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Relative risks of childhood developmental vulnerabilities in three Australian communities with exposure to per- and polyfluoroalkyl substances: data linkage study

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Abstract

Background
Aqueous film forming foams (AFFF) containing per- and polyfluoroalkyl substances (PFAS) caused local environmental contamination in three Australian residential areas: Katherine in the Northern Territory (NT), Oakey in Queensland (Qld) and Williamtown in New South Wales (NSW). We examined whether children who lived in these areas had higher risks of developmental vulnerabilities than children who lived in comparison areas without known contamination.

Methods
All children identified in the Medicare Enrolment File—a consumer directory for Australia's universal healthcare insurance scheme—who ever lived in exposure areas, and a sample of children who ever lived in selected comparison areas, were linked to the Australian Early Development Census (AEDC). The AEDC data were available from four cycles: 2009, 2012, 2015 and 2018. For each exposure area, we estimated relative risks (RRs) of developmental vulnerability on each of five AEDC domains and a summary measure, adjusting for sociodemographic characteristics and other potential confounders.

Findings
We included 2,429 children from the NT, 2,592 from Qld and 510 from NSW. We observed lower risk of developmental vulnerability in the Communication skills and general knowledge domain in Katherine (RR = 0.74, 95% confidence interval (CI) 0.57 to 0.97), and higher risks of developmental vulnerability in the same domain (RR = 1.49, 95% CI 1.18 to 1.87) and in the Physical health and wellbeing domain in Oakey (RR = 1.31, 95% CI 1.06 to 1.61). Risks of developmental vulnerabilities on other domains were not different from those in the relevant comparison areas or were uncertain due to small numbers of events.

Conclusion
There was inadequate evidence for increased risks of developmental vulnerabilities in children who ever lived in three PFAS-affected areas in Australia.

Keywords
PFAS; child health; developmental vulnerability; neurodevelopment; firefighting foams

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Background

Per- and polyfluoroalkyl substances (PFAS) are a group of man-made chemicals found in industrial and consumer products. PFAS are persistent organic pollutants and their movement through water and land has led to global contamination [1–3]. PFAS are resistant to environmental and biological degradation. The half-lives of PFAS in the human body are estimated to be 2–6 years for perfluorooctane sulfonic acid (PFOS) and 3–9 years for perfluorohexane sulfonic acid (PFHxS) [4, 5]. There is significant public concern about PFAS contamination as exposure has been linked to potential health effects in all age groups.

Pollution from PFAS production facilities or use of firefighting foams can lead to local populations facing considerable exposure. In Australia, aqueous film forming foams (AFFF) were used during training and fire emergencies on military bases since the 1970s. The AFFF used by the Australian Department of Defence contained PFOS and PFHxS as the main active ingredients. While foams with this particular formulation were phased out in the 2000s, PFAS remain detectable in water sources and land surrounding the bases [6–8]. The affected residential areas in Australia include Katherine in the Northern Territory (NT), Williamtown in New South Wales (NSW) and Oakey in Queensland (Qld).

The main sources of human exposure in these areas have been identified as the consumption of local bore water, or town water in the case of Katherine (both are extracted from groundwater contaminated with PFAS), and produce grown locally. Additionally, recreational use of local waterways and the consumption of fish and crustaceans from these waterways are other potential exposure pathways [6, 7, 9].

In 2016–2019, residents in these exposure areas had higher mean serum concentrations of PFOS and PFHxS than people living in selected comparison areas without known contamination, but residents of both areas had similar levels of perfluorooctanoic acid (PFOA). The geometric means of serum PFAS in Katherine, Williamtown and Oakey ranged from: 4.9 to 6.6 ng/ml for PFOS, 2.9 to 3.7 ng/ml for PFHxS and 1.3 to 1.8 ng/ml for PFOA. In the corresponding comparison communities of Alice Springs in the NT, Kiama and Shellharbour in NSW, and Dalby in Qld, the geometric means of serum PFAS (in adults $>$15 years) ranged from: 2.5 to 3.3 ng/ml for PFOS, 0.7 to 1.2 ng/ml for PFHxS and 1.2 to 1.4 ng/ml for PFOA [10]. Internationally, PFAS serum concentrations in the Australian exposure areas are comparable to those reported in three US communities [11–13], but much lower than residents in Ronneby, Sweden, also affected by AFFF use [14]. Measurements made in 2016–2019 provide some context for the levels of exposure, but may not reflect long-term cumulative exposure.

Exposures to environmental chemicals are increasingly thought to play a role in neurodevelopmental toxicity. The developing brain and nervous system are sensitive to toxic chemicals, and exposure during windows of developmental vulnerability in utero, infancy or early childhood may affect health throughout childhood and later in life [15, 16]. There is substantial evidence that industrial chemicals widely distributed in the environment are neurodevelopmental toxicants, including lead, methylmercury, arsenic, polychlorinated biphenyls and toluene [17]. Less is known about the role of PFAS.

Epidemiological studies have examined the associations between PFAS and measures of childhood neurodevelopment, including attention, behaviour, motor activity, learning and cognition. These studies were conducted among children living in highly exposed areas due to PFOA pollution from a local facility (C8 Health Project [18]) or children in the general population with background PFAS levels. Reviews suggest that the findings across studies are inconsistent—some studies observed positive associations, while others saw negative or null associations. Thus the evidence is inconclusive [19–22].

The aim of this study was to examine whether the risks of developmental vulnerability—as measured in the Australian Early Development Census (AEDC)—were higher in school-age children who had lived in one of the three PFAS exposure areas in Australia than in comparison areas without known contamination.

Methods

Data sources and study population

We selected the study populations based on their recorded addresses in the Medicare Enrolment File (MEF) (1983–2019). The MEF is a consumer directory for Medicare, Australia's universal health insurance scheme. It is estimated that 99% of children resident in Australia are enrolled by 12 months of age [23]. The MEF collects demographic information as well as address history from every consumer.

For our study, we selected all children with a recorded address in any Katherine, Williamtown or Oakey postcode (i.e. 0850, 0851, 0852, 0853, 2314, 2318, 4401), and a sample of children with an address in any comparison area postcode (see below), between July 2002 and December 2017, and at least five months prior to participating in any AEDC cycle (2009, 2012, 2015, 2018).

We defined the exposed populations in two ways. In the main analysis, we defined exposed children as those who had lived in the specific boundaries of exposure within Katherine, Williamtown and Oakey. These boundaries were defined by the Australian Department of Defence based on environmental sampling of land (sediment and soil) and water (groundwater and surface water) [6–8]. We extracted all street addresses from the Geocoded National Address File (G-NAF) [24] that fell inside these defined boundaries of exposure to compile a list of addresses for the purpose of data linkage.

In a second definition of exposure (sensitivity analysis), we expanded the definition of exposure areas to include all children who had lived in any Katherine, Williamtown or Oakey postcode, under the assumption that the nature of the contamination was more diffuse than the defined exposure boundaries.

We chose comparison areas (postcodes) on the basis that they had similar sociodemographic profiles to the exposure areas according to the Australian Bureau of Statistics' Census of Population and Housing data. We chose as many postcodes as necessary to obtain comparison populations that were approximately four times the size of the relevant exposed populations. Comparison children were sampled from the following postcodes and frequency-matched at a 4:1 ratio to the exposed children on sex, age, year of first living in an exposure or comparison area, and Aboriginal and Torres Strait Islander status; for Katherine: 0800, 0828, 0829, 0835, 0836, 0837, 0838, 0840, 0841, 0845, 0846, 0880, 0886; for Oakey: 4311, 4371, 4372, 4373, 4610; and for Williamtown: 2334, 2335, 2864, 2865, 2866, 2867, 2477. Figure 1 shows the locations of Katherine, Oakey and Williamtown, and the postcodes of their corresponding comparison areas.

The AEDC is a national census conducted every three years on individual children around Australia who are in their first year of full-time school. Therefore, we examined children who were exposed in the early childhood period prior to starting school, usually at the age of 5–6 years (or earlier for those who started school at an earlier age).

The AEDC collects demographic information and data on childhood development based on teacher ratings on a questionnaire adapted from the Canadian Early Development Instrument [25]. Teachers use their knowledge and observations of each child in their class to answer approximately 100 items across five key areas referred to as 'domains' (see Outcomes). A domain score is then calculated for each domain by combining information across all specific domain items. All teachers are provided with guidance, training and support materials to ensure they understand the AEDC. The AEDC data were available from four cycles: 2009, 2012, 2015 and 2018.

We did not include data from children if they were identified with special needs, as the centrally-derived cut-off scores for developmental vulnerability have not been validated or made available in the AEDC for children with special needs. Children with special needs are not included within AEDC domain indicators and categories because of the already identified substantial developmental needs of this group. We also excluded data from children who did not have at least one domain score due to insufficient valid responses by their teacher, or who had temporally inconsistent dates (such as where the date of birth on the AEDC was after the date of enrolment on the MEF).

The Australian Institute of Health and Welfare (AIHW) performed all data linkages. We obtained ethics approval for the study from the following institutions: AIHW (EO2019-3-1048), Australian National University (ANU) Human Research Ethics Committee (2019/565), NT Department of Health and Menzies School of Health Research Ethics Committee (2019–3472).

Variables

Outcomes

We examined six binary outcomes: developmentally vulnerable (or not) for each of the five AEDC domains and developmentally vulnerable on one or more domain(s). The five domains are: Physical health and wellbeing, Social competence, Emotional maturity, Language and cognitive skills (school-based), and Communication skills and general knowledge. In the first AEDC data collection cycle, a series of cut-off scores was established for each of the five domains: children falling below the 10th percentile were categorised as 'developmentally vulnerable', children falling between the 10th and 25th percentile were categorised as 'developmentally at risk' and all other children were categorised as 'developmentally on track'. Cut-off scores were defined based on age to account for age variations of children in their first year of full-time school [26].

Exposure and other variables

We classified children as exposed or comparison if their recorded address in the MEF was in an exposure or comparison area respectively. All covariates (see below) were as recorded in the AEDC.

Statistical analysis

We analysed all outcomes separately by exposure area. We used a modified Poisson approach with robust estimation of error variance to estimate relative risks (RR) and 95% confidence intervals (CI) for all outcomes [27].

We decided *a priori* not to pool study results across exposure areas as environmental risk assessments indicated that the nature and sources of exposure (e.g. contaminated ground water vs. contaminated town water) were different between the three exposure areas over the study period.

We specified two models for each outcome. In the first model we made adjustments for sex, Aboriginal and Torres Strait Islander status and AEDC collection year; we refer to this as a 'minimally-adjusted model'.

In the second model, which we refer to as a 'fully-adjusted model', we additionally adjusted for the following variables: English as a second language; socioeconomic disadvantage as measured by the Australian Bureau of Statistics' Index of Relative Socioeconomic Disadvantage (IRSD) quintile based on Statistical Area Level 1; and geographical remoteness as measured by the Accessibility and Remoteness Index of Australia 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.

In separate sensitivity analyses, we 1) limited the exposed populations to children who had lived in the exposure areas from birth with no record of moving out of the area, 2) expanded the exposed populations to children who had lived in Katherine, Oakey or Williamtown postcodes, rather than based on the specific boundaries defined by the Australian Department of Defence.

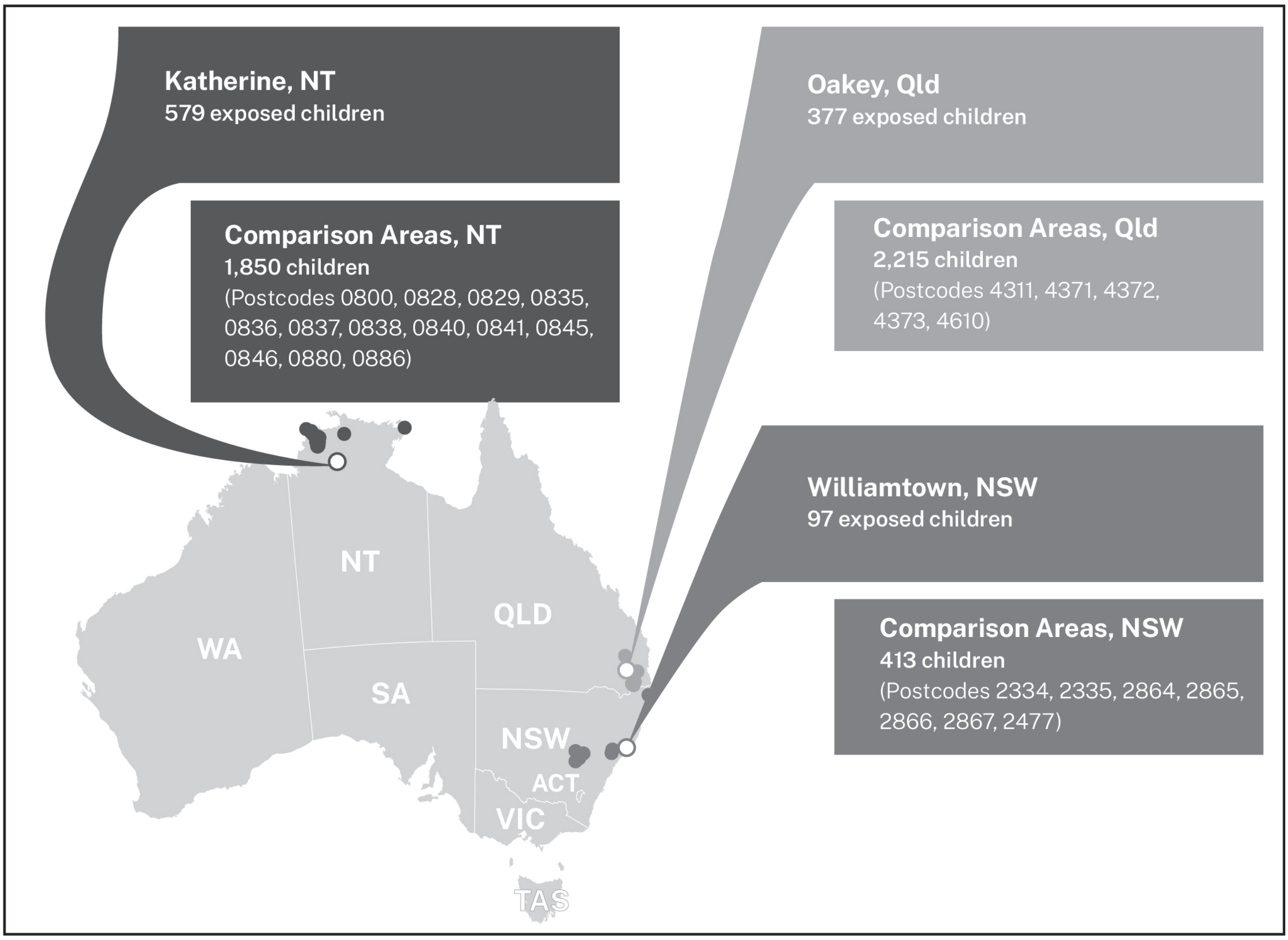
All data analyses and graphs were generated using SAS software (version 9.4).

Results

Description of the study population

After exclusions, we included 5,531 children in the main analysis where the largest sample was in the NT (579 in Katherine vs. 1,850 comparison), followed by Qld (377 in Oakey vs. 2,215 comparison) and NSW (97 in Williamtown vs. 413 comparison). A flow diagram of sample selection is shown in Figure 2.

Figure 1: Australian map showing locations of Katherine, Oakey and Williamtown and postcodes of their corresponding comparison areas



Each pair of exposed and comparison populations was similar in terms of demographic characteristics, including sex and age at AEDC measurement. The exposed and comparison populations in Qld and NSW were reasonably well-matched on remoteness category and area socioeconomic disadvantage (IRSD quintile). However, there was a higher proportion of Aboriginal and Torres Strait Islander children in Katherine, and of children living in remote areas and areas of most socioeconomic disadvantage, compared to its comparison population. Sample sizes and sociodemographic characteristics by area and exposure status can be seen in Table 1.

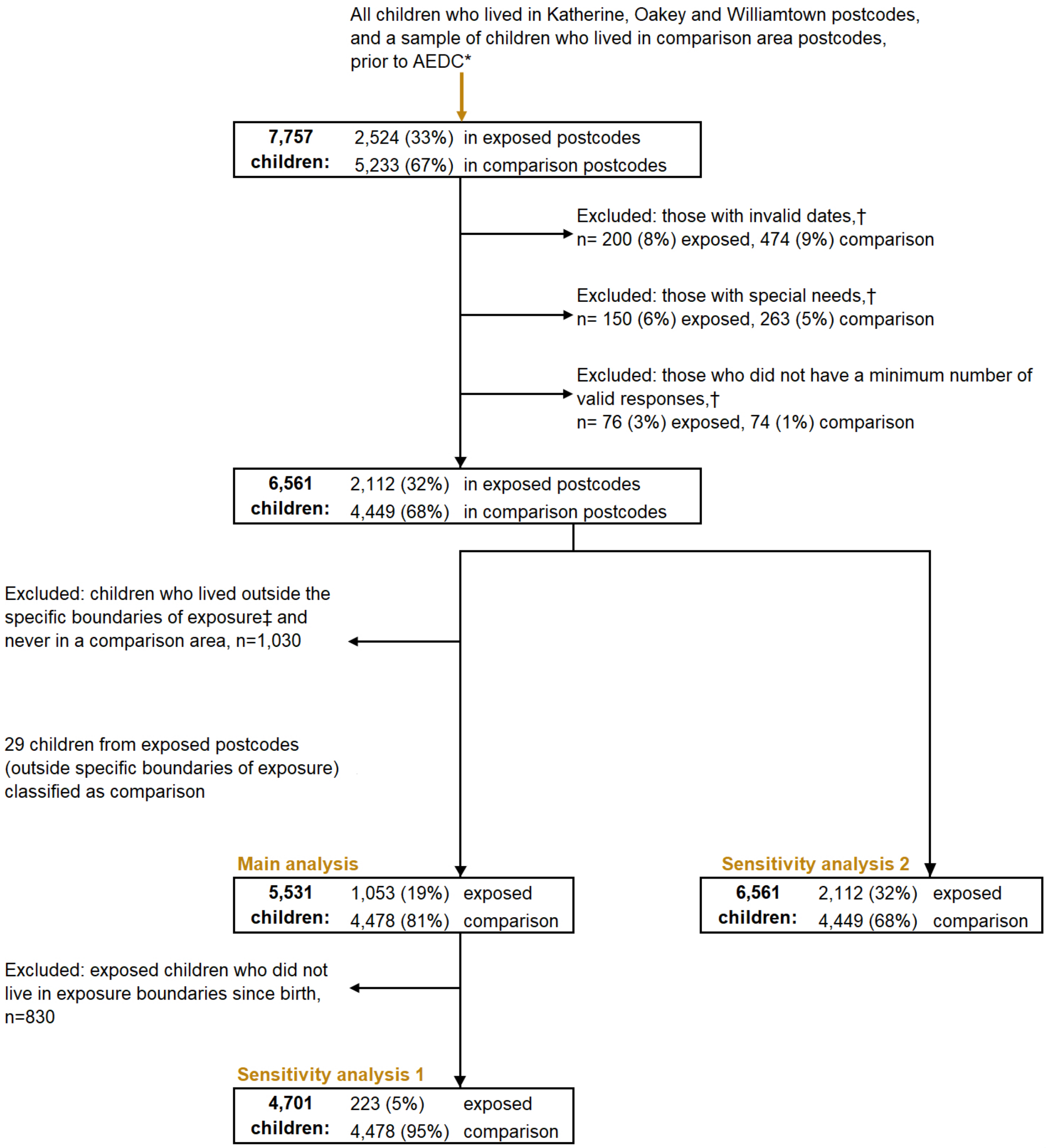
Childhood developmental outcomes in relation to living in exposure areas

The proportions of children in the exposed and comparison populations who were developmentally vulnerable in each domain, and adjusted RRs are shown in Table 2; a forest plot of adjusted RRs is shown in Figure 3.

In the NT, the proportions of children who were developmentally vulnerable in any domain 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 percentiles, all else being equal. After adjusting for sociodemographic characteristics, we estimated a 26% decreased risk of developmental vulnerability in the Communication skills and general knowledge domain among children who had lived in Katherine (fully-adjusted RR = 0.74, 95% CI 0.57 to 0.97). While the RR was also below 1 for the Language and cognitive skills (school-based) domain, the evidence pointing to a lower risk was uncertain (fully-adjusted RR = 0.83, 95% CI 0.68 to 1.01). In the remaining three domains, interval estimates suggested minimal or no differences in risks between children in Katherine compared to its comparison areas. Overall, there was a 14% reduced risk of developmental vulnerability on one or more domain(s) among children in Katherine (fully-adjusted RR = 0.86, 95% CI 0.75 to 0.98). Note that findings with respect to the number of domains were not necessarily independent of findings with respect to any unique domain.

In Qld, the proportions of children who were developmentally vulnerable in each domain 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: there was a 31% higher risk

Figure 2: Flow diagram of sample selection



* All children in the Medicare Enrolment File with a recorded address in any Katherine, Williamtown or Oakey postcode, and a sample of children with an address in any comparison area postcode (see Methods), between July 2002-December 2017, and at least five months prior to participating in any Australian Early Development Census (AEDC) cycle (2009, 2012, 2015, 2018).

† Exclusions not mutually exclusive.
‡ As defined by the Australian Department of Defence (see Methods).

Table 1: Sociodemographic characteristics of study populations for the main analysis, NT, Qld and NSW (2002–2018)

Characteristic	NT		Qld		NSW	
	Exposed n (%)	Comparison n (%)	Exposed n (%)	Comparison n (%)	Exposed n (%)	Comparison n (%)
Total sample	**A579**	**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 at 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 and above	18 (3)	98 (5)	11 (3)	40 (2)	0†	6 (1)
Age first lived in exposure 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)
3–6 and above	102 (18)	304 (16)	61 (16)	409 (18)	11 (11)	75 (18)
Age at AEDC measurement						
4y 7m–5y 0m	70 (12)	292 (16)	47 (12)	306 (14)	6 (6)	24 (6)
5y 1m–5y 6m	272 (47)	876 (47)	187 (50)	1,034 (47)	35 (36)	147 (36)
5y 7m–6y 0m	204 (35)	616 (33)	143 (38)	822 (37)	48 (49)	173 (42)
6y 1m -7y 5m	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)
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 disadvantaged)	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

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

1. Age at first registration with Medicare and age first lived in an exposure or comparison area were estimated from month and year of birth as recorded on the MEF, with day of birth assumed to be the 15^{th} of the month.
2. All characteristics except age first lived in an exposure or comparison area were sourced from the AEDC database. Therefore, geographic variables (Australian Bureau of Statistics' (ABS) 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 exposure areas. IRSD decile was based on the Statistical Area Level 1 of the child's usual residence coded according to ABS Australian Statistical Geography Standard 2016 Version for all cycles. No socioeconomic or remoteness information are collection in the MEF.
3. The discrepancies between variables with similar concepts on the MEF and AEDC are as below:
   - 5.0% (278/5,531) records differed in voluntary Aboriginal and Torres Strait Islander identification on the MEF vs. Aboriginal and Torres Strait Islander identification on the AEDC.
   - 0.7% (41/5,531) records differed in sex on the MEF vs. sex on the AEDC.
4. Denominators for proportions exclude missing values.
5. Cells have been suppressed or categories collapsed (†) to avoid reporting cell numbers with size $\leq$5.
6. Percentages were rounded to integer values.

Table 2: Comparison of childhood developmental outcomes in exposed and comparison populations: crude 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**		
Developmentally 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)

The RR is the risk in the exposed group divided by the risk in the 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 (NT only), 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 3.
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 (school-based) = NT: 8 (0.3%), Qld: 1 (0.0%)
    - Communication skills and general knowledge = Qld: 3 (0.1%).

of developmental vulnerability in the Physical health and wellbeing domain (fully-adjusted RR = 1.31, 95% CI 1.06 to 1.61), and a 49% higher risk of developmental vulnerability in the Communication skills and general knowledge domain (fully-adjusted RR = 1.49, 95% CI 1.18 to 1.87). While the RR was also above 1 for the Language and cognitive skills (school-based) domain, the evidence for a higher risk was uncertain (fully-adjusted RR = 1.24, 95% CI 0.98 to 1.57). In the remaining two domains, interval estimates were compatible with no effect. Overall, there was a 22% elevation in the risk of developmental vulnerability on one or more domain(s) among children in Oakey (fully-adjusted RR = 1.22, 95% CI 1.06 to 1.39).

In NSW, in contrast to the other two regions, the proportions of children who were developmentally vulnerable in any domain were at or below the national average, ranging from <4% to 10% in Williamtown and 5% to 11% in its comparison areas. After adjustments, interval estimates were too imprecise to make any conclusions about the size or direction of effects in all domains. We note the elevation in the risk of developmental vulnerability in the Language and cognitive skills (school-based) domain after minimal adjustment but did not have enough cases in the fully-adjusted model to make a conclusion.

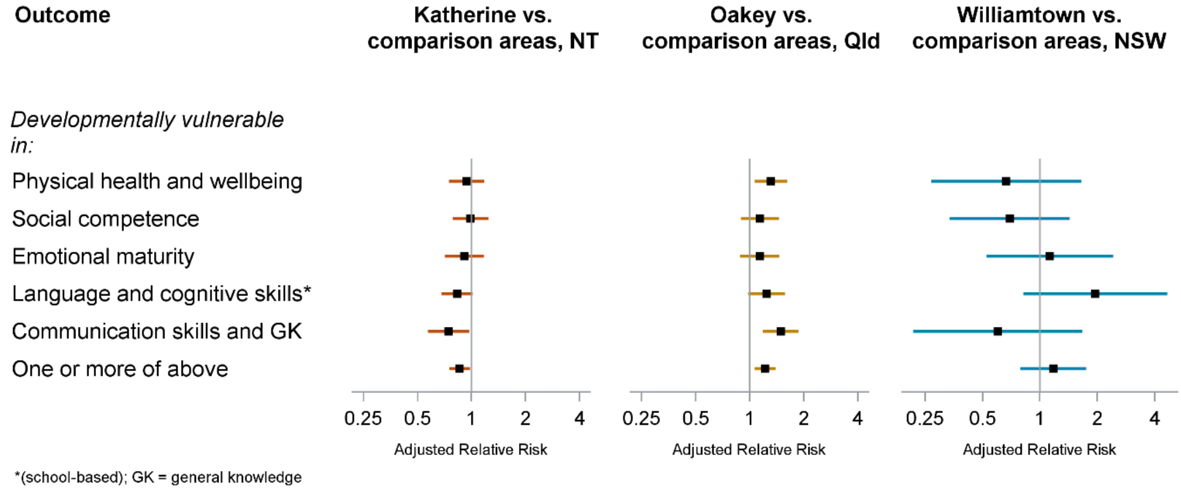
In the first sensitivity analysis, there was increased uncertainty in all estimates due to reductions in sample sizes when we included only children who had lived in the exposure areas since birth (Supplementary Table 1). Expanding the exposed population to all children who had lived in any Katherine, Oakey or Williamtown postcode had little material impact on results (Supplementary Table 2).

Discussion

We estimated increased risks of developmental vulnerability in two domains among children in Oakey, but a reduced risk in one of these domains among children in Katherine. For all remaining outcomes, we could not conclude that risks of developmental vulnerabilities were higher in the exposure areas than the relevant comparison populations. Overall, we found inadequate evidence for increased risks of developmental vulnerabilities among children who had lived in one of the three exposure areas of interest.

The discrepant findings that we observed for developmental vulnerability in the Communication skills and general knowledge domain—a reduced risk in Katherine, but an increased risk in Oakey—make interpretation difficult and reflects the variability in results seen in the literature. We are unaware of studies using the AEDC or a similar instrument to assess the relationship between PFAS and childhood communication or general knowledge. One study at lower (background) levels of exposure found both positive and negative associations between measured maternal serum PFAS concentrations and scores in language, intelligibility and communication. However, this study was conducted in girls at

Figure 3: Forest plot showing adjusted relative risks (RR) from Model 2



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 (NT only), Index of Relative Socioeconomic Disadvantage quintile and remoteness.
3. See Table 2 for sample sizes, crude risks and adjusted RRs.
4. Adjusted RRs are on a log scale.

much younger ages (15 and 38 months) and findings were not consistent across ages or individual PFAS type [28].

Other studies at background PFAS levels have reported largely mixed findings on measures of cognition in school-age children. Higher maternal serum PFOS concentration was associated with poorer executive function at 5–8 years [29], but this was not seen when child serum was measured in the same cohort at 3–8 years [30]. Other studies found that children with higher prenatal or childhood serum PFOS concentrations had higher reading scores at 5 and 8 years of age [31], while those with higher prenatal serum PFHxS had lower IQ score at seven years [32]. Exposure to other PFAS at background levels have also been associated with both better [31, 33] and poorer [30] cognitive outcomes.

We are unaware of any study on cognitive outcomes in children with community exposure to PFOS or PFHxS. For PFOA, studies of children exposed to drinking water contamination in the mid-Ohio Valley, US, found that those with higher estimated *in utero* PFOA levels had higher IQ scores at 6–12 years [34], while childhood serum levels were associated with both better and worse executive functions [35]. The inconsistent findings across studies are at least in part due to different methodologies and instruments used. This includes whether: PFAS exposure was measured or estimated, the timing of PFAS assessment, definition of outcomes, and the age at which these were assessed. While the variety of measurements across studies may be a strength in providing a comprehensive picture of neurodevelopment, direct comparisons across studies are difficult.

Our finding of increased risk of developmental vulnerability in the Physical health and wellbeing domain in Oakey is not supported by other evidence. In studies at background levels of exposure, prenatal and childhood serum PFAS concentrations were not related to motor difficulties or physical activity at 5–9 years of age [36–39].

In studies that focussed on social and behavioural outcomes, findings have been largely mixed. At background exposure, 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 type and timing of exposure measurement or outcomes [36, 37, 40–42]. Among children from the mid-Ohio Valley region who were highly exposed, inverse associations (decreased risks) were found between childhood serum PFAS concentrations and learning problems at 5–18 years [43].

The differences in outcomes used, study population demographics, exposure levels and timing of measurements, PFAS type, single versus multi-compound analyses and random error may explain the diverging results across studies, including the present study, examining childhood development. For example, the AEDC Language and cognitive skills (school-based) domain does not include a measure of IQ, and a previous validation study found that the AEDC emotional maturity domain or subdomains did not always correlate with constructs on the more widely used Strengths and Difficulties Questionnaire which measures children's emotional and behavioural difficulties [44]. It is also unclear if, or which, specific PFAS might be associated with neurodevelopmental outcomes and if there are heightened windows of vulnerability. Animal studies 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 in rodents; the mechanisms for such effects remain uncertain [45].

A strength of our study is the inclusion of a large majority of the eligible study population, as most children are enrolled on Medicare within their first year of birth. However, the AEDC is not collected every year, and children can start school at varying ages. This meant that we were unable to assess if exposure was related to starting school at a later age or not attending school at all, as some children may have started school in a non-census year.

The AEDC began only in 2009, therefore children who lived in the exposure areas prior to 2002 would not have been captured (even though PFAS exposure in Australia is possible as early as the 1970s). Compared to historical levels, contemporary PFOS and PFHxS exposure in children may be relatively lower due to the phasing out of AFFF products on military bases since the early 2000s. We do not know serum PFAS levels in the exposure areas during the period under study (2002–2017). However, in 2016–2019, the geometric means of serum PFAS among children 0–15 years in Katherine, Williamtown and Oakey ranged from: 2.6 to 4.0 ng/ml for PFOS and 1.3 to 4.1 ng/ml for PFHxS [10].

In comparison, arithmetic means of serum PFAS levels measured in a general Australian population in 2016–17 were: 2.5 ng/ml for PFOS and 1.3 ng/ml for PFHxS in children 1–4 years, and 3.0 ng/ml for PFOS and 1.6 for PFHxS in children 5–15 years [46]. It is possible that low exposure contrasts among children in this study made it difficult to observe measurable differences in outcomes. We attempted to examine the possible effect of continuous exposure since birth in a sensitivity analysis, but our sample sizes were considerably reduced.

Our use of an ecological measurement of exposure means that individual-level exposure is inaccurate, and we cannot be sure that children who were developmentally vulnerable had higher PFAS exposure than those who were not (or vice versa). However, this approach avoided confounding by individual factors that can occur when using personal measurements of exposure [47]. This includes physiological characteristics or behaviour that affect personal exposure, such as those that affect PFAS absorption in the body. Our approach also allowed the inclusion of a larger sample size, including historical populations, which would not have been possible in studies collecting personal exposure and individual confounding factors. However, the trade-off of this approach is increased exposure measurement error and the attendant potential bias towards the null.

We frequency-matched each exposed-comparison population pair on area-level socioeconomic status (SES) at the time of first exposure (first recorded address in an exposure area). However, area-level SES measured at the time of eventual AEDC participation several years later appeared dissimilar across groups (see Table 1). We included adjustments for SES at the time of AEDC participation, but this may not be reflective of the child's earlier years. We did not attempt to assign SES longitudinally.

We also lacked information on other potentially important confounding variables such as parental education, household income or community characteristics such as access to social support, health services and recreational facilities. We note the relatively high crude (unadjusted) risks of developmental vulnerability in all domains in both exposed and comparison children in the NT and Qld. This probably reflects the strong influences of socioeconomic factors on early development, notwithstanding environmental contamination.

Conclusion

We conclude that there is inadequate evidence for increased risks of developmental vulnerabilities (as assessed on the AEDC) among children who lived in three Australian areas where there has been exposure to PFAS from firefighting foams. The elevated risks observed in one area were not consistently seen in the other two exposure areas that we examined, were not supported by prior evidence and it is possible that they were due to chance or inadequately controlled socioeconomic factors.

Role of funding source

The Australian Government Department of Health funded the ANU to independently conduct this study and provided comment on the study protocol and final report. The study team was solely responsible for all outputs.

Ethics statement

We obtained ethics approval for the study from the following institutions: AIHW Ethics Committee (EO2019-3-1048), ANU Human Research Ethics Committee (2019/565), NT Department of Health and Menzies School of Health Research Ethics Committee (2019-3472).

Conflict of interests

MDK worked part-time for the Australian Government Department of Health between 2020–2022 on the national COVID-19 response. The other authors declare that they have no competing interests.

Link to study protocol

https://rsph.anu.edu.au/files/PFAS%20Health%20Study%20Data%20Linkage%20Study%20Research%20Protocol%20v1.0_Web_accessible%20for%20website_0.pdf#overlay-context=research/projects/pfas-health-study.

Data sharing

The data used in this study will not be made available to individuals other than nominated members of the study team under the Australian Government Department of Health Data Custodian requirements for data linked to the Medicare Enrolment File.

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the authors and should not be attributed to the Department or the Australian Government.

Author contributions

RK, MK, BA and HDL conceived the study; HDL, RK, BA, CD and MK contributed to study design; HDL did the analytical calculations; HDL, RH and KS did the literature search. HDL wrote the first draft of the manuscript and all authors provided critical feedback and approved the final manuscript.

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Supplementary Table 1: Comparison of childhood developmental outcomes in exposed (lived in exposure 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**
Developmentally 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)

The RR is the risk in the exposed group divided by 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 (NT only), 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).

Supplementary Table 2: Comparison of childhood developmental 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**		
Developmentally 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 by 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 (NT only), 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%).