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ABSTRACT

Objective
Some studies have reported increasing trends in certain brain tumours and a possible link with mobile phone use has been suggested. We examined the incidence time trends of brain tumour in Australia for three distinct time-periods to ascertain the influence of improved diagnostic technologies and increase in mobile phone use.

Design
In a population based ecological study we examined trends of brain tumour over the periods 1982-1992, 1993-2002 and 2003-2013. We further compared the observed incidence during the period of substantial mobile phone use (2003-2013) with predicted (modelled) incidence for the same period by applying various relative risks, latency periods and mobile phone use scenarios.

Setting
National incidence registration data on primary cancers of the brain diagnosed between 1982 and 2013.

Participants
16,825 eligible brain cancer cases aged 20 to 59 (10,083 males and 6,742 females).

Main Outcome Measures
Annual percent change (APC) in brain tumour incidence based on Poisson regression analysis.

Results
The overall brain tumour rates remained stable during all three periods. There was an increase in glioblastoma during 1993-2002 (APC = 2.3, 95% Confidence Interval = 0.8-3.7) which was likely due to advances in the use of MRI during that period. There were no increases in any brain tumour types or sub-types, including glioma (-0.6, -1.4-0.2) and glioblastoma (0.8, -0.4-2.0), during the period of substantial mobile phone use from 2003-2013. During that period there was also no increase in glioma of the temporal lobe (0.5, -1.3-2.3), which is the location most exposed when using a mobile phone. Predicted incidence rates were higher than the observed rates for latency periods up to 15 years.

Conclusions
In Australia, there has been no increase in any brain tumour histological type or glioma location that can be attributed to mobile phone use.

Strengths and limitations of this study

- This study investigated incidence time trends for different brain tumour histological types, grading and anatomical location over different time-periods.
- The study compared the observed brain tumour incidence rates with modelled predicted incidence rates assuming a causal association with mobile phone use.
- Mobile phone subscription data and information from surveys may not accurately represent mobile phone use patterns in adults.

INTRODUCTION

Since its introduction in the mid-80s mobile phone use has grown rapidly worldwide. When using a mobile phone against the head, the brain is exposed to much higher levels of radiofrequency (RF) radiation than the rest of the body and there has been continuing concern of a possible association with brain cancer. Several case–control and registry-based cohort studies have found little evidence to support such an association.(1) However a few other case-control studies, most notably the Interphone study (2010) and a Swedish study by Hardell et al (2011), have reported modest to large associations with glioma, the most common type of primary brain tumour.(2-4) These studies have generally found no association with other brain tumour types such as meningioma. Based on these results the International Agency for Research on Cancer (IARC) has classified RF as "possibly carcinogenic to humans".(5)

From a public health perspective, given that the majority of the population regularly uses mobile phones, even a relatively small excess risk would result in a significant number of additional brain tumour cases. In time, such an increase would be observable in cancer surveillance data sources.(6) The World Health Organization has previously identified as a high research priority the monitoring of brain tumour incidence trends through well-established population-based cancer registries and combined with population exposure data.(7)

Since the WHO recommendation a limited number of ecological studies have shown that although the prevalence of mobile phone use (usually measured through the number of mobile phone accounts) has seen a massive increase, the time trends of brain tumour incidence have remained fairly stable.(8, 9) Other studies have shown increases in certain brain tumour sub-types or specific anatomical locations.(9, 10) However, it has been suggested that the introduction of better diagnostic methods (computed tomography, CT; and magnetic resonance imaging, MRI) have improved the detection of brain cancers which leads to increased population incidence.(11) Further, a few recent studies, most notably in the US and Australia, have shown that predicted incidence rates based on the associations reported by the Interphone and Hardell studies for "heavy" mobile phone users are higher than the observed rates.(12, 13) Apart from the study by Little et al (2012) previous results have generally failed to show the incidence trends for different brain tumour histological and topographical types.(12) Further, the simulation of expected rates in these studies was only performed for a latency period of 10 years and if there is an association with mobile phone use the latency could be longer.

In this study, we analysed the incidence trends of brain tumour for three distinct time-periods to ascertain the influence of improved diagnostic methods and increase in mobile phone use. The analysis considered different histological types and sub-types, glioma grades and glioma anatomical sites. We further compared the observed incidence during the period of substantial mobile phone use (2003-2013) with predicted incidence for the same period based on relative risks (RRs) reported by the two epidemiological studies forming the basis of the IARC classification.(2, 3)

METHODS

Collection of Incidence Data

Incidence data on primary cancers of the brain and central nervous system diagnosed between 1982 and 2013 inclusive (the latest available) were obtained from the Australian Institute of Health and Welfare (AIHW). Reporting of incident invasive cancer is mandatory

in all Australian states and territories and the AIHW has been collecting and reporting national data on brain cancer incidence since 1982. The data included information on primary anatomical site (International Classification of Diseases version 10, ICD-10 topography codes, C70-C72), histology, diagnosis year and diagnosis age (in five-year groups: 0-4, 5-9 ….. 80-84, 85+). Data were not available for one Australian state (New South Wales) for the year 2013.

Patient and public involvement

Patients or the public were not involved in this study.

Statistical Analysis of Observed Incidence

Based on the results of the Interphone study we analysed intracranial brain cancer incidence in adults aged 20-59; neoplasms of the spinal cord, cranial nerves and other parts of central nervous system (ICD-10 code C72) were excluded. Annual age-standardized incidence rates per 100,000 person-years were calculated separately for males, females and both genders by using the World Health Organization's (WHO) standard population. Histology was analysed by categorising glioma, meningioma, other histological types and brain cancers with unspecified histology based on WHO's Classification of Tumors of the Central Nervous System.(14) We further analysed glioma by categorising glioblastoma (which is the most common brain tumour sub-type), glioma grade (low, high and unspecified) and glioma location (frontal lobe, temporal lobe, parietal lobe, other locations, overlapping lobes and unspecified). The categories analysed and their respective ICD-10 codes are shown in Table 1.

Table 1. ICD-10 Histology and Topography Codes

Histology	
Glioma	9380-9480
Glioblastoma	9440-9442
Meningioma	9530-9539
Other	8010-9371, 9490-9508, 9540-9561
Unspecified	8000-8004
Glioma Grade	
Low (I & II)	9384, 9391, 9393, 9400, 9410, 9411, 9420, 9421, 9424, 9425, 9450
High (III & IV)	9381, 9392, 9401, 9440-9442, 9451, 9470-9474, 9480
Unspecified	9380, 9382, 9390, 9423, 9430, 9460,
Topography	
Frontal	C711
Temporal	C712
Parietal	C713
Other locations	C700, C701, C709, C710, C714-C717
Overlapping	C718
Unspecified	C719

A large number of tumours had unspecified classifications, particularly for glioma grade and glioma location. We approximated the classification of unspecified tumours by recalculating the adjusted rates for each year by adding the unspecified group to the other groups in proportion to the distribution of specified tumours.

Analyses of incidence time trends were carried out using Poisson regression to estimate the annual percent change (APC) in the incidence, with corresponding 95% confidence intervals (CI) over three time-periods: 1982-1992 (representing increased CT and MRI use),

1993-2002 (representing advances in MRI) and 2003-2013 (representing substantial and increasing mobile phone use; more than 65% of the population).(15) Lowess smoothing was used in the graphical representation of the time trends.

Statistical Analysis of Predicted Incidence

With the assumption that mobile phone use is associated with glioma in adults as reported by the Interphone and Swedish studies, we calculated predicted incidence rates and time trends by applying various relative risks (RRs, 1.5, 2, 2.5, 3) and latency periods (1, 5, 10, 15, 20 years) for three different mobile phone use scenarios:

a) All users – RRs were applied to all mobile phone users
b) Heavy users – RRs were applied to heavy mobile phone users (defined as 19% of mobile phone users by the Interphone study)
c) Regular users and heavy users - RR of 1.5 applied to regular users (81% of all users) and RRs of 2, 2.5 and 3 applied to heavy users (19% of all users)

Mobile phone use was estimated using information on mobile phone accounts and survey data on actual use. Data on the annual number of mobile phone accounts from 1987 to 2013 was obtained from the national telecommunications regulator, the Australian Communications and Media Authority (ACMA). The number of mobile phone accounts per capita for each year was calculated by dividing the number of accounts by the total Australian population in that year (obtained from the Australian Bureau of Statistics), noting that since 2008 the annual number of accounts has been exceeding the number of people in the population. This data is not a true indication of mobile phone use as some users may have had more than one account and other users no account. A consumer survey conducted by ACMA reported that approximately 90% of the population used mobile phones in the years 2009 to 2013.(16) We estimated the annual prevalence of mobile phone use (shown in Figure 1) by multiplying the annual number of accounts per capita by a factor of 0.9.(16) It was not possible to stratify prevalence of use by age or gender; thus an overall estimate of prevalence is provided across the 20-59 age range and for both males and females.

The annual predicted incidence rates were calculated for the period 1987-2013 using the formula:

$$\text{Predicted Incidence} = (P \times RR \times I_B) + ((1 - P) \times I_B)$$

where P denotes the annual prevalence of mobile phone use, RR the relative risk and I_B the pre-mobile phone baseline incidence from 1982-1987. Confidence intervals and statistical significance of observed and expected incidence rates were calculated using formulas in.(17) Analyses of predicted incidence time trends were carried out by estimating the APC for the period 2003-2013, representing the time that mobile phone use increased rapidly.

We used Stata/SE 15.0 for all analyses. The reporting of our study conforms to the STROBE statement.(18)

RESULTS

Observed Incidence

There was a total of 16,825 eligible brain cancer cases aged 20 to 59 (10,083 males and 6,742 females) that were diagnosed between 1982 and 2013. Of these 15,758 (93.7%) were gliomas, 312 (1.9%) were meningiomas, 239 (1.4%) were other histological types and

516 (3.1%) were tumours of unspecified histology. The most common brain tumour sub-type was glioblastoma (7,326, 43.5%). Of the gliomas 4,699 (29.8%) were low grade, 9,300 (59%) were high grade and 1759 (11.2%) were of unspecified grade. The most common glioma anatomical location was the frontal lobe (4,422, 28.1%), followed by the temporal lobe (2,952, 18.7%) and parietal lobe (2272, 14.4%). There were 2,372 (15.1%) tumours in other locations, 968 (6.1%) overlapping locations and 2772 (17.6%) with unspecified location.

The observed incidence rates between 1982 and 2013 are shown in Figure 2 for both genders and Supplementary Figure A for males and females separately. Further, the observed incidence trends (given as APC) over the time-periods 1982-1992, 1993-2002 and 2003-2013 are shown in Table 2 for both genders and Supplementary Table A for males and females separately. The overall brain tumour rates remained stable in all three time-periods and the trends were similar for males and females. Glioblastoma increased during the period that saw advances in MRI (1993-2002) whilst it remained stable during the period of substantial mobile phone use (2003-2013); this later period also saw a decrease in other glioma sub-types. There was a strong decreasing trend in brain tumours with unspecified histology during the period of increased CT and MRI use (1982-1992). With the redistribution of unspecified tumours there were no significant changes to these histological trends (Table 3 for both genders and Supplementary Table B for males and females separately).

Table 2. Observed brain tumour incidence trends in adults (both genders, 20-59 years old) during increased CT and MRI use (1982-1982), advances in MRI use (1993-2002) and substantial mobile phone use (2003-2013)

	1982-1992			1993-2002			2003-2013		
	N	APC*	95% CI	N	APC	95% CI	N	APC	95% CI
All	4793	0.1	(-0.8,1)	5270	0.5	(-0.5,1.5)	6762	-0.8	(-1.6,0)
Histology									
Glioma	4347	1.1	(0.2,2.1)	4990	0.4	(-0.6,1.4)	6421	-0.6	(-1.4,0.2)
Glioblastoma	1638	1.4	(-0.1,2.9)	2397	2.3	(0.8,3.7)	3291	0.8	(-0.4,2)
Other glioma	2709	1	(-0.2,2.2)	2593	-1.2	(-2.6,0.1)	3130	-1.8	(-2.9,-0.7)
Meningioma	82	-0.4	(-6.9,6.6)	110	2.4	(-4.2,9.4)	120	-4.4	(-10.1,1.7)
Other	79	-7.3	(-13.6,-0.6)	66	-1.5	(-9.5,7.2)	94	-5.3	(-11.3,1)
Unspecified	285	-13.4	(-16.6,-10)	104	4.6	(-2.3,12)	127	-4.8	(-10.3,0.9)
Glioma Grade									
Low	1817	1.1	(-0.4,2.6)	1418	-3.8	(-5.5,-2)	1464	-3.1	(-4.7,-1.5)
High	1938	3.8	(2.3,5.2)	3151	2.1	(0.9,3.4)	4211	-0.1	(-1.1,1)
Unspecified	592	-6.9	(-9.2,-4.5)	421	2.2	(-1.2,5.7)	746	2	(-0.4,4.5)
Glioma Location									
Frontal	933	7.8	(5.6,10.1)	1345	3.7	(1.8,5.7)	2144	3	(1.6,4.5)
Temporal	599	7.3	(4.6,10.1)	982	2.8	(0.6,5.2)	1371	0.5	(-1.3,2.3)
Parietal	655	6.4	(3.9,9.1)	801	-1.3	(-3.7,1.1)	816	-0.4	(-2.7,2)
Other locations	605	5.1	(2.5,7.8)	778	0.5	(-1.9,3)	989	-1.7	(-3.8,0.3)
Overlapping	298	3.5	(-0.1,7.3)	296	-8.8	(-12.5,-5)	374	-2.3	(-5.6,1.1)
Unspecified	1257	-10.8	(-12.4,-9.2)	788	-2.9	(-5.2,-0.4)	727	-10.5	(-12.7,-8.2)

*APC = Annual percent change

Table 3. Observed brain tumour incidence trends in adults (both genders, 20-59 years old) after redistribution of unclassified tumours

	1982-1992			1993-2002			2003-2013		
	N	APC*	95% CI	N	APC	95% CI	N	APC	95% CI
All	4793	0.1	(-0.8,1)	5270	0.5	(-0.5,1.5)	6762	-0.8	(-1.6,0)
Histology									
Glioma	4623	0.2	(-0.7,1.2)	5094	0.5	(-0.5,1.5)	6547	-0.7	(-1.5,0.1)
Glioblastoma	1746	0.4	(-1.1,1.9)	2445	2.4	(0.9,3.8)	3353	0.7	(-0.5,1.9)
Other glioma	2886	0.1	(-1,1.2)	2649	-1.1	(-2.5,0.2)	3195	-1.9	(-3,-0.8)
Meningioma	84	-1.6	(-7.9,5.2)	110	2.4	(-4.2,9.4)	120	-4.4	(-10.1,1.7)
Other	82	-8.6	(-14.7,-2)	66	-1.5	(-9.5,7.2)	94	-5.3	(-11.3,1)
Glioma Grade									
Low	2107	-0.2	(-1.5,1.2)	1548	-3.6	(-5.3,-1.9)	1659	-2.8	(-4.3,-1.3)
High	2240	2.4	(1.1,3.7)	3442	2.3	(1.1,3.5)	4762	0.2	(-0.7,1.2)
Glioma Topography									
Frontal	1447	1.8	(0.2,3.5)	1719	2.3	(0.6,4)	2580	1.6	(0.3,2.9)
Temporal	929	1.8	(-0.2,3.9)	1252	1.5	(-0.5,3.5)	1656	-1.2	(-2.8,0.4)
Parietal	803	3.4	(1.2,5.7)	894	-2	(-4.2,0.3)	880	-1.1	(-3.3,1.1)
Other locations	948	-0.5	(-2.5,1.5)	996	-0.8	(-3,1.4)	1198	-3.3	(-5.1,-1.4)

*APC = Annual percent change

Looking at glioma grade in Table 2, high grade gliomas increased during both periods of improved diagnosis whilst low grade gliomas decreased during the periods of advances in MRI (1993-2002) and substantial mobile phone use (2003-2013). There was a strong decreasing trend in gliomas with unspecified grade during the period of increased CT and MRI use (1982-1992). The redistribution of unspecified tumours did not change the glioma grade trends (Table 3).

For glioma location in Table 2, there were increasing trends for all locations and a strong decreasing trend for unspecified location during the period of increased CT and MRI use (1982-1992). There were also increases in the frontal and temporal lobes and a smaller decrease in unspecified location during the period of advances in MRI (1993-2002); this period also had a very large decrease in gliomas with overlapping location. During the period of substantial mobile use there were no increases in any of the locations apart from the frontal lobe and there was a strong decrease in unspecified location. With the redistribution of a high number of gliomas with unspecified and overlapping location there was a much lower increasing trend only for gliomas in the frontal lobe during all three periods and a large increase in the parietal lobe during the first period (Table 3).

Predicted Incidence

Assuming a causal association between mobile phone use and glioma, the predicted incidence trends for both genders during 2003-2013 by applying various relative risks, latency periods and mobile phone use scenarios are shown in Table 4. The predicted incidence trends showed an increase for most mobile phone use scenarios and latency periods that were modelled apart from a 20-year latency period. There were also no statistically significant increases when applying the model to only heavy users for RRs less than 3. The highest expected trends were generally seen for a 10-year latency period, which was the latency period associated with mobile phones and brain tumour as reported in the Interphone and Swedish studies.

Table 4. Predicted glioma incidence trends for both genders (20-59 years) during 2003-2013

Scenario	Latency	RR=1.5		RR=2		RR=2.5		RR=3	
		APC*	95% CI	APC	95% CI	APC	95% CI	APC	95% CI
All Users	1	1.1	(0.3,1.8)	1.6	(1,2.3)	2.0	(1.4,2.6)	2.3	(1.7,2.8)
	5	2.8	(2,3.5)	4.5	(3.8,5.2)	5.7	(5.1,6.4)	6.6	(6,7.3)
	10	2.7	(1.9,3.6)	4.9	(4.1,5.7)	6.7	(5.9,7.5)	8.2	(7.4,8.9)
	15	1.3	(0.5,2.2)	2.5	(1.7,3.4)	3.7	(2.8,4.5)	4.8	(3.9,5.6)
	20	0.2	(-0.7,1)	0.3	(-0.5,1.2)	0.5	(-0.4,1.3)	0.6	(-0.2,1.5)
High Users	1	0.3	(-0.6,1.1)	0.5	(-0.3,1.3)	0.7	(-0.1,1.5)	0.9	(0.1,1.6)
	5	0.6	(-0.2,1.5)	1.2	(0.4,2)	1.8	(1,2.6)	2.2	(1.5,3)
	10	0.3	(-0.6,1.1)	0.5	(-0.3,1.4)	0.8	(-0.1,1.6)	1.0	(0.2,1.9)
	15	0.3	(-0.6,1.1)	0.5	(-0.3,1.4)	0.8	(-0.1,1.6)	1.0	(0.2,1.9)
	20	0.0	(-0.8,0.9)	0.1	(-0.8,0.9)	0.1	(-0.8,0.9)	0.1	(-0.7,1)
Regular users and high users		RR=1.5 (R), 2 (H)		RR=1.5 (R), 2.5 (H)		RR=1.5 (R), 3 (H)			
	1	1.2	(0.5,1.9)	1.3	(0.6,2)	1.4	(0.8,2.1)		
	5	3.2	(2.4,3.9)	3.5	(2.8,4.3)	3.9	(3.1,4.6)		
	10	3.2	(2.4,4)	3.6	(2.8,4.4)	4.0	(3.2,4.8)		
	15	1.5	(0.7,2.4)	1.8	(0.9,2.6)	2.0	(1.2,2.9)		
	20	0.2	(-0.7,1)	0.2	(-0.6,1.1)	0.2	(-0.6,1.1)		

*APC = Annual percent change

The observed and predicted glioma incidence rates for both genders from 1987 to 2013 are shown in Figure 3. With a RR of 2 for all mobile phone users and a latency of 10 years, the predicted incidence rate for both genders in 2013 was 7.3 per 100,000 people (95% confidence interval 6.7 to 7.9) compared to the observed 4.5 per 100,000. The predicted rates increase to 8.7 (8.1 to 9.3) and 10.2 (9.5 to 10.8) per 100,000 for RRs of 2.5 and 3 respectively. With a RR of 1.5 for regular users and a RR of 2 for heavy users and a latency of 10 years the predicted rate was 6.1 per 100,000 (5.6 to 6.6); increasing to 6.4 (5.9 to 6.9) and 6.7 (6.1 to 7.2) when applying RRs of 2.5 and 3 to heavy users, respectively. Assuming a latency of 15 years, the predicted incidence rates in 2013 were also higher compared to the observed rate. The model did not show an increasing trend for a latency of 20 years.

DISCUSSION

The results of our study showed that the overall brain tumour rates in adults aged 20 to 59 years showed no increasing or decreasing trend. This is in line with studies showing stable brain tumour trends in other countries.(9-11) Furthermore, the trends in our study were stable for different histological types, like glioma, which has been reported in some case-control studies as being associated with mobile phone use.(2, 3) The all glioma incidence rates were stable in both the periods before (1982-1992, 1993-2002) and the period after (2003-2013) substantial mobile phone use. For a causal relationship between mobile phone use and brain cancer, one would expect an increasing trend in the later period and no trend in the earlier periods.

There has been limited research showing the time trends of histological sub-types and particularly glioblastoma, which is the most common and most malignant brain tumour sub-type in adults.(4) Phillips et al (2018) reported that the incidence of glioblastoma more than doubled in England between 1995 and 2015; however the authors did not analyse different periods to investigate the impact of mobile phone use.(19) Dobes et al (2011) reported an increasing trend in glioblastoma incidence in Australia between 2000 and 2008 in people aged 65 years or older; noting that the cases were ascertained directly from neurological centres.(20) Our study used all the national incident brain cancer registrations available through Australia's high quality state and territory population-based cancer registration system. Registration is mandatory and histological verification rates exceed 85%.(13) In our study, which focused on the age group most likely to be affected by mobile phone use, there was no increase in the glioblastoma rates during the period of substantial mobile phone use but there was an increase in the glioblastoma rates in the earlier periods: 1982-1992, which saw increased use of CT and MRI, and, 1993-2002 which saw further advances in MRI. Technological developments in MRI during 1993-2002, including diffusion and perfusion imaging, improved significantly the discrimination of brain tumour types and sub-types.(15, 21) Other factors, such as improved access to care and an increase in the number of specialists, may also have played a role in the increase.(8) Earlier studies investigating trends in brain-tumour sub-types including glioblastoma have commented that increases in certain sub-types are accompanied by decreases in other sub-types whilst overall brain tumour incidence has remained stable.(22, 23) These studies suggest improvements in diagnostic technology as the reason for increasing trends in certain brain tumour sub-types.(22, 23)

The results on histology are consistent with the results by grade, as high-grade glioma is approximately equivalent to glioblastoma. During the period of advances in MRI there was an increase for high-grade lesions, and a decrease for low-grade, both which levelled off during the period of substantial mobile phone use. These results are consistent with

incidence trends reported by Barchana et al (2012) for low-grade and high grade gliomas in Israel between 1980 and 2009.(24) Furthermore, there was a strong decrease for unspecified histology, and for unspecified grade during the first period, and this is likely due to improvements in diagnosis using CT and histopathological classification.(25) There have also been shifts in classifying sub-types and grade in updated editions of the WHO classification; for example the WHO 2000 classification induced a shift from anaplastic astrocytoma to glioblastoma.

The results on anatomical location showed that there was a strong increase in gliomas located in the temporal and parietal lobes prior to the period of substantial mobile phone use, but not during it. There were increases for gliomas located in the frontal lobe both before and during increased mobile phone use, however the temporal and parietal lobes are more highly exposed to RF radiation than other brain sites when using mobile phones. Cardis et al (2008) reported that depending on the type of mobile phone and the manner in which it is used, the RF energy absorption is at least several times higher in the temporal lobe than in the frontal lobe.(26) In our data there was a large number of gliomas with unspecified or overlapping location. Reclassification of these did reduce the trends for the temporal lobe during the periods before substantial mobile phone use, and for the frontal lobe during all the periods.

In our study we also compared the observed incidence with a modelled predicted incidence assuming a causal association between mobile phone use and glioma as reported in the Interphone and Hardell studies. The results suggest that, if the effects of mobile phones on glioma risk are real, then the incidence rates would be far higher than those observed. Previous studies by Little et al (2012) and more recently by Chapman et al (2016) have also shown that when modelling the RRs from the Interphone and Hardell studies and assuming a latency of 10 years, the predicted incidence rates are much higher.(12, 13) The exact causes of brain cancer are unknown and so is the latency period for the disease. Ionising radiation has been shown to induce brain cancer by causing DNA damage with a latency period of about 5 or more years.(27) RF exposure is non-ionising radiation which doesn't cause direct DNA damage and it has been argued that a possible effect would have a latency shorter than 5 years.(12) However, it has also been argued that the latency for an increased risk of brain cancer could be both short and long, indicating tumour initiation and promotion, respectively.(28) In our study we modelled predicted incidence rates for a variety of latency periods up to 20 years. Our model found that the predicted incidence rates were higher than the observed rates for a latency period up to 15 years. A longer observation period is required in order to model longer latency periods.

The present study has some limitations. We estimated mobile phone use using information on mobile phone accounts, and this may not be a true indicator of actual use as some people may have multiple accounts and others may use a phone without having an account. We mitigated this by also using data from a consumer survey conducted by the national telecommunications regulator on the proportion of the population using mobile phones. Information from the survey was only available from the years 2009 to 2013 and this was applied to data on the annual number of mobile phone accounts from 1987. However, mobile phone use patterns have likely changed from 1987 to 2009. Further, the exposure metric is unclear when investigating whether mobile phone use is implicated in brain cancer risk. Prevalence of phone use is a de facto measure for the amount of RF energy a person is receiving when using a mobile phone, and changes in technology and patterns of individual use were not taken into account in this investigation. For example, advances in mobile telephony have resulted in greatly reduced output power of the phones

and the evolving use of mobile phones has resulted in less actual calling time with the phone against the head.

We estimated the prevalence of mobile phone use equally across the 20-59 age range and both males and females. The use of subscription data in early years is likely to underestimate prevalence of use in males and overestimate it in females given that users in early years were middle-aged working men on company mobile phone subscriptions.(13) In later years mobile phone use became equal between the two genders.(29)

For information on the proportion of regular and heavy mobile phone users we used data from the Interphone study, which also included data from Australia. Mobile phone use in the Interphone study was self-reported, relying on participants' recall of past phone use.(2) Sensitivity analyses on the Interphone methodology reported that for short term recall (up to a year) there was underestimation of phone use by regular users and overestimation by heavy users.(30) For longer recall (3 to 5 years) there was an underestimation of number of calls and an overestimation on the duration of calls for all users.(31) Based on these findings it is likely that the proportion of heavy users in our study is overestimated. Further, the real patterns of mobile phone use may be more complex than the scenarios we modelled.

Finally the results of our study are prone to the ecological fallacy and small risks in subgroups in the population may not have been detected. Further, the stable trend in brain tumour incidence could have concealed a true increasing risk related to mobile phone use which appeared flat due to declines in other risk factors.

In conclusion, we found no evidence that mobile phone use increased any brain tumour histological types or subtypes. There was an increase in the incidence of glioblastoma prior to the rapid increase in mobile phone use which was most likely due to improved diagnosis from MRI. Furthermore, there was no increase in gliomas of the temporal lobe, which is the most exposed location, during the period of substantial mobile phone use. The increase in gliomas of the temporal lobe and decrease in gliomas of unspecified location during the periods prior to substantial mobile phone use are in line with the theory of improved diagnosis from CT and MRI. Further, the predicted rates were higher than the observed rates for latency periods up to 15 years. These results do not support an association between mobile phone use and brain tumour, although the possibility of a small risk or a latency period of more than 15 years cannot be excluded. Future research should continue to investigate trends in brain tumour histological types, grading and anatomical location for a possible increase with a longer latency period.

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Author Contributors: KK, ME, GB and RC designed the study. KK and LT collected the data. KK and ME reviewed the literature. KK, ME, GB RC directed the analyses which were carried out by KK, MS and LT. KK wrote the initial draft. All authors critically revised the manuscript for intellectual content and approved the final version.

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Competing interests: ME has received personal fees from the New Zealand Government Health Department on an independent report on specified health issues of electric and magnetic fields. KK, GB, MS, LT and RC declare no conflict of interests.

Ethics Approval: Data from the AIHW had no personal identifying information. The data was collected by AIHW from each Australian state and territory cancer registry and ethics approval was required to use the data from South Australia (SA). The SA Department for Health and Ageing Human Research Ethics Committee granted ethics approval for use of the SA data (Reference Number: HREC/17/SAH/41).

Transparency: The lead author, KK, affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; no important aspects of the study have been omitted; and any discrepancies from the study as originally planned (and, if relevant, registered) have been explained.

Data sharing: No additional data available.

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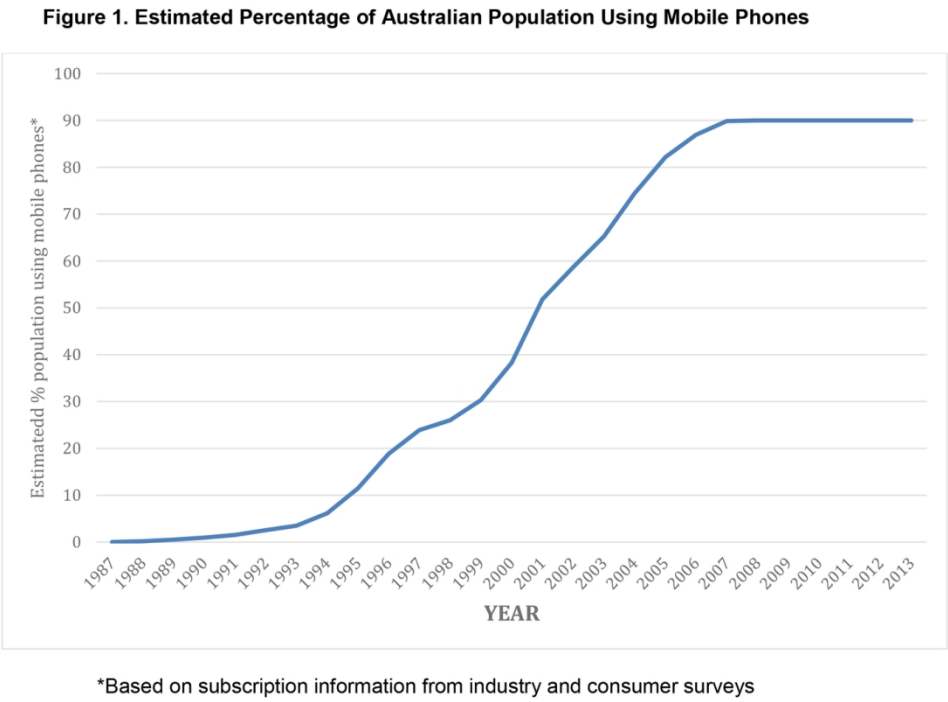


Figure 1. Estimated Percentage of Australian Population Using Mobile Phones

127x93mm (300 x 300 DPI)

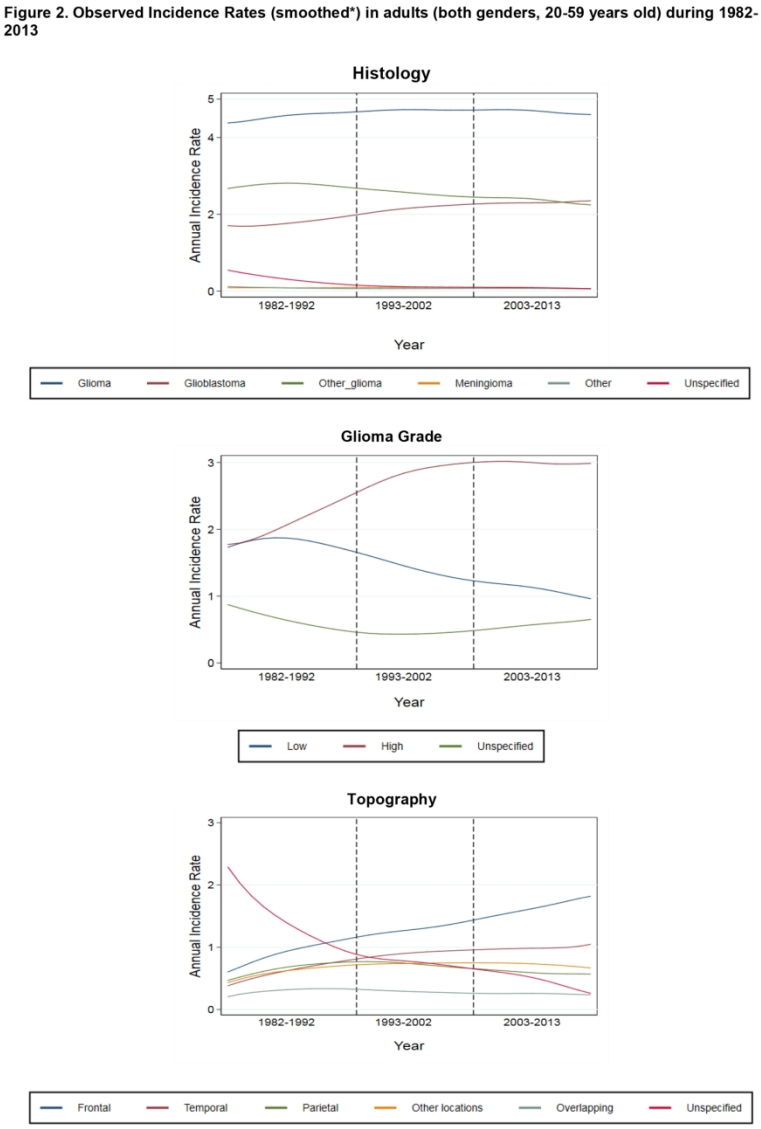


Figure 2. Observed Incidence Rates (smoothed*) in adults (both genders, 20-59 years old) during 1982-2013

233x346mm (300 x 300 DPI)

Figure 3. Observed (smoothed*) and predicted incidence rates in adults (both genders, 20-59 years old) during 1982-2013

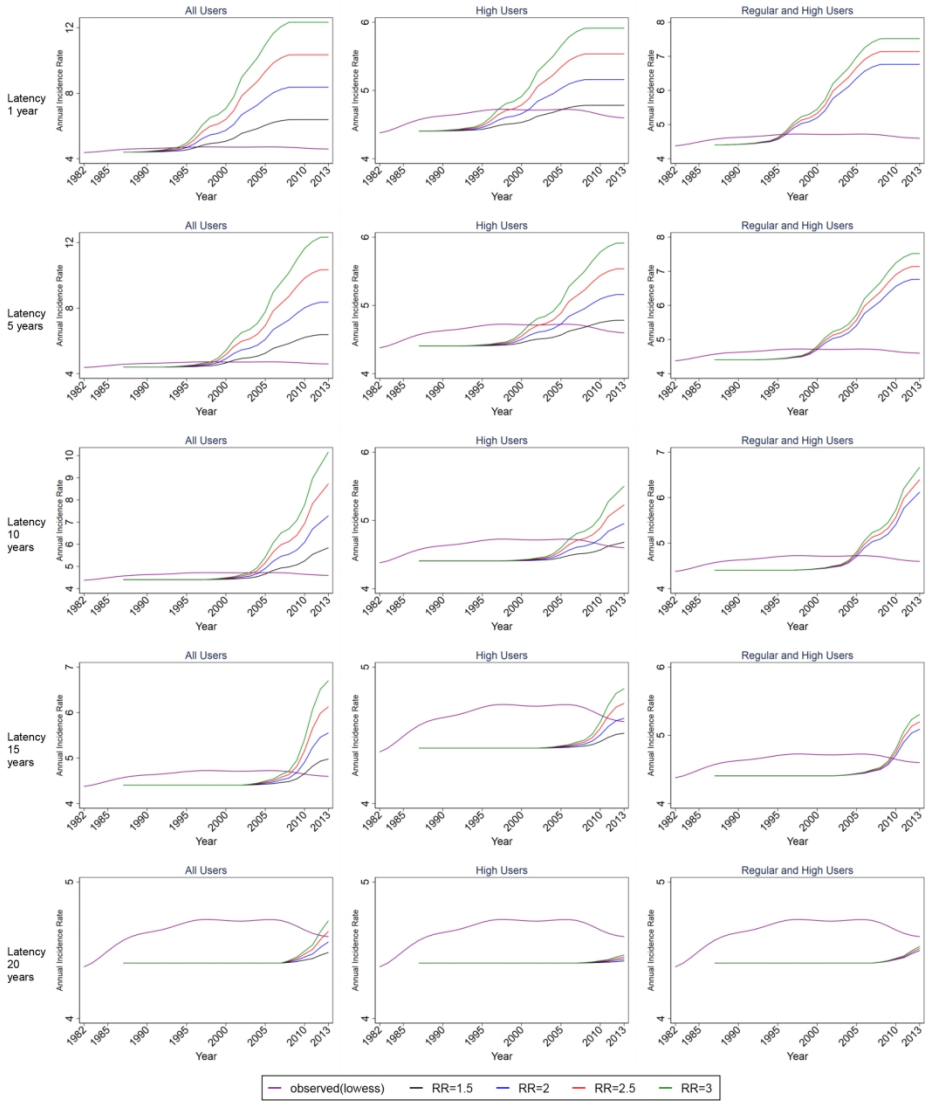
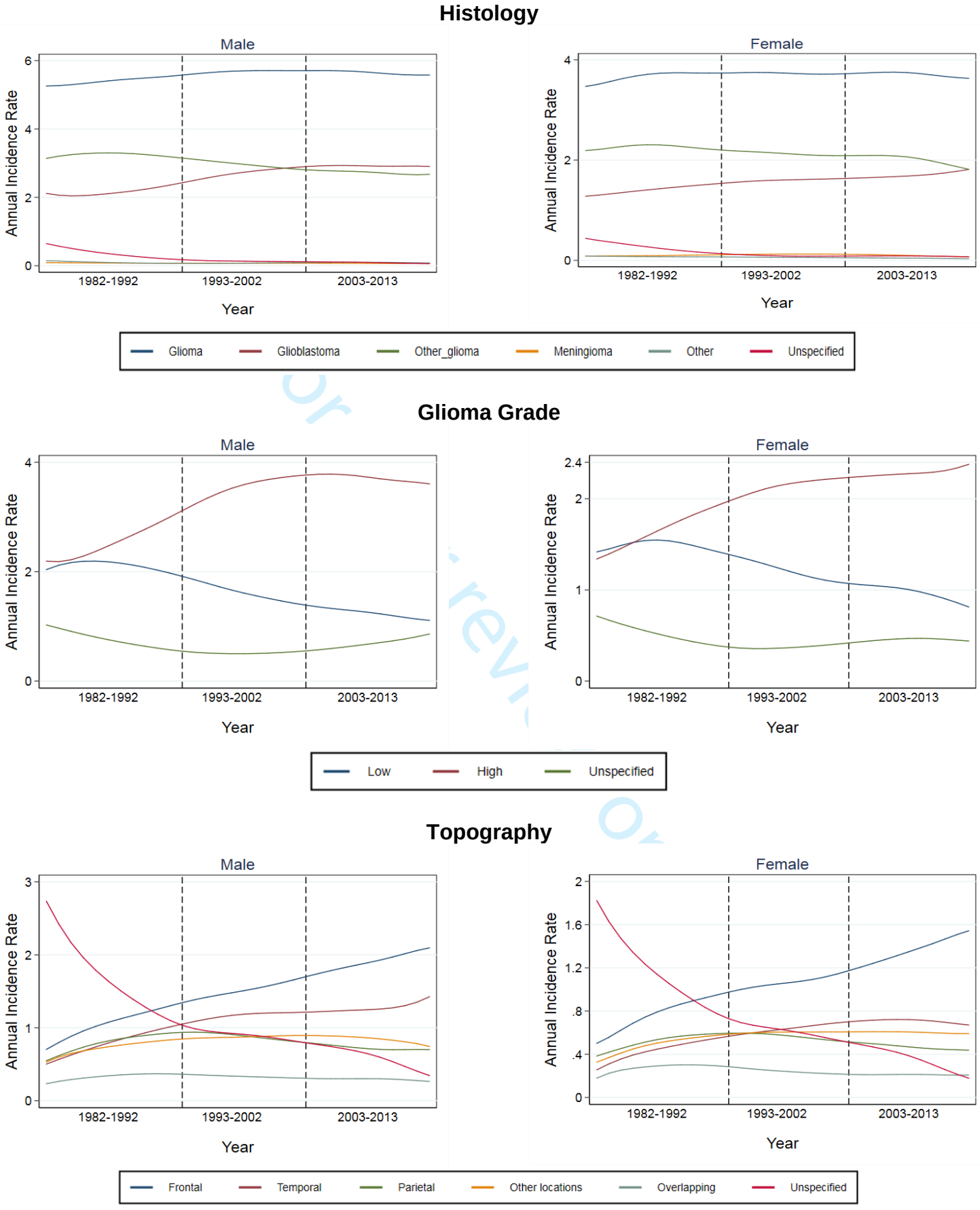


Figure 3. Observed (smoothed*) and predicted incidence rates during 1982-2013

223x289mm (300 x 300 DPI)

Supplementary Figure A. Observed Incidence Rates (smoothed*) in adults (males and females, 20-59 years old) during 1982-2013



*Lowess Smoothing

Supplementary Table A. Observed brain tumour incidence trends in adults (males and females, 20-59 years old) during increased CT and MRI use (1982-1982), advances in MRI use (1993-2002) and substantial mobile phone use (2003-2013)

	Male									female								
	1982-1992			1993-2002			2003-2013			1982-1992			1993-2002			2003-2013		
	N	APC*	95% CI	N	APC	95% CI	N	APC	95% CI	N	APC	95% CI	N	APC	95% CI	N	APC	95% CI
All	2841	-0.4	(-1.5,0.8)	3207	0.8	(-0.4,2.1)	4035	-0.5	(-1.6,0.5)	1952	0.7	(-0.7,2.1)	2063	0.1	(-1.4,1.6)	2727	-1.2	(-2.4,0.1)
Histology																		
Glioma	2597	0.8	(-0.4,2)	3064	0.7	(-0.5,2)	3857	-0.3	(-1.3,0.8)	1750	1.6	(0.1,3.1)	1926	-0.1	(-1.7,1.5)	2564	-1	(-2.3,0.3)
Glioblastoma	996	1.1	(-0.8,3.1)	1528	3.4	(1.5,5.3)	2083	0.6	(-0.9,2.1)	642	1.7	(-0.7,4.2)	869	0.5	(-1.9,2.9)	1208	1.2	(-0.7,3.2)
Other glioma	1601	0.6	(-0.9,2.2)	1536	-1.7	(-3.4,0)	1774	-1.2	(-2.7,0.3)	1108	1.6	(-0.3,3.5)	1057	-0.5	(-2.6,1.6)	1356	-2.7	(-4.4,-1)
Meningioma	39	-2.8	(-12,7.3)	40	1.5	(-9.1,13.4)	48	-1.2	(-10.3,8.9)	43	1.8	(-7.2,11.7)	70	2.9	(-5.4,11.8)	72	-6.5	(-13.8,1.3)
Other	44	-11.8	(-19.9,-2.8)	36	3.7	(-7.6,16.3)	63	-5.2	(-12.3,2.5)	35	-1.9	(-11.5,8.8)	30	-7.5	(-18.6,5.1)	31	-5.8	(-16.2,5.9)
Unspecified	161	-15.2	(-19.5,-10.8)	67	1.9	(-6.4,10.9)	67	-7.9	(-15.1,0)	124	-10.9	(-15.8,-5.8)	37	9.8	(-2.2,23.2)	60	-1.4	(-9.4,7.4)
Glioma Grade																		
Low	1066	0.4	(-1.5,2.3)	825	-4.1	(-6.4,-1.8)	812	-2.9	(-5,-0.7)	751	2.1	(-0.1,4.5)	593	-3.2	(-5.9,-0.4)	652	-3.5	(-5.9,-1)
High	1179	3.7	(1.9,5.6)	1987	2.9	(1.2,4.5)	2615	-0.3	(-1.6,1)	759	3.8	(1.5,6.1)	1164	1	(-1,3.1)	1596	0.3	(-1.4,2)
Unspecified	352	-7.2	(-10.2,-4.1)	252	1.2	(-3.1,5.7)	430	4.7	(1.5,8)	240	-6.4	(-10.1,-2.6)	169	3.7	(-1.7,9.4)	316	-1.5	(-5.1,2.1)
Glioma Location																		
Frontal	539	6.9	(4,9.8)	802	4.4	(1.9,7.1)	1252	2.9	(1,4.8)	394	9.2	(5.8,12.8)	543	2.7	(-0.3,5.9)	892	3.3	(1,5.6)
Temporal	384	7.5	(4.2,11)	655	3	(0.3,5.9)	856	1.9	(-0.4,4.3)	215	6.9	(2.4,11.6)	327	2.6	(-1.2,6.6)	515	-1.9	(-4.7,1.1)
Parietal	404	6.8	(3.5,10.1)	495	-1.1	(-4.1,2.1)	490	0.2	(-2.8,3.3)	251	5.9	(1.9,10.2)	306	-1.6	(-5.5,2.3)	326	-1.3	(-4.9,2.5)
Other locations	358	3.8	(0.4,7.2)	473	0.6	(-2.5,3.9)	583	-2	(-4.6,0.7)	247	7.2	(3,11.6)	305	0.4	(-3.5,4.4)	406	-1.4	(-4.6,1.8)
Overlapping	167	4.9	(0,10.1)	170	-7.7	(-12.5,-2.6)	217	-2.8	(-7.1,1.7)	131	1.9	(-3.4,7.5)	126	-10.3	(-15.7,-4.4)	157	-1.7	(-6.9,3.7)
Unspecified	745	-11.4	(-13.4,-9.3)	469	-3.2	(-6.3,-0.1)	459	-9.8	(-12.6,-6.9)	512	-10	(-12.4,-7.4)	319	-2.3	(-6,1.6)	268	-11.6	(-15.2,-7.8)

*APC = Annual percent change

Supplementary Table B. Observed brain tumour incidence trends in adults (males and females, 20-59 years old) after redistribution of unclassified tumours

	Male									female								
	1982-1992			1993-2002			2003-2013			1982-1992			1993-2002			2003-2013		
	N	APC*	95% CI	N	APC	95% CI	N	APC	95% CI	N	APC	95% CI	N	APC	95% CI	N	APC	95% CI
All	2841	-0.4	(-1.5,0.8)	3207	0.8	(-0.4,2.1)	4035	-0.5	(-1.6,0.5)	1952	0.7	(-0.7,2.1)	2063	0.1	(-1.4,1.6)	2727	-1.2	(-2.4,0.1)
Histology																		
Glioma	2755	-0.1	(-1.3,1.1)	3131	0.8	(-0.5,2)	3924	-0.4	(-1.5,0.6)	1868	0.8	(-0.6,2.2)	1963	0.1	(-1.5,1.7)	2623	-1	(-2.3,0.3)
Glioblastoma	1059	0.1	(-1.8,2)	1560	3.4	(1.6,5.3)	2118	0.4	(-1,1.9)	687	0.9	(-1.5,3.2)	885	0.6	(-1.7,3)	1235	1.2	(-0.7,3.2)
Other glioma	1699	-0.3	(-1.8,1.2)	1571	-1.7	(-3.4,0)	1806	-1.3	(-2.8,0.2)	1187	0.7	(-1.1,2.5)	1078	-0.3	(-2.4,1.8)	1389	-2.7	(-4.4,-1)
Meningioma	40	-4.1	(-13,5.8)	40	1.5	(-9.1,13.4)	48	-1.2	(-10.3,8.9)	44	0.7	(-8.1,10.4)	70	2.9	(-5.4,11.8)	72	-6.5	(-13.8,1.3)
Other	46	-12.9	(-20.8,-4.1)	36	3.7	(-7.6,16.3)	63	-5.2	(-12.3,2.5)	36	-3.2	(-12.6,7.2)	30	-7.5	(-18.6,5.1)	31	-5.8	(-16.2,5.9)
Glioma Grade																		
Low	1236	-0.8	(-2.5,0.9)	899	-4.1	(-6.3,-1.9)	914	-2.2	(-4.3,-0.2)	871	0.7	(-1.4,2.9)	649	-2.9	(-5.5,-0.3)	745	-3.5	(-5.7,-1.2)
High	1361	2.3	(0.6,4)	2165	2.9	(1.4,4.5)	2943	0.3	(-0.9,1.6)	879	2.5	(0.4,4.6)	1277	1.4	(-0.5,3.4)	1819	0.1	(-1.4,1.7)
Glioma Topography																		
Frontal	827	1.1	(-1.1,3.2)	1013	3	(0.8,5.3)	1515	1.4	(-0.3,3.1)	620	2.9	(0.4,5.5)	706	1.4	(-1.3,4)	1065	1.9	(-0.1,4)
Temporal	591	2	(-0.5,4.7)	827	1.6	(-0.8,4.1)	1036	0.2	(-1.9,2.3)	338	1.4	(-2,4.8)	425	1.3	(-2.1,4.8)	620	-3.4	(-5.9,-0.7)
Parietal	404	6.8	(3.5,10.1)	495	-1.1	(-4.1,2.1)	490	0.2	(-2.8,3.3)	399	0.2	(-2.8,3.3)	399	-3.1	(-6.4,0.3)	390	-2.7	(-6,0.6)
Other locations	556	-1.5	(-4.1,1.1)	599	-0.8	(-3.6,2.1)	710	-3.5	(-5.8,-1)	392	1	(-2.1,4.2)	397	-0.9	(-4.3,2.6)	488	-3	(-5.9,-0.1)

*APC = Annual percent change

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation	Met	Page	If not met, reasons why not
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	Yes	1	
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	Yes	2	
Introduction					
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	Yes	4	
Objectives	3	State specific objectives, including any prespecified hypotheses	Yes	4	
Methods					
Study design	4	Present key elements of study design early in the paper	Yes	4-5	
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	Yes	4-5	
Participants	6	*Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	Yes	4-5	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	Yes	5-6	
Data sources/ measurement	8	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	Yes	4-5	
Bias	9	Describe any efforts to address potential sources of bias	No		The study used all the available brain tumour data through Australia's high quality state and territory population-based cancer registration system. Other biases stemming from the inherent nature of the ecological study design are described in the Discussion section
Study size	10	Explain how the study size was arrived at	Yes	4-5	
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	Yes	5	

Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	Yes	5-6	
		(*b*) Describe any methods used to examine subgroups and interactions	Yes	5-6	
		(*c*) Explain how missing data were addressed	Yes	5	
		(*d*) *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	N/A		
		(*e*) Describe any sensitivity analyses	Yes	6	
Results					
Participants	13	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	Yes	6-7	
		(b) Give reasons for non-participation at each stage	N/A		This is not relevant for this study (all potentially available persons were included in the analysis).
		(c) Consider use of a flow diagram	N/A		This is not relevant for this study (all potentially available persons were included in the analysis).
Descriptive data	14	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Yes	6-7	
		(b) Indicate number of participants with missing data for each variable of interest	N/A		None of the included participants had missing data. There was no available data for one Australian state (New South Wales) for the year 2013.
Outcome data	15	*Cross-sectional study*—Report numbers of outcome events or summary measures	Yes	7-9	
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	No		Giving estimates unadjusted for age will result in biased results
		(*b*) Report category boundaries when continuous variables were categorized	N/A		
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	N/A		

Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	Yes	7-9
Discussion				
Key results	18	Summarise key results with reference to study objectives	Yes	10
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	Yes	11-12
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	Yes	12
Generalisability	21	Discuss the generalisability (external validity) of the study results	Yes	12
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Mobile phone use and incidence of brain tumour histological types, grading or anatomical location: A population-based ecological study

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ABSTRACT

Objective
Some studies have reported increasing trends in certain brain tumours and a possible link with mobile phone use has been suggested. We examined the incidence time trends of brain tumour in Australia for three distinct time-periods to ascertain the influence of improved diagnostic technologies and increase in mobile phone use on the incidence of brain tumours.

Design
In a population based ecological study we examined trends of brain tumour over the periods 1982-1992, 1993-2002 and 2003-2013. We further compared the observed incidence during the period of substantial mobile phone use (2003-2013) with predicted (modelled) incidence for the same period by applying various relative risks, latency periods and mobile phone use scenarios.

Setting
National Australian incidence registration data on primary cancers of the brain diagnosed between 1982 and 2013.

Population
16,825 eligible brain cancer cases aged 20 to 59 from all of Australia (10,083 males and 6,742 females).

Main Outcome Measures
Annual percent change (APC) in brain tumour incidence based on Poisson regression analysis.

Results
The overall brain tumour rates remained stable during all three periods. There was an increase in glioblastoma during 1993-2002 (APC = 2.3, 95% Confidence Interval = 0.8-3.7) which was likely due to advances in the use of MRI during that period. There were no increases in any brain tumour types, including glioma (-0.6, -1.4-0.2) and glioblastoma (0.8, -0.4-2.0), during the period of substantial mobile phone use from 2003-2013. During that period there was also no increase in glioma of the temporal lobe (0.5, -1.3-2.3), which is the location most exposed when using a mobile phone. Predicted incidence rates were higher than the observed rates for latency periods up to 15 years.

Conclusions
In Australia, there has been no increase in any brain tumour histological type or glioma location that can be attributed to mobile phones.

Strengths and limitations of this study

- This study investigated incidence time trends for different brain tumour histological types, grading and anatomical location over different time-periods.
- The study compared the observed brain tumour incidence rates with modelled predicted incidence rates assuming a causal association with mobile phone use.
- Mobile phone subscription data and information from surveys may not accurately represent mobile phone use patterns in adults.

INTRODUCTION

Since its introduction in the mid-80s mobile phone use has grown rapidly worldwide. When using a mobile phone against the head, the brain is exposed to much higher levels of radiofrequency (RF) radiation than the rest of the body (1) and there has been continuing concern of a possible association with brain cancer. Several case–control and registry-based cohort studies have found little evidence to support such an association.(1) However a few other case-control studies, most notably the Interphone study (2010) and a Swedish study by Hardell et al (2011), have reported modest to large associations with glioma, the most common type of primary brain tumour.(2-4) These studies have generally found no association with other brain tumour types such as meningioma. Based on these results the International Agency for Research on Cancer (IARC) has classified RF as "possibly carcinogenic to humans".(5)

From a public health perspective, given that the great majority of the population regularly uses mobile phones, even a relatively small excess risk would result in a significant number of additional brain tumour cases. In time, such an increase would be observable in cancer surveillance data sources.(6) The World Health Organization has previously identified as a high research priority the monitoring of brain tumour incidence trends through well-established population-based cancer registries and combined with population exposure data.(7)

Since the WHO recommendation a limited number of ecological studies have shown that although the prevalence of mobile phone use (usually measured through the number of mobile phone accounts) has seen a massive increase, the time trends of brain tumour incidence have remained fairly stable.(8, 9) Other studies have shown increases in certain brain tumour sub-types or specific anatomical locations.(9, 10) However, it has been suggested that the introduction of better diagnostic methods (computed tomography, CT; and magnetic resonance imaging, MRI) have improved the detection of brain cancers which leads to increased population incidence.(11) Further, a few recent studies, most notably in the US and Australia, have shown that predicted incidence rates based on the associations reported by the Interphone and Hardell studies for "heavy" mobile phone users are higher than the observed rates.(12, 13) Apart from the study by Little et al (2012) previous results have generally failed to show the incidence trends for different brain tumour histological and topographical types.(12) Further, the simulation of expected rates in these studies was only performed for a latency period of 10 years and if there is an association with mobile phone use the latency could be longer.

In this study, we analysed the incidence trends of brain tumour for three distinct time-periods to ascertain the influence of improved diagnostic methods and increase in mobile phone use. The analysis considered different histological types and sub-types, glioma grades and glioma anatomical sites. We further compared the observed incidence during the period of substantial mobile phone use (2003-2013) with predicted incidence for the same period based on relative risks (RRs) reported by the two epidemiological studies forming the basis of the IARC classification.(2, 3)

METHODS

Collection of Incidence Data

Incidence data on primary cancers of the brain and central nervous system diagnosed between 1982 and 2013 inclusive (the latest available) were obtained from the Australian Institute of Health and Welfare (AIHW). Reporting of incident invasive cancer is mandatory

in all Australian states and territories and the AIHW has been collecting and reporting national data on brain cancer incidence since 1982. The data included information on primary anatomical site (International Classification of Diseases version 10, ICD-10 topography codes, C70-C72), histology, diagnosis year and diagnosis age (in five-year groups: 0-4, 5-9 ….. 80-84, 85+). Data were not available for one Australian state (New South Wales) for the year 2013.

Patient and public involvement

Patients or the public were not involved in this study.

Statistical Analysis of Observed Incidence

Based on the results of the Interphone study we analysed intracranial brain cancer incidence in adults aged 20-59; neoplasms of the spinal cord, cranial nerves and other parts of central nervous system (ICD-10 code C72) were excluded. Annual age-standardized incidence rates per 100,000 person-years were calculated separately for males, females and both genders by using the World Health Organization's (WHO) standard population. Histology was analysed by categorising glioma, meningioma, other histological types and brain cancers with unspecified histology based on WHO's Classification of Tumors of the Central Nervous System.(14) We further analysed glioma by categorising glioblastoma (which is the most common brain tumour sub-type), glioma grade (low, high and unspecified) and glioma location (frontal lobe, temporal lobe, parietal lobe, other locations, overlapping lobes and unspecified). The categories analysed and their respective ICD-10 codes are shown in Table 1.

Table 1. ICD-10 Histology and Topography Codes

Histology	
Glioma	9380-9480
Glioblastoma	9440-9442
Meningioma	9530-9539
Other	8010-9371, 9490-9508, 9540-9561
Unspecified	8000-8004
Glioma Grade	
Low (I & II)	9384, 9391, 9393, 9400, 9410, 9411, 9420, 9421, 9424, 9425, 9450
High (III & IV)	9381, 9392, 9401, 9440-9442, 9451, 9470-9474, 9480
Unspecified	9380, 9382, 9390, 9423, 9430, 9460,
Topography	
Frontal	C711
Temporal	C712
Parietal	C713
Other locations	C700, C701, C709, C710, C714-C717
Overlapping	C718
Unspecified	C719

A large number of tumours had unspecified classifications, particularly for glioma grade and glioma location. We approximated the classification of unspecified tumours by recalculating the adjusted rates for each year by adding the unspecified group to the other groups in proportion to the distribution of specified tumours.

The incidence rates were low compared to the population at risk so the variability in the observed cases was assumed to follow a Poisson distribution.(15) Analyses of incidence time trends were carried out using Poisson regression to estimate the annual percent

change (APC) in the incidence, with corresponding 95% confidence intervals (CI) over three time-periods: 1982-1992 (representing increased CT and MRI use), 1993-2002 (representing advances in MRI) and 2003-2013 (representing substantial and increasing mobile phone use; more than 65% of the population).(16) Lowess smoothing was used in the graphical representation of the time trends.

Mobile Phone Use Data Sources

Mobile phone use was estimated using information on mobile phone accounts and survey data on actual use. Data on the annual number of mobile phone accounts from 1987, when mobile telephony first commenced in Australia, to 2013 was obtained from the national telecommunications regulator, the Australian Communications and Media Authority (ACMA). The number of mobile phone accounts per capita for each year was calculated by dividing the number of accounts by the total Australian population in that year (obtained from the Australian Bureau of Statistics), noting that since 2008 the annual number of accounts has been exceeding the number of people in the population. This data is not a true indication of mobile phone use as some users may have had more than one account and other users no account. A consumer survey conducted by ACMA reported that approximately 90% of the population used mobile phones in the years 2009 to 2013.(17) We estimated the annual prevalence of mobile phone use (shown in Figure 1) by multiplying the annual number of accounts per capita by a factor of 0.9.(17) It was not possible to stratify prevalence of use by age or gender; thus an overall estimate of prevalence is provided equally for all ages across the 20-59 age range and for both males and females.

Statistical Analysis of Predicted Incidence

With the assumption that mobile phone use is associated with glioma in adults as reported by the Interphone and Swedish studies, we calculated predicted incidence rates and time trends by applying various relative risks (RRs, 1.5, 2, 2.5, 3) and latency periods (1, 5, 10, 15, 20 years) for three different mobile phone use scenarios:

a) All users – RRs were applied to all mobile phone users
b) Heavy users – RRs were applied to heavy mobile phone users (defined as 19% of mobile phone users by the Interphone study)
c) Regular users and heavy users - RR of 1.5 applied to regular users (81% of all users) and RRs of 2, 2.5 and 3 applied to heavy users (19% of all users)

The annual predicted incidence rates were calculated for the period 1987-2013 using the formula:

$$\text{Predicted Incidence} = (P \times RR \times I_B) + ((1 - P) \times I_B)$$

where P denotes the annual prevalence of mobile phone use, RR the relative risk and I_B the pre-mobile phone baseline incidence from 1982-1987. Confidence intervals and statistical significance of observed and expected incidence rates were calculated using Poisson confidence intervals as described in Ulm (1990).(18) Analyses of predicted incidence time trends were carried out by estimating the APC for the period 2003-2013, representing the time that mobile phone use increased rapidly.

We used Stata/SE 15.0 for all analyses. The reporting of our study conforms to the STROBE statement.(19)

RESULTS

Observed Incidence

There was a total of 16,825 eligible brain cancer cases aged 20 to 59 (10,083 males and 6,742 females) that were diagnosed between 1982 and 2013. Of these 15,758 (93.7%) were gliomas, 312 (1.9%) were meningiomas, 239 (1.4%) were other histological types and 516 (3.1%) were tumours of unspecified histology. The most common brain tumour sub-type was glioblastoma (7,326, 43.5%). Of the gliomas, 4,699 (29.8%) were low grade, 9,300 (59%) were high grade and 1,759 (11.2%) were of unspecified grade. The most common glioma anatomical location was the frontal lobe (4,422, 28.1%), followed by the temporal lobe (2,952, 18.7%) and parietal lobe (2272, 14.4%). There were 2,372 (15.1%) tumours in other locations, 968 (6.1%) overlapping locations and 2772 (17.6%) with unspecified location.

The observed incidence rates between 1982 and 2013 are shown in Figure 2 for both genders and Supplementary Figure A for males and females separately. Further, the observed incidence trends (given as APC) over the time-periods 1982-1992, 1993-2002 and 2003-2013 are shown in Table 2 for both genders and Supplementary Table A for males and females separately. The overall brain tumour rates remained stable in all three time-periods and the trends were similar for males and females. Glioblastoma increased during the period that saw advances in MRI (1993-2002) whilst it remained stable during the period of substantial mobile phone use (2003-2013); this later period also saw a decrease in other glioma sub-types. The APC for glioblastoma in both genders for the entire observation period i.e. 1982-2013 (not shown in Table 2) was 1.45 (1.11-1.79). There was a strong decreasing trend in brain tumours with unspecified histology during the period of increased CT and MRI use (1982-1992). With the redistribution of unspecified tumours there were no significant changes to these histological trends (Table 3 for both genders and Supplementary Table B for males and females separately).

Table 2. Observed age-standardised brain tumour incidence trends in adults (both genders, 20-59 years old) during increased CT and MRI use (1982-1992), advances in MRI use (1993-2002) and substantial mobile phone use (2003-2013)

*APC = Annual percent change

	1982-1992			1993-2002			2003-2013		
	N	APC*	95% CI	N	APC	95% CI	N	APC	95% CI
All	4793	0.1	(-0.8,1)	5270	0.5	(-0.5,1.5)	6762	-0.8	(-1.6,0)
Histology									
Glioma	4347	1.1	(0.2,2.1)	4990	0.4	(-0.6,1.4)	6421	-0.6	(-1.4,0.2)
Glioblastoma	1638	1.4	(-0.1,2.9)	2397	2.3	(0.8,3.7)	3291	0.8	(-0.4,2)
Other glioma	2709	1	(-0.2,2.2)	2593	-1.2	(-2.6,0.1)	3130	-1.8	(-2.9,-0.7)
Meningioma	82	-0.4	(-6.9,6.6)	110	2.4	(-4.2,9.4)	120	-4.4	(-10.1,1.7)
Other	79	-7.3	(-13.6,-0.6)	66	-1.5	(-9.5,7.2)	94	-5.3	(-11.3,1)
Unspecified	285	-13.4	(-16.6,-10)	104	4.6	(-2.3,12)	127	-4.8	(-10.3,0.9)
Glioma Grade									
Low	1817	1.1	(-0.4,2.6)	1418	-3.8	(-5.5,-2)	1464	-3.1	(-4.7,-1.5)
High	1938	3.8	(2.3,5.2)	3151	2.1	(0.9,3.4)	4211	-0.1	(-1.1,1)
Unspecified	592	-6.9	(-9.2,-4.5)	421	2.2	(-1.2,5.7)	746	2	(-0.4,4.5)
Glioma Location									
Frontal	933	7.8	(5.6,10.1)	1345	3.7	(1.8,5.7)	2144	3	(1.6,4.5)
Temporal	599	7.3	(4.6,10.1)	982	2.8	(0.6,5.2)	1371	0.5	(-1.3,2.3)
Parietal	655	6.4	(3.9,9.1)	801	-1.3	(-3.7,1.1)	816	-0.4	(-2.7,2)
Other locations	605	5.1	(2.5,7.8)	778	0.5	(-1.9,3)	989	-1.7	(-3.8,0.3)
Overlapping	298	3.5	(-0.1,7.3)	296	-8.8	(-12.5,-5)	374	-2.3	(-5.6,1.1)
Unspecified	1257	-10.8	(-12.4,-9.2)	788	-2.9	(-5.2,-0.4)	727	-10.5	(-12.7,-8.2)

Table 3. Observed age-standardised brain tumour incidence trends in adults (both genders, 20-59 years old) after redistribution of unclassified tumours

	1982-1992			1993-2002			2003-2013		
	N	APC*	95% CI	N	APC	95% CI	N	APC	95% CI
All	4793	0.1	(-0.8,1)	5270	0.5	(-0.5,1.5)	6762	-0.8	(-1.6,0)
Histology									
Glioma	4623	0.2	(-0.7,1.2)	5094	0.5	(-0.5,1.5)	6547	-0.7	(-1.5,0.1)
Glioblastoma	1746	0.4	(-1.1,1.9)	2445	2.4	(0.9,3.8)	3353	0.7	(-0.5,1.9)
Other glioma	2886	0.1	(-1,1.2)	2649	-1.1	(-2.5,0.2)	3195	-1.9	(-3,-0.8)
Meningioma	84	-1.6	(-7.9,5.2)	110	2.4	(-4.2,9.4)	120	-4.4	(-10.1,1.7)
Other	82	-8.6	(-14.7,-2)	66	-1.5	(-9.5,7.2)	94	-5.3	(-11.3,1)
Glioma Grade									
Low	2107	-0.2	(-1.5,1.2)	1548	-3.6	(-5.3,-1.9)	1659	-2.8	(-4.3,-1.3)
High	2240	2.4	(1.1,3.7)	3442	2.3	(1.1,3.5)	4762	0.2	(-0.7,1.2)
Glioma Topography									
Frontal	1447	1.8	(0.2,3.5)	1719	2.3	(0.6,4)	2580	1.6	(0.3,2.9)
Temporal	929	1.8	(-0.2,3.9)	1252	1.5	(-0.5,3.5)	1656	-1.2	(-2.8,0.4)
Parietal	803	3.4	(1.2,5.7)	894	-2	(-4.2,0.3)	880	-1.1	(-3.3,1.1)
Other locations	948	-0.5	(-2.5,1.5)	996	-0.8	(-3,1.4)	1198	-3.3	(-5.1,-1.4)

*APC = Annual percent change

Looking at glioma grade in Table 2, high grade gliomas increased during both periods of improved diagnosis whilst low grade gliomas decreased during the periods of advances in MRI (1993-2002) and substantial mobile phone use (2003-2013). There was a strong decreasing trend in gliomas with unspecified grade during the period of increased CT and MRI use (1982-1992). The redistribution of unspecified tumours did not change the glioma grade trends (Table 3).

For glioma location in Table 2, there were increasing trends for all locations and a strong decreasing trend for unspecified location during the period of increased CT and MRI use (1982-1992). There were also increases in the frontal and temporal lobes and a smaller decrease in unspecified location during the period of advances in MRI (1993-2002); this period also had a very large decrease in gliomas with overlapping location. During the period of substantial mobile use there were no increases in any of the locations apart from the frontal lobe and there was a strong decrease in unspecified location. With the redistribution of a high number of gliomas with unspecified and overlapping location there was a much lower increasing trend only for gliomas in the frontal lobe during all three periods and a large increase in the parietal lobe during the first period (Table 3).

Predicted Incidence

Assuming a causal association between mobile phone use and glioma, the predicted incidence trends for both genders during 2003-2013 by applying various relative risks, latency periods and mobile phone use scenarios are shown in Table 4. The predicted incidence trends showed an increase for most mobile phone use scenarios and latency periods that were modelled apart from a 20-year latency period. There were also no statistically significant increases when applying the model to only heavy users for RRs less than 3. The highest expected trends were generally seen for a 10-year latency period, which was the latency period associated with mobile phones and brain tumour as reported in the Interphone and Swedish studies.

The observed and predicted glioma incidence rates for both genders from 1987 to 2013 are shown in Figure 3 for a 10 year latency and Supplementary Figure B for 1, 5, 15 and 20 year latencies. With a RR of 2 for all mobile phone users and a latency of 10 years, the predicted incidence rate for both genders in 2013 was 7.3 per 100,000 people (95% confidence interval 6.7 to 7.9) compared to the observed 4.5 per 100,000. The predicted rates increase to 8.7 (8.1 to 9.3) and 10.2 (9.5 to 10.8) per 100,000 for RRs of 2.5 and 3 respectively. With a RR of 1.5 for regular users and a RR of 2 for heavy users and a latency of 10 years the predicted rate was 6.1 per 100,000 (5.6 to 6.6); increasing to 6.4 (5.9 to 6.9) and 6.7 (6.1 to 7.2) when applying RRs of 2.5 and 3 to heavy users, respectively. Assuming a latency of 15 years, the predicted incidence rates in 2013 were also higher compared to the observed rate. The model did not show an increasing trend for a latency of 20 years.

Table 4. Predicted glioma incidence trends for both genders (20-59 years) during 2003-2013

Scenario	Latency	RR=1.5		RR=2		RR=2.5		RR=3	
		APC*	95% CI	APC	95% CI	APC	95% CI	APC	95% CI
All Users	**1**	1.1	(0.3,1.8)	1.6	(1,2.3)	2.0	(1.4,2.6)	2.3	(1.7,2.8)
	5	2.8	(2,3.5)	4.5	(3.8,5.2)	5.7	(5.1,6.4)	6.6	(6,7.3)
	10	2.7	(1.9,3.6)	4.9	(4.1,5.7)	6.7	(5.9,7.5)	8.2	(7.4,8.9)
	15	1.3	(0.5,2.2)	2.5	(1.7,3.4)	3.7	(2.8,4.5)	4.8	(3.9,5.6)
	20	0.2	(-0.7,1)	0.3	(-0.5,1.2)	0.5	(-0.4,1.3)	0.6	(-0.2,1.5)
High Users	**1**	0.3	(-0.6,1.1)	0.5	(-0.3,1.3)	0.7	(-0.1,1.5)	0.9	(0.1,1.6)
	5	0.6	(-0.2,1.5)	1.2	(0.4,2)	1.8	(1,2.6)	2.2	(1.5,3)
	10	0.3	(-0.6,1.1)	0.5	(-0.3,1.4)	0.8	(-0.1,1.6)	1.0	(0.2,1.9)
	15	0.3	(-0.6,1.1)	0.5	(-0.3,1.4)	0.8	(-0.1,1.6)	1.0	(0.2,1.9)
	20	0.0	(-0.8,0.9)	0.1	(-0.8,0.9)	0.1	(-0.8,0.9)	0.1	(-0.7,1)
Regular users and high users				**RR=1.5 (R), 2 (H)**		**RR=1.5 (R), 2.5 (H)**		**RR=1.5 (R), 3 (H)**	
	1			1.2	(0.5,1.9)	1.3	(0.6,2)	1.4	(0.8,2.1)
	5			3.2	(2.4,3.9)	3.5	(2.8,4.3)	3.9	(3.1,4.6)
	10			3.2	(2.4,4)	3.6	(2.8,4.4)	4.0	(3.2,4.8)
	15			1.5	(0.7,2.4)	1.8	(0.9,2.6)	2.0	(1.2,2.9)
	20			0.2	(-0.7,1)	0.2	(-0.6,1.1)	0.2	(-0.6,1.1)

*APC = Annual percent change

DISCUSSION

The results of our study showed that the overall brain tumour rates in adults aged 20 to 59 years showed no increasing or decreasing trend. This is in line with studies showing stable brain tumour trends in other countries.(9-11) Furthermore, the trends in our study were stable for different histological types, like glioma, which has been reported in some case-control studies as being associated with mobile phone use.(2, 3) The all glioma incidence rates were stable in both the periods before (1982-1992, 1993-2002) and the period after (2003-2013) substantial mobile phone use. For a causal relationship between mobile phone use and brain cancer, one would expect an increasing trend in the later period and no trend in the earlier periods.

There has been limited research showing the time trends of histological sub-types and particularly glioblastoma, which is the most common and most malignant brain tumour sub-type in adults.(4) Phillips et al (2018) reported that the incidence of glioblastoma more than doubled in England between 1995 and 2015; however the authors did not analyse different periods to investigate the impact of mobile phone use.(20) Dobes et al (2011) reported an increasing trend in glioblastoma incidence in Australia between 2000 and 2008 in people aged 65 years or older; noting that the cases were ascertained directly from neurological centres.(21) Our study used all the national incident brain cancer registrations available through Australia's high quality state and territory population-based cancer registration system. Registration is mandatory and histological verification rates exceed 85%.(13) In our study, which focused on the age group most likely to be affected by mobile phone use, there was an increasing trend for glioblastoma when looking at the entire observation period (1982-20130). However, when looking at different time periods there was no increase in the glioblastoma rates during the period of substantial mobile phone use but there was an increase in the glioblastoma rates in the earlier periods: 1982-1992 (non-statistically significant increase), which saw increased use of CT and MRI, and, 1993-2002 (statistically significant increase) which saw further advances in MRI. Technological developments in MRI during 1993-2002, including diffusion and perfusion imaging, improved significantly the discrimination of brain tumour types and sub-types.(16, 22) Other factors, such as improved access to care and an increase in the number of specialists, may also have played a role in the increase.(8) Earlier studies investigating trends in brain-tumour sub-types including glioblastoma have commented that increases in certain sub-types are accompanied by decreases in other sub-types whilst overall brain tumour incidence has remained stable.(23, 24) These studies suggest improvements in diagnostic technology as the reason for increasing trends in certain brain tumour sub-types.(23, 24)

The results on histology are consistent with the results by grade, as high-grade glioma is approximately equivalent to glioblastoma. During the period of advances in MRI there was an increase for high-grade lesions, and a decrease for low-grade, both which levelled off during the period of substantial mobile phone use. These results are consistent with incidence trends reported by Barchana et al (2012) for low-grade and high grade gliomas in Israel between 1980 and 2009.(25) Furthermore, there was a strong decrease for unspecified histology, and for unspecified grade during the first period, and this is likely due to improvements in diagnosis using CT and histopathological classification.(26) There have also been shifts in classifying sub-types and grade in updated editions of the WHO classification; for example the WHO 2000 classification induced a shift from anaplastic astrocytoma to glioblastoma.

The results on anatomical location showed that there was an increase in gliomas located in the temporal and parietal lobes prior to the period of substantial mobile phone use, but not during it. There were increases for gliomas located in the frontal lobe both before and during increased mobile phone use, however the temporal and parietal lobes are more highly exposed to RF radiation than other brain sites when using mobile phones. Cardis et al (2008) reported that depending on the type of mobile phone and the manner in which it is used, the RF energy absorption is at least several times higher in the temporal lobe than in the frontal lobe.(27) In our data there was a large number of gliomas with unspecified or overlapping location. Reclassification of these did reduce the trends for the temporal lobe during the periods before substantial mobile phone use, and for the frontal lobe during all the periods.

In our study we also compared the observed incidence with a modelled predicted incidence assuming a causal association between mobile phone use and glioma as reported in the Interphone and Hardell studies. The results suggest that, if the effects of mobile phones on glioma risk are real, then the incidence rates would be far higher than those observed. We modelled predicted incidence rates for a variety of latency periods up to 20 years whereas previous studies only included latencies up to 10 years. (12, 13) Previous studies by Little et al (2012) and more recently by Chapman et al (2016) have also shown that when modelling the RRs from the Interphone and Hardell studies and assuming a latency of 10 years, the predicted incidence rates are much higher.(12, 13) The exact causes of brain cancer are unknown and so is the latency period for the disease. Ionising radiation has been shown to induce brain cancer by causing DNA damage with a latency period of about 5 or more years.(28) RF exposure is non-ionising radiation which doesn't cause direct DNA damage and it has been argued that a possible effect would have a latency shorter than 5 years.(12) However, it has also been argued that the latency for an increased risk of brain cancer could be both short and long, indicating tumour initiation and promotion, respectively.(29) In our study we modelled predicted incidence rates for a variety of latency periods up to 20 years. Our model found that the predicted incidence rates were higher than the observed rates for a latency period up to 15 years. A longer observation period is required in order to model longer latency periods.

The present study has some limitations. The accuracy of the Australian cancer registration system in the early periods when it began in the 80s is unknown for all the states and territories. In Northern Territory mandatory notification of cancer cases by pathology laboratories was introduced in 1991. Case ascertainment was found to be approximately 40% incomplete for the period 1981-1986 and approximately 10% incomplete for the period 1987-1990. However the Northern Territory makes up a very small proportion of Australia's population (~ 1%).(30) All Australian state and territory registries conform to the International Agency for Research on Cancer's criteria for population based cancer registration, are "A" rated and have their data published in the "Cancer Incidence in Five Continents" series. (13, 31).

We estimated mobile phone use using information on mobile phone accounts, and this may not be a true indicator of actual use as some people may have multiple accounts and others may use a phone without having an account. We mitigated this by also using data from a consumer survey conducted by the national telecommunications regulator on the proportion of the population using mobile phones. Information from the survey was only available from the years 2009 to 2013 and this was applied to data on the annual number of mobile phone accounts from 1987. However, mobile phone use patterns have likely changed from 1987 to 2009. Further, the exposure metric is unclear when investigating whether mobile phone use is implicated in brain cancer risk. Prevalence of phone use is a de facto measure for the

amount of RF energy a person is receiving when using a mobile phone, and changes in technology and patterns of individual use were not taken into account in this investigation. For example, advances in mobile telephony have resulted in greatly reduced output power of the phones and the evolving use of mobile phones has resulted in less actual calling time with the phone against the head.

We estimated the prevalence of mobile phone use equally across the 20-59 age range and both males and females. The use of subscription data in early years is likely to underestimate prevalence of use in males and overestimate it in females given that users in early years were middle-aged working men on company mobile phone subscriptions.(13) In later years mobile phone use became equal between the two genders.(32)

For information on the proportion of regular and heavy mobile phone users we used data from the Interphone study, which also included data from Australia. Mobile phone use in the Interphone study was self-reported, relying on participants' recall of past phone use.(2) Sensitivity analyses on the Interphone methodology reported that for short term recall (up to a year) there was underestimation of phone use by regular users and overestimation by heavy users.(33) For longer recall (3 to 5 years) there was an underestimation of number of calls and an overestimation on the duration of calls for all users.(34) Based on these findings it is likely that the proportion of heavy users in our study is overestimated. Further, the real patterns of mobile phone use may be more complex than the scenarios we modelled.

Finally this is an ecological observational study, not based on individual data thus it is not possible to account for confounding factors. This study design is appropriate to define global trends. The results of our study are prone to the ecological fallacy and small risks in subgroups in the population may not have been detected. Further, the stable trend in brain tumour incidence could have concealed a true increasing risk related to mobile phone use which appeared flat due to declines in other risk factors.

In conclusion, we found no evidence that mobile phone use increased any brain tumour histological types or subtypes. There was an increase in the incidence of glioblastoma prior to the rapid increase in mobile phone use which was most likely due to improved diagnosis from MRI. Furthermore, there was no increase in gliomas of the temporal lobe, which is the most exposed location, during the period of substantial mobile phone use. The increase in gliomas of the temporal lobe and decrease in gliomas of unspecified location during the periods prior to substantial mobile phone use are in line with the theory of improved diagnosis from CT and MRI. Further, the predicted rates were higher than the observed rates for latency periods up to 15 years. These results do not support an association between mobile phone use and brain tumour, although the possibility of a small risk or a latency period of more than 15 years cannot be excluded. Future research should continue to investigate trends in brain tumour histological types, grading and anatomical location for a possible increase with a longer latency period.

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Author Contributors: KK, ME, GB and RC designed the study. KK and LT collected the data. KK and ME reviewed the literature. KK, ME, GB RC directed the analyses which were

carried out by KK, MS and LT. KK wrote the initial draft. All authors critically revised the manuscript for intellectual content and approved the final version.

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Competing interests: ME has received personal fees from the New Zealand Government Health Department on an independent report on specified health issues of electric and magnetic fields. KK, GB, MS, LT and RC declare no conflict of interests.

Ethics Approval: Data from the AIHW had no personal identifying information. The data was collected by AIHW from each Australian state and territory cancer registry and ethics approval was required to use the data from South Australia (SA). The SA Department for Health and Ageing Human Research Ethics Committee granted ethics approval for use of the SA data (Reference Number: HREC/17/SAH/41).

Transparency: The lead author, KK, affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; no important aspects of the study have been omitted; and any discrepancies from the study as originally planned (and, if relevant, registered) have been explained.

Data sharing: No additional data available.

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FIGURE LEGENDS

Figure 1. Estimated Percentage of Australian Population Using Mobile Phones

Figure 2. Observed Incidence Rates (smoothed*) in adults (both genders, 20-59 years old) during 1982-2013

Figure 3. Observed (smoothed*) and predicted (10 year latency) incidence rates in adults (both genders, 20-59 years old) during 1982-2013

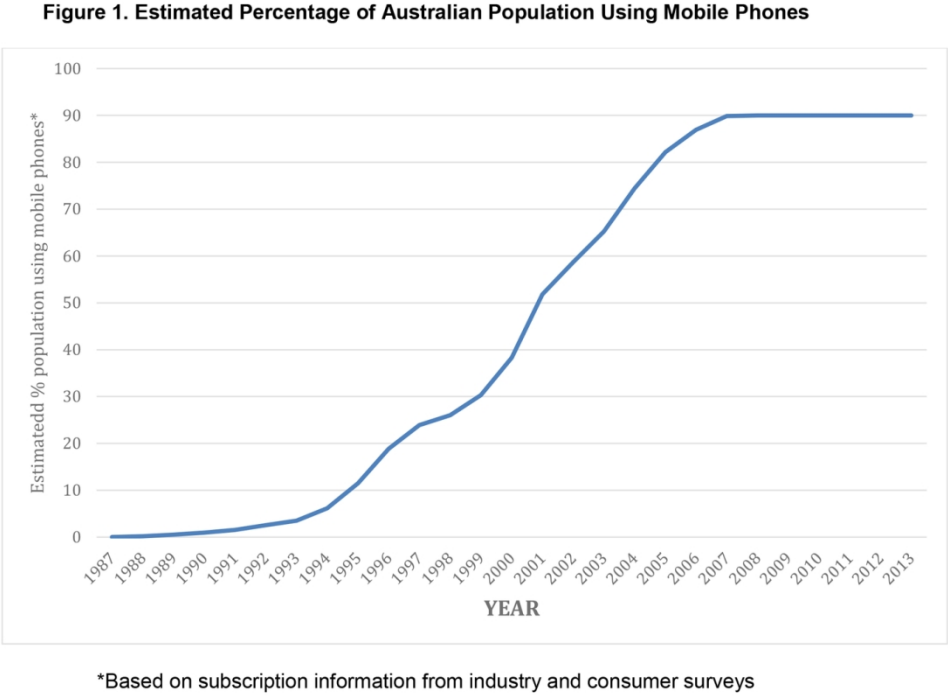


Figure 1. Estimated Percentage of Australian Population Using Mobile Phones

127x93mm (300 x 300 DPI)

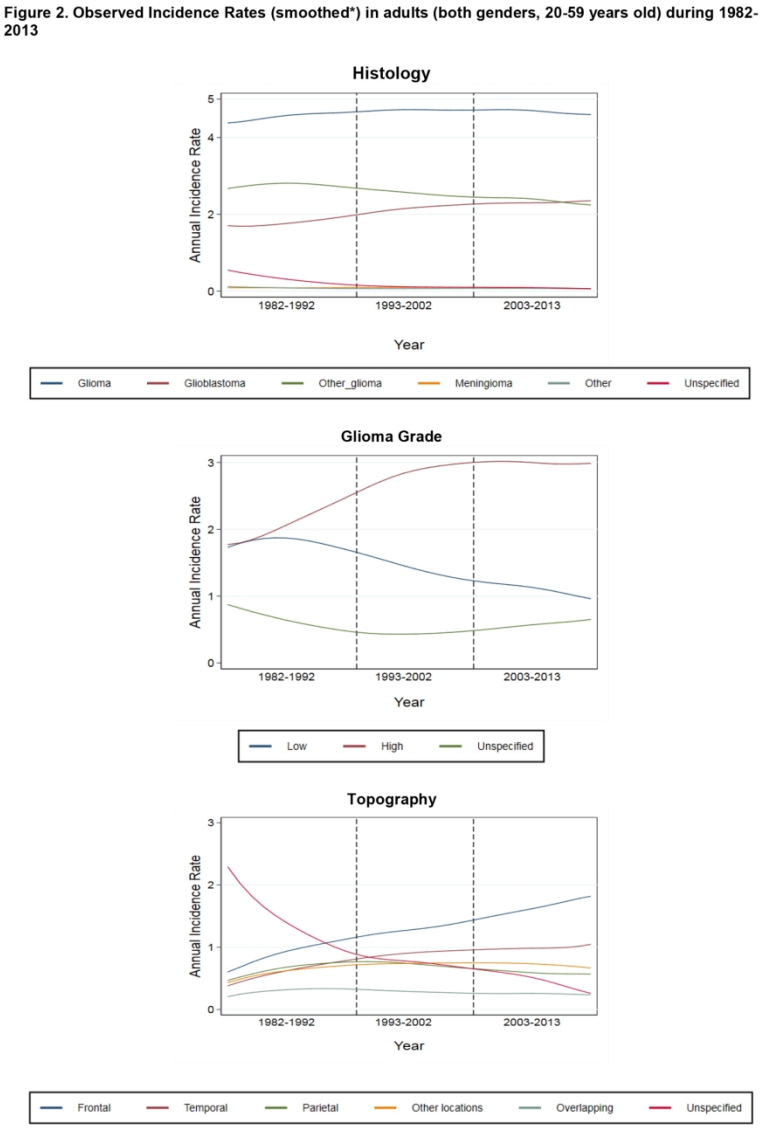


Figure 2. Observed Incidence Rates (smoothed*) in adults (both genders, 20-59 years old) during 1982-2013

233x346mm (300 x 300 DPI)

Figure 3. Observed (smoothed*) and predicted (10 year latency) incidence rates in adults (both genders, 20-59 years old) during 1982-2013

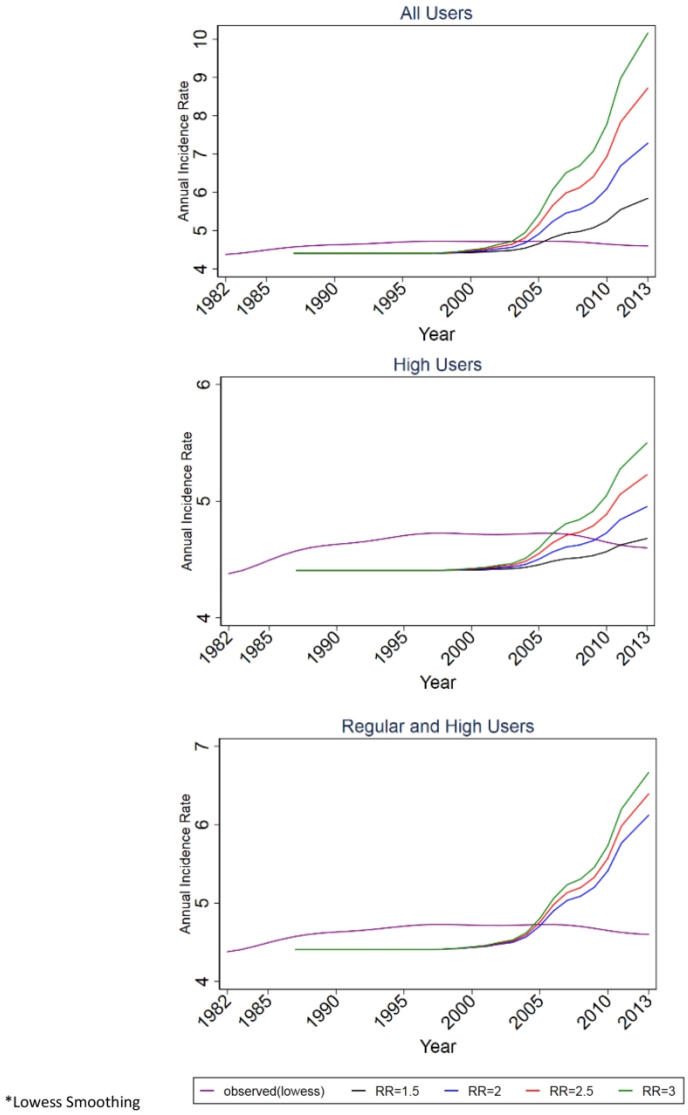
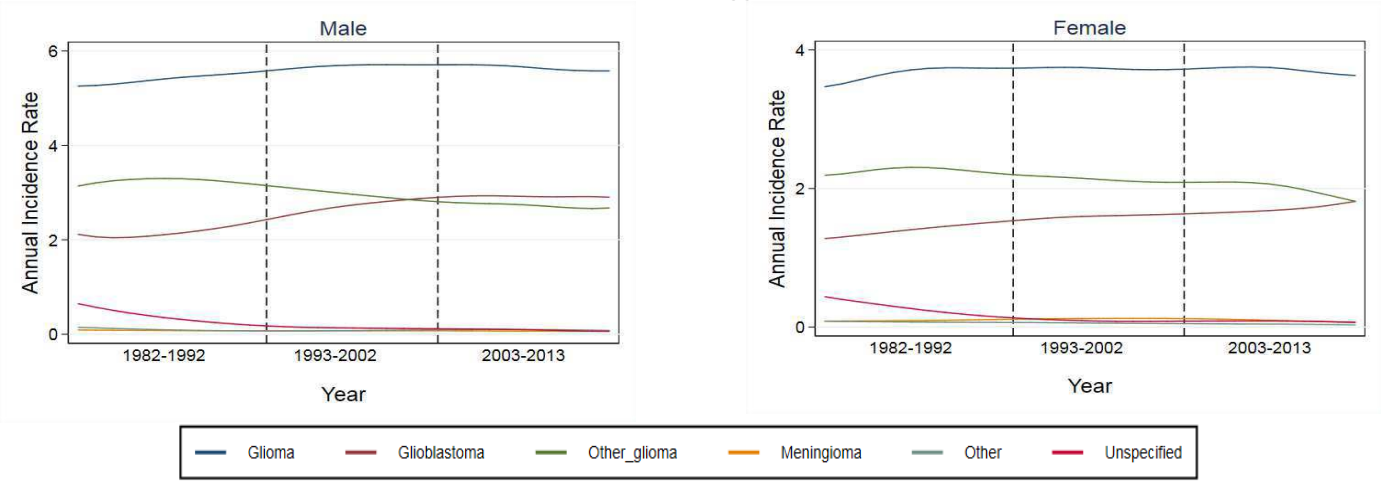


Figure 3. Observed (smoothed*) and predicted (10 year latency) incidence rates in adults (both genders, 20-59 years old) during 1982-2013

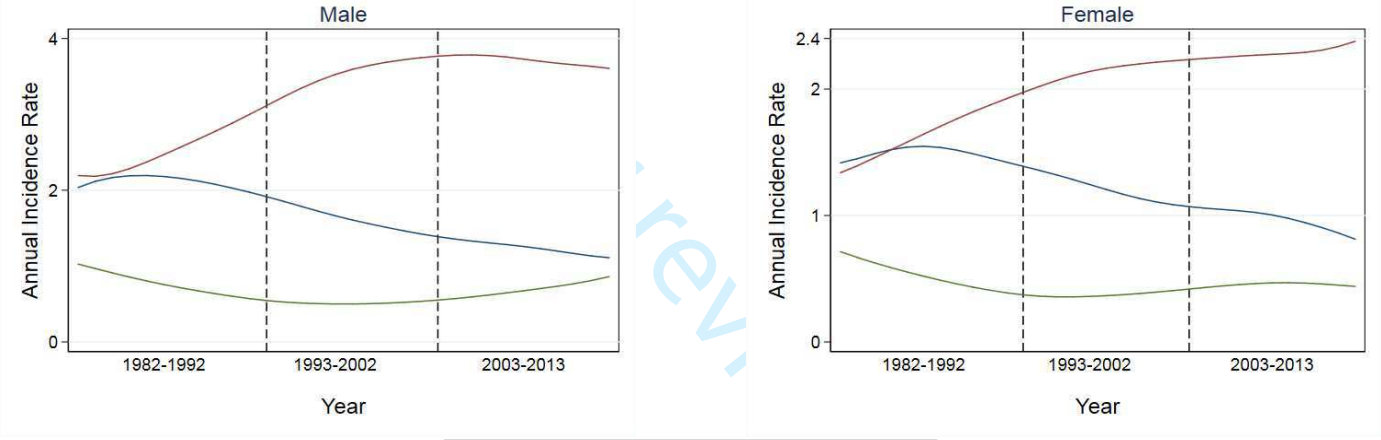
233x322mm (300 x 300 DPI)

Supplementary Figure A. Observed Incidence Rates (smoothed*) in adults (males and females, 20-59 years old) during 1982-2013

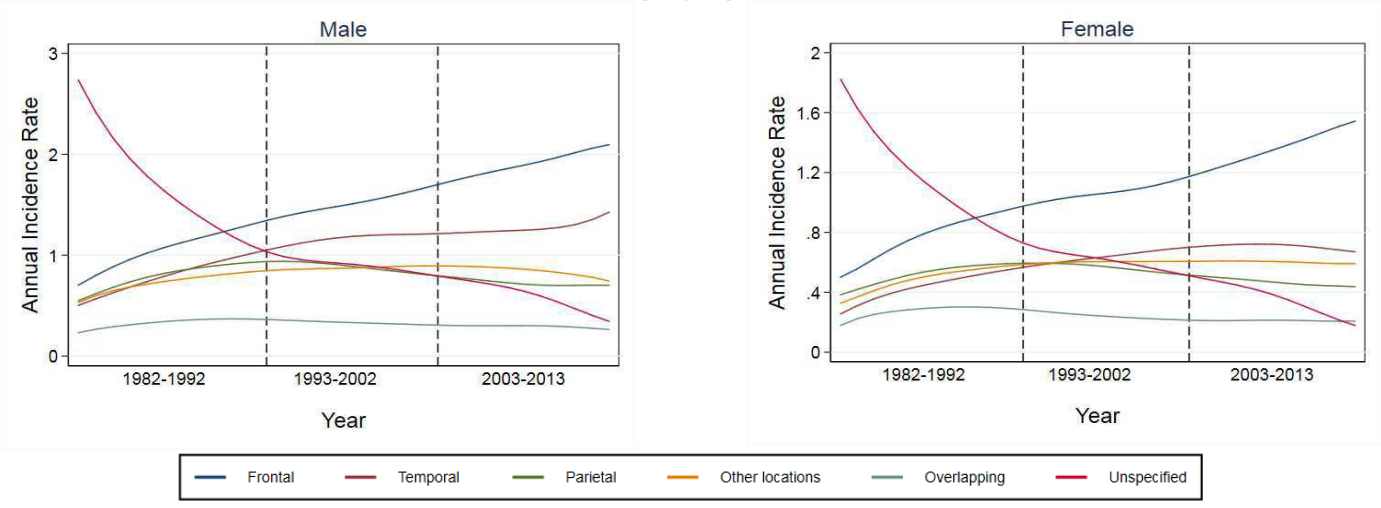
Histology



Glioma Grade

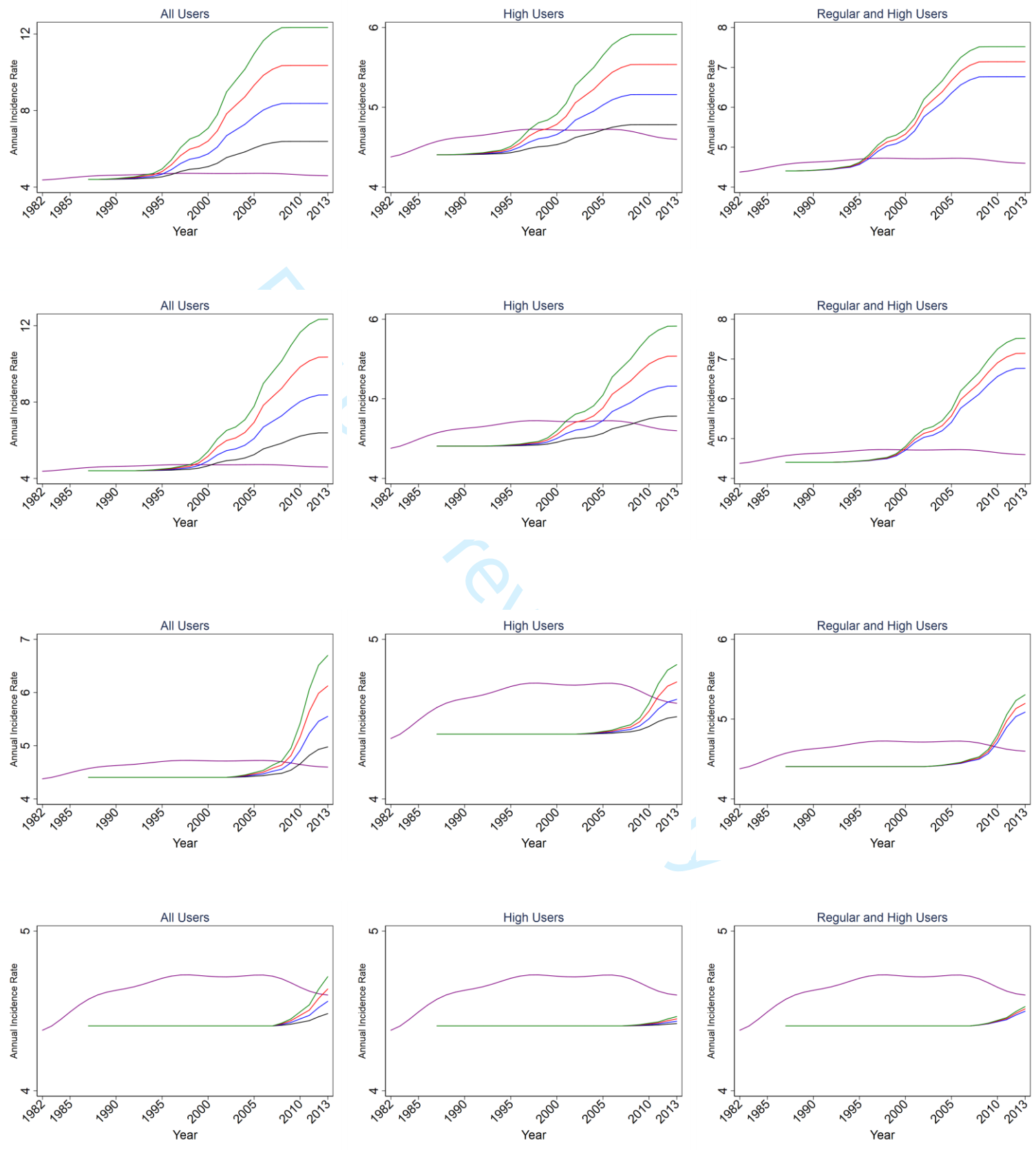


Topography



*Lowess Smoothing

Supplementary figure B. Observed (smoothed*) and predicted (1, 5, 10, 20 year latency) incidence rates in adults (both genders, 20-59 years old) during 1982-2013



*Lowess Smoothing

Supplementary Table A. Observed age-standardised brain tumour incidence trends in adults (males and females, 20-59 years old) during increased CT and MRI use (1982-1992), advances in MRI use (1993-2002) and substantial mobile phone use (2003-2013)

	Male									Female								
	1982-1992			1993-2002			2003-2013			1982-1992			1993-2002			2003-2013		
	N	APC*	95% CI	N	APC	95% CI	N	APC	95% CI	N	APC	95% CI	N	APC	95% CI	N	APC	95% CI
All	2841	-0.4	(-1.5,0.8)	3207	0.8	(-0.4,2.1)	4035	-0.5	(-1.6,0.5)	1952	0.7	(-0.7,2.1)	2063	0.1	(-1.4,1.6)	2727	-1.2	(-2.4,0.1)
Histology																		
Glioma	2597	0.8	(-0.4,2)	3064	0.7	(-0.5,2)	3857	-0.3	(-1.3,0.8)	1750	1.6	(0.1,3.1)	1926	-0.1	(-1.7,1.5)	2564	-1	(-2.3,0.3)
Glioblastoma	996	1.1	(-0.8,3.1)	1528	3.4	(1.5,5.3)	2083	0.6	(-0.9,2.1)	642	1.7	(-0.7,4.2)	869	0.5	(-1.9,2.9)	1208	1.2	(-0.7,3.2)
Other glioma	1601	0.6	(-0.9,2.2)	1536	-1.7	(-3.4,0)	1774	-1.2	(-2.7,0.3)	1108	1.6	(-0.3,3.5)	1057	-0.5	(-2.6,1.6)	1356	-2.7	(-4.4,-1)
Meningioma	39	-2.8	(-12,7.3)	40	1.5	(-9.1,13.4)	48	-1.2	(-10.3,8.9)	43	1.8	(-7.2,11.7)	70	2.9	(-5.4,11.8)	72	-6.5	(-13.8,1.3)
Other	44	-11.8	(-19.9,-2.8)	36	3.7	(-7.6,16.3)	63	-5.2	(-12.3,2.5)	35	-1.9	(-11.5,8.8)	30	-7.5	(-18.6,5.1)	31	-5.8	(-16.2,5.9)
Unspecified	161	-15.2	(-19.5,-10.8)	67	1.9	(-6.4,10.9)	67	-7.9	(-15.1,0)	124	-10.9	(-15.8,-5.8)	37	9.8	(-2.2,23.2)	60	-1.4	(-9.4,7.4)
Glioma Grade																		
Low	1066	0.4	(-1.5,2.3)	825	-4.1	(-6.4,-1.8)	812	-2.9	(-5,-0.7)	751	2.1	(-0.1,4.5)	593	-3.2	(-5.9,-0.4)	652	-3.5	(-5.9,-1)
High	1179	3.7	(1.9,5.6)	1987	2.9	(1.2,4.5)	2615	-0.3	(-1.6,1)	759	3.8	(1.5,6.1)	1164	1	(-1,3.1)	1596	0.3	(-1.4,2)
Unspecified	352	-7.2	(-10.2,-4.1)	252	1.2	(-3.1,5.7)	430	4.7	(1.5,8)	240	-6.4	(-10.1,-2.6)	169	3.7	(-1.7,9.4)	316	-1.5	(-5.1,2.1)
Glioma Location																		
Frontal	539	6.9	(4,9.8)	802	4.4	(1.9,7.1)	1252	2.9	(1,4.8)	394	9.2	(5.8,12.8)	543	2.7	(-0.3,5.9)	892	3.3	(1,5.6)
Temporal	384	7.5	(4.2,11)	655	3	(0.3,5.9)	856	1.9	(-0.4,4.3)	215	6.9	(2.4,11.6)	327	2.6	(-1.2,6.6)	515	-1.9	(-4.7,1.1)
Parietal	404	6.8	(3.5,10.1)	495	-1.1	(-4.1,2.1)	490	0.2	(-2.8,3.3)	251	5.9	(1.9,10.2)	306	-1.6	(-5.5,2.3)	326	-1.3	(-4.9,2.5)
Other locations	358	3.8	(0.4,7.2)	473	0.6	(-2.5,3.9)	583	-2	(-4.6,0.7)	247	7.2	(3,11.6)	305	0.4	(-3.5,4.4)	406	-1.4	(-4.6,1.8)
Overlapping	167	4.9	(0,10.1)	170	-7.7	(-12.5,-2.6)	217	-2.8	(-7.1,1.7)	131	1.9	(-3.4,7.5)	126	-10.3	(-15.7,-4.4)	157	-1.7	(-6.9,3.7)
Unspecified	745	-11.4	(-13.4,-9.3)	469	-3.2	(-6.3,-0.1)	459	-9.8	(-12.6,-6.9)	512	-10	(-12.4,-7.4)	319	-2.3	(-6,1.6)	268	-11.6	(-15.2,-7.8)

*APC = Annual percent change

Supplementary Table B. Observed age-standardised brain tumour incidence trends in adults (males and females, 20-59 years old) after redistribution of unclassified tumours

	Male									Female								
	1982-1992			1993-2002			2003-2013			1982-1992			1993-2002			2003-2013		
	N	APC*	95% CI	N	APC	95% CI	N	APC	95% CI	N	APC	95% CI	N	APC	95% CI	N	APC	95% CI
All	2841	-0.4	(-1.5,0.8)	3207	0.8	(-0.4,2.1)	4035	-0.5	(-1.6,0.5)	1952	0.7	(-0.7,2.1)	2063	0.1	(-1.4,1.6)	2727	-1.2	(-2.4,0.1)
Histology																		
Glioma	2755	-0.1	(-1.3,1.1)	3131	0.8	(-0.5,2)	3924	-0.4	(-1.5,0.6)	1868	0.8	(-0.6,2.2)	1963	0.1	(-1.5,1.7)	2623	-1	(-2.3,0.3)
Glioblastoma	1059	0.1	(-1.8,2)	1560	3.4	(1.6,5.3)	2118	0.4	(-1,1.9)	687	0.9	(-1.5,3.2)	885	0.6	(-1.7,3)	1235	1.2	(-0.7,3.2)
Other glioma	1699	-0.3	(-1.8,1.2)	1571	-1.7	(-3.4,0)	1806	-1.3	(-2.8,0.2)	1187	0.7	(-1.1,2.5)	1078	-0.3	(-2.4,1.8)	1389	-2.7	(-4.4,-1)
Meningioma	40	-4.1	(-13,5.8)	40	1.5	(-9.1,13.4)	48	-1.2	(-10.3,8.9)	44	0.7	(-8.1,10.4)	70	2.9	(-5.4,11.8)	72	-6.5	(-13.8,1.3)
Other	46	-12.9	(-20.8,-4.1)	36	3.7	(-7.6,16.3)	63	-5.2	(-12.3,2.5)	36	-3.2	(-12.6,7.2)	30	-7.5	(-18.6,5.1)	31	-5.8	(-16.2,5.9)
Glioma Grade																		
Low	1236	-0.8	(-2.5,0.9)	899	-4.1	(-6.3,-1.9)	914	-2.2	(-4.3,-0.2)	871	0.7	(-1.4,2.9)	649	-2.9	(-5.5,-0.3)	745	-3.5	(-5.7,-1.2)
High	1361	2.3	(0.6,4)	2165	2.9	(1.4,4.5)	2943	0.3	(-0.9,1.6)	879	2.5	(0.4,4.6)	1277	1.4	(-0.5,3.4)	1819	0.1	(-1.4,1.7)
Glioma Topography																		
Frontal	827	1.1	(-1.1,3.2)	1013	3	(0.8,5.3)	1515	1.4	(-0.3,3.1)	620	2.9	(0.4,5.5)	706	1.4	(-1.3,4)	1065	1.9	(-0.1,4)
Temporal	591	2	(-0.5,4.7)	827	1.6	(-0.8,4.1)	1036	0.2	(-1.9,2.3)	338	1.4	(-2,4.8)	425	1.3	(-2.1,4.8)	620	-3.4	(-5.9,-0.7)
Parietal	404	6.8	(3.5,10.1)	495	-1.1	(-4.1,2.1)	490	0.2	(-2.8,3.3)	399	0.2	(-2.8,3.3)	399	-3.1	(-6.4,0.3)	390	-2.7	(-6,0.6)
Other locations	556	-1.5	(-4.1,1.1)	599	-0.8	(-3.6,2.1)	710	-3.5	(-5.8,-1)	392	1	(-2.1,4.2)	397	-0.9	(-4.3,2.6)	488	-3	(-5.9,-0.1)

*APC = Annual percent change

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation	Met	Page	If not met, reasons why not
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	Yes	1	
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	Yes	2	
Introduction					
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	Yes	4	
Objectives	3	State specific objectives, including any prespecified hypotheses	Yes	4	
Methods					
Study design	4	Present key elements of study design early in the paper	Yes	4-5	
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	Yes	4-5	
Participants	6	*Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	Yes	4-5	This was an ecological study and details on the population used (not the participants) were provided
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	Yes	5-6	
Data sources/ measurement	8	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	Yes	4-5	
Bias	9	Describe any efforts to address potential sources of bias	No		The study used all the available brain tumour data through Australia's high quality state and territory population-based cancer registration system. Other biases stemming from the inherent nature of the ecological study design are described in the Discussion section
Study size	10	Explain how the study size was arrived at	Yes	4-5	
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	Yes	5	

Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	Yes	5-6	This was an ecological study that did not consider confounding
		(*b*) Describe any methods used to examine subgroups and interactions	Yes	5-6	
		(*c*) Explain how missing data were addressed	Yes	5	
		(*d*) *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	N/A		
		(*e*) Describe any sensitivity analyses	Yes	6	
Results					
Participants	13	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	Yes	6-7	This was an ecological study and population numbers were reported
		(b) Give reasons for non-participation at each stage	N/A		This is not relevant for this study (all potentially available persons were included in the analysis).
		(c) Consider use of a flow diagram	N/A		This is not relevant for this study (all potentially available persons were included in the analysis).
Descriptive data	14	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Yes	6-7	
		(b) Indicate number of participants with missing data for each variable of interest	N/A		None of the included participants had missing data. There was no available data for one Australian state (New South Wales) for the year 2013.
Outcome data	15	*Cross-sectional study*—Report numbers of outcome events or summary measures	Yes	7-9	
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	No		Giving estimates unadjusted for age will result in biased results
		(*b*) Report category boundaries when continuous variables were categorized	N/A		
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	N/A		

Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	Yes	7-9
Discussion				
Key results	18	Summarise key results with reference to study objectives	Yes	10
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	Yes	11-12
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	Yes	12
Generalisability	21	Discuss the generalisability (external validity) of the study results	Yes	12
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	Yes	12