

Identification of a Latitude Gradient in the Prevalence of Primary Biliary Cholangitis

Janine French, MBBS¹, Steve Simpson-Yap, BA, MPH, PhD^{2,3}, Ingrid van der Mei, BSc, MSc, PhD³, Justin Ng, MBBS¹, Peter Angus, MBBS, MD¹ and Paul J. Gow, MBBS, MD¹

INTRODUCTION: The prevalence of primary biliary cholangitis (PBC) reported in different countries varies significantly and seems to have a latitudinal gradient with the highest prevalence reported in higher latitudes, as has been observed with other autoimmune diseases. This study aimed to determine whether there is a latitudinal gradient of PBC prevalence in Australia using 2 methods of case ascertainment.

METHODS: We investigated the latitudinal variation of PBC prevalence across the states and territories of Australia (latitudinal range 18.0°–42.7°S) using pathology-based (private pathology antimitochondrial antibody results and PBC-specific prescription databases (prescriptions for ursodeoxycholic acid, the only publicly subsidized treatment for this disease).

RESULTS: PBC prevalence was significantly positively associated with latitude, and the postcodes in the highest quintile of latitude (encompassing the south coastal areas of the Australian mainland and Tasmania; latitude range –37.75° to –42.72°) had a prevalence estimate that was 1.78 times higher using the pathology-based prevalence estimation than those in the lowest quintile (encompassing tropical and southern Queensland; latitude range –18.02° to –27.59°). Comparing prevalence estimates between states/territories, the result was 2.53 and 2.21 times higher in Tasmania compared with Queensland when using the pathology-based and prescription-based methods, respectively.

DISCUSSION: Using 2 different case-ascertainment methods, we have demonstrated that prevalence estimates of PBC vary significantly with latitude in Australia. Further studies are needed to determine whether factors such as variations in ultraviolet radiation exposure and/or vitamin D levels are responsible for this observation and to investigate the latitudinal prevalence of PBC in other populations.

SUPPLEMENTARY MATERIAL accompanies this paper at <http://links.lww.com/CTG/A610>

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INTRODUCTION

Primary biliary cholangitis (PBC) is a chronic cholestatic liver disease of unknown etiology that causes immune-mediated bile duct destruction, a process that has the potential to progress to cirrhosis and liver failure. The disease is characterized by a female predominance, autoantibodies to mitochondrial antigens (AMA), and the distinctive histological finding of granulomatous portal tract inflammation with destruction of small bile ducts.

The etiology of this disease remains largely unknown; at present, it is believed to be a complex interplay between genetic susceptibility and environmental factors such as infection (1,2), xenobiotics (3,4), and tobacco smoking (2,5–7). Previous epidemiological studies in the north east of England have found clustering of disease, which is highly suggestive of an environmental

factor being linked to disease pathogenesis (8,9). Potential environmental factors linked to disease clustering have included toxic waste sites in New York City (10) and coal mines in Northeast England (11); however, these associations have not yet been replicated in other PBC populations.

The reported geographical prevalence of PBC varies markedly. A meta-analysis of 47 population-based studies has identified the prevalence in North America to be 218 per million and Europe to be 146 per million, both much higher than in the Asia-Pacific region with a prevalence of 98 per million (12). We have recently found the prevalence of PBC to be 81 per million in Victoria, Australia (13). This contrasts with Newcastle in the north of England where prevalence has been reported to be 335 per million (14) and the Calgary health region of Canada where the prevalence is reported to be 227

¹Department of Gastroenterology, Austin Hospital, Heidelberg, Australia; ²Department of Biostatistics and Epidemiology, Melbourne School of Population and Global Health, University of Melbourne, Carlton, Australia; ³Menzies Institute for Medical Research, University of Tasmania, Hobart, Tasmania, Australia.

Correspondence: Janine French, MBBS. E-mail: janine.french@austin.org.au.

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Table 1. Geographical variation in total PBC pathology-based prevalence

	Data points, n (%) ^a	Case number, n (%)	Population, n (%)	Prevalence/ million persons	IRR (95% CI)	aIRR (95% CI)
State						
QLD	9 (21.4%)	258 (15.9%)	4,297,330 (22.8%)	60.04	1.00 [reference]	1.00 [reference]
NSW/ACT	10 (23.8%)	474 (29.2%)	7,179,925 (38.0%)	66.02	1.10 (0.95, 1.28)	1.09 (0.94, 1.27)
VIC	10 (23.8%)	583 (35.9%)	5,328,052 (28.2%)	109.42	1.82 (1.57, 2.11)	1.78 (1.54, 2.07)
SA	8 (19.1%)	232 (14.3%)	1,591,722 (8.4%)	145.75	2.43 (2.03, 2.90)	2.39 (1.99, 2.87)
TAS	5 (11.9%)	75 (4.6%)	494,154 (2.6%)	151.77	2.53 (1.96, 3.27)	2.61 (2.01, 3.38)
					<i>P</i> < 0.001	
Region type						
Regional	32 (76.2%)	765 (47.2%)	4,375,269 (23.2%)	174.85	1.00 [reference]	
Metro	4 (9.5%)	446 (27.5%)	4,489,204 (23.8%)	99.35	1.30 (1.16, 1.46)	
Capital	6 (14.3%)	411 (25.3%)	10,031,219 (53.1%)	40.97	1.23 (1.09, 1.39)	
Trend:					<i>P</i> < 0.001	
Latitude (continuous)					1.05 (1.04, 1.06)	1.05 (1.03, 1.06)
					<i>P</i> < 0.001	<i>P</i> < 0.001
Latitude (quintiles)						
−18.02, −27.59	9 (21.4%)	272 (16.8%)	4,083,429 (21.6%)	66.61	1.00 [reference]	1.00 [reference]
<−27.59, −33.85	8 (19.1%)	272 (16.8%)	3,894,929 (20.6%)	69.83	1.05 (0.89, 1.24)	1.06 (0.90, 1.26)
<−33.85, −35.33	8 (19.1%)	364 (22.4%)	4,162,546 (22.0%)	87.45	1.31 (1.12, 1.54)	1.27 (1.08, 1.49)
<−35.33, −37.75	8 (19.1%)	190 (11.7%)	2,324,882 (12.3%)	81.72	1.23 (1.02, 1.48)	1.27 (1.05, 1.54)
<−37.75, −42.72	9 (21.4%)	524 (32.3%)	4,425,397 (23.4%)	118.41	1.78 (1.54, 2.06)	1.71 (1.47, 1.99)
Trend:					<i>P</i> < 0.001	<i>P</i> < 0.001
Sex						
Male		179 (11.0%)	9,697,783 (49.4%)	18.46	1.00 [reference]	1.00 [reference]
Female		1,443 (89.0%)	9,947,776 (50.6%)	145.06	7.86 (6.73, 9.18)	7.86 (6.73, 9.18)
					<i>P</i> < 0.001	<i>P</i> < 0.001
Age						
0–39		79 (4.9%)	10,044,474 (53.2%)	7.87	0.11 (0.09, 0.15)	0.11 (0.09, 0.15)
40–49		186 (11.5%)	2,666,185 (14.1%)	69.76	1.00 [reference]	1.00 [reference]
50–59		378 (23.3%)	2,412,864 (12.8%)	156.66	2.25 (1.88, 2.68)	2.27 (1.90, 2.70)
60–69		434 (26.8%)	1,885,486 (10.0%)	230.18	3.30 (2.78, 3.92)	3.36 (2.83, 3.99)
70–79		335 (20.7%)	1,122,231 (5.9%)	298.51	4.28 (3.58, 5.12)	4.36 (3.64, 5.21)
80–109		210 (13.0%)	758,655 (4.0%)	276.81	3.97 (3.26, 4.83)	3.99 (3.28, 4.87)
Trend:					<i>P</i> < 0.001	<i>P</i> < 0.001

Bold indicates statistical significance.

Analyses by Poisson regression, estimating an IRR (95% CI). Adjusted models adjusted for region type.

^aTwo-digit postcode regions within each state.

per million (15). This marked variation in disease prevalence is noteworthy, given the similarity in ethnicity between the Australian, UK, and Canadian populations, and raises the possibility that local environmental factors play a role in PBC pathogenesis. One of the obvious differences between the Australian, UK, and Canadian populations is the latitude at which they live and, therefore, levels of ambient ultraviolet radiation (UVR) exposure. There have been well-established precedents for increasing disease prevalence at higher latitudes in other immune mediated diseases, most notably multiple sclerosis (16,17). Latitudinal gradients of disease prevalence

have also been described with rheumatoid arthritis and celiac disease (18–22). A recent retrospective cohort study in the United Kingdom has demonstrated a strong association with PBC and latitude, with more than double the incidence over a 7° variation of latitude (23). Epidemiological studies in Australia have the added advantage of examining a huge variation in latitude, and therefore, it is an ideal geographic location to evaluate the relationship between latitude and PBC prevalence.

In this study, we explored whether the prevalence of PBC in Australia differed by latitude by examining the variation in PBC

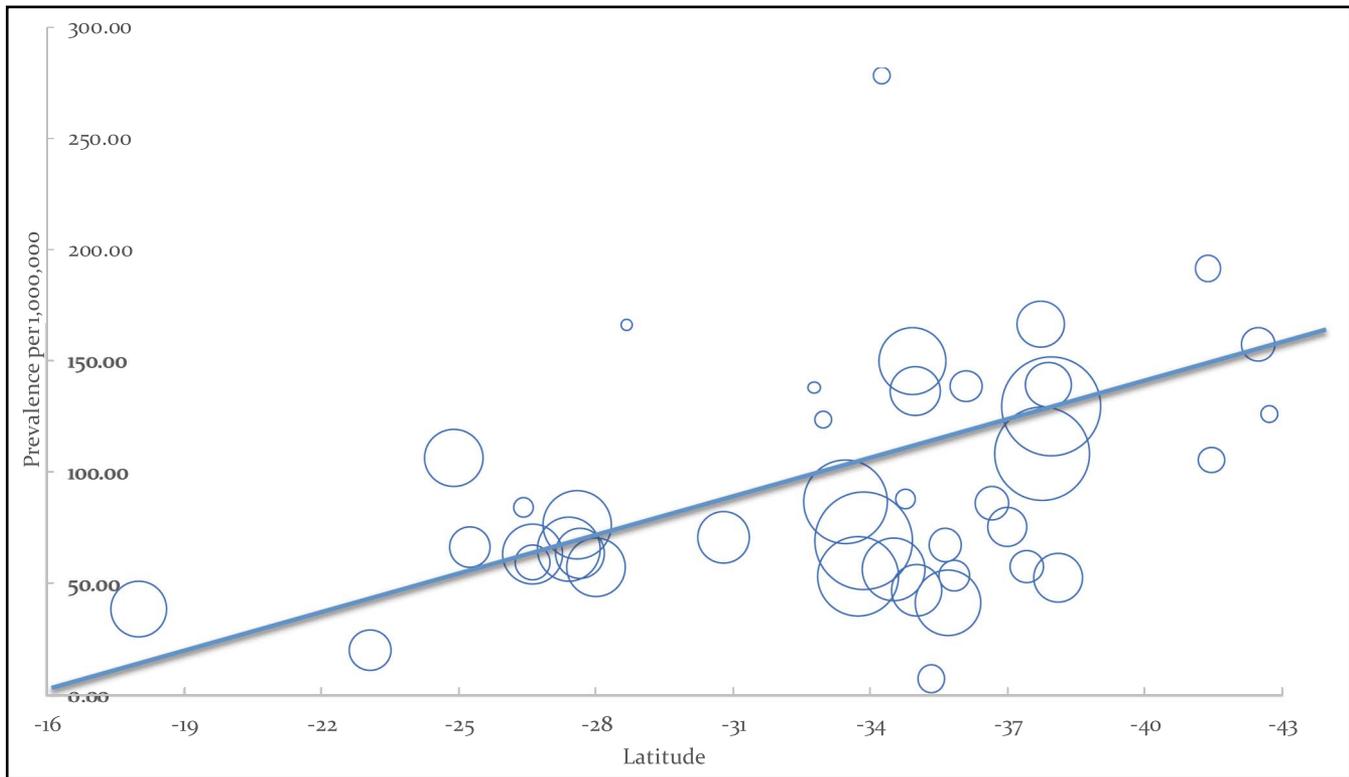


Figure 1. Latitudinal variation in PBC pathology-based prevalence by 2-digit postcode regions. Note: an outlier -74 postcode in western Tasmania has been excluded (see Supplementary Figure 2, Supplementary Digital Content 1, <http://links.lww.com/CTG/A610>). There was a linear relationship between PBC prevalence and latitude. The circle size in this bubble plot is proportional to the number of PBC cases at each 2-digit postcode region. PBC, primary biliary cholangitis.

prevalence estimates across the states and territories of Australia using pathology and PBC-specific prescription databases.

METHODS

Pathology-based PBC prevalence estimation by 2-digit postcode regions

All positive AMA results (titer > 1:40) and corresponding liver function tests were provided from the 3 major pathology companies in Australia for the states/territories of Queensland, New South Wales, the Australian Capital Territory, South Australia, Victoria, and Tasmania for a 3-year period (2010–2013). Patients fulfilling the diagnosis of probable PBC (defined as cholestatic liver function tests [elevation of serum alkaline phosphatase] and an AMA titer of at least 1:40) were included in this study. Latitude was geocoded based on patients' postcode at the time of their pathology results. Duplicates were excluded based on patient initials, postcode, and date of birth. Date of birth was used as a surrogate marker for age at diagnosis because the majority of AMA testing is performed during the diagnostic workup for PBC.

Services provided through the private sector represent approximately 60% of all pathology in Australia. Private pathology services are dominated by 3 large corporate providers (Sonic Healthcare, Primary Health Care, and Healthscope) which cover 77% of private pathology in Australia (24). The 3 major pathology companies provided a database of all positive AMA results from January 2010 to January 2013. For each positive AMA result, they also provided liver function tests for a period of 6 months, patient date of birth, sex, and postcode.

All Australian population data and population proportions of ancestry were sourced from the 2011 Australian census (25).

Two-digit postcode zones were used to divide Australia into geographical zones (see Supplemental Figure 1, Supplementary Digital File, <http://links.lww.com/CTG/A610>). Self-reported identification as Australian, English, Scottish, Welsh, and Irish ancestry was extracted for each 4-digit postcode in the states and territories in the study, and these then averaged for each of the 2-digit postcodes. This was performed, so that variation in ancestry could be evaluated in a multivariate analysis and to see whether variation in ancestry explained the difference in prevalence at decreasing latitudes.

PBC prevalence estimation was evaluated by state and also by quintiles of latitude. Each quintile of latitude represented 20% of the latitude range for the 2-digit postcode groups.

Ursodeoxycholic acid prescription-based prevalence estimation by state

The second method of PBC case identification used the ursodeoxycholic acid (UDCA) prescription data sourced from Medicare Australia by state from January 2010 to December 2013 (26). The Pharmaceutical Benefits Scheme (PBS) is part of the Australian universal health care system that provides subsidized medications to all Australians. A parallel system exists for Australian veterans: the Repatriation Pharmaceutical Benefits Scheme. PBC is the only condition for which UDCA is publicly subsidized in Australia. Although UDCA can be prescribed for several other rare liver conditions, government health care-reimbursed prescriptions are likely to be an accurate marker of PBC prevalence.

Medicare Australia provided the number of PBS and Repatriation Pharmaceutical Benefits Scheme prescriptions of UDCA prescribed in the 3-year period in each state and territory of

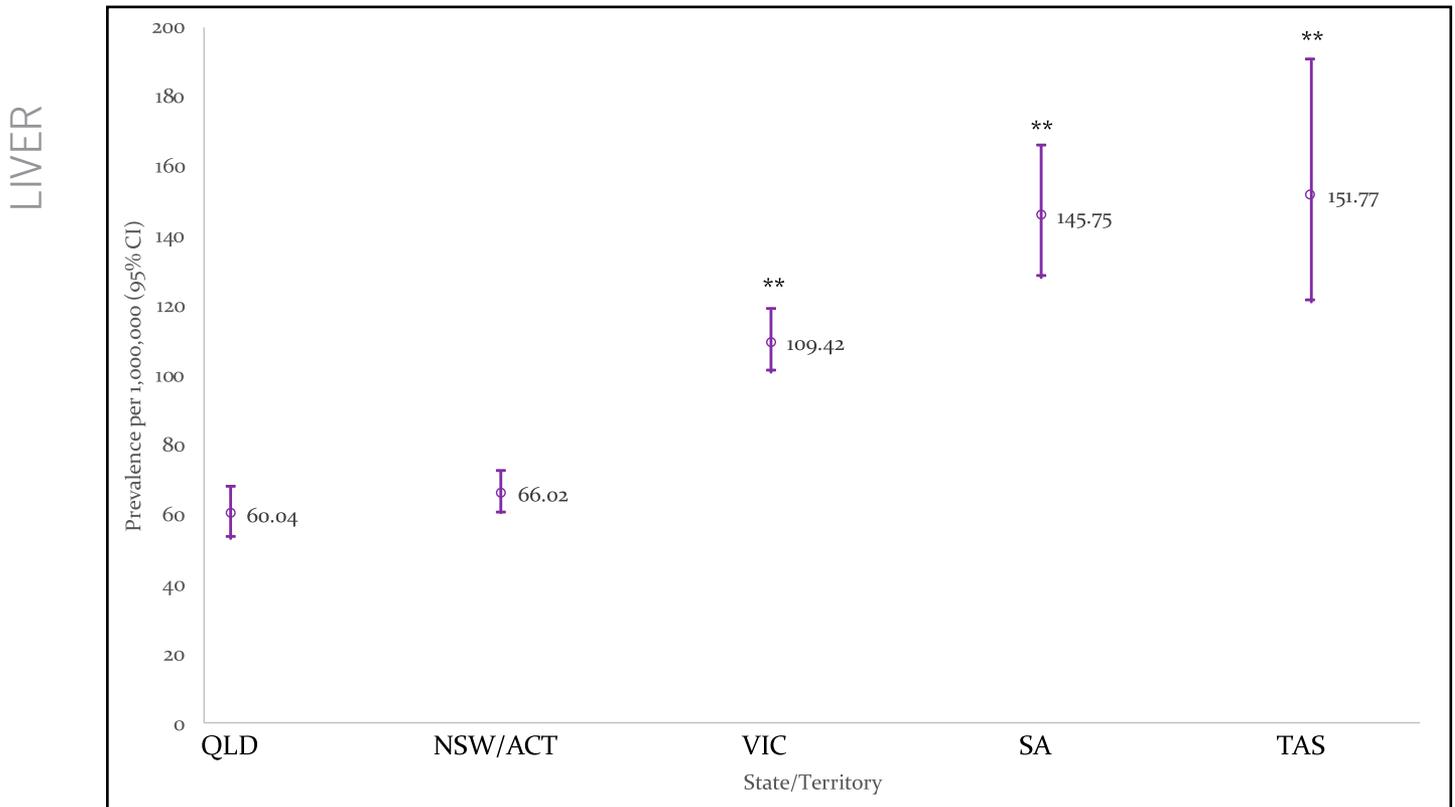


Figure 2. Pathology-based primary biliary cholangitis prevalence estimates showing a significant difference between VIC, SA, and TAS relative to Queensland. *P* values are tests for difference relative to QLD. * denotes significance $P < 0.05$, and ** denotes significance $P < 0.001$.

Australia from January 2010 to January 2013 inclusive. Repeat prescriptions of UDCA are issued every 50 days (based on an average dose of 500 mg bd). Cohort studies have indicated that 90% of PBC patients are on UDCA (27). Medicare was not able to provide age and sex of those who had received prescriptions for UDCA.

To estimate the total number of cases with PBC, the number of prescriptions dispensed over the 3-year period was divided by 7.31 (calculated by the number of days in the year divided by the days each individual script lasted, as all repeat prescriptions are for 50 days [365.25/50]) and then again by 3 (the number of years of the study period.) This was then divided by population and then the resultant prevalence multiplied by 0.9, assuming 90% of PBC cases were taking UDCA (Supplemental Table 4, <http://links.lww.com/CTG/A610>). Population denominators for each state were sourced from the 2011 Australian census, as was the state-based ancestry data.

The pathology-based UDCA prevalence estimates and rates of UDCA prescriptions were evaluated based on ancestry data from the 2011 census and mutually adjusted with the mean latitude of each state where the prescriptions were dispensed (Supplemental Table 5, <http://links.lww.com/CTG/A610>).

Statistical methods

Predictors of prevalence were evaluated by Poisson regression, estimating a prevalence ratio (PR). Tests for differences in association by sex and age were assessed by multiplicative interaction, the significance of the product term between the primary predictor and the terms for sex or age denoting the significance of the

difference between groups. All statistical analyses were undertaken in STATA/SE 15.0 (StataCorp, College Park, TX).

This study was approved by the Austin Health Human Research and Ethics Committee.

RESULTS

Pathology-based PBC prevalence estimates by state and latitude

There were 1,622 PBC cases identified using the private pathology company data, amounting to a prevalence of 85.9 per 1,000,000 (Table 1). In keeping with known disease characteristics, the majority of cases were female, comprising 88.9% of cases. The postcodes with the largest numbers of cases were the 30 and 31 postcode zones, encompassing the Melbourne metropolitan area, although the highest prevalence estimates were in the 74 postcode—encompassing western Tasmania—and the 55 postcode zone, which encompasses the north of Adelaide and the Yorke Peninsula across the St Vincent Gulf (see Supplementary Table 1, <http://links.lww.com/CTG/A610>). Figure 1 shows the latitudinal variation in PBC pathology-based prevalence estimates by 2-digit postcode regions, with an almost linear relationship between PBC prevalence and latitude ($\beta = 1.05$ [95% CI: 1.03–1.06], $P < 0.001$).

Evaluating pathology-based PBC prevalence estimates by state/territory (Table 1), compared with the QLD region (40–49 postcode zones), the prevalence of PBC was significantly higher in Victoria, South Australia, and Tasmania. The prevalence of PBC showed a significant positive latitudinal gradient ($p_{\text{trend}} < 0.001$), with the postcodes in Tasmania having a prevalence that was 2.53 times higher than those in Queensland (Figure 2). When the prevalence estimates were evaluated by quintiles, there was also a positive latitudinal

Table 2. Geographical variation in PBC pathology-based prevalence, by sex

	IRR (95% CI)		Test for difference
	Males	Females	
State			
QLD	1.00 [reference]	1.00 [reference]	
NSW/ACT	0.91 (0.59, 1.42)	1.11 (0.95, 1.31)	<i>P</i> = 0.44
SA	1.26 (0.81, 1.96)	1.87 (1.60, 2.19)	<i>P</i> = 0.16
VIC	1.65 (0.99, 2.76)	1.76 (1.44, 2.15)	<i>P</i> = 0.68
TAS	1.91 (0.84, 4.34)	2.79 (2.12, 3.66)	<i>P</i> = 0.45
Trend:	<i>P</i> = 0.010	<i>P</i> < 0.001	<i>P</i> = 0.82
Region type			
Regional	1.00 [reference]	1.00 [reference]	
Metro	1.48 (1.03, 2.13)	1.28 (1.13, 1.45)	<i>P</i> = 0.45
Capital	1.48 (1.04, 2.09)	1.01 (0.89, 1.14)	<i>P</i> = 0.043
Trend:	<i>P</i> = 0.019	<i>P</i> = 0.44	<i>P</i> = 0.054
Latitude (continuous)	1.01 (0.98, 1.05) <i>P</i> = 0.46	1.05 (1.04, 1.06) <i>P</i> < 0.001	<i>P</i> = 0.13
Latitude (quintiles)			
−18.02, −27.59	1.00 [reference]	1.00 [reference]	
<−27.59, −33.85	0.68 (0.40, 1.14)	1.15 (0.96, 1.37)	<i>P</i> = 0.070
<−33.85, −35.33	1.00 (0.64, 1.55)	1.09 (0.92, 1.31)	<i>P</i> = 0.93
<−35.33, −37.75	1.01 (0.57, 1.79)	1.29 (1.06, 1.58)	<i>P</i> = 0.22
<−37.75, −42.72	0.99 (0.63, 1.55)	1.86 (1.58, 2.19)	<i>P</i> = 0.031
Trend:	<i>P</i> = 0.64	<i>P</i> < 0.001	<i>P</i> = 0.057

Analyses by Poisson regression, estimating an IRR (95% CI). All models except region type adjusted for region type. Bold indicates statistical significance.

gradient with the postcodes in the highest quintile of latitude (encompassing the south coastal areas of the Australian mainland and insular Tasmania; latitude range −37.75 to −42.72°S) having a prevalence estimate that was 1.78 times higher than the lowest quintile of latitude (encompassing tropical and southern Queensland; latitude range −18.02 to −27.59°S) (Table 1). When we adjusted for population aggregation in metropolitan/capital city regions in a multivariate analysis, these associations persisted (Table 1).

Evaluating associations by sex (Table 2), it was evident that the regional variation in PBC prevalence was solely present in females, with males showing no material latitudinal variation. In relation to age at time of pathology testing (and thus likely age at diagnosis), the positive latitudinal gradient was present in all age groups from 40 years and above, both by state and by increments of latitude (Table 3).

PBC prevalence varied by ancestry of English, Irish, Scottish, Welsh, and Australian descent using ancestry data from the 2011 Australian Census (Supplemental table 5, <http://links.lww.com/CTG/A610>). However, using either the state/territory-based proportions of ancestry (Supplemental Table 2, <http://links.lww.com/CTG/A610>) or by 2-digit postcode (Supplemental Table 3, <http://links.lww.com/CTG/A610>), the latitudinal association was found to be independent of ancestry.

UDCA prescription prevalence estimation by location and latitude

The pharmaceutical benefit prescription data demonstrated that there was a statistically significant linear gradient with UDCA

prescriptions, with the prevalence estimation of PBC highest in Tasmania, followed by Victoria and NSW, and lowest in Queensland and the Northern Territory (Figure 3; Supplemental Table 4, <http://links.lww.com/CTG/A610>) The frequency of UDCA prescriptions was 2.21 times higher in the state with the highest median latitude, Tasmania (42.0°S), compared with Queensland (median latitude 22.5°S) and 4.17 times higher compared with the Northern Territory (mean latitude 19.5°S).

As with PBC prevalence by pathology, prevalence by UDCA prescription varied by ancestry of English, Irish, Scottish, Welsh, and Australian descent. We examined whether ancestry explained part of the association with latitude. We adjusted for ancestry and showed that latitude retained its independent association with PBC prevalence (Supplemental Table 5, <http://links.lww.com/CTG/A610>). The prescription-based prevalence estimation was not able to be evaluated by sex or age group because these parameters were not provided by Medicare Australia.

DISCUSSION

This study has demonstrated for the first time that the prevalence of PBC varies significantly with latitude in Australia. This finding was demonstrated using 2 separate methods, pathology (AMA-positive and cholestatic liver function tests) and prescription-based case identification for the PBC-specific medication UDCA with both methods demonstrating a strong association with increasing latitude and increasing prevalence of PBC. Postcodes at higher latitudes had significantly greater prevalence estimations

Table 3. Geographic variation in pathology-based PBC prevalence, by age group

	40–49 yo	50–59 yo	60–69 yo	70–79 yo	80–109 yo	Test for difference
State						
QLD	1.00 [reference]					
NSW/ACT	1.18 (0.75, 1.86)	1.25 (0.91, 1.72)	0.84 (0.63, 1.11)	1.43 (1.00, 2.04)	0.49 (0.32, 0.76)	P = 0.046
VIC	1.77 (1.13, 2.78)	2.12 (1.55, 2.90)	1.47 (1.12, 1.92)	2.04 (1.42, 2.92)	1.18 (0.80, 1.75)	<i>P = 0.19</i>
SA	2.92 (1.72, 4.95)	1.97 (1.31, 2.96)	1.60 (1.14, 2.26)	2.28 (1.48, 3.53)	1.91 (1.22, 2.99)	<i>P = 0.60</i>
TAS	3.16 (1.48, 6.72)	2.20 (1.26, 3.85)	1.51 (0.89, 2.55)	3.29 (1.90, 5.70)	2.03 (1.06, 3.90)	<i>P = 0.89</i>
Trend:	P < 0.001	<i>P = 0.84</i>				
Region type						
Regional	1.00 [reference]					
Metro	1.54 (1.11, 2.15)	1.15 (0.90, 1.48)	1.54 (1.23, 1.93)	1.55 (1.20, 1.99)	1.41 (1.01, 1.97)	<i>P = 0.55</i>
Capital	1.08 (0.74, 1.57)	1.29 (1.01, 1.64)	1.58 (1.26, 1.99)	1.39 (1.06, 1.81)	1.71 (1.25, 2.35)	<i>P = 0.090</i>
Trend:	<i>P = 0.37</i>	P = 0.040	P < 0.001	P = 0.004	P = 0.001	<i>P = 0.10</i>
Latitude (continuous)	1.06 (1.02, 1.09)	1.06 (1.03, 1.08)	1.04 (1.02, 1.07)	1.06 (1.04, 1.09)	1.04 (1.01, 1.08)	<i>P = 0.83</i>
	P = 0.002	P < 0.001	P < 0.001	P < 0.001	P = 0.019	
Latitude (quintiles)						
–18.02, –27.59	1.00 [reference]					
<–27.59, –33.85	1.11 (0.65, 1.90)	1.21 (0.84, 1.75)	1.25 (0.89, 1.75)	1.28 (0.85, 1.94)	0.62 (0.36, 1.07)	<i>P = 0.29</i>
<–33.85, –35.33	1.61 (0.98, 2.64)	1.28 (0.88, 1.85)	1.00 (0.70, 1.42)	1.58 (1.05, 2.37)	1.09 (0.67, 1.79)	<i>P = 0.65</i>
<–35.33, –37.75	1.11 (0.60, 2.07)	1.54 (1.03, 2.28)	1.36 (0.93, 2.00)	1.37 (0.86, 2.19)	0.83 (0.45, 1.54)	<i>P = 0.31</i>
<–37.75, –42.72	1.85 (1.15, 2.99)	2.08 (1.48, 2.92)	1.72 (1.26, 2.35)	1.95 (1.33, 2.86)	1.55 (0.98, 2.43)	<i>P = 0.64</i>
Trend:	P = 0.019	P < 0.001	P < 0.001	P = 0.001	P = 0.015	<i>P = 0.90</i>
Analyses by Poisson regression, estimating an IRR (95% CI). All models except region type adjusted for region type. Bold indicates statistical significance.						

of PBC compared with lower latitude postcodes. Using the pathology-based ascertainment, the prevalence estimates were 2.53 times higher in Tasmania compared with Queensland and 2.21 times higher using the prescription-based case identification.

Our findings are in keeping with a recently published study identifying a significant association with PBC incidence and distance from the equator in the United Kingdom (23) with an odds ratio that increased from 2.16 (95% CI 1.79–2.60) to 4.86 (95% CI 3.93–6.00) over 7° of latitude. There are also recent data to suggest that there may be an association with latitude and PBC symptomatology in a study examining the differences between reported symptoms in British, Italian, Spanish, and Japanese cohorts of PBC patients adding further weight to the role of latitude in etiopathogenesis (28).

The latitudinal gradient was found for each age group, but interestingly, it was only present for females and did not seem to exist for males. It is possible that this is due to the small sample size with only 179 male cases identified, compared with 1,443 female cases and thus could represent a type II error. We could not confirm this using the prescription-based case-ascertainment method because we did not have these data by age or sex.

There is also a well-established association between latitude and prevalence of multiple other immunologically based diseases including multiple sclerosis (MS) (17), rheumatoid arthritis, type I diabetes mellitus, inflammatory bowel disease, myasthenia gravis, and celiac disease (18–22). In multiple sclerosis, a latitude gradient has been recognized for more than 40 years. This

gradient was initially believed to be explained by geographically varying rates of viral infection that then went on to cause disease. More recently, it has been demonstrated that the gradient in disease prevalence in MS seems to be explained by differences in UV exposure, which then potentially leads on to long-term immunological effects. There have also been recent studies indicating that latitude may be associated with age of onset in both multiple sclerosis and rheumatoid arthritis (29–31).

As has been demonstrated with MS, it is possible that the explanation for the observed latitude gradient of PBC in Australia may be due to an effect of UVR or vitamin D₃, produced under the influence of UVR, exerting a protective effect against the disease (32,33). The potential protective association of UVR in MS (34) is believed to be due to an immunomodulatory effect of activated vitamin D (35). Vitamin D-independent UV modulation of the immune system has also been reported (36), suggesting there may be multiple mechanisms by which ambient UV could impact on immune function and thus potentially PBC risk. We have also previously found, in a prevalence study of PBC in Victoria, Australia, an average annual increase of 7.7 per million per year from 1991 to 2013 (95% CI: 5.74–8.12). This increased prevalence may be related to Australians decreasing their sun exposure and vitamin D levels due to effective SunSmart campaigns (37).

We examined whether differences in ancestry could explain the association of PBC prevalence with latitude and found that latitude remained independently associated with prevalence. The self-reported ancestry, as reported by the 2011 census, has

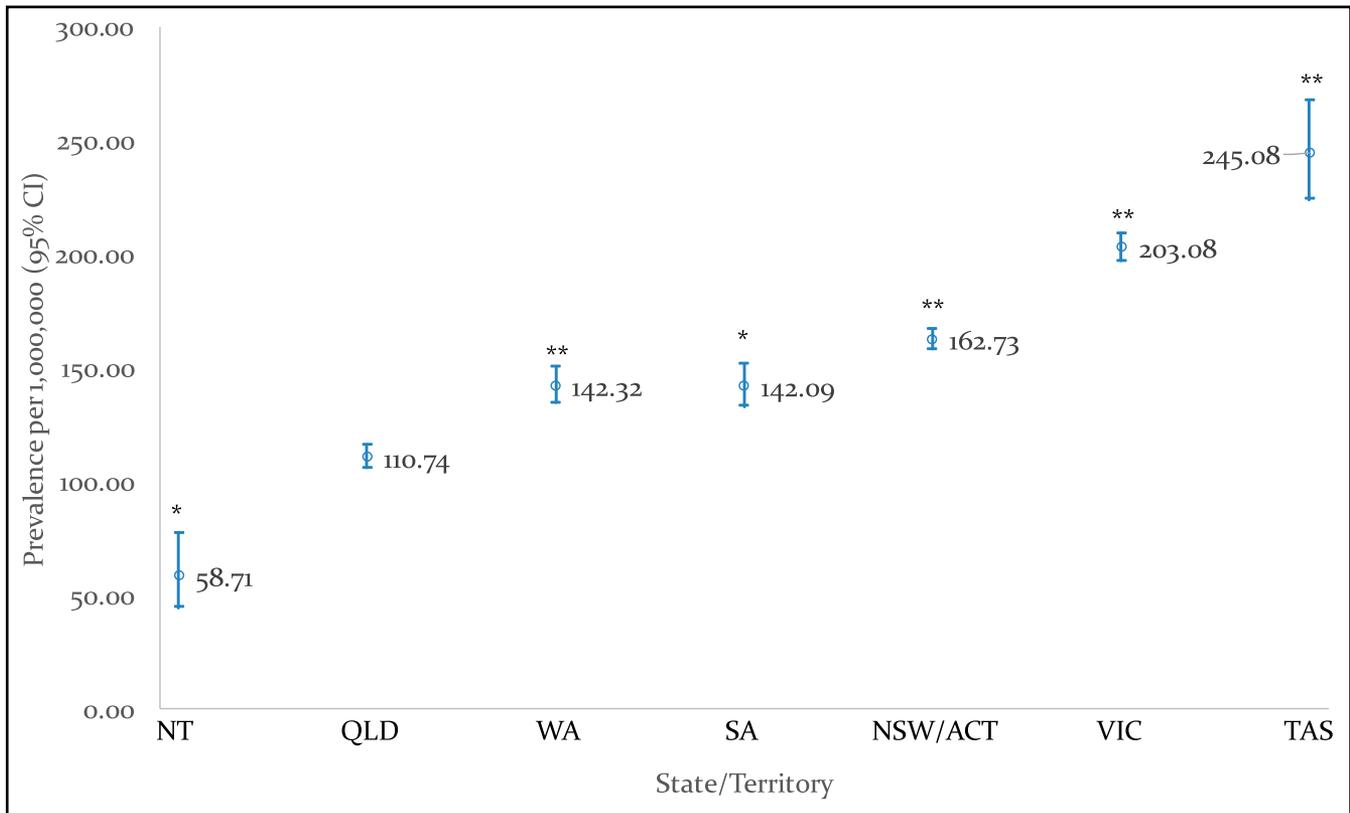


Figure 3. Prescription-based primary biliary cholangitis prevalence estimates by state showing a significant difference between WA, SA, NSW/ACT, VIC, and TAS relative to NT. *P* values are tests for difference relative to NT. * Denotes significance $P < 0.05$, and ** denotes significance $P < 0.001$.

considerable variation from state to state, and this could have been an explanation for the latitude gradient for PBC prevalence, i.e., populations from 1 particular ethnic group settling in particular regions of Australia. However, when the multivariate analysis was adjusted for ancestry, latitude was still associated with PBC prevalence.

One of the other possible explanations for the latitudinal gradient could be population aggregation in metropolitan/capital city regions; however, when we adjusted for population aggregation in a multivariate analysis, these associations persisted. It is also important to acknowledge that other environmental factors besides UVR such as toxic waste exposure, found to be associated with PBC is an American study (23) or coal mines, associated with clustering of disease in a population study in North East England (11), could be contributing to the association. These are avenues to be explored for future research.

A strength of our study is that Australia has a large latitudinal range while having a uniform health care system. Another strength is that this study used prevalence estimates from both positive AMA testing (pathology-based prevalence estimation) and UDCA prescriptions (prescription-based prevalence estimation). There are however a number of potential flaws in our data set. AMA-negative PBC (which comprise approximately 5% of PBC cases) will have not been captured in the pathology-based estimates. UDCA is also prescribed for a small percentage of patients who do not have PBC, and thus, these cases may have been included in the prevalence estimates. Patients who are not on UDCA would also not have been included in these estimates. In addition, our prevalence estimates generated from UDCA

dispensing data assume that patients refill their script once the current amount of medication is used. It is likely that some degree of poor compliance may compromise these estimates. We also acknowledge that the pathology-based estimates may vary from state to state as the 3 major private pathology providers did not necessarily have the same distribution in each state/territory at the time of this study. These data could not be publicly released. However, there was a very similar coverage of private health insurance across eastern Australia at the time of this study (38), and thus, there is no reason to believe that the distribution of the private pathology providers would differ between states. Furthermore, all these potential factors we would expect to affect the population uniformly, thus although we would expect them to affect the prevalence estimates, we would not expect them to affect the gradient of disease.

The latitude gradient that was evident in females with PBC was not identified in males. We believe that this at least partly explained by the small sample size of males in this study. This requires further evaluation with larger sample sizes, although this remains difficult in PBC populations with most cases occurring in females.

Data from the private pathology providers were not released in Western Australia or the Northern Territory, and thus, pathology-based prevalence estimation could not be performed for this state and territory. However UDCA prescription prevalence estimates were available for the Northern Territory and Western Australia and the latitudinal gradient was present when data from this territory and state were included. Western Australia comprises a huge range in latitude, and a limitation of this study was that we were not

able obtain pathology data for Western Australia, and thus the number of PBC cases per 2-digit postcode group, which would have enabled further evaluation of the association of latitude and prevalence on the west coast of Australia.

In conclusion, we have found for the first time that the prevalence estimates of PBC significantly varied with latitude in Australia using 2 different methods of case ascertainment. The next direction for future research would be to replicate this finding in other PBC populations and also to explore whether there is an association with latitude in other autoimmune liver diseases. This finding provides novel data to support the possibility that UVR or low vitamin D levels may play a role in disease etiology. Further case-control or cohort studies are needed to investigate this hypothesis.

CONFLICTS OF INTEREST

Guarantor of the Article: Janine French, MBBS.

Specific author contributions: J.F., P.A., and I.V.M.: conducted the research design. J.F. and J.N.: conducted the data acquisition. J.F. and S.S.: conducted the data interpretation, and all authors were involved with the manuscript preparation. All authors approved the final submitted draft.

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Potential competing interests: None to report.

Study Highlights

WHAT IS KNOWN

- ✓ Primary biliary cholangitis is a chronic progressive cholestatic liver disease, and there is widespread variation in worldwide prevalence.
- ✓ There is little known with regard to its etiology, and it is considered to be a complex interaction between genetic and environmental factors.

WHAT IS NEW HERE

- ✓ In Australia, there is a latitudinal gradient of prevalence.
- ✓ This was found using 2 different methods of case ascertainment.

TRANSLATIONAL IMPACT

- ✓ This provides novel data to support the possibility that ultraviolet radiation or low vitamin D levels may play a role in disease etiology.

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