Australian National University

PFAS HEALTH STUDY

PFAS Health Study

Component four: Data linkage study of health outcomes associated with living in PFAS exposure areas

December 2021

Hsei Di Law, Bruce Armstrong, Catherine D'Este, Deborah Randall, Rose Hosking, Nina Lazarevic, Susan Trevenar, Kayla Smurthwaite, Aparna Lal, Robyn Lucas, Jochen Mueller, Archie Clements, Martyn Kirk, Rosemary Korda

Acknowledgements

This research is a project of the National Centre for Epidemiology and Population Health, Research School of Population Health, the Australian National University. The PFAS Health Study was commissioned by the Australian Government Department of Health. The information and opinions contained in it do not necessarily reflect the views or policy of the Australian National University or the Australian Government Department of Health.

We thank Alice Wetherell for creating the infographics for this report and Eva Smeets for assisting with ethics applications. We also thank Matthew Sidebotham from workwisewords for his editorial advice.

We thank the Australian Institute of Health and Welfare Data Integration Services Centre, The Centre for Health Record Linkage, Data Linkage Queensland, and NT Department of Health for their data linkage services, selection of the study populations and provision of data.

We thank the data custodians of all the databases used in this study including the Australian Institute of Health and Welfare, NSW Health, NT Health, Qld Health, the Australian Government Department of Education and Training, and all Australian State and Territory cancer registries.

We also thank the entire PHXchange team at the Research School of Population Health for their advice on communication for this report. Lastly, we thank the entire PFAS Health Study team for their contributions to this project.

We acknowledge and celebrate the First Australians on whose traditional lands we meet, and pay our respect to the Elders past, present and future.

Suggested citation

Law HD, Armstrong B, D'este C, Randall D, Hosking R, Lazarevic N, Trevenar S, Smurthwaite K, Lal A, Lucas R, Mueller J, Clements A, Kirk M, Korda R. PFAS Health Study Component four: Data linkage study of health outcomes associated with living in PFAS exposure areas. Canberra (AU): Australian National University; 2021 Dec.

Contacts

Professor Martyn Kirk
Principal Investigator PFAS Health Study
National Centre for Epidemiology and Population Health
Research School of Population Health
The Australian National University
Acton ACT 2600 Australia

Telephone: 61 2 6125 5609
Email: martyn.kirk@anu.edu.au
Website: https://nceph.anu.edu.au

Ms Sue Trevenar
Senior Research Officer PFAS Health Study
National Centre for Epidemiology and Population Health
Research School of Population Health
The Australian National University
Acton ACT 2600 Australia

Telephone: 1800 430 903
Email: pfas.health.study@anu.edu.au
Website: https://pfas.anu.edu.au

Contents

Plain language summary

Per- and polyfluoroalkyl substances (PFAS) are man-made chemicals that may have adverse effects on the environment and human health. The primary aim of the PFAS Data Linkage Study was to examine whether adverse health outcomes were more common in people who had lived in towns with known PFAS contamination—Katherine in Northern Territory (NT), Oakey in Queensland (Qld) and Williamtown in New South Wales (NSW) (the 'exposure towns'). To do this, we compared rates of selected health outcomes in these towns, to rates in other separate but similar areas in Australia not known to have PFAS contamination (the 'comparison areas').

We conducted three separate studies that investigated four groups of health outcomes. Study 1 investigated maternal and infant (perinatal) health (15 outcomes); Study 2 examined childhood development (6); and Study 3 investigated cancer (23) and deaths due to specific causes (4)—a total of 48 outcomes. All studies used multiple data sources with records collected over many years, which were linked to create richer datasets for analyses. All data used were originally collected for administrative purposes. We only used data that did not identify individual people and no direct contact was made with anyone whose data were included in the studies.

Over the three separate studies, for most of the health outcomes studied we did not conclude that rates were higher in the towns than the comparison areas. For several health outcomes studied, we observed higher rates in one but not the other two towns. These were: in Katherine, prostate cancer; in Oakey, stillbirth, developmental vulnerability in two domains (physical health and wellbeing, and communication skills and general knowledge) and laryngeal cancer; and in Williamtown, postpartum haemorrhage (heavy blood loss following pregnancy), pregnancy-induced hypertension (high blood pressure), kidney cancer and lung cancer. Rates of death from coronary heart disease were higher in both Oakey and Williamtown.

For most of these health outcomes, we estimated the differences between the towns and comparison areas to be relatively small. For others, the differences were of modest size, but our estimates were imprecise, meaning the likely size of each difference could be anywhere between quite small to quite large. Even though our studies included almost everyone who had ever lived in the towns in the years we had available data (in some cases dating back to 1983), some of the conditions studied are uncommon and we observed only a few cases. For these outcomes, we could not precisely estimate the differences between the towns and comparison areas, and there is very little we can say about whether a difference really exists.

Due to the nature of our studies, there were certain design limitations. We were unable to fully account for certain risk factors (e.g. smoking) that could have led to observed differences in rates (or lack of them) between the towns and comparison areas ('confounding'). In particular, we were not able to account for socioeconomic factors as well as we would have liked. This is important, as socioeconomic conditions are strongly linked to health. In addition, some findings could have arisen just by chance alone and not because an association truly exists.

In light of the above, while there were higher rates of some adverse outcomes in individual towns, the evidence suggesting that this was due to living in these areas was limited. We did not have direct measurements of PFAS exposure and we cannot rule out that the higher rates were due to chance or confounding. Further, there was low consistency in our observations across the three towns (something we would not expect if PFAS caused an outcome), and there is limited evidence from other studies observing similar results or explaining how potential biological processes can result in PFAS causing these effects in humans. Overall, our findings are consistent with previous studies, which have not conclusively identified causative links between PFAS and these health outcomes.

Technical summary

Background

Per- and polyfluoroalkyl substances (PFAS) are synthetic chemicals classified as contaminants of emerging concern due to their potential adverse effects on the environment and human health. From 2013 to 2017, the Australian Government identified PFAS contamination affecting the local environments of Katherine in NT, Oakey in Qld, and Williamtown in NSW — known as the PFAS Management Areas. The primary aim of the PFAS Data Linkage Study was to examine whether rates of particular adverse health outcomes (candidate outcomes[a]) were higher among people who had lived in the PFAS Management Areas than among people who had lived in separate but similar areas in Australia not known to have PFAS contamination (the 'comparison areas').

Methods

We conducted three separate studies that investigated four groups of health outcomes. Study 1 investigated maternal and infant (perinatal) health (15 outcomes); Study 2 examined childhood development (6); and Study 3 investigated cancer (23) and cause-specific mortality (4) — a total of 48 outcomes. We also examined three control outcomes.[b]

For each study, we selected participants based on their place of residence as recorded in the State/Territory Perinatal Data Collections of NT (1986–2017), Qld (2007–2018) or NSW (1994–2018) at the time of giving birth (Study 1), or the national Medicare Enrolment File (1983–2019) (Studies 2 and 3). The 'exposed' populations included everyone who had a recorded address in the PFAS Management Areas. Those who had an address in a comparison area were eligible to be selected into the 'comparison' populations. Altogether, we analysed 16,970 pregnancies, 2,429 children, and 156,228 people (4 million person-years) in NT for Studies 1, 2 and 3 respectively; 4,654 pregnancies, 2,592 children, and 124,278 people (3.4 million person-years) in Qld; and 7,475 pregnancies, 510 children, and 38,381 people (1.1 million person years) in NSW.

We ascertained outcomes from the Perinatal Data Collections in Study 1. For the other two studies, we ascertained outcomes by linking the study populations to the Australian Early Development Census (AEDC) (2009, 2012, 2015, 2018) in Study 2; and to the Australian Cancer Database (1982–2017) and National Death Index (1980–2019) in Study 3. We used statistical methods to estimate adjusted relative risks (RR) for perinatal and childhood development outcomes, and standardised incidence ratios (SIR) for cancer and cause-specific mortality outcomes, taking into account potential confounders as far as was possible given the available data.

Results

For most candidate outcomes, we did not conclude that rates were higher in the PFAS Management Areas relative to the comparison areas, including where estimates were too imprecise to draw any inferences. For several outcomes, we estimated small to modest elevations in rates of individual outcomes, which were not consistently observed across the exposure areas. These were: in Katherine, prostate cancer (SIR = 1.76, 95% confidence interval (CI) 1.36 to 2.24); in Oakey, stillbirth (adjusted RR = 2.59, 1.25 to 5.39), developmental vulnerability in two AEDC domains (physical health and wellbeing , adjusted RR = 1.31, 1.06 to 1.61; and communication skills and general knowledge , adjusted RR = 1.49, 1.18 to 1.87), laryngeal cancer (SIR = 2.71, 1.30 to 4.98),

[a] Candidate outcomes were adverse health outcomes proposed by the study team based on The PFAS Health Study Systematic Literature Review and considerations of data availability.

[b] Control outcomes were health outcomes not known or thought to be associated with PFAS.

and coronary heart disease mortality (SIR = 1.22, 1.01 to 1.47); and in Williamtown, postpartum haemorrhage (adjusted RR = 1.94, 1.13 to 3.33), pregnancy-induced hypertension (adjusted RR = 1.88, 1.30 to 2.73), kidney cancer (SIR = 1.82, 1.04 to 2.96), lung cancer (SIR = 1.83, 1.39 to 2.38), and coronary heart disease mortality (SIR = 1.81, 1.46 to 2.33). For these key findings, adjusted absolute risks, which provide an indication of effects on the absolute scale, are provided in the main report. We also saw elevated rates of control outcomes: in Oakey, death from any external cause apart from self-harm (SIR = 1.38, 1.08 to 1.73) and death from intentional self-harm (SIR = 1.44, 1.08 to 1.89); and in Williamtown, death from intentional self-harm (SIR = 1.89, 1.04 to 3.18).

These findings should be interpreted in light of study weaknesses. Being observational studies, results could have been biased by differences between the exposed and comparison populations that we could not account for. We did not have complete information for certain risk factors (e.g. smoking) and were limited in our ability to control, other than crudely, for socioeconomic factors. Some findings may also have arisen purely by chance particularly as we studied a large number of outcomes.

Conclusion

There was limited support in these studies for effects of living in PFAS Management Areas on candidate health outcomes. While there were higher rates of some adverse outcomes in individual areas, the evidence suggesting that this was due to living in these areas was limited. We did not have direct measurements of PFAS exposure and we cannot rule out that the higher rates were due to chance or confounding. Further, there was low consistency in observed associations across the three PFAS Management Areas, some control outcomes were elevated, and at present, there is limited prior evidence or biological plausibility for PFAS causing these outcomes in humans. Overall, our findings are consistent with previous studies, which have not conclusively identified causative links between PFAS and these health outcomes.

Abbreviations

AARNET	Australian Academic and Research Network
ABS	Australian Bureau of Statistics
ACD	Australian Cancer Database
ACT	Australian Capital Territory
AEDC	Australian Early Development Census
AFFF	Aqueous film forming foam
AIHW	Australian Institute of Health and Welfare
ANU	Australian National University
APP	Australian Privacy Principles
ARIA+	Accessibility and Remoteness Index of Australia
ASGS	Australian Statistical Geography Standard
ATSDR	Agency for Toxic Substances and Disease Registry
BMI	Body mass index
CHeReL	Centre for Health Record Linkage
CI	Confidence interval
DISC	Data Integration Services Centre
GEE	Generalised estimating equations
G-NAF	Geocoded National Address File
HREC	Human Research Ethics Committee
ICD-9	International Statistical Classification of Diseases and Related Health Problems, Ninth Revision, Australian Modification
ICD-10	International Statistical Classification of Diseases and Related Health Problems, Tenth Revision
ICD-10-AM	International Statistical Classification of Diseases and Related Health Problems, Tenth Revision, Australian Modification
IQ	Intelligence Quotient
IR	Incidence ratio
IRSD	Index of Relative Socioeconomic Disadvantage
LDL	Low-density lipoprotein
LGA	Large for gestational age
MEF	Medicare Enrolment File
NDI	National Death Index
ng/ml	Nanograms per millilitre
NHMRC	National Health and Medical Research Council
NSW	New South Wales
NT	Northern Territory
PFAS	Per- and polyfluoroalkyl substances
PFHxS	Perfluorohexane sulfonic acid
PFOA	Perfluorooctanoic acid

PFOS	Perfluorooctane sulfonic acid
PFNA	Perfluorononanoic acid
PIH	Pregnancy-induced hypertension
PMA	PFAS Management Areas
PMKeyS	Personnel Management Key Solution database
PPARa	Peroxisome proliferator-activated receptor alpha
Qld	Queensland
RAAF	Royal Australian Air Force
RR	Risk ratio/relative risk
SA	South Australia
SA1	Statistical Area Level 1
SA2	Statistical Area Level 2
SD	Standard deviation
SDQ	Strengths and Difficulties Questionnaire
SES	Socioeconomic status
SGA	Small for gestational age
SIR	Standardised incidence ratio
SURE	Secure Unified Research Environment
Tas	Tasmania
USA	United States of America
Vic	Victoria
VII	Voluntary Indigenous Identifier database
WA	Western Australia

Introduction

Per- and polyfluoroalkyl substances (PFAS) are synthetic chemicals classified as contaminants of emerging concern due to their potential adverse effects on the environment and human health. Given their stability and useful properties, PFAS are used for a wide range of purposes, such as in the manufacture of fabric protectant, non-stick cookware and aqueous film forming foams (AFFF), which were used to extinguish liquid fuel fires in aviation settings. The extensive use of PFAS for household and industrial purposes since the 1950s, and the subsequent movement of PFAS through water sources and adjacent land, led to environmental contamination across the world.[3-5] In response, major manufacturers have phased many long-chain perfluoroalkyl substances out of production.[6,7]

Concerns over the potential for PFAS to adversely affect human health arise from the ease with which they are absorbed into, distributed through and retained in the body.[8,9] Human exposure to PFAS occurs predominantly through ingestion and absorption into the blood stream via the digestive tract, but may also occur through inhalation or skin absorption (dermal). The elimination half-life[c] in human blood varies with the type of PFAS, ranging from 3–5 years for perfluorooctane sulfonic acid (PFOS), 5–8 years for perfluorohexane sulfonic acid (PFHxS) and 2–3 years for perfluorooctanoic acid (PFOA).[10,11]

The epidemiological literature on the health effects of PFAS includes studies in three different types of populations: workers exposed in chemical plants that use or produce PFAS (occupational exposure), high-exposure communities in areas near plants with documented contamination of the local environment and drinking water supply (community exposure), and the general population (background exposure). Outside of Australia, key studies involving community exposure include those among residents of Ohio and West Virginia in the USA (C8 Health Project),[12] the Veneto Region of Northern Italy,[13-17] Uppsala in Sweden (the Prospective Investigation of the Vasculature in Uppsala Seniors Study),[18-20] and an ongoing study involving residents of Ronneby, Sweden.[21-24]

Epidemiological and toxicological investigations indicate a range of potential effects on metabolism, immunity, reproduction and development; specifically, disruptions to kidney and liver functions and uric acid metabolism, abnormal thyroid levels, suppression of some immune responses, higher total and low-density lipoprotein (LDL) cholesterol levels (hypercholesterolaemia) and small reductions in birth weight.[8,25-34] PFAS exposure may also contribute to pregnancy-induced hypertension, decreased male and female fertility[35-38] and testicular and kidney cancer.[39,40] Adverse psychological impacts associated with living in contaminated areas have also been suggested.[41] However, while epidemiological data suggest associations between PFAS and several health effects, most of the studies are cross-sectional in design and cannot establish causality.

In Australia, PFAS contaminations have occurred in environments surrounding firefighting training grounds, airports and military bases where AFFF were in frequent use. From the 1970s, Australian Department of Defence bases used AFFF products, mainly 3M Light Water™ for fire emergencies and training purposes.[42-44] Light Water™ contains PFOS and PFHxS as the main active ingredients.[45] In 2002, the 3M Company ceased production of Light Water™ due to environmental and human health concerns. In following years, the Department of Defence discontinued use of Light Water™ across Australian military bases.

From 2013 to 2017, the Australian Government identified PFAS contamination affecting the environment surrounding the Royal Australian Air Force (RAAF) bases at Tindal in Katherine,

[c] The length of time required for the body to eliminate half of a substance that has been taken into the body by normal physiological processes.

Northern Territory (NT) and Williamtown, New South Wales (NSW), and the Oakey Army Aviation Centre in Oakey, Queensland (Qld).[46-48] Environmental investigations of PFAS concentrations in ground and surface water, sediment, and soil showed PFAS concentrations were highest in water sources and land located near the military bases. The affected environments are referred to as PFAS Management Areas.

In response to the PFAS contamination in these areas, the Australian Department of Health commissioned the Australian National University (ANU) to conduct an epidemiological study to investigate exposure to and possible health effects of PFAS in Katherine, Oakey and Williamtown. During Phase I, the PFAS Health Study team conducted a systematic review to examine the health effects of PFAS in humans as reported in published literature.[49] Phase II included an epidemiological study of the three PFAS-affected communities, which comprised four studies; a focus group study,[50] a blood serum study,[51] a cross-sectional survey[52] and a data linkage study.

This document outlines the aims, methods, results and conclusions of the data linkage study.

Aims and objectives

The primary aim of the PFAS Data Linkage Study was to examine whether adverse health outcomes possibly caused by PFAS exposure (hereafter referred to as candidate outcomes) were more common among people who had lived in the Australian PFAS Management Areas of Katherine, Oakey and Williamtown (the exposure areas), than among people who had lived in separate but similar areas in Australia not known to have PFAS contamination (the comparison areas).

The candidate outcomes investigated were those determined *a priori* to be possibly associated with PFAS exposure based on The PFAS Health Study Systematic Literature Review,[53] and which could be measured in routinely collected administrative data. We also investigated several identified control outcomes, which were adverse health outcomes not known or thought to be associated with PFAS.

Research questions

1. What are the rates of candidate outcomes among people who have lived in the PFAS Management Areas of Williamtown, Oakey and Katherine, relative to people who have lived in comparison areas after adjusting for sociodemographic and other characteristics?
2. What are the rates of control outcomes among people who have lived in the PFAS Management Areas of Williamtown, Oakey and Katherine, relative to people who have lived in comparison areas after adjusting for sociodemographic and other characteristics?

We hypothesised that if living in the PFAS Management Areas of Katherine, Oakey or Williamtown increased the risk of adverse health outcomes, we would observe higher adjusted rates of candidate outcomes in these areas than in the comparison area, while the adjusted rates of control health outcomes would be similar across the exposure and comparison areas.

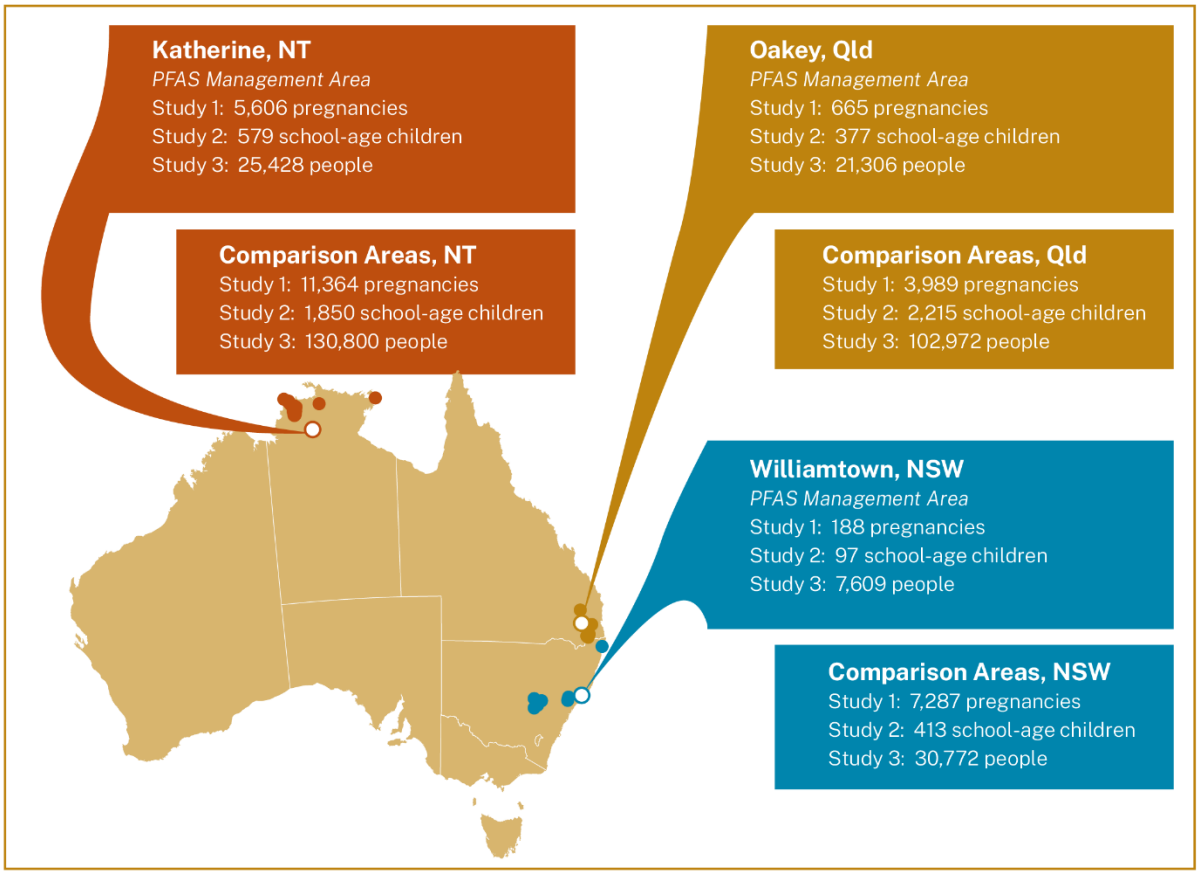
Overview of methods

We conducted three separate data linkage studies, investigating four groups of health outcomes. The first of these studies investigated perinatal outcomes; the second examined childhood development; and the third investigated cancer and death from specific causes (cause-specific mortality). Different data sources and analyses were used to study each group of outcomes.

We used routinely collected administrative data for all studies and no direct contact was made with study participants. For the first study, we used jurisdictional Perinatal Data Collections. For the other studies, we used data from the Medicare Enrolment File linked to the Australian Early Development Census (Study 2) or to the Australian Cancer Database and the National Death Index (Study 3).

For each study, we selected participants based on their place of residence as recorded in either the Perinatal Data Collections (Study 1) or the Medicare Enrolment File (Studies 2 and 3). Those who had a recorded residential or mailing address that matched any address in the PFAS Address Database (Box 1) were classified as being in the 'exposed' populations. Those who had a recorded residential or mailing address that matched any postcode in comparison areas were identified as eligible to be selected in the 'comparison' populations (Box 1). Figure 1 shows the locations of Katherine, Oakey and Williamtown, and the postcodes of the corresponding comparison areas. An illustration of how the study populations were selected is shown in Figure 2.

Figure 1. Map of Katherine, Oakey and Williamtown and corresponding postcodes of comparison areas, showing sample sizes for each of the three separate studies conducted under the PFAS Data Linkage Study



Data linkages were performed by a Commonwealth-accredited data integration authority and State/Territory data linkage nodes. More details on linkage authorities and application of the separation principle, a privacy protection measure, are available in Appendix 1.

In the following sections of this report, we describe the methods and findings for each study separately. Despite differences in methods, the main findings — from comparing outcomes in the exposed with the comparison populations — are presented in terms of a summary statistic of relative effect. The relative effect is the ratio of the rate of an outcome in the exposed population to the rate in the comparison population, expressed as either a risk ratio/relative risk (RR) or an incidence ratio (IR).[d] We estimated relative effects using statistical models to enable adjustment for sociodemographic and other potential confounding factors — that is, factors apart from PFAS exposure[e] that may account, at least in part, for differences in outcomes observed ('effects') between the exposed and comparison populations. These models also generate confidence (uncertainty) intervals around the estimates. Information on interpreting effect estimates and confidence intervals are presented in Box 2. A glossary of technical terms is available on page 62.

We analysed outcomes separately by State, rather than combining data across all States. We did this as the levels of exposure and sources of exposure (such as through consumption of food or bore water) are likely to have been different across Katherine, Oakey and Williamtown over the study period. All data analyses and graphs for this report were generated using SAS software.[f] A summary of the methods for each group of outcomes can be seen in Table 1.

The values of effect estimates are not the only information we use when interpreting the findings from these studies. It is also important to consider other factors such as biases due to measurement error and uncontrolled confounding. In addition, an observed association between exposure and outcome does not necessarily represent a causal relationship. Inferences of causality require data beyond that from a single study and involve considerations of the magnitude of estimates, the consistency of findings within and across other studies, and biological plausibility (among other criteria). We discuss this in the concluding section of the report.

The PFAS Data Linkage Study received approval from nine health research ethics committees, and a waiver of consent pursuant to section 95 of the *Privacy Act 1988* (Cth). More details on ethical approvals, data storage and secure access are available in Appendix 2.

[d] For simplicity, the term rate is used here to include incidence proportion (risk) as well as incidence rate (events per unit of person-time). Some perinatal outcomes are measured (such as birthweight). For these outcomes, the effect is reported as the difference between, rather than ratio of, the measured outcome in the exposed population and the comparison population.

[e] Defined in our studies as living in a PFAS Management Area.

[f] Version 9.4 of the SAS System for Windows. Copyright © 2017 SAS Institute Inc. SAS and all other SAS Institute Inc. product or service names are registered trademarks or trademarks of SAS Institute Inc., Cary, NC, USA.

Box 1. Address databases

The PFAS Address Database

The study team constructed a PFAS Address Database for the purposes of the PFAS Health Study. The boundaries of the PFAS Management Areas, defined by the Australian Department of Defence, were provided to the study team as a set of vector coordinates—longitude and latitude values—that demarcate the catchment areas. We used these coordinates to extract all relevant street addresses that fell inside the catchment areas, and those that lay on the boundaries, from the Geocoded National Address File (G-NAF).[1] The G-NAF contains address data for over 14 million physical addresses in Australia, including State, suburb, street, number and coordinates. The G-NAF does not contain any personal information or details relating to an individual or business.

The PFAS Address Database comprised a total of 5,883 street addresses: 3,007 addresses in Katherine, 1,958 in Oakey and 918 in Williamtown. We used ArcGIS v 10.7.1 software to facilitate the extraction of street addresses.

Comparison areas postcode list

The study team chose comparison areas separately for each of the three PFAS Management Areas. Comparison areas were selected from within the same State or Territory as each of the exposed areas, and had similar sociodemographic profiles to the corresponding exposed area in terms of the following characteristics: socioeconomic disadvantage measured by the Australian Bureau of Statistics' (ABS) Index of Relative Socioeconomic Disadvantage (IRSD) deciles, geographical remoteness measured by the Accessibility and Remoteness Index of Australia (ARIA+) categories (Very Remote, Remote, Outer Regional, Inner Regional and Major Cities), and estimated proportion of Aboriginal and/or Torres Strait Islander residents. Comparison areas were selected at the Statistical Area Level 2 geographical level (SA2) before being translated to postcodes. As many postcodes as necessary were then chosen, such that the expected comparison population was approximately four times that of the exposed population (see Appendix 3 for more detail).

The comparison area postcodes for the three exposed areas were:

- **For Katherine**: 0800, 0828, 0829, 0835, 0836, 0837, 0838, 0840, 0841, 0845, 0846, 0880, 0886
- **For Oakey**: 4311, 4371, 4372, 4373, 4610
- **For Williamtown**: 2334, 2335, 2864, 2865, 2866, 2867, 2477.

Box 2. Interpretation of effect sizes and confidence intervals

A relative effect measure — such as a risk ratio (RR) or incidence ratio (IR) — is the ratio of the rate of an outcome in the exposed population to the rate in the comparison population. Relative effect estimates include a point estimate and an accompanying 95% confidence interval (CI), which gives a range of probable values for the estimate (e.g. RR = 1.88, 95% CI 1.30 to 2.73). The width of the CI reflects the precision of an estimate: the narrower the CI, the more precise the estimate.

The point estimate and its CI are also collectively known as the interval estimate and can be interpreted as follows:

1. *If the point estimate and its CI are greater than 1*, the data point to the conclusion that the rate is higher in the exposed population than the comparison population. The further away from 1, the stronger the effect size.

2. *If the point estimate and its CI are below 1*, the data point to the conclusion that the rate is lower in the exposed population than the comparison population. The further away from 1, the stronger the effect size.

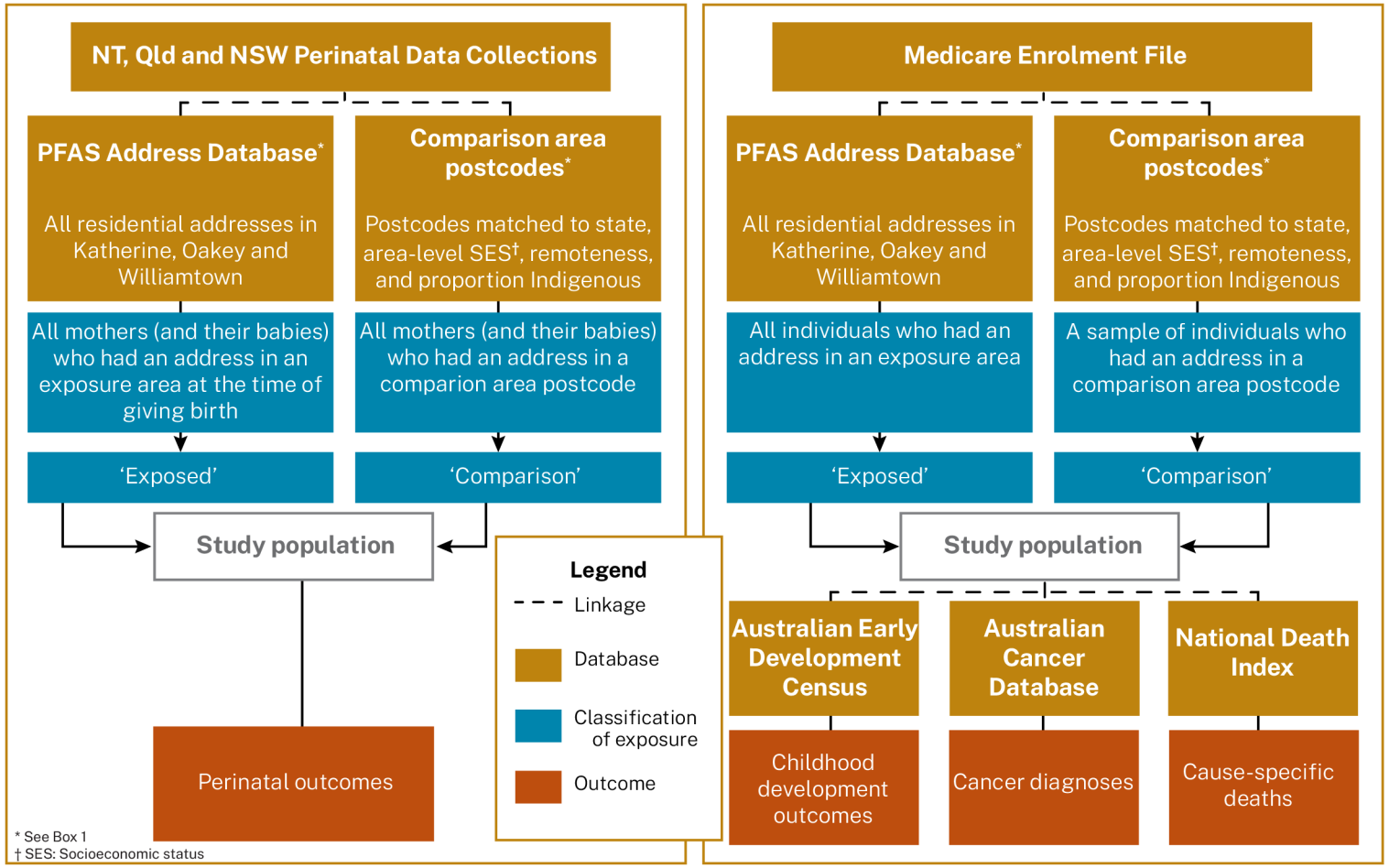
3. *If the CI includes 1*, the data are compatible with no difference ('no effect'). However, there are three possible interpretations:
   - If the upper and lower limits of the CI are close to 1 (e.g. 0.96 to 1.04), the data point to the conclusion that there is no (meaningful) difference in rates between the exposed and comparison populations.
   - If one of the CI limits is close to 1 (e.g. 0.95 to 3.90) rates are likely different, but too imprecise to confidently conclude there is an effect ('uncertain').
   - If the CI is wide and neither of its limits are close to 1 (e.g. 0.60 to 3.90), we are unable to conclude whether rates are different, and they could range from anywhere between much lower to much higher.

When an absolute difference measure is used rather than a ratio (e.g. difference in means), the reference point of no difference is 0 instead of 1. That is:

1. *If the point estimate and its CI are greater than 0*, the data are most compatible with the conclusion that the mean is higher in the exposed population than the comparison population.

2. *If the point estimate and its CI are below 0*, the data are most compatible with the conclusion that the mean is lower in the exposed population.

Figure 2. Selection of study populations, classification of exposure status and outcomes, showing linkages between databases



Data constructed to examine perinatal outcomes

Linkages were performed by CHeReL, NT Health and Data Linkage Queensland

Data constructed to examine childhood development, cancer and mortality outcomes

Linkages were performed by AIHW Data Integration Services Centre

Table 1. Overview of data sources and methods for each group of health outcomes, PFAS Data Linkage Study

Study	Health outcome	Data sources	Unit of analysis	Outcome measure	Statistical approach	Effect measure
Study 1	Perinatal outcomes	NSW PDC (1994–2018), NT Perinatal Trends (1986–2017), Qld PDC (2007–2018)	Singleton pregnancy	Proportion (risk) for binary outcomes	Modified Poisson regression	Adjusted relative risk
				Mean for continuous outcomes	Linear regression	Adjusted difference in means
Study 2	Childhood development	Linked MEF-AEDC (2002–2018)	Individual children	Risk	Modified Poisson regression	Adjusted relative risk
Study 3	Cancer	Linked MEF-ACD (1983–2017)	Person-years	Incidence rate	Indirect standardisation	Standardised incidence ratio
	Cause-specific mortality	Linked MEF-NDI (1983–2019)	Person-years	Incidence rate	Indirect standardisation	Standardised incidence ratio

Tables notes

1. A glossary of technical terms is available on page 62.
2. Abbreviations — PDC: Perinatal Data Collection, MEF: Medicare Enrolment File, AEDC: Australian Early Development Census, ACD: Australian Cancer Database, NDI: National Death Index

Study 1: Perinatal outcomes

This study included women who had lived in an exposure or comparison area and gave birth during that period of residence. We examined maternal and infant outcomes experienced during pregnancy and at or around the time of the infant's birth as recorded in the Perinatal Data Collection of the State or Territory where the mother was living at the time.

Methods

Data sources and study population

In this study, we used data from the NT, Qld and NSW Perinatal Data Collections, linked to the PFAS Address Database and comparison area postcodes (Box 1).

Perinatal Data Collections

Each State and Territory has a Perinatal Data Collection that captures information about each mother's pregnancy care, services accessed and pregnancy and birth outcomes. All live births and stillbirths of at least 400 grams birth weight or at least 20 weeks' gestation are included in these data collections. Information captured relating to the mother include demographic characteristics, and factors relating to the pregnancy, labour and birth. Information relating to the baby includes sex, birth status, gestational age at birth, birth weight, neonatal morbidity and fetal deaths.

The following jurisdictional Perinatal Data Collections, with data spanning 1986 to 2018, were available for the study:

- NT Perinatal Trends (January 1986–December 2017)
- Qld Perinatal Data Collection (July 2007–December 2018)
- NSW Perinatal Data Collection (January 1994–December 2018).

Selection of study populations

The study populations were selected and classified based on place of residence as described earlier (see Overview of methods and Figure 2). We included all pregnancies where the mother's residential address at the time of giving birth was in the PFAS Management Areas of Katherine, Oakey or Williamtown, or in a comparison area. As the NT Perinatal Trends database does not collect addresses at the street level, we selected mothers whose locality contained the string 'Katherine', thus encompassing Katherine, Katherine East and Katherine South. Pregnancies were excluded if they were from a multiple gestation to minimise potential confounding.

Study variables

Outcomes

We examined 15 outcomes: 12 adverse perinatal outcomes, coded as binary variables (outcome present or not present), and three growth measurements (continuous variables). All outcome variables were derived from information in the Perinatal Data Collections. The variables were either available directly (pre-defined in the datasets), derived from multiple variables, or based on the International Classification of Diseases Australian Modification, 10th revision (ICD-10-AM) codes. Table 2 shows all outcomes examined in this study and their definitions.

Table 2. Outcome definitions for the group of perinatal outcomes

Health outcome	Outcome type	Definition
Adverse perinatal outcome		
Gestational diabetes	Binary	As pre-defined in dataset or ICD-10-AM: O24.4
Pregnancy-induced hypertension	Binary	Gestational hypertension or pre-eclampsia, or ICD-10-AM: O13, O14
Caesarean/assisted vaginal	Binary	Caesarean or assisted vaginal birth (including forceps, vacuum extraction, vaginal breech)
Emergency caesarean	Binary	Caesarean after spontaneous or induced onset of labour
Postpartum haemorrhage	Binary	As pre-defined in dataset or ICD-10-AM: O72
Preterm birth	Binary	Gestation at birth <37 completed weeks
Spontaneous preterm	Binary	Gestation at birth <37 completed weeks with spontaneous onset of labour
Small for gestational age (SGA)	Binary	Birth weight below 10th percentile for age†
Large for gestational age (LGA)	Binary	Birth weight above 90th percentile for age†
Still birth	Binary	As pre-defined in dataset
Low Apgar* score at 5 minutes	Binary	Score <7
Term low Apgar* score at 5 minutes	Binary	Score <7 in babies born ≥37 weeks gestation
Growth measure		
Term birth weight	Continuous	Weight in grams in babies born ≥37 weeks gestation
Term birth length	Continuous	Length in cm in babies born ≥37 weeks gestation
Term head circumference	Continuous	Head circumference in cm in babies born ≥37 weeks gestation

Table notes

* Apgar is a mnemonic frame of reference to assess a neonate's vital signs: appearance (skin colour), pulse, grimace (reflex irritability), activity (muscle tone) and respiration.[54] Scores of six and lower indicate that medical attention is required.

† Percentile cut-offs taken from Dobbins et al. (2012).[55]

Exposure and other variables

The exposure variable in our analyses was residence in a PFAS Management Area (yes/no), as defined earlier. All other variables used to adjust for potential confounding (see analysis section below) were based on information in the relevant Perinatal Data Collection.

Statistical analysis

Main analyses

For each binary outcome, we calculated the proportions with the outcome (risk) in the exposed and comparison populations. Proportions were calculated as the number of cases (number of pregnancies/births with the outcome) divided by the total number of pregnancies/births. To estimate risk in the exposed pregnancies relative to the comparison pregnancies, we generated relative risks (RR) and 95% CIs using a modified Poisson approach with robust estimation of error variance.[56] For continuous outcomes, we measured the means and standard deviations for babies in the exposed and comparison populations. We used linear regression models to estimate the difference in means between groups and 95% CIs.

To take potential confounding into account in our RR and difference estimates, we specified two models for each outcome. Model 1 was a minimally adjusted model, with adjustments for maternal age (in years), maternal Aboriginal and Torres Strait Islander status (Indigenous, non-Indigenous),[g] and baby's year of birth for all outcomes; and additionally gestational age in completed weeks (37, 38, 39, 40, ≥41 weeks) for outcomes restricted to term babies (≥37 weeks) only. In Model 2 we additionally adjusted for the following where relevant: maternal country of birth (Australia, overseas), parity (0, 1, ≥2), marital status (married or de facto, other), pre-pregnancy body mass index (BMI in kg/m^2), any smoking during pregnancy (smoker, non-smoker), baby sex (male, female), and macrosomia (birth weight ≥4000g). Year of birth, maternal age, and pre-pregnancy BMI were treated as continuous covariates, all of which were modelled as natural cubic splines with three knots. Covariate data were available over varying periods for each jurisdictional Perinatal Data Collection. Therefore, Model 2 contained fewer years of data than minimally adjusted models.

For all outcomes, we used a generalised estimating equations (GEE) method with an exchangeable correlation structure to account for repeated measures (mothers who had more than one pregnancy over the study period).

Sensitivity analyses

We conducted the following sensitivity analyses:

a) Gestational diabetes was included as an additional covariate in Model 2 for the following outcomes: caesarean or assisted vaginal birth, large for gestational age and term birth weight.
b) Alternative parameterisation of continuous covariates as categorical variables: year of birth (10-year bands for NT and NSW, 5-year bands for Qld), maternal age (0–19, 20–24, 25–29, 30–34, ≥35 years) and pre-pregnancy BMI (0–<18.5, 18.5–<25, 25–<30, ≥30 kg/m^2).

Deviations from the original study protocol

There was one deviation from the original study protocol, outlined in Appendix 4.

Results

Description of the study population

From the NT, Qld and NSW Perinatal Data Collections, we identified 29,870 pregnancies in 21,187 mothers who were living in Katherine, Oakey or Williamtown, or a comparison area, at the time of giving birth. After excluding 771 instances of multiple pregnancies[h], we included 29,099 singleton pregnancies in 20,976 mothers in this analysis.

Overall, 22% (6,459/29,099) of the pregnancies were in mothers living in Katherine, Oakey or Williamtown at the time of giving birth, and were classified as the exposed population. We classified 78% (22,640/29,099) of pregnancies as comparison, as the mother was living in a comparison area at the time of birth. The largest number of pregnancies was in NT (5,606 (33%) exposed, 11,364 (67%) comparison), followed by Qld (665 (14%) exposed, 3,989 (86%) comparison) and NSW (188 (2.5%) exposed, 7,287 (97.5%) comparison). Sample sizes and characteristics by State/Territory and exposure status are shown in Table 3.

[g] Mothers who had two or fewer pregnancy records were coded as Aboriginal and Torres Strait Islander if the mother identified as Aboriginal and/or Torres Strait Islander at least once. Mothers who had more than two pregnancies were coded as Aboriginal and Torres Strait Islander if the mother identified as Aboriginal and/or Torres Strait Islander at least two times. This method was based on the multi-stage medium algorithm but as there was only one dataset, only the first stage was applied (Christensen, 2014).

[h] Twins, triplets or other multiples

Table 3. Characteristics of study populations for analysis of perinatal outcomes

	NT		Qld		NSW	
Characteristic	**Exposed n (%)**	**Comparison n (%)**	**Exposed n (%)**	**Comparison n (%)**	**Exposed n (%)**	**Comparison n (%)**
Mothers						
Total sample[1]	**4,083**	**8,607**	**513**	**2,876**	**144**	**4,871**
Country of birth						
Australia	3,529 (87)	6,825 (80)	463 (90)	2,642 (92)	130 (90)	4,522 (93)
Overseas	543 (13)	1,720 (20)	50 (10)	234 (8)	14 (10)	349 (7)
Missing/unknown	11	62	0	0	0	0
Indigenous status[2]						
No	2,916 (71)	6,795 (79)	424 (83)	2,707 (94)	139 (97)	4,651 (96)
Yes	1,167 (29)	1,806 (21)	89 (17)	169 (6)	≤5	206 (4)
Missing/unknown	0	6	0	0	≤5	14
Pregnancies						
Total sample[1]	**5,606**	**11,364**	**665**	**3,989**	**188**	**7,287**
Year of birth						
1985–1994	1,731 (31)	2,457 (22)	N/A	N/A	≤5	264 (4)
1995–2004	1,724 (31)	3,466 (31)	N/A	N/A	41 (22)	2,754 (38)
2005–2014	1,736 (31)	4,157 (37)	445 (67)	2,681 (67)	100 (53)	3,033 (42)
2015–latest	415 (7)	1,283 (11)	220 (33)	1,308 (33)	44 (23)	1,236 (17)
Missing/unknown	0	1	0	0	≤5	0
Mother's age (at baby's birth)[3]						
<20	606 (11)	925 (8)	87 (13)	360 (9)	≤5	332 (5)
20–24	1,344 (24)	2,182 (19)	201 (30)	961 (24)	22 (12)	1,284 (18)
25–29	1,714 (31)	3,187 (28)	194 (29)	1,281 (32)	60 (32)	2,374 (33)
30–34	1,315 (23)	3,252 (29)	121 (18)	865 (22)	60 (32)	2,105 (29)
35–39	526 (9)	1,534 (14)	62 (9)	522 (13)	39 (21)	976 (13)
40+	101 (2)	281 (2)	N/A	N/A	6 (3)	215 (3)
Missing/unknown	0	3	0	0	≤5	1
Gestation age (weeks)						
≤36	455 (8)	929 (8)	61 (9)	314 (8)	15 (8)	399 (5)
37–40	4,298 (77)	9,046 (80)	524 (79)	3,209 (80)	139 (74)	5,553 (76)
41+	827 (15)	1,300 (12)	80 (12)	465 (12)	34 (18)	1,332 (18)
Missing	26	89	0	1	0	3
Baby sex						
Female	2,688 (48)	5,607 (49)	329 (49)	1,899 (48)	94 (50)	3,552 (49)
Male	2,916 (52)	5,753 (51)	336 (51)	2,090 (52)	94 (50)	3,735 (51)
Missing/unknown	2	4	0	0	0	0

(Table continued over)

	NT		Qld		NSW	
Characteristic	Exposed n (%)	Comparison n (%)	Exposed n (%)	Comparison n (%)	Exposed n (%)	Comparison n (%)
Mothers						
Maternal parity						
No prior birth	2,087 (37)	4,683 (41)	190 (29)	1,033 (26)	72 (38)	2,595 (36)
One prior birth	1,676 (30)	3,501 (31)	160 (24)	1,054 (26)	69 (37)	2,436 (33)
≥Two prior births	1,840 (33)	3,156 (28)	315 (47)	1,902 (48)	47 (25)	2,246 (31)
Missing/unknown	3	24	0	0	0	10
Marital status (at birth)[4]						
Married/de facto	3,610 (65)	7,156 (64)	484 (73)	3,133 (79)	12 (80)	960 (87)
Other	1,959 (35)	4,014 (36)	181 (27)	856 (21)	3 (20)	148 (13)
Missing/unknown	37	194	0	0	173	6,179
Pre-pregnancy BMI[5]						
0–<18.5	13 (3)	48 (3)	25 (4)	210 (5)	≤5	34 (4)
18.5–<25	209 (43)	772 (53)	253 (41)	1,596 (41)	12 (41)	404 (44)
25–<30	139 (29)	393 (27)	160 (26)	1,012 (26)	≤10	244 (27)
30+	125 (26)	257 (17)	180 (29)	1,072 (28)	9 (31)	228 (25)
Missing/unknown	5,120	9,894	47	99	159	6,377
Smoking during pregnancy[6]						
No	2,293 (68)	5,623 (75)	471 (71)	2,959 (74)	158 (84)	5,909 (81)
Yes	1,092 (32)	1,912 (25)	191 (29)	1,025 (26)	30 (16)	1,355 (19)
Missing/unknown	2,221	3,829	3	5	0	23
IRSD[7] decile						
1	N/A	N/A	0	97 (2)	N/A	N/A
2	N/A	N/A	0	599 (15)	N/A	N/A
3	N/A	N/A	665 (100)	2,966 (74)	N/A	N/A
4	N/A	N/A	0	327 (8)	N/A	N/A
5–10	N/A	N/A	0	0	N/A	N/A
Remoteness						
Major city	N/A	N/A	0	0	N/A	N/A
Inner regional	N/A	N/A	0	0	N/A	N/A
Outer regional	N/A	N/A	0	43 (1)	N/A	N/A
Remote	N/A	N/A	665 (100)	3,946 (99)	N/A	N/A
Very remote	N/A	N/A	0	0	N/A	N/A

Table notes

Data sources: NSW Perinatal Data Collection (1994–2018), NT Perinatal Trends (1986–2017), Qld Perinatal Data Collection (2007–2018)

1. Mothers can move between exposure and comparison areas; therefore, totals are not for unique mothers.
2. Mothers who had two or fewer pregnancy records were coded as Aboriginal and Torres Strait Islander if the mother identified as Aboriginal and/or Torres Strait Islander at least once. Mothers who had more than two pregnancies were coded as Aboriginal and Torres Strait Islander if the mother identified as Aboriginal and/or Torres Strait Islander at least two times.
3. Mother's age is top-coded at 35 years in the Queensland Perinatal Data Collection.

4. Marital status is only available from 1994–1997 in the NSW Perinatal Data Collection, and thus was not used as a covariate due to insufficient data.
5. BMI is only available from 2014–2017 in the NT Perinatal Data Collection and 2016–2018 in the NSW Perinatal Data Collection, and thus was not used as a covariate in these states due to insufficient data.
6. Smoking during pregnancy is only available from 1996 in the NT Perinatal Data Collection.
7. Index of Relative Socioeconomic Disadvantage (IRSD) based on Statistical Area Level 2 of mother's usual address coded according to Australian Bureau of Statistics' Australian Statistical Geography Standard (ASGS) 2011 Version for births up to 2016/2017 and ASGS 2016 Version for births from 2017/2018.
8. Denominators for proportions exclude missing values.
9. Cells have been suppressed to avoid reporting cell numbers with size ≤5.
10. Percentages were rounded to zero decimal places.

Perinatal outcomes in relation to living in exposure areas

The proportions of the exposed and comparison populations with adverse perinatal outcomes (risks) and adjusted RRs, as well as mean growth measurements and adjusted difference in means, are shown in Table 4; a forest plot of adjusted RRs is shown in Figure 3. For information on interpreting effect estimates, see Box 2.

In NT, the crude (unadjusted) risks of adverse perinatal outcomes ranged from 1% for stillbirths to 31% (exposed) and 34% (comparison) for caesarean or assisted vaginal delivery. Risks were similar across mothers who had lived in Katherine and those who had lived in its comparison areas for all adverse perinatal outcomes. After adjusting for sociodemographic characteristics and other potential confounders, point estimates were not large and all interval estimates were compatible with no differences in risks between Katherine and its comparison areas. In terms of growth measurements, there was little to no meaningful difference in birth weight, birth length or head circumference between term babies (≥37 weeks' gestation) born to mothers who had lived in Katherine versus those who had lived in comparison areas.

In Qld, the crude risks of adverse perinatal outcomes ranged from 2% (exposed) and 1% (comparison) for stillbirths to 40% (exposed) and 36% (comparison) for caesarean or assisted vaginal delivery. With a few exceptions, the risks of adverse perinatal outcomes were similar across Oakey and its comparison areas, with point estimates small and interval estimates compatible with no effect. However, the estimated risk of stillbirth in Oakey was 2.6 times that of its comparison areas, although there was considerable uncertainty (imprecision) due to the small number of cases (Model 2 adjusted RR = 2.59, 95% CI 1.25 to 5.39). There was uncertain evidence of increased risk of low Apgar score (Model 2 adjusted RR = 1.47, 95% CI 0.95 to 2.26), and results were too imprecise to make any conclusions when restricted to term babies (Model 2 adjusted RR = 1.21, 95% CI 0.69 to 2.10). There was little to no meaningful difference between Oakey and its comparison areas in any growth measurement.

In NSW, the crude risks of adverse perinatal outcomes ranged from 1% (exposed) and <1% (comparison) for stillbirths to 38% (exposed) and 33% (comparison) for caesarean or assisted vaginal delivery. The risk of postpartum haemorrhage in Williamtown was almost twice that of its comparison areas (Model 2 adjusted RR = 1.94, 95% CI 1.13 to 3.33). Note that postpartum haemorrhage was only collected in the NSW Perinatal Data Collection from 2016; estimates were therefore based on a very small sample of 29 births in Williamtown between 2016 and 2018. The risk of pregnancy-induced hypertension in Williamtown was nearly twice that of comparison areas (Model 2 adjusted RR = 1.88, 95% CI 1.30 to 2.73). For the remaining adverse outcomes examined, interval estimates were compatible with no effect. While some point estimates were modest in size (for example, spontaneous preterm birth and term low Apgar score), interval estimates were too imprecise to conclude whether rates were likely to be different. This was due to the small sample size in Williamtown and rarity of these outcomes. We found no evidence of meaningful differences in growth measurements between Williamtown and its comparison areas.

Sensitivity analyses

In sensitivity analyses, where we re-examined the risks of caesarean or assisted vaginal births, large-for-gestational-age, and birth weight in term babies, including an additional adjustment for gestational diabetes, we observed little impact except for a marginal reduction in the adjusted RR for large-for-gestational-age in NT from 0.91 (95% CI 0.80 to 1.04) to 0.86 (95% CI 0.74 to 0.99) (Appendix Table 2). There were no appreciable changes in effect sizes or direction of findings when we treated year of birth, maternal age, and pre-pregnancy BMI as categorical instead of continuous covariates (Appendix Table 2).

Table 4. Comparison of perinatal outcomes in exposed and comparison populations: risks (%) and adjusted relative risks (RR) of adverse perinatal outcomes, and means and adjusted difference in means of growth measurements

	NT				Qld				NSW			
	Exposed % (n)	Comparison % (n)	Adjusted RR[1] (95% CI)	Adjusted RR[2] (95% CI)	Exposed % (n)	Comparison % (n)	Adjusted RR[1] (95% CI)	Adjusted RR[2] (95% CI)	Exposed % (n)	Comparison % (n)	Adjusted RR[1] (95% CI)	Adjusted RR[2] (95% CI)
Adverse perinatal outcome												
Total sample	**5,606**	**11,364**			**665**	**3,989**			**188**	**7,287**		
Gestational diabetes[3]	7% (215)	7% (505)	1.08 (0.92,1.28)	1.11 (0.94,1.32)	8% (53)	9% (361)	0.95 (0.71,1.27)	0.88 (0.66,1.19)	8% (13)	5% (306)	1.44 (0.85,2.44)	1.42 (0.84,2.41)
Pregnancy-induced hypertension	5% (294)	5% (607)	0.93 (0.80,1.07)	1.10 (0.92,1.32)	3% (17)	2% (99)	1.03 (0.62,1.72)	0.94 (0.56,1.59)	16% (30)	7% (527)	2.00 (1.36,2.93)	1.88 (1.30,2.73)
Caesarean/ assisted vaginal	31% (1,711)	34% (3,853)	0.99 (0.95,1.05)	0.97 (0.91,1.03)	40% (263)	36% (1,427)	1.13 (1.01,1.27)	1.12 (1.00,1.25)	38% (71)	33% (2,423)	1.03 (0.84,1.26)	0.98 (0.81,1.20)
Emergency caesarean	11% (607)	12% (1,306)	1.00 (0.90,1.10)	1.08 (0.96,1.21)	14% (90)	12% (490)	1.10 (0.88,1.37)	1.11 (0.89,1.39)	13% (25)	10% (747)	1.22 (0.83,1.81)	1.12 (0.76,1.65)
Postpartum haemorrhage[4]	8% (475)	9% (1,075)	0.96 (0.86,1.06)	1.01 (0.90,1.14)	6% (43)	7% (265)	0.96 (0.70,1.32)	0.89 (0.63,1.26)	34% (10)	19% (174)	1.97 (1.14,3.38)	1.94 (1.13,3.33)
Preterm birth	8% (455)	8% (929)	0.95 (0.85,1.07)	1.06 (0.92,1.22)	9% (61)	8% (314)	1.13 (0.85,1.49)	1.04 (0.77,1.41)	8% (15)	5% (399)	1.46 (0.89,2.39)	1.47 (0.90,2.40)
Spontaneous preterm birth	6% (310)	5% (586)	0.99 (0.86,1.14)	1.14 (0.96,1.36)	4% (29)	5% (180)	0.97 (0.65,1.44)	0.90 (0.58,1.39)	4% (7)	3% (234)	1.27 (0.60,2.68)	1.32 (0.63,2.77)
Small for gestational age (SGA)	13% (750)	14% (1,553)	0.87 (0.79,0.94)	0.92 (0.82,1.03)	5% (30)	5% (192)	0.93 (0.63,1.37)	1.02 (0.69,1.51)	7% (13)	9% (621)	0.87 (0.48,1.57)	0.86 (0.48,1.53)
Large for gestational age (LGA)	8% (453)	9% (1,028)	0.96 (0.86,1.08)	0.91 (0.80,1.04)	6% (39)	6% (259)	0.93 (0.66,1.32)	0.89 (0.63,1.27)	11% (20)	11% (836)	0.89 (0.58,1.37)	0.95 (0.62,1.45)

(Table continued over)

	NT				Qld				NSW			
	Exposed % (n)	Comparison % (n)	Adjusted RR[1] (95% CI)	Adjusted RR[2] (95% CI)	Exposed % (n)	Comparison % (n)	Adjusted RR[1] (95% CI)	Adjusted RR[2] (95% CI)	Exposed % (n)	Comparison % (n)	Adjusted RR[1] (95% CI)	Adjusted RR[2] (95% CI)
Stillbirth	1% (45)	1% (89)	0.94 (0.66,1.35)	0.90 (0.54,1.50)	2% (11)	1% (27)	2.43 (1.20,4.93)	2.59 (1.25,5.39)	≤5	<1% (34)	1.13 (0.15,8.29)	1.17 (0.16,8.61)
Low Apgar score at 5 min	3% (164)	3% (327)	0.93 (0.77,1.13)	1.07 (0.83,1.37)	4% (29)	3% (113)	1.50 (0.99,2.26)	1.47 (0.95,2.26)	≤5	2% (161)	0.98 (0.37,2.57)	0.95 (0.36,2.51)
Term (≥37 weeks) outcome												
Total sample	**5,125**	**10,346**			**604**	**3,674**			**173**	**6,885**		
Term low Apgar score at 5 min	2% (80)	2% (185)	0.77 (0.59,1.00)	0.84 (0.59,1.20)	2% (14)	2% (70)	1.15 (0.66,2.00)	1.21 (0.69,2.10)	≤5	2% (103)	1.57 (0.58,4.20)	1.51 (0.56,4.07)
	Exposed mean (SD)	**Comparison mean (SD)**	**Adjusted mean diff[1] (95% CI)**	**Adjusted mean diff[2] (95% CI)**	**Exposed mean (SD)**	**Comparison mean (SD)**	**Adjusted mean diff[1] (95% CI)**	**Adjusted mean diff[2] (95% CI)**	**Exposed mean (SD)**	**Comparison mean (SD)**	**Adjusted mean diff[1] (95% CI)**	**Adjusted mean diff[2] (95% CI)**
Growth measure												
Total sample	**5,125**	**10,346**			**604**	**3,674**			**173**	**6,885**		
Term birth weight (g)	3,423 (488.9)	3,405 (488.9)	31.1 (14.4,47.9)	11.22 (−8.9,31.3)	3,465 (448.8)	3,483 (468.9)	−9.6 (−49.7,30.6)	−11.1 (−48.7,26.5)	3,519 (479.6)	3,515 (477.4)	21.7 (−49.0,92.1)	35.7 (−29.4,100.8)
Term birth length (cm)[5]	50.7 (2.7)	50.3 (2.4)	0.3 (0.1,0.4)	0.2 (0.1,0.4)	51.6 (2.6)	51.4 (2.6)	0.3 (0.1,0.5)	0.3 (0.1,0.5)	Data not available			
Term head circumference (cm)[6]	34.7 (1.7)	34.6 (1.5)	0.1 (0.0,0.2)	0.0 (−0.1,0.1)	34.7 (1.6)	34.7 (1.5)	0.0 (−0.1,0.2)	0.0 (−0.1,0.2)				

Table notes

The RR is the risk in the exposed group divided by the risk in comparison group. The mean difference is the mean in the exposed group minus the mean in the comparison group.

1. RRs/Difference in means from Model 1: adjusted for year of birth, maternal age and mother's Aboriginal and Torres Strait Islander status (except NSW). Outcomes restricted to term babies included adjustment for gestational week.
2. RRs/Difference in means from Model 2: adjusted for year of birth, maternal age, maternal Aboriginal and Torres Strait Islander status (except NSW), parity, marital status (except NSW), maternal country of birth, maternal BMI (except NT and NSW) and maternal ever smoked during pregnancy. Caesarean/assisted vaginal, emergency caesarean and postpartum haemorrhage were additionally adjusted for macrosomia. Preterm birth, still birth, low Apgar and growth measures were

additionally adjusted for sex of baby. Outcomes restricted to term babies included adjustment for gestational week. RRs from Model 2 are represented in a forest plot in Figure 3.

3. Gestational diabetes is only available in the NSW Perinatal Data Collection from 1994–2015; the denominators for exposed and comparison are 159 and 6,345 respectively. Gestational diabetes is only available in the NT Perinatal Data Collection from 2000; the denominators for exposed and comparison are 2,943 and 7,229 respectively.
4. Postpartum haemorrhage is only available in the NSW Perinatal Data Collection from 2016; the denominators for exposed and comparison are 29 and 938 respectively. For this outcome, year was modelled as a categorical rather than continuous covariate.
5. Birth length is only available in the NT Perinatal Data Collection from 2008; the denominators for exposed and comparison are 1,422 and 3,024 respectively.
6. Head circumference is only available in the NT Perinatal Data Collection from 2008; the denominators for exposed and comparison are 1,391 and 2,954 respectively.
7. The reductions in sample sizes going from Model 1 to Model 2 were:
    - NT: 32% for all outcomes apart from gestational diabetes (6%), birth length (4%) and head circumference (5%)
    - Qld: 2.8 to 3.2% for all outcomes
    - NSW: 0.4 to 0.9% for all outcomes
8. Denominators for risks exclude missing values. The number of missing as a proportion of total data, n (%):
    - Caesarean/assisted vaginal = NT: 17 (0.1%); NSW: 1 (0.0%)
    - Emergency caesarean = NT: 15 (0.1%); NSW: 6 (0.0%)
    - Postpartum haemorrhage = NSW (available from year 2016 only): 4 (0.0%)
    - Preterm = NT: 115 (0.7%); Qld: 1 (0.0%); NSW: 3 (0.0%)
    - Spontaneous preterm = NT: 115 (0.7%); Qld: 1 (0.0%); NSW: 8 (0.0%)
    - SGA = NT: 121 (0.7%); Qld: 1 (0.0%); NSW: 3 (0.0%)
    - LGA = NT: 121 (0.7%); Qld: 1 (0.0%); NSW: 3 (0.0%)
    - Stillbirth = Qld: 13 (0.1%); NSW: 13 (0.1%)
    - Low Apgar score = NT: 74 (0.4%); Qld: 2 (0.0%); NSW: 50 (0.3%)
    - Term low Apgar score = NT: 46 (0.3%); Qld: 1 (0.0%); NSW: 45 (0.3%)
    - Term birth weight = NT: 2 (0.0%); NSW: 2 (0.0%)
    - Term birth length = NT (available from year 2008 only): 1,006 (18.5%); Qld: 42 (1.0%)
    - Term head circumference = NT (available from year 2008 only): 1,107 (20.3%); Qld: 37 (0.9%)

Figure 3. Forest plot showing Model 2 adjusted relative risks (RR) for adverse perinatal outcomes

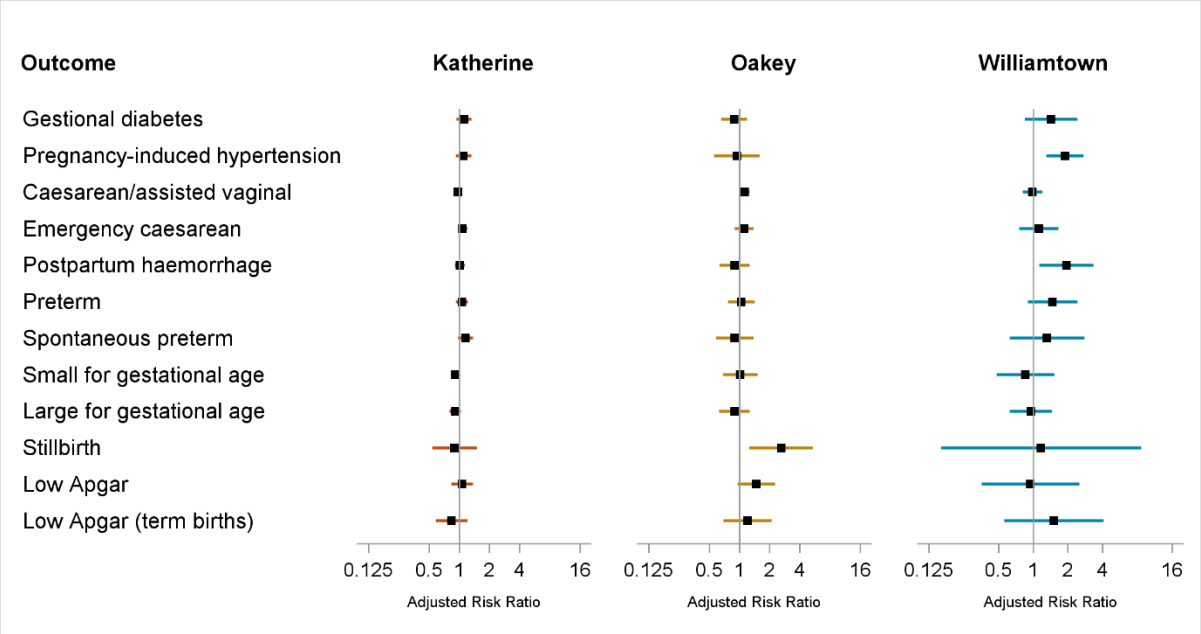


Figure notes

Data sources: NSW Perinatal Data Collection (1994–2018), NT Perinatal Trends (1986–2017), Qld Perinatal Data Collection (2007–2018)

1. Forest plot shows point estimates of adjusted RRs (filled squares) from Model 2 and associated 95% confidence interval (horizontal lines), and solid vertical line of no effect.
2. Model 2 RRs were adjusted for year of birth, maternal age, maternal Aboriginal and Torres Strait Islander status (except NSW), parity, marital status (except NSW), maternal country of birth, maternal BMI (except NT and NSW) and maternal ever smoked during pregnancy. Caesarean/assisted vaginal, emergency caesarean and postpartum haemorrhage were additionally adjusted for macrosomia. Preterm birth, still birth, low Apgar and growth measures were additionally adjusted for sex. Outcomes restricted to term babies included adjustment for gestational week.
3. See Table 4 for sample sizes, crude risks and adjusted RRs.
4. Adjusted RRs are on a log scale.

Discussion

Summary of main findings

We estimated that the risk of stillbirth in Oakey, Qld was 2.6-fold that of its comparison areas during the period 2007–2018, and that there was uncertain evidence for lower Apgar score in Oakey. In NSW, the risks for postpartum haemorrhage and pregnancy-induced hypertension in Williamtown were almost two times those in comparison areas over 1994–2018. For the remaining nine adverse perinatal outcomes examined in Qld, and the remaining 10 in NSW, we could not conclude that the risks were meaningfully different across the exposed and comparison populations. For several of these outcomes, in NSW in particular, this was because estimates were too imprecise to draw any conclusions. In NT, the results suggest no important differences between Katherine and its comparison areas for any of the adverse outcomes examined between 1987 and 2017. We did not find meaningful differences in growth measurements in babies born to mothers who had lived in Katherine, Oakey or Williamtown compared to the comparison areas.

The RRs for key findings are presented in Box 3, alongside which we have added the associated adjusted risks to provide an indication of effects on the absolute scale. It is important to note that while these estimates take random error (the play of chance) into account (confidence intervals

are available in Table 4), we cannot assume there was no bias from residual confounding. These issues are discussed in the section below on study strengths and weaknesses.

Box 3. Summary of key results: adjusted relative and absolute risks for selected perinatal outcomes

Outcome	Adjusted relative risk	Associated absolute risk
Oakey — Stillbirth	Risk 2.59-fold that of comparison population (159% increase)	Risk increase from 0.6 in 100 to 1.6 in 100 births
Williamtown — Postpartum haemorrhage	Risk 1.94-fold that of comparison population (94% increase)	Risk increase from 17 in 100 to 34 in 100 births
Williamtown — Pregnancy-induced hypertension	Risk 1.88-fold that of comparison population (88% increase)	Risk increase from 8 in 100 to 15 in 100 pregnancies
All other outcomes	No evidence of meaningful difference, uncertain or unable to determine due to imprecision.	

Notes

1. Adjusted relative and absolute risks were estimated from Model 2. Adjusted relative risks should be considered alongside their confidence intervals in Table 4.
2. Absolute risks were estimated assuming population characteristics of the exposed population (rather than those of the comparison population or average characteristics of the whole study population).

Interpretation of findings in the context of previous evidence

The largest relative effect estimated in our study was the increased risk of stillbirth in Oakey compared to its comparison areas, although the level of uncertainty suggested that the risk may have reasonably ranged anywhere from 25% to 440% higher. We are aware of only two previous studies from the C8 Health Project that have examined stillbirth in relation to PFAS. Neither study — both of which were conducted among women in the mid-Ohio Valley region who were highly exposed as a result of drinking water contaminated from a nearby PFOA facility — reported any association between estimated maternal serum PFAS and stillbirth, based on relatively large numbers of cases (approximately 100 stillbirths).[57,58] Consistent with this prior evidence, we did not find the risks of stillbirth to be elevated in the two other exposure areas of this study (Katherine and Williamtown) relative to their respective comparison areas.

Regarding the effects of PFAS exposure on caesarean section or assisted birth, one previous study reported an association between higher umbilical cord PFAS concentration and increased likelihood of vaginal delivery relative to caesarean, in principle a beneficial effect.[59] We did not find meaningful effects for this outcome in Katherine, Oakey or Williamtown.

The estimated elevated risks of pregnancy-induced hypertension (including pre-eclampsia, i.e. hypertension with proteinuria) and postpartum haemorrhage among mothers in Williamtown were not seen in Katherine nor Oakey in our study. Findings from previous studies are mixed. Among five studies conducted in highly exposed mothers from the mid-Ohio Valley region,[57,58,60-62] two suggested weak associations between estimated or measured maternal serum PFOA/PFOS and maternally reported pre-eclampsia,[57,60] and one found some evidence of a positive but not monotonic[i] association between measured maternal serum PFOA/PFOS and pregnancy-induced hypertension.[61] Using lifetime residential history and environmental/pharmacokinetic models to estimate PFOA exposure, Savitz and colleagues[58] did not report an association with pregnancy-induced hypertension. Pregnancy cohorts in Norway,[63] Sweden,[64] and Canada[65] at background levels of exposure have largely found no evidence of associations between various PFAS chemicals measured in blood sera and gestational hypertension or pre-eclampsia.

[i] A monotonic relationship is one where the value of one variable strictly increases (or decreases) as the value of the other variable increases (or decreases).

Elevated risks of pregnancy-induced hypertension and postpartum haemorrhage among pregnant mothers in Williamtown were accompanied by moderately elevated point estimates of risks of preterm birth and gestational diabetes, but with confidence intervals that were compatible with no effect, hence we consider these results uncertain. Gestational diabetes increases the risk of pregnancy-induced hypertension,[66] and preterm birth rates are higher in mothers with either diabetes or hypertension (or both).[67] Pregnancy-induced hypertension is also a risk factor for postpartum haemorrhage,[68] as is obesity,[69] which is also related to gestational diabetes. As such, it is probable that the increased risks observed in these adverse outcomes are related. There is, however, no consistent evidence to suggest the increased risks were related to PFAS exposure. They could be due to confounding by BMI, which we could not control due to insufficient data.

The few adverse outcomes we observed in this study in both mothers and infants, while not consistent across the exposure areas and to other studies, are hypothetically biologically plausible. PFAS have been shown to cross the placenta[70,71] and are hypothesised to disrupt placental growth and function, thereby increasing the risk of adverse perinatal outcomes.[72] Independently of PFAS exposure, placental dysfunction has been linked to hypertensive disorders of pregnancy[73] and low birth weight.[74] However, specific mechanisms for PFAS-induced placental damage as a driver of these outcomes have not yet been validated in experimental settings.

In terms of growth measurements, meta-analyses support a relationship between higher PFOA/PFOS serum concentrations and reduced birth weight,[32,33,75] although studies among highly exposed women in the mid-Ohio Valley region, and of female workers of a PFOS production facility, have not observed this association.[58,61,76,77] In another meta-analysis, Steenland and colleagues[78] suggest that associations between prenatal serum PFOA and decreased birth weight have been limited to studies with low background exposure or those with blood sampled later in pregnancy, where confounding and reverse causality are likely. Our findings for birth length are in the opposite direction to several general population birth cohort studies that found small decreases in length with increasing maternal serum PFAS concentrations,[79-82] although many studies have also not found evidence of associations.[79,81,83-86] While we found small increases in birth length (≤0.3 cm) in two exposure areas, we did not find concomitant increases in birth weight and head circumference; and all three measures are imperfect proxies for optimal fetal growth. We identified two studies that measured fetal growth by ultrasound, with neither reporting associations with PFAS exposure.[87,88] Either way, small differences in growth measurements within normal limits are likely to have low biological or clinical relevance and are doubtful as indicators of adverse impacts on health.[38]

Strengths and weaknesses

There are strengths and weaknesses of this study that should be kept in mind when interpreting findings and comparing them with results of other studies. These include considerations relating to selection of the study population, measurements of exposure and outcomes, and potential confounding.

Selection of study population

By using State/Territory Perinatal Data Collections to select the study populations, we were able to capture all mothers who had given birth over the last three decades in the exposure and comparison areas in Katherine and Williamtown, and over the last decade in Oakey (assuming low linkage error; see Appendix 1). Moreover, ascertainment of exposure by linkage of routinely collected datasets avoided selection bias and enhanced the internal validity of the estimates. The relatively small number of births in Oakey and Williamtown, and therefore few cases of some outcomes, meant we had low statistical power to make conclusions about these outcomes. There were larger numbers of exposed mothers and babies in Katherine, and thus more certainty in the

estimates. It is noteworthy, therefore, that none of the apparent increases in risks of perinatal outcomes we observed were in the Katherine population.

The NT, Qld and NSW Perinatal Data Collections were established well after the first exposures (PFAS exposure is possible as early as the 1970s). Therefore, mothers who had lived in exposure areas only before data collection began in their State[j] would not have been captured in this study.

Exposure measurement

State/Territory Perinatal Data Collections record no other data on residency except where mothers were living at the time of giving birth. There are limitations in relying on these data for exposure classification, which should be kept in mind when interpreting the study results.

First, without longitudinal information on residential history, we may not know whether the mother was living in an exposure area during the critical periods in pregnancy that may contribute to the development of adverse outcomes. If the critical window for exposure is during the gestational period, it is likely that misclassification was minimal, assuming that mothers do not usually move residences while pregnant. However, if the critical window is earlier in the mother's life, or accumulated over her lifetime, there would have been a higher rate of exposure misclassification and probably substantial under-coverage of the target population.

Secondly, it was not possible to measure duration of residency from address data in the Perinatal Data Collections. We do not know the correlation between 'ever resident' or duration of residency in an exposure area and cumulative serum levels of PFAS in the Australian context. Savitz and colleagues[57] report a moderate correlation (Spearman rank order correlation coefficient = 0.64) between estimated exposure based on lifetime residential history and maternal residence recorded on the baby's birth certificate in the mid-Ohio Valley region, but this is likely context specific.

Outcome measurement

Based on validation studies of the NSW Perinatal Data Collection,[89,90] we assume these data to have reasonably high levels of accuracy for reporting of most perinatal outcomes. However, pregnancy-induced hypertension may have been under-captured. When compared with medical records, the NSW Perinatal Data Collection identified about 63% of pregnancy-induced hypertension cases identified through medical chart review.[91] This under-ascertainment is likely to be the same in women in exposure and comparison areas ('non-differential misclassification'), meaning that while the risk will be underestimated to the same extent in both groups, the RR estimates are likely unaffected (not biased).

In addition, postpartum haemorrhage was only added to the NSW Perinatal Data Collection in 2016, limiting the data available to make inferences about this outcome in Williamtown. Finally, the scope of the Perinatal Data Collections includes live births and stillbirths of at least 20 weeks' gestation. If PFAS exposure is related to earlier outcomes, such as infertility or miscarriages,[92] this would not have been picked up in this study.

Potential confounding

Confounding is an issue in all observational studies, potentially biasing risk estimates and limiting the ability to draw causal inferences. This is discussed more fully in the final section of the report. In this study, we were able to adjust for many known confounders due to the richness of the data collected in the Perinatal Data Collections. Nevertheless, there were insufficient years of data collected for BMI and marital status in NT and NSW to allow statistical adjustments for these factors. We also lacked information on other potential confounders such as alcohol consumption, individual-level socioeconomic status (including maternal education), maternal height, ethnicity,

[j] Or collection of residential addresses in the case of the Qld Perinatal Data Collection.

model of obstetric care (i.e. private obstetrician, general practice shared care, public hospital) and detailed clinical information to classify high-risk pregnancies.

We expect our findings to have been particularly affected by confounding by factors related to socioeconomic status (SES). While every effort was made to draw a comparison population for each exposure area from comparable socioeconomic areas, this was based on area-level measures at one point in time, which may not have reflected changes over time. In addition, area-level SES measures are imprecise proxies of individual circumstances. We lacked information on individual-level SES to assess the comparability between the exposed and comparison populations on this dimension over the long study period.

We set out to select comparison areas that were also similar to the exposure areas on proportions of Aboriginal and Torres Strait Islander residents. However, there were smaller proportions of people of Aboriginal and Torres Strait Islander descent drawn from these areas in the resulting comparison populations in NT and Qld (Table 6). This was partly driven by limited number of areas to choose from, particularly in NT.

While in the analyses we also adjusted for the different proportions of Aboriginal and Torres Strait Islander women in the exposed and comparison populations, there were issues of under-identification in the Perinatal Data Collections over the study period.[93] The rates of under-identification were likely to be uneven across states and remoteness subgroups, and over time. Because of this, the extent and direction of residual confounding and resulting extent and direction of consequent bias are uncertain. Nonetheless, we expect it would have a bigger impact on results in NT than in Qld, and little to no effect in NSW given the low proportions of people of Aboriginal and Torres Strait Islander descent in Williamtown and its chosen comparison areas.

Summary

Overall, we found little support for higher risks of adverse perinatal outcomes in the PFAS Management Areas than comparison areas. We saw modest but inconsistent evidence of increased stillbirth, pregnancy-induced hypertension and postpartum haemorrhage. The inconsistencies observed in both size and direction of effects across the exposure areas, unknown PFAS levels in maternal blood, the potential for bias, and the lack of robust prior evidence for any associations observed, argue against PFAS causing these outcomes. Considerations of causality are discussed more fully in the final section of the report.

Study 2: Childhood development outcomes

This study included children who had lived in an exposure or comparison area and who subsequently took part in the Australian Early Development Census (AEDC) during their first year of full-time schooling. The outcomes were indicators of childhood development as recorded in the AEDC in any State or Territory where the child was living at the time of the AEDC.

Methods

Data sources and study population

We used data from the Medicare Enrolment File (Box 4) linked to the PFAS Address Database and comparison area postcodes (Box 1) to select study populations. The study populations were then linked to the AEDC to determine childhood development outcomes.

Australian Early Childhood Development Census (AEDC)

The AEDC is a nationwide data collection of early childhood development data made at the time children commence their first year of full-time schooling, generally in the year they turn five years of age. It is conducted nationally every three years. In each Census year, usually between 1 May and 31 July, teachers complete the AEDC for each child in their class, across five key areas of early childhood development referred to as 'domains'. The AEDC instrument is based on the Canadian Early Development Instrument (developed by McMaster University in Ottawa, Canada).[94]

The first AEDC was administered in 2009. Further collections were conducted nationally in 2012, 2015 and 2018. The AEDC datasets have near-complete national coverage of school entrants; more than 95% of schools with eligible children participated in each collection, with child participation rates of more than 96%.

On each of the five AEDC domains (see Table 5), each child receives a score from 0 to 10 which is calculated from teachers' responses to the relevant domain questions. AEDC results are reported as the number and proportion of children who are 'developmentally on track', 'developmentally at risk' and 'developmentally vulnerable' on each domain based on percentile cut-offs established using 2009 data, accounting for age variations in the population of children in their first year of schooling. The AEDC also collects sociodemographic information such as age, Aboriginal and Torres Strait Islander identification and English as a second language, among others.

Selection of study populations

The study populations were selected and classified based on place of residence as described earlier (see Overview of methods and Figure 2). We included all children in the Medicare Enrolment File who had lived in Katherine, Oakey or Williamtown,[k] and a sample of children who had lived in comparison areas, before taking part in any AEDC collection (2009, 2012, 2015 or 2018). As the AEDC is usually undertaken between 1 May and 31 July, we included only children who had lived in a PFAS Management Area or comparison area for at least five months before those dates. Thus, the study included children who had lived in a PFAS Management Area or comparison area between July 2002[l] and December 2017.

[k] We considered two exposed populations: where children lived in the PFAS Management Areas as defined by the PFAS Address Database (main analysis), and where children lived in Katherine, Oakey or Williamtown postcodes (sensitivity analysis).

[l] The oldest children in the first AEDC census year (2009) were 7 years old.

We selected a sample of individuals from the comparison areas (Box 1) rather than including everyone in these areas to meet ethical requirements pertaining to the Medicare Enrolment File. The comparison populations were frequency-matched at a 4:1 ratio to the exposed populations on age, sex, Aboriginal and Torres Strait Islander status, and year of first living in an exposure or comparison area.

Children were excluded from the study if they:

a) were identified as a child with special needs
b) had less than the minimum number of valid responses to questions in all domains of the instrument
c) had invalid dates — for example where the recorded date of birth occurred after the date of first registration with Medicare (allowing a 60-day buffer on either side), or where the disparity between the age recorded on the Medicare Enrolment File fell outside the age range recorded on the AEDC by >3 months.

Box 4. Medicare Enrolment File and associated Voluntary Indigenous Identifier database.

Medicare Enrolment File (1983–2019)

Medicare is Australia's universal health insurance provider, which is open to all Australian and New Zealand citizens living in Australia and permanent residents of Australia. The Medicare Enrolment File and associated Voluntary Indigenous Identifier database are held by Services Australia, which collects and stores personal details, including name, sex, date of birth and address, for each registered individual.

If an individual changes their address they are required to notify Services Australia by phone, online or in person. A history of these changes is stored in the Medicare Enrolment File, resulting in multiple address records for individuals who have moved. A *start date* is associated with each address record in the Medicare Enrolment File, which is the date Services Australia was notified of the change. There may be a delay between the actual change of address and this change being recorded in the Medicare Enrolment File.

Services Australia collects residential and mailing addresses for the Medicare Enrolment File. However, it is not mandatory for individuals to provide residential addresses. Consequently, only mailing addresses were provided to the Australian Institute of Health and Welfare (AIHW) for data linkage for this research. While mailing and residential addresses are likely to be the same for most of the population, a proportion of addresses on the data are non-residential, including post office box addresses. Multiple members of a family may be associated with a single Medicare registration, and the mailing address for all members is the address nominated by the card contact.

Voluntary Indigenous Identifier (VII) database (2002–2019)

The VII is a database of individuals with a Medicare record who elected to have their Aboriginal and Torres Strait Islander status recorded. Aboriginal and Torres Strait Islander people enrolled with Medicare have been able to have their status recorded confidentially on this database since 2002. By October 2019, about 599,000 people were enrolled on the VII database. This represents 75.5% of the estimated total population of Aboriginal and Torres Strait Islander people in Australia.[2]

Enrolment in VII database may occur through checking a box on the Medicare enrolment form, telephoning Medicare to provide this information, or completing and mailing a form located on the Services Australia website. Identification via the initial Medicare enrolment form is the most common way that individuals enrol on the VII database, which has led to higher rates of enrolment among infants and children.

The level of VII enrolment varies across age group, sex, remoteness and State/Territory subgroups, and over time. While the overall number of individuals with a VII record is increasing, individuals can also choose to have their identification information removed at any time. Other datasets record Aboriginal and Torres Strait Islander identification, such as the Perinatal Data Collections, Australian Early Development Census and Australian Cancer Database, but this information may not align with the VII database.

Study variables

Outcomes

We examined six outcomes: one for each of the five AEDC development domains (see Table 5), and a summary measure. For each outcome, we classified children as either developmentally vulnerable or not. A child was classified as 'vulnerable' on a particular domain of the AEDC if they scored below the 10th percentile, determined using the cut-off established in 2009 based on all

children who participated nationally.[95] Children were classified as developmentally vulnerable on the summary measure if they scored below the 10th percentile on any of the five domains.

Table 5. Descriptors of vulnerable category for the five AEDC childhood development domains

Domain	Descriptor of vulnerable category[96]
Physical health and wellbeing	Experience a number of challenges that interfere with their ability to physically cope with the school day. This may include being dressed inappropriately, frequently late, hungry or tired. Children are usually clumsy and may have fading energy levels.
Social competence	Experience a number of challenges with poor overall social skills. For example, children who do not get along with other children on a regular basis, do not accept responsibility for their own actions and have difficulties following rules and class routines. Children may be disrespectful of adults, children, and others' property, have low self-confidence and self-control, do not adjust well to change; and are usually unable to work independently.
Emotional maturity	Experience a number of challenges related to emotional regulation. For example, problems managing aggressive behaviour, being prone to disobedience and/or are easily distracted, inattentive, and impulsive. Children will usually not help others and are sometimes upset when left by their caregiver.
Language and cognitive skills (school-based)	Experience a number of challenges in reading/writing and with numbers; unable to read and write simple words, will be uninterested in trying, and often unable to attach sounds to letters. Children will have difficulty remembering things, counting to 20, and recognising and comparing numbers; and usually not interested in numbers.
Communication skills and general knowledge	Children will have poor communication skills and articulation; have limited command of English (or the language of instruction), have difficulties talking to others, understanding, and being understood; and have poor general knowledge.
Developmentally vulnerable on one or more domains	Scoring below 10th percentile in any of the above domains

Tables notes

A child who scores below the 10th percentile in a particular domain, determined using the cut-off established in 2009 based on all children who participated nationally, is classified as 'vulnerable' on that domain.[95]

Exposure and other variables

The exposure variable in our analyses was residence in a PFAS Management Area (yes/no), as defined earlier. All other variables used to adjust for potential confounding were based on information recorded in the AEDC. We coded Aboriginal and Torres Strait Islander status according to the AEDC rather than the VII database due to the higher rate of under-identification in the VII database. All demographic data in the AEDC, including Aboriginal and Torres Strait Islander status, were collected in the standard school enrolment process.

Statistical analysis

Main analysis

For each childhood development domain, we calculated the proportions of children who were developmentally vulnerable (risks) in the exposed and comparison populations. To estimate risk in the exposed children relative to the comparison children, we generated relative risks (RR) and 95% CIs using the modified Poisson approach with robust estimation of error variance.[56]

To take potential confounding into account in our RR estimates, we specified two models for each outcome. Model 1 was a minimally adjusted model, with adjustments for sex, Aboriginal and Torres

Strait Islander status and AEDC collection year. In Model 2 we additionally adjusted for the following variables: English as a second language; socioeconomic disadvantage as measured by the ABS Index of Relative Socioeconomic Disadvantage (IRSD) quintile based on Statistical Area Level 1 (SA1)[m]; and geographical remoteness as measured by the ARIA+ categories (Very Remote, Remote, Outer Regional, Inner Regional and Major Cities). We did not adjust for age as the nationally derived percentiles for domain scores had already been age-adjusted. All covariates were modelled as categorical variables.

Sensitivity analysis

We conducted the following sensitivity analyses:

a) The exposed populations were limited to children who had lived in the exposure areas of Katherine, Oakey or Williamtown continuously since birth—that is, children who were recorded on Medicare as living in these areas within 60 days of the date of birth, with no record of moving out of the area up to at least 1 January of the AEDC year in which the child was measured.
b) The exposed population was broadened to include children who had lived in Katherine, Oakey or Williamtown based on postcodes, rather than based on the PFAS Address Database. The relevant postcodes were: 2314, 2318, 4401, 0850, 0851, 0852 and 0853.

Results

Description of the study population

We identified two samples in this study: the main analysis sample comprised children who had lived at an address in the PFAS Address Database or a comparison area postcode, and a larger sensitivity analysis sample based on a broader definition of exposure, which included children who had lived in Katherine, Oakey and Williamtown postcodes.

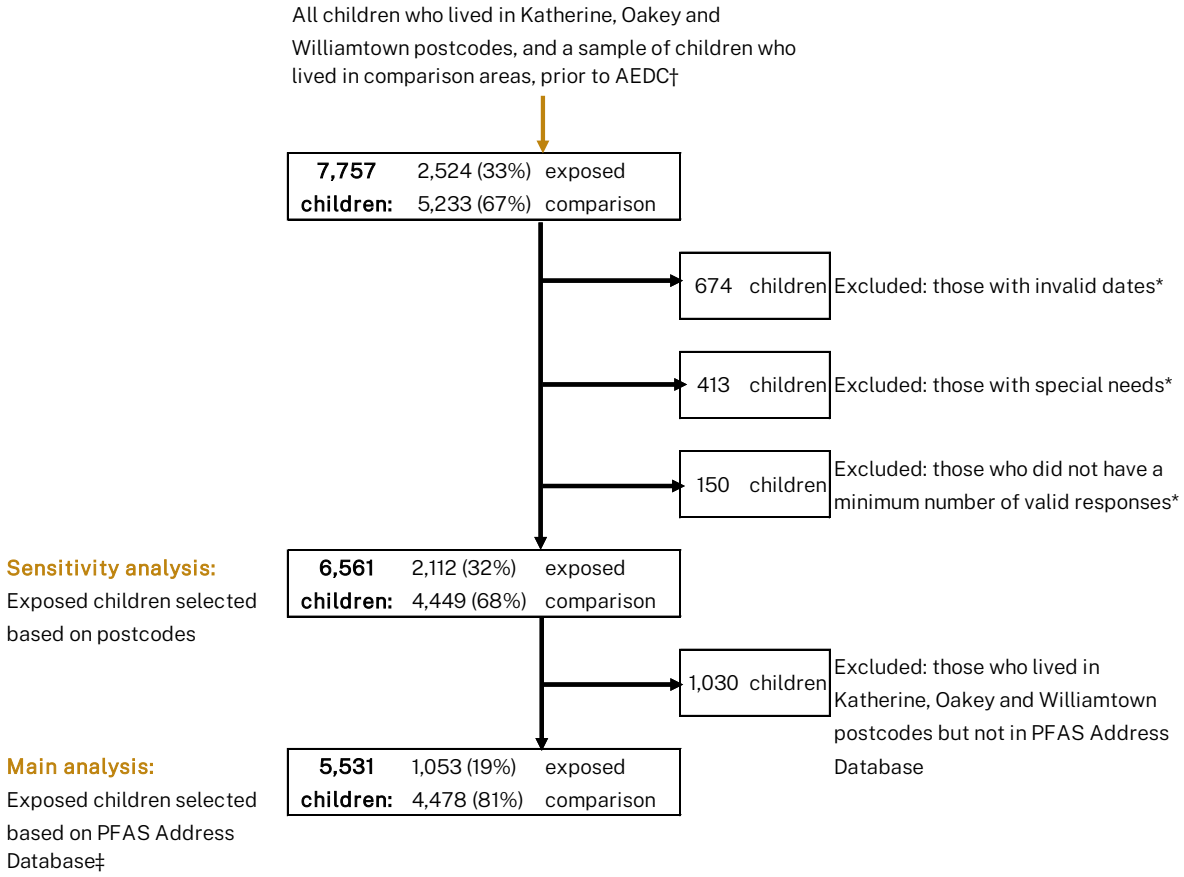
Between July 2002 and December 2017, a total of 7,757 children were identified in the Medicare Enrolment File as having lived in Katherine, Oakey or Williamtown postcodes (n = 2,524) or comparison areas (n = 5,233) at least five months prior to taking part in any AEDC collection year (2009, 2012, 2015 or 2018). After excluding 1,237 children with invalid dates (see (c) in Selection of study populations) or who were identified with special needs or did not have a minimum number of valid responses for instrument questions on all domains, we included 85% (6,561/7,757) of children in the sensitivity analysis sample, of whom 2,122 (32%) were from the exposure postcodes.

Our main analysis sample comprised 5,531 children, of whom 1,053 (19%) had lived at an address in the PFAS Address Database and 4,478 (81%) had lived in comparison areas. The largest number of exposed children was in NT (579 (24%) exposed, 1,850 (76%) comparison), followed by Qld (377 (15%) exposed, 2,215 (85%) comparison) and NSW (97 (19%) exposed, 413 (81%) comparison). Sample sizes and sociodemographic characteristics by State/Territory and exposure status can be seen in Table 6.

A flow diagram of sample selection is in Figure 4.

[m] IRSD quintile was based on the SA1 of the child's usual residence coded according to ASGS 2016 for all cycles.

Figure 4. Sample selection of study population for analysis of childhood development outcomes



† All children in the Medicare Enrolment File with a recorded address in Katherine, Oakey or Williamtown postcodes, and a sample of children from comparison area postcodes (see Box 1), between July 2002-December 2017, at least five months prior to participating in any AEDC cycle (2009, 2012, 2015, 2018).

‡ See Box 1.

* Exclusions not mutually exclusive

Table 6. Sociodemographic characteristics of study populations for analysis of childhood development outcomes

	NT		Qld		NSW	
Characteristic	**Exposed n (%)**	**Comparison n (%)**	**Exposed n (%)**	**Comparison n (%)**	**Exposed n (%)**	**Comparison n (%)**
Total sample	**579**	**1,850**	**377**	**2,215**	**97**	**413**
Sex						
Female	287 (50)	920 (50)	194 (51)	1,117 (50)	50 (52)	203 (49)
Male	292 (50)	930 (50)	183 (49)	1,098 (50)	47 (48)	210 (51)
AEDC cycle						
Cycle 1 (2009,2010)	110 (19)	281 (15)	60 (16)	372 (17)	12 (12)	59 (14)
Cycle 2 (2012)	168 (29)	543 (29)	105 (28)	596 (27)	16 (16)	90 (22)
Cycle 3 (2015)	143 (25)	517 (28)	95 (25)	642 (29)	37 (38)	136 (33)
Cycle 4 (2018)	158 (27)	509 (28)	117 (31)	605 (27)	32 (33)	128 (31)
Age first registration with Medicare[1]						
0–0.5	545 (95)	1,692 (91)	354 (94)	2,133 (96)	94 (97)	394 (95)
0.5–1	16 (3)	60 (3)	12 (3)	42 (2)	0†	13 (3)
1+	18 (3)	98 (5)	11 (3)	40 (2)	0†	6 (1)
Age first lived in PFAS Management Area or comparison area[1]						
0–1	377 (65)	1,165 (63)	243 (64)	1,389 (63)	66 (68)	267 (65)
1–2	50 (9)	203 (11)	40 (11)	204 (9)	12 (12)	38 (9)
2–3	50 (9)	178 (10)	33 (9)	213 (10)	8 (8)	33 (8)
3+	102 (18)	304 (16)	61 (16)	409 (18)	11 (11)	75 (18)
Age at AEDC measurement						
3–5	70 (12)	292 (16)	47 (12)	306 (14)	6 (6)	24 (6)
5–5.5	272 (47)	876 (47)	187 (50)	1,034 (47)	35 (36)	147 (36)
5.5–6	204 (35)	616 (33)	143 (38)	822 (37)	48 (49)	173 (42)
6+	33 (6)	66 (4)	0†	53 (2)	8 (8)	69 (17)
Indigenous status						
No	328 (57)	1,404 (76)	283 (75)	1,968 (89)	90 (93)	366 (89)
Yes	251 (43)	446 (24)	94 (25)	247 (11)	7 (7)	47 (11)
English as second language						
No	423 (73)	1,520 (82)	363 (96)	2,158 (97)	97 (100)	404 (98)
Yes	156 (27)	330 (18)	14 (4)	57 (3)	0†	9 (2)

(Table continued over)

	NT		Qld		NSW	
Characteristic	**Exposed n (%)**	**Comparison n (%)**	**Exposed n (%)**	**Comparison n (%)**	**Exposed n (%)**	**Comparison n (%)**
Remoteness						
Very remote	72 (12)	209 (11)	≤5	15 (1)	0	≤5
Remote	268 (46)	175 (9)	≤5	26 (1)	12 (12)	≤5
Outer regional	97 (17)	1,027 (56)	31 (8)	258 (12)	10 (10)	60 (15)
Inner regional	45 (8)	168 (9)	292 (77)	1,524 (69)	37 (38)	288 (70)
Major cities	97 (17)	271 (15)	45 (12)	392 (18)	38 (39)	61 (15)
IRSD[2] quintile						
1 (most disadvantage)	182 (32)	354 (19)	178 (47)	1,005 (45)	15 (15)	88 (21)
2	133 (23)	316 (17)	110 (29)	597 (27)	30 (31)	111 (27)
3	108 (19)	377 (21)	34 (9)	322 (15)	25 (26)	96 (23)
4	86 (15)	483 (26)	48 (13)	221 (10)	17 (18)	87 (21)
5	64 (11)	299 (16)	7 (2)	67 (3)	10 (10)	31 (8)
Missing	6	21	0	3	0	0

Table notes

Data sources: Medicare Enrolment File (July 2002–December 2017) linked to Australian Early Development Census (AEDC) (2009, 2012, 2015, 2018).

1. Age first registration with Medicare and age first lived in a PFAS Management Area (PMA) or comparison area was estimated from month and year of birth as recorded on the Medicare Enrolment File, with day of birth assumed to be the 15th of the month.
2. All characteristics except age first lived in a PMA or comparison area were sourced from the AEDC database. Geographic variables (Australian Bureau of Statistics' Index of Relative Socioeconomic Disadvantage (IRSD) quintile and remoteness) were based on where the child was living at the time of the AEDC, not at the time of living in PMAs. IRSD decile was based on the Statistical Area Level 1 of the child's usual residence coded according to Australian Bureau of Statistics' Australian Statistical Geography Standard (ASGS) 2016 Version for all cycles.
3. There is no socioeconomic or remoteness information on the Medicare Enrolment File.
4. The discrepancies between variables with similar concepts on the Medicare Enrolment File and AEDC are as below:
   - 5.0% (278/5531) records differed in voluntary Aboriginal and Torres Strait Islander identification on the Medicare Enrolment File vs. Aboriginal and Torres Strait Islander identification on the AEDC.
   - 0.7% (41/5531) records differed in sex on the Medicare Enrolment File vs. sex on the AEDC.
5. Denominators for proportions exclude missing values.
6. Cells have been suppressed or categories collapsed (†) to avoid reporting cell numbers with size ≤5.
7. Percentages were rounded to zero decimal places.

Childhood development outcomes in relation to living in exposure areas

The proportions of children in the exposed and comparison populations who were developmentally vulnerable in each domain (risks), and adjusted RRs are shown in Table 7; a forest plot of adjusted RRs is shown in Figure 5. For information on interpreting effect estimates, see Box 2.

In NT, the proportions of children who were developmentally vulnerable (crude risks) in the specific domains ranged from 12% to 20% among children in Katherine and 12% to 15% in its comparison areas. Notably, these crude risks were higher than 10%, the percentage that would be expected based on national percentile cut-offs, all else being equal. After adjusting for sociodemographic characteristics, we estimated a 26% lower risk of developmental vulnerability in the domain of communication skills and general knowledge among children in Katherine (Model 2 adjusted RR = 0.74, 95% CI 0.57 to 0.97). While the RR was also below 1 for the language and cognitive skills

domain, the evidence pointing to a lower risk was uncertain (Model 2 adjusted RR = 0.83, 95% CI 0.68 to 1.01). In the remaining three domains — physical health and wellbeing, social competence and emotional maturity — interval estimates suggested minimal or no differences in risks between children who had lived in Katherine compared to children who had lived in its comparison areas. Overall, there was a 14% lower risk of developmental vulnerability on one or more domains associated with childhood residence in Katherine (Model 2 adjusted RR = 0.86, 95% CI 0.75 to 0.98). Note that findings with respect to number of domains are not necessarily independent of findings with respect to any unique domain.

In Qld, the proportions of children who were developmentally vulnerable in the specific domains were also higher than the national average of 10%, ranging from 16% to 23% in Oakey and 13% to 17% in its comparison areas. After adjusting for sociodemographic factors, we estimated increased risks of developmental vulnerability in two domains in children who ever resided in Oakey compared to children in its comparison areas: there was a 31% higher risk of developmental vulnerability in physical health and wellbeing (Model 2 adjusted RR = 1.31, 95% CI 1.06 to 1.61), and a 49% higher risk of developmental vulnerability in communication skills and general knowledge (Model 2 adjusted RR = 1.49, 95% CI 1.18 to 1.87). While the RR was also above 1 for the language and cognitive skills domain, the evidence pointing to a higher risk was uncertain (Model 2 adjusted RR = 1.24, 95% CI 0.98 to 1.57). In the remaining two domains — social competence and emotional maturity — interval estimates were compatible with no effect. Overall, there was a 22% elevation in the risk of developmental vulnerability on one or more domains associated with residence in Oakey during childhood compared to residence in its comparison areas (Model 2 adjusted RR = 1.22, 95% CI 1.06 to 1.39).

In NSW, in contrast to the other two states, the proportions of children who were developmentally vulnerable in specific domains were at or below the national average, ranging from <4% to 10% in Williamtown and 5% to 11% in its comparison areas. After adjusting for sociodemographic factors, interval estimates were too imprecise to make any conclusions about the size or direction of effects in all domains. We note the elevation in risk of developmental vulnerability in the domain of language and cognition in Model 1 (minimally adjusted model) but did not have enough have cases in Model 2 to make a conclusion.

Sensitivity analyses

In the first sensitivity analysis, we limited the exposed populations in the PFAS Management Areas of Katherine and Oakey to children who had lived in these areas continuously since birth. This had the effect of increasing the uncertainty of all estimates (widening of confidence intervals) due to reductions in sample sizes (Appendix Table 3). This analysis was not performed for NSW due to limited sample size.

In the second sensitivity analysis, we broadened the definition of exposure to include all children who had lived in Katherine, Oakey or Williamtown postcodes, instead of just those at addresses captured in the PFAS Address Database. In this analysis, there was little material impact on effect sizes and direction of findings (Appendix Table 4).

Table 7. Comparison of childhood development outcomes in exposed and comparison populations: risks (%) and adjusted relative risks (RR)

	NT				Qld				NSW			
	Exposed % (n)	Comparison % (n)	Adjusted RR[1] (95% CI)	Adjusted RR[2] (95% CI)	Exposed % (n)	Comparison % (n)	Adjusted RR[1] (95% CI)	Adjusted RR[2] (95% CI)	Exposed % (n)	Comparison % (n)	Adjusted RR[1] (95% CI)	Adjusted RR[2] (95% CI)
Total sample	**579**	**1,850**			**377**	**2,215**			**97**	**413**		
Vulnerable in:												
Physical health and wellbeing	19% (109)	15% (283)	1.00 (0.82,1.22)	0.94 (0.75,1.18)	23% (87)	17% (377)	1.28 (1.04,1.58)	1.31 (1.06,1.61)	6% (6)	9% (38)	0.73 (0.32,1.65)	0.66 (0.27,1.64)
Social competence	18% (103)	14% (263)	1.05 (0.85,1.29)	0.99 (0.78,1.24)	18% (67)	15% (343)	1.10 (0.86,1.40)	1.14 (0.89,1.45)	9% (9)	11% (47)	0.87 (0.45,1.70)	0.69 (0.34,1.43)
Emotional maturity	15% (88)	14% (248)	0.96 (0.77,1.19)	0.91 (0.71,1.17)	16% (61)	14% (307)	1.10 (0.85,1.42)	1.13 (0.88,1.46)	10% (10)	8% (33)	1.31 (0.68,2.54)	1.12 (0.52,2.41)
Language and cognitive skills (school-based)	20% (114)	15% (281)	0.92 (0.76,1.10)	0.83 (0.68,1.01)	19% (73)	14% (313)	1.24 (0.99,1.57)	1.24 (0.98,1.57)	9% (9)	5% (21)	2.25 (1.11,4.57)	1.95 (0.82,4.64)
Communication skills and general knowledge	12% (72)	12% (222)	0.77 (0.61,0.99)	0.74 (0.57,0.97)	21% (78)	13% (293)	1.40 (1.12,1.76)	1.49 (1.18,1.87)	≤5	7% (30)	0.79 (0.31,1.98)	0.60 (0.22,1.67)
Developmentally vulnerable on one or more domains	36% (210)	32% (596)	0.93 (0.82,1.05)	0.86 (0.75,0.98)	40% (152)	32% (717)	1.19 (1.04,1.36)	1.22 (1.06,1.39)	27% (26)	22% (92)	1.30 (0.91,1.87)	1.17 (0.79,1.75)

Table notes

The RR is the risk in the exposed group divided the risk in comparison group.

1. RRs from Model 1: adjusted for sex, Aboriginal and Torres Strait Islander status and Australian Early Development Census (AEDC) year.
2. RRs from Model 2: adjusted for sex, Aboriginal and Torres Strait Islander status, AEDC year, English as second language (except Qld and NSW), Australian Bureau of Statistics' Index of Relative Socioeconomic Disadvantage (IRSD) quintile, and remoteness. In NSW, the two lowest remoteness categories, and the two highest IRSD quintiles were combined to avoid sparse categories. RRs from Model 2 are represented in a forest plot in Figure 5.
3. Denominators for risks exclude missing values. The number of missing as a proportion of total data, n (%):
    - Physical health and wellbeing = NT: 3 (0.1%), Qld: 1 (0.0%)
    - Social competence = NT: 7 (0.3%)
    - Emotional maturity = NT: 18 (0.7%), Qld: 6 (0.2%), NSW: 2 (0.4%)
    - Language and cognitive skills = NT: 8 (0.3%), Qld: 1 (0.0%)
    - Communication skills and general knowledge = Qld: 3 (0.1%)

Figure 5. Forest plot showing Model 2 adjusted relative risks (RR) for childhood development outcomes

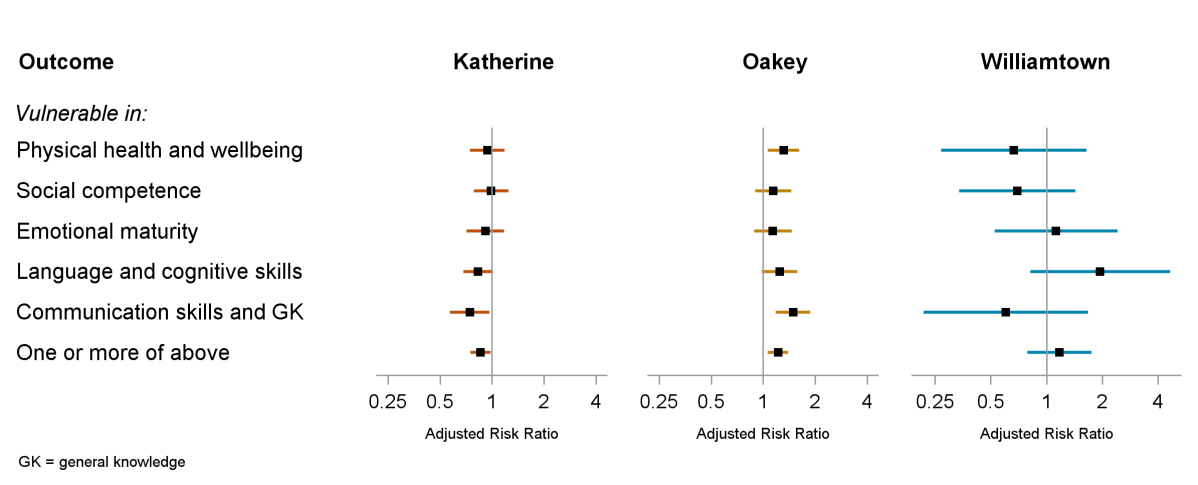


Figure notes

Data sources: Medicare Enrolment File (July 2002–December 2017) linked to Australian Early Development Census (2009, 2012, 2015, 2018). A child is classified as 'developmentally vulnerable' on a particular domain if they scored below the 10th percentile, determined using the cut-off established in 2009 based on all children who participated nationally.

1. Forest plot shows point estimates of adjusted RRs (filled squares) from Model 2 and associated 95% confidence interval (horizontal lines), and solid vertical line of no effect.
2. Model 2 RRs were adjusted for sex, Aboriginal and Torres Strait Islander status, AEDC year, English as second language (except Qld and NSW), Index of Relative Socioeconomic Disadvantage (IRSD) quintile, and remoteness.
3. See Table 7 for sample sizes, crude risks and adjusted RRs.
4. Adjusted RRs are on a log scale.

Discussion

Summary of main findings

In both the exposure and comparison areas in NT and Qld, the proportions of children assessed as developmentally vulnerable were higher than the national average in all domains. We estimated a 26% lower risk of developmental vulnerability in communication skills and general knowledge in children who had lived in Katherine, NT, compared to children who had lived in its comparison areas. Conversely, we estimated a 49% higher risk of developmental vulnerability in the same domain, and a 31% higher risk of developmental vulnerability in physical health and wellbeing among children in Oakey, Qld, compared with children in its comparison areas. We could not conclude that the risks were different across the exposed and comparison populations for any of the remaining domains in NT and Qld. In Williamtown (and its comparison areas), the proportions of children who were developmentally vulnerable in specific domains were at or below the national average, and RR estimates were essentially too imprecise to conclude whether risks were different.

The RRs for key findings are presented in Box 5, alongside which we have added the associated adjusted risks to provide an indication of effects on the absolute scale. It is important to note that while these estimates take random error (the play of chance) into account (confidence intervals are available in Table 7), we cannot assume there was no bias from residual confounding. These issues are discussed in the section below on study strengths and weaknesses.

Box 5. Summary of key results: adjusted relative and absolute risks for selected childhood development outcomes

Outcome	Adjusted relative risk	Associated absolute risk
Katherine — Developmental vulnerability in communication skills and general knowledge	Risk 0.74-fold that of comparison population (26% decrease)	Risk decrease from 16 in 100 to 12 in 100 children
Oakey — Developmental vulnerability in physical health and wellbeing	Risk 1.31-fold that of comparison population (31% increase)	Risk increase from 18 in 100 to 23 in 100 children
Oakey — Developmental vulnerability in communication skills and general knowledge	Risk 1.49-fold that of comparison population (49% increase)	Risk increase from 14 in 100 to 20 in 100 children
All other outcomes	No evidence of meaningful difference, uncertain or unable to determine due to imprecision.	

Notes

1. Adjusted relative and absolute risks were estimated from Model 2. Adjusted relative risks should be considered alongside their confidence intervals in Table 7.
2. Absolute risks were estimated assuming population characteristics of the exposed population (rather than those of the comparison population or average characteristics of the whole study population).

Interpretation of findings in the context of previous evidence

The discrepant findings that we observed for developmental vulnerability in communication skills and general knowledge — an increased risk in Oakey, but a lowered risk in Katherine — make interpretation difficult and reflects the variability in results seen in the current epidemiologic literature. We are unaware of any study that has used a similar instrument to measure the relationship between PFAS and communication skills or general knowledge in early school-age children. One British birth cohort study in girls examined the relationship between prenatal exposure to various PFAS and communication at two time points during very early childhood. This study found both positive and negative associations between measured maternal serum PFAS and scores in language, intelligibility and communication. The patterns were not consistent across the girls' ages at time of measurement (15 months and 38 months), or across types of PFAS.[97]

Previous birth cohort studies that have examined measures of cognition in their relationship to PFAS in the general population have reported largely mixed findings across PFAS type, timings of exposure and outcomes, and endpoints used. This is partly driven by the different methods that have been used in previous studies, making direct comparisons difficult. In a US birth cohort, higher prenatal serum concentration of PFOS was associated with poorer executive function in girls but not boys, with no associations reported for PFOA.[98] In the same cohort, Vuong and colleagues[99] later reported that higher blood levels of PFOA measured at eight years of age may be related to poorer executive function, but no associations were seen for PFOS or PFHxS. In a third study, no adverse relationships were noted between prenatal or childhood serum levels of some PFAS and cognitive function at eight years old, while those with higher levels of PFOA and PFNA had better outcomes on some measures including working memory, Intelligence Quotient (IQ) and perceptual reasoning.[100] In a different US birth cohort, children with higher measured serum PFOA, PFOS and PFNA levels, but not PFHxS, had higher reading scores at five and eight years of age.[101] In terms of IQ scores, a Swedish cohort study found that maternal blood concentration of PFHxS was associated with lower IQ scores at seven years[102]; however, there was no evidence supporting associations in Taiwan or Denmark between maternal PFAS levels and IQ scores at five or eight years.[103,104]

Among highly exposed children in the mid-Ohio Valley communities that experienced drinking water contamination from a nearby DuPont plant (C8 Health Project), those with higher estimated *in utero* PFOA levels were found to have higher IQ scores.[105] However, there was no support for associations to reading and mathematical skills.[105] Among the same population, another study suggested a relationship between PFOA and better executive function in boys but poorer function in girls.[106]

As far as we are aware, there is no robust evidence for an association between PFAS exposure and physical vulnerability. In two birth cohort studies among children in Greenland, Ukraine, Poland and Denmark, maternal serum PFOS and PFOA levels were not related to motor coordination difficulties at 5–9 years of age.[107,108] In a Danish cohort, no relationships were seen between levels of various PFAS types measured in children and physical activity at nine years.[109] A Chinese birth cohort study found that boys with higher maternal PFOA serum concentrations had a decreased risk of developmental problems in gross motor skills at four years of age, but no associations were observed to seven other PFAS chemicals measured.[110]

In other aspects of childhood social and behavioural development that are related to the measures used in this study, reported findings have again been largely mixed. In birth cohort studies that measured behaviour using the Strengths and Difficulties Questionnaire (SDQ), small to moderate associations have been observed between measured PFAS concentrations in maternal, infant or child sera and problem behaviour or pro-social difficulties at 5–9 years, however, effects were rarely consistent across PFAS chemical, timing of exposure or SDQ sub-scale measures.[107,108,111-113] Among children from the mid-Ohio Valley region who were highly exposed, no relationships were found between measured serum PFOA in children and mother/teacher reports of behavioural problems and emotional disturbances, although there may be gender differences in effects.[106] In another study in the same community, there were no associations — or even, inverse associations (decreased risk) — observed between PFAS levels in child sera and learning problems in children 5–18 years.[114]

The differences in instruments used, study population demographics, exposure levels and timing of measurement, PFAS type, single versus multi-compound analyses and random error may explain the diverging results across studies examining childhood development milestones. Studies on laboratory rodents have shown that prenatal and/or postnatal exposure to PFOA and PFOS can increase or decrease motor activity but does not appear to affect learning or memory; the mechanisms for such effects remain uncertain.[38]

Strengths and weaknesses

There are strengths and weaknesses of this study that should be kept in mind when interpreting findings and comparing them with results of other studies. These include considerations relating to selection of the study population, measurements of exposure and outcomes, and potential confounding.

Selection of study population

The AEDC began in 2009 and takes place every three years. Therefore, only children who were exposed after 2002 and who entered full-time schooling in an AEDC collection year were eligible to participate in the study. Thus, we cannot draw general conclusions from the study results regarding children who resided in the exposure areas prior to 2002. From this time, we probably captured a large proportion of the eligible study population by using the Medicare Enrolment File, as most children appear to have enrolled by the time they were one year old (Table 6). However, because children can start school at varying ages, and the AEDC is not collected every year, it was not possible to determine the proportion of children whose developmental outcomes were not measured, or were lost to follow up. For the same reason, we were not able to determine whether exposure is related to not attending school at all, or starting school at a later age, as children who

had lived in exposure or comparison areas but were not captured on the AEDC may have started school in a non-census year.

We did not include children with non-residential mailing addresses, such as post office boxes, in the main analyses — post office boxes were not captured in the PFAS Address Database. While we do not know how many children this applied to, in the sensitivity analysis where we included everyone in exposure areas based on postcodes including post office boxes, there was little material impact on effect sizes and direction of findings. Further, our study would have missed children who moved into an area without notifying Medicare of the change, but this is also unlikely to have affected RR estimates.[n] Another potential source of selection bias is linkage error, but we assume this error is small (see Appendix 1).

Exposure measurement

We relied on address data in the Medicare Enrolment File for exposure classification. While this is an objective method of attributing exposure, misclassification may occur if address details are incorrect. In particular, if a child lived in a comparison area and moved to an exposure area and this move was not registered, exposure would be misclassified; we assume such error was uncommon. Another limitation of our exposure measurement is we could only measure the fact of exposure, not duration. Although duration of exposure was of interest, there is insufficient evidence for a minimal duration of exposure that is potentially harmful in children, and the Medicare Enrolment File is not a reliable source of duration of residency. We attempted to examine the possible effect of duration in a sensitivity analysis by restricting the exposed population to children registered as living in an exposure area since birth, but this led to greater uncertainty in our estimates due to smaller sample sizes.

Outcome measurement

Linking to national AEDC data allowed complete ascertainment of outcomes among study participants who were linked, including outcomes in children who had moved away from the exposure or comparison areas. However, the accuracy of classifying outcomes using these data is potentially affected by the reality that, while the AEDC instrument has been validated within Australia and internationally, including through an extensive evaluation for Australian Aboriginal children,[115] all outcomes were teacher-reported and therefore subject to measurement error. Any measurement error from this is likely to have had a non-differential impact on estimates.

Moreover, teacher-level assessments are associated with a level of teacher/class level variation. As the school year progresses, there is some influence by the school/class/teacher on the children such that children tend to become similar in skills and capabilities.[116] This may have increased measurement error, especially in small communities where only a few teachers completed the data collection for that area. We estimated only two schools would have been eligible for AEDC participation in our catchment area for Oakey, and five to seven in Katherine and Williamtown.[117]

Potential confounding

Confounding is an issue in all observational studies, potentially biasing risk estimates and limiting the ability to draw causal inferences. This is discussed more fully in the last section of the report. There was a significant risk of confounding in this study, due to factors apart from exposure that may have led to differences (or lack of) in risks of childhood vulnerabilities. For example, we did not have information on other potentially important confounding variables including medical history, childcare experience, maternal education, household income and community characteristics such as access to social support, health services and recreational facilities.

[n] This under-capture of the eligible population could bias estimates in the unlikely scenario that a large proportion of individuals who were living in exposed areas did not register their address on Medicare, and they moved due to concerns regarding their health.

We expect our findings to have been particularly affected by confounding by SES-related factors. While every effort was made to draw a comparison population for each exposure area from comparable socioeconomic areas, this was based on area-level measures at one point in time. However, at the time of their AEDC participation, area-level characteristics of the child's residence (for example, remoteness) appear to be highly discrepant across the exposure and comparison areas (Table 6). Even though we adjusted for SES at the time of AEDC participation, this discrepancy reflects high mobility in these populations and presented challenges in assigning socioeconomic position longitudinally, which we did not attempt to do. Additionally, area-level SES measures do not represent individual circumstances, such as maternal education.

Summary

Comparing children from the three PFAS Management Areas with those from comparison areas, we estimated higher risks in two of the five domains of development assessed on the AEDC in Oakey and a lower risk in one domain in Katherine. The relatively high absolute risks of developmental vulnerability in all domains in both the exposure and comparison areas in NT and Qld are notable, probably reflecting influences of socioeconomic factors on early development. Selection and measurement errors are likely to have had relatively small effects on RR estimates; but it is possible that observed differences could be due to inadequately controlled socioeconomic and other confounding factors. Along with limited prior evidence, the overall evidence for a causal association between living in an exposure area and childhood development is weak and inconsistent. Considerations of causality are discussed more fully in the final section of the report.

Study 3: Cancer and cause-specific mortality outcomes

This study included people who had lived in an exposure or comparison area at any time during the period 1983–2019. The outcomes were cancer diagnoses and death from specific causes as recorded, respectively, in the Australian Cancer Database (ACD) and National Death Index (NDI) in any Australian State or Territory where the individual was living at the time.

Methods

Data sources and study population

In this study, we used data from the Medicare Enrolment File (Box 4), linked to the PFAS Address Database and comparison area postcodes (Box 1) to select the study populations. The study populations were then linked to the ACD and NDI to determine cancer and mortality outcomes.

Australian Cancer Database (ACD) (1982–2017)

The ACD contains data on new cases of cancer diagnosed in Australia since 1 January 1982, excluding basal and squamous cell carcinomas of the skin.[118]

Cancer is a notifiable disease in all Australian States and Territories. The relevant legislation requires certain individuals and organisations to notify all new cases of cancer to the jurisdiction's central cancer registry. These registries supply data annually to the Australian Institute of Health and Welfare (AIHW), which cleans and standardises the data, notifies the registries of inter-state duplicates and produces the ACD. Reporting of newly diagnosed cancers has been mandatory in most but not all jurisdictions since 1982.[o]

National Death Index (NDI) (1980–2019)

The NDI is a catalogue of death records that is used for epidemiological studies. Its use is strictly confined to AIHW Ethics Committee approved health and medical research. The NDI contains person-level records of all deaths occurring in Australia since 1980 obtained from the Registrars of Births, Deaths and Marriage in each State and Territory.[119]

NDI records are supplemented with cause of death information using a once-only data linkage with the National Mortality Database. This enhancement enables research that requires both fact of death (whether a person died) and cause of death (what the person died from).

Selection of study populations

The study populations were selected and classified based on place of residence as described earlier (see Overview of methods and Figure 2). We included all individuals in the Medicare Enrolment File who had lived in the PFAS Management Areas of Katherine, Oakey or Williamtown, and a sample of those who had lived in comparison areas, at any time between October 1983 (when the Medicare Enrolment file was established) and December 2019 (last available outcomes data).

As in Study 2, we selected a sample of individuals from the comparison areas (Box 1) rather than including everyone in these areas to meet ethical requirements pertaining to the Medicare Enrolment File. The comparison populations were frequency-matched at a 4:1 ratio to the exposed populations on sex, age and year of first living in an exposure or comparison area, and Aboriginal

[o] Mandatory reporting in: ACT — 1994; NSW — 1972; NT — 1991; Qld — 1982; SA — 1977; Tas — 1992; Vic — 1982; WA — 1981

and Torres Strait Islander status. Year and age were matched on 5-year bands, which were widened if there were too few individuals in the band to meet the 4:1 matching requirement.

Individuals were excluded from the study if they had:

a) missing data for their date of birth, date of death (if death recorded) or sex
b) invalid dates — for example, where the recorded date of birth occurred after entry into the study[p] or where the date of diagnosis occurred outside the interval from date of birth to date of death.

Study variables

Outcomes

We examined 30 separate outcomes: 20 candidate cancers, any candidate cancer, any other cancer apart from candidate cancers, any cancer (including any candidate or any other cancer), four candidate causes of death, and three control causes of death. Incident cancers (diagnosed age ≥25 years) and deaths (at any age) were ascertained from the ACD and the NDI, respectively, based on International Classification of Diseases and Related Health Problems, 10th revision (ICD-10) codes, or ICD-9 codes before year 1997. For time-to-event calculations (see below) we used date of diagnosis or date of death as reported on the ACD or NDI, respectively.

The candidate outcomes comprised all cancer and cause-specific death outcomes that were evaluated in PFAS Health Study Systematic Literature Review conducted in Phase I of the study,[53] apart from cancers of head and neck, uterine and ovarian, which were included due to community interest. Table 8 shows all cancer and mortality outcomes examined in this study and their ICD codes.

Table 8. Outcome definitions for the groups of cancer outcomes and cause-specific mortality outcomes

Health outcome[1]	International Classification of Diseases (ICD) codes
Cancer[2]	
Candidate outcomes	
Head and neck	C00–C14, C30–C32
Oesophageal	C15
Stomach	C16
Colorectal	C18–C20
Liver	C22
Pancreatic	C25
Laryngeal	C32
Lung	C33–C34
Bone	C40–C41
Breast	C50
Uterine	C54–C55
Ovarian	C56
Prostate	C61
Testicular	C62

(Table continued over)

[p] Entry into the study was defined as the date of first registration with Medicare, regardless of State/Territory of registration.

Health outcome[1]	International Classification of Diseases (ICD) codes
Cancer[2]	
Kidney	C64
Bladder	C67
Thyroid	C73
Hodgkin lymphoma	C81
Non-Hodgkin lymphoma	C82–C86
Leukaemia	C91–C95
Any above cancer	Any above ICD-10 code
Any other cancer	Any ICD-10 code from C00–C96 apart from the above
Any cancer	Any ICD-10 code from C00–C96
Cause-specific mortality[3]	
Candidate outcomes	
Chronic kidney disease[4]	ICD-10: E10.2, E11.2, E12.2, E13.2, E14.2, I12, I13, I15.0, I15.1, N18, N19 ICD-9: 250.3, 403, 404, 585–589
Coronary heart disease	ICD-10: I20–I25 ICD-9: 410–414
Stroke	ICD-10: I60–I64 ICD-9: 430–434, 436
Liver disease	ICD-10: K70–K76 ICD-9: 570–573
Control outcomes	
Infectious or parasitic diseases	ICD-10: A00, B99 ICD-9:001–139
All external causes apart from intentional self-harm	ICD-10: V01–Y98 ICD-9: 800–999
Intentional self-harm	ICD-10: X60–X84, Y87.0 ICD-9: 950–959

Table notes

1. Outcomes are ordered by ICD-10 codes.
2. As recorded in the Australian Cancer Database.
3. As recorded in the National Death Index as the underlying cause of death.
4. Includes diabetic nephropathy, hypertensive kidney disease, chronic kidney failure and unspecific kidney failure.

Exposure and other variables

Exposure, based on residence in a PFAS Management Area (as defined earlier) was classified at the person-time level (see analysis section). Sex, age and calendar year, used for adjustments in the analysis, were as recorded on the Medicare Enrolment File. Age and calendar year were treated as time-varying variables — that is, variables that have different values through follow-up time. Calendar- and age-at-risk periods (see below) were established at 5-year intervals (Lexis expansion[120]). Aboriginal and Torres Strait Islander status was coded according to the VII database (Box 4). Due to under-identification in the VII database, adjustment for Aboriginal and Torres Strait Islander status was performed in sensitivity analysis only.

Statistical analysis

Main analyses

For each cancer and cause-specific mortality outcome, we calculated the number of cases (number of incident cancer diagnoses or deaths), total person-time at risk and incidence rates (cases divided by total person-time), separately by exposure (exposed/non-exposed person-time). Person-time at risk is the time observed for every individual from study entry (date of first registration with Medicare regardless of State/Territory of registration) to study exit within the study period 1983–2019.

For each outcome, study exit for a particular individual occurred at the earliest occurrence of any of the following:

a) Date of cancer diagnosis (for cancer analyses only)
b) Date of death
c) Age 85
d) Date of change of address into a 'potential exposure'[q] area, unless already exposed prior to this date
e) End of the study period: 31 December 2017 for cancer outcomes, or 31 December 2019 for mortality outcomes.

All person-time was classified as either exposed or non-exposed.[r] For exposed individuals, we classified person-time *from time of first exposure* onwards as exposed (even if the individual subsequently moved out of an exposure area), allowing for a lag period, and classified all person-time *before time of first exposure or during the lag period* as non-exposed. For comparison individuals, we classified all person-time as non-exposed.

We used a lag period of 10 years as a minimum possible latency period — that is, an expected period between first exposure to PFAS (living in an exposure area) and onset of disease. We did not attribute health outcomes to exposure until after this lag period had passed. Individuals who were already living in an exposure address at the start of the observation period (that is, at inception of Medicare in 1983–1984) were assumed to had already lived there for at least 10 years, therefore a lag period was not applied for these individuals. In sensitivity analyses (see below), we varied the lag period but did not include zero lag (no lag period) because of the known latency from first exposure to a cause of chronic disease and occurrence of that disease. Figure 6 describes the classification of person-time under various scenarios.

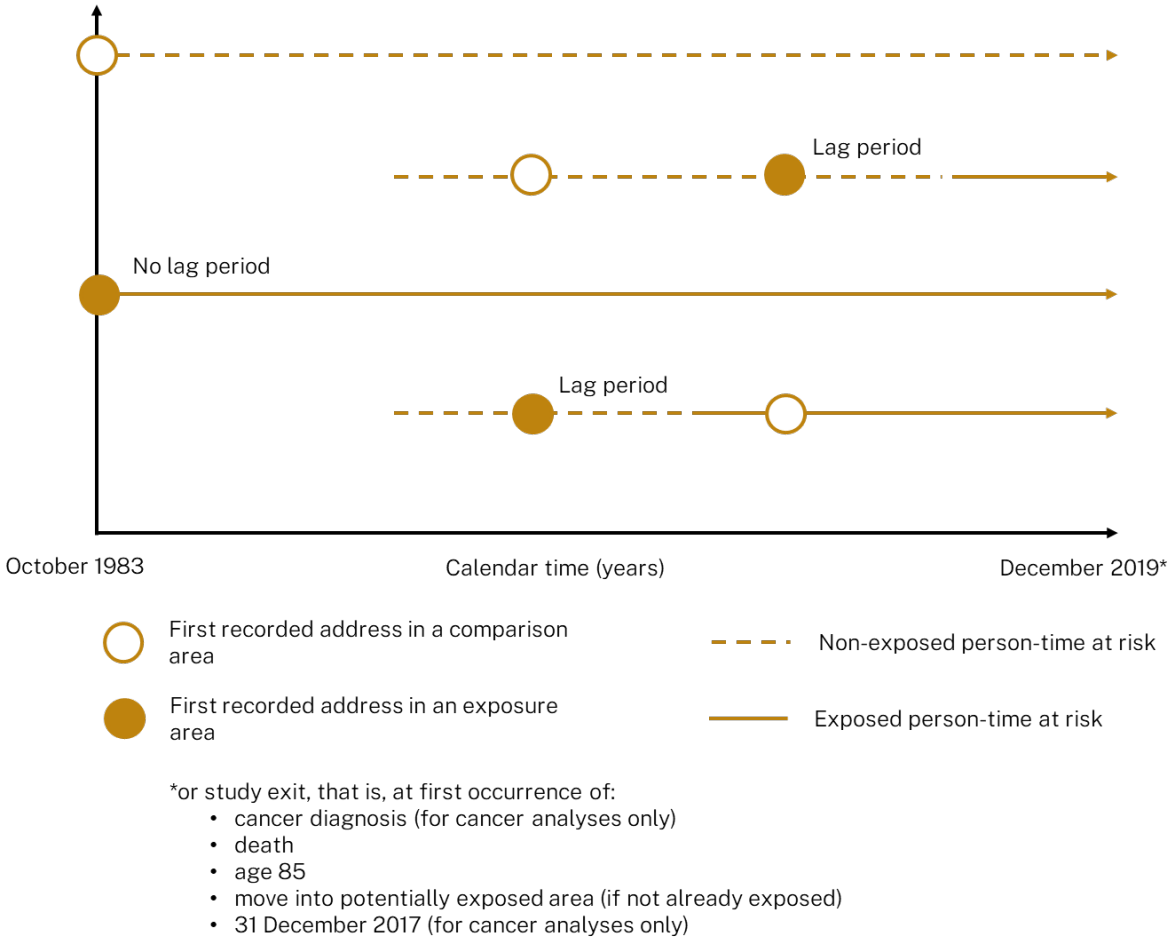
All cancer and cause-specific mortality outcomes were analysed separately by State/Territory, based on where the individual was first classified as living in an exposure or a comparison area. Those who had a cancer diagnosis before entry into the study (based on ACD records) were excluded from analysis of that cancer outcome. We used indirect standardisation to estimate the standardised incidence ratio (SIR) for each cancer and mortality outcome with Poisson 95% CIs. In this method, we calculated age-sex-calendar period-specific incidence rates in the non-exposed population. Five-year age and calendar stratifications were used and widened if there were no individuals in any stratum. We applied these rates to the exposed group, in order to generate an expected number of cases over the total amount of exposed person-time, i.e. the number of cases that would be expected if the exposed population experienced the same cancer or death rates as the comparison population. The SIR was then calculated as the ratio of observed cases in the exposed population to the expected cases calculated as described.

---

[q] Those who lived in Katherine, Oakey or Williamtown postcodes (2314, 2318, 4401, 0850, 0851, 0852, 0853), but were not found in the PFAS Address Database.

[r] In description of the study population, exposure was classified at the individual level — 'ever lived in Katherine, Oakey or Williamtown', or 'ever lived in comparison areas'.

Figure 6. Overview of attribution of person-time with application of lag period.



Sensitivity analyses

We conducted the following sensitivity analyses:

a) The exposed populations were limited to those who had lived in the PFAS Management Areas of Katherine, Oakey or Williamtown continuously for at least 10 years prior to the last available data in the ACD (31 December 2017) for cancer outcomes, or prior to the last available data in the NDI (31 December 2019) for cause-specific mortality outcomes, i.e. those who had moved out of exposure areas before 10 years had elapsed were excluded from the analysis. Those who were already living in PFAS Management Areas at the start of the observation period (1983–1984) were assumed to have been living there for at least 10 years and were therefore included in the exposed population for this analysis.
b) Aboriginal and Torres Strait Islander status, as recorded on the VII database, was included as an additional adjustment.
c) The lag period was varied from 10 years to 5 years and 15 years.
d) A 10-year lag period was applied to those who were already living in PFAS Management Areas at the start of the observation period (1983–1984).

Deviations from the original study protocol

There were several deviations from the original study protocol, as outlined in Appendix 4.

Results

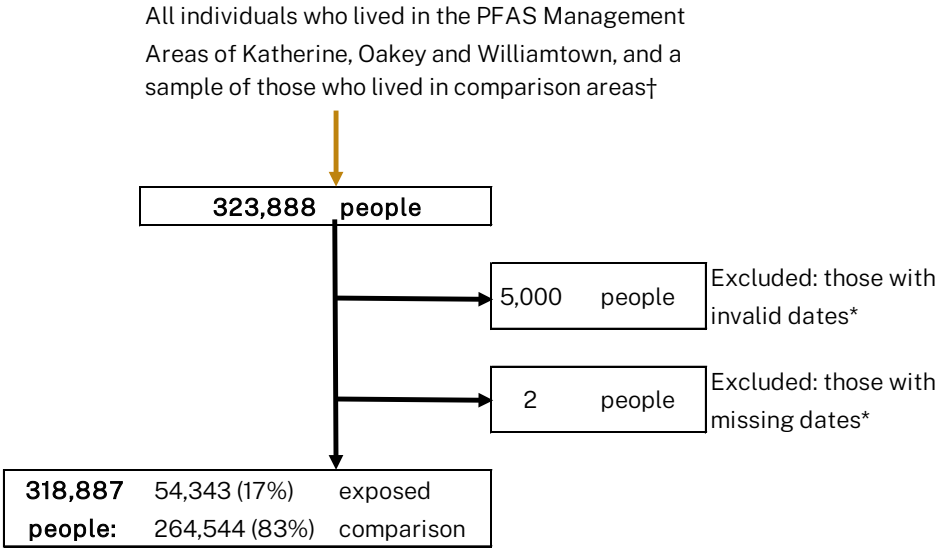
Description of the study population

Between 1 October 1983 and 31 December 2019, a total of 323,888 individuals were identified in the Medicare Enrolment File as having lived in the PFAS Management Areas of Katherine, Oakey or Williamtown and/or comparison areas. After excluding 5,001 individuals with missing or inconsistent dates (see (b) in Selection of study populations), we included 99% (318,887/323,888) of individuals, of whom 54,343 (17%) had lived at an address in the PFAS Address Database and 264,544 (83%) had lived in comparison areas.

The largest number of exposed individuals was in NT (25,428 (16%) exposed, 130,800 (84%) comparison), followed by Qld (21,306 (17%) exposed, 102,972 (83%) comparison) and NSW (7,609 (20%) exposed, 30,772 (80%) comparison). Sample sizes and sociodemographic characteristics by State/Territory and exposure status can be seen in Table 9.

A flow diagram of sample selection is in Figure 7.

Figure 7. Sample selection of study population for analysis of cancer and cause-specific mortality outcomes



† All individuals in the Medicare Enrolment File with a recorded address in the PFAS Address Database, or comparison area postcodes (see Box 1), between October 1983-

* Exclusions not mutually exclusive

Table 9. Sociodemographic characteristics of study populations for analysis of cancer and cause-specific mortality outcomes

	NT		Qld		NSW	
Characteristic	Exposed[1] n (%)	Comparison n (%)	Exposed n (%)	Comparison n (%)	Exposed n (%)	Comparison n (%)
Total sample	**25,428**	**130,800**	**21,306**	**102,972**	**7,609**	**30,772**
Sex						
Female	13,241 (52)	61,836 (47)	10,862 (51)	51,426 (50)	3,776 (50)	15,278 (50)
Male	12,187 (48)	68,964 (53)	10,444 (49)	51,546 (50)	3,833 (50)	15,494 (50)
Year first recorded as living PFAS Management Area or comparison area						
1983–1989	3,124 (12)	17,651 (13)	5,449 (26)	25,469 (25)	1,472 (19)	5,977 (19)
1990–1994	3,557 (14)	22,980 (18)	2,709 (13)	12,892 (13)	1,232 (16)	4,906 (16)
1995–1999	4,519 (18)	17,860 (14)	3,096 (15)	11,885 (12)	934 (12)	3,836 (12)
2000–2004	3,855 (15)	15,066 (12)	2,990 (14)	13,413 (13)	1,051 (14)	4,166 (14)
2005–2009	3,537 (14)	19,179 (15)	2,465 (12)	13,435 (13)	1,312 (17)	5,193 (17)
2010–2014	3,382 (13)	19,056 (15)	2,419 (11)	13,093 (13)	812 (11)	3,459 (11)
2015–2019	3,454 (14)	19,008 (15)	2,178 (10)	12,785 (12)	796 (10)	3,235 (11)
Age first recorded as living in PFAS Management Area or comparison area						
0–9	8,167 (32)	27,234 (21)	6,950 (33)	29,959 (29)	1,454 (19)	5,840 (19)
10–19	3,513 (14)	16,556 (13)	3,217 (15)	15,965 (16)	1,024 (13)	4,150 (13)
20–29	5,106 (20)	31,341 (24)	4,336 (20)	15,666 (15)	1,117 (15)	4,523 (15)
30–39	4,513 (18)	25,239 (19)	2,792 (13)	13,796 (13)	888 (12)	3,643 (12)
40–49	2,292 (9)	15,503 (12)	1,636 (8)	10,013 (10)	832 (11)	3,395 (11)
50–59	1,237 (5)	9,317 (7)	1,025 (5)	7,938 (8)	926 (12)	3,697 (12)
60–69	426 (2)	4,044 (3)	716 (3)	5,455 (5)	832 (11)	3,321 (11)
70–79	137 (1)	1,207 (1)	411 (2)	2,577 (3)	416 (5)	1,667 (5)
80–89	37 (0)	322 (0)	183 (1)	1,321 (1)	103 (1)	457 (1)
90+	0[†]	37 (0)	40 (0)	282 (0)	17 (0)	79 (0)
Indigenous status[2]						
No	20,084 (79)	11,7217 (90)	19,584 (92)	99,336 (96)	7,386 (97)	29,870 (97)
Yes	5,344 (21)	13,583 (10)	1,722 (8)	3,636 (4)	223 (3)	902 (3)

Table notes

Data sources: Medicare Enrolment File (October 1983–December 2019), Voluntary Indigenous Identifier (VII) database (2002–2019)

1. In this table, exposure was classified at the individual level (rather than at the person-time level). A person was 'exposed' if they ever lived at an address in the PFAS Address Database, and 'comparison' if they only ever lived in a comparison area.
2. These statistics were based on those Aboriginal and Torres Strait Islander people who had voluntarily identified in the VII database. The proportions presented have not been weighted for under-identification. These data were extracted on March 2021.
3. Categories were collapsed ([†]) to avoid reporting cell numbers with size ≤5.

4. Percentages were rounded to zero decimal places.

Although NT had the largest number of exposed individuals, Qld had the longest total duration of person-time at risk classified as exposed: (378,021 person-years), followed by NT (322,556 person-years) and NSW (115,373 person-years). Altogether, we observed a total of 4.0 million person-years in NT, 3.4 million person-years in Qld and 1.1 million person-years in NSW.

Among the 318,887 individuals included in the main sample, 8.4% (26,721/318,887) had a death recorded on the NDI over the study period, 1 October 1983 to 31 December 2019. Excluding individuals who entered the study after 31 December 2017 (n = 3,348), 6.7% (21,611/318,887) had at least one link to the ACD, with 24,166 cancers diagnosed in total over the study period, 1 October 1983 to 31 December 2017.

Cancer outcomes in relation to living in exposure areas

The number of observed and expected cases in the exposed population, and SIRs for all cancers examined are shown in Table 10; a forest plot of SIRs is shown in Figure 8. Number of cases, person-years of follow-up and crude rates are in Appendix Table 5-7. For information on interpreting effect estimates, see Box 2.

In NT, after adjusting for age, sex and calendar time, the rate of prostate cancer among those who had lived in Katherine was 76% higher than among those who had lived in the comparison areas (SIR = 1.76, 95% CI 1.36 to 2.24). The two composite outcomes, measuring the incidence of any of the 20 candidate cancers (SIR = 1.13, 95% CI 1.00 to 1.28), or of any cancer recorded on the ACD (SIR = 1.18, 95% CI 1.06 to 1.30), also indicated slightly higher rates of cancer among Katherine residents. However, when prostate cancer was removed from the composite measures, there was little or no differences in rates between the exposed and comparison populations (*any candidate cancer* SIR = 1.02, 95% CI 0.89 to 1.17; *any cancer* SIR = 1.10, 95% CI 0.98 to 1.23). For all other outcomes, interval estimates were compatible with no effect, and we were unable to conclude that rates of these cancers differed between Katherine and the comparison population. It is important to note that for most of these outcomes we observed only a small number of cases (reflecting the small median follow-up time once a 10-year lag had been taken into account) and estimates for these outcomes were too imprecise to determine the size or direction of effect. For example, the result for bone cancer, while appearing high (SIR = 2.11), was compatible with rates ranging from 95% lower to nearly 12-fold higher in Katherine residents compared to the comparison population (95% CI 0.05 to 11.76).

In Qld, after adjusting for age, sex and calendar time, the rate of laryngeal cancer in Oakey residents was 2.7-fold the rate among those who had lived in comparison areas (SIR = 2.71, 95% CI 1.30 to 4.98). However, this estimate was imprecise due to the small number of cases and a confidence interval suggesting that the rate may have ranged anywhere from 30% higher to 400% higher. For the other candidate outcomes in Oakey, effect sizes (in both directions) were not large and interval estimates were compatible with no effect. Composite measurements also suggested little or no differences in the rates of any of the 20 candidate cancers (SIR = 1.06, 95% CI 0.97 to 1.16) or of any cancer recorded on the ACD (SIR = 1.00, 95% CI 0.93 to 1.08) between Oakey residents and the comparison population.

In NSW, after adjusting for age, sex and calendar time, the rates of kidney and lung cancers in those who had lived in Williamtown were around 80% higher than the rates in those who had lived in its comparison areas (*kidney cancer* SIR = 1.82, 95% CI 1.04 to 2.96; *lung cancer* SIR = 1.83, 95% CI 1.39 to 2.38). For the other candidate outcomes, the precision of the estimates varied but all were compatible with no effect. Composite measurements suggested small or no differences in the rates of any of the 20 candidate cancers (SIR = 1.09, 95% CI 0.96 to 1.23) or of any cancer recorded on the ACD (SIR = 1.05, 95% CI 0.94 to 1.17) between Williamtown residents and the comparison population.

Table 10. Cancer and cause-specific mortality outcomes: observed (O) and expected (E) case numbers in the exposed populations, and standardised incidence ratios (SIR)

	Katherine, NT		Oakey, Qld		Williamtown, NSW	
	O\E cases	SIR (95% CI)	O\E cases	SIR (95% CI)	O\E cases	SIR (95% CI)
Cancer						
Candidate outcomes						
Head and neck	22\20	1.11 (0.69,1.67)	29\30	0.96 (0.65,1.38)	12\11	1.12 (0.58,1.96)
Oesophageal	7\5	1.33 (0.53,2.73)	12\8	1.57 (0.81,2.74)	≤5\≤5	0.46 (0.06,1.67)
Stomach	≤5\≤5	1.23 (0.40,2.86)	7\11	0.65 (0.26,1.34)	≤5\≤5	0.82 (0.22,2.10)
Colorectal	41\36	1.14 (0.82,1.54)	93\81	1.15 (0.93,1.41)	37\41	0.90 (0.63,1.24)
Liver	≤5\np	0.47 (0.13,1.20)	≤5\np	0.76 (0.25,1.77)	≤5\≤5	1.16 (0.32,2.97)
Pancreatic	≤5\np	0.74 (0.20,1.90)	17\12	1.37 (0.80,2.20)	13\8	1.58 (0.84,2.70)
Laryngeal	≤5\≤5	0.26 (0.01,1.45)	10\≤5	2.71 (1.30,4.98)	≤5\≤5	1.16 (0.14,4.17)
Lung	30\32	0.94 (0.64,1.34)	61\57	1.07 (0.82,1.37)	57\31	1.83 (1.39,2.38)
Bone	≤5\≤5	2.11 (0.05,11.76)	≤5\≤5	1.36 (0.03,7.60)	No observed events	
Breast	59\52	1.14 (0.87,1.47)	88\99	0.89 (0.71,1.09)	43\45	0.95 (0.69,1.29)
Uterine	9\6	1.56 (0.71,2.95)	18\13	1.38 (0.82,2.19)	7\5	1.30 (0.52,2.67)
Ovarian	≤5\≤5	1.65 (0.54,3.85)	7\8	0.87 (0.35,1.78)	≤5\≤5	0.27 (0.01,1.51)
Prostate	66\37	1.76 (1.36,2.24)	107\97	1.10 (0.90,1.33)	49\59	0.83 (0.61,1.09)
Testicular	≤5\≤5	0.51 (0.06,1.85)	6\6	0.92 (0.34,2.01)	≤5\≤5	0.64 (0.02,3.56)
Kidney	6\8	0.77 (0.28,1.67)	25\22	1.15 (0.74,1.69)	16\9	1.82 (1.04,2.96)
Bladder	8\≤5	2.02 (0.87,3.97)	12\14	0.89 (0.46,1.55)	14\9	1.63 (0.89,2.74)
Thyroid	≤5\np	0.66 (0.21,1.54)	22\18	1.20 (0.75,1.82)	6\≤5	1.66 (0.61,3.62)
Hodgkin lymphoma	≤5\≤5	0.49 (0.01,2.75)	≤5\≤5	0.78 (0.09,2.83)	≤5\≤5	0.81 (0.02,4.52)
Non-Hodgkin lymphoma	12\11	1.06 (0.55,1.84)	23\24	0.97 (0.61,1.45)	16\13	1.24 (0.71,2.02)
Leukaemia	≤5\np	0.41 (0.08,1.19)	23\20	1.12 (0.71,1.69)	10\10	0.96 (0.46,1.76)
Any above cancer	270\239	1.13 (1.00,1.28)	521\491	1.06 (0.97,1.16)	263\241	1.09 (0.96,1.23)
Any other cancer	103\80	1.29 (1.05,1.57)	174\192	0.90 (0.78,1.05)	88\89	0.99 (0.79,1.21)
Any cancer	358\305	1.18 (1.06,1.30)	656\653	1.00 (0.93,1.08)	325\310	1.05 (0.94,1.17)
Cause-specific mortality						
Candidate outcomes						
Chronic kidney disease	8\8	0.94 (0.41,1.86)	10\10	1.00 (0.48,1.83)	7\5	1.29 (0.52,2.65)
Coronary heart disease	40\37	1.07 (0.77,1.46)	114\93	1.22 (1.01,1.47)	92\51	1.81 (1.46,2.23)
Stroke	12\10	1.22 (0.63,2.13)	27\29	0.92 (0.60,1.33)	29\21	1.37 (0.92,1.97)
Liver disease	8\17	0.46 (0.20,0.91)	15\14	1.10 (0.62,1.82)	6\≤5	1.25 (0.46,2.71)
Control outcomes						
Infectious or parasitic	8\9	0.93 (0.40,1.82)	10\8	1.31 (0.63,2.41)	10\6	1.67 (0.80,3.07)
All external causes apart from self-harm	35\51	0.69 (0.48,0.96)	72\52	1.38 (1.08,1.73)	17\17	1.01 (0.59,1.62)
Intentional self-harm	30\31	0.98 (0.66,1.40)	53\37	1.44 (1.08,1.89)	14\7	1.89 (1.04,3.18)

Table notes

The standardised incidence ratio (SIR) is the ratio of the number of observed cancer cases in the exposed population to the number that would be observed ('expected') if the exposed population experienced the same cancer/death rates as the comparison population.

1. In this table, exposure was classified at the person-time level. In individuals who were 'ever exposed', we classified person-time *from time of first exposure onwards* as exposed (even if the individual subsequently moved out of an exposure area), allowing for a lag period, and classified all person-time *before time of first exposure or during the lag period* as non-exposed. In comparison individuals, we classified all person-time as non-exposed.
2. SIRs are adjusted for age, sex and calendar period. For death outcomes, the first age band was 15 years (0–15 years), and 5 years thereafter. For cancer outcomes, 5-year age bands were used from 25 years. The final age band for all outcomes was 70–85 years. A 10-year lag period was applied, therefore the first calendar period band was 15 years (1983–1998), and 5 years thereafter. SIRs are represented in forest plots in Figure 8 and Figure 9.
3. Number of cases, person-years of follow-up and crude rates are in Appendix Table 5–7.
4. Cells have been suppressed to avoid reporting cell numbers with size ≤5 (np: not provided).
5. Expected cases were rounded to zero decimal places.

Figure 8. Forest plot showing standardised incidence ratios (SIR) for cancer outcomes

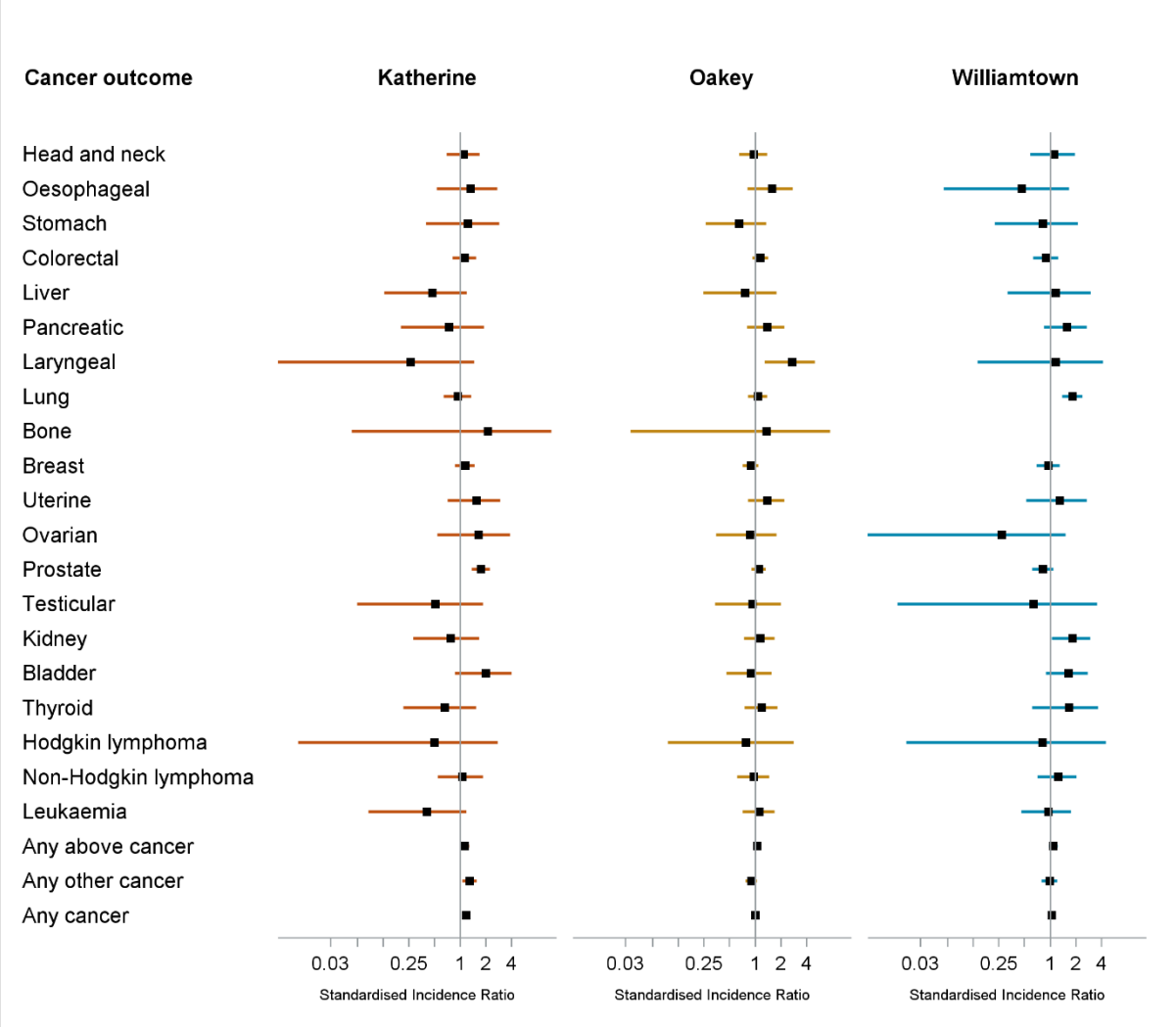


Figure notes

Data sources: Medicare Enrolment File (October 1983–December 2019) linked to Australian Cancer Database (up to December 2017).

1. Forest plot shows point estimates of SIRs (filled squares) and associated 95% confidence intervals (horizontal lines), and solid vertical line of no effect. SIRs were adjusted for age, sex and calendar period.
2. See Table 10 for numbers of observed and expected cases, and SIRs.

3. SIRs are on a log scale.

Mortality outcomes in relation to living in exposure areas

The number of observed and expected cases in the exposed population, and SIRs for all causes of death investigated are shown in Table 10; a forest plot of SIRs is shown in Figure 9. Number of cases, person-years of follow-up and crude rates are in Appendix Table 5–7. For information on interpreting effect estimates, see Box 2.

In NT, after adjusting for age, sex and calendar time, the rates of death from liver disease were 64% lower in those who had lived in Katherine compared to those who had lived in comparison areas (SIR = 0.46, 95% CI 0.20 to 0.91). The rate of death from external causes apart from self-harm was also 31% lower in Katherine (SIR = 0.69, 95% CI 0.48 to 0.96). For the other candidate outcomes (death from chronic kidney disease, coronary heart disease or stroke) and control outcomes (death from infections or intentional self-harm) effect sizes were generally small, and interval estimates imprecise, compatible with no effect.

In Qld, after adjustments, the rate of death from coronary heart disease was 22% higher in those who had lived in Oakey compared to those who had lived in comparison areas (SIR = 1.22, 95% CI 1.01 to 1.47). For the other candidate outcomes (death from chronic kidney disease, stroke or liver disease) point estimates were around 1, but estimates were too imprecise to make any conclusions about the size or direction of effects. For example, the data for chronic kidney disease mortality suggested that the rates were anywhere between 52% lower to 83% higher in the exposed population compared to the comparison population (SIR = 1.00, 95%CI 0.48 to 1.83). For two of three control outcomes examined, we estimated around 40% higher death rates associated with having lived in Oakey (*external causes apart from self-harm* SIR = 1.38, 95% CI 1.08 to 1.73; *intentional self-harm* SIR = 1.44, 95% CI 1.08 to 1.89).

In NSW, after adjusting for age, sex and calendar time, the rate of death from coronary heart disease was 81% higher in Williamtown residents compared to residents of comparison areas (SIR = 1.81, 95% CI 1.46 to 2.23). We also observed higher death rates from intentional self-harm in Williamtown (SIR = 1.89, 95% CI 1.04 to 3.18). For the remaining candidate and control causes of death studied, while all SIR point estimates were above 1, interval estimates were too wide to make any determinations about effects sizes or their direction, thus we were unable to conclude that rates of these outcomes differed between Williamtown residents compared to its comparison population.

Sensitivity analyses

In the first sensitivity analyses, we limited the exposed populations to those who had lived in the PFAS Management Areas continuously for at least 10 years. This had the effect of increasing the uncertainty of all estimates (widening of confidence intervals) due to reductions in sample sizes but did not change our conclusions. However, we note that the SIR estimate for bladder cancer in Williamtown increased from 1.63 (95% CI 0.89 to 2.74) in the main analysis to 2.27 (95% CI 1.04 to 4.31) in this sensitivity analysis (Appendix Table 8). In Oakey, SIR point estimates did not corroborate these results, where it was 0.89 (95% CI 0.46 to 1.55) in the main analysis and 1.20 (95% CI 0.58 to 2.21) in this analysis, but there was essentially not enough precision to make further inferences either way.

Our analysis was not sensitive to an increase in the lag period from 10 years to 15 years (Appendix Table 10). Decreasing the lag period from 10 years to five years largely did not have an impact on our conclusions. However, we estimated that the SIR of pancreatic cancer in Williamtown increased from 1.58 (95% CI 0.84 to 2.70) in the main analysis to 2.67 (95% CI 1.73 to 3.94) in this analysis (Appendix Table 9). In Oakey, the SIR for pancreatic cancer was above 1 in both the main

analysis (SIR = 1.37 95% CI 0.80 to 2.20) and this sensitivity analysis (SIR = 1.32 95% CI 0.80 to 2.07) however these intervals were still consistent with no differences.

In the third and fourth sensitivity analyses, where we included an additional adjustment for voluntary Aboriginal and Torres Strait Islander status (Appendix Table 11), and where we applied a lag period to those who were already living in PFAS Management Areas at the inception of Medicare[s] (Appendix Table 12) respectively, there was little to no impact on effect sizes and direction of findings. The third sensitivity analysis was not performed in NSW due to low proportions of Aboriginal and Torres Strait Islander residents.

Figure 9. Forest plot showing standardised incidence ratios (SIR) for cause-specific mortality outcomes

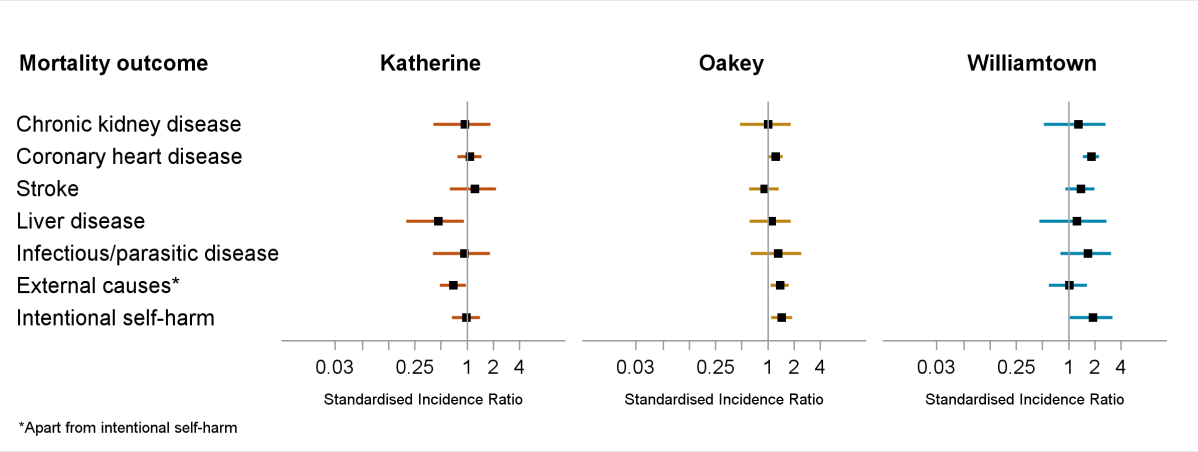


Figure notes

Data sources: Medicare Enrolment File (October 1983–December 2019) linked to National Death Index (up to December 2019).

1. Forest plot shows point estimates of SIRs (filled squares) and associated 95% confidence intervals (horizontal lines), and solid vertical line of no effect. SIRs were adjusted for age, sex and calendar period.
2. See Table 10 for numbers of observed and expected cases, and SIRs.
3. SIRs are on a log scale.

Discussion

Summary of main findings

In our analysis of cancer outcomes in the PFAS Management Areas between 1983–2017, we estimated higher-than-expected rates of prostate cancer in people who had lived in Katherine, of laryngeal cancer in people who had lived in Oakey, and of kidney and lung cancers—and from sensitivity analyses, possibly bladder and pancreatic cancers—in people who had lived in Williamtown. Otherwise, the overall standardised rates of any candidate cancer, or of any cancer, were very similar across the exposed and comparison populations, or too uncertain to draw conclusions.

For mortality outcomes, we estimated a lower-than-expected rate of death from liver disease in those who had lived in Katherine, and higher-than-expected rate of death from coronary heart disease in those who had lived in Oakey or Williamtown. Alongside this, we estimated higher-than-expected death rates for two control outcomes in Oakey (deaths from external causes apart from self-harm, and deaths from intentional self-harm), and in one control outcome in Williamtown (intentional self-harm). The implications of these findings are discussed below.

[s] In other words, we did not assume that these individuals had already been living at their first registered address on Medicare for at least 10 years.

It is important to note that for many of the candidate outcomes the numbers of cases analysed were small and estimates too imprecise to make any determination about whether rates were different across the exposed and comparison populations. The relative rates for key findings are presented in Box 6, alongside which we have added estimates of absolute rates to provide an indication of rate differences on the absolute scale. It is important to note that while these estimates take random error (the play of chance) into account (confidence intervals available in Table 10), we cannot assume there was no bias from residual confounding. These issues are discussed in the section below on study strengths and weaknesses.

Box 6. Summary of key results: adjusted relative and absolute rates for selected cancer and cause-specific mortality outcomes

	Adjusted relative rate	Associated absolute rate
Cancer		
Katherine — Prostate	Rate 1.76-fold that of comparison population (76% higher)	Rate increase from 9 to 15 cases in 10,000 person-years
Oakey — Laryngeal	Rate 2.71-fold that of comparison population (171% higher)	Rate increase from 0.2 to 0.7 cases in 10,000 person-years
Williamtown — Kidney	Rate 1.82-fold that of comparison population (82% higher)	Rate increase from 2 to 3 cases in 10,000 person-years
Williamtown — Lung	Rate 1.83-fold that of comparison population (83% higher)	Rate increase from 7 to 12 cases in 10,000 person-years
All other outcomes	No evidence of meaningful difference, uncertain or unable to determine due to imprecision.	
Cause-specific mortality		
Katherine — Liver disease	Rate 0.46-fold that of comparison population (64% lower)	Rate decrease from 1 to 0.5 death in 10,000 person-years
Oakey — Coronary heart disease	Rate 1.22-fold that of comparison population (22% higher)	Rate increase from 4 to 5 deaths in 10,000 person-years
Williamtown — Coronary heart disease	Rate 1.81-fold that of comparison population (81% higher)	Rate increase from 8 to 14 deaths in 10,000 person-years
All other outcomes	No evidence of meaningful difference, uncertain or unable to determine due to imprecision.	

Notes

1. Relative rates should be considered alongside their confidence intervals in Table 10.
2. 10,000 person-years is the equivalent of observing a population of 10,000 people for one year, or 1,000 people over 10 years, or 2,000 people for 5 years and so forth.
3. Absolute rates were estimated assuming population characteristics of the exposed over the study period (rather than the comparison or average characteristics of the whole study population).
4. In sensitivity analyses, the rate of bladder cancer and pancreatic cancer was 2.2-fold and 2.7-fold that of the comparison population respectively (confidence intervals in Appendix Table 8 and Appendix Table 9).

Interpretation of findings in the context of previous evidence

The largest relative effect estimated was the 2.7-fold (or 171% higher-than-expected) rate of laryngeal cancer in Oakey, although the level of uncertainty suggested that the rate may have been anywhere from 30% to 400% higher. The current evidence on the effects of PFAS exposure on laryngeal cancer is sparse. We are aware of one study that examined deaths from laryngeal cancer in a worker cohort with very high occupational exposure to PFOA,[121] and we are not aware of any study examining laryngeal cancer incidence. The worker cohort study observed only three deaths

due to laryngeal cancer and therefore, most likely did not have adequate statistical power to evaluate effects.[121] Similarly, we were limited by low numbers of events in Katherine and Williamtown, leading to very imprecise SIR estimates in these areas.

Prostate cancer had the highest incidence among the individual cancers investigated in this study, in all three exposure areas. This allowed SIRs for this outcome to be estimated with more precision, with results showing higher-than-expected rates in Katherine, but not in Oakey or Williamtown. Studies in highly exposed workers at a DuPont chemical plant in West Virginia, USA, which uses PFOA, and at facilities in Minnesota and Alabama, USA, which produce PFOA and PFOS respectively, did not find associations with prostate cancer incidence.[77,122,123] Studies among communities in the mid-Ohio Valley region (C8 Health Project) that were highly exposed to PFOA due to contaminated drinking water also did not see associations with prostate cancer.[124,125] In those with background levels of exposure, a case control general population study in Sweden did not detect overall associations with six types of measured serum PFAS, but did find associations in people who had a first-degree relative with a prostate cancer diagnosis;[126] a Danish population cohort study did not observe relationships between measured serum PFOS or PFOA and prostate cancer incidence.[127]

Mortality studies of prostate cancer have largely been based on small numbers of cases, and thus may have lacked sufficient power to detect effects. A decreased rate of death due to prostate cancer was seen among workers at a DuPont plant (12 deaths) when using the US population as a reference but not when using the state population or regional employees from the same company as the reference populations.[121] However, Steenland & Woskie[128] did not find an association between estimated cumulative serum PFOA and prostate cancer mortality (21 deaths) when they extended the follow-up of this cohort for an additional six years. In contrast, two studies reported higher risks of death from prostate cancer, based on six and 16 deaths in a different group of workers.[129,130] However, this was not corroborated in an updated study by Raleigh and colleagues[123] using the same cohort and additional employees, where they did not find evidence to support an association between exposure and prostate cancer mortality (24 deaths).

We estimated an elevated rate of kidney cancer in Williamtown. There is some prior evidence suggesting an association between PFOA and kidney cancer incidence, although not unequivocally. Excess kidney cancer was observed in the mid-Ohio Valley communities with known drinking water contamination, although there was some overlap in the cases examined in the two studies.[124,125] However, highly exposed workers at a PFOA-producing plant in Minnesota, USA, were not observed to have higher rates of kidney cancer.[123] In the US general population, where levels of exposure are low, a case-control study reported some evidence for a positive but not monotonic trend for kidney cancer with increasing levels of measured serum PFOA, but not for other PFAS.[131]

In terms of kidney cancer mortality, Steenland & Woskie[128] reported an association with estimated serum PFOA among employees in a facility that uses PFOA (12 deaths), but the same association was not seen among employees of a different PFOA-producing plant (6 deaths).[123] There is little published evidence for associations between PFOS and PFHxS to prostate and kidney cancers.

It is important to note that in other studies where associations between PFOA and increased rates of prostate and kidney cancers have been observed, PFOA concentrations are likely to be different to that in the PFAS Management Areas, making direct comparisons difficult. Median serum PFOA concentrations in occupational cohorts ranged from 113-5,200 ng/ml,[121-123,129,130] those in the mid-Ohio Valley communities ranged from 24.2-28.2 ng/ml[124,125] and median serum PFOA concentrations in general population studies in Sweden, Denmark and USA were 2.0–5.5 ng/ml.[126,127,131] We do not have historical data on PFAS concentrations in our study populations, however current median PFOA levels are between 1.3–1.9 ng/ml.[51]

Our finding of elevated lung cancer incidence in Williamtown is not supported by other evidence. As far as we are aware, there is no prior evidence for a relationship between PFAS exposure and

lung cancer. Studies in both occupational cohorts and in communities living in contaminated areas have not identified associations between PFAS and lung cancer incidence or mortality.[121,124,125,128,130,132,133]

We estimated an increased incidence of pancreatic cancer in Williamtown in a sensitivity analysis where a lag period of five years was applied. There is no prior support for a relationship between PFAS exposure and pancreatic cancer, although most studies have only investigated exposure to PFOA. Studies in workers exposed occupationally and in residents living in contaminated areas have not reported associations between PFAS and pancreatic cancer incidence or mortality.[121,123-125,128,130,134] It should be noted that most mortality studies have been based on very few cases (<20) and may have lacked statistical power to detect differences; the largest study was based on 18 deaths.[123] In a cohort study of the general population in Denmark, no associations were noted between measured serum PFOS and PFOA and pancreatic cancer incidence.[127]

We saw a higher rate of bladder cancer in Williamtown in a sensitivity analysis where we limited the exposed population to only those who had lived in the exposure area for at least 10 years. There is little support for a relationship between PFOA or PFOS and bladder cancer. In highly exposed employees of PFAS facilities, studies have not identified associations between PFAS and bladder cancer incidence or mortality or mortality,[121,123,128-130,135] apart from one study that found a lower risk of bladder cancer with increasing levels of estimated serum PFOA[122] and one study that found an increased rate of death associated with PFOS exposure based on 3 deaths.[133] Mortality studies (≤10 deaths) may have lacked statistical power to evaluate effects. There was no evidence to support an association between PFAS and bladder cancer incidence in communities living near manufacturing plants[124,125] or in the general population.[127]

With regard to the biological plausibility of potential causal links between PFAS exposure and cancer, animal studies have found PFOA exposure to promote hepatocellular adenomas, pancreatic acinar cell adenomas[136,137] and testicular Leydig cell adenomas,[137] with some differences in response between male and female rats.[136] However, the mechanism by which PFOA is thought to cause liver tumours in rats (peroxisome proliferator-activated receptor alpha (PPARa) activation) is considered to be unlikely in humans due to species differences in response to PPARa.[38] Animal studies have not detected kidney tumour in rats.[38] Possible mechanisms for PFAS carcinogenicity are largely unknown, and the relevance of alternative proposed modes of action in humans are similarly unknown.[38]

Findings on cause-specific mortality showed that coronary heart disease deaths, as expected, were much more common in the study populations than the other candidate causes studied, yielding the most precise estimates. The rates of death from coronary heart disease were elevated in both Oakey and Williamtown compared with their respective comparisons areas. There is no existing evidence for a link between PFAS and coronary heart disease mortality except for an indirect link by way of blood lipids (see below). Studies among workers with occupational exposure to PFOA did not find increased deaths from coronary heart disease or ischaemic heart disease.[123,128,130,138] Other studies examining incidence in worker cohorts, exposed communities and in the general population have not reported associations between PFOA, PFOS or PFHxS across a variety of endpoints, including ischaemic heart disease, coronary artery disease, angina and/or heart attack,[122,123,138-141] apart from one general population cohort study in the USA that reported an increased risk of coronary heart disease in those exposed to PFOA.[142] Studies in laboratory rodents have not reported any histological or morphological alterations in the heart.[38]

There is, however, some prior evidence for a relationship between PFAS and biomarkers of cardiovascular health including elevated levels of serum lipid, particularly total cholesterol, LDL and triglycerides.[8,31,143]

We assessed death rates for control outcomes based on biological plausibility — these deaths are unlikely to be attributable to the biological effects of PFAS exposure. Therefore, in the absence of

confounding, we would not expect to see any differences in the standardised death rates for these outcomes across the exposure and comparison areas. Therefore, the higher death rates of control outcomes in both Oakey and Williamtown bring into question the reason for increased rates of candidate outcomes in these areas, particularly given the multiple known risk factors for some outcomes (such as for coronary heart disease) which we could not account for in our analysis. Regardless, the findings of higher-than-expected rates of intentional self-harm in Oakey and Williamtown warrant further investigation, given possible social and psychological links to living in these areas by way of, for example, concerns for health and reduced property values due to PFAS contamination.

Importantly, even where we have observed elevated cancer or death rates among the exposed populations, and where there is some consistency with previous evidence, we cannot determine whether these effects are causal. This is discussed further in the strengths and weaknesses section below and in the general discussion of causality on page 58.

Strengths and weaknesses

There are strengths and weaknesses of this study that should be kept in mind when interpreting findings and comparing them with results of other studies. These include considerations relating to selection of the study population, measurements of exposure and outcomes, and potential confounding.

Selection of study population

A strength of this data linkage study is that by using the Medicare Enrolment File we likely captured a large proportion of the eligible study population who ever lived in Katherine, Oakey or Williamtown over the 35 years, from 1983 to 2019. It is equally likely that we captured a high proportion of the eligible comparison populations during this time. We would have missed people who moved into an area without notifying Medicare of the change, but this is unlikely to have affected relative effect estimates.[t] Further, those with non-residential mailing addresses only, such as post office boxes, were not included in the main analyses. The extent of exclusion from the study population due to this issue is unknown; however, we believe there to be a high percentage of Katherine residents who use post office boxes. In sensitivity analyses, we included everyone in Katherine, Oakey and Williamtown based on postcodes, which encompass post office box addresses. Another potential source of selection bias is linkage error; we assume this error to be small (see Appendix 1).

The Medicare Enrolment File started in late 1983, which means that we began observing the study population up to 15 years after the first exposures (PFAS exposure is possible as early as the 1970s). This is known as left-truncation of a cohort.[u] Individuals who were exposed earlier may have died or developed cancer before the start of the Medicare Enrolment File and would not be observed in this study. If PFAS exposure is related to disease and/or death, this may have led to underestimation of effect estimates — particularly for cancers with high fatality rates. However, PFAS exposure in Katherine, Oakey and Williamtown is thought to have peaked in the 2000s, around the time the Department of Defence commenced phasing out of the use of AFFF and before the public was made aware of contamination issues and advised to limit exposure — thus minimising the impact of left-truncation.

[t] This under-capture of the eligible population could bias estimates in the unlikely scenario that a large proportion of individuals who were living in exposed areas did not register their address on Medicare, and they moved due to concerns regarding their health.

[u] Left-truncation occurs when observation of the cohort begins after the time of first exposure.

Exposure measurement

We relied on address data in the Medicare Enrolment File to determine exposure status (residence in an exposure or comparison area). While this is an objective method of attributing exposure, misclassification may occur if address details are incorrect. Electronic reimbursements for Medicare-covered services have lessened the incentive for individuals to register changes in address, resulting in increasing delays between actual changes of residence and their recording by Medicare. The main effect of this is that exposed person-time and cases will be incorrectly attributed to the non-exposed. The extent of this error is unknown, but if rates are indeed different between the exposed and comparison populations, this error would have led to an under-estimation of effect sizes.

We were also unable to adequately measure duration of exposure due to left-truncation (there are no data before October 1983) and delays by individuals of notifying Medicare of address changes. We attempted to examine this in a sensitivity analysis by restricting the exposed population to individuals registered as living in exposure areas for at least 10 years, and note an increase in the SIR estimate for bladder cancer in Williamtown (estimates were in the same direction, but uncertain in the main analysis); but otherwise did not change our conclusions.

Outcome measurement

We ascertained incident cancers and deaths from national registries, thus allowing complete follow-up of cases (assuming no linkage error; see Appendix 1), including if study participants had moved away from the exposure or comparison areas.

The data in these registries are thought to be accurate, but the collection and classification of cancer and death data have changed over time, resulting in some measurement error. Mandatory reporting of cancer diagnoses began before the observation period for most States/Territories including NSW (1974) and Qld (1982), but not NT (1991). Thus, there will be under-ascertainment of cases, particularly among people living in the NT before 1991,[v] and possibly among those in the study populations that moved to the ACT or Tasmania in the early years, where reporting was only made mandatory in 1994 and 1992, respectively. Death data in the NDI were coded to ICD-9 from 1979 to 1996 and coded to ICD-10 from 1997 onward. There may have been more or fewer deaths due to a specific cause attributable to the change in coding standards.[w] These impacts were likely to have been non-differential with respect to the exposure, in which case SIRs would not have been affected.

A key issue was the small numbers of observed cases for many of the outcomes investigated, resulting in imprecise estimates and difficulties in our assessments of whether rates were different in the exposed versus comparison populations. Although we measured outcomes over a 35-year period and captured most individuals who were eligible to be included, the exposed populations, especially in Oakey and Williamtown, were small. Even in Katherine, despite a relatively large study population, there was insufficient follow-up time to observe differences, should they exist, in some cancers or causes of death that have long latency periods. Our data suggest that there was steady migration into Katherine over the study period, resulting in a shorter average follow-up time per resident than in Oakey and Williamtown, where higher proportions of residents had moved into these towns before the start of the study (Table 9).

[v] The proportions of total cancers in the study population diagnosed in NT for the period 1982–1991 and from 1991–2017 were 13% and 17% respectively. The proportions diagnosed in Qld were 48% in both periods, and in NSW, 24% and 26%. The remaining cancers (in the respective periods) were diagnosed in other states.

[w] The proportions of totals deaths in the study population for the period 1980–1997 (ICD-9) and 1997–2019 (ICD-10) were: external causes (15% and 12%), coronary heart disease (20% and 14%), chronic kidney disease (0.8% and 2%), liver disease (1.2% and 2%) and stroke (6% and 4.7%).

On average, each Oakey resident contributed 17.7 exposed follow-up years, followed by Williamtown (15.2 years) and Katherine (12.7 years). Note that the above figures do not reflect re-classification of exposure time due to application of a lag period; for example, in the main analysis the first 10 years after moving into an exposure area was attributed to the non-exposed to account for a latency period.

Potential confounding

Confounding is an issue in all observational studies, potentially biasing risk estimates and limiting the ability to draw causal inferences. This is additionally discussed in the last section of the report. There was a significant risk of confounding in this study, due to factors apart from exposure that may have led to differences (or lack of difference) in cancer and mortality rates. Use of administrative data meant that we did not have information on many participant characteristics, such as may be available from a survey study design. Apart from age and sex, we could not account for other risk factors related to the outcomes of interest, such as alcohol consumption, tobacco use, individual-level socioeconomic status, obesity and occupational exposure to PFAS.

We had indirect evidence of the probable unequal distribution of risk factors in the exposed and comparison populations, seen in the elevated death rates for control outcomes in both Oakey and Williamtown, and for non-candidate cancers in Katherine. These observations bring into question the reasons for elevated rates of candidate outcomes. We expect our findings to have been particularly affected by confounding by SES-related factors. While every effort was made to draw a comparison population for each exposure area from comparable socioeconomic areas, this was based on area-level measures at one point in time, which may not have reflected changes over time. The long study period and particularly mobile populations also presented challenges in assigning socioeconomic position longitudinally, which we did not attempt to do. In addition, area-level SES measures are imprecise proxies for individual circumstances. We lacked information on individual-level socioeconomic status to assess the comparability between the exposed and comparison populations on this dimension over the long study period.

We set out to select comparison areas that were similar to the exposure areas in terms of proportions of Aboriginal and Torres Strait Islander residents. However, there were smaller proportions of people of Aboriginal and Torres Strait Islander descent drawn from these areas in the resulting comparison populations in NT and Qld. This was partly driven by limited available comparison areas, particularly in NT, that were comparable to Katherine on other socioeconomic factors including proportions of Aboriginal and Torres Strait Islander peoples. We adjusted for individual-level voluntary Aboriginal and Torres Strait Islander status in sensitivity analyses. This adjustment did not materially affect estimates; but this may have reflected under-adjustment due to substantial under-identification.

Broadly, there appeared to be considerable under-identification of Aboriginal and Torres Strait Islander status in the study populations in NT and Qld as recorded in the VII database (Table 9), when compared to the Perinatal Data Collections (Table 3) and AEDC (Table 6), and when compared to Census 2011 data[x] — although noting differences in population demographics and/or time periods. Given the relatively high proportions of Aboriginal and Torres Strait Islander peoples in Katherine and Oakey, and the fact that cancer and mortality rates among the Aboriginal and Torres Strait Islander population generally differ substantially from rates in the non-Indigenous population, the impact of this under-identification may have been considerable.

[x] In 2011, the proportions of Aboriginal and Torres Strait Islander people in Katherine, Oakey and Williamtown/Salt Ash at the 'Urban Centre/Locality' level were 29.5%, 8.2% and 1.4%/2.7% respectively (Census, 2011).

Summary

In our analysis of cancer and mortality rates in the PFAS Management Areas between 1983 and 2017, we estimated higher-than-expected incidence rates of prostate cancer in people who had lived in Katherine; of laryngeal cancer and coronary heart disease deaths in Oakey; and of kidney cancer, lung cancer, and coronary heart disease deaths, and possibly bladder cancer and pancreatic cancer, in Williamtown. The overall standardised rates of any candidate cancer combined and of any cancer were very similar in the exposed and comparison populations across all States. For many of the candidate outcomes, the numbers of cases analysed were small and estimates too imprecise to make any determination about whether rates were different. The potential for bias in our estimates due to measurement error and confounding, the inconsistency in findings across the exposure areas, the elevated rates of control outcomes and the absence of robust prior evidence for an association between PFAS and outcomes highlighted in this study — apart from a suggestive link between PFOA and kidney cancer and plausible biological pathways for coronary heart disease — temper any suggestions of causality. This is discussed further in the final section of the report, below. The findings of elevated intentional self-harm in Oakey and Williamtown are likely to be concerning to current and previous residents of these areas and warrant further investigation.

Considerations of causality

Over the three separate data linkage studies, we did not find evidence to support an association between living in PFAS Management Areas and most candidate outcomes. For several outcomes, we estimated higher rates (relative to the comparison populations) of individual adverse health outcomes in one of the three exposure areas. These were: in Katherine, prostate cancer; in Oakey, stillbirth, developmental vulnerability in two AEDC domains (physical health and wellbeing, and communication skills and general knowledge), and laryngeal cancer; and in Williamtown, postpartum haemorrhage, pregnancy-induced hypertension, kidney cancer and lung cancer. We also estimated lower rates of liver disease mortality, and lower rates of developmental vulnerability in the AEDC domain of communication skills and general knowledge in individual exposure areas. For most of these outcomes, effect sizes were relatively small or imprecise. For coronary heart disease deaths, both Oakey and Williamtown had higher relative rates.

While we observed statistical evidence of higher rates of some adverse outcomes in exposure areas, this does not necessarily imply causal associations. In considering whether PFAS exposure could have caused any of these outcomes, we discuss the following:

- chance and statistical power
- bias
- consistency of findings across exposure areas
- consistency of findings with those of other studies
- biological plausibility.

Chance and statistical power

In these observational studies, we selected everyone who had ever lived in the exposure areas (rather than using a sample). However, because the populations of those who had ever lived in these areas were small, particularly in Oakey and Williamtown, many analyses were insufficiently powered to detect other than large differences in rates of outcomes between the exposed and comparison populations. Moreover, the perinatal, cancer and mortality studies included uncommon outcomes that would require large sample sizes to detect important risks associated with exposure. The estimated relative effects for stillbirth, and laryngeal cancer were based on ≤5 cases in the exposed population, while those for postpartum haemorrhage and kidney cancer were based on 10 and 16 cases respectively. Thus, these estimates are sensitive to even a small number of cases being missed or misclassified. These circumstances restricted our ability to answer the question of whether rates differed between the exposed and comparison populations.

We conducted multiple tests of association in these studies. Given the existence of a prior body of relevant evidence, we were able to interpret our results in the context of previous findings and did not perform a statistical correction for multiple comparisons. However, in general, there is a small chance (conventionally about 5% or 1 in 20) that the interval estimate will lead to the conclusion that the rate differed between the exposed and comparison populations when in fact they are not different, i.e. a false positive. The rate of false positives increases with the number of tests conducted.[y]

Bias

The strengths of these studies derive from using administrative data to select study participants and classify their exposure, and from linking data to State/Territory and national databases to identify incident outcomes. Consequently, we expect findings to have been minimally impacted by

[y] Assuming 60 tests (e.g. 20 individual cancers in 3 areas), there is a 95% chance, $1 - (0.95)^{60}$, that at least one finding is a false positive.

many of the common sources of bias in observational studies, including bias related to selection and loss to follow-up, and bias due to error in measurement of outcomes. However, the risk of bias due to confounding was a key concern in all studies in this report.

There are two potential sources of uncontrolled confounding in our studies: measurement error in the confounding variables (such as poor ascertainment of Aboriginal and Torres Strait Islander status), and omission of known and unknown confounding variables from the analysis.[144] The latter is the main issue in our studies because of the inability to control for differences in unknown confounders (this can only be done in randomised studies, never observational studies) and reliance on administrative data for information on known confounders. This last issue was less of a problem in the perinatal study, due to the availability of more risk factor information, and more of an issue in the cancer and mortality study, where we had only limited information on demographic characteristics, and no information on individual socioeconomic, behavioural and biological risk factors. For example, we did not have data on family history, smoking and diabetes, all of which are known risk factors for coronary heart disease deaths.

In particular, we were not able to account for socioeconomic factors as well as we would have liked. This is important, as socioeconomic conditions are strongly linked to health.[145] While we chose comparison areas that were similar to each exposure area on SES indexes (see Appendix 3), there was some indication that the populations drawn from these areas were dissimilar, and that this dissimilarity compounded over time due interstate movement and social mobility. This issue in selecting matching populations could have been minimised through statistical adjustment in the analysis; however assigning area-SES longitudinally is challenging and we lacked information on individual and household SES.

Additionally, we saw evidence of increased rates of the outcomes we designated as control outcomes in the cancer and mortality study, which further suggests that factors other than PFAS exposure could have led to differences in rates between the exposed and comparison populations. Thus, we cannot rule out with reasonable confidence that the findings of these studies, especially those based on small effect sizes, may have been generated by confounding. Small measurement errors in, or omission of, several confounders can cumulatively produce sizeable errors in estimates of risks.[144] We also cannot rule out that these issues could have masked real associations.

Our investigations pertained to living in an exposure area, and not necessarily to high PFAS exposure itself. Using this definition of exposure, measurement was assumed to be reasonably accurate as it was based on administrative data (for a fuller discussion on this, see pages 37 and 55). However, we lacked the necessary data to quantify the correlations between fact of residence ('ever lived' in an area), duration of residence, and serum PFAS concentrations over time, which would allow further considerations of causal links (see below).

Consistency of findings across exposure areas

In all three studies, we did not measure serum PFAS concentrations in the populations. However, measurements from the PFAS Health Study Blood Serum Study provide some context for the levels of exposure in the Australian context. Between 2016 and 2019, measured serum levels of PFAS showed that Katherine, Williamtown and Oakey had relatively similar exposure levels. The median PFAS levels, across the three exposure areas, ranged from: 4.8 to 6.1 ng/ml for PFOS, 2.9 to 3.9 ng/ml for PFHxS and 1.3 to 1.9 ng/ml for PFOA,[51] bearing in mind that serum levels measured at one point in time may not reflect cumulative exposure or changes over time. We did not have the necessary data to attempt historical reconstructions.

On the strong assumption that PFAS levels and composition were similar across the three exposure areas over the study period, if PFAS is causally linked to certain adverse outcomes, we would expect reasonably consistent findings on these outcomes across the three areas, at least in the direction of effect. This was not the case. We observed an effect on mortality due to coronary heart

disease in both Oakey and Williamtown (but also effects on control outcomes in these areas), while all other effects were seen in only one area, with some showing contradictory results — for example, we saw an increased risk of developmental vulnerability in communication skills and general knowledge in children in Oakey, but a decreased risk on this domain in Katherine.

Consistency of findings with other studies

There is limited previous evidence to draw definitive conclusions on the effects of PFAS on health. Considering our candidate outcomes, reviews have noted possible relationships between PFAS and reduced birthweight, pregnancy-induced hypertension, testicular cancer, kidney cancer, chronic kidney disease incidence and changes to cholesterol levels.[33,34,38-40]

Of the above, we saw higher rates of pregnancy-induced hypertension and kidney cancer, in Williamtown but not in the other two exposure areas. We probably did not have adequate statistical power to detect effects for testicular cancer and chronic kidney disease mortality in any of the exposure areas, and for kidney cancer in Katherine. For the other outcomes where statistical power may not have an issue, we did not see elevated rates (kidney cancer in Oakey, pregnancy-induced hypertension in Oakey and Williamtown); and we found little to no meaningful differences in birth weight in all exposure areas. One reason could be the possibly lower levels of PFAS in the Australian PFAS Management Areas[51] compared to other international reports of known residential drinking water contamination,[z] and thus potentially low exposure contrast between the exposed and comparison populations. Study populations with low exposure contrasts can make it difficult, if not impossible, to observe measurable differences in disease, if a difference exists. The possibility of confounding is also expected to be stronger in cohorts with low exposure, where some proportion of the variation in PFAS concentration could be due to physiological differences among individuals rather than environmental contact.[146] Additionally, for chronic kidney disease, we measured mortality not incidence, and differences in incidence are not necessarily reflected in mortality given people with kidney disease frequently die from other causes.

On the other hand, we observed several associations that have not been noted in reviews. These were for prostate, laryngeal and lung cancers, stillbirth and developmental vulnerabilities in the AEDC domains of physical health and wellbeing, and communication skills and general knowledge; all of which were observed in just one exposure area. We saw higher rates of coronary heart disease mortality in two exposure areas. Associations between PFAS and prostate and lung cancers,[77,122-125,130,132,133] stillbirth,[57,58] and death from coronary heart disease[123,128,130,138] have not been observed in highly exposed community cohorts, or worker cohorts with PFAS levels at orders of magnitude higher than community cohorts.[aa] While elevated cholesterol — a risk factor for coronary heart disease — has been associated with PFAS exposure, we obviously do not know to what extent, if any, this might explain the higher rates of coronary heart disease deaths observed in Oakey and Williamtown. While highly exposed children in the mid-Ohio Valley region have been observed to have poorer executive function, they have also been reported to have higher IQ and fewer learning problems[105,106,114]; noting these measurements may not be comparable to ours. The above null or equivocal patterns seen in highly exposed cohorts call into question the reason for the higher rates observed in our studies for these outcomes.

---

[z] The median PFAS levels in Ronneby, Sweden with environmental contamination from AFFF were: median (min-max) PFHxS: 277 ng/ml (12-1,660 ng/ml), PFOS: 245 ng/ml (24–1,500 ng/ml), PFOA: 18 ng/ml (2.4–92 ng/ml). The median PFAS levels in other communities affected by PFOA contamination associated with nearby manufacturing plants were: mid-Ohio valley, USA — median (min-max) PFOA: 28.2 ng/ml (0.2–22,412 ng/ml); Veneto region, Northern Italy — PFOA: 44 ng/ml (<0.5 — 1,400 ng/ml), PFHxS: 3.9 ng/ml (<0.5 — 127 ng/ml). (see Li, 2020; Viera, 2013; Pitter 2020)

[aa] Median PFOA in various groups of exposed workers: 113 — 2500 ng/ml, maximum concentration reported 92,030 ng/ml. (see Leonard 2018, Steenland 2015, Raleigh 2014, Gililand & Mandel 1993, Lundin 2009).

Overall, there was little consistency between the findings of our studies and those that have been noted in reviews, apart from the higher rates of pregnancy-induced hypertension and kidney cancer in Williamtown.

Biological plausibility

As far as we know, there are no confirmed or validated mechanisms for the effects of PFAS on those outcomes where we saw elevated rates. PFAS are hypothesised to disrupt placental growth and function, thus increasing the risk of adverse perinatal outcomes.[72] However, specific mechanisms for PFAS-induced placental damage leading to specific outcomes have not been experimentally validated. There are no known mechanisms for the effects of PFAS on early childhood developmental outcomes. PFOA has been reported to promote hepatocellular adenomas, pancreatic acinar cell adenomas[136,137] and testicular Leydig cell adenomas in rats.[137] However, the possible mechanisms for PFAS carcinogenicity in humans are largely unknown.

Overall conclusion

Of necessity, investigation of the health impacts of living in PFAS-contaminated areas relies on observational studies. Despite their limitations, our data linkage studies add to the body of evidence on this topic. Studies with long-term follow up of incident disease in large-sized cohorts with large exposure contrasts are the most likely to detect true associations, should they exist.

There was limited support in these studies for effects of living in PFAS Management Areas on candidate health outcomes. While there were higher rates of some adverse outcomes in individual areas, the evidence suggesting that this was due to living in these areas was limited. We did not have direct measurements of PFAS exposure and we cannot rule out that the higher rates were due to chance or confounding. Further, there was low consistency in observed associations across the three PFAS Management Areas, some control outcomes were elevated, and at present, there is limited prior evidence or biological plausibility for PFAS causing these outcomes in humans. Overall, our findings are consistent with previous studies, which have not conclusively identified causative links between PFAS and these health outcomes.

Glossary

Adjustment — the modification of an estimate to account for potential confounders (see *confounding*). For example, the crude relative risk of stillbirth was 0.99 in Katherine. After adjustment for year of birth, maternal age, and mother's Aboriginal and Torres Strait Islander status, the adjusted relative risk was 0.95.

Association — a relationship between two variables. A *positive association* is where the mean/rate of one variable tends to increase/is higher as the value of another variable increases. An *inverse association* is where the mean/rate of one variable tends to decrease/is lower as the value of another variable increases. A *null association* is where there is no relationship between two variables.

Bias — any systematic error that results in an incorrect effect estimate (see *effect estimate*).

Candidate outcomes — health outcomes investigated in this study that may be possibly associated with PFAS.

Causal relationship — where one variable (for example, exposure) causes another (for example, a health outcome). As opposed to 'association', where one variable is related to, but does not necessarily cause, the other.

Chance/random error — some study results may reflect a true effect; however, some results can arise simply because of chance (randomness).

Comparison areas — specific postcodes in NT, Qld and NSW that have similar sociodemographic characteristics to Katherine, Oakey and Williamtown respectively (see Box 1 for postcodes).

Comparison population — a sample of individuals who had lived in the comparison areas.

Confidence interval — a range of probable values for an estimate. The point estimate and its confidence interval are collectively known as the interval estimate.

Confounding — occurs if the characteristics of the exposed population do not match the characteristics of the comparison population, and it is these characteristics that cause an effect (see *effect*) to be observed. This makes the effect estimate biased (see *bias*). For example, if we compare an older population to a younger population, age may be the reason why a difference in rates of disease is observed. Age is a confounding factor here unless appropriately accounted for.

Control outcomes — health outcomes investigated in this study that were not known or thought to be associated with PFAS.

Crude statistic — an estimated statistic prior to any adjustments (see *adjustment*).

Data linkage — bringing together two or more records that relate to the same individual.

Difference in means — the difference in the means of an outcome between two populations.

Effect — the influence of one condition (for example, exposure) on another (for example, a health effect).

Effect estimate/point estimate — the value of a measurement used to estimate an effect (see *effect*). For example, the estimated relative rate, relative risk or mean difference.

Exposed population — all individuals who lived in the exposure areas.

Exposure areas — areas with known PFAS contamination, that is, the PFAS Management Areas. In some sensitivity analyses, we considered the wider areas that fall under Katherine, Oakey and Williamtown postcodes as the exposure areas.

Exposure levels — the level of a population's exposure to PFAS. *Background levels* reflect exposure to low levels of PFAS typically seen in the general population who have not experienced high levels

of exposure. *Community exposure levels* reflect exposure to high levels of PFAS through environmental contamination of residential areas located close to facilities that use or produce PFAS. *Occupational levels* represent exposure to very high levels of PFAS through work at facilities that use or produce PFAS.

Internal validity — the extent to which the findings of a study represent the population being studied, as opposed to 'external validity' which is whether findings of a study can be applied to a population beyond the study in a different setting.

Latency period — a period of time between first exposure and onset of disease.

Left-truncation — occurs when the study begins after the time of first exposure. For example, we began the cancer study in 1983 even though exposure to PFAS started in the 1970s. The implication is that individuals who were exposed to PFAS prior to 1983 may not have been included in the study.

Mean — the arithmetic mean or average is the central value of a set of values, i.e. the sum of the values divided by the number of values. For example, the mean of 1,2,2,2,4,4,5 is 2.85 (20 divided by 7).

Measurement error — incorrectly recorded values. For example, some teachers will be harder or softer in their judgement when scoring children on the AEDC (see also *misclassification*).

Median — the midpoint of a set of values. For example, the median value of 1,2,2,**2**,4,4,5 is 2. The median can be more useful than the mean when there are many extreme values.

Misclassification — when someone or something is assigned to an incorrect category. For example, someone could be misclassified as non-Indigenous if they did not identify as Aboriginal and/or Torres Strait Islander (see also *measurement error*).

Monotonic relationship — where one variable strictly increases (or strictly decreases) with another variable. If the variables also move at a constant rate, the monotonic relationship is also linear.

Non-differential — if misclassification error occurs in the same way in both the exposed and comparison populations.

Percentile — a score below which a certain percentage of the population falls. For example, 91% of the population falls below an IQ score of 120 (which is the 91st percentile).

Person-time — the total amount of time a person is observed. As epidemiological studies usually follow a group of individuals as they move through time, the total person-time is a combination of the number of people and amount of time. Total person-time is the denominator in calculation of the rate of the outcome.

PFAS Management Areas — the areas in Katherine, Oakey and Williamtown, within boundaries defined by the Australian Department of Defence, that have known PFAS contamination. All street addresses within the PFAS Management Areas are captured in the PFAS Address Database.

Potential exposure areas — locations nearby the PFAS Management Areas in Katherine, Oakey and Williamtown but not included in the PFAS Address Database.

Prenatal exposure — PFAS exposure that occurs before birth; for example, during pregnancy.

Rate (incidence) — the number of new cases per unit person-time (see *person-time*). For example, the rate of head and neck cancer was 2.33 cases per 10,000 person-years in Katherine.

Regression — a statistical method used to quantify the relationship between two variables.

Risk ratio (RR) or incidence ratio (IR) — the ratio of the risk/incidence of an outcome in one population divided by the risk/incidence in a reference population. The risk ratio is also known as the relative risk.

Risk/rate difference — the difference in the risk/rate of an outcome between two populations.

Risk — the number of new cases divided by the total number of individuals. For example, the risk of preterm birth was 455/5,606 or 8% in Katherine.

Selection bias — occurs when there is a systematic difference between people who are included in the study and those who are not.

Singleton baby/pregnancy — only one baby born at one birth, as opposed to a multiple such as twins or triplets.

Sociodemographic — a combination of social and demographic factors.

Socioeconomic — a combination of social and economic factors.

Standard deviation — a measure of the spread of a set of values relative to its mean. A low standard deviation means values are closer to the mean, while a large standard deviation means the values are spread over a wider range.

Standardised incidence ratio (SIR) — the number of observed cases in a population divided by the number of cases that would be expected if the population had the same disease rate as comparison population.

Statistical power — the ability of a study to detect an effect (see *effect*), if there is actually an effect. This depends on the number of people in the study (sample size), how common the health outcome is, how large the variance (spread) of the measure, and how large the expected effect is. The smaller the expected effect, the more power required.

Under-identification — occurs when fewer people in a minority group are recorded in a dataset than are truly present.

Variable — a characteristic that varies among individuals. A *binary variable* is a variable where there can only be two possible values (for example, 'yes' or 'no'). For example, bone cancer is a binary variable as person can either be diagnosed with it or not. A *categorical variable* is a variable where there can only be a limited number of values. For example, BMI is categorical variable with four possible values 'underweight', 'normal', 'overweight', and 'obese'). Note BMI can also be treated as a continuous variable. A *continuous variable* is a variable whose values can take any number including decimal places. For example, birth weight is a continuous variable.

Appendices

Appendix 1

Data Integration

Data linkage authorities

The Australian Institute of Health and Welfare Data Integration Services Centre (AIHW DISC)—a Commonwealth-accredited data integration authority—linked all study datasets involving the Medicare Enrolment File. Formal guidelines for integrating Commonwealth data for research projects were endorsed by the Commonwealth Secretaries Board in 2010. Full details, including how to apply for access to Medicare data for research purposes, are available on the Australian Government National Statistical Service webpage.[147]

The AIHW DISC performed the linkages between the Medicare Enrolment File to:

- the PFAS Address Database
- comparison area postcodes
- the Australian Cancer Database
- the Australian Early Development Census
- the National Death Index.

NT Health, Data Linkage Queensland and the Centre for Health Record Linkage (CHeReL) performed the linkages between the NT, Qld and NSW Perinatal Data Collections respectively, to:

- the PFAS Address Database
- comparison area postcodes.

Separation principle

The separation principle was in place throughout all data linkages performed for this study. The separation principle is an important strategy to protect privacy and provides data custodians with control over managing privacy and data access.

The cornerstone of handling confidential data is limiting access to data to those who need it. Consequently, staff have access to only those datasets required for their work. In particular, staff undertaking linkage have access only to identifying variables (such as names and dates of birth), staff undertaking data merging have access only to the content variables (such as clinical information, medical or pharmaceutical details) and data analysts have access only to non-identifiable and appropriately confidentialised integrated datasets. The separation principle ensures that no one working with the data is able to view both the linking (identifying) information and the merged analysis (content) data in an integrated dataset.

Linkage method

All linkages in this study were undertaken using probabilistic linkage methods. Probabilistic linkage is the linkage of records in two files based on the probabilities of agreement and disagreement, as opposed to exact agreement, between a range of linkage variables (fields used for comparison). It is based on the framework of Fellegi and Sunter[148] for linking records together using several fields. Linkage variables include identifying information such as name, address, date of birth and gender. No health or content data are used as linkage variables.

The linkage process involves running a series of passes that allow for variation in full name information and demographic data. Each pass consists of exact matching on selected 'blocking' variables and then calculating a comparison weight for each potential record pair. The comparison weight is calculated based on the level of agreement across multiple linkage variables.

Subsequently, manual clerical review of possible records pairs is undertaken to assign a decision of link or non-link to each record pair. In sample-based clerical review, only a sample of potential record pairs is reviewed in order to identify a comparison weight decision cut-off. This cut-off attempts to optimise the number of incorrect links that would be accepted against the number of correct links that would be missed.[149]

Linkage software

Commercial or open-source software can be used for probabilistic or more complex exact step-wise linkage. The CHeReL and Data Linkage Queensland uses ChoiceMaker software,[150] which is freely available; the AIHW has developed a bespoke linkage program, written in SAS.[149]

Linkage error

Despite use of probabilistic linkage techniques, all data linkages are subject to errors because of incorrect or omission of details in personal information; for example, changes in surname may not be captured, given names may be transposed, spelled incorrectly or partly replaced by nicknames, or the date of birth may be wrong. The extent of linkage error is largely unknown in this study, and the resulting direction of bias difficult to predict, as linkage error may manifest as false links (linkage to the wrong person) or missed records (failure to link at all).

We assumed linkage error to be small in this study and unlikely to differ in the exposed and comparison populations. Given this, it is likely that linkage error will have at most a small effect on estimates or, if anything, bias estimates towards the null (underestimation of effects).

The proportion of addresses in the PFAS Address Database that linked to the Perinatal Data Collections or the Medicare Enrolment File is presented in Appendix Table 1. We do not know the true proportion of households that experienced a pregnancy or birth event in the study period; therefore, we were unable to quantify the coverage of the study population for the analyses of perinatal outcomes. The proportion of addresses in the PFAS Address Database that linked to the Medicare Enrolment File was 98% (after excluding non-residential addresses). This means we would have captured at least one individual who ever lived in these addresses; however, we do not know the extent of missed individuals (many individuals could have lived in a given address over the long study period) due to missed or wrongly linked addresses.

Appendix Table 1: Proportion of addresses in the PFAS Address Database that linked to Perinatal Data Collections or Medicare Enrolment File

	Katherine	Oakey	Williamtown	Overall
Total addresses in PFAS Address Database	3,007	1,958	918	5,883
Linked to:				
Perinatal Data Collection	N/A	24% (465)	14% (121)	20%
Medicare Enrolment File	81% (2,444)	86% (1,684)	73% (673)	82%

Table notes

1. The NT Perinatal Data Collection does not collect address-level residential information; the Katherine study population for analyses of perinatal outcomes was selected on locality instead. Therefore, the proportion of Katherine addresses in the PFAS Address Database that would have linked to the NT Perinatal Data Collection is unknown.
2. Data linkers at the AIHW Data Integration Services Center deemed some addresses in the PFAS Address Database to be non-residential, duplicated or vacant blocks. After exclusion of these addresses, the overall linkage rate was 98% (5,750/5,883).

Appendix 2

Ethics

Ethics approvals

The PFAS Data Linkage Study involved linkages of Commonwealth databases and jurisdictional data collections. The Medicare Enrolment File, NDI, ACD, and the AEDC are Commonwealth data held by the AIHW, but State and Territory governments retain ownership of their jurisdiction's data in the ACD. The NT, Qld and NSW Perinatal Data Collections are held by the relevant States.

Ethical approvals were obtained from the following Committees:

- ACT Health Human Research Ethics Committee
- AIHW Ethics Committee
- ANU Human Research Ethics Committee
- NSW Population and Health Services Ethics Committee
- Aboriginal Health and Medical Research Council of NSW Ethics Committee
- NT Department of Health and Menzies School of Health Research Ethics Committee
- SA Department of Health and Ageing Human Ethics Committee
- Tasmanian Health and Medical Human Research Ethics Committee
- WA Aboriginal Health Ethics Committee.

Data custodian approvals were obtained for all databases used in this study. The AIHW DISC facilitated data custodian approvals for AIHW-held data including the NDI and the Medicare Enrolment File, and acquisition of a Public Interest Certificate signed by the Minister for Health of the Commonwealth. We obtained approvals from each Australian State/Territory cancer registry for the use of the ACD, and the Australian Department Education, Skills and Employment for the use of the AEDC.

Privacy and waiver of consent

This study was compliant with all Australian Privacy Principles (APP) except APP6 (use or disclosure of personal information). As this project was conducted without consent, which would breach APP6, a waiver of consent pursuant to section 95 of the Privacy Act 1988 was sought and granted on the basis of the large number of people involved, the high degree of privacy protection afforded by application of the separation principle, and additional measures relating to data access and use that aimed at minimising the re-identification risks of integrated data.

Secure data storage and access

All data linked to the Medicare Enrolment File were stored, accessed and analysed in the Secure Unified Research Environment (SURE) computing environment through the Sax Institute. SURE was accessed via the Australian Academic and Research Network (AARNET) or the internet using an encrypted connection from researchers' local computers, which must meet security requirements. Descriptive data and analysis results were downloaded from SURE under curator surveillance and stored on secure, password-protected networks at the ANU. Data from jurisdictional Perinatal Data Collections were stored on password-protected ANU secure servers. Only Hsei Di Law and Rosemary Korda had access to the data for this study.

Appendix 3

Selection of comparison areas

The study team chose comparison areas separately for each of the three PFAS Management Areas. Comparison areas were selected with the aim of ensuring the populations drawn from these areas were similar to the exposed populations in terms of sociodemographic factors.

We selected comparison areas from within the same State/Territory as each of the exposure areas, and had similar sociodemographic profiles to the corresponding exposure area[bb] in terms of the following characteristics at the SA2 geographical level: socioeconomic disadvantage, measured by the ABS IRSD deciles; geographical remoteness, measured by ARIA+ categories (Very Remote, Remote, Outer Regional, Inner Regional and Major Cities); and proportion Aboriginal and Torres Strait Islander in the year 2011.[cc]

Comparison areas were selected at the SA2 level before translation to postcodes due to the level of data available for sociodemographic characteristics. As many postcodes were chosen as necessary for the expected comparison population to reach approximately four times that of the exposed population.

The following tables published by the ABS were used to perform the above steps:

- SA2 Index of Relative Socio-economic Disadvantage 2011
- 2011 Estimated Resident Aboriginal and Torres Strait Islander and non-Indigenous population by SA2
- SA2 2011 to Remoteness Area 2011 correspondence file.

Apart from Katherine, Oakey and Williamtown, there are other sites under investigation for environmental contamination with PFAS. We coordinated with the PFAS Taskforce of the Department of Agriculture, Water and the Environment, NSW Environment Protection Authority, NSW Health, and Queensland Health to exclude potential comparison areas in NSW and Qld that had recorded exceedances of the National Health and Medical Research Council (NHMRC) drinking water guidelines for PFAS since testing began.[151] Results for comparison areas in the NT were checked against the Power and Water Corporation PFAS monitoring.[152]

Selected comparison SA2s were then mapped to postcodes using the ABS Postcode 2011 to SA2 2011 table. This was necessary as the data sources from which the study populations were chosen (Medicare Enrolment File, Perinatal Data Collections) do not record address information at the SA2 level. Final comparison area postcodes were selected where at least 50% of the postcode is donated to the SA2.

The comparison area postcodes for the three exposure areas were:

- **Katherine**: 0800, 0828, 0829, 0835, 0836, 0837, 0838, 0840, 0841, 0845, 0846, 0880, 0886
- **Oakey**: 4311, 4371, 4372, 4373, 4610
- **Williamtown**: 2334, 2335, 2864, 2865, 2866, 2867, 2477.

[bb] We selected the following SA2s to encompass the PFAS Management Areas: 'Jondaryan' for Oakey, 'Williamtown-Medowie-Karuah' for Williamtown and 'Katherine' for Katherine.

[cc] The SA2 statistical area structure first became available in 2011 under the Australian Statistical Geography Standard.

Appendix 4

Deviations to original study protocol

Perinatal

We measured the outcomes of postpartum haemorrhage and emergency caesarean, instead of the outcome of delivery complications (p. 27 of original study protocol[53]). We did not include the outcome of gender (p. 27) as we did not consider this meaningful.

Cancer and cause-specific mortality

- The linkage between Medicare Enrolment File to the Personnel Management Key Solution (PMKeyS) database, in order to identify Department of Defence personnel for adjustment purposes (p. 18 of original study protocol), was considered not feasible for this study. Further, as the PMKeyS database only contains Defence staff from 2001 onwards, the relevant analyses would likely not have sufficient length of follow-up to observe cases, and insufficient statistical power.
- Instead of the address list compiled by the Department of Defence and the NSW Environmental Protection Authority (p. 18), we used the PFAS Address Database created by the study team (Box 1). This was because the original list was not created for the purpose of identifying residences in the exposure areas and may have been incomplete.
- Instead of undertaking a search of the public domain and government documents to identify other areas of potential PFAS exposure apart from Katherine, Oakey and Williamtown, the study team coordinated with the PFAS Taskforce, NSW Environmental Protection Authority, NSW Health and Qld Health (p. 24).
- We did not examine the outcomes of first hospitalisation or death due to acute myocardial infarction, stroke, or major cardiovascular (p. 29). This was because we did not have access to hospitalisation data for this study. However, we examined the incidences of deaths due to coronary heart disease and stroke.
- For control outcomes, instead of deaths due to land transport accidents and accidental falls (p. 29–30), we measured the incidences of death due to all external causes (not only accidents and falls), death due to parasitic or infectious diseases, and death due to intentional self-harm.
- We estimated SIRs for all cancer and cause-specific mortality outcomes in order to avoid reporting relative effect estimates using a mixture of rate ratios, hazard ratios and SIRs (p. 32).
- We did not exclude those with a post office box address as a sensitivity analysis (p. 35), as the environmental exposure of PFAS is likely to be diffuse, and not dwelling-specific. Instead, in a sensitivity analysis, we classified everyone living in Katherine, Oakey or Williamtown postcodes (which encompass post office boxes) as exposed, assuming those using post office box addresses were living locally at the time.
- We did not conduct sensitivity analyses involving zero lag or censoring study participants at age 100 instead of 85 years (p. 35), as the results from these analyses would not have added meaningful data to the research questions.

Appendix 5

Sensitivity analyses tables

Appendix Table 2. Comparison of perinatal outcomes in exposed and comparison populations: and adjusted relative risks (RR) of adverse perinatal outcomes, and adjusted difference in means of growth measurements, where continuous covariates were modelled as categorical variables, and where gestational diabetes was included as an additional covariate

	NT			Qld			NSW		
	Adjusted RR[1] (95% CI)	Adjusted RR[2] (95% CI)	Adjusted RR[3] (95% CI)	Adjusted RR[1] (95% CI)	Adjusted RR[2] (95% CI)	Adjusted RR[3] (95% CI)	Adjusted RR[1] (95% CI)	Adjusted RR[2] (95% CI)	Adjusted RR[3] (95% CI)
Adverse perinatal outcome									
Gestational diabetes	1.07 (0.91,1.27)	1.10 (0.93,1.30)		0.95 (0.71,1.26)	0.93 (0.69,1.25)		1.45 (0.86,2.46)	1.43 (0.85,2.41)	
Pregnancy-induced hypertension	0.92 (0.80,1.07)	1.11 (0.93,1.33)		1.02 (0.61,1.71)	0.99 (0.59,1.67)		1.98 (1.35,2.90)	1.88 (1.29,2.73)	
Caesarean/assisted vaginal	0.99 (0.94,1.04)	0.96 (0.91,1.02)	0.98 (0.92,1.04)	1.13 (1.01,1.26)	1.13 (1.01,1.27)	1.12 (1.00,1.26)	1.03 (0.84,1.27)	0.99 (0.82,1.21)	0.92 (0.74,1.14)
Emergency caesarean	0.99 (0.90,1.09)	1.07 (0.96,1.20)		1.10 (0.89,1.38)	1.14 (0.91,1.42)		1.23 (0.83,1.81)	1.13 (0.77,1.67)	
Postpartum haemorrhage	0.95 (0.85,1.06)	1.01 (0.90,1.13)		0.96 (0.70,1.32)	0.90 (0.63,1.27)		1.89 (1.09,3.28)	1.87 (1.07,3.26)	
Preterm birth	0.95 (0.85,1.07)	1.06 (0.92,1.22)		1.12 (0.85,1.48)	1.05 (0.77,1.42)		1.47 (0.89,2.41)	1.48 (0.90,2.43)	
Spontaneous preterm birth	0.99 (0.86,1.14)	1.14 (0.96,1.36)		0.96 (0.65,1.44)	0.88 (0.57,1.36)		1.28 (0.61,2.70)	1.32 (0.63,2.79)	
Small for gestational age	0.87 (0.80,0.95)	0.92 (0.82,1.03)		0.94 (0.64,1.39)	1.01 (0.68,1.50)		0.88 (0.49,1.58)	0.87 (0.49,1.54)	
Large for gestational age	0.96 (0.86,1.08)	0.92 (0.80,1.04)	0.86 (0.74,0.99)	0.93 (0.66,1.31)	0.91 (0.64,1.30)	0.89 (0.62,1.27)	0.90 (0.58,1.38)	0.96 (0.63,1.46)	1.06 (0.69,1.63)
Stillbirth	0.95 (0.66,1.36)	0.90 (0.54,1.51)		2.42 (1.19,4.94)	2.59 (1.25,5.39)		1.22 (0.16,9.02)	1.29 (0.17,9.54)	
Low Apgar at 5 min	0.94 (0.78,1.13)	1.06 (0.83,1.36)		1.50 (0.99,2.27)	1.48 (0.96,2.29)		1.01 (0.38,2.65)	0.98 (0.37,2.60)	

(Table continued over)

Term (≥37 weeks) outcome

Term low Apgar score at 5 min	0.78 (0.60,1.01)	0.84 (0.59,1.20)		1.16 (0.66,2.02)	1.20 (0.69,2.10)		1.61 (0.60,4.32)	1.56 (0.58,4.22)	

	NT			Qld			NSW		
	Adjusted mean diff.[1] (95% CI)	Adjusted mean diff.[2] (95% CI)	Adjusted mean diff.[3] (95% CI)	Adjusted mean diff.[1] (95% CI)	Adjusted mean diff.[2] (95% CI)	Adjusted mean diff.[3] (95% CI)	Adjusted mean diff.[1] (95% CI)	Adjusted mean diff.[2] (95% CI)	Adjusted mean diff.[3] (95% CI)
Growth measure									
Term birth weight (g)	30.7 (14.0,47.4)	10.4 (−9.7,30.4)	−0.7 (−22.7,21.4)	−10.8 (−50.9,29.3)	−7.4 (−45.0,30.2)	−11.3 (−48.9,26.3)	22.2 (−48.0,92.4)	35.6 (−29.5,100.8)	52.3 (−19.1,123.7)
Term birth length (cm)	0.3 (0.1,0.4)	0.2 (0.1,0.4)		0.3 (0.1,0.5)	0.3 (0.1,0.6)				
Term head circumference (cm)	0.1 (0.0,0.2)	0.0 (−0.1,0.1)		0.0 (−0.1,0.2)	0.0 (−0.1,0.2)				

Table notes

The RR is the risk in the exposed group divided the risk in comparison group. The mean difference is the mean in the exposed group minus the mean in the comparison group.

1. RRs/Difference in means from Model 1: adjusted for year of birth, maternal age and mother's Aboriginal and Torres Strait Islander status (except NSW). Outcomes restricted to term babies included adjustment for gestational week. Year of birth and maternal age were treated as categorical covariates.
2. RRs/Difference in means from Model 2: adjusted for year of birth, maternal age, maternal Aboriginal and Torres Strait Islander status (except NSW), parity, marital status (except NSW), maternal country of birth, maternal BMI (except NT and NSW) and maternal ever smoked during pregnancy. Caesarean/assisted vaginal, emergency caesarean and postpartum haemorrhage were additionally adjusted for macrosomia. Preterm birth, still birth, low Apgar and growth measures were additionally adjusted for sex of baby. Outcomes restricted to term babies included adjustment for gestational week. Year of birth, maternal age and maternal BMI were treated as categorical covariates.
3. RR/Mean difference adjusted for year of birth, maternal age, maternal Aboriginal and Torres Strait Islander status (except NSW), parity, marital status (except NSW), maternal country of birth, maternal BMI (except NT and NSW) maternal ever smoke during pregnancy, and gestational diabetes. Caesarean/assisted vaginal were additionally adjusted for macrosomia. The analysis of term birthweight included adjustment for gestational week.

Appendix Table 3. Comparison of childhood development outcomes in exposed (lived in PFAS Management Areas since birth) and comparison populations: proportions and adjusted relative risks (RR)

	NT				Qld				NSW	
	Exposed % (n)	Comparison % (n)	Adjusted RR[1] (95% CI)	Adjusted RR[2] (95% CI)	Exposed % (n)	Comparison % (n)	Adjusted RR[1] (95% CI)	Adjusted RR[2] (95% CI)	Exposed % (n)	Comparison % (n)
Total sample	**121**	**1,850**			**90**	**2,215**			**12**	**413**
Vulnerable in:										
Physical health and wellbeing	21% (25)	15% (283)	1.08 (0.76,1.53)	0.91 (0.60,1.37)	21% (19)	17% (377)	1.17 (0.77,1.77)	1.18 (0.77,1.81)	0	9% (38)
Social competence	21% (26)	14% (263)	1.28 (0.89,1.84)	1.15 (0.78,1.70)	19% (17)	15% (343)	1.18 (0.75,1.87)	1.25 (0.79,1.98)	≤5	11% (47)
Emotional maturity	13% (16)	14% (248)	0.87 (0.55,1.38)	0.76 (0.46,1.25)	14% (13)	14% (307)	1.06 (0.63,1.77)	1.13 (0.67,1.90)	≤5	8% (33)
Language and cognitive skills (school-based)	21% (25)	15% (281)	0.93 (0.65,1.33)	0.82 (0.57,1.17)	18% (16)	14% (313)	1.19 (0.74,1.92)	1.09 (0.67,1.78)	≤5	5% (21)
Communication skills and general knowledge	12% (15)	12% (222)	0.78 (0.48,1.26)	0.77 (0.47,1.24)	27% (24)	13% (293)	1.80 (1.24,2.60)	1.91 (1.31,2.79)	0	7% (30)
Developmentally vulnerable on one or more domains	38% (46)	32% (596)	0.96 (0.77,1.20)	0.81 (0.64,1.03)	39% (35)	32% (717)	1.18 (0.90,1.54)	1.18 (0.91,1.55)	≤5	22% (92)

Table notes

The RR is the risk in the exposed group divided the risk in comparison group.

1. RRs from Model 1: adjusted for sex, Aboriginal and Torres Strait Islander status and Australian Early Development Census (AEDC) year.
2. RRs from Model 2: adjusted for sex, Aboriginal and Torres Strait Islander status, AEDC year, English as second language (except Qld and NSW), Australian Bureau of Statistics' Index of Relative Socioeconomic Disadvantage (IRSD) quintile, and remoteness. In NSW, the two lowest remoteness categories and the two highest IRSD quintiles were combined to avoid sparse categories.
3. Denominators for risks exclude missing values. The number of missing as a proportion of total data, n (%):
    - Physical health and wellbeing = NT: 2 (0.1), Qld: 1 (0.0)
    - Social competence = NT: 6 (0.3)
    - Emotional maturity = NT: 16 (0.8), Qld: 4 (0.2), NSW: 2 (0.5)
    - Language and cognitive skills (school-based) = NT: 6 (0.3), Qld: 1 (0.0)
    - Communication skills and general knowledge = Qld: 3 (0.1)
    - Developmentally vulnerable on one or more domains = NT: 7 (0.4), Qld: 6 (0.3)

Appendix Table 4. Comparison of childhood development outcomes in exposed (lived in Katherine, Oakey and Williamtown postcodes) and comparison populations: proportions and adjusted relative risks (RR)

	NT				Qld				NSW			
	Exposed % (n)	Comparison % (n)	Adjusted RR[1] (95% CI)	Adjusted RR[2] (95% CI)	Exposed % (n)	Comparison % (n)	Adjusted RR[1] (95% CI)	Adjusted RR[2] (95% CI)	Exposed % (n)	Comparison % (n)	Adjusted RR[1] (95% CI)	Adjusted RR[2] (95% CI)
Total sample	**1,471**	**1,824**			**467**	**2,212**			**174**	**413**		
Vulnerable in:												
Physical health and wellbeing	25% (372)	15% (277)	1.12 (0.97,1.28)	1.02 (0.87,1.21)	22% (101)	17% (377)	1.21 (1.00,1.48)	1.26 (1.03,1.53)	9% (16)	9% (38)	1.10 (0.63,1.92)	0.81 (0.43,1.54)
Social competence	24% (350)	14% (255)	1.19 (1.03,1.39)	1.08 (0.91,1.28)	16% (76)	16% (343)	1.02 (0.81,1.28)	1.06 (0.84,1.34)	9% (15)	11% (47)	0.82 (0.47,1.42)	0.63 (0.34,1.18)
Emotional maturity	20% (294)	13% (243)	1.06 (0.91,1.24)	0.93 (0.77,1.12)	15% (68)	14% (306)	1.01 (0.79,1.28)	1.06 (0.83,1.35)	9% (15)	8% (33)	1.13 (0.63,2.03)	0.95 (0.48,1.91)
Language and cognitive skills (school-based)	30% (440)	15% (276)	1.06 (0.93,1.20)	0.83 (0.72,0.95)	17% (81)	14% (313)	1.13 (0.90,1.41)	1.14 (0.91,1.44)	7% (13)	5% (21)	1.75 (0.90,3.39)	1.34 (0.59,3.06)
Communication skills and general knowledge	22% (328)	12% (216)	1.09 (0.93,1.27)	0.94 (0.79,1.13)	18% (86)	13% (293)	1.28 (1.03,1.60)	1.38 (1.11,1.72)	6% (11)	7% (30)	0.99 (0.51,1.94)	0.67 (0.32,1.44)
Developmentally vulnerable on one or more domains	48% (700)	32% (584)	1.02 (0.94,1.11)	0.89 (0.81,0.98)	37% (172)	32% (716)	1.10 (0.96,1.25)	1.14 (1.00,1.30)	25% (44)	22% (92)	1.24 (0.91,1.68)	1.06 (0.75,1.51)

The RR is the risk in the exposed group divided the risk in comparison group.

1. RRs from Model 1: adjusted for sex, Aboriginal and Torres Strait Islander status and Australian Early Development Census (AEDC) year.
2. RRs from Model 2: adjusted for sex, Aboriginal and Torres Strait Islander status, AEDC year, English as second language (except Qld and NSW), Australian Bureau of Statistics' Index of Relative Socioeconomic Disadvantage (IRSD) quintile, and remoteness. In NSW, the two lowest remoteness categories and the two highest IRSD quintiles were combined to avoid sparse categories.
3. Denominators for risks exclude missing values. The number of missing as a proportion of total data, n (%):
    - Physical health and wellbeing = NT: 12 (0.4%), Qld: 1 (0.0%)
    - Social competence = NT: 19 (0.6%)
    - Emotional maturity = NT: 40 (1.2%), Qld: 7 (0.3%), NSW: 2 (0.3%)
    - Language and cognitive skills (school-based) = NT: 18 (0.5%), Qld: 1 (0.0%)
    - Communication skills and general knowledge = NT: 1 (0.0%), Qld: 3 (0.1%)
    - Developmentally vulnerable on one or more domains = NT: 23 (0.7%), Qld: 8 (0.3%)

Appendix Table 5. Number of cases, person-years (PY) and crude rates for cancer and cause-specific mortality outcomes in relation to living in an exposure area, Northern Territory

NT	Exposed			Non-exposed		
	No.	PY(x10,000)	Crude rate (95%CI)	No.	PY(x10,000)	Crude rate (95% CI)
Cancer						
Candidate outcomes						
Head and neck	22	9.4	2.33 (1.46,3.47)	427	214.2	1.99 (1.81,2.19)
Oesophageal	7	9.5	0.74 (0.30,1.45)	102	214.5	0.48 (0.39,0.57)
Stomach	≤5	np	0.53 (0.17,1.16)	75	214.5	0.35 (0.28,0.44)
Colorectal	41	9.4	4.35 (3.12,5.84)	699	214.1	3.26 (3.03,3.51)
Liver	≤5	np	0.42 (0.12,1.01)	134	214.5	0.62 (0.52,0.74)
Pancreatic	≤5	np	0.42 (0.12,1.01)	104	214.5	0.48 (0.40,0.58)
Laryngeal	≤5	np	0.11 (0.00,0.49)	86	214.5	0.40 (0.32,0.49)
Lung	30	9.5	3.17 (2.14,4.47)	708	214.3	3.30 (3.07,3.55)
Bone	≤5	np	0.11 (0.00,0.49)	16	214.5	0.07 (0.04,0.12)
Breast	59	5.0	11.69 (8.90,14.97)	816	97.8	8.34 (7.78,8.93)
Uterine	9	5.1	1.76 (0.81,3.22)	91	98.4	0.92 (0.74,1.13)
Ovarian	≤5	np	0.98 (0.32,2.15)	70	98.5	0.71 (0.55,0.89)
Prostate	66	4.3	15.33 (11.86,19.38)	797	115.5	6.90 (6.43,7.39)
Testicular	≤5	np	0.46 (0.06,1.48)	100	115.9	0.86 (0.70,1.04)
Kidney	6	9.5	0.63 (0.23,1.31)	135	214.4	0.63 (0.53,0.74)
Bladder	8	9.5	0.85 (0.37,1.60)	98	214.5	0.46 (0.37,0.55)
Thyroid	≤5	np	0.53 (0.17,1.16)	119	214.4	0.55 (0.46,0.66)
Hodgkin lymphoma	≤5	np	0.11 (0.00,0.49)	39	214.5	0.18 (0.13,0.25)
Non-Hodgkin lymphoma	12	9.5	1.27 (0.66,2.15)	211	214.4	0.98 (0.86,1.12)
Leukaemia	≤5	np	0.32 (0.07,0.85)	143	214.4	0.67 (0.56,0.78)
Any above cancer	270	9.2	29.21 (25.83,32.85)	4,674	211.3	22.12 (21.49,22.76)
Any other cancer	103	9.4	11.01 (8.99,13.29)	1,656	213	7.78 (7.41,8.16)
Any cancer	358	9.1	39.13 (35.18,43.34)	6,110	209.8	29.12 (28.39,29.85)
Cause-specific mortality						
Candidate outcomes						
Chronic kidney disease	8	16.1	0.50 (0.21,0.94)	133	383.6	0.35 (0.29,0.41)
Coronary heart disease	40	16.1	2.49 (1.78,3.35)	833	383.6	2.17 (2.03,2.32)
Stroke	12	16.1	0.75 (0.39,1.26)	222	383.6	0.58 (0.51,0.66)
Liver disease	8	16.1	0.50 (0.21,0.94)	273	383.6	0.71 (0.63,0.80)
Control outcomes						
Infectious or parasitic	8	16.1	0.50 (0.21,0.94)	155	383.6	0.40 (0.34,0.47)
All external causes apart from self-harm	35	16.1	2.18 (1.52,2.99)	979	383.6	2.55 (2.39,2.72)
Intentional self-harm	30	16.1	1.87 (1.26,2.63)	503	383.6	1.31 (1.20,1.43)

Table notes

Sample sizes were approximately 150,100 individuals for cancer outcomes, and 152,200 for mortality outcomes.

Appendix Table 6. Number of cases, person-years (PY) and crude rates for cancer and cause-specific mortality outcomes in relation to living in an exposure area, Queensland

Qld	Exposed			Non-exposed		
	No.	PY(x10,000)	Crude rate (95%CI)	No.	PY(x10,000)	Crude rate (95% CI)
Cancer						
Candidate outcomes						
Head and neck	29	14.9	1.95 (1.31,2.76)	369	173.7	2.12 (1.91,2.35)
Oesophageal	12	14.9	0.81 (0.42,1.37)	92	174.1	0.53 (0.43,0.65)
Stomach	7	14.9	0.47 (0.19,0.92)	138	174	0.79 (0.67,0.93)
Colorectal	93	14.8	6.27 (5.06,7.65)	1,009	173.3	5.82 (5.47,6.19)
Liver	≤5	np	0.34 (0.11,0.74)	68	174.1	0.39 (0.30,0.49)
Pancreatic	17	14.9	1.14 (0.67,1.79)	150	174	0.86 (0.73,1.01)
Laryngeal	10	14.9	0.67 (0.32,1.19)	50	174	0.29 (0.21,0.38)
Lung	61	14.9	4.10 (3.14,5.23)	719	173.8	4.14 (3.84,4.45)
Bone	≤5	np	0.07 (0.00,0.31)	11	174.1	0.06 (0.03,0.11)
Breast	88	7.6	11.55 (9.26,14.16)	1,089	86.2	12.63 (11.89,13.40)
Uterine	18	7.7	2.34 (1.39,3.61)	159	87.1	1.82 (1.55,2.12)
Ovarian	7	7.7	0.91 (0.37,1.78)	99	87.2	1.14 (0.92,1.38)
Prostate	107	7.1	15.05 (12.33,18.10)	1,233	85.9	14.35 (13.56,15.17)
Testicular	6	7.2	0.84 (0.31,1.73)	73	86.7	0.84 (0.66,1.05)
Kidney	25	14.9	1.68 (1.09,2.44)	238	173.9	1.37 (1.20,1.55)
Bladder	12	14.9	0.81 (0.42,1.37)	182	173.9	1.05 (0.90,1.21)
Thyroid	22	14.9	1.48 (0.93,2.20)	181	173.9	1.04 (0.89,1.20)
Hodgkin lymphoma	≤5	np	0.13 (0.02,0.43)	27	174	0.16 (0.10,0.22)
Non-Hodgkin lymphoma	23	14.9	1.55 (0.98,2.28)	276	173.9	1.59 (1.41,1.78)
Leukaemia	23	14.9	1.55 (0.98,2.28)	243	173.9	1.40 (1.23,1.58)
Any above cancer	521	14.5	36.00(32.98,39.20)	5,934	169.3	35.05 (34.16,35.95)
Any other cancer	174	14.7	11.83 (10.13,13.68)	2,253	171.8	13.11 (12.58,13.66)
Any cancer	656	14.3	45.82 (42.38,49.43)	7,799	167.2	46.63 (45.60,47.68)
Cause-specific mortality						
Candidate outcomes						
Chronic kidney disease	10	23.1	0.43 (0.21,0.77)	114	318.2	0.36 (0.30,0.43)
Coronary heart disease	114	23.1	4.94 (4.08,5.91)	1,186	318.2	3.73 (3.52,3.94)
Stroke	27	23.1	1.17 (0.77,1.68)	372	318.2	1.17 (1.05,1.29)
Liver disease	15	23.1	0.65 (0.36,1.05)	128	318.2	0.40 (0.34,0.48)
Control outcomes						
Infectious or parasitic	10	23.1	0.43 (0.21,0.77)	77	318.2	0.24 (0.19,0.30)
All external causes apart from self-harm	72	23.1	3.12 (2.44,3.91)	536	318.2	1.68 (1.55,1.83)
Intentional self-harm	53	23.1	2.30 (1.72,2.98)	327	318.2	1.03 (0.92,1.14)

Table notes

Sample sizes were approximately 122,100 individuals for cancer outcomes, and 123,200 for mortality outcomes.

Appendix Table 7. Number of cases, person-years (PY) and crude rates for cancer and cause-specific mortality outcomes in relation to living in an exposure area, New South Wales

NSW	Exposed			Non-exposed		
	No.	PY(x10,000)	Crude rate (95%CI)	No.	PY(x10,000)	Crude rate (95% CI)
Cancer						
Candidate outcomes						
Head and neck	12	4.7	2.57 (1.33,4.35)	134	65.1	2.06 (1.72,2.43)
Oesophageal	≤5	np	0.43 (0.05,1.37)	44	65.3	0.67 (0.49,0.90)
Stomach	≤5	np	0.86 (0.23,2.03)	56	65.2	0.86 (0.65,1.11)
Colorectal	37	4.6	7.96 (5.61,10.85)	488	64.9	7.52 (6.87,8.21)
Liver	≤5	np	0.86 (0.23,2.03)	32	65.3	0.49 (0.34,0.68)
Pancreatic	13	4.7	2.78 (1.48,4.62)	78	65.3	1.20 (0.94,1.48)
Laryngeal	≤5	np	0.43 (0.05,1.37)	24	65.2	0.37 (0.24,0.54)
Lung	57	4.7	12.22 (9.26,15.72)	361	65.2	5.54 (4.98,6.13)
Bone	No observed events			≤5	np	0.05 (0.01,0.12)
Breast	43	2.3	18.48 (13.37,24.64)	536	32.1	16.69 (15.31,18.15)
Uterine	7	2.4	2.96 (1.19,5.81)	60	32.6	1.84 (1.40,2.35)
Ovarian	≤5	np	0.42 (0.01,1.97)	42	32.6	1.29 (0.93,1.72)
Prostate	49	2.3	21.61 (15.99,28.32)	656	32.1	20.42 (18.88,22.03)
Testicular	≤5	np	0.43 (0.01,2.03)	21	32.6	0.64 (0.40,0.97)
Kidney	16	4.7	3.43 (1.96,5.43)	94	65.2	1.44 (1.16,1.76)
Bladder	14	4.7	3.00 (1.64,4.90)	97	65.2	1.49 (1.21,1.81)
Thyroid	6	4.7	1.28 (0.47,2.65)	42	65.2	0.64 (0.46,0.86)
Hodgkin lymphoma	≤5	np	0.21 (0.01,1.00)	14	65.3	0.21 (0.12,0.35)
Non-Hodgkin lymphoma	16	4.7	3.43 (1.96,5.44)	155	65.1	2.38 (2.02,2.78)
Leukaemia	10	4.7	2.14 (1.03,3.80)	116	65.2	1.78 (1.47,2.13)
Any above cancer	263	4.5	58.76 (51.87,66.18)	2,811	63.1	44.56 (42.93,46.23)
Any other cancer	88	4.6	19.23 (15.42,23.57)	1,045	64.3	16.24 (15.27,17.25)
Any cancer	325	4.4	74.07 (66.23,82.46)	3,659	62.2	58.80 (56.91,60.72)
Cause-specific mortality						
Candidate outcomes						
Chronic kidney disease	7	6.4	1.09 (0.44,2.14)	49	101	0.49 (0.36,0.64)
Coronary heart disease	92	6.4	14.32 (11.54,17.47)	589	101	5.83 (5.37,6.32)
Stroke	29	6.4	4.51 (3.02,6.39)	208	101	2.06 (1.79,2.35)
Liver disease	6	6.4	0.93 (0.34,1.92)	46	101	0.46 (0.33,0.60)
Control outcomes						
Infectious or parasitic	10	6.4	1.56 (0.75,2.76)	51	101	0.50 (0.38,0.66)
All external causes apart from self-harm	17	6.4	2.65 (1.54,4.14)	181	101	1.79 (1.54,2.07)
Intentional self-harm	14	6.4	2.18 (1.19,3.56)	79	101	0.78 (0.62,0.97)

Table notes

Sample sizes were approximately 37,800 individuals for cancer outcomes, and 37,900 for mortality outcomes.

Appendix Table 8. Cancer and cause-specific mortality outcomes: observed (O) and expected (E) case numbers in the exposed populations (lived in PFAS Management Areas for ≥10 years), and SIRs

	Katherine, NT		Oakey, Qld		Williamtown, NSW	
	O\E cases	SIR (95% CI)	O\E cases	SIR (95% CI)	O\E cases	SIR (95% CI)
Cancer						
Head and neck	≤5\≤5	1.62 (0.33,4.74)	19\16	1.22 (0.74,1.91)	8\5	1.54 (0.67,3.04)
Oesophageal	No observed events		9\≤5	2.09 (0.95,3.96)	≤5\≤5	0.52 (0.01,2.91)
Stomach	No observed events		≤5\np	0.74 (0.24,1.74)	≤5\≤5	1.30 (0.27,3.81)
Colorectal	No observed events		57\47	1.20 (0.91,1.56)	15\20	0.74 (0.41,1.22)
Liver	No observed events		≤5\≤5	0.67 (0.08,2.40)	≤5\≤5	1.32 (0.16,4.76)
Pancreatic	≤5\≤5	1.96 (0.05,10.90)	8\7	1.13 (0.49,2.23)	7\≤5	2.00 (0.80,4.11)
Laryngeal	No observed events		≤5\≤5	1.77 (0.48,4.54)	No observed events	
Lung	≤5\≤5	0.93 (0.19,2.70)	32\34	0.93 (0.64,1.31)	32\14	2.25 (1.54,3.17)
Bone	No observed events		≤5\≤5	2.14 (0.05,11.93)	No observed events	
Breast	≤5\≤5	1.01 (0.28,2.59)	49\50	0.98 (0.72,1.29)	13\20	0.65 (0.34,1.11)
Uterine	No observed events		9\8	1.17 (0.53,2.22)	≤5\≤5	0.78 (0.09,2.81)
Ovarian	No observed events		≤5\≤5	0.66 (0.14,1.93)	≤5\≤5	0.62 (0.02,3.44)
Prostate	8\≤5	2.09 (0.90,4.12)	61\59	1.04 (0.79,1.33)	28\28	0.99 (0.65,1.42)
Testicular	No observed events		≤5\≤5	1.55 (0.42,3.98)	No observed events	
Kidney	No observed events		14\11	1.28 (0.70,2.16)	6\≤5	1.59 (0.58,3.47)
Bladder	No observed events		10\8	1.20 (0.58,2.21)	9\≤5	2.27 (1.04,4.31)
Thyroid	No observed events		11\8	1.45 (0.73,2.60)	≤5\≤5	1.93 (0.40,5.63)
Hodgkin lymphoma	No observed events		No observed events		No observed events	
Non-Hodgkin lymphoma	≤5\≤5	1.00 (0.03,5.56)	10\13	0.79 (0.38,1.45)	6\6	0.95 (0.35,2.07)
Leukaemia	No observed events		9\11	0.79 (0.36,1.50)	≤5\≤5	1.04 (0.34,2.44)
Any above cancer	20\22	0.92 (0.56,1.42)	288\272	1.06 (0.94,1.19)	125\112	1.12 (0.93,1.33)
Any other cancer	≤5\np	0.71 (0.23,1.66)	98\100	0.98 (0.80,1.19)	46\41	1.13 (0.83,1.51)
Any cancer	24\28	0.87 (0.55,1.29)	367\356	1.03 (0.93,1.14)	159\143	1.12 (0.95,1.30)
Cause-specific mortality						
Chronic kidney disease	≤5\≤5	1.30 (0.03,7.23)	7\6	1.19 (0.48,2.45)	≤5\≤5	2.06 (0.67,4.82)
Coronary heart disease	≤5\≤5	1.31 (0.43,3.06)	70\58	1.20 (0.94,1.52)	45\25	1.82 (1.32,2.43)
Stroke	≤5\≤5	1.85 (0.22,6.68)	17\19	0.91 (0.53,1.46)	11\10	1.10 (0.55,1.96)
Liver disease	≤5\≤5	1.34 (0.16,4.85)	6\6	1.03 (0.38,2.25)	≤5\≤5	0.52 (0.01,2.90)
Control outcomes						
Infectious or parasitic	No observed events		≤5\≤5	1.10 (0.30,2.82)	≤5\≤5	0.75 (0.09,2.71)
All external causes apart from self-harm	≤5\≤5	1.22 (0.40,2.84)	22\20	1.10 (0.69,1.67)	7\7	1.05 (0.42,2.17)
Intentional self-harm	≤5\≤5	0.43 (0.01,2.42)	20\12	1.61 (0.98,2.48)	≤5\≤5	0.87 (0.11,3.15)

Table notes

The standardised incidence ratio (SIR) is the ratio of the number of observed cancer cases in the exposed population to the number that would be observed ('expected') if the exposed population experienced the same cancer/death rates as the comparison population.

Appendix Table 9. Cancer and cause-specific mortality outcomes with a lag period of 5 years: observed (O) and expected (E) case numbers in the exposed populations, and SIRs

	Katherine, NT		Oakey, Qld		Williamtown, NSW	
	O\E cases	SIR (95% CI)	O\E cases	SIR (95% CI)	O\E cases	SIR (95% CI)
Cancer						
Head and neck	28\26	1.09 (0.72,1.57)	36\35	1.02 (0.71,1.41)	15\15	1.02 (0.57,1.69)
Oesophageal	10\6	1.55 (0.74,2.85)	13\9	1.47 (0.78,2.52)	6\5	1.11 (0.41,2.42)
Stomach	≤5\np	1.00 (0.32,2.32)	8\13	0.63 (0.27,1.24)	≤5\np	0.77 (0.25,1.79)
Colorectal	56\44	1.26 (0.95,1.64)	113\94	1.21 (0.99,1.45)	48\56	0.86 (0.63,1.14)
Liver	7\10	0.69 (0.28,1.43)	10\7	1.41 (0.68,2.60)	≤5\≤5	0.89 (0.24,2.27)
Pancreatic	≤5\np	0.60 (0.16,1.53)	19\14	1.32 (0.80,2.07)	25\9	2.67 (1.73,3.94)
Laryngeal	≤5\≤5	0.42 (0.05,1.52)	11\≤5	2.56 (1.28,4.58)	≤5\≤5	0.84 (0.10,3.03)
Lung	36\40	0.90 (0.63,1.25)	66\67	0.99 (0.77,1.26)	74\41	1.79 (1.40,2.24)
Bone	≤5\≤5	1.34 (0.03,7.45)	≤5\≤5	1.08 (0.03,6.04)	≤5\≤5	3.95 (0.10,22.02)
Breast	71\66	1.07 (0.84,1.35)	107\116	0.92 (0.76,1.12)	58\59	0.98 (0.74,1.27)
Uterine	9\7	1.23 (0.56,2.33)	20\15	1.31 (0.80,2.03)	9\7	1.29 (0.59,2.44)
Ovarian	≤5\≤5	1.18 (0.38,2.75)	9\10	0.93 (0.42,1.76)	≤5\≤5	0.64 (0.13,1.87)
Prostate	75\46	1.65 (1.30,2.06)	123\112	1.10 (0.91,1.31)	72\80	0.91 (0.71,1.14)
Testicular	≤5\np	0.94 (0.31,2.19)	9\8	1.15 (0.53,2.19)	≤5\≤5	0.49 (0.01,2.75)
Kidney	7\10	0.73 (0.29,1.50)	27\25	1.06 (0.70,1.55)	19\11	1.68 (1.01,2.63)
Bladder	9\≤5	1.83 (0.83,3.47)	16\16	1.02 (0.58,1.65)	18\11	1.60 (0.95,2.52)
Thyroid	10\9	1.05 (0.51,1.94)	30\21	1.42 (0.96,2.02)	7\≤5	1.54 (0.62,3.16)
Hodgkin lymphoma	≤5\≤5	0.37 (0.01,2.03)	≤5\≤5	0.98 (0.20,2.85)	≤5\≤5	0.64 (0.02,3.55)
Non-Hodgkin lymphoma	14\15	0.96 (0.53,1.62)	29\28	1.05 (0.70,1.51)	16\17	0.92 (0.52,1.49)
Leukaemia	7\9	0.77 (0.31,1.60)	27\24	1.13 (0.75,1.65)	16\14	1.18 (0.68,1.92)
Any above cancer	337\301	1.12 (1.00,1.25)	620\573	1.08 (1.00,1.17)	362\319	1.13 (1.02,1.26)
Any other cancer	133\104	1.28 (1.07,1.51)	219\226	0.97 (0.84,1.10)	131\117	1.12 (0.94,1.33)
Any cancer	450\389	1.16 (1.05,1.27)	792\763	1.04 (0.97,1.11)	458\410	1.12 (1.02,1.22)
Cause-specific mortality						
Chronic kidney disease	9\10	0.91 (0.41,1.72)	11\12	0.95 (0.48,1.70)	11\7	1.63 (0.81,2.92)
Coronary heart disease	61\46	1.31 (1.01,1.69)	140\108	1.30 (1.09,1.53)	122\68	1.78 (1.48,2.13)
Stroke	13\12	1.07 (0.57,1.83)	35\34	1.03 (0.71,1.43)	39\28	1.42 (1.01,1.93)
Liver disease	14\21	0.66 (0.36,1.10)	21\15	1.41 (0.87,2.15)	7\6	1.17 (0.47,2.41)
Control outcomes						
Infectious or parasitic	10\11	0.92 (0.44,1.70)	12\9	1.37 (0.71,2.40)	12\8	1.60 (0.82,2.79)
All external causes apart from self-harm	57\67	0.85 (0.64,1.10)	86\63	1.36 (1.09,1.69)	23\21	1.08 (0.69,1.62)
Intentional self-harm	42\39	1.08 (0.78,1.46)	64\43	1.49 (1.15,1.90)	20\9	2.25 (1.37,3.47)

Table notes

The standardised incidence ratio (SIR) is the ratio of the number of observed cancer cases in the exposed population to the number that would be observed ('expected') if the exposed population experienced the same cancer/death rates as the comparison population.

Appendix Table 10. Cancer and cause-specific mortality outcomes with a lag period of 15 years: observed (O) and expected (E) case numbers in the exposed populations, and SIRs

	Katherine, NT		Oakey, Qld		Williamtown, NSW	
	O\E cases	SIR (95% CI)	O\E cases	SIR (95% CI)	O\E cases	SIR (95% CI)
Cancer						
Head and neck	15\13	1.12 (0.63,1.84)	24\25	0.98 (0.62,1.45)	10\8	1.31 (0.63,2.41)
Oesophageal	≤5\≤5	1.32 (0.43,3.08)	11\6	1.72 (0.86,3.07)	≤5\≤5	0.33 (0.01,1.82)
Stomach	≤5\≤5	1.00 (0.21,2.92)	6\9	0.67 (0.24,1.45)	≤5\≤5	0.29 (0.01,1.62)
Colorectal	30\26	1.17 (0.79,1.67)	75\68	1.11 (0.87,1.39)	27\28	0.95 (0.63,1.39)
Liver	≤5\np	0.47 (0.10,1.38)	≤5\np	0.71 (0.19,1.83)	≤5\≤5	0.79 (0.10,2.84)
Pancreatic	≤5\≤5	0.52 (0.06,1.87)	13\11	1.24 (0.66,2.11)	8\6	1.42 (0.61,2.81)
Laryngeal	≤5\≤5	0.38 (0.01,2.10)	7\≤5	2.21 (0.89,4.55)	≤5\≤5	0.81 (0.02,4.50)
Lung	20\23	0.88 (0.54,1.36)	47\48	0.97 (0.72,1.29)	40\22	1.84 (1.31,2.50)
Bone	≤5\≤5	3.42 (0.09,19.05)	No observed events		No observed events	
Breast	41\35	1.18 (0.84,1.60)	76\81	0.94 (0.74,1.17)	29\32	0.91 (0.61,1.30)
Uterine	7\≤5	1.68 (0.67,3.45)	17\11	1.58 (0.92,2.53)	7\≤5	1.83 (0.74,3.77)
Ovarian	≤5\≤5	1.60 (0.33,4.69)	7\7	1.05 (0.42,2.17)	≤5\≤5	0.41 (0.01,2.27)
Prostate	51\27	1.88 (1.40,2.47)	91\82	1.11 (0.90,1.37)	34\41	0.83 (0.58,1.16)
Testicular	≤5\≤5	0.38 (0.01,2.14)	6\≤5	1.22 (0.45,2.65)	≤5\≤5	0.86 (0.02,4.82)
Kidney	≤5\np	0.71 (0.19,1.81)	19\18	1.05 (0.63,1.64)	12\6	1.89 (0.98,3.30)
Bladder	≤5\≤5	1.31 (0.36,3.35)	11\11	0.98 (0.49,1.75)	9\6	1.51 (0.69,2.87)
Thyroid	≤5\np	0.97 (0.32,2.27)	21\14	1.47 (0.91,2.24)	≤5\≤5	1.38 (0.38,3.54)
Hodgkin lymphoma	≤5\≤5	0.78 (0.02,4.36)	≤5\≤5	1.03 (0.13,3.73)	≤5\≤5	1.15 (0.03,6.38)
Non-Hodgkin lymphoma	10\8	1.30 (0.63,2.40)	19\20	0.97 (0.58,1.52)	11\9	1.21 (0.60,2.16)
Leukaemia	≤5\np	0.38 (0.05,1.39)	15\17	0.86 (0.48,1.42)	8\7	1.10 (0.48,2.18)
Any above cancer	191\166	1.15 (0.99,1.33)	430\409	1.05 (0.95,1.16)	184\170	1.09 (0.93,1.25)
Any other cancer	71\54	1.31 (1.02,1.65)	141\158	0.89 (0.75,1.06)	59\63	0.94 (0.72,1.21)
Any cancer	249\210	1.19 (1.04,1.34)	543\541	1.00 (0.92,1.09)	227\218	1.04 (0.91,1.18)
Cause-specific mortality						
Chronic kidney disease	6\7	0.91 (0.33,1.98)	9\8	1.07 (0.49,2.03)	6\≤5	1.65 (0.60,3.58)
Coronary heart disease	23\27	0.86 (0.54,1.29)	92\79	1.17 (0.94,1.43)	52\36	1.45 (1.08,1.90)
Stroke	6\7	0.81 (0.30,1.77)	23\25	0.93 (0.59,1.39)	20\15	1.36 (0.83,2.11)
Liver disease	≤5\np	0.41 (0.13,0.96)	10\12	0.86 (0.41,1.58)	≤5\≤5	1.37 (0.45,3.21)
Control outcomes						
Infectious or parasitic	≤5\np	0.81 (0.26,1.89)	8\6	1.27 (0.55,2.50)	≤5\≤5	0.63 (0.13,1.85)
All external causes apart from self-harm	21\33	0.64 (0.39,0.97)	53\41	1.29 (0.96,1.68)	13\12	1.12 (0.60,1.91)
Intentional self-harm	24\20	1.22 (0.78,1.81)	42\28	1.49 (1.07,2.01)	9\6	1.63 (0.75,3.10)

Table notes

The standardised incidence ratio (SIR) is the ratio of the number of observed cancer cases in the exposed population to the number that would be observed ('expected') if the exposed population experienced the same cancer/death rates as the comparison population.

Appendix Table 11. Cancer and cause-specific mortality outcomes: observed (O) and expected (E) case numbers in the exposed populations, and SIRs including adjustment for Aboriginal and Torres Strait Islander identification

	Katherine, NT		Oakey, Qld		Williamtown, NSW	
	O\E cases	SIR (95% CI)	O\E cases	SIR (95% CI)	O\E cases	SIR (95% CI)
Cancer						
Head and neck	22\20	1.12 (0.70,1.70)	29\30	0.96 (0.64,1.37)	12\10	1.17 (0.61,2.05)
Oesophageal	7\5	1.32 (0.53,2.72)	12\8	1.59 (0.82,2.78)	≤5\≤5	0.46 (0.06,1.68)
Stomach	≤5\≤5	1.24 (0.40,2.88)	7\11	0.64 (0.26,1.32)	≤5\≤5	0.86 (0.23,2.19)
Colorectal	41\37	1.11 (0.80,1.51)	93\81	1.15 (0.92,1.40)	37\40	0.93 (0.66,1.28)
Liver	≤5\np	0.47 (0.13,1.20)	≤5\np	0.76 (0.25,1.78)	≤5\≤5	1.18 (0.32,3.02)
Pancreatic	≤5\np	0.71 (0.19,1.82)	17\12	1.37 (0.80,2.20)	13\8	1.69 (0.90,2.89)
Laryngeal	≤5\≤5	0.26 (0.01,1.47)	10\≤5	2.70 (1.30,4.97)	≤5\≤5	1.18 (0.14,4.26)
Lung	30\33	0.91 (0.62,1.30)	61\57	1.07 (0.82,1.37)	57\30	1.88 (1.43,2.44)
Bone	≤5\≤5	1.99 (0.05,11.11)	≤5\≤5	1.20 (0.03,6.71)	No observed events	
Breast	59\51	1.15 (0.88,1.49)	88\99	0.89 (0.72,1.10)	43\45	0.96 (0.70,1.30)
Uterine	9\6	1.55 (0.71,2.94)	18\13	1.42 (0.84,2.24)	7\6	1.26 (0.51,2.59)
Ovarian	≤5\≤5	1.58 (0.51,3.68)	7\8	0.84 (0.34,1.72)	≤5\≤5	0.27 (0.01,1.53)
Prostate	66\38	1.73 (1.34,2.21)	107\96	1.11 (0.91,1.34)	49\58	0.84 (0.62,1.12)
Testicular	≤5\≤5	0.50 (0.06,1.79)	6\7	0.91 (0.33,1.98)	≤5\≤5	0.63 (0.02,3.51)
Kidney	6\8	0.77 (0.28,1.68)	25\22	1.14 (0.74,1.68)	16\9	1.88 (1.07,3.05)
Bladder	8\≤5	1.82 (0.79,3.59)	12\14	0.88 (0.45,1.53)	14\8	1.68 (0.92,2.83)
Thyroid	≤5\np	0.67 (0.22,1.56)	22\18	1.23 (0.77,1.86)	6\≤5	1.58 (0.58,3.45)
Hodgkin lymphoma	≤5\≤5	0.51 (0.01,2.82)	≤5\≤5	0.82 (0.10,2.96)	≤5\≤5	0.80 (0.02,4.46)
Non-Hodgkin lymphoma	12\11	1.06 (0.55,1.84)	23\24	0.97 (0.61,1.45)	16\13	1.24 (0.71,2.01)
Leukaemia	≤5\np	0.39 (0.08,1.15)	23\20	1.14 (0.72,1.71)	10\10	0.98 (0.47,1.81)
Any above cancer	270\241	1.12 (0.99,1.26)	521\490	1.06 (0.97,1.16)	263\236	1.11 (0.98,1.26)
Any other cancer	103\81	1.27 (1.03,1.54)	174\192	0.91 (0.78,1.05)	88\87	1.01 (0.81,1.25)
Any cancer	358\308	1.16 (1.04,1.29)	656\651	1.01 (0.93,1.09)	325\303	1.07 (0.96,1.20)
Cause-specific mortality						
Chronic kidney disease	8\9	0.91 (0.39,1.79)	10\10	0.96 (0.46,1.76)	7\≤5	1.43 (0.58,2.95)
Coronary heart disease	40\39	1.02 (0.73,1.40)	114\93	1.23 (1.01,1.48)	92\48	1.92 (1.55,2.36)
Stroke	12\11	1.09 (0.56,1.90)	27\30	0.91 (0.60,1.33)	29\19	1.49 (1.00,2.15)
Liver disease	8\17	0.47 (0.20,0.92)	15\14	1.09 (0.61,1.79)	6\≤5	1.22 (0.45,2.65)
Control outcomes						
Infectious or parasitic	8\9	0.93 (0.40,1.84)	10\8	1.28 (0.61,2.36)	10\6	1.81 (0.87,3.33)
All external causes apart from self-harm	35\51	0.69 (0.48,0.95)	72\52	1.38 (1.08,1.73)	17\16	1.07 (0.63,1.72)
Intentional self-harm	30\31	0.97 (0.66,1.39)	53\37	1.42 (1.06,1.85)	14\7	1.95 (1.07,3.27)

Table notes

The standardised incidence ratio (SIR) is the ratio of the number of observed cancer cases in the exposed population to the number that would be observed ('expected') if the exposed population experienced the same cancer/death rates as the comparison population.

Appendix Table 12. Cancer and cause-specific mortality outcomes, where a lag period of 10 years was applied to those already living in an exposure area at the inception of Medicare: observed (O) and expected (E) case numbers in the exposed populations, and SIRs

	Katherine, NT		Oakey, Qld		Williamtown, NSW	
	O\E cases	SIR (95% CI)	O\E cases	SIR (95% CI)	O\E cases	SIR (95% CI)
Cancer						
Head and neck	22\20	1.11 (0.69,1.68)	27\28	0.98 (0.64,1.42)	12\10	1.17 (0.61,2.05)
Oesophageal	7\5	1.33 (0.53,2.73)	12\7	1.69 (0.87,2.95)	≤5\≤5	0.47 (0.06,1.70)
Stomach	≤5\≤5	1.23 (0.40,2.86)	7\10	0.73 (0.29,1.51)	≤5\≤5	0.84 (0.23,2.16)
Colorectal	41\36	1.14 (0.82,1.54)	88\74	1.18 (0.95,1.46)	36\40	0.90 (0.63,1.25)
Liver	≤5\np	0.47 (0.13,1.20)	≤5\np	0.78 (0.25,1.81)	≤5\≤5	1.17 (0.32,2.99)
Pancreatic	≤5\np	0.74 (0.20,1.90)	15\11	1.31 (0.73,2.15)	13\8	1.60 (0.85,2.73)
Laryngeal	≤5\≤5	0.26 (0.01,1.46)	9\≤5	2.80 (1.28,5.32)	≤5\≤5	1.22 (0.15,4.42)
Lung	30\32	0.94 (0.64,1.35)	57\53	1.07 (0.81,1.39)	53\30	1.75 (1.31,2.29)
Bone	≤5\≤5	2.12 (0.05,11.83)	≤5\≤5	1.78 (0.05,9.94)	No observed events	
Breast	58\52	1.12 (0.85,1.45)	79\93	0.85 (0.67,1.06)	43\44	0.98 (0.71,1.32)
Uterine	9\6	1.56 (0.71,2.96)	17\12	1.40 (0.81,2.24)	7\5	1.33 (0.53,2.74)
Ovarian	≤5\≤5	1.65 (0.54,3.86)	6\7	0.83 (0.30,1.80)	≤5\≤5	0.28 (0.01,1.54)
Prostate	66\37	1.76 (1.36,2.24)	101\91	1.11 (0.91,1.35)	46\58	0.79 (0.58,1.06)
Testicular	≤5\≤5	0.51 (0.06,1.86)	6\6	1.00 (0.37,2.18)	≤5\≤5	0.69 (0.02,3.83)
Kidney	6\8	0.77 (0.28,1.67)	24\21	1.14 (0.73,1.69)	15\9	1.74 (0.98,2.87)
Bladder	8\≤5	2.02 (0.87,3.98)	12\12	1.00 (0.52,1.75)	13\8	1.56 (0.83,2.67)
Thyroid	≤5\np	0.66 (0.21,1.54)	21\18	1.19 (0.73,1.81)	6\≤5	1.72 (0.63,3.74)
Hodgkin lymphoma	≤5\≤5	0.49 (0.01,2.75)	≤5\≤5	0.83 (0.10,3.00)	≤5\≤5	0.83 (0.02,4.63)
Non-Hodgkin lymphoma	12\11	1.06 (0.55,1.85)	23\23	1.02 (0.65,1.53)	15\12	1.20 (0.67,1.99)
Leukaemia	≤5\np	0.41 (0.08,1.19)	21\19	1.10 (0.68,1.68)	9\10	0.88 (0.40,1.68)
Any above cancer	269\238	1.13 (1.00,1.27)	486\456	1.07 (0.97,1.17)	252\234	1.08 (0.95,1.22)
Any other cancer	102\80	1.28 (1.04,1.56)	160\178	0.90 (0.76,1.05)	85\86	0.99 (0.79,1.22)
Any cancer	356\304	1.17 (1.05,1.30)	610\605	1.01 (0.93,1.09)	311\300	1.04 (0.92,1.16)
Cause-specific mortality						
Chronic kidney disease	8\8	0.94 (0.41,1.86)	10\10	1.02 (0.49,1.88)	7\5	1.29 (0.52,2.67)
Coronary heart disease	40\37	1.07 (0.77,1.46)	103\85	1.21 (0.99,1.47)	88\49	1.79 (1.43,2.20)
Stroke	12\10	1.22 (0.63,2.13)	26\27	0.98 (0.64,1.43)	26\21	1.25 (0.81,1.83)
Liver disease	8\17	0.46 (0.20,0.91)	15\13	1.13 (0.63,1.87)	6\≤5	1.27 (0.46,2.76)
Control outcomes						
Infectious or parasitic	8\9	0.93 (0.40,1.83)	10\8	1.33 (0.64,2.44)	10\6	1.68 (0.80,3.09)
All external causes apart from self-harm	34\51	0.67 (0.46,0.94)	70\51	1.38 (1.08,1.75)	16\16	0.98 (0.56,1.59)
Intentional self-harm	30\31	0.98 (0.66,1.40)	50\36	1.40 (1.04,1.84)	14\7	1.95 (1.06,3.26)

Table notes

The standardised incidence ratio (SIR) is the ratio of the number of observed cancer cases in the exposed population to the number that would be observed ('expected') if the exposed population experienced the same cancer/death rates as the comparison population.

References

1. Geoscape Australia. Geo-coded National Address File (G-NAF) data product description. Available from: https://geoscape.com.au/wp-content/uploads/2021/08/G-NAF-Product-Description.pdf
2. Department of Health. Voluntary Indigenous Identifier (VII) Framework. A framework for the collection, release, use and publication of VII data. Canberra: Australian Government; 2020. 23p.
3. Bräunig J, Baduel C, Heffernan A, Rotander A, Donaldson E, Mueller JF. Fate and redistribution of perfluoroalkyl acids through AFFF-impacted groundwater. Sci Total Environ. 2017;596:360-8. doi: 10.1016/j.scitotenv.2017.04.095
4. Ahrens L. Polyfluoroalkyl compounds in the aquatic environment: a review of their occurrence and fate. J Environ Monit. 2011;13(1):20-31. doi: 10.1039/C0EM00373E
5. Giesy JP, Kannan K. Global distribution of perfluorooctane sulfonate in wildlife. Environ Sci Technol. 2001;35(7):1339-42. doi: 10.1021/es001834k
6. Buck RC, Franklin J, Berger U, Conder JM, Cousins IT, De Voogt P, et al. Perfluoroalkyl and polyfluoroalkyl substances in the environment: terminology, classification, and origins. Integr Environ Assess Manag. 2011;7(4):513-41. doi: 10.1002%2Fieam.258
7. De Silva AO, Armitage JM, Bruton TA, Dassuncao C, Heiger-Bernays W, Hu XC, et al. PFAS exposure pathways for humans and wildlife: a synthesis of current knowledge and key gaps in understanding. Environ Toxicol. 2021;40(3):631-57. doi: 10.1002/etc.4935
8. Sunderland EM, Hu XC, Dassuncao C, Tokranov AK, Wagner CC, Allen JG. A review of the pathways of human exposure to poly-and perfluoroalkyl substances (PFASs) and present understanding of health effects. J Expo Sci Environ Epidemiol. 2019;29(2):131-47. doi: 10.1038/s41370-018-0094-1
9. Jian J-M, Chen D, Han F-J, Guo Y, Zeng L, Lu X, et al. A short review on human exposure to and tissue distribution of per-and polyfluoroalkyl substances (PFASs). Sci Total Environ. 2018;636:1058-69. doi: 10.1016/j.scitotenv.2018.04.380
10. Li Y, Fletcher T, Mucs D, Scott K, Lindh CH, Tallving P, et al. Half-lives of PFOS, PFHxS and PFOA after end of exposure to contaminated drinking water. Occup Environ Med. 2018;75(1):46-51. doi: 10.1136/oemed-2017-104651
11. Olsen GW, Burris JM, Ehresman DJ, Froehlich JW, Seacat AM, Butenhoff JL, et al. Half-life of serum elimination of perfluorooctanesulfonate, perfluorohexanesulfonate, and perfluorooctanoate in retired fluorochemical production workers. Environ Health Perspect. 2007;115(9):1298-305. doi: 10.1289/ehp.10009
12. Steenland K, Fletcher T, Stein CR, Bartell SM, Darrow L, Lopez-Espinosa M-J, et al. Review: evolution of evidence on PFOA and health following the assessments of the C8 Science Panel. Environ Int. 2020;145:106125. doi: 10.1016/j.envint.2020.106125
13. Ingelido AM, Abballe A, Gemma S, Dellatte E, Iacovella N, De Angelis G, et al. Biomonitoring of perfluorinated compounds in adults exposed to contaminated drinking water in the Veneto region, Italy. Environ Int. 2018;110:149-59. doi: 10.1016/j.envint.2017.10.026
14. Dalla Zuanna T, Savitz DA, Barbieri G, Pitter G, Jeddi MZ, Daprà F, et al. The association between perfluoroalkyl substances and lipid profile in exposed pregnant women in the Veneto region, Italy. Ecotoxicol Environ Saf. 2021;209:111805. doi: 10.1016/j.ecoenv.2020.111805

15. Catelan D, Biggeri A, Russo F, Gregori D, Pitter G, Da Re F, et al. Exposure to perfluoroalkyl substances and mortality for COVID-19: a spatial ecological analysis in the Veneto Region (Italy). Int J Environ Res. 2021;18(5). doi: 10.3390/ijerph18052734

16. Di Nisio A, Sabovic I, Valente U, Tescari S, Rocca MS, Guidolin D, et al. Endocrine disruption of androgenic activity by perfluoroalkyl substances: clinical and experimental evidence. J Clin Endocrinol Metab. 2019;104(4):1259-71. doi: 10.1210/jc.2018-01855

17. Di Nisio A, Rocca MS, Sabovic I, De Rocco Ponce M, Corsini C, Guidolin D, et al. Perfluorooctanoic acid alters progesterone activity in human endometrial cells and induces reproductive alterations in young women. Chemosphere. 2020;242:125208. doi: 10.1016/j.chemosphere.2019.125208

18. Gyllenhammar I, Diderholm B, Gustafsson J, Berger U, Ridefelt P, Benskin JP, et al. Perfluoroalkyl acid levels in first-time mothers in relation to offspring weight gain and growth. Environ Int. 2018;111:191-9. doi: 10.1016/j.envint.2017.12.002

19. Miaz L, Plassmann M, Gyllenhammar I, Bignert A, Sandblom O, Lignell S, et al. Temporal trends of suspect- and target-per/polyfluoroalkyl substances (PFAS), extractable organic fluorine (EOF) and total fluorine (TF) in pooled serum from first-time mothers in Uppsala, Sweden, 1996-2017. Environ Sci Process Impacts. 2020;22:1071-83. doi: 10.1039/C9EM00502A

20. Lind PM, Salihovic S, Stubleski J, Kärrman A, Lind L. Changes in plasma levels of perfluoroalkyl substances (PFASs) are related to increase in carotid intima-media thickness over 10 years – a longitudinal study. J Environ Health. 2018;17(1):59. doi: 10.1186/s12940-018-0403-0

21. Li Y, Barregard L, Xu Y, Scott K, Pineda D, Lindh CH, et al. Associations between perfluoroalkyl substances and serum lipids in a Swedish adult population with contaminated drinking water. Environ Health. 2020;19(1):33. doi: 10.1186/s12940-020-00588-9

22. Xu Y, Li Y, Scott K, Lindh CH, Jakobsson K, Fletcher T, et al. Inflammatory bowel disease and biomarkers of gut inflammation and permeability in a community with high exposure to perfluoroalkyl substances through drinking water. Environ Res. 2020;181:108923. doi: 10.1016/j.envres.2019.108923

23. Xu Y, Jurkovic-Mlakar S, Lindh CH, Scott K, Fletcher T, Jakobsson K, et al. Associations between serum concentrations of perfluoroalkyl substances and DNA methylation in women exposed through drinking water: a pilot study in Ronneby, Sweden. Environ Int. 2020;145:106148. doi: 10.1016/j.envint.2020.106148

24. Xu Y, Jurkovic-Mlakar S, Li Y, Wahlberg K, Scott K, Pineda D, et al. Association between serum concentrations of perfluoroalkyl substances (PFAS) and expression of serum microRNAs in a cohort highly exposed to PFAS from drinking water. Environ Int. 2020;136:105446. doi: 10.1016/j.envint.2019.105446

25. Chang ET, Adami HO, Boffetta P, Wedner HJ, Mandel JS. A critical review of perfluorooctanoate and perfluorooctanesulfonate exposure and immunological health conditions in humans. Crit Rev Toxicol. 2016;46(4):279-331. doi: 10.3109/10408444.2015.1122573

26. Fragki S, Dirven H, Fletcher T, Grasl-Kraupp B, Bjerve Gützkow K, Hoogenboom R, et al. Systemic PFOS and PFOA exposure and disturbed lipid homeostasis in humans: what do we know and what not? Crit Rev Toxicol. 2021;51(2):141-64. doi: 10.1080/10408444.2021.1888073

27. Meneguzzi A, Fava C, Castelli M, Minuz P. Exposure to perfluoroalkyl chemicals and cardiovascular disease: experimental and epidemiological evidence. Front Endocrinol. 2021;12(850). doi: 10.3389/fendo.2021.706352

28. Priestly B. Literature review and report on the potential health effects of perfluroalkyl compounds, mainly perfluorooctane sulfonate (PFOS). Melbourne (AU): Monash University: 2017. 44p.

29. Rappazzo KM, Coffman E, Hines EP. Exposure to perfluorinated alkyl substances and health outcomes in children: a systematic review of the epidemiologic literature. Int J Environ Res Public Health. 2017;14(7):691. doi: 1660-4601/14/7/691

30. Schrenk D, Bignami M, Bodin L, Chipman JK, del Mazo J, Grasl-Kraupp B, et al. Risk to human health related to the presence of perfluoroalkyl substances in food. EFSA J. 2020;18(9):e06223. doi: 10.2903/j.efsa.2020.6223

31. Fenton SE, Ducatman A, Boobis A, DeWitt JC, Lau C, Ng C, et al. Per- and polyfluoroalkyl substance toxicity and human health review: current state of knowledge and strategies for informing future research. Environ Toxicol Chem. 2021;40(3):606-30. doi: 10.1002/etc.4890

32. Johnson PI, Sutton P, Atchley DS, Koustas E, Lam J, Sen S, et al. The Navigation Guide - evidence-based medicine meets environmental health: systematic review of human evidence for PFOA effects on fetal growth. Environ Health Perspect. 2014;122(10):1028-39. doi: 10.1289/ehp.1307893

33. Negri E, Metruccio F, Guercio V, Tosti L, Benfenati E, Bonzi R, et al. Exposure to PFOA and PFOS and fetal growth: a critical merging of toxicological and epidemiological data. Crit Rev Toxicol. 2017;47(6):482-508. doi: 10.1080/10408444.2016.1271972

34. Bach CC, Bech BH, Brix N, Nohr EA, Bonde JP, Henriksen TB. Perfluoroalkyl and polyfluoroalkyl substances and human fetal growth: a systematic review. Crit Rev Toxicol. 2015;45(1):53-67. doi: 10.3109/10408444.2014.952400

35. Bach CC, Vested A, Jørgensen KT, Bonde JPE, Henriksen TB, Toft G. Perfluoroalkyl and polyfluoroalkyl substances and measures of human fertility: a systematic review. Crit Rev Toxicol. 2016;46(9):735-55. doi: 10.1080/10408444.2016.1182117

36. Ding N HS, Randolph Jr JF, Loch-Caruso R, Park SK. Perfluoroalkyl and polyfluoroalkyl substances (PFAS) and their effects on the ovary. Hum Reprod. 2020;26(5):724-52. doi: 10.1093/humupd/dmaa018

37. Tarapore P, Ouyang B. Perfluoroalkyl chemicals and male reproductive health: do PFOA and PFOS increase risk for male infertility? Int J Environ Res Public Health. 2021;18(7):3794. doi: 1660-4601/18/7/3794

38. Agency for Toxic Substances and Disease Registry (ATDSR). Toxicological profile for perfluoroalkyls. Atlanta (GA): US Department of Health and Human Services, Public Health Service. 993p. doi: 10.15620/cdc:59198

39. Stanifer JW, Stapleton HM, Souma T, Wittmer A, Zhao X, Boulware EL. Perfluorinated chemicals as emerging environmental threats to kidney health. Clin J Am Soc Nephrol. 2018;13(10):1479. doi: 10.2215/CJN.04670418

40. Steenland K, Winquist A. PFAS and cancer, a scoping review of the epidemiologic evidence. Environ Res. 2021;194:110690. doi: 10.1016/j.envres.2020.110690

41. Schmitt HJ, Calloway EE, Sullivan D, Clausen WH, Tucker PG, Rayman J, et al. Chronic environmental contamination: a systematic review of psychological health consequences. Sci Total Environ. 2021;772:145025. doi: 10.1016/j.scitotenv.2021.145025

42. AECOM. Stage 2C environmental investigation - human health risk assessment – 2017 – Army Aviation Centre Oakey (AACO), Oakey QLD (Volume 1). Oakey (AU): AECOM; 2017. 214p.

43. AECOM. Off-site human health risk assessment December 2017 – RAAF Base Williamtown Stage 2B environmental investigation Defence. Williamtown (AU): AECOM; 2016. 1679p.

44. Coffey. RAAF Base Tindal human health risk assessment (HHRA). Victoria (AU): Coffey; 2018. 152p.

45. Ansul [Internet]. Data sheet: ansulite AFC-3DC 3% AFFF concentrate. Marinette (WI): Johnson Controls; 2018 [cited 2021 Jul 01]. Available from: https://docs.johnsoncontrols.com/specialhazards/api/khub/documents/5ue8e4Eok0Mxmvt2E_Axbg/content

46. Coffey. RAAF Base Tindal, detailed site investigation report. Victoria (AU): Coffey; 2018 Feb 12. 164p.

47. Parsons Brinckerhoff. Offsite risk assessment, PFOS and PFOA in groundwater: Stage 3 risk assessment and remediation design at Army Aviation Centre Oakey – remediation action plan – perfluorocarbons in groundwater. Victoria (AU); Parsons Brickerhoff; 2013 May 21. 56p.

48. GHD. Report for Transfield Services RAAF Williamtown, stage 1 – conceptual site model for AFFF contamination. Victoria (AU): GHD; 2013 Mar. 376p.

49. Kirk M, Smurthwaite K, Bräunig J, Trevenar S, D'Este C, Lucas R, et al. The PFAS Health Study: systematic literature review. Canberra (AU): The Australian National University; 2018. 256p.

50. Banwell C, Housen T, Smurthwaite K, Trevenar S, Walker L, Todd K, et al. The PFAS Health Study component one: Oakey, Williamtown and Katherine focus groups study. Canberra, (AU): The Australian National University; 2019. 62p.

51. Smurthwaite K, Lazarevic N, Bräunig J, Nilsson S, D'Este C, Lucas R, et al. The PFAS Health Study Component Two: Blood serum study of PFAS exposure, related risk factors and biochemical markers of health. Canberra (AU): The Australian National University; 2021.

52. Lazarevic N, Smurthwaite K, Trevenar S, D'Este C, Batterham P, Lane J, et al. The PFAS Health Study Component Three: Cross-sectional survey of self-reported physical and mental health outcomes and associations with blood serum PFAS. Canberra (AU): The Australian National University; 2021.

53. Korda RJ, Armstrong B, D'Este C, Smurthwaite K, Trevenar S, Lucas R, Miller A, Kirk M. The PFAS health study: data linkage study research protocol. Canberra (AU): Australian National University; 2019. 49p.

54. American Academy of Pediatrics Committee on Fetus and Newborn and American College of Obstetricians and Gynecologists Committee on Obstetric Practice. The Apgar score. Pediatr. 2015;136(4):819-22. doi: 10.1542/peds.2015-2651

55. Dobbins TA, Sullivan EA, Roberts CL, Simpson JM. Australian national birthweight percentiles by sex and gestational age, 1998-2007. Med J Aust. 2012;197(5):291-4. doi: 10.5694/mja11.11331

56. Zou G. A Modified Poisson regression approach to prospective studies with binary data. Am J Epidemiol. 2004;159(7):702-6. doi: 10.1093/aje/kwh090

57. Savitz DA, Stein CR, Bartell SM, Elston B, Gong J, Shin HM, et al. Perfluorooctanoic acid exposure and pregnancy outcome in a highly exposed community. Epidemiol. 2012;23(3):386-92. doi: 10.1097/EDE.0b013e31824cb93b

58. Savitz DA, Stein CR, Elston B, Wellenius GA, Bartell SM, Shin HM, et al. Relationship of perfluorooctanoic acid exposure to pregnancy outcome based on birth records in the mid-Ohio Valley. Environ Health Perspect. 2012;120(8):1201-7. doi: 10.1289/ehp.1104752

59. Arbuckle TE, Kubwabo C, Walker M, Davis K, Lalonde K, Kosarac I, et al. Umbilical cord blood levels of perfluoroalkyl acids and polybrominated flame retardants. Int J Hyg Environ Health. 2012;216(2):184-94. doi: 10.1016/j.ijheh.2012.03.004

60. Stein CR, Savitz DA, Dougan M. Serum levels of perfluorooctanoic acid and perfluorooctane sulfonate and pregnancy outcome. Am J Epidemiol. 2009;170(7):837-46. doi: 10.1093/aje/kwp212

61. Darrow LA, Stein CR, Steenland K. Serum perfluorooctanoic acid and perfluorooctane sulfonate concentrations in relation to birth outcomes in the mid-Ohio Valley, 2005-2010. Environ Health Perspect. 2013;121(10):1207-13. doi: 10.1289/ehp.1206372

62. Nolan LA, Nolan JM, Shofer FS, Rodway NV, Emmett EA. Congenital anomalies, labor/delivery complications, maternal risk factors and their relationship with perfluorooctanoic acid (PFOA)-contaminated public drinking water. Reprod Toxicol. 2010;29(2):147-55. doi: 10.1016/j.reprotox.2009.10.012

63. Starling AP, Engel SM, Richardson DB, Baird DD, Haug LS, Stuebe AM, et al. Perfluoroalkyl substances during pregnancy and validated preeclampsia among nulliparous women in the Norwegian Mother and Child Cohort Study. Am J Epidemiol. 2014;179(7):824-33. doi: 10.1093/aje/kwt432

64. Wikström S, Lindh CH, Shu H, Bornehag C-G. Early pregnancy serum levels of perfluoroalkyl substances and risk of preeclampsia in Swedish women. Sci Rep. 2019;9(1):9179. doi: 10.1038/s41598-019-45483-7

65. Borghese MM, Walker M, Helewa ME, Fraser WD, Arbuckle TE. Association of perfluoroalkyl substances with gestational hypertension and preeclampsia in the MIREC study. Environ Int. 2020;141:105789. doi: 10.1016/j.envint.2020.105789

66. Sullivan SD, Umans JG, Ratner R. Hypertension complicating diabetic pregnancies: pathophysiology, management, and controversies. J Clin Hypertens. 2011;13(4):275-84. doi: 10.1111/j.1751-7176.2011.00440.x

67. Roberts CL, Ford JB, Henderson-Smart DJ, Algert CS, Morris JM. Hypertensive disorders in pregnancy: a population-based study. Med J Aust. 2005;182(7):332-5. doi: 10.5694/j.1326-5377.2005.tb06730.x

68. Durmaz A, Komurcu N. Relationship between maternal characteristics and postpartum hemorrhage: a meta-analysis study. J Nurs Res. 2018;26(5):362-72. doi: 10.1097/jnr.0000000000000245

69. Fyfe EM, Thompson JMD, Anderson NH, Groom KM, McCowan LM. Maternal obesity and postpartum haemorrhage after vaginal and caesarean delivery among nulliparous women at term: a retrospective cohort study. BMC Pregnancy Childbirth. 2012;12(1):112. doi: 10.1186/1471-2393-12-112

70. Midasch O, Drexler H, Hart N, Beckmann MW, Angerer J. Transplacental exposure of neonates to perfluorooctanesulfonate and perfluorooctanoate: a pilot study. Int Arch Occup Environ Health. 2007;80(7):643-8. doi: 10.1007/s00420-006-0165-9

71. Rovira J, Martínez MÁ, Sharma RP, Espuis T, Nadal M, Kumar V, et al. Prenatal exposure to PFOS and PFOA in a pregnant women cohort of Catalonia, Spain. Environ Res. 2019;175:384-92. doi: 10.1016/j.envres.2019.05.040

72. Blake BE, Fenton SE. Early life exposure to per- and polyfluoroalkyl substances (PFAS) and latent health outcomes: A review including the placenta as a target tissue and possible

driver of peri- and postnatal effects. Toxicol. 2020;443:152565. doi: 10.1016/j.tox.2020.152565

73. Pijnenborg R, Anthony J, Davey DA, Rees A, Tiltman A, Vercruysse L, et al. Placental bed spiral arteries in the hypertensive disorders of pregnancy. Br J Obstet Gynaecol. 1991;98(7):648-55. doi: 10.1111/j.1471-0528.1991.tb13450.x

74. Cuffe JSM, Holland O, Salomon C, Rice GE, Perkins AV. Review: Placental derived biomarkers of pregnancy disorders. Placenta. 2017;54:104-10. doi: 10.1016/j.placenta.2017.01.119

75. Cao T, Qu A, Li Z, Wang W, Liu R, Wang X, et al. The relationship between maternal perfluoroalkylated substances exposure and low birth weight of offspring: a systematic review and meta-analysis. Environ Sci Pollut Res. 2021. doi: 10.1007/s11356-021-15061-4

76. Nolan LA, Nolan JM, Shofer FS, Rodway NV, Emmett EA. The relationship between birth weight, gestational age and perfluorooctanoic acid (PFOA)-contaminated public drinking water. Reprod Toxicol. 2009;27(3-4):231-8. doi: 10.1016/j.reprotox.2008.11.001

77. Grice MM, Alexander BH, Hoffbeck R, Kampa DM. Self-reported medical conditions in perfluorooctanesulfonyl fluoride manufacturing workers. J Occup Environ Med. 2007;49(7):722-9. doi: 10.1097/JOM.0b013e3180582043

78. Steenland K, Barry V, Savitz D. Serum perfluorooctanoic acid and birthweight: an updated meta-analysis with bias analysis. Epidemiol. 2018;29(6):765-76. doi: 10.1097/ede.0000000000000903

79. Fei C, McLaughlin JK, Tarone RE, Olsen J. Fetal growth indicators and perfluorinated chemicals: a study in the Danish National Birth Cohort. Am J Epidemiol. 2008;168(1):66-72. doi: 10.1093/aje/kwn095

80. Lauritzen HB, Larose TL, Øien T, Sandanger TM, Odland JØ, van de Bor M, et al. Maternal serum levels of perfluoroalkyl substances and organochlorines and indices of fetal growth: a Scandinavian case-cohort study. Pediatr Res. 2017;81(1):33-42. doi: 10.1038/pr.2016.187

81. Maisonet M, Terrell ML, McGeehin MA, Christensen KY, Holmes A, Calafat AM, et al. Maternal concentrations of polyfluoroalkyl compounds during pregnancy and fetal and postnatal growth in British girls. Environ Health Perspect. 2012;120(10):1432-7. doi: 10.1289/ehp.1003096

82. Kashino I, Sasaki S, Okada E, Matsuura H, Goudarzi H, Miyashita C, et al. Prenatal exposure to 11 perfluoroalkyl substances and fetal growth: A large-scale, prospective birth cohort study. Environ Int. 2020;136:105355. doi: 10.1016/j.envint.2019.105355

83. Bach CC, Bech BH, Nohr EA, Olsen J, Matthiesen NB, Bonefeld-Jørgensen EC, et al. Perfluoroalkyl acids in maternal serum and indices of fetal growth: the Aarhus birth cohort. Environ Health Perspect. 2016;124(6):848-54. doi: 10.1289/ehp.1510046

84. Manzano-Salgado CB, Casas M, Lopez-Espinosa MJ, Ballester F, Iñiguez C, Martinez D, et al. Prenatal exposure to perfluoroalkyl substances and birth outcomes in a Spanish birth cohort. Environ Int. 2017;108:278-84. doi: 10.1016/j.envint.2017.09.006

85. Lind DV, Priskorn L, Lassen TH, Nielsen F, Kyhl HB, Kristensen DM, et al. Prenatal exposure to perfluoroalkyl substances and anogenital distance at 3 months of age in a Danish mother-child cohort. Reprod Toxicol. 2017;68:200-6. doi: 10.1016/j.reprotox.2016.08.019

86. Chen M-H, Ha E-H, Wen T-W, Su Y-N, Lien G-W, Chen C-Y, et al. Perfluorinated compounds in umbilical cord blood and adverse birth outcomes. PLoS One. 2012;7(8):e42474-e. doi: 10.1371/journal.pone.0042474

87. Ouidir M, Buck Louis GM, Kanner J, Grantz KL, Zhang C, Sundaram R, et al. Association of maternal exposure to persistent organic pollutants in early pregnancy with fetal growth. JAMA Pediatr. 2020;174(2):149-61. doi: 10.1001/jamapediatrics.2019.5104

88. Costa O, Iñiguez C, Manzano-Salgado CB, Amiano P, Murcia M, Casas M, et al. First-trimester maternal concentrations of polyfluoroalkyl substances and fetal growth throughout pregnancy. Environ Int. 2019;130:104830. doi: 10.1016/j.envint.2019.05.024

89. Roberts CL, Bell JC, Ford JB, Morris JM. Monitoring the quality of maternity care: how well are labour and delivery events reported in population health data? Paediatr Perinat Epidemiol. 2009;23(2):144-52. doi: 10.1111/j.1365-3016.2008.00980.x

90. Taylor L, Pym M, Bajuk B, Sutton L, Travis S, Banks C. Part 8: Validation study NSW Midwives Data Collection 1998. NSW Public Health Bull Supplementary Series 2000;11(1):97-99. doi: 10.1071/NB00S11

91. Roberts CL, Bell JC, Ford JB, Hadfield RM, Algert CS, Morris JM. The accuracy of reporting of the hypertensive disorders of pregnancy in population health data. Hypertens Pregnancy. 2008;27(3):285-97. doi: 10.1080/10641950701826695

92. Liew Z, Luo J, Nohr EA, Bech BH, Bossi R, Arah OA, et al. Maternal plasma erfluoroalkyl substances and miscarriage: a nested case control study in the Danish National Birth Cohort. Environ Health Perspect. 2020;128(4):047007. doi: 10.1289/EHP6202

93. NSW Ministry of Health. Reporting of Aboriginality in perinatal data [Internet]. NSW Government; 2020 Nov 19 [cited 2021 Jun 6]. Available from: http://www.healthstats.nsw.gov.au/Indicator/dqi_era_pdc/dqi_era_pdc?&topic=Aboriginal%20health&topic1=topic_aboriginal_health&code=atsi%20dqi%20hlp

94. Australian Early Development Census: an Australian Government initiative [Internet]. Commonwealth of Australia; 2019 [cited 2021 Jul 01]. Available from: https://www.aedc.gov.au/

95. How to understand the AEDC results [Internet]. Commonwealth of Australia; 2019 [cited 2021 Jul 22]. Available from: https://www.aedc.gov.au/about-the-aedc/how-to-understand-the-aedc-results

96. About the AEDC domains [Internet]. Commonwealth of Australia; 2019 [cited 2021 Aug 26]. Available from: https://www.aedc.gov.au/about-the-aedc/about-the-aedc-domains

97. Jeddy Z, Hartman TJ, Taylor EV, Poteete C, Kordas K. Prenatal concentrations of perfluoroalkyl substances and early communication development in British girls. Early Hum Dev. 2017;109:15-20. doi: 10.1016/j.earlhumdev.2017.04.004

98. Vuong AM, Yolton K, Webster GM, Sjödin A, Calafat AM, Braun JM, et al. Prenatal polybrominated diphenyl ether and perfluoroalkyl substance exposures and executive function in school-age children. Environ Res. 2016;147:556-64. doi: 10.1016/j.envres.2016.01.008

99. Vuong AM, Yolton K, Wang Z, Xie C, Webster GM, Ye X, et al. Childhood perfluoroalkyl substance exposure and executive function in children at 8 years. Environ Int. 2018;119:212-9. doi: 10.1016/j.envint.2018.06.028

100. Vuong A, Yolton K, Xie C, Kim N, Braun J, Webster G, et al. Prenatal and childhood exposure to poly- and perfluoroalkyl substances (PFAS) and cognitive development in children at age 8 years. Environ Res. 2019;172. doi: 10.1016/j.envres.2019.02.025

101. Zhang H, Yolton K, Webster GM, Ye X, Calafat AM, Dietrich KN, et al. Prenatal and childhood perfluoroalkyl substances exposures and children's reading skills at ages 5 and 8 years. Environ Int. 2018;111:224-31. doi: 10.1016/j.envint.2017.11.031

102. Tanner EM, Hallerbäck MU, Wikström S, Lindh C, Kiviranta H, Gennings C, et al. Early prenatal exposure to suspected endocrine disruptor mixtures is associated with lower IQ at age seven. Environ Int. 2020;134:105185. doi: 10.1016/j.envint.2019.105185

103. Liew Z, Ritz B, Bach CC, Asarnow RF, Bech BH, Nohr EA, et al. Prenatal exposure to perfluoroalkyl substances and IQ scores at age 5; a study in the Danish National Birth Cohort. Environ Health Perspect. 2018;126(6):067004. doi: 10.1289/EHP2754

104. Wang Y, Rogan WJ, Chen HY, Chen PC, Su PH, Chen HY, et al. Prenatal exposure to perfluroalkyl substances and children's IQ: The Taiwan maternal and infant cohort study. Int J Hyg Environ Health. 2015;218(7):639-44. doi: 10.1016/j.ijheh.2015.07.002

105. Stein CR, Savitz DA, Bellinger DC. Perfluorooctanoate and neuropsychological outcomes in children. Epidemiol. 2013;24(4):590-9. doi: 10.1097/EDE.0b013e3182944432

106. Stein CR, Savitz DA, Bellinger DC. Perfluorooctanoate exposure in a highly exposed community and parent and teacher reports of behaviour in 6–12-year-old children. Paediatr Perinat Epidemiol. 2014;28(2):146-56. doi: 10.1111/ppe.12097

107. Fei C, Olsen J. Prenatal exposure to perfluorinated chemicals and behavioral or coordination problems at age 7 years. Environ Health Perspect. 2011;119(4):573-8. doi: 10.1289/ehp.1002026

108. Høyer BB, Ramlau-Hansen CH, Obel C, Pedersen HS, Hernik A, Ogniev V, et al. Pregnancy serum concentrations of perfluorinated alkyl substances and offspring behaviour and motor development at age 5–9 years – a prospective study. Environ Health. 2015;14(1):2. doi: 10.1186/1476-069X-14-2

109. Domazet SL, Jensen TK, Wedderkopp N, Nielsen F, Andersen LB, Grøntved A. Exposure to perfluoroalkylated substances (PFAS) in relation to fitness, physical activity, and adipokine levels in childhood: The European Youth Heart Study. Environ Res. 2020;191:110110. doi: 10.1016/j.envres.2020.110110

110. Niu J, Liang H, Tian Y, Yuan W, Xiao H, Hu H, et al. Prenatal plasma concentrations of perfluoroalkyl and polyfluoroalkyl substances and neuropsychological development in children at four years of age. Environ Health. 2019;18(1):53. doi: 10.1186/s12940-019-0493-3

111. Ghassabian A, Bell EM, Ma WL, Sundaram R, Kannan K, Buck Louis GM, et al. Concentrations of perfluoroalkyl substances and bisphenol A in newborn dried blood spots and the association with child behavior. Environm Pollut. 2018;243(Pt B):1629-36. doi: 10.1016/j.envpol.2018.09.107

112. Høyer BB, Bonde JP, Tøttenborg SS, Ramlau-Hansen CH, Lindh C, Pedersen HS, et al. Exposure to perfluoroalkyl substances during pregnancy and child behaviour at 5 to 9 years of age. Horm Behav. 2018;101:105-12. doi: 10.1016/j.yhbeh.2017.11.007

113. Oulhote Y, Steuerwald U, Debes F, Weihe P, Grandjean P. Behavioral difficulties in 7-year old children in relation to developmental exposure to perfluorinated alkyl substances. Environ Int. 2016;97:237-45. doi: 10.1016/j.envint.2016.09.015

114. Stein CR, Savitz DA. Serum perfluorinated compound concentration and attention deficit/hyperactivity disorder in children 5–18 years of age. Environ Health Perspect. 2011;119(10):1466-71. doi: 10.1289/ehp.1003538

115. Silburn S, Brinkman S, Ferguson-Hill S, Styles I, Walker R, Shepherd C. The Australian Early Development Index (AEDI) Indigenous Adaptation Study. 2009. Perth (AU): Curtin University of Technology and Telethon Institute for Child Health Research. 34p.

116. Gregory T, Brinkman, S. Exploring change in the Australian version of the Early Development Instrument: the estimation of a critical difference for the 'vulnerable', 'at risk' and 'on track' categories. Adelaide (AU): Telethon Kids Institute 2016.

117. AEDC Data Explorer (Katherine NT) [Internet]. Commonwealth of Australia; 2019 [cited 2021 Jul 01]. Available from: https://www.aedc.gov.au/data/data-explorer?id=135674

118. About Australian Cancer Database [Internet]. Australian Institute of Health and Welfare; 2021 [cited 2021 Jul 01]. Available from: https://www.aihw.gov.au/about-our-data/our-data-collections/australian-cancer-database/about-australian-cancer-database

119. About National Death Index [Internet]. Australian Institute of Health and Welfare; 2021 [cited 2021 Jul 01]. Available from: https://www.aihw.gov.au/about-our-data/our-data-collections/national-death-index/about-national-death-index

120. Nitika, Mishra SS, Lohani P. Lexis expansion: a prerequisite for analyzing time changing variables in a cohort study. Nepal J Epidemiol. 2017;7(2):681-4. doi: 10.3126/nje.v7i2.17974

121. Leonard RC, Kreckmann KH, Sakr CJ, Symons JM. Retrospective cohort mortality study of workers in a polymer production plant including a reference population of regional workers. Ann Epidemiol. 2008;18(1):15-22. doi: 10.1016/j.annepidem.2007.06.011

122. Steenland K, Zhao L, Winquist A. A cohort incidence study of workers exposed to perfluorooctanoic acid (PFOA). J Occup Environ Med. 2015;72(5):373-80. doi: 10.1136/oemed-2014-102364

123. Raleigh KK, Alexander BH, Olsen GW, Ramachandran G, Morey SZ, Church TR, et al. Mortality and cancer incidence in ammonium perfluorooctanoate production workers. J Occup Environ Med. 2014;71(7):500-6. doi: 10.1136/oemed-2014-102109

124. Vieira VM, Hoffman K, Shin HM, Weinberg JM, Webster TF, Fletcher T. Perfluorooctanoic acid exposure and cancer outcomes in a contaminated community: a geographic analysis. Environ Health Perspect. 2013;121(3):318-23. doi: 10.1289/ehp.1205829

125. Barry V, Winquist A, Steenland K. Perfluorooctanoic acid (PFOA) exposures and incident cancers among adults living near a chemical plant. Environ Health Perspect. 2013;121(11-12):1313-8. doi: 10.1289/ehp.1306615

126. Hardell E, Kärrman A, van Bavel B, Bao J, Carlberg M, Hardell L. Case–control study on perfluorinated alkyl acids (PFAAs) and the risk of prostate cancer. Environ Int. 2014;63:35-9. doi: 10.1016/j.envint.2013.10.005

127. Eriksen KT, Sørensen M, McLaughlin JK, Lipworth L, Tjønneland A, Overvad K, et al. Perfluorooctanoate and perfluorooctanesulfonate plasma levels and risk of cancer in the general Danish population. J Nat Cancer Inst. 2009;101(8):605-9. doi: 10.1093/jnci/djp041

128. Steenland K, Woskie S. Cohort mortality study of workers exposed to perfluorooctanoic acid. Am J Epidemiol. 2012;176(10):909-17. doi: 10.1093/aje/kws171

129. Gilliland FD, Mandel JS. Mortality among employees of a perfluorooctanoic acid production plant. J Occup Med. 1993;35(9):950-4. doi: 10.1097/00043764-199309000-00020

130. Lundin JI, Alexander BH, Olsen GW, Church TR. Ammonium perfluorooctanoate production and occupational mortality. Epidemiol. 2009;20(6):921-8. doi: 10.1097/EDE.0b013e3181b5f395

131. Shearer JJ, Callahan CL, Calafat AM, Huang W-Y, Jones RR, Sabbisetti VS, et al. Serum Concentrations of per- and polyfluoroalkyl substances and risk of renal cell carcinoma. J Nat Cancer Inst. 2020;113(5):580-7. doi: 10.1093/jnci/djaa143

132. Girardi P, Merler E. A mortality study on male subjects exposed to polyfluoroalkyl acids with high internal dose of perfluorooctanoic acid. Environ Res. 2019;179:108743. doi: 10.1016/j.envres.2019.108743

133. Alexander BH, Olsen GW, Burris JM, Mandel JH, Mandel JS. Mortality of employees of a perfluorooctanesulphonyl fluoride manufacturing facility. J Occup Environ Med 2003;60(10):722-9. doi: 10.1136/oem.60.10.722

134. Consonni D, Straif K, Symons JM, Tomenson JA, van Amelsvoort LGPM, Sleeuwenhoek A, et al. Cancer risk among tetrafluoroethylene synthesis and polymerization workers. Am J Epidemiol. 2013;178(3):350-8. doi: 10.1093/aje/kws588

135. Alexander BH, Olsen GW. Bladder cancer in perfluorooctanesulfonyl fluoride manufacturing workers. Ann Epidemiol. 2007;17(6):471-8. doi: 10.1016/j.annepidem.2007.01.036

136. National Toxicology Program (NTP). NTP technical report on the toxicology and carcinogenesis studies of perfluorooctanoic acid (CASRN 335-67-1) administered in feed to Sprague Dawley (Hsd:Sprague Dawley® SD®) rats. NTP Technical Report Series (598); 2020. doi: 10.22427/NTP-TR-598

137. Biegel LB, Hurtt ME, Frame SR, O'Connor JC, Cook JC. Mechanisms of extrahepatic tumor induction by peroxisome proliferators in male cd rats. Toxicol Sci. 2001;60(1):44-55. doi: 10.1093/toxsci/60.1.44

138. Sakr CJ, Symons JM, Kreckmann KH, Leonard RC. Ischaemic heart disease mortality study among workers with occupational exposure to ammonium perfluorooctanoate. J Occup Environ Med. 2009;66(10):699-703. doi: 10.1136/oem.2008.041582

139. Mattsson K, Rignell-Hydbom A, Holmberg S, Thelin A, Jönsson BA, Lindh CH, et al. Levels of perfluoroalkyl substances and risk of coronary heart disease: findings from a population-based longitudinal study. Environ Res. 2015;142:148-54. doi: 10.1016/j.envres.2015.06.033

140. Melzer D, Rice N, Depledge MH, Henley WE, Galloway TS. Association between serum perfluorooctanoic acid (PFOA) and thyroid disease in the US National Health and Nutrition Examination Survey. Environ Health Perspect. 2010;118(5):686-92. doi: 10.1289/ehp.0901584

141. Winquist A, Steenland K. Modeled PFOA exposure and coronary artery disease, hypertension, and high cholesterol in community and worker cohorts. Environ Health Persp. 2014;122(12):1299-305. doi: 10.1289/ehp.1307943

142. Shankar A, Xiao J, Ducatman A. Perfluorooctanoic acid and cardiovascular disease in US adults. Arch Int Med. 2012;172(18):1397-403. doi: 10.1001/archinternmed.2012.3393

143. Lind PM, Lind L. Are persistent organic pollutants linked to lipid abnormalities, atherosclerosis and cardiovascular disease? A review. J Lipid Atheroscler. 2020;9(3):334-48. doi: 10.12997/jla.2020.9.3.334

144. Fewell Z, Davey Smith G, Sterne JAC. The impact of residual and unmeasured confounding in epidemiologic studies: a simulation study. Am J Epidemiol. 2007;166(6):646-55. doi: 10.1093/aje/kwm165

145. Braveman P, Gottlieb L. The social determinants of health: it's time to consider the causes of the causes. Public Health Rep. 2014;129 (Suppl 2):19-31. doi: 10.1177/00333549141291S206

146. Savitz DA, Wellenius GA. Invited commentary: exposure biomarkers indicate more than just exposure. Am J Epidemiol. 2017;187(4):803-5. doi: 10.1093/aje/kwx333

147. National Statistical Service. A guide for data integration projects involving Commonwealth data for statistical and research purposes [Internet]; 2014 [cited 2021 Jul 01]. Available from: https://statistical-data-integration.govspace.gov.au/

148. Fellegi IP, Sunter AB. A theory for record linkage. J Am Stat Assoc. 1969;64(328):1183-210. doi: 10.1080/01621459.1969.10501049

149. Overview of AIHW data integration methods. Canberra (AU): Australian Institute of Health and Welfare; 2020.

150. Goldeberg A, Borthwick A. The Choicemaker 2 record matching system. ChoiceMaker Technologies, Inc; 2004 [cited 2021 Jul 01]. Available from: http://citeseerx.ist.psu.edu/viewdoc/download?doi=10.1.1.121.2691&rep=rep1&type=pdf

151. National Health and Medical Research Council, National Resource Management Ministerial Council. Australian drinking water guidelines. Paper 6 National water quality management strategy. Canberra (AU): Australian Governemnt, 2021. Available from: https://www.nhmrc.gov.au/about-us/publications/australian-drinking-water-guidelines.

152. Power and Water Corporation [Internet]. PFAS monitoring: Power and Water; 2020 [cited 2021 Jul 01]. Available from: https://www.powerwater.com.au/about/what-we-do/water-supply/drinking-water-quality/pfas