Vehicle refuelling, use of domestic wood heaters and the risk of childhood brain tumors: results from an Australian case-control study

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ABSTRACT

Background

The etiology of childhood brain tumors (CBT) is largely unknown. Damage to germ cells after parental exposure to airborne carcinogens such as volatile organic compounds and polycyclic aromatic hydrocarbons is one plausible pathway. This analysis aimed to investigate whether parental refuelling of vehicles or the use of domestic wood heaters in key time periods relating to the child's birth was associated with an increased risk of CBT.

Procedure

Cases <15 years of age were recruited through 10 pediatric oncology centres around Australia; controls were recruited through nationwide random-digit dialling, frequency matched to cases on age, sex and State of residence. Exposure to refuelling and wood heaters was ascertained through questionnaires from both parents. Odds ratios (ORs) and confidence intervals (CIs) were estimated using unconditional logistic regression, adjusting for relevant covariates.

Results

Exposure data were available for 306 case and 950 control families. Paternal refuelling ≥4 times/month was associated with an increased risk of CBT (OR 1.59, 95% CI: 1.11, 2.29), and a dose-dependent trend was observed (P=0.004). No association was seen for maternal refuelling. Use of closed, but not open, wood heaters before (OR 1.51, 95% CI: 1.05, 2.15), and after (OR 1.44, 95% CI: 1.03, 2.01) the child's birth was associated with increased risk of CBT, but dose-response relationships were weak or absent.

Conclusions

Paternal refuelling of vehicles ≥4 times/month and the use of closed wood heaters before the child's birth may increase the risk of CBT. Replication in larger studies is needed.

INTRODUCTION

Childhood brain tumors (CBT) are the second most common type of childhood cancer, and have the highest mortality rate of all the childhood cancers. Despite this, very little is known of their etiology, apart from a few genetic syndromes and high dose ionising radiation to the head [1]. Given the early onset of many CBT cases, it is likely that prenatal and antenatal factors are involved in their etiology. Parental or childhood exposure to volatile organic compounds (VOCs) such as benzene, and to other air pollutants, have been identified as a possible risk factors for CBT [2-4]. Exposure to exhaust emissions and petrol fuel vapour are a major source of VOCs in non-smoking people [5, 6].

The International Agency for Research on Cancer (IARC) has classed diesel exhausts as carcinogenic to humans (Group 1) while petrol exhausts are possibly carcinogenic to humans (Group 2B) [7]. These fuels when combusted emit gaseous (e.g. carbon monoxide, nitrogen oxides, and VOCs: including benzene, toluene, ethylbenzene and xylenes (BTEX)) and particulate emissions [7]. Polycyclic aromatic hydrocarbons (PAHs) are also an important component of both types of emissions (both gaseous and particulate bound) [7]. The uncombusted fuels also contain a variety of VOCs and PAHs, many of which are classified as carcinogens [7, 8].

Previous studies have suggested an association between paternal occupation involving hydrocarbon exposure and/or vehicle emission exposure and the risk of CBT, although many of these studies have low numbers of exposed cases (reviewed [9, 10]). While occupational exposure to motor exhaust emissions have been studied extensively, there has been little investigation into the health effects of non-occupational fuel exposure – especially through direct contact or inhalation of unburnt vapour. One study reported a positive association between maternal kerosene use and the risk of astrocytoma [11]; while another study found no association

between car repairs carried out by the father at home and the risk of medulloblastomas or primitive neuroectodermal tumors (PNETs) [12].

Domestic wood heaters and open fires are sources of benzene and other potential airborne carcinogens. IARC has classified household biomass fuel combustion as probably carcinogenic to humans (Group 2A), although the main cancer site was the lung; this assessment was based largely on data from low-income countries with a high reliance on solid fuel heating and cooking [13]. Wood smoke contains similar carcinogens to fuel emissions, such as benzo[a]pyrene and benzene [14]. An Australian study reported that wood smoke from domestic wood heaters are a major source of personal VOC exposure in non-smokers [5]. There have been no previous studies on the association between the use of domestic wood heaters and the risk of CBT.

The Australian Study of Childhood Brain Tumors (Aus-CBT) was a nationwide case-control study designed to investigate the genetic, dietary and environmental risk factors for CBT. The aim of this analysis was to investigate whether parents' refuelling of vehicles or the use of domestic wood heaters during key periods relating to the child's birth were associated with an increased risk of CBT. We also sought to determine if any such associations varied across histological subtypes of CBT.

METHODS

Study participants

Aus-CBT was a nationwide case-control study conducted between 2005 and 2010. Incident cases of CBT were identified via all 10 pediatric oncology centers in Australia. Controls were recruited by national random digit dialling (RDD) and frequency matched to cases by child's age, sex and state of residence. The recruitment process has been described in detail previously [15]. Families were eligible to participate if they resided in Australia and had a biological parent

who could complete questionnaires in English. Controls recruited in 2005 and 2006 were originally matched to cases in our concurrent national case-control study of childhood acute lymphoblastic leukemia (Aus-ALL; 2003-2007), which used identical RDD recruitment methods [16]. Aus-CBT and Aus-ALL were approved by the Human Research Ethics Committees at all participating hospitals.

Data collection

Information about refuelling and the use of domestic wood heaters and open fires, in addition to other personal exposures and demographics, was obtained through parental questionnaires. Both parents were asked to indicate the number of times a month they refuelled a vehicle in the 12 months before the pregnancy and, for the mothers, during pregnancy. The type of fuel (petrol (gasoline)/diesel fuel/liquefied petroleum gas (LPG)) was also requested. Use of wood heaters was reported by the mother for the household, including the total number of times used in the 12 months before pregnancy, during the pregnancy, and after the child's birth but before diagnosis. These questions were asked for both open (i.e. open fireplace) and closed heaters (eg enclosed heater with a glass door, or 'potbelly' stove). If the parents had lived at separate addresses in the pre-pregnancy period, the father was asked about exposure in his own home. In addition to these exposure variables, we also had the area-based 'Index of Relative Socioeconomic Disadvantage' (IRSD) obtained from population census data for the household address [17].

Statistical analysis

Odds ratios (ORs) and 95% confidence intervals (CIs) were estimated using unconditional logistic regression. ORs were estimated for each parent refuelling a vehicle with *any* fuel and with each individual type of fuel in the relevant time periods. Frequency categories were assigned based on the median frequency of refuelling for each fuel type among controls where

any exposure was reported. Very few mothers had refuelled vehicles only before or only during pregnancy, so exposures during these time periods were combined.

ORs were estimated for *any* use of a wood heater in the home, and for use of open and closed heaters separately. Data on frequency of use were heavily right skewed, so categories were created where the cut-point was the median frequency of use in controls (if frequency>0). Medians were calculated separately for any, open and closed burners. Only 17 case and 33 control parents reported using a wood heater only before or only during pregnancy, so these periods were combined.

All models were adjusted for the frequency matching variables (child's age, sex and State of residence) and other potential confounders. Demographic variables considered *a priori* to be potential confounders were: parental age, year of birth, child's ethnicity, parental education, household income, IRSD and birth order. We also investigated confounding by the following exposures that have previously been associated with CBT risk in our study: maternal pre-pregnancy folic acid supplementation, parental alcohol consumption, household exposure to pesticides and, for paternal refuelling, paternal occupational exposure to diesel exhaust or solvents [15, 18-21]. Variables that were independently associated with exposure to maternal/paternal refuelling or wood heater use in controls, and to case/control status or to participation, were included in models as potential confounders. Although parental smoking does not appear to be associated with CBT risk [22], we investigated its inclusion in models because it is an important source of VOCs; however, the results did not change so it was not included in final models. Confounders included in the final models vary by exposure and are listed in the footnotes to results tables. Interactions between the main exposures and child's age and parental smoking status were investigated by stratifying the analysis by categories of these variables, and by fitting interaction terms into the models. Trend *P*-values were calculated by fitting ordinal frequency categories to the model as continuous variables with 1 degree of

freedom. All analyses were carried out using IBM SPSS Statistics for Windows, version 22 (IBM Corp., Armonk, New York, 2013).

RESULTS

Detailed results of recruitment and participation have been published previously [15]. Briefly, 730 eligible cases were identified between 2005 and 2010, 568 of whom were invited to participate by their physicians and 374 (65.8% of invited, 51.2% of eligible) of whom consented to participate. RDD identified 3624 eligible controls in the same period; 2,255 (62.2%) agreed to participate. In accordance with our frequency-matching quotas, 1,467 of these control families were recruited.

Information on maternal refuelling of vehicles, wood heater use, other exposures of interest and demographic factors was obtained by written questionnaire from 302 (81% of those recruited) case mothers, and 941 control mothers (61% of recruited). Information on paternal refuelling of vehicles was available from 247 case fathers (66% of recruited), and 801 control fathers (55% of recruited).

Table I shows the demographic characteristics of families who returned a written questionnaire. Controls were more likely than cases to be of European ethnicity, have older parents, and to have parents who completed secondary school. There were proportionally more controls who were female and aged less than 5 years compared with case children, as controls for cases diagnosed in 2005 and 2006 were matched to cases from our study of ALL [15].

Refuelling

Refuelling vehicles was a regular activity for both parents; approximately half of the mothers and 70% of fathers refuelled a vehicle once a week or more on average. For mothers,

approximately 92% of refuelling occasions was for gasoline, and 4% each for diesel and LPG; while for fathers, 69% of refuelling was with gasoline, 25% with diesel and 6% with LPG.

There was no evidence of any association between risk of CBT and maternal refuelling of vehicles in the 12 months before or during pregnancy (Table II). Estimates for diesel and LPG were imprecise due to small numbers of exposed mothers.

As less than 3% of fathers never refuelled a vehicle, the reference category was modified to 'refuelling <4 times per month' (Table III). The OR for refuelling ≥4 times/month overall was 1.59 (95% CI: 1.11, 2.29), with a significant dose-response trend (P_{trend}=0.004), and the ORs for gasoline and diesel (≥4 times/month vs <4/month of any type) were similar to the overall OR when analysed separately and statistically significant for gasoline. The OR for LPG was almost double that of gasoline or diesel, and although statistically significant was based on very small numbers of exposed fathers (Table III).

Associations with both parents' refuelling of vehicles (≥ vs <4 times/month) were investigated across CBT subgroups (Supplementary Table I). The results were consistent across subgroups and similar to the main results reported above. The OR for paternal refuelling was higher among children aged ≤4 years (OR 2.13, 95% CI 1.18, 3.83) than children 5-14 years (OR 1.33, 95% CI 0.83, 2.12), although the age-interaction *P*-value was 0.14. The OR for paternal refuelling among non-smokers was 1.86 (95% CI: 1.21, 2.86), compared with 0.99 (95% CI: 0.49, 2.03) among smokers, but the interaction term *P*-value was only 0.23.

Use of domestic wood heaters

Approximately 30% of participating families reported use of a wood heater in the year before the pregnancy, during the pregnancy or after the child's birth. On average, closed wood heaters were used more often than open fires. The mean number of times (±SDs) for use of closed and

open wood heaters were used in the year before or during pregnancy were: 25.8 (±75.5) and 5.4 (±28.4) respectively; the mean number of times they were used after birth were 78.7 (±244.3) and 12.1 (±70.9) respectively.

The use of wood heaters in the home before or during the index pregnancy, or after the child's birth, was associated with a modest increase in risk of CBT (Table IV). The ORs for use of closed wood heaters were generally higher than those for open fires, and the only evidence of a dose-response relationship was for closed wood heaters used before the birth ($P_{trend} = 0.03$). When the same frequency categories were used for open and closed heaters as for 'any' heater use, the results were similar; however, few families reported using open heaters >110 times. As 60% of families who used wood heaters used them both before and after the child's birth, we estimated the ORs for use exclusively before or exclusively after the birth. The ORs for any wood heater use and closed heater use only before the birth were slightly higher than use only after birth (Table IV).

When stratified by CBT subtype, the elevated ORs for wood heater use were seen across all types except high-grade glioma (Supplementary Table II). There was no evidence of interactions by child's age at diagnosis or parental smoking.

DISCUSSION

This study provides evidence that a higher frequency of fathers' vehicle refuelling in the year before conception may increase risk of CBT, with a possible dose-response relationship. Positive associations with risk of CBT were seen for paternal refuelling with all fuel types investigated (gasoline, diesel and LPG). The prenatal use of domestic wood heaters was also associated with an increased risk of CBT. This association appeared to be restricted to use of closed heaters, although use of open fires was quite limited.

The association between paternal self-reported vehicle refuelling and risk of CBT is novel, although previous studies have found positive associations between paternal occupations involving exposure to petroleum or polycyclic aromatic hydrocarbons (PAHs) and risk of CBT or other childhood cancers [23-25]. It is possible that paternal exposure to PAHs and other chemicals found in petroleum products such as VOCs could increase the risk of childhood cancer by causing DNA damage to the sperm. DNA damage has been found in the sperm of men occupationally exposed to PAHs [26, 27]. The higher OR for paternal refuelling seen among younger children is consistent with a biological mechanism involving a paternal germline effect, as such cancers might be expected to develop earlier in life. The current results are consistent with previously reported results from our study for paternal occupational exposure to solvents (OR: 1.55, 95% CI: 0.99, 2.43) [21] and diesel exhaust (OR: 1.39, 95% CI: 0.97, 1.99) [20] (which were adjusted for in the current analysis) – all of which are suggestive of a paternal germline effect. Maternal refuelling did not appear to be associated with CBT risk, and it was noted that fewer mothers than fathers reported any refuelling and that their frequency of refuelling was lower than for fathers.

Wood smoke emissions consist of numerous particles and gases, include known and potential carcinogens such as benzo[a]pyrene, 1,3 butadiene, benzene and PAHs [28]. A Swedish group reported that indoor PAH [29] and benzene/1,3-butadiene [30] levels were higher in houses using wood heaters than houses heated by electricity, indicating that even in developed countries wood burning can increase exposure to potential carcinogens. The apparent difference in results for open and closed heaters is difficult to explain, and may have occurred due to chance. However, there are likely to be quantitative and qualitative differences in the emissions produced by the two types of heater. Closed heaters are able to burn wood slowly for longer periods as air flow around the fuel is reduced, and this can result in less complete combustion and greater emissions, particularly of VOCs [30, 31]. In addition there is a smoke spillage effect with closed

wood heaters, potentially releasing high concentrations of products of incomplete combustion [32]. Inefficient combustion has been associated with increased PAH emissions and greater amounts of DNA damage in human and mouse cells compared with efficient combustion [33, 34]. Our findings for closed burners suggest only a weak dose-response association; thus, if causal, there may be a threshold effect. Open wood fires were used much less frequently than closed burners in our study population, so power to detect any effect for this type was limited.

The OR for the use of domestic wood heaters exclusively before the child's birth was slightly higher than for exposure only during childhood. While any difference in risk between the two periods would be etiologically important as different biological mechanisms would be involved, the observed difference was not large and may be due to chance. As well as PAH related damage to sperm, noted above, associations have been reported between ambient air pollution levels and PAH-DNA adducts in the cells of mothers and newborns [35] as well as the placenta [36], indicating that maternal exposure to PAHs during pregnancy could have genotoxic effects on the child. It is plausible, therefore, that wood smoke exposure may act on the germ cell, the fetus in utero, or directly on the child. Despite being unable to identify any previous studies of use of domestic wood heaters and risk of CBT, similar results were seen in our concurrent study of childhood ALL for use of closed wood heaters before the child's birth (OR 1.41, 95% CI: 1.02, 1.94) [37].

The strengths of this study are the comprehensive data collected on a range of exposures related to refuelling and wood heater use, including types of fuel and heater, frequency of use, and period of exposure, and fathers and mothers filled in questionnaires relating to their own exposures independently. In addition, Aus-CBT recruited controls nationally using the most representative methods available in Australia, and we were able to adjust for a variety of potential confounders related to socioeconomic status and other relevant exposures.

Nevertheless, this study also has some limitations. Our participation rate was fairly low, particularly among controls, and the different distributions of some variables (e.g. parental age and education) among cases and controls may be attributable to these differences in participation. If participation was in some way related to the exposures of interest, our findings may be affected by selection bias. We have previously reported that, on average, our controls had higher IRSD scores than the Australian population [15], indicating that low socioeconomic status households are underrepresented in our control group. In our study, maternal refuelling was associated with higher IRSD and paternal refuelling was associated with lower IRSD. This could have caused some underestimation of refuelling ORs for mothers and overestimation of refuelling ORs for fathers. However, IRSD scores were very similar among cases and controls [15], and we adjusted for at least one socioeconomic measure (parental education/IRSD) in every analysis, which would limit the effect such bias would have on our results. The use of wood heaters was not associated with socioeconomic status in our data; if differential participation affected our results, we are unable to predict the direction this might take.

Our study relied on parental reports of refuelling and wood heater use, and our results are therefore subject to exposure misclassification; however, this is likely to be non-differential between cases and controls. Case-control studies are susceptible to recall bias due to the potential for more detailed reporting by cases compared with controls. However, our questionnaires were designed to enhance recall by providing tick-boxes and detailed prompts, making recall bias unlikely to account for our results. As neither refuelling nor wood heater use is known to increase the risk of childhood cancer, we believe it unlikely that our results were affected by response bias due to underreporting of exposures by case parents.

Because of the relatively small numbers of exposed parents in this study, our findings could be considered inconclusive; nonetheless, there is some consistency. Refuelling vehicles and wood

heater use release PAHs and VOCs into the air [5, 8, 28], which can result in human exposure; hence the potential exists for impacts on human health.

Conclusions

Higher paternal exposure to vehicle refuelling before conception and use of closed domestic wood heaters before or during the index pregnancy may increase the risk of CBT. These novel findings require replication in larger studies before any public health recommendations could be considered. There is also a need to establish the sources, contributors and concentrations of prenatal parental and childhood exposure to hazardous air pollutants.

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Conflict of Interest Disclosure: Nothing to declare.

REFERENCES

1. Baldwin RT, and Preston-Martin S. Epidemiology of brain tumors in childhood--a review. Toxicol Appl Pharmacol 2004: 199: 118-131.
2. Cordier S, Lefeuvre B, Filippini G, Peris-Bonet R, Farinotti M, Lovicu G, and Mandereau L. Parental occupation, occupational exposure to solvents and polycyclic aromatic hydrocarbons and risk of childhood brain tumors (Italy, France, Spain). Cancer Causes Control 1997: 8: 688-697.
3. Feychting M, Svensson D, and Ahlbom A. Exposure to motor vehicle exhaust and childhood cancer. Scand J Work Environ Health 1998: 24: 8-11.
4. Savitz DA, and Feingold L. Association of childhood cancer with residential traffic density. Scand J Work Environ Health 1989: 15: 360-363.
5. Hinwood AL, Berko HN, Farrar D, Galbally IE, and Weeks IA. Volatile organic compounds in selected micro-environments. Chemosphere 2006: 63: 421-429.
6. Horton A, Murray F, Bulsara M, Hinwood A, and Farrar D. Personal monitoring of benzene in Perth, Western Australia: the contribution of sources to non-industrial personal exposure. Atmos Environ 2006: 40: 2596-2606.
7. International Agency for Research on Cancer. Diesel and gasoline engine exhausts and some nitroarenes. Volume 105. IARC monographs on the evaluation of carcinogenic risk to humans. Lyon, France: World Health Organisation, 2013.
8. Brewer R, Nagashima J, Kelley M, Heskett M, and Rigby M. Risk-based evaluation of total petroleum hydrocarbons in vapor intrusion studies. Int J Environ Res Public Health 2013: 10: 2441-2467.
9. Colt JS, and Blair A. Parental occupational exposures and risk of childhood cancer. Environ Health Perspect 1998: 106 Suppl 3: 909-925.

10. Savitz DA, and Chen JH. Parental occupation and childhood cancer: review of epidemiologic studies. Environ Health Perspect 1990: 88: 325-337.

11. Bunin GR, Buckley JD, Boesel CP, Rorke LB, and Meadows AT. Risk factors for astrocytic glioma and primitive neuroectodermal tumor of the brain in young children: a report from the Children's Cancer Group. Cancer Epidemiol Biomarkers Prev 1994: 3: 197-204.

12. Rosso AL, Hovinga ME, Rorke-Adams LB, Spector LG, and Bunin GR. A case-control study of childhood brain tumors and fathers' hobbies: a Children's Oncology Group study. Cancer Causes Control 2008: 19: 1201-1207.

13. International Agency for Research on Cancer. Household Use of Solid Fuels and High Temperature Frying. Volume 95, IARC Monographs on the Evaluation of Carcinogenic Risks to Humans Lyon, France: World Health Organization, 2010.

14. Straif K, Baan R, Grosse Y, Secretan B, El Ghissassi F, and Cogliano V. Carcinogenicity of household solid fuel combustion and of high-temperature frying. Lancet Oncol 2006: 7: 977-978.

15. Milne E, Greenop KR, Bower C, Miller M, van Bockxmeer FM, Scott RJ, de Klerk NH, Ashton LJ, Gottardo NG, and Armstrong BK. Maternal use of folic acid and other supplements and risk of childhood brain tumors. Cancer Epidemiol Biomarkers Prev 2012: 21: 1933-1941.

16. Bailey H, Milne E, de Klerk N, Fritschi L, Bower C, Attia J, and Armstrong B. Representativeness of child controls recruited by random digit dialing. Paediatr Perinat Epidemiol 2010: 24: 293-302.

17. Australian Bureau of Statistics. Information Paper: An Introduction to Socio-Economic Indexes, 2006. Commonwealth of Australia.

http://www.ausstats.abs.gov.au/Ausstats/subscriber.nsf/0/D729075E079F9FDECA2574170011B088/$File/20390_2006.pdf. Published 2008, Accessed 13 January 2012.

18. Milne E, Greenop KR, Scott RJ, de Klerk NH, Bower C, Ashton LJ, Heath JA, and Armstrong BK. Parental alcohol consumption and risk of childhood acute lymphoblastic leukemia and brain tumors. Cancer Causes Control 2013: 24: 391-402.

19. Greenop KR, Peters S, Bailey HD, Fritschi L, Attia J, Scott RJ, Glass DC, de Klerk NH, Alvaro F, Armstrong BK, and Milne E. Exposure to pesticides and the risk of childhood brain tumors. Cancer Causes Control 2013: 24: 1269-1278.

20. Peters S, Glass DC, Reid A, de Klerk NH, Armstrong BK, Kellie S, Ashton LJ, Milne E, and Fritschi L. Parental occupational exposure to engine exhausts and childhood brain tumors. Int J Cancer 2013: 132: 2975-2979.

21. Peters S, Glass DC, Greenop KR, Armstrong BK, Kirby M, Milne E, and Fritschi L. Childhood brain tumors: Associations with parental occupational exposure to solvents. Br J Cancer 2014; doi:10.1038/bjc.2014.358.

22. Milne E, Greenop KR, Scott RJ, Ashton LJ, Cohn RJ, De Klerk NH, and Armstrong BK. Parental smoking and risk of childhood brain tumors. Int J Cancer 2013: 133: 253-260.

23. Cordier S, Monfort C, Filippini G, Preston-Martin S, Lubin F, Mueller BA, Holly EA, Peris-Bonet R, McCredie M, Choi W, Little J, and Arslan A. Parental exposure to polycyclic aromatic hydrocarbons and the risk of childhood brain tumors: The SEARCH International Childhood Brain Tumor Study. Am J Epidemiol 2004: 159: 1109-1116.

24. Fabia J, and Thuy TD. Occupation of father at time of birth of children dying of malignant diseases. Br J Prev Soc Med 1974: 28: 98-100.

25. Johnson CC, Annegers JF, Frankowski RF, Spitz MR, and Buffler PA. Childhood nervous system tumors--an evaluation of the association with paternal occupational exposure to hydrocarbons. Am J Epidemiol 1987: 126: 605-613.

26. Gaspari L, Chang SS, Santella RM, Garte S, Pedotti P, and Taioli E. Polycyclic aromatic hydrocarbon-DNA adducts in human sperm as a marker of DNA damage and infertility. Mutat Res 2003: 535: 155-160.

27. Ji G, Gu A, Zhu P, Xia Y, Zhou Y, Hu F, Song L, Wang S, and Wang X. Joint effects of XRCC1 polymorphisms and polycyclic aromatic hydrocarbons exposure on sperm DNA damage and male infertility. Toxicol Sci 2010: 116: 92-98.

28. Naeher LP, Brauer M, Lipsett M, Zelikoff JT, Simpson CD, Koenig JQ, and Smith KR. Woodsmoke health effects: a review. Inhal Toxicol 2007: 19: 67-106.

29. Gustafson P, Ostman C, and Sallsten G. Indoor levels of polycyclic aromatic hydrocarbons in homes with or without wood burning for heating. Environ Sci Technol 2008: 42: 5074-5080.

30. Gustafson P, Barregard L, Strandberg B, and Sallsten G. The impact of domestic wood burning on personal, indoor and outdoor levels of 1,3-butadiene, benzene, formaldehyde and acetaldehyde. J Environ Monit 2007: 9: 23-32.

31. McDonald JD, Zielinska B, Fujita EM, Sagebiel JC, Chow JC, and Watson JG. Fine particle and gaseous emission rates from residential wood combustion. Environ Sci Technol 2000: 34: 2080-2091.

32. Longley I, and Gadd J. Preliminary exploration of high resolution PM10 measured inside wood-burning New Zealand homes. Air Quality and Climate Change 2011: 45: 21-26.

33. Kocbach Bolling A, Pagels J, Yttri KE, Barregard L, Sallsten G, Schwarze PE, and Boman C. Health effects of residential wood smoke particles: the importance of combustion conditions and physicochemical particle properties. Part Fibre Toxicol 2009: 6: 29. doi: 10.1186/1743-8977-6-29.

34. Tapanainen M, Jalava PI, Maki-Paakkanen J, Hakulinen P, Lamberg H, Ruusunen J, Tissari J, Jokiniemi J, and Hirvonen MR. Efficiency of log wood combustion affects the

toxicological and chemical properties of emission particles. Inhal Toxicol 2012: 24: 343-355.

35. Whyatt RM, Santella RM, Jedrychowski W, Garte SJ, Bell DA, Ottman R, Gladek-Yarborough A, Cosma G, Young TL, Cooper TB, Randall MC, Manchester DK, and Perera FP. Relationship between ambient air pollution and DNA damage in Polish mothers and newborns. Environ Health Perspect 1998: 106 Suppl 3: 821-826.

36. Topinka J, Binkova B, Mrackova G, Stavkova Z, Benes I, Dejmek J, Lenicek J, and Sram RJ. DNA adducts in human placenta as related to air pollution and to GSTM1 genotype. Mutat Res 1997: 390: 59-68.

37. Bailey HD, de Klerk NH, Fritschi L, Attia J, Daubenton JD, Armstrong BK, and Milne E. Refuelling of vehicles, the use of wood burners and the risk of acute lymphoblastic leukaemia in childhood. Paediatr Perinat Epidemiol 2011: 25: 528-539.

Table I. Distribution of demographic characteristics in the current analysis of the Australian Study of Childhood Brain Tumors (Aus-CBT).

Variable	Category	Case n (%)	Control n (%)
Any written questionnaire returned		306	950
Mother Questionnaire returned		302	941
Father Questionnaire returned		247	801
Case diagnosis	Low grade gliomas	146 (47.7)	
	High grade gliomas	27 (8.8)	
	Embryonal tumors	72 (23.5)	
	Germ cell tumors	20 (6.5)	
	Ependymomas	22 (7.2)	
	Other	19 (6.2)	
Child gender	Female	123 (40.2)	450 (47.4)
	Male	183 (59.8)	500 (52.6)
Child age group	0-1	30 (9.8)	110 (11.6)
	2-4	85 (27.8)	304 (32.0)
	5-9	92 (30.1)	294 (30.9)
	10-14	99 (32.4)	242 (25.5)
Child state of residence	NSW/ACT	103 (33.7)	286 (30.1)
	Victoria/Tasmania	86 (28.1)	251 (26.4)
	SA/NT	19 (6.2)	78 (8.2)
	Western Australia	42 (13.7)	114 (12.0)
	Queensland	56 (18.3)	221 (23.3)
Child birth year	1990-1998	86 (28.1)	229 (24.1)
	1998-2003	127 (41.5)	472 (49.7)
	2004-2010	93 (30.4)	249 (26.2)
Maternal age group	<25	47 (15.4)	87 (9.2)
	25-34	188 (61.6)	598 (63.0)
	35+	70 (23.0)	264 (27.8)

Paternal age group	<25	16 (6.0)	26 (3.2)
	25-34	154 (57.0)	436 (54.2)
	35+	100 (37.0)	342 (42.5)
Ethnic group[a]	European	186 (60.8)	682 (71.8)
	At least 50% European	76 (24.8)	176 (18.5)
	At least 50% non-European	12 (3.9)	30 (3.2)
	Indeterminate	32 (10.5)	62 (6.5)
Maternal Education	< complete secondary school	73 (24.0)	180 (19.0)
	Complete secondary school/ trade qualification	100 (32.9)	312 (32.9)
	University/College	131 (43.1)	457 (48.2)
Paternal Education	< complete secondary school	49 (19.8)	123 (15.4)
	Complete secondary school/ trade qualification	101 (40.9)	375 (46.8)
	University/College	97 (39.3)	303 (37.8)
IRSD population quartiles	1	62 (20.5)	150 (16.0)
	2	68 (22.5)	213 (22.7)
	3	79 (26.2)	298 (31.7)
	4	93 (30.8)	278 (29.6)

ACT, Australian Capital Territory; IRSD, Index of relative socioeconomic disadvantage; NSW, New South Wales; NT, Northern Territory; SA, South Australia. [a]European: at least 3 European grandparents; 50% European: 2 European grandparents; at least 50% non-European: 2 non-European grandparents and ethnicity of 2 other grandparents unknown; indeterminate: no 2 grandparents of same ethnicity (i.e European or non-European) and 2+ grandparents of unknown ethnicity.

Table II. Mothers' refuelling of vehicles in the 12 months before or during pregnancy and risk of childhood brain tumors

Exposure	Cases n (%)	Controls n (%)	OR[a] (95% CI)
	302	941	
No refuelling	42 (13.9)	107 (11.4)	1.00
Any refuelling	260 (86.1)	834 (88.6)	0.97 (0.64, 1.47)
1-3 times/month	105 (34.8)	378 (40.2)	0.90 (0.58, 1.41)
≥4 times/month	155 (51.3)	456 (48.5)	1.02 (0.67, 1.57)
Refuelling <4 times/month	147 (48.7)	485 (51.5)	1.00
Refuelling ≥4 times/month	155 (51.3)	456 (48.5)	1.11 (0.84, 1.45)
Fuel Types			
Any Gasoline[b]	250 (85.6)	801 (88.2)	0.95 (0.63, 1.44)
Any Diesel[b]	12 (22.2)	56 (34.4)	0.54 (0.24, 1.26)
Any LPG[b]	15 (26.3)	35 (24.6)	1.49 (0.64, 3.44)
Gasoline ≥4 times/month[c]	147 (50.0)	425 (46.7)	1.11 (0.84, 1.46)
Diesel ≥4 times/month[c]	4 (2.6)	18 (3.6)	0.69 (0.21, 2.28)
LPG ≥4 times/month[c]	6 (3.9)	17 (3.4)	1.43 (0.51, 3.99)

CI, confidence Interval; LPG, liquefied petroleum gas; OR, odds ratio. [a]Adjusted for matching variables (child's age, gender, State of residence), child's year of birth, child's ethnicity, mother's age, mother's education, maternal alcohol use in the year prior to pregnancy. [b]Referent category is no refuelling of vehicles. [c]Referent category is refuelling with any fuel <4 times/month.

Table III. Fathers' refuelling of vehicles in the 12 months before the index pregnancy and risk of childhood brain tumors

Exposure	Cases n (%)	Controls n (%)	OR[a] (95% CI)
	241	795	
Any Refuelling <4 times/month	53 (22.0)	238 (29.9)	1.00
Any Refuelling ≥4 times/month	192 (78.0)	558 (70.1)	1.59 (1.11, 2.29)
4-5.9 times/month	81 (33.6)	275 (34.6)	1.43 (0.96, 2.13)
6+ times/month	107 (44.4)	282 (35.5)	1.83 (1.21, 2.77)
Fuel Types			
Gasoline ≥4 times/month[b]	150 (73.9)	461 (66.0)	1.50 (1.04, 2.19)
Diesel ≥4 times/month[b]	36 (40.4)	111 (31.8)	1.49 (0.82, 2.72)
LPG ≥4 times/month[b]	18 (25.4)	39 (14.1)	2.94 (1.33, 6.49)

CI, confidence Interval; OR, odds ratio. [a]Adjusted for matching variables (child's age, gender, State of residence), father's age, father's education, paternal occupational exposure to diesel exhaust or solvents up to 2 years prior to the birth. 1 case missing education, 5 cases and 6 controls missing diesel exhaust and solvent variable. [b]Referent category is refuelling (with any fuel) <4 times/month.

Table IV. Domestic wood heater use and the risk of childhood brain tumors

	Cases n	Controls n	OR (95% CI)
12 months before/during pregnancy[a]			
No wood heater use	189	656	1.00
Any wood heater use	81	208	1.39 (1.01, 1.91)
≤110 times	42	106	1.39 (0.92, 2.10)
>110 times	39	102	1.39 (0.91, 2.12)
Only before birth	14	30	1.79 (0.90, 3.55)
Any Open	26	84	1.12 (0.69, 1.82)
≤25 times	14	42	1.12 (0.58, 2.14)
>25 times	12	42	1.13 (0.57, 2.23)
Only before birth	3	13	1.01 (0.27, 3.71)
Any Closed	61	144	1.51 (1.05, 2.15)
≤120 times	30	73	1.44 (0.90, 2.32)
>120 times	31	71	1.57 (0.98, 2.53)
Only before birth	11	18	2.18 (0.98, 4.83)
After the child's birth[b]			
No wood heater use	186	655	1.00
Any wood heater use	95	242	1.34 (0.99, 1.81)
≤180 times	52	125	1.48 (1.01, 2.15)
>180 times	43	117	1.19 (0.78, 1.79)
Only after birth	28	65	1.27 (0.77, 2.09)
Any Open	31	95	1.06 (0.67, 1.67)
≤38 times	15	47	1.07 (0.57, 1.99)
>38 times	16	48	1.05 (0.57, 1.93)
Only after birth	11	28	1.08 (0.52, 2.28)
Any Closed	74	177	1.44 (1.03, 2.01)
≤240 times	40	91	1.59 (1.04, 2.42)
>240 times	34	86	1.28 (0.80, 2.03)

Only after birth	22	44	1.52 (0.86, 2.68)

IRSD: Index of socioeconomic disadvantage; CI, confidence Interval; OR, odds ratio. [a]Adjusted for matching variables (child's age, sex, State of residence), child's year of birth, maternal age, child's ethnicity, IRSD quartiles. 4 cases and 11 controls missing IRSD data. Referent is no wood heater use from 12 months before the birth to the censoring date. [b]Adjusted for matching variables (child's age, sex, State of residence), child's year of birth, maternal age, child's ethnicity, IRSD quartiles, maternal folate supplementation 1 month prior pregnancy. Seven cases and 14 cases missing IRSD/folate data. Referent is no wood heater use from 12 months before the birth to the censoring date.

Supplementary Table I. Parental Refuelling and the risk of childhood brain tumors by tumor subtype

		Maternal refuelling		Paternal refuelling	
	Refuelling	n case/control	OR[a] (95% CI)	n case/control	OR[b] (95% CI)
Low grade gliomas	<4/month	66/485	1.00	28/238	1.00
	≥4/month	78/456	1.21 (0.84, 1.74)	88/557	1.46 (0.90, 2.37)
High grade gliomas	<4/month	12/485	1.00	3/238	1.00
	≥4/month	14/456	1.11 (0.49, 2.55)	19/557	2.28 (0.62, 8.35)
Embryonal tumors	<4/month	38/485	1.00	11/238	1.00
	≥4/month	33/456	0.93 (0.56, 1.53)	44/557	1.65 (0.81, 3.39)
Germ cell tumors	<4/month	10/485	1.00	2/238	1.00
	≥4/month	10/456	1.12 (0.42, 3.02)	9/557	2.49 (0.50, 12.32)
Ependymomas	<4/month	12/485	1.00	5/238	1.00
	≥4/month	10/456	0.84 (0.35, 2.03)	15/557	1.41 (0.48, 4.18)

CI, confidence Interval; OR, odds ratio. [a]Adjusted for matching variables, birth year, maternal age, maternal education, child's ethnicity, maternal alcohol use 12 months before pregnancy. [b]Adjusted for matching variables, paternal age, paternal education, paternal occupational exposure to diesel exhausts or solvents up to 2 years prior to the birth.

Supplementary Table II. Household wood burning and risk of childhood brain tumors by tumor subtype

		Before/during pregnancy[a]		After birth[b]	
	Wood heater use	n case/control	OR (95% CI)	n case/control	OR(95% CI)
Low grade gliomas	None	83/656	1.00	82/655	1.00
	Any	44/208	1.73 (1.14, 2.63)	51/242	1.59 (1.06, 2.37)
High grade gliomas	None	19/656	1.00	19/655	1.00
	Any	6/208	0.90 (0.33, 2.43)	7/242	0.87 (0.33, 2.28)
Embryonal tumors	None	46/656	1.00	45/655	1.00
	Any	17/208	1.38 (0.75, 2.53)	20/242	1.28 (0.72, 2.28)
Germ cell tumors	None	12/656	1.00	12/655	1.00
	Any	6/208	1.81 (0.56, 5.81)	6/242	1.42 (0.44, 4.59)
Ependymomas	None	14/656	1.00	14/655	1.00
	Any	6/208	1.74 (0.63, 4.75)	8/242	2.01 (0.79, 5.08)

CI, confidence Interval; IRSD: Index of socioeconomic disadvantage; OR, odds ratio. [a] Adjusted for matching variables, year of birth, maternal age, child's ethnicity, IRSD quartiles. [b] Adjusted for matching variables, year of birth, maternal age, child's ethnicity, maternal pre-pregnancy folate supplementation, IRSD quartiles.