high- and intermediate-risk medical conditions for progression to TB disease. High-risk conditions for progression to TB disease included (1) HIV infection based on ICD 9th and 10th edition (ICD-9: 079.53, 042, V08, 795.71; ICD-10: B20, B97.71, Z21, O98.7) codes; (2) solid organ transplantation ICD codes (ICD-9: V42.0, V42.1, V42.6, V42.7, V42.83, V42.84; ICD-10: Z94.0-Z94.4); (3) hematologic malignancy based on ICD codes (ICD-9: 200–208; ICD-10: C81–C96); (4) receipt of tumor necrosis factor alpha inhibitors (TNFα) based on pharmacy records, including adalimumab, certolizumab, etanercept, golimumab, infliximab; (5) receipt of high-dose corticosteroids, defined as ≥20 mg prednisone equivalents of oral or systemic corticosteroids daily for ≥30 days based on pharmacy

records; (6) receipt of other immunosuppressants based on pharmacy records, including receipt of abatacept, anakinra, auranofin, azathioprine, baricitinib, canakinumab, cyclosporine, fingolimod, guselkmab, leflunomide, mycophenolate mofetil, riskankizumab, rituximab, secukinumab, sirolimus, tacrolimus, thalidomide, tofacitinib, tocilizumab, and ustekinumab. Intermediate-risk conditions for progression to TB disease included (1) diabetes mellitus using ICD codes (ICD-9: 249, 250;

Table 1. Persons With and Without Incident Tuberculosis Disease, Kaiser Permanente Northern California, 2004–2022

	All Persons		With TB Disease		Without TB Disease	
	No.	%	No.	%	No.	%
Total	4 761 427	…	1463	…	4 759 964	…
Sex						
Male	2 321 581	48.7	854	58.4	2 320 727	48.7
Female	2 439 846	51.2	609	41.6	2 439 237	51.2
Age						
18–29 y	1 128 764	23.7	178	12.2	1 128 586	23.7
30–39 y	1 109 859	23.3	221	15.1	1 109 638	23.3
40–49 y	943 465	19.8	276	18.9	943 189	19.8
50–59 y	795 682	16.7	318	21.7	795 364	16.7
60–69 y	465 598	9.78	251	17.2	465 347	9.78
70–79 y	216 391	4.54	171	11.7	216 220	4.54
80+ y	101 668	2.14	48	3.28	101 620	2.13
Race/ethnicity						
White	2 161 648	45.4	107	7.31	2 161 541	45.4
Black	289 666	6.08	81	5.54	289 585	6.08
Hispanic	872 276	18.3	212	14.5	872 064	18.3
Asian	831 600	17.5	981	67.1	830 619	17.5
American Indian/Alaska Native	21 700	.46	5	0.34	21 695	0.46
Native Hawaiian/Pacific Islander	32 389	0.68	18	1.23	32 371	0.68
Other/unknown/multiracial	552 148	11.6	59	4.03	552 089	11.6
Charlson comorbidity index score						
0	3 132 597	65.8	781	53.4	3 131 816	65.8
1	490 045	10.3	266	18.2	489 779	10.3
2	144 302	3.03	104	7.11	144 198	3.03
3+	98 506	2.07	69	4.72	98 437	2.07
No visits prior year	895 977	18.8	243	16.6	895 734	18.8
Nativity categories						
Born in TB-endemic country	584 801	12.3	896	61.2	583 905	12.3
Non-US-born by language only	210 982	4.43	75	5.13	210 907	4.43
Non-US-born in non-TB-endemic country	58 171	1.22	11	0.75	58 160	1.22
US-born	1 597 656	33.6	203	13.9	1 597 453	33.6
Unknown (by country or language)	2 309 817	48.5	278	19.0	2 309 539	48.5
High- or intermediate-risk medical conditions for progression to TB						
Any high-risk condition	262 827	5.52	299	20.4	262 528	5.52
Any intermediate-risk condition	740 195	15.6	607	41.5	739 588	15.5
Any high- or intermediate-risk conditions	919 911	19.3	764	52.2	919 147	19.3
No high- or intermediate-risk conditions	3 841 516	80.7	699	47.8	3 840 817	80.7
Specific high-risk conditions						
HIV infection	15 842	0.3	18	1.23	15 824	0.3
Solid organ transplantation	11 083	0.2	19	1.30	11 064	0.2
Hematologic malignancy	57 007	1.2	58	4.1	56 919	1.2
TNFα inhibitor use	9562	0.2	9	0.6	9553	0.2
High-dose corticosteroid use	136 502	2.9	100	7.1	136 402	2.9
Other immunosuppressant use	122 884	2.6	130	9.0	122 754	2.6
Specific intermediate-risk conditions						
Diabetes mellitus	728 643	15.3	478	35.2	728 165	15.3
End-stage renal disease	39 880	0.8	56	4.0	39 824	0.8

For all variables, those with TB disease and without TB disease were significantly different ($P < .0001$, chi-square test). Race and ethnicity were mutually exclusive, and all race categories were defined as non-Hispanic.

Abbreviations: TB, tuberculosis; TNFα, tumor necrosis factor alpha.

Table 2. Incidence and Risk of Tuberculosis Disease, Kaiser Permanente Northern California, 2004–2022

	No. of TB Disease Cases	No. of Persons in Denominator	Follow-up Time in Person-Years	TB Disease Incidence Rate (95% CI)	Adjusted Hazard Ratio (95% CI)
Total	1463	4 761 427	35 591 565	4.11 (3.90–4.32)	N/A
Sex					
Male	854	2 321 581	16 706 234	5.11 (4.77–5.47)	1.95 (1.62–2.34)
Female	609	2 439 846	18 885 330	3.22 (2.97–3.49)	Ref
Age					
18–29 y	178	1 128 764	5 868 376	3.03 (2.60–3.51)	Ref
30–39 y	221	1 109 859	7 516 137	2.94 (2.57–3.36)	0.82 (0.68–1.00)
40–49 y	276	943 465	7 910 835	3.49 (3.09–3.93)	1.03 (0.85–1.24)
50–59 y	318	795 682	7 167 807	4.44 (3.96–4.96)	1.43 (1.19–1.72)
60–69 y	251	465 598	4 410 951	5.69 (5.01–6.44)	1.90 (1.57–2.31)
70–79 y	171	216 391	2 080 508	8.22 (7.03–9.55)	2.93 (2.37–3.63)
80+ y	48	101 668	636 950	7.54 (5.56–9.99)	3.37 (2.46–4.66)
Race/ethnicity					
White	107	2 161 648	18 262 312	0.586 (0.48–0.708)	N/A
Black	81	289 666	2 296 275	3.53 (2.80–4.38)	N/A
Hispanic	212	872 276	6 195 205	3.42 (2.98–3.92)	N/A
Asian	981	831 600	6 201 931	15.8 (14.8–16.8)	N/A
American Indian/Alaska Native	5	21 700	146 513	3.41 (1.11–7.96)	N/A
Native Hawaiian/Pacific Islander	18	32 389	216 384	8.32 (4.93–13.15)	N/A
Other/unknown/multiracial	59	552 148	2 272 946	2.60 (1.98–3.35)	N/A
Charlson comorbidity index score					
Score 0	781	3 132 597	24 047 810	3.25 (3.02–3.48)	N/A
Score 1	266	490 045	3 872 926	6.87 (6.07–7.75)	N/A
Score 2	104	144 302	1 158 816	8.97 (7.33–10.9)	N/A
Score 3+	69	98 506	626 110	11.0 (8.58–13.9)	N/A
No visits prior year	243	895 977	5 885 903	4.13 (3.63–4.68)	N/A
Country of birth categories					
Born in TB-endemic country	896	584 801	5 095 331	17.6 (16.5–18.8)	15.3 (13.2–17.9)
Non-US-born by language only	75	210 982	1 165 820	6.43 (5.06–8.06)	5.83 (4.46–7.63)
Non-US-born in non-TB-endemic country	11	58 171	653 744	1.68 (0.840–3.01)	1.15 (0.62–2.10)
US-born	203	1 597 656	15 992 024	1.27 (1.10–1.46)	Ref
Unknown (by country or language)	278	2 309 817	12 684 646	2.19 (1.94–2.47)	1.95 (1.62–2.34)
High- or intermediate-risk medical conditions for progression to TB					
Any high-risk condition	299	262 827	2 648 848	11.3 (10.0–12.6)	N/A
Any intermediate-risk condition	607	740 195	7 235 389	8.39 (7.74–9.08)	N/A
Any high- or intermediate-risk conditions	764	919 911	8 982 293	8.51 (7.91–9.13)	N/A
No high- or intermediate-risk conditions	699	3 841 516	26 609 272	2.63 (2.44–2.83)	N/A
Specific high-risk conditions					
HIV infection	18	15 842	103 784	17.34 (10.3–27.4)	3.77 (2.07–3.89)
Solid organ transplantation	19	11 083	62 324	30.5 (18.4–47.6)	0.634 (0.359–1.12)
Hematologic malignancy	58	57 007	254 903	22.8 (17.3–29.4)	1.62 (1.17–2.22)
TNFα inhibitor use	9	9562	45 424	19.8 (9.06–37.6)	1.49 (0.721–3.06)
High-dose corticosteroid use	100	136 502	757 152	13.2 (10.7–16.1)	1.39 (1.10–1.77)
Other immunosuppressant use	130	122 884	865 928	15.0 (12.5–17.8)	2.37 (1.73–3.24)
Specific intermediate-risk conditions					
Diabetes mellitus	478	729 127	4 573 532	10.5 (9.54–11.4)	2.85 (2.53–3.20)
End-stage renal disease	56	39 880	115 903	48.3 (36.5–62.7)	2.84 (2.07–3.89)

Race and ethnicity were mutually exclusive, and all race categories were defined as non-Hispanic. TB disease incidence rate is per 100 000 person-years. Adjusted hazard ratio was based on Cox proportional hazards model estimating risk of TB disease by nativity categories as baseline variables and high- and intermediate-risk medical conditions as time-dependent variables adjusted for age group and sex.

Abbreviations: aHR, adjusted hazard ratio; TB, tuberculosis; TNFα, tumor necrosis factor alpha.

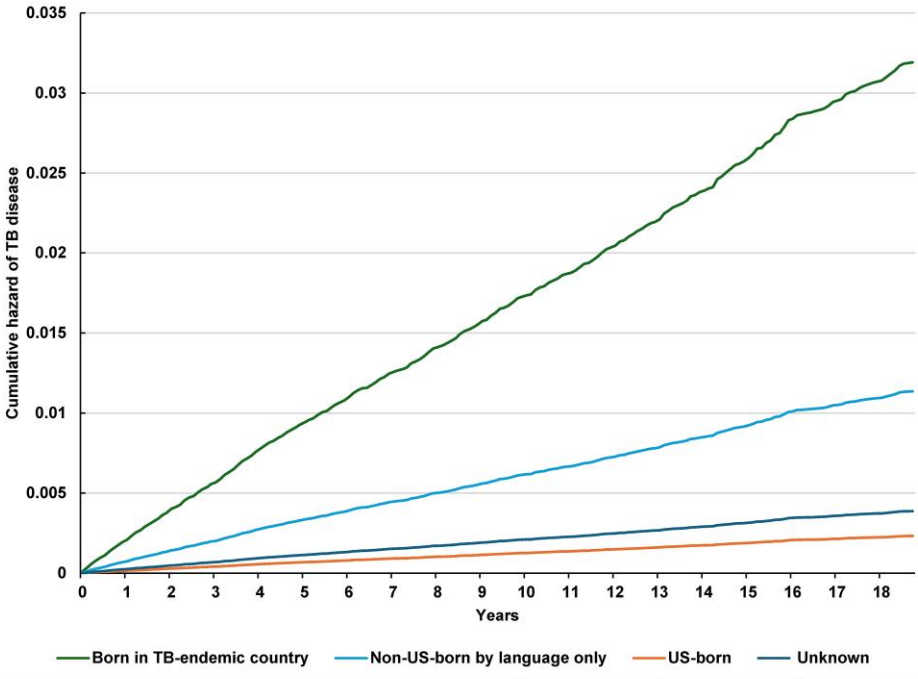
ICD-10: E08–E11, E13); (2) end-stage renal disease using ICD codes (ICD-9: 585.6; ICD-10: N18.6). Other covariates included demographic characteristics (age, sex, race/ethnicity) and Charlson comorbidity index score [15].

Statistical Analysis

We calculated the crude incidence rate of TB disease during the follow-up period by dividing the number of TB cases by the total number of person-years and used an exact method to estimate the 95% CIs [16]. Using Cox proportional hazards models with a Nelson-Aalen estimator, we produced cumulative hazard curves stratified by nativity categories and medical conditions. To assess the risk of incident TB disease among persons born in TB-endemic countries and persons with medical conditions, we estimated adjusted hazard ratios (aHRs) and CIs using Cox proportional hazards models adjusting for potential confounders defined a priori, including age in years and sex. High- and intermediate-risk medical conditions were included in all models as time-dependent covariates as the onset date could occur after the index date but before the date of TB disease or end of follow-up. Moreover, to assess possible effect modification between nativity and high/intermediate-risk categories for TB progression, we fit separate Cox models among persons born in TB-endemic countries and US-born persons. In all models, we assessed the proportional hazards assumption by testing for slopes in Schoenfeld residuals [17]. All analyses used SAS software, version 9.4 (SAS Institute Inc., Cary, NC, USA). All comparisons were 2-tailed, with $P < .05$ considered significant.

RESULTS

In all, 4 761 427 persons with 35 591 565 person-years of follow-up were included in this analysis over the 18-year study period, and 1463 persons were diagnosed with TB disease (incidence rate, 4.11/100 000PY) (Tables 1 and 2). In the overall study population, 53.0% were age >40 years (median age [interquartile range {IQR}], 41 [29–53] years), 51.2% were female, 45.4% were non-Hispanic White, 6.08% were Black, 18.3% were Hispanic, and 17.5% were Asian. In all, 12.3% were born in TB-endemic countries, 4.43% were non-US-born by language only, 33.6% were US-born, and 48.5% had unknown nativity. Only 5.52% had a high-risk condition, and 15.6% had an intermediate-risk condition. Persons with incident TB disease were significantly more likely to be older (median age [IQR], 51 vs 41 [26 vs 24] years), male (58.4% vs 48.7%), Asian (67.1% vs 17.5%), born in a TB-endemic country (61.2%



	Year 0	Year 5	Year 10	Year 15	Year 18
Born in TB-endemic country	584 800	360 680	217 208	137 371	79 507
Non-US-born by language only	210 982	82 677	32 294	17 051	8640
US-born	1 597 656	1 107 527	739 193	493 959	305 730
Unknown	2 309 817	830 696	367 841	219 940	136 344

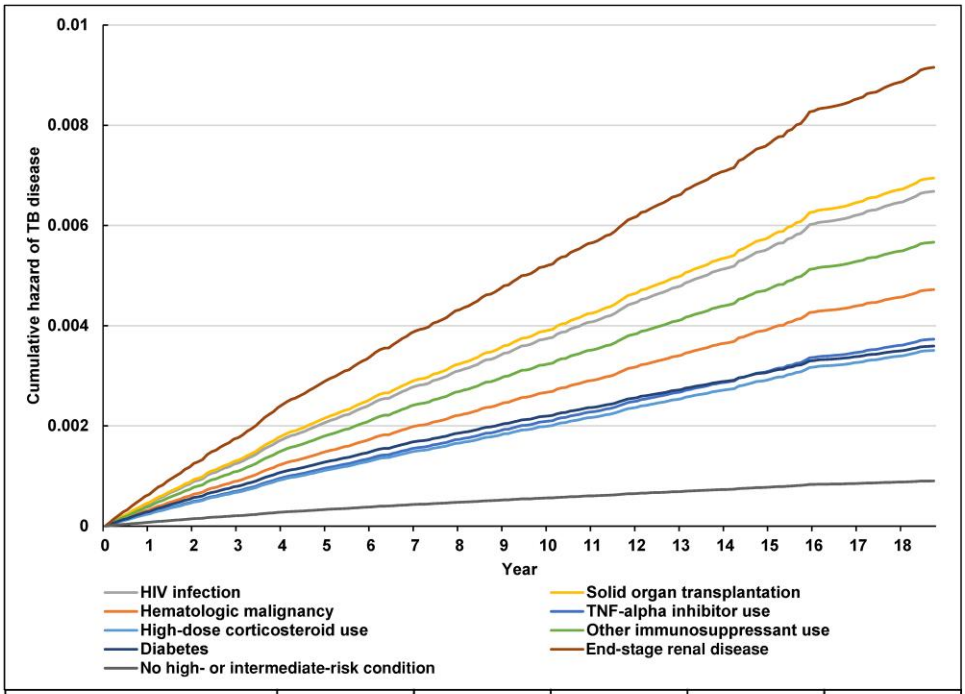
Figure 1. Cumulative hazard of TB disease by nativity, Kaiser Permanente Northern California, 2004–2022. Abbreviation: TB, tuberculosis.

vs 12.3%), and to have a high-risk (20.4% vs 5.52%) or intermediate-risk (41.5% vs 15.5%) medical condition ($P < .0001$ for all comparisons). Only 13.9% of all TB cases were among US-born persons. Persons with unknown nativity comprised 48.5% of the population and accounted for 19.0% of all persons with TB disease.

The incidence of TB disease increased with age, from 2.94 (95% CI, 2.55–3.33) per 100 000PY among persons aged 30–39 years to 7.54 (95% CI, 5.40–9.67) per 100 000PY among persons aged 80–89 years (Table 2). Asian persons had the highest incidence rate among all race/ethnicity groups (IR, 15.8/100 000PY; 95% CI, 14.8–16.8/100 000PY). Persons born in TB-endemic countries (IR, 17.6/100 000PY; 95% CI, 16.4–18.7/100 000PY) or non-US-born by language only (IR, 6.43/100 000PY; 95% CI, 4.98–7.89/100 000PY) had substantially higher rates of TB disease than US-born persons (IR, 1.27/100 000PY; 95% CI, 1.09–1.44/100 000PY) or persons with unknown nativity (IR, 2.19/100 000PY; 95% CI, 1.93–2.45/100 000PY). TB disease incidence rates were higher for persons with high-risk (IR, 11.3/100 000PY; 95% CI, 10.0–12.6/100 000PY) medical conditions than for persons who had no high- or intermediate-risk medical conditions (IR, 2.63/100 000PY; 95% CI, 2.43–2.82/100 000PY).

The adjusted hazard ratio of TB disease was 15.3 (95% CI, 13.2–17.9) times higher for persons born in TB-endemic countries and 5.83 (95% CI, 4.46–7.63) times higher for non-US-born persons by language only compared with US-born persons (Table 2, Figure 1). Persons with HIV infection (aHR, 3.77; 95% CI, 2.7–3.89), diabetes (aHR, 2.85; 95% CI, 2.53–3.20), end-stage renal disease (aHR, 2.84; 95% CI, 2.07–3.89), and those who had received high-dose corticosteroids (aHR, 1.39; 95% CI, 1.10–1.77) or other immunosuppressants (aHR, 2.37; 95% CI, 1.73–3.24) had significantly increased risk of TB disease compared with persons without those conditions (Table 2, Figure 2).

Among persons born in TB-endemic countries, TB incidence rates were substantially higher among persons with high-risk (IR, 49.7/100 000PY; 95% CI, 42.8–56.6/100 000PY) and intermediate-risk (IR, 27.5/100 000PY; 95% CI, 24.9–30.1/100 000PY) medical conditions compared with persons without



	Year 0	Year 5	Year 10	Year 15	Year 18
HIV infection	11 732	8040	5207	3139	1657
Solid organ transplantation	22 261	17 742	12 813	7856	3980
Hematologic malignancy	111 149	89 830	62 487	37 804	18 056
TNF-alpha inhibitor use	16 475	14 252	10 646	7104	4061
High-dose corticosteroid use	224 432	178 717	125 087	77 155	40 433
Other immunosuppressants use	113 220	93 463	68 223	45 228	25 004
Diabetes mellitus	780 027	648 091	486 358	341 196	204 856
End-stage renal disease	74 553	61 636	43 133	24 633	9711
No high- or intermediate-risk condition	4302 228	2058 228	1109 290	664 347	383 959

Figure 2. Cumulative hazard of TB disease by high- and intermediate-risk medical conditions for progression to TB disease, Kaiser Permanente Northern California, 2004–2022. Abbreviations: TB, tuberculosis; TNFα, tumor necrosis factor alpha.

Table 3. Incidence and Risk of Tuberculosis Disease by High- and Intermediate-Risk Medical Conditions Among Persons Born in TB-Endemic Countries and US-Born Persons, Kaiser Permanente Northern California, 2004–2022

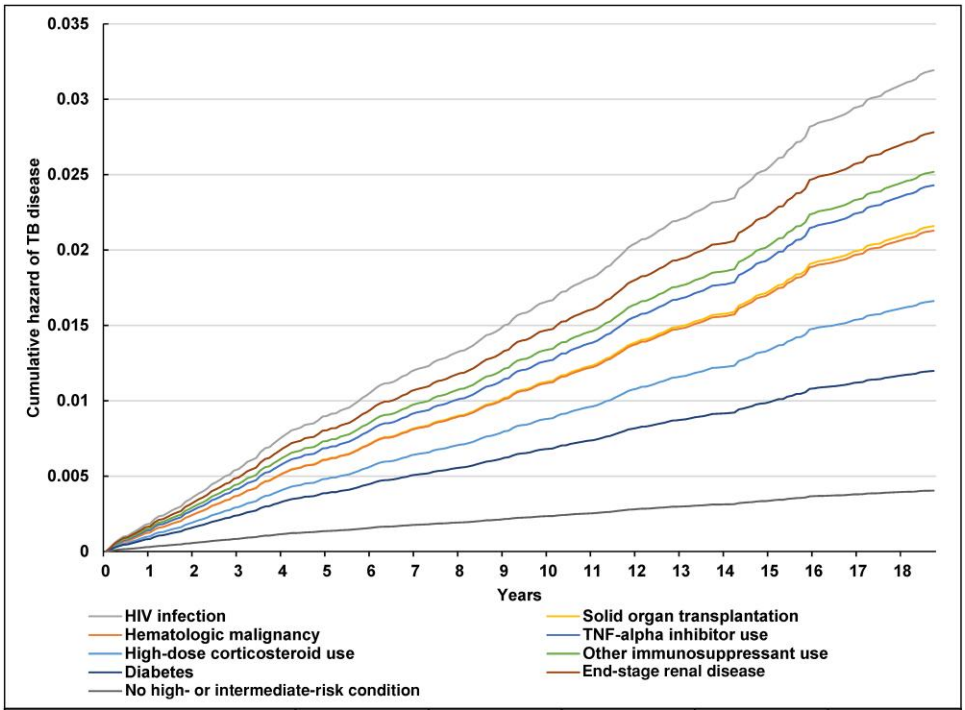
	No. of TB Disease Cases	No. of Persons in Denominator	Follow-up Time in Person-Years	TB Disease Incidence Rate (95% CI)	Adjusted Hazard Ratio (95% CI)
Born in TB-endemic countries	896	584 801	5 095 331	17.6 (16.4–18.7)	…
HIV infection	8	1603	9983	80.1 (34.6–158)	4.73 (2.25–9.96)
Solid organ transplantation	16	2915	15 919	101 (57.4–163)	0.493 (0.261–0.930)
Hematologic malignancy	37	8055	32 241	115 (80.8–158)	1.46 (0.971–2.21)
TNFα inhibitor use	7	1311	5148	136 (54.7–280)	1.91 (.827–4.42)
High-dose corticosteroid use	71	19 402	105 596	67.2 (52.5–84.8)	1.53 (1.15–2.03)
Other immunosuppressant use	94	21 241	144 587	65.0 (52.5–79.6)	2.67 (1.86–3.89)
Diabetes mellitus	344	147 435	967 212	35.6 (31.9–39.5)	2.01 (1.74–2.31)
End-stage renal disease	56	39 800	115 903	48.3 (37.5–62.7)	2.35 (1.66–3.33)
Any high-risk condition	200	38 740	402 225	49.7 (43.7–57.1)	N/A
Any intermediate-risk condition	424	149 714	1 540 683	27.5 (24.9–30.3)	N/A
Any high- or intermediate-risk conditions	518	172 077	1 763 688	29.4 (26.9–32.0)	N/A
No high- or intermediate-risk conditions	378	412 724	3 331 643	11.3 (10.2–12.5)	N/A
US-born	203	1 597 656	15 992 024	1.27 (1.09–1.44)	…
HIV infection	7	7773	62 352	11.2 (4.51–23.1)	6.91 (2.56–18.7)
Solid organ transplantation	1	6433	38 901	2.57 (0.065–14.3)	0.636 (0.0710–5.68)
Hematologic malignancy	10	35 275	173 698	5.76 (2.76–10.6)	1.74 (0.807–3.73)
TNFα inhibitor use	2	6613	33 701	5.93 (0.719–21.4)	2.62 (0.599–11.5)
High-dose corticosteroid use	16	81 392	501 278	3.19 (1.82–5.18)	1.42 (0.783–2.58)
Other immunosuppressant use	17	71 082	561 824	3.03 (1.76–4.85)	1.51 (0.630–3.61)
Diabetes mellitus	49	325 707	2 461 689	1.99 (1.47–2.63)	1.53 (1.09–2.15)
End-stage renal disease	5	24 884	75 392	6.63 (2.15–15.5)	1.27 (0.376–4.30)
Any high-risk condition	53	151 977	1 764 273	3.00 (2.25–3.93)	N/A
Any intermediate-risk condition	71	332 834	3 848 290	1.85 (1.44–2.33)	N/A
Any high- or intermediate-risk conditions	103	434 529	5 003 166	2.06 (1.68–2.50)	N/A
No high- or intermediate-risk conditions	100	1 163 127	10 988 858	0.910 (0.740–1.11)	N/A

Race and ethnicity were mutually exclusive, and all race categories were defined as non-Hispanic. TB disease incidence rate is per 100 000 person-years. Adjusted hazard ratio was based on Cox proportional hazards model estimating risk of TB disease among persons with high- and intermediate-risk medical conditions as time-dependent variables adjusted for age group and sex. For all high- and intermediate risk-conditions, the referent is persons who do not have the condition.

Abbreviations: aHR, adjusted hazard ratio TB, tuberculosis; TNFα, tumor necrosis factor alpha.

any high-risk or intermediate-risk conditions (IR, 11.4/100 000PY; 95% CI, 10.2–12.5/100 000PY) (Table 3, Figure 3). Similarly, among US-born persons, TB incidence rates were substantially higher among persons with high-risk (IR, 3.00/100 000PY; 95% CI, 2.20–3.81/100 000PY) and intermediate-risk (IR, 1.85/100 000PY; 95% CI, 1.42–2.27/100 000PY) medical conditions compared with persons without any high- or intermediate-risk conditions (IR, 0.910/100 000PY; 95% CI, 0.732–1.09/100 000PY) (Figure 4). Among persons born in TB-endemic countries, HIV infection (aHR, 4.73; 95% CI, 2.25–9.96), high-dose corticosteroid use (aHR, 1.53; 95% CI, 1.15–2.03), other immunosuppressant use (aHR, 2.67; 95% CI, 1.86–3.89), diabetes mellitus (aHR, 2.01; 95% CI, 1.74–2.31), and end-stage renal disease (aHR, 2.35; 95% CI, 1.66–3.33) were independent risk factors for TB disease. Among US-born persons, only HIV infection (aHR, 6.91, 95% CI, 2.56–18.7) and diabetes mellitus (aHR, 1.53; 95% CI, 1.09–2.15) were independent risk factors for TB disease. Persons born in TB-endemic countries accounted for the majority of all TB cases among persons with high-risk (200/253; 79.1%) or intermediate-risk medical conditions (424/495; 85.7%).

Among the 584 801 persons born in TB-endemic countries, we assessed the incidence and risk of TB disease among persons from selected TB-endemic countries and geographic regions (Table 4). Persons born in Ethiopia (IR, 63.9/100 000PY; 95% CI, 34.0–109/100 000PY), Burma (IR, 48.2/100 000PY; 95% CI, 26.3–80.8/100 000PY), the Philippines (IR, 39.6/100 000PY; 95% CI, 35.9–43.7/100 000PY), and Vietnam (IR, 33.0/100 000PY; 95% CI, 27.1–39.8/100 000PY) had the highest incidence of TB disease. By region of birth, persons born in Africa and Eastern, South, or Southeast Asia had the highest incidence of TB disease, while persons born in the Caribbean, Central or Western Asia, or Eastern Europe had the lowest



	Year 0	Year 5	Year 10	Year 15	Year 18
HIV infection	1382	976	613	362	182
Solid organ transplantation	5788	4710	3421	2125	1074
Hematologic malignancy	15 717	13 275	9312	5531	2444
TNF-alpha inhibitor use	2032	1692	1234	786	436
High-dose corticosteroid use	33 208	27 962	19 869	12 171	6084
Other immunosuppressants use	20 176	16 688	11 987	7786	4097
Diabetes mellitus	160 374	138 663	105 638	73 435	42 767
End-stage renal disease	17 942	15 361	10 907	6352	2543
No high- or intermediate-risk condition	497 540	285 991	159 196	90 786	47 720

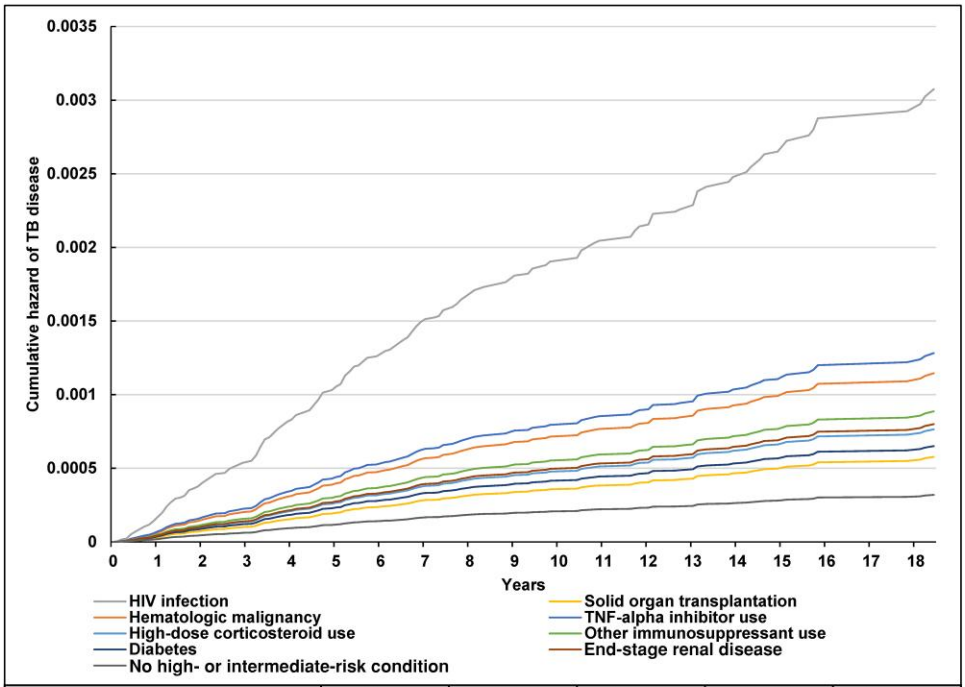
Figure 3. Cumulative hazard of TB disease by high- and intermediate-risk conditions for progression to TB disease among persons born in TB-endemic countries, Kaiser Permanente Northern California, 2004–2022. Abbreviations: TB, tuberculosis; TNFα, tumor necrosis factor alpha.

incidence of TB disease. Adjusted Cox models produced aHRs similar to these incidence rates.

DISCUSSION

This large US-based retrospective cohort study with >4.7 million persons and 35 million PY of follow-up adds to our understanding of the risk of incident TB disease in California in several ways. First, using available data on country of birth and preferred language in the EHR, we have identified populations at high risk (born in a TB-endemic country based on recorded country of birth or preferred language) and low risk (US-born; unknown country of birth) of incident TB disease. Second, we report that risk of TB disease is significantly higher in persons born in TB-endemic countries and among persons with medical conditions associated with progression to TB disease than among persons without those risk factors. Moreover, we report that >79% of all TB cases among persons with high- or intermediate-risk medical conditions for progression to TB disease occur among non-US-born persons at TB risk. Third, we report that risk of TB disease is substantially higher in persons born in Africa as well as East, South, and Southeast Asia.

LTBI screening guidelines recommend LTBI screening of persons who were born in, or are former residents of, countries with high TB disease incidence, but few US-based studies in a general health system have assessed the incidence of TB disease among persons born in TB-endemic countries [4–6]. In this analysis, we demonstrate that persons born in TB-endemic countries based on country of birth or preferred language in the EHR have significantly higher risk of TB disease than US-born persons and might have substantial benefit from screening and treatment for LTBI. As many health systems do not routinely collect data on country of birth, demonstrating that language as a proxy for country of birth is also associated with high risk of progression has practical utility for identifying persons who are at increased risk of progression to TB disease [18]. The absolute risk of TB disease was 13.88 times higher among persons born in TB-endemic countries compared with US-born persons, and this group accounted for 61% of all incident TB disease cases. However, risk of incident TB



	Year 0	Year 5	Year 10	Year 15	Year 18
HIV infection	6820	5213	3559	2153	1140
Solid organ transplantation	13 891	11 832	8710	5320	2665
Hematologic malignancy	73 808	65 869	46 820	28 174	13 360
TNF-alpha inhibitor use	11 977	10 621	8130	5463	3101
High-dose corticosteroid use	143 093	127 626	91 919	56 405	29 217
Other immunosuppressants use	73 498	65 018	48 782	32 506	17 875
Diabetes mellitus	394 148	357 109	280 094	197 520	117 205
End-stage renal disease	47 072	42 600	30 343	17 299	6790
No high- or intermediate-risk condition	1399 882	907 905	571 366	357 300	210 051

Figure 4. Cumulative hazard of TB disease by high- and intermediate-risk conditions for progression to TB disease among US-born persons, Kaiser Permanente Northern California, 2004–2022. Abbreviations: TB, tuberculosis; TNFα, tumor necrosis factor alpha.

disease differed substantially by country as well as region, with persons from Eastern, Southeast, and South Asia and Africa having the highest rates of TB disease, as has been shown in other studies [19]. Our analysis supports current guidelines specifying that persons born in TB-endemic countries are at highest risk of TB disease and should be prioritized for LTBI screening and treatment, but it offers insights into differences among persons born in TB-endemic countries that could be used to prioritize particular subgroups for screening and treatment.

LTBI and disease-specific treatment guidelines recommend LTBI screening and treatment for persons with medical factors associated with progression to TB disease such as a medical condition (eg, HIV infection, solid organ transplantation, hematologic malignancy) or treatment (eg, receipt of TNFα inhibitors, corticosteroids, or other immunosuppressants) [5, 20]. In a stratified analysis, persons born in TB-endemic countries with medical risk factors for TB progression had significantly higher TB incidence than persons born in TB-endemic countries without medical risk factors, and >79% of all TB cases among those with medical risk factors were concentrated among persons born in TB-endemic countries. In addition, we highlight the increased risk of TB disease among persons with diabetes and end-stage renal disease among persons born in TB-endemic countries. Although the number of TB cases among US-born persons was small, US-born persons with high- or intermediate-risk medical conditions associated with progression to TB disease did not have significantly higher risk of TB disease compared with persons without medical risk factors, except among persons with HIV infection and diabetes. These data reinforce that birth in a TB-endemic country is the main risk factor for TB disease and TB disease risk is especially high among persons born in TB-endemic countries with high or intermediate risk of progression to TB disease. Unfortunately, even this very high-risk group is often not screened appropriately for LTBI [11].

Many rigorously conducted epidemiologic studies have suggested that the risk of incident TB disease is greatest in the first 2 years after primary infection and thus time since primary infection is a critical risk factor for incident TB disease [21].

Table 4. Incidence and Risk of Tuberculosis Disease by Country and Region of Birth, Kaiser Permanente Northern California, 2004–2022

	No. of TB Disease Cases	No. of Persons in Denominator	Follow-up Time in Person-Years	TB Disease Incidence Rate (95% CI)	Adjusted Hazard Ratio (95% CI)
Total No. (%)	1463	4 761 427	35 591 565	4.11	N/A
Select TB-endemic countries					
Mexico	49	144 858	1 120 423	4.37 (3.24–5.78)	3.98 (2.91–5.44)
Philippines	409	103 355	1 031 760	39.6 (35.9–43.7)	34.8 (29.4–41.2)
India	96	61 236	436 236	22.0 (17.8–26.9)	20.9 (16.3–26.7)
China	130	99 438	824 045	15.8 (13.2–18.7)	12.7 (10.1–15.8)
Vietnam	110	41 704	333 173	33.0 (27.1–39.8)	31.2 (24.7–39.4)
El Salvador	2	20 398	170 903	1.17 (0.142–4.23)	1.06 (0.264–4.27)
South Korea	18	14 472	117 865	15.3 (9.05–24.1)	13.2 (8.17–21.5)
Iran	2	10 180	85 866	2.33 (0.282–8.41)	1.79 (0.445–7.22)
Russia	3	9456	65 891	4.55 (0.939–13.3)	4.15 (1.33–13.0)
Nicaragua	5	7767	73 693	6.78 (2.20–15.83)	5.85 (2.41–14.2)
Guatemala	3	7029	51 753	5.80 (1.20–16.9)	5.25 (1.68–16.4)
Peru	7	6237	54 175	12.9 (5.20–26.6)	11.1 (5.23–23.6)
Laos	6	5873	50 722	11.8 (4.34–25.7)	12.0 (5.32–27.1)
Thailand	9	5618	42 819	21.0 (9.61–39.9)	22.7 (11.6–45.0)
Pakistan	5	4985	36 257	13.8 (4.48–32.2)	12.6 (5.19–30.1)
Afghanistan	4	4234	27 215	14.7 (4.01–37.6)	14.1 (5.24–38.0)
Cambodia	9	3428	28 915	31.1 (14.2–59.1)	31.9 (16.3–62.2)
Myanmar (Burma)	14	3162	29 074	48.2 (26.3–80.8)	41.3 (24.0–71.1)
Brazil	1	2874	20 056	4.99 (0.126–27.8)	5.19 (0.727–37.0)
Ethiopia	13	2761	20 333	63.9 (34.0–109)	66.0 (37.6–116)
United States	203	1 597 656	15 992 024	1.27 (1.01–1.46)	Ref
Select TB-endemic regions					
Caribbean	1	6326	61 931	1.61 (0.041–9.00)	1.21 (0.169–8.62)
Central America	60	183 954	1 450 084	4.14 (3.16–5.33)	3.75 (2.81–5.00)
South America	13	18 057	154 716	8.40 (4.47–14.4)	7.14 (4.07–12.5)
Africa	21	15 109	120 345	17.5 (10.8–26.7)	16.2 (10.3–25.3)
Eastern Europe	11	27 082	222 616	4.94 (2.47–8.84)	4.06 (2.21–7.45)
Asia					
Eastern Asia	159	130 754	1 113 763	14.3 (12.1–16.7)	11.7 (9.49–14.4)
South Asia	104	69 415	491 151	21.2 (17.3–25.7)	20.0 (15.8–25.5)
Southeast Asia	565	168 268	1 564 149	36.1 (33.2–39.2)	32.5 (27.7–38.2)
Central and Western Asia	9	30 343	238 030	3.78 (1.73–7.18)	3.13 (1.60–6.10)
Oceania	11	15 690	140 490	7.83 (3.91–14.0)	7.06 (3.85–13.0)
United States	203	1 597 656	15 992 024	1.27 (1.10–1.46)	Ref

Race and ethnicity were mutually exclusive, and all race categories were defined as non-Hispanic. TB disease incidence rate is per 100 000 person-years. Adjusted hazard ratio was based on Cox proportional hazards model estimating risk of TB disease by nativity categories as baseline variables and high- and intermediate-risk medical conditions as time-dependent variables adjusted for age group and sex.

Abbreviations: aHR, adjusted hazard ratio; TB, tuberculosis; TNFα, tumor necrosis factor alpha.

Thus, proxies for time since primary infection such as time since initial TB exposure (eg, close contact with a TB case), immigration to the United States, or most recent travel to a TB-endemic country might be useful in defining overall TB risk [22]. However, these data are often not collected routinely within health systems in the United States and are often hard to ascertain in routine clinical practice. Our analysis suggests that for persons residing in a low-incidence setting such as California, the risk of TB disease appears to remain stable over an 18-year observation period and suggests that reactivation TB from remote infection is the primary driver of incident TB in California.

Our study has several limitations. We only included persons with TB disease who were diagnosed within our health system and thus might have missed some persons with incident TB disease. We did not assess all possible previously reported risk factors for TB disease, including travel to a TB-endemic country, close contact with a known TB case, homelessness, injection drug use, and incarceration. Data on these risk factors were not available in our EHR and thus could not be included in this analysis. In addition, we did not explore other possible risk factors for TB disease, and thus some residual confounding might remain. Lastly, we only assessed risk in persons who have not been previously treated for LTBI as treatment reduces the

risk of progression to TB disease, and we did not explore differential access to treatment among the different risk groups.

In summary, this study provides a detailed report of risk of TB disease in a general health system and highlights the need to focus our prevention efforts on patients at highest risk of developing TB disease, persons born in TB-endemic countries, and especially those with medical factors associated with progression to TB disease.

Supplementary Data

Supplementary materials are available at *Open Forum Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

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Author contributions. All contributed to conceptual ideas. All contributed to methodology. J.S. and Y.N. contributed to formal analysis. J.S. and Y.N. contributed to writing and original draft preparation. All authors contributed to writing, reviewing, and editing the manuscript. J.S. supervised the work.

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Data sharing. Anonymized data that support the findings of this study may be made available from the investigative team in the following conditions: (1) agreement to collaborate with the study team on all publications, (2) provision of external funding for administrative and investigator time necessary for this collaboration, (3) demonstration that the external investigative team is qualified and has documented evidence of training for human subjects protections, and (4) agreement to abide by the terms outlined in data use agreements between institutions.

Patient consent. The study was approved by the Kaiser Permanente Southern California and the KPNC Institutional Review Boards with waivers of the requirement for informed consent.

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Potential conflicts of interest. All authors: no conflicts of interest.

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