Childhood Cancer 2018

12th - 14th September 2018
Westminster, London

Cancer in Children and Young People

A landmark conference examining the way we understand cancer, exploring the way forward within the full US NIH definition of Precision Medicine

Children with Cancer UK
Keeping families together

Registered Charity Number: 298405.

Traffic-related air pollution and risk of childhood leukaemia: A systematic review and dose-response meta-analysis

Marco Vinceti[1,2], Tommaso Filippini[1]

[1]Environmental, Genetic and Nutritional Epidemiology Research Center (CREAGEN) - University of Modena and Reggio Emilia Medical School, Modena, Italy; [2]Department of Epidemiology, Boston University School of Public Health, Boston, Massachusetts

marco.vinceti@unimore.it

Introduction

Childhood leukaemia is the most frequent childhood cancer, and its incidence is continuing to increase through most recent years (Siegel *et al*, 2016). The aetiology of childhood leukaemia is still largely unknown, although increasing evidence suggests a major role of environmental factors (Schüz *et al*, 2016). In addition to established and putative risk factors such as ionizing and non-ionizing radiation, infections, pesticides, and parental smoking, there is concern about the etiologic role of outdoor air pollution and, in particular, exposure to contaminants released by motorized traffic, a nearly ubiquitous exposure (Metayer *et al*, 2016). In this review, we updated a prior systematic review on the effect of air pollution on childhood leukemia risk (Filippini *et al*, 2015), and we performed a dose-response meta-analysis based on several proxies of air pollution exposure.

Methods

We performed a systematic scientific database search using the terms 'childhood leukaemia' and 'air pollution' to retrieve relevant case-control and cohort studies through June 30, 2018. We assessed the risk of bias of the retrieved studies using the Newcastle-Ottawa scale. From these studies, we extracted population size, characteristics and effect estimates, also taking into account leukaemia subtype and exposure window. We computed a summary disease risk ratio (RR) along with its 95% confidence limits (CL) from all studies or their subsets, by inputting in a random-effect model the disease odds ratio or RR in the highest exposure category compared to the lowest one. We also performed a dose-response meta-analysis to assess the shape of the relation between air pollutants and disease risk.

Results

We retrieved 28 eligible studies (25 case-control and 3 cohort studies), overall including over 12,000 cases and (for the case-control studies) 138,000 controls allocated worldwide, with year of diagnosis from 1960 to 2012. To assess exposure to traffic exhaust contaminants, these studies used two basic proxies: traffic density, as assessed through distance from major roads or their length or the number of vehicles on these roads, and measured or modeled levels of traffic-related air toxics such as nitrogen dioxide (NO_2), fine particulate matter ($PM_{2.5}$), benzene and 1,3-butadiene exposure. Fourteen studies were carried out in children aged less than 6 or presented age-stratified analyses. Most studies used residential address at leukaemia diagnosis to assess exposure. The methodological quality of these studies was generally high. The summary RR of leukaemia from studies using traffic density to assess air pollution exposure was 1.07 (95% CL 0.98 – 1.17), and the dose-response analysis suggested a roughly linear positive association between such exposure and risk. Considering benzene exposure, the highest exposure category was associated with a summary RR of 1.27 (95% CL 1.03 – 1.56), which in subgroup analysis was 1.09 (95% CL 0.88 – 1.36) for Acute Lymphoblastic Leukaemia and 1.84 (95% CL 1.31 – 2.59) for Acute Myeloid Leukaemia. The dose-response meta-analysis showed an increasing risk even at the lowest exposure level, with a linear relation between exposure and disease risk in the entire range investigated (1-14 $\mu g/m^3$). For NO_2, RR of leukaemia in the highest exposure group compared with the lowest exposure group showed little departure from the unit (summary RR 1.03, 95% CL 0.90 – 1.18), though spline regression suggested a non-linear positive association with risk starting to increase from around 40 $\mu g/m^3$. An excess risk was also associated to 1,3-butadiene exposure in the highest versus the lowest category, though based on two studies, with a summary RR of 1.45 (95% CL 1.08 – 1.95). A slight indication of a higher RR emerged for $PM_{2.5}$ of 1.05 (95% CL 0.94 – 1.16).

When we took into account the exposure window, studies assessing exposure on the basis of either child residence at diagnosis or their longest place of residence yielded higher summary RRs compared with studies based on maternal residence at birth, or during pregnancy. We also found a higher RR when we

restricted the analysis to children aged less than 6 years compared with older children. Overall, funnel plots based on the different exposure assessment methods and Egger's test did not indicate a substantial publication bias.

Discussion

The addition to the previous assessment of the six most recent epidemiologic studies, three of which were carried out in Europe and three in the US, appear to support and strengthen the already suggested relation between outdoor air pollution, mainly from motorized traffic, and risk of childhood leukaemia. Our results also suggest a greater influence on risk from exposure to outdoor air pollutants in the post-natal period compared with prenatal and perinatal period. However, while exposure to pollutants such as benzene, an established leukaemogen in adults, clearly suggested a link with disease risk (particularly for Acute Myeloid Leukaemia), exposure assessed through 'traffic' indicators showed less evidence of such association. This might be due to a weakness of the latter approach in capturing actual exposure to outdoor air pollutants compared to modelled exposure assessment methods. In addition, because air pollution is a complex mixture of multiple, often highly correlated, pollutants, assessment of single pollutants may obscure true etiologic associations. This is clearly true particularly for NO_2, which is a non-carcinogenic air pollutant, and which may be a poor surrogate of established carcinogens such as benzene, 1,3-butadiene and particulate matter. In addition, all the reviewed studies could have been potentially affected by unmeasured confounding, for example, due to parental smoking and socioeconomic status, or to pesticide and electromagnetic field exposure. Moreover, exposure misclassification may have occurred due to indoor air pollution (including passive smoke), time spent away from home, and inaccuracies generated by the air pollution models.

Overall, study findings indicate a role of outdoor air pollution, mainly due to motorized traffic, in childhood leukaemia aetiology. This relation has biological plausibility, due to the presence in traffic exhausts of known genotoxics and carcinogens such as benzene, benzopyrene, 1,3-butadiene, heavy metals and particulate matter (Navasumrit *et al*, 2005; Calderon-Garciduenas *et al*, 2008; Andreoli *et al*, 2012; Vattanasit *et al*, 2016; Luyten *et al*, 2018). However, further epidemiologic research is needed for a precise assessment of the role of air pollution in disease etiology, particularly about the specific pollutants responsible for this excess risk and the critical thresholds of exposure.

References

Andreoli *et al* (2012) Med Lav 103: 324 – 327

Calderon-Garciduenas *et al* (2008) Toxicol Pathol 36: 289 – 310.

Filippini *et al* (2015) J Environ Sci Health C Environ Carcinog Ecotoxicol Rev 33: 36 – 66.

Luyten *et al* (2018) Environ Res 166:310 – 323

Metayer *et al* (2016) Pediatrics 138: S45 – S55

Navasumrit *et al* (2005) Chem Biol Interact 153 – 154: 75–83

Schüz *et al* (2016) Arch Med Res 47: 607 – 614

Siegel *et al* (2016) CA Cancer J Clin 66: 7 – 30

Vattanasit *et al* (2016) Int J Hyg Environ Health 217: 23 – 33