Geographic distribution of malignant mesothelioma incidence and survival in Australia

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Colour figures: Figures 2, 3 and 4

Abstract

Objectives: To understand the geographic distribution of and area-level factors associated with malignant mesothelioma incidence and survival in Australia.

Materials and Methods: Generalised linear models and Bayesian spatial models were fitted using population registry data. Area-level covariates were socioeconomic quintile, remoteness category and state or territory. The maximised excess events test was used to test for spatial heterogeneity.

Results: There was strong evidence of spatial differences in standardised incidence rates for malignant mesothelioma but survival was uniformly poor. Incidence rates varied by state or territory and were lower in remote areas. Patterns in the geographic distribution of modelled incidence counts for malignant mesothelioma differed substantially from patterns of standardised incidence rates.

Conclusions: Geographic variation in the modelled incidence counts of malignant mesothelioma demonstrates varying demand for diagnostic and management services. The long latency period for this cancer coupled with migration complicates any associations with patterns of exposure, however some of the geographic distribution of diagnoses can be explained by the location of historical mines and asbestos-related industries.

Key words

Mesothelioma; cancer; incidence; survival; spatial modeling; statistical modeling.

1. Introduction[1]

Malignant mesothelioma (hereafter referred to as "mesothelioma") is a cancer of the tissue lining the cavities of the torso[1] and usually affects the lungs ("pleural", 93% of cases) or abdomen ("peritoneal", 4% of cases).[2, 3] In 2020, malignant mesothelioma caused an estimated 26,278 deaths worldwide, including 886 in Australia and New Zealand.[4] Life expectancy and quality of life following a diagnosis of mesothelioma are poor,[5] with median survival typically less than a year[3, 6] and five-year relative survival less than 10%[2] but depends on histological subtype and anatomical site.[3, 6] Incidence rates among males are substantially higher than among females.[2]

Mesothelioma is usually caused by exposure to asbestos, a naturally occurring mineral, the mining and usage of which has now been banned in many industrialised countries including Australia. Exposure to asbestos typically occurred during mining, building and manufacturing,[7-9] or during the repair, renovation and demolition of buildings that contain asbestos,[10] with around 90% of Australian cases having a known history of exposure to asbestos.[2, 11] Of people diagnosed with mesothelioma since 2005, most have a history of working with asbestos as a miner, as a trades person or in the land or water transport industries.[12, 13] However, the specific risk of diagnosis with mesothelioma also depends on exposure characteristics such as the type of asbestos, air concentration levels, intensity and duration of exposure, which are in turn associated with anatomical site and histological subtype.[11] Historically, Luxembourg and Australia had the highest per capita rates of asbestos use internationally[14] and these countries also have among the highest incidence rates of mesothelioma in the world (see Table A1 of the Appendix).[15] Characteristics of asbestos exposure vary geographically, because of variation in geology or because of the location of mining, manufacturing, shipping and other industries.

The median latency period between first exposure and diagnosis of mesothelioma has been estimated to be 30 years but can range from ten to as long as 60 years.[16, 17] The long and highly variable latency makes it difficult to establish direct links between known previous patterns of exposure with currently observed patterns of diagnosis and survival.

While the incidence of mesothelioma varies by state or territory in Australia,[2] little is known of how it varies at smaller area levels, limiting the ability to appropriately target health and supportive care

[1] Abbreviations
CI: Confidence interval
EHR: Excess hazard ratio
MEET: Maximised excess events test
Mesothelioma: Malignant mesothelioma
SIR: Standardised incidence ratio

services and prioritise interventions. To address this gap in knowledge, particularly given Australia's history of high levels of asbestos use, we used population-based cancer registry data to quantify how incidence and survival for mesothelioma varied by small geographical areas and according to area-level characteristics across Australia. We aim to describe the spatial variation in the burden of mesothelioma in Australia and identify area-level covariates associated with higher burden. The burden of mesothelioma in Australia by small geographic area has not been studied previously.

2. Material and methods

2.1 Ethics

Approval was obtained from Australia's state and territory Data Custodians and the following human research ethics committees: NSW Population & Health Services Research Ethics Committee (EC00410, Reference: 2019/ETH01656), Australian Capital Territory Health Human Research Ethics Committee (EC00100, Reference: ETHLR.16.235), Human Research Ethics Committee for the Northern Territory Department of Health and Menzies School of Health Research (EC00153, Ref: 2016-2720) and Griffith University Human Research Ethics Committee (EC00162, Reference:2018/280).

2.2 Data

Data on all diagnosed cases of malignant mesothelioma in Australia between 2002 and 2016 were obtained from the Australian Cancer Database[18] using ICD-O-3 morphology codes 9050-9053. The time period was selected to facilitate calculation of five-year survival using the most recent data available. The data included individuals' sex, age and residential location at time of diagnosis, geocoded by Statistical Area 2, as defined in the Australian Bureau of Statistics 2011 Geography Standard.[19] Individuals' mortality status was obtained through routine data linkage of cancer records with the Australian National Death Index, censored at 31 December 2016.

All analyses used only the records of individuals aged over 15 years at diagnosis and survival analyses were also limited to persons aged 89 or less at diagnosis. Estimated resident population data by age, sex and area were obtained from the Australian Bureau of Statistics[20] and mortality data by age, sex and area were obtained from the Office of Births, Deaths and Marriages.[21]

2.3 Statistical analysis

Directly age-standardised incidence rates were calculated using the 2001 Australian standard population distribution and all incidence analyses were carried out on the diagnoses occurring between 2007 and 2016, inclusive.[22] Relative survival was calculated using the period approach.[23] The 'at risk' period for survival analyses was 2007 to 2016, so that individuals were included in the

population at risk for each year between 2007 and 2016 that they survived after having been diagnosed no more than 5 years previously (earliest diagnosis year was 2002).

2.3.1 Regional and demographic associations

Broad patterns in incidence and survival were explored by constructing multivariable generalized linear models with a Poisson distribution. The proportional hazards assumption was assessed via visual inspection of the survival curves (for example, see Figure A3 of the Appendix). Associations between both incidence and survival and the following covariates were assessed using likelihood ratio tests: sex, age group, remoteness, area-level socioeconomic status, state or territory and, for the survival model, year since diagnosis ("risk interval"), histological sub-type (as defined by ICD-O-3 codes) and anatomical site using ICD-10 coding.

Likelihood ratio tests were used to assess univariable associations between candidate covariates and the outcome using Poisson regression. Multivariable Poisson models were then constructed via backwards elimination using covariates with evidence of a univariable association with the outcome at the conservative $p = 0.2$ level. Interactions between several pairs of factors were tested using likelihood ratio tests; however, since these interactions were either not significant at the $p = 0.2$ level or their inclusion did not alter the regression coefficients, they were omitted in favour of a more parsimonious model. For the incidence model, the offset was the log of the population at risk. Negative binomial models were also fitted to both incidence and survival data; however, there was no change in the coefficients or their variances, nor was there an improvement in the log likelihood or pseudo R^2 and so the results of the Poisson models are reported. A random effect for area was also trialed in the models for incidence and survival but did not improve model fit substantially and had a negligible effect on the coefficients and their confidence intervals. This suggests area-level variability was adequately explained by the area-level factors.

The excess hazard resulting from the survival model was the modelled number of deaths exceeding the age- and sex-matched population mortality (details are provided in the Appendix). We tested for evidence of an interaction between risk interval and the other covariates graphically, using likelihood ratio tests and by assessing the impact of interaction on the covariates. While some showed weak evidence of an interaction ($0.05 < p \leq 0.20$), the impact on coefficients by risk interval was negligible. For this reason, the proportional hazards method was deemed suitable. Confidence intervals for the summary statistics and generalised linear modelling of survival were calculated using the Ederer II estimator.[24]

Remoteness categories were as defined by the Australian Bureau of Statistics 2011 Geography Standard, with the remote and very remote categories combined.[25] The quintiles of the index of

relative socioeconomic advantage and disadvantage, as measured in the 2011 census, were used to quantify area-level socioeconomic status.[26]

2.3.2 Spatial models

Bayesian spatial incidence and survival models with Leroux priors on the spatial random effect were applied, as per the Australian Cancer Atlas,[27, 28] to assess patterns by small geographical area across Australia. The results of the models were standardized incidence ratios (incidence) or excess hazard ratios (survival), smoothed over neighbouring areas to protect confidentiality and distinguish underlying spatial patterns from random noise. Spatial models for females did not converge, owing to small numbers and insufficient statistical power, so sex-specific spatial results are not reported. Convergence was checked by inspecting the trace plots and posterior distributions of the model parameters and calculating the Geweke statistic[29] for the areal random effects. If more than 10% of areas had significant Geweke diagnostics at the 5% level or the trace plots suggested poor convergence, the number of Markov chain Monte Carlo iterations was increased. The 90% credible intervals for the standardised incidence ratios (SIRs) are provided as evidence both supporting and against real differences.

A statistical test for evidence of spatial heterogeneity, the Maximised Excess Events Test (MEET), was conducted. The MEET compares the modelled numbers of diagnoses and deaths with the expected counts, based on the national age-specific observed rates and the age-specific population of each area.[30]

3. Results

3.1 Incidence

An average of 717 cases of mesothelioma were diagnosed annually in Australia among persons aged 15 years and older between 2007 and 2016 inclusive, with 584 cases among males and 133 among females. The corresponding age-standardised incidence rates were 3.6 (95% CI: 3.5 – 3.7) cases per 100 000 person years among all persons, 6.4 (6.2 – 6.6) among males and 1.2 (1.2 – 1.3) among females. Epithelioid mesothelioma accounted for 42% of cases, 13% were fibrous mesothelioma, 10% were biphasic and 35% were not otherwise specified. A breakdown of the histological subtype by state or territory is provided in Table A2. The majority of cases, 93.8%, were pleural mesothelioma, 5.6% were peritoneal and 0.6% were mesothelioma of the pericardium, other sites or not specified. Hence, anatomical site could not be included in the incidence models, but was included in the relative survival generalised linear model, which used individual-level data.

3.1.1 Regional and demographic associations

Each of the variables considered explained substantive variation ($p \leq 0.03$) in the incidence rates according to the univariable and multivariable likelihood ratio tests. The residual deviance indicated good model fit ($p > 0.99$) and the pseudo R^2 (0.41) indicated an improvement in the likelihood compared with the null model. The results of the final model are shown as incidence rate ratios (Table 1) and marginal age- and sex-adjusted incidence rates (Figure 1). The adjusted incidence rate ratio for males versus females was 5.3 (95% CI: 5.0 – 5.6). Age group was omitted from Table 1 for clarity; however, the adjusted incidence rate ratios increased rapidly with age group (Table A3). Incidence rates were highest in Western Australia (12.2 cases / 100 000 person-years, 95% CI: 9.9-14.4) and lowest in Tasmania (5.1 / 100 000 person-years, 95% CI: 3.8-6.4). Incidence rates were lower in remote and very remote areas and lower in the most affluent areas (Table 1), although the difference in the area-level socioeconomic quintiles was not evident in the marginal incidence rates (Figure 1).

3.1.2 Spatial patterns

Smoothed SIRs for mesothelioma are shown in Figure 2. Areas that appear as creamy-yellow have incidence rates similar to the average area. Areas in blue have lower incidence than average and areas in orange and red have higher incidence than average. There was strong evidence of spatial variability in incidence of mesothelioma according to the MEET ($p < 0.001$). Consistent with the multivariable model, incidence was higher than average in many areas of Western Australia and lower in many areas of Tasmania (see Figure A1 for the SIRs and their 90% credible intervals for each area, grouped by state or territory).

The colour scales for Figure 2 (A) and (C) were capped at 1.5 to highlight practically important differences, however, most areas of Western Australia's state capital, Perth, had an incidence at least 50% higher than the Australian average. To highlight the differences within this state, Figure 2 (B) shows SIRs in Western Australia (right), the greater Perth region (bottom left) and Karratha and surrounds (top left), where the colour scales were capped at 2.0 so that the darkest red areas have incidence rates twice the average. The highest incidences in the state occurred around the Mandurah, Joondalup and Armadale regions on the outskirts of Perth and Karratha, the coastal centre near the former asbestos mine at Wittenoom.

Figure 2 (C) shows SIRs near the former asbestos mines at Baryulgil (operational 1944-1979[23, 31]) and Woodsreef (operational 1971-1983[9]) in north-eastern New South Wales and near the power station in Yallourn where asbestos products were used extensively until 1979[32]. SIRs in the areas around

Yallourn were consistently high, while those around Baryulgil and Woodsreef were low; although SIRs were elevated in Grafton, the city nearest Baryulgil.

Smoothed counts of mesothelioma diagnoses are plotted in Figure 3, in which areas with 3 or fewer diagnoses over 10 years are coloured cream, magenta areas have approximately 10 diagnoses and black areas have more than 15 diagnoses over 10 years. Most of Australia's landmass was cream coloured, reflecting the sparsity of the population. Areas with larger counts tend to be in coastal areas, which are more densely populated. Counts were low outside Perth in Western Australia, including in Karratha. Counts were relatively high around the former power plant at Yallourn and high around the former asbestos mines at Baryulgil and Woodsreef and in Grafton.

3.2 Survival

The 5-year relative survival for people who were 'at risk' between 2007 and 2016 was 6.2% (95% CI: 5.5-6.8%) for all persons, for males was 5.5% (4.8-6.2%) and for females 8.8% (7.1-10.6%). Between 2007 and 2016, on average 628 deaths occurred annually among persons who had been diagnosed with mesothelioma in the preceding five years, which was 603 deaths more than expected given the mortality in the age- and sex-matched population.

3.2.1 Regional and demographic associations

There were significant associations ($p < 0.01$), based on likelihood ratio tests, between the excess hazard of death after a diagnosis of mesothelioma and the following variables: sex, age group, morphology, risk interval (the number of years since diagnosis) and area-level socioeconomic quintile. The residual deviance indicated good model fit ($p > 0.99$). The excess hazard was higher among males, older persons, persons living in areas in the second most disadvantaged socioeconomic quintile and among those diagnosed with fibrous or biphasic mesotheliomas (Table 2). While state and territory appeared to explain some of the variation in the excess hazard, this association could have been by chance ($p = 0.19$). There was no evidence that remoteness category was associated with relative survival ($p > 0.2$). Morphology was tabulated against anatomical site in the Appendix, Table A4.

3.2.2 Spatial modelling

A map of the sex-adjusted and age-standardised excess hazard ratios according to the spatial survival model is shown in Figure 4, with credible intervals shown in Figure A2. As with incidence, cream-coloured areas have similar survival to the national average, red areas have poorer survival and blue areas have better survival compared with the national average. There was no evidence of spatial variation in 5-year survival following a diagnosis of mesothelioma (MEET: $p > 0.99$).

4. Discussion

Our study found strong evidence of geographical variation in the incidence of mesothelioma in Australia, with areas of high incidence being concentrated in Western Australia, along with some coastal areas in southeast Queensland, New South Wales and Victoria. In contrast, there was little evidence of geographical variation in survival, with the poor survival being consistent across all areas of the country.

Consistent with previous reports,[33] SIRs were highest in many areas of Western Australia, which has a history of mining and use of crocidolite, the most carcinogenic form of asbestos. Lower rates but high counts were observed around the chrysotile mines in northern New South Wales that were active mines more recently.[9] High rates and counts were observed around Yallourn, where the power station used asbestos extensively and where asbestos dust permanently suspended in the air was considered "ordinary conditions" of work.[32] This association of high mesothelioma incidence in geographical areas with a history of asbestos exposure has also been reported internationally.[34-41] For example, in Belgium there were higher incidence rates near a former asbestos processing plant,[37] or higher mortality rates in towns containing asbestos-consuming companies, shipbuilding companies or international ports.[40]

Although ecological associations have been reported in many regions, the long latency between exposure and disease onset means that an individual's residential location at time of diagnosis may be different to the location of their exposure (as exemplified by the few incident cases in residents of towns near the crocidolite mining and milling area of Western Australia and the concentration of cases in popular retirement areas on the outskirts of Perth, the capital of Western Australia). As with most population-based cancer registries, these previous residential data are not collected by cancer registries within Australia and hence, caution is needed when interpreting the findings in terms of potential exposures. It is likely that the extent of migration also varies by geographical area. For example, the mining and milling operations at Wittenoom ceased in 1966 and most workers left the area.[42] The town of Wittenoom was slowly phased out from the 1990s by state authorities and so the persons exposed at the mine or from the asbestos contamination in the town have migrated from that area.[43] In contrast, there were high SIRs in Yallourn, where there is a continuing community[5] and evidence that many persons exposed to asbestos in Yallourn remain in the area.

While spatial maps of SIRs provide information about the varying population risk of being diagnosed with cancer, they do not always reflect the geographic distribution of the absolute diagnostic and treatment burden associated with mesothelioma. For example, several areas of Western Australia had high SIRs but low numbers of diagnoses because of their small populations. Additionally, some

areas with low SIRs but higher counts of diagnoses may reflect exposure of specific sub-populations in those areas, for example the Aboriginal population at Baryulgil.[31]

5. Conclusions

Historical mining, high importation and use of raw and manufactured asbestos in Australia present an ongoing risk of asbestos exposure and mesothelioma. Some of the geographical variation in incidence of mesothelioma is because of the location of historical mines and industries using asbestos products, however migration after exposure complicates the interpretation. Survival rates were uniformly poor and without evidence of spatial differences. Regional differences in the modelled number of cases indicates varying demand for diagnostic and management services for mesothelioma. The poor prognosis for people diagnosed with mesothelioma should motivate clear, consistent and comprehensive management of exposure risk to minimise future diagnoses.

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Figures

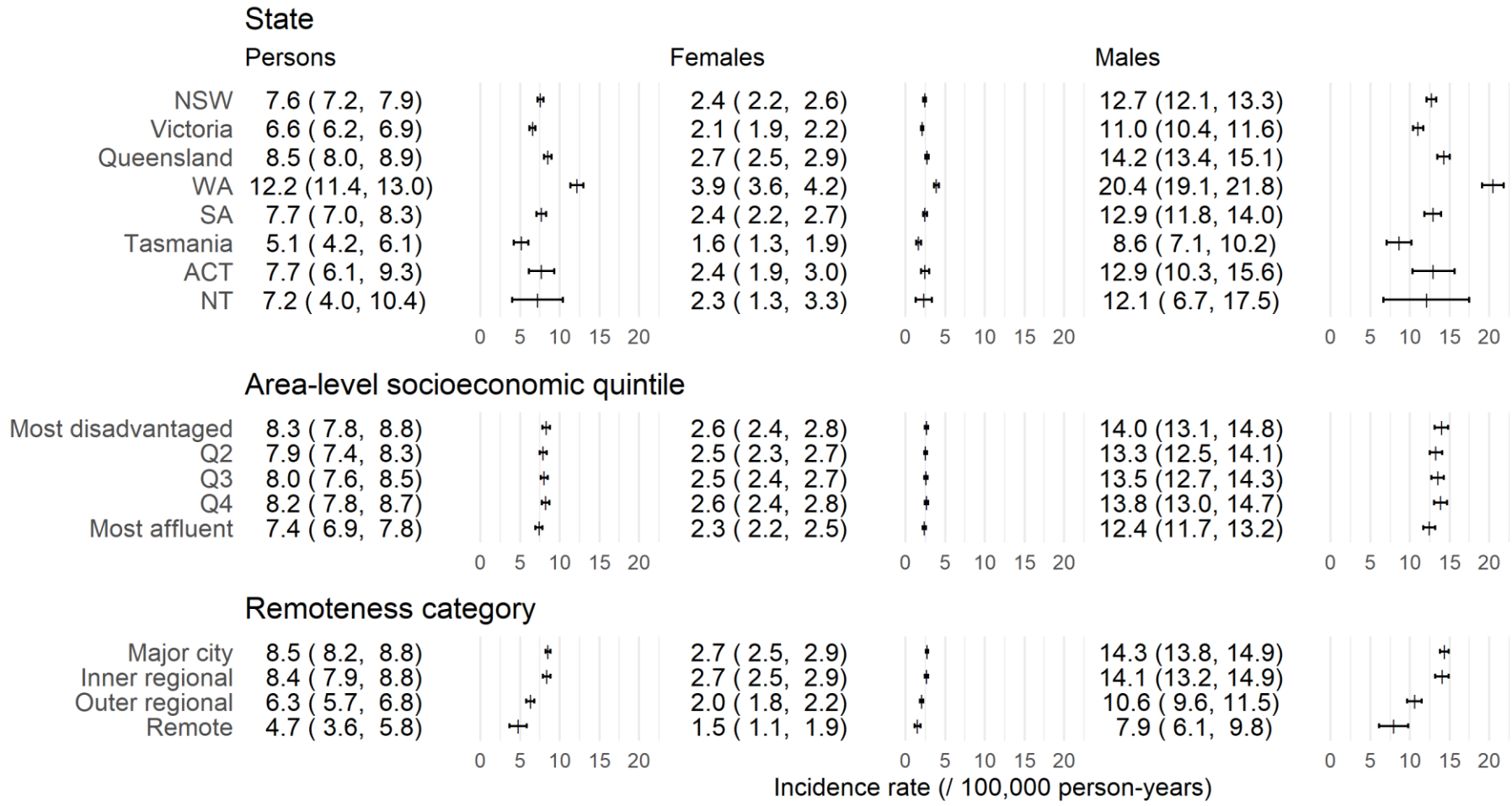

Figure 1; Age-adjusted incidence rates for mesothelioma (per 100,000 person-years) by sex and state or territory, area-level socioeconomic quintile and remoteness category, with 95% confidence intervals. Abbreviations for states/territories are NSW: New South Wales, WA: Western Australia, SA: South Australia, ACT: Australian Capital Territory, NT Northern Territory.

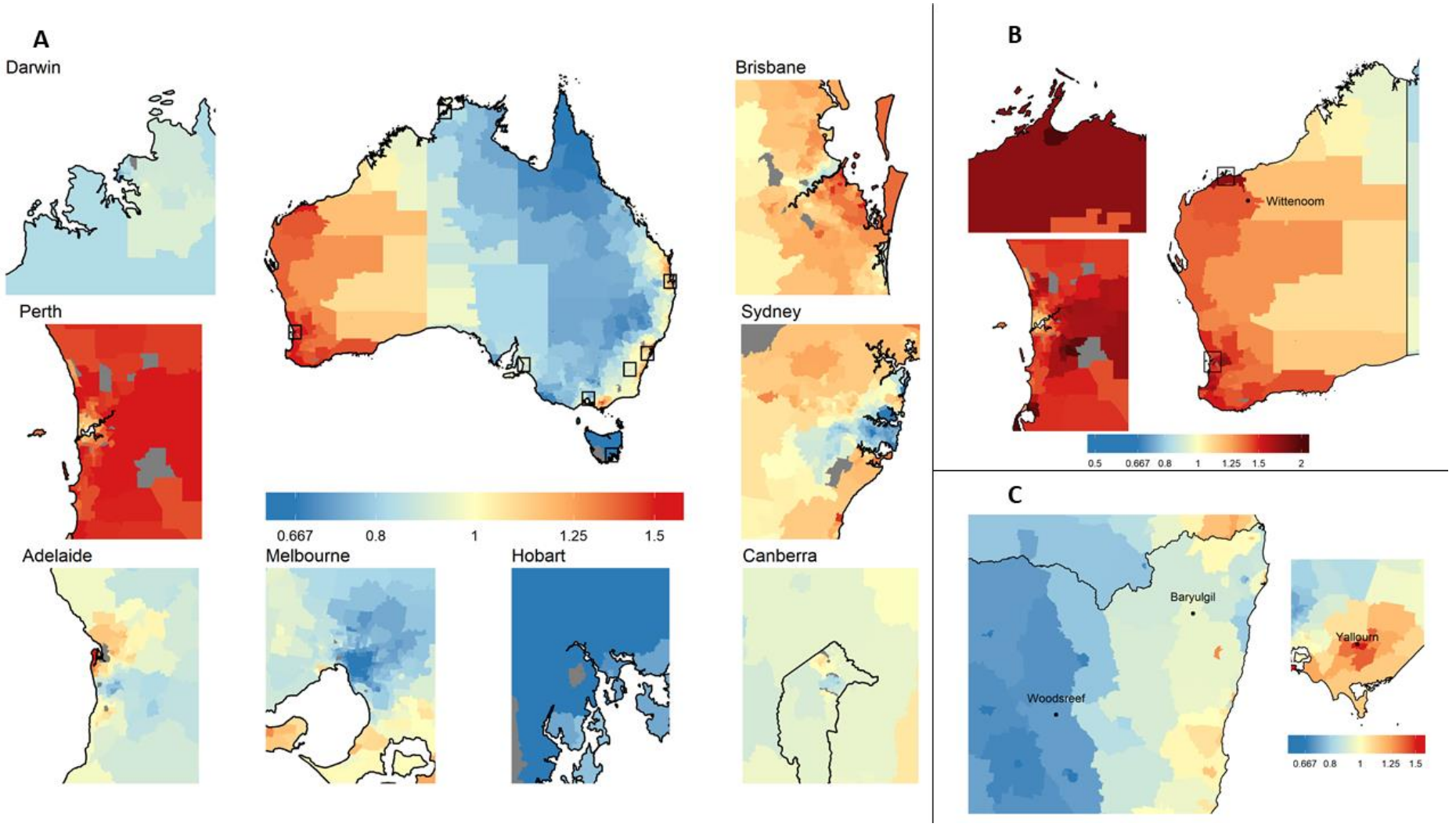

Figure 2; Smoothed standardised incidence ratios for mesothelioma for persons, standardised by age and sex. (A) shows the map for all of Australia, with insets of the state and territory capitals and the location of these insets are marked on the map of Australia. (B) uses an extended colour scale and shows Western Australia (right) including the location of the historical asbestos mine at Wittenoom, Perth (bottom left) and Karratha (top left). (C) shows north eastern New South Wales (left) and the locations of the former Baryulgil and Woodsreef asbestos mines and south eastern Victoria and the location of the Yallourn power station.

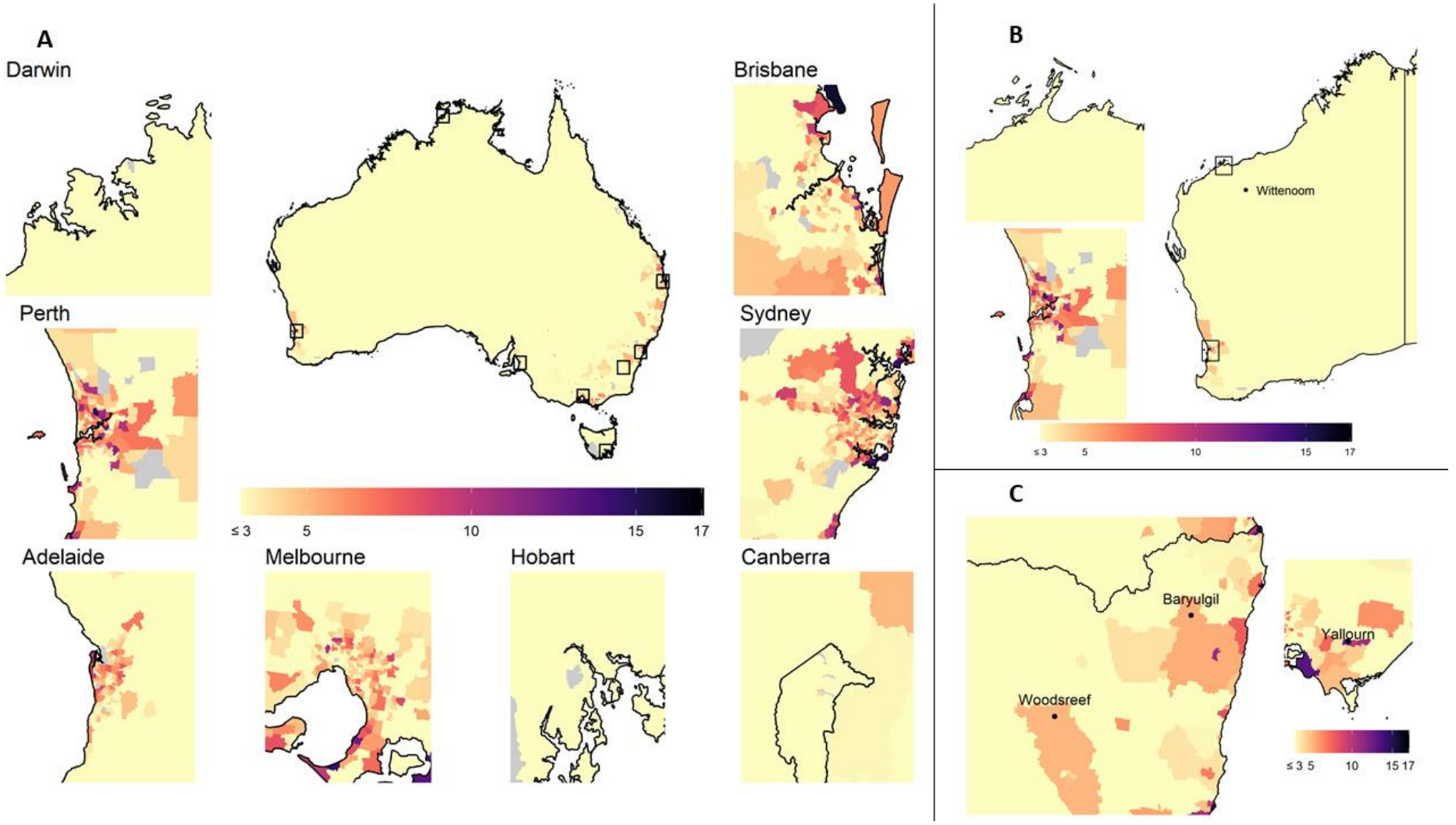

Figure 3; Smoothed number of diagnoses for mesothelioma for persons, censored below counts of 3. (A) shows Australia, with insets show the counts for the areas around the state and territory capitals and the location of these insets are marked on the map of Australia.(B) shows Western Australia (right), Perth and surrounds (bottom left) and the Karratha region (top right). (C) shows the region around Yallourn in south eastern Victoria and the areas around the asbestos mines in north eastern New South Wales.

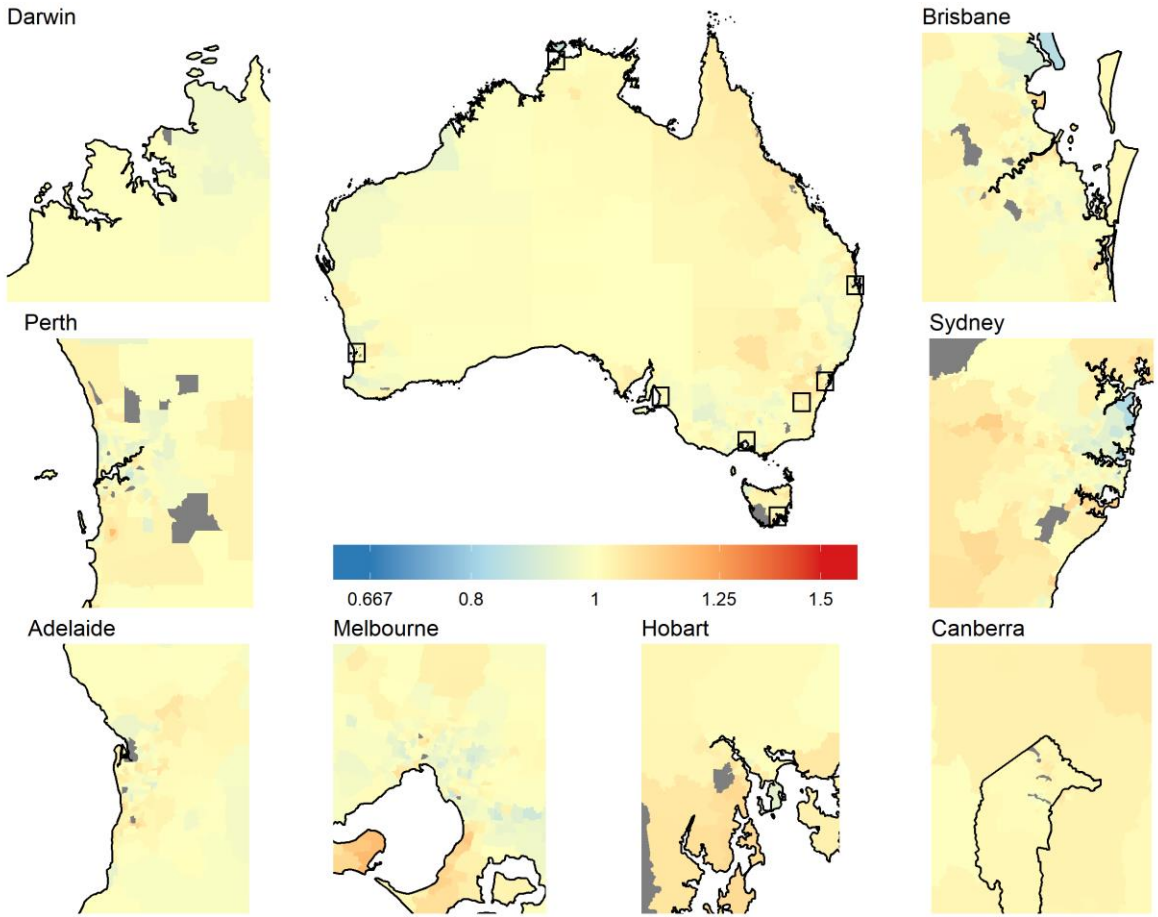

Figure 4; Excess hazard ratios for persons within 5 years of a mesothelioma diagnosis. Insets show the excess hazard ratios for the areas of the state and territory capitals and the location of these insets are marked on the map of Australia.

Tables

Table 1; Age-adjusted results of the generalised linear model for diagnoses: the incidence rate ratios for each level of the categorical variables with 95% confidence intervals (CIs), z-statistic and p-values. See Table A3 for additional age effects.

	Incidence rate ratio (95% CI)	*z*	*P*[1]
State			**< 0.0001**
New South Wales	0.62 (0.58, 0.67)	-12.0	< 0.001
Victoria	0.54 (0.50, 0.59)	-14.7	< 0.001
Queensland	0.70 (0.64, 0.76)	-8.4	< 0.001
Western Australia	1	-	-
South Australia	0.63 (0.57, 0.70)	-8.8	< 0.001
Tasmania	0.42 (0.35, 0.51)	-8.7	< 0.001
Australian Capital Territory	0.63 (0.51, 0.78)	-4.2	< 0.001
Northern Territory	0.59 (0.38, 0.93)	-2.3	0.02
Sex			**< 0.0001**
Females	1	-	-
Males	5.29 (4.98, 5.62)	53.7	< 0.001
Area-level socioeconomic quintile			**0.03**
Most disadvantaged	1.12 (1.03, 1.22)	2.8	0.006
Q2	1.07 (0.98, 1.16)	1.6	0.1
Q3	1.09 (1.00, 1.17)	2.1	0.04
Q4	1.11 (1.03, 1.20)	2.7	0.007
Most affluent	1	-	-
Remoteness			**< 0.0001**
Major city	1.80 (1.42, 2.28)	4.9	< 0.001
Inner regional	1.77 (1.39, 2.24)	4.7	< 0.001
Outer Regional	1.33 (1.04, 1.69)	2.3	0.02
Remote	1	-	-

1. Bold p-values represent the statistical significance of each covariate based on likelihood ratio test comparing the final model with the model after removing the corresponding covariate; other p-values are the significance of category-specific incidence rate ratios

Table 2; Results of the generalised linear model for relative survival: the excess hazard ratios (EHRs) for each level of the categorical variables with 95% confidence intervals (CIs), z-statistic and p-values.

	EHRs (95% CI)	*z*	*p*[1]
Risk interval (years since diagnosis)			**< 0.0001**
0-1	1	-	-
1-2	1.13 (1.06, 1.21)	3.9	< 0.001
2-3	0.86 (0.78, 0.95)	-3.0	0.003
3-4	0.60 (0.52, 0.69)	-7.0	< 0.001
4-5	0.46 (0.38, 0.56)	-7.7	< 0.001
Sex			**0.003**
Females	1	-	-
Males	1.11 (1.04, 1.19)	3.0	0.003
Age group			**< 0.0001**
15-54	0.78 (0.68, 0.89)	-3.6	< 0.001
55-64	1	-	-
65-74	1.08 (1.00, 1.17)	2.1	0.04
75-89	1.57 (1.46, 1.69)	11.9	< 0.001
Histological subtype			**< 0.0001**
Mesothelioma NOS[2] *(9050)*	1	-	-
Fibrous mesothelioma (9051)	1.96 (1.81, 2.13)	16.3	< 0.001
Epithelioid mesothelioma (9052)	0.77 (0.72, 0.82)	-8.3	< 0.001
Mesothelioma, biphasic (9053)	1.27 (1.16, 1.40)	5.2	< 0.001
Site			**0.009**
Pleural (C45.0)	1	-	-
Peritoneal (C45.1)	0.87 (0.77, 0.99)	-2.2	0.03
Other or NOS[2] *(C45.2, C45.7, C45.9)*	0.67 (0.44, 1.02)	-1.9	0.06
Area-level socioeconomic quintile			**0.01**
Most disadvantaged	0.91 (0.84, 0.98)	-2.4	0.02
Q2	1	-	-
Q3	0.91 (0.84, 0.98)	-2.4	0.02
Q4	0.90 (0.83, 0.98)	-2.6	0.01
Most affluent	0.86 (0.79, 0.93)	-3.6	< 0.001
State or territory			**0.19**
New South Wales	1	-	-
Victoria	0.93 (0.86, 1.00)	-2.0	0.05
Queensland	1.00 (0.93, 1.08)	0.0	> 0.99
Western Australia	1.02 (0.94, 1.11)	0.5	0.59
South Australia	1.00 (0.90, 1.11)	0.0	0.99

Tasmania	1.16 (0.95, 1.42)	1.4	0.15
Australian Capital Territory	1.07 (0.85, 1.34)	0.6	0.57
Northern Territory	0.76 (0.48, 1.21)	-1.2	0.24

1. Bold p-values represent the statistical significance of variable based on likelihood ratio test comparing the final model with the model after removing the corresponding covariate; other p-values are the significance of category-specific excess hazard ratios.
2. NOS: Not otherwise specified. This category is likely a mixture of fibrous, epithelial, biphasic and non-specific mesothelioma.

Conflict of interest statement

Declarations of interest: none

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Appendix

Tables

Table A1; Age standardised incidence rates of malignant mesothelioma among persons aged 15 and over by country using the World Health Organisation world age structure. Countries with highest incidence only.[1]

Country	ASR (/10,000 person-years)
Luxembourg	6
United Kingdom	2.7
The Netherlands	1.9
Australia	1.9
New Zealand	1.8
Belgium	1.7
Switzerland	1.6
Italy	1.5
Malta	1.5
New Caledonia (France)	1.5
Slovenia	1.4
Croatia	1.3
Denmark	1.3
Turkey	1.3
Finland	1.2
Bahrain	1.1
France	1
Norway	0.99
Canada	0.99
Cyprus	0.98
World	0.3

[1] Ferlay J, Ervik M, Lam F, et al. Global Cancer Observatory: Cancer Today Lyon, France: International Agency for Research on Cancer; 2020. Accessed March 1st 2022. [Available from: https://gco.iarc.fr/today].

Table A2; Percentage[2] of cases of malignant mesothelioma for each histological subtype by state or territory.

	NOS 9050	Fibrous 9051	Epithelioid 9052	Biphasic 9053
New South Wales	42%	12%	37%	8%
Victoria	41%	12%	39%	9%
Queensland	36%	14%	39%	11%
Western Australia	< 10%	14%	> 60%	16%
South Australia	40%	14%	38%	8%
Tasmania	47%	9%	32%	13%
Australian Capital Territory	> 40%	21%	32%	< 10%
Northern Territory	> 60%	13%	17%	< 10%
Total	35%	13%	42%	10%

Table A3; Incidence rate ratios for the age groups (rounded to 2 significant figures) from the results of the generalised linear model for diagnoses with 95% confidence intervals (CIs), p-values.

	Incidence rate ratio (95% CI)	*p[1]*
Age group		**< 0.0001**
15 – 19	2.9 (2.5, 3.4) x 10^{-8}	< 0.001
20 – 24	0.010 (0.0025, 0.041)	< 0.001
25 – 29	0.030 (0.013, 0.067)	< 0.001
30 – 34	0.057 (0.031, 0.11)	< 0.001
35 – 39	0.11 (0.071, 0.17)	< 0.001
40 – 44	0.22 (0.16, 0.31)	< 0.001
45 – 49	0.34 (0.25, 0.45)	< 0.001
50 – 54	1	-
55 – 59	2.3 (1.9, 2.7)	< 0.001
60 – 64	4.9 (4.1, 5.7)	< 0.001
65 – 69	9.1 (7.7, 11)	< 0.001
70 – 74	14 (12, 17)	< 0.001
75 – 79	20 (17, 23)	< 0.001
80 – 84	25 (21, 29)	< 0.001
85+	25 (21, 29)	< 0.001

[2] In states with low numbers of cases and low percentages of at least one sub-type, precise percentages are suppressed to prevent disclosure.

1. Bold p-values represent the statistical significance of the variable based on likelihood ratio test; other p-values are the significance of category-specific incidence rate ratios

Table A4; Number (and row percentage) of cases of malignant mesothelioma for each histological subtype (defined by ICD-O-3 code) by anatomical site.

Anatomical site (ICD-10)	NOS 9050	Fibrous 9051	Epithelioid 9052	Biphasic 9053
Pleural (C45.0)	2312 (34%)	919 (14%)	2812 (42%)	681 (10%)
Peritoneal (C45.1)	181 (45%)	10 (2%)	177 (44%)	34 (8%)
Pericardium (C45.2)	4 (36%)	4 (36%)	3 (27%)	0
Other sites (C45.7)	8 (40%)	6 (30%)	6 (30%)	0
Unspecified (C45.9)	9 (90%)	0	1 (10%)	0

Figures

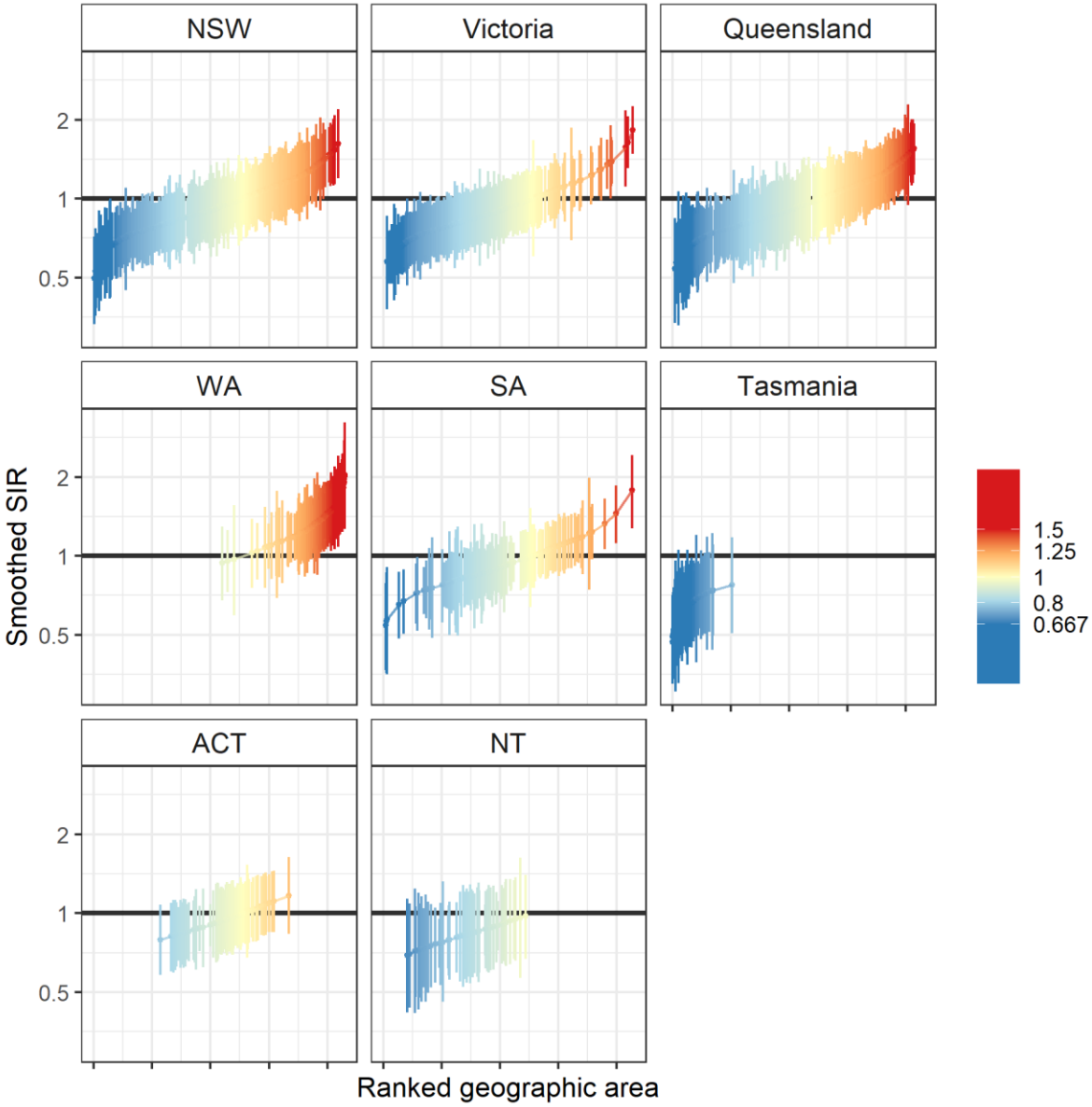


Figure A1; Standardised incidence rates (SIRs) and the associated 90% credible interval for each small geographical area, ranked by the median SIR and plotted by state or territory.

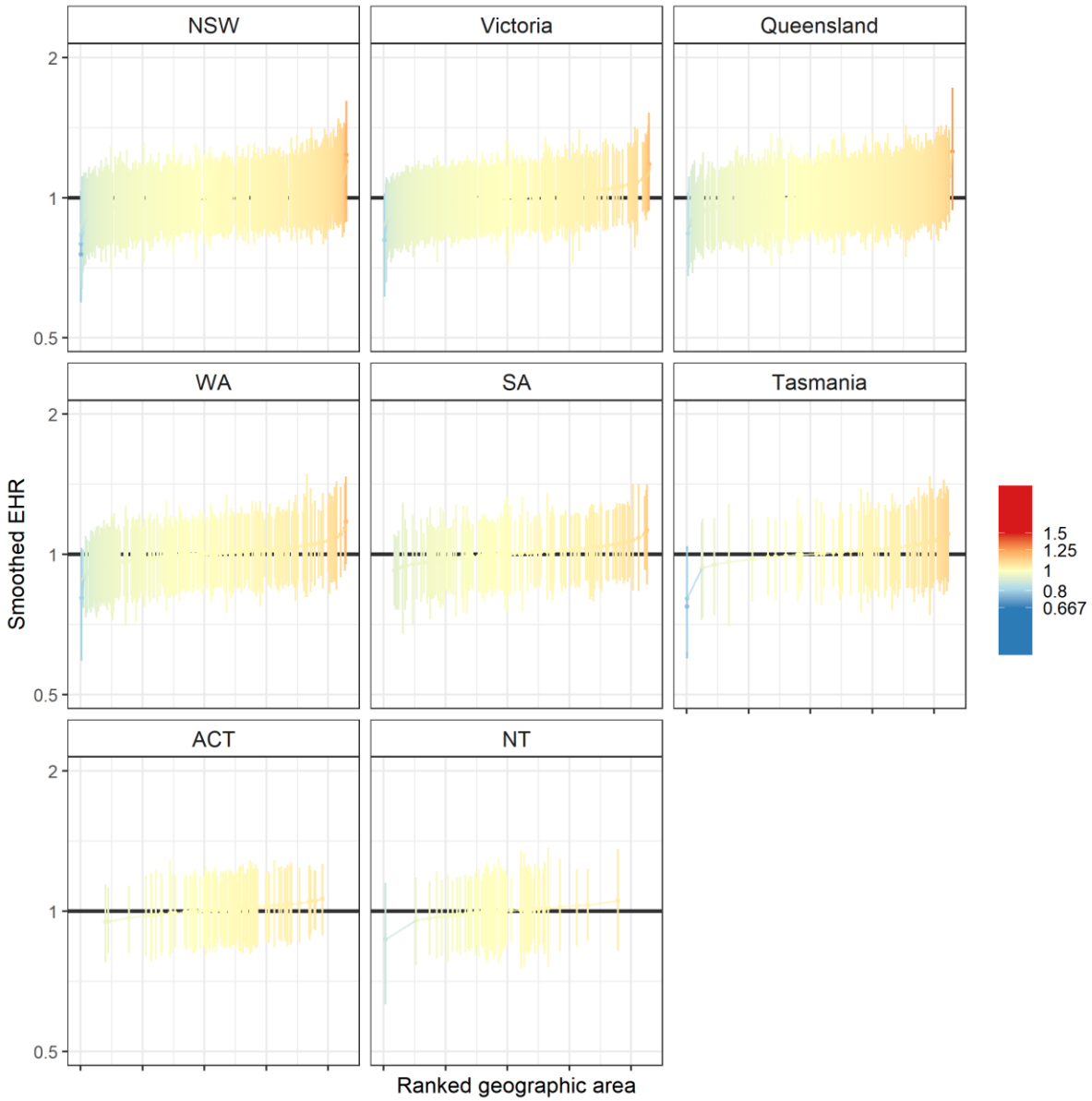
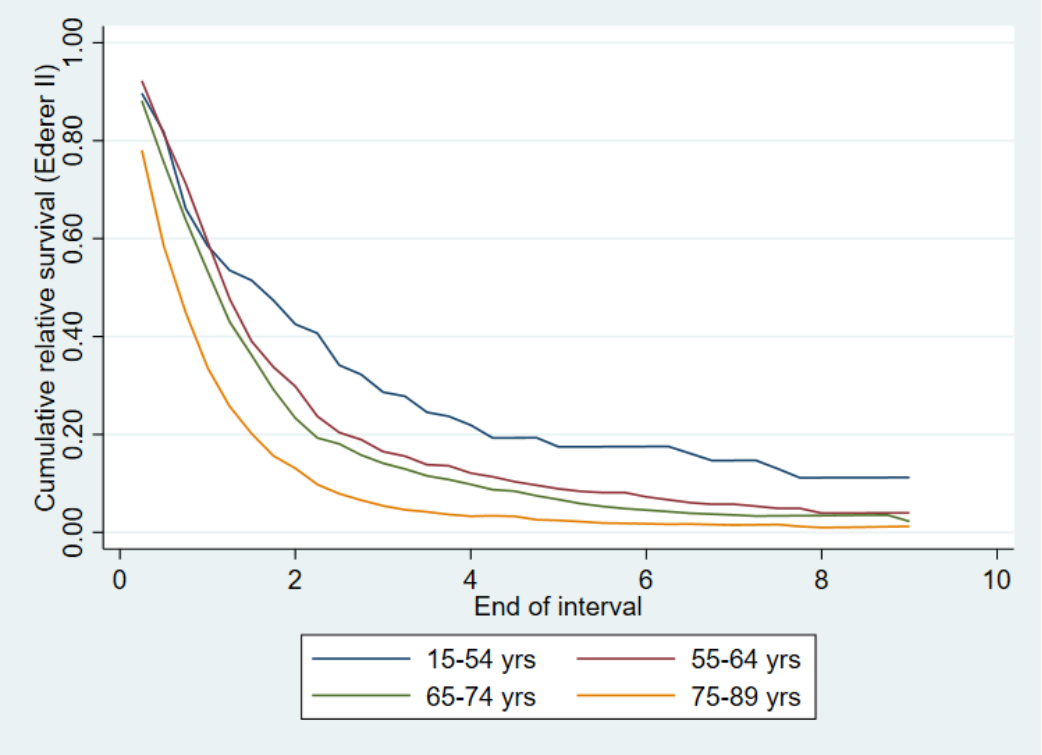
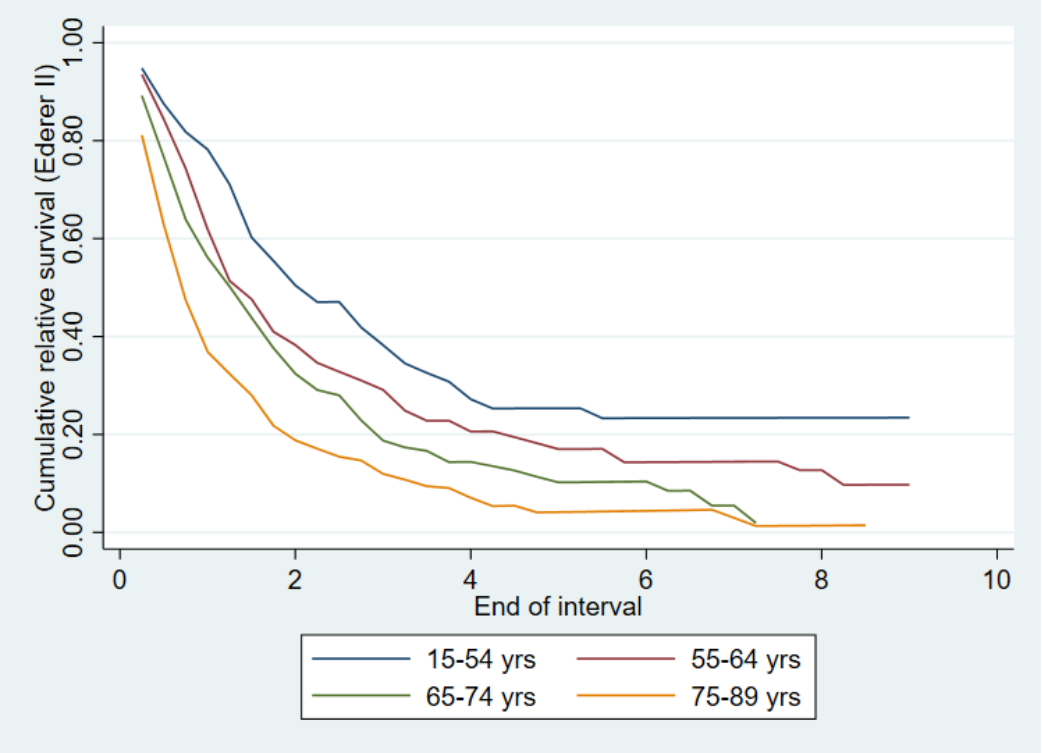


Figure A2; Excess hazard ratios (EHRs) and the 90% credible interval for each small geographical area, ranked by the median EHR and plotted by state or territory.



(a)



(b)

Figure A3; Survival curves by age group for males (a) and females (b) aged 15 or over and diagnosed with malignant mesothelioma between 2007 and 2016.

Methods

Generalised linear modelling for excess deaths

Excess mortality by area-level factors was modelled using Poisson regression, as shown in **Error! Reference source not found.** and described in greater detail by Dickman *et al*. (2004) and Dickman and Coviello (2015).[24, 44] The model was fitted to individual-level data, where d_j was the number of deaths for observation j, d_j^* was the expected mortality in the sex- and age-matched population and y_j was the person-time at-risk period. The covariate matrix, X, included risk interval, individual- and area-level factors and β was the coefficient matrix.

$$d_j \sim Poisson(\mu_j)$$

$$\ln(\mu_j - d^*) = \ln(y_j) + X_j\beta$$

Equation A1

Spatial model for diagnoses

The Bayesian spatial model for diagnoses is provided in Equation A2, where y_i is the number of diagnoses observed in area i, E_i is the expected number of counts, n_k is the number of cases in Australia in age group k, pop_k is the total Australian population for age group k, pop_{ik} is the population in area i for age group k and IG refers to the inverse gamma distribution.

$$y_i \sim Poisson(E_i\lambda_i)$$

$$\log(\lambda_i) = \beta + S_i$$

$$E_i = \sum_{k=1}^{K} \frac{n_k}{pop_k} pop_{ik}$$

$$\beta \sim N(0,100000)$$

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

$$\sigma_S^2 \sim IG(1, 0.01)$$

$$\rho \sim Uniform(0,1)$$

Equation A2

The standardised incidence ratio (SIR) is then the posterior median of λ_i.

Spatial model for excess deaths

The spatial model for excess deaths is provided in Equation A3Equation A2, where d_{ijk} is the number of deaths observed in area i in age group k and risk interval j, d^*_{ijk} is the expected number of deaths according to the area- and age-specific population mortality, y_{ijk} is the person-time at risk, β_j is the risk interval-specific intercept, x is the covariate matrix, including indicator variables for age category and sex and HN refers to the half-normal distribution.

$$d_{ijk} \sim Poisson(\mu_{ijk})$$

$$\log(\mu_{ijk} - d^*_{ijk}) = \log(y_{ijk}) + \beta_j + x\beta_k + S_i$$

$$\beta_j \sim N(0,0.01)$$

$$\beta_k \sim N(0,0.01)$$

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

$$\sigma_S^2 \sim HN(1, 0.2)$$

$$\rho \sim Uniform(0,1)$$

Equation A3

The excess hazard ratio (EHR) is then the posterior median of S_i.

Code

Diagnosis model

```
library(CARBayes)
library(spdep)


W <- nb2mat(aust, style = "B")   # where aust is a neighbourhood structure
(i.e. class = nb)
file.input = data.frame(obs = file$count, expect = file$expect, id =
file$grid)
formula <- obs ~ offset(log(expect))
model.ler <- S.CARleroux(
  formula = formula,
  data = file.input,
  family = "poisson",
  W = W,
  burnin = 50000,
```

```
  n.sample = 150000,
  thin = 10)
```

Excess deaths model

R code

```
library(R2WinBUGS)

# Fixed values
bugs.dat <- list(
  N = N,                # Number of areas (SA2s)
  T = T,                # Number of risk years
  N.d = N.d,            # Number of data rows (N * T * # of covariates)
  d = d,                # Number of deaths
  d.star = d.star,      # Expected number of deaths due to causes other
than cancer of interest
  y = y,                # Person-time at risk offset
  RiskYear = RiskYear,
  Area = Area,
  adj = adj$adj,
  num = adj$num,
  cum = c(cumsum(adj$num) - adj$num, sum(adj$num)),
  sumnum = sum(adj$num),
  agegp2 = x1,
  agegp3 = x2,
  agegp4 = x3)

# Initial values
inits <- function() {list(
  alpha = rep(-3, 5),
  u = rep(0, N),
  sigma.u2 = 0.2,
  rho = 0.5,
  beta = rep(0, 3))}

# Parameters to monitor in WinBUGS
parameters <- c("alpha", "u", "sigma.u2", "beta", "rho")

# Run WinBUGS
  bugs(
    data = bugs.dat,
    inits = inits,
    parameters.to.save = parameters,
    model.file = "Leroux.bug",
```

```
    n.chains = 1,
    n.iter = 150000,
    n.burnin = 50000,
    n.thin = 10,
    debug = FALSE,
    bugs.directory = "C:/WinBUGS/",
    program = "WinBUGS",
    DIC = FALSE)
```

WinBUGS Code

```
model{
  for(i in 1:N.d){
    d[i] ~ dpois(mu[i])
    mu[i] <- d.star[i] + d.excess[i]
    log(d.excess[i]) <- log(y[i]) + alpha[RiskYear[i]] + beta[1] *
agegp2[i] + beta[2] * agegp3[i] + beta[3] * agegp4[i] + u[Area[i]]}


  # Leroux prior for spatial random effects
  for(j in 1:N){
    u[j] ~ dnorm(mean.u[j], prec.u[j])
    A[j] <- (rho * num[j] + 1 - rho)
    prec.u[j] <- A[j] / sigma.u2
    mean.u[j] <- rho * sum(W.u[cum[j] + 1:cum[j+1]]) / A[j]}
  for(h in 1:sumnum){
    W.u[h] <- u[adj[h]]}

  # Other priors
  sigma.u2 ~ dnorm(0, 0.2)I(0,)
  rho ~ dunif(0, 1)
  for(t in 1:T){
    alpha[t] ~ dnorm(0, 0.01)}
  for(k in 1:3){
    beta[k] ~ dnorm(0, 0.01)}}
```