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Residential traffic exposure and lymphohematopoietic malignancies among children in the city of São Paulo, Brazil: An ecological study

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ABSTRACT

Background: Despite widespread evidence that air pollution is carcinogenic, there is little evidence from low-middle income countries, especially related to childhood malignancies. We examined the role of traffic related pollution on lymphohematopoietic malignancies among under-14 s in Sao Paulo.

Methods: All incident cases between 2002 and 2011 were collected from a population-based registry. Exposures were assigned on residential address at diagnosis via traffic density database (for the year 2008) and a satellite derived NO_2 land use regression model (averaged between 1997 and 2011). Incidence rate ratios (IRRs) were calculated via Poisson Regression adjusted by age, gender and socioeconomic status (SES), with additional stratification by SES.

Results: A positive association between traffic and NO_2 with some lymphohematopoietic malignancies was observed with the degree of effect differing by SES. For example, lymphoid leukemia IRRs in the lower SES group were 1.21 (95 % CI: 1.06, 1.39) for traffic density and 1.38 (95 % CI: 1.13, 1.68) for NO_2. In the higher group they were 1.06 (95 % CI: 1.00, 1.14) and 1.37 (95 % CI: 1.16, 1.62).

Conclusion: NO_2 and traffic density were associated with Hodgkin lymphoma and lymphoid leukemia among children in São Paulo. Differing IRRs by gender and SES group indicate differences in underlying risk and/or exposure profiles.

1. Introduction

There is evidence associating the emissions from motor-vehicles with various health outcomes [1]. Of note, exposure to traffic-related air pollution is an important risk factor for cancer incidence [2], including childhood cancers [3–5].

Previous studies have also established that residential proximity to roadways with high traffic volume and exposure to traffic-related air pollution are both linked to lymphohematopoietic cancer in children [6–11] with environmental exposure during pregnancy often considered responsible for increasing the risk of cancers in early childhood [12–14]. Different traffic measures have been used to assess the relationship with childhood cancer and several studies have detected a positive association between nitrogen dioxide (NO_2) and childhood leukemia [4,6,8,12,15,16].

However, the evidence thus far has primarily been derived from studies conducted in high-income countries, with a dearth of evidence from low- and middle-income countries (LMIC). Our previous study showed the impact of air pollution in the occurrence of respiratory malignancies in São Paulo, Brazil [17]. Thus, to further address the research gaps in LMIC and as an ongoing examination of the health effects of air pollution in São Paulo, we conducted an ecological study to

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examine the role of residential exposure to traffic-related air pollution (using traffic density and estimates of NO_2 as exposure metrics) on the incidence on lymphohematopoietic malignancies among children.

2. Methods

2.1. Study area and population

The municipality of São Paulo is highly urban being the largest and most populous city in Brazil. It has a fleet of approximately 9.0 million vehicles (of which approximately 16 % are diesel operated), which circulate daily on approximately 18,000 km of routes. Following the protocol of our previous study, the municipality was divided into 6384 grid cells, each 500m × 500m in size. Grid cell size was based on the consideration that the greatest exposures occur at a distance of up to 500 m from high-traffic roads [1]. The study population consisted of the approximately 2.3 million children identified in the 2010 Census, conducted by the Brazilian Institute of Geography and Statistics (IBGE) [18]. A "child" was defined as per the Brazilian National Cancer Institute to be an individual 14 years or younger [19]. Grid cells with zero population (n = 1399) were excluded from further analysis.

2.2. Case ascertainment

Cases were defined as all incident cases (between 2002 and 2011) of lymphohematopoietic malignancy including Hodgkin's lymphoma (C81), Non-follicular lymphoma (C83), other and unspecified types of non-Hodgkin lymphoma (C85), lymphoid leukemia (C91), myeloid leukemia (C92), and other leukemias (C93, C94, C95), in São Paulo residents up to the age of 14. Case information was obtained from the Population-based Cancer Registry of São Paulo (2002–2011). Cases' addresses were geocoded using ArcGIS, version 9.3 (Esri, Redlands, CA, USA), and the existing set of georeferenced points within São Paulo (Multispectral, São Paulo, Brazil).

2.3. Evaluation of exposure

Exposure to traffic-related air pollution at the home street of incident cases at diagnosis was assigned as the volume and density of traffic for the year 2008, by vehicle counts, and as the annual estimates of NO_2 averaged between 1997 and 2011. All exposures were averaged for the aforementioned 500m × 500m cells. The development of the traffic density dataset has been described elsewhere [17,20]. Briefly, the traffic volume and density databases were generated during a previous project, developed in partnership with the São Paulo State Health Department and the São Paulo Department of Transportation, which conducted vehicle counts on a variety of roadways, classified according to their function as expressway, arterial-1, arterial-2, arterial-3, collector-1, collector-2, and local. We complemented this standard data with vehicle counts for other streets evenly distributed throughout the city, employing the same method used by the São Paulo Department of Transportation. In total, vehicle counts were obtained for 681 roadways with no counts made near traffic lights or when traffic was interrupted. Annual estimates of NO_2 were obtained from a global NO_2 land use regression (LUR) model, which included satellite observations (via the SCIAMACHY and GOME-2 satellites) and geographic predictor variables (e.g. length of roads, population density, green spaces etc.) predicting NO_2 at a 100 × 100 m resolution. A detailed description of this model has been described elsewhere [17,21].

The Municipal Human Development Index (MHDI), for the year 2010, was calculated as a marker of socioeconomic status. The MHDI contains 3 components (longevity, income, and education) which were grouped by geometric mean, following the methodology of the United Nations Development Programme [22] to generate an indicator of development, which ranges from 0 to 1. For the longevity component, we used data referring to mortality in the city for the triennium 2009–2011, obtained from the São Paulo Municipal Health Department. For the income and education components, we used data from the 2010 census [18].

2.4. Statistical analysis

The effect of traffic density and NO_2 exposure on the incidence of lymphohematopoietic cancers was quantified by means of incidence rate ratios (IRRs) and corresponding 95 % confidence intervals (CI), calculated using Poisson Regression models. The dependent variable was the number of incident lymphohematopoietic cancer cases, offset by population up to the age of 14, and adjusted by age group (0−4, 5−9 and 10−14), gender and MHDI, per grid cell. To investigate the role of SES, models were also stratified by two MHDI categories (above/below median). Analyses were performed using Stata version 12 (StataCorp 2011).

3. Results

A total of 2.3 million individuals were examined in this study (Table 1), of which 30.4 % were aged 0–4 years, 32.5 % were 5–9 years, and 37.1 % were 10–14 years. There was an approximately 50/50 divide in both gender and MHDI strata. Between 2002 and 2011, 1145 cases of lymphohematopoietic malignancy matching our ICD criteria were recorded. Lymphoid leukemia was the most common (n = 558, 48.7 %), followed by myeloid leukemia (n = 186, 16.3 %), Hodgkin lymphoma (n = 120, 10.5 %) and other and unspecified types of non-Hodgkin lymphoma (n = 117, 10.2 %). The frequencies for leukemias were 42.4 %, 31.4 % and 26.2 % for the age groups 0−4, 5−9 and 10−14, whereas for lymphomas were they 22.4 %, 33.5 % and 44.1 %, respectively.

The geographic distribution of MHDI is shown in Fig. 1a where areas with the highest index were typically concentrated in the central regions with the index declining towards the peripheral regions. Figs. 1b and 1c show the traffic density and annual NO_2 estimates for São Paulo respectively. In general, traffic density and NO_2 were higher in the central regions than the peripheral regions. Traffic density ranged from 0 to 163 m.vehicles.hour/m^2 (the number of vehicles for each street

Table 1
Distribution of the study population, stratified by age group, gender and MHDI (2010)[a], and the incidence of lymphohematopoietic malignancies by ICD-10 from 2002 to 2011 (São Paulo, Brazil).

Total people in study population	2,322,472	
Age group, n (%)		
0−4	706,641	30.4
5−9	753,747	32.5
10−14	862,084	37.1
Gender, n (%)		
Male	1,178,574	50.7
Female	1,143,898	49.3
MHDI category, n (%)		
Below median	1,165,070	50.2
Above median	1,157,402	49.8
Incidence of lymphohematopoietic malignancies	1145	
ICD-10, n (%)		
C81 – Hodgkin lymphoma	120	10.5
C83 – Non-follicular lymphoma	94	8.2
C85 – Other and unspecified types of non-Hodgkin lymphoma	117	10.2
C91 – Lymphoid leukemia	558	48.7
C92 – Myeloid leukemia	186	16.3
C93, C94, C95 – Other leukemia[b]	70	6.1

[a] MHDI (2010) – Municipal Human Development Index.
[b] C93 (monocytic leukemia), C94 (other cell leukemias of specified type) and C95 (leukemia of unspecified cell type).

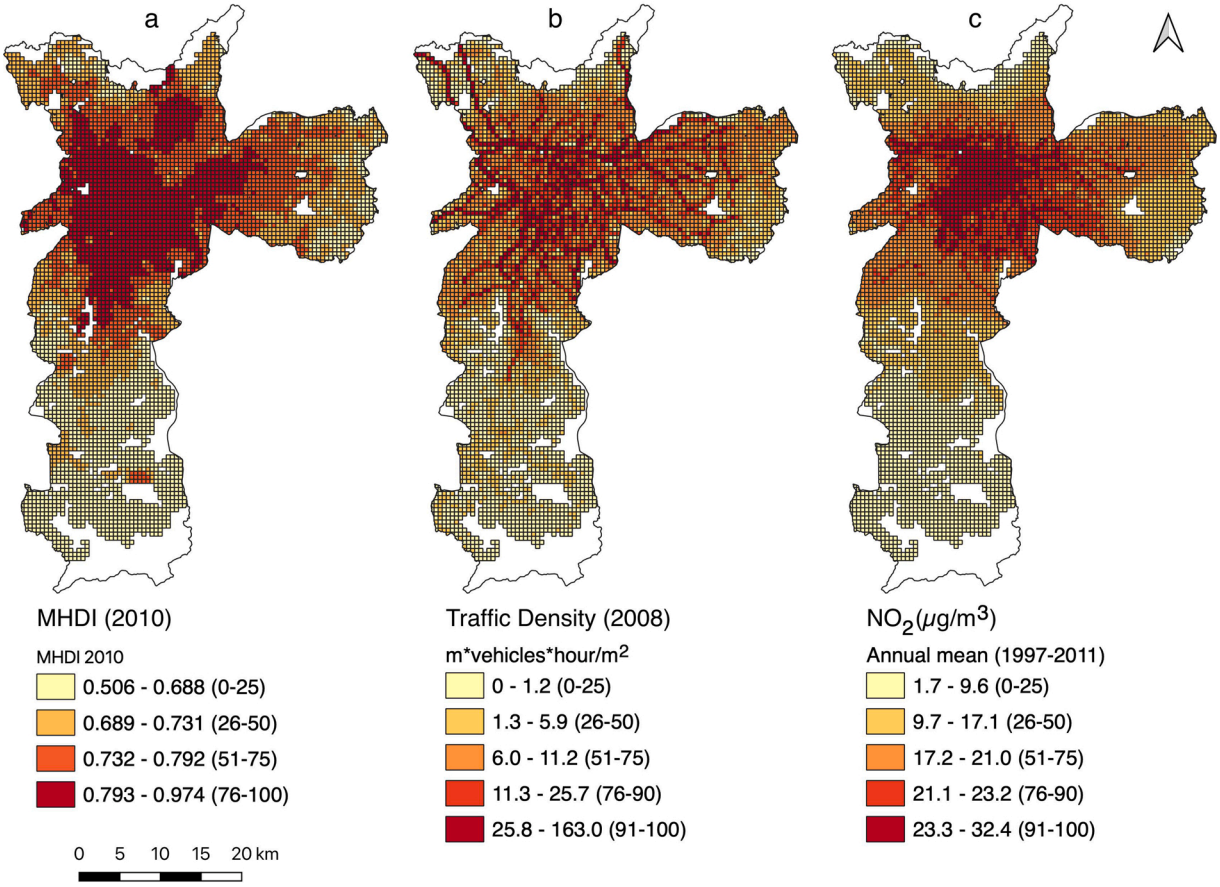

Fig. 1. (a) Municipal Human Development Index – MHDI (2010), (b) traffic density (2008) and (c) annual mean NO_2 concentrations (1997–2011), by grid cells (500m × 500m), in São Paulo, Brazil.

segment within one hour divided by the area in square meters) and ambient NO_2 concentrations ranged from 1.7 to 32.4 μg/m^3.

There was a generally positive relationship between traffic density and NO_2 and lymphohematopoietic cancer (Table 2). An increase in traffic density of 10 m.vehicles.hour/m^2 was associated with IRRs of 1.17 (95 % CI: 1.05, 1.30) for Hodgkin lymphoma and 1.05 (0.99, 1.12) for lymphoid leukemia. Similarly, a 5 μg/m^3 increase in NO_2 resulted in IRRs of 1.55 (1.15, 2.09), and 1.24 (1.08, 1.43) respectively. When stratifying by gender, males had an IRR of 1.43 (1.18, 1.72) for NO_2 and lymphoid leukemia, and females had a significantly positive IRR for Hodgkin lymphoma and both traffic density (1.30 [1.15, 1.48] and NO_2 (2.36 [1.46, 3.79]. Females also had an IRR of 1.16 (1.02, 1.31) for myeloid leukemia in relation to traffic density increase.

Stratifying by MHDI group (above/below median) indicated that the degree of effect of traffic density and NO_2 on IRR differed between the two groups. A 10 m.vehicles.hour/m^2 increase in traffic density was associated with IRRs for Hodgkin's lymphoma of 1.21 (95 % CI: 1.09, 1.34) for the high MHDI and 0.84 (0.50, 1.40) for the low MHDI group. For NO_2, the IRR for the high MHDI group was 1.97 (1.36, 2.85) and 1.16 (0.79, 1.70) in the low MHDI group. However, the degree of effect was not always consistent. For Lymphoid leukemia, the effect of traffic was more pronounced in the low MHDI group (IRR: 1.21 [1.06, 1.39] vs 1.06 [1.00, 1.14]) whereas the effect of NO_2 was similar for both groups (1.38 [1.13, 1.68] in the low MHDI vs. 1.37 [1.16, 1.62] in the high group). Further, in the high MHDI group, myeloid leukemia was significantly linked to both traffic density (1.11 [1.01, 1,23]) and NO_2 (1.46 [1.09, 1.97]).

4. Discussion

This study found that traffic density and ambient NO_2 concentrations were associated with an increased incidence of Hodgkin lymphoma and lymphoid leukemia among individuals up to the age of 14 in São Paulo. Stratifying by gender and MHDI showed that the effect of exposure was more pronounced for females and the high SES group.

The influence that residential proximity to roadways with high traffic volume has on the occurrence of lymphohematopoietic cancer in children has been the subject of several previous studies based in high income countries, with findings largely reflective of what has been reported in the current paper. An association between exposure to traffic-related air pollution and an increased risk of acute childhood leukemia was observed in two French case-control studies (the ESCALE and the GEOCAP studies [6,7], in a national cohort study from Switzerland [9], and a Spanish case control study which reported that living within 50 m of the busiest motorways was associated with a more than 3-fold increased odds of childhood leukemia [10]. However, by contrast, a recent case control study of maternal exposure in Texas, USA, found no association between maternal proximity to major roadways and acute childhood leukemia [14].

As our study was ecological and with a single assigned value (per grid) for NO_2 and traffic we were unable to differentiate between prenatal exposures and childhood exposures in terms of effect. However, both antenatal and life-course exposures have been found to be relevant for childhood lymphohematopoietic cancer. For example, the SCALE study reported a relationship between childhood leukemia and NO_2 concentrations [6], a study conducted in Taiwan observed a significant exposure-response relationship between exposure to NO_2 concentrations and the risk of leukemia among young children [15], and a recent

Table 2
Incidence rate ratio (IRR)[a] (and 95 % CI) for incidence of lymphohematopoietic malignancies among individuals up to 14 years of age by proximity to traffic density and NO_2 concentrations (São Paulo, Brazil).

Incidence (2002−2011)		Traffic Density		NO_2	
Study population = 2,322,472		(10-unit increase)		(5-μg/m^3 increase)	
	n	IRR	CI 95 %	IRR	CI 95 %
All[b]					
Hodgkin lymphoma	120	1.17	(1.05–1.30)	1.55	(1.15–2.09)
Non-follicular lymphoma	94	1.12	(0.97–1.29)	1.13	(0.81–1.57)
Other and unspecified types of non-Hodgkin lymphoma	117	1.04	(0.90–1.19)	1.29	(0.95–1.74)
Lymphoid leukemia	558	1.05	(0.99–1.12)	1.24	(1.08–1.43)
Myeloid leukemia	186	1.09	(0.98–1.21)	1.20	(0.95–1.52)
Other leukemia[e]	70	1.13	(0.98–1.30)	1.12	(0.76–1.66)
Male[c]					
Hodgkin lymphoma	72	1.02	(0.85–1.24)	1.18	(0.81–1.73)
Non-follicular lymphoma	61	1.15	(0.97–1.36)	1.35	(0.89–2.05)
Other and unspecified types of non-Hodgkin lymphoma	80	1.06	(0.91–1.23)	1.34	(0.93–1.95)
Lymphoid leukemia	317	1.07	(0.99–1.17)	1.43	(1.18–1.72)
Myeloid leukemia	96	1.01	(0.85–1.20)	1.04	(0.75–1.44)
Other leukemia	38	1.16	(0.97–1.39)	1.37	(0.81–2.32)
Female[c]					
Hodgkin lymphoma	48	1.30	(1.15–1.48)	2.36	(1.46–3.79)
Non-follicular lymphoma	33	1.06	(0.81–1.38)	0.82	(0.48–1.40)
Other and unspecified types of non-Hodgkin lymphoma	37	0.97	(0.71–1.32)	1.17	(0.69–2.00)
Lymphoid leukemia	241	1.02	(0.93–1.13)	1.04	(0.84–1.28)
Myeloid leukemia	90	1.16	(1.02–1.31)	1.40	(0.99–1.98)
Other leukemia	32	1.10	(0.88–1.37)	0.87	(0.49–1.57)
MHDI below median[d]					
Hodgkin lymphoma	49	0.84	(0.50–1.40)	1.16	(0.79–1.70)
Non-follicular lymphoma	45	1.27	(0.98–1.64)	1.34	(0.88–2.03)
Other and unspecified types of non-Hodgkin lymphoma	37	1.25	(0.93–1.68)	1.18	(0.76–1.85)
Lymphoid leukemia	202	1.21	(1.06–1.39)	1.38	(1.13–1.68)
Myeloid leukemia	70	1.01	(0.73–1.41)	0.97	(0.71–1.32)
Other leukemia	21	1.20	(0.78–1.85)	1.21	(0.67–2.19)
MHDI above median[d]					
Hodgkin lymphoma	71	1.21	(1.09–1.34)	1.97	(1.36–2.85)
Non-follicular lymphoma	49	1.09	(0.92–1.29)	1.01	(0.64–1.59)
Other and unspecified types of non-Hodgkin lymphoma	80	1.05	(0.91–1.21)	1.55	(1.09–2.21)
Lymphoid leukemia	356	1.06	(1.00–1.14)	1.37	(1.16–1.62)
Myeloid leukemia	116	1.11	(1.01–1.23)	1.46	(1.09–1.97)
Other leukemia	49	1.16	(1.01–1.33)	1.26	(0.80–1.99)

[a] Estimates from Poisson Regression models.
[b] Adjusted by age, gender and Municipal Human Development Index – MHDI (2010).
[c] Adjusted by age and Municipal Human Development Index – MHDI (2010).
[d] Adjusted by age and gender.
[e] C93 (monocytic leukemia), C94 (other cell leukemias of specified type) and C95 (leukemia of unspecified cell type).

study observed a higher risk of this exposure with non-Hodgkin lymphoma in children aged 0–19 years [16]. However, a study conducted in Oklahoma, USA, did not find any significant association between exposure to nitrogen oxides or road density and childhood acute leukemia [8] and a recent study in Iran observed a positive association between PM_{10} exposure and childhood cancers and a positive, but not statistically significant association with NO_2 exposure [4]. With regards to maternal exposure, the relationship between maternal exposure to ambient NO_2 and childhood lymphohematopoietic cancer was reported by a study conducted in Ontario, Canada who reported a positive association between exposure during the first trimester of pregnancy and acute lymphoblastic leukemia [13]. A case control study of maternal exposure from California, USA, reported that the odds of acute lymphoblastic leukemia increased by 9 %, 23 %, and 8 % for each 25-ppb increase in average nitric oxide, nitrogen dioxide, and nitrogen oxide levels, respectively, over the entire pregnancy [12].

In terms of aetiological mechanisms, the causes of childhood neoplasms, including leukemias and lymphomas, are largely unknown and only 5% of tumors can be associated with hereditary origin, requiring the investigation of specific mutation profiles that are possibly related to environmental carcinogens [23]. Our results align with those reported in a review of genotoxicity biomarkers which reported a greater amount of DNA damage in children exposed to outdoor air pollution in urban areas or who attended schools within 500 m of a high-traffic road, compared with children in relatively unpolluted area [24]. Many childhood cancers, like in those in adults, are thought to be activated by somatic mutations, and compared with adults, children are more vulnerable to environmental agents because of their unique activity patterns, behavior, and physiology, as well as the immaturity of their organs [23].

São Paulo has a pollutant monitoring network that includes 17 fixed stations with regular measurements for: PM_{10}, SO_2, NO_X, CO, O_3 and $PM_{2.5}$ but the number and geographical distribution of these stations are insufficient to measure exposures to these pollutants on a fine spatial scale. Despite the lack of other sources of air pollution data, a major strength of our study was the use of the global NO_2 land use regression model that allowed estimating NO_2 concentrations at a relatively fine spatial scale (100 m resolution), the ability to estimate traffic density at a fine spatial scale, which might be used as a proxy for traffic exposure in São Paulo [25], and detailed information on socio-economic factors. This enabled us to observe differences in effect estimates by MHDI group. In general, the traffic metrics were higher within the high MHDI group, where we found more significant IRRs for lymphohematopoietic cancer. These differences can be seen for Hodgkin lymphoma and myeloid leukemia.

Despite our findings, this ecological study has certain limitations, most notably a lack of individual information, meaning we were unable to consider other potentially confounding factors that were not available in the registry data (ex. cytogenetic factors, other environmental exposures, race, ethnicity, family history of cancer, etc.). Furthermore, we assumed that all individuals within the 500m × 500m grid cells had the same level of exposure, however as it was not possible to assess the variation of individual exposures during daily movements within the city, some exposure misclassification is likely to have occurred. However, individuals up to 14 years of age are less likely to move between the regions of the city than working-age adults, which reduces the influence of this factor. Another limitation is that averaging NO_2 exposures over the years may also induce bias if the exposure is highly variable over the study period. However, we used small area units and the NO_2 measurements had a higher stability during the assessment period, probably because the road system has been running at full capacity in the last years. Although, we could not evaluate the exposure occurred before 1997, the historical air quality data reported pollutants level higher in previous years of this study with NO_2 concentrations above 50 μg/m^3 from 1982 to 1996 [26], meaning that the exposure assigned here likely under-estimate historical exposures.

In summary, NO_2 and traffic density were positively associated with an increased incidence of Hodgkin lymphoma and lymphoid leukemia. Differing IRRs by gender and SES group indicate differences in underlying risk and/or exposure profiles.

Authorship contribution

AGR, ACN and GD were responsible for designing the study, working on the analysis, interpreting the findings and writing the manuscript. RV, MRAC, MRDOL and PH worked on the acquisition of data,

interpretation the findings and reviewed critically the manuscript. All authors have revised and approved the version to be published.

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CRediT authorship contribution statement

Adeylson Guimarães Ribeiro: Conceptualization, Methodology, Formal analysis, Investigation, Writing - original draft, Writing - review & editing, Visualization. **Roel Vermeulen:** Methodology, Investigation, Writing - review & editing. **Maria Regina Alves Cardoso:** Methodology, Data curation, Validation, Writing - review & editing, Funding acquisition. **Maria do Rosario Dias de Oliveira Latorre:** Data curation, Investigation, Writing - review & editing. **Perry Hystad:** Methodology, Data curation, Validation, Writing - review & editing. **George Stanley Downward:** Investigation, Writing - original draft, Writing - review & editing, Visualization, Supervision. **Adelaide Cássia Nardocci:** Conceptualization, Methodology, Validation, Writing - review & editing, Project administration, Funding acquisition.

Declaration of Competing Interest

None.

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