Geographical and Temporal Distribution of Prostate Specific Antigen Testing Across Australia

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A thesis submitted to fulfil requirements for the degree of Doctor of Philosophy

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Statement of originality

This is to certify that to the best of my knowledge and belief, the research showcased in this thesis is my own work, with the exception of the acknowledged content. I confirm that I have not previously submitted this thesis, in part or in full, for any degree or other purposes.

I certify that the intellectual content of this thesis is the product of my own work and that all the assistance received in preparing this thesis and sources have been acknowledged.

Signature:

Ankur Kohar

30 June 2023

Thesis abstract

Prostate cancer is the second most diagnosed cancer worldwide among men and the most diagnosed in Australia. Despite controversies surrounding its low specificity, the Prostate-specific antigen (PSA) test remains the most commonly used test for prostate cancer. In Australia, PSA "screening" test rates have consistently been high among men living in socio-economically advantaged and urban areas compared to disadvantaged and rural areas. Long term national level data on these trends has not been available. Additionally, there is limited information about the prevalence of PSA testing at the small geographical area level, limiting the ability to appropriately understand the role of PSA testing in the observed geographical patterns of prostate cancer incidence. The aim of this thesis was to investigate spatial and temporal patterns of PSA testing in Australia.

We utilized the population-based Medicare Benefit Schedule dataset on PSA testing, developed complex methods to transform postcodes into smaller areas and used Bayesian models to identify key underlying patterns. We first computed a general PSA testing trend across Australia, as well as by area-specific regions, including socio-economic status, remoteness, and states and territories. Then, we investigated whether the national patterns were evident in smaller areas across Australia over time. Finally, to understand the impact of PSA testing on prostate cancer incidence, we examined the association between PSA testing and prostate cancer incidence by small areas.

This population-based study identified substantial variation in the participation rate of PSA testing by small geographical areas across Australia and over time. However, there was a low association between PSA testing and prostate cancer incidence at the smaller area level. This information can help in reviewing and developing evidence-based strategies to reduce any identified disparities in prostate cancer indicators across Australia.

List of publications arising from thesis

This thesis contains four manuscripts which have either been published or are currently under internal peer-review.

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- Kohar, A., Cramb, S. M., Pickles, K., Smith, D. P., & Baade, P. D. (2023). Changes in prostate specific antigen (PSA) "screening" patterns by geographic region and socio-economic status in Australia: Analysis of medicare data in 50-69 year old men. *Cancer epidemiology*, *83*, 102338. https://doi.org/10.1016/j.canep.2023.102338

- Kohar, A., Cramb, S. M., Pickles, K., Smith, D. P., & Baade, P. D. (2023). Spatial patterns of prostate-specific antigen testing in asymptomatic men across Australia: a population-based cohort study, 2017-2018. *Public health*, *217*, 173–180. https://doi.org/10.1016/j.puhe.2023.01.039

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Statement on author's contribution

Chapter 1 - Introduction and background. This chapter of the thesis provides an introduction and background on the epidemiology of Prostate-specific antigen (PSA) testing and prostate cancer. We also address the controversies surrounding the use of PSA testing and changes in screening guidelines over the years. It provides the context upon which Chapters 3 through to 7 are based, outlining the background to the use of PSA testing and potential influences on testing use and screening prevalence in Australia.

I, Ankur Kohar, conceptualized the approach, developed the structure, conducted a literature search and wrote the original draft of this chapter. Associate Professor David Smith, Professor Peter Baade, and Dr Susanna Cramb provided guidance, feedback, and comments on the chapter.

Chapter 2 – Spatial and Spatio-temporal literature review. This chapter provides a literature review of smoothing approaches available for spatial and spatio-temporal analysis. It presents the methodological approach that will be used for the analysis in Chapters 4 to 6, highlighting the reasons for selecting of these models to calculate rates for PSA testing and prostate cancer data in smaller areas across Australia.

I, Ankur Kohar, conducted literature research, created the search terms, identified appropriate manuscripts and reports, and wrote the original draft of this chapter. Associate Professor David Smith, Professor Peter Baade, and Dr Susanna Cramb provided guidance, feedback and comments on the chapter.

Chapter 3 - Trend analysis. This Chapter of the thesis was published in Cancer Epidemiology in 2023 (Cancer Epidemiol. 2023 Apr;83:102338. doi: 10.1016/j.canep.2023.102338. Epub 2023 Feb 24.).

This chapter provides the national trends of PSA testing across Australia, states and territories, remoteness categories, and socio-economic status. The chapter is formatted as the final accepted manuscript by Cancer Epidemiology. It illustrates the "big picture" of how PSA testing has changed over time and broad region in Australia, upon which the next two chapters provide more detailed investigation.

I, Ankur Kohar, was the first author and was responsible for programming, cleaning data, performing data analysis, preparing tables and figures, checking results, and drafting the original manuscript. Ankur Kohar, Associate Professor David Smith, Professor Peter Baade, and Dr Susanna Cramb were responsible for the conceptualization and design of the study. Moreover, Associate Professor David Smith, Professor Peter Baade, and Dr Susanna Cramb were equally responsible for guiding, revising, and refining the manuscript. Additionally, Professor Peter Baade was responsible for data acquisition. All the authors mentioned above, and Dr Kristen Pickles were responsible for writing and editing the manuscript. All authors approved the final submitted version and acknowledged its inclusion in this thesis.

Chapter 4 - Spatial analysis. This Chapter of the thesis was published in Public Health in 2023 (Public Health. 2023 Apr;217:173-180. doi: 10.1016/j.puhe.2023.01.039. Epub 2023 Mar 8).

This chapter provides the geographical variation of PSA testing by small areas across Australia. Furthermore, it examines the variation in PSA testing rates within and between broad regions, including states and territories, remoteness categories, and socio-economic status. The chapter is formatted as the final accepted manuscript by Public Health. It determines the extent of variation in PSA testing between small geographical areas across Australia and underscores the potential contributing factors. This chapter forms the foundation for the subsequent chapter, which aims to explore how geographical patterns have changed over time.

I, Ankur Kohar, was the first author and was responsible for programming, cleaning data, performing data analysis, preparing tables and figures, checking results, and drafting the original manuscript. Ankur Kohar, Associate Professor David Smith, Professor Peter Baade, and Dr Susanna Cramb were responsible for the conceptualization and design of the study. Moreover, Associate Professor David Smith, Professor Peter Baade, and Dr Susanna Cramb were equally responsible for guiding, revising, and refining the manuscript. Additionally, Professor Peter Baade was responsible for data acquisition. All the authors mentioned above, and Dr Kristen Pickles were responsible for writing and editing the manuscript. All authors approved the final submitted version and acknowledged its inclusion in this thesis.

Chapter 5 - Spatio-temporal analysis. This chapter is formatted as a manuscript in preparation for submission to a peer-reviewed journal. The chapter provides the geographical variation of PSA testing by smaller areas over time across Australia. It identifies the PSA testing variation in small areas and the extent to which it varies over time across Australia. This analysis raises a question to be examined in the next chapter: Does the variation in PSA testing rates correlate with prostate cancer incidence in small areas across Australia?

I, Ankur Kohar, am the first author and am responsible for programming, cleaning data, performing data analysis, preparing tables and figures, checking results, and drafting the original manuscript. Ankur Kohar, Associate Professor David Smith, Professor Peter Baade, and Dr Susanna Cramb were responsible for the conceptualization and design of the study. Moreover, Associate Professor David Smith, Professor Peter Baade, and Dr Susanna Cramb were equally responsible for guiding, revising, and refining the manuscript. Additionally, Professor Peter Baade was responsible for data acquisition. All the authors mentioned above, including Dr Kristen Pickles, were responsible for writing and editing the manuscript. All authors approved the final submitted version and acknowledged its inclusion in this thesis.

Chapter 6 - Spatial associations. This chapter is formatted as a manuscript in preparation for submission to a peer-reviewed journal. This chapter provides the spatial association between PSA testing and prostate cancer incidence by small areas across Australia. It reveals that there is no evidence of a direct relationship between the use of PSA testing and prostate cancer incidence in smaller areas across Australia. These findings provide the motivation to further discuss and draw conclusions in the next chapter, highlighting the significant discoveries of this thesis.

I, Ankur Kohar, am the first author and am responsible for programming, cleaning data, performing data analysis, preparing tables and figures, checking results, and drafting the original manuscript. Ankur Kohar, Associate Professor David Smith, Professor Peter Baade, and Dr Susanna Cramb were responsible for the conceptualization and design of the study. Moreover, Associate Professor David Smith, Professor Peter Baade, and Dr Susanna Cramb were equally responsible for guiding, revising, and refining the manuscript. Additionally, Professor Peter Baade was responsible for data acquisition. All the authors mentioned above, including Dr Kristen Pickles, were responsible for writing and editing the manuscript. All authors approved the final submitted version and acknowledged its inclusion in this thesis.

Chapter 7 - Discussion and conclusions. This chapter provides a discussion of the principal findings in this thesis, the significance of this research, and explores directions for future research. It highlights the important implications and findings regarding the variation in PSA testing rates in Australia, also raising further questions for future research to delve into the underlying reasons behind these variations.

I, Ankur Kohar, wrote the original draft of the chapter. Associate Professor David Smith, Professor Peter Baade, and Dr Susanna Cramb reviewed and provided feedback on the chapter.

As supervisor of the candidature upon which this thesis is based, I can confirm that the authorship attribution statements above are correct.

Primary supervisor: Associate Professor David P. Smith

Signature: David P. Smith **Date:** 30 June 2023

Ethics and Data custodian approval

Ethics approval to access prostate-specific antigen testing data was obtained from the Griffith University Human Research Ethics Committee (GU Ref no: 2017/777).

Ethics approval to access prostate cancer incidence data was obtained from four committees.

- New South Wales Population & Health Services Research Ethics Committee (2017/HREC0203),
- QUT University Human Research Ethics Committee (1600000880),
- Human Research Ethics Committee for the Northern Territory Department of Health and Menzies School of Health Research ((2016-2720),
- The Australian Capital Territory Health Human Research Ethics Committee (ETHLR.16.235).

Ethics and data custodian approval letters are provided in Appendix A.

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List of Abbreviations

ABS	Australian Bureau of Statistics
AHTAC	Australian Health Technology Advisory Committee
ANOVA	Analysis Of Variance
ARIA+	Accessibility/Remoteness Index of Australia Plus
ASGS	Australian Statistical Geography Standard
BUGS	Bayesian inference Using Gibbs Sampling
BYM	Besag, York and Mollié
CAP	Comparison Arm for ProtecT
CAR	Conditional Autoregressive
DIC	Deviance Information Criterion
DRE	Digital Rectal Examination
EP	Exceedance Probabilities
ERSPC	European Randomized Study of Screening for Prostate Cancer
GP	General Practitioner
GWMMR	Geographically Weighted Multivariate Multiple Regression
GWR	Geographically Weighted Regression
HPOS	Health Professional Online Services
ICAR	Intrinsic Conditional Autoregressive
IQR	Interquartile Range
IRSAD	Index of Relative Socio-Economic Advantage and Disadvantage
MBS	Medicare Benefit Schedule
MCMC	Markov Chain Monte Carlo
MGWR	Multiscale Geographically Weighted Regression
MRI	Magnetic Resonance Imaging
NIMBLE	Numerical Inference for statistical Models using Bayesian and Likelihood Estimation
PCA3	Prostate Cancer Antigen 3
PCFA	Prostate Cancer Foundation of Australia

PCOR-ANZ	Prostate Cancer Outcomes Registry - Australia and New Zealand
PLCO	Prostate, Lung, Colorectal and Ovarian
POA	Postal Area
PSA	Prostate Specific Antigen
PSMA PET-CT	Prostate Specific Membrane Antigen Positron Emission Tomography–Computed Tomography
RACGP	Royal Australian College of General Practitioners
SA2	Statistical Area Level 2
SAR	Spatial Autoregressive
SEIFA	Socio-Economic Indexes for Areas
SES	Socio-Economic Status
SIR	Standardised Incidence Rates
SURE	Secure Unified Research Environment
TRUS	Trans Rectal Ultrasound
UK	United Kingdom
US	United States
USPSTF	United States Preventive Services Task Force
WAIC	Watanabe-Akaike Information Criterion

Chapter 1

1 INTRODUCTION AND BACKGROUND

1.1 Chapter overview

Chapter 1 provides an overview of prostate-specific antigen (PSA) testing and prostate cancer. It begins by explaining what PSA testing is and highlights the significance of elevated PSA levels in detecting early prostate cancer and other conditions. The types and reasons for PSA testing are discussed, including the use of novel markers and alternative methods. The chapter emphasizes the limitations of these modifications in detecting aggressive disease.

The debates surrounding PSA testing are explored, focusing on its high sensitivity, low specificity, and the challenges in distinguishing between cancer and non-cancer conditions. The issue of overdiagnosis and overtreatment is addressed, highlighting the detection of slow-growing tumors that may not cause harm and the potential negative impact on patients' quality of life and mental health. The benefits and harms of PSA testing are examined, including the limitations of false positives and false negatives. False positives lead to unnecessary tests, procedures, treatments, and adverse effects, while false negatives can result in missed high-risk diseases, poor outcomes, and medico-legal issues for clinicians. The chapter emphasizes the need for careful consideration of the benefits and harms of screening programs.

This chapter further discusses international guidelines for PSA testing, highlighting the varying recommendations across different countries, including the US, UK, Canada, and Australia. It outlines the changes in Australian guidelines over time and the differing recommendations from organizations such as the Royal Australian College of General Practitioners and the Prostate Cancer Foundation of Australia. Finally, the chapter explores the overall and area-specific patterns of PSA testing, noting the variability in usage across Western countries and the disparities between advantaged and disadvantaged areas.

Chapter 1 also provides an introduction to prostate cancer, outlining a summary of what is known about the natural history of the disease and the role of PSA in its detection. It discusses the different tests used for diagnosing prostate cancer, such as digital rectal examination, PSA testing, prostate biopsy, and Magnetic Resonance Imaging (MRI) scans. The epidemiology of prostate cancer on an international scale is examined, highlighting its incidence rates across different regions and the impact of PSA testing on detection rates. The chapter emphasizes the geographical variation in prostate cancer incidence and mortality rates.

Overall, this chapter provides the necessary background and sets the agenda for understanding the complexities and controversies surrounding PSA testing and prostate cancer, providing a foundation for the subsequent chapters of the thesis.

1.2 Prostate-specific antigen testing

1.2.1 What is Prostate-specific antigen testing?

The prostate-specific antigen (PSA) test is a blood examination designed to assess the levels of a protein known as "prostate-specific antigen." This particular protein is predominantly synthesized within the prostate gland and plays a crucial role in providing nourishment to sperm (National Cancer Institute 2022). Increased concentrations of PSA can serve as an indication of the presence of early-stage prostate cancer, in addition to other conditions such as benign prostatic hyperplasia, urinary tract infections, or recent ejaculation (Brett 2011). Through the utilization of the PSA test, early detection of prostate cancer can occur, leading to the implementation of more efficacious treatment strategies. The initial introduction of the PSA test occurred in the United States in 1987, and subsequently, it has been extensively employed for opportunistic screening in numerous developed countries, including Australia in 1989, with the objective of reducing prostate cancer mortality rates (Alberts *et al.,* 2015, Pathirana *et al.,* 2022). Prior to the integration of PSA testing, prostate cancer diagnoses primarily relied on the practice of digital rectal examination (DRE), which exhibited suboptimal sensitivity, limited specificity, and substantial interobserver variability in the detection of prostate cancer (Alberts *et al.,* 2015).

1.2.2 Types and reasons for prostate-specific antigen testing

The PSA test is often used for screening asymptomatic men for prostate cancer and used extensively in the monitoring and surveillance of men with prostate cancer, in those on active surveillance but also those who have had treatment (surgery, radiation, androgen deprivation therapy) to assess disease control (National Cancer Institute 2022). An elevated PSA level is classified as abnormal when it exceeds 2.5 ng/ml for men aged 40 to 59 and 4.0 ng/ml for men in their 60s (Pavlovich 2023). Furthermore, a yearly increase of 0.35 ng/ml in PSA is also considered an abnormal finding. In such instances, additional testing may be advised by the healthcare professional. Recognizing the limitations associated with PSA testing, extensive efforts have been devoted over the past few decades to enhance the reliability of prostate cancer screening markers. Numerous novel markers are currently under investigation, with prostate cancer antigen 3 (PCA3), Prostate Health Index, and TMPRSS2:ERG gene fusion being among the most extensively studied (Borza *et al.,* 2013).

Alternatives or variations to the PSA test include:

- PSA Velocity: This method, if used optimally, involves obtaining a minimum of three sequential PSA readings over an 18-month period to calculate the rate of PSA increase.

- Free PSA: The ratio of free-PSA to total PSA is calculated, as benign prostatic tissue produces more free-PSA compared to prostate cancer. This test is usually used in the case of men with PSA levels between 3 and 10 ng/ml. Consequently, patients with prostate cancer exhibit lower ratio values.
- Complexed PSA: It serves as an adjunct to total PSA; however, it offers limited additional benefits over total PSA in differentiating between benign and malignant conditions.
- PSA Density: PSA density is a calculation of the PSA level to the size of the prostate. This is employed to enhance the performance of PSA testing since prostate cancer has been reported to produce up to 10 times more PSA per unit volume of tissue compared to benign conditions.

These modifications have demonstrated improved cancer detection rates. Unfortunately, most of them possess limited capability in predicting or detecting aggressive disease. Despite the limitations of the test, PSA remains the foremost predictive tumor marker for identifying men at an elevated risk of prostate cancer (Alberts *et al.,* 2015).

1.2.3 Prostate-specific antigen testing debates

Sensitivity and specificity

The utilization of the PSA test for detecting prostate cancer is a subject of extensive debate (Coory and Baade 2005). This debate arises from concerns regarding its high sensitivity and low specificity (Ankerst and Thompson 2006) in asymptomatic people as well as its limited ability to differentiate between cancers that will progress and those that are unlikely to cause symptoms (Stamey *et al.,* 2004). One of the original developers of the PSA test, Richard Albin, described the test as a “hugely expensive mistake and never thought that it would lead to profit driven public health disaster” (Albin 2010). Although the PSA test remains the prevailing method for prostate cancer detection, its use is accompanied by these controversies.

Overdiagnosis and overtreatment

PSA testing has had a substantial influence on the recorded incidence rates of prostate cancer in western nations (Alberts *et al.,* 2015). This testing method aims to detect prostate cancer in asymptomatic individuals, leading to earlier diagnosis compared to cases that would have otherwise been identified later. However, it also detects indolent tumors that may not have exhibited symptoms before the patient's demise from unrelated causes, resulting in the identification of overdiagnosed cancers (Alberts *et al.,* 2015). The term "overdiagnosis" refers to the identification of cancer that would not have presented clinically or led to cancer-related mortality during a patient's lifetime. The detection of such overdiagnosed cases artificially inflates the observed incidence rate of prostate cancer by including

instances that would have otherwise gone undetected (Carter *et al.,* 2015). Overdiagnosis poses a notable concern in prostate cancer due to its high prevalence and low mortality rates (Borza *et al.,* 2013). The diagnosis of insignificant tumors can lead to unnecessary invasive treatments like radical prostatectomy or radiotherapy, which may entail side effects such as incontinence and impotence. The overtreatment of clinically insignificant prostate cancer significantly impacts the patient's quality of life (Alberts *et al.,* 2015). Moreover, PSA testing and prostate cancer diagnosis have been associated with adverse effects on mental well-being, including anxiety and depression, which in turn elevate the risk of cardiovascular events and suicide (Borza *et al.,* 2013).

Benefits and harm of testing

The drawbacks associated with PSA testing encompass the occurrence of false positives and false negatives, where false positives can trigger the need for further tests, procedures, treatments, and the adverse effects associated with radiation exposure, surgery, or active surveillance (Ilic *et al.,* 2013). On the other hand, the effects of false negatives are quite different from false positives. Missing the opportunity to detect high-risk disease can have serious outcomes for the man, such as a poor prognosis, aggressive treatment, poor quality of life, and the risk of premature death. A false negative test can also present medico-legal issues for clinicians (Nash *et al.,* 2009). These outcomes have the potential to cause physical and emotional harm (Lin *et al.,* 2008). Initially, it was believed that the majority of tumors detected through PSA testing had the potential to be clinically significant. However, it has become evident over time that many of these tumors resemble those identified in autopsy studies, which were deemed to be clinically insignificant (Borza *et al.,* 2013).

Nonetheless, uncertainties persist regarding the potential benefits of early detection, improved prognosis, reduction in disease incidence, and cost-effectiveness in terms of whether prostate cancer necessitates treatment and whether early detection leads to enhancements in the duration or quality of life (Lin *et al.,* 2008).

However, the reason PSA testing is still not part of a formal structured screening program may be attributed to the results of international randomized controlled trials that examined whether PSA testing reduces prostate cancer-specific mortality and its impact on the quality of life (Ilic *et al.*, 2013). The European Randomized Study of Screening for Prostate Cancer (ERSPC) has reported prostate-specific mortality benefits at 16years of follow up for men randomized to receive screening compared to the control group (Hugosson, Roobol *et al.,* 2019). All three international randomized controlled trials, including the European Randomized Study of Screening for Prostate Cancer (ERSPC), the United States' Prostate, Lung, Colorectal and Ovarian (PLCO), and the UK's Comparison Arm for ProtecT (CAP) study, reported that the harms likely outweigh the benefits. Moreover, the evidence shows that treatment-related quality of life issues for men treated for early-stage disease have traditionally been the main concern due to the harms associated with aggressive therapy (Smith *et al.,* 2009, Donovan *et al.,* 2016). Various

modeling-based studies have estimated that up to 42% of men have been considered to be "overdiagnosed," and when these men are "overtreated" with aggressive therapy, it creates harm (Glasziou *et al.,* 2020). A recent Australian study reported, for every man aged 50-69 years who avoids prostate cancer-specific mortality, two will experience overdiagnosis (Caruana, Gulati *et al.,* 2023). However, recent changes in the use of mpMRI, different approaches to biopsy techniques, and the use of active surveillance in low-risk disease have altered the balance of harms to benefits (Chiam *et al.,* 2021).

In conclusion, although screening programs hold promise for significant benefits, they also carry the risk of harm to patients. The careful evaluation of the advantages and disadvantages of screening programs is crucial both in the clinical context and within screening trials to ensure that the benefits outweigh the harm and that patients receive optimal and equitable care (Alberts *et al.,* 2015).

1.2.4 Prostate-specific antigen testing guidelines

International guidelines

Due to the contentious nature of PSA testing, it is not recommended as a widespread screening approach. However, international guidelines exist that recommend informed decision-making regarding testing considering risk factors such as age, family history, race, and ethnicity when determining whether to perform the screening test.

The US Preventive Services Task Force (USPSTF) in 2018 stated that while there are potential benefits of prostate cancer testing, however, these advantages did not outweigh the expected harms enough to recommend routine testing (Grossman *et al.,* 2018). Testing was not recommended for men aged 70 or older. However, the guideline stated that if men aged 55-69 expressed a desire for the PSA test, they should be provided with information about the benefits and risks of testing prior to offering it. Similar recommendations were provided by other US guidelines, including the American Cancer Society (American Cancer Society 2020), The American Urological Association (Carter *et al.,* 2013), The American Academy of Family Physicians (American Academy of Family Physicians 2020), The American College of Physicians (Qaseem *et al.,* 2013) and National Comprehensive Cancer Network (Mohler *et al.,* 2019) although the frequency of offering the test varied.

The UK's National Screening Committee advised against population-based screening and instructed general practitioners not to initiate discussions related to testing. However, if men inquired about the test, they should be informed about its benefits and risks before it was offered (UK National Screening Committee 2020). The Canadian Task Force on Preventive Health Care did not support PSA-based testing for prostate cancer (The Canadian Task Force on Preventive Health Care 2019). In 2020, the European Association of Urology recommended an individualized risk-adapted approach for well-informed men aged 50 or older (Jackson *et al.,* 2022). The New Zealand Prostate Cancer Working Group and Ministry

of Health, in 2015, recommended testing men aged 50-70 every 2-4 years following a discussion (Jackson *et al.,* 2022).

Australian PSA guidelines overtime

The guidelines in Australia have changed over time since 1996. Generally, Australian guidelines for PSA testing have evolved in response to changes in the United States Preventive Services Task Force guidelines, likely resulting in substantial fluctuations in testing rates.

In 1996, the Royal Australian College of General Practitioners (RACGP) acknowledged that PSA testing could detect early cases of prostate cancer but there was uncertainty as to whether early cancer detection could improve outcomes (Royal Australian College of General Practitioners 1996). In 2002, RACGP discouraged the use of PSA test for screening prostate cancer and described it as unsuitable due to known risks and adverse effects of therapies (Royal Australian College of General Practitioners 2002). By 2005, the RACGP recommended PSA tests for men aged 50-75 years (Royal Australian College of General Practitioners 2005), likely leading to a further increase in testing until 2008. However, in 2009, the RACGP advised against testing men aged 75 or older, possibly contributing to the observed decline in testing rates (Royal Australian College of General Practitioners 2009). This recommendation was further reinforced in 2012, when the RACGP discouraged PSA testing for men of all ages and advised against raising the issue of PSA testing with patients (Royal Australian College of General Practitioners 2012). A further decrease in testing rates was observed. In 2016, the RACGP continued to not recommend PSA testing and advised general practitioners that they are not obliged to offer the test (Royal Australian College of General Practitioners 2016).

Conversely, the Prostate Cancer Foundation of Australia and Cancer Council Australia guidelines (Prostate Cancer Foundation of Australia and Cancer Council Australia PSA Testing Guidelines Expert Advisory Panel 2016) released in 2016 and endorsed by the National Health and Medical Research Council, recommend that men aged 50-69 years at average risk of prostate cancer be offered a PSA test every two years if they make an informed decision to do so. However, as explored in a later chapter of this thesis, this recommendation did not appear to result in a significant change in testing rates.

The guidelines in Australia have resulted in conflicting messages due to inconsistent phrasing of recommendations. A recent commentary discussing the need for a review of these guidelines suggests that the interpretation of these two sets of Australian based recommendations can lead to differences in primary care (Rashid *et al.,* 2023).

1.2.5 Area-specific patterns of prostate-specific antigen testing

PSA testing is widely practiced in various western countries, including Australia; however, there is notable variation in the utilization of PSA testing based on the geographic location of individuals (Coory

and Baade 2005, Calopedos *et al.,* 2019). Studies have shown that testing rates tend to be higher among men residing in advantaged and urban areas, while lower rates are observed among those living in disadvantaged and rural regions (Calopedos *et al.,* 2019, Dasgupta *et al.,* 2019). Furthermore, variations in testing patterns are evident at both the inter-state and intra-state levels, influenced by factor such as the accessibility to prostate cancer services for men residing in remote or regional areas (Calopedos *et al.,* 2019).

1.3 Prostate cancer

1.3.1 What is prostate cancer?

Prostate cancer is a malignancy that originates in the prostate gland (Figure 1.1) (Prostate anatomy), an essential component of the male reproductive system located near the base of the bladder (Healthdirect 2022). Typically, about the size of a golf ball, the prostate gland can undergo enlargement as men age and due to conditions, such as prostatitis or benign prostatic hypertrophy. Within the prostate, specialized cells produce a protein called prostate-specific antigen (PSA), which can be detected through a blood test (Cancer Research UK 2019). The development of cancer in the prostate is characterized by the abnormal growth and proliferation of cells, which can invade nearby tissues and potentially metastasize to distant parts of the body (Prostate anatomy). The most common type of prostate cancer is acinar adenocarcinoma, originating from the glandular cells in the outer regions of the prostate (Prostate anatomy). Prostate cancer encompasses various subtypes, with many exhibiting slow growth and remaining asymptomatic for long periods, while others display aggressive behavior and pose a significant risk to overall health and survival (Healthdirect 2022).

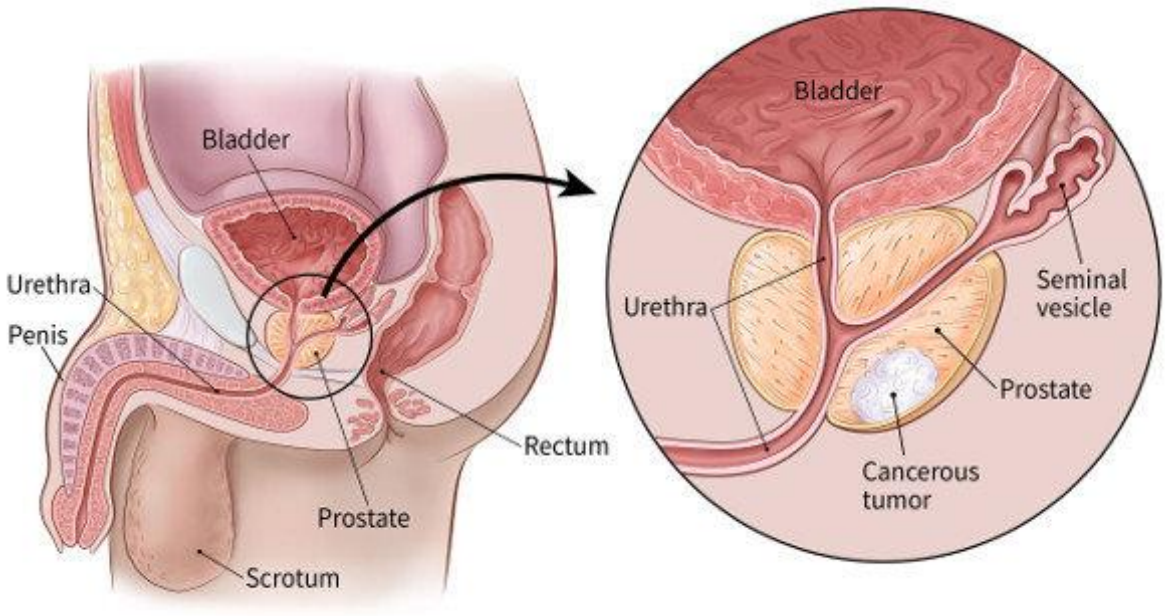

Figure 1.1: *Location of prostate gland in men body (left) and cancerous tumor in prostate gland (right), adapted from American Cancer Society.*

The Prostate Cancer Outcomes Registry - Australia and New Zealand (PCOR-ANZ) serves as a comprehensive registry for prostate cancer, gathering data on care and outcomes for men diagnosed with prostate cancer in Australia and New Zealand (Prostate Cancer Outcomes Registry Australia and New Zealand 2023). Its primary goal is to enhance the quality of care and health outcomes for individuals diagnosed with prostate cancer. Presently, the registry contains data pertaining to 91,941 men who received prostate cancer diagnoses between 2015 and 2022 in Australia (excluding Western Australia) and New Zealand (Prostate Cancer Outcomes Registry Australia and New Zealand 2022). Among the diverse treatment options available, including Active Surveillance, Watchful Waiting, Surgery, Radiation Therapy, Androgen Deprivation Therapy, and Chemotherapy, PCOR-ANZ has described a notable shift towards the utilization of Active Surveillance among men with low-risk prostate cancer. Additionally, there has been a clear shift in the trend from transrectal biopsy to transperineal biopsy over the period 2015 to 2019. Investigating the prevalence of PSA testing in smaller geographic areas holds the potential to shed light on small area differences in the utilization of biopsies and treatments.

1.3.2 How prostate cancers are diagnosed?

There are several tests available to evaluate the prostate health:

- Digital rectal examination (DRE): During a DRE, a doctor inserts a lubricated, gloved finger into the rectum to assess the size and detect any abnormalities in the prostate. Although Australian guidelines do not recommend routine addition of DRE to PSA testing in asymptomatic men (Royal Australian College of General Practitioners 2016) in primary care, it can still detect some cancers, even in individuals with low PSA levels (Ong *et al.,* 2020). The DRE is often performed by a urologist in the investigation of suspicious cancer.
- Prostate-specific antigen (PSA) test: This blood test measures the levels of a protein called prostate-specific antigen, which is produced by the prostate gland. Elevated PSA levels can indicate the possibility of prostate cancer.
- Prostate biopsy: To confirm a diagnosis of prostate cancer, a urologist performs a prostate biopsy. This procedure involves the removal of a sample of cells from the prostate by passing a biopsy needle through the rectal mucosa (Wei *et al.,* 2015). The cells are then examined for cancer. However, there has been a shift in techniques for biopsy, from Trans Rectal Ultrasound (TRUS) towards Trans Perineal. The resulting change appears to reduce the risk of infection.
- MRI scan: An MRI scan provides a detailed image of the prostate, helping to identify potential signs of cancer. Multiparametric MRI of the prostate has improved the accuracy of biopsy results and reduced the number of unnecessary benign biopsies (Thompson *et al.,* 2016). It has shown high sensitivity and negative predictive value of 87% and 72%, respectively, compared to TRUS biopsy with sensitivity and negative predictive value of 60% and 65% (Ahmed *et al.,* 2017).

- Prostate-specific membrane antigen positron emission tomography–computed tomography (PSMA PET-CT): PSMA is a glycoprotein expressed in prostate tissue. However, no significant difference was found between PSMA PET-CT and multiparametric MRI in detecting primary tumors, clinically significant tumors, or transition zone tumors (Kalapara *et al.,* 2020) and is not currently systematically offered in the diagnostic pathway.

1.3.3 Risk factors for prostate cancer

Several risk factors have been linked to the incidence of prostate cancer, including age (Milonas *et al.,* 2019), race or ethnicity (Rebbeck *et al.,* 2013), family history (Ang *et al.,* 2020), and inherited genetic factors. The risk of developing aggressive prostate cancer tends to increase with age, as older men often have higher Gleason scores than younger men (Milonas *et al.,* 2019). Gleason score is a prostate cancer grading system where pathologists take two samples from different locations of the prostate gland and assign grades on a scale of 1 to 5 based on their similarity to healthy cells (Munjal and Leslie 2023). The final score is the sum of both grades, and a low score indicates lower prostate malignancies. Worldwide, prostate cancer is most commonly observed in black men of African descent (Rebbeck *et al.,* 2013) and incidence rates are highest among black men in the United States and the Caribbean (Sung *et al.,* 2021). However, mortality rates are highest among Caribbean and sub-Saharan African men (Sung *et al.,* 2021), possibly due to differences in healthcare access, diagnosis, and testing practices (Rebbeck *et al.,* 2013). Having a positive family history of prostate cancer has been associated with an increased risk of developing the disease, but not with cancer-specific mortality (Ang *et al.,* 2020). Additionally, having a single first-degree relative with prostate cancer raises the risk of developing prostate cancer by a factor of 2.5, while having two affected relatives increases the risk by 3.5-fold (Johns and Houlston 2003).

1.3.4 International epidemiology of prostate cancer

Globally, prostate cancer (ICD-10 code C61) ranks as the second most prevalent cancer among men, just behind lung cancer (Figure 1.2). In 2020, approximately 1.4 million new cases were estimated worldwide, corresponding to an incidence rate of 37.5 per 100,000 men (Sung *et al.,* 2021). Additionally, prostate cancer is the most commonly diagnosed cancer in 112 countries worldwide (Figure 1.3). Incidence rates of prostate cancer exhibit significant variation, ranging from 6.3 to 83.4 per 100,000 men across different regions. Developed countries such as Australia, the United States (US), and Scandinavian countries demonstrate particularly high incidence rates (Figure 1.4), while Asia and Northern Africa exhibit the lowest rates. The incidence of prostate cancer shows an approximately 25-fold variation between countries with high and low incidence (Center *et al.,* 2012, Ferlay *et al.,* 2015). Notably, mortality rates from prostate cancer display different patterns internationally, with the highest mortality rates observed among black populations in the Caribbean and sub-Saharan Africa (Figure 1.4) (Dasgupta *et al.,* 2019). The variation in diagnostic practices is likely an important factor contributing to the divergent prostate cancer incidence rates worldwide.

Following the introduction of prostate-specific antigen (PSA) testing in the USA and subsequently in Australia as a rebateable item on Medicare Benefit Schedule (MBS) in 1988, these two countries experienced a rapid increase in incidence rates as preclinical cancers were detected (Center *et al.,* 2012). However, there was a subsequent sharp decline in the late 2000s, which has been attributed to a decrease in the utilization of PSA testing (Kvåle *et al.,* 2007, Center *et al.,* 2012, Zhou *et al.,* 2016). These reductions in testing rates reflect changes in recommendations regarding PSA-based testing for asymptomatic men (U.S. Preventive Services Task Force 2008, Royal Australian College of General Practitioners 2009, Moyer 2012, Royal Australian College of General Practitioners 2012, Prostate Cancer Foundation of Australia and Cancer Council Australia PSA Testing Guidelines Expert Advisory Panel 2016, Royal Australian College of General Practitioners 2016).

Area-level patterns and trends

Men living in urban areas of Western and European countries, including the USA (Fogleman *et al.,* 2015, Zahnd *et al.,* 2018), Denmark (Marsa *et al.,* 2008) and Spain (Ocaña-Riola *et al.,* 2004), showed high incidence rates compared to rural areas. Similarly, men residing in affluent areas of the USA (Kish *et al.,* 2014, Houston *et al.,* 2018), Netherlands (Aarts *et al.,* 2010), Denmark (Meijer *et al.,* 2013), the UK (Maringe *et al.,* 2013) and Scotland (Morgan *et al.,* 2013) demonstrate higher prostate cancer incidence compared to those in disadvantaged areas. In contrast to prostate cancer incidence, prostate cancer mortality rates tend to be higher among men living in rural and disadvantaged areas compared to urban and affluent areas (Baade *et al.,* 2015). In addition, survival rates also exhibit consistent patterns, with men residing in urban areas or affluent areas demonstrating higher survival rates compared to those living in rural or disadvantaged areas (Marsa *et al.,* 2008, Shafique and Morrison 2013, Xiao *et al.,* 2015). However, there are some studies that showed no difference in survival (Marsh *et al.,* 2017, Vetterlein *et al.,* 2017).

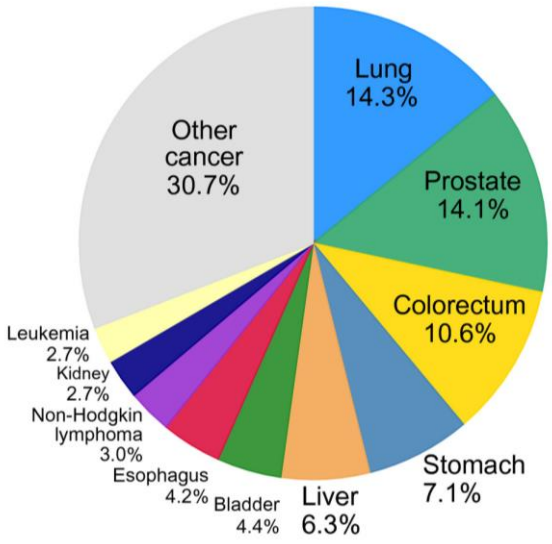

Figure 1.2: *Worldwide distribution of incidence cases of top 10 common cancers in males. Source: GLOBOCAN 2020.*

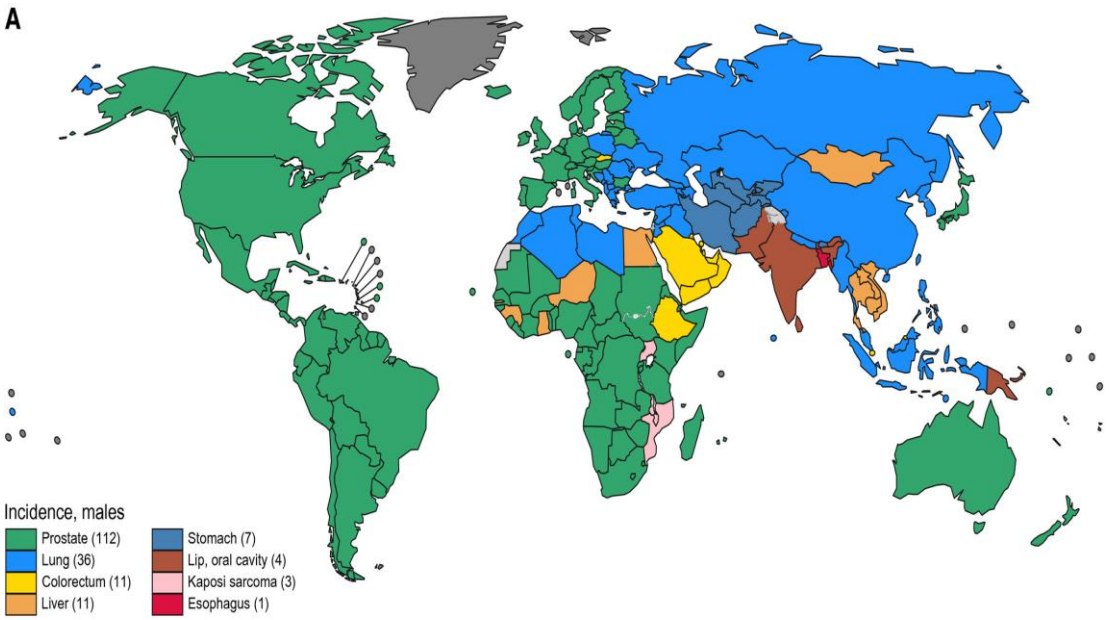

Figure 1.3: *Most commonly diagnosed cancers worldwide among men (excluding keratinocyte cancers). Digits with cancer type in legend represents number of countries. Source: GLOBOCAN 2020.*

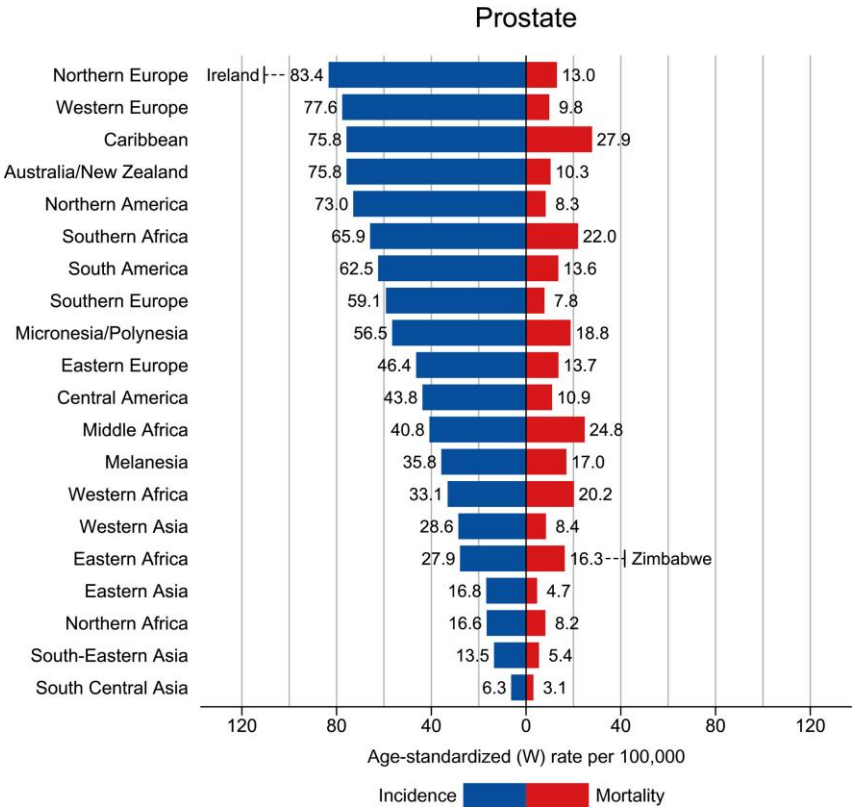

Figure 1.4: *Region-specific incidence and mortality age-standardized rates for prostate cancer. Source: GLOBOCAN 2020.*

1.3.5 Epidemiology of prostate cancer in Australia

In Australia, the occurrence of new prostate cancer cases has consistently been high compared to other developed countries (Feletto *et al.,* 2015). It was estimated that 24,217 men in Australia will be diagnosed

with prostate cancer in 2022, with an incidence rate of 150.8 cases per 100,000 men (Australian Institute of Health and Welfare 2022). Additionally, highest incidence rates were observed in men aged 70-74, followed by those aged 65-69. However, the incidence rate in 2018 varied by state and territory, being highest in Queensland (161.8 cases per 100,000 men) and lowest in the Northern Territory (95.3 cases per 100,000 men) compared to the national average (Australian Institute of Health and Welfare 2022).

The overall incidence of prostate cancer over time showed a notable pattern with its first peak observed in 1994, followed by a decline until 1997 (Australian Institute of Health and Welfare 2022, Pathirana *et al.,* 2022). The incidence remained stable until 2002 when it started to rise and reached a second peak in 2009. Subsequently, it declined until 2014. Since 2014, there has been a plateau in the overall national incidence trend. This trend is generally observed in all states and territories, but the magnitude varied by State or Territory (Australian Institute of Health and Welfare 2022, Pathirana *et al.,* 2022). The peak in prostate cancer incidence in 1994 was associated with the introduction of the PSA test in 1989 (Pathirana *et al.,* 2022), while the 2009 peak correlates with rise in biopsy rates and a change in the number of cores sampled at biopsy (Pathirana *et al.,* 2022) and could be due to changes in Australian PSA testing guidelines in 2005 (Royal Australian College of General Practitioners 2005), which recommended that general practitioners inform patients of risk and benefits of PSA test for men aged 50 to 75.

Area-level patterns and trends

There is significant variability in the incidence and mortality rates of prostate cancer within Australia. Prior to 1990, the incidence of prostate cancer was similar in Australian regional/rural and urban areas (Coory and Baade 2005). However, more recent patterns indicate that men living in urban areas had higher incidence rates compared to those in rural areas (Baade *et al.,* 2015, Calopedos *et al.,* 2019). Similarly, men residing in affluent areas demonstrated higher prostate cancer incidence compared to those in disadvantaged areas (Cramb *et al.,* 2011). In contrast to prostate cancer incidence, prostate cancer mortality rates tended to be higher among men living in rural and disadvantaged areas compared to urban and affluent areas of Australia (Baade *et al.,* 2011, Singh *et al.,* 2011). It was recently forecasted that there would be a continued rise in the incidence count of prostate cancer in Australia, as well as at the small area level (local government area), in the coming years (Wah, Papa *et al.,* 2022). This increase was attributed to three main factors: population growth, an aging population, and an increased rate of detection, in addition to PSA testing. Conversely, the decline in mortality rates associated with prostate cancer was attributed to early detection and improved treatment options (Earnest, Evans *et al.,* 2019). Survival rates exhibited consistent patterns, with men residing in urban areas, more accessible regions, or affluent areas demonstrating higher survival rates compared to those living in rural, less accessible, or disadvantaged areas (Tervonen *et al.,* 2017).

Small-area geographical patterns

To date, the highest geographical resolution of prostate cancer incidence and survival estimates are available in the Australian Cancer Atlas (atlas.cancer.org.au). These areas were defined using the Statistical Area level 2 (SA2) classification (2,148 areas across Australia), as specified by the Australian Bureau of Statistics (ABS) (Australian Bureau of Statistics 2016, 12 July), and revealed marked variation in rates across the nation (see Section 1.4, Australian geography).

Since July 1, 2011, the Australian Statistical Geography Standard (ASGS) (Figure 1.6), a comprehensive framework developed by the Australian Bureau of Statistics (ABS), has been used to categorize and interpret geographical statistics (Australian Bureau of Statistics 2011). The ASGS Main Structure comprises Statistical Area Levels 1 – 4, with Statistical Areas Level 2 (SA2) being medium-sized general-purpose regions formed by aggregating entire Statistical Areas Level 1. Additionally, whole SA2s are combined to create Statistical Areas Level 3 (SA3).

SA2s represent the smallest geographical units for releasing non-Census and Intercensal statistics by the ABS (Australian Bureau of Statistics Jul2021-Jun2026). This data includes information such as the Estimated Resident Population and Health & Vitals data. The primary objective of SA2s is to group people with similar characteristics either socially or economically. In cases where large areas, typically with negligible or no population, such as ports, airports, commercial zones, water bodies, industrial areas, defense lands, and national parks, are designated by the ABS as 'zero SA2s.' They serve the purpose of representing extensive unpopulated regions that cannot be easily merged with adjacent populated SA2s (Australian Bureau of Statistics Jul2021-Jun2026).

In this thesis, the term SA2 will be referred to as ‘small area’. The incidence map revealed lower-than-average rates in numerous areas of western and northern Australia, as well as parts of Victoria and Tasmania (Figure 1.5) (Australian Cancer Atlas (https://atlas.cancer.org.au)). Conversely, higher-than-average rates of prostate cancer diagnosis were observed in areas of New South Wales, south-western Western Australia, and Central Queensland. Capital cities, such as Sydney, Melbourne, and Perth, exhibited areas with increased incidence rates, with the exception of Darwin. The Atlas also illustrated that prostate cancer survival rates were generally lower than average across central, western, and northern Australia, with notably low rates in several areas of Victoria (Figure 1.5) (Australian Cancer Atlas (https://atlas.cancer.org.au)). The Atlas showed that many areas with high incidence had high survival (low excess mortality), and likewise for low incidence. This suggests that PSA testing may play a role in the early detection of prostate cancers within specific regions.

(A) Prostate Cancer Incidence

(B) Prostate Cancer Excess Mortality within 5 years of diagnosis

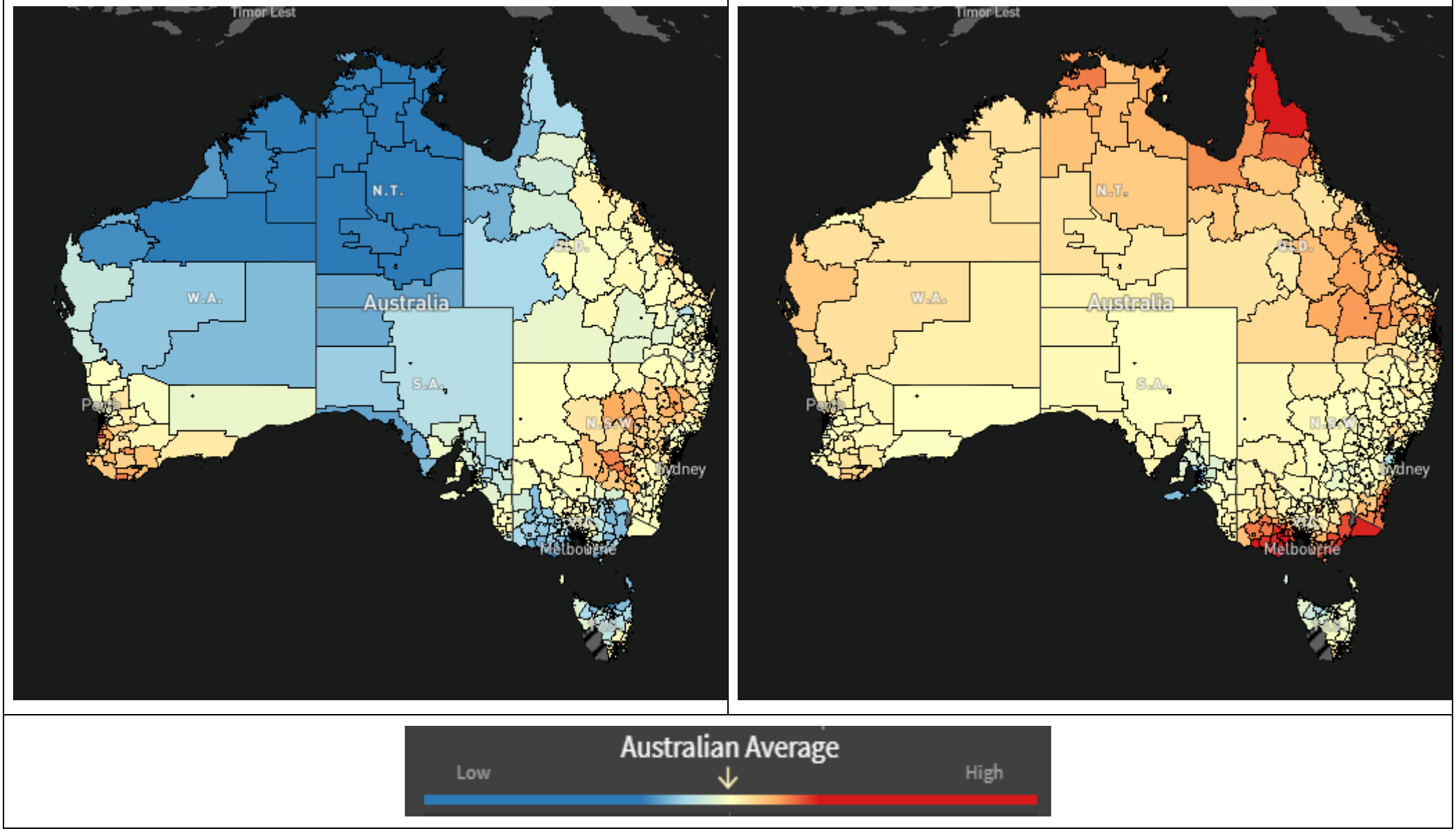

Figure 1.5: *Spatial pattern of (A) Prostate cancer incidence, and (B) Prostate cancer excess mortality (a survival measure) by small areas across Australia, Adapted from the Australian Cancer Atlas.*

1.4 Australian geography

The Australian Statistical Geography Standard (ASGS) is a classification system established by the Australia Bureau of Statistics (ABS) to categorize geographical areas within Australia. It comprises two components: ABS Structures and non-ABS Structures (Figure 1.6). ABS Structures are geographies for which the ABS collects data to analyze social, demographic, and economic statistics, releasing them accordingly. In contrast, non-ABS Structures generally represent administrative regions that are not defined by the ABS and provide a limited range of statistics, such as postal areas, which approximate postcode boundaries. The blue shaded boxes represent the key areas used in this work: Postal Areas in Non ABS Structure (Figure 1.6) approximate the postcodes provided in the dataset, and these are converted to Statistical Areas level 2 (SA2s) in the ABS Structure for small area analysis. The conversion process of postal areas (approximation of postcodes) to SA2s is discussed in further detail later in Section 1.5.1.

Australia is geographically divided into six states (New South Wales, Queensland, South Australia, Tasmania, Victoria, and Western Australia) and two territories (Australian Capital Territory and Northern Territory) (Figure 1.7(A)). The Greater Capital City Statistical Areas represent the functional areas of the eight state and territory capital cities (Australia Bureau of Statistics 2016). These areas include people living in urban areas as well as those who regularly visit the cities but reside in surrounding areas.

In 2011, the Australia Bureau of Statistics divided Australia into 2,196 SA2 regions as part of ASGS 2011, ensuring there were no gaps or overlaps in the delineation (Figure 1.7(B)) (Australian Bureau of Statistics Jul2021-Jun2026). Generally, SA2s have an average population of around 10,000 individuals, with populations ranging from 3,000 to 25,000 persons. Notably, in the 2017-2018 period, the median population for men aged 50-79 within SA2s was 1,479 (IQR: 895 - 2,296), while the mean population was 1,668 (Range: 4 - 6,191). SA2s located in remote and regional areas typically have smaller populations but larger geographical area compared to those in urban areas.

Remoteness Areas categorize Australia into five classes based on their relative access to services (Figure 1.7(C)). These areas are determined using the Accessibility/Remoteness Index of Australia Plus (ARIA+) (Australia Bureau of Statistics 2011). Additionally, the socio-economic characteristics of each SA2 are classified based on the Index of Relative Socio-Economic Advantage and Disadvantage (IRSAD) (Figure 1.7(D)) (Australia Bureau of Statistics 2013). This comprehensive index combines measures of both relative advantage and disadvantage. It is one of four Socio-Economic Indexes for Areas (SEIFA) indexes, each of which captures a distinct facet of the socio-economic conditions in an area based on different Census data. Due to the diverse variables considered, the same area may receive varying scores across these indexes. The IRSAD specifically provides an overview of the economic and social conditions experienced by individuals and households within a given area.

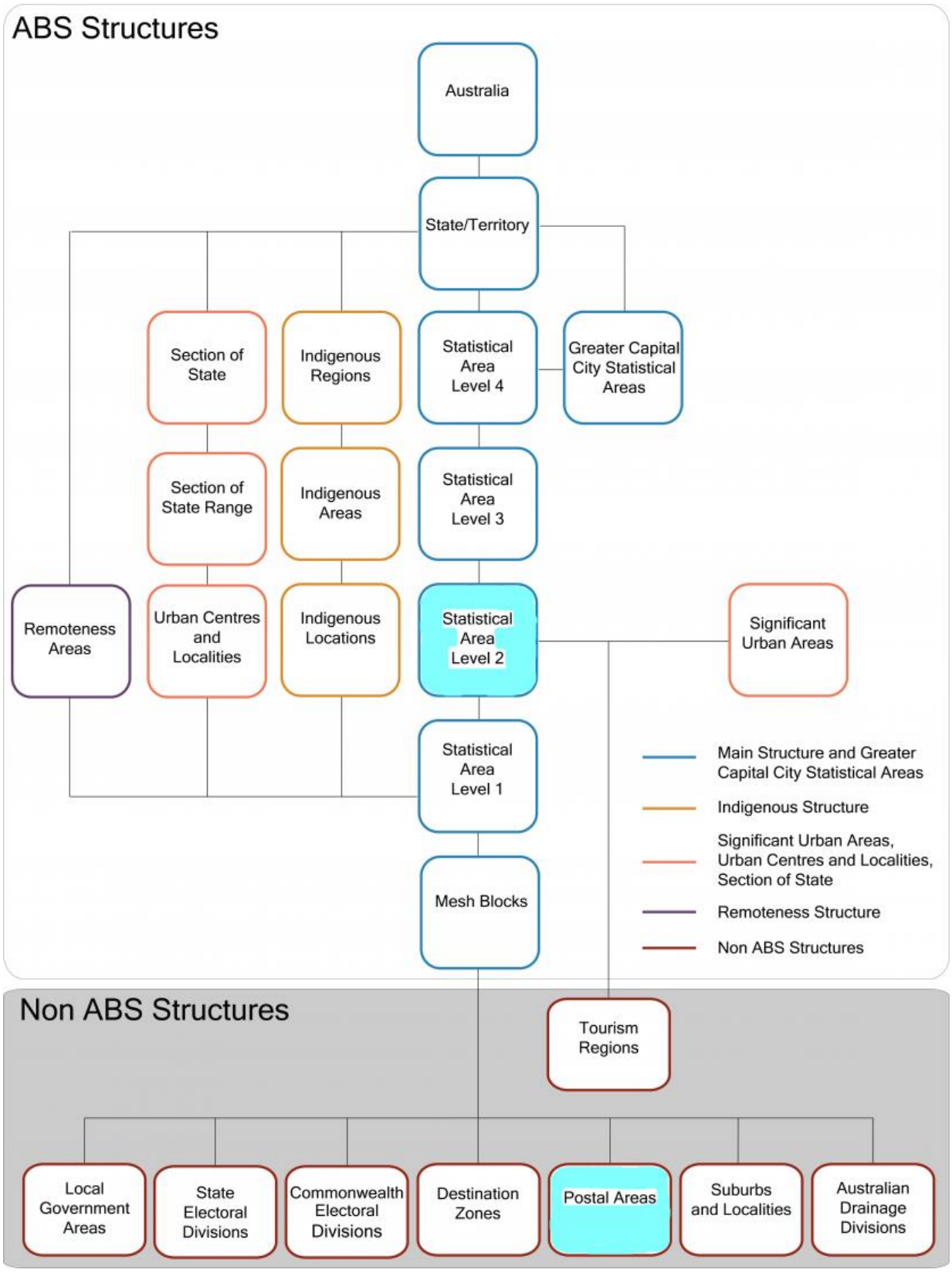

Figure 1.6: *Hierarchies of ABS and Non ABS Structures. The blue box in Non ABS and ABS Structures represents the hierarchical level of the collected data and the modified data for small area analysis. Adapted from Australia Bureau of Statistics.*

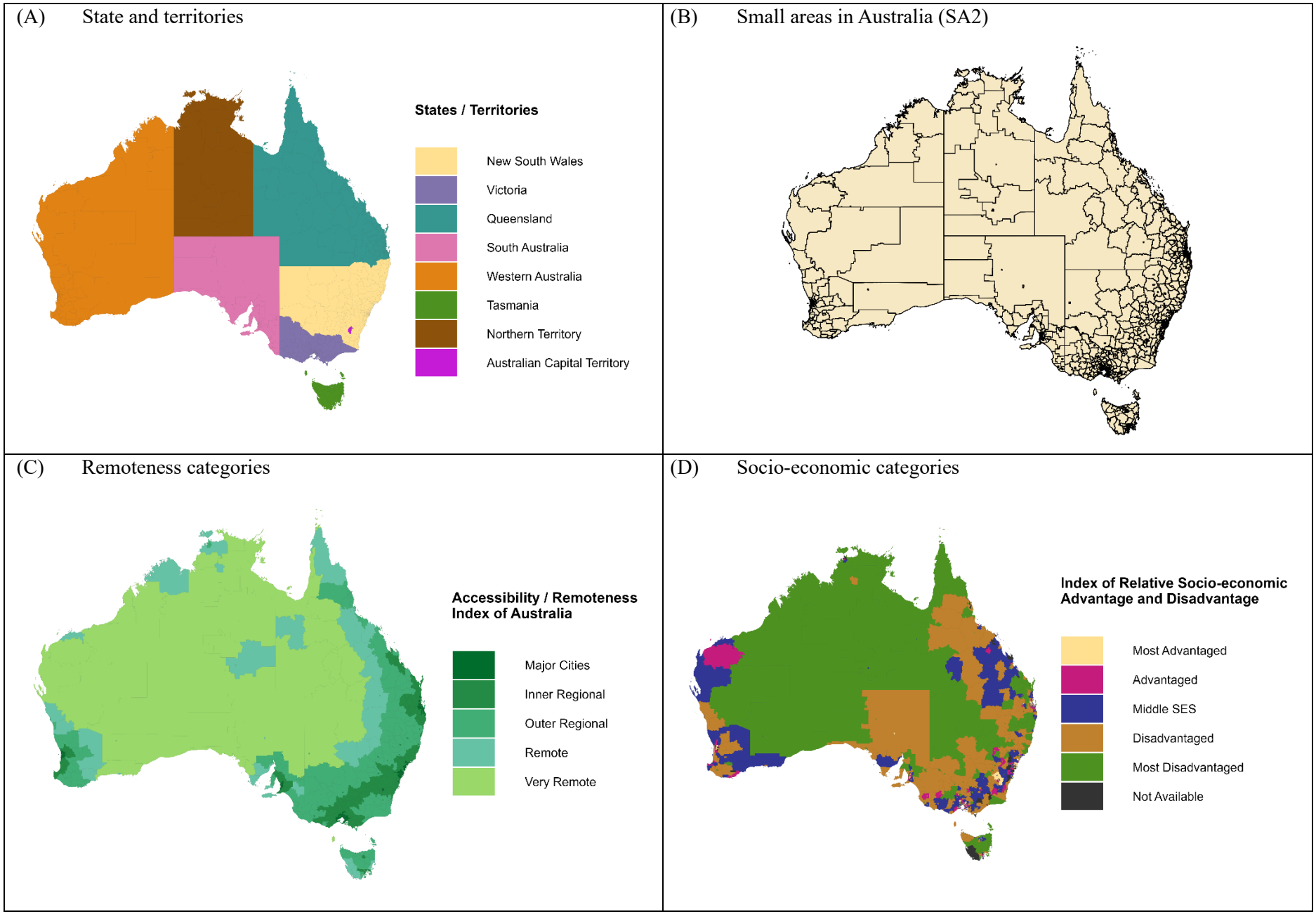

Figure 1.7: *Geographical representation of (A) States and territories, (B) Small areas, (C) Remoteness categories and (D) Socio-economic status in Australia.*

1.5 Data

1.5.1 Medicare Benefit Schedule

Prostate-specific antigen screening

The Medicare Benefits Schedule (MBS) comprises a detailed itemized list of healthcare services that are subsidized by the Australian government, aiming to provide benefits to patients seeking various health services. These benefits are available to individuals holding a Medicare card, which is exclusively issued to citizens and permanent residents of Australia.

Data from the MBS pertaining to Prostate Specific Antigen (PSA) testing among males aged 50-79 years in 10-year age groups (50-59, 60-69, 70-79) was obtained for the period of 2002-2018. Approval for the population data of PSA testing was obtained from the Department of Health and Aged Care, Australia. The dataset comprises Medicare items, which represent the Medicare services subsidized by the Australian government for prostate cancer testing. Medicare collect four items under PSA testing (66655, 66656, 66659, 66660). This study primarily focuses on the specific MBS item with code 66655, commonly referred to as "PSA screening," "screening," or "Prostate specific antigen - quantitation - 1 of this item in a 12-month period". The item number “66655” is specifically collected for the PSA test in asymptomatic men. Whereas item no 66656 is used for monitoring purposes and 66659-60 are used for follow-up of ambiguous PSA tests, generally referred to as the “free to total ratio”.

Throughout this thesis the terms “PSA testing” and “PSA screening” are used in context. Testing refers to the broad term of PSA testing and “PSA screening tests” more specifically to those tests undertaken in men without symptoms likely used for screening or case finding purposes. When using the term “screening” we are not implying a formal system and organised screening programme such as is used for bowel, breast, or cervical screening. Generally, Chapters 1, 2, and 7 will use the term "PSA testing" as it is commonly used. However, the published (or soon to be published) Chapters 3, 4, 5, and 6 begin by referring to “testing”, but use the term "PSA screening" after a description in the methods section as these chapters analyse data that are based on Item number 66655, which is considered the “de facto screening” measure.

In Australia, Medicare Benefit Schedule data have been used previously in research for various purpose. For instance, investigating differences in prostate cancer incidence, mortality and relative survival rates in relation to PSA testing (Threlfall *et al.,* 1998, Luo *et al.,* 2022), costs of diagnosing prostate cancer (Mervin *et al.,* 2017), the effect of COVID-19 on prostate cancer

testing (Jain *et al.,* 2022), factor associated with PSA testing (Nair-Shalliker *et al.,* 2018) and patterns of PSA testing by remoteness and socioeconomic status (Calopedos *et al.,* 2019).

The primary strength of Medicare data is their accuracy and reliability (Gool *et al.,* 2015). The Australian Medicare program includes over 5,700 medical services, each identified by its unique Medicare Benefits Schedule (MBS) item number. This list of Medicare items and their associated fees are regularly updated. All medical services, whether delivered in an out-of-hospital context (such as GP or specialist consultations) or within private or public hospitals, are included within the Medicare data. These data are maintained and stored by state and territory government agencies. Researchers can gain access to this valuable resource upon reasonable request (Gool *et al.,* 2015).

Notably, Australians are unable to purchase additional insurance for Medicare-eligible out-of-hospital services, making the government the exclusive insurer for such services. Additionally, the Medicare data have individual identifiers for each record, enabling individual-based analyses, instead of service-based analyses (Gool *et al.,* 2015).

The primary strength of both Medicare data sources lies in their accuracy, as these data rely on payment processes. In many instances, data collection occurs in real-time and is automated, significantly reducing the likelihood of errors. Additionally, Medicare Australia has implemented multiple processes to validate and verify the data. While not completely immune to errors, this system has proven to be more reliable than alternative self-reporting methods and is likely a more efficient approach to data collection (Gool *et al.,* 2015).

Medicare data provide accurate insights into healthcare costs and access to services, including monitoring and medication compliance. It also provides insights into the out-of-pocket costs associated with these services (Gool *et al.,* 2015).

However, there are some limitations in using Medicare data. Not all screening tests are captured in the Medicare database due to the impact of "coning". The primary purpose of establishing the Medicare database was for administrative functions rather than research oriented. Consequently, to limit the pathology benefit paid, only the three most expensive tests are documented, or "coned" within an episode of care. Additionally, the PSA test is associated with a low scheduled fee ($AUD 20.15). As a result, not all PSA tests are included in the MBS, potentially leading to a 22% coning rate for PSA tests (Trevena *et al.,* 2013). Moreover, postcodes provide the most detailed geographical information available in the Medicare data. To conduct analyses on smaller areas, such as SA2s, the data was subject to probabilistic allocation transformation, which introduces the possibility of misassigning some cases to

incorrect small areas. There are recording delays in Medicare claims data, resulting in a gap between service date and claim date (Gool *et al.,* 2015).

Converting postcodes to SA2s

Medicare enrolment requires all eligible people to provide their postal address, including postcodes, as a mandatory step (Services Australia - Enrolling 2022). Medicare records patient's enrolled postcode to assess services, rather than the location of healthcare services. Patients have the option to update their information, including their postal address, on the government website (https://my.gov.au/) under the Medicare tab (Services Australia - Medicare Update 2023). Alternatively, patients can provide an updated postal address when prompted by healthcare professionals to access services.

Since 2009, healthcare professionals have had access to Medicare details through the Health Professional Online Services (HPOS) system, particularly when patients don't have their physical Medicare card with them (Services Australia - HPOS 2023). HPOS offers a secure web portal that grants healthcare providers real-time access to various online services offered by the Department of Human Services, including the ability to look up or verify a patient's Medicare number.

However, the accuracy of a patient's Medicare enrolment postcode may not necessarily correspond to their primary residence and cannot be consistently determined (Shergold, Seidel *et al.,* 2017). For instance, people who change residences are not necessarily updating their address, or the Medicare enrolment postcode could be a PO box address. The analysis in this thesis has not been adjusted for non-updated addresses. To increase the reliability of our estimates, we excluded postcodes associated with PO boxes from our analysis. Moreover, postcodes can change over time, with new postcodes introduced, old postcodes retired, or existing postcodes modified, leading to variations in how patients are assigned to geographic regions (Australian Institute of Health and Welfare 2020).

The available geographical information in the Medicare Benefit Schedule (MBS) data was limited to postcodes. However, since the estimated resident population data, which is used as the denominator for rate calculations, was defined by the SA2 classification, concordance files between postcodes and SA2 were applied in this study. This was necessary to establish the correspondence between postcodes and SA2 boundaries. It should be noted that SA2 boundaries could span multiple postcodes, resulting in some uncertainty regarding the specific SA2 in which each individual resided. To address this, a postcode to SA2 concordance file based on the 2011 boundaries released by the ABS (Australia Bureau of Statistics 2016) was utilized. This file provided the approximate proportion of the population in each postcode that

belonged to each SA2. Simulation methods were employed to quantify the level of uncertainty associated with the final assignment of SA2. Furthermore, methodologies were developed to incorporate this uncertainty into the estimated prevalence of PSA testing for each SA2. In this thesis the term SA2 will be referred to as 'small area'.

1.5.2 Australian cancer database

Prostate cancer incidence data

We obtained prostate cancer incidence (ICD-10 C61) data from the Australian Cancer Database, which combines information from state and territory cancer registries, for all men diagnosed aged 50-79 years between 2012 and 2016. As cancer is a notifiable disease in Australia, this dataset encompasses all diagnosed prostate cancers. The data provided SA2 information using the 2011 Australian Statistical Geography Standard (ASGS) and were categorized into 5-year age groups (50-54, 55-59, 60-64, 65-69, 70-74, 75-79) for the most recent 5-year period available at the time of extraction (January 2012 to December 2016).

We limited our analysis of prostate cancer data to men aged 50-79 years to be consistent with PSA testing data, as there is a low incidence of prostate cancer among men younger than 50 years and guidelines regarding prostate cancer testing generally focus on men aged 50-69 or with at least 7 years life expectancy.

1.5.3 Estimated resident population

Population data necessary for this study for men aged 50-79 years was sourced from the Estimated Resident Population database (Australia Bureau Of Statistics 2019) maintained by the Australian Bureau of Statistics (ABS). The data was securely stored, and all analyses were conducted within the Secure Unified Research Environment (SURE) facility managed by The Sax Institute (The Sax Institute).

1.6 Motivation, aims, and structure of thesis

1.6.1 Motivation for this study

Quantifying the spatial variation in PSA testing, particularly in relation to temporal changes, will offer valuable insights into the uptake of PSA testing across the nation and identify disparities. Without this knowledge, the development of evidence-based strategies to address identified inequity in prostate cancer indicators across Australia is hindered. It is essential to interpret variations in testing rates within the framework of the actual effectiveness of PSA as a screening tool and adherence to current national guidelines. Through a collaborative effort

between the research team and the Australian Cancer Atlas project, the study's findings will be integrated into the Atlas, providing greater dissemination of results.

The primary objective of this analysis is to quantify the trends, spatial patterns, spatio-temporal patterns in PSA testing and association between PSA testing and prostate cancer incidence across Australia. This study is timely as a systematic review of prostate cancer testing guidelines is currently underway, with an expected timeline for completion by late 2024. Baseline evidence on the distribution of PSA testing tests is important for future policy and planning in this area.

1.6.2 Specific aims

1. Describe PSA testing patterns and trends by State and Territory, remoteness of residence and socio-economic status (Chapter 3).
2. To quantify how PSA testing rates vary by small geographical areas across Australia during the period following the release of the 2016 Australian clinical guidelines on PSA testing (Chapter 4).
3. To identify the change in PSA testing rates by small geographic areas over time in Australia during the period 2002-2018 (Chapter 5).
4. To quantify the association between PSA testing and prostate cancer incidence rates at the small area level in Australia for men aged 50-79 during the period 2012-2016 (Chapter 6).

1.6.3 Chronology of thesis chapters

Chapter 1 provides an overview of PSA testing and prostate cancer, covering its significance, limitations, debates, benefits, and harms. It discusses international guidelines and variations in recommendations, including changes in Australian guidelines. The chapter explores patterns of PSA testing and introduces prostate cancer development, diagnostic tests, and epidemiology. Emphasizing geographical variations, it sets the foundation for understanding complexities and controversies regarding testing for prostate cancer.

Chapter 2 presents a literature review and narrative on the methods focusing on the spatial and spatio-temporal methodologies appropriate in the analysis of small area level data. The chapter aims to explore the various modeling approaches available, with particular emphasis on kriging and Bayesian methods. It highlights the preference for Bayesian modeling due to its ability to incorporate prior information and handle confidentiality concerns. Moreover, the advantages of adopting a Bayesian framework are discussed, potentially in contrast to alternative modeling approaches. Additionally, the chapter outlines the distinction between SAR (Spatial

Autoregressive) and CAR (Conditional Autoregressive) models. It also outlines the criteria used for evaluating the goodness of fit of Bayesian models, encompassing the Watanabe-Akaike information criterion (WAIC) and Deviance information criterion (DIC). The text further addresses the identification of spatial autocorrelation following model fitting. Finally, the chapter concludes by identifying existing gaps in the literature that require further exploration.

Chapter 3 is a manuscript published in *Cancer Epidemiology* titled "Changes in prostate-specific antigen (PSA) 'screening' patterns by geographic region and socioeconomic status in Australia: Analysis of Medicare data in 50–69-year-old men." This population-based cohort study aimed to examine trends in PSA testing rates among Australian men aged 50-69 from 2002 to 2018. The study analyzed data from over 2.7 million men and assessed geographical differences across Australia, including state and territories, remoteness, and socioeconomic status. This study addressed persisting geographical disparities in prostate cancer incidence and survival, emphasizing the need for consistent diagnostic strategies regardless of location of residence.

Chapter 4 is a manuscript published in *Public Health* titled "Spatial patterns of prostate-specific antigen testing in asymptomatic men across Australia: a population-based cohort study, 2017-2018". This study provides a comprehensive analysis of the variation in prostate-specific antigen (PSA) testing across small geographical areas in Australia, focusing on categories of remoteness and socio-economic status. It is a retrospective population-based cohort study that includes data from nearly 1 million men aged 50-79 years who underwent PSA testing between 2017 and 2018. By utilizing Bayesian spatial Leroux model, the study generated smoothed indirectly standardized incidence ratios to examine the variation in PSA testing rates. Notably, this is the first population-based study to map and describe the small-area geographical variation of PSA testing in Australia.

Chapter 5 is a manuscript ready for submission titled "Spatio-temporal patterns of prostate-specific antigen testing in asymptomatic men: a population-based cohort study, Australia, 2002-2018". This retrospective population-based cohort study focuses on examining how the geographical variation in prostate-specific antigen (PSA) testing rates across Australia has changed over time from 2002 to 2018. The study utilizes data from the Medicare Benefit Schedule, involving more than 9 million men aged 50-79. By mapping postcodes to statistical area level 2 and utilizing a Bayesian spatio-temporal Separate model, standardized incidence ratios are generated for each small area and each calendar year over the study period. This study is the first of its kind to provide insights into the temporal changes in PSA testing rates at the small area level. It underscores the evolving geographic variation in PSA testing rates and

emphasizes the importance of further research to ensure equitable access to prostate cancer testing services.

Chapter 6 is a manuscript ready for submission titled “Spatial associations between prostate cancer incidence rates and prostate-specific antigen screening test use in Australia, 2012-2016: a population-based study”. This study aims to examine the relationship between prostate-specific antigen (PSA) testing and prostate cancer incidence rates at the small area level in Australia, focusing on men aged 50-79 from 2012 to 2016. The study utilizes a dataset of over 2.5 million men, combining Medicare data on PSA testing and prostate cancer incidence data from state and territory cancer registries. Using a Bayesian spatial model, the study calculates standardized incidence ratios for PSA testing and prostate cancer incidence for each small area and explores the correlation between them. The findings offer valuable insights at the local as well as at national level, highlight the need for further research to understand geographical disparities and evaluate national PSA guidelines in order to improve prostate cancer mortality rates in Australia.

Chapter 7 offers a summary of the thesis, highlighting its primary focus on examining the patterns and inequalities in prostate-specific antigen (PSA) testing for prostate cancer in Australia. The chapter starts with an introductory overview of the entire thesis, followed by a discussion on the key findings and their implications. Additionally, the strengths and limitations of the study are acknowledged. The chapter emphasizes the significance of the research findings and suggests future research directions, specifically exploring the influence of age groups on spatial and spatio-temporal PSA testing patterns.

The appendix section encompasses essential study documents necessary for the completion of the thesis. It includes ethical approval letters that were obtained for conducting the study on PSA testing and prostate cancer data. Additionally, it contains a list of conferences where presentations were made throughout the PhD candidature. Lastly, it incorporates a list of other research publications achieved during the candidature period. The purpose of the appendix is to provide detailed supporting information that supplements the main body of the thesis.

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CHAPTER 2

2 LITERATURE REVIEW OF SPATIAL AND SPATIO-TEMPORAL MODELS

2.1 Chapter Overview

Chapter 2 is a methodology-focused review chapter that outlines the diverse options and approaches currently available for modeling spatial and spatio-temporal data, and then ultimately choosing the most suitable approach for the analysis in this thesis. We are not aware that anyone has previously explored or published on the spatial or spatio-temporal patterns of prostate-specific antigen (PSA) testing. As outlined in this chapter, there are numerous available options for the analyses of these data.

In addition, this chapter highlights the advantages and disadvantages of non-modeling approaches, such as kriging, and model-based approaches, including frequentist and Bayesian methods. The chapter discusses various types of kriging methods and their assumptions. It emphasizes that kriging can be an optimal interpolator under certain conditions but has limitations when assumptions are not met or there are few observations.

The chapter then explains why the Bayesian framework is preferred in spatial modeling due to its ability to incorporate prior information and handle confidentiality and privacy concerns. It discusses the challenges associated with frequentist models and the computational obstacles in calculating likelihood for generalized linear mixed models. The chapter further categorizes spatial models into geostatistical models and lattice models and discusses simultaneous autoregressive (SAR) models for spatial variation analysis. It highlights the limitations of SAR models and introduces conditional autoregressive (CAR) models as a simpler approach for modeling autocorrelated geo-referenced areal data.

The advantages of Bayesian spatial and spatio-temporal models are discussed, including the ability to incorporate diverse sources of information, provide direct probabilistic statements, and offer reliable estimates even with limited case counts. The chapter summarizes the computational challenges of Bayesian models and discusses user-friendly software options for implementing them. The chapter concludes by discussing the importance of checking the

convergence of Markov Chain Monte Carlo (MCMC) chains in Bayesian models and provides approaches for assessing convergence. It also covers global spatial smoothing and the potential issues of oversmoothing in CAR-based models. Finally, the chapter briefly mentions Bayesian model fitting criteria, such as the Watanabe-Akaike information criterion (WAIC) and deviance information criterion (DIC), for assessing model performance.

Overall, the chapter discusses different smoothing approaches for spatial and spatio-temporal data, highlights the advantages of Bayesian models, and provides insights into model fitting and convergence assessment in spatial modeling.

2.2 Spatial data characteristics

Spatial data are commonly observed in two forms: point data, such as the addresses of patients at specific spatial locations, and areal data, which involves aggregating data over geographical subregions like counties or postal codes (Moraga *et al.,* 2017).

In Australia, postcodes are used by Australia Post for mail delivery, but they lack precise geographic boundaries (Australian Bureau of Statistics July 2021 - June 2026). While they cover most of Australia, exceptions exist, such as western Tasmania having no designated postcodes; this is because there are no people living there. To facilitate comparisons between Australian Bureau of Statistics (ABS) data and other datasets using postcodes, the ABS introduced Postal Areas (POAs) as approximations of postcode boundaries (Australian Bureau of Statistics 2016). Postal Areas exclude certain postcodes that do not pertain to street delivery areas. This category incorporates post office boxes, entries for mail back competitions, locations catering to large volume receivers, and specialized delivery postcodes. These specific postcodes are exclusively applicable to postal addresses and do not represent valid locations for population data.

POAs are integrated into the Australian Statistical Geography Standard (ASGS) as non-ABS structures, representing areas approximating administrative or environmental boundaries. POAs are created by grouping one or more Statistical Areas Level 1 (SA1s), the smallest units for Census data release, based on dwelling distribution (Australian Bureau of Statistics 2016). POAs aim to encompass all of geographic Australia, but 'Unclassified POAs' exist, representing areas not tied to specific postcodes. These are not depicted as spatial entities within POA digital boundaries. This occurs when no SA1 can be definitively linked to a specific postcode, for example, when one SA1 covers multiple postcodes, or multiple SA1s partially overlap a postcode and are allocated to different postcodes they share areas with.

According to 2021 census, the total area of Australia is 7,692,024 km², encompassing 2,644 postal areas with a population of 25,422,789 people and an average of 3.1 people per household (CYBO Company 2005-2023). The average area for postal codes in Australia is 2,910.9 km² (Range: 0.561 km² to 1,002,280.6 km²). In Australia, the average population and population density for a postal code are 9,075 (Max: 114,408) and 672.5 / km² (Max: 12,528 / km²), respectively (Australian Bureau of Statistics 2021). The average number of households per postal area is 2,927 (= 9,075 / 3.1).

In epidemiology, point data are often restricted due to concerns related to confidentiality, privacy, or ethics surrounding health records. It is crucial to address these concerns when sharing information about small numbers in small areas. As a result, areal data are commonly utilized by aggregating point data within geographical subregions (Lawson 2012). Spatial data can be sparse, particularly when dealing with smaller areas, leading to noise and unreliable estimates. To mitigate this issue, applying smoothing approaches is essential to obtain reliable estimates. Smoothing sparse data in epidemiology is critical for data visualization, estimation, addressing spatial heterogeneity, identifying clusters or hotspots with higher disease occurrences, and facilitating statistical modeling. By reducing noise and capturing underlying trends, smoothing techniques enhance model performance and improve the accuracy of predictions and inferences. This enhances the quality and reliability of data analysis, contributing to a better understanding of disease patterns and informing public health interventions. Ultimately, the objective is to comprehend the underlying patterns.

2.3 Spatial smoothing: Kriging

There are several approaches available for performing smoothing, one of which is a simple spatial smoothing technique known as kriging. This method was developed to smooth over point data, but some variants also allow for area-level data to be used.

Kriging is a geostatistical interpolation technique that reduces prediction errors by calculating a weighted average of known function values in the vicinity of a point. It involves two steps: first, fitting a variogram to account for spatial correlation, and second, using this information to predict or interpolate attribute values at unsampled locations (Bailey and Gatrell 1995). While kriging effectively filters out noise and provides uncertainty estimates in most cases, its primary purpose is not to estimate the risk within each area (Goovaerts 2005). However, kriging has some limitations. Kriging was originally developed to estimate values based on limited set of sampled data across a continuous spatial region (Shao 2011). It is sensitive to variogram model misspecification, and the assumptions of the kriging model may not be met in many

environmental exposures. Additionally, the accuracy of kriging interpolation is limited when there are few sampled observations or inadequate spatial correlation (Waller and Gotway 2004).

Kriging is considered an optimal interpolator when certain conditions are met, such as normally distributed data without trends, spatial autocorrelation, and stationarity (consistent mean and range across the study area). Table 2.1 presents various types of kriging methods and their assumptions, but it is not an exhaustive list, as different combinations are possible.

Previous studies have utilized kriging methods to examine oral cancer in men and female breast cancer in Taiwan between 1997 and 2017 (Tsai *et al.,* 2022). Kriging estimates are based on the assumption that the data are located at the centroids of areas (Nagle 2010). Kriging is particularly advantageous when the objective is data exploration, ease of use and simplicity (Lawson *et al.,* 2000). However, Bayesian methods have several advantages when more detailed inferential analyses are required (Lawson *et al.,* 2000); these are described in Section 2.4.

Sl No.	Kriging type	Assumptions
1	Simple kriging (Waller and Gotway 2004)	Most basic form of kriging that assumes a known mean.
2	Ordinary kriging (Zhang *et al.,* 2011)	Assumes that the mean and variance of the values are constant across the spatial field.
3	Universal kriging (Zhang *et al.,* 2011)	An extension of ordinary kriging that allows the mean of the values to differ for different locations, while only the variance is held constant across the entire field.
4	Block kriging (Waller and Gotway 2004)	Estimates averaged values over gridded "blocks" rather than single points.
5	Cokriging (Waller and Gotway 2004, Zhang *et al.,* 2011)	Cokriging is a multivariate linear prediction, allows additional observed variables to enhance the precision of the interpolation of the variable of interest at each location. It is best suited when co-variables are strongly correlated, and the secondary variable is more densely sampled compared with the primary variable.
6	Filtered Kriging, or kriging with measurement error (Waller and Gotway 2004)	Used for smoothing and prediction for noisy data.
7	Lognormal Kriging (Waller and Gotway 2004)	Produces optimal spatial prediction based on the lognormal distribution.

8	Trans-Gaussian kriging (Waller and Gotway 2004)	Used for spatial prediction based on transformation of data.
9	Indicator kriging (Waller and Gotway 2004)	Probability mapping based on indicator function of data.
10	Probability kriging (Waller and Gotway 2004)	Probability mapping based on indicator function of the data.
11	Disjunctive kriging (Waller and Gotway 2004)	Non-linear prediction based on univariate functions of data.
12	Bayesian kriging (Waller and Gotway 2004)	Incorporates prior information about mean and covariance into spatial predictions.
13	Binomial Cokriging (Oliver *et al.,* 1998)	Utilizes both ordinary and conditional unbiased cokriging for estimation.
14	Poisson kriging (Goovaerts and Gebreab 2008)	Used for point and area-to-area implementations to calculate incidence counts and disease rates.

Table 2.1: *Types of kriging and their assumptions.*

2.4 Spatial smoothing: Modeling

Spatial models can be categorized into two main groups: (i) Geostatistical models, which use point data, and (ii) lattice models or areal models, which use area-level data (Cressie 2015). An example of the latter is disease incidence in predefined geographic regions. Since health data are usually available by areas, we will focus on area-level models. Among the lattice models, the most commonly used are the simultaneous autoregressive (SAR) and conditional autoregressive (CAR) models (Hooten *et al.,* 2014).

2.4.1 Frequentist vs Bayesian approach

Spatially varying phenomena have been analyzed using both frequentist (classical) and Bayesian analytical methods. However, the Bayesian approach is often preferred due to its ability to incorporate information from diverse sources. Within the Bayesian framework, questions are addressed through an estimation procedure that combines multiple sources of information, such as prior knowledge and the observed data, known as the likelihood (Louzada *et al.,* 2021).

Bayesian spatial models enhance the stability and precision of estimates by incorporating information from neighboring geographical areas, resulting in smoothed estimates for small areas. This assumption relies on the notion that people residing in one area share similar characteristics, such as exposures and lifestyles, with those in nearby areas (Leroux *et al.,* 2000, Cramb *et al.,* 2020, Lines *et al.,* 2022). Bayesian models allow for ranking estimates, comparing regions, and providing reliable estimates with associated uncertainty (Kang *et al.,* 2016). Numerous Bayesian spatial models are available, differing in terms of neighbor definition, model specification, smoothing type, and parametric or semi-parametric forms (Leroux *et al.,* 2000, Cramb *et al.,* 2020). The selection of final models will involve assessing multiple options and comparing their suitability based on goodness of fit, plausibility of estimates, computational time, and feasibility (Kang *et al.,* 2016). Smoothing is desirable as it reduces estimation uncertainty and reveals underlying spatial trends that may otherwise be obscured by noise and other variables (Cramb *et al.,* 2020).

When mapping diseases, employing a Bayesian approach offers numerous advantages. It allows for direct probabilistic statements, such as estimating the probability of increased disease risk in a specific area (Kang *et al.,* 2016). The utilization of prior distributions ensures reliable and robust estimates, even in scenarios with limited case counts in a particular area, as they provide well-defined and stable results (Kang *et al.,* 2016).

2.4.2 Simultaneous autoregressive (SAR) models

Simultaneous autoregressive (SAR) models have a general objective of revealing and quantifying spatial variation within data, providing summaries of geographical areas by identifying spatial clustering and evaluating the influence of explanatory variables on quantities of interest. SAR models are capable of simultaneously modeling the distribution of predicted values. Detailed discussions on SAR models can be found in the works of Anselin (1988), Haining (1990) and Cressie (1993). SAR models have found applications in various fields such as ecology, epidemiology, sociology, and environmental science, particularly for data with areal spatial support. It is worth noting that any SAR model can be represented as a CAR model, but the reverse is not necessarily true.

In classical mixed model framework, we consider a dataset $y = (y_1, y_2, \dots, y_n)^T$ that originates from a data-generating process incorporating both first-moment (mean) and second-moment (covariance) structures, where they exhibit linear relationships with a set of covariates x_i for $i = 1, 2, \dots, n$ along with additive components. An autoregressive model can be formulated as:

$$y = X\beta + z + \epsilon$$

Here β represents the coefficient vector, z denotes the structured random effect, and ϵ represents the unstructured error term. In mixed model specifications, it is common to assume normality for z and ϵ due to the ease of implementation and inference. The covariance matrixΣ_z, for the autoregressive process can be expressed as:

$$\sum\nolimits_z = \sigma_z^2((I - B)(I - B^T))^{-1}$$

In this equation, the diagonal matrix is considered as the identity matrix I and B captures the second-moment dependence in the process.

SAR models have certain drawbacks, as they are more suitable for maximum likelihood estimation or cases with second-order dependency and global spatial autocorrelation, but not well-suited for MCMC fitting of Bayesian models (Shekhar and Xiong 2007). Furthermore, SAR models do not adhere to the spatial version of the Markov property, which assumes that a given geographical area is influenced only by its immediate neighbors and not by neighbors of neighbors. In situations where the spatial Markov property holds, conditional autoregressive (CAR) models offer a simpler approach to modeling autocorrelated geo-referenced areal data (Goodchild and Haining 2004).

2.4.3 Conditional autoregressive (CAR) models

Global spatial smoothing refers to the application of consistent smoothing parameters across the entire region (Lee and Mitchell 2012). Conditional autoregressive (CAR) models, a type of global spatial model, assume a common variance for the smoothing term across the entire region while also permitting local smoothing of estimates in neighboring areas (Kang *et al.,* 2016). This approach is appropriate when a consistent spatial trend exists across the region, although it may not hold true for large areas that exhibit spatial heterogeneity.

While global CAR-based models are straightforward to implement using various software, they have drawbacks. One such disadvantage is the potential for oversmoothing, where discontinuities between adjacent areas are smoothed over. Oversmoothing can be defined as the process of hiding the underlying spatial patterns. The extent to which oversmoothing occurs may depend on the specific context and the objectives of the analysis. For all CAR-based models, the strength of the partial autocorrelation depends on the number of neighbouring areas rather than on any underlying relationship (Lee and Mitchell 2013). Table 2.2 provides details of Bayesian spatial models using global spatial smoothening.

Sl. No.	Bayesian Spatial Models	Key Features	Advantage / Disadvantage
Conditional autoregressive (CAR) models: Global smoothing			
1	Intrinsic CAR	Structured spatial random effect is the only random effects.	Unstructured random effect is not considered thus have tendency to oversmooth estimates and can produce biased parameter estimates.
2	BYM model (Besag *et al.,* 1991)	Random effects will be the sum of structured and unstructured spatial random effects.	The two separate random effects components cannot be individually identified – only their sum is identifiable.
3	Modified BYM or BYM2 model (Simpson *et al.,* 2017)	Enables the use of meaningful penalized complexity priors and addresses the scaling issue of the original BYM model by incorporating a scaled spatially structured component and an unstructured component.	It allows for an intuitive parameter interpretation and facilitates prior assignment.
4	Leroux model (Leroux *et al.,* 2000)	Requires only a single set of random effects.	A single set of random effects incorporates both structured and unstructured random effects thus avoiding identifiability issues.
5	Proper CAR model (Besag 1974)	Precision matrix is redefined because the joint distribution becomes improper due to the singularity of the precision matrix.	It may limit the breadth of the posterior spatial pattern. For a reasonable amount of spatial association, ρ is likely to be very close to 1.
Variant of CAR models: Local smoothing			
6	CAR dissimilarity models (Lee and Mitchell 2012)	The spatial weights matrix are modeled to reduce the partial autocorrelations between certain adjacent random effects.	Excluding covariates can ensure the spatial structure is consistent in both the risk surface and the random effects surface.
7	Weighted sum of spatial priors (Lawson and Clark 2002)	An extension to the BYM model, which incorporates both a spatially structured component and an unstructured spatial component.	Model allows for the detection of abrupt discontinuities.
8	Leroux scale mixture model (Congdon 2017)	It combines a scale mixture model with a Leroux prior.	If $\rho = 0$, this reduces to an unstructured independent and identically distributed scale mixture.
9	Skew-elliptical areal spatial models (Nathoo and Ghosh 2013)	Two versions were proposed, first aims to ensure each random effect parameter has a skew-elliptical distribution. Second, it uses an approximation to a Dirichlet process to allow for data-driven	It accommodates uncertainty in the mixing structure, and gives greater flexibility in the tail behaviour of marginal distributions.

		departures from the parametric version.	
10	Localised autocorrelation or cluster model (Lee and Sarran 2015)	The random effects are spatially smoothed and augmented with a piecewise constant intercept.	The clustering is solely non-spatial, while the CAR prior on the Structured spatial random effects term accounts for spatial autocorrelation.
11	Locally adaptive model (Lee and Sarran 2015)	The boundaries between areas are not identified using additional information, and the spatial weights matrix is binary.	It is more computational feasible compared to existing boundary analysis methods because spatial weights matrix is updated at each iteration.
Other models: Global smoothing			
12	Geostatistical model (Clements *et al.,* 2006)	The residual spatial structure in this model is represented by a Gaussian process.	By setting the upper and lower bounds of rate of decay, a range of possible values for the spatial correlation is considered in the model.
13	Global spline models (Lang and Brezger 2004)	Model assumes that the incidence cases (counts) are located at the centroid of each area.	The coefficients are penalized to control for the level of "wiggliness" through a penalty matrix.
Other models: Local smoothing			
14	Hidden Potts model (Green and Richardson 2002)	Model the spatial random effect on the log scale as K-components mixture model.	Model impose discontinuities on the risk surface, potentially leading to unrealistic representations. However, it is computationally challenging as the spatial grid size increases.
15	Spatial partition model (Knorr-Held and Rasser 2000)	Similar to Hidden Potts model but the clusters and the specifications of the hyperpriors are defined differently.	Model assume a constant relative risk within each cluster, which may not accurately capture the underlying variability.
16	Local spline models (Goicoa *et al.,* 2012)	An expansion of the global spline models. It involves the incorporation of unstructured random effects.	The random effect vector follows a multivariate normal distribution, capturing the unstructured heterogeneity.

Table 2.2: *Types of Bayesian spatial model, their advantages/disadvantages.*

Intrinsic CAR model

The intrinsic conditional autoregressive (ICAR) is a subclass of CAR model that is widely used and consider global smoothing over the neighbors of area. This model is employed when the areal data comprises a single aggregated measure per areal unit, such as a binary, count, or continuous value. The model specifies the following set of conditional distributions for the spatial random effect parameter (Besag *et al.,* 1991):

$$\mathrm{R}_i = \mathrm{S}_i \; for \; areas \; i = 1, \ldots, N$$

$$S_i | s_{\setminus i} \sim \mathcal{N}\left(\frac{1}{\sum_j w_{ij}} \sum_j w_{ij} s_j, \frac{\sigma_s^2}{\sum_j w_{ij}}\right)$$

$$w_{ij} = \begin{cases} 1 & \text{if areas } i \text{ and } j \text{ are adjacent} \\ 0 & \text{otherwise} \end{cases}$$

Here, S_i is structured spatial random effects and w_{ij} is the element of a spatial weights matrix. This model implies that the conditional expectation of S_i is equal to the mean of the random effects at neighbouring locations. Alternatives to ICAR model are possible and one of them is the Proper CAR model, which will be discussed later in the chapter.

BYM Model

One of the most popular model used in disease mapping is the Besag, York and Mollié (BYM) model (Besag *et al.,* 1991). Successfully applied in the Atlas of Cancer in Queensland report (Cramb *et al.,* 2011), the BYM model includes both an ICAR component for spatial smoothing and an ordinary random-effects component for non-spatial heterogeneity. Including an unstructured effect as well as the structured effect helps minimise biases in parameter estimates (Latouche *et al.,* 2007). Here the random effect parameters will be the sum of structured and unstructured spatial random effects.

$$\mathrm{R}_i = \mathrm{S}_i + \mathrm{U}_i$$

$$U_i \sim \mathrm{N}(0, \sigma_U^2)$$

A disadvantage of this model is that the two separate random effects components cannot be individually identified only their sum is identifiable (Eberly and Carlin 2000). This model has also been widely applied in mapping cancers, including investigating factors associated with skin cancers in Germany during 2009-2015 (Augustin *et al.,* 2018).

Modified BYM or BYM2 model

A new modification was proposed to the parametrization of the BYM model, known as BYM2, which improves the identifiability and interpretability of the model's parameters. BYM2 also enables the use of meaningful Penalized Complexity priors and addresses the scaling issue of the original BYM model by incorporating a scaled spatially structured component (u_*) and an unstructured component (v_*) (Simpson *et al.,* 2017). In BYM2, the random effect (b) is defined as:

$$b = \frac{1}{\sqrt{T_b}}\left(\sqrt{1-\phi}v_* + \sqrt{\phi}u_*\right)$$

with a covariance matrix given by:

$$Var(b|T_b, \phi) = T_b^{-1}((1-\phi)I + \phi Q_*^-$$

Here Q_* is the precision matrix of the Besag model that is scaled to provide a modified version of the random effect.

In this formulation, the precision parameter ($T_b > 0$) controls the contribution of the weighted sum of u_* and v_* to the marginal variance. The mixing parameter ($0 \geq \phi \leq 1$) measures the proportion of the marginal variance explained by the structured effect u_* (Moraga 2019). The spatial random effect (b) represents a compromise between pure overdispersion and spatially structured correlation, with ϕ indicating the proportion of the marginal variance explained by the structured effect. The BYM2 model can be considered as a purely spatial model (BYM) when $\phi = 1$, and it reduces to pure overdispersion with only unstructured spatial noise when $\phi = 0$ (Riebler *et al.,* 2016, Moraga 2019).

By using the standardized Q_*^- and the scaled structured effect (u_*), the marginal variances become approximately equal to $\frac{1-\phi}{T_b} + \frac{\phi}{T_b}$. The scaling of the random effect b and the interpretation of the prior imposed on T_b are consistent in this formulation. Moreover, the hyperparameters T_b and ϕ are now interpretable and no longer confounded (Riebler *et al.,* 2016).

This model was used to determine the spatial incidence of cervical cancer and the risk factors among HIV positive women in South Africa during 2004-2014 (Tafadzwa *et al.,* 2021).

Leroux model

Another alternative to the BYM, which allows a single set of random effects, is the Leroux model.

The Leroux model requires only a single set of random effects (Lee 2011), thus avoiding identifiability challenges (Riebler *et al.,* 2016), but allows for both spatial and non-spatial smoothing like the BYM. The conditional distribution of Si under the Leroux model can be expressed as:

$$S_i|s_{\setminus i} \sim \mathcal{N}\left(\frac{\rho\sum_{j=1}^{N} w_{ij}s_j + (1-\rho)\mu_0}{\rho\sum_j w_{ij} + 1 - \rho}, \frac{\sigma_s^2}{\rho\sum_j w_{ij} + 1 - \rho}\right)$$

The precision matrix can be written as:

$$T = \frac{1}{\sigma_S^2}[\rho(D - W) + (1 - \rho)I]$$

Consequently, S_i has a conditional expectation that combines a weighted average of both the independent random effects and the spatially structured random effects.

The difference between the Leroux model and the BYM2 model lies in the inclusion of the factor ϕ, which is calculated based on the spatial structure of the data (Riebler *et al.,* 2016). It should be noted that the Leroux model cannot be scaled due to its construction, as the scaling would depend on the value of ϕ.

This model has been previously applied to describe spatial changes by small area in cervical cancer screening rates in Queensland state of Australia, during 2008-2017 (Dasgupta *et al.,* 2020), and also in the Australian Cancer Atlas (https://atlas.cancer.org.au).

Proper CAR model

The Proper CAR model uses the full conditionals for the ICAR model, but due to the singularity of the precision matrix, the joint distribution becomes improper (Besag 1974). There are certain disadvantages associated with the Proper CAR prior. One potential disadvantage is that it may limit the breadth of the posterior spatial pattern (Banerjee *et al.,* 2003). Additionally, for a moderate level of spatial association, ρ is expected to be close to 1 (Banerjee *et al.,* 2003). This model has been used to analyse the small area spatial pattern of cancer mortality in Spain and its association with social inequalities during 2002-2013 (Santos-Sánchez *et al.,* 2020).

2.4.4 Variant of CAR models

While all the previous CAR models described uses global smoothing, assuming the same level of smoothing across the entire region of interest, variants have been developed to allow for discontinuities in smoothing to occur. 'Local' spatial smoothing models allows for differential smoothing depending on neighbourhood characteristics. There are many options available, and more being developed, but some commonly used approaches are described further in this section and are listed in Table 2.2.

CAR dissimilarity models

This model is based on the Leroux conditional autoregressive (CAR) prior (Lee and Mitchell 2012), with ρ set to be 0.99 to ensure strong global spatial smoothing. In this model, the elements in the weight matrix (W) are modeled to reduce the partial autocorrelations between

certain adjacent random effects (Lee and Mitchell 2012). The approach allows for both binary and non-binary elements in W.

When this model bases discontinuities on a characteristic of the areas (for instance, socioeconomic status), then this characteristic should not also be included as a covariate, to ensures that the spatial structure is consistent in both the risk surface and the random effects surface (Lee and Mitchell 2012). This model was applied to Pennsylvania Cancer Registry data to study prostate cancer incidence during 2000-2011 in both Pennsylvania and Philadelphia at county level (Wang *et al.,* 2017).

Weighted sum of spatial priors

An extension was introduced to the BYM model, which incorporates both a spatially structured component, denoted as S_i, and an unstructured spatial component, denoted as U_i (Lawson and Clark 2002). This extension allows for the detection of abrupt discontinuities. The augmented model can be expressed as:

$$R_i = p_i S_i + (1 - p_i) Z_i + U_i$$

It is important to note that when $p_i = 1$, the model reduces to the original BYM model. Conversely, when $p_i = 0$, the model exhibits complete discontinuity.

This method was used to address the spatial variation in incidence of cervical cancer at municipalities level in San Luis Potosí, a state in Mexico (Terán-Hernández *et al.,* 2016).

Leroux scale mixture model

A new model was proposed, which incorporates a scale mixture model with a Leroux prior (Congdon 2017). Specifically, modifications were made to the normality assumption for area random effects by incorporating a scale mixture version of the Leroux model. This modification enables the model to handle both heterogeneity and clustering within a single set of random effects. Additionally, the scale mixture component introduces adaptivity to local discontinuity and spatial outliers, enhancing the model's robustness and ability to capture complex spatial patterns.

Skew-elliptical areal spatial models

In this model, the observed response R_i is defined as:

$$R_i = \eta_i^{-\frac{1}{2}} (\delta |Z_i| + S_i)$$

where $\delta|Zi|$ represents the skewing component, with Zi denoting a set of skewing variables drawn independently from a standard normal distribution. η serves as a scale mixing parameter, and S_i follows a Conditional Autoregressive (CAR) model. Two versions of the model were proposed. The first version aims to ensure that each R_i follows a skew-elliptical distribution, where the marginal distribution for each spatial effect belongs to the skew-t family of distributions (Nathoo and Ghosh 2013). The second version is a semiparametric approach that utilizes an approximation to a Dirichlet process. This allows for data-driven deviations from the parametric version, accommodating uncertainty in the mixing structure and providing greater flexibility in the tail behavior of marginal distributions (Nathoo and Ghosh 2013).

Localised autocorrelation

The random effects in this model are spatially smoothed and augmented with a piecewise constant intercept, known as a cluster model. This allows for significant changes in the mean surface between adjacent areas if they belong to different clusters. The approach involves partitioning the areas into a maximum clusters approach (Lee and Sarran 2015). We must specify the maximum number of clusters, but model may choose to use fewer clusters. It is important to note that the clustering is solely non-spatial, while the CAR prior on the S_i term accounts for spatial autocorrelation (Lee and Sarran 2015).

Locally adaptive model

A similar approach to the dissimilarity model described above is used in this thesis, but with some differences. Here, the boundaries between areas are not identified using additional information, and the w_{ij} values are binary only (Lee and Sarran 2015). The model is based on the Leroux CAR model with $\mu_0 = 0$ (Lee and Mitchell 2013).

In this model, ρ can be estimated or fixed at a specified value, typically recommended as 0.99 (Lee and Mitchell 2013). The spatial weights matrix, W, initially takes the form of a binary, first-order adjacency matrix. However, this matrix is updated at each iteration, allowing the weights corresponding to neighbors to be estimated as either 1 or 0. By estimating weights only for neighboring areas, this approach offers improved computational feasibility compared to areal wombling (Lu *et al.,* 2007), where all values in W, are estimated.

2.4.5 Other model: Global smoothing

There are alternatives to the CAR priors as well, which were developed for point level data, so assume all cases occur at the centroid of areas. Options include the geostatistical model, spline

based areal distance smoothing, but these are quite difficult to work on in the Australian context with dramatically varying area sizes.

Geostatistical model

The residual spatial structure in this model is represented by a Gaussian process using a geostatistical design (Clements *et al.,* 2006). The random effects follow a Gaussian distribution. This model was applied to investigate the spatial variation and affecting factors of Gastric cancer in Shanxi, China, 2014-2016 (Zhang *et al.,* 2018).

Global spline models

Two primary methods used in spline modeling are smoothing splines and P-splines (MacNab 2007). Smoothing splines are penalized splines that incorporate knots at all data points. On the other hand, P-splines allow for a reduced number of knots and are typically formulated as penalized spline regressions using a "difference penalty" based on coefficients of adjacent B-spline bases or other spline bases (MacNab 2007).

This model was used to identify spatial variation in breast cancer survival patients in New Jersey, USA, between 2010-2014 (Wiese *et al.,* 2019), and at geographic variation in colon cancer survival among patients from 2006 to 2011 using cancer registry data of New Jersey, USA (Wiese *et al.,* 2020).

2.4.6 Other models: Local smoothing

Hidden Potts model

The aim of this model is to represent the relative risk as a mixture model with K components (Green and Richardson 2002). Each component represents a distinct risk category, and the assignment of areas to components follows a spatially correlated process. This model was used to map colorectal cancer incidence at county-level and identify risk factors associated with the colorectal cancer incidence in Florida, 2018 (Dagne 2022).

Spatial partition model

The spatial partition models, which are closely related to the Hidden Potts model, share similarities but have distinct characteristics (Knorr-Held and Rasser 2000, Denison and Holmes 2001). Like the Hidden Potts model, they involve K clusters of non-overlapping areas, with each cluster representing a constant relative risk. The value of K is unknown and estimated by the model (Best *et al.,* 2005). However, the main differences lie in how the clusters are defined and the specifications of the hyperpriors (Best *et al.,* 2005).

It is important to note that both the Hidden Potts model and the spatial partition models have faced criticism. One criticism is that they impose discontinuities on the risk surface, potentially leading to unrealistic representations. Additionally, these models assume a constant relative risk within each cluster, which may not accurately capture the underlying variability (Lawson and Clark 2002).

This method was applied to analyse late-stage diagnosis of breast cancer risks among women in Illinois, USA in 2000 (Wang *et al.,* 2012).

Local spline models

An expansion of the global spline models mentioned earlier, aimed at achieving a less smooth surface, involves the incorporation of unstructured random effects known as the Penalized Random Individual Dispersion Effects model (Perperoglou and Eilers 2010).

$$R_i = f(c_{1i}, c_{2i}) + \gamma_i$$

The random effect vector γ_i follows a multivariate normal distribution, capturing the unstructured heterogeneity. The covariance matrix of the random effects includes an identity matrix multiplied by a variance component, along with the eigenvalues obtained from the P-spline model component (Goicoa *et al.,* 2012).

This model was used to predict prostate cancer mortality cases in regions of Spain during 1975-2008 (Etxeberria *et al.,* 2015).

2.4.7 Bayesian model applied to other topics

The Bayesian modeling approach has not only been applied to cancer-related topics but has also been extensively applied in other areas of health research. For instance, the utilization of Bayesian hierarchical models has facilitated meta-analyses examining the occurrence and prevalence of psoriasis (Parisi *et al.,* 2020). Additionally, a Bayesian hierarchical model was employed to determine the prevalence of metabolic syndrome among children and adolescents (Noubiap *et al.,* 2022). Bayesian regression models were utilized to gain insights into the care experiences of individuals with cancer who received mental health services (Lines *et al.,* 2022). The Bayesian approach was also employed to estimate the global prevalence of dry eye disease, as well as its prevalence within specific sub-groups (Papas 2021). Furthermore, Bayesian multivariate regression analysis was employed to estimate national health expenditures pertaining to healthcare services (Schneider *et al.,* 2021). Moreover, there is an increasing interest in utilizing Bayesian spatial models in meta-analyses of brain imagery. This application

aims to pinpoint regions of consistent activation in the brain, which can be valuable for diagnosis and treatment purposes (Kang *et al.,* 2011).

2.5 Spatio-temporal smoothing: Modeling

In this section, Bayesian spatial models are expanded by incorporating a temporal component to investigate the changes in prevalence and geographical patterns of PSA testing over time. We will develop, evaluate, and apply Bayesian spatio-temporal models using a methodology similar to that employed for the spatial models. The general hierarchical model utilized for fitting spatio-temporal data is expressed as follows:

$$Y_{kt}|\mu_{kt} \sim f(y_{kt}|\mu_{kt}, v^2) \qquad for\ k = 1, \dots, K\ areas, \quad t = 1, \dots, N\ time\ points$$

$$g(\mu_{kt}) = x_{kt}^T\beta + O_{kt} + \psi_{kt}$$

$$\beta \sim N(\mu_\beta, \Sigma_\beta)$$

Here, μ_{kt} represents the expected value of Y_{kt}. The regression parameters β are represented as a vector, and they follow a multivariate Gaussian prior distribution. The term ψ_{kt} represents a latent component associated with a specific areal unit (*k*) and time period (*t*), which encompasses one or more collections of spatio-temporally autocorrelated random effects. These random effects are denoted by

$$\psi = (\psi_1, \dots, \psi_N), \text{ where } \psi_t = (\psi_{1t}, \dots, \psi_{kt})$$

Further, an overview of the range of univariate spatio-temporal models incorporating space-time random effects are presented (Table 2.3).

2.5.1 Spatio-temporal models: Global spatial smoothing

Linear models

The model presented is an alteration of the one proposed by Bernardinelli in 1995 (Bernardinelli *et al.,* 1995). It introduces the estimation of autocorrelated linear time trends for each areal unit and this model is suitable when the objective is to estimate the areas that demonstrate increasing or decreasing linear trends in the response variable over time. The random effects for this model include the following structure:

$$\psi_{kt} = \phi_k + (\alpha + \delta_k)\frac{t - \bar{t}}{N}$$

The random effects $\phi = (\phi_1, \ldots, \phi_K)$ and $\delta = (\delta_1, \ldots, \delta_K)$ are modeled by Leroux prior. Here t represents the time period, and N is the total time period, and α is the overall slope parameter.

This model was used to analyze stomach cancer incidence for people living in Southern Portugal between 1998 and 2006 (Papoila *et al.,* 2014). In practice, most area estimates do not change monotonically, which makes the model less reliable, especially for prostate cancer and PSA testing which exhibit substantial temporal fluctuations. Therefore, we need to consider alternative models, such as ANOVA or separate spatial models, because of their advantages in incorporating space-time interactions or a separate spatial surface at each time period, compared to the linear model.

ANOVA models

This model is an alteration of the one proposed by Knorr-Held in 2000 (Knorr-Held 2000). It breaks down the spatio-temporal variation in the data into an overall spatial effect shared across all time periods, an overall temporal trend shared across all spatial units, and a set of independent space-time interactions. The spatio-temporal autocorrelation is modelled by a common set of spatial random effects ϕ and a common set of temporal random effects δ, and both are modelled by the CAR prior proposed by Leroux (Leroux *et al.,* 2000). The model can incorporate an optional set of independent space-time interactions γ. Additionally, ρ_S, ρ_T are the dependence parameters and $\tau_S^2, \tau_T^2, \tau_I^2$ are the variance parameter. This model is suitable when the objective is to estimate overall time trends and spatial patterns. However, the random effects calculations in ANOVA model involve three terms, making the model more complex compared to a separate spatial model. The model formulation is as follows:

$$\psi_{kt} = \phi_k + \delta_t + \gamma_{kt}$$

$$\phi_k | \phi_{-k}, W \sim N\left(\frac{\rho_S \sum_{j=1}^{K} w_{kj}\phi_j}{\rho_S \sum_{j=1}^{K} w_{kj} + 1 - \rho_S}, \frac{\tau_S^2}{\rho_S \sum_{j=1}^{K} w_{kj} + 1 - \rho_s}\right)$$

$$\delta_t | \delta_{-t}, D \sim N\left(\frac{\rho_T \sum_{j=1}^{N} d_{tj}\delta_j}{\rho_T \sum_{j=1}^{N} d_{tj} + 1 - \rho_T}, \frac{\tau_T^2}{\rho_T \sum_{j=1}^{N} d_{tj} + 1 - \rho_T}\right)$$

$$\gamma_{kt} \sim N(0, \tau_I^2)$$

$$\tau_S^2, \tau_T^2, \tau_I^2 \sim \text{InverseGamma}(a, b)$$

$$\rho_S, \rho_T \sim \text{Uniform}(0, 1)$$

$$\phi = (\phi_1, \phi_2, \ldots, \phi_K),$$

$$\delta = (\delta_1, \delta_2, \dots, \delta_N)$$

$$\gamma = (\gamma_{11}, \gamma_{12}, \dots, \gamma_{KN})$$

This model was used to evaluate breast cancer incidence in 30 provinces of Iran during 2004-2008 (Jafari-Koshki *et al.,* 2014).

Separate spatial models

The separate spatial model is a generalisation of the one proposed by Napier in 2016 (Napier *et al.,* 2016). It represents the data as an overall temporal trend and separate spatial surfaces for each time period. These spatial surfaces share a common spatial dependence parameter but have different spatial variances.

In this model, an overall temporal trend δ is fitted to the data, which is common to all areal units. Additionally, at each time period t, a separate (uncorrelated) spatial surface ϕ_t is introduced. The overall temporal trend and each spatial surface are modeled using the conditional autoregressive (CAR) prior suggested by Leroux in 2000 (Leroux *et al.,* 2000). The spatial surfaces have a common spatial dependence parameter ρ_S but their variance parameter τ_T^2 varies over time.

The collection of variance parameters $(\tau_1^2, \dots, \tau_N^2)$ allows for an examination of the changes in the magnitude of spatial variation in the data over time. This model is suitable when the objective is to estimate both a common overall temporal trend and the degree to which the spatial variation in the response has changed over time. The separate spatial model has the advantage of being parsimonious, requiring fewer terms to calculate random effects. The model specification is provided below.

$$\psi_{kt} = \phi_{k_t} + \delta_t$$

$$\phi_{kt} | \phi_{-kt}, W \sim N\left(\frac{\rho_S \sum_{j=1}^{K} w_{kj}\phi_{jt}}{\rho_S \sum_{j=1}^{K} w_{kj} + 1 - \rho_S}, \frac{\tau_t^2}{\rho_S \sum_{j=1}^{K} w_{kj} + 1 - \rho_s}\right)$$

$$\delta_t | \delta_{-t}, D \sim N\left(\frac{\rho_T \sum_{j=1}^{N} d_{tj}\delta_j}{\rho_T \sum_{j=1}^{N} d_{tj} + 1 - \rho_T}, \frac{\tau_T^2}{\rho_T \sum_{j=1}^{N} d_{tj} + 1 - \rho_T}\right)$$

$$\tau_1^2, \dots, \tau_N^2, \tau_T^2 \sim \text{InverseGamma}(a, b)$$

$$\rho_S, \rho_T \sim \text{Uniform}(0, 1)$$

$$\phi_{-k,t} = (\phi_{1,t}, \ldots, \phi_{k-1,t}, \phi_{k+1,t}, \ldots, \phi_{K,t})$$

$$\delta = (\delta_1, \delta_2, \ldots, \delta_N)$$

$$\phi_t = (\phi_{1t}, \ldots, \phi_{Kt})$$

This model was employed to analyze the spatio-temporal pattern of hospital admissions involving patients diagnosed with both cancer and dementia in New York State from 2007 to 2017 (Liu *et al.,* 2021).

Autoregressive models

Two versions of the Autoregressive model exist, distinguished by their utilization of either a first-order or second-order temporal autoregressive process. The model proposed by Rushworth (Rushworth *et al.,* 2014) captures the spatio-temporal structure through a multivariate first-order autoregressive process. This model incorporates a precision matrix that exhibits spatial autocorrelation. The second model builds upon the first model by including a multivariate second-order autoregressive process, which also utilizes a precision matrix demonstrating spatial autocorrelation. These models are particularly suitable when the objective is to estimate the changes in the spatial random effects surface over time. By applying these models, valuable insights can be gained regarding the variations in spatial patterns and random effects across different time periods. The random effects for first order temporal autoregressive process is given by:

$$\psi_{kt} = \phi_{k_t}$$

$$\phi_t | \phi_{t-1} \sim \mathrm{N}(\rho_T \phi_{t-1}, \tau^2 Q(W, \rho s)^{-1}) \qquad t = 2, \ldots, N$$

The vector $\phi_t = (\phi_{1t}, \ldots, \phi_{kt})$ represents the random effects at time period t. $Q(W, \rho_S)$ is the precision matrix, $\rho s \; and \; \rho_T$ are the dependence parameters. τ^2 is the variance parameter.

2.5.2 Spatio-temporal models: Local spatial smoothing

Adaptive models

This model is an extension of the earlier described Autoregressive model. It is also proposed by Rushworth (Rushworth *et al.,* 2017) to incorporate spatially adaptive smoothing. This model is suitable when the residual spatial autocorrelation in the response, after accounting for the covariates, remains consistent over time but exhibits a localized structure. In other words, autocorrelation may be strong in certain parts of the study region while weak in others. Autoregressive random effects in the model follows a similar structure to the first-order

Autoregressive model. However, the key distinction lies in the presence of a single level of spatial dependence in autoregressive model that is controlled by the parameter ρ_S, which accounts for the spatial variability in the model.

$$\psi_{kt} = \phi_{k_t}$$

$$\phi_t|\phi_{t-1} \sim \mathrm{N}(\rho_T\phi_{t-1}, \tau^2 Q(W, \rho s)^{-1}) \qquad t = 2, \ldots, N$$

The model allows for localized spatial autocorrelation by introducing correlation or conditional independence among spatially neighboring random effects, which induces smoothness.

This model was used to investigate spatiotemporal patterns of the incidence in breast and cervix uteri cancers in Iranian women during 2004-2009 (Raei *et al.,* 2019).

Localised models

The localised model was proposed by Lee and Lawson in 2016 (Lee and Lawson 2016), and enhances the smooth spatiotemporal variation in Autoregressive models by incorporating a piecewise constant intercept process ($\lambda_{Z_{kt}}$). The random effects $\phi_t = (\phi_{1t}, \ldots, \phi_{kt})$ at time period t is modeled by autoregressive model. This model is suitable to identify clusters of areas that exhibit reduced or elevated values of the response compared to their geographical and temporal neighbors. The mean function in the model allows to capture any step-changes in the response and its random effects are defined as follows:

$$\psi_{kt} = \lambda_{Z_{kt}} + \phi_{kt}$$

Clustrends models

This model is proposed by Napier in 2019 (Napier *et al.,* 2019), the random effects uses a mixture of temporal trend with fixed parametric forms such as linear or step-change otherwise constrained shapes such as monotonically increasing and an overall spatial pattern. One disadvantage of this model is it cannot include covariates due to identifiability issues. Model can identify clusters of areas that exhibit similar temporal trends. The random effects of this model are:

$$\psi_{kt} = \phi_k + \sum_{s=1}^{S} \omega_{ks} f_s(t|\gamma_s)$$

This model fits an overall spatial pattern, ϕ_k to the data that is common across all time periods. The spatial pattern is modeled using the conditional autoregressive (CAR) prior proposed by

Leroux (Leroux *et al.,* 2000). The model clusters areas based on their temporal trends, where the S trends are specified by the user in $\left(f_1(t|\gamma_1), \ldots, f_S(t|\gamma_S)\right)$. Each area k is assigned to one of the S trends through the binary indicator $\omega_k = (\omega_{k1}, \ldots, \omega_{ks})$.

Sl. No.	Bayesian spatio-temporal model	Features	Objective
Spatio-temporal models: Global spatial smoothing			
1	Linear models (Bernardinelli *et al.,* 1995)	It introduces the estimation of autocorrelated linear time trends for each areal unit.	To estimate the areas that demonstrate increasing or decreasing linear trends in the response variable over time.
2	ANOVA models (Knorr-Held 2000)	The spatio-temporal autocorrelation is modelled by a common set of spatial random effects and a common set of temporal random effects.	To estimate overall spatial effect shared across all time periods, an overall temporal trend shared across all spatial units, and a set of independent space-time interactions.
3	Separate spatial models (Napier *et al.,* 2016)	An overall temporal trend is fitted to the data, which is common to all areal units.	To estimate an overall temporal trend and separate spatial surfaces for each time period.
4	Autoregressive models (Rushworth *et al.,* 2014)	There are two versions, first captures the spatio-temporal structure through a multivariate first-order autoregressive process. The second model extends this by incorporating a multivariate second-order autoregressive process.	To estimate the evolution of the spatial random effects surface over time. They provide valuable insights into how the spatial patterns and random effects change over different time periods.
Spatio-temporal models: Local spatial smoothing			
5	Adaptive models (Rushworth *et al.,* 2017)	It extends the Autoregressive models to incorporate spatially adaptive smoothing.	Suitable when the residual spatial autocorrelation in the response, after accounting for the covariates, remains consistent over time but exhibits a localized structure.
6	Localised models (Lee and Lawson 2016)	It enhances the smooth spatiotemporal variation in Autoregressive models by incorporating a	To identify clusters of areas that exhibit elevated or reduced values of the response compared to their geographical and temporal neighbors.

		piecewise constant intercept process.	
7	Clustrends models (Napier *et al.,* 2019)	It represents the latent random effects using an overall spatial pattern and a mixture of temporal trend functions with fixed parametric forms or constrained shapes.	To identify clusters of areas that exhibit similar temporal trends.

Table 2.3: *Types of Bayesian spatio-temporal model and their applications.*

2.5.3 Computation of Bayesian models

Before recent advances in computational capacity, the computation of Bayesian models was a difficult and time-consuming task. However, with the progress in computational power, the Bayesian method, particularly the non-informative Bayesian approach where priors and hyperprior distributions aim to be non-informative, has gained popularity. Nonetheless, the implementation of the non-informative Bayesian approach requires careful attention (Torabi 2012).

The estimation of Bayesian models involves dealing with the intricate complexity of the posterior marginal distribution, for which the Markov Chain Monte Carlo (MCMC) method is commonly employed for numerical integration (Louzada *et al.,* 2021). However, there are challenges associated with MCMC estimation, one of which involves assessing the convergence of the MCMC chain. Several methods can be utilized for this purpose, although none of them are flawless (Cowles and Carlin 1996).

The two most common approaches to Markov chain Monte Carlo (MCMC) simulation involve Gibbs sampling and Metropolis-Hastings's algorithm which is generalized version of the Metropolis algorithm (Nicholas Burke 2018). Gibbs sampling is a specific instance of the Metropolis-Hastings algorithm, where conditional distributions are utilized as proposal distributions. This method is applicable when the joint distribution is unknown or challenging to sample directly, but the conditional distribution of each variable is known and easily sampled. On the other hand, the Metropolis-Hastings algorithm employs a full joint density distribution to generate a sequence of random samples. It has the capability to draw samples from any probability distribution that is symmetric, provided that the function value can be computed.

There exist several software options such as R, Bayesian inference Using Gibbs Sampling (BUGS), Stan and Numerical Inference for statistical Models using Bayesian and Likelihood Estimation (NIMBLE) for effectively implementing fully Bayesian spatial or spatio-temporal models. These software solutions are user-friendly, computationally efficient, and support

various model types, including those with discontinuities. With the continuous improvement in data collection and computational tools for spatial data analysis, Bayesian spatial statistics are expected to make further inroads into various fields and emerge as one of the leading methods for data analysis (Louzada *et al.,* 2021).

2.5.4 Convergence

Convergence pertains to the concept that eventually, the chosen Markov Chain Monte Carlo (MCMC) technique will reach a stationary distribution. Once in this state, it remains within the distribution and fluctuates. When the model has achieved convergence, additional samples from a parameter's posterior distribution should not impact the calculation of the mean. To account for potential convergence delays, it is recommended to discard the initial MCMC observations until convergence is achieved. In some cases, running MCMC chains for an extended period is advised since Bayesian models often require more time to converge (Cowles and Carlin 1996). However, it is impossible to definitively prove convergence; we can only ascertain when convergence has not occurred. It is also important to note that convergence does not indicate a good model.

When analyzing trace plots, one should look for patterns. If the model has converged, the trace plot will exhibit movement around the mode of the distribution. Conversely, the presence of any patterns suggests a lack of convergence. Trace plots have a limitation: although they may indicate convergence, the chain might be temporarily trapped in a local region instead of exploring the entire posterior.

Geweke diagnostics (Geweke 1991) can be used to evaluate convergence. After simulating a large number of draws, if a model has converged, the mean and variance of a parameter's posterior distribution from the first half of the chain will be equivalent to those from the second half. A value ranging from -2 to 2 indicates convergence.

Another method for testing MCMC chain convergence is the Gelman-Rubin convergence diagnostic (Gelman and Rubin 1992), which involves running two or more parallel chains (Cowles and Carlin 1996) initialized with different values. By comparing the variance within and between chains for each variable, this test can assess convergence. Generally, parameters with approximately normal marginal posterior densities yield more reliable indications of convergence (Gelman and Rubin 1992).

2.6 Bayesian models fitting criteria

To evaluate model performance and compare predictive accuracy across different models, various measures of goodness of fit are considered. The goal is to identify the best-fitting model that explains the maximum amount of variation while utilizing the fewest independent variables. Commonly used measures include the Watanabe-Akaike information criterion (Watanabe and Opper 2010), deviance information criterion (DIC) (Spiegelhalter *et al.,* 2002), Bayesian information criterion BIC (Schwarz 1978), Akaike information criterion AIC (Akaike 1974) and adjusted R-squared.

Commonly used in frequentist models, adjusted R-squared is a corrected goodness-of-fit measure specifically designed for linear models. It penalizes the inclusion of independent variables that do not contribute significantly to predicting the dependent variable in regression analysis. Similarly, AIC penalizes models with excessive parameters to avoid overfitting. However, both AIC and adjusted R-squared have limitations, as they may include variables that are not statistically significant but perform better in predictions. To address overfitting, BIC introduces a penalty term for the number of parameters in the model. Compared to AIC, BIC imposes a larger penalty, favoring more parsimonious models.

While DIC and BIC are commonly used for comparing Bayesian models. DIC is defined as $-2\log p(y|\theta)$, where $p(y|\theta)$ represents likelihood (Spiegelhalter *et al.,* 2002, Mallick and Yi 2013). BIC on the other hand, is defined as $-2\log likelihood + p\log(n)$, where n represents the data and p denotes the number of parameters (Wit *et al.,* 2012, Mallick and Yi 2013). BIC aims to determine the true model, necessitating the specification of the parameters count, and offer model averaging procedure. In contrast, DIC focuses on short-term predictive ability and estimates the effective number of parameters. Additionally, DIC does not provides a procedure for model averaging (Mallick and Yi 2013). However, WAIC offers several advantages over DIC and BIC. WAIC closely approximates Bayesian cross-validation, utilizes the entire posterior distribution, and remains invariant to parameterization (Vehtari *et al.,* 2017). Moreover, WAIC provides a more comprehensive Bayesian approach for estimating out-of-sample expectations (Gelman *et al.,* 2014). Smaller values for both DIC and WAIC indicate a better fit for the model.

If a model fits well, then the residuals should not have any remaining spatial autocorrelation. Commonly Moran's I (Moran 1950) statistic is employed to assess the presence of spatial autocorrelation in residuals. Values close to 0 indicate very low or no spatial autocorrelation, while values above 0.2 were considered indicative of some positive spatial autocorrelation

(Anderson and Ryan 2017). However, it is important to note that Moran's I can be sensitive to the spatial weights matrix to define spatial dependencies between areas. Determining an appropriate spatial dependency structure for calculating residual spatial autocorrelation is challenging, and therefore it may be preferred for this measure to carry less weight in the goodness of fit process.

2.7 Conclusion

In conclusion, this chapter has explored various Bayesian approaches for spatial and spatio-temporal modeling in the context of investigating small-area geographical patterns in the prevalence of PSA testing and how they have changed over time. Each presented model has its own advantages and considerations.

The Bayesian approach is often preferred for analyzing areal data as it allows for the incorporation of information from diverse sources, resulting in smoothed estimates that enhance the stability and precision of the estimates. This approach is particularly useful in small areas where data may be limited.

Previous research has demonstrated that Bayesian models offer numerous advantages in mapping diseases. They enable direct probabilistic statements, such as estimating the probability of increased disease risk in a specific area. Additionally, Bayesian models are straightforward to implement using software, making them accessible for researchers and practitioners.

To uncover spatial trends across regions, conditional autoregressive (CAR) models such as the BYM and Leroux models use global spatial smoothing. These models assume a common variance for the smoothing term across the entire region while allowing for local smoothing in neighboring areas. However, considering the objectives of the analysis, the Leroux model is parsimonious and has an advantage over BYM as it employs single spatial random effect parameter, allowing for variation in both structured and unstructured spatial random effects between geographical areas.

While the BYM2 model is also parsimonious, the Leroux model has been previously implemented and performed well in the Australian context, such as in the Australian Cancer Atlas (https://atlas.cancer.org.au/) for multiple cancer types.

Furthermore, separate spatial and ANOVA models incorporate an overall temporal trend and separate spatial surfaces for each time period. However, the separate spatial model is preferred

due to its parsimonious nature and the requirement of fewer terms to calculate random effects. Moreover, the separate spatial model takes less time to run and converges more quickly compared to the ANOVA model.

Overall, this chapter has not only expanded our understanding of Bayesian approaches for spatial and spatio-temporal modeling but has also provided a practical guide to selecting the Leroux model and the separate spatial model as the most suitable approaches for spatial and spatio-temporal analysis, respectively. This selection is based on careful consideration of the type of data and the advantages these models offer in capturing random effects while maintaining a parsimonious framework. In addition, the appropriateness of a model lies in the trade-offs between smoothness, interpretability, and computational efficiency.

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CHAPTER 3

3 Changes in prostate specific antigen (PSA) "screening" patterns by geographic region and socio-economic status in Australia: analysis of Medicare data in 50–69 year old men

3.1 Chapter overview

This chapter examines the trends in prostate-specific antigen (PSA) screening among men aged 50-69 in Australia from 2002 to 2018. The analysis was conducted at the area-specific level, taking into account categories including socio-economic status, remoteness, and state/territories. In addition, we compare PSA screening rates during two distinct periods: high screening (2005-2009) and low screening (2014-2018). By focusing on these area-specific categories, we aim to understand the regional variations in PSA screening rates and identify potential areas for improvement in screening practices. The comparison of high and low screening periods also provides insights into the impact of changes in screening recommendations and policies over time. Our findings contribute to the ongoing discussion on the effectiveness and appropriateness of PSA screening for prostate cancer, particularly for men in the age group of 50-69. The chapter has been published and presented as a final accepted manuscript.

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3.2 Manuscript cover page

Changes in prostate specific antigen (PSA) "screening" patterns by geographic region and socio-economic status in Australia: Analysis of Medicare data in 50-69 year old men.

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3.3 Highlights of this manuscript

- Analysis of individual-level Medicare data in Australia
- PSA screening tests have declined since 2007
- Assessed trends by states/territories, remoteness and area disadvantage
- Trends by geographical area were consistent with the national trends
- National factors more likely to influence trends than local factors

3.3.1 What is known before this manuscript

- Released in 2016, the most recent Australian guidelines state that the current evidence does not support a national prostate cancer screening program (a program that offers prostate-specific antigen (PSA) testing to all men of a certain age group). However, for men at average risk of prostate cancer who have been informed of the benefits and harms of testing and who decide to undergo regular testing for prostate cancer, they support offering PSA testing every 2 years from ages 50 to 69.
- Modelled PSA screening rates in Australia peaked in 2007 and have decreased since then until 2017.
- Previous reports using data up to 2009 have shown that for men aged 40 years and over, and more specifically 50-79 years, those living in metropolitan and more socioeconomically advantaged areas of Australia have higher PSA screening rates when compared to men living in rural/remote and disadvantaged areas.

3.3.2 What is new in this manuscript

- These results focus on changes over time in the numbers and rates of men aged 50-69 years who have received a screening PSA test, rather than simply the numbers of PSA tests carried out.
- Overall reductions in PSA screening rates in Australia since 2007 were observed across each of the state and territories, remoteness categories and area-level socioeconomic quintiles.
- Remoteness differentials have remained unchanged between 2005-2009 and 2014-2018. Socio-economic differences in PSA screening rates have reduced over this time.
- There is some variation in the use of PSA as a screening test by Australian States and Territories.

- Results suggest that the reasons for the decrease in PSA screening rates over time, while unknown, are likely to be similar across jurisdiction, remoteness and area level socioeconomic categories.
- While it is likely that MBS episode coning explains at least some of the differentials by remoteness, similar reductions over time between the remoteness categories suggests that the main drivers of the temporal changes were independent of coning.

3.4 Abstract

Background: While it is known that national PSA testing rates have decreased in Australia since 2007, it is not known whether these trends are consistent by broad geographical areas, nor whether previously reported area-specific differences have remained in more recent time periods.

Methods: Population-based cohort study of Australian men (n=2,793,882) aged 50-69 who received at least one PSA test (Medicare Benefit Schedule item number 66655) during 2002-2018. Outcome measures included age-standardised participation rate, annual percentage change using JoinPoint regression and indirectly standardised participation rate ratio using multivariable Poisson regression.

Results: During 2005-09, two thirds (68%) of Australian men aged 50-69 had at least one PSA test, reducing to about half (48%) during 2014-18. In both periods, testing rates were highest among men living in major cities, men aged 50-59 years, and among men living in the most advantaged areas. Nationally, the Australian PSA testing rate increased by 9.2% per year between 2002 and 2007, but then decreased by 5.0% per year to 2018. This pattern was generally consistent across States and Territories, and socio-economic areas, however the magnitude of the trends was less pronounced in remote and very remote areas.

Conclusions: The decreasing trends are consistent with a greater awareness of the current guidelines for clinical practice in Australia, which recommend a PSA test be done only with the informed consent of individual men who understand the potential benefits and risks. However, given there remain substantial geographical disparities in prostate cancer incidence and survival in Australia, along with the equivocal evidence for any benefit from PSA screening, there remains a need for more effective diagnostic strategies for prostate cancer to be implemented consistently regardless of where men live.

3.5 Introduction

Prostate-specific antigen (PSA) testing in asymptomatic men can instigate an early diagnosis of prostate cancer, potentially avoiding higher risk disease and enabling the management to be more effective. While it remains the most commonly used test for prostate cancer screening or monitoring after a prostate cancer diagnosis or its treatment, its use as a screening test for prostate cancer is widely debated (Albertsen 2020) due to its high sensitivity and a low specificity (Ankerst and Thompson 2006), its inability to distinguish between cancers and non-cancer conditions, and the known harms associated with overdiagnosis and over-treatment of screen detected cancers (Stamey *et al.,* 2004). Increased rates of PSA testing are typically associated with increases in prostate cancer diagnoses and higher observed cause specific survival (Alberts *et al.,* 2015).

While population-based screening for prostate cancer is not endorsed internationally nor implemented as policy in any country in the world, during 2005-2009 52% of Australian men aged 40 years and over had at least one Medicare-funded PSA "screening" test (Calopedos *et al.,* 2019). Medicare reimburses four categories of PSA tests (66655, 66656, 66659 and 66660) and for the purposes of this paper we refer to item 66655 as de-facto "screening" tests (henceforth referred to as PSA screening tests), as it relates to tests undertaken on asymptomatic men. In 2016, the Prostate Cancer Foundation of Australia and Cancer Council Australia (Prostate Cancer Foundation of Australia 2016) released national evidence-based guidelines that did not recommend a population-based prostate screening program, and instead advised informed individual decision-making regarding PSA testing. The guidelines state that men aged 50 to 69 years who make an informed decision to have a PSA test be offered biennial PSA testing. These recommendations are generally consistent with similar USA (Qaseem *et al.,* 2013, American Academy of Family Physicians 2018, Grossman *et al.,* 2018) and Canadian recommendations (The Canadian Task Force on Preventive Health Care 2019).

In Australia, PSA screening rates have been consistently lower among men living in less accessible regional and remote areas of Australia versus the rest of the country (Baade *et al.,* 2011, Calopedos *et al.,* 2019), and lower in socioeconomically disadvantaged populations (Calopedos *et al.,* 2019), however these estimates relate to the period of highest PSA testing rates more than ten years ago. While modelled rates have decreased nationally since around 2007 (Calopedos *et al.,* 2019) it is not known whether these trends are consistent across geographical areas, and whether the geographical disparities reported previously (Baade *et al.,* 2015, Calopedos *et al.,* 2019, Dasgupta *et al.,* 2019) have persisted over time.

The aim of this study is to describe Medicare-funded PSA screening test patterns and trends by State and Territory, remoteness of residence and socio-economic status. This information may be used to guide policy makers about temporal changes in PSA testing and its implementation, and thus inform the development of recommendations or future revisions of the Australian PSA testing guidelines.

3.6 Methods

3.6.1 Data collection

A de-identified unit record dataset extracted from the Medicare Benefits Schedule was provided by the Commonwealth Department of Health covering the period January 2002 to December 2018 for specific items numbers related to PSA testing. This included MBS item numbers 66655, 66656, 66659 and 66660. For the purposes of this paper, we selected just those tests categorised as 66655. Data included a unique (deidentified) person number, age at treatment (10-year age groups), month and year of service and postcode of residence. Estimated resident population data at the SA2 level were obtained from the Australian Bureau of Statistics (abs.gov.au). SA2s are small geographical areas covering the entire geographical area of Australia without gap or overlap. In Australia there were 2,196 small areas in 2011 (Australia Bureau Of Statistics 2011). The median population of included SA2s in 2011 was 505 (IQR: 312, 795) for men aged 50-69.

3.6.2 Geographic definitions

We used a concordance file obtained from the Australian Bureau of Statistics to map postcodes to SA2 boundaries. Of the 2,653 postcodes included in the concordance, 1,177 (44%) mapped completely (>99.9% overlap) to an individual SA2. For each individual we used the population weighted proportions to randomly allocate the postcode to a SA2. We repeated this random allocation to assess the potential impact of this non-exact concordance on the results. Geographic location information was categorised into State/Territory, remoteness of residence and area socioeconomic status based on the Index of Relative Socioeconomic Advantage and Disadvantage derived by the Australian Bureau of Statistics (abs.gov.au).

3.6.3 Statistical analysis

We calculated the average number of men having a PSA screening test in any given calendar year, rather than the number of screening tests in that year. Men who had multiple PSA screening tests within a single calendar year were counted only once for that year. We restricted

the analysis on men aged 50-69 for consistency with the 2016 Australian PSA testing guidelines (Prostate Cancer Foundation of Australia 2016).

We present PSA screening rates as average annual rates per year for two periods; 2005-2009 representing the period of highest PSA screening rates (and reported previously for different age groups (Calopedos *et al.,* 2019)), and 2014-2018 representing the most recent data available at the time of data extraction.

Directly age-standardised screening rates were calculated using two 10-year age groups and standardised to the Australian 2001 population, with standard errors calculated using the modified gamma method. Trends were quantified by calculating annual percentage change by calendar year using Joinpoint regression (https://surveillance.cancer.gov/joinpoint/) which employs a series of regression models using the observed age-standardised testing rates as the outcome measure and including their standard errors to determine the best combination of linear line segments that fit the data. A maximum of 3 joinpoints (or 4-line segments) were used for this analysis. One PSA test for each man per calendar year were included in these trend analyses.

Incidence rate ratios of receiving a PSA screening test over the study period were calculated by exponentiating the coefficients from Poisson models. The outcome measure for the Poisson model was the observed number of men receiving at least one PSA test during the time period and used an offset term defined by the log of the age-specific male population. The significance level for each variable was tested using the likelihood ratio test; comparing the model to a reduced model where each variable is excluded one at a time. These models also included year of testing, 10-year age group, remoteness, area socioeconomic status and State/territory, as well as an interaction term between Remoteness and Area socioeconomic status.

Analyses were conducted using R (version 3.5.3), Joinpoint (version 4.8.0.1) and Stata (version 16) software. Ethics approval for this study was obtained from the Griffith University Human Research Ethics committee (GU Ref no: 2017/777). Data custodian approval was provided by the Commonwealth Department of Health after approval from the Chief Data Steward under the Health Insurance Act 1973.

3.7 Results

In total, there were 7,438,720 Medicare records of PSA screening tests among men aged 50-69 years between 2002 and 2018. Records were excluded from the study if the provided postcode was used exclusively for Post Office boxes rather than a residential street address (n=51,016,

0.69%), an invalid postcode (n=43,983, 0.59%) or was a repeated screening test for an individual man within the same calendar year (n=2,870, 0.04%). After these exclusions, the final study cohort included 7,340,851 PSA screening tests among 2,793,882 men between 2002 to 2018, counted as one screening test per man per year.

3.7.1 Trends over time

Nationally, the Australian PSA screening rate among men aged 50-69 years increased by 9.2% per year between 2002 and 2007, but then decreased by 5.0% per year between 2007 and 2018 (Figure 3.1, Table ST 3.1). The pattern of increasing trend followed by a decrease was generally consistent across the Australian states and territories, remoteness categories and socio-economic areas, however the magnitude of the trends were less pronounced in remote and very remote areas (Figure 3.1, Table ST 3.1). The decreasing trend plateaued since the early-mid 2010s for men living in Remote areas, as well as those in the more socioeconomically advantaged areas.

The peak in modelled PSA screening rates occurred in Australia in 2007. The number of men receiving at least one Medicare funded PSA screening test during a five-year period decreased nationally from nearly 1.5 million men in the period between 2005 and 2009 to 1.3 million men between 2014 and 2018 (Table 3.1). The corresponding age-standardized screening rates reduced from 676 men receiving at least one PSA screening test (95% CI: 675.3-677.5) to 482 per 1,000 men (480.8-482.4). Decreases in both the number and rate of men receiving at least one screening test between 2005-2009 and 2014-2018 were observed across all age groups, states/territories, remoteness, and socio-economic areas (Table 3.1).

3.7.2 Differences by population subgroup

In both 5-year time periods, the screening rate among men aged 60-69 years was 8% lower than the rate among men aged 50-59 years (Table 3.1). Screening rates varied across the states and territories, with age-standardised rates being higher in Western Australia, Victoria, Queensland and South Australia during 2014 to 2018. In both time periods, PSA screening rates were highest among men living in major cities, and then reduced with increasing remoteness. While screening rates were up to 11% higher among men living in the most advantaged areas in the 2005-2009 time period, during 2014-2018 the differentials were attenuated with the maximum differential being 4% (Table 3.1).

There was statistically significant evidence ($p<0.001$ for both time periods) that the association between area disadvantage and PSA screening rates varied by geographical remoteness (Table 3.2). This interaction was highlighted by the limited variability across quintiles of

socioeconomic disadvantage in major city, inner regional and outer regional areas, however among remote areas PSA screening rates were particularly low in the most disadvantaged areas while the rates in very remote areas were low in most disadvantaged and advantaged areas. There were generally similar trends over time between the different combinations of remoteness and area disadvantage (Figure 3.1, Table ST 3.2), and given the relatively low number of PSA tests conducted among men in remote and very remote areas compared to men in the other remoteness categories, some caution is needed when interpreting these interactions.

3.8 Discussion

3.8.1 Interpretation

Using a population-based cohort of nearly three million Australian men who had at least one Medicare-funded PSA screening test, we found consistency in PSA screening patterns over time across states and territories, geographical regions, and area-level socioeconomic status. This suggests that the key factors influencing these trends in the use of PSA screening are more likely to be driven at a national level such as clinical practice guides, rather than being influenced by local or regional factors. There were, however, key differences in the prevalence of PSA screening across population groups in the five years up to 2018, with higher rates among men aged 50-59 compared to those aged 60-69, men living in major cities compared to regional and remote areas, and men living in Western Australia, Victoria, Queensland and South Australia compared to other States/Territories, while differences by area level disadvantage were less pronounced compared with the peak screening period of 2005-2009, particularly in non-remote areas.

Importantly, this work provides more contemporary information about the differences in PSA screening participation across geographical population subgroups than what has been reported previously by Calopedos and colleagues (Calopedos *et al.,* 2019). While most of the population-subgroup patterns have remained, disparities by area level socioeconomic status have decreased over the last decade. In addition, while reductions in PSA screening rates over the last decade have been previously reported for Australia (Calopedos *et al.,* 2019), Canada (Winnipeg) (Wang *et al.,* 2020), Argentina (Martinez *et al.,* 2019), and the United States (Frendl *et al.,* 2020), our work highlights that the temporal reductions in PSA screening in Australia are generally consistent across broad geographical regions of remoteness, area socioeconomic disadvantage quintiles and state/territory jurisdictions.

Shared decision making has been recommended since the mid-1990s (Australian Health Technology Advisory Committee (AHTAC) 1996, The Royal Australian College of General

Practitioners (RACGP) 2016). This suggests that the widespread decline in PSA testing may be less due to changes in shared decision making and more due to changes in the recommendations regarding informed decision making from international organisations such as the United States Preventive Services Task Force and Royal Australian College of General Practitioners that happened around the same time (Herget *et al.,* 2016).

The lower rates of PSA screening among men living in the less accessible regional and remote areas of Australia are consistent with differences reported in previous years (Baade *et al.,* 2011, Calopedos *et al.,* 2019) although a recent systematic review (Dasgupta *et al.,* 2019) found the patterns by remoteness were not consistent internationally. One possible explanation for the differences by remoteness, particularly in Australia with often large distances to medical services, is that men and general practitioners in regional and remote areas might be more focused on medical tests or interventions that are motivated by existing symptoms rather than including pre-emptive tests or interventions such as PSA screening. In addition to uncertain benefits and recognised potential harms, the results of PSA screening may then require long-distance travel for further clinical work-up or treatment (Baldwin *et al.,* 2013, Calopedos *et al.,* 2019).

3.8.2 Strengths and limitations

Australia's Medicare database was established and maintained for administration purposes, rather than for the purposes of research. As such, the impact of coning, in which the number of claims made per episode of care is capped to limit the cost of Medicare benefits paid in a single episode, may have impacted the observed results. If, for example, men living in regional and remote areas combine multiple tests during a single visit general practitioner visit, the PSA test (which is relatively inexpensive) might be excluded from the claims in favour of other, more expensive tests. Even still, it has been estimated that up to 40% of PSA tests might be coned (Trevena *et al.,* 2013). The extent to which coning varies by geographical area is not known. However, a NSW study showed that men who visited general practitioners more often were more likely to have a PSA test (Nair-Shalliker *et al.,* 2018), while Australians living in outer regional and remote areas were 2.5 and 6 times more likely to report that not having a general practitioner nearby was a barrier to seeing one (AIHW 2019). In addition, the use of general practitioners is higher in major city areas, and the number of non-hospital medical services per capita reduces with increasing remoteness (AIHW 2019). Combined, these suggest that while coning may explain at least some of the observed disparities in PSA screening by remoteness, the consistency of temporal trends across remoteness categories suggests the recent reductions in each category are unlikely to be impacted by coning.

3.8.3 Implications

We specifically focussed on screening participation among Australian men aged 50-69 for consistency with the Australian guidelines (Prostate Cancer Foundation of Australia 2016), which in turn is guided by the previous evidence (Schroder *et al.,* 2012) that any mortality benefit from the early diagnosis of prostate cancer due to PSA testing is not seen within 7 years of testing. However, that there is some evidence of a mortality benefit after 7 years of PSA testing means that the net benefit of PSA testing is equivocal for those men who are likely to live another 7 years. With life expectancy among Australian men continuing to increase (AIHW 2021), the substantial numbers of men aged over 70 who have had a PSA test (Calopedos *et al.,* 2019) is not surprising, and it is important that guidance be provided for these men and their clinicians as to their decision-making process.

The debate over the most appropriate use of the PSA test for screening purposes is likely to continue. While the 2016 Australian Guidelines (Prostate Cancer Foundation of Australia 2016) and similar international guidelines (Qaseem *et al.,* 2013, American Academy of Family Physicians 2018, Grossman *et al.,* 2018, The Canadian Task Force on Preventive Health Care 2019) recommend informed decision making regarding testing for men, a number of more recent changes to the way in which men are diagnosed and treated for early stage prostate cancer have potentially altered the balance of harms and benefits of screening. The changes include the routine use of MRI in the diagnosis of men, a shift in the technical approach to prostate biopsy from transrectal to transperineal thus reducing the risk of biopsy related infection, and evidence of a significant proportion of men with low-risk disease being managed with active surveillance (Papa *et al.,* 2021). As a result, the guidelines are in need of review to account for these recent changes in screening, diagnosis, and treatment of prostate cancer. The patterns described in this paper provide the most relevant background to any proposed changes to Australia's approach to prostate cancer screening.

3.9 Conclusion

Despite current recommendations in Australia supporting individual informed decision-making regarding PSA testing rather than the use of the test as a screening tool, about half of Australian men aged 50-69 years had at least one Medicare-funded PSA test over the five-year period up to 2018. The consistent decreasing trends across State/Territory, geographical remoteness and area-level disadvantage are consistent with a greater awareness of the current guidelines for clinical practice in Australia. On current evidence, more efficient, informed targeted use of PSA testing and post-testing follow-up, in relation to both the potential benefits and harms, could help improve prostate cancer outcomes and reduce inequities. Prostate cancer remains the

second-leading cause of cancer death in Australian men, with significant disparities in mortality between men from different regional and socioeconomic groups. More research is urgently needed on ways to utilise existing technologies, including targeted use of PSA testing and patient management, diagnostic technology such as MRI and on the development of improved risk assessment tools.

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Figure 3.1: *Trends in annual PSA screening test rates for Australian men aged 50 to 69 years, 2002 to 2018, for Australia, by State, Remoteness, and Area-level Socio-economic Status.*

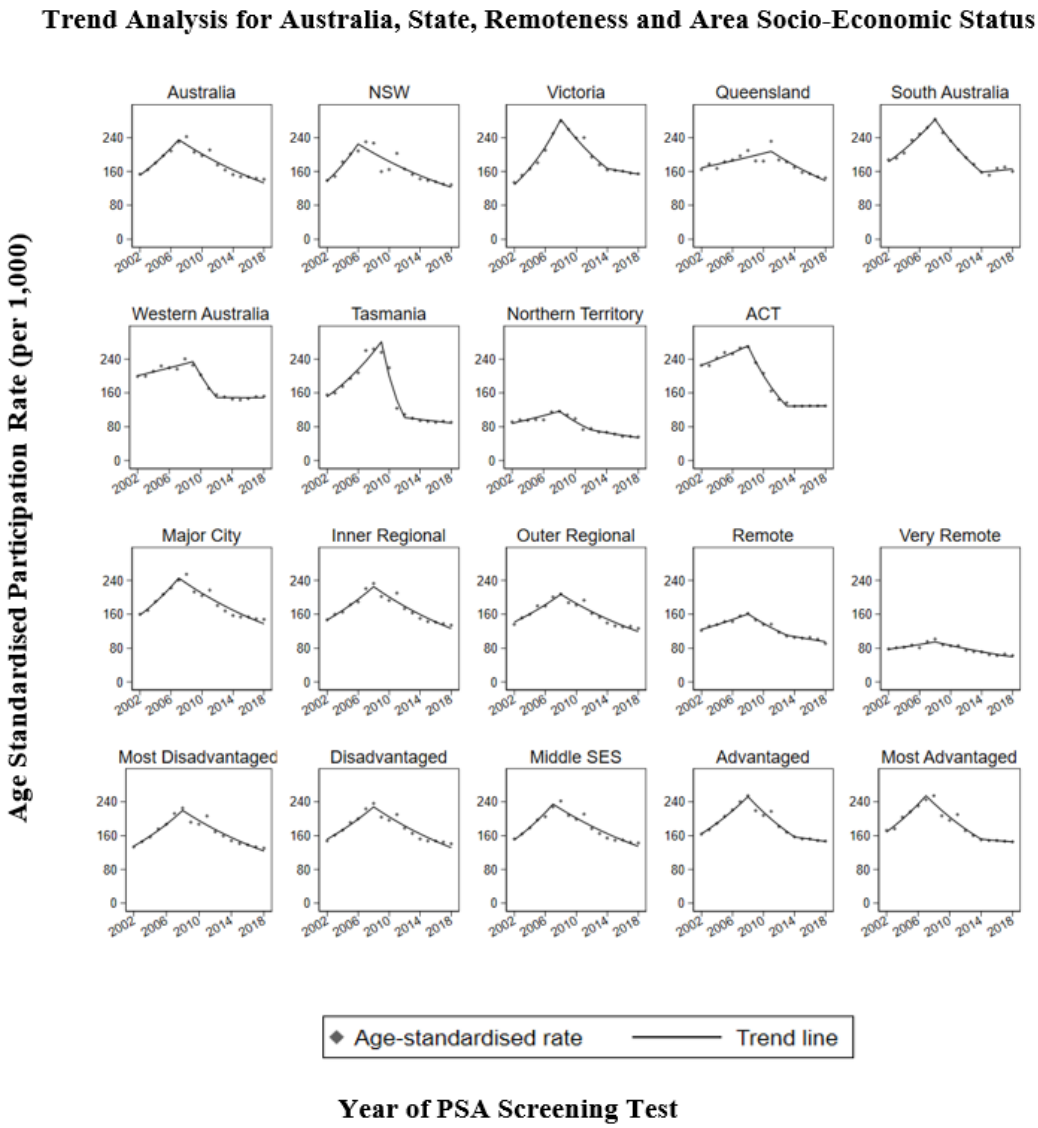

Table 3.1: *Characteristics of PSA screening participation1 among Australian men aged 50-69 years for 2005-09 and 2014-18.*

Year	**2005-09**				**2014-18**			
Category	**N[2]**	**Crude %[3]**	**ASR/1000[4]**	**IRR[5] [95% CI]**	**N[2]**	**Crude %[3]**	**ASR/1000[4]**	**IRR[5] [95% CI]**
Australia	1,510,096	67.6	676.4		1,303,898	48.3	481.6	
Age Group								
50-59 years	898,770	68.6	686.0	1.00	704,343	47.5	474.5	1.00
60-69 years	611,326	66.2	661.7	0.92 [0.92, 0.92]	599,555	49.2	492.4	0.92 [0.92, 0.92]
State / Territory[5]								
New South Wales	485,420	66.3	663.1	1.00	400,188	46.0	459.7	1.00
Victoria	387,415	71.7	717.4	1.15 [1.14, 1.15]	340,773	51.2	510.1	1.23 [1.23, 1.24]
Queensland	277,880	62.5	626.5	0.91 [0.91, 0.92]	270,909	49.7	496.4	1.19 [1.19, 1.20]
South Australia	131,958	74.9	748.8	1.34 [1.34, 1.35]	109,419	53.1	525.6	1.38 [1.37, 1.39]
Western Australia	152,827	67.1	671.0	1.11 [1.10, 1.11]	137,614	48.8	487.5	1.16 [1.15, 1.16]
Tasmania	42,219	71.5	715.5	1.28 [1.27, 1.30]	22,094	32.2	325.0	0.63 [0.62, 0.64]
Northern Territory	7,118	35.5	355.6	0.67 [0.66, 0.69]	5,357	22.2	221.7	0.58 [0.56, 0.60]
Australia Capital Territory	25,259	74.7	745.8	1.15 [1.14, 1.17]	17,544	44.0	439.1	0.96 [0.95, 0.98]
Remoteness of residence								
Major City	1,038,169	70.1	701.7	1.00	897,575	49.8	497.6	1.00
Inner Regional	305,648	65.4	655.5	0.93 [0.93, 0.93]	264,592	46.8	467.1	0.96 [0.96, 0.97]

Outer Regional	145,419	61.2	611.9	0.91 [0.90, 0.91]	124,327	44.5	443.1	0.94 [0.94, 0.95]
Remote	15,609	48.2	482.6	0.76 [0.75, 0.77]	12,834	34.6	343.7	0.78 [0.77, 0.79]
Very Remote	5,251	31.5	317.4	0.52 [0.50, 0.53]	4,570	23.3	234.1	0.58 [0.57, 0.60]
Area Socio-Economic Status								
Most Disadvantaged	279,675	64.1	641.3	1.00	236,576	46.4	461.9	1.00
Disadvantaged	298,252	65.9	659.3	1.05 [1.05, 1.06]	261,642	48.5	483.6	1.02 [1.02, 1.03]
Middle SES	310,638	67.3	673.4	1.09 [1.08, 1.09]	275,714	48.7	485.6	1.03 [1.02, 1.03]
Advantaged	298,964	70.2	702.2	1.11 [1.10, 1.11]	262,145	49.3	491.6	1.04 [1.03, 1.04]
Most Advantaged	322,567	70.5	704.7	1.10 [1.09, 1.10]	267,821	48.4	483.8	1.00 [0.99, 1.00]

Notes:

[1] Jervis Bay area was excluded due to no state information.

[2] Total number of men receiving at least one PSA test during the time period.

[3] Percentage of men aged 50-69 years (not age adjusted).

[4] Directly age-standardised rates using the 2001 Australian Standard Population. Note that age-specific ASR are equivalent to crude rates.

[5] IRR = Adjusted Incidence Rate Ratio

Table 3.2: *Age-standardized incidence rates, and adjusted[1] incidence rate ratios showing interaction between Remoteness and SEIFA categories on PSA screening rates for Australian men aged 50-69 years, 2005-09 and 2014-18.*

	2005-09				2014-18			
Characteristics	**Count[2] (%)**	**ASR[3]**	**IRR[4] [95% CI[5]]**	**P-value[6]**	**Count[2] (%)**	**ASR[3]**	**IRR[4] [95% CI[5]]**	**P-value[6]**
Major City				< 0.001				< 0.001
Most Disadvantaged	132,059 (8.7)	670.39	1.00		114,810 (8.8)	483.95	1.00	
Disadvantaged	138,126 (9.1)	691.91	1.02 [1.01, 1.03]		122,083 (9.4)	505.72	1.03 [1.02, 1.04]	
Middle SES	209,472 (13.9)	699.45	1.04 [1.04, 1.05]		186,913 (14.3)	505.84	1.03 [1.03, 1.04]	
Advantaged	251,698 (16.7)	717.32	1.06 [1.05, 1.07]		219,296 (16.8)	503.53	1.02 [1.02, 1.03]	
Most Advantaged	306,814 (20.3)	708.65	1.05 [1.04, 1.06]		254,473 (19.5)	489.21	1.01 [1.00, 1.02]	
Outer Regional				< 0.001				< 0.001
Most Disadvantaged	82,475 (5.5)	636.89	1.00		69,442 (5.3)	462.52	1.00	
Disadvantaged	98,825 (6.5)	661.02	1.03 [1.02, 1.04]		85,966 (6.6)	476.73	0.98 [0.97, 0.99]	
Middle SES	76,205 (5.0)	658.32	1.02 [1.01, 1.03]		66,946 (5.1)	467.12	0.98 [0.97, 0.99]	
Advantaged	36,452 (2.4)	669.25	1.03 [1.01, 1.04]		32,422 (2.5)	463.28	1.00 [0.99, 1.01]	
Most Advantaged	11,691 (0.8)	686.25	1.04 [1.02, 1.06]		9,816 (0.8)	431.85	0.92 [0.90, 0.94]	
Inner Regional				< 0.001				< 0.001
Most Disadvantaged	59,302 (3.9)	646.43	1.00		48,160 (3.7)	458.80	1.00	
Disadvantaged	53,050 (3.5)	597.33	0.97 [0.96, 0.98]		46,064 (3.5)	447.14	0.97 [0.96, 0.98]	
Middle SES	19,882 (1.3)	584.25	1.03 [1.01, 1.05]		17,532 (1.3)	425.86	0.97 [0.95, 0.98]	
Advantaged	10,096 (0.7)	582.60	1.09 [1.07, 1.11]		9,821 (0.8)	424.32	1.03 [1.01, 1.05]	

Most Advantaged	3,089 (0.2)	535.61	1.11 [1.07, 1.16]		2,750 (0.2)	339.64	0.96 [0.92, 1.01]	
Remote				< 0.001				< 0.001
Most Disadvantaged	3,196 (0.2)	414.67	1.00		2,040 (0.2)	239.39	1.00	
Disadvantaged	6,618 (0.4)	580.00	1.41 [1.33, 1.49]		5,982 (0.5)	453.69	1.52 [1.42, 1.62]	
Middle SES	4,352 (0.3)	432.60	1.37 [1.28, 1.45]		3,688 (0.3)	315.41	1.43 [1.33, 1.53]	
Advantaged	470 (< 0.1)	383.20	1.69 [1.52, 1.89]		342 (0.0)	246.91	1.73 [1.53, 1.96]	
Most Advantaged	973 (0.1)	504.04	1.56 [1.43, 1.70]		782 (0.1)	305.96	1.39 [1.26, 1.53]	
Very Remote				< 0.001				< 0.001
Most Disadvantaged	2,643 (0.2)	271.54	1.00		2,124 (0.2)	193.65	1.00	
Disadvantaged	1,633 (0.1)	537.32	1.38 [1.28, 1.48]		1,547 (0.1)	458.41	1.37 [1.27, 1.48]	
Middle SES	727 (< 0.1)	370.64	1.39 [1.28, 1.52]		635 (< 0.1)	292.51	1.34 [1.22, 1.47]	
Advantaged	248 (< 0.1)	142.65	0.69 [0.61, 0.79]		264 (< 0.1)	91.99	0.60 [0.52, 0.68]	
Most Advantaged	Not Applicable[7]				Not Applicable[7]			

[1] Adjusted for age group, state, and year.

[2] Jervis Bay area was excluded due to no state information.

[3] ASR = Age standardised rate per 1000 men.

[4] IRR = Adjusted Incidence Rate Ratio.

[5] CI = Confidence Interval.

[6] P-value = Based on χ^2chi test, < 0.05 is considered as significant.

[7] There are no very remote SA2s in Australia that are also within the most advantaged socioeconomic category.

3.11 Supplementary material

Figure SF 3.1: *Interaction between Remoteness and Area-level Socio-economic Status on trends in annual PSA screening test rates for Australian men aged 50 to 69 year, 2002 to 2018.*

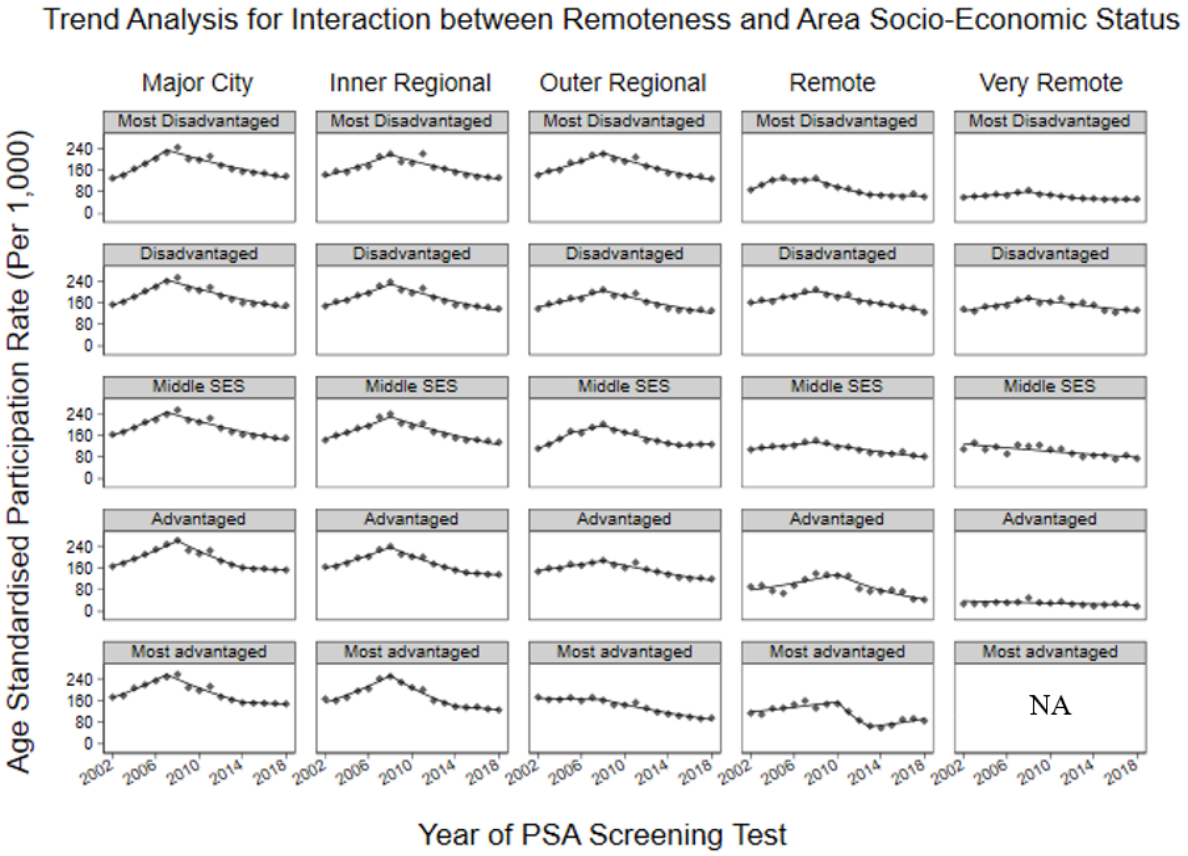

Table ST 3.1: *Annual percentage changes in PSA screening rates between 2002 and 2018 by Australia, State/Territory, Remoteness and Socio-economic Status categories, Australian men aged 50 to 69 years.*

Variable	N	Trend 1		Trend 2		Trend 3	
		Year	APC [95% CI][1]	Year	APC [95% CI] [1]	Year	APC [95% CI] [1]
Australia	7,339,858	2002-2007	9.2 [4.8, 13.8][2]	2007-2018	-5.0 [-6.1, -4.0][2]		
Remoteness							
Major City	5,060,721	2002-2007	9.2 [4.5, 14.1][2]	2007-2018	-5.1 [-6.3, -4.0][2]		
Inner Regional	1,485,004	2002-2008	7.4 [4.4, 10.6][2]	2008-2018	-5.6 [-6.8, -4.4][2]		
Outer Regional	698,043	2002-2008	6.6 [3.7, 9.5][2]	2008-2018	-5.4 [-6.5, -4.2][2]		
Remote	72,790	2002-2008	4.4 [2.4, 6.5][2]	2008-2013	-7.2 [-10.3, -4][2]	2013-2018	-3.0 [-5.5, -0.3][2]
Very Remote	23,300	2002-2008	3.5 [1.0, 6.0][2]	2008-2018	-4.6 [-5.6, -3.6][2]		
Socio-economic Status							
Most Disadvantaged	1,326,605	2002-2008	8.4 [5.4, 11.5][2]	2008-2018	-5.6 [-6.7, -4.4][2]		
Disadvantaged	1,466,735	2002-2008	7.1 [4.3, 9.8][2]	2008-2018	-5.3 [-6.4, -4.3][2]		
Middle SES	1,526,637	2002-2007	9.3 [5.1, 13.7][2]	2007-2018	-4.9 [-5.9, -3.9][2]		
Advantaged	1,470,661	2002-2008	7.4 [5.1, 9.9][2]	2008-2014	-7.6 [-10.1, -5.1][2]	2014-2018	-1.7 [-5.7, 2.4][2]
Most Advantaged	1,549,220	2002-2007	8.5 [4.2, 13][2]	2007-2014	-7.1 [-9.7, -4.5][2]	2014-2018	-1.1 [-6.6, 4.8][2]
State / Territory							
New South Wales	2,233,285	2002-2006	13.1 [2.5, 24.7][2]	2006-2018	-4.9 [-6.5, -3.3][2]		
Victoria	1,923,615	2002-2008	14 [11.1, 17][2]	2008-2014	-8.4 [-11, -5.8][2]	2014-2018	-2.0 [-6.3, 2.5]
Queensland	1,454,340	2002-2011	2.3 [0.9, 3.8][2]	2011-2018	-5.6 [-7.4, -3.8][2]		

South Australia	653,471	2002-2008	7.5 [5.6, 9.5][2]	2008-2014	-9.2 [-11.2, -7.2][2]	2014-2018	1.2 [-2.3, 4.9]
Western Australia	766,203	2002-2009	2.2 [0.9, 3.5][2]	2009-2012	-13.9 [-21.5, -5.5][2]	2012-2018	-0.1 [-1.7, 1.6]
Tasmania	164,905	2002-2009	9.3 [7.4, 11.2][2]	2009-2012	-28.8 [-37.8, -18.4][2]	2012-2018	-2.2 [-5.0, 0.7]
Northern Territory	29,643	2002-2008	4.8 [1.8, 7.8][2]	2008-2012	-11.2 [-18.0, -3.7][2]	2012-2018	-4.8 [-7.7, -1.8][2]
Australia Capital Territory	114,396	2002-2008	3.1 [1.9, 4.4][2]	2008-2013	-13.8 [-15.9, -11.8][2]	2013-2018	0.1 [-1.8, 2.0]

Notes:

1. 95% confidence intervals
2. Significant ($p<0.05$) linear trend

Table ST 3.2: *Annual percentage changes in PSA screening rates between 2002 and 2018 by Remoteness and Socio-economic Status categories, Australian men aged 50 to 69 years.*

Category	N	Trend 1		Trend 2		Trend 3		Trend 4	
		Year	APC [95% CI][1]	Year	APC [95% CI] [1]	Year	APC [95% CI] [1]	Year	APC [95% CI] [1]
Major City									
Most Disadvantaged	627,798	2002-2007	13.0 [8.5, 17.7][2]	2007-2018	-5.1 [-6.1, -4.1][2]				
Disadvantaged	679,693	2002-2007	10.2 [5.9, 14.7][2]	2007-2018	-4.9 [-5.9, -3.9][2]				
Middle SES	1,039,304	2002-2007	9.0 [4.7, 13.4][2]	2007-2018	-4.9 [-5.9, -3.8][2]				
Advantaged	1,239,088	2002-2008	7.7 [5.2, 10.2][2]	2008-2014	-7.7 [-10.3, -5.1][2]	2014-2018	-1.4 [-5.5, 2.9]		
Most Advantaged	1,474,838	2002-2007	8.5 [4.1, 13.2][2]	2007-2014	-7.1 [-9.7, -4.4][2]	2014-2018	-1.0 [-6.7, 5.0]		
Inner Regional									
Most Disadvantaged	393,902	2002-2008	7.7 [3.3, 12.4][2]	2008-2018	-5.3 [-7.0, -3.5][2]				
Disadvantaged	484,674	2002-2008	7.4 [4.4, 10.4][2]	2008-2018	-5.5 [-6.6, -4.3][2]				
Middle SES	371,137	2002-2008	7.6 [4.9, 10.4][2]	2008-2018	-5.8 [-6.8, -4.8][2]				
Advantaged	179,462	2002-2008	6.8 [4.9, 8.8][2]	2008-2015	-7.0 [-8.5, -5.5][2]	2015-2018	-1.7 [-6.6, 3.4]		
Most Advantaged	55,829	2002-2008	8.7 [5.8, 11.8][2]	2008-2014	-9.5 [-12.4, -6.5][2]	2014-2018	-2.2 [-7.0, 2.8]		
Outer Regional									
Most Disadvantaged	281,596	2002-2008	7.5 [4.8, 10.4][2]	2008-2018	-5.7 [-6.8, -4.6][2]				
Disadvantaged	259,669	2002-2008	6.1 [2.7, 9.5][2]	2008-2018	-5.1 [-6.4, -3.8][2]				
Middle SES	92,909	2002-2005	15.2 [6.4, 24.7][2]	2005-2008	5.1 [-7.4, 19.3]	2008-2015	-6.6 [-8.5, -4.5][2]	2015-2018	1.4 [-5.2, 8.5]

Advantaged	49,253	2002-2008	3.7 [0.8, 6.7][2]	2008-2018	-4.7 [-5.9, -3.6][2]				
Most Advantaged	14,616	2002-2008	-0.5 [-3.3, 2.3]	2008-2018	-5.8 [-6.9, -4.6][2]				
Remote									
Most Disadvantaged	12,518	2002-2004	19.6 [-3.7, 48.6]	2004-2008	-0.1 [-8.7, 9.2]	2008-2013	-11.3 [-16.8, -5.4][2]	2013-2018	-1.3 [-6.4, 4.0]
Disadvantaged	34,611	2002-2008	4.3 [2.3, 6.3][2]	2008-2018	-4.4 [-5.2, -3.6][2]				
Middle SES	19,843	2002-2008	3.6 [0.7, 6.6][2]	2008-2018	-5.1 [-6.2, -3.9][2]				
Advantaged	1,881	2002-2010	7.1 [1.3, 13.3][2]	2010-2018	-13.1 [-18.2, -7.6][2]				
Most Advantaged	3,937	2002-2010	3.5 [-0.1, 7.1]	2010-2013	-25.8 [-44.2, -1.2][2]	2013-2018	7.9 [0.1, 16.4][2]		
Very Remote									
Most Disadvantaged	10,791	2002-2008	5.2 [3.0, 7.4][2]	2008-2013	-7.5 [-10.8, -4.1][2]	2013-2018	-1.0 [-3.7, 1.9]		
Disadvantaged	8,088	2002-2008	5.2 [1.6, 9.0][2]	2008-2018	-3.0 [-4.5, -1.5][2]				
Middle SES	3,444	2002-2018	-3.0 [-4.2, -1.7][2]						
Advantaged	977	2002-2018	-3.1 [-5.5, -0.6][2]						

Notes:

1. 95% confidence intervals
2. Significant ($p<0.05$) linear trend

CHAPTER 4

4 SPATIAL PATTERNS OF PROSTATE-SPECIFIC ANTIGEN TESTING IN ASYMPTOMATIC MEN ACROSS AUSTRALIA: A POPULATION-BASED COHORT STUDY, 2017-2018

4.1 Chapter overview

This chapter presents a spatial analysis of prostate-specific antigen testing across Australia from 2017-2018 conducted at a smaller area level. The investigation looks into the degree of geographical variation within area-based categories, including socio-economic status, remoteness, and states/territories, while utilizing the Bayesian spatial Leroux model. Additionally, it explores the geographical differences between greater capital cities and areas outside greater capital cities. The chapter aims to address the potential reasons that contribute to the variation in PSA testing. It has been published and presented as a final accepted manuscript.

Chapter 4 was published:

Kohar, A., Cramb, S. M., Pickles, K., Smith, D. P., & Baade, P. D. (2023). Spatial patterns of prostate-specific antigen testing in asymptomatic men across Australia: a population-based cohort study, 2017-2018. *Public Health*, *217*, 173–180. https://doi.org/10.1016/j.puhe.2023.01.039

4.2 Manuscript cover page

Spatial patterns of prostate-specific antigen testing in asymptomatic men across Australia: a population-based cohort study, 2017-2018

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4.3 Highlights of this manuscript

Using Medicare claims data, this is the first study to quantify how patterns of PSA "screening" tests varied by small geographical areas in the Australian male population. The marked geographical variation in screening within the broader categories of remoteness suggests that small area-specific factors, such as GP attitudes and community perceptions, may play a role in this variation. Given the national focus of Australian PSA guidelines, reasons for the area variation should be explored further.

4.3.1 What is known before this manuscript

Worldwide, prostate cancer is the second most diagnosed cancer in men. In many developed countries the prostate-specific antigen (PSA) test has been associated with an increase in the diagnosis of asymptomatic prostate cancers.

We searched articles published in English on PubMed using terms ("PSA testing"[All Fields] OR "Prostate cancer screening"[All Fields] OR "PSA screening"[All Fields]) AND ("Geographic inequalities"[All Fields] OR "Spatial"[All Fields] OR "Geospatial"[All Fields] OR "Small area"[All Fields] OR "recurrence"[MeSH Terms]) NOT ("review"[Heading]) for articles published between 1 January 2002 and 1 July 2022.

Our search identified 20 articles, but only two focussed on spatial variation in PSA testing. One found substantial variation in PSA screening rates by smaller areas within the United States of America. Other study was based on broad geographical patterns of PSA screening in Switzerland. The majority of excluded studies focused on the spatial pattern of prostate cancer incidence and mortality, with a number of studies posing the question of PSA screening variability being a potential driver for incidence or mortality patterns, however no studies quantify the geographical associations in this variability.

In Australia, PSA testing rates vary by broad geographical areas, men living in advanced socio-economic status and major cities areas generally have high rates of PSA testing compared to their counterpart living in disadvantaged and remote areas. Presently, to our knowledge, there are no published studies from Western Pacific countries that quantify PSA screening variation by smaller areas.

Current guidelines for PSA screening in Australia released by the Cancer Council Australia and Prostate Cancer Foundation of Australia (PCFA) in 2016 recommend that men aged 50 to 69 years at risk of prostate cancer, having made an informed decision to have a PSA test, should be offered a test every two years. These are similar to international guidelines in other developed countries. Following the release of the 2016 Australian guidelines, it is not currently known how the use of PSA testing varies by small geographical areas across Australia, or within broad geographical areas of remoteness categories and area disadvantage.

4.3.2 What is new in this manuscript

This is the first study to quantify how patterns of PSA "screening" tests in the Australian male population varied across 2,129 small geographical areas across the country. Bayesian spatial Leroux models were used to provide modelled estimates with increased stability and precision. The CARBayes package used for analysis incorporated Markov Chain Monte Carlo methods to compute smoothed small area-specific standardised incidence ratios (SIRs). Estimates were combined over 50 iterations due to probabilistic allocation of postcode to small statistical areas. The model gave consistent results when different hyperpriors such as (IG(shape=1, scale=0·1; default in CARBayes), IG(0·1, 0·01) and IG(0·5, 0·0005) were used.

We found 20-fold variation in PSA screening rates between small areas across Australia. On an average 26·1% Australian men aged 50-79 had a PSA screening test during 2017 and 2018. Among those, men aged 60-69 (28·9%) had highest population percent screening compared to age groups 50-59 (23·7%) and 70-79 (26·1%). Screening rates in most small areas (83·2%) in Australia were likely to differ from the Australian average; either having higher (exceedance probability>80%) than average rates (45·0%) or lower (exceedance probability<20%) than average rates (38·2%).

Compared with major city regions, the median area-specific PSA screening rate was lower in more regional and remote regions, however the between-area variation increased. There was little difference in the area-specific distributions of PSA screening between the socio-economic categories. The PSA screening rates in almost all small areas in Northern Territory (65 out of 66) and Tasmania (95 out of 95) were lower than the national average. In contrast, screening rates were higher than the national average in the majority of small areas in the south of Victoria (276 of 427), South Australia (134 of 163), south-west Queensland (268 of 512) and coastal areas of Western Australia (150 of 234), along with some small areas in north-east New South Wales (144 of 526). There was also considerable variation in screening rates evident both between and within capital cities.

4.4 Abstract

Objectives: In Australia, while prostate-specific antigen (PSA) testing rates vary by broad area-based categories of remoteness and socio-economic status, little is known about the extent of variation within them. This study aims to describe the small-area variation in PSA testing across Australia.

Study design: Retrospective population-based cohort study.

Methods: We received data for PSA testing from the Australian Medicare Benefit Schedule. The cohort included men (n=925,079) aged 50-79 years who had at least one PSA test during 2017-2018. A probability-based concordance was applied across multiple iterations (n=50) to map each postcode to small areas (Statistical Areas 2 (SA2); n=2,129). For each iteration, a Bayesian spatial Leroux model was used to generate smoothed indirectly standardized incidence ratios (SIRs) across each small area, with estimates combined using model-averaging.

Results: About a quarter (26%) of the male population aged 50-79 had a PSA test during 2017-2018. Testing rates among small areas varied 20-fold. Rates were higher (exceedance probability>0·8) compared to the Australian average in the majority of small areas in southern Victoria and South Australia, south-west Queensland and some coastal regions of Western Australia but lower (exceedance probability<0·2) in Tasmania and Northern Territory.

Conclusions: The substantial geographical variation in PSA testing rates across small areas of Australia may be influenced by differences in access to and guidance provided by clinicians, and attitudes and preferences of men. Greater understanding of PSA testing patterns by subregions and how these patterns relate to health outcomes could inform evidence-based approaches to identifying and managing prostate cancer risk.

4.5 Introduction

Prostate-specific antigen (PSA) testing is regularly used opportunistically to test asymptomatic men for risk of prostate cancer (Australian Institute of Health and Welfare 2019), however it has a low positive predictive value that makes it difficult to distinguish between cancerous and benign prostatic conditions (Bryant and Lilja 2014). Consequently, this is a test that is undertaken ad hoc rather than in organized population-wide screening programs (Alberts *et al.,* 2015).

In 2016, the Prostate Cancer Foundation of Australia (PCFA) and Cancer Council Australia released national guidelines that recommend if men at average risk of prostate cancer aged 50 to 69 years make an informed decision to have a regular PSA test, it should be offered every two years (Prostate Cancer Foundation of Australia and Cancer Council Australia PSA Testing Guidelines Expert Advisory Panel 2016). Summary guidelines from the Royal Australian College of General Practitioners (The Royal Australian College of General Practitioners 2016) advise GPs that, due to screening of asymptomatic men with PSA not being recommended, GPs are not obliged to offer the test. Most international guidelines on screening and early detection of prostate cancer are similar to Australian PCFA guidelines including United States (Grossman *et al.,* 2018), Europe (European Association of Urology 2018), Canada (Bell *et al.,* 2014), and the United Kingdom (National Institute for Health and Care Excellence 2014).

Higher PSA testing rates have been reported among men living in socio-economically advantaged areas compared to those living in disadvantaged areas. In addition, testing rates have been shown to be higher for men living in urban areas compared to rural areas (Calopedos *et al.,* 2019, Dasgupta *et al.,* 2019). However, the lack of robust estimates for PSA testing at the small area level makes it difficult to interpret prostate cancer incidence and survival information in recent disease atlases such as the Australian Cancer Atlas (Australian Cancer Atlas 2021).

This study, using PSA testing data from the Medicare Benefit Schedule, Australian Government's universal health funding scheme, aims to address this gap in knowledge. It will quantify how PSA testing rates vary by small geographical areas across Australia during the time period following the release of the 2016 Australian clinical guidelines on PSA testing (Prostate Cancer Foundation of Australia and Cancer Council Australia PSA Testing Guidelines Expert Advisory Panel 2016).

4.6 Methods

4.6.1 Data

Medicare reimbursed PSA test data for men aged 50-79 years, tested in Australia between January 2017 and December 2018 were obtained from the Commonwealth Department of Health (under the Health

Insurance Act 1973). In Australia, the Medicare Benefits Schedule reimburses item number 66655, since it is specifically used for detecting asymptomatic prostate disease in men, which will refer to it as a "screening" test. The unit-record data extract contained a deidentified unique person-level ID number, postcode of residence recorded by Medicare Benefits Schedule at the time of PSA test, 10-year age group, year, and month of the conducted screening test.

4.6.2 Geography

A probability-based geographical correspondence file (Australia Bureau of Statistics 2012) was used to transform the 2011 postcode information into Statistical Areas 2 (SA2s) information from the 2011 Australian Statistical Geography Standard (ASGS). In this study, the term SA2 will be referred to as "small area".

The correspondence file, containing the proportions of the population within each postcode that were allocated to each small area, was merged with the postcode-specific PSA dataset. The postcode for each record was then randomly assigned to a small area according to these probabilities based on the uniform distribution, with the random process carried out 50 times.

The small areas were categorized by the ABS Remoteness Index and the Index of Relative Socio-Economic Advantage and Disadvantage (Australia Bureau of Statistics 2011, Australia Bureau of Statistics 2011).

4.6.3 Exclusions

We selected PSA tests that were undertaken on men aged 50-79 during the period 2017-2018 (Figure 4.1). Postcodes that were exclusively used for post office boxes were excluded since it was impossible to determine its exact geographical catchment area. This study is based on the number of men rather than the number of screening tests, therefore only the first test per individual during the study period was considered. Records where postcodes did not match with the postcode-small area concordance were removed from the cohort.

We excluded records from 67 SA2s because of male population ≤ 3 men or were classified as remote islands (n=3). The final dataset included 2,129 small areas.

4.6.4 Population

Estimated resident population (Australian Bureau of Statistics 2021) by small area for men aged 50-79 years old during 2017-18 were concorded from 2016 ASGS classification to the 2011 ASGS using a population-weighted correspondence file (Australian Bureau of Statistics 2016). The included 2,129 small areas had a median population of 1,479 (interquartile range: 895 - 2,296) men.

4.6.5 Statistical analysis

Spatial models

Spatial data commonly exhibits autocorrelation, or clustering, and ignoring this can lead to biased results (Duncan *et al.,* 2019). To allow for spatial autocorrelation in the data, three Bayesian spatial models, all variants of the Intrinsic Conditional Auto-Regressive model, were initially considered to model the standardized incidence ratio (SIR): Leroux (Leroux 1999), Besag, York and Mollié (BYM) (Besag 1991), and Localised (Lee and Sarran 2015). Each of these models allow for autocorrelation through random effect terms on each area. Of the three, the Leroux model was preferred over the Localised model due to its more stable estimates (Figure SF 4.1 (a) and (b)). Also, the Leroux model is more parsimonious than the BYM model, since it has only one spatial random effect parameter for each area, rather than the two per area in BYM, yet still allows for both spatial autocorrelation and random variation between areas.

The Leroux model (File SFile 1) applied a Poisson distribution with an offset of the logged expected counts in each small area. Expected counts were calculated by multiplying national age-specific rates (total observed count / total population) by the age-specific population in each small area, then summing all age-specific expected counts. The expected counts and observed counts were input to the Bayesian model to calculate smoothed SIR estimates for each small area compared to the Australian average.

We undertook modelling using the CARBayes package (version 5·2·3) (Lee 2013) in R (version 4·0·0) (R Core Team 2022), which uses Markov Chain Monte Carlo (MCMC) methods for computation. Since Bayesian spatial models are too complex to compute analytically, MCMC algorithms are used to sample from probability distributions to approximate the desired distribution. There were 150,000 MCMC iterations run, with the first 50,000 iterations excluded as burn-in before selecting every 10th iteration to generate 10,000 iterations for each model. These small area-specific iterations from 50 models were combined with equal weighting, resulting in 500,000 iterations for each small area. Most small area results are based on the median value (SIR) of these 500,000 iterations. Markov chain convergence was checked by visual inspection of trace plots (Figure SF 4.2).

Visualization

Maps

The R package ggplot2 (version 3·3·6) (Wickham 2016) was used to visualize the results. The color scale on the SIR maps ranged from 0·67 to 1·5 including color breaks at 0·8, 1 and 1·25. Blue and red shades indicate low and high PSA screening rates respectively compared to the Australian average, as shown in yellow.

The exceedance probability is equal to the posterior probability of the modelled SIR being above 1 for each small area (Cramb *et al.,* 2016). In the exceedance probability thematic map, green represents low (<20%) exceedance probabilities and suggests a true lower-than-average PSA screening rate and purple represents high (>80%) suggesting a real higher-than-average PSA screening rate.

Graphs

Boxplots were used to show how the small area-specific distribution of modelled estimates varied according to the categories of remoteness, socio-economic status, states/territories, and greater capital cities.

4.7 Results

During 2017-18, 1,052,900 PSA screening tests were performed on 938,622 Australian men aged 50-79 years (Figure 4.1). Of these, 8,398 (0·80%) screening tests were removed due to the postcode containing only post office boxes (n=177), 113,366 (10·77%) were duplicate screening tests, 5,997 (0·57%) tests that were linked to a postcode that did not match with ABS postcode to small area correspondence files and 60 (<0·01%) tests were in small areas that had male population aged 50-79 years less than or equal to three. The final dataset included 925,079 men (one PSA test per man) aged 50-79 years, tested during 2017-18, giving an overall crude screening rate of 260·6 per 1000 (26·1%) men.

The highest population percent of men screened was among men aged 60-69 (Table 4.1). Population screening percentages decreased substantially with remoteness, while screening rates were relatively consistent across the area-level socio-economic categories. Population PSA screening rates by states and territories were between 23·4% and 31·2%, except for lower rates in Tasmania (16·2%) and the Northern Territory (11·1%).

4.7.1 Prostate-specific antigen screening patterns by smaller areas

There was a 20-fold (=2/0·1) variation in PSA screening rates (based on the modelled SIRs) across small areas of Australia (Figure 4.2), with low (SIR<1) PSA screening rates in many remote areas. Approximately 5·3% of the small areas had screening rates that were more than 50% lower (SIR<0·5) than the Australian average (SIR=1), and these were more likely to be outside capital cities, in remote and very remote areas, and most disadvantaged areas in Tasmania and Northern Territory (Table ST 4.1). The screening rates in about 1·8% of small areas were more than 50% higher (SIR>1·5) than average (Table ST 4.1). Sensitivity analyses showed similar SIR estimates by small area regardless of the choice of hyperpriors within the statistical models (Figure SF 4.3 (a) and (b)).

Northern Territory (65/66 small areas) and Tasmania (95/95) had consistently lower screening rates than the national average. In contrast, screening rates were higher than the national average in the majority of small areas in the south of Victoria (276/427), South Australia (134/163), south-west Queensland (268/512) and coastal areas of Western Australia (150/234), along with some small areas in north-east New South Wales (144/526) (Figure 4.2). Considerable variation in screening rates was evident both between and within capital cities. In most small areas within Sydney, PSA rates were lower than the national average, along with those within Hobart, Darwin, and Canberra, whereas higher than average PSA screening rates were observed in many areas within Melbourne, Brisbane, Adelaide, and Perth (Figure 4.2 and SF 4.4 (b)).

The majority (83%) of small areas had a screening rate likely to differ from the national average (Figure 4.3). PSA screening in 957/2129 small areas was considered likely to be lower (<20% probability of being higher, Figure 4.2) than the national average, and higher (>80% probability, Figure 4.2) in 814/2129 small areas. Screening rates in the remaining 358 small areas were considered unlikely to be different to the national average.

4.7.2 Distribution of small area-specific estimates within broader areas

There was no difference in the distribution of small area-specific estimates across categories of socio-economic status (Figure 4.4 (a)) and this was consistent outside and inside greater capital cities (Figure SF 4.4 (c)). However, within some capital cities including Hobart and Adelaide, there was a suggestion of contrasting patterns of socio-economic gradients (Figure SF 4.4 (e)) while more populated capital cities of Sydney, Melbourne and Brisbane had little variation. Likewise, there was less variability between greater capital cities and outside greater capital cities (Figure 4.4 (d)), whereas small areas within greater capital cities and outside greater capital cities of Victoria and South Australia consistently had higher screening rates than the national average (Figure SF 4.4 (a) and (b)). The small area-specific distribution shows lower screening rates and increasing heterogeneity within categories with rising remoteness (Figure 4.4 (b)) as well as for outside greater capital cities and greater capital cities by remoteness (Figure SF 4.4 (d)). While screening rates in remote areas were generally lower than the national average, there were some notable exceptions in remote areas in southern South Australia and northwest Victoria (Figure 4.4 (c)), which had very high PSA screening rates compared to the national average (Figure 4.2 and Figure 4.3).

4.8 Discussion

4.8.1 Interpretation

This is, to our knowledge, the first population-based study to map and describe the substantial variation in PSA screening tests in Australia by small geographical areas and the characteristics of this variation within broader socio-economic groups, remoteness categories, and states and territories.

Our results of testing patterns relating to the broad geographical classifications of urban and rural differences are consistent with international studies from Switzerland (Ulyte *et al.,* 2020), New Zealand (Obertová *et al.,* 2016) and the United Kingdom (Williams *et al.,* 2011). These studies found that men living in urban areas and regions with high health service supply had higher PSA screening rates. While we found limited variation between area-based socio-economic categories, other international studies (Williams *et al.,* 2011, Ulyte *et al.,* 2020) have reported generally increased use of PSA testing among men living in more affluent areas.

While previous research (Calopedos *et al.,* 2019, Kohar *et al.,* 2023) has demonstrated variation between large geographical regions or remoteness categories in Australia, the results of this study highlight the extent of variation within those broad regions. For example, the variation within socio-economic categories indicates that the PSA screening rate in some 'disadvantaged' small areas was higher than in some 'advantaged' small areas, and vice versa. In addition, not all small areas within remote and very remote categories had lower PSA screening rates than the Australian average. This emphasizes the importance of examining geographical variation between smaller geographical areas, otherwise the heterogeneity within the larger regions is ignored.

The current Australian prostate cancer screening guidelines (Prostate Cancer Foundation of Australia and Cancer Council Australia PSA Testing Guidelines Expert Advisory Panel 2016, The Royal Australian College of General Practitioners 2016) do not incorporate any geographical area characteristics. Therefore, if the decision-making processes for men and their general practitioners across Australia consistently followed the recommended guidelines and had equity in access to the resulting follow-up consultations and procedures, we might expect only a small amount of geographical variation in testing. Thus, while untangling the likely multifaceted reasons for the substantial geographical variation observed in our study requires more detailed investigations, it is likely that at least some of the reasons would relate to local area influences rather than factors operating at the national level. These could include variations in behaviours and attitudes of general practitioners (GPs), who are the gatekeeper to medical services including PSA testing (The Royal Australian College of General Practitioners 2016), as well as factors relating to men living in each area, such as the activities of local PSA testing advocacy groups, and accessibility to primary care and specialist services.

In general, while GPs in Australia have a good understanding of the benefits and limitations of PSA screening, many have limited knowledge of the current guidelines (Ilic *et al.,* 2013). Previous studies have highlighted substantial variation in attitudes and practices by Australian GPs toward PSA testing (Pickles *et al.,* 2015, Pickles *et al.,* 2018), so this may have contributed to our observed results.

Some explanations proposed for this variability between Australian GPs relate to the uncertainty about the evidence base for PSA testing and the ambiguity in PSA screening guidelines (Pickles *et al.,* 2015), personal beliefs or experiences relating to PSA screening (Ilic *et al.,* 2013), clinician motivation to avoid either overdiagnosis or underdiagnosis, perceived medicolegal risks during decision-making process (Pickles *et al.,* 2015) and financial implications and incentives (Pickles *et al.,* 2018). This variation between Australian GPs appears to be in contrast to GPs in the United Kingdom, who are advised not to proactively initiate the screening discussion with men, however they can provide information if specifically requested (Pickles *et al.,* 2016). UK GPs are more likely than Australian GPs to follow organizational guidelines that recommend to only provide PSA testing at the patient request (Pickles *et al.,* 2016, Jackson *et al.,* 2022). This may suggest that, in terms of PSA testing, Australian GPs operate with greater levels of individual discretion, contributing to the large geographical variation in PSA screening observed in this study.

Another possible explanation for the observed variation could be in Australian men's knowledge, attitudes and behaviors regarding prostate health and prostate cancer testing, although little is known about how this varies by geography. Previous surveys tend to suggest low levels of knowledge about prostate cancer risks. For example, a survey conducted among Australian men in 2012 (Prostate Cancer Foundation of Australia 2012) reported that prostate cancer was considered to be the most important health issue facing Australian men by 51% of respondents, and that 55% of men felt they knew at least a reasonable amount about testing for prostate cancer. About three quarters (72%) indicated they would 'probably or definitely' have a PSA test sometime in the future (Prostate Cancer Foundation of Australia 2012).

Advocacy and awareness campaigns, particularly if locally targeted, may contribute to the observed geographic variability in screening participation. While some have a national focus, others have a local or regional focus. Various multistate awareness programmes (Prostate Cancer Foundation of Australia 2022) include the aim of raising awareness in men about prostate cancer and PSA testing. Other more targeted community campaigns use celebrity or sporting identities to endorse community participation in screening (Brewer 2021) or involve prominent members of the local community encouraging greater involvement in testing in communities where mortality rates are high (Denham *et al.,* 2010) such as the 'Little Prick' campaign in the Hunter region of New South Wales (Beaumont 2019). While there are no data on the varying impact of these campaigns on PSA testing rates by geographical area, it is plausible

to expect that the reach and impact of campaigns on men's PSA testing behaviour would not be consistent across the country.

Some of the variations in PSA screening observed between small geographical areas, particularly the patterns by remoteness, may also result from differences in access to primary care practitioners, or GPs, who usually instigate the screening pathway. Outlying communities are well documented as having a lower GP supply (70·5 GPs per 100,000 people in very remote areas compared to 103·5 per 100,000 in major cities) (The Royal Australian College of General Practitioners 2019), and men in rural areas typically have longer wait times to see a GP (Australian Institute of Health and Welfare 2019 2019). Moreover, there are fewer medical specialists (22 per 100,000 people) in very remote areas compared to major cities (143 per 100,000 people) (Australian Institute of Health and Welfare 2019 2019). This may impact rural residents' decision whether to be tested, since they would likely have to travel great distances to access follow up diagnostic and treatment services (Australian Institute of Health and Welfare 2019 2019).

4.8.2 Strengths and limitations

One of the main strengths of this study was the use of population-based data that captured the vast majority of PSA tests among the eligible Australian male population and is not subject to known limitations of self-reported data (Zavala *et al.,* 2016). In addition, reporting on person-based screening history, rather than test-based use as in other studies (Pathirana *et al.,* 2022), removed any impact of multiple tests over the 2-year study period. Also, the Bayesian modelling approach provides more robust estimates of the underlying small-area rates, rather than being unduly impacted by the increased random fluctuations associated with small area data (Duncan *et al.,* 2017).

Medicare claims are restricted to benefits paid to pathology during a single episode of care, known as episode coning. It is possible that coning results in differential testing patterns based on geography. For example, it may be more common in less accessible areas, because men who travel greater distances to see a GP might combine multiple more expensive tests into a single visit (Trevena *et al.,* 2013). However, it is less likely to explain small area variation compared with broader variation between urban and regional or remote areas. While up to 19% of PSA tests may be coned and hence not included in the Medicare data (Trevena *et al.,* 2013), it is not known to what extent this would vary by small geographical area. Additionally, Medicare data only captured the postcode of residence, and the probabilistic allocation of certain postcodes to multiple SA2s may have misassigned some cases to an incorrect area. For this study, the data (2017-18) was received in the fourth quarter of 2019. We were not able to receive an updated data extract prior to completion of this study. In addition, by focusing on a period before the COVID-19 pandemic it enables us to access the underlying PSA testing patterns independently of any behavioral changes through the various COVID-19 management directives.

4.9 Conclusion

In summary, this population-based study identified substantial variation in the PSA screening participation rate by small geographical areas across Australia. The challenge remains to ensure that all males at risk of prostate cancer have access to the same clinical decision-making process, regardless of where they live. This will likely require the development and implementation of more effective resources, policies and communication strategies that have broader engagement and application than those currently in place.

4.10 References

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Figure 4.1: *Flowchart showing selection of men in analysis aged 50-79, Australia, 2017-18.*

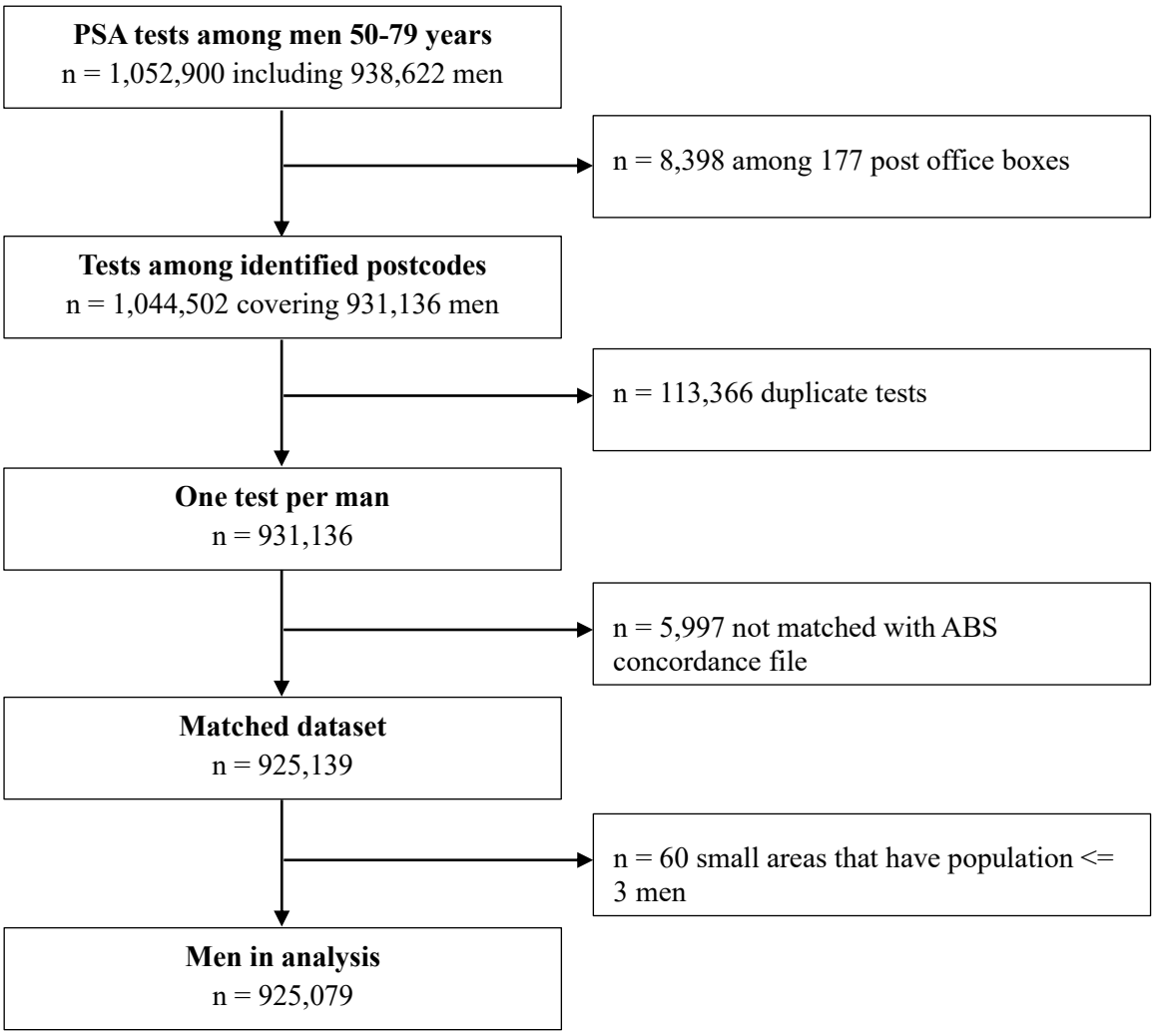
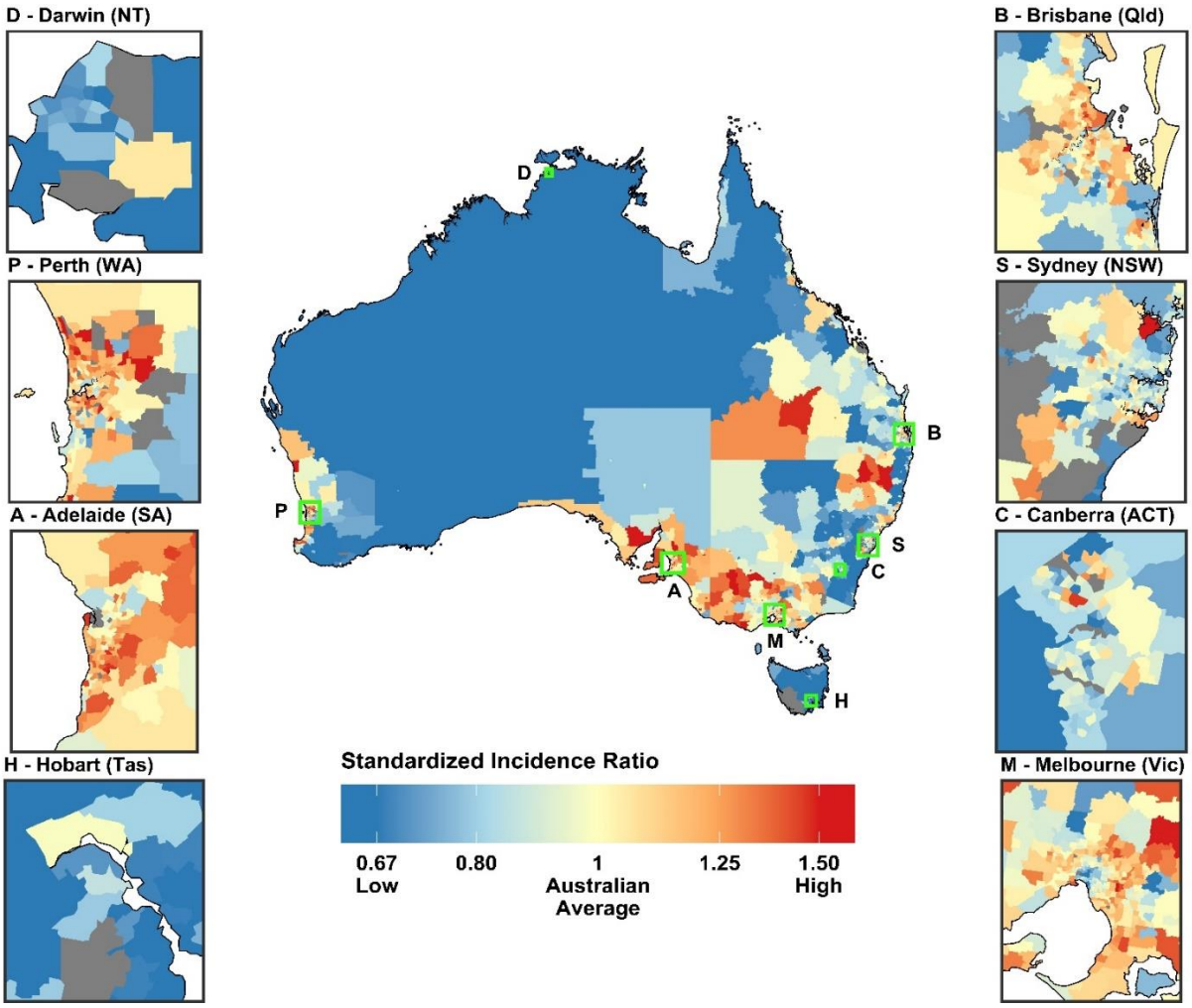


Table 4.1: *Demographic characteristics of men aged 50-79 years having at least one Medicare-funded prostate-specific antigen (PSA) screening test, Australia, 2017-18.*

Characteristics	Men Tested (%)	Population[a] (%)	Population percent of Men Tested (%)
Australia	925,079 (100)	3,549,392 (100)	26·1
Age group (years)			
50 - 59	354,339 (38·3)	1,494,873 (42·1)	23·7
60 - 69	358,708 (38·8)	1,242,648 (35·0)	28·9
70 - 79	212,032 (22·9)	811,871 (22·9)	26·1
Remoteness			
Major City	633,310 (68·5)	2,353,258 (66·3)	26·9
Inner Regional	191,095 (20·7)	761,985 (21·5)	25·1
Outer Regional	88,979 (9·6)	366,005 (10·3)	24·3
Remoteness	8,673 (0·9)	45,084 (1·3)	19·2
Very Remote	3,022 (0·3)	23,059 (0·6)	13·1
Socio-economic Status[b]			
Most Advantaged	187,547 (20·3)	714,676 (20·1)	26·2
Advantaged	186,199 (20·1)	691,652 (19·5)	26·9
Middle SES[c]	195,772 (21·2)	743,578 (20·9)	26·3
Disadvantaged	189,307 (20·5)	717,915 (20·2)	26·4
Most Disadvantaged	166,181 (18·0)	681,437 (19·2)	24·4
State / Territory[d]			
New South Wales	269,171 (29·1)	1,143,786 (32·2)	23·5
Victoria	249,597 (27·0)	880,935 (24·8)	28·3
Queensland	189,527 (20·5)	719,050 (20·3)	26·4
South Australia	84,978 (9·2)	271,968 (7·7)	31·2
Western Australia	101,958 (11·0)	363,522 (10·2)	28·0
Tasmania	14,741 (1·6)	90,845 (2·6)	16·2
Northern Territory	3,143 (0·3)	28,240 (0·8)	11·1
Australian Capital Territory	11,952 (1·3)	50,969 (1·4)	23·4

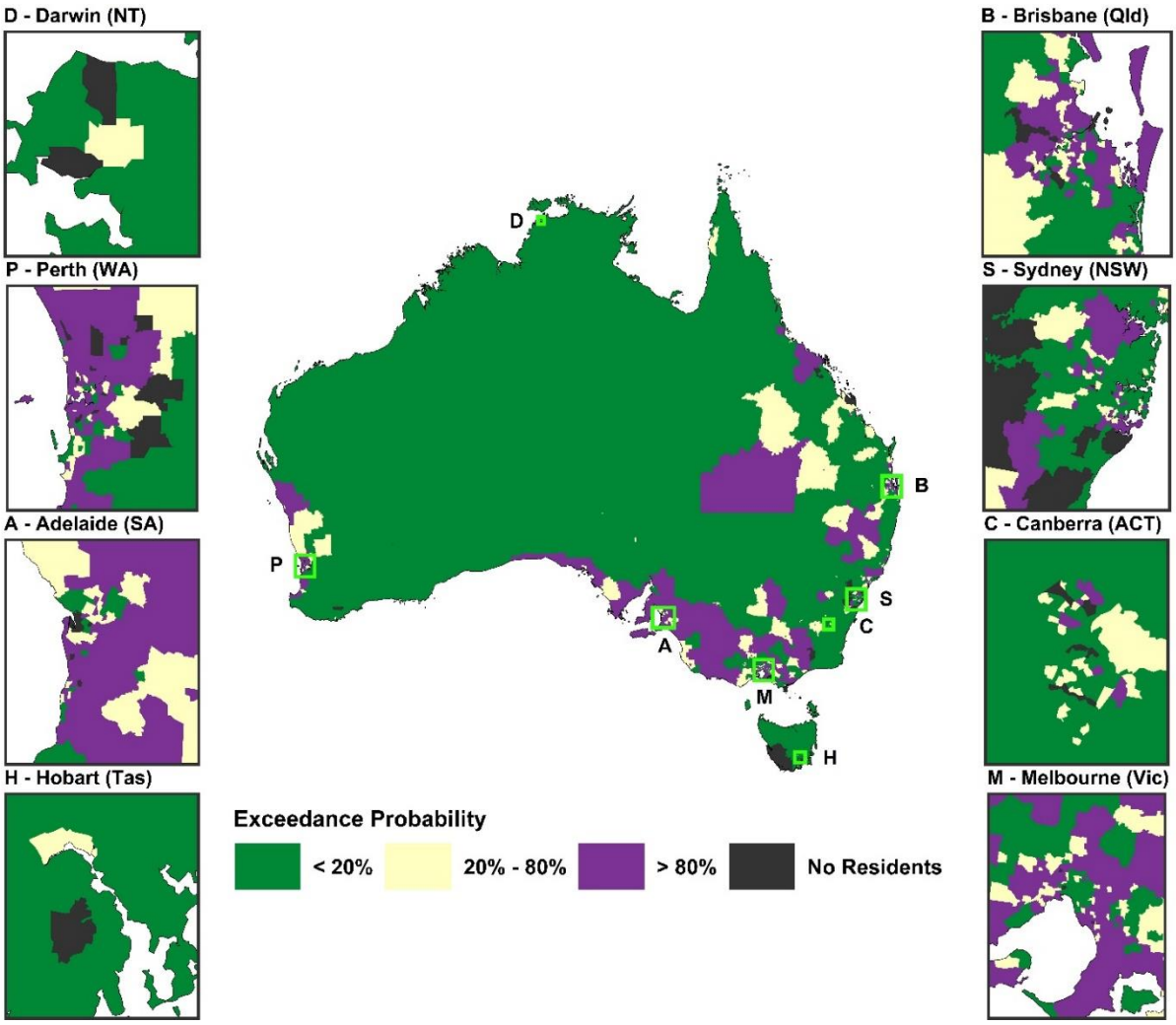
[a] Average estimated resident population of Australia for 2017-18.
[b] Records were excluded that do not have Index of Relative Socio-Economic Advantage and Disadvantage.
[c] Middle SES means Middle Socio-Economic Status.
[d] Records from Jervis Bay area were excluded due to classified as Other Territory.

Figure 4.2: *Standardized Incidence Ratios (SIR) of prostate-specific antigen (PSA) screening by small area[a,b], Australia, 2017-18.*



[a] Insets show capital cities of each state and territory.
[b] NT – Northern Territory, WA – Western Australia, SA – South Australia, Tas. - Tasmania, Qld. - Queensland, NSW – New South Wales, ACT – Australia Capital Territory, Vic. – Victoria.

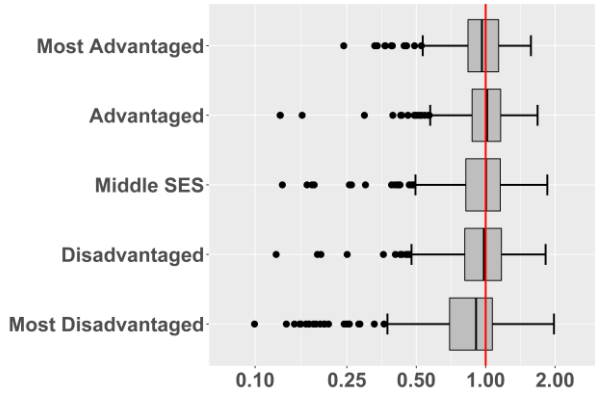
Figure 4.3: *Exceedance probabilities of prostate-specific antigen (PSA) screening by small area[a,b], Australia, 2017-18.*



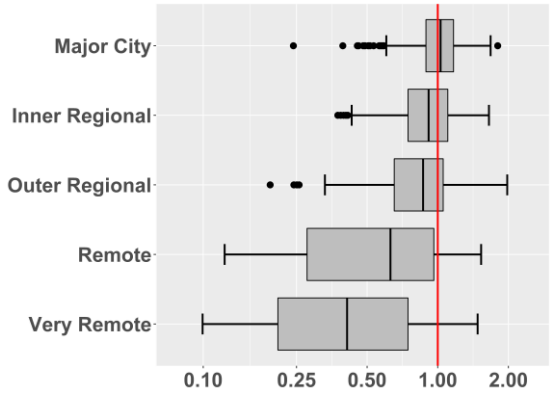
[a] Insets show capital cities of each state and territory.
[b] NT – Northern Territory, WA – Western Australia, SA – South Australia, Tas. - Tasmania, Qld. - Queensland, NSW – New South Wales, ACT – Australia Capital Territory, Vic. – Victoria.

Figure 4.4: *Standardized Incidence Ratio of prostate-specific antigen (PSA) screening for 2129 small area during 2017-18 grouped by (a) Socio-economic Status, (b) Remote Areas, (c) States / Territories, (d) Outside Greater Capital Cities Vs Greater Capital Cities*

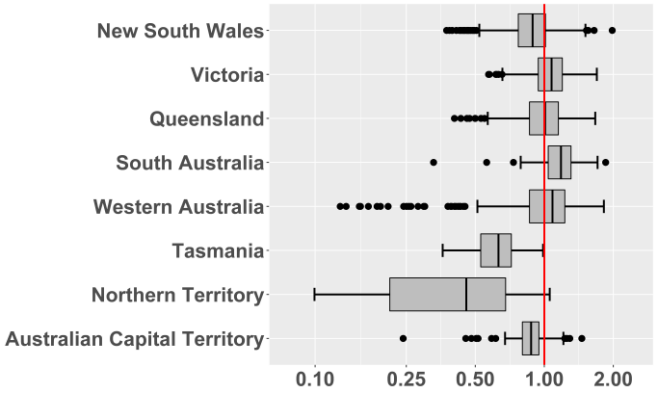
(a) Socio-economic Status[a]



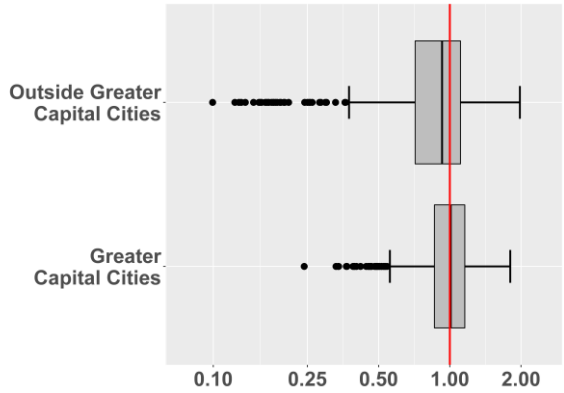
(b) Remoteness



(c) States / Territories



(d) Outside Greater Capital Cities Vs Greater Capital Cities



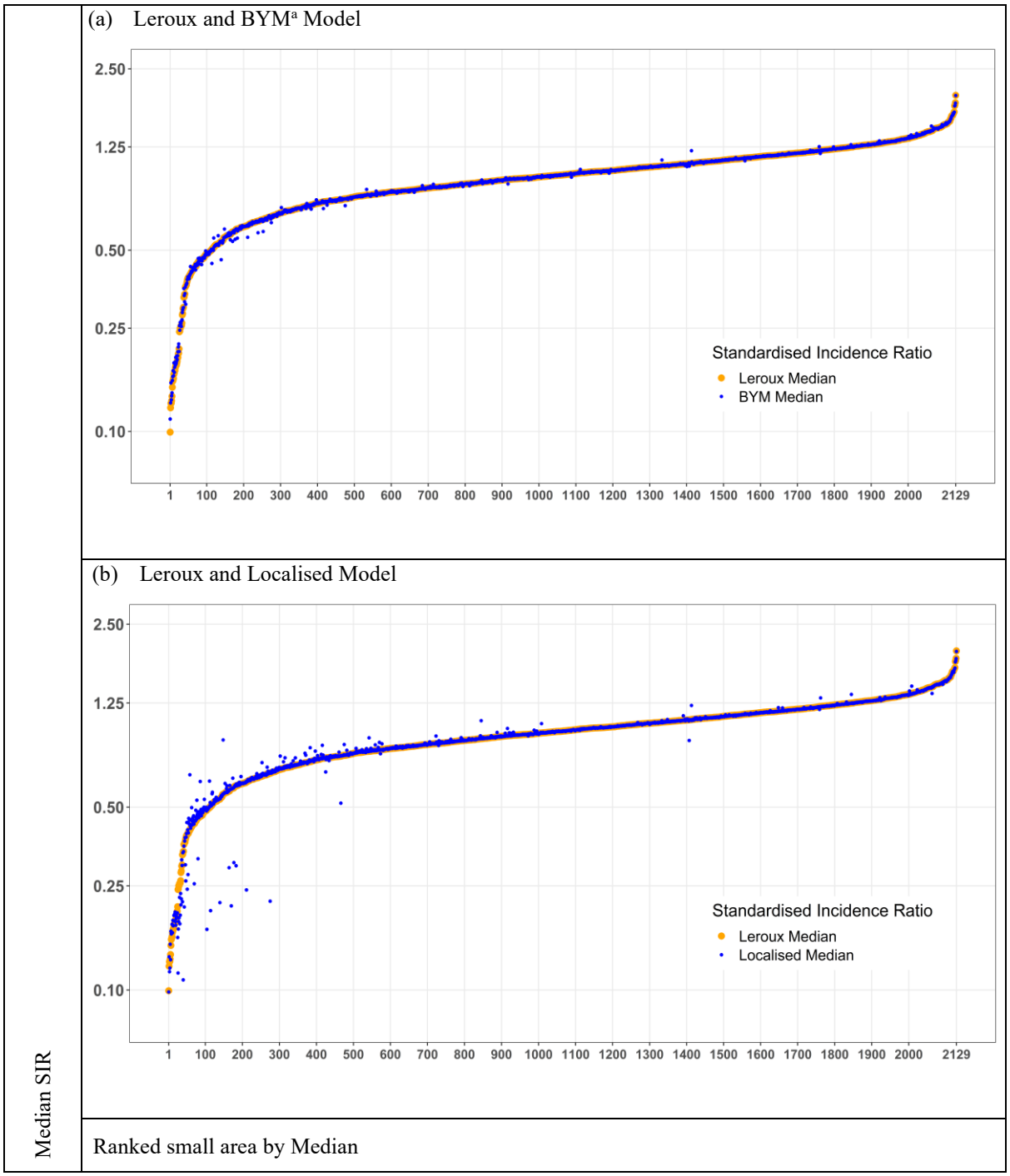
Standardized Incidence Ratio

Note: Australian average is shown as a red vertical line at SIR = 1

[a] Middle SES in plot means Middle Socio-Economic Status.

4.11 Supplementary material

Figure SF 4.1: *Standardized Incidence Ratio (SIR) median comparisons for 2129 small areas between (a) Leroux and BYM[a] model and (b) Leroux and Localised model.*



[a] BYM means Besag, York and Mollié.

File SFile 1: Leroux Model

$$y_i \sim \text{Poisson}(E_i \theta_i)$$

$$\log(\theta_i) = \text{intercept} + S_i$$

$$S_i | S_{\setminus i} \sim \mathcal{N}\left(\frac{\rho \sum_j w_{ij} s_j}{\rho \sum_j w_{ij} + 1 - \rho}, \frac{\sigma_s^2}{\rho \sum_j w_{ij} + 1 - \rho}\right)$$

$$\sigma_s^2 \sim \text{InverseGamma}(1, 0 \cdot 01)$$

$$\rho \sim \text{Uniform}(0, 1)$$

i = 1 to 2129 small area

j = Neighbouring small area of i

y_i = Count data

E_i = Expected counts

θ_i = Standardized incidence ratio

S_i = Structured spatial random effects

ρ = Spatial dependence parameter

σ_s^2 = Variance parameter

w_{ij} = Elements of spatial weight matrix ,

$$= \begin{cases} 1 & \text{if areas } i \text{ and } j \text{ are adjacent} \\ 0 & \text{otherwise} \end{cases}$$

s_j = Spatial autocorrelation random effects

Figure SF 4.2: *Trace plot and density plot (one model as an example) showing Markov Chain Monte Carlo samples distribution for beta parameter.*

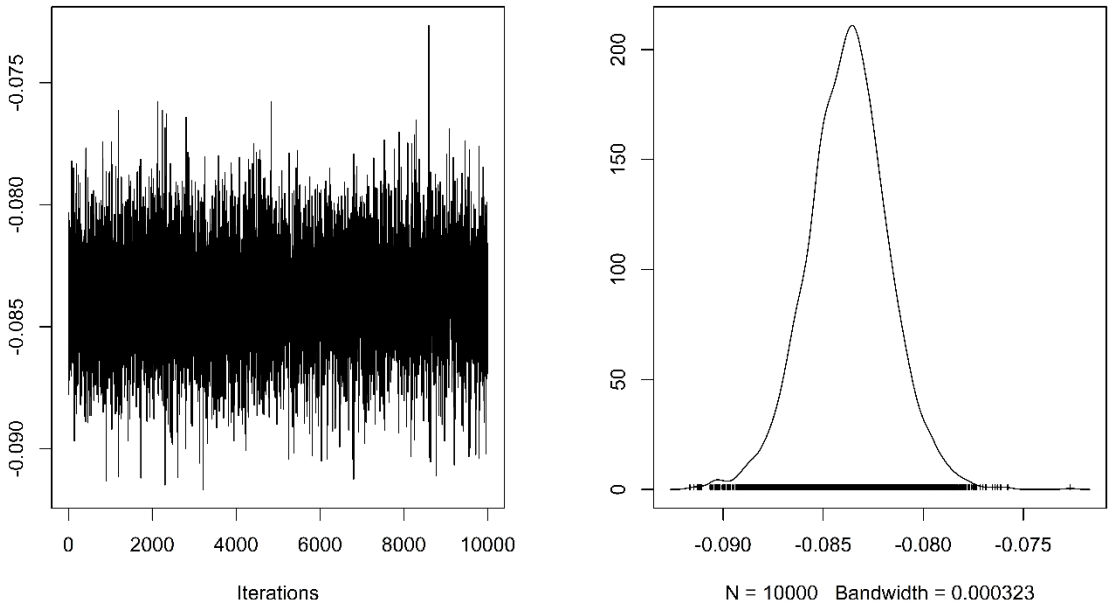
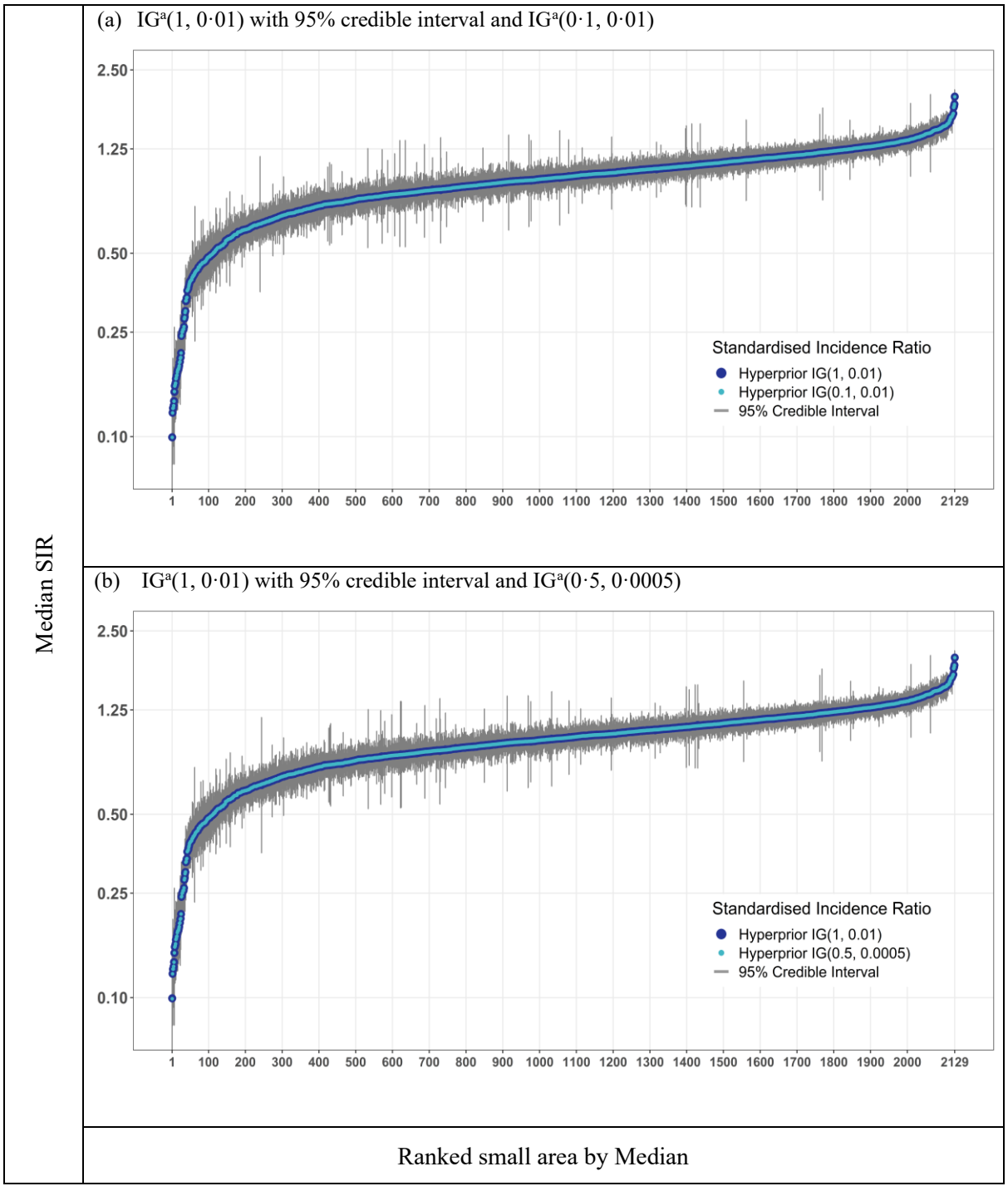


Figure SF 4.3: *Sensitivity analysis showing comparisons of standardized incidence ratio (SIR) for 2129 small areas using hyperpriors (a) IG[a](1, 0·01) with 95% credible interval and IG[a](0·1, 0·01) (b) IG[a](1, 0·01) with 95% credible interval and IG[a](0·5, 0·0005).*



[a] IG means Inverse-Gamma.

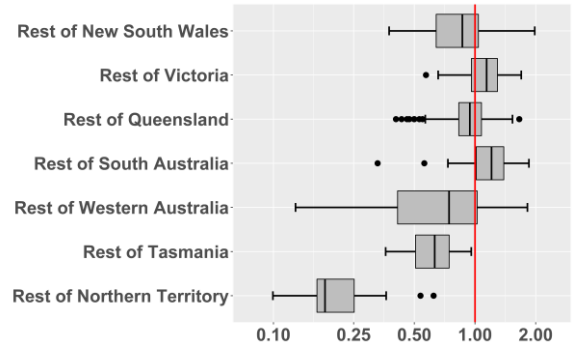
Table ST 4.1: *Small area comparisons for screening rates that were more than 50% higher (SIR>1·5) and more than 50% lower (SIR<0·5) than the Australian average (SIR=1) by Australia, capital cities, remoteness, socio-economic status, and state/territory.*

Characteristics	**Small Areas (n(%))**	**SIR[1] > 1·5 (n (%))**	**SIR[a] < 0·5 (n (%))**
Australia	2129 (100)	38 (1·8)	113 (5·3)
Capital Cities			
Outside Greater Capital Cities	908 (42·6)	25 (2·8)	89 (9·8)
Greater Capital Cities	1221 (57·4)	13 (1·1)	24 (2·0)
Remoteness			
Major City	1233 (57·9)	15 (1·2)	6 (0·5)
Inner Regional	483 (22·7)	5 (1·0)	21 (4·3)
Outer Regional	317 (14·9)	16 (5·0)	40 (12·6)
Remote	47 (2·2)	2 (4·3)	17 (36·2)
Very Remote	49 (2·3)	0	29 (59·2)
Socio-economic Status[b]			
Most Disadvantaged	419 (19·7)	10 (2·4)	46 (11·0)
Disadvantaged	421 (19·8)	9 (2·1)	20 (4·8)
Middle SES[c]	419 (19·7)	8 (1·9)	21 (5·0)
Advantaged	420 (19·7)	5 (1·2)	11 (2·6)
Most Advantaged	421 (19·8)	6 (1·4)	11 (2·6)
State / Territory[d]			
New South Australia	526 (24·7)	6 (1·1)	21 (4·0)
Victoria	427 (20·1)	10 (2·3)	0
Queensland	512 (24·0)	6 (1·2)	6 (1·2)
South Australia	163 (7·7)	8 (4·9)	1 (0·6)
Western Australia	234 (11·0)	8 (3·4)	25 (10·7)
Tasmania	95 (4·5)	0	16 (16·8)
Northern Territory	66 (3·1)	0	40 (60·6)
Australian Capital Territory	105 (4·9)	0	3 (2·9)

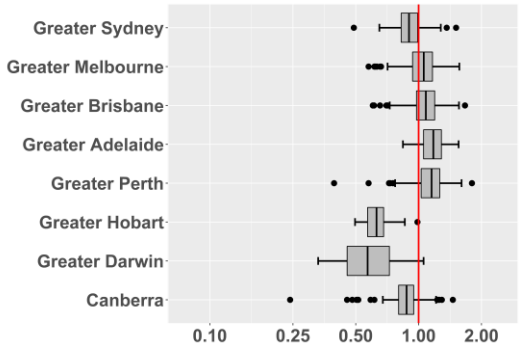
[a] SIR means Standardised incidence ratio.
[b] Small areas were excluded that do not have Index of Relative Socio-Economic Advantage and Disadvantage.
[c] Middle SES means Middle Socio-Economic Status.
[d] Jervis Bay area was excluded due to classified as Other Territory.

Figure SF 4.4: *Standardized incidence ratio (SIR) of prostate-specific antigen (PSA) screening for 2129 small areas during 2017-18 grouped by combinations of Greater Capital Cities, States/Territories, Socio-economic Status and Remoteness.*

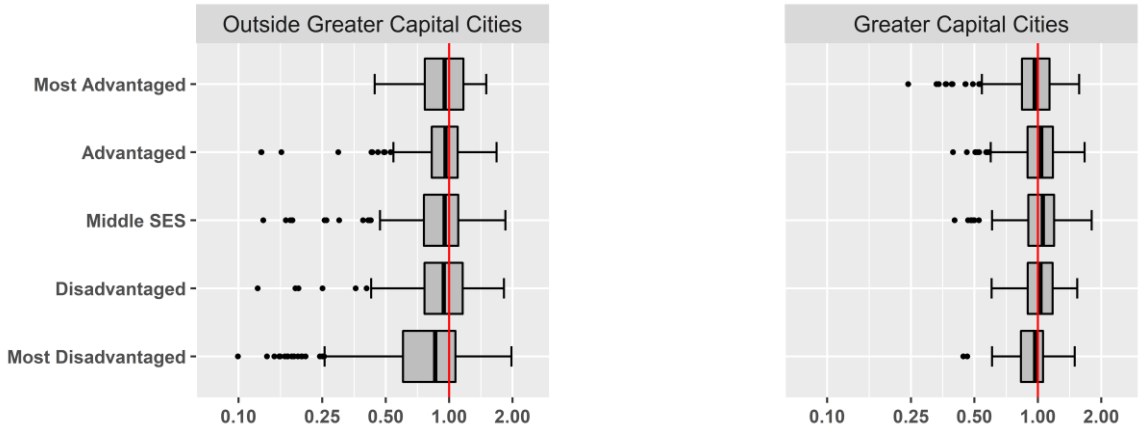
(a) Outside Greater Capital Cities by State/Territory



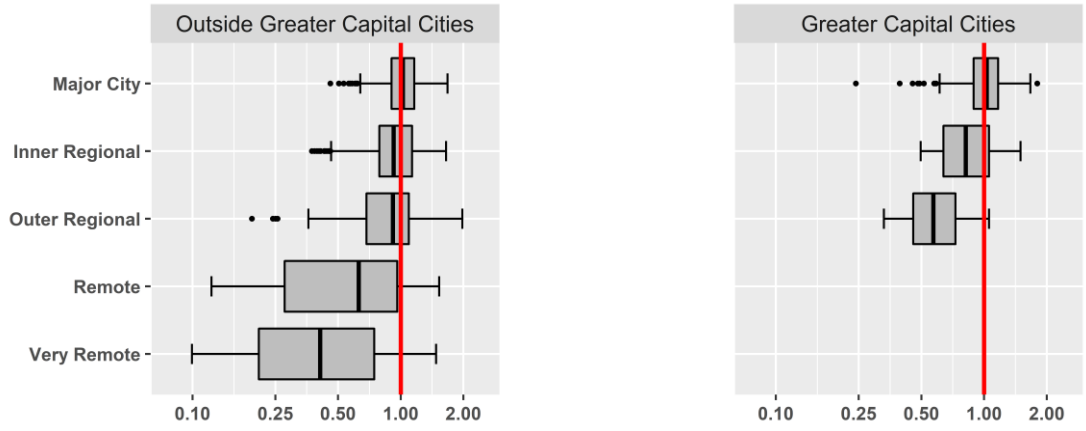
(b) Greater Capital Cities by State/Territory



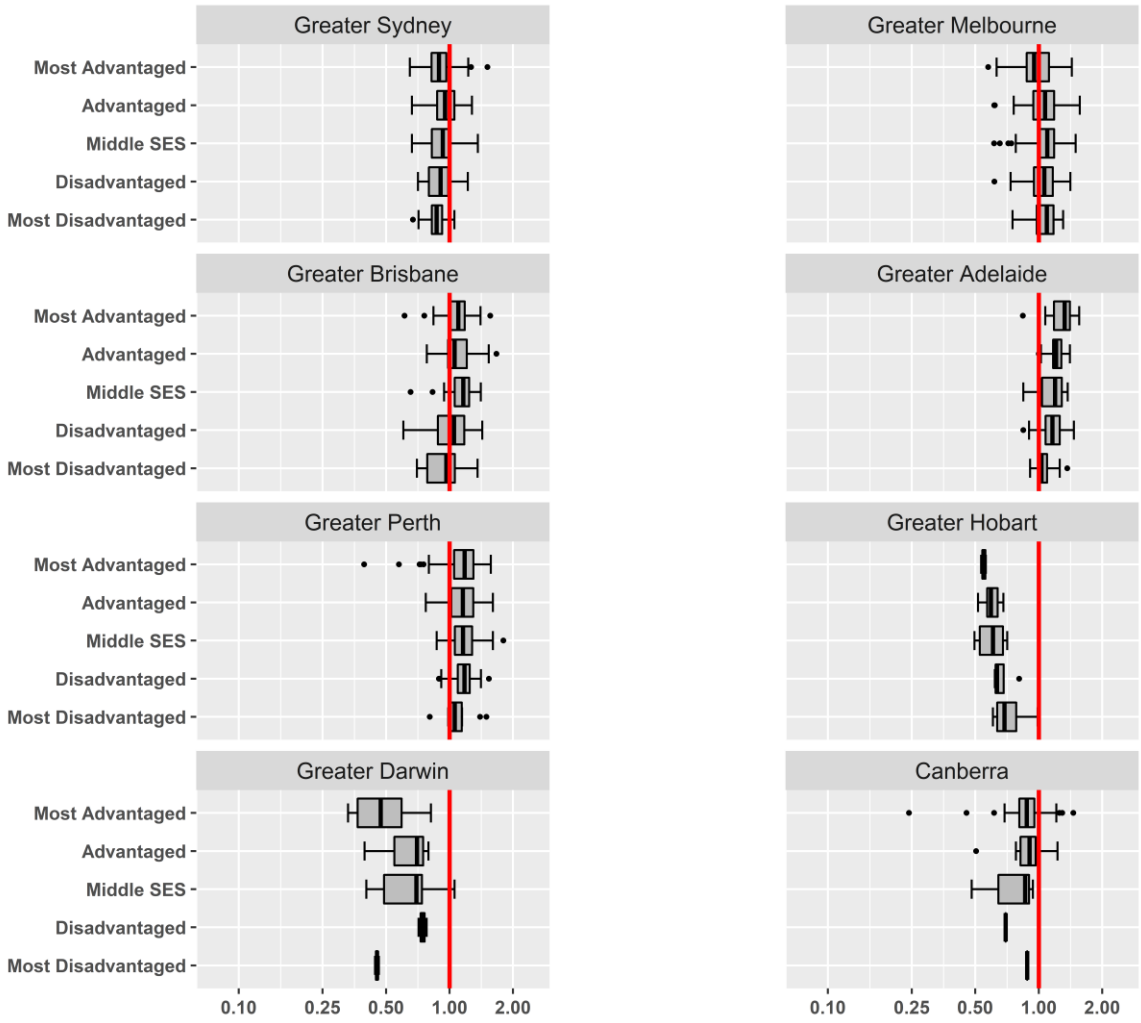
(c) Outside Greater Capital Cities and Greater Capital Cities by Socio-economic Status



(d) Outside Greater Capital Cities and Greater Capital Cities by Remoteness



(e) Greater Capital Cities by Socio-economic Status



Standardized Incidence Ratio

Note: Australian average is shown as a red vertical line at SIR = 1.

CHAPTER 5

5 SPATIO-TEMPORAL PATTERNS OF PROSTATE-SPECIFIC ANTIGEN TESTING IN ASYMPTOMATIC MEN: A POPULATION-BASED COHORT STUDY, AUSTRALIA, 2002-18

5.1 Chapter overview

This chapter presents a spatio-temporal analysis to identify the variation in prostate-specific antigen (PSA) testing rates by smaller areas and over time across Australia during the period 2002 to 2018. It explains the process of mapping postcodes to statistical areas and the statistical model used, which involves Bayesian spatio-temporal models to analyze the data and generate standardized incidence ratios for each small area. It represents the first population-based study conducted worldwide. This smaller area study utilizes Medicare data to highlight the temporal trends in PSA testing rates, the variations in testing rates among small areas, and the observed geographic patterns. It also discusses the regions that showed divergent trends and those with consistently low testing rates. The chapter has been published and presented as a final accepted manuscript.

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5.2 Manuscript cover page

Spatio-temporal patterns of prostate-specific antigen testing in asymptomatic men: a population-based cohort study, Australia, 2002-2018

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5.3 Highlights of this manuscript

- This manuscript analyzes Medicare data from the entire Australian population at an individual-level.
- It is the first population-based study to describe changes in small area PSA screening rates over time.
- The scope and patterns of geographic disparities in PSA testing rates across small areas have changed over time.

5.3.1 What is known before this manuscript

- In Australia, national PSA testing rates rose between 2002 and 2008, followed by a decline.
- Testing rates varied significantly by state and territory and remoteness category but were relatively consistent among area-level socio-economic groups.
- There was substantial variation in PSA testing rates between small areas during 2017-2018.
- Area-specific PSA screening rates were lower in remote areas compared to major cities. Socio-economic categories showed little difference in area-specific PSA screening distributions.

5.3.2 What is new in this manuscript

- This study identifies changes over time in small-area geographical patterns of PSA screening among men aged 50-79 years. The novelty is in the methods used. The manuscript presents the rate of men tested, rather than just the absolute number of tests conducted.
- The study revealed substantial variation in the geographic patterns of PSA screening over time.
- Not all small areas followed the national trend; from 2002 to 2008, 51% of small areas experienced an increase in testing rates, while 29% saw a decrease from 2009 to 2018.
- Differences in PSA testing behaviors across time and geographic areas likely contribute to these small-area variations.

5.4 Abstract

Objectives: In Australia, while prostate-specific antigen (PSA) testing rates vary by small geographical area, little is known regarding the extent of change in variations over time. This study aims to examine this in Australia during 2002-2018.

Study design: Retrospective population-based cohort study.

Methods: We received Medicare Benefit Schedule data on PSA testing (n=9,342,134) from the Commonwealth Department of Health, Australia for men aged 50-79, in the period 2002 to 2018. Postcodes were mapped to statistical area level 2 (n=2133) using a probability-based correspondence file and multiple (n=50) iterations. Bayesian spatio-temporal models were used to generate indirectly standardized incidence ratios for each small area over time, allowing comparisons with the national average testing rates.

Results: The annual percentage of men aged 50-79 who received PSA testing in small areas increased until 2008, peaking at 24.5%, before declining. Geographical patterns of PSA testing varied substantially over time, with some areas deviating from the national trend. Between 2002 and 2008, 50.87% of small areas experienced increased testing rates, while 29% showed a decrease from 2009 to 2018. Regions on the east coast and southwest, primarily major cities and regional areas, exhibited the most divergent temporal trends, while many remote areas maintained consistently low testing rates.

Conclusions: The extent and patterns of geographic variation in PSA testing rates across small areas has changed over time. Given the reasons for this variation are likely multifactorial and complex, it remains a priority to understand the reasons for this variation and help ensure all men at risk of prostate cancer have equitable access to relevant decision-making information.

5.5 Introduction

Prostate cancer is the second most common diagnosed cancer among men worldwide (Zhou *et al.,* 2016). Incidence rates have been consistently high in Australia compared to other developed countries (Feletto *et al.,* 2015), and approximately 24,000 new prostate cancer cases were estimated to be diagnosed in Australia in 2022 (Australian Institute of Health and Welfare 2022). Prostate cancer incidence rates also vary markedly across the country (Australian Cancer Atlas 2021).

One postulated cause of these varying rates is differences in rates of prostate-specific antigen (PSA) testing across the nation (Kohar *et al.,* 2023). The PSA test is a blood test that can be used to screen asymptomatic men for prostate cancer risk. PSA testing has been controversial over the years due to its low sensitivity and issues surrounding potential harms of diagnosis and treatment (Denham *et al.,* 2010). The PSA test became a reimbursable item on Medicare, Australia's universal health care system, in the late 1980s and was rapidly adopted as a test used to indicate the presence of prostate abnormalities. Although PSA testing guidelines in Australia have changed over time, contemporary guidelines from both the Royal Australian College of General Practitioners (The Royal Australian College of General Practitioners 2016) as well as Prostate Cancer Foundation of Australia and Cancer Council Australia (Prostate Cancer Foundation of Australia and Cancer Council Australia PSA Testing Guidelines Expert Advisory Panel 2016) recommend that men aged 50-69 years should make an informed decision whether to have a PSA test, after carefully considering the risks and benefits.

In Australia, PSA testing rates have changed over time, with national PSA testing rates increasing from 2002 to 2008 and then declining (Kohar *et al.,* 2023). Testing rates varied substantially by state or territory and remoteness category but were relatively similar between area-level socio-economic groups (Kohar *et al.,* 2023). In addition, the trends over time for individual states and territories, area-level socio-economic status and remoteness were generally consistent with the national trends (Kohar *et al.,* 2023).

A recent Australian based study (Wah *et al.,* 2021) evaluated spatio-temporal variations in prostate cancer incidence in Victoria and concluded that temporal changes in PSA testing have contributed to an increasing temporal trend in prostate cancer incidence. However, prostate cancer incidence patterns over time are unclear across small areas in Australia. While there was a large variation in PSA testing rates between small areas during 2017-2018, following the introduction of the 2016 Australian guidelines (Kohar *et al.,* 2023), there is currently no understanding of how small area patterns have changed over time in Australia. This information is particularly relevant and timely as national guidelines are being reviewed as it may help to inform future communications and decision making about testing Australian men for prostate cancer.

The aim of this study is to identify how the variation in PSA testing rates by smaller areas has changed over time in Australia during the period 2002 to 2018.

5.6 Methods

5.6.1 Data

This study used data on prostate-specific antigen (PSA) testing obtained from the Medicare Benefits Schedule (MBS) managed by the Australian Department of Health and Aged Care. The data extract included details for Australian men aged 50 to 79 years who had a PSA test funded by the MBS over the time period 2002 to 2018. During the study period there were four MBS item numbers related to PSA testing (66655, 66656, 66659 and 66660). Item 66655 was defined as "Prostate specific antigen (test) – quantitation – 1 of this item in a 12 month period" which was generally used in asymptomatic men. The other PSA test items are recommended for monitoring of previously diagnosed prostate disease (66656), or the follow up of equivocal PSA results (66659, 66660). In this paper we solely focus on item number 66655 and refer to it hereafter as a "screening" PSA test. The other variables obtained in this dataset were year and month of test, updated residential postcodes of each man, age grouped in 10-year age bands (50-59, 60-69 and 70-79) and unique ID number for each individual man. Data were stored and accessed through the Secured Unified Research Environment (SURE) (The Sax Institute 2022) for the purposes of security and confidentiality. Ethics approval was obtained from Griffith University Human Research Ethics Committee (GU Ref no: 2017/777).

5.6.2 Geography and concordance

The postcode where each man resided at the time of screening was provided in the Medicare data. We used the population-weighted 2011 Australian Bureau of Statistics (ABS) Geographical Correspondence File (Australia Bureau of Statistics 2012) to convert the postcodes into the Statistical Area Level 2 (SA2) geographic units of the 2011 Australian Statistical Geography Standard (ASGS). Generally, SA2s are relatively homogenous small areas with population data available across Australia. The median population of all SA2s in 2011 was 400 (IQR: 225, 665) for men aged 50 to 79. Throughout the manuscript we refer to SA2 as a "small area". In 2011, there were 2,196 small areas covering the entire geography of Australia without gap or overlap. For this analysis we assumed 2002-2018 postcode boundaries were the same as the 2011 boundaries.

5.6.3 Exclusions

So that the final dataset was based on the number of men screened per year rather than the number of screening tests undertaken, we excluded duplicate tests for an individual in any given calendar year (Figure 5.1). Screening tests were also excluded if the postcode was solely identified as a Post Office Box, since it did not reflect a residential geographical area. Tests were also excluded if the postcode did not match with the 2011 ABS concordance file.

5.6.4 Small area allocation

A postcode in Australia can encompass either a whole or partial section of one or more SA2s. For each postcode, the proportion of the population allocated to each SA2 was defined in the correspondence file (Australia Bureau of Statistics 2012). Using these proportions, each record was randomly allocated to a relevant SA2 according to the uniform distribution. The allocation process was repeated 50 times to incorporate the uncertainty in the postcode-to-SA2 correspondence via the probabilistic allocation of SA2s, generating 50 different allocated datasets. For some SA2s with small male populations during 2002-2018 (n=1 to 15 for different years), this process resulted in the allocated number of men tested being higher than the eligible population. For those 31 combinations of small area and year where this occurred, the 2,025 men from these areas were modified to be equal to the eligible population of those areas (n=664).

5.6.5 Population

The annual estimated resident population of each SA2 for men aged 50-79 years between 2002 and 2018 was obtained from the ABS [5]. Data for 2002 to 2016 was provided for 2011 ASGS boundaries, while data for 2017 to 2018 (provided based on the 2016 ASGS) were concorded to the 2011 ASGS using an ABS population correspondence file [6].

5.6.6 Small area exclusion

In total, we excluded 63 small areas (532 men) from the analysis including areas that had an average annual population from 2002-2018 (for men aged 50-79) up to three men (n=60) or were remote islands (n=3) that do not have a spatial relationship with the mainland (Christmas, Cocos, and Lord Howe Islands). The final population dataset had an average annual population of 473 (Range: 0, 3253) men aged 50-79 years per small area during the period 2002-2018 across 2,133 small areas.

5.6.7 Statistical model

Bayesian spatio-temporal models were used to examine changes in PSA screening over time and by small area. We considered two models, the first included an overall time trend and separate geographical patterns for each time period (Model 1, based on Napier et al (Napier *et al.,* 2016)). The second model had an overall time trend and geographical pattern with a space-time interaction term (Model 2, based on Knorr-Held et al (Knorr-Held 2000)). The spatial smoothing was achieved using a Leroux prior while temporal effects were given a random walk 1 (RW1) prior. Adjacent small areas were considered neighbors if they shared a boundary. Model 1 was preferred over Model 2 based on its stability in estimates and the simplicity of the model, which favored parsimony. Results of this study are based on Model 1 and include Standardized Incidence Ratio (SIR) maps, exceedance probability maps and temporal analysis. Full details for Models 1 and 2 are provided, including priors and hyperpriors (File Sfile 1), sensitivity checks (Figure SF 5.1 and SF 2) and a comparison of modelled results (Figure SF 5.3).

5.6.8 Expected counts

The baseline for the SIRs was the Australian average rates over the whole study period. This was achieved by calculating the expected counts using national rates that were averaged over the whole study period. The resulting SIRs compare an areas' annual rates with the Australian rates averaged over the whole period, 2002-2018. Consequently, the baseline will be referred to as the "2002-2018 Australian average".

In detail, national age-specific testing rates for each 10-year age group were calculated based on the number of screens in the eligible population over the whole time period. Expected counts for each small area and year were calculated by multiplying the national age-specific rates by each area's annual age-specific population and summing across the age groups. These were calculated for each of the 50 datasets generated by the reallocation from postcode to SA2.

5.6.9 Model computation and testing

Spatio-temporal models were run separately on each of the 50 datasets generated by the reallocation process. Each dataset contained both expected and observed counts and the models were run for 150,000 iterations with the first 50,000 discarded and only every 10^{th} sample kept. The models produced modelled SIRs of PSA screening for each small area by year. Modeling was performed in R software version 4.1.3 (R Core Team 2020) using the CARBayesST package version 3.3 (Lee *et al.,* 2018). Model 1 used the function ST.CARsepspatial, and model 2 ST.CARanova. Convergence of the Markov chains was checked using Geweke diagnostics (value between -2 and 2 indicated convergence). Further, we examined trace plots and histograms as a graphical check of convergence of the global parameters. With convergence

confirmed, the MCMC samples kept from each of the 50 datasets were pooled to produce overall distributions of the parameters. To check model goodness-of-fit, the Moran's I statistic (Anderson and Ryan 2017) was used to measure the amount of spatial autocorrelation in the residuals for each year.

A sensitivity analysis was performed on the 50 datasets for Model 1 to check the robustness of the results, specifically the influence of using three different hyperpriors on the variance term in the Leroux prior: IG(1, 0.01), IG(0.1, 0.01) and IG(0.5, 0.0005) where the Inverse-Gamma distribution is shown as (shape, scale).

5.6.10 Visualization

Maps

Spatial maps of modelled SIRs were generated for each year in the study period (2002-2018) to provide an overall description of PSA screening patterns in Australia. The SIR reflects the standardized incidence rates of PSA testing for small areas at a specific time point, compared with the Australian average over the whole time period (2002-2018). For every fifth year from 2003 (2003, 2008, 2013, 2018), insets for the spatial maps were generated for the capital city areas to illustrate geographical patterns in these densely populated but geographically small areas that are not visible on the national map. The gradient color scale of SIR maps uses shades of orange/red color for values greater than one, while values lower than one are represented by shades of blue/light blue. In addition, Australian average at SIR=1 is represented by pale yellow.

Exceedance probability maps

While SIRs show the magnitude of variation, they do not indicate if it is likely to differ from the Australian average. We used exceedance probabilities (EP) which are the posterior-probability that the SIR is greater than 1, to determine which areas were likely to be truly different to the whole-period Australian average. Conversely, 1-EP reflects the posterior probability that the SIR is lower than 1. National maps of exceedance probabilities by small areas were shown for each calendar year, with insets provided for the same four years as above. Purple and green respectively represent evidence that the rates are truly higher (>80% probability) than the national average and lower (<20% probability of higher; which equates to >80% probability of lower) than the national average for the small areas (Richardson *et al.,* 2004). Using this categorization and color coding for the exceedance probabilities, the number of small areas (on y-axis) in each category (<20%, 20% - 80% and >80%) was plotted against year (on x-axis). R package Ggplot2 version 3.3.6 (Wickham 2016) was used for visualization.

Temporal plot and Sankey diagrams

Boxplots were used to visualize the distribution of small area-specific PSA screening estimates for each year compared to the Australian average (SIR=1). The Sankey diagram visualizes temporal change in PSA screening estimates for each small area by categorizing SIR values as 0.67-0.79 (blue), 0.80-0.94 (light blue), 0.95-1.05 (yellow), 1.06-1.24 (orange) and 1.25-1.50 (red). Cutpoints below 1 are the inverse of those above 1. Colors in the vertical bar represent the current status of small areas ranked by the categories, whereas the gap between bars shows the path of small areas changing their category each year. Likewise change in exceedance probabilities over time for each small area were represented as <20% (green), 20% - 80% (yellow) and >80% (purple).

5.7 Results

In Australia, during the period 2002 to 2018, a total of 9,458,168 PSA screening tests were performed on 3,270,817 men aged 50-79 years (Figure 5.1). Records were excluded from the study (totaling 0.64%) if their residential postcode was solely a Post Office Box (n=6.84%), if they were a duplicate test for a man in a single calendar year (0.04%), if the residential postcode did not match with the ABS concordance file (0.55%) or if the matched SA2 of residence had an average population of men aged 50-79 of three or less (0.01%). The final dataset included 9,342,134 screening tests among 3,243,849 Australian men aged 50-79 years with an overall crude rate of 181.53 men screened per 1000 men per year.

The annual percentage of the male population aged 50-79 having a PSA screening test in a given year varied substantially between 2002-2018, with a peak in 2008 (Table 5.1). While men aged 50-59 had the most screening tests of the three age groups, they had the lowest screening rate per capita. The percentage of eligible men who had a PSA screening test differed by state and territory (Table 5.1).

There was strong variation in the spatial patterns of PSA screening rates over time (Figure 5.2 (A) and Figure 5.3). The maps are visually dominated by the geographically large, but sparsely populated central, northern and western areas of the country, however the main changes over time are visible in the smaller, more densely populated south-eastern corner of the country. In particular, the PSA screening rate in the majority of the areas in the south-eastern part of Australia during 2003 were lower than the 2002-2018 Australian average. By 2008, however, the screening rates in much of the south-east were higher than the 2002-2018 combined Australian average. After 2008, many of these areas' screening rates decreased until they were lower than the 2002-2018 Australian average. Similar changes in patterns were also observed in smaller pockets of Western Australia, and Queensland. (Figure 5.2 (A), Figure 5.3 and Figure SF 5.4).

The exceedance probabilities (Figure 5.2 (B), Figure 5.5 and Figure SF 5.5) provide strong evidence that these changes in geographical patterns over time are likely to be real, with the vast majority of areas across all calendar years having PSA screening rates considered likely to be truly different to the 2002-2018 Australian average. Only a few small areas had any year-specific exceedance probabilities between 20 and 80% (so unlikely to reflect a true difference to the Australian average).

These area-level temporal patterns are highlighted by the distribution of smoothed SIRs for each small area over the study period (Figure 5.6). For example, in 2008 all the interquartile ranges were above the 2002-2018 Australian average, while from 2015 onward they were all below the 2002-2018 Australian average.

The trends over time can also be viewed at the small area level (Figure 5.4 (A)), with the trend lines being ranked and colored by their screening rates in 2002. There is substantial variation in the small area-specific trends over time, with only a small proportion of areas having screening rates that remained relatively low over the entire study period. Similarly, the trend lines for changes in exceedance probabilities can also be viewed at the small area level (Figure 5.4 (B)). There is substantial variation in the trends of exceedance probabilities over time, with most areas initially having rates that were truly below the Australian average, peaking above average, and then returning to below average compared to areas with no-real difference. However, the timing of this trajectory varied considerably among small areas. Nonetheless, only a few small areas consistently exhibited lower (<20%) or higher (>80%) exceedance probabilities over time.

Although the number of small areas likely to be different to the combined Australian average remained fairly constant over time (Figure SF 5.6), the specific small areas within the higher and lower groups changed considerably each year.

Sensitivity analysis suggested the results were robust in terms of the initial model assumptions made, with little or no variation in SIR results when different hyperpriors were applied (Figure SF 5.1 and SF 5.2). Similar geographical patterns and exceedance probabilities were observed for both models (Model 1 and Model 2) over time (Figure SF 5.6).

5.8 Discussion

To our knowledge this is the first population-based study to describe the change in PSA screening rates by small area over time. Australia is well placed to undertake a study of this type because almost all PSA tests were reimbursed by Medicare for the entire study period and the data are available at relatively small geographical areas (SA2). This study identified that the geographic patterns of PSA screening varied substantially over time. From 2002 to 2008, more than half (50.87%) of the small areas displayed an

increase in screening rates, and 29% of small areas showed a decrease in screening rates from 2009 to 2018. These small areas that followed the national trend were predominantly in major cities and regional areas, while many remote areas' PSA screening rates remained low throughout the study period.

While reasons for the different temporal trends for PSA screening cannot be determined from this study, they may be influenced by factors relating to the local area such as population characteristics or availability of services, systematic changes in screening awareness or behaviours, changes in the interpretation or application of the guidelines or variation in the socio-demographic characteristics of small area populations. For example, new housing estates may alter the demographic, socio-economic or ethnic composition of certain areas thus altering composition of the base population likely to be available and interested in screening.

General practitioner's attitude and behaviour:

In Australia, PSA screening tests are most often offered by general practitioners (GPs), so any variations in their clinical advice and behaviour is likely to contribute to differences in PSA screening rates. Differences in test ordering behaviors by time and geographical areas are likely to result in small area variations. Some GPs in the Australian context have reported feeling inadequately supported by the healthcare system when making decisions about PSA testing (Pickles *et al.*, 2016) and perceive confusion about whether to test individual asymptomatic men. This can often manifest as a dilemma between seeking to avoid overdiagnosis (i.e. less PSA testing), compared to trying to prevent a missed or late diagnosis (i.e. more PSA testing) and potential harmful outcomes to the patient and possible medico-legal issues that could follow (Pickles *et al.*, 2015). As a result, some GPs only initiate discussions within the recommended age range, while others discuss screening beyond this range (either initiated by the GP or patient) (Smith *et al.*, 2022). GPs can also have varying attitudes regarding the optimal age to begin PSA screening (Crowe *et al.*, 2015). While the two most commonly referenced current Australian guidelines have similarities in the general principles of informed decision making, they differ in the way in which this is expressed. RACGP guidelines (Royal Australian College of General Practitioners 2016) recommend that GPs are not obligated to offer PSA tests to asymptomatic men, while the PCFA/Cancer Council guidelines (Prostate Cancer Foundation of Australia and Cancer Council Australia PSA Testing Guidelines Expert Advisory Panel 2016) take no position on "whether, or how, primary care doctors should raise the topic of prostate cancer testing with their male patients. Both guidelines advise that screening with PSA tests is acceptable in men who make an informed decision. Elsewhere, in popular media and medical journals, authors have incorrectly portrayed the PCFA/Cancer Council guidelines as including a positive recommendation for GPs to actively offer screening (Rashid *et al.*, 2023, Timms and Gregory, 2022). Thus, apparently conflicting

advice may have compelled some GPs to apply their own screening protocols (Ranasinghe *et al.,* 2015). At the time of writing, preparations were underway to update the PCFA/Cancer Council guidelines with a view to more consistent and practical messaging for all clinicians involved in PSA testing.

However, PSA testing rates in Australia are not solely determined by individual GP attitudes towards screening or interpretation of published guidelines. Qualitative research has suggested that GP behaviour is often more directly influenced by internalised guidelines which are individually developed and socially reinforced by personal experience, colleagues, opinion leaders and patients than research publications (Gabbay and May, 2004). Thus, some of the clustering of PSA testing we observed may reflect the socially-mediated influences of GPs' local community of practice. Current and past healthcare structures, systems, and, regulations also significantly influence the attitudes and behaviours that GPs adopt in their practice (Pickles *et al.,* 2016). In Australia, GPs are remunerated based on the number of patient care services provided, resulting in higher income with an increased number of appointments. Additionally, various system factors such as screening culture, funding models, media exposure, referral system, and the influence of local or reginal urological specialists may contribute to the variation in prevalence of PSA screening in Australia (Pickles *et al.,* 2016). Temporal variations may also be linked to the relocation of GPs to or from that area. For instance, an influx of GP registrars to a small area could lead to a rise in screening rates as previous work has shown a higher likelihood of registrars ordering PSA tests than more experienced GPs in Australia (Magin *et al.,* 2017). However, these explanations are speculative, as data on these less tangible measures of practice are not available at smaller geographical areas, nor do we have information about how those factors have changed over time.

Change in men's PSA screening awareness over the period:

Previous research has shown that men generally view PSA screening positively (Howard *et al.,* 2013, Thomas *et al.,* 2014, James *et al.,* 2017). Men with high anxiety levels, uncertainties associated with PSA testing, and those with more concerns about poor outcomes were found to be more likely to undergo PSA testing during follow-up visits with their GPs (Pedersen *et al.,* 2015). Many men living in rural areas may have less awareness and knowledge regarding prostate cancer screening (Ojewola *et al.,* 2017, Maladze *et al.,* 2023), whereas those with higher socioeconomic status, education levels, and income have been noted to have higher awareness and knowledge regarding screening (Musalli *et al.,* 2021). A survey found that 55% of men reported being informed about their right to choose whether or not to undergo testing, 22% were informed that some doctors recommend PSA testing while others do not, and 14% were informed that the effectiveness of PSA testing in saving lives is still uncertain. Only 10% of men reported receiving this information about PSA testing (Leyva *et al.,* 2016). It has been suggested that Australian men are often

willing to participate in prostate cancer screening, especially when supported by their social networks or healthcare providers (James *et al.,* 2017). While there is no information about how these attitudes have changed over time, the very large variation in attitudes among Australian men between different geographical and sociodemographic subgroups suggests the potential for these attitude and behaviours to have altered over time.

5.8.2 Strengths and limitations

This study has several notable strengths. Firstly, it draws on population-based data that covers the entire nation of Australia for a 17-year period, from 2002 to 2018. To ensure accuracy and mitigate the impact of multiple tests in our analysis, we limited our data to one test per man per year, enabling us to focus on the number of men screened annually, rather than the total number of screening tests administered. The use of Bayesian spatio-temporal modeling techniques is key strength, a technique designed to produce robust estimates. Through combining the dataset available and these methods, we captured a significant proportion of PSA tests among eligible Australian males and were able to provide more reliable estimates of the underlying small-area rates.

The study also had some limitations. A small proportion of PSA tests will not have been captured in this dataset. Under Medicare, only the three most expensive pathology items in a care episode can be claimed during a single episode of care, referred to as 'episode coning', potentially resulting in under-reporting of pathology tests in less accessible areas where men and their GPs may bundle a number of tests into a single episode of care (Hajati *et al.,* 2018). The PSA test can be particularly susceptible to this under-reporting due to its low schedule fee ($AUD 20.15) and the extent of variation by small geographical area is unknown. Furthermore, Medicare address details may not be updated, so if men move, these changes may not be reflected in the results.

5.9 Conclusion

To summarize, this study identified significant changes in the geographic disparities in PSA screening rates over time. Not all areas followed the national trend, and the reasons behind these disparities are likely multifaceted and complex. These findings emphasize the need for further research to better understand the underlying factors and ensure equitable access to clinical decision-making for all men at risk of prostate cancer, regardless of their area of residence. Achieving this goal will require the development and implementation of more effective resources, policies, and communication strategies with broader reach and applicability.

5.10 References

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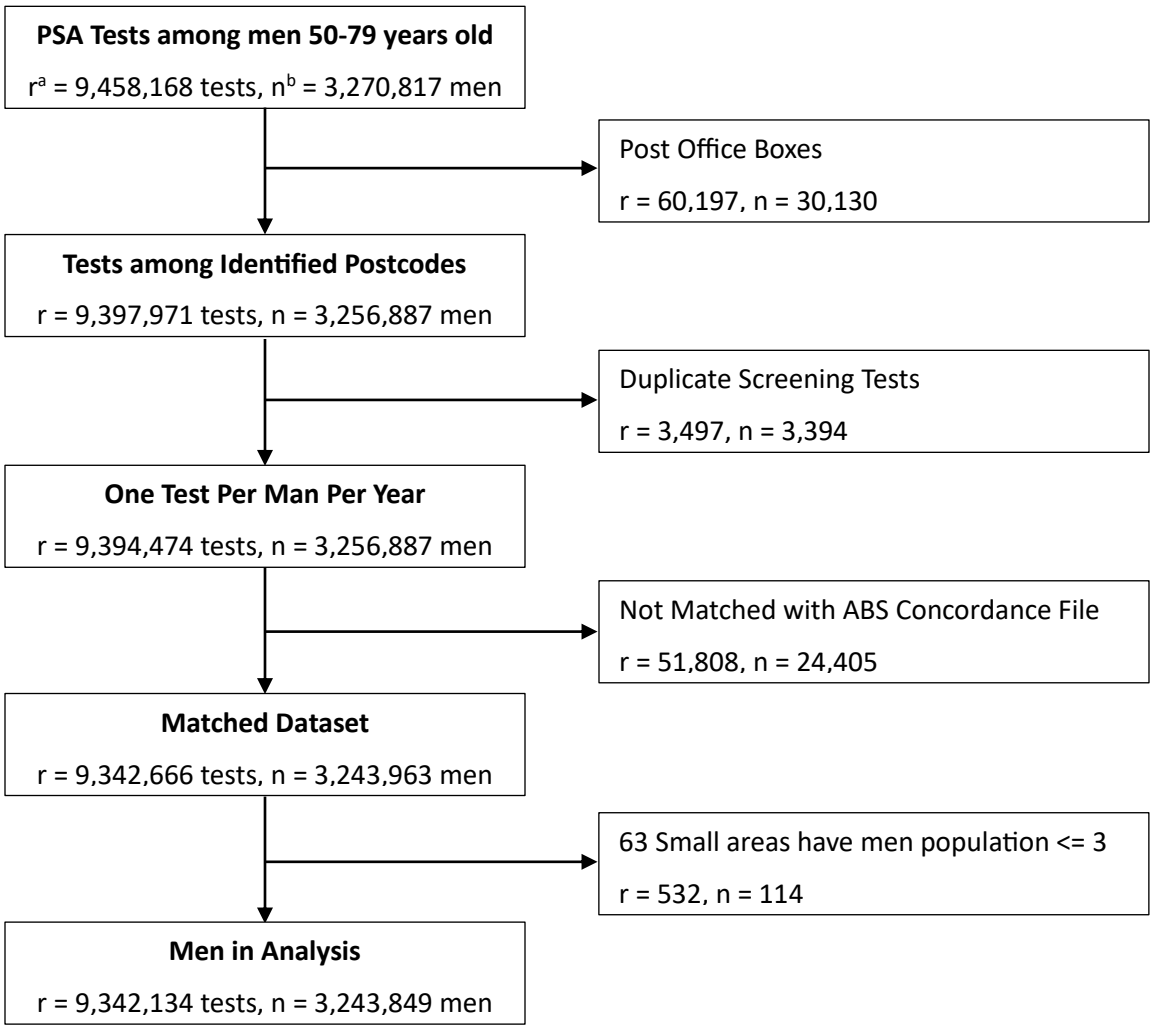
Figure 5.1: *Flowchart showing selection of men aged 50-79 in analysis, 2002-18, Australia.*



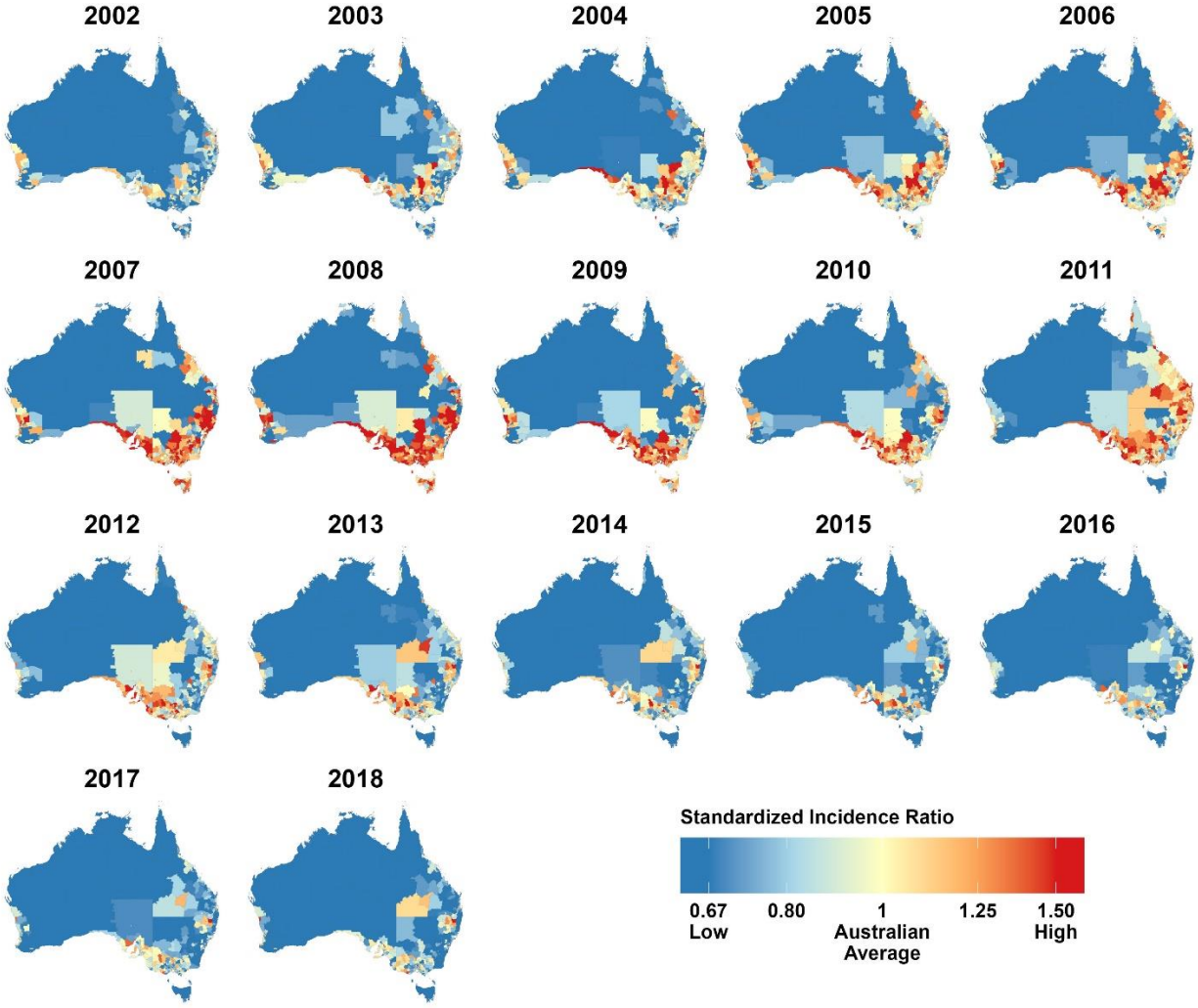
[a] r = Records of PSA screening test
[b] n = Number of men

Table 5.1: *Demographic characteristics of men aged 50-79 with a record of at least one PSA test reimbursed by Medicare per year, 2002-18, Australia.*

Characteristics	Number of individual men[a] tested	Number of PSA tests[b]	Total eligible population over study period[c]	Average annual percentage of men having a PSA Test[d]
Australia	3,243,849	9,342,134	51,463,109	18.2
Age group (years)				
50 - 59	1,935,621	3,788,193	23,295,346	16.3
60 - 69	1,616,084	3,552,231	17,474,943	20.3
70 - 79	961,462	2,001,710	10,692,820	18.7
State / Territory				
New South Wales	1,085,269	2,850,754	16,918,211	16.9
Victoria	826,014	2,460,682	12,603,465	19.5
Queensland	670,159	1,827,650	10,171,674	18.0
South Australia	273,440	864,252	4,062,456	21.3
Western Australia	325,570	959,139	5,191,447	18.5
Tasmania	82,224	206,719	1,350,213	15.3
Northern Territory	16,739	34,683	420,307	8.3
Australian Capital Territory	51,000	138,255	745,336	18.5
Year				
2002	387,239	387,239	2,487,305	15.6
2003	426,899	426,899	2,546,339	16.8
2004	475,292	475,292	2,602,030	18.3
2005	528,982	528,982	2,660,811	19.9
2006	576,347	576,347	2,721,899	21.2
2007	651,503	651,503	2,792,627	23.3
2008	701,549	701,549	2,864,224	24.5
2009	613,300	613,300	2,939,948	20.9
2010	605,760	605,760	3,018,126	20.1
2011	671,837	671,837	3,102,361	21.7
2012	569,408	569,408	3,181,075	17.9
2013	543,075	543,075	3,258,849	16.7
2014	519,011	519,011	3,330,897	15.6
2015	513,460	513,460	3,395,409	15.1
2016	520,644	520,644	3,457,265	15.1
2017	517,801	517,801	3,520,322	14.7
2018	520,027	520,027	3,583,622	14.5

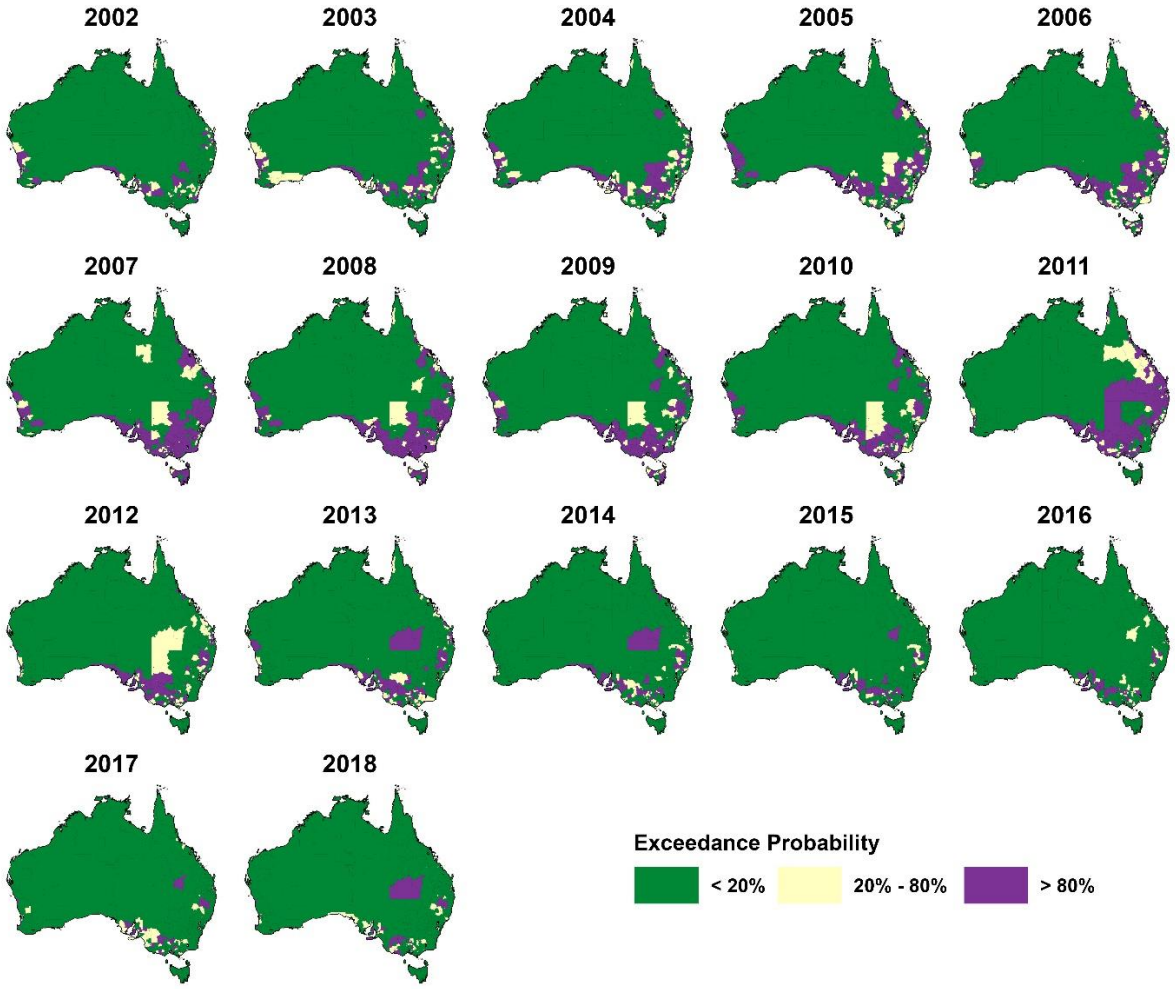
[a] Men counted once over the whole time period.
[b] Each man only had one test counted per year.
[c] Sum of the eligible population over the whole study period.
[d] Number of PSA tests divided by the total eligible population

Figure 5.2: *(A) Spatial patterns by year of prostate-specific antigen screening as modelled Standardized Incidence Ratios compared to the Australian average[a] between 2002-18.*



[a] Average Australian prostate specific antigen screening participation rate between 2002 and 2018

(B) Exceedance probabilities by smaller area[a,b,c] of prostate-specific antigen screening, 2002-18, Australia. The exceedance probability provides evidence that the annual SIRs were truly different to the 2002-2018 Australian average.



[a] < 20% - Areas where prostate specific antigen screening participation rates were likely to be lower than the 2002-2018 Australian average .
[b] 20% - 80% - Unlikely to be different from Australian average between 2002 and 2018
[c] > 80% - Areas where prostate specific antigen screening participation rates were likely to be higher than the 2002-2018 Australian average.

Figure 5.3: *Map showing standardized incidence ratios of prostate specific antigen screening for the selected years 2003, 2008, 2013, 2018, Australia.*

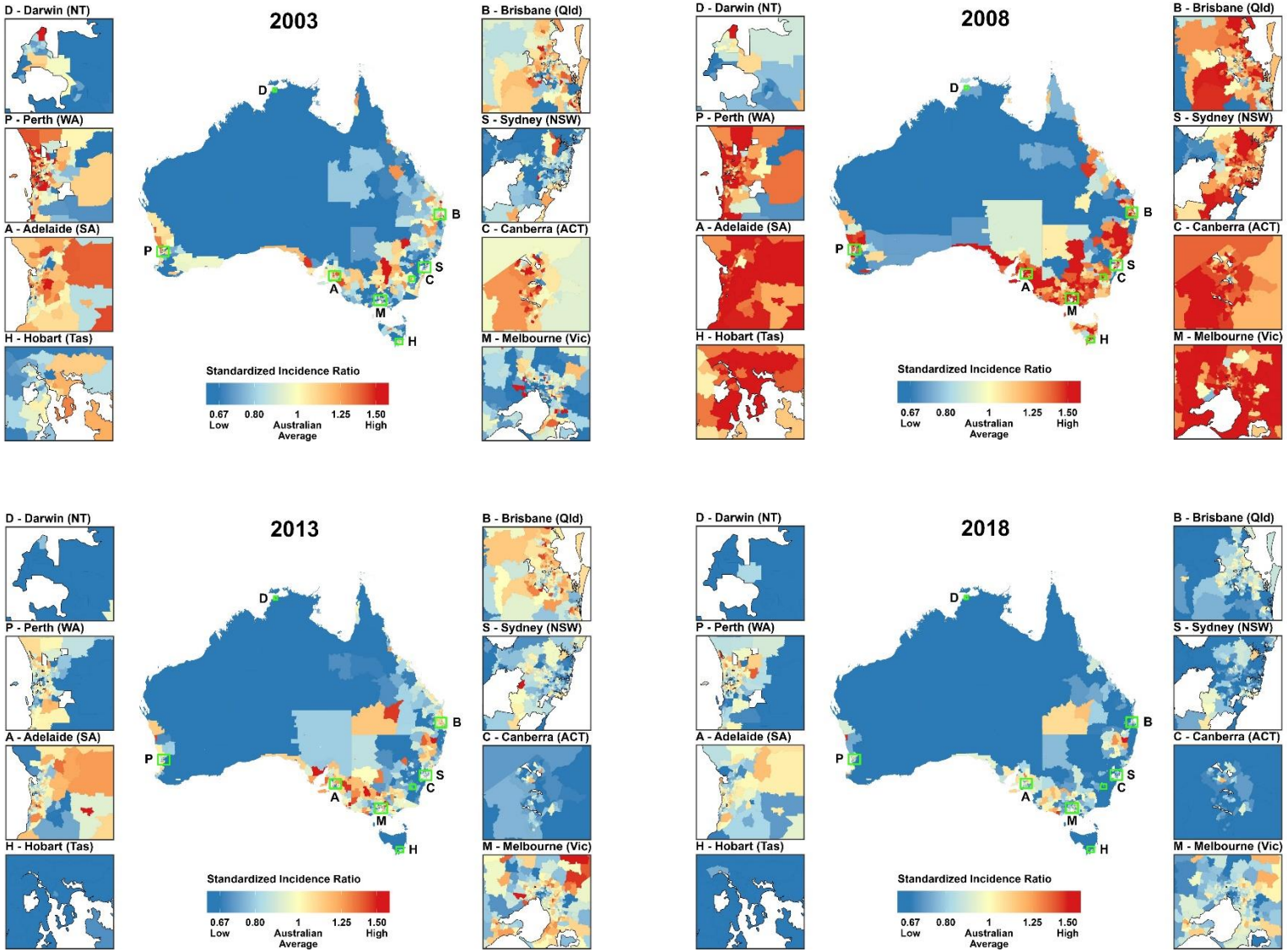
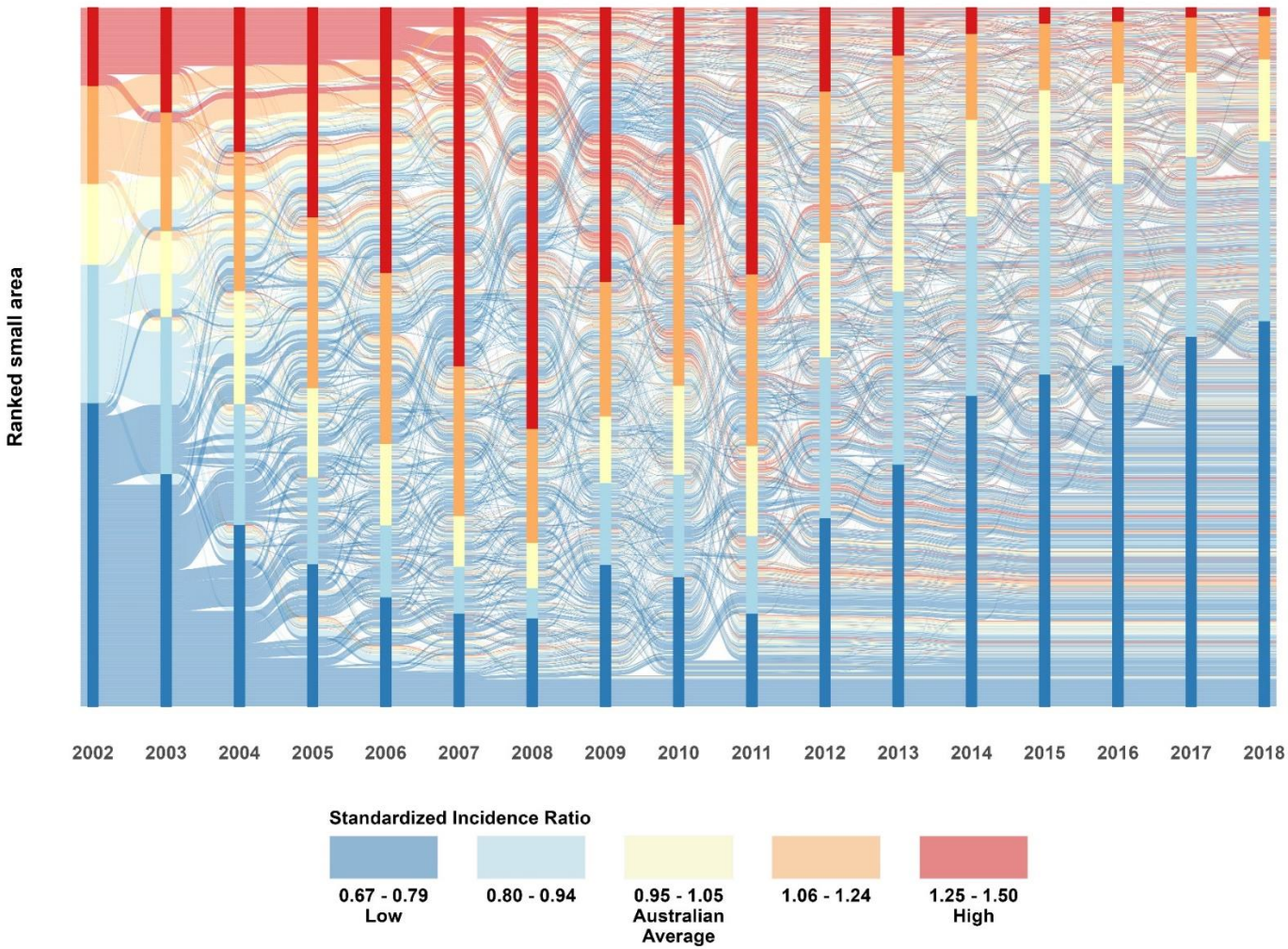
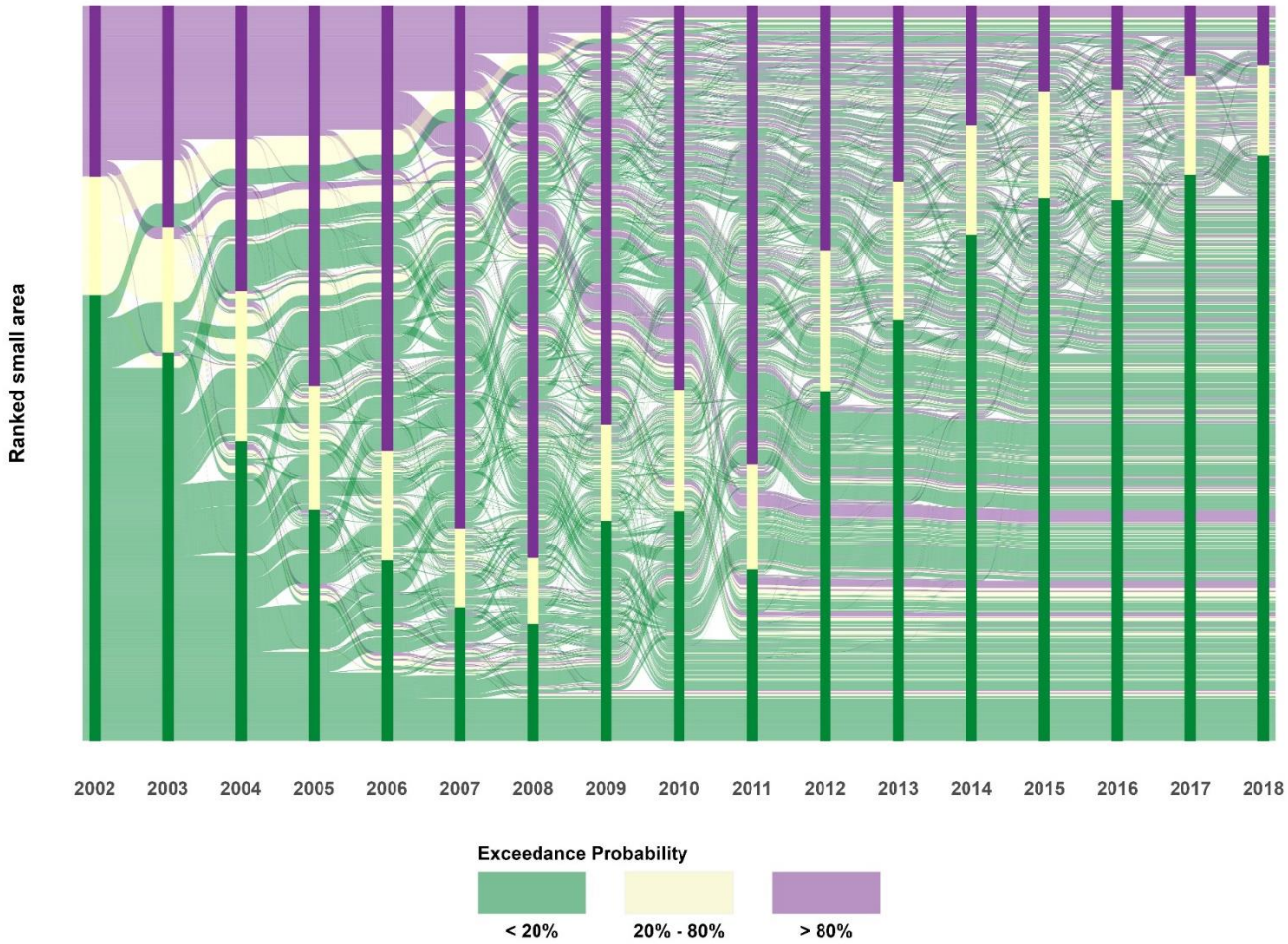


Figure 5.4: *(A) Change in small area rates of prostate-specific antigen screening as modelled Standardized Incidence Ratios compared to the 2002-2018 Australian average*[a].



[a] Average Australian prostate specific antigen screening participation rate between 2002 and 2018

(B) Change in small area exceedance probabilities[a,b,c] of prostate-specific antigen screening, 2002-18, Australia. The exceedance probability provides evidence that age-standardized screening rates were truly different to the 2002-2018 Australian average.



[a] < 20% - Prostate specific antigen screening participation rates were likely lower than the Australian average between 2002 and 2018.

[b] 20% - 80% - Unlikely to be different from Australian average between 2002 and 2018

[c] > 80% - Prostate specific antigen screening participation rates were likely to be higher than Australian average between 2002 and 2018.

Figure 5.5: *Map showing exceedance probabilities of prostate specific antigen screening for the selected years 2003, 2008, 2013, 2018, Australia. Exceedance probabilities provide evidence that rates were truly different to the 2002-2018 Australian average.*

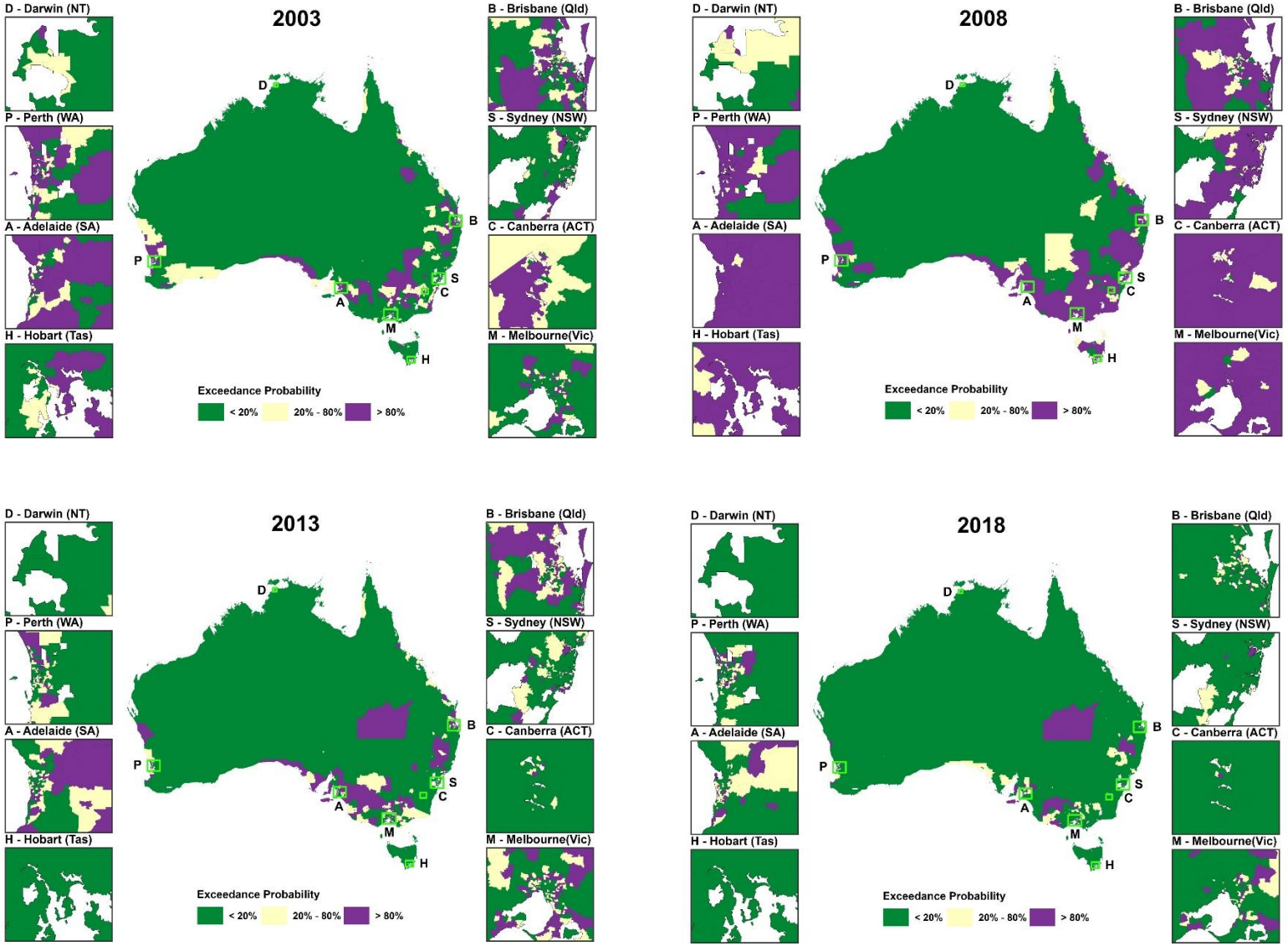
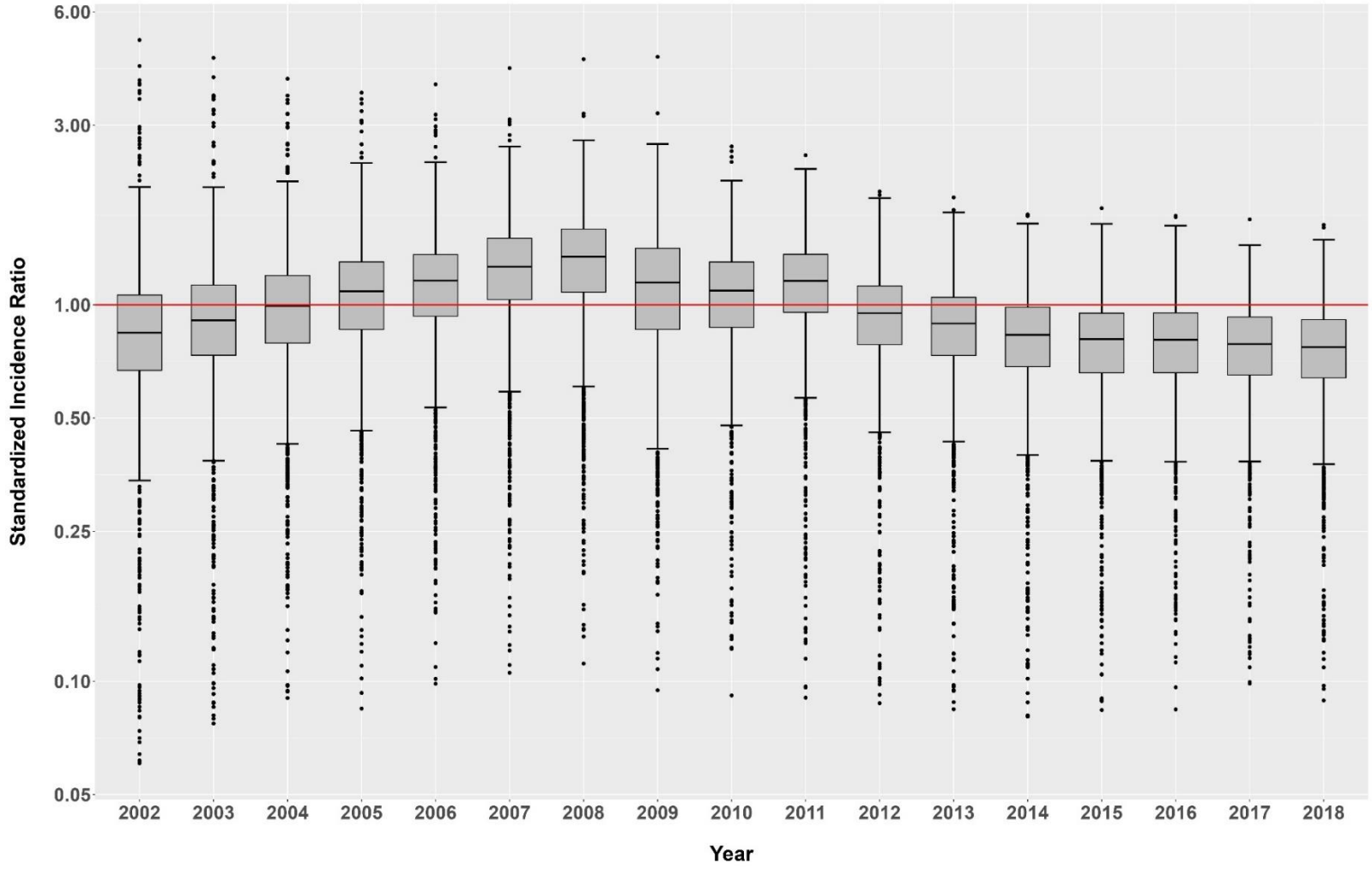


Figure 5.6: *Boxplots showing the temporal trend in standardized incidence ratios of prostate specific antigen testing by small area and year, 2002-18, Australia.*



* The temporal trend shows the modelled rates for all small areas on the y-axis using a log-transformed scale by individual years on x-axis with the red horizontal line at SIR = 1 representing the 2002-2018 Australian average.

5.11 Supplementary material

File SFile 1: *Model 1 (ST.CARsepspatial)*

$Y_{kt} \sim \text{Poission}(E_{kt}\theta_{kt})$

$\log(\theta_{kt}) = \text{Intercept} + \psi_{kt}$

$\text{Intercept} \sim \mathcal{N}(0, 100000)$

$\boldsymbol{\psi_{kt}} = \boldsymbol{\phi_{k_t}} + \boldsymbol{\delta_t}$

$\boldsymbol{\delta_t} = (\boldsymbol{\delta_1}, \boldsymbol{\delta_2}, \ldots, \boldsymbol{\delta_N})$

$\boldsymbol{\phi_{k_t}} = (\boldsymbol{\phi_{1_1}}, \boldsymbol{\phi_{1_2}}, \ldots, \boldsymbol{\phi_{K_t}})$

$$\phi_{k_t}|\phi_{-k_t}, W \sim N\left(\frac{\rho_S \sum_{j=1}^{K} w_{kj}\phi_{j_t}}{\rho_S \sum_{j=1}^{K} w_{kj} + 1 - \rho_S}, \frac{\tau_t^2}{\rho_S \sum_{j=1}^{K} w_{kj} + 1 - \rho_s}\right)$$

$$\delta_t|\delta_{-t}, D \sim N\left(\frac{\rho_T \sum_{J=1}^{N} d_{tj}\delta_j}{\rho_T \sum_{j=1}^{N} d_{tj} + 1 - \rho_T}, \frac{\tau_T^2}{\rho_T \sum_{j=1}^{N} d_{tj} + 1 - \rho_T}\right)$$

$\tau_1^2, \ldots, \tau_N^2, \tau_T^2 \sim \text{InverseGamma}(1, 0.01)$

$\rho_S, \rho_T \sim \text{Uniform}(0, 1)$

k = 1, 2, …, K i.e. 1 to 2133 small areas

t = 1, 2, …, N i.e. 1 to 17 years for 2002 to 2018

Y_{kt} = Spatio-temporal count data

E_{kt} = Spatio-temporal expected count data

θ_{kt} = Spatio-temporal standardized incidence ratio

ψ_{kt} = Spatio-temporal random effects

ϕ_k = Spatial random effects

δ_t = Temporal random effects

W = Spatial neighborhood matrix

D = Temporal neighborhood matrix

ρ_S = Spatial dependence parameter

ρ_T = Temporal dependence parameter

w_{kj} = Elements of spatial weight matrix = $\begin{cases} 1 & \text{if areas } i \text{ and } j \text{ are adjacent} \\ 0 & \text{otherwise} \end{cases}$

d_{tj} = Elements of temporal weight matrix = $\begin{cases} 1 & \text{if years } t \text{ and } j \text{ are adjacent} \\ 0 & \text{otherwise} \end{cases}$

τ_t^2 = Spatial varying variance parameter

τ_T^2 = Temporal varying variance parameter

Model 2 (ST.CARanova)

$Y_{kt} \sim \text{Poission}(E_{kt}\theta_{kt})$

$\log(\theta_{kt}) = \text{Intercept} + \psi_{kt}$

$\text{Intercept} \sim \mathcal{N}(0, 100000)$

$\boldsymbol{\psi_{kt} = \phi_k + \delta_t + \gamma_{kt}}$

$\boldsymbol{\delta_t = \delta_1, \delta_2, \ldots, \delta_N}$

$\boldsymbol{\phi_k = \phi_1, \phi_2, \ldots, \phi_K}$

$\boldsymbol{\gamma_{kt} = \gamma_{11}, \gamma_{12}, \cdots, \gamma_{KN}}$

$$\phi_k|\phi_{-k}, W \sim N\left(\frac{\rho_S \sum_{j=1}^{K} w_{kj}\phi_j}{\rho_S \sum_{j=1}^{K} w_{kj} + 1 - \rho_S}, \frac{\tau_S^2}{\rho_S \sum_{j=1}^{K} w_{kj} + 1 - \rho_s}\right)$$

$$\delta_t|\delta_{-t}, D \sim N\left(\frac{\rho_T \sum_{j=1}^{N} d_{tj}\delta_j}{\rho_T \sum_{j=1}^{N} d_{tj} + 1 - \rho_T}, \frac{\tau_T^2}{\rho_T \sum_{j=1}^{N} d_{tj} + 1 - \rho_T}\right)$$

$\gamma_{kt} \sim N(0, \tau_I^2)$

$\tau_S^2, \tau_T^2, \tau_I^2 \sim \text{InverseGamma}(1, 0.01)$

$\rho_S, \rho_T \sim \text{Uniform}(0, 1)$

k = 1, 2, …, K i.e. 1 to 2133 small areas

t = 1, 2, …, N i.e. 1 to 17 years for 2002 to 2018

Y_{kt} = Spatio-temporal count data

E_{kt} = Spatio-temporal expected count data

θ_{kt} = Spatio-temporal standardized incidence ratio

ψ_{kt} = Spatio-temporal random effects

ϕ_k = Spatial random effects

δ_t = Temporal random effects

γ_{kt} = Spatio-temporal interactions

W = Spatial neighborhood matrix

D = Temporal neighborhood matrix

ρ_S = Spatial dependence parameter

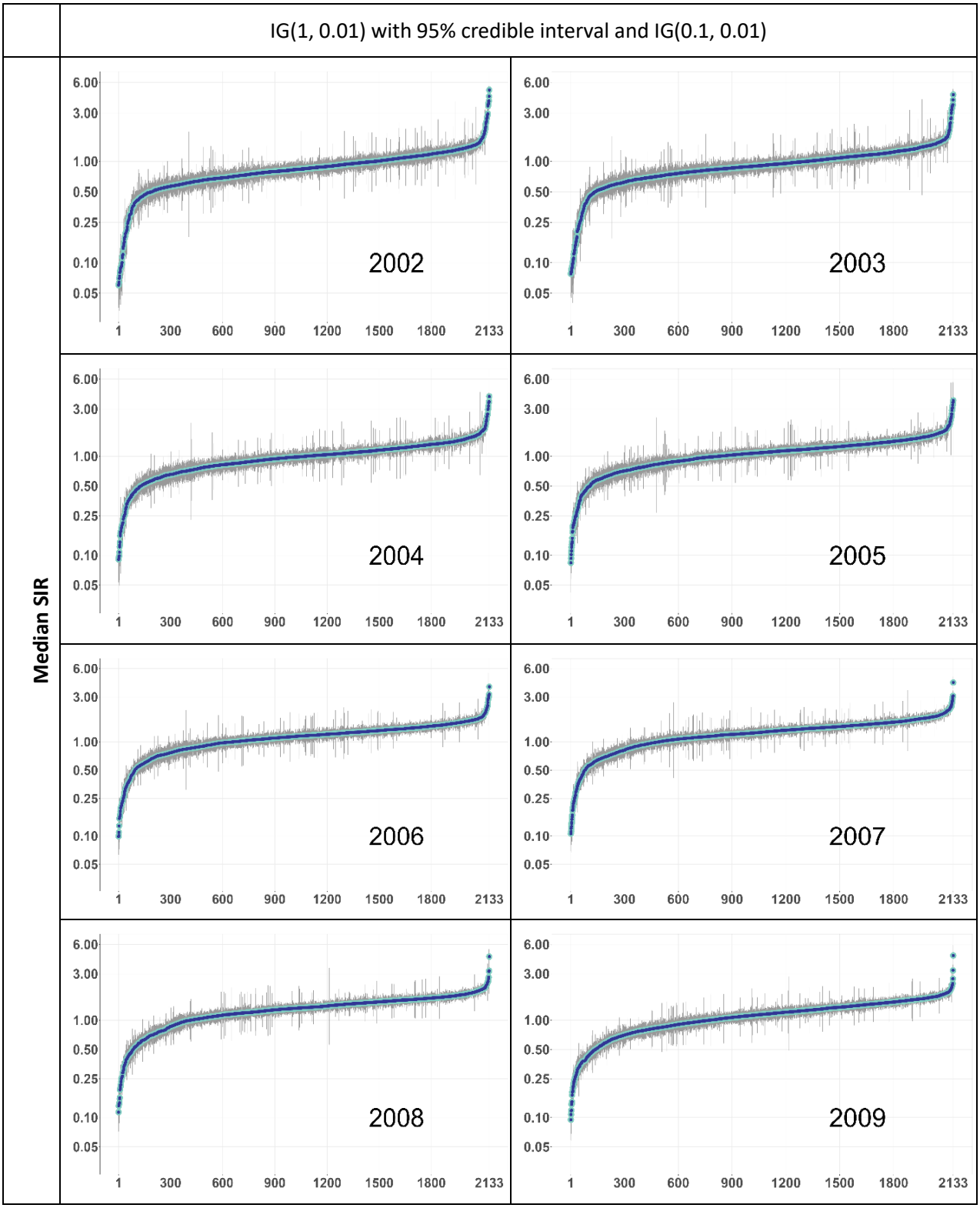
ρ_T = Temporal dependence parameter

w_{kj} = Elements of spatial weight matrix = $\begin{cases} 1 & \text{if areas } i \text{ and } j \text{ are adjacent} \\ 0 & \text{otherwise} \end{cases}$

d_{tj} = Elements of temporal weight matrix = $\begin{cases} 1 & \text{if years } t \text{ and } j \text{ are adjacent} \\ 0 & \text{otherwise} \end{cases}$

$\tau_S^2, \tau_T^2, \tau_I^2$ = Spatial, Temporal and Spatio-temporal interaction varying variance parameter respectively

Figure SF 5.1: *Sensitivity analysis showing comparison between Standardized incidence ratio (SIR) of hyperpriors IG(1, 0.01) with 95% credible interval and IG(0.1, 0.01) for 2133 small areas.*



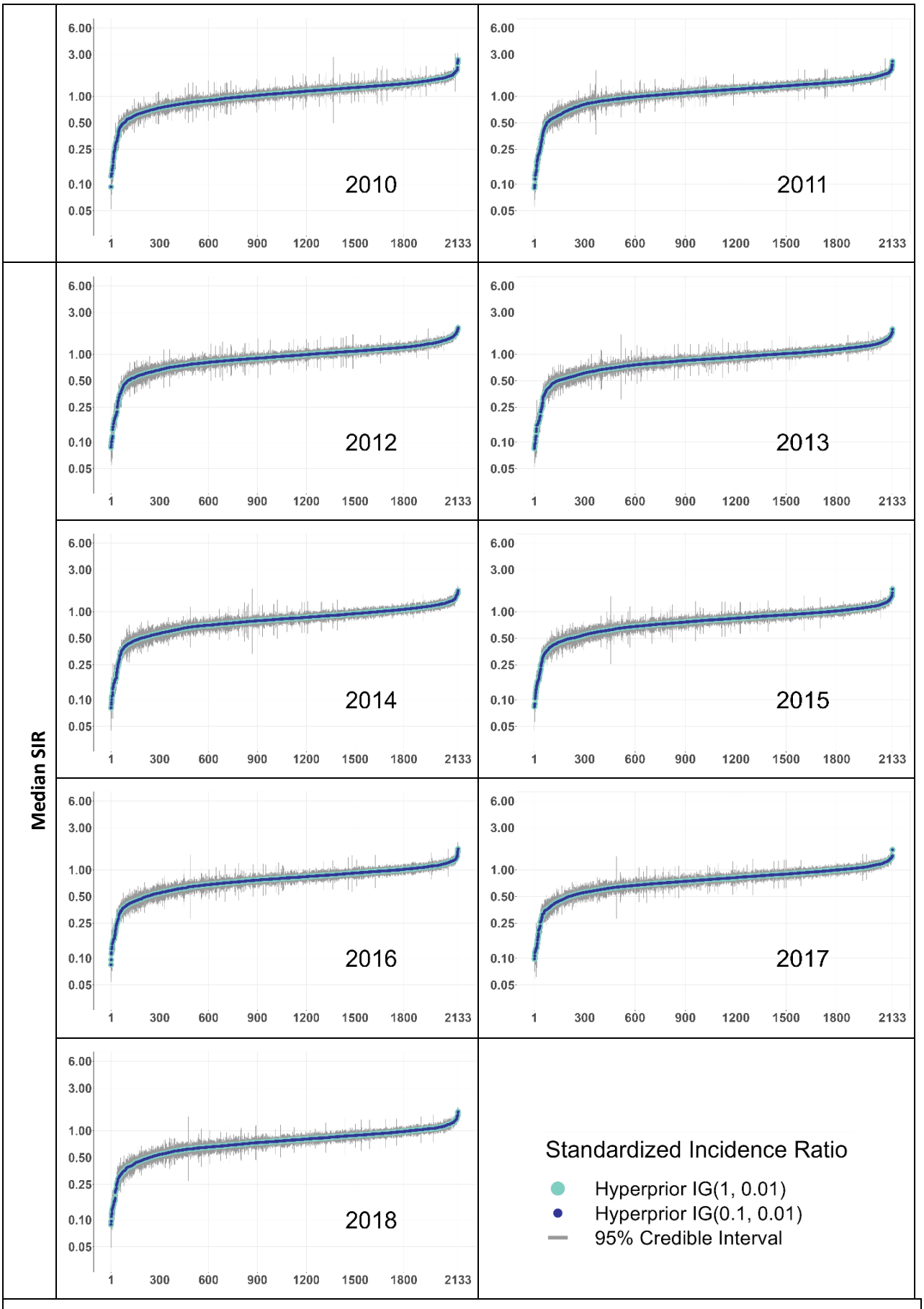
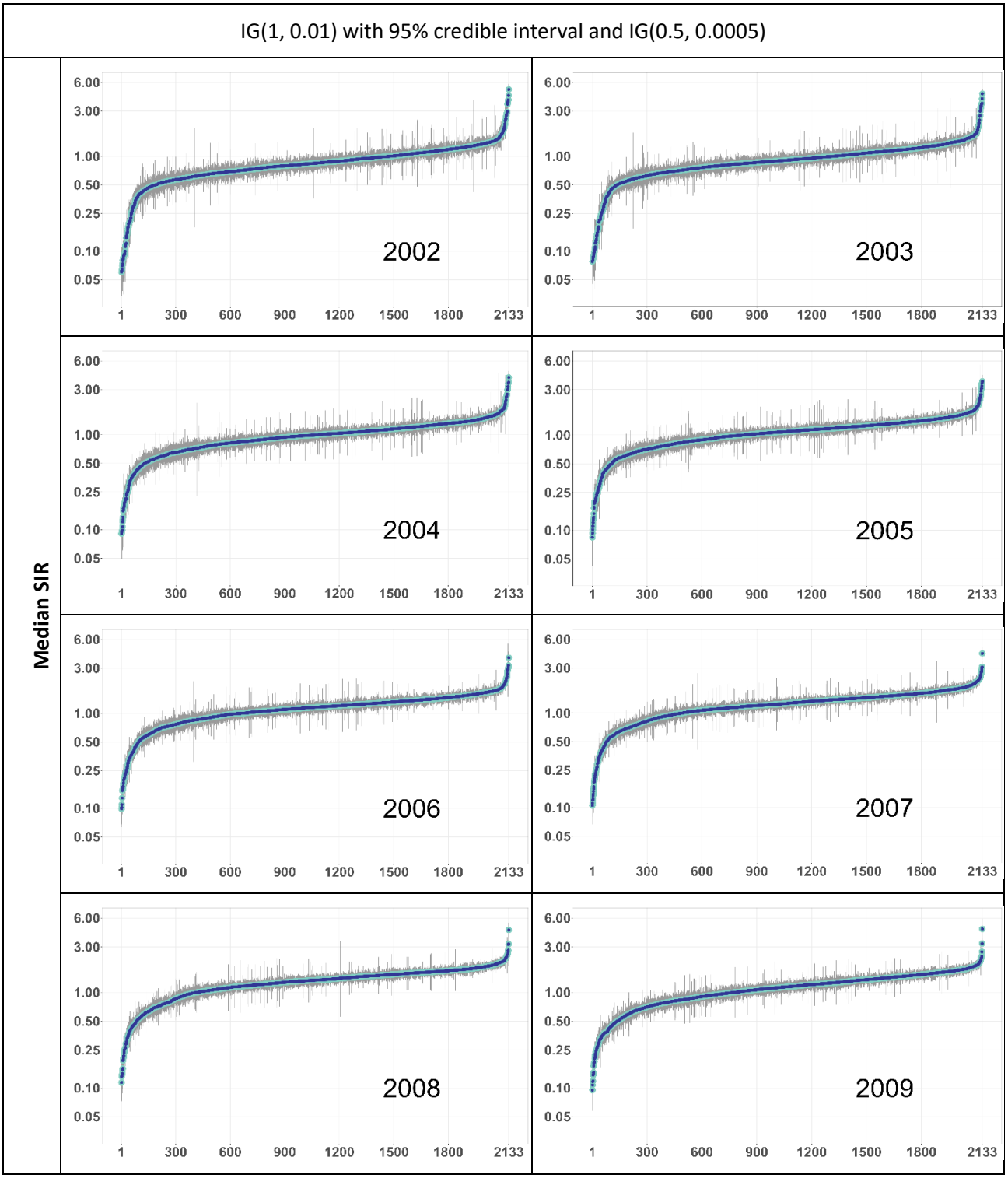

Median SIR
6.00
3.00
1.00
0.50
0.25
0.10
0.05
1
300
600
900
1200
1500
1800
2133
2010
2011
2012
2013
2014
2015
2016
2017
2018
Standardized Incidence Ratio
Hyperprior IG(1, 0.01)
Hyperprior IG(0.1, 0.01)
95% Credible Interval
Ranked Small Areas

Figure SF 5.2: *Sensitivity analysis showing comparison between Standardized incidence ratio (SIR) of hyperpriors IG(1, 0.01) with 95% credible interval and IG(0.5, 0.0005) for 2133 small areas.*



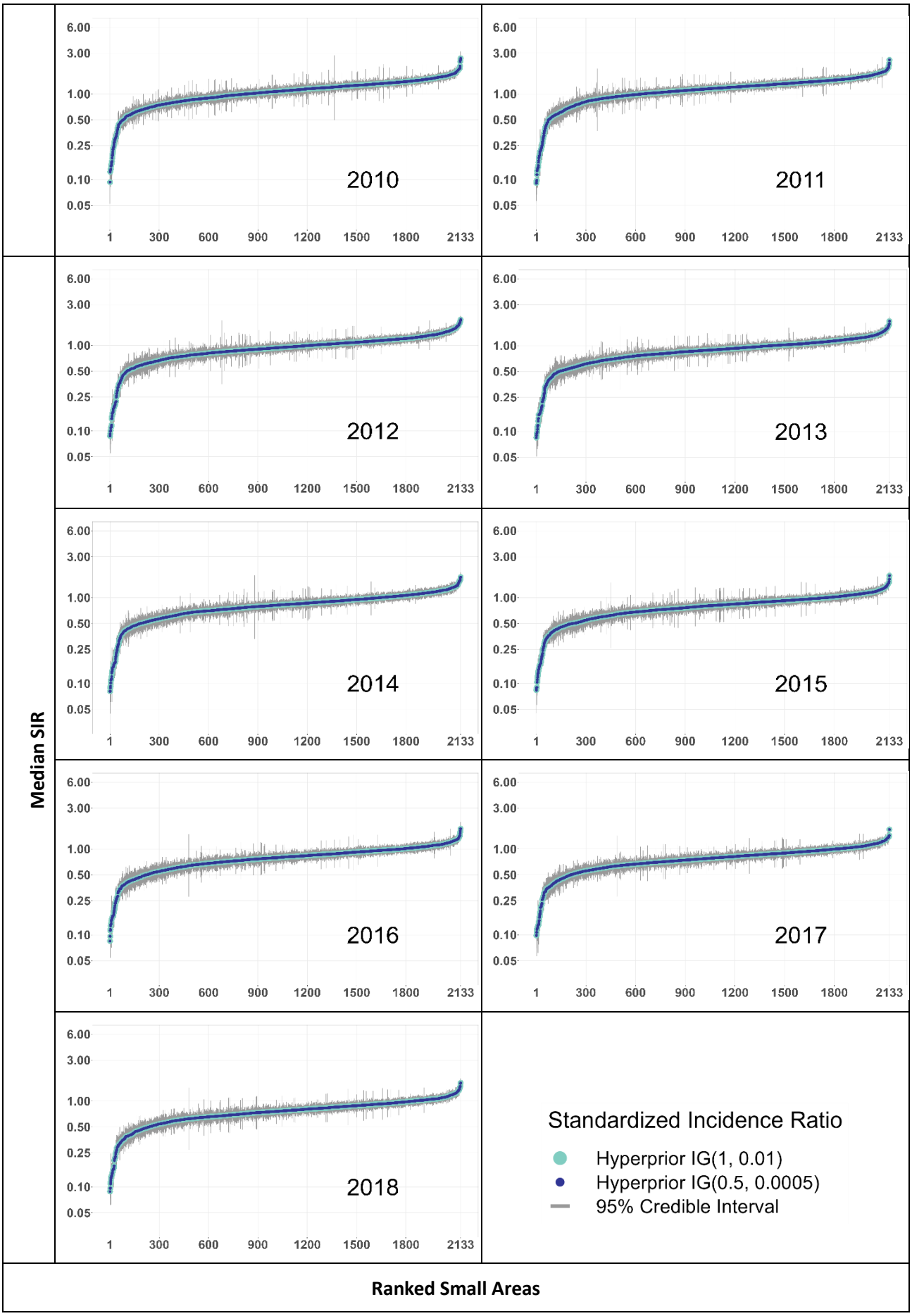
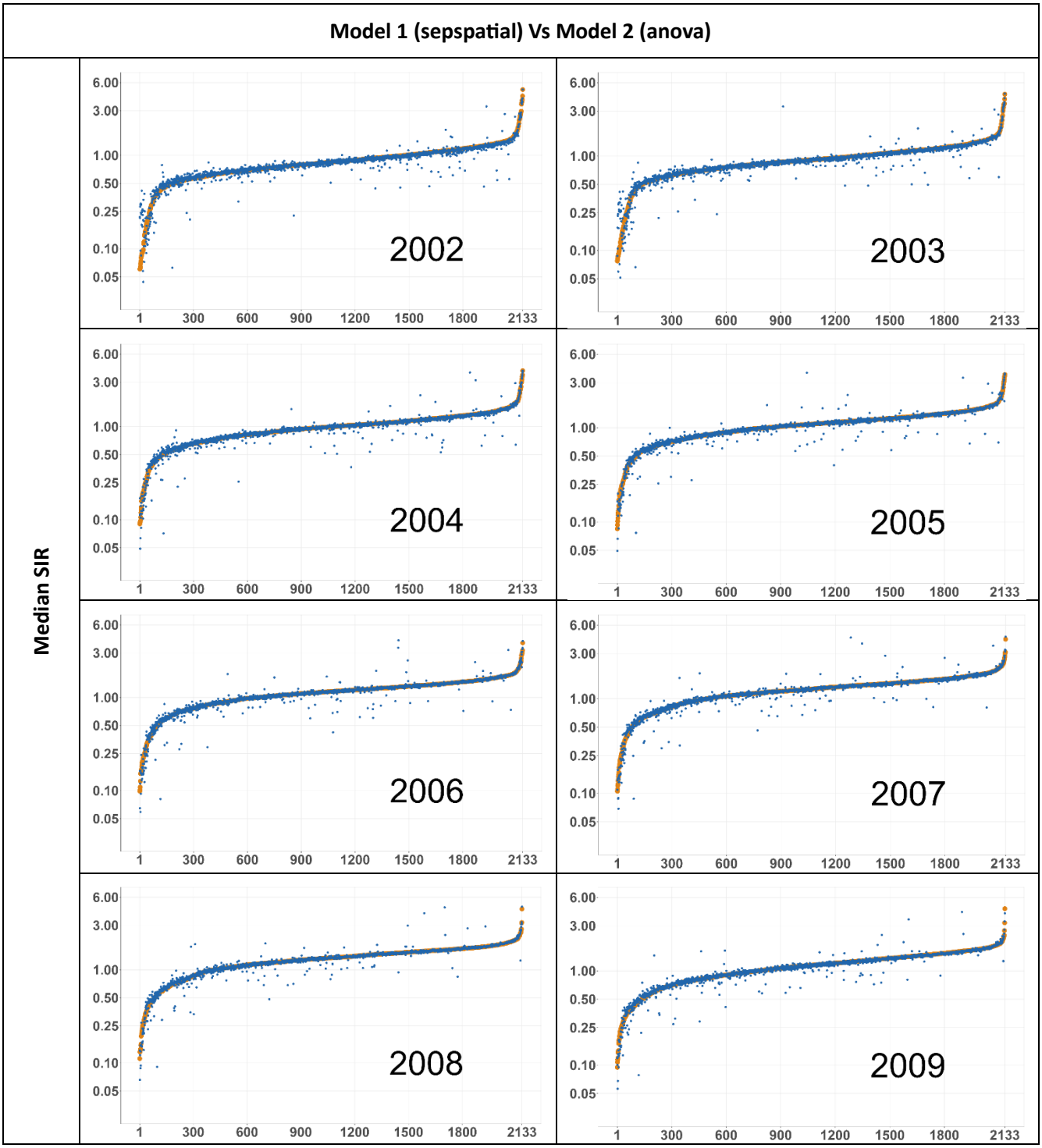

2010
2011
2012
2013
2014
2015
2016
2017
2018
6.00
3.00
1.00
0.50
0.25
0.10
0.05
1
300
600
900
1200
1500
1800
2133
Median SIR
Standardized Incidence Ratio
Hyperprior IG(1, 0.01)
Hyperprior IG(0.5, 0.0005)
95% Credible Interval
Ranked Small Areas

Figure SF 5.3: *Median comparison of Standardized incidence ratio between ST.CARsepspatial and ST.CARanova model for 2133 small areas.*



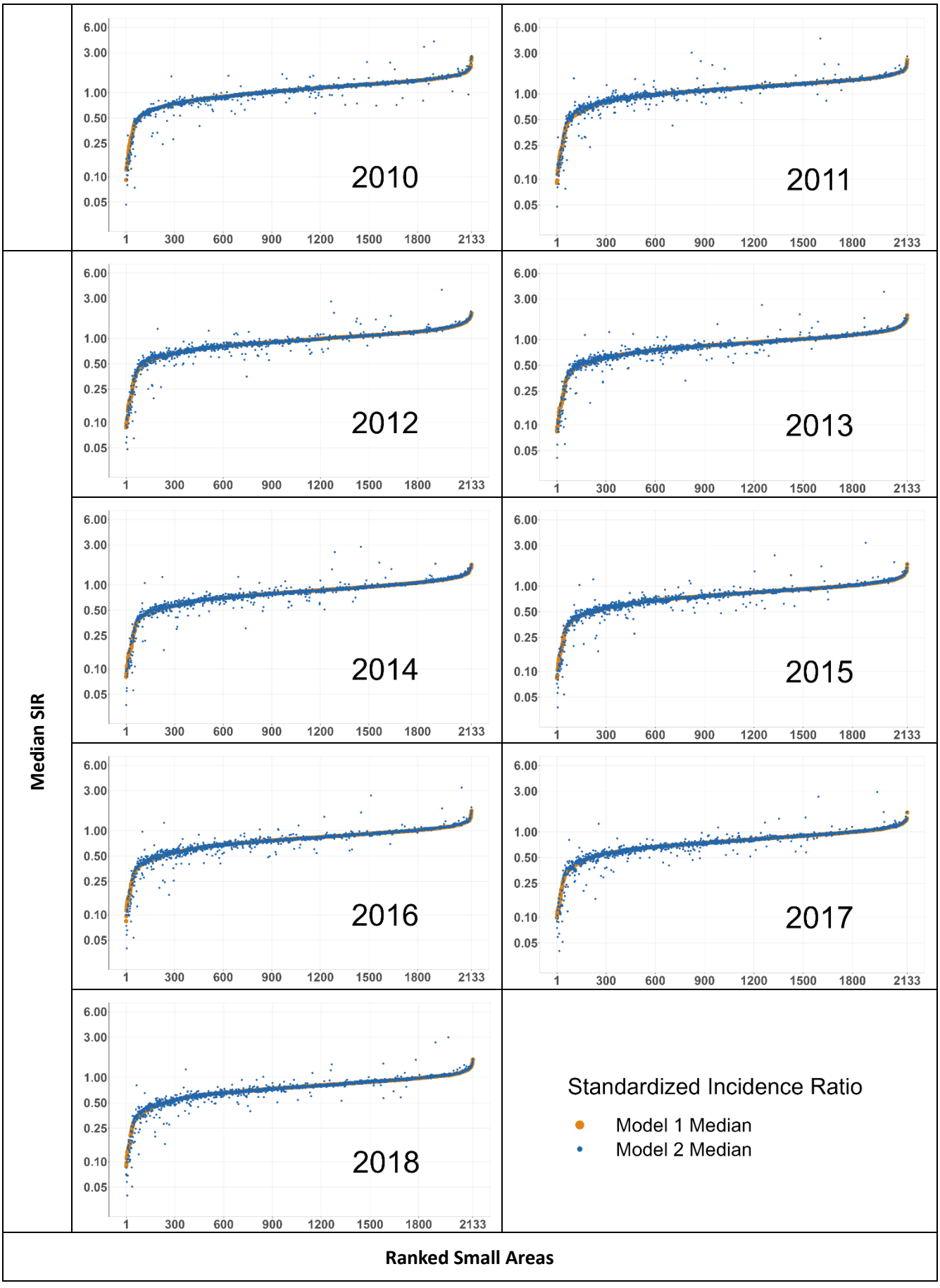
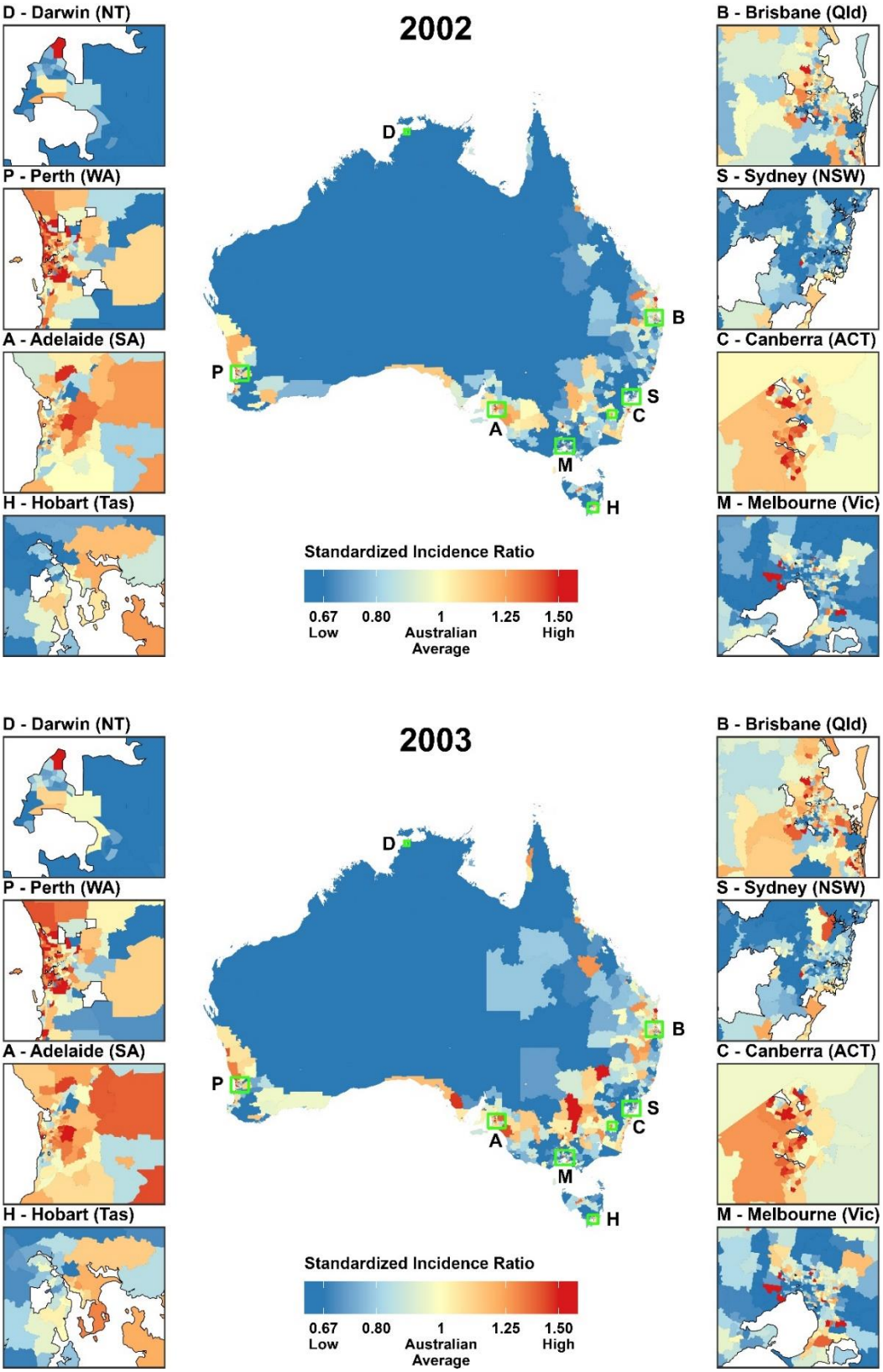
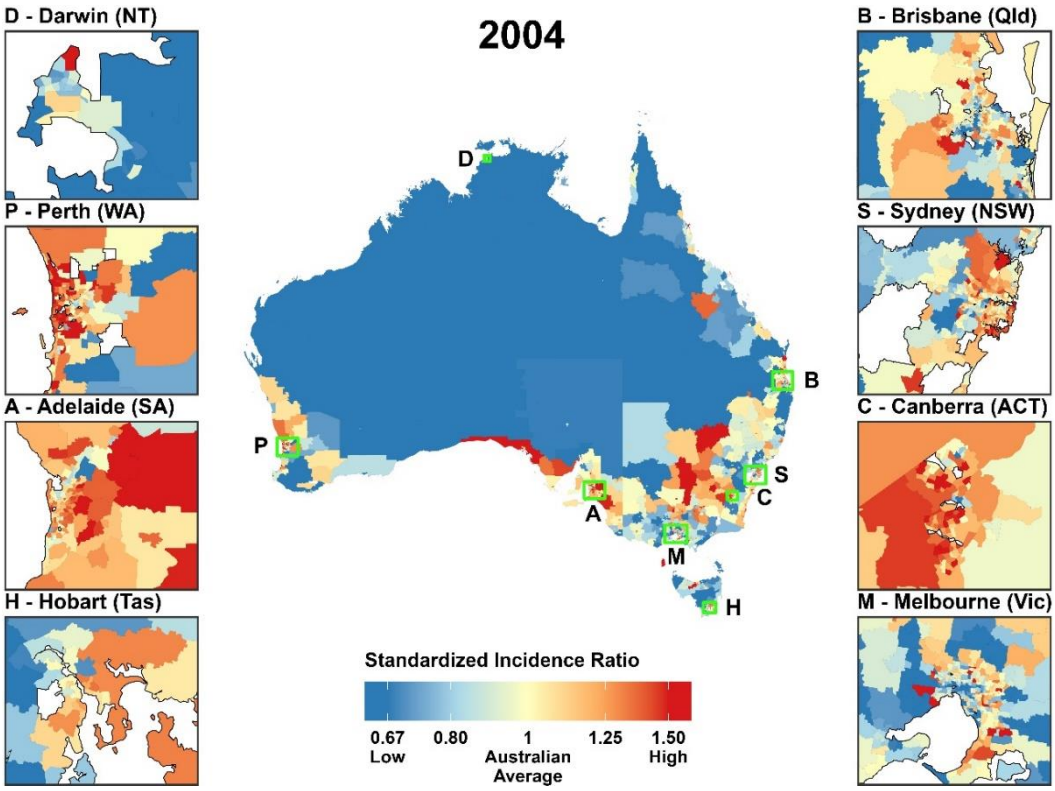
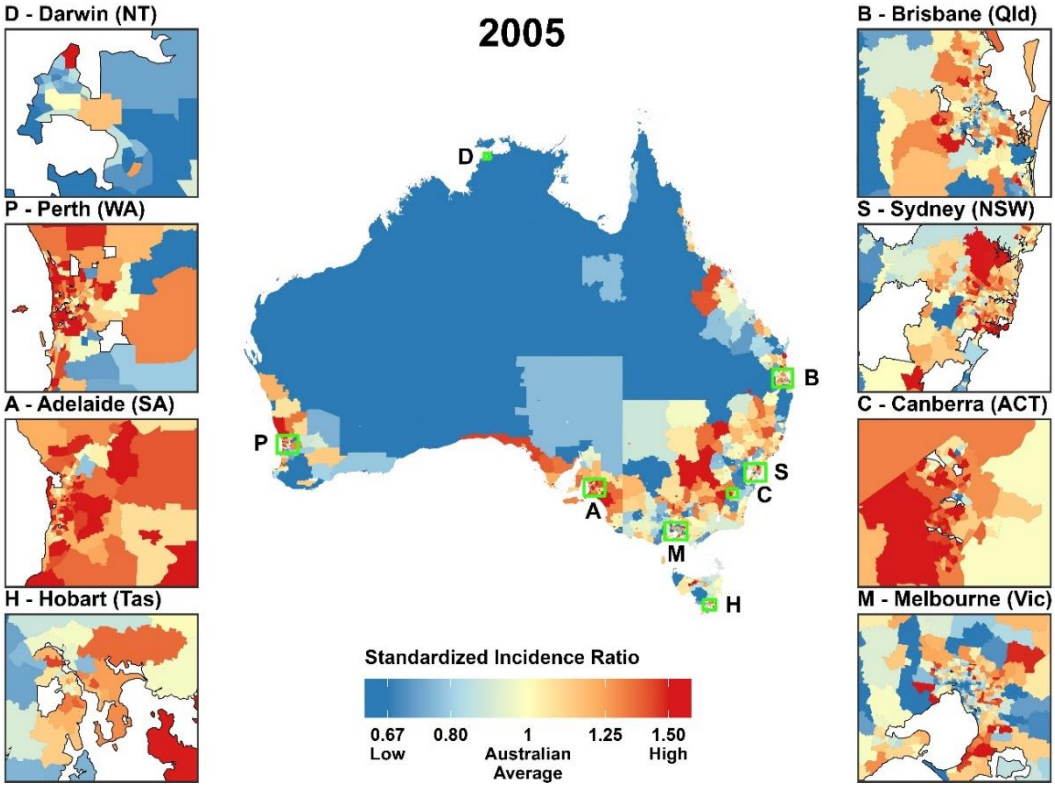
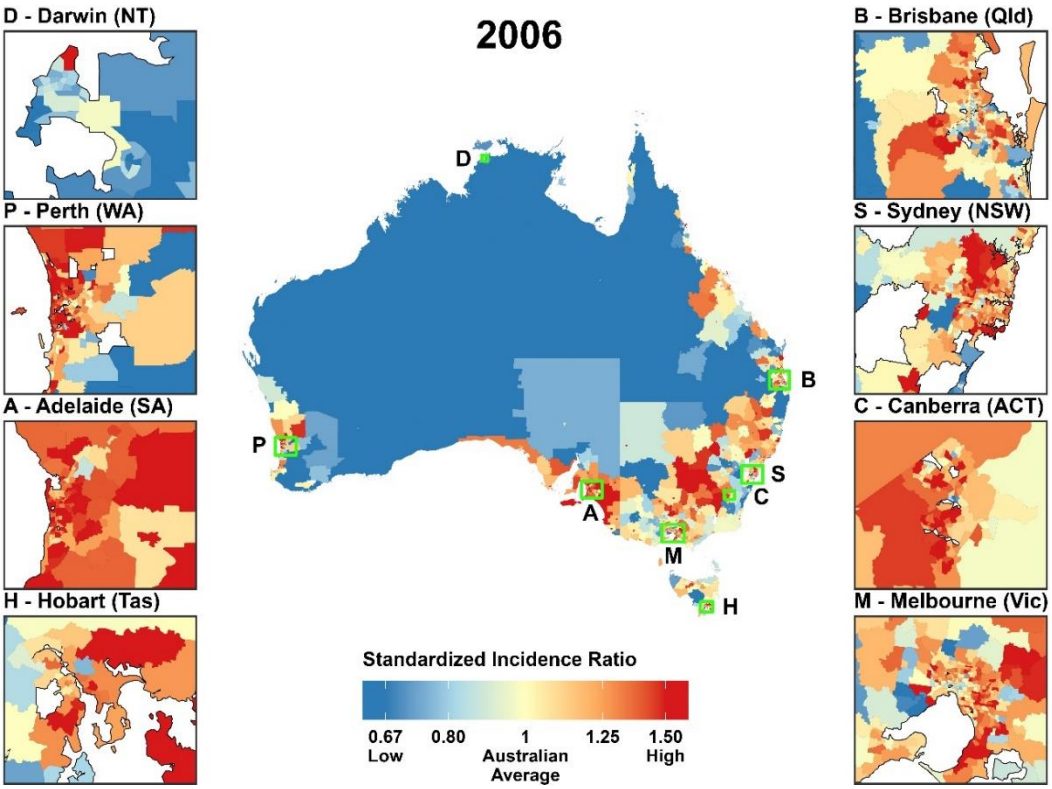

Median SIR
2010
2011
2012
2013
2014
2015
2016
2017
2018
6.00
3.00
1.00
0.50
0.25
0.10
0.05
1
300
600
900
1200
1500
1800
2133
Standardized Incidence Ratio
Model 1 Median
Model 2 Median
Ranked Small Areas

Figure SF 5.4: *Map showing standardized incidence ratios of prostate specific antigen screening, 2002-2018, Australia.*




2004
D - Darwin (NT)
P - Perth (WA)
A - Adelaide (SA)
H - Hobart (Tas)
B - Brisbane (Qld)
S - Sydney (NSW)
C - Canberra (ACT)
M - Melbourne (Vic)
D
P
A
M
H
B
S
C
Standardized Incidence Ratio
0.67 Low
0.80
1 Australian Average
1.25
1.50 High


2005
D - Darwin (NT)
P - Perth (WA)
A - Adelaide (SA)
H - Hobart (Tas)
B - Brisbane (Qld)
S - Sydney (NSW)
C - Canberra (ACT)
M - Melbourne (Vic)
D
P
A
M
H
B
S
C
Standardized Incidence Ratio
0.67 Low
0.80
1 Australian Average
1.25
1.50 High


2006
D - Darwin (NT)
P - Perth (WA)
A - Adelaide (SA)
H - Hobart (Tas)
B - Brisbane (Qld)
S - Sydney (NSW)
C - Canberra (ACT)
M - Melbourne (Vic)
D
P
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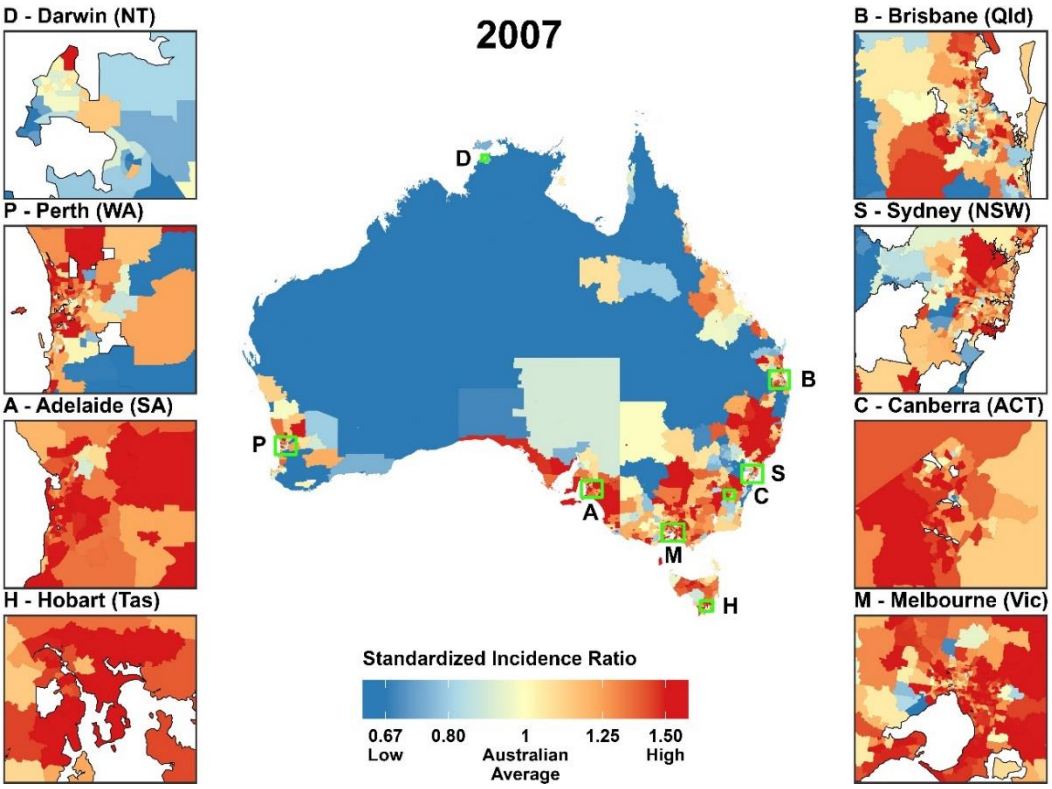
M
H
B
S
C
Standardized Incidence Ratio
0.67 Low
0.80
1 Australian Average
1.25
1.50 High


2007
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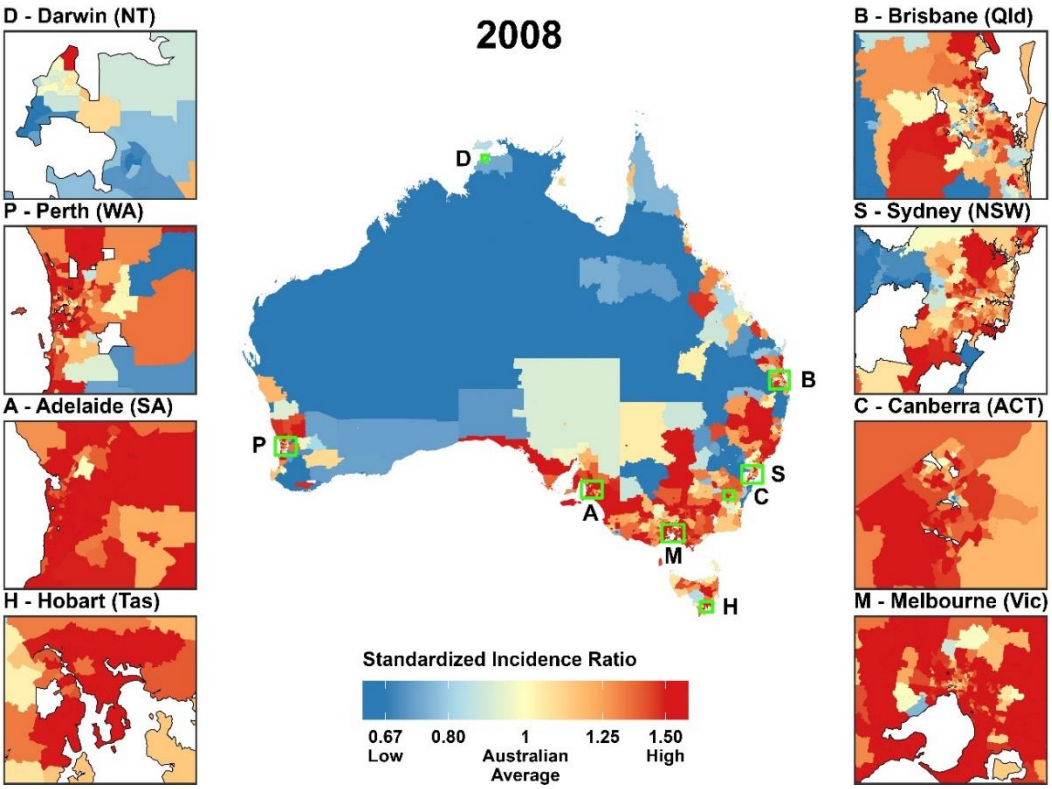
Standardized Incidence Ratio
0.67 Low
0.80
1 Australian Average
1.25
1.50 High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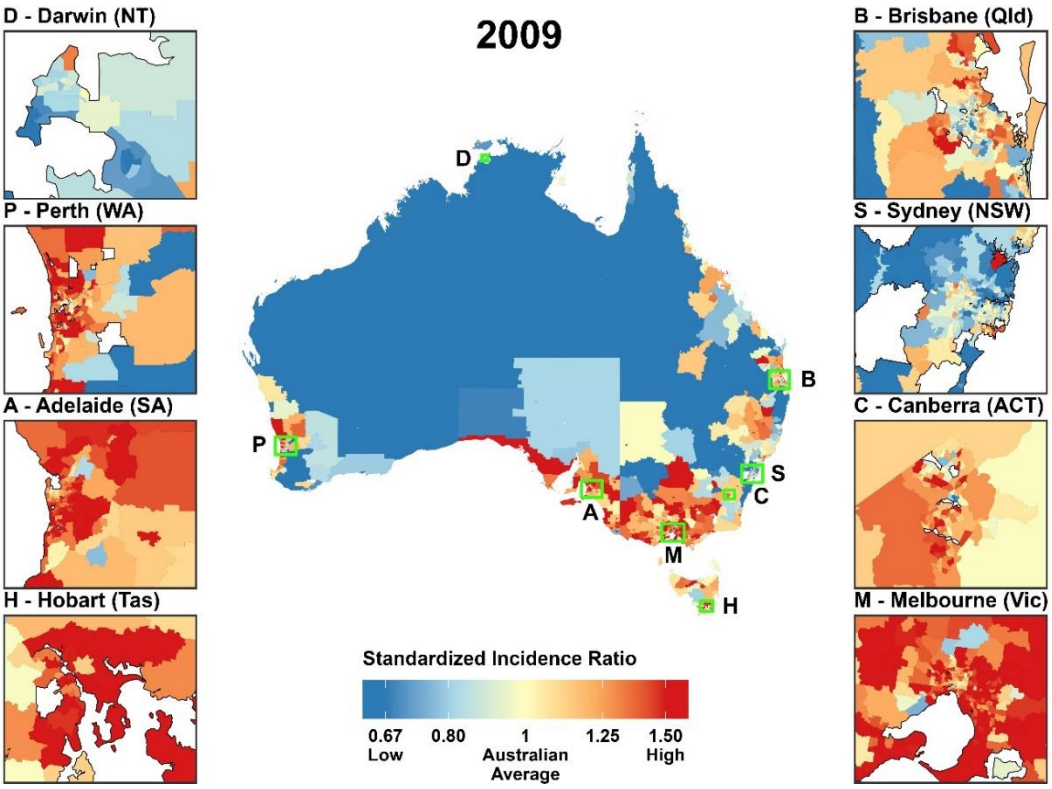
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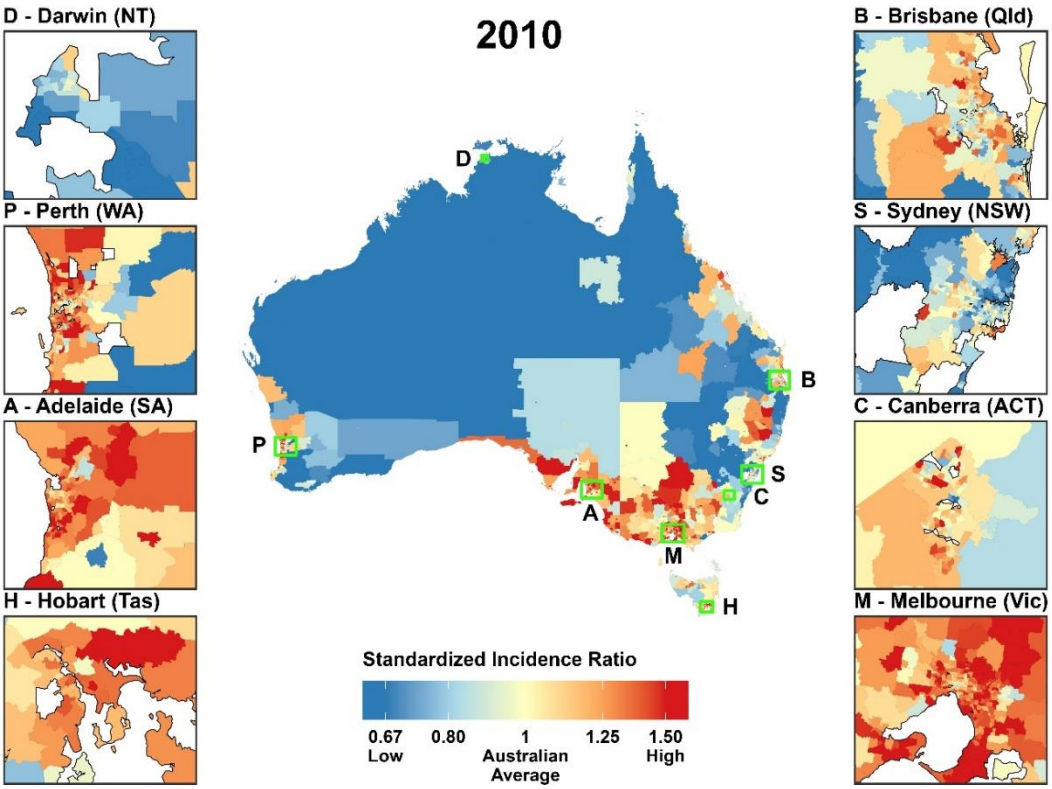
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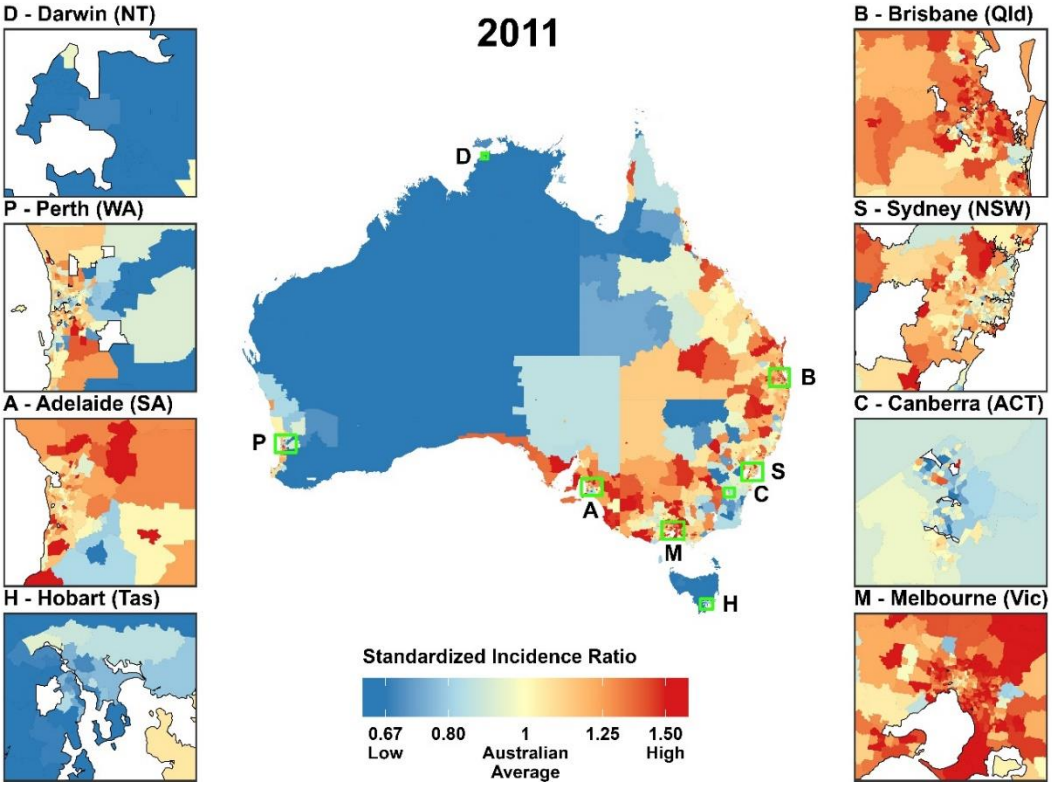
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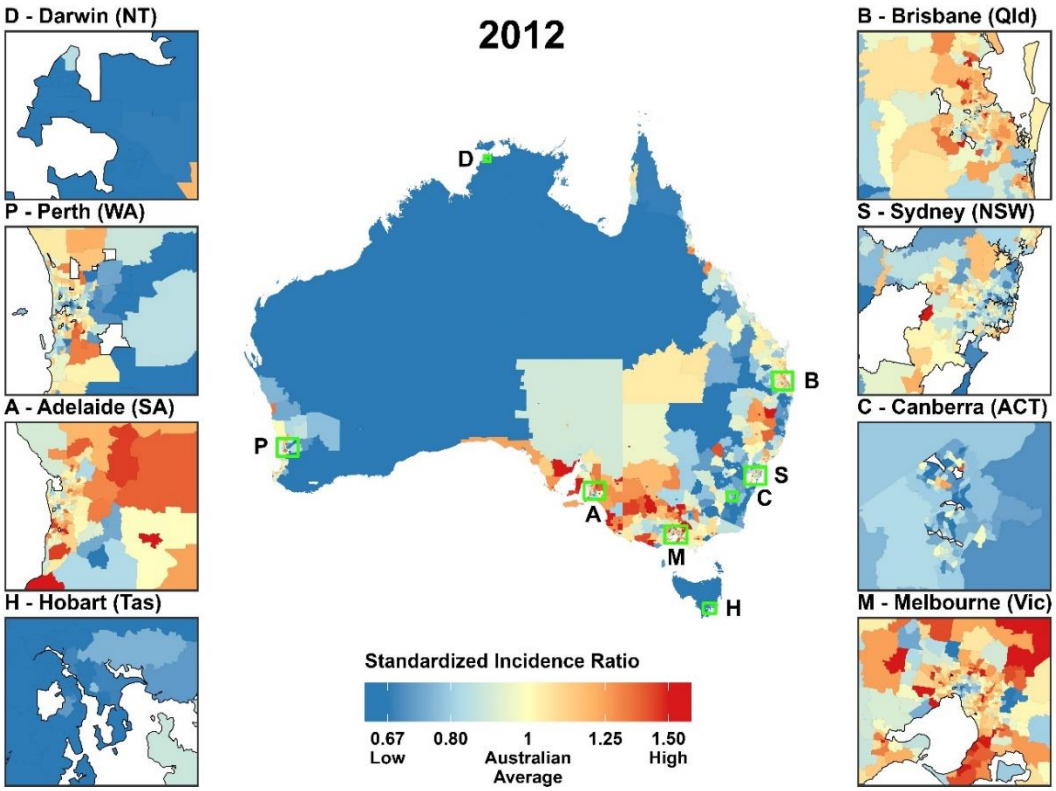
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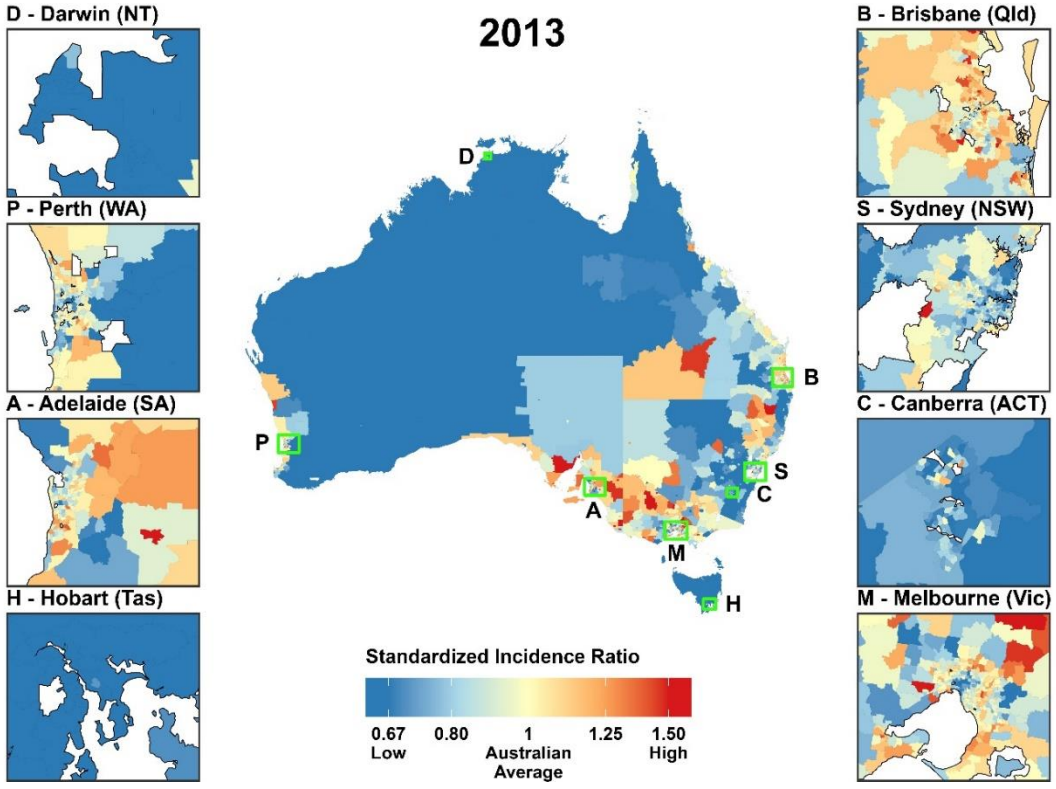
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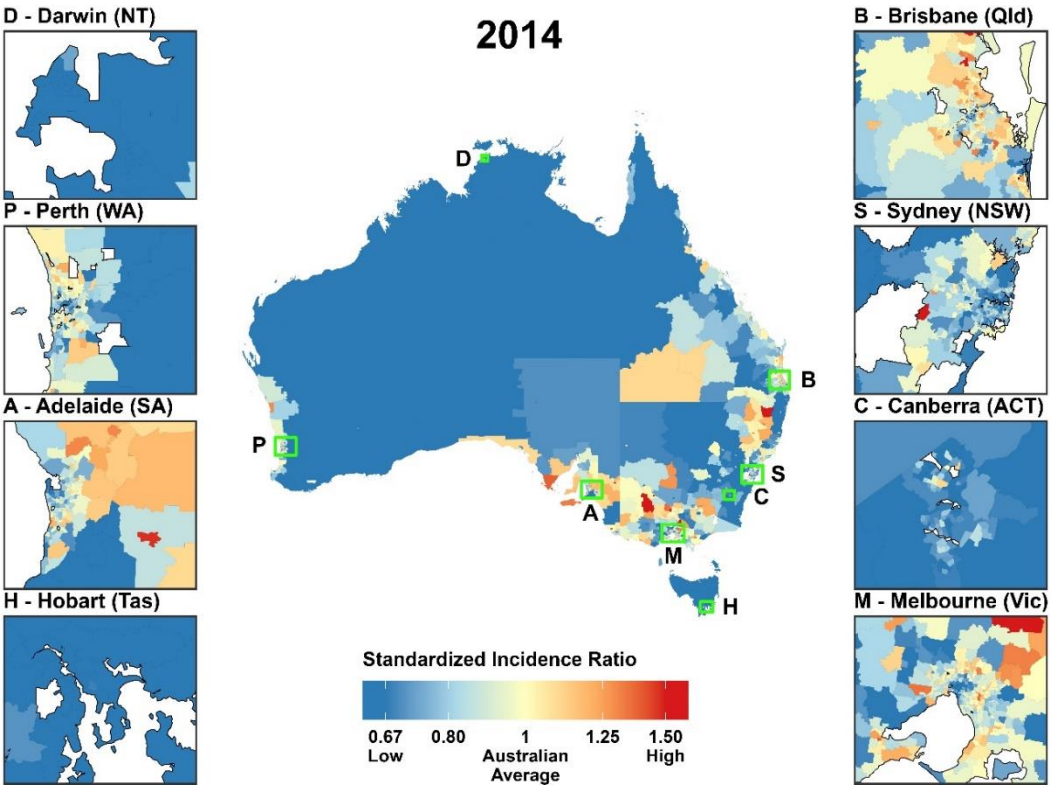
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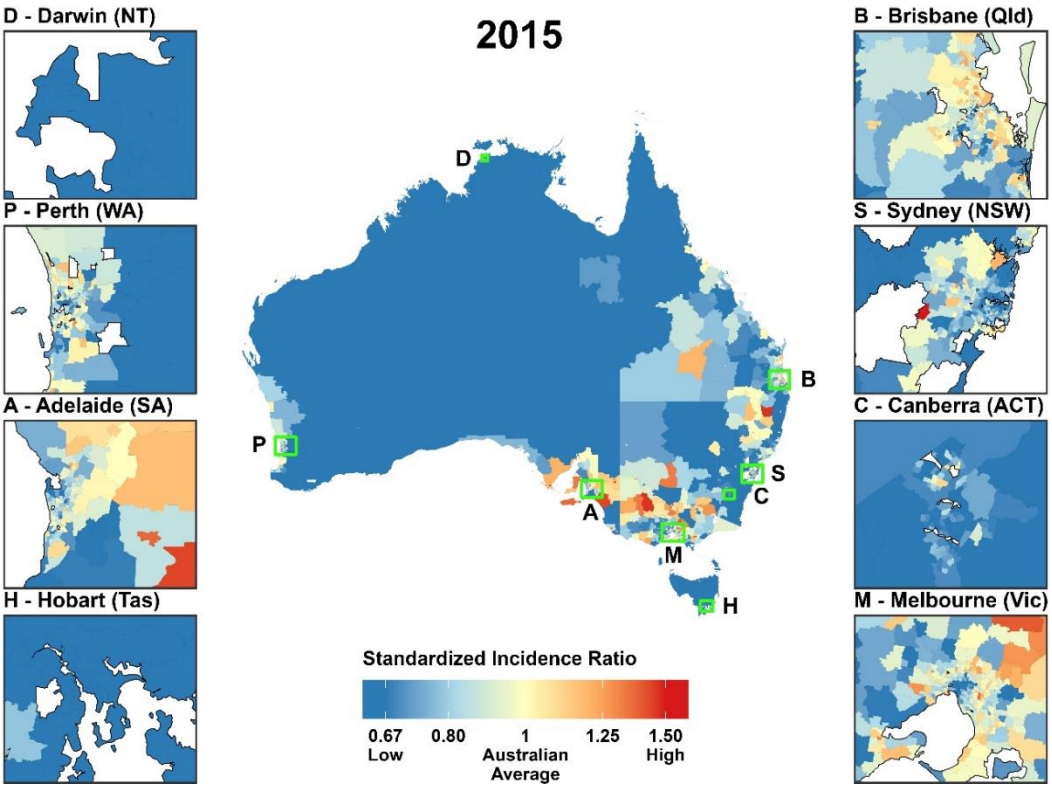
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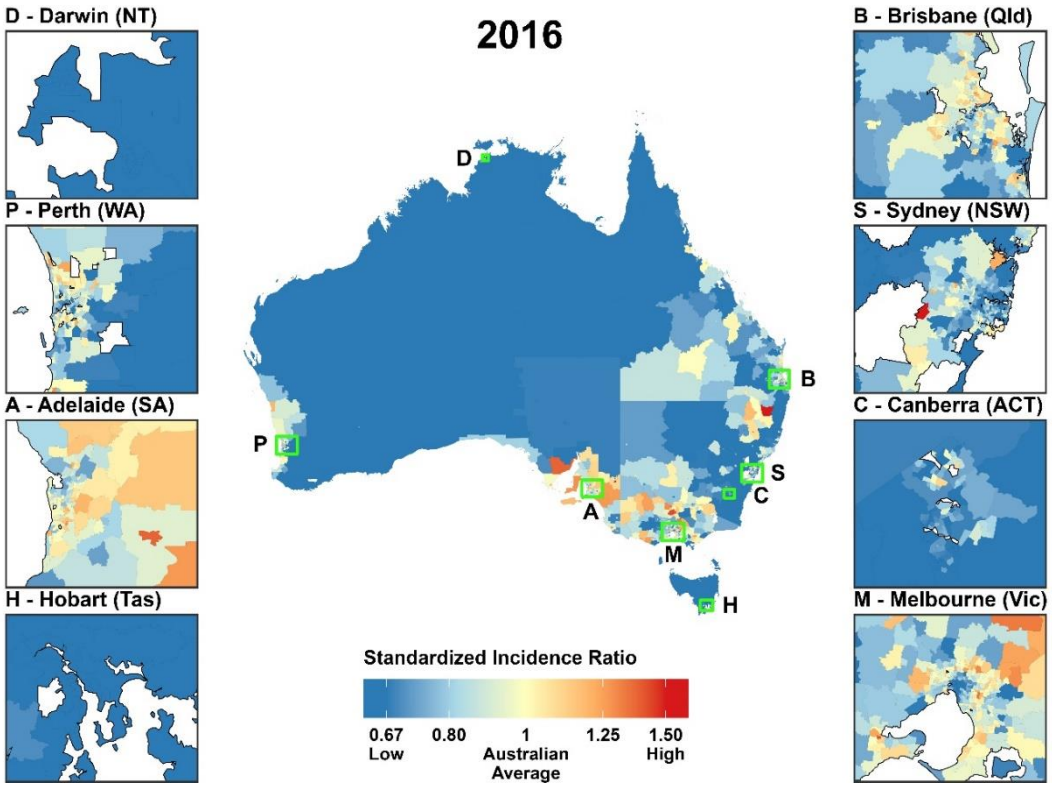
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Standardized Incidence Ratio
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1 Australian Average
1.25
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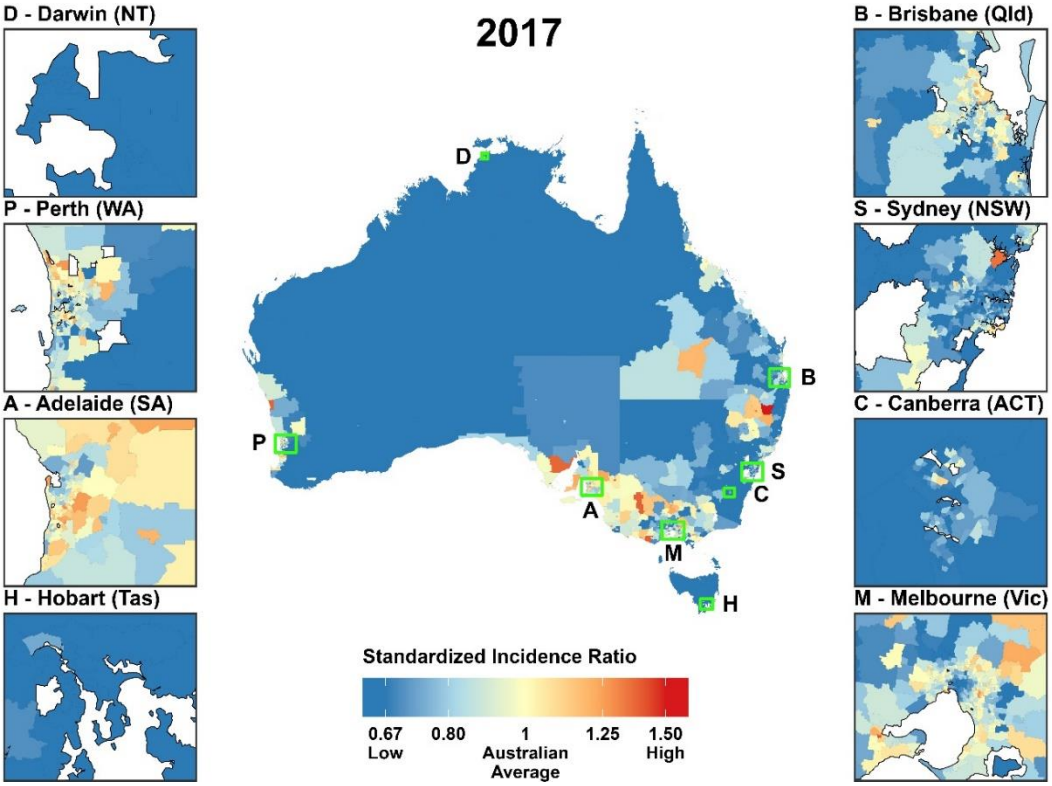
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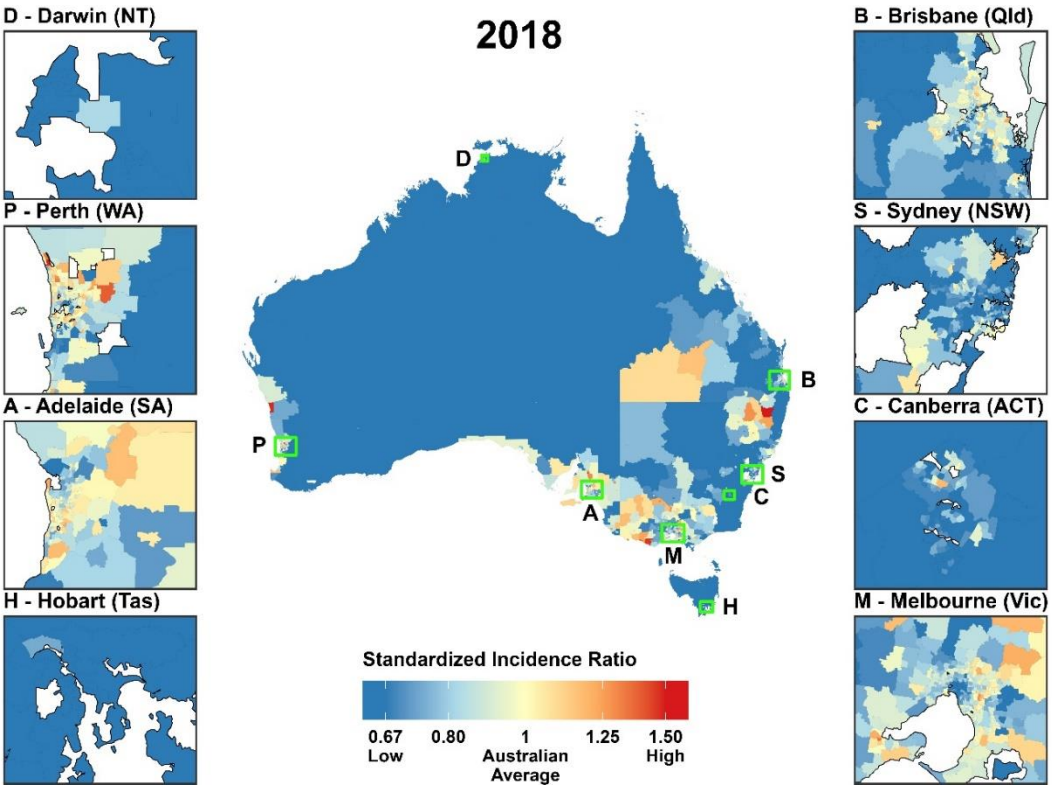
2018
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H - Hobart (Tas)
B - Brisbane (Qld)
S - Sydney (NSW)
C - Canberra (ACT)
M - Melbourne (Vic)
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Standardized Incidence Ratio
0.67
Low
0.80
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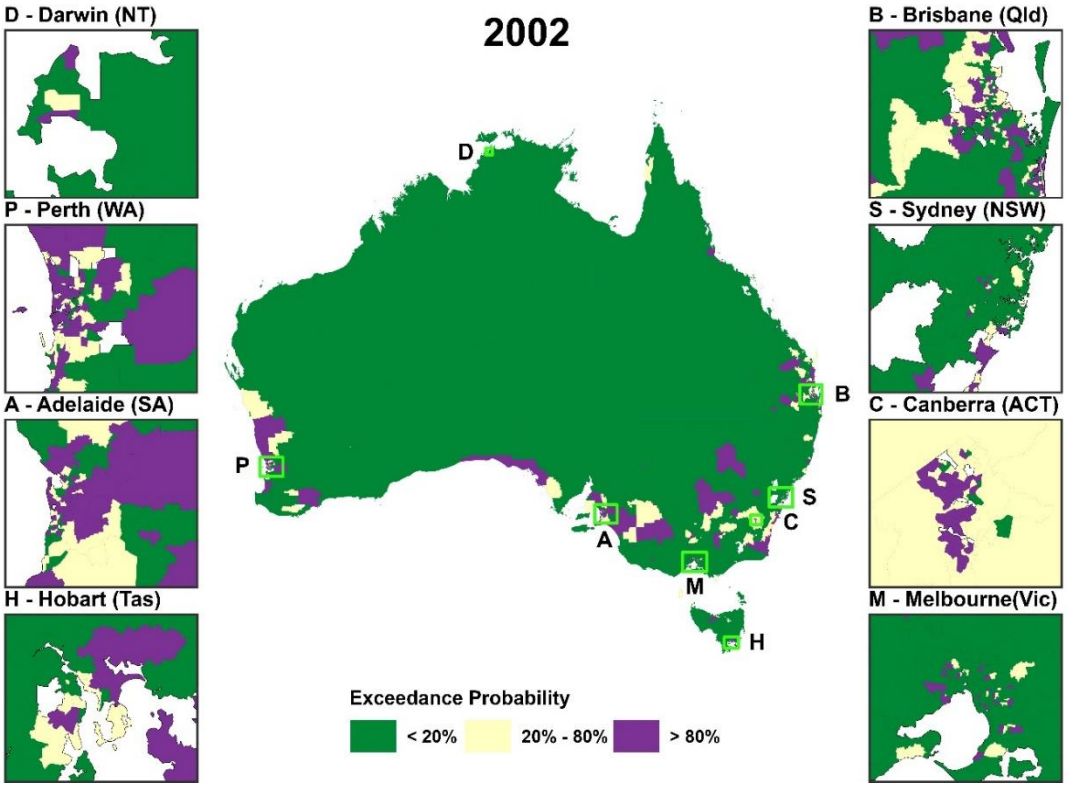
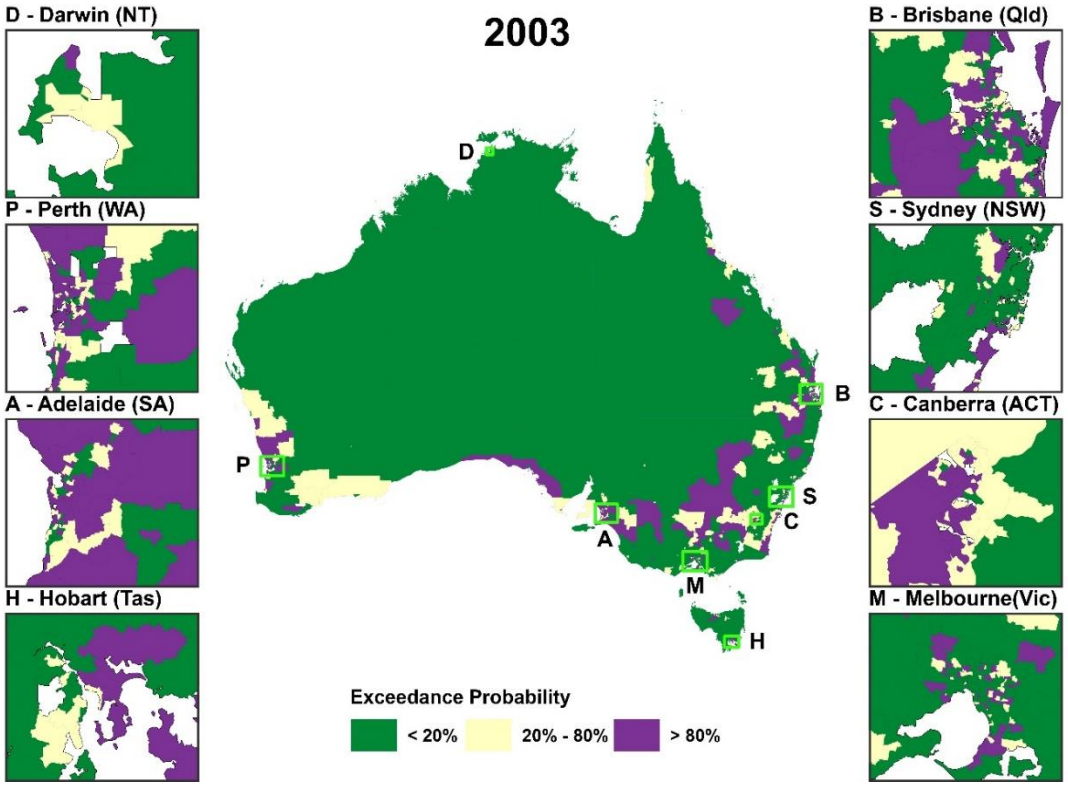
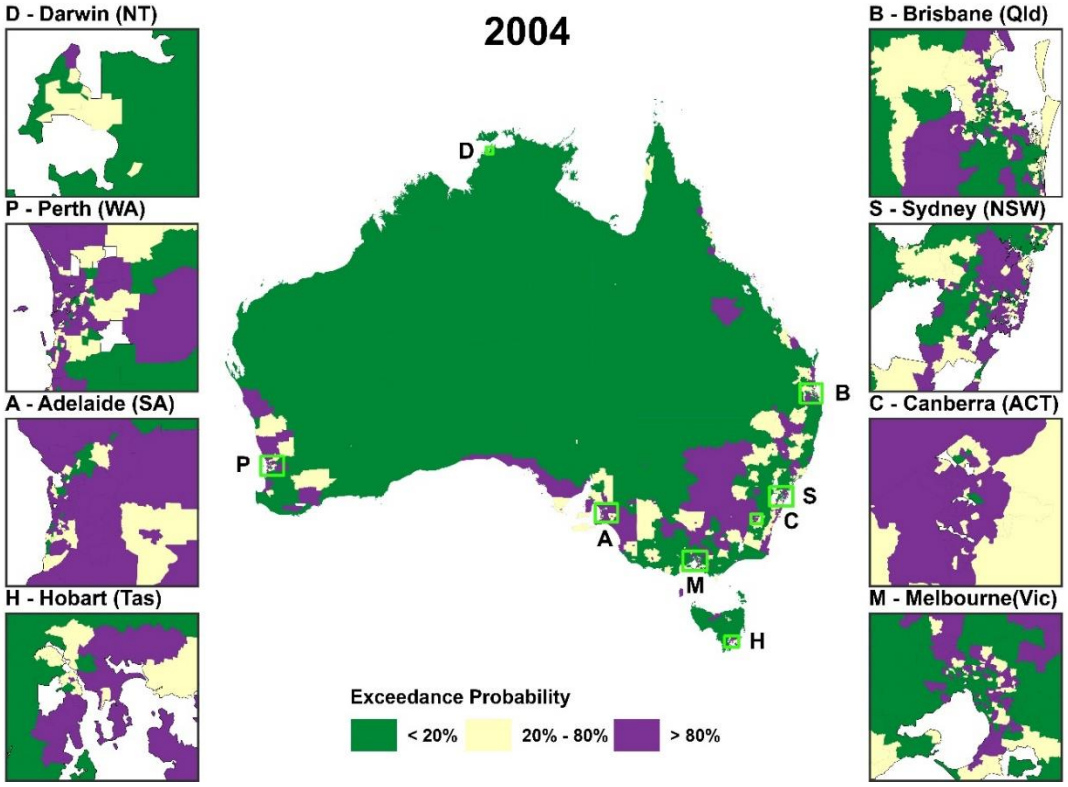
Australian
Average
1.25
1.50
High

Figure SF 5.5: *Map showing Exceedance probabilities of prostate specific antigen screening for 2002-2018, Australia.*



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Exceedance Probability
< 20%
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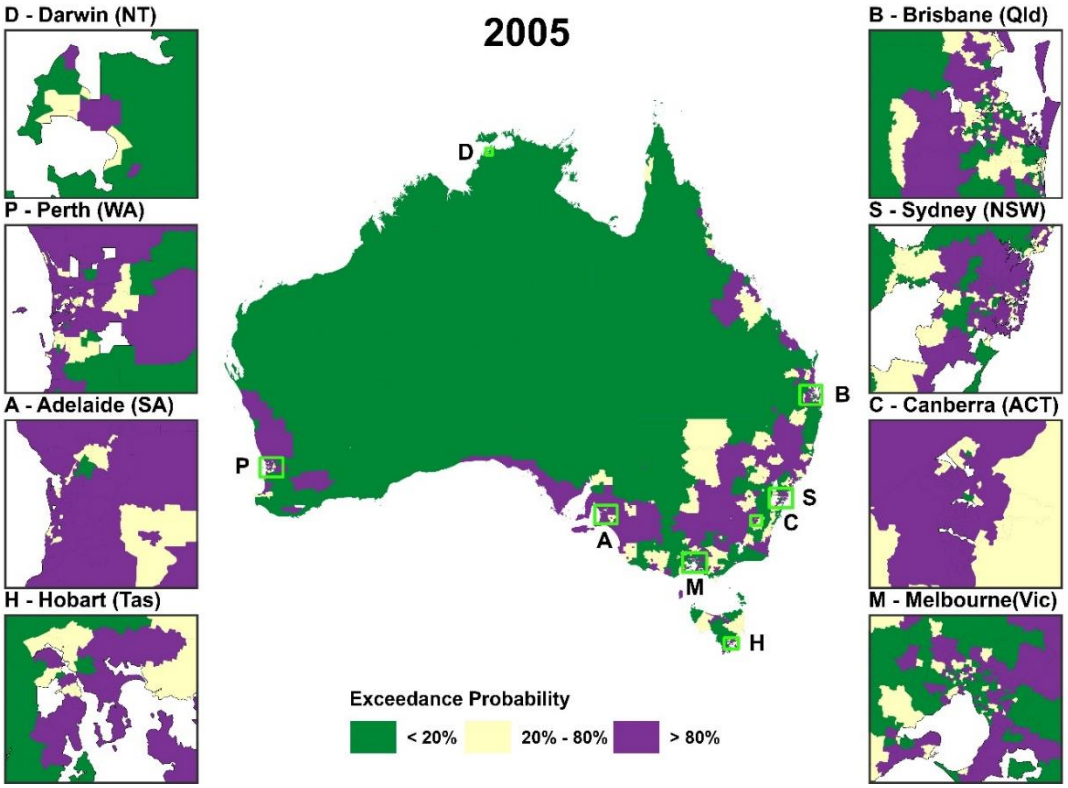
> 80%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Exceedance Probability
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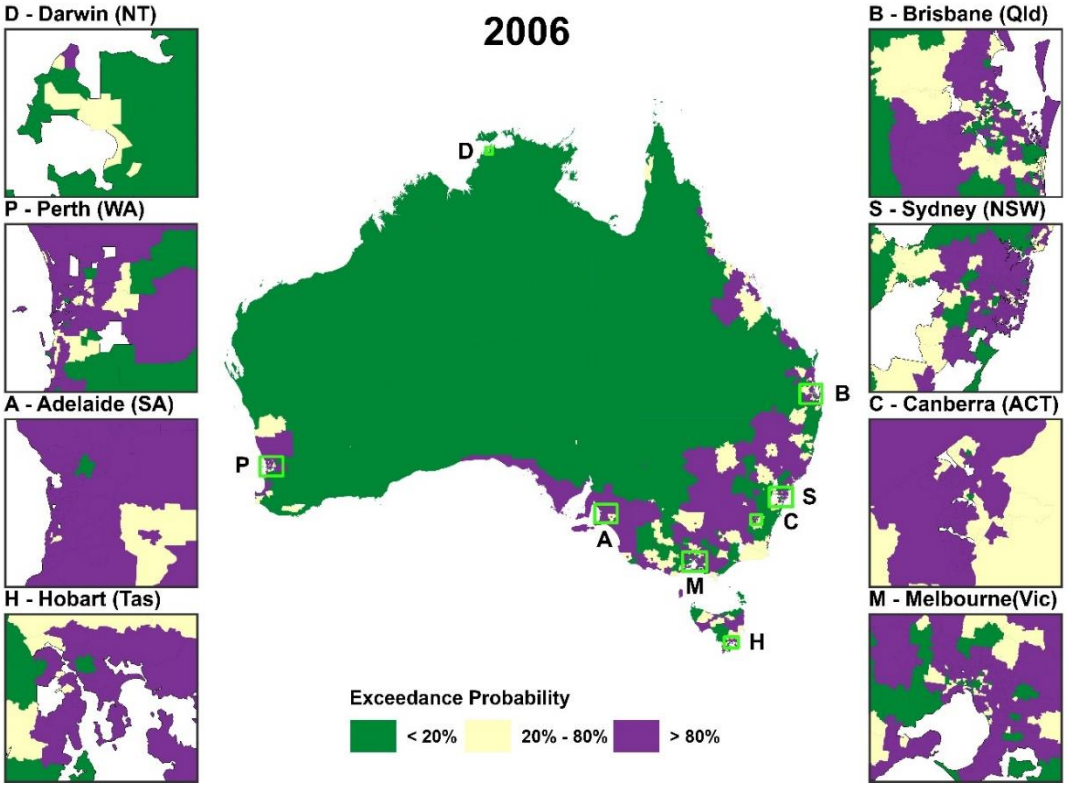
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Exceedance Probability
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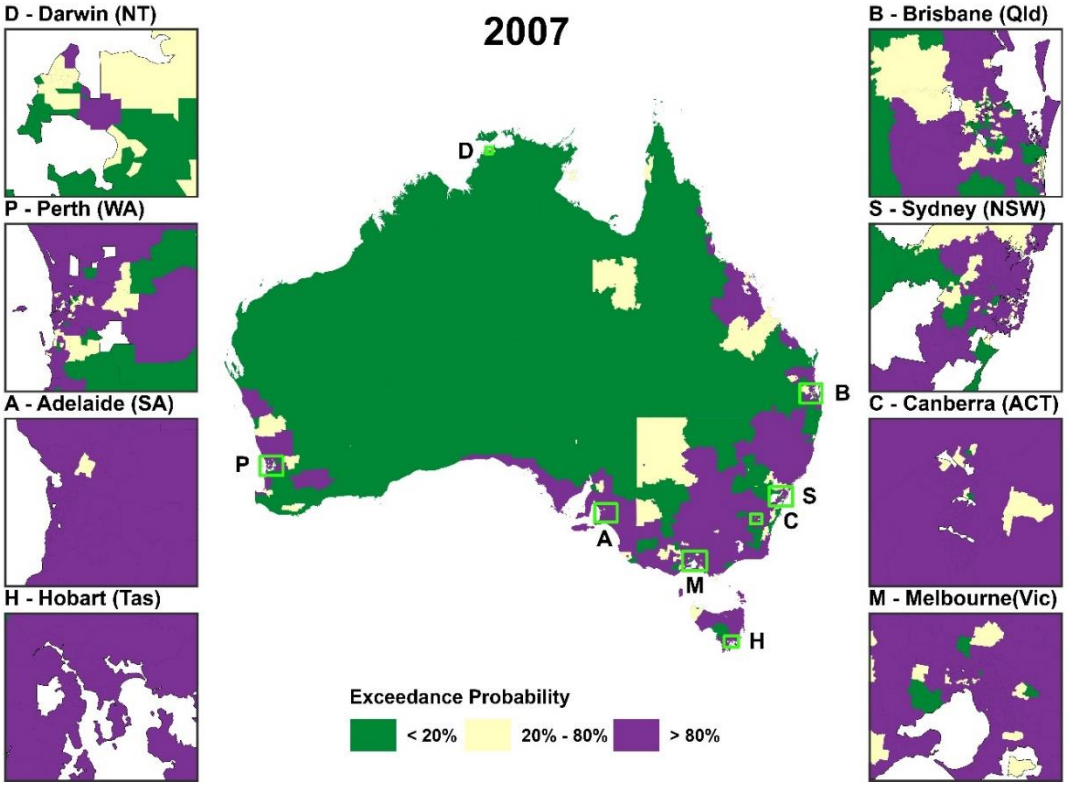
2007
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Exceedance Probability
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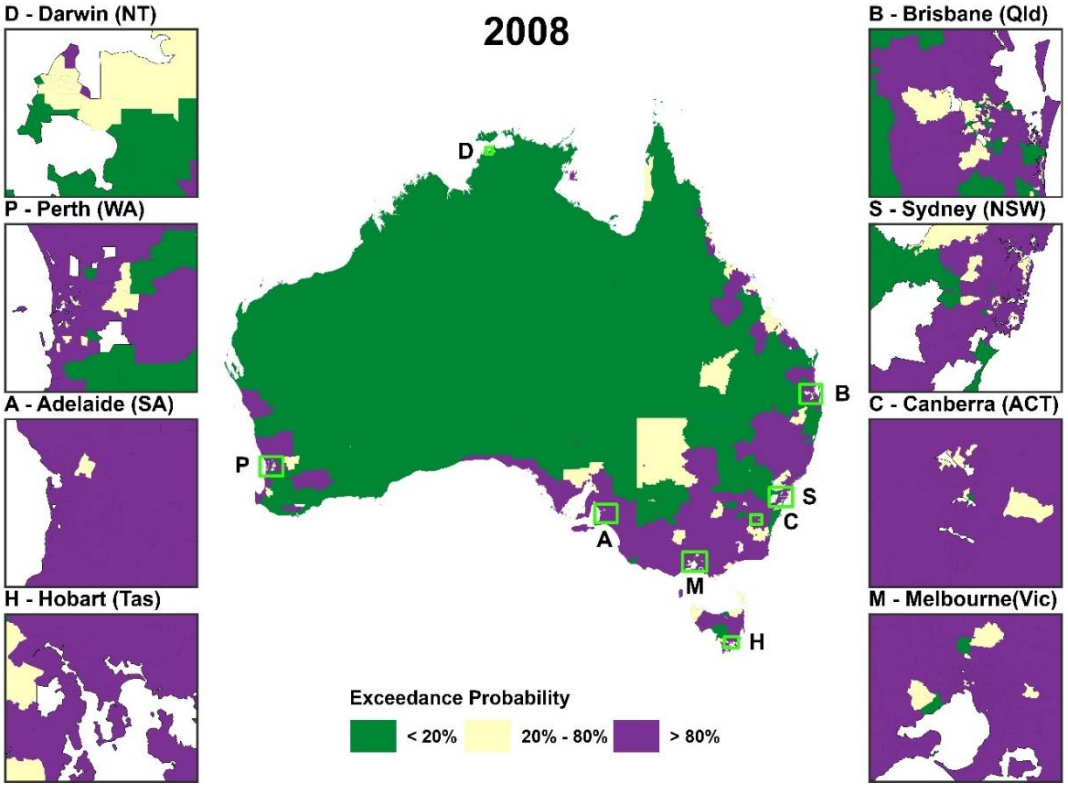
2008
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Exceedance Probability
< 20%
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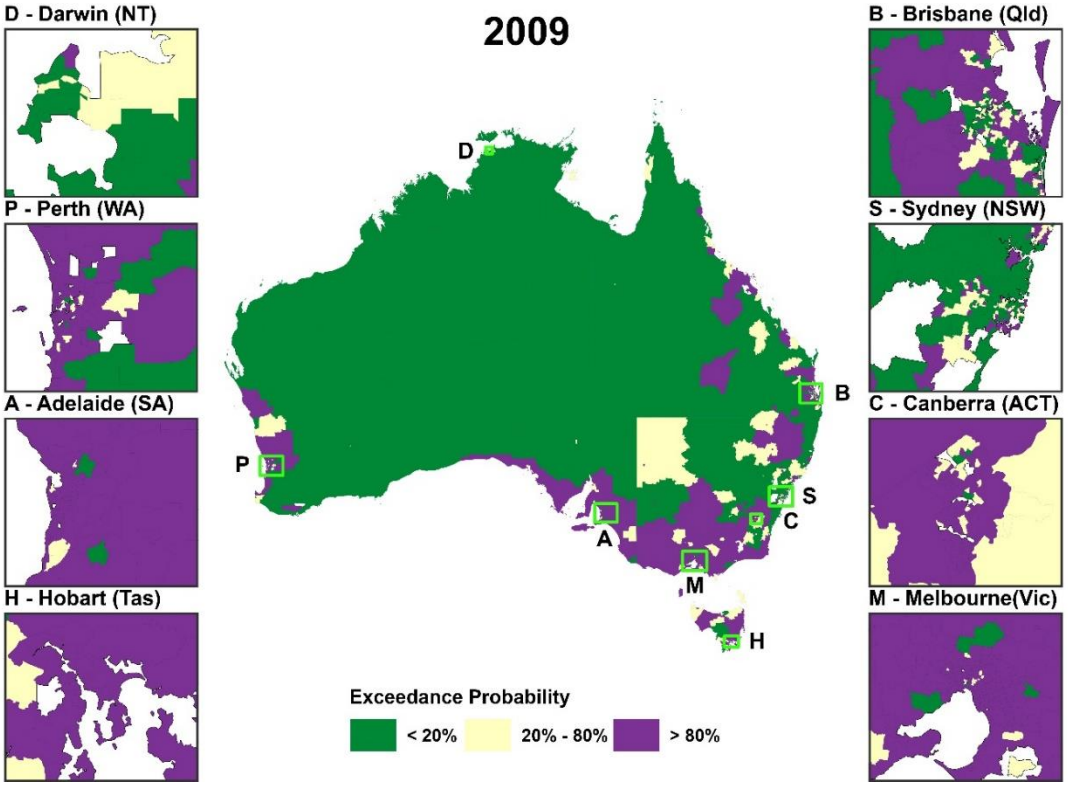
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Exceedance Probability
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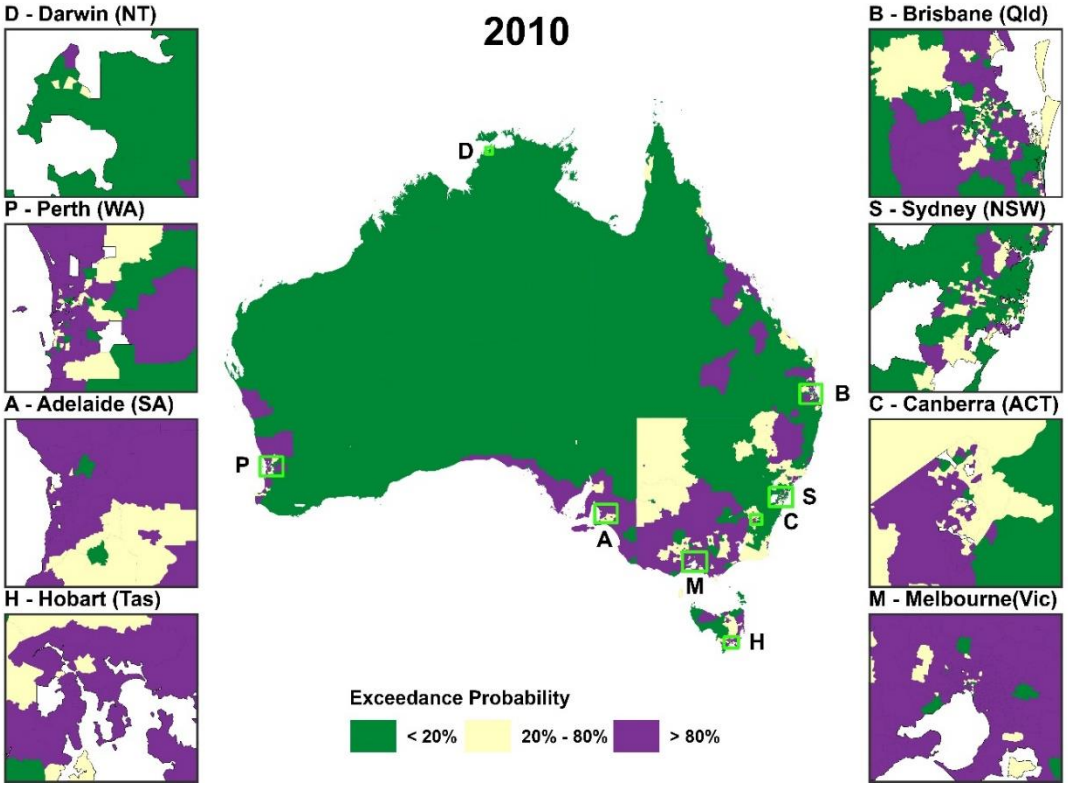
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Exceedance Probability
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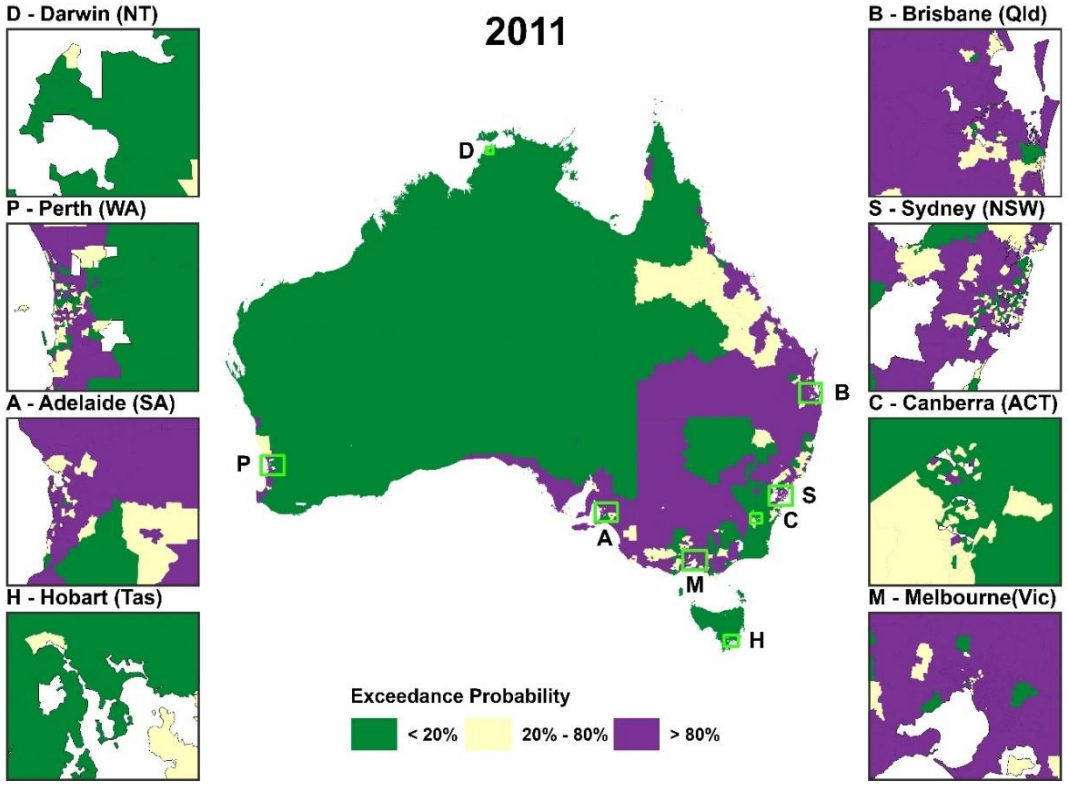
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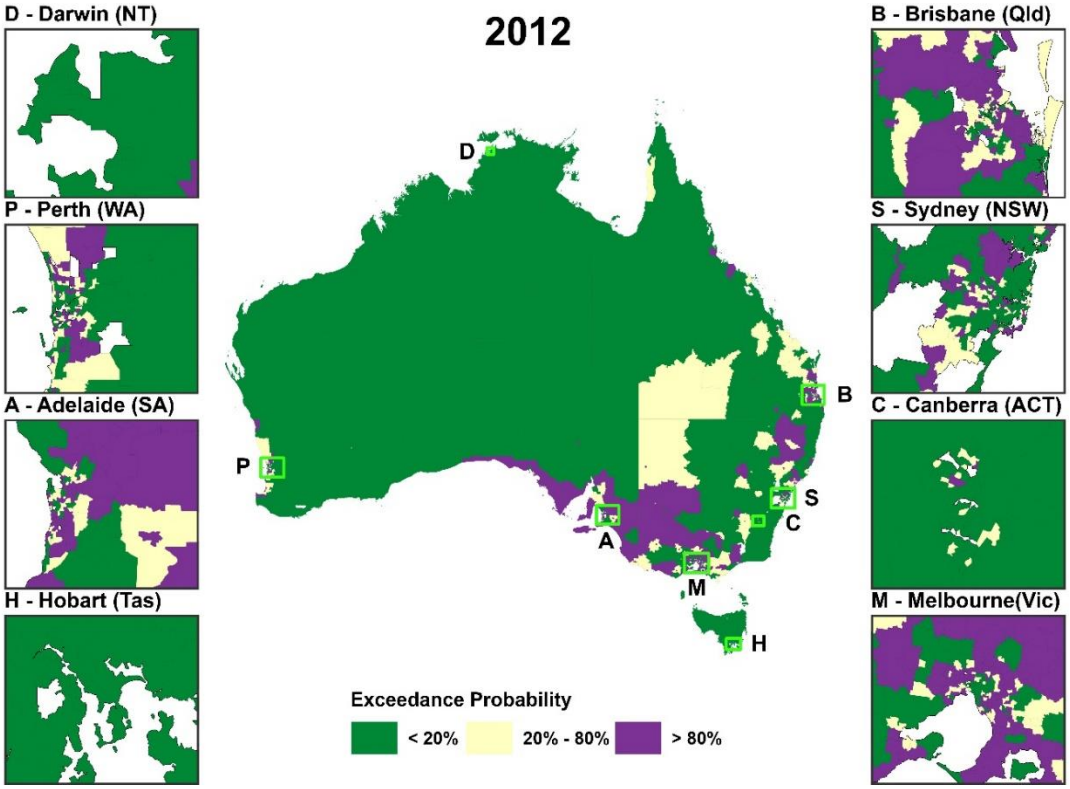
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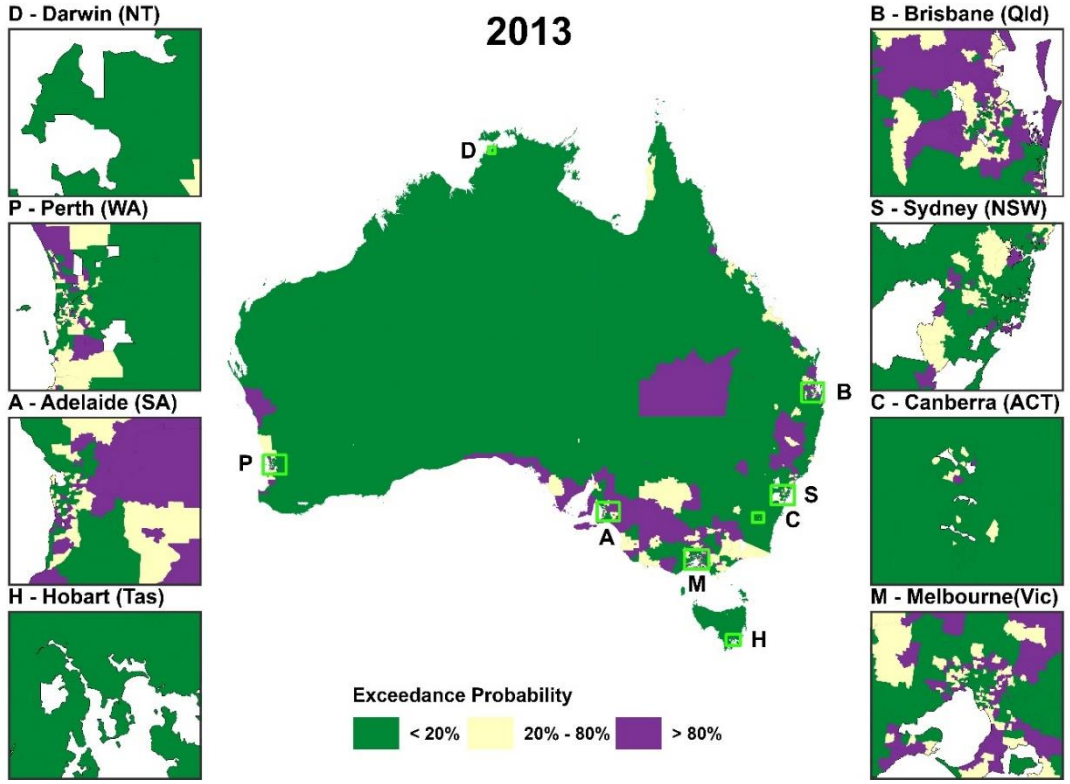
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Exceedance Probability
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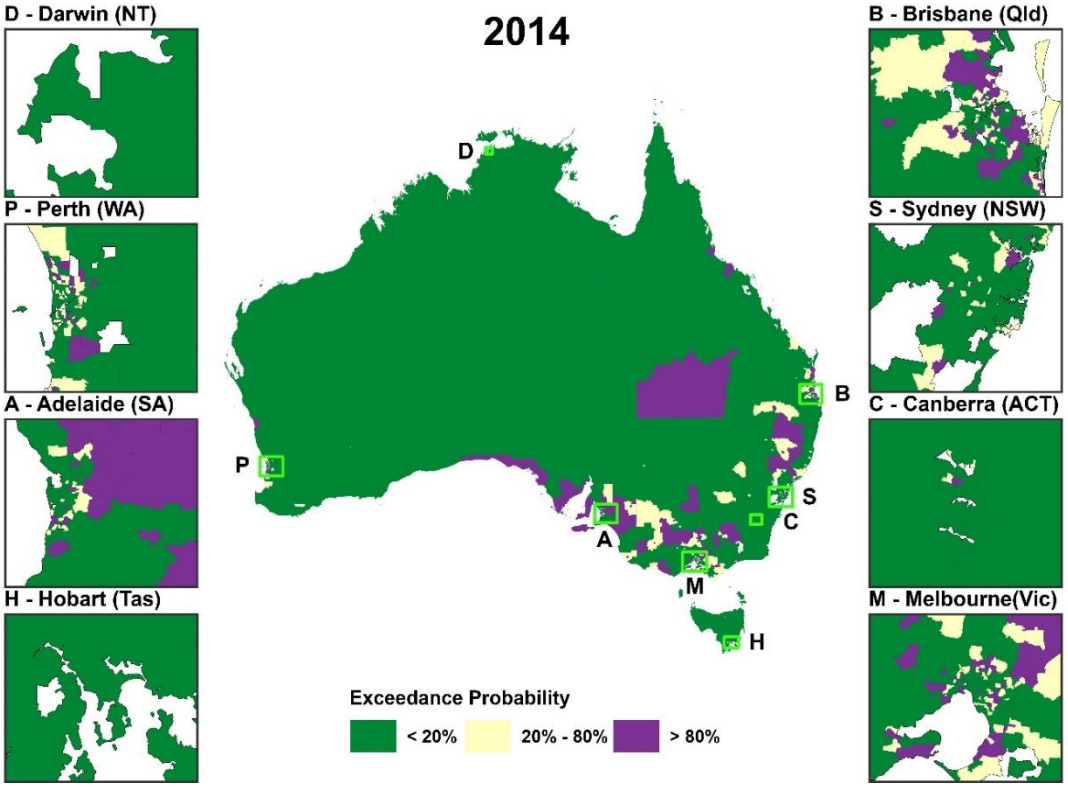
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Exceedance Probability
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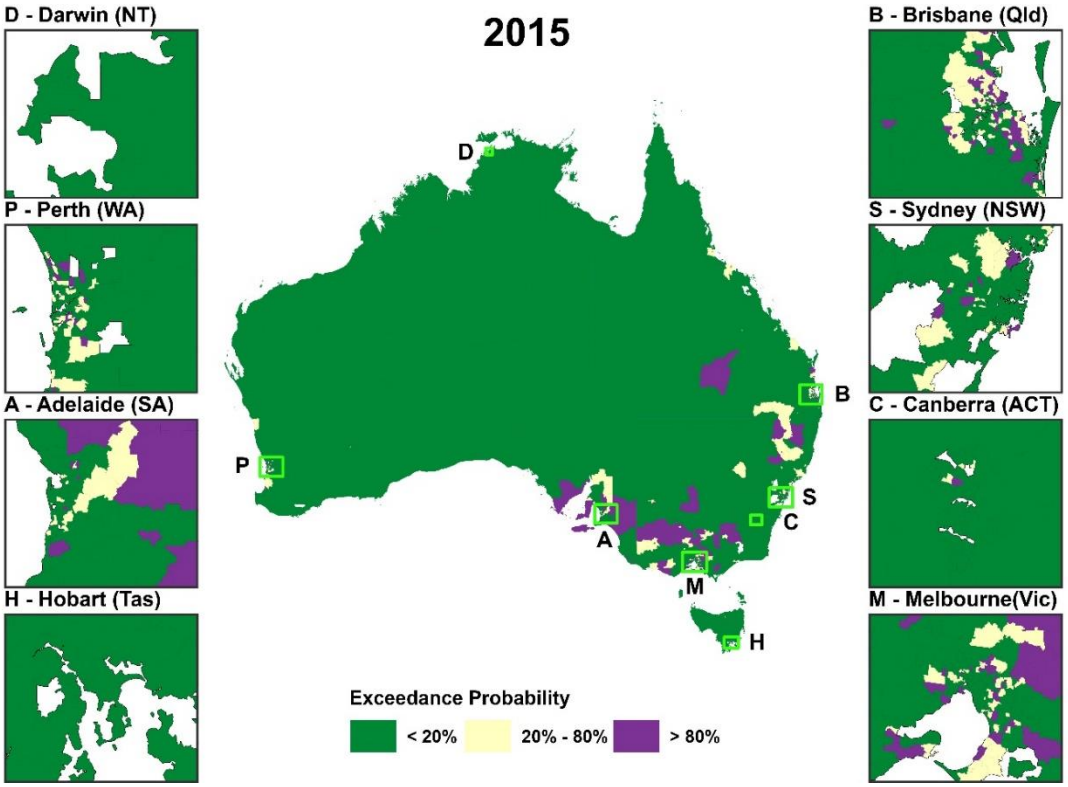
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Exceedance Probability
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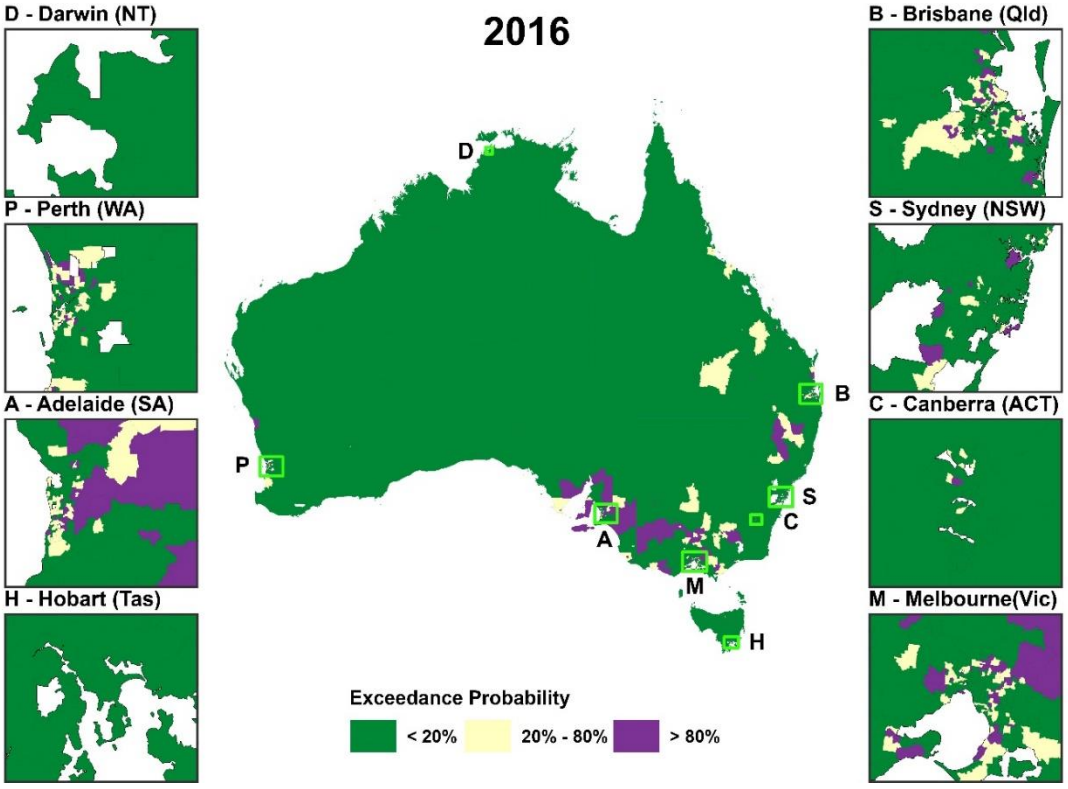
2016
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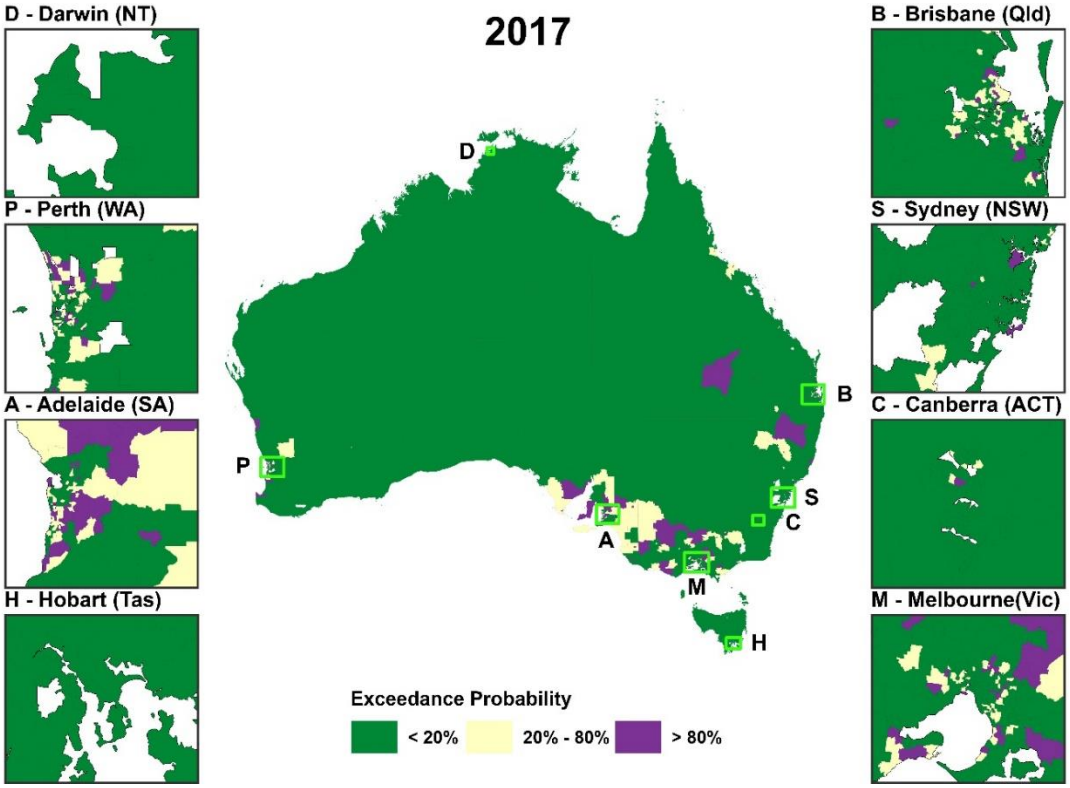
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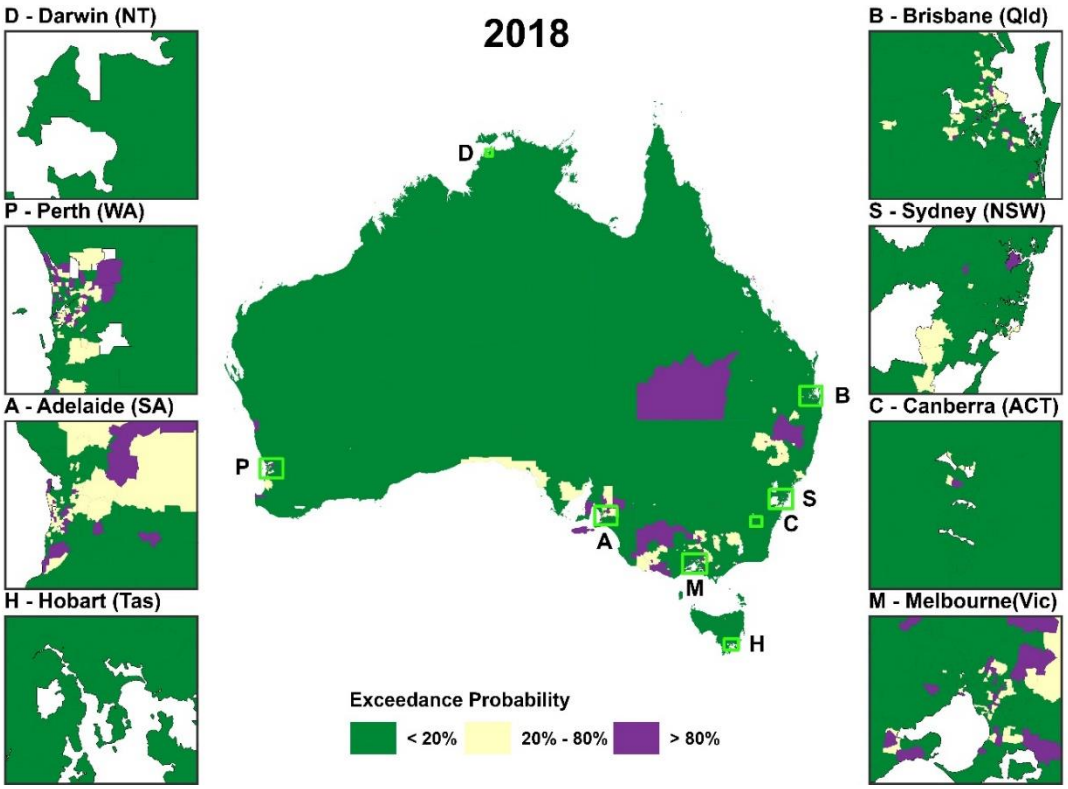
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Exceedance Probability
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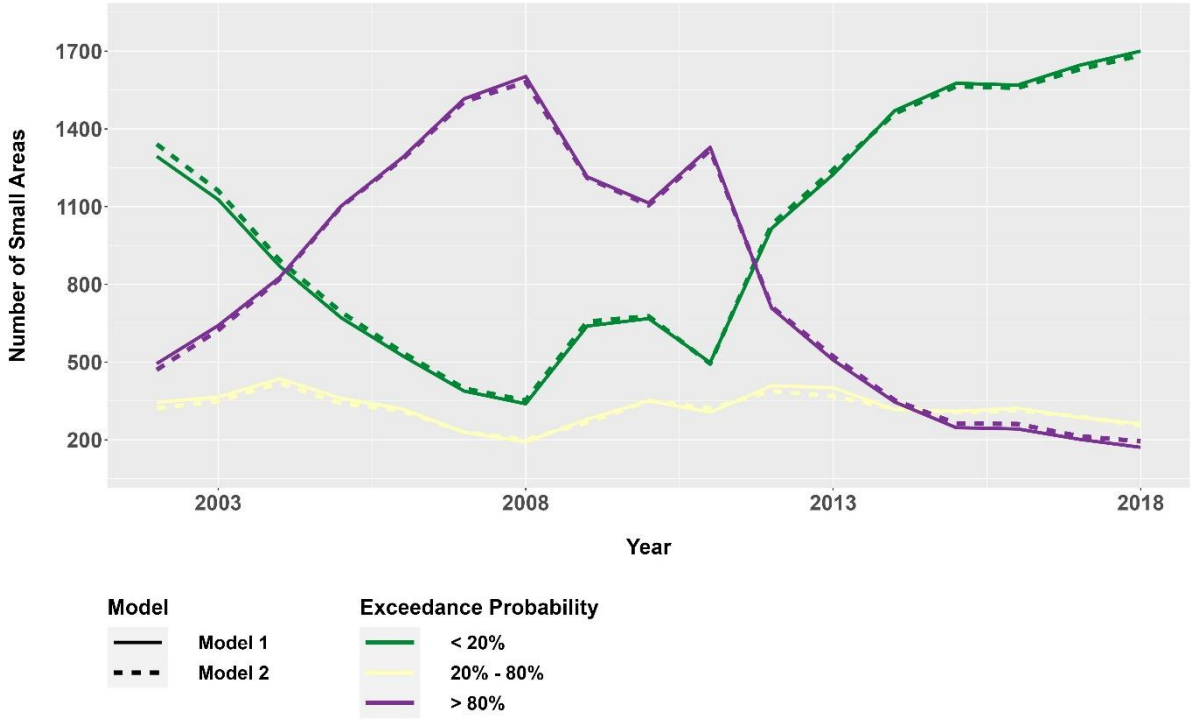
Figure SF 5.6: *Comparison of small areas by Exceedance Probabilities for Model 1 and Model 2.*



CHAPTER 6

6 SPATIAL ASSOCIATIONS BETWEEN PROSTATE CANCER INCIDENCE RATES AND PROSTATE-SPECIFIC ANTIGEN SCREENING TEST USE IN AUSTRALIA, 2012-2016: SMALL AREA POPULATION BASED COMPARISON

6.1 Chapter overview

Bayesian spatial models will be expanded to combine, at the statistical area level 2 (SA2) ecological level, the smoothed estimates from the prostate cancer incidence, prostate cancer survival and the prostate-specific antigen (PSA) testing to determine the extent of association between those three measures, and the direction of that association.

Chapter 6 is under internal peer-review as:

Kohar, A., Cramb, S. M., Pickles, K., Baade, P. D., Smith, D. P., & (2023). Small area associations between prostate cancer incidence rates and prostate-specific antigen screening test use in Australia, 2012-2016: a population based study.

6.2 Manuscript cover page

Small area associations between prostate cancer incidence rates and prostate-specific antigen screening test use in Australia, 2012-2016: a population based study

Authors: Ankur Kohar, MStat[a,b], Susanna M Cramb, PhD[b,c,d,e], Kristen Pickles, PhD[b], Peter D Baade, PhD[c,f,g,], David P Smith, PhD[a,h]

Affiliations:

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e. Australian Centre for Health Services Innovation & Centre for Healthcare Transformation, Queensland University of Technology, Brisbane, Australia

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g. Menzies Health Institute, Griffith University, Gold Coast, Australia

h. School of Public Health and Preventive Medicine, Monash University, Melbourne, Victoria, Australia.

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Phone : +612 93341711

E-mail : aank6528@uni.sydney.edu.au

Keywords: prostate specific antigen, prostate cancer incidence, geographical, bayesian, small area

6.3 Highlights of this manuscript

- This manuscript explores the small-area geographical association between PSA testing and prostate cancer incidence.
- It is the first population-based study of its kind at the small-area level.
- The analysis is based on the number of men rather than the screening test count in Australia.
- Not all small areas exhibited similar trends in the correlation between PSA screening and prostate cancer incidence rates.

6.3.1 What is known before this manuscript

- PSA testing and prostate cancer incidence rates exhibit significant variation across small geographical areas.
- Incidence rates vary within socio-economic and remoteness categories.
- National and broad geographical patterns and trends in PSA testing have generally been consistent with prostate cancer incidence rates.

6.3.2 What is new in this manuscript

- Overall, a weak correlation existed between PSA testing and prostate cancer incidence across Australia at the small area level for men aged 50-79 during the period 2012-2016.
- This weak correlation persisted when examining area-specific categories, including socio-economic status and remoteness.
- Small areas with low rates (SIR<0.5) typically displayed a broader range of estimates and more noticeable differences between prostate cancer incidence and PSA screening than areas with high rates (SIR>1.5).

6.4 Abstract

Objectives: In Australia, prostate-specific antigen (PSA) testing and prostate cancer incidence rates vary substantially by small geographical area, but little is known about the association between them. This study aims to quantify the association between PSA testing and prostate cancer incidence rates at the small area level in Australia for men aged 50-79 during the period 2012-2016.

Study design: Retrospective population-based cohort study.

Methods: We obtained Medicare data on PSA testing (n=2,665,656) from the Commonwealth Department of Health, Australia. We converted (n=50) the postcodes in the PSA data into statistical area level 2 (n=2158) using 2011 geographical concordance file. We also obtained prostate cancer incidence data from all state and territory cancer registries, Australia. We employed a Bayesian spatial model (Leroux model) to calculate the indirectly standardized incidence ratios for PSA testing and prostate cancer incidence for each small area.

Results: Approximately half of the male population aged 50-79 underwent PSA testing at least once in the study period and 4.5% of men received a prostate cancer diagnosis. Overall, there was a weak (r=0.1) correlation between prostate testing and cancer incidence across Australia at the small area level. Additionally, the correlation remained weak when stratified by area-specific categories, including socio-economic status (r= -0.09to0.17), remoteness (r= 0.01to0.26).

Conclusions: Despite strong consistency in temporal trends, the low correlation between PSA testing and prostate cancer incidence at the small area level in this study highlights the complex interaction between ad hoc testing and diagnosis for this disease. Further investigation is needed to describe this relationship and better understand the drivers of geographical variation in prostate cancer incidence by place of residence.

6.5 Introduction

Globally, prostate cancer is the second most diagnosed cancer among males with more than 1.4 million new cases diagnosed in 2020 (Sung *et al.,* 2021), and the most common cancer diagnosed in males in Australia (Australian Institute of Health and Welfare 2022). Incidence rates often vary within countries: in high income countries, more affluent areas generally have higher prostate cancer incidence rates and men from higher socio-economic areas (SES) tend to be diagnosed at earlier stages (Kilpeläinen *et al.,* 2016, Khadhra *et al.,* 2021) than those from lower SES areas. Similarly, men living in remote areas of Australia have lower prostate cancer incidence rates but a slightly higher risk of being diagnosed at later stages compared to men from more urban areas (Foley *et al.,* 2022).

While not part of a formal screening program, the Prostate-Specific Antigen (PSA) test is a blood test commonly used to detect prostate abnormalities in asymptomatic men (Albertsen 2020). Use of the test peaked in Australia in 2008, where nearly one quarter (24.5%) of men aged 50-79 had a "screening" PSA test, with annual rates reducing to 14.5% in 2018 (Kohar *et al.,* 2023). In wealthy countries, higher PSA testing rates have been reported among men living in more socio-economically advantaged and urban areas compared to those living in more disadvantaged and rural areas (Calopedos *et al.,* 2019, Dasgupta *et al.,* 2019).

Since its introduction in the late 1980's, reported temporal trends in PSA testing have generally been consistent with prostate cancer incidence rates (Hu *et al.,* 2017, Pathirana *et al.,* 2022). For example, increases in PSA testing have been followed by increases in prostate cancer incidence (Patasius *et al.,* 2019, Kensler *et al.,* 2021, Ko *et al.,* 2022, Luo *et al.,* 2022). Similarly, a decline in PSA testing rates was followed by a decline in prostate cancer incidence in many high-income countries (Culp *et al.,* 2020, Pathirana *et al.,* 2022, Kohar *et al.,* 2023). In addition, declines in PSA testing in the USA were associated with an increase in late stage or aggressive prostate cancer rates (Kelly *et al.,* 2018, Wang *et al.,* 2020).

To date, only a single study has examined the geographical variation in PSA testing rates at a small area-based level. Furthermore, this population-based study found substantial variation in PSA testing rates between smaller areas across Australia for men aged 50-79 for the period 2017-18 (Kohar *et al.,* 2023). The study reported that the distribution of small area testing rates was similar across socio-economic categories but generally lower in more remote areas.

In Australia there is an established association between prostate cancer incidence and PSA testing over time, both nationally and within broad geographical areas (Luo *et al.,* 2022, Pathirana *et al.,* 2022, Wah *et al.,* 2022). However, very little is understood about the association between small area geographical patterns of PSA testing and the corresponding patterns for prostate cancer incidence. This study addresses

that gap using population-based data on PSA testing collected by Australia's Medicare Benefit Schedule, compared with whole-population prostate cancer incidence data from the Australian Cancer Database.

6.6 Methods

6.6.1 Data

As part of the Australian Cancer Atlas project (Australian Cancer Atlas 2023), data for all prostate cancers (ICD-10 C61) diagnosed among men aged 50-79 years during 1 January 2012 to 31 December 2016 were obtained from the Australian Cancer Database which combines data from all state and territory cancer registries. Since cancer is a notifiable disease in Australia, this contains all prostate cancers diagnosed. Data for the most recent 5-year time period available at the time of data extraction, January 2012 to December 2016 were obtained. The data were supplied with Statistical Area Level 2 (SA2) information using the 2011 Australian Statistical Geography Standard (ASGS) in 5-year age groups (50-54, 55-59, 60-64, 65-69, 70-74, 75-79). Ethics approval for the prostate cancer incidence data was obtained from four ethics committees (New South Wales Population & Health Services Research Ethics Committee (2017/HREC0203), QUT University Human Research Ethics Committee (1600000880), Human Research Ethics Committee for the Northern Territory Department of Health and Menzies School of Health Research ((2016-2720) and the Australian Capital Territory Health Human Research Ethics Committee (ETHLR.16.235).

We obtained data on PSA testing from the Medicare Benefit Schedule (MBS), Commonwealth Department of Health, Australia. The data were for all Medicare reimbursed PSA tests received between 1 January 2012 and 31 December 2016 for men aged between 50 and 79 years. There are four PSA testing-related MBS items (66655-56, 66659-60) with 66655 generally regarded as the item that best classifies tests for "screening" purposes (Kohar *et al.,* 2023). The other three items are primarily used for follow-up of previous prostate disease or for monitoring purposes. The data were supplied with a unique identification for each man, postcode of residence and age categorized in 10-year age groups. Ethics approval to access these PSA data was obtained from the Griffith University Human Research Ethics Committee (2017/777). Analyses of both the PSA screening and prostate cancer incidence data were performed within the Secured Unified Research Environment managed by The Sax Institute (The Sax Institute 2023).

6.6.2 Population

Estimated annual resident populations by SA2 based on 2011 ASGS boundaries for men aged 50-79 by 5-year age groups between 2012 to 2016 were obtained from the Australian Bureau of Statistics (ABS) (Australia Bureau of Statistics 2023).

6.6.3 Concordance and small area allocation

The SA2s (also referred to here as "small area") are the smallest area for which the ABS releases age-specific population statistics. In 2011, there were 2,196 small areas covering the entire geographical area of Australia without gap and overlap. SA2s vary in area and population size. During 2012-16, the median male population aged 50-79 living in those small areas was 1,353 (IQR: 816, 2,134).

The prostate cancer incidence data extract included SA2 information. For the MBS PSA data, the only recorded geographical information was postcode. These postcodes were converted to the 2011 SA2 classification using an ABS geographical concordance file (Australia Bureau of Statistics 2012). For each postcode, the population proportions of each SA2 within that postcode were used to generate a probability distribution, and individual men allocated accordingly to an SA2. This postcode to SA2 allocation was carried out 50 times to incorporate randomness due to probabilistic allocation of individuals to SA2. Each small areas were assigned an ABS Remoteness Area value (Australia Bureau of Statistics 2011) and an Index of Relative Socio-Economic Advantage and Disadvantage quintile (Australia Bureau of Statistics 2011).

6.6.4 Exclusions

Small areas that did not match with the ABS concordance file or had an average annual population of three or fewer men aged 50-79 years during 2012-16 were excluded from the analysis (n=37) (Figure SF 6.1(A)). Lord Howe Island was also excluded, due to its distance from the mainland, leaving 2158 small areas for both prostate cancer incidence and PSA screening data. Additionally, for the PSA data, men were excluded from the study if their listed residential postcode was solely identified as a post office box postcode since it was impossible to identify the correct small area of the individual's residence (Figure SF 6.1(B)). We removed duplicate PSA screening tests in a single year to count only one test per man per year therefore each man could be included a maximum of up to five times in the study period. Due to the probabilistic allocation of men receiving PSA screening tests, when more men appeared to receive a screening PSA test than resided in an area, the number of men having tests was adjusted to be equal to the population. This affected three small areas, removing 0.01% (n=53) of the total men.

6.6.5 Statistical model for spatial estimates

We used Bayesian spatial hierarchical models for the spatial analysis because they borrow information from neighboring areas to 'smooth' the estimates and generate robust and reliable estimates even when data are sparse (Kang *et al.,* 2016). The Leroux model has been shown to perform well for both cancer and PSA small-area analyses previously (Cramb *et al.,* 2018, Kohar *et al.,* 2023), and is a parsimonious way to incorporate both spatially structured (local neighbourhood smoothing) and unstructured (global mean smoothing) effects. A spatial weights matrix for the Leroux model was calculated for 2158 small areas. For full details on model specifications refer to SFile 1.

6.6.6 Data input

For each small area, and separately for prostate cancer incidence and PSA screening, expected counts (based on the Australian average) for men aged 50-79 years were calculated by multiplying the relevant age-specific national rate by the age-specific population of each small area, and then summing across all age groups. The Poisson regression for Leroux model used the log of the expected counts as the offset for each small area. For PSA screening, the expected counts were calculated and used similarly to incidence data, however these calculations were carried out for each (n=50) random small area allocations.

6.6.7 Model computation and testing

To compute our Bayesian models, we used the CARBayes package (version 5.3) (Lee 2013) in R (version 4.1.3) (R Core Team (2022) 2022) that implements Markov Chain Monte Carlo (MCMC) methods. Out of a total of 150,000 iterations, the first 50,000 were excluded to let the model converge. We then selected every tenth sample to reduce autocorrelation between samples, providing a total of 10,000 samples for each of the 2158 small areas.

For PSA screening tests this process was performed for each of the 50 probabilistic allocations, resulting in 500,000 estimates for each small area. Subsequently, a median was calculated from these 500,000 estimates for each small area. Convergence of MCMC chain, indicating that the samples generated are similar to the true posterior distribution and are no longer influenced by their initial conditions, was checked by visually scanning trace plots of the samples of regression parameter (beta) for both the screening (n=50) and incidence (n=1) models (Figure SF 6.2).

6.6.8 Visualization

The R package ggplot2 (version 3.3.6) (Wickham 2016) was used for visualizing results. Using a combination of maps and graphs we present the SIRs for both prostate cancer incidence and PSA screening separately, and also the small-area specific correlation between these SIRs.

6.6.9 Small area correlation

The overall correlation between modelled small area-specific PSA screening and prostate cancer incidence across Australia, and correlations stratified by broader regions, were calculated using Pearson correlation coefficient based solely on the median estimates obtained from the spatial models.

Bivariate maps

The bivariate spatial map with insets (showing relatively small but densely populated areas of Australia) of greater capital cities was used to visualize the associations between PSA screening tests and prostate cancer incidence for many highly populated areas in Australia. The small areas in the map are coloured according to the exceedance probabilities for the nine combinations of PSA screening and Prostate cancer

incidence: Low (Exceedance probability <0.2), Average (0.2≥ Exceedance probability ≤0.8) and High (Exceedance probability >0.8) for PSA screening and prostate cancer incidence (Table ST 5.1).

Bivariate graphs

The bivariate scatterplot shows the modeled small-area SIR estimates for PSA screening and prostate cancer incidence for Australia and by broad regions. These plots were colour-coded by the same nine combinations of Low, Average and High exceedance probabilities described above for the bivariate maps where each circle represents a small area.

6.7 Results

6.7.1 Exclusions

There were 73,073 Australian men aged 50-79 diagnosed with prostate cancer in the study period (Figure SF 6.1(A)). Forty-six men (0.06%) were excluded due to missing geographical information and in an additional to 2 (<0.01%) men from 38 excluded small areas were excluded, leaving 73,025 individuals. The average annual age standardized incidence rate was 5.1 prostate cancer cases per 1,000 men.

In total, 2,703,168 PSA screening tests were undertaken during the study period on 1,671,823 men aged 50-79 years (Figure SF 6.1(B)). Records of PSA tests were excluded for post office box postcodes (n=181, 0.75%), duplicate tests (n=346, 0.02%), postcodes not matching to the ABS concordance file (n=11,439, 0.68%) or low populated small areas (n=91, <0.01%). The final PSA screening dataset included 2,665,656 screening tests among 1,649,427 men aged 50-79 with an average age standardized participation rate of 159.5 screening tests per 1,000 men per year.

6.7.2 Demography

Nearly half of the male population aged 50-79 years had a PSA screening test at least once during 2012-2016. Over the same time period, approximately 4.5% of men in this age group were diagnosed with prostate cancer (Table 6.1). Those aged 70-79 years had the lowest population percent of screening, with 45.6 tests per 100 men. Conversely, men aged 60-69 years had the highest rate of screening, with 51.1 tests per 100 men. The highest ratio of diagnoses to men tested was observed among men aged 70-79 years, with 12.4 diagnoses per 100 tests compared to 0.9 diagnoses per 100 tests in men aged 50-59 years (Table 6.1).

Residents of the major cities had the highest percentage of men screened, while those in very remote areas had the lowest percentage (Table 6.1 and Figure SF 6.3). Due to the smaller sample sizes, very remote areas have more variability in the median estimates, resulting in a larger IQR rather than high uncertainty (Figure SF 6.3). However, the proportion of men diagnosed over the total screened was higher in men living in very remote areas compared to men living in major cities. There was little difference in the

percentage of men screened across categories of socio-economic status. The proportion of men diagnosed over the total screened was higher in the most advantaged areas and lowest in the most disadvantaged areas (Table 6.1 and Figure SF 6.3).

6.7.3 Associations or correlation between prostate-specific antigen screening and prostate cancer incidence by smaller areas

There was considerable spatial variation in both PSA screening and prostate cancer incidence between small areas across Australia and within most greater capital cities (Figure 6.1 and SF 6.4). For PSA screening, 90% of areas had rates likely to differ from the national average, and almost 60% of areas for prostate cancer (Table ST 6.2) were likely to differ from the average. Overall, there was a weak ($r = 0.1$) correlation as well as lower value of kappa statistics (< 0) between PSA screening and prostate cancer incidence by small areas across Australia during the study period (Figure 6.2). Moreover, kappa statistics showed low association when small areas were categorized into one of the nine combinations of low/average/high for prostate cancer incidence and PSA screening (Table ST 6.1). Additionally, when stratified by area-specific categories, the correlation remained weak across most of the categories, including socio-economic status ($r = -0.09$ to 0.17), remoteness ($r = 0.01$ to 0.26), greater capital cities ($r = -0.1$ to 0.20) and outside greater capital cities ($r = 0.09$ to 0.34) (Figure 6.3). Overall, small areas with low rates (SIR<0.5) tended to have a wider range of estimates and differed more between prostate cancer incidence and PSA screening than areas with high rates (SIR>1.5) (Figure 6.2 and 6.3).

When small areas were categorized into one of nine combinations of low/average/high for prostate cancer incidence and PSA screening, there was a large variation across the categories distributed throughout Australia (Figures 6.4 and 6.2). Visually, the map (Figure 4) and bottom left quadrant of scatter plot (Figure 6.2) were dominated by the areas in dark green that indicate both low prostate cancer incidence and low screening (Table ST 6.3). However, these small areas were predominately sparsely populated (15.4% of study population), representing 63.6% of the total Australia's land area, but only 16.7% of the total number of mapped small areas.

In addition, those areas with both high incidence and high screening (top right quadrant; Figure 6.2) (presented in red) constituted 11.8% of total areas mapped (Table ST 6.3) and 13.7% of the male population aged 50-79 years. These areas are less than 1% of total land area and are mainly from greater capital cities of Brisbane, Sydney, Melbourne, Perth, and some areas of Adelaide (Figure 6.4). Furthermore, small areas in light green (bottom right quadrant), representing 13.6% of the total small areas (4.7% of total land area) with low incidence but high screening rates, accounted for nearly 17% of the population and are mainly situated in eastern, south-eastern, and some western parts of Australia (Figure 6.4 and Table ST 6.3). Finally, the small areas (11.8% of the total or 4.4% of total land area) which have high incidence-low screening rates (top left quadrant) in orange were mainly evident in the north-east of Queensland, south-

eastern Australia, and the south-west of Western Australia (Figure 6.4 and Table ST 6.3). These areas include small areas both outside and inside greater capital city regions.

6.8 Discussion

6.8.1 Interpretation

To the best of our knowledge, this study is the first of its kind to examine the relationship between PSA screening and prostate cancer incidence rates at a small area level in a whole-population setting. The chosen methodology was the most suitable when dealing with small numbers. While there was significant variability in both screening and incidence rates, our findings reveal very low correlation (r = 0.1) between these variables by small areas across Australia. Additionally, the correlation at the small area level remained low across the different levels of remoteness and socio-economic status. In the study period it appeared that variation in prostate cancer incidence rates at small areas was not related to the prevalence of PSA screening.

This consistently low correlation was surprising, because the temporal patterns of prostate cancer incidence has been strongly associated with the temporal patterns in PSA screening in Australia. This was particularly evident after the initial listing of PSA as a rebateable item on Medicare in 1988, with a resulting significant increase in incidence to a peak in 1993 (McCaul *et al.,* 1995). Notably, studies conducted during that period demonstrated a strong correlation between the number of PSA tests performed and the incidence of prostate cancer in New South Wales (Smith and Armstrong 1998) and Western Australia (Threlfall *et al.,* 1998). The temporal change in rates in prostate cancer incidence from 1993 (first peak) to the early 2000s aligned, initially with changes in the way in which prostate biopsy was conducted (Royal Australian College of General Practitioners 2012) and then with the reduced frequency of PSA screening (Luo *et al.,* 2022). Furthermore, following the modification of the Royal Australian College of General Practitioners' guidelines for PSA testing in 2009 (Royal Australian College of General Practitioners 2009) (after the second peak in 2008) and 2012 (Royal Australian College of General Practitioners 2012), there was a subsequent decline in prostate cancer incidence rates (Pathirana *et al.,* 2022). The Australian situation is consistent with the correlation observed between temporal patterns in PSA screening and prostate cancer incidence in multiple countries at the national level, including the United States of America (Zhou *et al.,* 2016), Canada (Zhou *et al.,* 2016), Brazil (Zhou *et al.,* 2016), New Zealand (Zhou *et al.,* 2016) and the United Kingdom (Zhou *et al.,* 2016).

To help with the interpretation of the relationships between screening intensity and prostate cancer incidence, we divided areas into categories. There was inconsistency in the relationship between screening and incidence. We observed that only 25% of small areas had either a high-high or low-low association between PSA screening and prostate cancer incidence. There were 13.6% (n=293/2158) of small areas that demonstrated high screening and low incidence, indicating a high level of awareness regarding PSA

screening in those areas. Potential explanation for these areas could be that testing prior to the study period had already diagnosed cancers in this population, or that organised testing campaigns (Beaumont 2019), celebrities backing mass screening programs (Brewer 2021) or dedicated prostate cancer organisation organizing annual events (Prostate Cancer Foundation of Australia 2022) may have encouraged higher rates of testing. As opposed, there was a group of 11.8% (n=255/2158) of small areas that had low screening and high incidence, suggesting again that incidence was not strongly related to screening uptake. However, 98.4% of small areas in this group are from major cities and regional areas.

The remaining half of the total small areas (n=1069/2133) displayed no evidence that their rates were different to the Australian average for either screening, incidence, or both.

The lack of an association between testing and incidence could potentially be due to the complexity between screening patterns and cancer incidence. Additionally, the low association could be attributed to the selected time period, which is approximately two decades after the initial major peak for prostate cancer incidence in 1993. It is possible that men at risk may have been detected earlier and subsequently removed from the at-risk group during the study period. It is plausible that associations may have been stronger in an earlier period preceding our study, although we lack the necessary data to substantiate this claim.

The changes in diagnostic procedures around 2002 may have also contributed to the dissociation between testing and incidence. Specifically, the broad threshold for further investigation of PSA levels 4.0 ng/ml was reduced to a range of 2.6-4.0 ng/ml depending more on age-specific ranges. This modification resulted in a significant rise in the identification of clinically significant cancers by up to 22% and a corresponding 59% increase in the number of prostate biopsies conducted in New South Wales between 2000 and 2004 (Smith *et al.,* 2008). These outcomes highlight the impact of diagnostic protocol changes on prostate cancer detection and subsequent clinical interventions. Hence, men screened were potentially diagnosed at an earlier time period than they would have been if the threshold value had not been changed, and those men were not included in our analysis. It is not clear whether the shift in diagnostic practices would have differed by geographic regions in Australia.

The demographic variations in small areas may have influenced testing behaviour and cancer risk differentially in small areas. For example, one potential explanation for the limited correlation could be the variation in screening rates and cancer risk between migrant men and Australian-born men. Among most migrant groups, prostate cancer incidence rates were lower compared to Australian-born males, particularly among males originating from Southern and North-East Asian countries, where incidence rates were 50-60% lower (Yu *et al.,* 2023). These patterns might be influenced by the lower prevalence of prostate-specific antigen (PSA) screening reported among urban-dwelling males from East Asia and China, around 30% and 50% less respectively, compared to Australian-born males (Weber *et al.,* 2014). However, a recent analysis based on Medicare claims indicated minimal differences in PSA screening across major migrant

groups (Nair-Shalliker *et al.,* 2018). Additionally, it is possible that there is a lower uptake of screening in areas with a higher concentration of non-English speaking households (Khan *et al.,* 2021). Future work should focus on the association between testing behaviour and cancer incidence in both migrant and first nations men.

In this study, the limited number of observations in small areas, especially for prostate cancer, may pose a challenge in establishing a strong association. The size of a correlation can be influenced by the sample size, with larger samples generally leading to more stable correlations (Hung *et al.,* 2017). While the average number of modelled incident prostate cancer cases in the small areas was 33.8 (range: 0.02-135.2), this was below the recommended sample size of at least 150 to 200 for correlation analyses (Hung *et al.,* 2017). However, numbers were 'borrowed' between neighbouring areas in the modelling of estimates, leading to greater reliability than the low numbers imply.

While no studies have explored small-area associations between PSA and prostate cancer, several studies have explored small-area associations between screening and incidence for other cancer types. For instance, a study conducted in the United States identified significant inverse associations between colorectal cancer screening and incidence rates (Warren Andersen *et al.,* 2019). Similarly, a study utilizing data from the California health care system observed a strong correlation between undergoing screening colonoscopy and a decreased risk of death from colorectal adenocarcinomas in the colon and rectum (Doubeni *et al.,* 2018). Furthermore, in South Korea, a positive association was found between increased incidence rates and the extent of screening practices for thyroid cancer (Park *et al.,* 2016). These countries have far higher population numbers than Australia and much greater population density in small areas.

6.8.2 Strengths and limitations

This study has several notable strengths. Firstly, the analysis relies on population-based data for both PSA screening and prostate cancer incidence, sourced from comprehensive datasets such as Medicare Benefit Schedule and the cancer registry in Australia, which capture nearly all cases. Secondly, we employed a Bayesian modeling approach, which enables the generation of robust estimates for the underlying spatial patterns at the small-area level, while mitigating the impact of random fluctuations often associated with small area data. The use of Bayesian spatial models also offers the advantage of flexibility in calculating appropriate estimates.

This study is subject to several limitations that warrant consideration. Firstly, it is important to recognize that this is an ecological study, therefore, caution is required when interpreting the results, as unmeasured and uncontrolled confounding factors may influence the findings. Additionally, there is a possibility of underreporting of some PSA tests due to the nature of Medicare claims, which only capture benefits paid to pathology during a single episode of care, referred to as episode coning. This may result in differential screening patterns based on geographical factors. For instance, it is plausible that men residing in less

accessible areas may combine multiple, more expensive tests into a single visit due to the need to travel greater distances to see a general practitioner. The geographical information captured by Medicare is limited to the postcode of residence, and although we performed probabilistic allocation, there is a possibility of misassignment of postcodes to incorrect small areas. However, to mitigate this issue, we conducted the analysis 50 times and considered the median. One potential drawback of spatial smoothing is the potential for geographic homogeneity to be established between neighboring places, which may make it challenging to distinguish between different small areas. Another limitation is the lack of national data on the stage of disease at presentation, which could have provided insights into whether higher screening rates were associated with higher incidence of lower risk disease and conversely lower screening rates associated with more late-stage disease. Moreover, introducing bias in results when rezoning boundaries of areal units or aggregating data from smaller areal units to estimate values for larger units is a possibility; this phenomenon is commonly known as the Modifiable Areal Unit Problem (Ye and Rogerson 2022). The results presented in this study are valid when using the 2011 ASGS SA2 boundaries but may alter under different geographical boundaries.

6.8.3 Implications

The findings of this study have important implications, indicating substantial variation in both screening practices and incidence rates, but little association between them at the small area level. One of the enduring questions about prostate cancer screening is whether it results in lower prostate cancer mortality. Based on the lack of correlations in this study it is unlikely this study design would be useful in measuring the association between screening intensity and prostate cancer mortality. Measuring the relationship between screening and mortality would be further challenged by the long latency period between testing and death, the possibility of movement of the population between testing and death. Nevertheless, this study design can be valuable in investigating other screening methods and cancer types to determine if disparities in access to early detection influence incidence rates and potentially impact outcomes such as later stage disease or treatment patterns.

6.9 Conclusion

This study is the first to examine the geographical association between PSA screening and prostate cancer incidence rates by small areas across Australia. Despite observing consistent temporal trends, the low correlation between PSA testing and prostate cancer incidence at the small area level emphasizes the intricate interplay between ad hoc testing and disease diagnosis. These findings offer valuable insights at both local and national levels. Further research is needed to explore the underlying factors that contribute to geographical disparities, allowing for a better comprehension of the drivers behind the variation in prostate cancer incidence based on residential location. Additionally, a review and reflection on national PSA guidelines are warranted to enhance prostate cancer outcomes in Australia.

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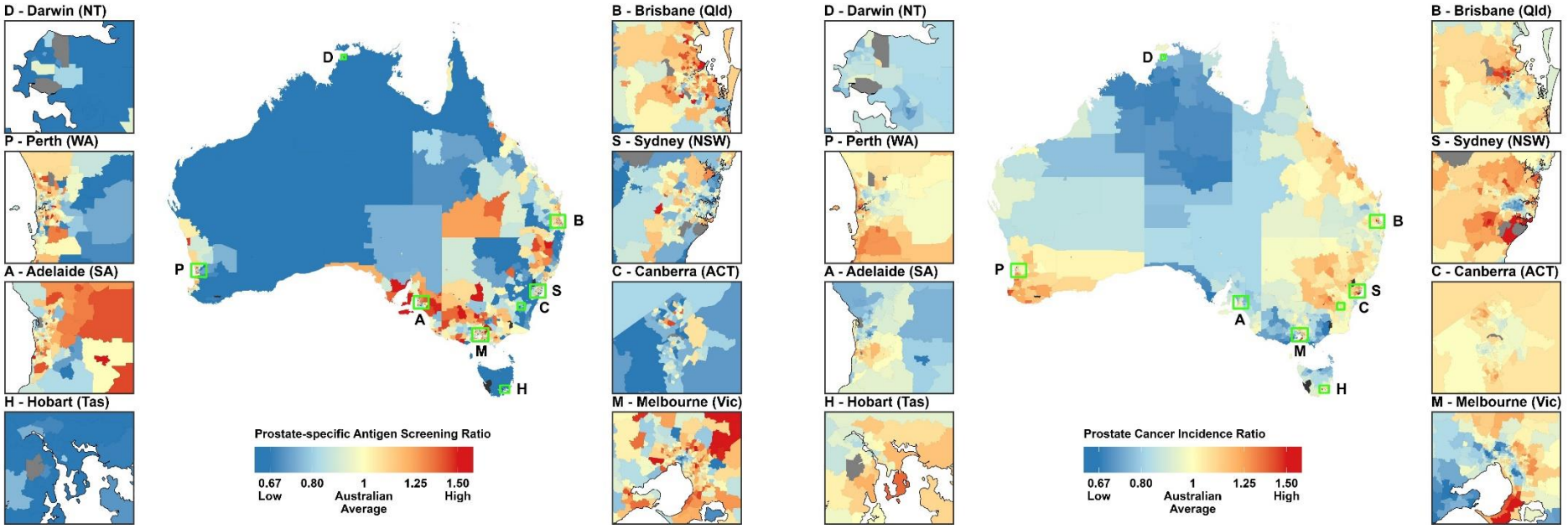
Table 6.1: *Demographic characteristics of men who had at least one Medicare-funded prostate-specific antigen (PSA) screening test and those who diagnosed with prostate cancer aged 50-79 years, Australia, 2012-16.*

Data Source	Australia Bureau of Statistics Data	Medicare Benefit Schedule Data		Cancer Registry Data	Calculated Data	
Characteristics	**Estimated Resident Population[a] (n)**	**PSA Screening Tests[b] (n)**	**Number of Men Screened[c] (n)**	**Men Diagnosed[c] (n)**	**Population Percent of Men Screened[d] (%)**	**Proportion of Men Diagnosed over the Total Screened[e] (%)**
Australia	3,324,744	2,665,656	1,648,707	73,025	49.6	4.4
Age group (years)						
50 - 59	1,462,362	1,048,087	734,819	6,829	50.2	0.9
60 - 69	1,174,675	1,048,854	600,459	27,339	51.1	4.6
70 - 79	687,707	568,715	313,429	38,857	45.6	12.4
Remoteness						
Major City	2,192,526	1,812,150	1,119,394	48,080	51.1	4.3
Inner Regional	714,011	560,298	345,641	16,176	48.4	4.7
Outer Regional	349,170	259,244	161,627	7,638	46.3	4.7
Remote	45,333	25,650	16,229	817	35.8	5.0
Very Remote	23,703	8,314	5,816	314	24.5	5.4
Socio-Economic Status[f]						
Most Advantaged	666,884	523,660	326,064	16,527	48.9	5.1
Advantaged	638,163	528,300	324,842	14,212	50.9	4.4
Middle SES[g]	693,053	562,934	346,906	14,939	50.1	4.3
Disadvantaged	677,042	549,265	338,247	14,495	50.0	4.3
Most Disadvantaged	649,243	501,218	312,468	12,837	48.1	4.1

[a] Average estimated resident population of Australian men aged 50-79 for 2012-16.
[b] One test per man per year.
[c] Men counted once over 2012-16.
[d] Ratio of Number of men tested and Estimated Resident Population.
[e] Ratio of Men Diagnosed and Number of Men Tested.
[f] 279 PSA tests were excluded for postcodes that could not be allocated an Index of Relative Socio-Economic Advantage and Disadvantage.
[g] SES = Socio-Economic Status.

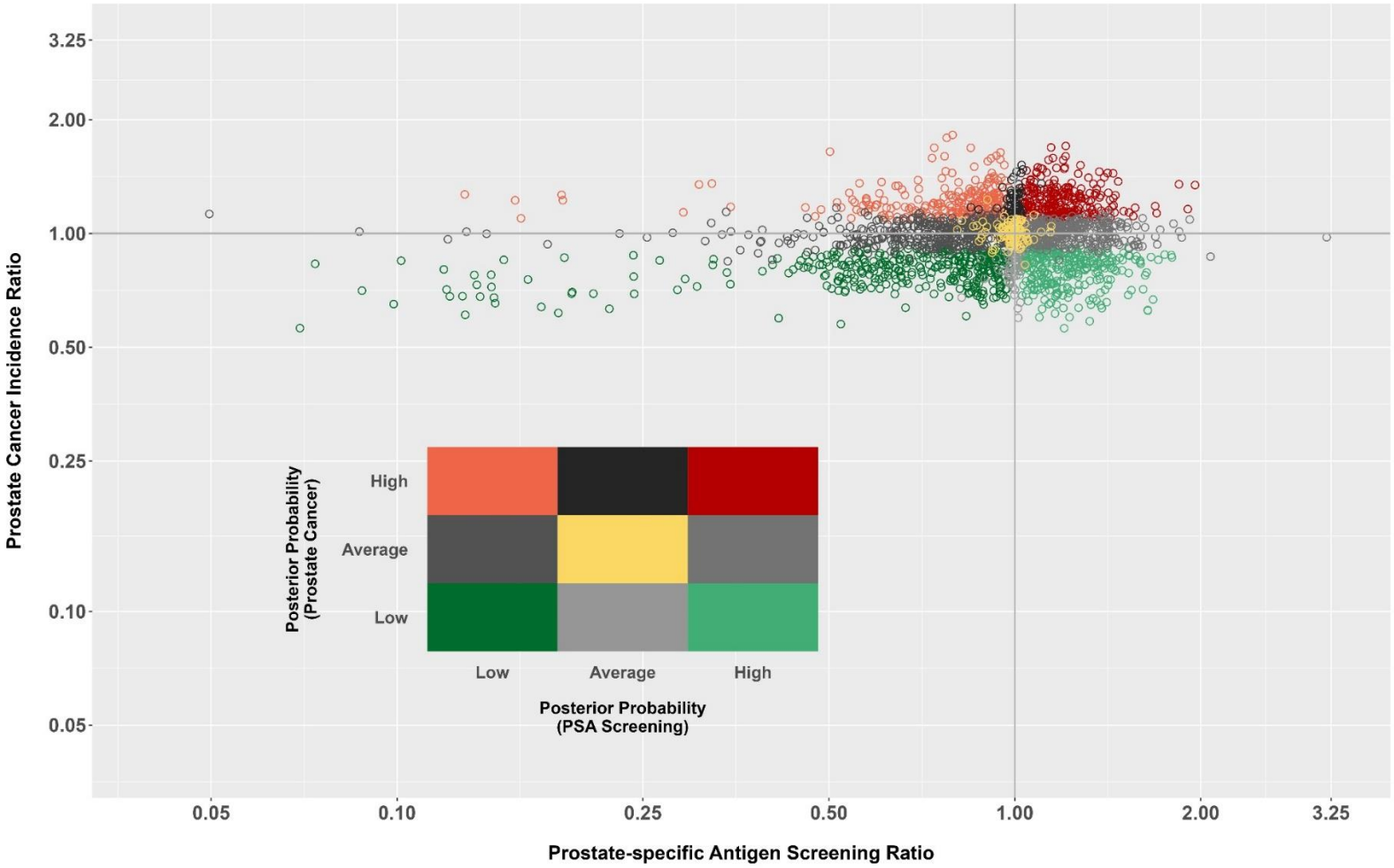
Figure 6.1: *Spatial variation* in standardized incidence ratios of prostate-specific antigen screening and prostate cancer incidence by small area[a,b] for men aged 50-79 years, Australia, 2012-16.*



[a] Insets show capital cities of each state and territory.
[b] NT – Northern Territory, WA – Western Australia, SA – South Australia, Tas - Tasmania, Qld - Queensland, NSW – New South Wales, ACT – Australia Capital Territory, Vic - Victoria

*Spatial maps, including insets for capital city regions, show blue and red shades representing modeled SIRs that are lower (SIR<1) and higher (SIR>1) than the Australian average (SIR=1) in yellow respectively. For spatial maps and insets, the small areas that have SIR values below 0.67 and above 1.5 were truncated at those values.

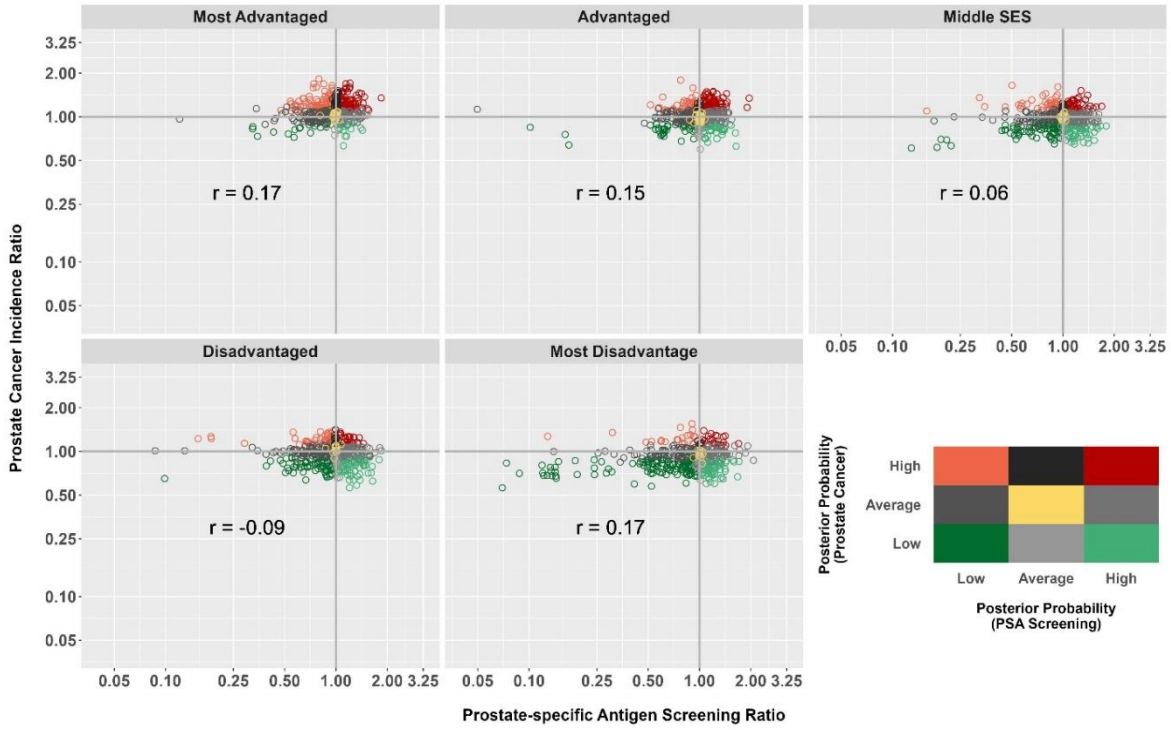
Figure 6.2: *Small area correlation[a] between prostate cancer incidence and prostate-specific antigen screening for men aged 50-79, Australia, 2012-16.*



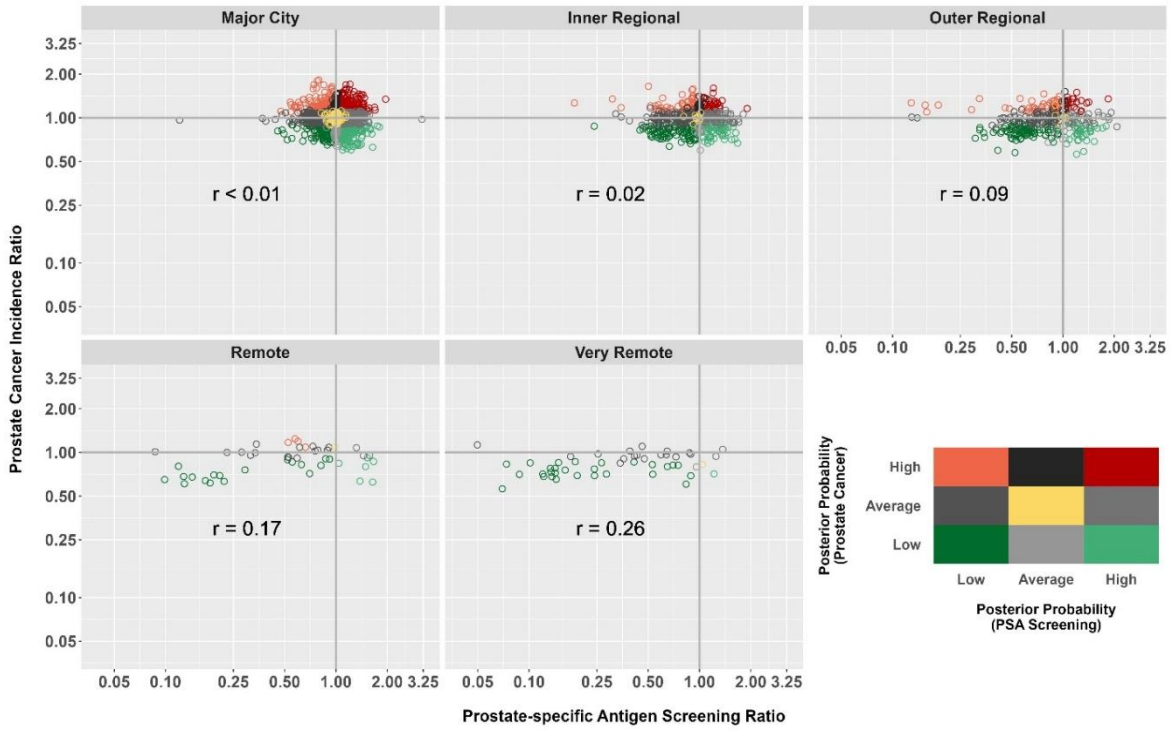
[a] Low: Exceedance probability < 0.2, Average: 0.2 ≤ Exceedance probability ≥ 0.8, High: Exceedance probability > 0.8.

Figure 6.3: *Associated[a] correlation between small areas of prostate cancer incidence and prostate-specific antigen screening for men aged 50-79 during 2012-16 by (A) Socio-Economic Status, (B) Remoteness, (C) Greater Capital Cities, (D) Outside Greater Capital Cities.*

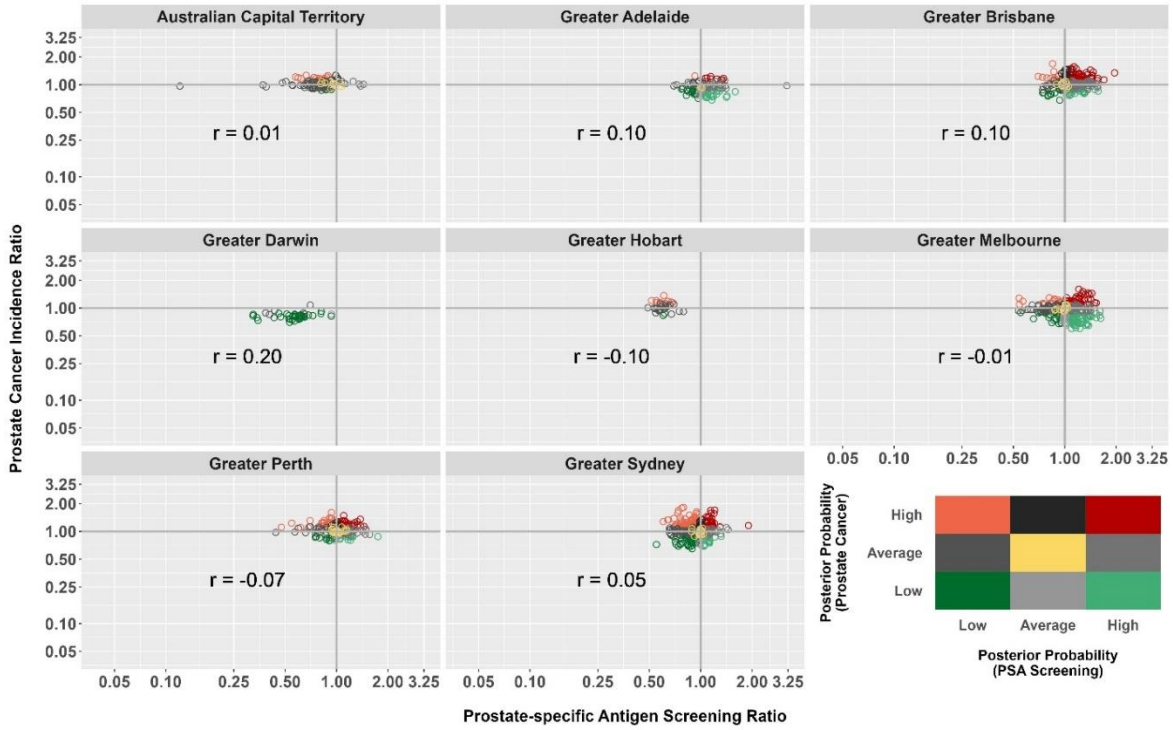
(A) Socio-Economic Status



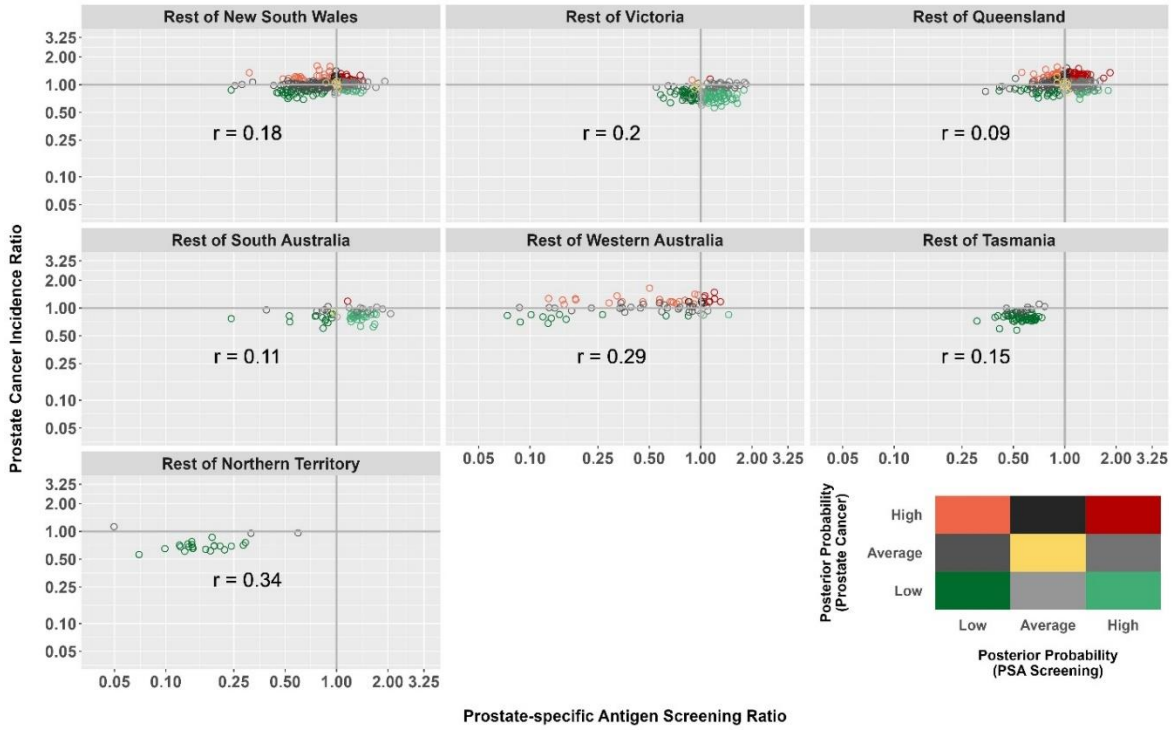
(B) Remoteness



(C) Greater Capital Cities

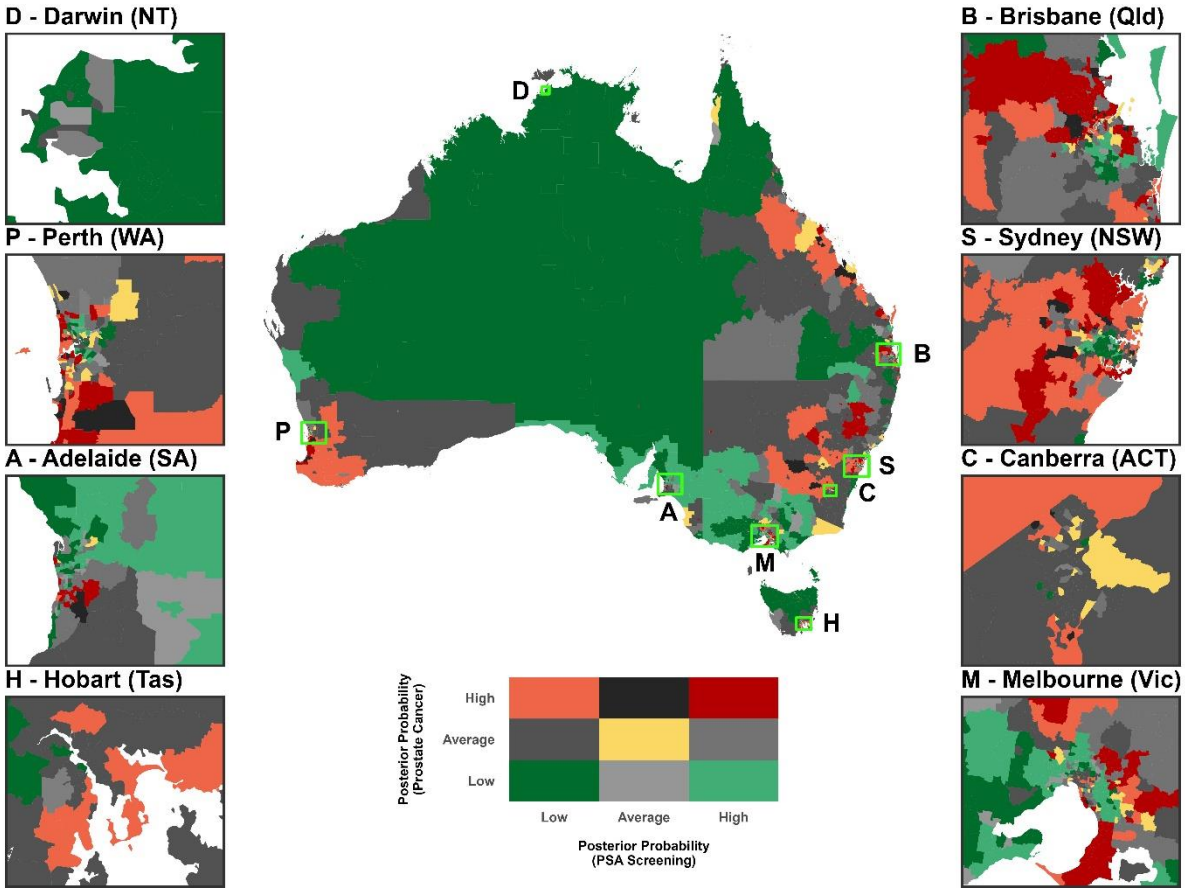


(D) Outside Greater Capital Cities



[a] Low: Exceedance probability < 0.2, Average: 0.2 ≥ Exceedance probability ≤ 0.8, High: Exceedance probability > 0.8.

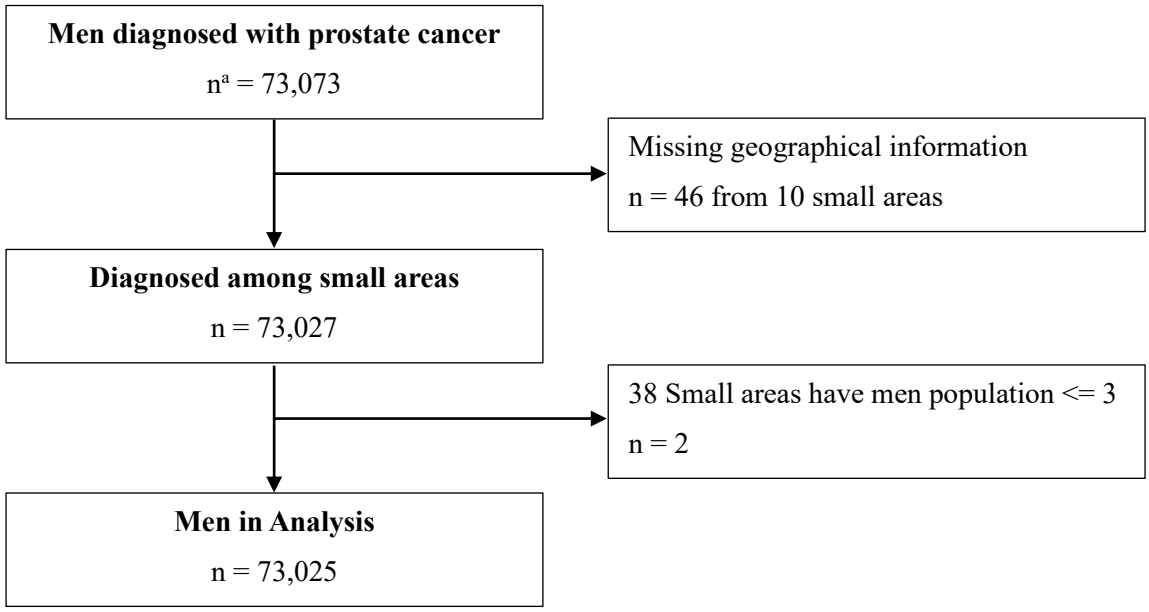
Figure 6.4: *Spatial associations[a] between prostate cancer incidence and prostate-specific antigen screening by small area[b,c] for men aged 50-79 years, Australia, 2012-16.*



[a] Low: Exceedance probability < 0.2, Average: 0.2 ≥ Exceedance probability ≤ 0.8, High: Exceedance probability > 0.8.
[b] Insets show capital cities of each state and territory.
[c] NT – Northern Territory, WA – Western Australia, SA – South Australia, Tas - Tasmania, Qld - Queensland, NSW – New South Wales, ACT – Australia Capital Territory, Vic - Victoria

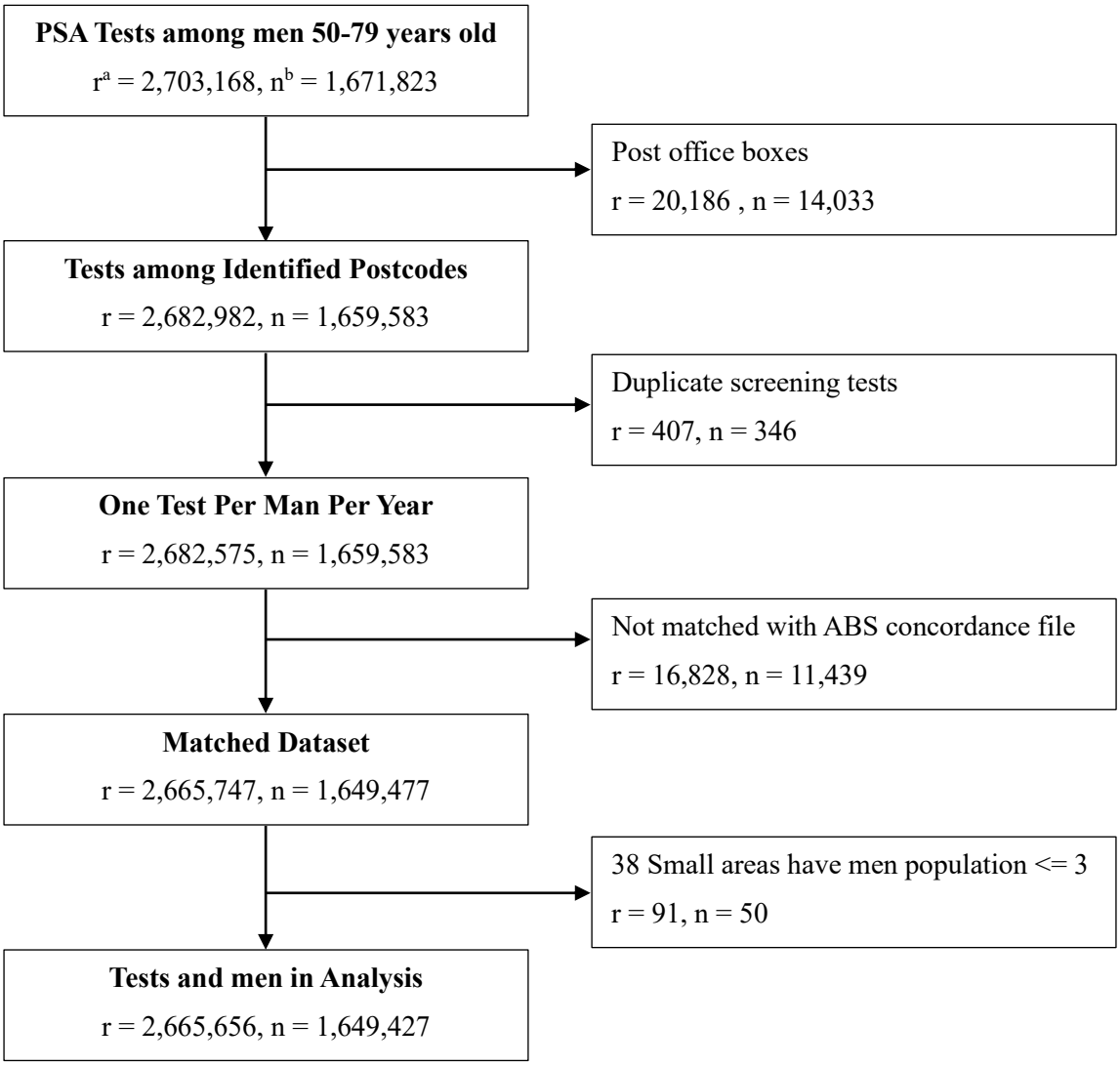
6.11 Supplementary material

Figure SF 6.1: *(A) Flowchart displaying selection of prostate cancer incidence cases for men aged 50-79, 2012-16, Australia.*



[a] n = Number of men diagnosed

(B) Flowchart displaying selection of prostate-specific antigen (PSA) screened men aged 50-79, 2012-16, Australia.



[a] r = Number of prostate-specific antigen screening tests

[b] n = Number of men tested

File SFile 1: *Leroux Model*

$y_i \sim \text{Poisson}(E_i \theta_i)$

$\log(\theta_i) = \text{Intercept} + S_i$

$\text{Intercept} \sim \mathcal{N}(0, 100000)$

$$S_i | S_{\setminus i} \sim \mathcal{N}\left(\frac{\rho \sum_j w_{ij} s_j}{\rho \sum_j w_{ij} + 1 - \rho}, \frac{\sigma_s^2}{\rho \sum_j w_{ij} + 1 - \rho}\right)$$

$\sigma_s^2 \sim \text{InverseGamma}(1, 0.01)$

$\rho \sim \text{Uniform}(0, 1)$

i = 1 to 2129 small area

j = Neighboring small area of i

y_i = Count data

E_i = Expected counts

θ_i = Standardized incidence ratio

Intercept = Overall fixed effects

S_i = Structured spatial random effects

ρ = Spatial dependence parameter

σ_s^2 = Variance parameter

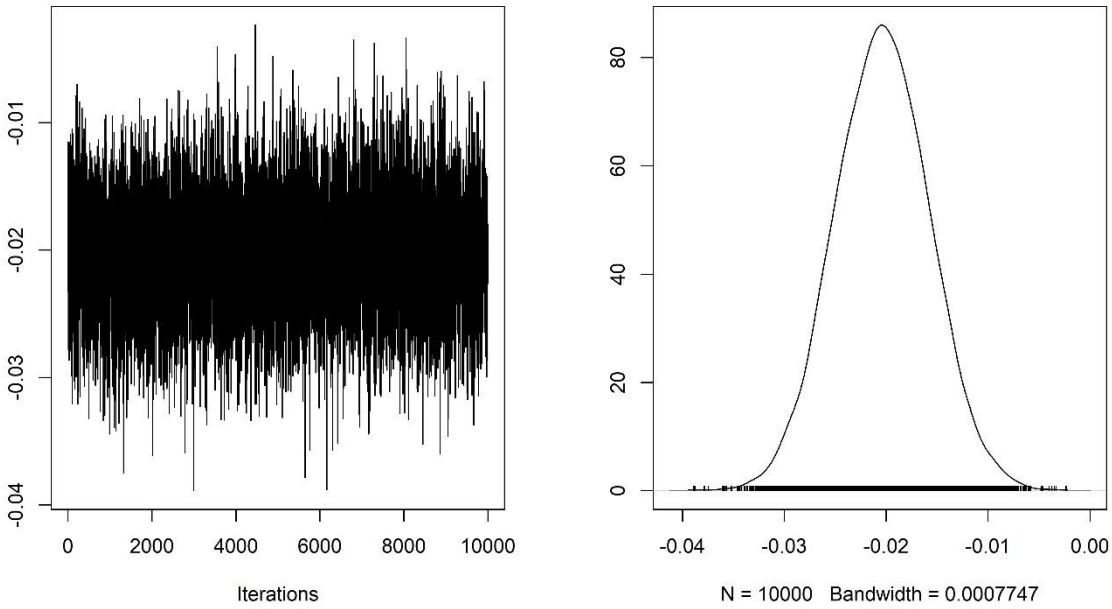
w_{ij} = Elements of spatial weight matrix ,

$$= \begin{cases} 1 & \text{if areas } i \text{ and } j \text{ are adjacent} \\ 0 & \text{otherwise} \end{cases}$$

s_j = Spatial autocorrelation random effects

Figure SF 6.2: *Trace and density plot showing Markov Chain Monte Carlo samples distribution of beta parameters for prostate cancer incidence and prostate-specific antigen screening.*

(A) Prostate cancer incidence



(B) Prostate-specific antigen Screening

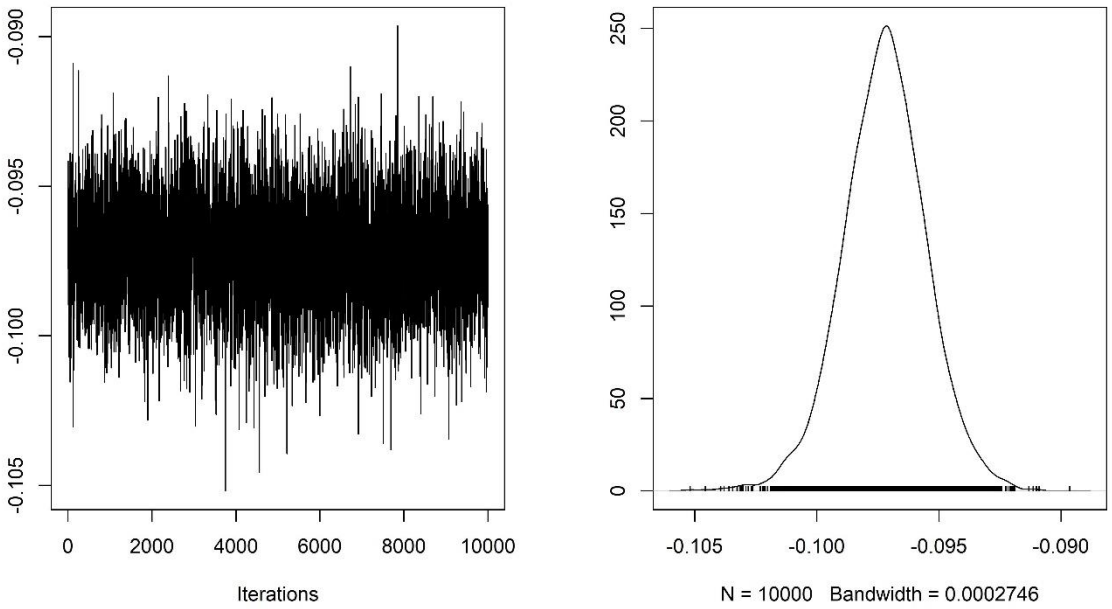
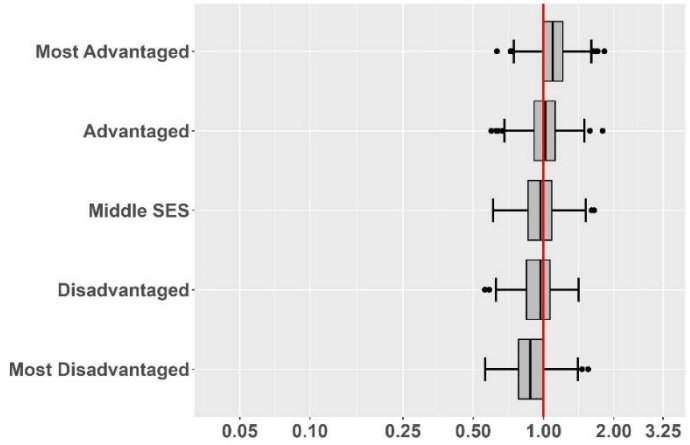
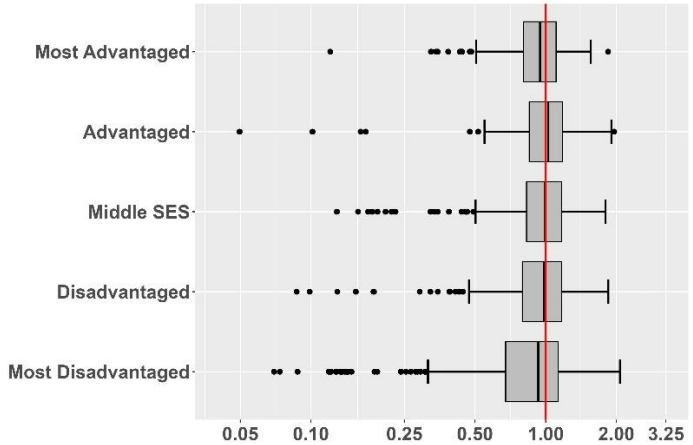
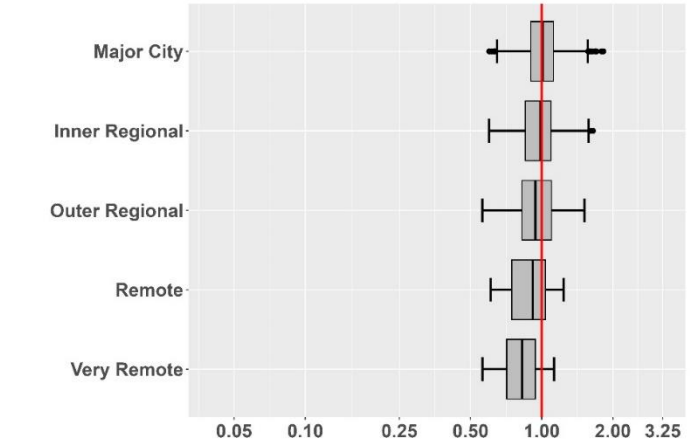
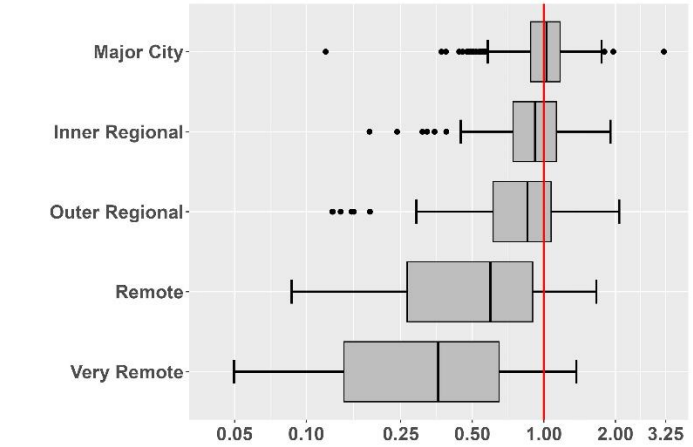


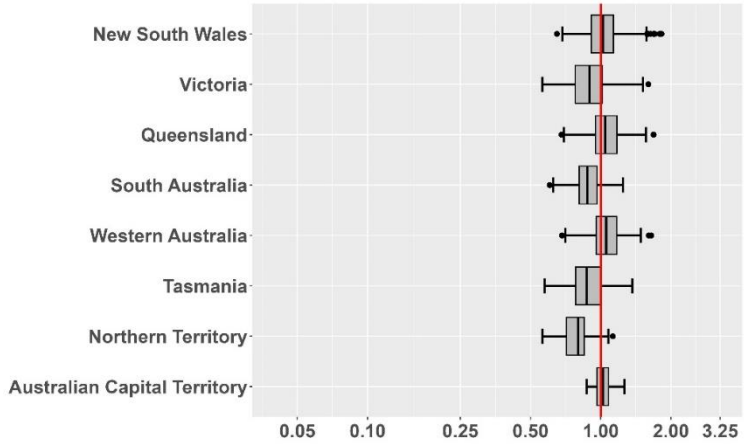
Table ST 6.1: *Description of kappa statistics in each category between prostate cancer incidence and prostate-specific antigen screening.*

Exceedance probability of prostate cancer incidence (PCI)	High (> 0.8)	0.0	0.0	< 0.01
	Average (0.2 ≤ PCI ≥ 0.8)	0.0	0.0	0.0
	Low (< 0.2)	< 0.0	0.0	0.0
		Low (< 0.2)	Average (0.2 ≤ PSA ≥ 0.8)	High (> 0.8)
	Exceedance probability of prostate-specific antigen (PSA) screening			

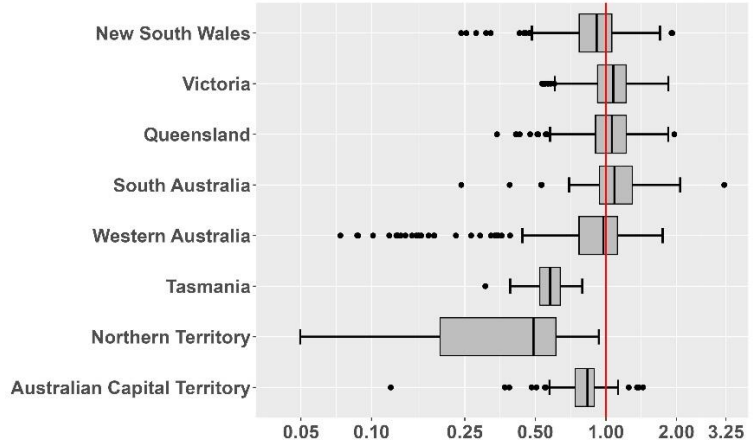
Figure SF 6.3: *Boxplots* showing small area median standardized incidence ratio estimates by (A) Socio-economic status, (B) Remoteness, (C) States / Territories, (D) Outside Greater Capital Cities Vs Greater Capital Cities for prostate cancer incidence and prostate-specific antigen screening, 2012-16.*

Prostate Cancer Incidence	**Prostate-Specific Antigen Screening**
(A1) Socio-economic status	(A2) Socio-economic status
	
(B1) Remoteness	(B2) Remoteness
	

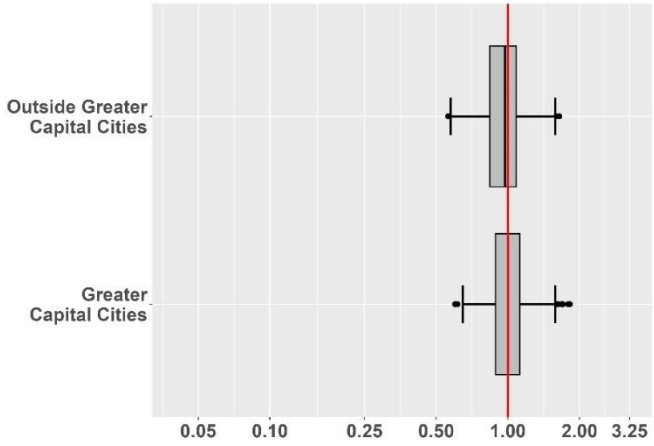
(C1) States / Territories



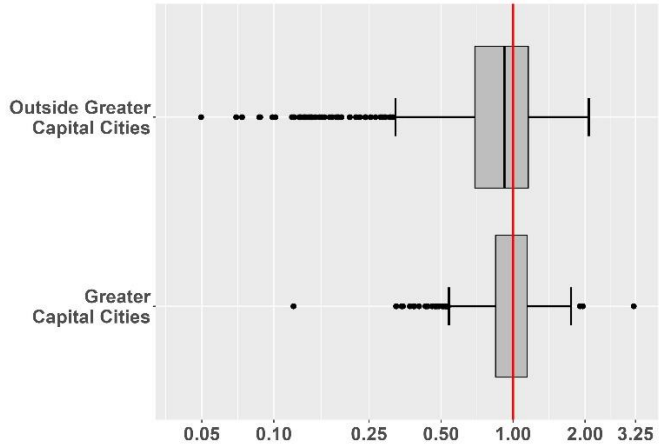
(C2) States / Territories



(D1) Outside Greater Capital Cities Vs Greater Capital Cities



(D2) Outside Greater Capital Cities Vs Greater Capital Cities



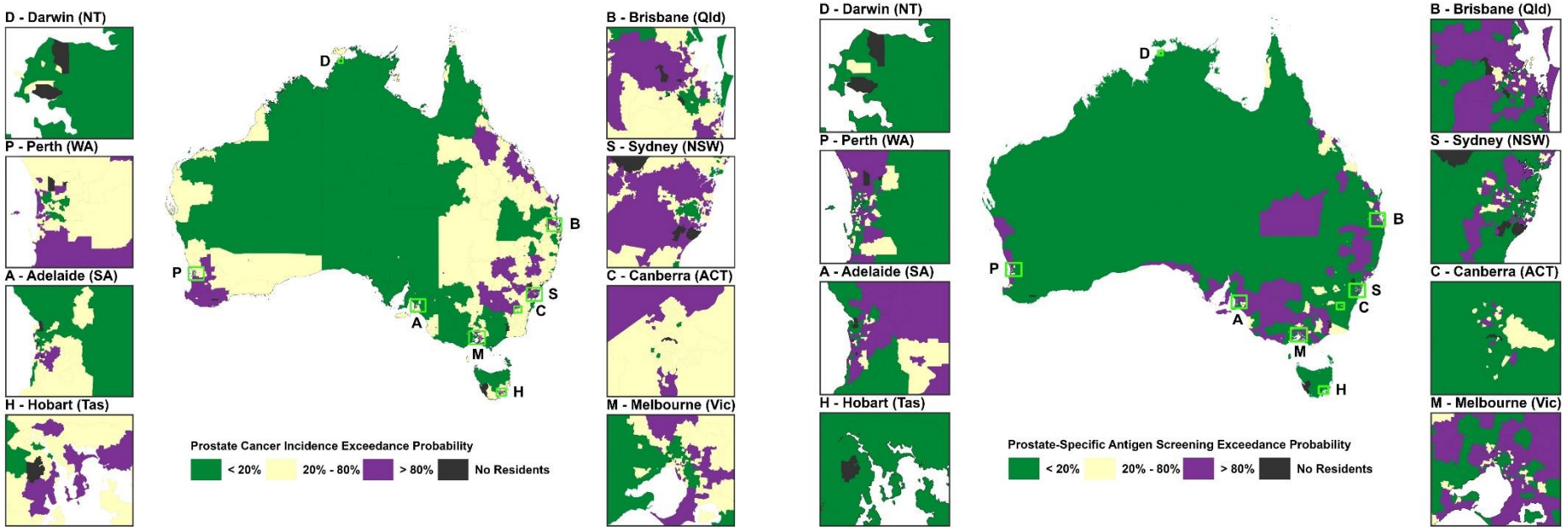
Prostate cancer incidence ratio

Prostate-specific antigen screening ratio

Note: Australian average is represented as red vertical line at SIR = 1

*Area-specific boxplot shows inconsistent patterns in socio-economic status as the distribution of small area-specific incidence rates are higher among most advantaged areas compared with most disadvantages areas, however there was less variability in the distributions of PSA screening by area disadvantage (Figure SF 6.3). In addition, the remoteness patterns for incidence and screening were consistent where rates decrease gradually from major city to very remote area however screening is more pronounced than incidence. No specific pattern was noted between outside and inside greater capital cities, incidence and screening ratios were nearly equal to Australian average.

Figure SF 6.4: *Exceedance probabilities* of prostate cancer incidence and prostate-specific antigen (PSA) screening by small area[a,b], Australia, 2012-16.*



[a] Insets show capital cities of each state and territory.
[b] NT – Northern Territory, WA – Western Australia, SA – South Australia, Tas - Tasmania, Qld - Queensland, NSW – New South Wales, ACT – Australia Capital Territory, Vic - Victoria

*The exceedance probability map shows the posterior probability of the area-specific SIR being higher than 1 (national average). Green and purple represent those small areas that likely to be genuinely lower (exceedance probability <20%) or higher (>80%) rates than the national average.

Table ST 6.2: *Comparison of 2158 small areas by exceedance probabilities for prostate cancer incidence and prostate-specific antigen screening, Australia, 2012-16.*

Exceedance probabilities	Number of small areas for prostate cancer incidence (n (%))	Number of small areas for prostate-specific antigen screening (n (%))
< 0.2	706 (32.7)	1048 (48.6)
0.2 ≤ EP ≥ 0.8	879 (40.7)	214 (9.9)
> 0.8	573 (26.6)	896 (41.5)
TOTAL	**2158 (100)**	**2158 (100)**

Table ST 6.3: *Comparison of 2158 small areas by categories of association between prostate cancer incidence (PCI) and prostate-specific antigen (PSA) screening rates, Australia, 2012-16.*

Characteristics	Number of small areas (n (%))	Land area[a] (%)	Average Median SIR[b] (PCI – PSA)
Prostate cancer incidence - Prostate-specific antigen screening			
Low - Low	361 (16.7)	63.6	0.80 - 0.69
Low - Average	52 (2.4)	20.3	0.81 - 0.99
Low - High	293 (13.6)	4.4	0.81 - 1.22
Average - Low	432 (20.0)	0.4	1.00 - 0.75
Average - Average	99 (4.6)	0.7	1.01 - 0.99
Average - High	348 (16.1)	0.3	1.00 - 1.24
High - Low	255 (11.8)	4.7	1.23 - 0.79
High - Average	63 (2.9)	4.9	1.22 - 1.00
High - High	255 (11.8)	0.7	1.23 - 1.21

[a] Sum of land area of Category / Total area of Australia * 100

[b] SIR means Standardized Incidence Ratio.

CHAPTER 7

7 DISCUSSION AND CONCLUSION

7.1 Chapter overview

Chapter 7 of the thesis provides an overview of the entire thesis and summarizes the key findings. The implications and significance of these findings are addressed, along with the strengths and limitations of the research. Overall, the thesis provides essential insights into PSA testing for prostate cancer and identifies disparities that can inform evidence-based strategies for addressing them.

7.2 Overview of the thesis

Using PSA tests to screen for prostate cancer has both champions and opponents and remains controversial. Prior to this thesis, there was limited understanding of PSA testing uptake across Australia. This thesis utilizes the comprehensive Medicare Benefit Schedule dataset, encompassing almost all male residents of Australia, to offer unique insights into testing patterns for prostate cancer and shed light on geographical and temporal disparities in these patterns. This objective is achieved through four distinct steps. Firstly, the study describes the patterns and trends of Medicare-funded PSA testing tests nationally, by state and territory, remoteness of residence, and socio-economic status. Secondly, the research quantifies the geographical variability in PSA testing rates across small geographical areas in Australia. Thirdly, it investigates how the geographical variation in PSA testing rates among smaller areas has evolved over time in Australia. Lastly, the study quantified the geographical association between PSA testing and prostate cancer incidence rates at the small area level in Australia. In conclusion, this thesis presents a comprehensive overview of geographical and temporal variation of PSA testing for prostate cancer, providing novel information useful for the development or implementation of evidence-based strategies to address disparities in prostate cancer indicators and outcomes across Australia.

7.3 Recapitulation

7.3.1 Introduction and background (Chapter 1)

This chapter provides an overview of the epidemiology, background issues and associated concerns regarding prostate-specific antigen (PSA) testing and prostate cancer incidence, both in Australia and worldwide. While this chapter does not contain novel findings it sets out the context for why an examination of PSA testing rates by small areas is important. Prostate cancer is the most prevalent cancer in Australia and holds a similar rank in developed countries. This is likely due, in part, to PSA testing. Although guidelines offer recommendations for PSA testing at a national level, it seems that geographical-based outcomes, such as incidence rates, may be influenced by differences in detection practices. Evidence from international randomized controlled trials, including ERSPC, PLCO, and CAP, indicate that the harms of PSA testing likely outweigh the benefits. This evidence is crucial in guiding our current approach to quantifying the patterns of PSA testing behavior in Australia. Differential usage of PSA is likely responsible for the observed variations across countries and over time. Overall, this chapter establishes the foundation for comprehending the complexities and controversies surrounding PSA testing and prostate cancer in the subsequent chapters.

7.3.2 Literature review of spatial and spatio-temporal models (Chapter 2)

This chapter provides an overview of various approaches for smoothing spatial and spatio-temporal data, with a particular emphasis on Bayesian models. It discusses their advantages, disadvantages, and considerations when selecting a model for analysis. The choice of model appropriateness depends on the

trade-offs between smoothness, interpretability, and computational efficiency. Bayesian models offer benefits such as the incorporation of prior information and the ability to handle limited case counts. Considering the objectives of the analysis in chapters 3 to 6 and the structure of the MBS data, this chapter serves as a practical guide for selecting the most suitable models. These include conditional autoregressive models, the Leroux spatial model, and the Separate spatial model. These models assume a common variance for the smoothing term across the entire region while allowing for local smoothing in neighboring areas. Moreover, the selected models are parsimonious and possible to implement using free, readily-available software. The decision to choose these models was based on a careful consideration of the data type and the advantages they offer in capturing random effects.

7.4 Key Findings

7.4.1 Consistent prostate-specific antigen testing trends by broad region (Chapter 3)

We found consistent trends in PSA testing over time throughout Australia, states and territories, remoteness groups, and socioeconomic status levels. However, the magnitude of PSA testing rates varied across different geographical regions. This suggests that while national clinical practice guidelines for PSA testing are broadly followed, there is regional variation in the manner and extent to which they are applied. Disparities in socioeconomic status at the area level have decreased over the past decade, but disparities between rural and urban areas persisted. Men living in remote areas were less likely to be tested compared to those residing in major cities. While not available in this study, having data on men's testing intentions could have provided further clarity, revealing the underlying reasons for seeking or not seeking testing, as well as identifying factors contributing to low testing rates in rural areas, such as limited healthcare facilities or longer travel times.

Additionally, there were differences in the prevalence of PSA testing among population groups during two different time periods: 2014-2018 and 2005-2009. Men between the ages of 50 and 59 exhibited higher testing rates compared to those aged 60-69. Data on shared decision making could have revealed underlying reasons for age and time-specific variation, such as the influence of general practitioners, persuasion by general practitioners or their peer group, or men's awareness about PSA testing.

7.4.2 Large variation in spatial patterns of prostate-specific antigen testing (Chapter 4)

We found significant variation in PSA testing rates across Australia, as well as within broader regions encompassing diverse socioeconomic groups, remoteness categories, and states and territories.

The findings indicated that, overall, there were no noticeable variations in the distribution of PSA testing rates in small areas when examined across different socioeconomic status. This pattern held true for both greater capital cities and areas outside the greater capital cities. However, contrasting patterns by socioeconomic status were observed in Hobart and Adelaide which had strong gradients by SES (higher

PSA testing in affluent areas) compared to the more densely populated capital cities, such as Sydney, Melbourne, and Brisbane, where minimal variation was observed. Furthermore, substantial heterogeneity present within these broader regions, with some "disadvantaged" small areas exhibiting higher PSA testing rates compared to some "advantaged" small areas, and vice versa. Similarly, not all small areas within remote and very remote categories demonstrated lower PSA testing rates compared to the national average. These results emphasize the importance of investigating geographical variation at smaller scales, as neglecting heterogeneity within larger regions would overlook crucial insights.

The outcomes of this study potentially suggest the influence of local area factors, such as testing campaigns, on PSA participation. Moreover, previous research has shown that testing rates can be influenced by general practitioners' attitudes, perspectives, and practices regarding PSA testing, as well as accessibility to primary care practitioners, and the differences in knowledge, attitudes, and behaviors of Australian men based on their geographical location. Furthermore, these findings are consistent with a range of diverse influences likely impacting decision-making processes concerning PSA testing across different regions of the country.

Additionally, there exists ambiguity between the recommendations of Prostate Cancer Foundation of Australia (PCFA) and the Royal Australian College of General Practitioners (RACGP) PSA testing guidelines, as subtle differences in wording send different messages to general practitioners regarding the approach to testing in Australian men. All of these results are consistent with the hypothesis that Australian men are not receiving equal opportunities to be tested based on where they live; otherwise, we would expect only a small amount of geographical variation in testing.

7.4.3 Variation in spatio-temporal patterns of prostate-specific antigen testing (Chapter 5)

We found substantial evidence that the geographic variations in PSA testing rates have changed over time. These small-area geographic patterns of PSA testing varied substantially over time, with the most significant changes observed in densely populated areas, while rates remained consistently low in many remote areas. Our study is the first of its kind to examine testing rates at the small-area level over time. Notably, not all small areas followed the same temporal trend. Between 2002 and 2008, nearly half of the smaller areas showed an increase in testing rates, while almost 29% experienced a decrease from 2009 to 2018. These changes were primarily observed in major cities and regional areas. Some of the geographical differences in temporal trends aligned with trends previously noted in broader geographical regions, but not all.

The variation in PSA testing rates over time suggests the existence of disparities among small areas of Australia, both geographically and temporally. This is consistent with men not receiving equal opportunities to make shared decisions regarding testing depending on where they live.

7.4.4 Low spatial association between prostate-specific antigen testing and prostate cancer incidence (Chapter 6)

We observed considerable geographic variability in both testing and incidence rates, but there was a low correlation (r = 0.1) between these variables across small areas in Australia. This suggests that PSA testing does not appear to be associated with the variation in prostate cancer incidence at the small-area level. Furthermore, the correlation remains low even when stratifying by area-specific factors such as remoteness and socioeconomic status.

The low correlation underscores the complex interaction between PSA testing and prostate cancer diagnosis. This indicates that there must be some other underlying factors or reason influencing their relationship at the smaller area level. One possible explanation for the lack of a strong association could be attributed to the selected time period, which is approximately two decades after the initial peak in prostate cancer incidence in 1993. It is possible that men at risk were detected earlier and subsequently excluded from the at-risk group during the study period.

7.5 Strengths and limitations

7.5.1 Strengths

This research study has several notable strengths. Firstly, it utilized population-based data from the Medicare Benefit Schedule, covering the entirety of Australia over a period of 17 years from 2002 to 2018. This comprehensive dataset effectively captured the majority of PSA tests conducted among eligible Australian males, thereby avoiding the limitations associated with self-reported data (Zavala *et al.,* 2016). Furthermore, by using an administrative population-based dataset, the likely occurrence of missing data was minimised.

Additionally, the analysis incorporated population-based data on prostate cancer incidence, sourced from the Australian Cancer Database, which through the state- and territory-based cancer registries is considered to provide a comprehensive record of all cases of prostate cancer diagnosed within the country (Australian Institute of Health and Welfare (AIHW) 2023).

Another significant strength of our study lies in the utilization of a Bayesian modeling approach. While various modeling options were available, we opted for the Bayesian approach due to its robustness in handling the unique characteristics of data based on smaller geographical areas. The Bayesian modeling approach has the ability to incorporate information from neighboring geographical areas, generating smoothed estimates for small areas that are considered to have greater stability and precision for the underlying small-area rates, along with measures of uncertainty. By employing this approach, the reported estimates in this study were not unduly influenced by random fluctuations associated with small-area data

(Duncan *et al.,* 2017). Furthermore, the application of Bayesian spatial models offered the advantage of flexibility in specifying the parameters in the model to calculating appropriate estimates.

Previous reports have described PSA testing trends in Australia. To provide a more relevant interpretation of our results, we imposed a restriction of one test per man per year, mitigating the impact of multiple tests within the same year. This approach allowed us to focus on a person-based testing history, specifically examining the annual number of men screened, as opposed to the total number of screening tests administered reported in other studies (Pathirana *et al.,* 2022). This method provided reliable estimates when considering the participation in PSA testing by Australian men compared to artificially inflated estimates, minimizing the potential for biased results.

7.5.2 Limitations

This study is subject to several limitations that necessitate careful consideration. Firstly, the claims made through Medicare are restricted to pathology benefits paid during a single episode of care, known as episode coning. This means that only the three most expensive pathology items within a care episode can be claimed at once, potentially leading to an under-reporting of pathology tests in less accessible areas (Hajati *et al.,* 2018). This coning practice may have influenced the observed results, as men residing in regional and remote areas who travel longer distances to see a general practitioner may need to combine multiple tests during a single visit (Trevena *et al.,* 2013). It has been estimated that up to 19% of PSA tests may be coned and thus not included in the Medicare data (Trevena *et al.,* 2013). It is also possible that coning leads to differential testing patterns based on geography. However, the extent to which coning varies by geographical area remains unknown.

Furthermore, the available Medicare data only captured the postcode of residence, meaning that there was an additional measure of uncertainty of the final estimates due to the imprecision of the postcode to SA2 concordance and possible misassignment of postcodes to SA2 areas. To address this, we employed probabilistic allocation to transform postcodes into small areas (statistical area level 2), and then conducted the Bayesian analysis 50 times, combined the MCMC iterations, and considered both the median and the distribution of those combined iterations to quantify the greater uncertainty. Additionally, it should be noted that the correspondence between postcode and SA2 was not specific to age or sex, so it is possible that the probabilities were not always reflective of the 50-79 year old males in our cohort due to the individual demographic characteristics of the small areas in the study.

The study timeframe itself was defined due to the availability of data and to focus on more contemporary data. However, it means that we did not have information about the time period when PSA testing was initially introduced and reimbursed by Medicare during the late 1980s and 1990s. It is likely that the early uptake of the test in certain areas during the "early PSA era" would have influenced the long-term testing behaviors of men still living in those area, thus making it difficult to determine which areas were "early adopters" of PSA testing prior to the study period.

Another limitation arises from the fact that the design is an ecological study, which requires careful interpretation of the results due to the potential impact of unmeasured and uncontrolled confounding factors on the findings. Ecological studies are vulnerable to the ecological fallacy, where data analyzed at a group level are mistakenly assumed to apply at the individual level, leading to potential shortcomings or biases in the results (Sedgwick 2014). Adjusting for confounding factors that influence the outcome is not feasible in ecological studies. As a result, an observed correlation or, as was the case in this study, the absence of a correlation can be misleading. That we did not observe a correlation between PSA testing and prostate cancer incidence at the small area level does not mean no association exists; more that we have not been able to capture the specific association with the data we were using.

Furthermore, the lack of national data on the stage of disease at the time of diagnosis for prostate cancer is a limitation for the geographical correlation analyses, as comparing localized cancers to PSA testing patterns could have offered greater insights into whether testing was being excessively used in certain areas. In Australia, Cancer Australia has explored the potential of collecting and reporting national data on the stage of certain types of cancer at diagnosis, including prostate cancer, based on pathology records (National Cancer Control Indicator 2018). However, this is currently only available at a national level for the 2011 calendar year.

It is worth noting that one potential drawback of spatial smoothing is the assumption of geographic homogeneity between neighboring areas, which can present challenges in distinguishing between different small areas. Bayesian spatial models incorporate information from neighboring geographical areas, resulting in smoothed estimates for small areas. This assumption is based on the idea that individuals residing in one area share similar characteristics with those in the surrounding areas (Leroux *et al.,* 2000, Cramb *et al.,* 2020, Lines *et al.,* 2022). However, the Localised model performed poorly in spatial analysis and yielded misleading results.

In future analyses, it is worth considering alternative approaches for Bayesian spatial modeling, such as Geographically Weighted Regression (GWR) models. The Bayesian GWR model separately samples for each location, which means that the parameter dimension does not scale with the number of locations, irrespective of the generalized linear model employed (Liu Y *et al.,* 2023). This model works on the principle that it reduces random errors but introduces systematic errors. Various variants of the GWR model exist, differentiated by their approach to estimate calculation, such as using weighted log-likelihood (Liu Y *et al.,* 2023) or weighted least squares (Ma *et al.,* 2020). However, they come with certain limitations, including computational cost, potential inference challenges in case of limited observations, and the use of a globally fixed geographical bandwidth. The latter can be problematic when the true data generating process varies considerably in some areas but only slightly in others (Liu Y *et al.,* 2023).

GWR models examine how a relationship varies spatially, making them applicable to models with covariates. They are well-suited for exploratory analyses rather than serving as a formal model (Brunsdon *et al.,* 1996). Extensions to the GWR model include the Multiscale Geographically Weighted Regression (MGWR) and Geographically Weighted Multivariate Multiple Regression (GWMMR). The former model offers a flexible and scalable framework for examining multiscale processes, while the latter analyzes multiple interrelated response variables and considers correlations across multivariate responses.

Lastly, the data utilized for this study was obtained in the fourth quarter of 2019, and no updated data extract was available before the completion of the study. However, in Australia, during the first half of 2020, there was a significant decrease in PSA testing rates across all states and territories associated with the outbreak of the COVID-19 virus (Cancer Australia 2020). This means that by focusing on a period preceding the COVID-19 pandemic, it enabled us to examine the underlying patterns of PSA testing independently of any behavioral changes resulting from COVID-19 management directives.

7.6 Implications and significance of research findings

This thesis makes a significant contribution to the current understanding of prostate-specific antigen (PSA) testing patterns across Australia, specifically within smaller geographical areas. We observed substantial variation in the utilization of PSA testing across smaller areas of Australia, both spatially and temporally. Furthermore, our findings indicate that men residing in smaller areas of major cities exhibited higher testing rates in comparison to those residing in remote areas, but testing rates were consistent across socioeconomic categories.

There was a notable lack of published studies documenting changes in PSA patterns at smaller areas across the country and variations within area-specific categories such as remoteness and socioeconomic status, so this study fills an important gap in knowledge.

While several studies have described PSA patterns at a national level or in broad areas such as by state, territory, or socioeconomic status (Calopedos *et al.,* 2017, Luo *et al.,* 2022, Pathirana *et al.,* 2022), the research conducted in this thesis aims to address these knowledge gaps by providing information for smaller areas within those large regions. Clinicians and policymakers can utilize these findings as evidence to interpret different outcomes of PSA testing for prostate cancer. Our results suggest significant variation in PSA testing rates. Therefore, targeted campaigns focusing on improved education and communication regarding informed decision-making for men can be implemented in areas that have been identified as being higher or lower than the national average, potentially reducing geographical disparities in the coming years.

The results of this study have provided a comprehensive national perspective on the geographical and temporal variations in PSA testing across Australia and its association with observed geographical patterns in prostate cancer incidence. This will have the following implications:

- Establishing a robust and ongoing evidence base to support advocacy efforts aimed at reducing inequalities across Australia is crucial. Testing is just the beginning; our goal is to ensure that men have equal opportunities for informed decision-making, follow-up, support, and treatment in relation to prostate cancer wherever they live.
- Useful evidence for the current review of the Australian PSA testing guidelines. Our study provides valuable insights into the changing patterns of PSA testing at the small area level in Australia over time. While the guidelines are provided at a national level, our results highlight that there must be different, currently unmeasured, factors that impact on the participation in PSA testing by Australian men. Our research findings highlight the importance of effective communication and engagement with health professionals and the general public to ensure the rationale and recommendations within current guidelines is widely understood.
- Motivating and directing research efforts towards understanding and addressing the underlying causes of observed geographical disparities in participation in PSA testing.
- Informing health planners and government policymakers at both state and national levels to allocate resources based on the best available evidence. The results of this study and the variation in geographic patterns do not necessarily imply over testing or under testing. The difference in testing rates are suggestive of differences in behaviors of health care providers and men. While informed decision-making regarding PSA testing remains the recommended the approach from peak bodies, the challenge is to ensure that the process is equally available to all men, irrespective of where they live. So, resources should be allocated to better inform GPs and raise awareness among men. For instance, helping health professionals and the general public better understand the significance of prostate cancer and the process of PSA testing information in the management of prostate cancer is crucial (Chiam *et al.,* 2023).

Furthermore, this work has the potential to motivate international research collaborations to examine how spatial patterns in PSA testing vary between countries. PSA testing has been common in many developed countries for the last three decades. Little has been done at the international level to evaluate PSA testing levels and the association with prostate cancer incidence. The results of our analyses will hopefully motivate other similar studies internationally utilising similar methods to enable direct comparisons between the findings.

For Australian policymakers, the Australian Cancer Atlas already serves as a trusted and nationally uniform evidence base for making informed decisions regarding broad-based health and spatial inequalities. With appropriate approvals of the data custodians, the results of this study have the potential to be included within this existing online platform to enrich the wider understanding of PSA testing patterns and their geographic distribution across the country. This enhanced knowledge can assist

policymakers in formulating targeted interventions, strategies to address any identified disparities, ensuring that decisions about testing are equally available across the country.

Australian guidelines on PSA testing are national in scope. While specific recommendations focus on men at higher risk of prostate cancer, they do not suggest different approaches by socio-demographic or geographic characteristics. Therefore, the geographical variability described in this study is either suggestive of variation in practices in primary care or variation in attitudes of individual men. Variation in clinical practice is not ideal as it can cascade into real differences in outcomes. Future developments in guideline development, communication and dissemination should take note of the variations in testing practice by geography and tailor resources appropriately.

7.7 Future directions for research in PSA testing

To gain a deeper understanding of the variation in PSA testing rates, the following research directions are highly recommended based on the findings of this research:

7.7.1 Exploring the influence of age groups on geographical and temporal patterns in PSA testing

Currently, the highest prevalence of PSA testing in Australia is observed among individuals aged 55-64 (Calopedos *et al.,* 2017). However, the geographical patterns of PSA testing across different age groups remain unknown. To address this gap, Bayesian spatial and spatio-temporal models can be utilized to examine how age groups influence these patterns. This can be achieved by conducting stratified analyses or incorporating additional interaction terms involving spatial and temporal parameters. Furthermore, a future research project using these data could also explore spatial variations in testing utilization beyond the recommended PSA testing age groups to identify geographical areas where over-testing is more prevalent, such as regions where men under 40 or over 80 are screened at high rates.

7.7.2 Identifying key novel methods to extend research on observed geographical and temporal patterns in PSA testing

To explore the factors underlying geographical variation in PSA testing prevalence, an important step is to incorporate information about the characteristics of small geographical areas into spatial models. These ecological factors may include measures of distance from major services, area disadvantage, and accessibility to specific healthcare services. Additionally, it would be valuable to consider the area-specific demographic characteristics such as the percentages of men from non-English speaking backgrounds, those who identify as First Nations individuals or where gender diversity is more common. All of which may have an influence in early detection related behaviours. Furthermore, conducting a comparative analysis can provide insights into the ecological factors associated with areas exhibiting very low PSA testing rates in comparison to those with very high rates.

The growing use of extensively linked datasets also opens up further possibilities for answering policy relevant research questions regarding prostate cancer testing and prostate cancer outcomes. Large, linked datasets, that can identify and track an individual's testing history, cancer registration, hospital admissions, radiotherapy episodes, pharmaceuticals use, Medicare reimbursements and death information are already being trialled or used in some jurisdictions (O'Callaghan *et al.,* 2021, Cancer Institute NSW 2022). While still in their infancy these resources are likely to offer many advantages over and above ecological analysis in the future.

It is also important to examine other factors that would not be collected in standard datasets, such as psychosocial and cultural factors at the individual level. These might require more a mixed methods type of approach, including the possible use of artificial intelligence methods to synthesize large amounts of qualitative data.

7.7.3 Investigating intentions to undergo PSA testing

In-depth qualitative analysis is recommended to investigate men's intentions to undergo PSA screening test, as the currently available data lacks information in this regard. Understanding the factors that influence men's decision-making processes regarding PSA testing can provide valuable insights into whether areas with low testing rates reflect missed opportunities or if areas with high testing rates reflect over-servicing. Face-to-face, online and telephone interviews would be one option, as they would likely yield higher completion rates and ensure a higher level of result authenticity (Curasi 2001, Vogl 2013). Research questions targeted towards men residing in all remoteness categories, socioeconomic categories, and men aged 40 to 80, as this would encompass a broad range of individuals. Questions could include: How did you become aware of PSA testing? Did you have prior knowledge about PSA before undergoing the test? Do you want to undergo the PSA test? What are your reasons for wanting to undergo the test? What are your reasons for not wanting to undergo the test? Do you believe PSA testing can save your life? Has your general practitioner offered you a test? How often do you intend to undergo testing in the future?

7.7.4 Researching attitudes and behaviors of general practitioners

In addition to investigating men's intentions to undergo PSA screening tests, it is also important to research the attitudes and behaviors of general practitioners. Understanding how healthcare providers perceive and approach PSA testing can provide valuable insights into the factors influencing testing practices. Previous studies have examined general practitioners' practices regarding prostate-specific antigen (PSA) testing at a national level in the UK and Australia (Pickles *et al.,* 2016), including variation in communication with men regarding PSA testing (Pickles *et al.,* 2018) and their approach to PSA testing and overdiagnosis (Pickles *et al.,* 2015). Furthermore, exploring general practitioners' attitudes nationally on a large scale and within smaller geographical areas is likely to provide even greater insights. However, this area presents challenges due to poor response rates in primary care research. Obtaining

comprehensive and representative data from general practitioners can be difficult, and addressing this issue is crucial for a more comprehensive understanding of the factors influencing PSA testing decisions. Efforts should be made to engage primary care providers in research studies to enhance our knowledge in this domain.

7.8 Overall conclusion

This thesis comprehensively explored PSA testing patterns by small areas over time and its association with prostate cancer incidence. Prostate cancer and prostate cancer testing are likely to continue to be a major public health issue requiring high quality local evidence upon which policy decisions can be based. This research is unique in providing evidence to advance our knowledge of the landscape of PSA testing over the last two decades. This study has demonstrated that PSA testing varies substantially by smaller geographical areas, and the characteristics of that variation have changed over time. However, regardless of the overall PSA uptake, not all small areas follow the national trends over time. Furthermore, this research highlighted a low correlation between PSA testing and prostate cancer when assessed at the small area level. This thesis has also identified areas for potential future research focus that aim to continue improving prostate cancer mortality rates by understanding PSA testing patterns and their underlying reasons correctly. In conclusion, this research has provided novel findings and insights that will form important benchmarks and motivation for further investigations, including international collaborations.

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APPENDICES

Appendix A: Ethical approval letters

Data custodian approval letters

Appendix B: Published manuscript of Chapter 3

Appendix C: Published manuscript of Chapter 4

Appendix D: List of conference presentations during Ph.D. candidature

Appendix E: Other research publications during Ph.D. candidature

Appendix A: Ethical approval letters

Working together to lessen the impact of cancer

14 March 2017

Professor Peter Baade
Cancer Council Queensland
PO Box 201
Spring Hill QLD 4004

Dear Professor Baade,

NSW Population & Health Services Research Ethics Committee

AU RED Reference: HREC/17/CIPHS/3

Cancer Institute NSW reference number: 2017/HRE0203

Project Title: National Cancer Atlas

Thank you for your correspondence dated 10 March 2017 responding to a request for further information/clarification of the above referenced study, submitted to the NSW Population & Health Services Research Ethics Committee. The Committee has reviewed your response and has agreed that the aforementioned application meets the requirements of the *National Statement on Ethical Conduct in Human Research (2007)*. This approval is for a maximum of five years from the date of this letter, after which time a renewal application will be required if the protocol has not been completed.

The Committee granted a waiver of the usual requirement of consent for the use of re-identifiable information held by NSW agencies, in line with the State Privacy Commissioner's Guidelines for Research and the Health Records and Information Privacy Act 2002 (NSW).

The documents reviewed and approved include:

- Letter of Response, dated 10 March 2017
- Cover Letter, dated 27 January 2017
- NSW National Ethics Application Form, v2.2, submission code AU/1/2B5B28, dated 24 January 2017
- Protocol version 3, dated 10 March 2017
- NSW CR Data Request
- NSW CR Data Variable Checklist
- NSW CR Data Custodian Sign Off Form, dated 30 January 2017
- NSW Health Privacy Form – Updated version submitted 10 March 2017
- Peter Baade CV
- Kerrie Mengersen CV
- Joanne Frances Aitken CV
- Pamela Burrage CV
- Susanna Cramb CV
- James McGee CV
- Paula Moraga CV

Cancer Institute NSW
ABN 48 538 442 594
Level 9, 8 Central Avenue, Australian Technology Park, Eveleigh NSW 2015
PO Box 41, Alexandria, NSW 1435
t +61 (0)2 8374 5600 f +61 (0)2 8374 3600 e information@cancerinstitute.org.au
www.cancerinstitute.org.au

- Jessie Roberts CV
- Nicole White CV

The Committee noted the following documents:

- ACT Ethics Approval and Low-Risk Application
- QLD Ethics Approval and NEAF
- Menzies School of Health Research Letter of Approval and NEAF

Approval is now valid for the following sites:

- Cancer Council Queensland
- Queensland University of Technology

The NSW Population & Health Services Research Ethics Committee has been accredited by the NSW Ministry of Health to provide single ethical and scientific review of research proposals conducted within the NSW public health system.

The Committee is a joint initiative of the Cancer Institute NSW and NSW Ministry of Health. The Committee has been constituted and operates in accordance with the National Health and Medical Research Council's *National Statement on Ethical Conduct in Human Research (2007)* and relevant legislation and guidelines.

Please note that ethical approval is valid for **5 years**, conditional on the following:

- Principal investigators will immediately report anything which might warrant a review of ethical approval of the research, including unforeseen events that might affect continued ethical acceptability.
- Proposed amendments to the research proposal or conduct of the research which may affect the ethical acceptability of the research are to be provided to the NSW Population & Health Services Research Ethics Committee for review.
- The NSW Population & Health Services Research Ethics Committee will be notified giving reasons, if the research is discontinued before the expected date of completion.
- The Principal Investigator will provide a progress report to the NSW Population & Health Services Research Ethics Committee annually and at the completion of the study.

Your first progress report will be due on 14/03/2018 and the duration of approval is until **14/03/2022**, after which time a new submission to the Ethics Committee will be required.

You are reminded that this letter constitutes *'ethical approval'* only. This research project must not commence at a site until separate authorisation from the Chief Executive or delegate of that site has been obtained. It is your responsibility to forward a copy of this letter together with any approved documents as enumerated above, to all site investigators for submission to the site's Research Governance Officer. Where relevant, copies will also need to be provided to the CHeReL and the data custodian.

For further information about the NSW Population & Health Services Research Ethics Committee, please refer to our website https://www.cancerinstitute.org.au/Data-research/Research-ethics-committee.

Should you have any queries about the ethical review of your research proposal, please contact ethics at ethics@cancerinstitute.org.au.

Yours sincerely,

[redacted]

Professor Sallie-Anne Pearson
Chairperson
NSW Population & Health Services Research Ethics Committee

2019/ETH01656: Notification of an amendment to a research study - Request for extension of HREC Approval - (104412) - Approved (ethics and NSW site acknowledgement)

no_reply@regis.health.nsw.gov.au <no_reply@regis.health.nsw.gov.au>
Fri 8/26/2022 5:24 PM

To: Peter Baade <PeterBaade@cancerqld.org.au>

Cc: Habtamu Bizuayehu <habtamubizuayehu@cancerqld.org.au>;Upeksha Chandrasiri <UpekshaChandrasiri@cancerqld.org.au>;cinsw-ethics@health.nsw.gov.au <cinsw-ethics@health.nsw.gov.au>;CINSW-DARenquiries@health.nsw.gov.au <CINSW-DARenquiries@health.nsw.gov.au>

Date of Decision Notification: **26 Aug 2022**

Dear Professor Peter Baade,

Thank you for submitting an Amendment for the following study;
2019/ETH01656: National Cancer Atlas

The Amendment has been reviewed on **26 Aug 2022**, by the Executive Officer as delegated by the HREC Chair and has been **approved**.

Notification of an amendment to a research study - Request for extension of HREC Approval - (104412)
Previous HREC expiry date: 31/12/2022
New HREC expiry date: **31/12/2024**

The NSW Population and Health Services Research Ethics Committee is constituted and operates in accordance with the National Statement on Human Conduct in Research (NH&MRC, 2007).

This notification is on behalf of the NSW Population and Health Service Research Ethics Committee and each NSW site listed in REGIS.
The new end date has been updated across the system, you are not required to submit to any NSW sites (listed in REGIS) and will not receive individual acknowledgements.
Each NSW Principal Investigator and Administration Contact will receive this notification.

If contract changes or site specific documents require RGO authorisation please submit a Site Amendment Form to each individually affected site.
See QRG: Site Amendment - Completing and Submitting

Please contact us if you would like to discuss any aspects of this process further, as per the contact details below.

Yours Sincerely,
Secretariat on behalf of David Roder, Chairperson, NSW Population and Health Services Research Ethics Committee
T (02) 8374 5689 / 8374 3610 **F** (02) 8374 3600 **E** cinsw-ethics@health.nsw.gov.au

Cancer Institute NSW
Level 4, 1 Reserve Road, St Leonards NSW 2065

Locked Bag 2030 St Leonards NSW 1590
cancer.nsw.gov.au

We acknowledge the traditional custodians of the lands on which we work and live, and pay our respect to Elders past, present and future.
Please consider the environment before printing this email.

23 November 2022

Dear Adpro Peter Baade

We are pleased to advise that your application has been reviewed and approved by the University Human Research Ethics Committee (UHREC) as meeting the requirements of the National Statement on Ethical Conduct in Human Research (2007, updated 2018). In addition, the UHREC approved a waiver of consent to access and use health data to be justified in accordance with the National Statement 2.3.10 and S95 of the Cth Privacy Act Part 3.3 (Weighing the Public Interest) a); b); c); e); f) i; g); h) i, iii, iv, v.

Project title:	National Cancer Atlas (renewal)
Approval number:	6398
Approval date:	23/11/2022
Expiry date:	*23/11/2027
	**subject to receipt of satisfactory progress or conditional reports*

Documents approved:

Document Type	File Name	Date	Version
Evidence of the outcome	QUT ethics extension Dec 2022	11/12/2020	6
Evidence of the outcome	ACT_6.1.1 - ETHLR.16.235 - Baade - PPR	23/11/2021	6
Evidence of the outcome	HREC 16-2720 Annual Report with Extension Acceptance 21.12.21	20/12/2021	7
Evidence of the outcome	NSW Ethics extenssion to 31_12_2024	29/08/2022	8
Signature	PB certification	13/10/2022	1
Curriculum vitae (CV)	Peter Baade CV	19/10/2022	1
Curriculum vitae (CV)	Kerrie Mengersen CV	19/10/2022	1
Curriculum vitae (CV)	Joanne Aitken CV	19/10/2022	1
Curriculum vitae (CV)	Jessica Cameron CV	19/10/2022	1
Curriculum vitae (CV)	David Smith CV	19/10/2022	1
Curriculum vitae (CV)	Paramita Dasgupta CV	19/10/2022	1
Curriculum vitae (CV)	Susanna Cramb_CV	19/10/2022	1
Protocol	Project Description V8_23_11_2022	23/11/2022	8
Cover letter	Cover Letter HREC 23_11_2022	23/11/2022	1

Research team approved:

Professor Peter Baade, Professor Joanne Aitken, Mr Jamie Hogg, Mr Ankur Kohar, Ms Yuxin Huang, Doctor Susanna Cramb, Doctor Jessica n Camero, Doctor Paramita Dasgupta, Associate Professor David Smith,

Distinguished Professor Kerrie Mengersen

This approval is subject to the following standard conditions of approval as well as any additional conditions of approval indicated by the UHREC.

Additional conditions of approval:

- Nil

QUT's UHREC is constituted and operates in accordance with the National Health and Medical Research Council's (NHMRC) *National Statement on Ethical Conduct in Human Research (2007, updated 2018)*, NHMRC and Universities Australia *Australian Code for the Responsible Conduct of Research (2018)*.

QUT Human Research Ethics Advisory Team | humanethics@qut.edu.au | +61 (0)7 3138 5123

Government of South Australia
SA Health

Office for Research
Level 5, Citi-Centre Building
11 Hindmarsh Square
ADELAIDE SA 5000
Telephone: (08) 8226 7461

Professor Peter Baade
Cancer Council Queensland
PO Box 201
Spring Hill
QUEENSLAND 4004

Dear Professor Baade

RE: SITE SPECIFIC ASSESSMENT – AUTHORISATION

Project title: National Cancer Atlas

SSA reference: SSA/17/SAH/28

HREC reference HREC/17/CIPHS/3

Site Name: Department for Health and Ageing (SA Cancer Registry data)

Thank you for submitting the Site Specific Assessment (SSA) form and associated documentation for the above named project.

Following a review of the submission, and noting the protocol was ethically approved in full by NSW Population and Health Services Research Ethics Committee, I am pleased to advise your project has received research governance approval for the research activities outlined in the SSA.

This approval encompasses the following documentation:

- SSA Form (AU/12/F5BB210)
- Protocol Version 2, dated 24/01/2017
- Approval letters, NSW Population & Health Services Research Ethics Committee (HREC/17/CIPHS/3), dated 14/03/2017, and revised version, dated 24/03/2017
- Certificate of currency, QUT, Broadform Public & Products Liability, dated 1/11/16
- Certificate of currency, QUT, Professional Indemnity, dated 1/11/16
- Certificate of currency, CCQ, Professional Indemnity, dated 20/12/16
- C.V., Prof Peter Baade, dated September 2016

Please note the following conditions of authorisation:

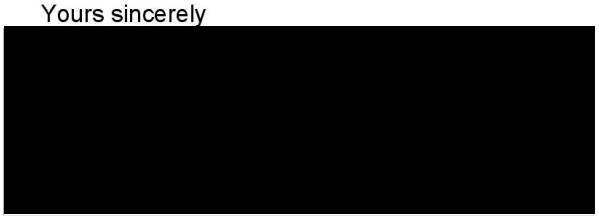
- Authorisation is limited to the activities described in the application provided. Any changes to the project involving the site should be submitted as a

research governance amendment, separate to any requirements of the reviewing HREC.

- Project authorisation is granted for the term of the project specified in the application.
- Any requirements of the data custodian/s, including signing of a Deed of Confidentiality for use of the data provided, must be followed.
- You should advise the Research Governance Officer via HealthResearchGovernance@sa.gov.au of any changes to the status of the project within a timely manner, including discontinuation or withdrawal of the study at the site, or changes to the scope of the project including the participants, research staff, data required, site resources or other governance matters affecting the site.
- The study must be conducted in accordance with the conditions of ethical approval provided by the lead HREC, and in conjunction with the standards outlined in the *National Statement on Ethical Conduct in Human Research* (2007) and the *Australian Code for the Responsible Conduct of Research* (2007).
- You are required to provide annual progress reports and/or a final report for the project. A copy of the reporting template may be requested from the Research Governance Officer. These progress reports should be submitted directly to HealthResearchGovernance@sa.gov.au. **Your first report will be due on 1/05/18 (or when the project is completed, if earlier than this date).**

Should you have any queries regarding these requirements, please contact HealthResearchGovernance@sa.gov.au or (08) 8226 7461.

Yours sincerely



David Van der Hoek
RESEARCH GOVERNANCE OFFICER
DEPARTMENT FOR HEALTH AND AGEING

01/05/17

Cc: *Upeksha Chandrasiri, Data Analyst, Cancer Council Queensland*
Dr. Katina D'Onise, Director, Epidemiology Branch, SA Dept for Health and Ageing

menzies
school of health research

Postal: PO Box 41096, Casuarina NT 0811, Australia
Location: John Mathews Building (Bldg 58),
Royal Darwin Hospital Campus, Rocklands Drv, Casuarina NT 0810
Ph: (08) 8946 8600 Fax: (08) 8946 8464
Website: menzies.edu.au
ABN: 70 413 542 847

20 December 2021

Ethics Administration Office
File Reference Number: HREC-2016-2720
Phone: (08) 8946 8687 or (08) 8946 8692
Email: ethics@menzies.edu.au

Professor Peter Baade
Cancer Council Queensland
PeterBaade@cancerqld.org.au
CC: UpekshaChandrasiri@cancerqld.org.au
Via Email

Dear Professor Baade,

HREC Reference Number: 2016-2720
Project Title: *National Cancer Atlas*

The Human Research Ethics Committee of the Northern Territory Department of Health and Menzies School of Health Research (HREC) thanks you for taking the time to complete and return your annual progress report for the above project.

The report has been reviewed and noted.

The following amendment has been approved:

- An extension of the completion date from *31/12/2022 to 31/12/2024*

Approval is granted for the above research project until the next report due date.

Annual progress report due: *31/12/2022*

Approved timeframe (subject to compliance and annual reporting): *31/01/2017 to 31/12/2024*

APPROVAL IS SUBJECT TO the following conditions being met:

1. The Coordinating Principal Investigator will **immediately report anything that might warrant review** of ethical approval of the project.

2. The Coordinating Principal Investigator will notify the Human Research Ethics Committee of the Northern Territory Department of Health and Menzies School of Health Research (HREC) of any event that requires a **modification or amendment to the protocol or other project documents** and submit any required amendments in accordance with the instructions provided by the HREC. These instructions can be found on the Menzies' website.

3. The Coordinating Principal Investigator will submit any necessary reports related to the **safety of research participants (e.g. protocol deviations, protocol violations)** in accordance with the HREC's policy and procedures. These guidelines can be found on the Menzies' website.

4. The Coordinating Principal Investigator will **report** to the HREC **annually** and notify the HREC when the project is completed at all sites using the specified forms. Forms and instructions may be found on the Menzies' website.

5. The Coordinating Principal Investigator will notify the HREC if the project is **discontinued at a participating site before the expected completion date**, and provide the reason/s for discontinuance.

6. The Coordinating Principal Investigator will notify the HREC of any plan to **extend the duration of the project past the approval period listed above** and will submit any associated required documentation. The preferred time and method of requesting an extension of ethical approval is during the **annual progress report**. However, an extension may be requested at any time.

7. The Coordinating Principal Investigator will notify the HREC of his or her **inability to continue as Coordinating Principal Investigator**, including the name of and contact information for a replacement.

8. The safe and ethical conduct of this project is entirely the responsibility of the investigators and their institution(s).

9. Researchers should immediately report anything which might affect continuing ethical acceptance of the project, including:

    - Adverse effects of the project on participants and the steps taken to deal with these;
    - Other unforeseen events;
    - New information that may invalidate the ethical integrity of the study; and
    - Proposed changes in the project.

10. Approval for a further twelve months, within the original proposed timeframe, will be granted upon receipt of an annual progress report if the HREC is satisfied that the conduct of the project has been consistent with the original protocol.

11. Confidentiality of research participants should be maintained at all times as required by law.

12. The Patient Information Sheet and the Consent Form shall be printed on the relevant site letterhead with full contact details.

13. The Patient Information Sheet must provide a brief outline of the research activity including: risks and benefits, withdrawal options, contact details of the researchers and must also state that the Human Research Ethics Administrators can be contacted (telephone and email) for information concerning policies, rights of participants, concerns or complaints regarding the ethical conduct of the study.

14. You must forward a copy of this letter to all Investigators and to your institution (if applicable).

This letter constitutes ethical approval only. This project, including amendments to the research protocol or conduct of the research which may affect the site acceptability of the project, cannot proceed at any site until separate research governance authorisation has been obtained from the CEO or Delegate of the institution under whose auspices the research will be conducted at that site, if not already obtained. Should you wish to discuss the above research project further, please contact the Ethics Administrators via email: ethics@menzies.edu.au or telephone: (08) 8946 8687 or (08) 8946 8692.

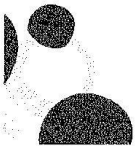
The Human Research Ethics Committee of the Northern Territory Department of Health and Menzies School of Health Research wishes you every continued success in your research.

Yours sincerely,

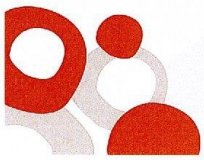
[redacted]

Dr Mary Morris
Chair
Human Research Ethics Committee
of the Northern Territory Department of Health
and Menzies School of Health Research
http://www.menzies.edu.au/ethics

This HREC is registered with the Australian National Health and Medical Research Council (NHMRC) and operates in accordance with the NHMRC *National Statement on Ethical Conduct in Human Research (2007)*. NHMRC Reg no. EC00153



menzies.edu.au



menzies
school of health research

Postal: PO Box 41096, Casuarina NT 0811, Australia
Location: John Mathews Building (Bldg 58),
Royal Darwin Hospital Campus, Rocklands Drv, Casuarina NT 0810
Ph: (08) 8946 8600 Fax: (08) 8946 8464
Website: menzies.edu.au
ABN: 70 413 542 847

31 January 2017

Professor Peter Baade
Cancer Council Queensland
PO Box 201
Spring Hill QLD 4004

Ethics Administration Office
File Reference Number: HREC-2016-2720
Phone: (08) 8946 8687 or (08) 8946 8692
Email: ethics@menzies.edu.au

Dear Professor Baade,

HREC Reference Number: 2016-2720
Project Title: *National Cancer Atlas*

Thank you for your letter dated 31/01/2017 and taking the time to respond to the issues of concern identified by the Fast Track sub-committee of the Human Research Ethics Committee of the Northern Territory Department of Health and Menzies School of Health Research (HREC). This project was considered by members of the HREC and the Aboriginal Ethics Sub-Committee (AESC), and assessed against guidelines for human research including the NHMRC *National Statement on Ethical Conduct in Human Research 2007.*

I am pleased to advise that **full ethical approval** of this research project has been granted following assessment by representatives of both the AESC and the HREC. Please note that approval applies only to research conducted after the date of this letter and continued approval is dependent on annual reporting.

Please note: A condition of this approval is that the Principal Investigator will, at the annual report stage, report what the results of the discussions with A/Professor Gail Garvey were, and what other sources were used to generate the plan for communicating results.

Approval Date: ***31/01/2017***

Approved Timeline: ***31/01/2017 – 31/12/2018***

Annual progress report due: ***31/01/2018***

The nominated participating site in this project is:

- **Northern Territory Cancer Registry**

The documents listed below are approved:

Document	Version	Date
HREC Application	1	9Nov2016

The documents listed below are noted:

Document	Version	Date
Letter of Support – Northern Territory Cancer Registry	-	12Jan2017

APPROVAL IS SUBJECT TO the following conditions being met:

1. The Coordinating Principal Investigator will **immediately report anything that might warrant review** of ethical approval of the project.
2. The Coordinating Principal Investigator will notify the Human Research Ethics Committee of the Northern Territory Department of Health and Menzies School of Health Research (HREC) of any event that requires a **modification or amendment to the protocol or other project documents** and submit any required amendments in accordance with the instructions provided by the HREC. These instructions can be found on the Menzies' website.
3. The Coordinating Principal Investigator will submit any necessary reports related to the **safety of research participants (e.g. protocol deviations, protocol violations)** in

accordance with the HREC's policy and procedures. These guidelines can be found on the Menzies' website.

4. The Coordinating Principal Investigator will **report** to the HREC **annually** and notify the HREC when the project is completed at all sites using the specified forms. Forms and instructions may be found on the Menzies' website.
5. The Coordinating Principal Investigator will notify the HREC if the project is **discontinued at a participating site before the expected completion date**, and provide the reason/s for discontinuance.
6. The Coordinating Principal Investigator will notify the HREC of any plan to **extend the duration of the project past the approval period listed above** and will submit any associated required documentation. The preferred time and method of requesting an extension of ethical approval is during the **annual progress report**. However, an extension may be requested at any time.
7. The Coordinating Principal Investigator will notify the HREC of his or her **inability to continue as Coordinating Principal Investigator**, including the name of and contact information for a replacement.
8. The safe and ethical conduct of this project is entirely the responsibility of the investigators and their institution(s).
9. Researchers should immediately report anything which might affect continuing ethical acceptance of the project, including:
    - Adverse effects of the project on participants and the steps taken to deal with these;
    - Other unforeseen events;
    - New information that may invalidate the ethical integrity of the study; and
    - Proposed changes in the project.
10. Approval for a further twelve months, within the original proposed timeframe, will be granted upon receipt of an annual progress report if the HREC is satisfied that the conduct of the project has been consistent with the original protocol.
11. Confidentiality of research participants should be maintained at all times as required by law.
12. The Patient Information Sheet and the Consent Form shall be printed on the relevant site letterhead with full contact details.
13. The Patient Information Sheet must provide a brief outline of the research activity including: risks and benefits, withdrawal options, contact details of the researchers and must also state that the Human Research Ethics Administrators can be contacted (telephone and email) for information concerning policies, rights of participants, concerns or complaints regarding the ethical conduct of the study.
14. You must forward a copy of this letter to all Investigators and to your institution (if applicable).

This letter constitutes ethical approval only. This project cannot proceed at any site until separate research governance authorisation has been obtained from the CEO or Delegate of the institution under whose auspices the research will be conducted at that site.

Should you wish to discuss the above research project further, please contact the Ethics Administrators via email: ethics@menzies.edu.au or telephone: (08) 8946 8687 or (08) 8946 8686.

Yours sincerely,

[redacted]

Dr Lewis Campbell
Chair
Human Research Ethics Committee
of the Northern Territory Department of Health
and Menzies School of Health Research
http://www.menzies.edu.au/ethics

menzies.edu.au

ACT Government
Health

ACT Health
Research Ethics and Governance Office
Low Risk Sub-Committee

Professor Peter Baade
Cancer Research Centre
Cancer Council Queensland
PO Box 201
Spring Hill QLD 4004

Dear Professor Baade

ETHLR.16.235

The ACT Health Human Research Ethics Committee's Low Risk Sub-Committee received notification of the proposed study:

National Cancer Atlas at its meeting of 16 November 2016.

I am pleased to inform you that your application has been approved.

The Committee noted a waiver of consent request and advised this is not required for access to de-identified unit record data.

The Sub-Committee agreed that the application is for low risk research and determined that the research meets the requirements of the National Statement on Ethical Conduct in Human Research and is ethically acceptable.

I attach for your records an Outcome of Consideration of Protocol form.

I confirm that the ACT Health Human Research Ethics Committee is constituted according to the National Statement on Ethical Conduct in Human Research 2007 and is certified for single review of multi-centre clinical trials. ACT Health HREC operates in compliance with applicable regulatory requirements and the International Conference on Harmonization Guidelines on Good Clinical Practice.

Yours sincerely

[redacted]

Louise Morauta PSM PhD
Chair
ACT Health Human Research Ethics Committee
Low Risk Sub-Committee

16 November 2016

PO Box 11 Woden ACT 2606 | Phone: 6174 7968 or 6174 5659 | E: acthealth-hrec@act.gov.au

ACT HEALTH HUMAN RESEARCH ETHICS COMMITTEE

Outcome of Consideration of Protocol

Submission No: **ETHLR. 16.235** **Date of Approval:** 16 November 2016

Project Title: National Cancer Atlas

Submitted by: Professor Peter Baade

Your project was considered by the ACT Health Human Research Ethics Committee and Approved for a period of 3 years from 16 November 2016 to 16 November 2019.

First Annual Review due: 1 November 2017

For the duration of the approval period you will be required to report any amendments and breaches as per the reporting requirements below.

Reporting requirements:

- Annual project progress report
- Amendments to the protocol or project plan
- Changes to project personnel
- Breaches of security of records
- Breaches of compliance with approved consent procedures and documentation
- Breaches of compliance with other approved procedures
- Unexpected adverse effects on participants
- Unforeseen events that might affect continued ethical acceptability of the project
- Final report and closure notification

All published reports to carry an acknowledgement stating:

- Approved on 16 November 2016 by the ACT Health Human Research Ethics Committee's Low Risk Sub-Committee.

[redacted]

Louise Morauta PSM PhD
Chair
ACT Health Human Research Ethics Committee
Low Risk Sub-Committee

16 November 2016

PO Box 11 Woden ACT 2606 | Phone: 6174 7968 or 6174 5659 | E: acthealth-hrec@act.gov.au

Data custodian approval letters

Declaration & Undertaking by the Data Custodian and the Chief Investigator

Title of Project: National Cancer Atlas

(Amendments Only) CI NSW Ref:

Name of the Database to be sourced: NSW Cancer Registry

Declaration of Data Custodian(s)

I have discussed the proposal with the Chief Investigator. I confirm that the request as stated in this proposal is feasible and I will give due regard to any ethical conditions imposed by the NSW Population & Health Services Research Ethics Committee when deciding whether, and in what form, I will release data to the investigator.

[redacted]

Declaration of Chief Investigator

I am applying for approval to conduct the project. If approval is granted, it will be undertaken in accordance with this application and other relevant laws, regulations and guidelines.

I agree to ensure that all members of the research team (Principal investigators/researchers, Associate investigators/researchers and other personnel) working on the above project are aware of the provisions of this Undertaking and the need to comply with them.

Specifically I will comply as relevant with:

i) NSW *Health Records & Information Privacy Act 2002* and statutory guidelines
ii) NSW *Privacy and Personal Information Protection Act 1998*
iii) NSW Health *Privacy Management Plan, Version 2, 2005*
iv) *NSW Aboriginal Health Information Guidelines*
v) *NHMRC National Statement on Ethical conduct in Research Involving Humans, 2007*
vi) *Australian Code for the Responsible Conduct of Research, 2007*
vii) Any conditions imposed by the NSW Population & Health Services Research Ethics Committee in conducting this project.

I will not use identified or re-identifiable data collected for the purpose of this project for any other purpose, or supply it to any third party not specified in this proposal, without the approval of the Data Administrator/Data Custodian, where relevant, and a properly constituted Ethics Committee with jurisdiction and relation to these data.

[redacted]

TRIM Record: E13/25682

From: Peter Baade
To: Upeksha Chandrasiri
Subject: FW: Request for approval to provide data for the National Cancer Atlas project [SEC= UNCLASSIFIED]
Date: Thursday, 31 August 2017 3:45:13 PM
Attachments: image017.png

FYI

From: Vicky Thursfield [mailto:Vicky.Thursfield@cancervic.org.au]
Sent: Tuesday, 11 April 2017 8:42 AM
To: Peter Baade <PeterBaade@cancerqld.org.au>
Subject: RE: Request for approval to provide data for the National Cancer Atlas project [SEC=UNCLASSIFIED]

Many thanks Peter – this is perfect. I will run these past Helen today and Hopefully send final approval to AIHW for release of the data.

With kind regards, Vicky

Vicky Thursfield
Reporting and Quality Manager
Victorian Cancer Registry
T: (03) 9514 6226
Monday-Thursday
615 St Kilda Rd, Melbourne Vic 3004 Australia
www.cancervic.org.au
Prevent Cancer. Empower Patients. Save Lives.

Cancer Council Victoria acknowledges the Traditional Owners of the land and waters throughout Victoria and pays respect to them, their culture and their Elders past, present and future.

From: Peter Baade [mailto:PeterBaade@cancerqld.org.au]
Sent: Monday, 10 April 2017 8:40 PM
To: Vicky Thursfield
Subject: RE: Request for approval to provide data for the National Cancer Atlas project [SEC= UNCLASSIFIED]

Hi Vicky,

I have attached the ethics application and protocol document that we supplied to NSW HREC.

Let me know if this answers your questions. The choice of cancers was primarily to include the most common cancer types, and is similar to those reported in the 2011 Atlas of Cancer in Queensland.

Thanks,

Peter.

From: Vicky Thursfield [mailto:Vicky.Thursfield@cancervic.org.au]
Sent: Monday, 10 April 2017 11:55 AM
To: Peter Baade <PeterBaade@cancerqld.org.au>
Subject: FW: Request for approval to provide data for the National Cancer Atlas project [SEC=UNCLASSIFIED]

Hi Peter

Before Helen signs off final approval for data provision for your project, can you just confirm the cancer sites/site groups you are intending to include in your atlas, and/or the basis on which you are making the decision as to which cancers will be displayed. I have a feeling that you may have answered this previously so please forgive me if you have. We have lost key staff in Data Access area so are currently rather under-staffed and sometimes bamboozled by others' filing systems!

With many thanks.

With kind regards, Vicky

Cancer Council Victoria

Vicky Thursfield
Reporting and Quality Manager
Victorian Cancer Registry
T: (03) 9514 6226
Monday-Thursday
615 St Kilda Rd, Melbourne Vic 3004 Australia
www.cancervic.org.au
Prevent Cancer. Empower Patients. Save Lives.

From: Harvey, Justin [mailto:justin.harvey@aihw.gov.au]

Sent: Thursday, 6 April 2017 5:15 PM
To: ACT - Group address; Phung, Hai; Newman, Leah; ACT - Liz Chalker; NSW - Aisling Forrest; NSW - Richard Walton; NSW - Sheena Lawrance; NSW - Shelley Rushton; Wendy Thomson; Condon, John; NT - Sarah Dugdale; NT - Shu Li; QLD - Joanne Aitken; QLD - Peta Gordon; SA - Katina D'Onise; SA - Kevin Priest; TAS - Alison Venn; TAS - Brian Stokes; Helen Farrugia; Vicky Thursfield; WA - Group address; WA - John Dowling
Cc: Cancer Data Team
Subject: Request for approval to provide data for the National Cancer Atlas project
[SEC= UNCLASSIFIED]

Dear Registry Directors (or equivalent),

I refer to the 'National Cancer Atlas' project being conducted by researchers from Cancer Council Queensland and Queensland University of Technology. It is AIHW's understanding that the team has now obtained all required registry-specific approvals (such as ethics committee approval) pertaining to this project except for the SSA approval required in SA. However please advise us if there are any other outstanding matters. We are now seeking final permission from each registry to extract the data from the ACD as per the attached data specifications and to provide the dataset to the SURE environment as agreed with the researchers (details currently being finalised).

Except for SA, could you please send your final approval to me (and cc to cancer@aihw.gov.au) by COB Thursday 13 April if possible.

For SA, we will await confirmation that SSA approval has been given before seeking final approval.

Thanks,
Justin Harvey
Head of the Cancer and Screening Unit
Australian Institute of Health and Welfare
Ph: (02) 6244 1063

Enquiries to: Sharon Knight
Principal Policy Officer
Office of Research and Innovation
Telephone: (07) 3199 3175
File Ref: PHA 7924.4

Queensland Government

Queensland Health

Professor Peter Baade
Cancer Council Queensland
PO Box 201
Spring Hill QLD 4004

Email: peterbaade@cancerqld.org.au

Dear Professor Baade

Research Title: **National Cancer Atlas**

HREC / Project Number: **QUT UHREC 6398 (HREA 2023-6398-12519)**

I am writing to inform you that, having considered your application, received on the 13 February 2023 under section 282 of the Public Health Act 2005 (the Act) to be given health information held by a health agency specified below (Information) for research in relation to the project listed above, your amended application has been granted under section 284 of the Act by the Director-General's delegate. Consequently, the Information can be given to the persons specified below, providing they act in accordance with Part 4 of the Act and within the limits detailed in your now granted application and this letter.

This grant PHA 7924.4 commences on the date of this letter and is for the information described and date range stated in the approved application. It is valid for the period of the Human Research Ethics Committee (HREC) approval in place for this project and expires at the end of that period (i.e., refer to condition (a)(v) on page two (2) of this grant).

This grant relates to information for the period listed from the following repositories:

Name of site	Name of repository	Time period
Queensland University of Technology	Australian Cancer Database	1 Jan 96 to 31 Dec 20

The following persons may be given the information as noted in section 4 of the above-mentioned amended application:

Name of person	Position title	Person's institution
Professor Peter Baade	Principal Coordinating Investigator	Cancer Council Queensland
Professor Kerrie Mengersen	Investigator	Queensland University of Technology
Professor Joanne Aitken	Investigator	Cancer Council Queensland
Dr Susanna Cramb	Investigator	Queensland University of Technology
Dr Jessica Cameron	Investigator	Cancer Council Queensland
Dr Paramita Dasgupta	Investigator	Cancer Council Queensland
A/Professor David Smith	Investigator	Cancer Council NSW
Ms Yuxin Huang	Investigator	Queensland University of Technology
Mr Ankur Kohar	Investigator	Cancer Council NSW

This grant requires you to act in accordance with the provisions of Part 4 of the Act, including adhering to the following conditions:

a) You must:
   i. provide notification of any change in the names of persons who will be given the Information for the research specified above;
   ii. ensure that the Information is kept confidential, is not disclosed (whether directly or indirectly) to persons not named in this letter and is handled securely, including in relation to storage or disposal of the Information;
   iii. protect the privacy of any individual capable of being identified by the Information; and
   iv. provide an annual progress report and a final report at the completion of your project, to Office of Precision Medicine and Research, Clinical Planning and Service Strategy Division. Templates can be found on the web page http://www.health.qld.gov.au/ohmr/html/regu/aces_conf_hth_info.asp.
   v. provide annually to the PHA office evidence of ongoing HREC approval (Please note: The PHA grant expires on the due date of the annual report to the HREC every year unless the Principal Investigator provides the OPMR office with evidence of the HREC's receipt of an annual report and subsequent ongoing HREC approval. Failure to do so may result in the grant being rescinded).

b) You must not:
   i. use the Information in a way that is inconsistent with the research for which it is given as described in the application to which this letter relates; or
   ii. disclose the Information where the disclosure is not permitted by the Act.

Failure to act in accordance with a condition stated above may constitute an offence under the Act for which you may be prosecuted and incur a penalty.

When conducting research within the Queensland public health system, a copy of this letter must be provided to the relevant Research Governance Officer as part of your research governance application in accordance with Queensland Health policies.

Please note: This letter constitutes a grant only for the purposes of Part 4 of the Act. The project cannot proceed until separate Research Governance authorisation has been obtained from the relevant authority in accordance with Queensland Health policies.

Please display this letter and a copy of the application to which this letter relates when requesting the Information from the relevant data custodian.

Should you wish to amend the project protocol, you will need to seek approval of these amendments from the HREC that has ethical oversight of the project and submit a new application for a grant to be given for health information held by a health agency in accordance with the provisions of Part 4 of the Act. Amendments include seeking to use the Information in a way, or for an additional research purpose, not listed in the application to which this letter relates or seeking to give the Information for the research to additional persons not named in this letter. Please provide a copy of your HREC approval of the amendments when re-applying.

Please contact the Office of Research and Innovation, Clinical Planning and Service Strategy Division on email PHA@health.qld.gov.au or phone 07 3199 3175 if you have any queries on this matter.

Melissa Hagan
Director
Office of Research and Innovation
Clinical Planning and Service Strategy Division

Peter Baade

From: Harvey, Justin <justin.harvey@aihw.gov.au>
Sent: Thursday, 17 November 2016 10:55 AM
To: Peter Baade; Joanne Aitken
Cc: Cancer Data Team
Subject: FW: Update on the National Cancer Atlas project [SEC=UNCLASSIFIED]

Hi Peter/Joanne,

Sorry I thought I'd forwarded this to you but it appears I hadn't.

Justin

From: D'Onise, Katina (Health) [mailto:Katina.D'Onise@sa.gov.au]
Sent: Saturday, 5 November 2016 10:43 AM
To: Harvey, Justin
Subject: RE: Update on the National Cancer Atlas project [SEC=UNCLASSIFIED]

Not for SA
Regards
Katina

From: Harvey, Justin [mailto:justin.harvey@aihw.gov.au]
Sent: Friday, 4 November 2016 1:48 PM
To: 'NSW - Richard Walton'; Wendy Thomson; 'QLD - Carly Scott'; 'QLD - Joanne Aitken'; D'Onise, Katina (Health); Priest, Kevin (Health); 'TAS - Alison Venn'; 'TAS - Brian Stokes'; Farrugia, Helen; 'VIC - Vicky Thursfield'; 'WA - Group address'; 'WA - John Dowling'
Cc: Cancer Data Team
Subject: RE: Update on the National Cancer Atlas project [SEC=UNCLASSIFIED]

Hi,

Can you please advise whether further ethics committee approvals (in addition to those already obtained) need to be sought to enable the data for your state to be provided for this project?

Thanks,
Justin

From: Harvey, Justin
Sent: Tuesday, 25 October 2016 9:34 AM
To: Newman, Leah; ACT - Liz Chalker; NSW - Richard Walton; Wendy Thomson; NT - Josette Chor; NT - Sarah Dugdale; QLD - Carly Scott; QLD - Joanne Aitken; SA - Katina D'Onise; SA - Kevin Priest; TAS - Alison Venn; TAS - Brian Stokes; Farrugia, Helen; VIC - Vicky Thursfield; WA - Group address; WA - John Dowling
Cc: Cancer Data Team
Subject: Update on the National Cancer Atlas project [SEC=UNCLASSIFIED]

Dear cancer registries

This email is to provide you with an update on the National Cancer Atlas project.

We are pleased to provide you with an update on some changes to the stakeholder arrangements for this project. As some of you may know, the National Cancer atlas project was a collaborative initiative between the Collaborative Research Centre for Spatial Information (CRCSI), Cancer Council Queensland (CCQ), Queensland University of Technology (QUT) and the National Health Performance Authority (NHPA). Following the transfer of

NHPA functions to the AIHW, the AIHW has taken on some of NHPA's previous responsibilities and is now part of the collaborating team and a contributing partner in this work. We are pleased that this will enable the AIHW to be more actively involved in shaping the process and delivery of this project and we will continue to work closely with registries.

You have provided in-principle support for this work previously and subsequently some registries have indicated that ethics committee approval was also likely to be required. Since then, the project has obtained a low-risk ethics committee approval from the Queensland University of Technology (QUT) human research ethics committee (see attachment). It has also obtained PHA approval (see attachment) from Queensland Health to access the required data from the Queensland Cancer Registry.

The researchers intend to utilise the Secure Unified Research Environment (SURE) facility run by the SAX Institute to store and analyse the required data. An information sheet on this facility is also attached.

Would you please advise whether further approvals from other ethics committees would be required in addition to the above? If so, we would recommend that the lead investigators liaise directly with you regarding the specifications of the project and what information needs to be included in the relevant ethics committee applications. Professor Peter Baade will contact you directly about this, as required.

Once all necessary ethics approvals have been obtained, the AIHW will proceed with the data extraction and will co-ordinate the request for final approval from registries for the release of the data.

Please let us know if you would like to discuss further.

Kind regards
Theresa

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Peter Baade

From: Dowling, John <John.Dowling@health.wa.gov.au>
Sent: Monday, 12 December 2016 10:31 AM
To: Harvey, Justin
Cc: Chau, Theresa; Satti, Tony; Peter Baade
Subject: RE: Update on the National Cancer Atlas project [SEC=UNCLASSIFIED]

Hi Justin

We have now reviewed this project and can approve this request as the items involved aren't likely to enable individuals to be identified.

Once again, apologies for my misunderstanding and subsequent delay.

With warm regards . . . John

John Dowling | A / Assistant Director,
Data Collections Directorate | PURCHASING AND SYSTEM PERFORMANCE DIVISION
Department of Health
Level 1, C Block, 189 Royal Street, East Perth, WA 6004
T: (08) 9222 4249 Mb: 0407 099 071

From: Dowling, John
Sent: Thursday, 8 December 2016 10:15 AM
To: 'Harvey, Justin'
Cc: Chau, Theresa; Satti, Tony; 'PeterBaade@cancerqld.org.au'
Subject: RE: Update on the National Cancer Atlas project [SEC=UNCLASSIFIED]

Hi Justin

My sincere apologies for misunderstanding your email of 25 October and the delay it has generated.

Peter has just called me and we have had a further valuable discussion.

I have also re-read the attached Ethics QUT HREC Application that clearly defines the method statement.

WA Health usually endorses similar AIHW data provision projects without the need for WA ethics approval, especially when the data release will be provided 'de-identified but in a unit record form.'

It is likely that a number of my WA Health colleagues will be most interested in the 'novel visualisation techniques' outcomes of this project and I would like a few extra days to liaise with them in reviewing these documents. Peter has also kindly offered to provide some earlier question and answer information that may enrich our understanding of this important project.

We anticipate providing this final approval from WA by mid-week next week.

With warm regards and thank you for your patience . . . John

John Dowling | A / Assistant Director, WA Cancer Registry
Data Collections Directorate | PURCHASING AND SYSTEM PERFORMANCE DIVISION
Department of Health
Level 1, C Block, 189 Royal Street, East Perth, WA 6004
T: (08) 9222 4249 Mb: 0407 099 071

From: Harvey, Justin [mailto:justin.harvey@aihw.gov.au]
Sent: Thursday, 8 December 2016 9:17 AM
To: Dowling, John
Cc: Chau, Theresa; Satti, Tony
Subject: RE: Update on the National Cancer Atlas project [SEC=UNCLASSIFIED]

Hi John,

This enquiry is in relation to another geospatial project (see the details in the email below), not the CIMAR books which are scheduled for release on 14/12. I know it's a bit confusing at the moment with several geographical cancer projects occurring concurrently. The project referred to in the email below is in the early stages where the approvals required to provide the data to the researchers are being determined currently.

Please let me know if you have any questions or need to clarify anything.

Regards,
Justin

From: Dowling, John [mailto:John.Dowling@health.wa.gov.au]
Sent: Thursday, 8 December 2016 12:07 PM
To: Harvey, Justin
Cc: Chau, Theresa; Satti, Tony
Subject: RE: Update on the National Cancer Atlas project [SEC=UNCLASSIFIED]

Hi Justin,

Further to my email to Theresa and you on 7 November, ethics approval for this release is not required by WA Health, based on the previous precedents used by the WA Cancer Registry.

We have thoroughly reviewed the embargoed material for publication and are preparing a briefing note for our Director General focusing, on the SA3 summaries comparing Western Australia's highest incident results with other similar State results. We have also recently briefed the Co-Director of the WA Cancer and Palliative Care Network on online information that will be made available next week.

We are looking forward to the public interest that this important information will generate.

With warm regards . . . John

John Dowling | A / Assistant Director, WA Cancer Registry
Data Collections Directorate | PURCHASING AND SYSTEM PERFORMANCE DIVISION
Department of Health
Level 1, C Block, 189 Royal Street, East Perth, WA 6004
T: (08) 9222 4249 Mb: 0407 099 071

From: Harvey, Justin [mailto:justin.harvey@aihw.gov.au]
Sent: Thursday, 8 December 2016 7:43 AM
To: Dowling, John
Cc: WA Cancer Registry
Subject: FW: Update on the National Cancer Atlas project [SEC=UNCLASSIFIED]
Importance: High

Hi John,

Have you made any progress on this?

Justin

From: Harvey, Justin
Sent: Friday, 11 November 2016 4:34 PM
Cc: Cancer Data Team; Chau, Theresa
Subject: FW: Update on the National Cancer Atlas project [SEC=UNCLASSIFIED]

Hi,

Have you had a chance to consider whether or not any additional ethics committee approvals will be required for this data request?

Thanks,
Justin

From: Harvey, Justin
Sent: Tuesday, 25 October 2016 9:34 AM
To: Newman, Leah; ACT - Liz Chalker; NSW - Richard Walton; Wendy Thomson; NT - Josette Chor; NT - Sarah Dugdale; QLD - Carly Scott; QLD - Joanne Aitken; SA - Katina D'Onise; SA - Kevin Priest; TAS - Alison Venn; TAS - Brian Stokes; Farrugia, Helen; VIC - Vicky Thursfield; WA - Group address; WA - John Dowling
Cc: Cancer Data Team
Subject: Update on the National Cancer Atlas project [SEC=UNCLASSIFIED]

Dear cancer registries

This email is to provide you with an update on the National Cancer Atlas project.

We are pleased to provide you with an update on some changes to the stakeholder arrangements for this project. As some of you may know, the National Cancer atlas project was a collaborative initiative between the Collaborative Research Centre for Spatial Information (CRCSI), Cancer Council Queensland (CCQ), Queensland University of Technology (QUT) and the National Health Performance Authority (NHPA). Following the transfer of NHPA functions to the AIHW, the AIHW has taken on some of NHPA's previous responsibilities and is now part of the collaborating team and a contributing partner in this work. We are pleased that this will enable the AIHW to be more actively involved in shaping the process and delivery of this project and we will continue to work closely with registries.

You have provided in-principle support for this work previously and subsequently some registries have indicated that ethics committee approval was also likely to be required. Since then, the project has obtained a low-risk ethics committee approval from the Queensland University of Technology (QUT) human research ethics committee (see attachment). It has also obtained PHA approval (see attachment) from Queensland Health to access the required data from the Queensland Cancer Registry.

The researchers intend to utilise the Secure Unified Research Environment (SURE) facility run by the SAX Institute to store and analyse the required data. An information sheet on this facility is also attached.

Would you please advise whether further approvals from other ethics committees would be required in addition to the above? If so, we would recommend that the lead investigators liaise directly with you regarding the specifications of the project and what information needs to be included in the relevant ethics committee applications. Professor Peter Baade will contact you directly about this, as required.

Once all necessary ethics approvals have been obtained, the AIHW will proceed with the data extraction and will co-ordinate the request for final approval from registries for the release of the data.

Please let us know if you would like to discuss further.

Kind regards
Theresa

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From:	Peter Baade
To:	Upeksha Chandrasiri
Subject:	FW: Tassie approval for National Cancer Atlas [SEC=UNCLASSIFIED]
Date:	Thursday, 31 August 2017 3:46:29 PM

FYI

From: Cancer Data Team [mailto:cancer@aihw.gov.au]
Sent: Thursday, 29 June 2017 12:34 PM
To: Peter Baade <PeterBaade@cancerqld.org.au>; Watson, Bill <bill.watson@aihw.gov.au>; Ougrinovski, Elena <elena.ougrinovski@aihw.gov.au>; Hampel, Kirk <kirk.hampel@aihw.gov.au>
Cc: Cancer Data Team <cancer@aihw.gov.au>
Subject: Tassie approval for National Cancer Atlas [SEC=UNCLASSIFIED]

I just got approval from Alison Venn, Director of the Tasmanian Cancer Registry, to include the TCR data in the National Cancer Atlas. So, Elena and Kirk, hold your horses with the upload to SURE. I'll have to prepare and send you a new csv file. Probably this afternoon.

(This is just like when you hold off washing your sheets and hanging them on the line for a few days because it looks like it might rain. But it doesn't rain on those days. Then you can't wait any longer so you do it, and it rains! Conclusion: hanging sheets on the line MAKES it rain.)

Cheers,

Mark Short
Manager, Australian Cancer Database
Cancer and Screening Unit
Australian Institute of Health and Welfare
Ph: (02) 6244 1063

NORTHERN TERRITORY GOVERNMENT

DEPARTMENT OF HEALTH

Strategy and Reform Division
Health Gains Planning
Level 2 Health House
87 Mitchell Street
DARWIN NT 0800

Postal Address:
PO Box 40596
CASUARINA NT 0811

T 08 89858082
E josette.chor@nt.gov.au

Our Ref:
Your Ref:

Peter Baade, PhD
Senior Research Fellow
Viertel Cancer Research Centre
Cancer Council Queensland
Australia

Dear Professor Baade,

RE: SUPPORT BY THE NORTHERN TERRITORY CANCER REGISTRY

I am writing to confirm the Northern Territory Cancer Registry's support in principle for the proposed project "National Cancer Altas" which is a descriptive study using routinely collected data that aims to 1) describe the geographical variation in cancer incidence and survival across Australia using complex statistical models, and 2) present these results using cutting-edge visualisation methods through a web-based, interactive digital product.

Please note that Section 17 of the Cancer (Registration) Act 2009 specifies that authorisation by the Chief Health Officer (CHO) is required before the NTCR is permitted to disclose personal information for research. The final authorization letter of the release of data will be available once we receive your conditional and final approval letter from HREC.

If you have any question, please do not hesitate and contact me.

Yours sincerely

[redacted]

Josette Chor
Cancer Registrar, NT Government Department of Health
12 Jan 2017

ACT Government
Health

Professor Peter Baade
Viertel Cancer Research Centre
Cancer Council Queensland
PO Box 201
Spring Hill, QLD, 2004

Dear Professor Baade,

RE: 2017-724 National Cancer Atlas

In reply to your application of 6 February 2017, please accept this letter as data custodian approval for the Australian Institute of Health and Welfare to provide de-identified unit record data for the years 1996-2013 from the Australian Cancer Database for this project.

Yours sincerely

[redacted]

Dr Hai Phung
Director
ACT Cancer Registry

22/ February 2017

Req No: 2017-724

cc: Cancer Data Team,
Australian Institute of Health and Welfare

Appendix B: Published manuscript of Chapter 3

Cancer Epidemiology 83 (2023) 102338

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Cancer Epidemiology

journal homepage: www.elsevier.com/locate/canep

Changes in prostate specific antigen (PSA) "screening" patterns by geographic region and socio-economic status in Australia: Analysis of medicare data in 50–69 year old men

Ankur Kohar [a,b], Susanna M. Cramb [c,d,h], Kristen Pickles [e], David P. Smith [a,f], Peter D. Baade [g,h,i,*]

[a] The Daffodil Centre, The University of Sydney, a joint venture with Cancer Council NSW, Sydney, New South Wales, Australia
[b] Sydney School of Public Health, The University of Sydney, Australia
[c] School of Public Health and Social Work, Queensland University of Technology, Brisbane, Australia
[d] Australian Centre for Health Services Innovation & Centre for Healthcare Transformation, Queensland University of Technology, Brisbane, Australia
[e] Faculty of Medicine and Health, Sydney Health Literacy Lab, School of Public Health, The University of Sydney, Sydney, Australia
[f] School of Public Health and Preventive Medicine, Monash University, Melbourne, Victoria, Australia
[g] Cancer Council Queensland, Brisbane, Australia
[h] Centre for Data Science, Queensland University of Technology, Brisbane, Australia
[i] Menzies Health Institute, Griffith University, Gold Coast, Australia

ARTICLE INFO

Keywords:
PSA screening
Prostate cancer
Trends
Remoteness
Area-disadvantage

ABSTRACT

Background: While it is known that national PSA testing rates have decreased in Australia since 2007, it is not known whether these trends are consistent by broad geographical areas, nor whether previously reported area-specific differences have remained in more recent time periods.
Methods: Population-based cohort study of Australian men (n = 2793,882) aged 50–69 who received at least one PSA test (Medicare Benefit Schedule item number 66655) during 2002–2018. Outcome measures included age-standardised participation rate, annual percentage change using JoinPoint regression and indirectly standardised participation rate ratio using multivariable Poisson regression.
Results: During 2005–09, two thirds (68%) of Australian men aged 50–69 had at least one PSA test, reducing to about half (48%) during 2014–18. In both periods, testing rates were highest among men living in major cities, men aged 50–59 years, and among men living in the most advantaged areas. Nationally, the Australian PSA testing rate increased by 9.2% per year between 2002 and 2007, but then decreased by 5.0% per year to 2018. This pattern was generally consistent across States and Territories, and socio-economic areas, however the magnitude of the trends was less pronounced in remote and very remote areas.
Conclusions: The decreasing trends are consistent with a greater awareness of the current guidelines for clinical practice in Australia, which recommend a PSA test be done only with the informed consent of individual men who understand the potential benefits and risks. However, given there remain substantial geographical disparities in prostate cancer incidence and survival in Australia, along with the equivocal evidence for any benefit from PSA screening, there remains a need for more effective diagnostic strategies for prostate cancer to be implemented consistently regardless of where men live.

1. Introduction

Prostate-specific antigen (PSA) testing in asymptomatic men can instigate an early diagnosis of prostate cancer, potentially avoiding higher risk disease and enabling the management to be more effective. While it remains the most commonly used test for prostate cancer screening or monitoring after a prostate cancer diagnosis or its treatment, its use as a screening test for prostate cancer is widely debated [1] due to its high sensitivity and a low specificity [2], its inability to distinguish between cancers and non-cancer conditions, and the known

* Correspondence to: Cancer Council Queensland, PO Box 201 Spring Hill, Queensland 4004, Australia.
E-mail address: peterbaade@cancerqld.org.au (P.D. Baade).

https://doi.org/10.1016/j.canep.2023.102338
Received 7 August 2022; Received in revised form 30 January 2023; Accepted 10 February 2023
Available online 24 February 2023

harms associated with overdiagnosis and over-treatment of screen detected cancers [3]. Increased rates of PSA testing are typically associated with increases in prostate cancer diagnoses and higher observed cause specific survival [4].

While population-based screening for prostate cancer is not endorsed internationally nor implemented as policy in any country in the world, during 2005–2009 52% of Australian men aged 40 years and over had at least one Medicare-funded PSA "screening" test [5]. Medicare reimburses four categories of PSA tests (66655, 66656, 66659 and 66660) and for the purposes of this paper we refer to item 66655 as de-facto "screening" tests (henceforth referred to as PSA screening tests), as it relates to tests undertaken on asymptomatic men. In 2016, the Prostate Cancer Foundation of Australia and Cancer Council Australia [6] released national evidence-based guidelines that did not recommend a population-based prostate screening program, and instead advised informed individual decision-making regarding PSA testing. The guidelines state that men aged 50–69 years who make an informed decision to have a PSA test be offered biennial PSA testing. These recommendations are generally consistent with similar USA [7–9] and Canadian recommendations [10].

In Australia, PSA screening rates have been consistently lower among men living in less accessible regional and remote areas of Australia versus the rest of the country [5,11], and lower in socioeconomically disadvantaged populations[5], however these estimates relate to the period of highest PSA testing rates more than ten years ago. While modelled rates have decreased nationally since around 2007[5] it is not known whether these trends are consistent across geographical areas, and whether the geographical disparities reported previously[5, 12,13] have persisted over time.

The aim of this study is to describe Medicare-funded PSA screening test patterns and trends by State and Territory, remoteness of residence and socio-economic status. This information may be used to guide policy makers about temporal changes in PSA testing and its implementation, and thus inform the development of recommendations or future revisions of the Australian PSA testing guidelines.

2. Methods

2.1. Data collection

A de-identified unit record dataset extracted from the Medicare Benefits Schedule was provided by the Commonwealth Department of Health covering the period January 2002 to December 2018 for specific items numbers related to PSA testing. This included MBS item numbers 66655, 66656, 66659 and 66660. For the purposes of this paper we selected just those tests categorised as 66655. Data included a unique (deidentified) person number, age at treatment (10-year age groups), month and year of service and postcode of residence. Estimated resident population data at the SA2 level were obtained from the Australian Bureau of Statistics (abs.gov.au). SA2s are small geographical areas covering the entire geographical area of Australia without gap or overlap. In Australia there were 2196 small areas in 2011 [14]. The median population of included SA2s in 2011 was 505 (IQR: 312, 795) for men aged 50–69.

2.2. Geographic definitions

We used a concordance file obtained from the Australian Bureau of Statistics to map postcodes to SA2 boundaries. Of the 2653 postcodes included in the concordance, 1177 (44%) mapped completely (>99.9% overlap) to an individual SA2. For each individual we used the population weighted proportions to randomly allocate the postcode to a SA2. We repeated this random allocation to assess the potential impact of this non-exact concordance on the results. Geographic location information was categorised into State/Territory, remoteness of residence and area socioeconomic status based on the Index of Relative Socioeconomic Advantage and Disadvantage derived by the Australian Bureau of Statistics (abs.gov.au).

2.3. Statistical analysis

We calculated the average number of men having a PSA screening test in any given calendar year, rather than the number of screening tests in that year. Men who had multiple PSA screening tests within a single calendar year were counted only once for that year. We restricted the analysis on men aged 50–69 for consistency with the 2016 Australian PSA testing guidelines [6].

We present PSA screening rates as average annual rates per year for two periods; 2005–2009 representing the period of highest PSA screening rates (and reported previously for different age groups[5]), and 2014–2018 representing the most recent data available at the time of data extraction.

Directly age-standardised screening rates were calculated using two 10-year age groups and standardised to the Australian 2001 population, with standard errors calculated using the modified gamma method. Trends were quantified by calculating annual percentage change by calendar year using Joinpoint regression (https://surveillance.cancer.gov/joinpoint/) which employs a series of regression models using the observed age-standardised testing rates as the outcome measure and including their standard errors to determine the best combination of linear line segments that fit the data. A maximum of 3 joinpoints (or 4 line segments) were used for this analysis. One PSA test for each man per calendar year were included in these trend analyses.

Incidence rate ratios of receiving a PSA screening test over the study period were calculated by exponentiating the coefficients from Poisson models. The outcome measure for the Poisson model was the observed number of men receiving at least one PSA test during the time period and used an offset term defined by the log of the age-specific male population. The significance level for each variable was tested using the likelihood ratio test; comparing the model to a reduced model where each variable is excluded one at a time. These models also included year of testing, 10-year age group, remoteness, area socioeconomic status and State/territory, as well as an interaction term between Remoteness and Area socioeconomic status.

Analyses were conducted using R (version 3.5.3), Joinpoint (version 4.8.0.1) and Stata (version 16) software. Ethics approval for this study was obtained from the Griffith University Human Research Ethics committee (GU Ref no: 2017/777). Data custodian approval was provided by the Commonwealth Department of Health after approval from the Chief Data Steward under the Health Insurance Act 1973.

3. Results

In total, there were 7,438,720 Medicare records of PSA screening tests among men aged 50–69 years between 2002 and 2018. Records were excluded from the study if the provided postcode was used exclusively for Post Office boxes rather than a residential street address (n = 51,016, 0.69%), an invalid postcode (n = 43,983, 0.59%) or was a repeated screening test for an individual man within the same calendar year (n = 2870, 0.04%). After these exclusions, the final study cohort included 7,340,851 PSA screening tests among 2,793,882 men between 2002 and 2018, counted as one screening test per man per year.

3.1. Trends over time

Nationally, the Australian PSA screening rate among men aged 50–69 years increased by 9.2% per year between 2002 and 2007, but then decreased by 5.0% per year between 2007 and 2018 (Fig. 1, Table S1). The pattern of increasing trend followed by a decrease was generally consistent across the Australian states and territories, remoteness categories and socio-economic areas, however the magnitude of the trends were less pronounced in remote and very remote areas

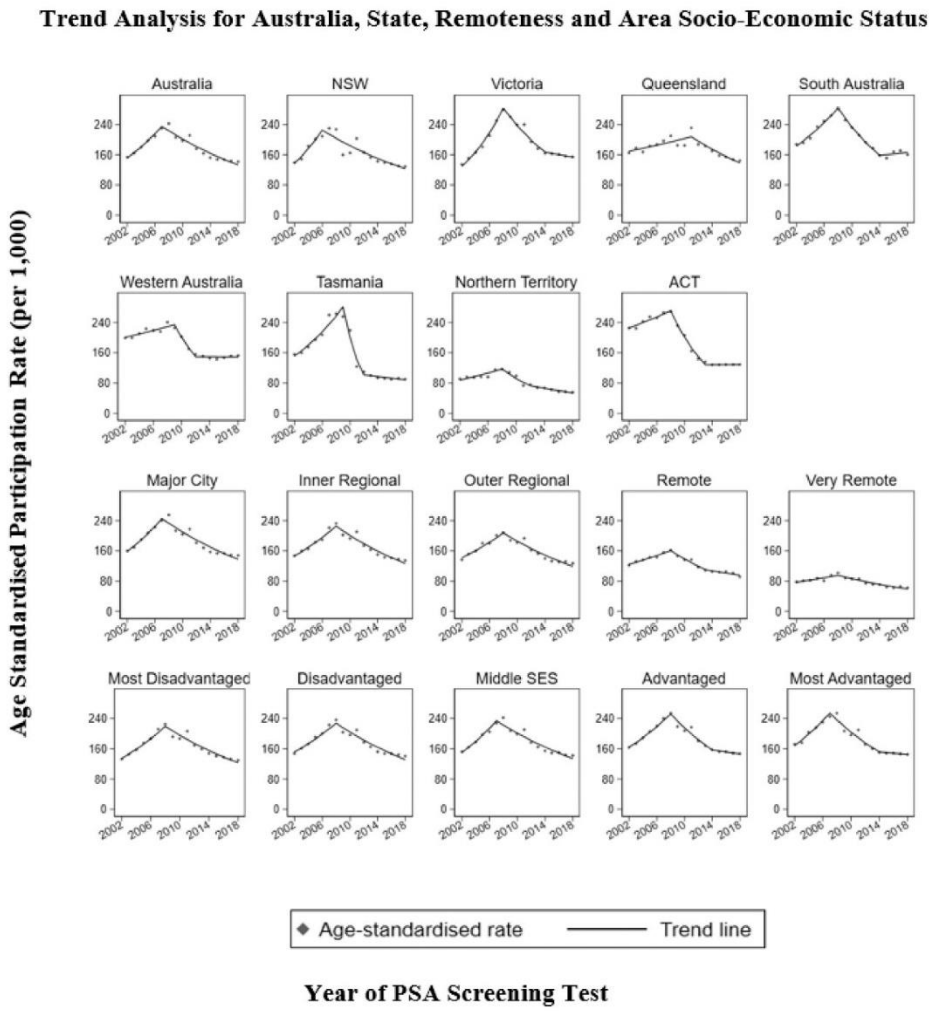

Fig. 1. Trends in annual PSA screening test rates for Australian men aged 50–69 years, 2002–2018, for Australia, by State, Remoteness, and Area-level Socio-economic Status.

(Fig. 1, Table S1). The decreasing trend plateaued since the early-mid 2010 s for men living in Remote areas, as well as those in the more socioeconomically advantaged areas.

The peak in modelled PSA screening rates occurred in Australia in 2007. The number of men receiving at least one Medicare funded PSA screening test during a five year period decreased nationally from nearly 1.5 million men in the period between 2005 and 2009–1.3 million men between 2014 and 2018 (Table 1). The corresponding age-standardized screening rates reduced from 676 men receiving at least one PSA screening test (95% CI: 675.3–677.5) to 482 per 1000 men (480.8–482.4). Decreases in both the number and rate of men receiving at least one screening test between 2005 and 2009 and 2014–2018 were observed across all age groups, states/territories, remoteness, and socio-economic areas (Table 1).

3.1.1. Differences by population subgroup

In both 5-year time periods, the screening rate among men aged 60–69 years was 8% lower than the rate among men aged 50–59 years (Table 1). Screening rates varied across the states and territories, with age-standardised rates being higher in Western Australia, Victoria, Queensland and South Australia during 2014–2018. In both time periods, PSA screening rates were highest among men living in major cities, and then reduced with increasing remoteness. While screening rates were up to 11% higher among men living in the most advantaged areas in the 2005–2009 time period, during 2014–2018 the differentials were attenuated with the maximum differential being 4% (Table 1).

There was statistically significant evidence ($p < 0.001$ for both time periods) that the association between area disadvantage and PSA screening rates varied by geographical remoteness (Table 2). This

Table 2
Age-standardized incidence rates, and adjusted[1] incidence rate ratios showing interaction between Remoteness and SEIFA categories on PSA screening rates for Australian men aged 50–69 years, 2005–09 and 2014–18.

	2005–09				2014–18			
Characteristics	Count[2] (%)	ASR[3]	IRR[4] [95% CI[5]]	P-value[6]	Count[2] (%)	ASR[3]	IRR[4] [95% CI[5]]	P-value[6]
Major City				< 0.001				< 0.001
Most Disadvantaged	132,059 (8.7)	670.39	1.00		114,810 (8.8)	483.95	1.00	
Disadvantaged	138,126 (9.1)	691.91	1.02 [1.01, 1.03]		122,083 (9.4)	505.72	1.03 [1.02, 1.04]	
Middle SES	209,472 (13.9)	699.45	1.04 [1.04, 1.05]		186,913 (14.3)	505.84	1.03 [1.03, 1.04]	
Advantaged	251,698 (16.7)	717.32	1.06 [1.05, 1.07]		219,296 (16.8)	503.53	1.02 [1.02, 1.03]	
Most Advantaged	306,814 (20.3)	708.65	1.05 [1.04, 1.06]		254,473 (19.5)	489.21	1.01 [1.00, 1.02]	
Outer Regional				< 0.001				< 0.001
Most Disadvantaged	82,475 (5.5)	636.89	1.00		69,442 (5.3)	462.52	1.00	
Disadvantaged	98,825 (6.5)	661.02	1.03 [1.02, 1.04]		85,966 (6.6)	476.73	0.98 [0.97, 0.99]	
Middle SES	76,205 (5.0)	658.32	1.02 [1.01, 1.03]		66,946 (5.1)	467.12	0.98 [0.97, 0.99]	
Advantaged	36,452 (2.4)	669.25	1.03 [1.01, 1.04]		32,422 (2.5)	463.28	1.00 [0.99, 1.01]	
Most Advantaged	11,691 (0.8)	686.25	1.04 [1.02, 1.06]		9816 (0.8)	431.85	0.92 [0.90, 0.94]	
Inner Regional				< 0.001				< 0.001
Most Disadvantaged	59,302 (3.9)	646.43	1.00		48,160 (3.7)	458.80	1.00	
Disadvantaged	53,050 (3.5)	597.33	0.97 [0.96, 0.98]		46,064 (3.5)	447.14	0.97 [0.96, 0.98]	
Middle SES	19,882 (1.3)	584.25	1.03 [1.01, 1.05]		17,532 (1.3)	425.86	0.97 [0.95, 0.98]	
Advantaged	10,096 (0.7)	582.60	1.09 [1.07, 1.11]		9821 (0.8)	424.32	1.03 [1.01, 1.05]	
Most Advantaged	3089 (0.2)	535.61	1.11 [1.07, 1.16]		2750 (0.2)	339.64	0.96 [0.92, 1.01]	
Remote				< 0.001				< 0.001
Most Disadvantaged	3196 (0.2)	414.67	1.00		2040 (0.2)	239.39	1.00	
Disadvantaged	6618 (0.4)	580.00	1.41 [1.33, 1.49]		5982 (0.5)	453.69	1.52 [1.42, 1.62]	
Middle SES	4352 (0.3)	432.60	1.37 [1.28, 1.45]		3688 (0.3)	315.41	1.43 [1.33, 1.53]	
Advantaged	470 (< 0.1)	383.20	1.69 [1.52, 1.89]		342 (0.0)	246.91	1.73 [1.53, 1.96]	
Most Advantaged	973 (0.1)	504.04	1.56 [1.43, 1.70]		782 (0.1)	305.96	1.39 [1.26, 1.53]	
Very Remote				< 0.001				< 0.001
Most Disadvantaged	2643 (0.2)	271.54	1.00		2124 (0.2)	193.65	1.00	
Disadvantaged	1633 (0.1)	537.32	1.38 [1.28, 1.48]		1547 (0.1)	458.41	1.37 [1.27, 1.48]	
Middle SES	727 (< 0.1)	370.64	1.39 [1.28, 1.52]		635 (< 0.1)	292.51	1.34 [1.22, 1.47]	
Advantaged	248 (< 0.1)	142.65	0.69 [0.61, 0.79]		264 (< 0.1)	91.99	0.60 [0.52, 0.68]	
Most Advantaged	Not Applicable[7]				Not Applicable[7]			

1. Adjusted for age group, state, and year.
2. Jervis Bay area was excluded due to no state information.
3. ASR = Age standardised rate per 1000 men.
4. IRR = Adjusted Incidence Rate Ratio.
5. CI = Confidence Interval.
6. P-value = Based on χ^2chi test, < 0.05 is considered as significant.
7. There are no very remote SA2s in Australia that are also within the most advantaged socioeconomic category.

uncertain benefits and recognised potential harms, the results of PSA screening may then require long-distance travel for further clinical work-up or treatment [5,21].

Australia's Medicare database was established and maintained for administration purposes, rather than for the purposes of research. As such, the impact of coning, in which the number of claims made per episode of care is capped to limit the cost of Medicare benefits paid in a single episode, may have impacted the observed results. If, for example, men living in regional and remote areas combine multiple tests during a single visit general practitioner visit, the PSA test (which is relatively inexpensive) might be excluded from the claims in favour of other, more expensive tests. Even still, it has been estimated that up to 40% of PSA tests might be coned [22]. The extent to which coning varies by geographical area is not known. However, a NSW study showed that men who visited general practitioners more often were more likely to have a PSA test [23], while Australians living in outer regional and remote areas were 2.5 and 6 times more likely to report that not having a general practitioner nearby was a barrier to seeing one [24]. In addition, the use of general practitioners is higher in major city areas, and the number of non-hospital medical services per capita reduces with increasing remoteness [24]. Combined, these suggest that while coning may explain at least some of the observed disparities in PSA screening by remoteness, the consistency of temporal trends across remoteness categories suggests the recent reductions in each category are unlikely to be impacted by coning.

We specifically focussed on screening participation among Australian men aged 50–69 for consistency with the Australian guidelines [6], which in turn is guided by the previous evidence [25] that any mortality benefit from the early diagnosis of prostate cancer due to PSA testing is not seen within 7 years of testing. However, that there is some evidence of a mortality benefit after 7 years of PSA testing means that the net benefit of PSA testing is equivocal for those men who are likely to live another 7 years. With life expectancy among Australian men continuing to increase [26], the substantial numbers of men aged over 70 who have had a PSA test [5] is not surprising, and it is important that guidance be provided for these men and their clinicians as to their decision making process.

The debate over the most appropriate use of the PSA test for screening purposes is likely to continue. While the 2016 Australian Guidelines [6] and similar international guidelines [7–10] recommend informed decision making regarding testing for men, a number of more recent changes to the way in which men are diagnosed and treated for early stage prostate cancer have potentially altered the balance of harms and benefits of screening. The changes include the routine use of MRI in the diagnosis of men, a shift in the technical approach to prostate biopsy from transrectal to transperineal thus reducing the risk of biopsy related infection, and evidence of a significant proportion of men with low-risk disease being managed with active surveillance [27]. As a result, the guidelines are in need of review to account for these recent changes in screening, diagnosis, and treatment of prostate cancer. The patterns described in this paper provide the most relevant background to any proposed changes to Australia's approach to prostate cancer screening.

Table 1
Characteristics of PSA screening participation[1] among Australian men aged 50–69 years for 2005–09 and 2014–18.

Year	2005–09				2014–18			
Category	N[2]	Crude %[3]	ASR/1000[4]	IRR[5] [95% CI]	N[2]	Crude %[3]	ASR/1000[4]	IRR[5] [95% CI]
Australia	1,510,096	67.6	676.4		1,303,898	48.3	481.6	
Age Group								
50–59 years	898,770	68.6	686.0	1.00	704,343	47.5	474.5	1.00
60–69 years	611,326	66.2	661.7	0.92 [0.92, 0.92]	599,555	49.2	492.4	0.92 [0.92, 0.92]
State / Territory[5]								
New South Wales	485,420	66.3	663.1	1.00	400,188	46.0	459.7	1.00
Victoria	387,415	71.7	717.4	1.15 [1.14, 1.15]	340,773	51.2	510.1	1.23 [1.23, 1.24]
Queensland	277,880	62.5	626.5	0.91 [0.91, 0.92]	270,909	49.7	496.4	1.19 [1.19, 1.20]
South Australia	131,958	74.9	748.8	1.34 [1.34, 1.35]	109,419	53.1	525.6	1.38 [1.37, 1.39]
Western Australia	152,827	67.1	671.0	1.11 [1.10, 1.11]	137,614	48.8	487.5	1.16 [1.15, 1.16]
Tasmania	42,219	71.5	715.5	1.28 [1.27, 1.30]	22,094	32.2	325.0	0.63 [0.62, 0.64]
Northern Territory	7118	35.5	355.6	0.67 [0.66, 0.69]	5357	22.2	221.7	0.58 [0.56, 0.60]
Australia Capital Territory	25,259	74.7	745.8	1.15 [1.14, 1.17]	17,544	44.0	439.1	0.96 [0.95, 0.98]
Remoteness of residence								
Major City	1,038,169	70.1	701.7	1.00	897,575	49.8	497.6	1.00
Inner Regional	305,648	65.4	655.5	0.93 [0.93, 0.93]	264,592	46.8	467.1	0.96 [0.96, 0.97]
Outer Regional	145,419	61.2	611.9	0.91 [0.90, 0.91]	124,327	44.5	443.1	0.94 [0.94, 0.95]
Remote	15,609	48.2	482.6	0.76 [0.75, 0.77]	12,834	34.6	343.7	0.78 [0.77, 0.79]
Very Remote	5251	31.5	317.4	0.52 [0.50, 0.53]	4570	23.3	234.1	0.58 [0.57, 0.60]
Area Socio-Economic Status								
Most Disadvantaged	279,675	64.1	641.3	1.00	236,576	46.4	461.9	1.00
Disadvantaged	298,252	65.9	659.3	1.05 [1.05, 1.06]	261,642	48.5	483.6	1.02 [1.02, 1.03]
Middle SES	310,638	67.3	673.4	1.09 [1.08, 1.09]	275,714	48.7	485.6	1.03 [1.02, 1.03]
Advantaged	298,964	70.2	702.2	1.11 [1.10, 1.11]	262,145	49.3	491.6	1.04 [1.03, 1.04]
Most Advantaged	322,567	70.5	704.7	1.10 [1.09, 1.10]	267,821	48.4	483.8	1.00 [0.99, 1.00]

Notes:
1. Jervis Bay area was excluded due to no state information.
2. Total number of men receiving at least one PSA test during the time period.
3. Percentage of men aged 50–69 years (not age adjusted).
4. Directly age-standardised rates using the 2001 Australian Standard Population. Note that age-specific ASR are equivalent to crude rates.
5. IRR = Adjusted Incidence Rate Ratio

interaction was highlighted by the limited variability across quintiles of socioeconomic disadvantage in major city, inner regional and outer regional areas, however among remote areas PSA screening rates were particularly low in the most disadvantaged areas while the rates in very remote areas were low in most disadvantaged and advantaged areas. There were generally similar trends over time between the different combinations of remoteness and area disadvantage (Supplementary Fig 1, Supplementary Table 2), and given the relatively low number of PSA tests conducted among men in remote and very remote areas compared to men in the other remoteness categories, some caution is needed when interpreting these interactions.

4. Discussion

Using a population-based cohort of nearly three million Australian men who had at least one Medicare-funded PSA screening test, we found consistency in PSA screening patterns over time across states and territories, geographical regions, and area-level socioeconomic status. This suggests that the key factors influencing these trends in the use of PSA screening are more likely to be driven at a national level such as clinical practice guides, rather than being influenced by local or regional factors. There were, however, key differences in the prevalence of PSA screening across population groups in the five years up to 2018, with higher rates among men aged 50–59 compared to those aged 60–69, men living in major cities compared to regional and remote areas, and men living in Western Australia, Victoria, Queensland and South Australia compared to other States/Territories, while differences by area level disadvantage were less pronounced compared with the peak screening period of 2005–2009, particularly in non-remote areas.

Importantly, this work provides more contemporary information about the differences in PSA screening participation across geographical population subgroups than what has been reported previously by Calopedos and colleagues [5]. While most of the population-subgroup patterns have remained, disparities by area level socioeconomic status have decreased over the last decade. In addition, while reductions in PSA screening rates over the last decade have been previously reported for Australia [5], Canada (Winnipeg) [15], Argentina [16], and the United States [17], our work highlights that the temporal reductions in PSA screening in Australia are generally consistent across broad geographical regions of remoteness, area socioeconomic disadvantage quintiles and state/territory jurisdictions.

Shared decision making has been recommended since the mid-1990 s[18,19] This suggests that the widespread decline in PSA testing may be less due to changes in shared decision making and more due to changes in the recommendations regarding informed decision making from international organisations such as the United States Preventive Services Task Force and Royal Australian College of General Practitioners that happened around the same time [20].

The lower rates of PSA screening among men living in the less accessible regional and remote areas of Australia are consistent with differences reported in previous years [5,11], although a recent systematic review [13] found the patterns by remoteness were not consistent internationally. One possible explanation for the differences by remoteness, particularly in Australia with often large distances to medical services, is that men and general practitioners in regional and remote areas might be more focused on medical tests or interventions that are motivated by existing symptoms rather than including pre-emptive tests or interventions such as PSA screening. In addition to

5. Conclusions

Despite current recommendations in Australia supporting individual informed decision-making regarding PSA testing rather than the use of the test as a screening tool, about half of Australian men aged 50–69 years had at least one Medicare-funded PSA test over the five-year period up to 2018. The consistent decreasing trends across State/Territory, geographical remoteness and area-level disadvantage are consistent with a greater awareness of the current guidelines for clinical practice in Australia. On current evidence, more efficient, informed targeted use of PSA testing and post-testing follow-up, in relation to both the potential benefits and harms, could help improve prostate cancer outcomes and reduce inequities. Prostate cancer remains the second-leading cause of cancer death in Australian men, with significant disparities in mortality between men from different regional and socio-economic groups. More research is urgently needed on ways to utilise existing technologies, including targeted use of PSA testing and patient management, diagnostic technology such as MRI and on the development of improved risk assessment tools.

CRediT authorship contribution statement

(see https://www.elsevier.com/authors/policies-and-guidelines/credit-author-statement).

Ankur Kohar: Methodology, Formal analysis, Writing – original draft. **Susanna M. Cramb:** Writing – review & editing. **Kristen Pickles:** Writing – review & editing. **David P. Smith:** Writing – review & editing, Supervision. **Peter D. Baade:** Conceptualization, Data curation, Writing – review & editing, Supervision.

Declaration of interest

None.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.canep.2023.102338.

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Appendix C: Published manuscript of Chapter 4

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Original Research

Spatial patterns of prostate-specific antigen testing in asymptomatic men across Australia: a population-based cohort study, 2017–2018

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ABSTRACT

Objectives: In Australia, while prostate-specific antigen (PSA) testing rates vary by broad area-based categories of remoteness and socio-economic status, little is known about the extent of variation within them. This study aims to describe the small-area variation in PSA testing across Australia.
Study design: This was a retrospective population-based cohort study.
Methods: We received data for PSA testing from the Australian Medicare Benefits Schedule. The cohort included men (n = 925,079) aged 50–79 years who had at least one PSA test during 2017–2018. A probability-based concordance was applied across multiple iterations (n = 50) to map each postcode to small areas (Statistical Areas 2; n = 2,129). For each iteration, a Bayesian spatial Leroux model was used to generate smoothed indirectly standardized incidence ratios across each small area, with estimates combined using model averaging.
Results: About a quarter (26%) of the male population aged 50–79 years had a PSA test during 2017–2018. Testing rates among small areas varied 20-fold. Rates were higher (exceedance probability>0.8) compared with the Australian average in the majority of small areas in southern Victoria and South Australia, south-west Queensland, and some coastal regions of Western Australia but lower (exceedance probability<0.2) in Tasmania and Northern Territory.
Conclusions: The substantial geographical variation in PSA testing rates across small areas of Australia may be influenced by differences in access to and guidance provided by clinicians and attitudes and preferences of men. Greater understanding of PSA testing patterns by subregions and how these patterns relate to health outcomes could inform evidence-based approaches to identifying and managing prostate cancer risk.

Introduction

Prostate-specific antigen (PSA) testing is regularly used opportunistically to test asymptomatic men for the risk of prostate cancer;[1] however, it has a low positive predictive value that makes it difficult to distinguish between cancerous and benign prostatic conditions.[2] Consequently, this is a test that is undertaken ad hoc rather than in organized population-wide screening programs.[3]

In 2016, the Prostate Cancer Foundation of Australia and Cancer Council Australia released national guidelines that recommend if men at average risk of prostate cancer aged 50–69 years make an informed decision to have a regular PSA test, it should be offered every 2 years.[4] Summary guidelines from the Royal Australian College of General Practitioners[5] advise general practitioners (GPs) that due to screening of asymptomatic men with PSA not being recommended, GPs are not obliged to offer the test. Most international guidelines on screening and early detection of prostate

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cancer are similar to Australian Prostate Cancer Foundation of Australia guidelines, including the United States,[6] Europe,[7] Canada,[8] and the United Kingdom.[9]

Higher PSA testing rates have been reported among men living in socio-economically advantaged areas compared with those living in disadvantaged areas. In addition, testing rates have been shown to be higher for men living in urban areas compared with rural areas.[10,11] However, the lack of robust estimates for PSA testing at the small area level makes it difficult to interpret prostate cancer incidence and survival information in recent disease atlases, such as the Australian Cancer Atlas.[12]

This study, using PSA testing data from the Medicare Benefits Schedule, Australian Government's universal health funding scheme, aims to address this gap in knowledge. It will quantify how PSA testing rates vary by small geographical areas across Australia during the period following the release of the 2016 Australian clinical guidelines on PSA testing.[4]

Methods

Data

Medicare-reimbursed PSA test data for men aged 50–79 years, tested in Australia between January 2017 and December 2018, were obtained from the Commonwealth Department of Health (under the Health Insurance Act 1973). In Australia, the Medicare Benefits Schedule reimburses item number 66655, since it is specifically used for detecting asymptomatic prostate disease in men, which will refer to it as a "screening" test. The unit-record data extract contained a deidentified unique person-level ID number, postcode of residence recorded by Medicare Benefits Schedule at the time of PSA test, 10-year age group, year, and month of the conducted screening test.

Geography

A probability-based geographical correspondence file[13] was used to transform the 2011 postcode information into Statistical Areas 2 (SA2s) information from the 2011 Australian Statistical Geography Standard (ASGS). In this study, the term SA2 will be referred to as "small area".

The correspondence file, containing the proportions of the population within each postcode that were allocated to each small area, was merged with the postcode-specific PSA data set. The postcode for each record was then randomly assigned to a small area according to these probabilities based on the uniform distribution, with the random process carried out 50 times.

The small areas were categorized by the ABS Remoteness Index and the Index of Relative Socio-Economic Advantage and Disadvantage.[14,15]

Exclusions

We selected PSA tests that were undertaken on men aged 50–79 years during the period 2017–2018 (Fig. 1). Postcodes that were exclusively used for post office boxes were excluded because it was impossible to determine its exact geographical catchment area. This study is based on the number of men rather than the number of screening tests; therefore, only the first test per individual during the study period was considered. Records where postcodes did not match with the postcode-small area concordance were removed from the cohort.

We excluded records from 67 SA2s because of male population of three men or less or were classified as remote islands ($n = 3$). The final data set included 2,129 small areas.

Population

Estimated resident population[16] by small area for men aged 50–79 years during 2017–2018 were concorded from 2016 ASGS classification to the 2011 ASGS using a population-weighted correspondence file.[17] The included 2,129 small areas had a median population of 1,479 (interquartile range: 895–2,296) men.

Statistical analyses

Spatial models

Spatial data commonly exhibit autocorrelation, or clustering, and ignoring this can lead to biased results.[18] To allow for spatial autocorrelation in the data, three Bayesian spatial models, all variants of the Intrinsic Conditional Auto-Regressive model, were initially considered to model the standardized incidence ratio (SIR): Leroux,[19] Besag, York, and Mollié (BYM),[20] and Localised.[21] Each of these models allow for autocorrelation through random effect terms on each area. Of the three, the Leroux model was preferred over the Localised model because of its more stable estimates (Figure SF 1a and b). Also, the Leroux model is more parsimonious than the BYM model because it has only one spatial random effect parameter for each area, rather than the two per area in BYM, yet still allows for both spatial autocorrelation and random variation between areas.

The Leroux model (File SFile 1) applied a Poisson distribution with an offset of the logged expected counts in each small area. Expected counts were calculated by multiplying national age-specific rates (total observed count/total population) by the age-specific population in each small area, then summing all age-specific expected counts. The expected counts and observed counts were input to the Bayesian model to calculate smoothed SIR estimates for each small area compared with the Australian average.

We undertook modeling using the CARBayes package (version 5.2.3)[22] in R (R Core Team (2020), version 4.0.0),[23] which uses Markov Chain Monte Carlo (MCMC) methods for computation. As Bayesian spatial models are too complex to compute analytically, MCMC algorithms are used to sample from probability distributions to approximate the desired distribution. There were 150,000 MCMC iterations run, with the first 50,000 iterations excluded as burn-in before selecting every 10th iteration to generate 10,000 iterations for each model. These small area–specific iterations from 50 models were combined with equal weighting, resulting in 500,000 iterations for each small area. Most small area results are based on the median value (SIR) of these 500,000 iterations. Markov chain convergence was checked by visual inspection of trace plots (Figure SF 2).

Visualization

Maps

The R package ggplot2 (version 3.3.6)[24] was used to visualize the results. The color scale on the SIR maps ranged from 0.67 to 1.5, including color breaks at 0.8, 1, and 1.25. Blue and red shades indicate low and high PSA screening rates, respectively, compared with the Australian average, as shown in yellow.

The exceedance probability is equal to the posterior probability of the modeled SIR being above 1 for each small area.[25] In the exceedance probability thematic map, green represents low (<20%) exceedance probabilities and suggests a true lower-than-average PSA screening rate, and purple represents high (>80%), suggesting a real higher-than-average PSA screening rate.

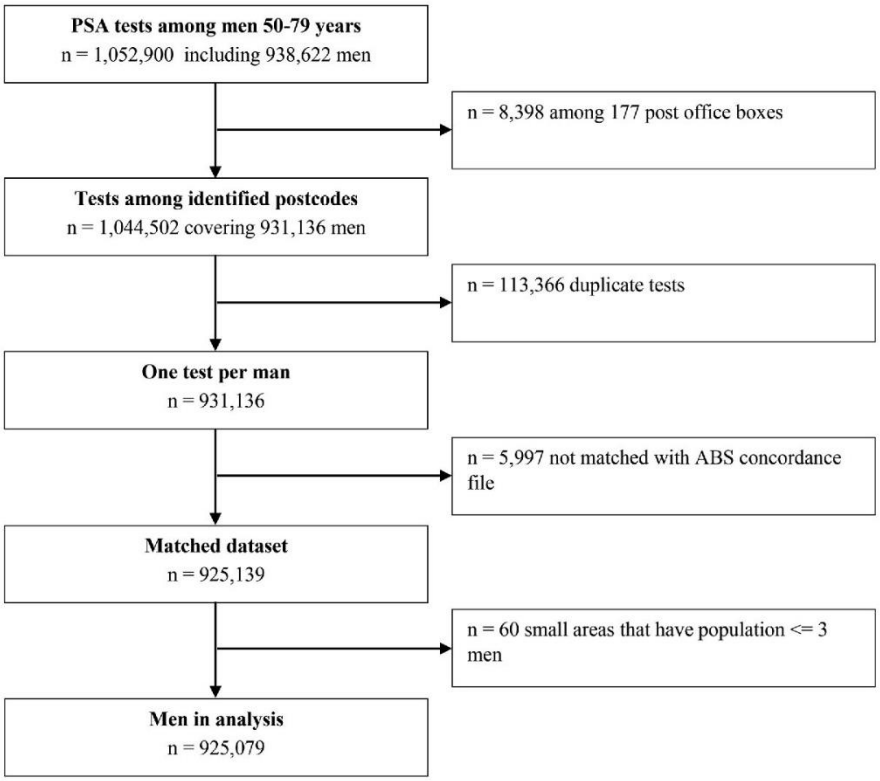

Fig. 1. Flowchart showing selection of men in analysis aged 50–79 years, Australia, 2017–2018.

Graphs

Boxplots were used to show how the small area–specific distribution of modeled estimates varied according to the categories of remoteness, socio-economic status, states/territories, and greater capital cities.

Results

During 2017–2018, 1,052,900 PSA screening tests were performed on 938,622 Australian men aged 50–79 years (Fig. 1). Of these, 8,398 (0.80%) screening tests were removed due to the postcode containing only post office boxes (n = 177), 113,366 (10.77%) were duplicate screening tests, 5,997 (0.57%) tests that were linked to a postcode that did not match with ABS postcode to small area correspondence files, and 60 (<0.01%) tests were in small areas that had male population aged 50–79 years less than or equal to three. The final data set included 925,079 men (one PSA test per man) aged 50–79 years, tested during 2017–2018, giving an overall crude screening rate of 260.6 per 1000 (26.1%) men.

The highest population percent of men screened was among men aged 60–69 (Table 1). Population screening percentages decreased substantially with remoteness, whereas screening rates were relatively consistent across the area-level socio-economic categories. Population PSA screening rates by states and territories were between 23.4% and 31.2%, except for lower rates in Tasmania (16.2%) and the Northern Territory (11.1%).

PSA screening patterns by smaller areas

There was a 20-fold (=2/0.1) variation in PSA screening rates (based on the modeled SIRs) across small areas of Australia (Fig. 2), with low (SIR <1) PSA screening rates in many remote areas. Approximately 5.3% of the small areas had screening rates that were more than 50% lower (SIR <0.5) than the Australian average (SIR = 1), and these were more likely to be outside capital cities, in remote and very remote areas, and most disadvantaged areas in Tasmania and Northern Territory (Table ST 1). The screening rates in about 1.8% of small areas were more than 50% higher (SIR >1.5) than average (Table ST 1). Sensitivity analyses showed similar SIR estimates by small area regardless of the choice of hyperpriors within the statistical models (Figure SF 3a and b).

Northern Territory (65/66 small areas) and Tasmania (95/95) had consistently lower screening rates than the national average. In contrast, screening rates were higher than the national average in the majority of small areas in the south of Victoria (276/427), South Australia (134/163), south-west Queensland (268/512), and coastal areas of Western Australia (150/234), along with some small areas in north-east New South Wales (144/526; Fig. 2). Considerable

Table 1
Demographic characteristics of men aged 50–79 years having at least one Medicare-funded prostate-specific antigen screening test, Australia, 2017–2018.

Characteristics	Men tested (%)	Population[a] (%)	Population percent of men tested (%)
Australia	925,079 (100)	3,549,392 (100)	26.1
Age group (years)			
50–59	354,339 (38.3)	1,494,873 (42.1)	23.7
60–69	358,708 (38.8)	1,242,648 (35.0)	28.9
70–79	212,032 (22.9)	811,871 (22.9)	26.1
Remoteness			
Major city	633,310 (68.5)	2,353,258 (66.3)	26.9
Inner regional	191,095 (20.7)	761,985 (21.5)	25.1
Outer regional	88,979 (9.6)	366,005 (10.3)	24.3
Remote	8,673 (0.9)	45,084 (1.3)	19.2
Very remote	3,022 (0.3)	23,059 (0.6)	13.1
Socio-economic status[b]			
Most advantaged	187,547 (20.3)	714,676 (20.1)	26.2
Advantaged	186,199 (20.1)	691,652 (19.5)	26.9
Middle SES[c]	195,772 (21.2)	743,578 (20.9)	26.3
Disadvantaged	189,307 (20.5)	717,915 (20.2)	26.4
Most disadvantaged	166,181 (18.0)	681,437 (19.2)	24.4
State/territory[d]			
New South Wales	269,171 (29.1)	1,143,786 (32.2)	23.5
Victoria	249,597 (27.0)	880,935 (24.8)	28.3
Queensland	189,527 (20.5)	719,050 (20.3)	26.4
South Australia	84,978 (9.2)	271,968 (7.7)	31.2
Western Australia	101,958 (11.0)	363,522 (10.2)	28.0
Tasmania	14,741 (1.6)	90,845 (2.6)	16.2
Northern Territory	3,143 (0.3)	28,240 (0.8)	11.1
Australian Capital Territory	11,952 (1.3)	50,969 (1.4)	23.4

[a] Average estimated resident population of Australia for 2017–2018.
[b] Records were excluded that do not have Index of Relative Socio-Economic Advantage and Disadvantage.
[c] Middle SES means middle socio-economic status.
[d] Records from Jervis Bay area were excluded due to classified as Other Territory.

variation in screening rates was evident both between and within capital cities. In most small areas within Sydney, PSA rates were lower than the national average, along with those within Hobart, Darwin, and Canberra, whereas higher-than-average PSA screening rates were observed in many areas within Melbourne, Brisbane, Adelaide, and Perth (Fig. 2 and SF 4b).

The majority (83%) of small areas had a screening rate likely to differ from the national average (Fig. 3). PSA screening in 957/2129 small areas was considered likely to be lower (<20% probability of being higher, Fig. 2) than the national average and higher (>80% probability, Fig. 2) in 814/2129 small areas. Screening rates in the remaining 358 small areas were considered unlikely to be different from the national average.

Distribution of small area–specific estimates within broader areas

There was no difference in the distribution of small area–specific estimates across categories of socio-economic status (Fig. 4a), and this was consistent outside and inside greater capital cities (Figure SF 4c). However, within some capital cities, including Hobart and Adelaide, there was a suggestion of contrasting patterns of socio-economic gradients (Figure SF 4e), whereas more populated capital cities of Sydney, Melbourne, and Brisbane had little variation. Likewise, there was less variability between greater capital cities and outside greater capital cities (Fig. 4d), whereas small areas within greater capital cities and outside greater capital cities of Victoria and South Australia consistently had higher screening rates than the national average (Figure SF 4a and b). The small area–specific distribution shows lower screening rates and increasing heterogeneity within categories with rising remoteness (Fig. 4b) as well as for outside greater capital cities and greater capital cities by remoteness (Figure SF 4d). While screening rates in remote areas were generally lower than the national average, there were some notable exceptions in remote areas in southern South Australia and northwest Victoria (Fig. 4c), which had very high PSA screening rates compared with the national average (Figs. 2 and 3).

Discussion

This is, to our knowledge, the first population-based study to map and describe the substantial variation in PSA screening tests in Australia by small geographical areas and the characteristics of this variation within broader socio-economic groups, remoteness categories, and states and territories.

Our results of testing patterns relating to the broad geographical classifications of urban and rural differences are consistent with international studies from Switzerland,[26] New Zealand,[27] and the United Kingdom.[28] These studies found that men living in urban areas and regions with high health service supply had higher PSA screening rates. Although we found limited variation between area-based socio-economic categories, other international studies[26,28] have reported generally increased use of PSA testing among men living in more affluent areas.

Although previous research[10,29] has demonstrated variation between large geographical regions or remoteness categories in Australia, the results of this study highlight the extent of variation within those broad regions. For example, the variation within socio-economic categories indicates that the PSA screening rate in some "disadvantaged" small areas was higher than in some "advantaged" small areas, and vice versa. In addition, not all small areas within remote and very remote categories had lower PSA screening rates than the Australian average. This emphasizes the importance of examining geographical variation between smaller geographical areas; otherwise, the heterogeneity within the larger regions is ignored.

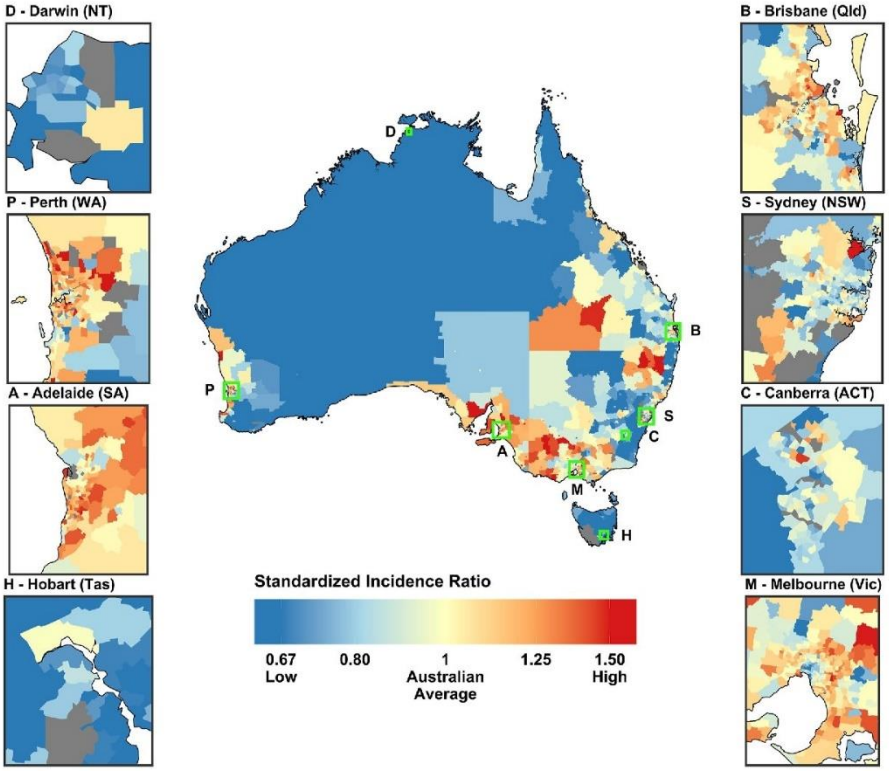

Fig. 2. Standardized incidence ratios (SIRs) of prostate-specific antigen (PSA) screening by small area[a,b], Australia, 2017–2018. [a]Insets show capital cities of each state and territory. [b]NT, Northern Territory; WA, Western Australia; SA, South Australia; Tas., Tasmania; Qld., Queensland; NSW, New South Wales; ACT, Australian Capital Territory; Vic., Victoria.

The current Australian prostate cancer screening guidelines[4,5] do not incorporate any geographical area characteristics. Therefore, if the decision-making processes for men and their GPs across Australia consistently followed the recommended guidelines and had equity in access to the resulting follow-up consultations and procedures, we might expect only a small amount of geographical variation in testing. Thus, while untangling the likely multifaceted reasons for the substantial geographical variation observed in our study requires more detailed investigations, it is likely that at least some of the reasons would relate to local area influences rather than factors operating at the national level. These could include variations in behaviors and attitudes of GPs, who are the gatekeeper to medical services, including PSA testing,[5] as well as factors relating to men living in each area, such as the activities of local PSA testing advocacy groups and accessibility to primary care and specialist services.

In general, although GPs in Australia have a good understanding of the benefits and limitations of PSA screening, many have limited knowledge of the current guidelines.[30] Previous studies have highlighted substantial variation in attitudes and practices by Australian GPs toward PSA testing,[31,32] so this may have contributed to our observed results.

Some explanations proposed for this variability between Australian GPs relate to the uncertainty about the evidence base for PSA testing and the ambiguity in PSA screening guidelines,[31] personal beliefs or experiences relating to PSA screening,[30] clinician motivation to avoid either overdiagnosis or underdiagnosis, perceived medicolegal risks during decision-making process,[31] and financial implications and incentives.[32] This variation between Australian GPs appears to be in contrast to GPs in the United Kingdom, who are advised not to proactively initiate the screening discussion with men; however, they can provide information if specifically requested.[33] UK GPs are more likely than Australian GPs to follow organizational guidelines that recommend to only provide PSA testing at the patient request.[33,34] This may suggest that in terms of PSA testing, Australian GPs operate with greater levels of individual discretion, contributing to the large geographical variation in PSA screening observed in this study.

Another possible explanation for the observed variation could be in Australian men's knowledge, attitudes, and behaviors regarding prostate health and prostate cancer testing, although little is known about how this varies by geography. Previous surveys tend to suggest low levels of knowledge about prostate cancer risks. For example, a survey conducted among Australian men in 2012[35] reported that prostate cancer was considered to be the most important health issue facing Australian men by 51% of respondents and that 55% of men felt they knew at least a reasonable amount about testing for prostate cancer. About three-fourths (72%) indicated they would "probably or definitely" have a PSA test sometime in the future.[35]

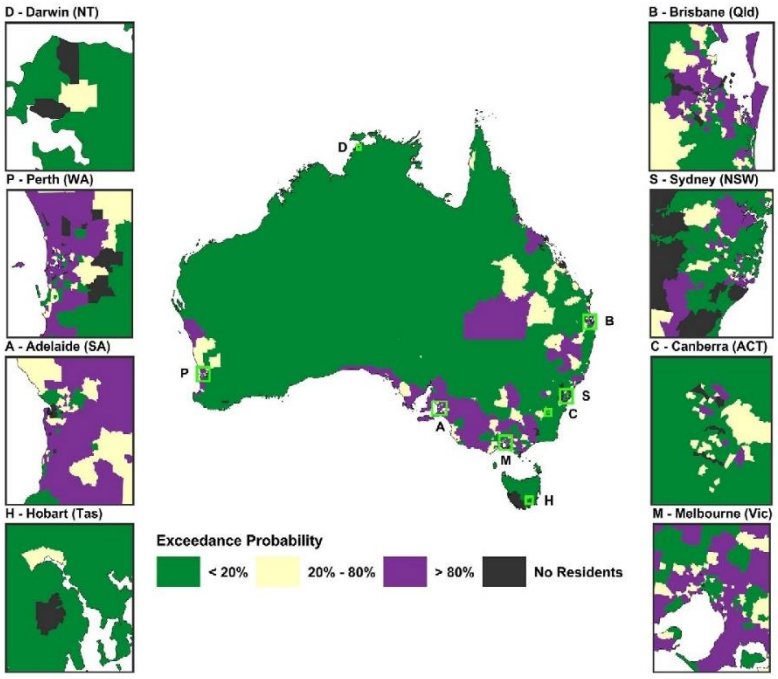

Fig. 3. Exceedance probabilities of prostate-specific antigen (PSA) screening by small area[a,b], Australia, 2017–2018. [a]Insets show capital cities of each state and territory. [b]NT, Northern Territory; WA, Western Australia; SA, South Australia; Tas., Tasmania; Qld., Queensland; NSW, New South Wales; ACT, Australian Capital Territory; Vic., Victoria.

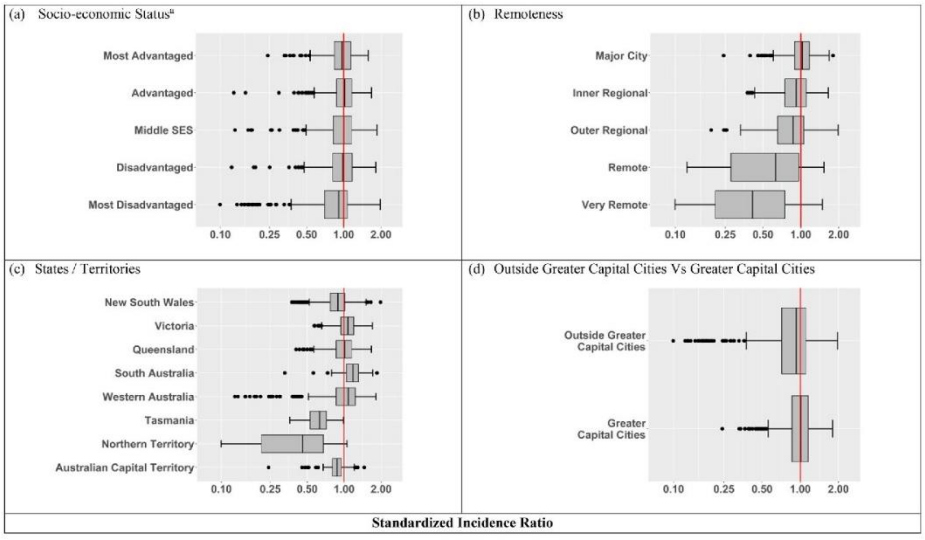

Fig. 4. Standardized incidence ratio (SIR) of prostate-specific antigen (PSA) screening for 2129 small area during 2017–2018 grouped by (a) socio-economic status, (b) remote areas, (c) states/territories, (d) outside greater capital cities vs greater capital cities. [a]Middle SES in plot means middle socio-economic status.

Advocacy and awareness campaigns, particularly if locally targeted, may contribute to the observed geographic variability in screening participation. While some have a national focus, others have a local or regional focus. Various multistate awareness programs[36] include the aim of raising awareness in men about prostate cancer and PSA testing. Other more targeted community campaigns use celebrity or sporting identities to endorse community participation in screening[37] or involve prominent members of the local community, encouraging greater involvement in testing in communities where mortality rates are high,[38] such as the "Little Prick" campaign in the Hunter region of New South Wales.[39] Although there are no data on the varying impact of these campaigns on PSA testing rates by geographical area, it is plausible to expect that the reach and impact of campaigns on men's PSA testing behavior would not be consistent across the country.

Some of the variations in PSA screening observed between small geographical areas, particularly the patterns by remoteness, may also result from differences in access to primary care practitioners, or GPs, who usually instigate the screening pathway. Outlying communities are well documented as having a lower GP supply (70.5 GPs per 100,000 people in very remote areas compared with 103.5 per 100,000 in major cities),[40] and men in rural areas typically have longer wait times to see a GP.[41] Moreover, there are fewer medical specialists (22 per 100,000 people) in very remote areas compared with major cities (143 per 100,000 people).[41] This may impact rural residents' decision whether to be tested because they would likely have to travel great distances to access follow-up diagnostic and treatment services.[41]

Strengths and limitations

One of the main strengths of this study was the use of population-based data that captured the vast majority of PSA tests among the eligible Australian male population and is not subject to known limitations of self-reported data.[42] In addition, reporting on person-based screening history, rather than test-based use as in other studies,[43] removed any impact of multiple tests over the 2-year study period. Also, the Bayesian modeling approach provides more robust estimates of the underlying small-area rates rather than being unduly impacted by the increased random fluctuations associated with small area data.[44]

Medicare claims are restricted to benefits paid to pathology during a single episode of care, known as episode coning. It is possible that coning results in differential testing patterns based on geography. For example, it may be more common in less accessible areas because men who travel greater distances to see a GP might combine multiple more expensive tests into a single visit.[45] However, it is less likely to explain small area variation compared with broader variation between urban and regional or remote areas. While up to 19% of PSA tests may be coned and hence not included in the Medicare data,[45] it is not known to what extent this would vary by small geographical area. In addition, Medicare data only captured the postcode of residence, and the probabilistic allocation of certain postcodes to multiple SA2s may have misassigned some cases to an incorrect area. For this study, the data (2017–2018) were received in the fourth quarter of 2019. We were not able to receive an updated data extract before the completion of this study. In addition, by focusing on a period before the COVID-19 pandemic, it enables us to access the underlying PSA testing patterns independently of any behavioral changes through the various COVID-19 management directives.

In summary, this population-based study identified substantial variation in the PSA screening participation rate by small geographical areas across Australia. The challenge remains to ensure that all males at risk of prostate cancer have access to the same clinical decision-making process, regardless of where they live. This will likely require the development and implementation of more effective resources, policies, and communication strategies that have broader engagement and application than those currently in place.

Author statements

Ethical approval

The ethics approval for this study was obtained from Griffith University Human Research Ethics Committee (GU Ref no: 2017/777).

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Competing interests

None declared.

Data statement

Original data are not able to be supplied by the authors due to data sharing agreement with the custodians. Those seeking original data are advised to contact the custodians. Modeled estimates may be available on reasonable request to the principal investigator (P.B.).

Author contributions

A.K., S.C., D.S., and P.B. were responsible for the conceptualization and design of the study. P.B. was responsible for data acquisition. A.K., S.C., D.S., and P.B. were responsible for data analysis and preparing the tables and figures. All authors were responsible for writing and editing the article.

Author agreement

This original article comprises unpublished work and is not under consideration elsewhere. All authors of this study have read and agreed to the submission.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.puhe.2023.01.039.

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Appendix D: List of conference presentations during Ph.D. candidature

During my candidacy, I have regularly showcased my PhD research at several online and in-person conferences, as well as competitions.

1. Kohar A, Smith DP, Baade PD, Cramb SM, editors. The Geography of Prostate Specific Antigen Testing in Australia: Spatial Analyses of Medicare Claims Data. 2022 Postgraduate Student Cancer Research Symposium; 2022, 17th November; Cancer Research Network at the University of Sydney, Australia.

2. Kohar A, Cramb SM, Smith DP, Baade PD, editors. Spatial Analysis of Medicare Reimbursed Prostate-Specific Antigen Tests by Small Areas in Australia. 2nd Early Career Researcher Cancer Epidemiology Conference; 2022, 15th November; Federation of Cancer Councils and Australasian Epidemiological Association (Online conference), Australia.

3. Kohar A, Cramb SM, Baade PD, Smith DP, editors. How the reductions in PSA testing participation in Australia vary by geographical location. 1st Cancer Council Epidemiology Conference; 2021, 9th February; Federation of Cancer Councils (Online conference), Australia.

4. Kohar A, Cramb SM, Smith DP, Baade PD, editors. How the reductions in PSA testing participation in Australia vary by geographical location. Postgraduate & ECR Cancer Research Symposium 2020; 2020, 10th, 17th, and 24th November, The University of Sydney, Australia.

5. Kohar A, Cramb SM, Baade PD, Smith DP, editors. Prostate Specific Antigen (PSA) Testing Across Australia: Does It Vary by Geographical Area and Over Time? 3-Minute Thesis Competition; 2019, 29 November; Cancer Council NSW, Australia.

Appendix E: Other research publications during Ph.D. candidature

During the course of my PhD research, I additionally provided significant inputs to various cancer research publications. Although these publications are relevant to my area of study, they are not directly incorporated in this thesis.

1. Chiam, K., Crowe, J., Grogan, P., Vaneckova, P., Kohar, A., Mazariego, C., Nair-Shalliker, V., & Smith, D. P. (2023). Making informed decisions about prostate cancer testing: Locally tailored factsheets on the burden of prostate cancer in Australia. *Australian journal of general practice*, *52*(3), 102–105. https://doi.org/10.31128/AJGP-07-22-6500

2. Feletto, E., Kohar, A., Mizrahi, D., Grogan, P., Steinberg, J., Hughes, C., Watson, W. L., Canfell, K., & Yu, X. Q. (2022). An ecological study of obesity-related cancer incidence trends in Australia from 1983 to 2017. *The Lancet regional health. Western Pacific*, *29*, 100575. https://doi.org/10.1016/j.lanwpc.2022.100575