Estimating Exposure to Traffic-Related Air Pollution and Its Consequences on Respiratory Health in Population Working or Living along the Trunk Road: A Systematic Review

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Abstract

Introduction: Urban Air pollution is increasingly becoming a major health and sustainable development issue. Several studies showed that Traffic-related air pollution (TRAP) is one of the main sources of urban air pollution and has serious consequences on respiratory health. As no systematic review focused on the traffic-related air pollution and respiratory health in the target population of individuals working in a shop or in an office or individuals living along the trunk road, the authors conducted the current study to try to fill this gap. Methods: A systematic review search was conducted using MEDLINE (PubMed), Scientific Research Publishing: SCIRP, Web of Science, Google scholar. Studies were included if they meet the following selection criteria: 1) focus on population working or living along a major/trunk road; 2) studies had reported clearly at least on the exposure variables related to TRAP; 3) the association between TRAP and development of respiratory symptoms or respiratory diseases was established. Results: 13 articles were selected on the 192 articles that were retrieved in the initial research. Exposure to traffic-related air pollution was determined by using distance to road, traffic intensity and pollutants measured. The main respiratory health problems found were cough, wheeze, asthma and bronchitis. No article discussed about roundabouts in characterizing exposure to traffic-related air pollution. Conclusion: Distance to road, traffic density and pollutants measured are the usual methods to characterize the exposure to traffic-related air pollution and its consequences on respiratory health. Regarding the context of area occupations in African cities, it is necessary to focus on population around roundabouts and see if they are not more exposed to TRAP.
1. Introduction

Urban Air pollution is increasingly becoming a major health and sustainable development issue. Compared to all other forms of environmental pollution, air pollution causes the largest number of environmental pollution-related deaths [1]. Ninety-two per cent of the world’s population is living in places where levels exceed recommended limits [2]. The World Health Organization (WHO) estimates that ambient (outdoor) air pollution was estimated to cause 4.2 million premature deaths worldwide per year in 2016 [3]. Traffic-related air pollution (TRAP) is one of the main sources of urban air pollution [4] [5] [6] [7] [8]. In major African cities, the air quality has deteriorated significantly. In a study conducted from 2015 to 2017 in Benin and Côte d’Ivoire, 24-hour PM$_{2.5}$ concentrations were found to consistently exceed WHO guidelines [9]. In Ethiopia, Kenya and Uganda, PM pollution levels were estimated to have increased by 182%, 162% and 62% respectively since the 1970s to the current period [10]. The increase in number of obsolete vehicles [11], the urbanization plan that does not keep up with the rapid population growth and the rural exodus are among the main reasons for this situation.

The relationship between TRAP exposure and respiratory morbidity has been studied worldwide [8] [12] [13] [14] [15] [16] and several systematic reviews have examined the relationship between exposure to traffic-related air pollution and respiratory health [17]-[23]. But to the author’s knowledge, there were not enough systematic reviews that focused on the target population of individuals working or living along the trunk road. The current review is an attempt to fill this gap. The first step will be to take stock of the different approaches used to estimate the exposure of this target group to traffic-related air pollution and to identify the different pollutants that have been studied. Secondly, the different respiratory health problems are identified.

The aim of this review is to examine if the different approaches used to estimate exposure to traffic-related air pollution and its consequences on respiratory health fully respond to the context of West Africa’s cities such as Cotonou.

2. Methodology

This systematic review adhered to the recommendations outlined in the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement [24].

2.1. Data Sources and Search Strategy

Searches were performed using a systematic literature search strategy with the
removal of duplicates, identifying the available data on the topic. The following electronic scientific databases were primarily searched: MEDLINE (PubMed), Scientific Research Publishing: SCIRP (Open Journal of Air Pollution; Open Journal of Respiratory Diseases), Web of Science. Data sources such as the Google Scholar, search on internet for available grey literature, the table of contents of Environmental Health Perspectives and Atmospheric Environment were searched. The authors also hand-searched references list from included studies in order to found any relevant titles. Medical search terms (MeSH) and keywords such as “traffic” AND (“Air pollution” OR “TRAP”) AND (“respiratory symptoms” OR “respiratory diseases”) AND (“major road” OR “trunk road” OR “main road” OR “busy road” OR “main street” OR “major street”) were used as combinations of text or thesaurus terms to conduct search in the various databases, with the aim of identifying eligible articles for inclusion in the review.

2.2. Studies Selection

All original studies, published in English or French including observational or epidemiological studies (cross-sectional, cohort, case-control studies) published from inception January 2000 to December 2019, which discussed about traffic-related air pollution and respiratory symptoms in population working or living along major or trunk roads were eligible for this review. The authors have only included those studies that mentioned clearly the exposure variable addressed. Another inclusion criterion was that the article should address the various respiratory symptoms or respiratory diseases that were associated with traffic-related air pollution.

These different selection criteria concerning specifically the type of study and all expected characteristics of the results are clearly summarized and detailed in Table 1.

Table 1. Selection criteria.

| Inclusion criteria                                                                 | Exclusion criteria                                                                 |
|-----------------------------------------------------------------------------------|-----------------------------------------------------------------------------------|
| • Original articles                                                                | • Non-research studies, off-topic studies, studies concerning populations not exclusively exposed to traffic-related air pollution |
| • Epidemiological or observational studies such as cross-sectional, cohort, or case-control studies | • Review, commentaries                                                            |
| • Only human studies                                                               | • Animal studies                                                                  |
| • Articles published in English, French                                             | • Abstract or full articles not available                                         |
| • Focus on traffic related air pollution                                           | • Studies about TRAP but not on major/trunk road                                 |
| • Focus on population working or living along a major/trunk road                   | • Studies that measured exclusively pollution exposure to non-traffic related air pollution |
| • Studies had reported clearly at least one of the exposure variables related to TRAP |                                                                                   |
| • Studies had reported respiratory symptoms or respiratory diseases                |                                                                                   |
| • Studies examined the association between traffic related air pollution (TRAP) and development of respiratory symptoms or respiratory diseases |                                                                                   |

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The selection process of the articles was done iteratively in three stages, based on all the inclusion criteria previously defined. In the first stage, one author screened all titles and removing the titles of publications that are not relevant, and then the others authors screened the remaining publications based on abstract. Thus, after having screening the publications based on titles and abstracts, the last step will be to evaluate the eligibility of the full articles remaining.

2.3. Data Extraction, Management and Synthesis

For all included studies, according to the inclusion criteria on consensus of two reviewers (HL & VA), data have been extracted and synthesized in a table. Data extracted included authors, year of publication, the location, the study design, the type of exposure variable and the different respiratory symptoms or respiratory diseases found in these studies as health outcomes.

3. Results

3.1. Search Results and Flow Chart

The initial research produced a total of 192 publications from the various databases and other sources. After removing 18 duplicates, 136 publications were excluded after an evaluation, based on a title analysis, and abstract analysis. This left a final total of 38 studies whose full text articles were reviewed for eligibility. At the end of the review process, 13 publications met the eligibility criteria and were included in the review. The PRISMA flow diagram below (Figure 1) summarizes the study selection process, including the number of publications found, the review process, and the reasons for exclusion of publications.
3.2. Study Design, Site and Population Studied

On the 13 articles included (see Table 2), 6 were a cohort study and 6 were a cross-sectional study; one article used a case-control study and a cross-sectional study. The studies were implemented in Europe (Switzerland, UK, Netherlands, Sweden, Italy, Germany), in USA, in Asia (China, Japan) and in Oceania (Australia). Different populations were studied such as residents or children in class.

3.3. Exposure Variables Measured in Studies Included in the Review

Three variables were used to estimate the exposure to traffic-related air pollution: distance or proximity from a major road, traffic intensity and pollutants measured. As shown in Table 2, most of articles (11 on 13) based the characterization of the exposure to traffic-related air pollution on the distance by using different approaches. Among them were distance to closet main street per 100 m, distance to nearest main road (≤30 m; 60 m; 90 m; 120 m; 150 m) [26], distance to major road (<200 m or ≥200 m) [28], distance from trunk road (0 - 49 m, ≥50 m) [35].

Six articles used traffic intensity to characterize the exposure to traffic-related air pollution. Traffic intensity were defined by Truck traffic density, car traffic density, <10,000 vehicles per day versus ≥10,000 vehicles per days [12], number of cars per minute (0 - 1 cars/min; 2 - 5 cars/min; 6 - 10 cars/min and >10 cars/min) [31] or per 12 hours [35].

Seven articles used pollutants measure to appreciate the exposure to traffic-related air pollution. Several pollutants were measured such as PM$_{10}$ [25] [30] [34]; PM$_{2.5}$ [29] [30]; NO$_x$ [30] [31], NO$_2$ [28] [29] [30] [32] [34] [35], NO [30], Benzene [29], BC [30] [32] and SO$_2$ [35].

3.4. Effects on Respiratory Health

Articles included showed effects of traffic-related air pollution on respiratory health.

These effects could be mostly classified in two groups: effects found based on the distance to road (Table 3) and effects found based on the concentrations of pollutants (Table 4).

Hu et al. found that compared to participants with a home road distance of >200 m, participants with a home road distance of <100 m or 100 - 200 m had a higher prevalence of chronic cough, with an odds ratio of 2.54 (95% CI: 1.57 - 4.10) and 1.97 (95% CI: 1.16 - 3.37), respectively [27]. In the same vein, Bowate et al. also found that living < 200 m from a major road and NO$_2$ exposure was associated with increased current asthma and current wheeze prevalence (adjusted OR 1.49; 95% CI: 1.09 - 2.05 and 1.61, 95% CI: 1.19 - 2.19, respectively) [28]. Regarding the results reported by Mc Connell et al., living < 75 m was significantly associated with a higher prevalence of asthma (adjusted OR 1.29; 95% CI: 1.01 - 1.66), and a current wheeze (adjusted OR 1.40; 95% CI: 1.09 - 1.78)
Table 2. Studies about TRAP and respiratory health on population living/working along trunk road included in the review.

| Author          | Year of publication | Type of study          | Location (city) | Population studied | Exposure variables | Key Health Outcomes | Key findings                                                                                                                                 |
|-----------------|---------------------|------------------------|-----------------|--------------------|--------------------|---------------------|-----------------------------------------------------------------------------------------------------------------------------------------------|
| Bayer-Oglesby   | 2006                | Cohort study           | Switzerland     | Adults             | Distance (distance to closest main street (per 100 m); living within 20 m of a main street) | RS, RS, RS          | The risk of attacks of breathlessness increased for all subjects by 13% per 500-m increment in the length of main street segments within 200 m of the home and decreased in never smokers by 12% per 100 m increment in distance from home to a main street. Living within 20 m of a main street increased the risk of regular phlegm by 15% and wheezing with breathing problems by 34% in never smokers. These findings among a general population provide strong confirmation that living near busy streets leads to adverse respiratory health effects. Among children living within 150 m of a main road, the risk of wheeze increased. And most of the increased risk was localized to within 90 m of the roadside. Living within approximately 90 m of a main road is associated with a proximity-related increase in the risk of wheezing illness in children. Participants living a shorter distance from major roads had lower percentage of predicted FEV in 1 s. Long term exposure to traffic related air pollution in people living near major roads in Beijing is associated with lower lung function, airway acidification, and a higher prevalence of chronic cough. |
| Venn et al.     | 2001                | Case control/Cross sectional | UK (Nottingham) | Children and adolescents | Distance to nearest main road (≤30 m; 60 m; 90 m; 120 m; 150 m) | RD, RS              |                                                                                                                                                             |
| Hu et al.       | 2016                | Cohort study           | China (Beijing) | Adults long-term residents | Distance (<100 m; 100 - 200 m, or >200 m) | RS, RS              |                                                                                                                                                             |
Bowate et al. [28] 2017 Longitudinal study (data from established cohort study) Australia (Tasmania) Adults (45 - 50 years) - **Distance to major road** (<200 m; ≥ 200 m) - **Pollutant measured** - NO₂ - **RS** - Wheeze - **RD** - Asthma

- **Traffic intensity** - Truck traffic density (vehicles/weekday) - Car traffic density (vehicles/weekday) - **Distance** - Distance schools motorways (m) - Distance home - motorway (m) - **Pollutants measured** - PM₂.₅ - NO₂ - Benzene

- **RS** - Wheeze - Asthma ever - Current conjunctivitis - Hay fever ever - Current itchy rash - Ecema ever - Current phlegm - Current bronchitis - **RD** - Bronchial Hyper responsiveness (BHR)

- Air pollutants that increased near motorways with high truck traffic counts - Respiratory symptoms were increased also near motorways with high truck traffic counts.

- Men living within 50 m of a major roadway were more likely to report persistent wheeze compared with those living more than 400 m away - The risk was observed only for those living within 50 m of heavily trafficked road (≥10,000 vehicles/24h) - Exposure to vehicular emissions by living near busy roadways contribute to symptoms of chronic respiratory diseases in adults

Janssen et al. [29] 2003 Cross-sectional study Netherlands Children in classes 4 - 8 (7 - 12 years old) - **Traffic intensity** - Truck traffic density (vehicles/weekday) - Car traffic density (vehicles/weekday) - **Distance** - Distance schools motorways (m) - Distance home - motorway (m) - **Pollutants measured** - PM₂.₅ - NO₂ - Benzene

- **RS** - Wheeze - Asthma ever - Current conjunctivitis - Hay fever ever - Current itchy rash - Ecema ever - Current phlegm - Current bronchitis - **RD** - Bronchial Hyper responsiveness (BHR)

- Air pollutants that increased near motorways with high truck traffic counts - Respiratory symptoms were increased also near motorways with high truck traffic counts.

Garshick et al. [12] 2003 Cross-sectional study US (Southeastern Massachusetts) Adults Male (Veterans) - **Traffic intensity** (<10,000 veh/day; ≥10,000 veh/day) - **Distance from roadway** (50 m; 50 - 400 m; >400 m) - **RS** - Wheeze - Chronic cough - Chronic phlegm - **RD** - Chronic Respiratory Disease (CRD)

- Living < 200 m from a major road was associated with increased prevalence of current asthma and wheeze, and lower lung function - Over the 5-year period, higher NO₂ exposures were associated with increased asthma prevalence

- Men living within 50 m of a major roadway were more likely to report persistent wheeze compared with those living more than 400 m away - The risk was observed only for those living within 50 m of heavily trafficked road (≥10,000 vehicles/24h) - Exposure to vehicular emissions by living near busy roadways contribute to symptoms of chronic respiratory diseases in adults
| Study Authors      | Year | Study Design       | Location          | Population Details                                      | Traffic Intensity                     | Distance (downwind) | Pollutants Measured | Findings                                                                 |
|--------------------|------|--------------------|-------------------|---------------------------------------------------------|---------------------------------------|---------------------|---------------------|--------------------------------------------------------------------------|
| Kim et al. [30]    | 2004 | Cross-sectional    | US (San Francisco) | Children                                                | Traffic intensity (90,000 - 210,000 veh/day) | Distance (<300 m)  | PM10, PM2.5, BC, NOx, NO2, NO | Observation of difference concentrations between schools nearby versus more distant (or upwind) from major roads |
| Lindgren et al. [31]| 2009 | Cross-sectional    | Southern Sweden    | Adults (18 - 77 years)                                   | Traffic intensity (0 - 1 cars/min; 2 - 5 cars/min; 6 - 10 cars/min and >10 cars/min based upon 24-hour mean levels) | Distance (within 100 m of a road with >10 cars/minute) was associated with prevalence of asthma diagnosis and COPD diagnosis, and symptoms of asthma and bronchitis. |
| Hoek et al. [32]   | 2002 | Cohort study       | Netherlands        | Adults (55 - 69 years)                                   | Distance (<300 m downwind)            | Pollutants measured | NOx modeled exposure | Cardiopulmonary mortality was associated with living near a major road. |
| Migliore et al. [33]| 2009 | Cross-sectional    | Italy              | Children (6 - 7 years) and adolescents (13 - 14 years)   | Traffic intensity                      | Pollutants measured | BC, NO2 | Traffic density was weakly associated with asthma symptoms but there was a stronger association with cough or phlegm. | Children living in zones with intense traffic are at higher risk for respiratory effects. |
| Study                | Year | Study Design         | Country       | Population          | Exposure Measures                                                                 | Findings                                                                                                                                 |
|---------------------|------|----------------------|---------------|---------------------|------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------|
| Schikowski et al.   | 2005 | Cross-sectional study | Germany       | Adults (Women)       | Distance (<100 m, ≥100 m); Pollutants measured - NO₂, PM₁₀                           | COPD and pulmonary function were strongest affected by PM₁₀ a traffic related exposure. Women living less than 100 m from a busy road also had a significantly decreased lung function and COPD was 1.79 times more likely than for those living farther away. Chronic exposure to PM₁₀, NO₂ and living near a major road might increase the risk of developing COPD and can have a detrimental effect on lung function. |
| McConnel et al.     | 2006 | Cohort study         | US (Southern California) | Children (5 - 7 years) | Distance (<75 m; 75 - 150 m; 150 m - 300 m; >300 m)                              | Residence within 75 m of a major road was associated with an increased risk of lifetime asthma.                                             |
| Shima et al.        | 2003 | Cohort study         | Japan         | Children (6 - 9 years) | Traffic intensity (number of vehicles/12 hours); Distance from trunk road (0 - 49 m; ≥50 m; rural area); Pollutants measured - NO₂, SPM, SO₂ | The prevalence of asthma increased with increases of air pollution. Findings suggest that traffic-related air pollution may be of a particular importance in the development of asthma among children living near major trunk roads with heavy traffic |
Table 3. Some significant associations between respiratory symptoms or diseases and distance to major road.

| Authors        | RS/RD              | Exposure (Distance) | OR (95% CI)         |
|----------------|--------------------|---------------------|---------------------|
| **Hu et al.**  | Chronic cough      |                     |                     |
|                | <100 m             | 2.54 (1.57 - 4.10)  |                     |
|                | 100 - 200 m        | 1.97 (1.16 - 3.37)  |                     |
|                | >200 m             | 1                   |                     |
| **Current asthma** |                   |                     |                     |
| **Bowate et al.** | Living < 200 m from a major road | 1.49 (1.09 - 2.05) |                     |
| **Current wheeze**  |                     |                     |                     |
| **McConnell et al.** | Living < 200 m from a major road | 1.61 (1.19 - 2.19) |                     |
| **Lifetime asthma** | >300               | 1                   |                     |
|                | 150 - 300          | 0.92 (0.73 - 1.15)  |                     |
|                | 75 - 150           | 1.06 (0.82 - 1.36)  |                     |
|                | <75                | 1.29 (1.01 - 1.66)  |                     |
| **Prevalent asthma** |                     |                     |                     |
|                | >300               | 1                   |                     |
| **Frequent cough** |                     |                     |                     |
| **Schikowski et al.** | <100 m from major road with 10,000 cars/day compared to >100 m | 1.24 (1.03 - 1.49) |                     |
| **COPD**       |                     |                     |                     |

RS: Respiratory symptoms; RD: Respiratory diseases; OR: Odd ratio; COPD: Chronic Obstructive Pulmonary Disease.

(adjusted OR 1.25; 95% CI: 1.00 - 1.58), frequent cough (adjusted OR 1.13; 95% CI: 1.01 - 1.27) and COPD (adjusted OR 1.39; 95% CI: 1.20 - 1.63). Another result found by Schikowski et al. is the association between PM10 and COPD. He found that an increase of 7 of µg/m3 PM10 was associated with an increased risk of COPD (adjusted OR 1.33; 95% CI: 1.03 - 1.72) [34].
Table 4. Some significant associations between respiratory symptoms or diseases and air pollution concentrations.

| Authors          | RS/RD | Exposure (Pollutants) | OR (95% CI)         |
|------------------|-------|-----------------------|---------------------|
| *Kim et al.*     |       | **Bronchitis**        |                     |
|                  |       | NO₂                   | 1.05 (1.01, 1.08)   |
|                  |       | NO                    | 1.05 (1.02, 1.09)   |
| *Schikowski et al.* | Chronic bronchitis by physician diagnosis | NO₂ [16 µg/m³] | 1.25 (1.00 - 1.58) |
|                  |       | Frequent cough        |                     |
|                  |       | NO₂ [16 µg/m³]        | 1.13 (1.01 - 1.27)  |
| *Janseens et al.* |       | COPD                  |                     |
|                  |       | NO₂ [16 µg/m³]        | 1.39 (1.20 - 1.63)  |
|                  |       | PM₁₀ [7 µg/m³]        | 1.33 (1.03 - 1.72)  |
|                  |       | **Hay fever ever**    |                     |
|                  |       | PM₂.⁵                 | 2.28 (1.13 - 4.57)  |

RS: Respiratory symptoms; RD: Respiratory diseases; OR: Odd ratio; COPD: Chronic Obstructive Pulmonary Disease.

In the rest of this paragraph, we presented some results that combined the effects of distance to major road, the concentrations of pollutants or the intensity of traffic on respiratory health. Bowate et al. also found that living < 200 m from a major road and NO₂ exposure was associated with increased current asthma prevalence (adjusted OR 1.49; 95% CI: 1.09 - 2.05 and aOR 1.10, 95% CI: 0.96 - 1.27, respectively) [28]. In the same vein, Garshick et al. reported that exposure to vehicular emissions by living near busy roadways contribute to symptoms of chronic respiratory diseases in adults [12] and Hu et al. reported that long-term exposure to traffic-related air pollution in people living near major roads in Beijing is associated with lower lung function, airway acidification and a higher prevalence of chronic cough [27]. Lindgren et al. found that living close to traffic (within 100 m of a road with >10 cars/minute) and annual average NOₓ was associated with prevalence of asthma diagnosis and COPD diagnosis and symptoms of asthma and bronchitis [31]. Concerning the children’s, Migliore et al. found that children living in zones with intense traffic are at higher risk for respiratory effects [33] and Kim et al. also reported an observation of a difference concentrations between schools nearby versus more distant (or upwind) from major roads and association between respiratory symptoms and traffic related pollutants [30]. Shima et al., findings confirmed that traffic-related air pollution may be of a particular importance in the development of asthma among children living near major trunk roads with heavy traffic [35]. Hoek et al. goes much deeper by establishing that long-term exposure to traffic-related air pollution may shorten life expectancy due to fact that cardiopulmonary mortality was associated with living near a major road [32].
The different effects reported in this review can be classified in respiratory symptoms and respiratory diseases. The main respiratory symptoms found were wheezing [12] [25] [26] [28] [29] [36], cough [12] [25] [27] [33] [34] [35]. As respiratory diseases, the articles mentioned asthma [26] [28] [30] [31] [35] [36], bronchitis ([30] [31] [34], chronic respiratory diseases [12] [31] [34].

4. Discussion

This systematic review focused on different methods to estimate the exposure to traffic-related air pollution and its consequences on respiratory health in population working or living along or near the trunk road. So, what we were going to discuss in this paper was not the degree of association between exposure to traffic-related and respiratory health but we would like to highlight the different approaches used for these relationships.

The authors found only 13 studies that meet the criteria and no study in Africa. To characterize the exposure to traffic-related air pollution, studies used distance to road [12] [25]-[30] [32] [34] [35] [36], traffic density [12] [26] [29] [30] [31] [33] [35] and pollutants measure [25] [28] [29] [30] [31] [32] [34] [35]. Several previous systematic reviews came to the same conclusion in their study [20] [37] [38].

Based on these three characterization approaches, the authors of different papers have estimated the health outcomes.

The main health outcomes found were wheeze and cough for respiratory symptoms, asthma and bronchitis for respiratory diseases. This is consistent with some results in literature. Indeed Weinmayr et al., found that cough was one of key health respiratory symptom outcome [39]. Sylla et al. and Weinmayr et al. found in their review that asthma was one of key health respiratory disease outcome [20] [39].

Whether to characterize exposure to air pollution related to road traffic or to determine the effects of this exposure on respiratory health, the different articles included did not specifically address the particularity of roundabouts. Certainly, because these studies did not take place in the context of major West African cities. In fact, in these cities, urbanization is not always well carried out and the populations are enthusiastic to settle along the roads but also around the roundabouts with heavy traffic for their commercial activities [40] [41]. But living or working closet to high-traffic may have an additional risk depending on the location in relation to roundabouts and this situation has not been considered in different studies included.

5. Conclusion

In the present study, the authors found that distance to road, traffic density and pollutants measure are the usual methods to characterize the exposure to traffic-related air and his consequences on respiratory health. No study mentioned the situation about specifically populations around the roundabouts. But the
situation in Africa’s cities is different regarding the urbanization and the enthusiasm of population to settle along high traffic road and roundabouts. The authors suggest that it would be very useful if research focused on the populations living around the roundabouts in order to determine their possible overexposure to air pollution linked to traffic.

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Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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