Gliwice, 05.02.2025

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PETYCJA O ZMIANĘ PRZEBIEGU TRASY OBWODNICY OSTROPA ORAZ ZMIANĘ PRZEZNACZENIA TERENU W MPZP DLA OBRĘBU OSTROPA POLA Z PRZEMYSŁOWEGO NA BUDOWLANO- USŁUGOWY

Szanowna Pani Prezydent,

Ponieważ bez jednoznacznego podania przyczyny termin składania wniosków do planu ogólnego został wydłużony jedynie dla okolic dzielnicy Sikornik, jako przedstawiciele społeczności Ostropy składamy własne zastrzeżenie do obecnego MPZP oraz wnioski, których uwzględnienia oczekujemy w powstającym planie ogólnym.

Nie negując konieczności inwestycji i rozwoju miasta, musimy zwrócić uwagą, że powinny się one odbywać z uszanowaniem głosu mieszkańców i norm środowiskowych. Dlatego w niniejszej petycji przedstawimy argumenty mieszkańców, mające na celu wypracowanie kompromisu, który nie zablokuje Państwa planów, ale też nie zniszczy unikalnego charakteru dzielnicy i nie obniży jakości życia jej mieszkańców.

Zarówno obwodnica miasta jak i strefa przemysłowa w części od autostrady A4 do szybu KWK Gliwice, powstają w odległości zaledwie 200 metrów od domów mieszkalnych. Spowoduje to, wzrost zanieczyszczenia powietrza, hałasu oraz tzw. smogu świetlnego. Biorąc pod uwagę, że w pobliżu jest autostrada A4, Ostropa stanie się miejscem gdzie hałas i zanieczyszczenia zaczną mieć bardzo negatywny wpływ na zdrowie i życie mieszkańców. Budowa kolejnego szlaku komunikacyjnego dla pojazdów osobowych i ciężarowych sprawi, że w tym rejonie zacznie występować więcej zanieczyszczeń TRAP, co znacząco wpłynie na poziom zanieczyszczenia powietrza i zdrowie mieszkańców. W załączeniu nr 1 do niniejszej petycji przedstawiamy zastrzeżenia oraz argumenty podważające wydaną dla rzeczonej inwestycji drogowej decyzję środowiskową. W załącznikach od 2 – 10 przedstawiamy badania naukowe ukazujące bezpośredni, negatywny wpływ zanieczyszczeń TRAP na zdrowie dzieci i dorosłych.

Dodatkowo, patrząc na plany dotyczące budowy obwodnicy miasta nawsuwa się wniosek, że nie do końca jest to obwodnica służąca mieszkańcom miasta. Nowa droga zwana obwodnicą ma stanowić głównie dojazd do powstającej strefy przemysłowej, a tym samym dedykowana będzie transportowi ciężkiemu. Po otwarciu w ub. roku części obwodnicy prowadzącej od ulicy Rybnickiej do ulicy Swoińskiego, jasno wynika, że niewielki procent kierowców jadących Daszyńskiego wybiera skręt w lewo (jadąc od Ostropy). Większość kierowców jedzie prosto w stronę centrum miasta. Tak więc nowa obwodnica w niewielkim stopniu odciąży ulicę Daszyńskiego.

Dlatego założenie, że obwodnica ma odciążyć drogi lokalne i nie wpłynie na zwiększenie zanieczyszczenia powietrza jest fałszywe, ponieważ wygenerowany zostanie nowy ruch drogowy stanowiący dojazd do hal przemysłowych. To z pewnością wpłynie na zwiększenie hałasu i emisji

szkodliwych substancji. Dowody naukowe jednoznacznie wskazują, że zanieczyszczenie powietrza ma związek z epidemią chorób takich jak nowotwory, udary mózgu, choroby serca, astma i przewlekła obturacyjna choroba płuc.

Z informacji telefonicznej uzyskanej w ub. roku w ZDM Gliwice, wynika, że miasto planując budowę obwodnicy nie uwzględniło przebudowy lokalnych dróg zjazdowych w rejonie skrzyżowania ulic Tokarskiej i Ciesielskiej, tak aby mieszkańcy, zwłaszcza dzieci, mogli bezpiecznie przejść na drugą stronę ulicy, zmierzając do szkoły, pracy czy na przystanek autobusowy.

Reasumując powyższe- mieszkańcy znacznej części Ostropy zostaną zamknięci w kleszczach Autostrady A4, obwodnicy, i hal przemysłowych, które drastycznie obniżą jakość ich życia, uniemożliwiając bezpieczne wydostanie się z tej „enklawy".

Planowane inwestycje pozabawiają także mieszkańców całego miasta zielonych i spokojnych terenów rekreacyjnych, które w drastycznym tempie znikają z mapy Gliwic. To tutaj gliwiczanie po ciężkim dniu pracy przyjeżdżają na rowerach, spacerują, biegają, organizują się grupy nordic walking. W pobliży planowanej obwodnicy i strefy przemysłowej, działają trzy stadniny, gdzie jedna z nich prowadzi hipoterapię dla dzieci z niepełnosprawnościami.

Na terenie pól Ostropy swoje siedliska mają różne gatunki zwierząt - ptaków, gadów, saren, nietoperzy. To na terenach przeznczonych pod inwestycje przemysłowe, znajdują się także zasoby wody dla mieszkańców Gliwic. Ponad to obszar Ostropa Pola w Audycie Krajobrazowym Województwa Śląskiego został uznany za obszar krajobrazu priorytetowego ze względu na swój unikatowych charakter. Powyższe jasno sugeruje, że teren ten zasługuje na szczególne traktowanie i ochronę.

Ostropa jest wyjątkową dzielnicą z silną tradycją rolniczą, gdzie kultywuje się zwyczaje przekazywane z pokolenia na pokolenie. To tutaj, na polach na których już niedługo mają stanąć hale przemysłowe i jeździć TIR-y, każdego roku od setek lat przejeżdża słynna na całą Polskę wielkanocna procesja konna zwana Osterritt. Na stronach UM Gliwice czytamy:

Ten zwyczaj uznawany jest za jeden z najstarszych zachowanych na Śląsku i Łużycach i czyni Ostropę miejscem szczególnym w Polsce. Ostropska tradycja wpisana została na krajową listę niematerialnego dziedzictwa kulturowego.

Miasto Gliwice szczyci się, że jest jedną z najbogatszych gmin w Polsce, jednocześnie nie przekłada się to na podniesienie jakości życia jej mieszkańców. Wręcz przeciwne kolejne inwestycje skutecznie odstraszają, zwłaszcza młodych ludzi do tego, aby pozostać w mieście. Świadczy o tym wyludnianie się miasta. Z danych GUS wynika, że Gliwice są w czołówce miast w Polsce, które w alarmującym tempie tracą mieszkańców, zwłaszcza młodych. Od 2000 roku Gliwice straciły ponad 24 tysiące mieszkańców! Pomimo, że działa tutaj jedna z najlepszych uczelni w Polsce, miasto nie potrafi zatrzymać młodych ludzi, którzy tu studiują. Jednym z czynników jest z pewnością betonowanie miasta, brak miejsc rekreacji, tworzenie stref przemysłowych w pobliżu osiedli mieszkaniowych oraz kurczący się obszar stref zielonych. Nikt nie chce mieszkać w miejscu gdzie jest hałas, zanieczyszczenia powietrza, a przejścia dla pieszych nie są realizowane w miejscach strategicznych.

Biorąc jednak pod uwagę, że nie uciekniemy od rozwoju chcemy z miastem wypracować kompromis.

Nasze postulaty:

- domagamy się przesunięcia budowanej obwodnicy za rejon dawnej kopalni KWK Gliwice, czyli w stronę ulicy Ciesielskiej. To jest około 100 metrów dalej od zabudowań mieszkalnych przy ulicy Tokarskiej,

- zmiany przeznaczenia terenu w MPZP dla obrębu Ostropa Pola, między autostradą A4, planowaną obwodnicą, a ulicą Tokarską z przemysłowego na budowlano usługowy,

- utworzenie pomiędzy ulicą Tokarską, a obwodnicą strefy zabudowy jednorodzinnej.

Wnosimy, aby miasto zachowało rolniczy charakter dzielnicy oraz jej zielony potencjał, wykorzystując go z korzyścią dla miasta i jego mieszkańców, tworząc tu zamiast kolejnej dzielnicy przemysłowej, dzielnicę spokojną, zieloną słynącą z tradycji jeździeckich.

Współpraca UM z lokalną społecznością oraz istniejącymi tu od lat licznymi stadninami i szkółkami jeździeckimi oraz prywatnymi hodowcami koni ma ogromny potencjał, aby powstały tu tereny do uprawniania sportów konnych w pięknej lokalizacji wśród zieleni, w dobrze zorganizowanej przez miasto przestrzeni, podnosząc tym samym prestiż miasta i dzielnicy.

Obecny plan zagospodarowania przestrzennego nie chroni zieleni ani założeń ekologicznych, a przecież **zdrowie i jakość życia mieszańców oraz ochrona terenów cennych przyrodniczo stanowić powinna nadrzędną rolę** w stosunku do inwestycji przemysłowych. Jesteśmy na takim etapie rozwoju miasta, gdzie mieszkańcy mogą zacząć korzystać z dobrodziejstw rozwoju gospodarczego. Dlatego prosimy o uwzględnienie naszych postulatów.

Pragniemy również nadmienić, że niniejsze pismo składane jest w formie uproszczonej, aby zgłosić nasz sprzeciw w terminie 07.02.2025. W nadchodzących tygodniach złożone zostanie kolejne pismo z pełną listą mieszkańców popierających zmiany obecnego MPZP.

Wiemy, że obecny stan oraz plany wobec Ostropy są pokłosiem decyzji poprzedniej władzy, z czym Państwo musicie się mierzyć. Jednak głęboko wierzymy, że możliwe jest zachowanie Ostropy nienaruszonej przemysłem, poszanowanie jej wiekowych już tradycji co będzie korzystne dla całego miasta.

Z poważaniem mieszkańcy Dzielnicy Ostropa.

- ZAŁĄCZNIK NR 1 -

Gliwice 28.01.2025

Odnosząc się do treści decyzji środowiskowej wydanej dla inwestycji drogowej, którą jest powstanie Obwodnicy Gliwic w Ostropie wnosimy zastrzeżenia do jej treści oraz przedstawiamy argumentację naszego stanowiska.

„Eksploatacja planowanej drogi wiązała się będzie z emisją hałasu i zanieczyszczeń gazowo – pyłowych do powietrza, której źródłem będzie ruch pojazdów.
Celem planowanej inwestycji jest przejęcie potoku samochodów, które obecnie poruszają się po drogach lokalnych, które często są w złym stanie technicznym. Samochody po projektowanej obwodnicy poruszały się będą płynnie co wpłynie na ograniczenie emisji zanieczyszczeń do powietrza w stosunku do sytuacji gdyby samochody poruszały się po drogach w złym stanie technicznym. Biorąc pod uwagę powyższe można przyjąć za autorami karty informacyjnej przedsięwzięcia, że eksploatacja planowanej obwodnicy nie wpłynie znacząco na jakość powietrza."

Powyższe stwierdzenie nie posiada żadnej wartości naukowej i jest pozbawione podstaw merytorycznych. Budowa nowej drogi lokalnej nie doprowadzi do redukcji emisji związanych z samochodami spalinowymi. Wręcz przeciwnie, realizacja obwodnicy przyczyni się do zwiększenia liczby pojazdów poruszających się w pobliżu obszarów zamieszkałych, co znacząco wpłynie na poziom zanieczyszczenia powietrza. Chociaż istnieje możliwość zmniejszenia emisji pyłów związanych z abrazyjnym zużyciem opon, nie wpłynie to na redukcję emisji spalin samochodowych. W Gliwicach najczęściej stosowanym paliwem jest benzyna, która stanowi 50% wszystkich zmierzonych samochodów osobowych w 2022 roku[1]. Na kolejnych miejscach znajdują się pojazdy z silnikiem diesla (34%) oraz napędzane gazem płynnym (LPG) (14%). Samochody hybrydowe stanowiły jedynie 2%, a elektryczne – mniej niż 1%. Zgodnie z ustaleniami Environmental Protection Agency, ruch drogowy ma istotny wpływ na jakość powietrza w promieniu kilkuset metrów – około 200 metrów od dróg o dużym natężeniu ruchu w kierunku pod wiatr lub wzdłuż dróg o znacznym natężeniu ruchu ciężarowego[2].

Nowe źródło zanieczyszczenia powietrza nie zostało uwzględnione w decyzji o środowiskowych uwarunkowaniach. Tymczasem dowody naukowe przedstawione przez ekspertów jednoznacznie wskazują na związek między zanieczyszczeniem powietrza a epidemią chorób niezakaźnych, takich jak nowotwory, udary mózgu, choroby serca, astma i przewlekła obturacyjna choroba płuc. Jest to jedna z nielicznych kwestii środowiskowych, w których epidemiolodzy i toksykolodzy są zgodni co do negatywnego wpływu zanieczyszczenia powietrza na zdrowie.

W 2012 roku International Agency for Research on Cancer (IARC), będąca międzyrządową agencją WHO specjalizującą się w badaniach nad nowotworami, sklasyfikowała emisje spalin silników Diesla zostały jako czynnik rakotwórczy dla ludzi (Grupa 1) na podstawie wystarczających dowodów naukowych **(IARC 2012)**. W Gliwicach 34% pojazdów to samochody z silnikami Diesla[3]. Rok później, ta sama agencja sklasyfikowała generalne zanieczyszczenie powietrza jako „czynnik rakotwórczy dla ludzi" (Group 1), podkreślając, że stanowi ono „jedną z głównych środowiskowych przyczyn zgonów z powodu raka" **(IARC 2013)**.

Znaczenie dowodów naukowych jest tak duże, że w 2019 roku WHO uznała zanieczyszczenie powietrza za największe zagrożenie dla zdrowia ludzi[4]. Od trzech dekad gromadzone są obszerne dane, które jednoznacznie dowodzą, że zanieczyszczenie powietrza stanowi poważne zagrożenie dla zdrowia. Już w latach 1990, renomowana grupa epidemiologów wykazała, że każda, nawet najmniejsza ekspozycja na zanieczyszczenie

powietrza, wywiera negatywny wpływ na zdrowie. Badania te potwierdziły, że nie istnieje próg ekspozycji, poniżej którego zanieczyszczenie powietrza byłoby obojętne dla zdrowia (Zobacz plik zip "APHEA study").

Wpływ zanieczyszczenia powietrza, zwłaszcza pochodzącego z ruchu drogowego, na zdrowie jest szczególnie dotkliwe w przypadku małych dzieci. Negatywnie oddziałuje ono na wiele układów w organizmach dzieci, prowadząc do zwiększonej zachorowalności i śmiertelności, zwłaszcza wśród noworodków. Kobiety w ciąży narażone na zanieczyszczenie powietrza mają większe ryzyko przedwczesnego porodu, a ich dzieci mogą mieć niską masę urodzeniową i ryzyko wystąpienia zaburzeń ze spektrum autyzmu. Zanieczyszczenie powietrza wpływa również negatywnie na rozwój układu nerwowego oraz zdolności poznawcze, a także zwiększa ryzyko wystąpienia astmy obniżoną funkcję płuc, infekcje dróg oddechowych oraz alergie u dzieci i młodzieży. Ponadto zwiększa ryzyko wystąpienia przewlekłych chorób w wieku dorosłym, takie jak schorzenia układu krążenia (Zobacz zip "Trafic related health impact").

Warto dodać, że decyzja o środowiskowych uwarunkowaniach zdaje się bardziej koncentrować na ochronie drzew i ich zabezpieczeniu niż na ochronie zdrowia ludzi mieszkających w pobliżu planowanej obwodnicy. Podobnie, w przypadku zwierząt, takich jak nietoperze, ptaki, płazy, gady i inne, ochrona ich siedlisk wydaje się być traktowana priorytetowo w porównaniu do zdrowia mieszkańców Ostropy.

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[1] chrome-extension://oemmndcbldboiebfnladdacbdfmadadm/https://theicct.org/wp-content/uploads/2024/09/ID-226-%E2%80%93-LEZ-Gliwice_final.pdf

[2] chrome-extension://oemmndcbldboiebfnladdacbdfmadadm/https://www.epa.gov/sites/default/files/2015-11/documents/420f14044_0.pdf ◊ strona 2

[3] chrome-extension://oemmndcbldboiebfnladdacbdfmadadm/https://theicct.org/wp-content/uploads/2024/09/ID-226-%E2%80%93-LEZ-Gliwice_final.pdf

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ZAŁĄCZNIK NR 2

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Short communication

Long-term exposure to traffic-related air pollution and selected health outcomes: A systematic review and meta-analysis

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ABSTRACT

The health effects of traffic-related air pollution (TRAP) continue to be of important public health interest. Following its well-cited 2010 critical review, the Health Effects Institute (HEI) appointed a new expert Panel to systematically evaluate the epidemiological evidence regarding the associations between long-term exposure to TRAP and selected adverse health outcomes. Health outcomes were selected based on evidence of causality for general air pollution (broader than TRAP) cited in authoritative reviews, relevance for public health and policy, and resources available.

The Panel used a systematic approach to search the literature, select studies for inclusion in the review, assess study quality, summarize results, and reach conclusions about the confidence in the evidence. An extensive search was conducted of literature published between January 1980 and July 2019 on selected health outcomes. A new exposure framework was developed to determine whether a study was sufficiently specific to TRAP.

In total, 353 studies were included in the review. Respiratory effects in children (118 studies) and birth outcomes (86 studies) were the most commonly studied outcomes. Fewer studies investigated cardiometabolic effects (57 studies), respiratory effects in adults (50 studies), and mortality (48 studies).

The findings from the systematic review, meta-analyses, and evaluation of the quality of the studies and potential biases provided an overall high or moderate-to-high level of confidence in an association between long-term exposure to TRAP and the adverse health outcomes all-cause, circulatory, ischemic heart disease and lung cancer mortality, asthma onset in children and adults, and acute lower respiratory infections in children. The evidence was considered moderate, low or very low for the other selected outcomes.

In light of the large number of people exposed to TRAP – both in and beyond the near-road environment - the Panel concluded that the overall high or moderate-to-high confidence in the evidence for an association between long-term exposure to TRAP and several adverse health outcomes indicates that exposures to TRAP remain an important public health concern and deserve greater attention from the public and from policymakers.

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1. Introduction

Motor vehicles are a significant source of urban air pollution and are important contributors of anthropogenic carbon dioxide and other greenhouse gases. Traffic-related air pollution (TRAP) is a complex mixture of gases and particles resulting from the use of motor vehicles. Motor vehicles emit a variety of pollutants including nitrogen dioxide (NO_2), elemental carbon (EC), ultrafine particles (UFP) and fine particle matter ($PM_{2.5}$). These pollutants can be emitted directly through the vehicle exhaust as tailpipe emissions. They can also be emitted from non-exhaust sources such as evaporative emissions of fuel, the resuspension of dust, the wear of brakes and tires, and the abrasion of road surfaces, which are collectively referred to as non-tailpipe emissions (Harrison et al., 2021; HEI, 2010).

Tailpipe emissions from motor vehicles and ambient concentrations of most monitored traffic-related pollutants have decreased steadily over the last several decades in most high-income countries. This trend is a result of air quality regulations and improvements in vehicular emission control technologies and is likely to continue (Frey, 2018). These positive developments, however, have not been able to compensate fully for the rapid growth and increased vehicular congestion of the motor vehicle fleet due to population growth, urbanization, and economic activity, in addition to the continued presence of older or malfunctioning vehicles on the roads. The introduction of new technologies such as electric vehicles, promises alleviation of some components of TRAP. Adoption has been constrained so far, however, due to the pace and cost of developing battery technology and infrastructure, electricity decarbonization, and fleet turn-over (Khreis et al., 2020). For the foreseeable future, a substantial number of people globally will continue to be exposed to tailpipe and non-tailpipe TRAP, especially in urban settings and locations in proximity to busy roadways, where detectable increases extend to about 500 m.

In 2010, HEI published Special Report 17, *Traffic–Related Air Pollution: A Critical Review of the Literature on Emissions, Exposure, and Health Effects*. This 2010 review, developed by the HEI Panel on the Health Effects of Traffic–Related Air Pollution summarized and synthesized research on emissions, exposure, and health effects from TRAP and drew conclusions about whether the associations between exposure and health outcomes were causal. The 2010 Panel reviewed both toxicological and epidemiological evidence. At that time, the Panel concluded that the evidence was sufficient to support a causal relationship between short and long-term exposure to TRAP and exacerbation of asthma in children. The Panel found suggestive evidence of a causal relationship between exposure to TRAP and other outcomes, including all-cause and cardiovascular mortality, and limited evidence of associations for some other outcomes, such as birth outcomes (HEI, 2010).

Since the 2010 HEI review, regulations and vehicular technology have advanced significantly, exposure assessment has been enhanced, and many additional studies investigating the health effects of exposure to TRAP have been published. Therefore, HEI formed a new Panel, consisting of 13 experts in epidemiology, exposure assessment, and statistics at institutions in North America and Europe, to conduct a new review. This review is the largest systematic effort to date to evaluate the epidemiological evidence regarding the associations between long-term exposure to TRAP and selected adverse health outcomes. The report will be published later this year (HEI, 2022). Here, we summarize the main findings of the review.

2. Objective

The objective of this review was to systematically evaluate the epidemiological evidence regarding the associations between long-term exposure to ambient TRAP and selected adverse health outcomes. Results were quantitatively combined to evaluate the strength of the evidence, where appropriate. The Panel was charged with drawing conclusions about the confidence in the quality of the body of evidence and with assessing the level of confidence in the presence of an association.

3. General methods

The Panel used a systematic approach to search the literature, select studies for inclusion in the review, assess study quality, summarize results, and reach conclusions about the confidence in the body of evidence, based largely on standards set by Cochrane, World Health Organization, and the National Institute of Environmental Health Sciences. To this end, a review protocol was published in 2019 (HEI, 2019) and registered in Prospero.

Health outcomes were selected by the Panel based on evidence of causality (causal or likely causal) according to the latest determination for *general* air pollution (broader than TRAP) from available authoritative integrated science assessments (e.g., Health Canada, 2016; IARC, 2016; U.S. EPA, 2016, 2019), and other considerations such as relevance for public health and policy, and resources available. The selected health outcomes were clinical outcomes (rather than preclinical) and included birth outcomes (e.g., term low birth weight: <2,500 g for infants born at term > 37 weeks of gestation), respiratory outcomes (e.g., asthma onset), cardiometabolic outcomes (e.g., ischemic heart disease and diabetes) and all-cause and cause-specific (e.g., circulatory, respiratory) mortality. The Panel acknowledged the limitations in the selection of health outcomes.

A PECOS (Population, Exposure, Comparator, Outcome and Study) question was developed and inclusion and exclusion criteria were listed for each PECOS domain in relation to the selected health effects of long–term exposure to TRAP (months to years). The focus of the review was on health effects observed in the general population. Cohort, case-control, cross-sectional, and intervention studies using individual-level data were included.

An extensive search was conducted of literature published between January 1980 and July 2019. Studies were checked for eligibility for inclusion by two reviewers. Data from all included studies were extracted and evaluated extensively, including key information for meta-analysis. Effect estimates from single pollutant models were selected for the meta-analysis. Results from multi-pollutant models were de-emphasized as we were not interested in the associations of single pollutants *independent* of other pollutants. Instead, we considered the associations of single pollutants to represent the associations of the TRAP mixture. We performed random-effects meta-analysis when at least three estimates were available for a specific exposure-outcome pair. The Panel decided to use the pollutant concentration increments from the ESCAPE study to reflect a realistic range of exposure contrasts in most studies (Beelen et al., 2014, 2015). The following increments were used: 10 $\mu g/m^3$ for NO_2, 1 $\mu g/m^3$ for EC, and 5 $\mu g/m^3$ for $PM_{2.5}$. The increments used are in the same range as other reviews (e.g., Chen and Hoek, 2020; Huangfu and Atkinson, 2021; Khreis et al., 2017).

We assessed risk of bias for all exposure-outcome associations that were included in the meta–analyses, using a modified version of the tool developed for the risk of bias assessment in the WHO Air Quality Guidelines review (WHO, 2020, 2021).

Where possible, the Panel performed additional analyses to assess consistency of the association, for example, across geographic region, within time period, by level of risk of bias, and with more extensive adjustment for individual-level lifestyle factors (i.e., smoking). An adapted GRADE (Grading of Recommendations Assessment, Development and Evaluation) assessment of the confidence in the quality of the body of evidence was made using the Office of Health Assessment and Translation (OHAT) method as a guide (OHAT, 2019). Because the OHAT assessment was heavily geared towards the studies entering a meta-analysis, and it focused on the quality of the body of evidence and less on the presence of an association, the Panel deemed it necessary to accompany the OHAT assessment with a broader approach. Hence, we developed a narrative assessment to evaluate the level of confidence in

the presence of an association, considering the meta-analyzed studies as well as all other studies not included in the meta-analysis. Subsequently, we combined the findings from the narrative assessment and the modified OHAT assessment into an overall confidence assessment, with the two approaches considered complementary.

4. Exposure assessment framework

Assessing exposure to TRAP is challenging because TRAP is a complex mixture of particulate matter and gaseous pollutants and exhibits high spatial and temporal variability. The Panel developed a new exposure framework to define, as transparently as possible, exposure characterization approach(es) most likely to specifically assess TRAP as opposed to air pollution exposure more generally. Studies meeting the framework's criteria were considered TRAP-specific and thus eligible for inclusion in the current review. The exposure assessment framework included three strategies to determine whether a study was sufficiently TRAP-specific, namely the selection of traffic-related air pollutants, the exposure assessment method, and the spatial resolution. None of the pollutants considered are uniquely traffic-specific and therefore these additional criteria were needed.

Broadly, emissions from motorized traffic may affect air quality at the local, neighborhood, urban and regional scale. The Panel judged, however, that epidemiological studies that focused on exposure contrasts at the local and neighborhood scale offered the greatest potential in determining associations with outcomes that are most confidently derived from TRAP emissions.

In brief, the Panel included studies that evaluated exposure to NO_2, EC (including related metrics such as black carbon, black smoke and PM absorbance), carbon monoxide (CO), UFP, and other pollutants and indirect traffic measures (distance and density), as well as $PM_{2.5}$ and PM_{10} (particles smaller than 2.5 and 10 μm, respectively). For studies that evaluated exposure to $PM_{2.5}$ and PM_{10}, but not to other pollutants, even more stringent requirements for inclusion were needed regarding exposure assessment and study setting to indicate that the exposure contrasts were likely due to variation in traffic emissions. For example, the Panel excluded PM studies where the exposure assessment was solely derived from monitoring data. The Panel also excluded nationwide studies on any pollutant where the primary exposure contrast was due to between-cities variations, rather than within-cities.

5. Main findings of the systematic review

In total, 353 studies were included in this review. Respiratory effects in children (118 studies, 33%) and birth outcomes (86 studies, 24%) were the most common outcomes studied. Fewer studies investigated cardiometabolic effects (57 studies, 16%), respiratory effects in adults (50 studies, 14%), and mortality (48 studies, 13%). The studies were conducted in populations residing in a wide range of countries, though the majority were done in Europe (163 studies, 46%), and North America (130 studies, 37%). Studies in Asia (predominantly China) emerged more recently (41 studies, 12%). More TRAP studies in low- and middle-income countries are needed. Most meta-analyses by outcome pertained to NO_2, followed by EC and $PM_{2.5}$. Few studies were identified for some pollutants, in particular non-tailpipe PM indicators and UFP, and such studies were identified as a future research need.

The results of the meta-analyses of associations between long-term exposure to the most commonly studied TRAP exposure indicators (NO_2, EC and $PM_{2.5}$) and selected health outcomes are displayed in Table 1. We use the term relative risk to describe effect estimates, as it is easier to communicate, even if in some of the included studies it would be technically more correct to refer to an odds ratio, or hazard ratio.

Following are important considerations while reviewing the results: 1) Although the results are presented by pollutant, the individual pollutants are considered indicators of the TRAP mixture. 2) Effect estimates cannot be compared directly across traffic-related pollutants since selected increments do not necessarily represent the same contrast in exposure. 3) Studies included in a meta-analysis represent only about half of all studies considered, such as when multiple studies conducted in the same population, <3 studies were available for a particular exposure-outcome pair, or definitions of indirect traffic measures varied across studies. Thus, the Panel did not pursue meta-analyses of indirect traffic measures. Despite not being included in the meta-analyses, the remaining studies added important information to the overall assessment.

For each health outcome, Fig. 1 and Table 1 also provide the overall level of confidence in an association with long-term exposure to TRAP, based on a combination of the narrative assessment and the modified OHAT assessment (see above). Detailed descriptions of the overall confidence assessment are listed in Table 2. Below, we describe the main findings for each broad health outcome category.

5.1. Birth outcomes

The summary estimates showed that $PM_{2.5}$ exposure over the entire pregnancy is most clearly associated with measures of fetal growth restriction. The summary relative risk was 1.11 (95% CI: 1.03; 1.20) for term low birth weight and 1.09 (1.04; 1.14) for small for gestational age (birth weight below the 10th percentile for a gestational age and sex according to national growth curves, for example), and a mean difference in term birth weight of −17.3 (−33.2; −1.5) grams per 5 μg/m^3. The $PM_{2.5}$ associations are supported by consistent associations with PM_{10} as well. Associations for preterm birth were largely null, though a few studies of traffic-PM and indirect traffic measures (distance and density measures) supported an association. Associations for the other meta-analyzed traffic-related air pollutants, including NO_2, NO_X, and EC, with all four birth outcomes were mostly null, with the exception of an association of NO_X with term low birth weight. Studies that were not included in the meta-analyses broadly agreed with the summary estimates for the various pollutants.

The majority of studies of TRAP and birth outcomes were conducted in North America and Europe. Most used a cohort study design and registry data and therefore lacked potentially important confounder information on lifestyle factors, such as maternal smoking during pregnancy and pre-pregnancy body mass index. As a result, those studies were rated high risk of bias for potential confounding, which reduced confidence in the body of evidence, particularly for term birth weight and preterm birth (births < 37 weeks of gestation).

The Panel concluded that there was an overall moderate level of confidence in the evidence for an association between exposure to TRAP and term low birth weight (categorical outcome) and small for gestational age, and low confidence for term birth weight (continuous outcome) and preterm birth.

5.2. Respiratory outcomes

The summary estimates for NO_2 per 10 μg/m^3 were 1.05 (95% CI: 0.99; 1.12) for asthma onset in children and 1.10 (95% CI:1.01; 1.21) for asthma onset in adults, and 1.09 (95% CI: 1.03; 1.16) for acute lower respiratory infections in children. For these outcomes, positive associations were also reported for other traffic-related air pollutants, either in meta-analyses or in single large studies. Most were cohort studies that were conducted in different populations and had low or moderate risk of bias.

The Panel concluded that the overall level of confidence in the evidence for an association of exposure to TRAP with asthma onset in both children and adults and with acute lower respiratory infections in children was considered moderate-to-high. Studies examining exposure to NO_2 made the greatest contribution to this evaluation. The overall level of confidence in the evidence was moderate for prevalence of asthma ever and active asthma in children. Asthma ever refers to lifetime asthma prevalence and active asthma refers to prevalence of asthma in the last 12 months. For most of the other respiratory outcomes investigated, including incidence of chronic obstructive pulmonary disease, acute lower respiratory infections in adults, wheeze outcomes as well as exacerbation of asthma and chronic obstructive pulmonary disease in diseased adults, the confidence was very low or low for an association with TRAP, hampered in part by the small number of qualifying studies.

Table 1
Overall confidence assessment and meta-analytical summary estimates of associations between long-term exposure to the most common traffic-related air pollutants (NO_2, EC, $PM_{2.5}$) and health outcomes. (NOTE: the individual pollutants are considered indicators of TRAP).

Health outcome			Overall confidence assessment	NO_2 per 10 μg/m^3 N	NO_2 per 10 μg/m^3 Relative risk	EC per 1 μg/m^3 N	EC per 1 μg/m^3 Relative risk	$PM_{2.5}$ per 5 μg/m^3 N	$PM_{2.5}$ per 5 μg/m^3 Relative risk
Birth outcomes		Term low birth weight	Moderate	12	1.01 (0.99;1.03)	5	1.01 (0.99;1.04)	7	1.11 (1.03;1.20)
		Term birth weight	Low	8	−3.2 (−11.0;4.6)[3]	4	−2.6 (-6.1;0.9)[3]	6	−17.3 (−33.2;-1.5)[3]
		Small for gestational age	Moderate	11	1.00 (0.98;1.02)	3	1.02 (0.92;1.14)	4	1.09 (1.04;1.14)
		Preterm birth	Low	14	1.00 (0.96;1.04)	5	1.02 (0.97;1.07)	4	0.99 (0.90;1.09)
Respiratory outcomes	Children	Asthma onset[1]	Moderate-to- high	12	1.05 (0.99;1.12)	5	1.11 (0.94;1.31)	5	1.33 (0.90;1.98)
		Asthma ever[2]	Moderate	21	1.09 (1.01;1.18)	3	1.30 (0.56;3.04)	3	1.29 (0.58;2.87)
		Active asthma[2]	Moderate	12	1.12 (1.02;1.23)	3	1.25 (0.98;1.59)	<3	NA
		Acute lower respiratory infections[1]	Moderate-to-high	11	1.09 (1.03;1.16)	4	1.30 (0.78;2.18)	<3	NA
	Adults	Asthma onset[1]	Moderate-to- high	7	1.10 (1.01;1.21)	<3	NA	<3	NA
		Acute lower respiratory infections[1]	Very low-to-low	3	1.07 (0.71; 1.61)	<3	NA	<3	NA
		Chronic obstructive pulmonary disease[1]	Low	7	1.03 (0.94;1.13)	<3	NA	4	0.91 (0.62;1.36)
Cardiometabolic outcomes		Ischemic heart disease events[1]	Moderate	5	0.99 (0.94;1.05)	5	1.01 (0.99;1.03)	4	1.09 (0.86;1.39)
		Coronary events[1]	Low	7	1.03 (0.95;1.11)	<3	NA	<3	NA
		Stroke events[1]	Low-to-moderate	7	0.98 (0.92;1.05)	6	1.03 (0.98;1.09)	4	1.08 (0.89;1.32)
		Diabetes[1]	Moderate	7	1.04 (0.96;1.13)	3	1.16 (0.57;2.36)	4	1.05 (0.96;1.15)
		Diabetes[2]		7	1.09 (1.02;1.17)	<3	NA	3	1.08 (0.70;1.67)
Mortality		All-cause	High	11	1.04 (1.01;1.06)	11	1.02 (1.00;1.04)	12	1.03 (1.01;1.05)
		Circulatory	High	10	1.04 (1.00;1.09)	9	1.02 (1.00;1.04)	11	1.04 (1.01;1.08)
		Respiratory	Moderate	8	1.05 (1.00;1.09)	8	1.01 (0.98;1.05)	7	1.03 (0.97;1.10)
		Lung cancer	Moderate-to-high	5	1.04 (1.01;1.07)	3	1.02 (0.88;1.19)	6	1.06 (0.99;1.13)
		Ischemic heart disease	High	6	1.05 (1.03;1.08)	6	1.05 (0.99;1.11)	7	1.07 (1.04;1.10)
		Stroke	Low-to- moderate	6	1.01 (0.98;1.04)	<3	NA	3	1.04 (1.01;1.07)
		Chronic obstructive pulmonary disease	Low	3	1.03 (1.00;1.05)	<3	NA	<3	NA

[1] Incidence.
[2] Prevalence.
[3] Mean difference in g. NA = not applicable.

5.3. Cardiometabolic outcomes

The summary estimates were consistent with an association of PM_{10} with ischemic heart disease: 1.14 (95% CI: 0.99; 1.31) per 10 μg/m^3, with evidence suggesting a monotonic exposure–response function. Evidence was suggestive for EC and $PM_{2.5}$, but was less consistent overall. Associations were reported between NO_2 and diabetes prevalence with a summary estimate of 1.09 (95% CI: 1.02; 1.17) per 10 μg/m^3, supported by consistent but imprecise estimates for the other pollutants. The summary estimates of EC, PM_{10} and $PM_{2.5}$ with stroke incidence were slightly less precise, but the evidence was strengthened by several high-quality studies with a monotonic exposure–response function. Studies that were not included in meta-analyses provided additional support for an association between TRAP and ischemic heart disease, diabetes and stroke. In contrast, for coronary events, the number of studies was smaller and insufficient for meta-analyses, except for NO_2, which yielded a positive, though imprecise association.

Because cardiometabolic outcomes are likely influenced by traffic noise, some studies investigated possible confounding or effect modification by noise with mostly similar results after adjustment for co-exposure to noise.

The Panel had overall moderate confidence in the evidence for an association between long-term exposure to TRAP and ischemic heart disease, and diabetes, low-to-moderate confidence in the evidence for an association of TRAP with stroke, and low confidence in the evidence for an association of TRAP with coronary events.

5.4. Mortality

The summary estimates showed that NO_2, EC, and $PM_{2.5}$ were associated with all-cause, circulatory, ischemic heart disease, respiratory and lung cancer mortality, with relative risks ranging from 1.01 to 1.07 (Table 1). Associations of those pollutants with stroke and COPD mortality were less certain because fewer studies were available for consideration. The studies on pollutants not included in the meta-analyses and the studies with indirect traffic measures supported those associations. All studies on mortality had cohort designs, with outcome during follow-up determined by linkage with mortality registries. Most studies were conducted in North America and Europe; some were set in Asia. The majority of studies accounted for a large number of individual and area-level covariates, including smoking, body mass index and individual and area-level socio-economic status, and were judged at a low or moderate risk for bias.

The overall confidence in the evidence for an association between TRAP exposure and mortality was high for all-cause, circulatory, and IHD mortality. The Panel's overall confidence was moderate-to-high for lung cancer, moderate for respiratory, low-to-moderate for stroke, and low for COPD mortality.

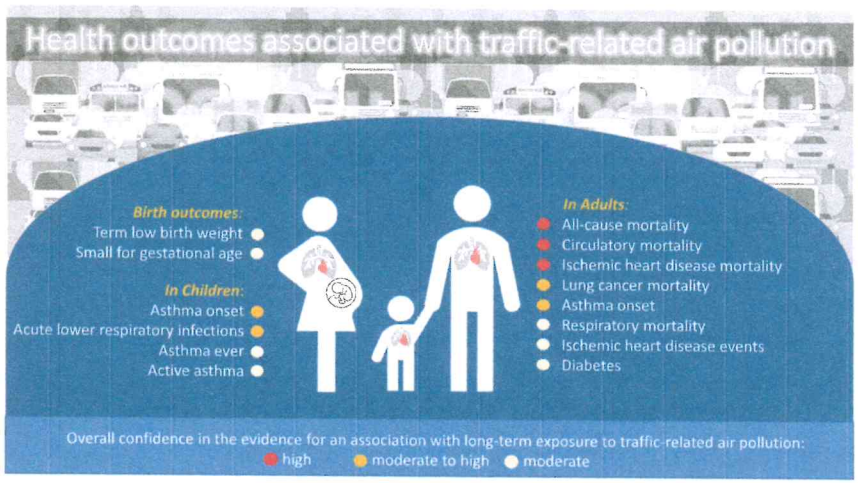

Fig. 1. Overall confidence in the evidence for an association between long-term exposure to ambient TRAP and selected health outcomes. Footnote: health outcomes for which the overall confidence in the evidence was low-to-moderate, low or very low are not in Fig. 1.

Table 2
Overall confidence assessment – Descriptions of the level of confidence in the evidence for an association.[1]

High	Evidence is sufficient to conclude that the strength of the evidence for an association is high, that is, the exposure has been shown to be associated with health effects in studies in which chance, confounding, and other biases could be ruled out with reasonable confidence. The determination is based on multiple high-quality studies conducted in different populations and geographical areas with consistent results for multiple exposure indicators.
	High confidence in the association between exposure and the outcome.
Moderate	Evidence is sufficient to conclude that an association is likely to exist, that is, the exposure has been shown to be associated with health effects in studies where results are not explained by chance, confounding, and other biases, but uncertainties remain in the evidence overall. The determination is based on some high-quality studies in different populations and geographical areas, but the results are not entirely consistent across areas and for multiple exposure indicators.
	Moderate confidence in the association between exposure and the outcome.
Low	Evidence is suggestive but limited, and chance, confounding, and other biases cannot be ruled out. Generally, the body of evidence is relatively small, with few high-quality studies available and at least one high-quality epidemiologic study shows an association with a given health outcome and/or when the body of evidence is relatively large but the evidence from studies of varying quality and across multiple exposure indicators is generally supportive but not entirely consistent.
	Low confidence in the association between exposure and the outcome.
Very low	Evidence is inadequate to determine if an association exists with the relevant exposures. The available studies are of insufficient quantity, quality, consistency, or statistical power to permit a conclusion regarding the presence or absence of an association.
	Very low confidence in the association between exposure and the outcome.

[1] The overall confidence assessment of the association of each health outcome with long-term exposure to TRAP is a combination of the narrative assessment and the modified OHAT assessment. The descriptors are modified from U.S. EPA (2015) and OHAT (2019).

6. Overall conclusions

The findings from the systematic review, meta-analyses, and evaluation of the quality of the studies and potential biases provided an overall high or moderate-to-high level of confidence in an association between long-term exposure to TRAP and the adverse health outcomes all-cause, circulatory, ischemic heart disease and lung cancer mortality, asthma onset in children and adults, and acute lower respiratory infections in children. The Panel's confidence in the evidence was considered moderate, low or very low for the other selected outcomes. The findings add to the growing evidence base of a range of other health outcomes associated with long-term exposure to TRAP.

Tailpipe emissions from motor vehicles and ambient concentrations of most monitored traffic-related pollutants have decreased steadily over the last several decades in most high-income countries. The Panel's main findings were derived from studies conducted when exposure levels were generally higher than present-day levels in high-income countries, and comparable to or lower than present-day levels in low-income countries.

In light of the large number of people exposed to TRAP – both in and beyond the near-road environment - the Panel concluded that the overall high or moderate-to-high confidence in the evidence for an association between long-term exposure to TRAP and several adverse health outcomes indicates that exposures to TRAP remain an important public health concern and deserve greater attention from the public and from policymakers.

Credit authorship contribution statement

H. Boogaard: Conceptualization, Methodology, Writing, Supervision. **A.P. Patton:** Methodology, Writing. **R.W. Atkinson:** Conceptualization, Methodology, Formal analysis, Writing. **J.R. Brook:** Conceptualization, Methodology, Writing. **H.H. Chang:** Conceptualization, Methodology, Writing. **D.L. Crouse:** Writing. **J.C. Fussell:** Writing. **G. Hoek:** Conceptualization, Methodology, Writing. **B. Hoffmann:** Conceptualization, Methodology, Writing. **R. Kappeler:** Investigation. **M. Kutlar Joss:** Investigation. **M. Ondras:** Visualization, Writing. **S.K. Sagiv:** Conceptualization, Methodology, Writing. **E. Samoli:** Conceptualization, Methodology, Formal analysis, Writing. **R. Shaikh:** Writing. **A. Smargiassi:** Conceptualization, Methodology, Writing. **A.A. Szpiro:** Conceptualization, Methodology, Writing. **E.D.S. Van Vliet:** Writing. **D. Vienneau:** Conceptualization, Methodology, Writing. **J. Weuve:** Conceptualization, Methodology, Writing. **F.W. Lurmann:** Conceptualization, Methodology, Writing. **F. Forastiere:** Conceptualization, Methodology, Writing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Early postnatal exposure to traffic-related air pollution and asthma in adolescents: vulnerability factors in the PARIS birth cohort

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ABSTRACT

Background: Associations between early traffic-related air pollution (TRAP) exposure and respiratory and allergic morbidity in adolescents are inconsistent. However, sub-groups might be more vulnerable to the health effects of this exposure.

Objectives: We investigated associations between early exposure to TRAP and respiratory and allergic morbidity at age 13 years in the PARIS birth cohort, and potential modifying effects of sex, parental allergy, stressful family event and lower respiratory tract infections (LRTI).

Methods: This study deals with data from 732 children of the PARIS birth cohort followed up using repeated questionnaires until 13 years of age. Prenatal TRAP exposure was assessed by measuring daily concentrations of nitrogen dioxide at the nearest station to mother's home. Early postnatal TRAP exposure was calculated for each child during the first year of life by a nitrogen oxides (NO_x) air dispersion model taking into account both residence and daycare. Associations between TRAP exposures and asthma, rhinitis and related symptoms were assessed using multivariable logistic regression models adjusted for potential confounding factors. Effect modification was explored by testing multiplicative interactions.

Results: An increase in interquartile range (17.0 $\mu g/m^3$) of early postnatal NO_x exposure was positively related to current asthma (adjusted odds ratio aOR = 1.21; 95% confidence interval CI: 1.02, 1.43), severe wheeze (aOR = 1.23; 95% CI: 1.02, 1.47) and persistent asthma at 13 years old (aOR = 1.26; 95% CI: 1.03, 1.55) and tended to be associated with asthma ever. Parental history of allergy, asthma, early stressful family event and LRTI modified these associations with TRAP exposure. No relationship with rhinitis was found. Prenatal TRAP exposure did not show any association with respiratory and allergic morbidity.

Discussion: This study is one of the first to show several modifiers of the association between early postnatal TRAP exposure and asthma at adolescence. Not all adolescents seem equally affected by early postnatal TRAP exposure: those presenting parental history of allergy, especially asthma, those with early stressful family event or LRTI appear to be more vulnerable.

Abbreviations: AIRPARIF, Paris air quality monitoring network; aOR, Adjusted Odds Ratio; BAMSE, Children, Allergy, Milieu, Stockholm, Epidemiological Survey; CI, Confidence Interval; CSTB, French Scientific and Technical Center for Building; DAG, Directed Acyclic Graph; ETS, Environmental Tobacco Smoke; ETV, Exposure To Violence; IFSTTAR, French Institute of Science and Technology for Transport, Development and Networks; IQR, Interquartile range; ISAAC, International Study of Asthma and Allergies in Childhood; LRTI, Lower Respiratory Tract Infections; LUR, Land-Use Regression; MeDALL, Mechanisms of the Development of ALLergy; NO_2, Nitrogen dioxide; NO_x, Nitrogen oxides; OR, Odds Ratio; PARIS, Pollution and Asthma Risk: an Infant Study; PIAMA, Prevention and Incidence of Asthma and Mite Allergy; SES, Socioeconomic Status; TRAP, Traffic-Related Air Pollution.

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1. Introduction

In recent decades, the prevalence of respiratory and allergic diseases has been increasing worldwide (Asher et al., 2006; Eder et al., 2006) and diseases such as asthma and allergic rhinitis are among the most common chronic conditions in adolescents (Ait-Khaled et al., 2009; Pearce et al., 2007). The origins of these diseases result from multiple interacting factors including genetic predispositions, and behavioral and environmental factors. Regarding these environmental factors especially the increase in road traffic, the question of the role of traffic-related air pollution (TRAP) on respiratory and allergic morbidity arises (Chair et al., 2010).

There is now sufficient evidence that TRAP exposure can exacerbate pre-existing asthma (Guarnieri and Balmes, 2014; Tétreault et al., 2016a) and many studies investigated the association between TRAP and respiratory and allergic morbidity in children (Bowatte et al., 2015; Han et al., 2021; Khreis et al., 2019). However, the impact of TRAP on this morbidity in adolescents has been rarely investigated. A few studies have shown associations between TRAP exposure and incident asthma from birth to 13 years of age (Tétreault et al., 2016b), or from 10 to 18 years of age (Jerrett et al., 2008). In the PIAMA birth cohort, an association was found between nitrogen dioxide (NO_2) levels at the birth address and incident asthma up to the age of 12 (Gehring et al., 2015a) and up to the age of 14 (Yang et al., 2016). In another birth cohort, BAMSE, Gruzieva et al. (2013) observed significant associations between TRAP exposure during the first year of life and prevalent and incident asthma at 12 years of age. In contrast, a pooled European study of four birth cohorts described associations with incident asthma at 14–16 years of age but not with prevalent asthma at this age (Gehring et al., 2015b). He et al. (2019) did not establish any association with asthma at adolescence. Regarding the association between TRAP and adolescent rhinitis, results are few in number and also inconsistent (Gehring et al., 2015b; Yang et al., 2016). All these studies are difficult to compare. They use many different exposure assessment methods: pollutant measurements from air quality monitoring stations (He et al., 2019); indoor air measurements (Jerrett et al., 2008); statistical regression models such as land-use regression (LUR) (Gehring et al., 2015a,b; Tétreault et al., 2016b; Yang et al., 2016) and air pollution dispersion models (Gruzieva et al., 2013). Outcomes were defined at different ages and in different ways using administrative health databases (Tétreault et al., 2016b), standardized questions similar to those used in the International Study of Asthma and Allergies in Childhood (ISAAC) and the MeDALL (Mechanisms of the Development of ALLergy) consortium (Gehring et al., 2015a,b; He et al., 2019; Jerrett et al., 2008; Yang et al., 2016) or other specific questions (Gruzieva et al., 2013). Nevertheless, an early exposure window is most often associated with respiratory and allergic morbidity in these studies (Gehring et al., 2015b; Gruzieva et al., 2013; Tétreault et al., 2016b; Yang et al., 2016). Moreover, a few studies suggested the potential role of effect modifiers on these associations in children (Bougas et al., 2018; Cakmak et al., 2016; Kravitz-Wirtz et al., 2018; Oudin et al., 2017; Rancière et al., 2017). Our team has previously shown in the Pollution and Asthma Risk: an Infant Study (PARIS) birth cohort, that some sub-groups of children, those with male sex, parental history of allergy, early postnatal stressful family events and repeated lower respiratory tract infections (LRTI), are more vulnerable to TRAP than others regarding asthma prevalence at 4 years old (Rancière et al., 2017) and reduced lung function at 8–9 years old (Bougas et al., 2018). However, these potential modifying effects on respiratory morbidity in adolescents need further study.

In this context, the aims of this study were to investigate associations between early exposure to TRAP and respiratory and allergic morbidity at the age of 13 years in the PARIS birth cohort, and then to explore potential modifying effects of sex, parental history of allergy, early postnatal exposure to a stressful family event and early repeated LRTI.

2. Methods

2.1. Study design

The prospective follow-up of the PARIS birth cohort is based on standardized questionnaires completed by parents on inclusion, then every three months for the first year, at 18 months and every year until 8 years of age. At 13 years old, a self-administered questionnaire was completed by the adolescents in addition to a questionnaire filled in by their parents. At 18 months old and 8–9 years old, children benefited from a free medical examination, including a blood test and a lung function test at 8–9 years old. The French Ethics Committees approved the PARIS study and parents gave written informed consent (permission nos. 031153, 051289, and ID-RCB, 2009-A00824-53).

2.2. Participants

The PARIS birth cohort consists of 3840 healthy newborns recruited between 2003 and 2006 in five Paris maternity hospitals. Information about medical and sociodemographic eligibility criteria and methods of selection has been previously published (Clarisse et al., 2007). The present study deals with families who answered at least one questionnaire when children were 13 years old (parents and/or adolescent).

2.3. Health outcomes

Standardized questions from the ISAAC study used in the European consortium MeDALL were used to assess respiratory and allergic morbidity. Adolescents reported symptoms occurring in the previous 12 months such as wheeze ("Have you had wheezing or whistling in the chest in the past 12 months?") and rhinitis symptoms ("In the past 12 months, have you had a problem with sneezing, or a runny, blocked nose when you did not have a cold or flu?"). Wheeze was considered as severe when adolescents reported at least one of the following in the preceding 12 months: sleep disturbance due to wheezing, wheezing severe enough to limit speech to only one or two words at a time between breaths or discomfort due to wheezing greater than 4 on a scale from 0 to 10. Rhinitis symptoms were classified as severe when adolescents reported discomfort due to these nasal problems greater than 4 on a scale from 0 to 10 in the previous 12 months. Parents reported ever-diagnosed asthma and allergic rhinitis for their child and use of asthma medication during the preceding 12 months. Current asthma was defined as a positive answer to at least two of the three questions regarding doctor-diagnoses asthma, asthma medication during the previous 12 months and wheezing in the preceding 12 months. Based on the repeated questionnaires from birth, persistent asthma was defined as asthma diagnosed between birth and 5 years old and still current at 13 years old.

2.4. TRAP exposure assessment

The ExTra index assessed cumulated exposure over time in front of the different residences and daycare (Sacre et al., 1995). It was developed by the French Scientific and Technical Center for Building (CSTB) and the French Institute of Science and Technology for Transport, Development and Networks (IFSTTAR) and has previously been validated by our team (Reungoat et al., 2003). The ExTra index was used to estimate ambient air concentrations of nitrogen oxides (NO_x) in front of children's residences. It includes a regional component corresponding to background levels measured by the Paris air quality monitoring network (AIRPARIF) and a local component modeled using an air pollution dispersion model adapted from the Danish operational street pollution model (Hertel and Berkowicz, 1989). This model requires topographical data, data on traffic intensity and meteorological data related to each residence. The geographical information system of Paris municipality was used to collect topographical data: height of buildings and width of pavements and road. The average daily street traffic density was

provided by the Observatory on Mobility in the Île-de-France Region from counting or modeling. Meteorological data included a wind rose, constructed as a matrix of frequencies of occurrence of wind speeds and directions observed at the local weather bureau (Paris-Montsouris station). Specific questionnaires throughout the follow-up made it possible to document location addresses (residence and daycare) and time spent at each location. The ExTra index is composed of sub-indices corresponding to the maximum periods during which no change in location occurred. The early postnatal exposure was calculated for each child during the first year of life. It is expressed in $\mu g/m^3$ NO_2 equivalent. In addition, prenatal TRAP exposure was assessed from the daily concentrations of NO_2 measured by the nearest station to mother's home and applying an inverse distance weighting. For each mother, average NO_2 exposure levels were calculated for the entire pregnancy.

2.5. Potential confounders and effect modifiers

Sex and anthropometric parameters of the newborn were collected at the maternity hospital. The mother was asked about family characteristics: maternal education level, parents' origins, parental history of allergy (at least one parent with history of asthma or allergic rhinitis or atopic dermatitis), parental history of asthma (at least one parent with asthma history), maternal smoking and exposure to environmental tobacco smoke (ETS) during pregnancy. Family socioeconomic status (SES) was determined according to parents' occupations classified in three categories (low: unemployed/student/blue-collar workers/low-level white-collar workers; medium: craftsmen/shopkeepers/intermediate-level white-collar workers; high: high-level white-collar workers), with the highest SES of the two parents taken as the SES for the family.

When children were one month old, family living conditions were described during a phone interview including presence of humidity/mold in the home and presence of a cat at home. During the first year of life, repeated questionnaires documented residential and daycare addresses, the occurrence of early repeated LRTI (bronchitis/bronchiolitis) and early exposure to ETS at home. The occurrence of a stressful family event was defined as a separation/divorce, a job loss, a serious health problem (e.g., chronic-disease, cancer, depression, surgery, hospitalization) in any family member or close relative or the death of a family member or a close relative. Early postnatal stressful family event occurrences were considered during the first two years of life. At 13 years of age, information was collected regarding the presence of humidity/mold in the home and active smoking of the adolescent.

2.6. Statistical analyses

Using chi-squared tests or Students' t-tests, the baseline characteristics recorded at birth and health data collected at the 8–9-year medical examination were compared between adolescents participating in this study and those still followed up at 13 years old but not participating.

Associations of early TRAP exposure (prenatal NO_2 exposure and/or early postnatal NO_x exposure) with asthma and rhinitis outcomes at 13 years old were assessed using multivariable logistic regression models adjusted for confounding factors. Both single-exposure window (either prenatal NO_2 or early postnatal NO_x exposure) and multi-exposure windows (both prenatal NO_2 and early postnatal NO_x exposure) models were performed. The adjustment variables required for statistical models were selected by a Directed Acyclic Graph (DAG) produced using the online tool DAGitty version 3.0 (Textor et al., 2011) (see Supplemental Figure S1). Relationships between each variable were assigned based on knowledge of the literature regarding these associations. We identified the minimal sufficient set of adjustment variables for estimating the total effect of TRAP exposure on respiratory health. The selected variables for the models were: parental history of allergy (no, yes), family SES (low/medium, high), presence of humidity/mold in the home at birth (no, yes), presence of a cat at home at birth (no, yes), daycare attendance before 6 months of age (no, yes), season of birth (spring, summer, autumn, winter) and maternal smoking during pregnancy (no, yes). For statistical models evaluating current asthma and symptoms at 13 years old, an additional adjustment was made for adolescents active smoking (no, yes) and presence of humidity/mold in the home at 13 years old (no, yes). Results were expressed as crude and adjusted odds ratios (aOR) and their 95% confidence intervals (CI). They are presented for an interquartile range (IQR) increase in NO_x levels during the first year of life or NO_2 prenatal levels. As previously shown in the PARIS cohort at age 4 years and 8–9 years, effect modification by sex, parental history of allergy, parental history of asthma, early stressful family events (no, yes) and early repeated LRTI (less than two, two or more) were explored using interactions terms ($p < 20\%$) and stratified models. All analyses were performed using Stata/SE version 15.0 (StataCorp).

3. Results

3.1. Participants

Among the 1916 families still followed up who were sent self-administrated questionnaires for 13-year-old children, 732 returned at least one of the two questionnaires "parents" or "adolescent". Fig. 1 shows the flowchart of the study population at 13 years of age.

Table 1 presents baseline characteristics of adolescents. Compared to families who did not respond to the questionnaires, responding families were more likely to have a high SES, were more often of French origin, and mothers at birth were older, had a higher level of education and less likely to be lone mother households at inclusion; during pregnancy, mothers also smoked less often and were less exposed to ETS. No differences were observed at birth concerning sex, weight and height, place of residence, parity, breastfeeding and parental history of allergy, asthma, allergic rhinitis or atopic dermatitis.

Adolescents included and not included in this study did not differ with regard to asthma and rhinitis outcomes at 8–9 years of age nor to spirometric parameters measured at the medical examination (see Supplemental Table S1).

3.2. Levels of TRAP exposure

The distribution of prenatal and early postnatal TRAP exposure is presented in Table 2.

3.3. Associations between early TRAP exposure and respiratory health

Overall, early postnatal TRAP exposure was positively associated with current asthma (aOR = 1.21; 95% CI: 1.02, 1.43), severe wheeze (aOR = 1.23; 95% CI: 1.02, 1.47) and tended to be associated with any wheeze (aOR = 1.14; 95% CI: 0.97, 1.34) and asthma ever (aOR = 1.09; 95% CI: 0.93, 1.28) at 13 years of age. In addition, early postnatal TRAP exposure had a positive association with persistent asthma at 13 years of age (aOR = 1.26; 95% CI: 1.03, 1.55) (Table 3). Regarding associations to prenatal TRAP exposure, none were significant despite a trend for wheeze and asthma outcomes. There was no association between early TRAP exposure and allergic rhinitis outcomes in 13-year-old adolescents of the PARIS birth cohort. The results of the single-exposure window models were similar and are presented in the supplementary file (see Supplemental Table S2).

Associations between early postnatal exposure to TRAP and asthma were modified by parental history of allergy, parental history of asthma, early stressful family events and early repeated LRTI. TRAP exposure was positively associated with asthma ever, current asthma and persistent asthma only in adolescents whose parents reported parental history of allergy, especially asthma. In the same way, associations between early postnatal TRAP exposure and asthma outcomes were reinforced in adolescents whose parents reported an early stressful family event or early repeated LRTI (Fig. 2). In addition, associations between asthma symptoms (any wheeze and severe wheeze) and early postnatal TRAP exposure were modified by parental history of asthma. Early postnatal TRAP exposure was positively associated with any wheeze and severe wheeze in adolescents whose parents reported parental history of asthma but not in adolescents without parental history of asthma. Adolescents' sex did not modify associations ($p > 0.20$).

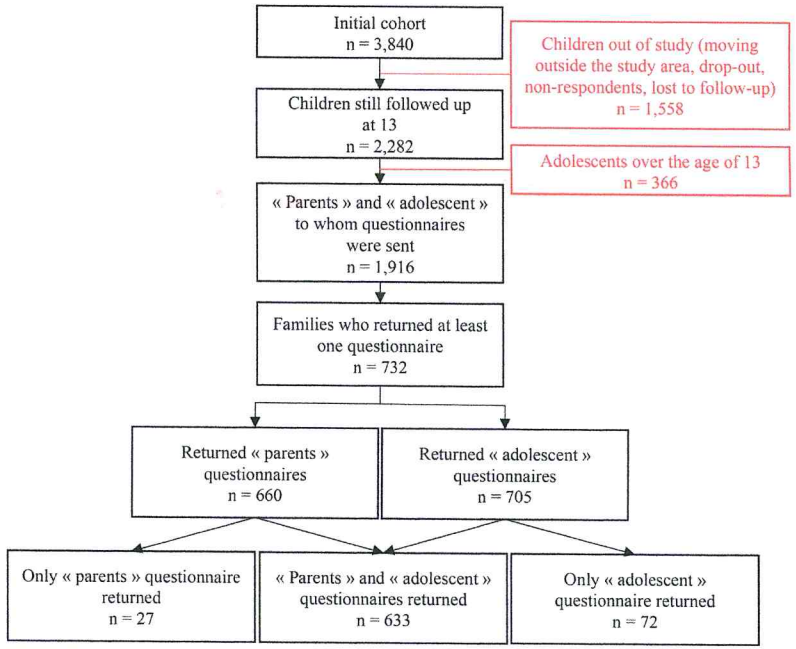

Fig. 1. Flowchart of the study population at 13 years old in the PARIS birth cohort.

4. Discussion

4.1. Key results

In this study, we showed positive associations between early postnatal TRAP exposure and the prevalence of current asthma, severe wheeze and persistent asthma in 13-year-old adolescents of the PARIS birth cohort. In addition, associations between early postnatal TRAP exposure and asthma ever, current asthma and persistent asthma at 13 years of age were clearly reinforced in certain subgroups of adolescents: those with parental history of allergy, especially asthma; early stressful family event; and early repeated LRTI. No associations with rhinitis outcomes were found at 13 years of age. Prenatal TRAP exposure did not show any association with asthma nor rhinitis outcomes.

Consistent with our results, there are several studies that also indicate that early life TRAP exposure has substantial effects on the long-term respiratory health of adolescents. In the Swedish birth cohort BAMSE, Gruzieva et al. (2013) showed a positive association between early postnatal TRAP exposure (evaluated by a dispersion model of NO_x) and prevalent asthma at 12 years of age. However, they did not find any association with wheeze at the same age, perhaps due to parents' underestimating symptom prevalence compared to adolescents' reports. In the Dutch birth cohort PIAMA, Yang et al. (2016) observed associations between NO_2 levels at birth address (evaluated by a LUR model) and incident asthma during the first 14 years of life and asthma-related symptoms at 14 years old. Moreover, pooled analysis of four European cohorts of MeDALL consortium found that early postnatal NO_2 exposure tended to be associated with asthma ever at 14–16 years of age, and was significantly associated with incident asthma between birth and 14–16 years of age (Gehring et al., 2015b).

Our present results confirm those previously observed at 4 and 8–9 years of age in the prospective follow-up of the PARIS birth cohort. In line with our findings, we had yet pointed out the role of early postnatal TRAP exposure on respiratory health. Early postnatal TRAP exposure was positively associated with asthma ever and persistent wheeze at 4 years of age, especially in children with parental history of allergy or with an occurrence of early stressful family event (Rancière et al., 2017). Additionally, at 8–9 years of age, associations between early postnatal TRAP levels and PARIS cohort children's lung function were modified by early repeated LRTI (Bougas et al., 2018). All these modifying effects clearly persist at 13 years of age, which has not been previously described in the literature. Few cohort studies have focused on interactions that may modify the associations between early postnatal TRAP exposure and respiratory health in adolescents. Gruzieva et al. (2013) were not able to demonstrate a modifying effect of parental history of allergy including asthma in the BAMSE cohort at 12 years old.

Table 1
Baseline characteristics of adolescents form the PARIS birth cohort included and not included in the study at 13 years of age.

Baseline characteristics at birth	*Respondents at 13 years(n = 732)*	*Non-respondents at 13 years(n = 1184)*	*p-Value*
Male sex, n (%)	381 (52.1)	615 (51.9)	0.96
Birth weight, g (mean ± SD)	3417 ± 15	3421 ± 12	0.84
Birth height, cm (mean ± SD)	50.2 ± 1.8	50.1 ± 1.9	0.27
Place of residence			0.24
Paris city, n (%)	458 (62.6)	709 (59.9)	
Paris suburbs, n (%)	274 (37.4)	475 (40.1)	
Family socioeconomic status			<0.001
Low, n (%)	32 (4.4)	116 (9.8)	
Medium, n (%)	164 (22.4)	356 (30.1)	
High, n (%)	536 (73.2)	712 (60.1)	
Geographic origins of parents			0.001
Two parents born in France, n (%)	558 (76.4)	820 (69.7)	
At least one parent born outside France, n (%)	172 (23.6)	357 (30.3)	
Maternal education			<0.001
Primary, n (%)	6 (0.8)	17 (1.4)	
Secondary, n (%)	52 (7.1)	173 (14.7)	
Post-secondary, n (%)	673 (92.1)	992 (83.9)	
Mother's age, years (mean ± SD)	33.3 ± 3.9	32.4 ± 4.0	<0.001
Primiparous mother, n (%)	375 (51.2)	641 (54.1)	0.22
Lone mother households, n (%)	4 (0.6)	20 (1.7)	0.03
Exposure to smoking during pregnancy			
Maternal active smoking, n (%)	42 (5.7)	119 (10.1)	0.001
Exposure to ETS, n (%)	146 (20.0)	298 (25.3)	0.008
Breastfeeding, n (%)	591 (82.1)	948 (80.8)	0.49
Parental history of allergy, n (%)*	392 (53.6)	637 (54.0)	0.86
Asthma, n (%)	149 (20.4)	226 (19.2)	0.52
Allergic rhinitis, n (%)	273 (37.4)	435 (36.9)	0.85
Atopic dermatitis, n (%)	131 (17.9)	245 (20.8)	0.12

Definition of abbreviation: SD = standard deviation; ETS = environmental tobacco smoke. *Asthma, allergic rhinitis and/or atopic dermatitis.

However, susceptibility to TRAP in children exposed to stress has been suggested in different studies. The Children's Health Study cohort showed the effect of TRAP exposure during childhood on incident asthma at 5–9 years of age and pulmonary function (mean age 11.2 years) only in children with high parental stress (Islam et al., 2011; Shankardass et al., 2009). Using exposure to violence (ETV) as a proxy for chronic stressor, Clougherty et al. (2007) reported that NO_2 levels in the year of diagnosis were associated with asthma in children with above-median ETV exposure. Nevertheless, these studies did not focus on early postnatal exposure windows. To the best of our knowledge, no study has investigated vulnerability to TRAP exposure in adolescents who have suffered from repeated LRTI in early life.

All these results are biologically plausible. The exact mechanisms by which TRAP affects respiratory health are complex and not fully understood. TRAP exposure could play a role on asthma onset by various mechanisms: TRAP can induce airway inflammation and airway hyperresponsiveness, two characteristics of asthma. Moreover, TRAP induces oxidative stress through the formation of reactive oxygen species (Mann et al., 2021). This oxidative stress causes chronic inflammation of airway epithelial cells and potentiates the allergic response (Guarnieri and Balmes, 2014). As suggested in this study, parental history of allergy, asthma, early stressful family events, and early repeated LRTI could potentiate the effect of early postnatal TRAP exposure. It is now well known that heredity is a major contributor to the development of asthma (Ober and Yao, 2011). This combined with TRAP exposure, may increase the risk of developing asthma during childhood. Similar to TRAP, early exposure to stress is another potential driver for respiratory disorders such as asthma. The potential mechanisms linking stress and respiratory problems have been extensively studied (Rosa et al., 2018). Chronic stress has been shown to result in biological changes such as the expression of immunologic genes, alterations in the hypothalamic pituitary axis and cortisol levels (Barnthouse and Jones, 2019). This stress response together with TRAP exposure may influence long-term respiratory and allergic health and the development of asthma in exposed children. Finally, early LRTI are known to have long-term sequelae, including the development of asthma in children (Edmond et al., 2012; Stein et al., 1999). It has been suggested that LRTI at an early stage of lung development may impair lung growth and reduce subsequent lung function. Thus, the harmful effect of early repeated LRTI combined with early postnatal TRAP exposure may promote the development of asthma later in life.

Regarding TRAP exposure windows, we focused on early life exposure. The early postnatal period is a crucial time in the development of asthma. It corresponds to a critical time in lung and immune system development when chronic TRAP exposure could lead to airway damage and induce an airway remodeling leading to asthma. Pregnancy is also a vulnerable period for TRAP exposure but, despite a trend, no association between prenatal TRAP exposure and respiratory health in adolescents was found in this study. This could be due to the use of a less accurate method of exposure assessment. Indeed, the absence of topographic data relating to mothers' residence and workplace during pregnancy meant it was not possible to model prenatal TRAP exposure by the ExTra index.

Table 2
Distribution of prenatal and early postnatal TRAP exposure in the PARIS birth cohort children included in the study at 13 years old (n = 732).

	Minimum	25th Percentile	Median	75th Percentile	Maximum	IQR
Prenatal NO_2, µg/m^3	34.3	39.0	41.1	44.0	50.0	5.0
Early postnatal NO_x, µg/m^3 NO_2 equivalent	42.1	66.0	72.1	83.0	246.0	17.0

Definition of abbreviations: IQR = interquartile range; NO_x = nitrogen oxides; NO_2 = nitrogen dioxide. "Prenatal NO_2" corresponds to average NO_2 exposure during the entire pregnancy, weighted by inverse distance. Prenatal levels are based only on background stations. "Early postnatal NO_x" corresponds to average NO_x exposure during the first year of life.

Table 3
Associations of prenatal and early postnatal TRAP exposure with respiratory health in the PARIS birth cohort at 13 years: multi-exposure windows model.

		Prenatal NO_2		Early postnatal NO_x	
Outcomes	n	Crude OR (95% CI)	aOR (95% CI)	Crude OR (95% CI)	aOR (95% CI)
Wheeze in the last 12 months					
No (reference)	611	1	1	1	1
Any wheeze	90	1.00 (0.71, 1.41)	1.11 (0.60, 2.04)	1.22 (1.06, 1.40)**	1.14 (0.97, 1.34)
No (reference)	611	1	1	1	1
Severe wheeze	44	0.87 (0.53, 1.41)	1.11 (0.49, 2.53)	1.32 (1.12, 1.55)***	1.23 (1.02, 1.47)*
Current asthma					
No (reference)	485	1	1	1	1
Yes	64	0.80 (0.53, 1.21)	1.49 (0.76, 2.94)	1.26 (1.08, 1.47)**	1.21 (1.02, 1.43)*
Asthma					
No (reference)	562	1	1	1	1
Asthma ever	90	0.92 (0.66, 1.29)	1.19 (0.69, 2.03)	1.12 (0.96, 1.31)	1.09 (0.93, 1.28)
No (reference)	562	1	1	1	1
Persistent asthma at 13	27	0.77 (0.42, 1.43)	1.40 (0.53, 3.68)	1.33 (1.10, 1.61)**	1.26 (1.03, 1.55)*
Rhinitis symptoms in the last 12 months					
No (reference)	461	1	1	1	1
Any rhinitis symptoms	240	1.03 (0.81,1.31)	0.80 (0.53, 1.16)	1.03 (0.92, 1.15)	1.02 (0.89, 1.16)
No (reference)	461	1	1	1	1
Severe rhinitis symptoms	69	1.11 (0.75, 1.64)	0.70 (0.35, 1.20)	0.92 (0.74, 1.15)	0.93 (0.73, 1.20)
Allergic rhinitis ever					
No (reference)	551	1	1	1	1
Yes	100	0.99 (0.72, 1.37)	0.93 (0.54, 1.11)	0.97 (0.82, 1.16)	0.92 (0.76, 1.11)

Definition of abbreviations: OR = odds ratio; aOR = adjusted odds ratio; CI = confidence interval. Odds ratios are calculated for an interquartile range (5.0 µg/m^3 NO_2 for prenatal exposure and 17.0 µg/m^3 NO_2 equivalent for early postnatal exposure). Symptom outcomes are based on adolescents' questionnaires (n = 705), asthma ever and rhinitis ever are based on parents' questionnaires (n = 660), current asthma is based on both adolescents' and parents' questionnaires (n = 633). Models are adjusted for parental history of allergy, family SES, presence of humidity/mold in the home at birth, presence of a cat in the home at birth, daycare attendance before 6 months of age, season of birth and maternal smoking during pregnancy. Associations with prenatal NO_2 exposure were also adjusted for early postnatal NO_x. Associations with early postnatal NO_x were also adjusted for prenatal NO_2 exposure. Supplementary adjustments on adolescents' active smoking and the presence of humidity/mold in the home at age 13 are made in models evaluating current asthma and symptoms associations. *$p \leq 0.05$. **$p \leq 0.01$. ***$p \leq 0.001$.

Consequently, we used NO_2 concentrations measured by the air quality network background station closest to the mother's address. In the literature, exposure to prenatal TRAP appears to impair fetal immune system development and contribute to the development of childhood wheezing and asthma (García-Serna et al., 2020; Hehua et al., 2017). However, the impact of prenatal TRAP has been studied primarily in young children. No studies have reported consistent associations between prenatal exposure and asthma in adolescence.

Concerning rhinitis in adolescents, the role of TRAP exposure is unclear. Most studies to date are cross-sectional (Shirinde et al., 2015; Skrzypek et al., 2019) and, to our knowledge, only two studies have dealt with early postnatal TRAP exposure in association with adolescent rhinitis using a prospective design. Yang et al. (2016) reported an association between NO_2 levels at birth address and rhinitis in children up to the age of 14. Gehring et al. (2015b) found no association between TRAP and incident nor prevalent rhinoconjunctivitis at 14–16 years of age. Since allergic rhinitis develops later in childhood, an exposure window closer to adolescence may be more appropriate to assess the impact of TRAP.

4.2. Strengths and limitations

This study has multiple strengths. First, this is one of the few cohort studies to focus on adolescent respiratory and allergic morbidity and its relationship with early TRAP exposure. The prospective follow-up of the PARIS birth cohort makes reporting the chronology of events possible, thus reducing classification bias. In addition, the use of parental questionnaires for medical information and adolescent questionnaires for symptoms facilitates the capture of complementary features of this morbidity at the age of 13. Indeed, we can assume that symptoms are better described by those who feel them and that questions about medical information such as medications or diagnoses since birth are better documented by parents, with less memory bias than adolescents. Another strength lies in the method used to assess early postnatal TRAP exposure which was considered as a whole without focusing on one specific pollutant. It was expressed with regard to NO_x, which are the best traffic indicators in the Paris area where 56% of total background NO_x levels are attributed to traffic (against 23% for $PM_{2.5}$) (Airparif, 2020). Early postnatal TRAP exposure was precisely estimated taking into account multiple addresses (residence and daycare) by a dispersion model of NO_x. Indeed, modeling of NO_x levels by the ExTra index showed excellent performance in the validation study previously conducted by our team (Reungoat et al., 2003). However, these air pollution dispersion models require a large amount of data and are time-consuming. Most of the studies use LUR exposure models (Gehring et al., 2015b; Mölter et al., 2013; Zhao et al., 2020). In LUR models it is difficult to take into account street canyon effects, meteorology and atmospheric chemistry of the pollutants and generally children's mobility is not considered (Khreis and Nieuwenhuijsen, 2017). Finally, our study has detailed information on family, home and lifestyle characteristics, allowing the adjustment of statistical models for many potential confounding factors. We selected the most relevant confounders from a DAG including prenatal exposure to TRAP. This made it possible to distinguish effects of postnatal exposure from those of *in utero* exposure. Moreover, it is assumed that respiratory morbidity results from multiple interacting causes. For this reason, many interactions have been tested in order to identify modifiers.

Regarding limitations, the analysis of results at 13 years old was conducted on a subgroup of 732 participants who answered questionnaires without any reminder. The attrition rate, inherent to longitudinal surveys, in the PARIS birth cohort is mainly due to a move out of the study area. In fact, families in large conurbations, such as Paris and its suburbs, have a high rate of residential mobility. Another weakness lies in the homogeneity of our population mainly of moderate to high SES, thus limiting us to investigate the interaction between TRAP exposure and social deprivation previously described in the literature (Cakmak et al., 2016; Kravitz-Wirtz et al., 2018).

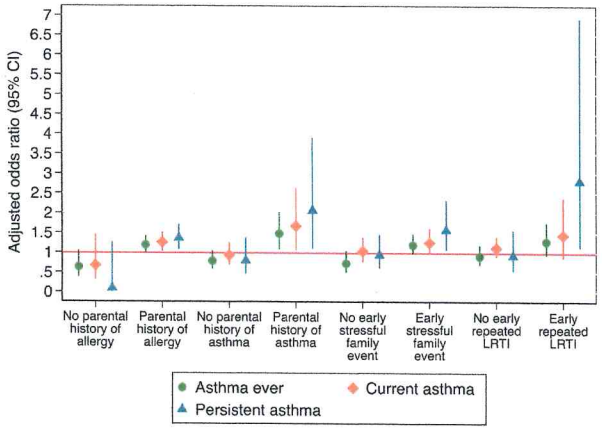

Fig. 2. Associations between early postnatal TRAP exposure and asthma at 13 years old in relation to parental history of allergy, parental history of asthma, the occurrence of an early stressful family event and the occurrence of early repeated LRTI in the PARIS birth cohort. Odds ratios are calculated for an interquartile range (17.0 $\mu g/m^3$ NO_2 equivalent) increase in average NO_x levels during the first year of life. Models are adjusted for parental history of allergy, family SES, presence of humidity/mold in the home at birth, presence of a cat at the home at birth, daycare attendance before 6 months of age, season of birth, maternal smoking during pregnancy and prenatal NO_2 exposure. Supplementary adjustments on adolescents' active smoking and presence of humidity/mold in the home at the age of 13 are made in models evaluating current asthma.

5. Conclusion

In conclusion, higher levels of TRAP exposure during the first year of life increase the risk of asthma at 13 years old but are not associated with rhinitis. All adolescents are not equally affected by early postnatal TRAP exposure. Adolescents presenting parental history of allergy especially asthma, those with an early stressful family event or early repeated LRTI appear to be more vulnerable to the effects of early postnatal TRAP exposure. Therefore, these results strength the need of preventive measures to reduce TRAP levels in urban areas, including public space planning and research to replace fossil energy with clean energy.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envres.2021.111473.

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Early Exposure to Traffic-Related Air Pollution, Respiratory Symptoms at 4 Years of Age, and Potential Effect Modification by Parental Allergy, Stressful Family Events, and Sex: A Prospective Follow-up Study of the PARIS Birth Cohort

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BACKGROUND: The relation between traffic-related air pollution (TRAP) exposure and the incidence of asthma/allergy in preschool children has been widely studied, but results remain heterogeneous, possibly due to differences in methodology and susceptibility to TRAP.

OBJECTIVES: We aimed to study the relation of early TRAP exposure with the development of respiratory/allergic symptoms and asthma during preschool years, and to investigate parental allergy, "stressful" family events, and sex as possible effect modifiers.

METHODS: We examined data of 2,015 children from the PARIS birth cohort followed up with repeated questionnaires completed by parents until age 4 years. TRAP exposure in each child's first year of life was estimated by nitrogen oxides (NO_x) air dispersion modeling, taking into account both home and day care locations. Association between TRAP exposure and patterns of wheezing, dry night cough, and rhinitis symptoms was studied using multinomial logistic regression models adjusted for potential confounders. Effect modification by parental history of allergy, stressful family events, and sex was investigated.

RESULTS: An interquartile range (26 $\mu g/m^3$) increase in NO_x levels was associated with an increased odds ratio (OR) of persistent wheezing at 4 years (adjusted OR = 1.27; 95% confidence interval: 1.09, 1.47). TRAP exposure was positively associated with persistent wheeze, dry cough, and rhinitis symptoms among children with a parental allergy, those experiencing stressful family events, and boys, but not in children whose parents did not have allergies or experience stressful events, or in girls (all interaction p-values < 0.2).

CONCLUSIONS: This study supports the hypothesis that not all preschool children are equal regarding TRAP health effects. Parental history of allergy, stressful family events, and male sex may increase their susceptibility to adverse respiratory effects of early TRAP exposure.

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Introduction

The prevalence of respiratory and allergic diseases in early childhood has been rising globally, which is unlikely to be attributable to genetic changes only. These multifactorial diseases are associated with both individual and environmental factors. Recent decades have seen a change in air pollution profile in western urban areas, with motor vehicle traffic emissions now as a major source of air pollution (Mayer 1999). Traffic-related air pollution (TRAP) is known to worsen existing respiratory disease (Weinmayr et al. 2010). However, despite substantial literature on the relation between TRAP and the development of asthma and allergy in preschool years, results are still heterogeneous and some uncertainties persist (Bråbäck and Forsberg 2009). For instance, although a meta-analysis of 19 published studies showed evidence for a relationship between TRAP exposure and wheezing in preschool children (Gasana et al. 2012), pooled analyses of five European birth cohorts within the European Study of Cohorts for Air Pollution Effects (ESCAPE) project revealed no significant association of TRAP exposure in early years of life with asthma prevalence at 4–5 years (Mölter et al. 2015) or sensitization to inhalant or food allergens at 4 years (Gruzieva et al. 2014). These inconsistencies in findings may be attributable to methodological issues such as variability in the assessment of TRAP exposure (Brauer 2010) and the definition of health outcomes, and to the possible existence of susceptible subgroups.

In birth cohort studies, TRAP exposure of preschool children has been studied using various indicators: distance to traffic, land-use regression (LUR) models, and, less often, air dispersion models (Bowatte et al. 2015). There are also differences in TRAP pollutants that authors considered [e.g. nitrogen dioxide (NO_2), nitrogen oxides (NO_x), particulate matter with an aerodynamic diameter ≤ 10 μm (PM_{10}) or ≤ 2.5 μm ($PM_{2.5}$), soot, black carbon], as well as in place and timing of exposure, with most studies only considering the home address at birth, and a few studies considering residential mobility and/or other locations where infants spend time such as day care center. Furthermore, asthma may be difficult to reliably diagnose at preschool age when the clinical symptoms of asthma are variable and nonspecific, and asthma-like or allergy-like symptoms other than wheeze have not been extensively explored.

Besides methodological considerations, another explanation may be related to differences in vulnerability to TRAP. Even if early childhood is a critical period of vulnerability for everyone because of continued development and maturation of the lung and immune system, certain children may be at increased risk for adverse health effects from TRAP (Sacks et al. 2011). In particular, atopy may play a role as an effect modifier, but results from the literature are not entirely consistent. Stronger associations between TRAP exposure and asthma were observed in atopic children in some studies (Dell et al. 2014; Janssen et al. 2003; Schultz et al. 2012) and in nonatopic children in other studies (Gruzieva et al. 2013; McConnell et al. 2006; Nordling et al. 2008). Moreover, emerging research indicates that stress may play a role in increasing the deleterious effect of TRAP on school-age children's respiratory health (Chen et al. 2008; Clougherty et al. 2007; Islam et al. 2011; Shankardass et al. 2009); but, to our knowledge, no such studies have been conducted in preschool children. Further, whether the susceptibility to the effects of TRAP differs between preschool boys and girls remains unclear. Some authors reported evidence of stronger effects in boys (Gehring et al. 2002) or in girls (Nordling et al. 2008), whereas others did not find any evidence for an effect measure modification by sex (Gruzieva et al. 2014). Last, gene–environment interactions may also partially explain observed heterogeneity in associations between TRAP exposure and the incidence of asthma and allergic outcomes, as suggested by findings from the Traffic, Asthma, and Genetics (TAG) study (Fuertes et al. 2013; MacIntyre et al. 2014).

Consequently, much needed are longitudinal studies with refined assessment of TRAP exposure and insight into factors that may modify the effect of children's TRAP exposure on respiratory and allergic morbidity. Especially, birth cohort studies are essential to understand the life course and childhood predictors of asthma and allergy, and the complex interplay between heritable and environmental factors (Bousquet et al. 2014).

As part of the Pollution and Asthma Risk: an Infant Study (PARIS) birth cohort, the aims of this study were *a*) to investigate the association between TRAP exposure in early life and the history of respiratory symptoms and asthma during the preschool years, and *b*) to explore whether certain groups of preschool children are more prone to develop respiratory symptoms and asthma in relation to TRAP exposure, focusing on parental allergy, "stressful" family events, and sex.

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Methods

Study Design and Setting

Data were collected from birth to age 4 years, including a face-to-face interview with the mother at the maternity hospital, a phone interview at 1 month, and regular self-administered questionnaires filled in by parents when their child was 1, 3, 6, 9, 12, and 18 months and 2, 3, and 4 years of age.

Participants

PARIS is a population-based birth cohort study that enrolled 3,840 newborn babies born between 2003 and 2006 in five Paris maternity hospitals. Information about medical and sociodemographic eligibility criteria and methods of selection was previously published (Clarisse et al. 2007). Briefly, PARIS included single-birth, full-term newborns, without malformation, and with an uncomplicated birth and neonatal period. Exclusion criteria included infants whose mothers were < 18 years of age, did not receive medical care during pregnancy, had alcohol or drug addiction, or had difficulty speaking French. The French Ethics Committee approved the study protocol and written informed consent was obtained from the parents.

Variables

Health outcomes. Respiratory symptoms suggestive of asthma or allergy were assessed by standardized questions from the International Study of Asthma and Allergies in Childhood (Asher et al. 1995), used in the European consortium MeDALL (Mechanisms of the Development of ALLergy) (Antó et al. 2012; Pinart et al. 2014). At ages 1, 2, 3 and 4 years, parents were asked about the occurrence in the previous year of wheezing ("In the last 12 months, has your child had wheezing or whistling in the chest?"), dry night cough ("In the last 12 months, has your child had a dry cough at night, apart from a cough associated with a cold or chest infection?"), and rhinitis symptoms ("In the last 12 months, has your child had a problem with sneezing, or a runny or blocked nose when he/she did not have a cold or the flu?").

We hypothesized that the effects of TRAP exposure on respiratory health during preschool years may differ depending on the time of onset and the persistence of the symptoms. To account for the temporality of symptoms during preschool years, children were categorized into four classes according to the trajectory of each of these three symptoms between 0 and 4 years:

- No symptom
- Early-transient: symptom occurring between 0 and 2 years of age and not persisting later;
- Late-onset: symptom occurring between 2 and 4 years of age;
- Persistent: symptom occurring between 0 and 2 years of age and persisting later.

Each year, parents were asked whether a doctor had ever diagnosed their child with asthma. Asthma ever at 4 years was defined as asthma ever doctor-diagnosed between 0 and 4 years. Asthma ever with current respiratory symptoms at 4 years was defined as asthma ever in addition to respiratory symptoms (wheezing, dry night cough) in the previous year at 4 years.

TRAP exposure. We used the ExTra index developed by Sacre et al. (1995) to estimate ambient concentrations of traffic-related air pollutants such as nitrogen oxides [NO_x = nitrogen monoxide (NO) + NO_2], taking into account the different places (home and day care) attended by children during their first year of life.

At each follow-up time point, the parents provided in a specific questionnaire the home and day care addresses (including the floor number), as well as the time spent at day care (number of hours per week). We derived the time spent at home as the remaining time. Addresses were geocoded using traditional maps (scale: 1/15,000 or 1/12,500), cadastral maps, and/or the geographic information system (GIS) of the Paris municipality.

Briefly, the ExTra index relies on an air dispersion model adapted from the Danish Operational Street Pollution Model (OSPM) by the French Scientific and Technical Center for Building (CSTB) and the French Institute of Science and Technology for Transport, Development and Networks (IFSTTAR), and has been validated by our research team (Reungoat et al. 2003). Briefly, NO_x concentrations measured over 6 weeks with passive samplers were compared with NO_x concentrations modeled using the ExTra index, at 100 sites in four French cities including Paris. There were highly significant correlations ($r = 0.89$, $p < 10^{-4}$ in Paris) and good intraclass correlation coefficients ($R = 0.89$ in Paris) between the two series of values.

The ExTra index integrates a regional component corresponding to the background NO_x levels measured by the Paris air quality monitoring network (AIRPARIF) and a local component modeling NO_x levels in front of the different locations attended by children. The modeling step required the preliminary collection of a large amount of data such as topographical features of each relevant location (residence, day care) for each child in the cohort (height of buildings and width of pavements and road collected using a GIS), meteorological data (wind direction and speed supplied by the local weather bureau), and traffic density in the street (resulting from counting or estimating).

The ExTra index is composed of subindices corresponding to the different life periods of each child. A life period is defined as the maximum time period during which no change in locations (home, day care) or time spent in these locations occurred. The ExTra index, expressed in $\mu g/m^3$ NO_2 equivalent, was then calculated for each child's first year of life as the weighted average of the different subindices. In summary, the concentration assigned to each child can be expressed as following, for all life periods i, with C the concentration of NO_x, T the percent of time spent in the place during the period, and D the duration of the period in days.

$$\sum_i [C(home)_i \times T(home)_i + C(day\ care)_i \times T(day\ care)_i] \times \frac{D_i}{365}$$

The modeling of TRAP exposure during the fourth year of life taking into account home, day care and school locations is ongoing in our study.

Family and home characteristics. At the maternity hospital, the mother was questioned about family characteristics including presence of older siblings, parental education, occupation, and history of asthma, eczema, and allergic rhinitis, and maternal active and passive smoking during pregnancy. Family socioeconomic status (SES) was based upon the highest position among the two parents and divided into three categories (low/medium/high) as previously described (Rancière et al. 2013b). Parental history of allergy was defined as at least one parent with a history of asthma, eczema, or allergic rhinitis.

When the child was 1 month old, a trained interviewer administered a phone questionnaire to one of the parents about housing characteristics and living habits, and occurrence of "stressful" family events. The self-administered questionnaires mailed to the families between 3 months and 4 years of age produced an update of previously collected data and documented duration of breastfeeding and type of day care setting. We considered a child to be exposed to "stressful" family events if the parents reported a separation/divorce, a loss of job, a serious health problem (e.g., chronic disease, cancer, depression, surgery, hospitalization) in any family member or close relative or the death of a family member or a close relative, during the first 2 years of life.

Statistical Methods

The main characteristics of PARIS children, whether or not included in the present study, were analyzed using chi-squared tests or Student's *t*-tests.

The association of early-life TRAP exposure with asthma and patterns of respiratory symptoms was assessed using multinomial logistic regression (for the wheeze, dry cough, and rhinitis outcomes) or logistic regression (for the dichotomous asthma outcomes) adjusted for the relevant variables. Covariates were selected for inclusion in the statistical models using a directed acyclic graph (DAG) built using DAGitty version 2.2 (Textor et al. 2011). The DAG is presented in Figure S1. Relationships between each of the variables were assigned based on knowledge of the literature regarding these associations. Given the assumptions described in the DAG theory, we identified the minimal sufficient set of adjustment variables for estimating the direct effect of TRAP exposure on respiratory health. Covariates selected for inclusion in the multivariable models were sex, birth weight (continuous), family SES (low, medium, high), maternal education (high school education or less, at least some college), exclusive breastfeeding during the first 3 months (no, yes), type of day care during the first 6 months (no day care, at home, at a childminder's home, in a day care center), maternal smoking during pregnancy (no, yes), exposure to environmental tobacco smoke at home during the first year (no, yes), body mass index ≥ 85th percentile for age and sex at 2–3 years (no, yes), visible mold in the home at birth (no, yes), gas for cooking/heating in the home at birth (no, yes), and stressful family events (no, yes). Given our research question, models were also adjusted for maternal and paternal history of allergy (no, yes), which did not result in any biasing path.

Children with complete data for all covariates were included in the final multivariable models. Results were expressed as adjusted odds ratios (OR) and their 95% confidence intervals (CI). TRAP exposure levels were entered as a continuous variable, and results are presented for an interquartile range (IQR) increase in NO_x levels within the PARIS birth cohort (26 $\mu g/m^3$ NO_2 equivalent).

Possible effect measure modification by parental history of allergy (based on either parent, or based on the mother only, father only, or both), stressful family events, and sex was explored by testing multiplicative interactions using an alpha of 0.2.

In a subsample of about 800 children for whom TRAP exposure during the fourth year of life has already been modeled, we performed a sensitivity analysis including TRAP exposure levels during both the first year (early exposure) and the fourth year (later exposure).

All analyses were performed using Stata/SE version 13.1 (StataCorp).

Results

Participants

Results are given for 2,015 children for whom information about TRAP exposure level during the first year and natural history of at least one respiratory symptom during the first 4 years were available. Twenty-eight percent of the children not included had to stop the follow-up before their 4th birthday because they moved outside the study area, a withdrawal criterion specified in the protocol (Clarisse et al. 2007). The main characteristics of children included in this study are presented in Table 1. Compared with children from the PARIS birth cohort not included, the 2,015 children included in this study were more likely to live in a family with a high SES and less likely to have been exposed to maternal smoking during pregnancy. Parents of children included in the study more often reported a paternal history of asthma, eczema, or allergic rhinitis.

Levels of TRAP Exposure

Levels of early exposure to NO_x ranged from 39 to 257 $\mu g/m^3$ NO_2 equivalent, with a median (IQR) of 75 (66–89) $\mu g/m^3$. Children exposed to NO_x levels above the median level were more likely to be from families with a high SES, to have been exposed to maternal smoking during pregnancy, and to live in a home with gas used for heating and/or cooking (Table 2). TRAP exposure levels were significantly higher in the inner city than in the suburbs, with a median (IQR) of 77 (69–91) $\mu g/m^3$ and 68 (58–86) $\mu g/m^3$ NO_2 equivalent, respectively ($p = 0.008$).

Main Results

Overall, early TRAP exposure was significantly associated with persistent wheeze at age 4 years (OR = 1.27; 95% CI: 1.09, 1.47) compared with children without wheeze during the first 4 years of life (Table 3). No such associations were observed for early-transient and late-onset wheeze. In addition, TRAP exposure was significantly associated with increased OR for asthma ever (OR = 1.15; 95% CI: 1.01, 1.31) and asthma ever with current respiratory symptoms at 4 years (OR = 1.20; 95% CI: 1.02, 1.41). There was no significant association of TRAP exposure with any patterns of dry night cough or rhinitis symptoms.

Associations of TRAP exposure with persistent respiratory symptoms appeared to be modified by parental history of allergy and stressful family events (Table 4). TRAP exposure was positively associated with all persistent respiratory symptoms, asthma ever, and asthma ever with current respiratory symptoms in children whose parents reported a history of allergy, but not in children whose parents did not have a history of allergy (all interaction p-values ≤ 0.15). Associations also were positive for the same outcomes among children with a history of stressful family events, but not among children without a history of stressful events, though interactions were not significant (interaction $p > 0.2$) for the two asthma outcomes. The highest ORs were observed for persistent wheeze. Furthermore, we explored whether maternal and paternal allergy had different implications for the risk of asthma ever in relation with TRAP exposure, and they did not appear to have differential effects (Figure 1). TRAP exposure was positively associated with asthma ever in children with allergy in one or both parents, but not in children without parental allergy (p for interaction = 0.12). The association between TRAP exposure and asthma ever appeared stronger when both parents had a history of allergy (OR = 1.71; 95% CI: 1.23, 2.38) than when only one parent had a history of allergy (OR = 1.17; 95% CI: 0.97, 1.40).

Associations also differed by sex regarding persistent respiratory symptoms and asthma (Table 5). TRAP exposure was significantly associated with persistent wheeze (OR = 1.39; 95% CI: 1.15, 1.69), persistent dry night cough (OR = 1.21; 95% CI: 1.01, 1.45), and persistent rhinitis symptoms (OR = 1.21; 95% CI: 1.03, 1.43) among boys but not girls (all interaction $p \leq 0.12$). The association with asthma ever was also significant in boys (OR = 1.22; 95% CI: 1.05, 1.43) but not in girls (OR = 1.04; 95% CI: 0.83, 1.32), even though the interaction was not significant (interaction $p > 0.20$). Moreover, TRAP exposure was positively associated with early-transient wheeze in boys but not in girls, and late-onset wheeze in girls but not in boys (interaction p-values = 0.09), although the ORs were not significant.

Preliminary results on a subgroup of the cohort ($n = 768$) showed that TRAP exposure levels during the first and fourth years were correlated with a correlation coefficient of 0.64 ($p < 10^{-5}$). Early TRAP exposure was still positively associated with persistent wheezing when later TRAP exposure was further included in the model (OR = 1.22; 95% CI: 0.87, 1.72 compared with OR = 1.27; 95% CI: 1.00, 1.62 when later exposure was not included), although the OR estimate was no longer statistically significant. This additional adjustment did not result in improvement in model fit (p from likelihood-ratio test = 0.74). The OR estimate associated with later TRAP exposure was closer to 1 and was not statistically significant (OR = 1.09; 95% CI: 0.66, 1.79).

Table 1. Baseline characteristics of children from the PARIS cohort included ($n = 2,015$) and not included ($n = 1,825$) in the present study.

Baseline characteristics	Included	Not included	*p*-Value
Male sex	1,032 (51.2)	941 (51.6)	0.83
Birth weight (kg)	3.40 ± 0.39	3.40 ± 0.40	0.77
Family socioeconomic status			< 0.001
Low	122 (6.0)	244 (13.4)	
Medium	525 (26.1)	555 (30.4)	
High	1,368 (67.9)	1,026 (56.2)	
Place of residence at birth			0.98
Paris city	1,277 (63.4)	1,156 (63.3)	
Paris suburbs	738 (36.6)	669 (36.7)	
Older siblings	885 (43.9)	776 (42.5)	0.38
Maternal history of asthma, eczema, or allergic rhinitis	759 (37.7)	651 (35.7)	0.20
Paternal history of asthma, eczema, or allergic rhinitis	745 (37.1)	603 (32.2)	0.01
Maternal use of antibiotics during pregnancy	296 (14.7)	261 (14.3)	0.73
Maternal smoking during pregnancy	203 (10.1)	230 (12.6)	0.01
Cat allowed in the child's bedroom just after birth	160 (8.0)	124 (7.2)	0.36
Visible mold in the home just after birth	312 (15.5)	284 (16.4)	0.46
Use of gas for cooking or heating in the home just after birth	1,096 (55.5)	960 (57.2)	0.28

Data are shown as *n* (%) or mean ± SD. Total numbers may not be equal to 2,015 and 1,825 for some characteristics due to missing data.

Discussion

Key Results

In the PARIS prospective birth cohort study, we aimed to explore the association of early-childhood TRAP exposure with the time course of respiratory/allergic symptoms in the first 4 years and asthma ever at 4 years. In

Table 2. Characteristics of children from the PARIS cohort included in the study according to median level of traffic-related air pollution exposure during the first year ($n = 2,015$).

Characteristics[a]	$NO_x < 75$ $\mu g/m^3$ ($n = 973$)	$NO_x \geq 75$ $\mu g/m^3$ ($n = 1,042$)	*p*-Value
Sex			0.84
Male	496 (51.0)	536 (51.4)	
Female	477 (49.0)	506 (48.6)	
Birth weight	3.42 ± 0.39	3.39 ± 0.40	0.12
Family socioeconomic status			0.01
Low	69 (7.1)	53 (5.1)	
Medium	274 (28.2)	251 (24.1)	
High	630 (64.7)	738 (70.8)	
Maternal education			0.58
High school education or less	109 (11.2)	109 (10.5)	
At least some college	862 (88.8)	933 (89.5)	
Missing (*n*)	2	0	
Maternal history of asthma, eczema, or allergic rhinitis			0.56
No	600 (61.7)	655 (62.9)	
Yes	373 (38.3)	386 (37.1)	
Missing (*n*)	0	1	
Paternal history of asthma, eczema, or allergic rhinitis			0.72
No	606 (62.5)	656 (63.3)	
Yes	364 (37.5)	381 (36.7)	
Missing (*n*)	3	5	
Maternal smoking during pregnancy			0.04
No	889 (91.4)	923 (88.6)	
Yes	84 (8.6)	119 (11.4)	
Visible mold in the home			0.92
No	822 (84.6)	877 (84.4)	
Yes	150 (15.4)	162 (15.6)	
Missing (*n*)	1	3	
Use of gas for cooking or heating in the home			0.003
No	455 (48.0)	425 (41.3)	
Yes	493 (52.0)	603 (58.7)	
Missing (*n*)	25	14	
Exclusive breastfeeding during the first 3 months			0.65
No	678 (70.2)	736 (71.1)	
Yes	288 (29.8)	299 (28.9)	
Missing (*n*)	7	7	
Day care during the first 6 months			0.87
No	374 (39.8)	379 (38.4)	
Yes, at home	158 (16.8)	174 (17.6)	
Yes, at a childminder's home	208 (22.1)	229 (23.2)	
Yes, in a day care center	200 (21.3)	206 (20.8)	
Yes, but type not specified (*n*)	33	54	
Exposure to smoking at home during the first year			0.13
No	717 (75.3)	735 (72.3)	
Yes	235 (24.7)	282 (27.7)	
Missing (*n*)	21	25	
Stressful family events during the first 2 years[b]			0.51
No	521 (54.8)	540 (53.3)	
Yes	430 (45.2)	473 (46.7)	
Missing (*n*)	22	29	
Body mass index ≥ 85th percentile for age and sex at 2–3 years			0.06
No	755 (79.5)	770 (75.9)	
Yes	195 (20.5)	245 (24.1)	
Missing (*n*)	23	27	

Data are shown as *n* (%) or mean ± SD.
[a]Characteristics are at birth unless otherwise specified.
[b]Among parental separation/divorce, parental loss of job, serious health problem, or death of a family member or close relative.

the whole study population, TRAP exposure was associated with asthma and persistent wheezing at 4 years of age. We were also interested in determining whether certain groups of preschool children are more likely to be affected by TRAP exposure, and we found evidence for effect modification by parental allergy, occurrence of stressful family events, and sex. Our analyses suggest that adverse respiratory effects of TRAP exposure may be evident only in preschool children with parental history of allergy, in those who experienced stressful family events, or in boys.

Table 3. Association between traffic-related air pollution exposure during the first year and respiratory health during preschool years in the PARIS cohort.

Respiratory health during the first 4 years of life	*n* (%)	aOR (95% CI)	*p*-Value
Wheeze			
No (reference)	1,181 (69.1)	1	
Early-transient	317 (18.5)	1.03 (0.91, 1.17)	0.67
Late-onset	86 (5.0)	1.09 (0.89, 1.33)	0.40
Persistent	126 (7.4)	1.27 (1.09, 1.47)	0.002
Dry night cough			
No (reference)	1,032 (60.6)	1	
Early-transient	190 (11.2)	1.01 (0.87, 1.18)	0.87
Late-onset	265 (15.5)	1.03 (0.91, 1.18)	0.63
Persistent	217 (12.7)	1.11 (0.97, 1.27)	0.13
Rhinitis symptoms			
No (reference)	934 (55.3)	1	
Early-transient	300 (17.7)	0.95 (0.83, 1.09)	0.45
Late-onset	175 (10.4)	1.06 (0.91, 1.24)	0.45
Persistent	281 (16.6)	1.09 (0.96, 1.24)	0.18
Asthma ever at 4 years			
No (reference)	1,517 (87.2)	1	
Yes	223 (12.8)	1.15 (1.01, 1.31)	0.03
Asthma ever with current respiratory symptoms at 4 years			
No (reference)	1,595 (93.1)	1	
Yes	119 (6.9)	1.20 (1.02, 1.41)	0.03

Notes: aOR, adjusted odds ratio; CI, confidence interval. Odds ratios are calculated for an interquartile range (26 μg/m³ NO_2 equivalent) increase in average NO_x levels during the first year of life. The categorical outcomes were modeled using multinomial logistic regression models. Models were adjusted for sex, birth weight, family socioeconomic status, maternal education level, maternal history of asthma, allergic rhinitis, or eczema, paternal history of asthma, allergic rhinitis, or eczema, maternal smoking during pregnancy, exposure to environmental tobacco smoke at home during the first year, exclusive breastfeeding during the first 3 months, type of child care during the first 6 months, stressful family events during the first 2 years, body mass index ≥ 85th percentile for age and sex at 2–3 years, use of gas for cooking or heating in the home, and visible mold in the home.

Strengths and Limitations

A major strength of our study is the TRAP exposure assessment. Early TRAP exposure was finely modeled using an air dispersion model. Modeling NO_x levels through the ExTra index showed excellent performance in the study of validation (Reungoat et al. 2003). In the literature, these types of models were relatively little used compared to LUR models due to a complicated and time-consuming implementation. Few cohort studies have estimated children's TRAP exposure by dispersion model: BAMSE (Children, Allergy, Milieu, Stockholm, Epidemiology) in Sweden [NO_x and PM_{10} (Nordling et al. 2008)], Oslo birth cohort in Norway [NO_2 (Oftedal et al. 2009)], Generation R in the Netherlands [NO_2 and PM_{10} (Sonnenschein-van der Voort et al. 2012)], and the Children's Health Study in California [NO_x (McConnell et al. 2010)]. Only the BAMSE and PARIS cohorts have studied the impact of TRAP exposure on the respiratory health of preschool children.

Another important strength is the inclusion of all the different places in which each child spent time during his/her first year of life as it should reduce misclassification in TRAP exposure, contrary to other studies where only the home address at birth was considered to assess the TRAP exposure during the first year (Brauer et al. 2007; Morgenstern et al. 2007). In older children, McConnell et al. (2010) showed that TRAP exposure at home and school may both contribute to the development of asthma. Results from the Canadian Healthy Infant Longitudinal Development (CHILD) study suggest that accounting for day care to assess early TRAP exposure might reduce exposure misclassification because participants for whom exposure misclassification was less likely (i.e., those spending more than the city median time at home and those who did not attend day care) had stronger associations between exposure to NO_2 at home and allergic sensitization at age 1 year (Sbihi et al. 2015). However, in preschool children, TRAP exposure at day care has been rarely considered. The reason for this can be cultural, as in the BAMSE birth cohort in Sweden, where only 1% of the children in the study started day care before 12 months of age (Nordling et al. 2008), compared with about two-third in our study.

Moreover, the NO_x levels were predicted at the front windows of each home and day care place and not at the ground level, as in LUR models, resulting in a more precise estimation of the actual level of exposure. In birth cohort studies, nitrogen oxides were mostly reported in the form of NO_2 and more rarely as both NO_2 and NO (Bowatte et al. 2015), although gas exhaust from traffic contains NO_x composed primarily of NO. Another strength of our study is the adjustment of statistical models for variables related to other sources of children's exposure to NO_x (i.e., use of gas and smoking in the home).

Regarding windows of TRAP exposure, we focused on early childhood, a period of high susceptibility due to the immaturity of the lung and immune system (Dietert et al. 2000). In the literature, the impact of TRAP on the development of asthma and allergy appears stronger for exposure during the first year of life than for exposure later, and TRAP exposure occurring in early life has been linked to long-term respiratory manifestations (Gruzieva et al. 2012; Schultz et al. 2012). We present data on TRAP exposure during the first year, before possible asthma diagnosis. As already highlighted in the BAMSE cohort at the same age of 4 years (Melén et al. 2008; Nordling et al. 2008), considering exposure during the first year of life only is a way to minimize possible reverse causality induced by avoidance behavior due to the child's disease. However, we cannot state with certainty that exposure during the first year alone is responsible for the observed associations, and later exposure between 1 and 4 years may also contribute to the associations observed in our study. In a subgroup of 769 children from the PARIS cohort, we performed a preliminary model including TRAP exposure levels during two time windows (first and fourth years). After adjusting for later TRAP exposure, early TRAP exposure was still positively associated with persistent wheezing, even though our sample size was most probably too small to have sufficient statistical power to detect a significant association.

One limitation of our study is participation. We observed a substantial attrition rate during follow-up. As previously described (Rancière et al. 2013a), this is partly attributable to families moving outside the study area, consistent with the high residential mobility rates observed in Paris. Previous studies found that associations between TRAP and respiratory diseases and asthma were stronger among individuals of lower socioeconomic status (Burra et al. 2009; Wheeler and Ben-Shlomo 2005). Children enrolled in the PARIS cohort were mainly of high SES, and we were unable to study the interaction between TRAP exposure and social deprivation. However, as observed in the BAMSE cohort, children from families of high SES had

Table 4. Association between traffic-related air pollution exposure and respiratory health according to parental history of allergy and stressful family events in the PARIS cohort.

Respiratory health during the first 4 years of life	Parental history of allergy[a]					Stressful family events[b]				
	No		Yes		*p* for interaction	No		Yes		*p* for interaction
	n	aOR (95% CI)	*n*	aOR (95% CI)		*n*	aOR (95% CI)	*n*	aOR (95% CI)	
Wheeze										
No (reference)	507	1	677	1		659	1	522	1	
Early-transient	112	0.99 (0.80, 1.23)	205	1.06 (0.90, 1.25)	0.64	162	1.01 (0.85, 1.20)	155	1.02 (0.85, 1.24)	0.98
Late-onset	35	0.96 (0.69, 1.34)	51	1.16 (0.90, 1.50)	0.35	46	0.94 (0.68, 1.30)	40	1.26 (0.97, 1.63)	0.19
Persistent	44	1.05 (0.78, 1.41)	82	1.42 (1.18, 1.71)***	0.12	62	1.06 (0.82, 1.37)	64	1.46 (1.19, 1.79)***	0.08
Dry night cough										
No (reference)	458	1	576	1		574	1	458	1	
Early-transient	72	1.00 (0.78, 1.28)	118	1.04 (0.85, 1.27)	0.81	99	0.99 (0.79, 1.23)	91	1.05 (0.84, 1.31)	0.68
Late-onset	96	0.89 (0.71, 1.12)	170	1.13 (0.96, 1.32)	0.10	155	1.07 (0.90, 1.27)	110	1.00 (0.81, 1.23)	0.52
Persistent	63	0.85 (0.64, 1.15)	154	1.22 (1.04, 1.44)**	0.03	102	0.97 (0.78, 1.20)	115	1.29 (1.08, 1.55)**	0.09
Rhinitis symptoms										
No (reference)	415	1	520	1		532	1	402	1	
Early-transient	113	0.94 (0.76, 1.15)	188	0.95 (0.79, 1.14)	0.98	161	0.96 (0.80, 1.15)	139	0.97 (0.79, 1.19)	0.91
Late-onset	74	0.98 (0.78, 1.25)	101	1.11 (0.91, 1.36)	0.41	91	1.06 (0.85, 1.31)	84	1.06 (0.85, 1.33)	0.91
Persistent	78	0.79 (0.59, 1.04)	203	1.21 (1.04, 1.40)**	0.01	134	0.95 (0.77, 1.16)	147	1.26 (1.06, 1.49)**	0.04
Asthma ever at 4 years										
No (reference)	642	1	878	1		828	1	689	1	
Yes	63	0.97 (0.74, 1.27)	160	1.23 (1.06, 1.43)**	0.15	117	1.06 (0.88, 1.29)	106	1.25 (1.05, 1.49)**	0.26
Asthma ever with current symptoms at 4 years										
No (reference)	668	1	930	1		862	1	733	1	
Yes	27	0.76 (0.47, 1.25)	92	1.32 (1.11, 1.58)**	0.04	72	1.09 (0.86, 1.38)	47	1.34 (1.07, 1.68)**	0.29

Notes: aOR, adjusted odds ratio; CI, confidence interval. Odds ratios are calculated for an interquartile range (26 μg/m³ NO_2 equivalent) increase in average NO_x levels during the first year of life. The categorical outcomes were modeled using multinomial logistic regression models. Models were adjusted for the same variables as in Table 3 (except for the stratification variables).
[a]Among asthma, allergic rhinitis, and eczema in the mother and/or the father.
[b]Among parental separation or divorce, parental loss of job, serious health problem, or death of a family member or close relative during the child's first 2 years of life.
**$p \le 0.01$. ***$p \le 0.001$.

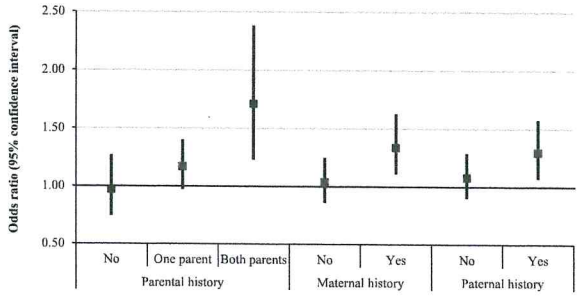

Figure 1. Association between traffic-related air pollution exposure and asthma ever at 4 years according to several definitions of parental history of allergy in the PARIS cohort.
Odds ratios were calculated for an interquartile range (26 μg/m³ NO_2 equivalent) increase in average NO_x levels during the first year of life. Models were adjusted for the same variables as in Table 3, except maternal and paternal history of allergy for the parental history models, maternal history of allergy for the maternal history models, and paternal history of allergy for the paternal history models.

Table 5. Association between traffic-related air pollution exposure and respiratory health according to the child's sex in the PARIS cohort.

Respiratory health during the first 4 years of life	Sex				
	Boys		Girls		*p* for interaction
	n	aOR (95% CI)	*n*	aOR (95% CI)	
Wheeze					
No (reference)	564	1	617	1	
Early-transient	180	1.12 (0.95, 1.32)	137	0.87 (0.71, 1.08)	0.09
Late-onset	49	0.92 (0.66, 1.28)	37	1.24 (0.96, 1.62)	0.09
Persistent	77	1.39 (1.15, 1.69)***	49	1.09 (0.82, 1.44)	0.12
Dry night cough					
No (reference)	506	1	526	1	
Early-transient	104	1.02 (0.83, 1.26)	86	0.97 (0.76, 1.23)	0.79
Late-onset	154	1.04 (0.87, 1.24)	111	1.02 (0.84, 1.24)	0.94
Persistent	104	1.21 (1.01, 1.45)*	113	0.99 (0.80, 1.23)	0.12
Rhinitis symptoms					
No (reference)	450	1	484	1	
Early-transient	162	0.92 (0.75, 1.11)	138	0.98 (0.81, 1.19)	0.57
Late-onset	101	1.05 (0.85, 1.30)	74	1.08 (0.85, 1.35)	0.87
Persistent	146	1.21 (1.03, 1.43)*	135	0.93 (0.76, 1.14)	0.06
Asthma ever at 4 years					
No (reference)	745	1	772	1	
Yes	147	1.22 (1.05, 1.43)**	76	1.04 (0.83, 1.32)	0.26
Asthma ever with current symptoms at 4 years					
No (reference)	798	1	797	1	
Yes	76	1.25 (1.02, 1.53)*	43	1.12 (0.85, 1.49)	0.53

Notes: aOR, adjusted odds ratio; CI, confidence interval. Odds ratios are calculated for an interquartile range (26 μg/m³ NO_2 equivalent) increase in average NO_x levels during the first year of life. The categorical outcomes were modeled using multinomial logistic regression models. Models were adjusted for the same variables as in Table 3, except for sex.
*$p \le 0.05$. **$p \le 0.01$. ***$p \le 0.001$.

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REVIEW Open Access

The first 1000 days of life: traffic-related air pollution and development of wheezing and asthma in childhood. A systematic review of birth cohort studies

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Abstract

Background: The first 1000 days of life -including pregnancy and the first 2 years after birth- represent a critical window for health interventions.
This systematic review aimed to summarize the evidence on the relationship between traffic-related air pollutants exposure in the first 1000 days of life and the development of wheezing and asthma, with a particular focus on windows of exposure.

Methods: Medline and Embase were searched from January 2000 to May 2020 to retrieve population-based birth-cohort studies, including registries, providing quantitative information on the association between exposure to traffic-related air pollutants during pregnancy or early life, and the risk of developing wheezing and asthma in childhood. Screening and selection of the articles were completed independently by three reviewers. The quality of studies was assessed using the Newcastle-Ottawa scale.

Results: Out of 9681 records retrieved, 26 studies from 21 cohorts were included. The most common traffic-related air pollutant markers were particulate matter (PM) and nitric oxides (NOx). The variability in terms of pollutants, exposure assessment methods, and exposure levels chosen to present the results did not allow a meta-analysis. Exposure to PM and NOx in pregnancy (10 cohorts) was consistently associated with an increased risk of asthma development, while the association with wheezing development was unclear. The second trimester of pregnancy seemed to be particularly critical for asthma risk. As for exposure during early life (15 cohorts), most studies found a positive association between PM (7/10 studies) and NOx (11/13 studies) and the risk of asthma development, while the risk of wheezing development was controversial. The period of postnatal exposure, however, was less precisely defined and a partial overlap between the period of exposure measurement and that of outcome development was present in a consistent number of studies (14 out of 15) raising doubts on the associations found.

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Conclusions: Traffic-related air pollution during pregnancy is associated with an increased risk of asthma development among children and adolescents. The relationship between exposure in the first two years of life and the development of wheezing and asthma needs to be confirmed in studies with more precise exposure assessment.

Keywords: Air pollution, Asthma, Children, Cohort studies, Early life, Pregnancy, Wheezing

Background

The period from conception to the child's second year of life (the first 1000 days) is a window for intervention to improve child and adult health [1]. This has been suggested for different exposures and outcomes, especially in the field of nutrition, cognitive development, and respiratory health [2, 3]. Several programmes have therefore been undertaken worldwide with the aim of promoting early life interventions for children and families [1, 4].

Among early risk factors critical for respiratory health, tobacco smoke exposure, especially during pregnancy and in the first months after birth, is well known to be associated with an abnormal lung development and with an increased risk of both wheezing and asthma in offspring [5, 6]. In fact, although lung growth occurs from conception to early adulthood, prenatal and early postnatal periods might be particularly vulnerable time windows [7].

Tobacco smoke and air pollution exposures are not equivalent, but air pollution exposure might have similar consequences for the lungs [7]. The advent of new technologies with a detailed assessment of exposure to air pollutants and a more precise spatial resolution allows nowadays to better explore the association between exposure to air pollutants from conception through infancy and respiratory outcomes later in life. Prospective birth cohorts represent the best design to assess the temporal relationship between early life exposures and the onset of respiratory diseases in childhood.

To date only one systematic review considering birth cohort studies published until March 2014 has focused on the relationship between childhood traffic-related air pollution exposure and subsequent asthma, wheeze, and allergic diseases [8]. Among the 11 cohort studies included in this systematic review [8], eight were population-based, while three were high-risk cohorts (i.e. including only subjects with a family history of asthma or allergies). Furthermore, almost all studies evaluated postnatal exposure, as studies on pregnancy exposure have been published later.

Since 2014, several birth cohort studies have focused on the association between exposure to traffic-related air pollutants, including gases - in particular nitrogen oxides (NO_X)- and particulate matter (PM) in pregnancy and in the first 2 years after birth and development of respiratory problems in childhood, namely wheezing and asthma.

On these bases, we aimed to systematically review the evidence from population-based birth cohort studies on the relationship between traffic-related air pollutants exposure in utero and in the first 2 years after birth (the first 1000 days of life) and the subsequent development of wheezing and asthma in childhood, with a particular focus on the critical time windows of exposure. A precise identification of the more vulnerable periods of exposure would be important to choose more efficacious preventive measures.

Methods

We searched Medline and Embase for papers published in English between January 1st 2000 and May 5th 2020.

We considered as eligible only prospective unselected pregnancy or birth cohort studies, including population-based registries, providing quantitative information on the association between exposure to traffic-related air pollutants during pregnancy or during the first 2 years of infant's life, and the risk of developing wheezing and/or asthma in children and adolescents (aged 1 to 17 years). Cohorts of susceptible populations, such as offspring of parents with asthma and/or allergies, were excluded. We considered exposures to any established traffic-related air pollutant, including black carbon (BC), carbon monoxide (CO), elemental carbon (EC), NOx, nitric oxide (NO), nitrogen dioxide (NO_2), hydrocarbons, and PM such as Ultra-Fine Particles ≤0.1 μm in diameter (UFPs), PM < 2.5 and < 10 μm in diameter ($PM_{2.5}$, PM_{10}), PM between 2.5 and 10 μm in diameter (PM coarse), and soot (i.e., black substance formed by combustion or separated from fuel during combustion, rising in fine particles). We excluded studies that: a) were reviews, commentaries, governmental reports, letters, animal and experimental studies; b) only examined adulthood asthma; c) only examined non-traffic-related air pollutants including ozone (O_3) which is not emitted directly from automobiles, sulphur dioxide (SO_2), indoor air pollution, proximity to point sources and wood smoke; d) only examined the association between the exposure to the selected pollutants and asthma exacerbations or severity; e) did not report the estimates of the

quantitative association between traffic-related air pollutants and wheezing or asthma development.

The strategies used for Medline and Embase literature search are reported in supplementary Table 1. Briefly, search terms related to the three main thematic areas "traffic-related air pollutants", "wheezing/asthma" and "paediatric population" were combined through the Boolean operator "AND".

Titles and abstracts of all records retrieved by the search were screened by three co-authors (AB, EG, EM). We retrieved the full-text and supplementary material of all articles initially identified for potential inclusion. All potentially relevant full texts were independently screened by two pairs of co-authors to check the fulfilment of the inclusion criteria. Discrepancies were resolved through discussion.

In addition, we checked the reference list of previous published systematic reviews on this topic, to identify additional original research papers not retrieved by our search.To avoid study duplication, the following rules were adopted: a) where multiple publications were based on the same birth cohort or registry and considered the same exposures and outcomes within the same children's age group, only the most recent publication was included; b) where multiple publications were based on the same birth cohort or registry and evaluated the same exposures and respiratory outcomes for different age groups, we selected the publication with the earliest period of wheezing assessment, and the latest period of asthma assessment. The rationale for this choice was that wheezing occurring in the first years of life could have a different meaning in terms of prognosis with respect to wheezing and asthma at older ages and that asthma can be hardly diagnosed in the earlies years of life.

Data were extracted using a standardized form. Two authors (AB, EG) independently extracted the following data:

1. Exposure data: traffic-related air pollutants studied; mean or median or interquartile range (IQR) concentrations; period of exposure; method for exposure assessment.
2. Outcome data: outcome definition; method used to assess the outcome; period of outcome assessment; relevant adjusted effect estimates and 95% Confidence Intervals (CI).
3. Other information: study population; year of publication; sample size; country in which participants were recruited.

The methodological quality of the studies was assessed by two authors (EM and AB) using the Newcastle-Ottawa Quality Assessment Scale for cohort studies [9].

Results

Our search yielded to 9738 records. After removing duplicates, 9681 unique articles were identified. Of them, 9609 records were excluded after title and abstract screening, whereas 72 articles were selected for full-text reviewing. Among these, 26 articles [10–35] fulfilled the inclusion criteria (Fig. 1).

The 26 articles included in the review were based on 21 pregnancy or birth cohorts.

Nine birth cohorts were registry-based [14–17, 20, 21, 27, 28, 34, 35]. Two studies were case-control study, nested in a registry-based birth cohort [21, 35].

Ten cohorts were based in Europe [11, 13, 22–26, 29–34] and eight were based in North America [14, 16–21, 27, 28, 35]. Of the remaining three cohorts, two were based in Asiatic countries [10, 15] and one in Mexico [12]. Only four birth cohorts reported exposure to air pollutants both in pregnancy and in the first 2 years after delivery [13, 15–17].

The association between exposure to traffic-related air pollutants during pregnancy and the first 2 years of the child's life and subsequent asthma was evaluated in six [14–21] and 13 cohorts [15–17, 22, 23, 27–35], respectively (Tables 1 and 2).

Wheezing development was evaluated in nine cohorts: four after exposure in utero [10–13] and five after exposure in the first 24 months of child's life [13, 22–25] (Tables 3 and 4).

A large variability in the air pollutants studied and in the methods of exposure assessment was observed across studies. (supplementary Tables 2 and 3) The most common traffic-related air pollutant markers were PM (PM_{10}, $PM_{2.5}$, PM coarse, and $PM_{2.5}$ abs) and NO_2. A few studies considered also other pollutants: NOx, NO_3^-, CO and UFPs.

We observed a moderate variability in the methods for exposure assessment among studies that considered PM; most of the studies published in the last 5 years used models based on satellite data with a spatial resolution of 1-km^2, considering a complex and flexible modelling approach (supplementary Tables 2 and 3). For less recent studies on PM and for most of the studies on NO_2 the most common method for exposure assessment was Land use regression (LUR) model. One study assessed exposure to NO_3^- in pregnancy using a hybrid model of a chemical transport model (GEOS-Chem) and land-use regression [19]. Two studies during pregnancy [17, 21] and eight in the first 2 years after delivery [17, 22–24, 26, 33–35] studied exposure to NOx, NO, CO, BC, soot and EC attributed to traffic (ECAT) applying different methods for exposure assessment (supplementary Tables 2 and 3).

The variability in terms of pollutants, exposure assessment methods, and exposure levels chosen to present

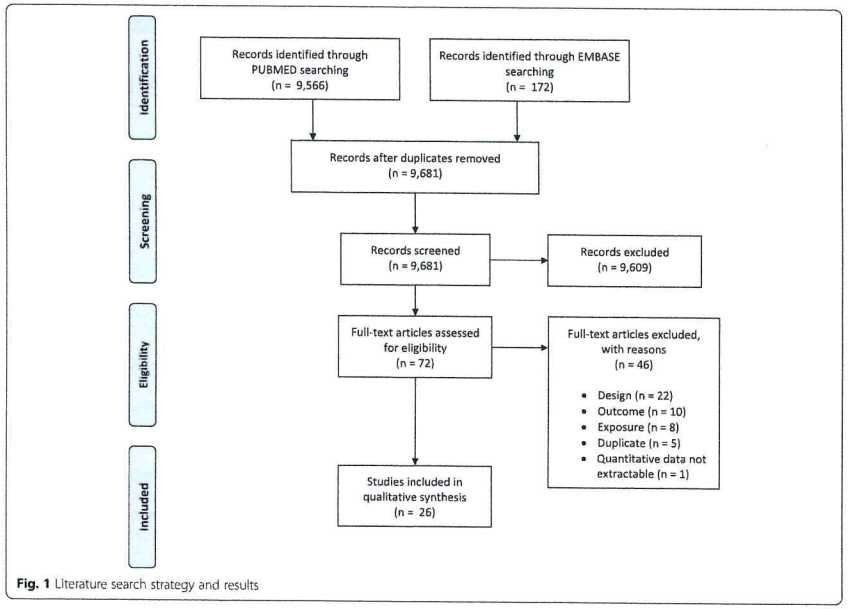

Fig. 1 Literature search strategy and results

the results (e.g. interquartile range increase, mean or median levels etc.) as reported in detail in supplementary Tables 2 and 3 did not allow to do a meta-analysis.

Data on study quality are presented in supplementary Tables 4 and 5.

Regarding the "Selection" items, all the studied cohorts were considered representative of the general population, as cohorts of susceptible populations were excluded.

In cohorts evaluating exposure in pregnancy the outcome of interest (wheezing or asthma in offspring) was, by definition, not present at the beginning of the study. Conversely, in all except one study [13, 15, 16, 22–35] which evaluated exposures in early life, there was an

Table 1 Association between exposure to traffic related air pollutants in pregnancy and wheezing development

References	Type of study, country	Subjects, no	Pollutants and exposure assessment	Outcome	Positive association with the outcome	Sensitivity windows
Soh S et al., 2018 [10]	GUSTO birth cohort, Singapore	953	$PM_{2.5}$ Daily exposure	Wheezing (birth up to 2 years)	Yes	No sensitive trimester
Madsen C et al., 2017 [11]	MoBa, pregnancy cohort, Norway	17,533	NO_2 Annual average estimates at residential address at birth	Wheezing (6 to 18 months)	No	NA
Rosa MJ et al., 2017 [12]	PROGRESS pregnancy cohort, Mexico	552	$PM_{2.5}$ Daily exposure	Wheezing (birth up to 4 years)	No	No sensitive trimester
Aguilera I et al., 2013 [13]	Four birth cohorts of the INMA project, Spain	2199	NO_2 Annual average estimates at residential address in pregnancy	Wheezing (birth up to 12–18 months)	No	NA

$PM_{2.5}$ Particulate matter < 2.5 μm in diameter; *NO_2* Nitrogen dioxide, *NA* Not assessed

Table 2 Association between exposure to traffic related air pollutants in pregnancy and asthma development

References	Type of study, Country	Subjects, no	Pollutants and exposure assessment	Outcome	Positive association with the outcome	Sensitivity windows
Lavigne E et al., 2019 [14]	Registry-based birth cohort, Toronto, Canada	160,641	UFPs, $PM_{2.5}$, NO_2 Daily exposure	Asthma (birth up to < 6 years)	Yes	Second trimester
Jung CR et al., 2019 [15]	TMCHD registry-based birth cohort, Taiwan	184,604	$PM_{2.5}$ Daily exposure	Asthma (birth up to 3–10 years)	Yes	Weeks 6–22
Lavigne E et al., 2018 [16]	Registry-based birth cohort, Ontario, Canada	222,864	$PM_{2.5}$, NO_2 Daily exposure	Asthma (birth up to < 6 years)	Yes	Second trimester
Pennington AF et al., 2018 [17]	KAPPA, registry-based birth cohort, Atlanta, USA	19,951	$PM_{2.5}$, NO_x, CO Annual average	Asthma (2 to 6 years)	Yes	NA
Lee A et al., 2018 [18]	ACCESS pregnancy cohort, Boston, USA	736	$PM_{2.5}$ Daily exposure	Asthma (birth up to 6 years)	Yes	Weeks 19–23 in exposed to maternal prenatal stress
Bose S et al., 2017 [19]	ACCESS pregnancy cohort, Boston, USA	752	NO_3^- Daily exposure	Asthma (birth up to 6 years)	Yes in boys exposed to prenatal maternal stress	7–19 and 33–40 weeks
Sbihi H et al., 2017 [20]	Registry-based birth cohort, Vancouver, Canada	65,254	NO_2, $PM_{2.5}$ Daily exposure aggregated over the pregnancy period	Asthma trajectories (birth up to 7–10 years)	Yes	NA
Sbihi H et al., 2016 [21]	Case-control nested in a registry-based birth cohort, Vancouver, Canada	Pre-schoolers: 6948 cases, 34,621 controls; School-age: 1711 and 8577	BC, CO, NO, NO_2, $PM_{2.5}$, PM_{10} Daily exposure aggregated over the pregnancy period	Asthma (birth up to 6–10 years)	Yes only in preschoolers and only for PM_{10}	NA

BC Black carbon, *CO* Carbon monoxide, $PM_{2.5}$ Particulate matter < 2.5 μm in diameter, PM_{10} Particulate matter < 10 μm in diameter; NO_x Nitrogen oxides, *NO* Nitric oxide, NO_2 Nitrogen dioxide, NO_3 Nitrate, *UFPs* Ultra-Fine Particles ≤ 0.1 μm in diameter; *NA* Not assessed

Table 3 Association between exposure to traffic related air pollutants in early life and wheezing development

References	Type of study, Country	Subjects, no	Pollutants and exposure assessment	Outcome	Positive association with the outcome
Rancière F et al., 2017 [22]	PARIS birth cohort, France	2015	NO_x Exposure assessed in the first year of life	Wheezing phenotypes (birth up to 4 years)	Yes only for persistent wheezing
Aguilera I et al., 2013 [13]	Four birth cohorts, INMA project, Spain	2199	NO_2 Annual average exposure estimated at address in the first year of life	Wheezing (birth up to 12–18 months)	No
Gehring U et al., 2010 [23]	PIAMA birth cohort, the Netherlands	3863	$PM_{2.5}$, NO_2, Soot Annual average exposure estimated at birth address	Wheezing phenotypes (birth up to 8 years)	Yes only for $PM_{2.5}$ and early transient and late onset wheezing
Nordling E et al., 2008 [24]	Birth cohort, Sweden	3515	PM_{10}, NO_x Annual average exposure estimated at address in the first year of life	Wheezing phenotypes (birth up to 4 years)	Yes only for NO_x and persistent wheezing.
Morgenstern V et al., 2007 [25]	GINI/LISA birth cohorts, Munich, Germany	3577	$PM_{2.5}$ mass, $PM_{2.5}$ absorbance, NO_2 Annual average exposure estimated at birth address	Wheezing (birth up to 2 years)	No
Brauer M et al., 2002 [26]	PIAMA birth cohort, the Netherlands	3730	$PM_{2.5}$, NO_2, Soot Annual average exposure estimated at birth address	Wheezing (birth up to 2 years)	No

$PM_{2.5}$ Particulate matter < 2.5 μm in diameter, PM_{10} particulate matter < 10 μm in diameter, *NOx Nitrogen oxides, NO Nitric oxide,* NO_2 *Nitrogen dioxide*

Table 4 Association between exposure to traffic related air pollutants in early life and asthma development

References	Type of study, Country	Subjects, no	Pollutant and exposure assessment	Outcome	Positive association with the outcome
To T et al., 2020 [27]	T-CHEQ registry-based birth cohort, Ontario, Canada	1286	$PM_{2.5}$, NO_2 Average exposure assessed in the first 3 years of life	Asthma (birth up to 15–20 years)	Yes only for NO_2
Jung CR et al., 2019 [15]	TMCHD registry-based birth cohort, Taiwan	184,604	$PM_{2.5}$ Exposure assessed in the first year of life	Asthma (birth up to 3–10 years)	Yes
Lavigne E et al. 2018 [16]	Registry-based birth cohort Ontario, Canada	222,864	$PM_{2.5}$, NO_2 Exposure assessed in the first year of life	Asthma (birth up to < 6 years)	Yes only for NO_2
Pennington AF et al., 2018 [17]	KAPPA registry- based birth cohort, Atlanta, USA	23,100	$PM_{2.5}$, NO_x, CO Annual average exposure estimated in the first year of life	Asthma (2 to 6 years)	Yes
Rancière F et al., 2017 [22]	PARIS birth cohort, France	2015	NOx Exposure assessed in the first year of life	Asthma (birth up to 4 years)	Yes
Tétreault L-F et al., 2016 [28]	Registry-based birth cohort, Quebec, Canada	1,183,865	$PM_{2.5}$, NO_2 Annual average exposure estimated at birth address	Asthma (birth up to 1–12 years)	Yes
Gehring U et al., 2015 [30]	PIAMA birth cohort, the Netherlands	3702	$PM_{2.5}$ abs, $PM_{2.5}$, PM_{10}, PM coarse, NO_2, elemental composition of $PM_{2.5}$ and PM_{10} Annual average exposure estimated at birth address	Asthma (birth up to 11 years)	Yes only for NO_2, K $PM_{2.5}$, K PM_{10}, S $PM_{2.5}$, Zn PM_{10}
Gehring U et al., 2015 [29]	BAMBSE, GINI plus, LISA plus and PIAMA birth cohorts, Sweden, Germany, the Netherlands	14,126	$PM_{2.5}$ abs, $PM_{2.5}$, PM_{10}, PM coarse, NO_2 Annual average exposure estimated at birth address	Asthma (birth up to 14–16 years)	Yes only for NO_2, $PM_{2.5}$ abs
Ranzi A et al., 2014 [31]	GASPII birth cohort, Italy	672	NO_2 Annual average exposure estimated at birth address	Asthma (birth up to 7 years)	No
Fuertes E et al., 2013 [32]	GINI plus and LISA plus birth cohorts, Germany	6604	$PM_{2.5}$ mass, $PM_{2.5}$ abs, NO_2 Annual average exposure estimated at birth address	Asthma (birth up to 10 years)	No
Gruzieva O et al., 2013 [33]	BAMSE birth cohort, Sweden	3633	NO_x, PM_{10} Annual average exposure estimated at birth address	Asthma (birth up to 12 years)	Yes
Lindgren A et al., 2013 [34]	Registry-based birth cohort, southern Sweden	7898	NO_x Annual average exposure estimated at birth address	Asthma (birth up to 1–6 years)	Negative association
Clark NA et al., 2010 [35]	Case-control study, nested in a cohort (administrative databases), British Columbia, Canada	3482 cases, 17,410 controls	$PM_{2.5}$, PM_{10}, NO, NO_2, CO, BC Exposure estimated at address in the first year of life	Asthma (birth up to 36–59 months)	Yes only for NO_2, BC, CO, PM_{10}
Gehring U et al., 2010 [23]	PIAMA birth cohort, the Netherlands	3863	$PM_{2.5}$, NO_2, Soot Annual average exposure estimated at birth address	Asthma (birth up to 8 years)	Yes

Abs Absorbance, *BC* Black carbon, *CO* Carbon monoxide, $PM_{2.5}$ Particulate matter < 2.5 μm in diameter, PM_{10} *Particulate matter < 10* μm *in diameter,* NO_x *Nitrogen oxides, NO* Nitric oxide, NO_2 Nitrogen dioxide, NO_3 Nitrate, *UFPs Ultra-Fine Particles ≤ 0.1 μm in diameter, NA* Not assessed

overlap between the period of exposure measurement and that of outcome development. This might represent a relevant risk of bias, especially for studies in which the outcome of interest was wheezing evaluated in the first few months/years of life.

Regarding the "Comparability" domain (supplementary Tables 4 and 5), except for five studies assessing in utero exposure [17–21] and two studies assessing exposure in early life [17, 28] all the other studies adjusted for both second-hand smoking and asthma predisposition, important potential confounders of the association between exposure to traffic-related air pollutants and wheezing and asthma. Five of 12 studies on pregnancy exposure to air pollutants adjusted for exposure during early life [10, 12, 14–16] while only three of 16 studies on early life exposures also accounted for it in their analysis exposure

during pregnancy [15, 16, 35]. Moreover, several cohorts considered - often in sensitivity analyses - also changes of home address for a more precise evaluation of exposure to air pollutants [11, 13–21, 23, 26–32, 34, 35].

As for the "Outcome" domain (supplementary Tables 4 and 5), we defined that a follow-up of 2 and of 6 years was long enough to detect the occurrence of wheezing and asthma, respectively. According to this definition, for exposure in pregnancy follow-up was not long enough for wheezing or asthma to occur in two [11, 13] and two cohorts [15, 17], respectively. For exposures in the first 2 years of life follow up was not long enough for wheezing to occur in all the subjects in one cohort [13] and for asthma in four cohorts [15, 17, 34, 35].

Only three cohorts had a follow-up rate ≤ 60%, considered as likely to introduce a bias [17, 22, 31].

Tables 1 and 2 and supplementary Table 2 provide a summary of the 12 studies evaluating the association between exposure to traffic-related air pollutants in pregnancy and wheezing and asthma development [10–21].

The sample sizes ranged from 552 to 222,864, being the largest cohorts based on registries. Most of the studies evaluated exposures to particulate matter (9/12 studies) and eight to gases including NO_2 (six studies), NOx, NO_3^-, NO, and CO.

Follow-up periods varied according to the outcome, ranging from 6 to 48 months for wheezing and from 2 to 10 years for asthma, though in the majority of studies on asthma incidence children were followed up at least up to school age.

Only 4 studies examined the development of wheezing after exposure to traffic-related air pollutants in pregnancy [10–13]. One study (GUSTO birth cohort, Singapore; 953 subjects) [10] reported an association between $PM_{2.5}$ measured at eight stations and wheezing in the first 2 years of life. This was not confirmed in another small birth cohort (PROGRESS pregnancy cohort, Mexico; 552 subjects) [12]. No association was found for exposure to NO_2 in pregnancy either in the INMA birth cohort in Spain (2199 subjects) [13] and in the MoBa pregnancy cohort in Norway [11]; this was a large cohort (17.533 subjects) exposed to low levels of NO_2 (mean: 13.6 μg/m3).

Conversely, a positive association between exposure to both particulate and gases during pregnancy and asthma development was found in all the studies.

Five studies tried to identify "sensitive time periods" for exposure to air pollutants during the prenatal period and asthma development [14–16, 18, 19]. A sensitive window was found in four studies [14–16, 18] in the second trimester of pregnancy (weeks 13 to 24) for exposures either to UFP, $PM_{2.5}$, or to NO_2. Notably, the susceptibility during this sensitive window seemed to be more critical for boys with elevated maternal stress during gestation [18].

Tables 3 and 4 and supplementary Table 3 describe the 19 studies [13, 15–17, 23–26, 28–35] evaluating the association between exposure to traffic-related pollutants in the first 2 years of children's life and wheezing and asthma development.

The sample sizes ranged from 672 to 1.183.865 subjects. Seventeen studies evaluated exposures to gases and 14 to PM.

Follow-up periods varied according to the outcome, being from 12 months to 8 years for wheezing and from 12 months to 16 years for asthma.

Three studies that followed children up to 4–8 years of life focused on wheezing phenotypes (Table 3): two found an association between exposure to NOx and persistent wheezing [22, 24] and one between $PM_{2.5}$ and early transient and late-onset wheezing [23]. No association was found in three studies that evaluated exposure to NO_2 or $PM_{2.5}$ and wheezing in the first 2 years of children's life with no mention of phenotypes [13, 25, 26].

Eleven [15–17, 22, 23, 27–30, 33, 35] of 14 studies found an association with exposure to one or more pollutants at the birth address or in the first year(s) of life and development of asthma. (Table 4) A positive association with asthma incidence was found more often for NO_2 and $PM_{2.5}$. One study performed in Italy [31] on a small cohort (672 subjects) did not find an association between exposure to NO_2 measured at the birth address and development of asthma in the first 7 years of life. A study in the GINA plus and LISA plus birth cohorts (6604 subjects) [32] also did not find an association between exposure to $PM_{2.5}$ and NO_2 at the birth address and asthma incidence from birth up to 10 years. However, in another study [29] where data from the same cohorts collected over a longer follow-up period (14 to 16 years) were put together to those of other larger cohorts (BAMSE and PIAMA) and meta-analyzed, an association was found for NO_2 and $PM_{2.5}$. Finally, Lindgren and colleagues [34] found a negative association between exposure to NOx at birth and the development of asthma in children aged 2 to 6 years, though the study, also according to authors, might have been subjected to several biases.

Discussion

Our systematic review summarized current published evidence from prospective unselected cohort studies on the association between exposure to traffic-related air pollutants in the first 1000 days of life -including pregnancy and the first 2 years after birth- and the subsequent risk of developing asthma and wheezing in childhood. We found consistent results for exposure to both NOx and PM in pregnancy and asthma development in childhood [14–21], with a more vulnerable window of exposure in the weeks corresponding to the second trimester of pregnancy [14–16, 18]. The susceptibility during this window of exposure seems to be modified by gender and stress-related factors; in fact, air pollution exposure during thesecond trimester of pregnancy (weeks 19–23) seems more critical in case of elevated maternal stress during gestation, particularly for male newborns [18].

The relationship between exposure to air pollutants in pregnancy and development of wheezing in childhood was evaluated in only four studies [10–13], and a significant association was found with exposure to $PM_{2.5}$ in only one [10], while two studies did not find an association with exposure to NO_2 [11, 13].

Also, for exposures to traffic-related air pollutants in the first 2 years after birth, the results were not concordant for wheezing development, while a positive association was found in most of the studies evaluating PM and NOx and the risk of asthma development [15–17, 23, 27–30, 33, 35].

As previously discussed, a large variability among studies in terms of pollutants considered, exposure assessment, and air pollutants levels, prevented us to perform a meta-analysis.

On the other hand, an accurate evaluation of the characteristics and the quality of the studies included in this systematic review gave interesting hints and allowed several important considerations.

The association found for exposure in pregnancy and asthma at school age is concordant with findings of an adverse impact of prenatal air pollution exposure on lung function [36–38]. In three studies [14, 16, 19] the second trimester of pregnancy was identified as a vulnerable period for asthma development both for exposure to PM and NO_2. In studies evaluating lung function, the evidence of a more vulnerable trimester is weaker, though two studies also mentioned the second trimester [38, 39]. A recent Editorial [40] on inconclusive results on the most vulnerable time-period of exposure in pregnancy for lung function outcome in childhood pointed out methodological issues, highlighting the need of a more precise exposure assessment and statistical methods able to identify weeks of gestation rather than specific trimesters. In four studies included in our review [14–16, 18] which identified the second trimester of pregnancy as a vulnerable period, daily exposures were available, and distributed lag nonlinear models were used to identify susceptible weeks, thus allowing a precise definition of time windows of exposure. The availability of only two studies based on small birth cohorts [10, 12] evaluating the association between intrauterine $PM_{2.5}$ exposure and wheezing in offspring as the outcome, and which found opposite results, does not permit to derive any conclusion. Exposure to LUR-modelled prenatal traffic-related NO_2 was also evaluated in two larger birth cohorts [11, 13] and no association was found for the development of wheezing in the first 18 months of life. Mean NO_2 exposures in the two cohorts were quite different being 39.1 $\mu g/m^3$ for the INMA cohort and only 13.6 $\mu g/m^3$ for the MoBa cohort, in this case largely below the EU air quality standard of 40 $\mu g/m^3$. The fact that wheezing incidence in early childhood was not associated with in utero exposure to traffic related air pollutants, whereas asthma incidence at school age was, allows several considerations: the lack of large studies and hence a problem of potency, the fact that wheezing in childhood and asthma are different disease entities or latency in disease manifestation.

There is little doubt on the relationship between acute exposure to high levels of air pollution and increased respiratory symptoms in children, including cough and wheeze, and visits to emergency departments for respiratory illnesses [7]. Whether there is also an association between early postnatal exposure to air pollution and wheezing and asthma development is a more contentious issue. In our systematic review an association between exposure to gases, in particular to NO_2, but also in a number of studies to PM, in particular to $PM_{2.5}$, and asthma incidence has been reported in most of the studies.

In their systematic review and metanalysis, Bowatte and colleagues [8] concluded that exposure to traffic-related air pollutants (NO_2, $PM_{2.5}$, and BC) from birth up to 5 years of age was associated with new onset of asthma throughout childhood. The association found between exposure to NO_2 in the five studies meta-analysed was modest (OR 1.09; 95% CI 0.96 to 1.23 per 10 mcg/m^3 increase) with a high heterogeneity between the studies. Association between $PM_{2.5}$ (four studies) and BC (only three studies) and asthma incidence was slightly higher with an OR 1.14 (95% CI 1.00 to 1.30) per 2 $\mu g/m^3$ increase and OR 1.20 (95% CI 1.05 to 1.38) per $1 \times 10^{-5} m^{-1}$ increase, respectively. Only few studies in the review of Bowatte and colleagues are included also in the present study, the others being on selected cohorts or evaluating exposure to pollutants beyond the first 2 years of children's life, raising a problem of overlap between the period of exposure measurement and that of outcome development. Among the more recent studies in our review (Tables 3 and 4 and supplementary Table 3), the association is expressed per one IQR increase of the air pollutants and a formal comparison among these studies and the older ones is difficult. Other methodological issues that could affect comparability among studies in our review are exposure models and age at outcome measurement. While more recent

studies used models based on satellite data [12, 14–16, 18, 19, 28], allowing to obtain daily data and hence reliable exposure estimates in the first one or 2 years of life, studies published before 2015 mostly considered an average annual exposure estimated at the birth address. Furthermore, in most of these studies, exposure models based on air pollution measurements taken in different sampling campaigns done during several periods of one/two weeks and then averaged to represent annual mean were used to assess exposure to air pollution at the birth address, and this could represent a problem for the assessment of a narrow exposure period like the first one or 2 years of life.

As for children age at asthma diagnosis, a study by Gehring et al. [29] aimed at assessing the longitudinal associations between exposure to air pollution and development of asthma, noticed that the effects of air pollution on asthma incidence were larger after the age of 4 years, where asthma diagnosis is more likely to be made. Though most of the studies in our review evaluating the association between air pollution exposure in the first 2 years of life and asthma incidence followed children up to school age, in some [14–21, 23, 27–34] a follow-up and hence asthma diagnosis was limited to the first years of life in all or in part of the subjects studied. This resulted also in a partial overlapping between the period of exposure and the development of the outcome. As already discussed, this overlap is more critical for studies that evaluated wheezing as an outcome. Interestingly, in two [22, 24] of the three studies [22–24] that evaluated wheezing phenotypes, there was an association between exposure to NOx and persistent wheezing at 4 years of life, a condition often associated with asthma.

Conclusions

Traffic-related air pollution during pregnancy increases the risk of asthma development among children and adolescents. This is in line with studies that considered lung function as an outcome. Also, in line with part of the studies on lung function is the finding of a susceptible time-window in the second trimester of pregnancy which corresponds to a period of intense airways development. We also confirmed a relationship between exposure in the first 2 years of life and asthma, although the time frame and hence the relationship between air pollutants exposure and asthma incidence needs to be further confirmed in studies with more precise exposure assessment. This is crucial for setting up more efficacious preventive strategies. Few studies with inconsistent results are available on the relationship between exposure to air pollutants either in pregnancy or in the 2 years after birth and wheezing development.

Abbreviations

BC: Black Carbon; CI: Confidence Intervals; CO: Carbon Monoxide; EC: Elemental Carbon; ECAT: Elemental Carbon Attributed To Traffic; IQR: Interquartile Range; LUR: Land Use Regression; NO: Nitric Oxide; NO_2: Nitrogen Dioxide; NOx: Nitric Oxides; O_3: Ozone; PM: Particulate Matter; SO_2: Sulphur Dioxide; UFPs: Ultra-Fine Particles

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12940-021-00728-9.

Additional file 1: Supplementary Tables.

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Authors' contributions

FR conceived of the study and oversaw the analysis. AB and EG conducted the literature review. AB, EG and EM screened the literature records and assessed studies for eligibility. AB and EM extracted relevant data from the included studies and evaluated the risk of bias. FA and FR reviewed the extracted data and contributed to data interpretation. FR wrote the manuscript; AB, EG, EM and FA contributed to the manuscript writing. The authors read and approved the final manuscript.

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Availability of data and materials

All data are available within the article and supplemental material.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Publisher's Note

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Traffic-related Air Pollution and Lung Function in Children at 8 Years of Age

A Birth Cohort Study

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***Rationale*: Long-term exposure to air pollution has been related to lung function decrements in children, but the role of timing of exposure remains unknown.**

***Objectives*: To assess the role of long-term exposure to air pollution on lung function in school-age children.**

***Methods*: More than 1,900 children in the Swedish birth cohort BAMSE were followed with repeated questionnaires, dynamic spirometry, and IgE measurements until 8 years of age. Outdoor concentrations of particulate matter with an aerodynamic diameter less than 10 μm (PM_{10}) from road traffic were estimated for residential, day care, and school addresses from birth and onward using dispersion modeling. The relationship between time-weighted average exposure during different time windows and FEV at 8 years was analyzed by linear regression, adjusting for potential confounding factors, including short-term exposure to air pollution.**

***Measurements and Main Results*: A 5th to 95th percentile difference in time-weighted average particulate matter less than 10 μm in aerodynamic diameter exposure during the first year of life was associated with a reduced FEV_1 of −59.3 ml (95% confidence interval, −113 to −5.6) at 8 years of age. The negative association was particularly pronounced in children concomitantly sensitized to common inhalant or food allergens (−136.9 ml; 95% confidence interval, −224.1 to −49.7). Exposure after the first year of life seemed to have less impact on lung function at 8 years.**

***Conclusions*: Our results indicate that exposure to traffic-related air pollution during infancy affects lung function in children up to 8 years of age and particularly in those sensitized to common inhalant or food allergens.**

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Author Contributions: E.S.S. was responsible for the practical conduct of the project including planning, coordination, and analyzing of the data, which was supervised by E.M. and G.P. E.S.S. and O.G. wrote a first version of the manuscript. O.G. was responsible for the long-term exposure assessment after consultancy from T.B. M.B. contributed with statistical consultancy in general. J.H. and M.S. provided consultancy regarding lung physiology and had overall responsibility for the lung function measurements. I.K., E.M., and G.P. designed the study. I.K. and G.P. planned the initial cohort and supervised the collection of data. All authors contributed to the interpretation of the data, revised the manuscript, and approved the final manuscript.

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AT A GLANCE COMMENTARY

Scientific Knowledge on the Subject

Long-term exposure to ambient air pollution has been associated with reduced lung function in children. However, the role of timing of exposure remains unclear, as does possible effect modification by allergic status and other factors.

What This Study Adds to the Field

In this prospective birth cohort study, we found an association between traffic-related air pollution exposure during infancy and decreased lung function in children up to 8 years of age. Our results suggest stronger effects in children sensitized to common allergens. Early life exposure to traffic-related air pollution seems to have long-term respiratory consequences in susceptible groups, such as children with atopy.

Keywords: spirometry; forced expiratory volume; sensitization; dispersion modeling; particulate matter

A considerable body of research has shown adverse effects of long-term exposure to ambient air pollution on children's respiratory health (1–7). However, the evidence on lung function effects seems inconsistent because some of the larger studies reported no associations (8, 9). Heterogeneity in study designs, exposure assessment, and spirometric measures used across the studies may have contributed to the different results (10). Furthermore, the impact of air pollution on lung function development in the context of concomitant respiratory symptoms and sensitization has attained only limited consideration in prospective studies. The Children's Health Study from California showed associations between community-average pollutant concentrations and diminished lung function development in children aged 10–18 years (11). The observed effect remained statistically significant in the subgroup of children without asthma, but the children with asthma were too few for precise risk estimation. A birth cohort study from Oslo indicated stronger air pollution effects in children with asthma compared with those without asthma. However, because of wide confidence intervals (CIs) the findings have to be interpreted with caution (1). Studies have demonstrated associations between traffic-related air pollution and sensitization (12–16), but to our knowledge, no prospective study has evaluated effect modification by sensitization status on lung function effects related to air pollution exposure.

Early exposure to ambient air pollution seems to be important for respiratory effects in later life (6, 17–19). However, only one prospective study has investigated different aspects of timing of traffic-related air pollution exposure in relation to lung function (1). Recent data show that alveoli are formed not only during early postnatal period, but also throughout childhood and adolescence (20), which may contribute to age-related vulnerability. In addition, effects of long- and short-term air pollution exposure have generally not been considered in the same study. In the two cohort studies that included short- and long-term exposure simultaneously, only the long-term effect remained significant after adjustments (1, 11). There is a need for additional epidemiologic evidence on vulnerable time periods for air pollution exposure, particularly during childhood, and on effect modification by short-term exposure.

We have previously reported an association between exposure to traffic-related air pollution during the first year of life and lower peak expiratory flow at age 4 years in a Swedish birth cohort, BAMSE (12). In the present study from the same cohort, lung function data from extended follow-up to 8 years are analyzed together with effect modification by sex, allergic sensitization, and asthma. Furthermore, assessment of several time windows enabled evaluation of critical time periods of increased susceptibility to the adverse effects of air pollution exposure. Some of the results from this study have been previously reported in the form of an abstract (21).

METHODS

More details are provided in the online supplement.

Study Subjects and Measurements

During 1994–1996, 4,089 new-born infants were recruited to the prospective cohort study BAMSE (Children, Allergy, Milieu, Stockholm, Epidemiological Survey) from four municipalities in Stockholm County. A detailed description of the study design, enrolment criteria, and procedures for data collection is provided elsewhere (22). Briefly, data on background characteristics were requested in a questionnaire at baseline (median child age, 2 mo). Questionnaires focusing on the children's respiratory health and allergic diseases, and on various exposure factors, were completed at 1, 2, 4, and 8 years of age. The response rates were from 96% and 84%, for the 1- and 8-year questionnaires, respectively. In addition, 2,630 children (64% of the original cohort) attended a clinical examination at age 8 years including maximum expiratory flow volume tests and blood sampling. Moving out of the study area and unwillingness to participate were the main reasons for drop out from the clinical follow-up. The maximal values of FVC, FEV_1, and $FEV_{0.5}$ were used for analysis. In addition, we computed FEV below 80% and 85% of the predicted value based on the present study population and using age, sex, height, and weight as predictors. Also, standard deviation scores for FEV_1 were calculated taking age, sex, height, and ethnicity into consideration (23). The Ethics Committee of Karolinska Institute, Stockholm, Sweden, approved the study.

The methodology for calculating individual long-term exposure to local traffic-related particulate matter less than 10 μm in aerodynamic diameter (PM_{10}) and NO_x has been described in detail elsewhere (13). In short, the lifetime residential, day care, and school addresses were geocoded, and time-weighted average outdoor levels for the different time windows were calculated using emission inventories and a gaussian air dispersion model. Short-term exposure was estimated using daily air quality measurements and meteorologic data from urban background and rural monitoring stations.

Statistical Analyses

Associations between air pollution and lung function were analyzed using linear regression and results are presented as β values and 95% CIs. Air pollution concentrations were entered as continuous variables without transformation and the results are provided as change in lung function per 7 $\mu g/m^3$ increase in PM_{10} concentration (corresponding to the 5th to 95th percentile difference in time-weighted average concentration). The final models were adjusted for covariates based on study design or on earlier literature if they were shown to lead to more than 10% change in the β coefficient. Only municipality, sex, age, height, and heredity for asthma or allergy fulfilled these criteria. To account for possible influence by short-term effects of air pollution, we fitted a model that adjusted for the average ozone and PM_{10} levels, temperature, and relative humidity for lags of 1–3 and 1–7 days before each child's lung function test.

Long-term exposure time windows were defined as the first year of life, 1–4 years, and 4–8 years. We explored the inclusion of several exposure time windows simultaneously into the model, but because of substantial collinearity the main analyses shown use models unadjusted for the other time windows.

A total of 1,924 subjects (47%) were included in the analyses with information on exposure, confounders, and lung function measurements. All analyses were performed with STATA 11 software package (StataCorp LP, College Station, TX).

RESULTS

Table 1 illustrates some main characteristics of the study population. The distribution of covariates was comparable among all children in the cohort and those with lung function measurements included in the present analyses. Furthermore, estimated exposure levels were similar in children included in the study and in those of the whole cohort. A description of lung function and anthropometry data obtained at the 8-year clinical examination is given in Table 2. A total of 6.8% and 10.5% of subjects with spirometric measurements had less than 85% predicted FEV_1 and $FEV_{0.5}$ levels, respectively, and approximately half of these had less than 80% predicted levels.

Exposure to traffic-PM_{10} during the first year of life was associated with FEV deficit of 59.3 ml (−113 to −5.6) in FEV_1 and −62.4 ml (−113.7 to −11.1) in $FEV_{0.5}$ for a 5th to 95th percentile difference in time-weighted exposure. Similar effects were seen for FVC, but not statistically significant. However, no clear effects on lung function were seen in relation to air pollution exposure after infancy (Figure 1). A sensitivity analysis using FEV_1 expressed as standard deviation scores confirmed the negative effect of traffic-PM_{10} exposure on lung function ($P = 0.04$). Further analyses suggested stronger effects in boys, in those sensitized against any common inhalant or food allergens, and in those with asthma, with deficits in FEV_1 of −79.6 ml (−155.7 to −3.5), −136.9 ml (−224.1 to −49.7), and −90.6 ml (−293.4 to 112.3), respectively (Table 3). However, the apparent effect modification was not statistically significant ($P = 0.35$, 0.13, and 0.69, respectively). No association was seen between sensitization *per se* and the lung function measurements (data not shown).

We also analyzed effects at less than 80% and 85% of predicted FEV_1 and $FEV_{0.5}$ to determine whether exposure to air pollution was associated with clinically important lung function deficits. Strong associations were indicated between exposure to traffic-PM_{10} during the first year of life and FEV less than 80% and 85% of predicted. Corresponding odds ratios of 4.1 (95% CI, 0.8–20.3) and 6.1 (95% CI, 2.3–16.5) and 4.0 (95% CI, 1.2–13.1) and 2.5 (95% CI, 1.0–6.3) were seen for FEV_1 and $FEV_{0.5}$, respectively (Figure 2). First year exposure remained significant after adjusting for the other exposure time periods (data not shown).

Additional adjustment for temperature, relative humidity, ozone, and PM_{10} levels during 3–7 days before each child's pulmonary function test showed little effect on the estimates of the long-term effects of air pollution (see Table E1 in the online supplement).

TABLE 1. DESCRIPTIVE DATA FOR THE BAMSE COHORT AND OF THOSE WITH DATA ON LUNG FUNCTION AT 8 YEARS OF AGE

Covariates*	Full Cohort (n = 4,089)	Study Population at 8 Years (n = 1,924)†
Girls, n (%)	2,024 (49.5)	937 (48.7)
Birth weight, g; mean (SD)	3,530 (558)	3,538 (548)
Birth length, cm; mean (SD)	50.2 (2.6)	50.2 (2.5)
Length of pregnancy, wk; mean (SD)	39.8 (2)	39.8 (1.8)
Mother's smoking during pregnancy or at birth of child, n (%)	563 (13.8)	252 (13.1)
Socioeconomic status of parents, n (%)		
Unskilled blue-collar workers	260 (6.4)	103 (5.4)
Skilled blue-collar workers	435 (10.7)	180 (9.4)
Low level white collar workers	605 (14.9)	264 (13.8)
Intermediate level white collar workers	1,179 (29)	588 (30.6)
High level white collar workers	1,539 (37.8)	769 (40.1)
Others (students, unemployed)	54 (1.3)	16 (0.8)
Heredity, n (%)		
No parental allergy or asthma	2,841 (70.5)	1,308 (68)
One parent with allergy or asthma	1,066 (26.4)	551 (28.6)
Both parents with allergy or asthma	125 (3.1)	65 (3.4)
Traffic-PM_{10}, mean/median (5th–95th percentile)‡		
Exposure during first year of life	4.2/3.7 (0.9–8.1)§	4.2/3.8 (0.9–7.9)
Exposure between 1–4 yr of life	3.7/3.4 (0.8–7.6)‖	3.7/3.5 (0.9–7.6)
Exposure between 4–8 yr of life	3.5/3.1 (0.7–7.5)¶	3.5/3.2 (0.8–7.4)

Definition of abbreviations: BAMSE = Children, Allergy, Milieu, Stockholm, Epidemiological Survey; PM_{10} = particulate matter less than 10 μm in aerodynamic diameter.

* Covariates relate to the first year of child's life.

† Includes subjects with data on lung function measurements, municipality, heredity, sex, age, length at 8-year examination, and exposure information for all time periods.

‡ Source-specific contribution to residential outdoor levels estimated from local traffic with dispersion models. Presented in μg/m³.

§ Data for 4,017 children who had complete exposure information for the first year of life.

‖ Data for 3,515 children who had complete exposure information for 1–4 years of life period.

¶ Data for 3,103 children who had complete exposure information for 4–8 years of life period.

Results using traffic-NO_x as exposure indicator were consistent with those using traffic-PM_{10}, although the level of statistical significance varied. For example, exposure during the first year of life was associated with a deficit of −34.9 ml (−80.1 to 10.4) in FEV_1 for a 5th to 95th percentile difference in time-weighted exposure to traffic-NO_x (47 μg/m³), whereas the corresponding deficit was −98.9 ml (−169.4 to −28.4) among those sensitized at 8 years. The odds ratios associated with 80% and 85% of predicted FEV_1 were 2.1 (95% CI, 0.6–8.1) and 3.4 (95% CI, 1.6–7.4), respectively, for first year exposure to traffic-NO_x.

DISCUSSION

In this prospective birth cohort study, exposure to traffic-related air pollution during infancy was associated with a decreased lung function in children at 8 years of age. There was a tendency toward stronger effects in boys, in those with asthma, and particularly in those sensitized to allergens. No significant impact of short-term air pollution exposure on the estimates of the long-term effects of air pollution was found. Our results are in general concordance with the findings from the Children's Health Study in Southern California (3, 11) and from the Oslo Birth Cohort (1), which indicated that exposure to pollution from traffic has adverse effects on children's lung function development. Several studies did not find any effect of air pollution on the pulmonary function, which might in part be attributable to their cross-sectional design and less refined exposure assessment (8, 9).

It has been shown that children are particularly susceptible to the adverse effects of air pollution and environmental tobacco smoke and that timing of exposure plays a critical role (1, 6, 12, 13, 19, 24, 25). Prenatal exposure and during infancy seems particularly harmful. Children may also be more exposed to many air pollutants compared with adults because of their higher ventilation per minute in relation to body size and often higher physical activity. In addition, the development of mature systemic immune responses during early childhood could be of importance (26). Our findings provide further support that early life exposure has long-lasting impact on lung function development.

We mainly found effects on FEV_1 and $FEV_{0.5}$, which reflect the mechanical properties of the airways and not as much on FVC, representing lung size. This is in line with the California health study (3, 11) and the Oslo cohort findings (1), even though the California study found the largest effect on midexpiratory flow, possibly more representing the bronchioles. Differences in effects on lung function variables from air pollution

TABLE 2. LUNG FUNCTION AND ANTHROPOMETRY DATA FROM 8-YEAR EXAMINATION IN THE BAMSE COHORT

Variable	N	Mean	SD	%
Length, m	1,924	1.32	0.06	
Age, yr	1,924	8.3	0.5	
FEV_1, ml	1,851	1,781	269	
$FEV_{0.5}$, ml	1,670	1,326	213	
FVC, ml	1,879	2,068	327	
FEV_1/FVC, %	1,812	86.2	5.7	
$FEV_{0.5}$/FVC, %	1,633	64.3	7.4	
FEV_1, <85% pred	125			6.8
$FEV_{0.5}$, <85% pred	176			10.5
FVC, <85% pred	116			6.2
FEV_1, <80% pred	50			2.7
$FEV_{0.5}$, <80% pred	90			5.4
FVC, <80% pred	56			3.0

Definition of abbreviations: % pred = % of predicted based on age, sex, height, and weight and interactions of sex with age, height, and weight; BAMSE = Children, Allergy, Milieu, Stockholm, Epidemiological Survey.

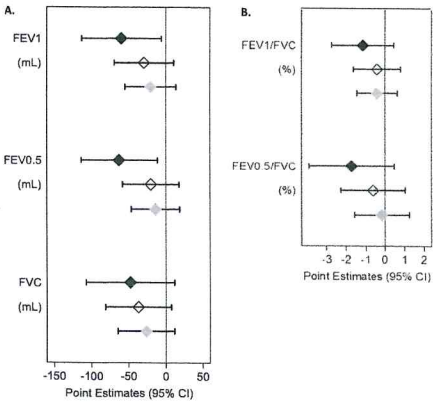

Figure 1. Lung function measurements in relation to traffic particulate matter less than 10 μm in aerodynamic diameter (PM_{10}) exposure during different time periods of life (*black*, first year of life exposure; *white*, first to fourth year exposure; *gray*, fourth to eighth year exposure). CI = confidence interval. Adjusted for municipality, sex, age, height, and heredity. Results are presented in milliliters (*A*) and percentages (*B*) for a difference in PM_{10} level from 5th to 95th percentile, corresponding to 7 μg/m³.

might partly be explained by the mixture of components in traffic-related emission. We have in our study focused on PM_{10} as exposure estimate, which in Stockholm is primarily influenced by coarse particles (>2.5 μm), although it also contains fine and ultrafine particles. Our results are in general agreement with the other studies considering that levels of smaller particles, such as $PM_{2.5}$, correlate to PM_{10} and are also supported by our findings for traffic-NO_x, which correlate with fine particulate emissions from motor vehicles.

From an individual perspective the estimated effect on lung function seen in our study is rather small (−3.3% for FEV_1 and −4.7% for $FEV_{0.5}$), but even a slight shift in the population distribution of lung function can substantially increase the prevalence of subjects exhibiting respiratory function below clinical thresholds. In our study this is indicated by the sharply increased risks of having a lung function below 80% and 85% of predicted. The cut point 80% of predicted was chosen because it is generally used in clinical settings to identify persons who are at increased risk for adverse respiratory effects. However, few children were identified with this lung function reduction and 85% of predicted was also used, but the results remained similar. Our analyses were internally adjusted for age, height, and sex but results were consistent also when the lung function analyses were based on external reference data using standard deviation scores (23).

We also investigated the effect modification by including interaction terms with sex, current asthma, and allergic sensitization. Although the interactions were not statistically significant, there was a tendency for a stronger effect on lung function in subjects sensitized to common allergens. We have earlier shown in this cohort that air pollution exposure during the first year of life is associated with sensitization at 4 years of age (12, 13), but not at 8 years of age; however, no association was found between sensitization *per se* and FEV_1. Thus, the effects from PM_{10} on lung function do not seem to be explained by sensitization affecting lung function. Data regarding the role of allergic sensitization as a risk factor for lung function loss in relation to air pollution exposure in children are limited. Several cross-sectional studies have reported larger effects of air pollution exposure on lung function in children with a diagnosis of asthma, allergies, eczema, or any combination (i.e., in children with a predisposing bronchial sensitivity) (27, 28). Although the exact mechanisms are unclear, it has been suggested that air pollution and sensitization might be independently involved in the induction of Th2 immune response. For instance, it has been shown that diesel exhaust particles stimulate an unfavorable Th2-skewed immune response to allergens and that allergic children experience subclinical asthma-like changes in their lung function (29, 30). Thus, air pollution exposure in allergic children may exert a synergistic effect on the allergic inflammation response to specific allergens or an irritative effect on the airways.

Several studies have shown an association between short-term exposure to outdoor air pollution and lung function impairment in children (31); however, simultaneous effects of long- and short-term exposures on lung function have rarely been investigated within the same study. We included short- and long-term air pollution exposures in the models to exclude possible confounding or decreased precision of the long-term exposure estimates by short-term exposure. The sensitivity analysis with adjustment for temperature, relative humidity, and short-term exposures (previous days' concentrations of O_3 and PM_{10}) showed,

TABLE 3. ASSOCIATION BETWEEN EXPOSURE TO TRAFFIC PM_{10} DURING THE FIRST YEAR OF LIFE AND FEV_1 AT 8 YEARS OF AGE (N = 1,851)

	N	Traffic PM_{10} Point Estimates in Milliliters (95% CI)*	*P* Value
All subjects	1,851	−59.3 (−113 to −5.6)	0.03
Girls	902	−37.1 (−112.7 to 38.4)	0.34
Boys	949	−79.6 (−155.7 to −3.5)	0.04
Sensitized at 8 yrs†	606	−136.9 (−224.1 to −49.7)	<0.01
Not sensitized at 8 yrs	1,119	−44.8 (−116.6 to 26.9)	0.22
Asthma at 8 yrs‡	144	−90.6 (−293.4 to 112.3)	0.38
No asthma at 8 yrs	1,696	−55.4 (−111.2 to 0.3)	0.05

Definition of abbreviations: CI = confidence interval; PM_{10} = particulate matter less than 10 μm in aerodynamic diameter.

* Results are presented in milliliters for a difference in PM_{10} level from 5th to 95th percentile, corresponding to 7 μg/m³. Adjusted for municipality, sex, age, height, and heredity.

† Defined as IgE values for phadiatop greater than or equal to 0.35 kU/L or IgE value for food-mix greater than or equal to 0.35 kU/L.

‡ Defined as at least four episodes of wheeze in the last 12 months or at least one episode in combination with prescription of inhaled corticosteroids.

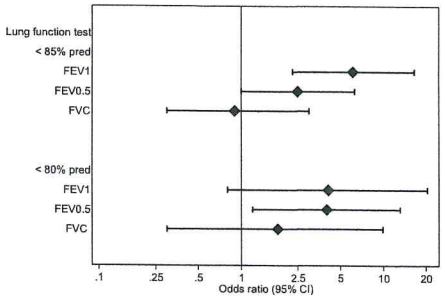

Figure 2. Association between first year of life exposure to traffic. PM_{10} and FEV less than 80% and 85% of predicted. % pred = % of predicted based on age, sex, height, and weight and interactions of sex with age, height, and weight; CI = confidence interval; PM_{10} = particulate matter less than 10 μm in aerodynamic diameter. Odds ratios are calculated for a 7 $\mu g/m^3$ difference in PM_{10} level corresponding to a 5th to 95th percentile difference. Adjusted for municipality and heredity.

however, little influence of short-term exposure on the effect estimates for long-term exposure on lung function. Similar findings were reported from the California health study and Oslo cohort (1, 11). Our study has several advantages, including its combination of a prospective design; large number of participants; individual long-term exposure to air pollutants (incorporating their time-activity patterns); objective measurement of lung function; evaluation of effect modification by sex, asthma, or increased IgE levels to common allergens; and influence of the short-term variation in air pollution exposure. In particular, the exposure estimates for each study subject were obtained from a time- and space-resolved dispersion model enhanced by addition of street canyon contribution for addresses in the most polluted street segments, and by including not only residential addresses but also addresses of day care and schools.

Some potential weaknesses of this study should be recognized. One is that model calculations of PM_{10} concentrations were only done for 2004 and extrapolated to the other years of follow-up. The most important local source of PM_{10} in many urban areas in Sweden is coarse particles resulting from road surface erosion by cars with studded tires and sanding or salting of roads in the winter (32). Because of the stable use of studded tires in the Stockholm area during the study period, and traffic load in the inner city, the emissions of PM_{10} have not changed substantially (33). Road moisture has a crucial impact on the yearly variations of PM_{10} concentrations. Unfortunately, this could not be taken into consideration because of lack of relevant data (32). However, several validation studies have shown good agreement between modeled and measured air pollution concentrations (34, 35). Results were supported by analyses using traffic-NO_x as indicator, where the exposure assessment was based on dispersion modeling at repeated occasions during the observation period (13). This is expected because of the high correlation between the two exposure measures.

Some misclassification of true individual exposure levels has probably affected the results, especially because no indoor environments were characterized and no individual time-activity data were used. However, the errors in the assessments of exposure and disease are most likely to be independent and making such misclassification would thus be expected to weaken any true associations. Imprecision in the lung function measurements primarily results from its dependence on the children's cooperation. However, because one trained team examined all the children using the same equipment and method of measuring, masked to the exposure, such bias is likely unimportant. Selective participation is probably of limited concern because subjects in air pollution studies are generally unaware of their precise level of exposure, and lung function is objectively evaluated (36). We tested a comprehensive set of known risk factors for childhood respiratory disorders with regard to possible confounding effects, including socioeconomic status, home environment characteristics, maternal smoking, and so forth, but none except those included in the models showed clear confounding effect. Still, the possibility of residual confounding cannot be ruled out.

To conclude, our results indicate that exposure to ambient air pollution from traffic during the first year of life is associated with lung function deficits in children up to 8 years, particularly in those sensitized to common allergens.

Author disclosures are available with the text of this article at www.atsjournals.org.

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International Agency for Research on Cancer

World Health Organization

PRESS RELEASE
N° 213

12 June 2012

IARC: DIESEL ENGINE EXHAUST CARCINOGENIC

Lyon, France, June 12, 2012 -- After a week-long meeting of international experts, the International Agency for Research on Cancer (IARC), which is part of the World Health Organization (WHO), today classified diesel engine exhaust as **carcinogenic to humans (Group 1)**, based on sufficient evidence that exposure is associated with an increased risk for lung cancer.

Background
In 1988, IARC classified diesel exhaust as *probably carcinogenic to humans (Group 2A)*. An Advisory Group which reviews and recommends future priorities for the IARC Monographs Program had recommended diesel exhaust as a high priority for re-evaluation since 1998.

There has been mounting concern about the cancer-causing potential of diesel exhaust, particularly based on findings in epidemiological studies of workers exposed in various settings. This was re-emphasized by the publication in March 2012 of the results of a large US National Cancer Institute/National Institute for Occupational Safety and Health study of occupational exposure to such emissions in underground miners, which showed an increased risk of death from lung cancer in exposed workers (1).

Evaluation
The scientific evidence was reviewed thoroughly by the Working Group and overall it was concluded that there was *sufficient evidence* in humans for the carcinogenicity of diesel exhaust. The Working Group found that diesel exhaust is a cause of lung cancer (*sufficient evidence*) and also noted a positive association (*limited evidence*) with an increased risk of bladder cancer (Group 1).

The Working Group concluded that gasoline exhaust was possibly carcinogenic to humans (Group 2B), a finding unchanged from the previous evaluation in 1989.

Public health
Large populations are exposed to diesel exhaust in everyday life, whether through their occupation or through the ambient air. People are exposed not only to motor vehicle exhausts but also to exhausts from other diesel engines, including from other modes of transport (e.g. diesel trains and ships) and from power generators.

Given the Working Group's rigorous, independent assessment of the science, governments and other decision-makers have a valuable evidence-base on which to consider environmental standards for diesel exhaust emissions and to continue to work with the engine and fuel manufacturers towards those goals.

Increasing environmental concerns over the past two decades have resulted in regulatory action in North America, Europe and elsewhere with successively tighter emission standards for both diesel and gasoline engines. There is a strong interplay between standards and technology – standards drive technology and new technology enables more stringent standards. For diesel engines, this required changes in the fuel such as marked decreases in sulfur content, changes in engine design to burn diesel fuel more efficiently and reductions in emissions through exhaust control technology.

However, while the amount of particulates and chemicals are reduced with these changes, it is not yet clear how the quantitative and qualitative changes may translate into altered health effects; research into

this question is needed. In addition, existing fuels and vehicles without these modifications will take many years to be replaced, particularly in less developed countries, where regulatory measures are currently also less stringent. It is notable that many parts of the developing world lack regulatory standards, and data on the occurrence and impact of diesel exhaust are limited.

Conclusions
Dr Christopher Portier, Chairman of the IARC working Group, stated that "The scientific evidence was compelling and the Working Group's conclusion was unanimous: diesel engine exhaust causes lung cancer in humans." Dr Portier continued: "Given the additional health impacts from diesel particulates, exposure to this mixture of chemicals should be reduced worldwide."(2)

Dr Kurt Straif, Head of the IARC Monographs Program, indicated that "The main studies that led to this conclusion were in highly exposed workers. However, we have learned from other carcinogens, such as radon, that initial studies showing a risk in heavily exposed occupational groups were followed by positive findings for the general population. Therefore actions to reduce exposures should encompass workers and the general population."

Dr Christopher Wild, Director, IARC, said that "while IARC's remit is to establish the evidence-base for regulatory decisions at national and international level, today's conclusion sends a strong signal that public health action is warranted. This emphasis is needed globally, including among the more vulnerable populations in developing countries where new technology and protective measures may otherwise take many years to be adopted."

Summary evaluation
The summary of the evaluation will appear in The Lancet Oncology as an online publication ahead of print on June 15, 2012.

(1) JNCI J Natl Cancer Inst (2012) doi:10.1093/jnci/djs034
http://jnci.oxfordjournals.org/content/early/2012/03/05/jnci.djs034.abstract; and
JNCI J Natl Cancer Inst (2012) doi: 10.1093/jnci/djs035
http://jnci.oxfordjournals.org/content/early/2012/03/05/jnci.djs035.abstract

(2) Dr Portier is Director of the National Center for Environmental Health and the Agency for Toxic Substances and Disease Registry at the Centers for Disease Control and Prevention (USA).

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Link to the **audio file** posted shortly after the media briefing:
http://terrance.who.int/mediacentre/audio/press_briefings/

About IARC
The International Agency for Research on Cancer (IARC) is part of the World Health Organization. Its mission is to coordinate and conduct research on the causes of human cancer, the mechanisms of carcinogenesis, and to develop scientific strategies for cancer control. The Agency is involved in both epidemiological and laboratory research and disseminates scientific information through publications, meetings, courses, and fellowships.

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Annexes

Evaluation groups - Definitions

Group 1: *The agent is carcinogenic to humans.*
This category is used when there is *sufficient evidence of carcinogenicity* in humans. Exceptionally, an agent may be placed in this category when evidence of carcinogenicity in humans is less than *sufficient* but there is *sufficient evidence of carcinogenicity* in experimental animals and strong evidence in exposed humans that the agent acts through a relevant mechanism of carcinogenicity.

Group 2.
This category includes agents for which, at one extreme, the degree of evidence of carcinogenicity in humans is almost *sufficient*, as well as those for which, at the other extreme, there are no human data but for which there is evidence of carcinogenicity in experimental animals. Agents are assigned to either Group 2A (*probably carcinogenic to humans*) or Group 2B (*possibly carcinogenic to humans*) on the basis of epidemiological and experimental evidence of carcinogenicity and mechanistic and other relevant data. The terms *probably carcinogenic* and *possibly carcinogenic* have no quantitative significance and are used simply as descriptors of different levels of evidence of human carcinogenicity, with *probably carcinogenic* signifying a higher level of evidence than *possibly carcinogenic*.

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  This category is used when there is *limited evidence of carcinogenicity* in humans and *sufficient evidence of carcinogenicity* in experimental animals. In some cases, an agent may be classified in this category when there is *inadequate evidence of carcinogenicity* in humans and *sufficient evidence of carcinogenicity* in experimental animals and strong evidence that the carcinogenesis is mediated by a mechanism that also operates in humans. Exceptionally, an agent may be classified in this category solely on the basis of *limited evidence of carcinogenicity* in humans. An agent may be assigned to this category if it clearly belongs, based on mechanistic considerations, to a class of agents for which one or more members have been classified in Group 1 or Group 2A.

- **Group 2B:** The agent is *possibly carcinogenic to humans.*
  This category is used for agents for which there is *limited evidence of carcinogenicity* in humans and less than *sufficient evidence of carcinogenicity* in experimental animals. It may also be used when there is *inadequate evidence of carcinogenicity* in humans but there is *sufficient evidence of carcinogenicity* in experimental animals. In some instances, an agent for which there is *inadequate evidence of carcinogenicity* in humans and less than *sufficient evidence of carcinogenicity* in experimental animals together with supporting evidence from mechanistic and other relevant data may be placed in this group. An agent may be classified in this category solely on the basis of strong evidence from mechanistic and other relevant data.

Group 3: The agent is *not classifiable as to its carcinogenicity to humans.*
This category is used most commonly for agents for which the evidence of carcinogenicity is *inadequate* in humans and *inadequate* or *limited* in experimental animals.
Exceptionally, agents for which the evidence of carcinogenicity is *inadequate* in humans but *sufficient* in experimental animals may be placed in this category when there is strong evidence that the mechanism of carcinogenicity in experimental animals does not operate in humans.
Agents that do not fall into any other group are also placed in this category.

An evaluation in Group 3 is not a determination of non-carcinogenicity or overall safety. It often means that further research is needed, especially when exposures are widespread or the cancer data are consistent with differing interpretations.

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IARC: Diesel engines exhaust carcinogenic

Group 4: The agent is *probably not carcinogenic to humans.*
This category is used for agents for which there is *evidence suggesting lack of carcinogenicity* in humans and in experimental animals. In some instances, agents for which there is *inadequate evidence of carcinogenicity* in humans but *evidence suggesting lack of carcinogenicity* in experimental animals, consistently and strongly supported by a broad range of mechanistic and other relevant data, may be classified in this group.

Evidence for studies in humans - Definition

As shown previously, the evidence relevant to carcinogenicity is evaluated using standard terms. For studies in humans, evidence is defined into one of the following categories:

Sufficient evidence of carcinogenicity: The Working Group considers that a causal relationship has been established between exposure to the agent and human cancer. That is, a positive relationship has been observed between the exposure and cancer in studies in which chance, bias and confounding could be ruled out with reasonable confidence. A statement that there is *sufficient evidence* is followed by a separate sentence that identifies the target organ(s) or tissue(s) where an increased risk of cancer was observed in humans. Identification of a specific target organ or tissue does not preclude the possibility that the agent may cause cancer at other sites.

Limited evidence of carcinogenicity: A positive association has been observed between exposure to the agent and cancer for which a causal interpretation is considered by the Working Group to be credible, but chance, bias or confounding could not be ruled out with reasonable confidence.

Inadequate evidence of carcinogenicity: The available studies are of insufficient quality, consistency or statistical power to permit a conclusion regarding the presence or absence of a causal association between exposure and cancer, or no data on cancer in humans are available.

Evidence suggesting lack of carcinogenicity: There are several adequate studies covering the full range of levels of exposure that humans are known to encounter, which are mutually consistent in not showing a positive association between exposure to the agent and any studied cancer at any observed level of exposure. The results from these studies alone or combined should have narrow confidence intervals with an upper limit close to the null value (e.g. a relative risk of 1.0). Bias and confounding should be ruled out with reasonable confidence, and the studies should have an adequate length of follow-up. A conclusion of *evidence suggesting lack of carcinogenicity* is inevitably limited to the cancer sites, conditions and levels of exposure, and length of observation covered by the available studies. In addition, the possibility of a very small risk at the levels of exposure studied can never be excluded.

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ZAŁĄCZNIK NR 8

International Agency for Research on Cancer

World Health Organization

PRESS RELEASE
N° 221

17 October 2013

IARC: Outdoor air pollution a leading environmental cause of cancer deaths

Lyon/Geneva, 17 October 2013 – The specialized cancer agency of the World Health Organization, the International Agency for Research on Cancer (IARC), announced today that it has classified outdoor air pollution as *carcinogenic to humans* (Group 1). [1]

After thoroughly reviewing the latest available scientific literature, the world's leading experts convened by the IARC Monographs Programme concluded that there is *sufficient evidence* that exposure to outdoor air pollution causes lung cancer (Group 1). They also noted a positive association with an increased risk of bladder cancer.

Particulate matter, a major component of outdoor air pollution, was evaluated separately and was also classified as *carcinogenic to humans* (Group 1).

The IARC evaluation showed an increasing risk of lung cancer with increasing levels of exposure to particulate matter and air pollution. Although the composition of air pollution and levels of exposure can vary dramatically between locations, the conclusions of the Working Group apply to all regions of the world.

A major environmental health problem
Air pollution is already known to increase risks for a wide range of diseases, such as respiratory and heart diseases. Studies indicate that in recent years exposure levels have increased significantly in some parts of the world, particularly in rapidly industrializing countries with large populations. The most recent data indicate that in 2010, 223 000 deaths from lung cancer worldwide resulted from air pollution. [2]

The most widespread environmental carcinogen
"The air we breathe has become polluted with a mixture of cancer-causing substances," says Dr Kurt Straif, Head of the IARC Monographs Section. "We now know that outdoor air pollution is not only a major risk to health in general, but also a leading environmental cause of cancer deaths."

The IARC Monographs Programme, dubbed the "encyclopaedia of carcinogens", provides an authoritative source of scientific evidence on cancer-causing substances and exposures. In the past, the Programme evaluated many individual chemicals and specific mixtures that occur in outdoor air pollution. These included diesel engine exhaust, solvents, metals, and dusts. But this is the first time that experts have classified outdoor air pollution as a cause of cancer.

"Our task was to evaluate the air everyone breathes rather than focus on specific air pollutants," explains Dr Dana Loomis, Deputy Head of the Monographs Section. "The results from the reviewed studies point in the same direction: the risk of developing lung cancer is significantly increased in people exposed to air pollution."

IARC Monographs evaluations
Volume 109 of the IARC Monographs is based on the independent review of more than 1000 scientific papers from studies on five continents. The reviewed studies analyse the carcinogenicity of various pollutants present in outdoor air pollution, especially particulate matter and transportation-related pollution. The evaluation is driven by findings from large epidemiologic studies that included millions of people living in Europe, North and South America, and Asia.

[1] Please note that the summary evaluation will be published by The Lancet Oncology online on Thursday 24 October 2013
[2] http://www.iarc.fr/en/publications/books/sp161/index.php

IARC: Outdoor air pollution a leading environmental cause of cancer deaths

The predominant sources of outdoor air pollution are transportation, stationary power generation, industrial and agricultural emissions, and residential heating and cooking. Some air pollutants have natural sources, as well.

"Classifying outdoor air pollution as carcinogenic to humans is an important step," stresses IARC Director Dr Christopher Wild. "There are effective ways to reduce air pollution and, given the scale of the exposure affecting people worldwide, this report should send a strong signal to the international community to take action without further delay."

For more information, please contact

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The International Agency for Research on Cancer (IARC) is part of the World Health Organization. Its mission is to coordinate and conduct research on the causes of human cancer, the mechanisms of carcinogenesis, and to develop scientific strategies for cancer control. The Agency is involved in both epidemiological and laboratory research and disseminates scientific information through publications, meetings, courses, and fellowships. If you wish your name to be removed from our press release e-mailing list, please write to com@iarc.fr.

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Full-chain health impact assessment of traffic-related air pollution and childhood asthma

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ABSTRACT

Background: Asthma is the most common chronic disease in children. Traffic-related air pollution (TRAP) may be an important exposure contributing to its development. In the UK, Bradford is a deprived city suffering from childhood asthma rates higher than national and regional averages and TRAP is of particular concern to the local communities.

Aims: We estimated the burden of childhood asthma attributable to air pollution and specifically TRAP in Bradford. Air pollution exposures were estimated using a newly developed full-chain exposure assessment model and an existing land-use regression model (LUR).

Methods: We estimated childhood population exposure to NO_x and, by conversion, NO_2 at the smallest census area level using a newly developed full-chain model knitting together distinct traffic (SATURN), vehicle emission (COPERT) and atmospheric dispersion (ADMS-Urban) models. We compared these estimates with measurements and estimates from ESCAPE's LUR model. Using the UK incidence rate for childhood asthma, meta-analytical exposure-response functions, and estimates from the two exposure models, we estimated annual number of asthma cases attributable to NO_2 and NO_x in Bradford, and annual number of asthma cases *specifically* attributable to traffic.

Results: The annual average census tract levels of NO_2 and NO_x estimated using the full-chain model were 15.41 and 25.68 μg/m^3, respectively. On average, 2.75 μg/m^3 NO_2 and 4.59 μg/m^3 NO_x were specifically contributed by traffic, without minor roads and cold starts. The annual average census tract levels of NO_2 and NO_x estimated using the LUR model were 21.93 and 35.60 μg/m^3, respectively. The results indicated that up to 687 (or 38% of all) annual childhood asthma cases in Bradford may be attributable to air pollution. Up to 109 cases (6%) and 219 cases (12%) may be specifically attributable to TRAP, with and without minor roads and cold starts, respectively.

Conclusions: This is the first study undertaking full-chain health impact assessment of TRAP and childhood asthma in a disadvantaged population with public concern about TRAP. It further adds to scarce literature exploring the impact of different exposure assessments. In conservative estimates, air pollution and TRAP are estimated to cause a large, but largely preventable, childhood asthma burden. Future progress with childhood asthma requires a move beyond the prevalent disease control-based approach toward asthma prevention.

Abbreviations: AD, atmospheric dispersion; ADMS-Urban, atmospheric dispersion modeling system; COPERT, COmputer Programme to calculate Emissions from Road Transport; E&W, England and Wales; ESCAPE, European Study of Cohorts for Air Pollution Effects; GIS, geographic information systems; HIA, health impact assessment; IMD, Index of Multiple Deprivation; LUR, land-use regression; PAF, population attributable fraction; RR, relative risk; SATURN, simulation and assignment of traffic in urban road networks; TRAP, traffic-related air pollution

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1. Introduction

Asthma is a chronic disease of the air passages leading to and from the lung, and is a condition that is often cited as the most common chronic disease of childhood (Gasana et al., 2012; Fabian et al., 2012; Gaffin and Phipatanakul, 2014). A recent meta-analysis showed statistically significant exposure-response relationships between traffic-related air pollution (TRAP) and development of asthma in children from birth to 18 years of age (Khreis et al., 2017c). The public health relevance of these relationships is largely unknown and the impact of TRAP exposures on the burden of childhood asthma is poorly documented. Due to the ubiquity of TRAP and the number of exposed children, the relatively small individual risks of TRAP-associated asthma could translate into significant public health impact.

Little work has been undertaken to estimate the burden of childhood asthma attributable to TRAP. Only four published studies, coming from the same research group, quantified the number of *prevalent* asthma cases attributable to TRAP (Perez et al., 2009; Perez et al., 2013; Künzli et al., 2008; Perez et al., 2012). Three of these studies were conducted in California, in Long Beach, Riverside and Los Angeles county (Künzli et al., 2008; Perez et al., 2009; Perez et al., 2012). The fourth study was conducted in 10 European cities (Perez et al., 2013). All four studies estimated the impacts of exposure to TRAP, characterized by proximity to major roadways, on asthma prevalence in children between birth and 18 years old. These studies suggested that 6% to 14% of prevalent childhood asthma cases were attributable to TRAP exposures; as characterized by traffic proximity (Table S1).

Despite pioneering in studying asthma as an outcome in the burden of disease assessment of TRAP, these studies relied on residential proximity to major roadways as the TRAP exposure metric. Proximity to major roadways is a crude exposure metric (Beevers et al., 2013; Jerrett et al., 2005) and alternative improved approaches are now more readily available (Khreis and Nieuwenhuijsen, 2017). Individual measurements are the preferred exposure assessment method, but since it is often not possible to measure air pollution exposures for the large populations included in health impact assessment and most epidemiological studies, many rely on less costly and more practical modeling approaches. Land-use regression (LUR) (Eeftens et al., 2012; Beelen et al., 2013; De Hoogh et al., 2014) and atmospheric dispersion (AD) modeling (Rancière et al., 2017; Yamazaki et al., 2014; De Hoogh et al., 2014) are two common modeling methods used to obtain air pollution exposure estimates for relatively large areas and number of people.

These two exposure modeling methods are fundamentally different and vary in their spatial and temporal resolution, specificity to traffic and advantages and disadvantages (Khreis and Nieuwenhuijsen (2017). AD models rely on mathematical formula and an understanding of underlying emission and dispersion processes to estimate air pollution exposures (Nieuwenhuijsen, 2015). On the other hand, LUR is an empirical method that uses least squares regression to combine air pollution measurements with geographic information system (GIS)-based predictor variables which reflect pollutant sources (for example, road, traffic and buildings density, green space etc.). The practical and policy advantage of AD modeling is that it allows for easier estimation of the contribution of different sources, such as traffic, to air pollution exposure estimates. On the other hand, the true contribution of traffic to the regression in LUR models is not always known or reported (Health Effects Institute, 2010).

In this study, we aimed to construct a full-chain health impact assessment model (Nieuwenhuijsen et al., 2017), to estimate the annual number of childhood asthma cases in Bradford, UK, attributable to air pollution, and specifically to TRAP. In the full-chain health impact assessment model, we combined four distinct models of traffic, emission, AD and health impact assessment (HIA), which covered the full-chain from the source of air pollution to the health impacts (Fig. 1). We then compared the burden of disease estimates obtained using the full-chain model with those obtained using exposure estimates from a LUR model, instead.

2. Methods

2.1. Setting

The study was set in Bradford, a city in the North of England, with an estimated 534,300 inhabitants (City of Bradford Metropolitan District Council, 2017). Bradford's population has a notably different structure from other cities in England and Wales (E&W) with more people under the age of 16 (Bradford has 22.6% whilst E&W have 18.7%) (Fielding, 2012). Based on the British government's residential area Index of Multiple Deprivation (IMD) (ESRI, 2017) and considering factors like income, employment, education and health deprivation, crime, barriers to housing and services and living environment deprivation, Bradford is one of the 10% most deprived local authorities in the UK, with significant deprivation discrepancy between the different neighborhoods (Fielding, 2012; Wright et al., 2013). The major sources of air pollution in the district have been identified as regional rural concentrations, traffic, industry, and domestic, institutional and commercial space heating. Less important sources include point sources, rail, and aircrafts (Department for Environment Food and Rural Affairs, 2010).

The work presented in this paper is part of ongoing work in Bradford assessing the emissions and air quality profile in the district and the associated childhood health effects and population-based impacts. The analysis year was 2009; when the LUR model and the traffic model used to construct the AD model were available.

2.2. Health impacts assessment framework

The HIA followed classical HIA methodology combining information on exposure estimates, baseline incidence rates of the outcome of interest and meta-analytical exposure-response functions (Mueller et al., 2017).

NO_x and NO_2 were the exposures studied and were estimated using:

- an existing LUR model and
- a newly developed AD model.

To validate and enhance the AD model's estimates, we used information gained from measured NO_x data from the ESCAPE project (Cyrys et al., 2012), as will be described next.

2.3. Land-use regression model

The first set of exposure estimates were derived using NO_2 and NO_x LUR models which were developed in Bradford as part of the ESCAPE project (European Study of Cohorts for Air Pollution Effects, 2014). These models were based on NO_2 and NO_x measurements at 41 sites across Bradford, using Ogawa passive samplers (www.ogawausa.com). The passive samplers were administered between *1 June 2009* and *15 December 2009* and contained two collection filters, one for sampling NO_2 and the other for NO_x (Cyrys et al., 2012).

The measurement sites were classified into regional background ($n = 2$), urban background ($n = 24$) and traffic sites ($n = 15$) (Table 1 and Fig. 2). At each site, measurements were made for three 14-day periods, with each period representing a different season namely the warm, cold and intermediate seasons. The measurements were adjusted for temporal variability using measurements obtained from a reference fixed-site monitoring station which was operated all year around (Cyrys et al., 2012; Beelen et al., 2013).

The summary statistics of the adjusted measurements made at the 41 sites are shown in Table 1. The cross-validation R^2s of the NO_x and NO_2 LUR models were 0.88 and 0.80, respectively, and a full validation description has been reported elsewhere (Beelen et al., 2013). The final

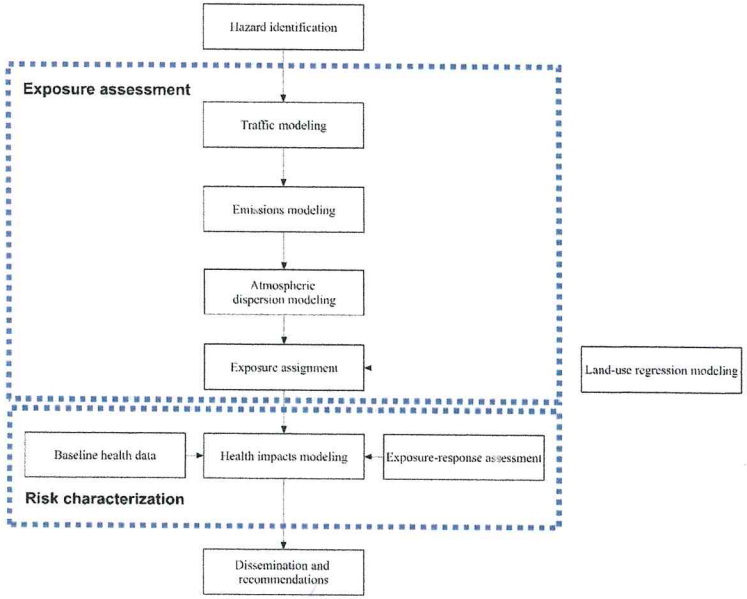

Fig. 1. Full-chain health impact assessment of TRAP.
Source: Modified after Nieuwenhuijsen et al. (2017).

LUR models used in Bradford and adopted in this study were as follows (Beelen et al., 2013):

$$NO_2 = 16.52 + 7.81E - 5*BUILDINGS300 + 5.86E - 6*TRAFLOAD25 + 3.20E - 8*TRAFLOAD251000 - 1.09E - 4*NATURAL300 + 7.43E - 4*HEAVYTRAFMAJOR$$

$$NO_x = 19.76 + 1.68E - 5*TRAFLOAD25 + 1.90E - 6*TRAFLOAD25100 + 2.74E - 4*BUILDINGS300 - 2.48E - 3*NATURAL100 + 1.92E - 4*TRAFMAJOR$$

where BUILDINGS = Area of the land use in that buffer / number of buildings (m^2/number).

TRAFLOAD = Total traffic load of all roads in a buffer (sum of (traffic intensity * length of all segments)) (veh·day^{-1} * m), NATURAL = Semi-natural and forested areas in that buffer (m^2), HEAVYTRAFMAJOR = Heavy-duty traffic intensity on nearest major road (veh·day^{-1}), and TRAFMAJOR = Traffic intensity on nearest major road (veh·day^{-1}).

Table 1
Summary statistics of adjusted measured NO_2 and NO_x concentrations at the 41 ESCAPE sites of Bradford.

ESCAPE site type	Rural background	Urban background	Traffic
Definition	Measurements in the smaller towns and villages of the cohort	A site with fewer than 3000 vehicles per day passing within a 50 m radius	A site in a major road carrying at least 10,000 vehicles per day
Number	2	24	15
Average adjusted NO_2 (μg/m^3)	16.9	24.1	29.7
Average adjusted NO_x (μg/m^3)	23.6	38.4	59.4
Average NO_2/NO_x ratio (μg/m^3)	0.72	0.63	0.50
Minimum adjusted NO_2 (μg/m^3)	16.7	17.2	19.4
Maximum adjusted NO_2 (μg/m^3)	17.0	34.1	44.9
Minimum adjusted NO_x (μg/m^3)	22.4	25.1	33.6
Maximum adjusted NO_x (μg/m^3)	24.7	59.1	110.5

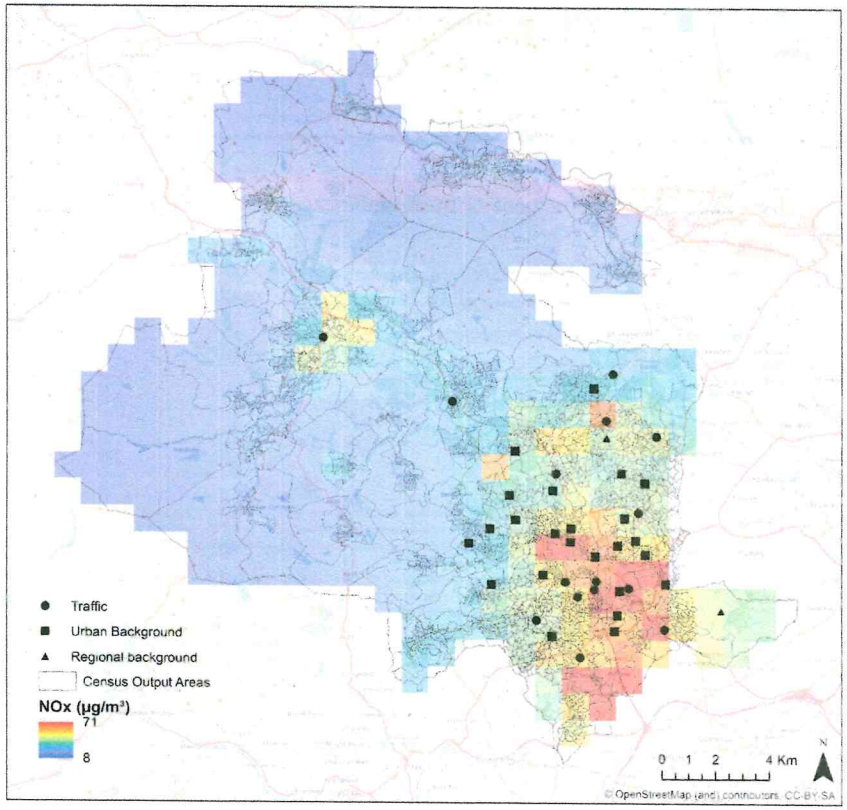

Fig. 2. Locations and types of the ESCAPE measurement sites, underlying 1 km × 1 km background NO_x concentrations grids and census output areas in Bradford.

2.4. Atmospheric dispersion model

The second set of exposure estimates were derived using a newly developed AD model. The key inputs for the AD model were:

1. link-based traffic flows and average traffic speeds obtained from a previously validated SATURN traffic simulation and assignment model (van Vliet, 1982; Steer Davies Gleave, 2009);
2. NO_x exhaust emission estimates based on average-speed-emission functions sourced from the COPERT emission model (Samaras et al., 2014; Khreis et al., 2017b);
3. hourly sequential meteorological data covering year 2009.

The dispersion modeling was undertaken using the software ADMS-Urban version 3.0.0. (Cambridge Environmental Research Consultants Ltd, 2010). The AD model has been previously described and validated in Khreis et al. (2017a), so here, we only briefly describe the various steps.

2.4.1. SATURN traffic flows and average traffic speeds

A validated SATURN traffic model covering the Bradford District was used to extract geographical locations of 4500 road links and to estimate link-based traffic flows (vehicles/h) and average speeds (km/h) (Steer Davies Gleave, 2009). The model was run in SATURN version 11.1.09 and was independently validated at 19 automatic traffic counters with complete traffic flow data for a neutral week in 2009 (Khreis et al., 2017b). The R^2 for the validation was 0.77. Overall the model tended to under estimate traffic flows at smaller/lower-level roads compared to major roads. The model was found to be a simplistic schematic of the underlying road network as the geographical locations of the road links were not very accurate and road links were represented as straight lines (rather than curved paths). The model simulated traffic flows and average speeds for three times on an average weekday:

- AM peak,
- inter-peak and
- PM peak.

For all hours outside the simulation periods, a scaling factor from traffic flow observations at the 19 validation automatic traffic counters was developed and applied to estimate an average diurnal traffic profile (Khreis et al., 2017b). The estimated traffic flows were split into different vehicle classes using 2009 standard fleet compositions in Urban England (National Atmospheric Emissions Inventory and Ricardo Energy and Environment, 2014). The Bradford's SATURN model AM peak simulated actual flows and net speeds are shown in Fig. S1 and Fig. S2.

2.4.2. COPERT NOx exhaust emissions

NO_x emissions were estimated using NO_x average-speed-emission functions from the COPERT 4 version 10.0 emission model (spreadsheets are freely available at: http://naei.beis.gov.uk/data/ef-transport). Based on Urban England's 2009 fleet compositions, there were 167 applicable average-speed-emission functions that were sourced and coded onto an Excel spreadsheet. In this spreadsheet, the user can enter the SATURN link-based average traffic speed (km/h) and traffic flow (vehicles/h) under each vehicle type (for example, a EURO 4 diesel passenger car) so that its NO_x emission factor (g/km) is calculated.

The link-based NO_x emission rates in g/km were converted into g/km/s, using a time conversion factor (1 h/3600 s) to align with ADMS-Urban input requirements. This process was undertaken 48 times corresponding to the 24 h in an average weekday and the 24 h in an average weekend; using the weekday and weekend hourly traffic flows as estimated or derived from the SATURN outputs (see "SATURN traffic flows and average traffic speeds" section above). This data was used to develop time varying emission factors as shown in Fig. S3 (Cambridge Environmental Research Consultants Ltd, 2014). The AM, inter-peak and PM peak speeds, as estimated by the SATURN model, were directly used to calculate emissions at those three time periods. For all other hours outside the SATURN's simulation periods (for which no speeds existed), the inter-peak speed was used.

The emission contribution of the specific vehicle categories has been verified and reported in detail in a another paper dealing with the impacts of using different vehicle emission factors on local emission inventories (Khreis et al., 2017b): 21% of all traffic NO_x came from petrol passenger cars, 26.5% from diesel passenger cars, 17.1% from light goods vehicles, 18.5% from heavy goods vehicles and 16.9% from buses and coaches.

2.4.3. ADMS-Urban set-up and runs

The ADMS-Urban model required input data on the modeling site and meteorological conditions. The inputs used in this model are given in Table S2 and are compared to the model's default values (Cambridge Environmental Research Consultants Ltd, 2010). The meteorological data was hourly sequential and was obtained from the Bingley Samos weather station, which was at a distance of 9.7 km west-north from the city center (Bradford City Hall) (metoffice.gov.uk, ND).

Road source emission rates from the 4500 available road links were entered into the ADMS-Urban model. The ADMS-Urban model only allowed for one road source emissions dataset from one period (for example, AM peak) to be entered directly in a single model run. As such, it was not possible to enter the 48-hour weekday and weekend estimated emission datasets to be modeled at once. Instead, the AM peak hour was the hour selected to be directly entered in the model's run and an additional modeling option specifying time varying emission factors was used (Cambridge Environmental Research Consultants Ltd, 2010). The time varying emissions represented the differing traffic flows and associated emissions across the different hours of an average weekday and the weekend (Fig. S3). During the dispersion simulations, the ADMS-Urban model used the provided time varying emission factors (Fig. S3) to multiply the entered AM peak hour emission rates at each road link by the appropriate factor, as specified for each hour.

The model was used to estimate annual 2009 average NO_x concentrations only. NO_2 concentrations were not directly modeled in ADMS-Urban, mainly because Ozone background concentration data, which are required to run the Chemical Reaction Scheme module (Cambridge Environmental Research Consultants Ltd, 2010), were not available for Bradford.

2.4.4. NOx background data

To account for air pollution concentrations originating from all sources *other* than road traffic, annual (2010) average background NO_x concentrations were added to the ADMS-Urban modeled NO_x estimates. These concentration values were obtained from a national modeling study by the UK Department for Environment, Food and Rural Affairs (DEFRA) on emissions sources like industry, rail, domestic and aircraft. The NO_x concentrations were spatially varying values, modeled at 1 km × 1 km grids (Fig. 2) (Department for Environment Food and Rural Affairs, 2016). The varying NO_x background concentrations were considered more realistic than using a constant background concentration (i.e. one value) across the whole city, as often used in other studies. In work reported elsewhere (Khreis et al., 2017a), we also validated the AD modeled NO_x estimates twice; once complementing the AD estimates with the varying NO_x background concentrations described above, and once complementing the AD estimates with a constant urban background concentration of 38.4 μg/m^3, as measured in the ESCAPE campaign (Table 1). Our results suggested that, overall, using the varying NO_x background concentrations resulted in better model performance, and as such, these varying estimates were used in our final models and analyses (Khreis et al., 2017a).

The varying NO_x background concentrations ranged from about 8.5 to 71 μg/m^3, with an average of 14.73 μg/m^3 (Fig. 2). These concentrations originated from the following sources: industry, domestic, aircraft, rail, point sources, rural sources and "others", as described in more detail in Department for Environment Food and Rural Affairs (2016) and as summarized in Table S3.

We excluded all the traffic sources from the final NO_x background concentrations used, to avoid any double counting of TRAP. The traffic sources excluded were motorways, trunk A roads, primary A roads and minor roads and cold starts, as detailed in Table S3. The exclusion of minor roads and cold starts, however, may result in a worse performance of the AD model as these sources were not explicitly included in the SATURN traffic network which was focused on main and strategic roads. As such, we further explored the impact of adding minor road and cold start concentrations to the AD estimates in a sensitivity analysis (Table S3).

2.4.5. NO_x to NO_2 conversion data

In this study, the final AD modeling estimates of NO_x concentrations were converted to NO_2 concentrations using the average NO_2/NO_x ratio of 0.60 (range = 0.39 to 0.75), as calculated from local ESCAPE's measurements in Bradford in the same year of analysis (2009) (Table 1 and Fig. 2). This average ratio was consistent with the average ratio of 0.59 calculated for the whole of the 36 European study areas in the ESCAPE project and with ratios in English cities like Manchester (0.58) and London/Oxford (0.58) (Cyrys et al., 2012).

2.4.6. Validation

The AD modeling estimates were validated against the ESCAPE measurements (Table 1). Excluding two influential outliers, a good correlation was found (R^2 = 0.60) and the validation was reported in detail elsewhere (Khreis et al., 2017a). However, the AD model underestimated NO_x at 36 out of the 41 ESCAPE sites by between 3.7% to 71.1%; or on average by 23.5% (12.3 μg/m^3 NO_x) across all ESCAPE sites (Fig. S4).

This under estimation, in big part, was likely due to under estimation in the traffic-related component as 15 of the 36 sites where an under estimation was recorded were traffic sites where NO_x was underestimated by about 32%, 20 were urban background sites, where NO_x was underestimated by 24% and one was a regional background site, where NO_x was underestimated by < 10%, *on average* (Table S4). The key reasons behind this under estimation were thought to be the unrealistically low vehicle emission factors, the underestimated SATURN traffic flows at smaller/lower-level roads, disregarding the impacts of road gradient on vehicle emissions and the impacts of street canyons and terrain on air pollution concentrations. Further, the exclusion of many minor roads in the Bradford's SATRUN traffic network may have led to under estimation of NO_x, but this latter point was specifically explored in sensitivity analysis.

2.5. Geographical resolution of analysis

2.5.1. Exposure estimates

Both the AD and LUR models were used to estimate NO_x and NO_2 at 46,452 specified output points (X, Y pairs) throughout the city, covering a box of ≈ 40 * 33 km. Each specified output point was the centroid of a 100 m × 100 m grid. At each 100 m × 100 m grid, the centroid's NO_x and NO_2 estimate, from the two models (AD and LUR), was applied to whole 100 m × 100 m grid and raster air pollution maps were developed with a resolution of 100 m × 100 m. This process was undertaken in ArcMap version 10.4 using the Point to Raster conversion tool.

2.5.2. Census data

In terms of census population, the "output area" was the lowest/smallest geographical level at which census data was provided (Fig. 2) (Office for National Statistics, 2016). This was the geographical level used to assign childhood population data (birth to 18 years old), exposure data, population attributable fraction and attributable number of asthma cases (see next).

The 2011 census data were used as these were considered more compatible with the 2009 exposure estimates than the 2001 census data; the only other dataset available. The characteristics of Bradford's output areas are shown in Table 2. There were 1528 output areas in which 143,472 children, aged 0 to 18 years old, lived.

2.5.3. Intersection between exposure and census maps and excluded data

Each output area was intersected with the raster air pollution maps, produced by the AD and the LUR models and complemented with the background NO_x concentrations. The 100 m × 100 m raster cell values contained within each census output area were averaged, resulting in one average annual air pollution estimate at each output area. This process was undertaken Geospatial Modelling Environment suite version 0.7.4.0. using the "isectpolyrst" (intersect polygons with raster) tool.

There were 156 output areas where there was no intersection between the raster air pollution maps and the output areas' boundaries (Fig. 2). The reason behind this was that the air pollution maps, from both the AD and the LUR models, covered a lesser extent than the census maps, as no traffic and other necessary GIS-based predictor variables were available for the whole area that was covered by the census. These 156 output areas, where 10,089 children, or ≈7%, of all children lived, were excluded from the analysis. This exclusion underestimates the burden of childhood asthma attributed to air pollution in Bradford but does not affect the percentage of attributable cases reported.

2.6. Baseline childhood asthma incidence rates

The incidence rate of asthma in children from birth to 18 years old *in Bradford* was not found in the peer reviewed or the grey literature. As such, the national incidence rate of childhood asthma (birth to 18 years old), as reported by Punekar and Sheikh (2009) in the UK, was used instead. This equaled 137 clinician-diagnosed asthma cases per 10,000 person-years, by the age of 18 years, as identified for 43,473 children indexed in the General Practice Research Database.

We, however, found another Bradford specific publication, where Mebrahtu et al. (2015) identified asthma, based on diagnostic and prescription codes in the primary care database, for 13,734 children ages 0 to 7 years old, participating in the Born in Bradford cohort (Wright et al., 2013). Using the data reported in this paper, we calculated an asthma incidence rate of 123 per 10,000 person-years, by the age of 7 years. However, and as the authors note, this figure is likely to be conservative due to diagnosis difficulties in this younger age group (Mebrahtu et al., 2015).Bradford is indeed known to have childhood asthma rates higher than national and regional averages (Yorkshire and Humber Public Health Observatory, 2012). Hence, Mebrahtu et al. (2015) also established another outcome termed "wheezing disorders based on treatment" which identifies the existence of at least two drug prescriptions indicated for the treatment of asthma, a minimum of 1 week, and a maximum of 12 months apart. Based on this definition, an asthma incidence rate of 442 per 10,000 person-years, by the age of 7 years, was calculated.

Both incidence rates calculated from data reported in Mebrahtu et al. (2015) were used in sensitivity analyses to explore the influence of the background incidence rates in the HIA assessment (Künzli, 2002).

Table 2
Characteristics of Bradford's census output areas.

Number of total output areas	1528 output areas
Output areas excluded	156
Total number of children in all output areas (birth–18 y.o.)	143,472 children
Total number of children in excluded output areas (birth–18 y.o.)	10,089 children
Average number of children in all output areas (birth–18 y.o.)	94 children
Minimum number of children in an output area (birth–18 y.o.)	3 children
Maximum number of children in an output area (birth–18 y.o.)	468 children
Percentage of children ≤6 years old (pre-school age) in all output areas	44.7%
Percentage of children > 6 years old (school age) in all output areas	55.3%
Average area of all output areas (m^2)	239,802
Minimum area of an output area (m^2)	3817
Maximum area of an output area (m^2)	15,395,650

2.7. Exposure-response functions

Exposure-response functions for the association between exposure to air pollution and the subsequent development of childhood asthma from birth to 18 years old were extracted from random effects meta-analyses undertaken by Khreis et al. (2017c). The NO_2 exposure-response function was based on 20 studies and equaled 1.05 (95% CI, 1.02, 1.07), per 4 μg/m^3 NO_2. The NO_x exposure-response function was based on 7 studies and equaled 1.48 (95% CI, 0.89, 2.45), per 30 μg/m^3 NO_x. More information on the derivation of these exposure-response functions can be found in the original paper (Khreis et al., 2017c).

It is worth noting here that the studies included in the underlying meta-analyses *did not* adjust for co-pollutants. As such, the numbers of asthma cases attributable to NO_2 and the numbers of asthma cases attributable to NO_x we estimate should *not* be added up, but instead should be viewed as independent estimates of the potential impact of traffic-related air pollutants on childhood asthma burden.

2.8. Estimation of population attributable fraction and attributable number of cases

Using the exposure-response function above, the risk estimates for asthma development were scaled to the difference in exposure level between the counterfactual (no exposure) and the reference (current exposure) scenarios. To scale a risk estimate to the exposure difference between the reference and the counterfactual scenarios, standard methods were used (Mueller et al., 2017), where:

$$RR_{exposure\,difference} = e^{\left(\left(\frac{\ln RR}{E_{RR\,unit}}\right) \times E_{exposure\,difference}\right)}$$

where *RR* is the relative risk obtained from the exposure-response function;

E_{RR_unit} is the exposure unit that corresponds to the RR obtained from the exposure-response function;

$E_{exposure\_difference}$ is the difference in the exposure level between the counterfactual scenario and the reference scenario;

$RR_{exposure\_difference}$ is the scaled relative risk that corresponds to the difference in exposure level between the counterfactual (no exposure) and reference (current exposure) scenario.

The population attributable fraction (PAF) was then calculated, as below. The PAF defines the proportional reduction in morbidity that would occur if the exposure to air pollution was reduced to the counterfactual (no exposure) scenario:

$$PAF = \frac{\sum_{i=1}^{n} P(RR_{exposure\,difference} - 1)}{\sum_{i=1}^{n} P(RR_{exposure\,difference} - 1) + 1}$$

where P is the proportion of the exposed population;

$RR_{exposure\_difference}$ is the previously scaled RR that corresponds to the difference in exposure level between the counterfactual (no exposure) and reference (current exposure) scenario.

n is the number of exposure levels.

Finally, the number of childhood asthma cases attributable to the excess exposure compared to the counterfactual (no exposure) scenario was calculated as follows:

Attributable number of asthma cases
= PAF∗expected asthma cases due to all causes

where

Expected asthma cases due to all causes = childhood population
∗baseline childhood asthma incidence rate

3. Results

3.1. NO_2 and NO_x exposures

The annual average census tract levels of NO_2 and NO_x estimated with the AD model were 15.41 and 25.68 μg/m^3, respectively. On average, 2.75 μg/m^3 NO_2 and 4.59 μg/m^3 NO_x were specifically contributed by traffic. The annual average census tract levels of NO_2 and NO_x estimated with the LUR models were higher and equaled 21.93 and 35.60 μg/m^3, respectively. Table 3 shows the distribution of NO_2 and NO_x exposures across the census tracts, from the two exposure models.

3.2. Attributable number of cases

Using the full-chain HIA model, we estimated that an average of 321 (range = 139, 428) childhood asthma cases per year, or 18% of all childhood asthma cases in Bradford, are attributable to NO_2 (Table 4). For NO_x, we estimated an average of 530 (range = −201, 976) attributable childhood asthma cases per year, or 29% of all childhood asthma cases in Bradford. The traffic component of this air pollution was estimated to be responsible for a small percentage of the overall air pollution attributable childhood asthma burden: 62 cases or 3% of all childhood asthma cases were attributable to traffic-NO_2 whilst 109 cases or 6% of all childhood asthma cases were attributable to traffic-NO_x (Table 4).

Using the LUR HIA model, we estimated that an average of 435 (range = 191, 573) childhood asthma cases per year, or 24% of all childhood asthma cases in Bradford, were attributable to NO_2. For NO_x, we estimated an average of 687 (range = −279, 1196) attributable asthma cases per year, or 38% of all childhood asthma cases in Bradford. The contribution of traffic to this burden was not quantifiable (Table 4).

Table 3
Annual average census tract NO_2 and NO_x levels from the two exposure models: AD and LUR models.

Statistic	Minimum	1st quartile	Median	Mean	3rd quartile	Maximum
NO_2 (AD)	6.45	11.34	14.72	15.41	17.98	45.62
NO_2 (LUR)	12.42	20.15	21.63	21.93	23.70	37.09
NO_x (AD)	10.75	18.90	24.53	25.68	29.97	76.03
NO_x (LUR)	0.00	31.29	35.22	35.60	40.28	73.32

3.3. Sensitivity analyses

3.3.1. Influence of adding minor road and cold start concentrations

In our first sensitivity analysis, we explored the impact of adding minor roads and cold start concentrations (Table S3) to the AD estimates. The exclusion of minor roads (and cold starts) from the adopted SATURN traffic network was believed to be one reason behind the AD under estimation of NO_x (Table S4), and this was investigated further in this analysis.

Adding minor roads and cold start concentrations to the AD estimates did not improve the validation metric (R^2) and left it almost unchanged as compared to the main analysis (Khreis et al., 2017a). However, the under estimation at the ESCAPE validation sites, as recorded in Table S4, was notably lessened (Table S5), suggesting that the addition of minor roads and colds starts to the SATURN network may improve the model's performance, whilst their exclusion may be an important reason behind the model's under estimation.

Table S5 shows that when minor road and cold start concentrations were added to the AD estimates, only 21, instead of 36 sites (Table S4), had a NO_x under estimation. Of those, 10 sites (instead of 15 sites as in the main analysis) were traffic sites where NO_x was underestimated by about 31%, on average, and 11 sites (instead of 20 sites as in the main analysis) were urban background sites, where NO_x was underestimated by almost 12%, on average. Across all the ESCAPE sites combined, NO_x estimates from the AD model with minor road and cold start concentrations were underestimated by 4.9% or 4.7 μg/m^3, on average, as compared to 23.5% or 12.3 μg/m^3, on average, in the main analysis (without minor road and cold start concentrations).

Fig. S5 and Table S6 further show the underlying data and the linear regression between the measured and the modeled NO_x (μg/m^3), with the inclusion of minor road and cold start concentrations, at the 41 ESCAPE sites. As shown in Fig. S5 and Table S6, the largest deviations between measured and modeled NO_x is generally apparent at the measurement points where NO_x was highest.

Based on these different results, we rerun the HIA using the AD models' NO_2 and NO_x exposures, with minor road and cold start concentrations added. The results are reported in Table 5 and show that that the addition of minor road and cold start concentrations almost doubled the asthma cases attributable to traffic, bringing the burden of disease from 3% to 7% for traffic-NO_2 and from 6% to 12% for traffic-NO_x. Interestingly, the inclusion of minor roads and cold starts also brought the estimates of the two exposure models, the AD and LUR models, closer.

Table 4
Estimated annual attributable asthma cases in Bradford using the AD model (first 2 rows) and the LUR model (last 2 rows) (using national baseline asthma incidence rate = 137 per 10,000 person-years).

Model	Pollutant	Attributable cases	Attributable cases lower CI	Attributable cases upper CI	Percentage of all cases	Attributable cases to traffic
Full-chain AD	NO_2	321	139	428	18%	62 (3%)
Full-chain AD	NO_x	530	−201	976	29%	109 (6%)
LUR	NO_2	435	191	573	24%	NA
LUR	NO_x	687	−279	1196	38%	NA

Table 5
Estimated annual attributable asthma cases in Bradford using the AD model *when complemented by minor road and cold start concentrations* (using national baseline asthma incidence rate = 137 per 10,000 person-years).

Model	Pollutant	Attributable cases	Attributable cases lower CI	Attributable cases upper CI	Percentage of all cases	Attributable cases to traffic
Full-chain AD	NO_2	394	173	520	22%	128 (7%)
Full-chain AD	NO_x	638	−256	1125	35%	219 (12%)

3.3.2. Influence of baseline childhood asthma incidence rates

Table S6 shows the asthma cases attributable to NO_x and NO_2, from the two available exposure models (AD and LUR models), as estimated using two different baseline childhood asthma incidence rates calculated from Mebrahtu et al. (2015). Compared to the main analyses (Table 4), the number of the estimated attributable asthma cases drops by approximately 10% when using the first lower asthma incidence rate (123 per 10,000 person-years) whilst it increases by up to 223% when using the second higher asthma incidence rate (442 per 10,000 person-years). The attributable percentage of all cases remains the same but the differences in the absolute number of attributable asthma cases, and hence the reported burden of asthma, is significant.

3.4. Further estimation of the contribution of traffic

As the contribution of traffic to the percentage of attributable asthma cases in the AD BoD model was small and smaller than we expected, we further explored the plausibility of these results utilizing the ESCAPE's NO_x measurements; which were directly comparable to the AD model's NO_x estimates, using a few different scenarios (Table 6).

As overviewed in the methods and shown in Table S4, NO_x estimates from the AD model were underestimated by 23.5% or 12.3 μg/m^3, on average. To a large extent, this under estimation may be due to under estimation in the contribution of traffic, which, on average, accounted for 2.5 μg/m^3 or 13% of all NO_x in the final AD model (without the minor roads and cold starts) (Table 6, row 3).

Although under estimation of background NO_x in some areas cannot be excluded, this is not addressed further in the following analysis.

Based on the difference between the average urban background and average traffic sites' NO_x recorded in the ESCAPE campaign, traffic is likely to contribute to up to 35% of (or 21 μg/m^3) ambient NO_x (Table 6, row 1). Based on this contribution, and for simplicity assuming a linear relation between the percentage of traffic NO_x and asthma cases attributable to traffic NO_x, 240 (i.e. 35% ∗ 687) out of the total 687 asthma cases attributable to the LUR's NO_x, may be attributed to traffic-NO_x. This represents 13% of all asthma cases.

Table 6, row 2, presents another plausible estimation. As the ESCAPE design allowed urban background sites to be within 50 m of roads with < 3000 vehicles/day (Table 1), the ESCAPE's average urban background NO_x may also include a traffic-related component and therefore can be underestimating the traffic component/contribution calculated above (Table 6, row 1). Therefore, we re-did the estimation using the average urban background NO_x value of 17 μg/m^3 from the NO_x background maps which also went into the main AD model and excluded all traffic sources (Table S3). Using this urban background NO_x value and the ESCAPE's average NO_x from the traffic *and* the urban background sites, traffic was estimated to contribute 63% of (or 29.4 μg/m^3) NO_x. As above and for simplicity, assuming a linear relation between the percentage of traffic NO_x and the asthma cases attributable to traffic NO_x, 433 (i.e. 63% ∗ 687) out of the total 687 asthma cases attributable to the LUR's NO_x, may be to traffic-NO_x. This represents 24% of all asthma cases in Bradford.

These calculations are only indicative of what the contribution of traffic to the percentage of attributable asthma cases can realistically be, based on the ratios between urban background and traffic NO_x levels in the study area. More work is clearly needed to address the underlying reasons behind the AD (and the LUR) models under estimation, and therefore improve the exposure and the associated burden of disease estimates.

4. Discussion

4.1. Summary

This study provides the first full-chain HIA of TRAP and childhood asthma; using pollutant-specific exposure estimates (rather than exposure surrogates) and pollutant-specific meta-analytic exposure-response functions, whilst considering the full-chain of events from exposure source, through pathways to population health impacts.

The results indicate that between 18% to 38% of all childhood asthma cases in Bradford may be attributable to air pollution (Table 4), whilst 7% and 12% may be specifically attributable to traffic-NO_2 and traffic-NO_x, respectively (Table 5). The results of the full-chain model presented here are, however, likely to underestimate the real impact of air pollution, especially the impacts of its traffic-related component, and especially at the locations where TRAP is highest. We explored this further by adjusting the traffic-related component modeled by the AD model to the ESCAPE background/traffic measurement ratios in the same study area and showed that up to 24% of all childhood asthma cases in Bradford may be specifically attributable to air pollution from traffic (Table 6). We also showed that the exclusion of minor roads (and cold starts) from the SATURN traffic network may be one important reason for the documented under estimation in the AD model exposure estimates and associated health impacts. Rerunning the full-chain HIA model using the AD NO_2 and NO_x estimates, with minor road and cold start concentrations added, the results from the LUR and AD became very similar (Tables 4 and 5).

4.2. Addition to the literature

This study adds to very scarce literature documenting the impact of TRAP on the intra-urban burden of disease of childhood asthma. Further, it addresses some limitations in past research and sheds new light on crucial areas that require further work.

Table 6
Average urban background and traffic NO_x concentrations ($\mu g/m^3$) from the different datasets/models and TRAP attributable asthma cases.

Row number Scenario description	Urban background dataset Traffic dataset	Average NO_x at urban background sites ($\mu g/m^3$)	Average NO_x at traffic sites ($\mu g/m^3$)	Average traffic contribution ($\mu g/m^3$) (= Traffic NO_x – Urban background NO_x)	Average percentage of traffic contribution (Traffic contribution / Traffic NO_x)	Overall NO_x attributable asthma cases	Assumed traffic-related NOx attributable asthma cases, based on linear relations (% traffic contribution * overall attributable cases)
Row 1	ESCAPE measurements	38.4	59.4	21	35%	687 (38%) using LUR	240 (13%) (=35% * 687)
Using only ESCAPE measurements	ESCAPE measurements						
Row 2	DEFRA map	17	46.4	29.4	63%	687 (38%) using LUR	433 (24%) (=63% * 687)
Using ESCAPE measurements at traffic and urban background sites and DEFRA background map	ESCAPE measurements						
Row 3	DEFRA map	17	19.5	2.5	13%	530 (29%) using COPERT-based dispersion model	109 (6%)
Using COPERT-based dispersion modeling including DEFRA background map	COPERT-based dispersion model (snapped)						

The previously published studies (Perez et al., 2009; Perez et al., 2013; Künzli et al., 2008; Perez et al., 2012), despite pioneering in studying asthma as an outcome in TRAP burden of disease assessment, had limitations which we addressed in the present work. First, previous studies relied on residential proximity to major roadways as the TRAP exposure metric. Proximity to major roadways is a crude exposure measure which cannot provide information on the impacts of specific sources and actual pollutants and lacks consideration of significant local emissions and dispersion processes that might have great influence on air pollution levels and subsequent human exposures (Beevers et al., 2013; Khreis and Nieuwenhuijsen, 2017). Indeed, proximity models were previously shown to result in exposure misclassification, as compared to LUR models (Ryan et al., 2007).

Second, the exposure-response function used in previous studies was sourced from an individual study rather than a meta-analysis (i.e. a pooled estimate). This may be argued as preferable in the Southern Californian studies (Künzli et al., 2008; Perez et al., 2009; Perez et al., 2012), where the use of a location-specific exposure-response function to calculate a location-specific attributable fraction is appropriate. However, in the European-wide study, the use of an individual U.S. study's exposure-response function for a European population is less appropriate (Perez et al., 2013). The use of the single study's exposure-response estimate also resulted in large statistical uncertainty around the estimated burden, but at the time, there were no meta-analytical exposure-response functions that could be used.

Third, uncertainties in the health impact estimates due to uncertainties in the exposure assessments and the underlying baseline childhood asthma incidence rates have not been examined. These are important issues (Künzli, 2002; Khreis et al., 2017c), especially in the context of childhood asthma, but are generally issues that are underexplored in the literature.

Finally, these previous HIA studies examined prevalent asthma rather than incident asthma and therefore did not give indication of how many cases could be avoided, if for example TRAP was reduced or eliminated.

In this study, we used highly resolved modeled estimates of NO_2 and NO_x for the HIA. We specifically explored the contribution of traffic to the overall levels of these pollutants and associated health impacts. Furthermore, we used newly generated exposure-response functions combining information from studies specifically focused on TRAP exposures as a risk factor for the development of subsequent childhood asthma, the strengths and applicability of which have been described in full elsewhere (Khreis et al., 2017c). We used asthma incidence rather than prevalence rates and gave an indication of the impacts of:

1. using national versus local baseline childhood asthma incidence rates with differing underlying asthma definitions;
2. using exposure estimates from two different and commonly used exposure models: a LUR versus an AD model;
3. including versus excluding minor road and cold start concentrations in the exposure and HIA assessment.

4.3. Strengths

This study has strengths and limitations as follows.

This is one of the very few studies undertaking full-chain HIA assessment that considers the full-chain from exposure source (vehicle emissions), through pathways (air pollution and exposure levels) to health impacts (development of childhood asthma) (Nieuwenhuijsen et al., 2017). Such assessment is important for policy decision making as it gives indication of the contribution of different sources and can inform effective mitigation policies. In this work, an explicit quantification of burden of disease attributable to the traffic component of air pollution was given, as the use of the full-chain model allowed to specifically attribute the estimated health impacts to traffic, and even to minor roads' traffic and associated cold starts in the sensitivity analysis.

Further, this work adds to the literature by exploring the differences between estimated health impacts associated with AD models' and LUR models' exposure estimates. The attributable burden resulting from the use of the LUR models was 6% to 9% higher than that estimated with the full-chain model, in the main analyses (Table 4). However, when the AD model was complemented by minor road and cold start concentrations, the burden resulting from the use of the LUR models was only 2% to 3% higher than that estimated with the AD model (Table 5). Considering the fundamental differences between these two models (Khreis and Nieuwenhuijsen, 2017), this result could be viewed as a very good agreement. We believe this agreement may be further improved by addressing the overall under estimation of NO_x by the AD models. The relatively good agreement between these two models is in line with the scarce literature showing similar HIA estimates when using LUR and AD models' exposure estimates (Rojas-Rueda et al., 2012).

Another key strength of the current study is the use of meta-analytical exposure-response functions to estimate the attributable health impacts (Khreis et al., 2017c). Meta-analytical exposure-response functions are recommended in burden of disease and health impact assessments (Nieuwenhuijsen et al., 2017), are more precise than single study estimates (Perez et al., 2009) and are considered more generalizable and arguably preferable in this study area where no local exposure-response functions for Bradford's population are currently available. Further, the use of the meta-analytical exposure-response functions derived in this study allowed exploring the specific impacts of different pollutants, something which was restricted by the lack of pollutant-specific exposure-response functions in the past.

Both NO_x and NO_2 here are perhaps best viewed as signatures of TRAP and interpreting the estimated impacts as a certain pollutant's impact is not possible as NO_x and NO_2 are highly correlated with other pollutants, and each other, in traffic exhaust (Beckerman et al., 2008). Further, whilst the studies included in the underlying meta-analysis controlled for key potential confounders, an important limitation was the lack of adjustment for co-pollutants (Khreis et al., 2017c), which makes a distinction of pollutant-specific effects not possible. As such, the numbers of cases attributable to NO_2 and NO_x we estimate in this study should *not* be added up, but instead viewed as independent estimates of the potential impact of TRAP on childhood asthma. We are in the process of repeating this analysis using other pollutants including particulate matter and black carbon, which should shed more light on the importance of pollutant selection in similar BoD assessments. A final addition of this work related to the sensitivity analyses conducted to demonstrate the impact that different baseline asthma incidence rates have on the burden of disease estimates. This issue has not been explored in previous literature and, as shown here, the impacts of the baseline incidence rates were significant. These impacts are particularly relevant as underlying asthma incidence rates are uncertain, partly due to difficulties in asthma diagnosis and assessment, in addition to the poor consensus on the definition of asthma (Khreis et al., 2017c; van Schayck and Boudewijns, 2017). The relevance of these differences to policy decision making would be significant if the estimated burden of disease was transformed in monetary values to inform the health benefit-risk tradeoff of public policies. Similar work has been reported in Lomas et al. (2016).

4.4. Limitations

This study also has its limitations. The key limitation of this work is that air pollution due to traffic is likely to have been underestimated and therefore the contribution of air pollution due to traffic to the attributable asthma cases is likely underestimated as well. We were, however, fortunate to have the ESCAPE measurements and modeled data for validation and adjustment. We further rerun the analyses complementing the AD estimates with minor roads and cold start concentrations and give insight into the potential range of impacts, which we still believe is underestimated.

The under estimation we report is likely due to the unrealistically low vehicle emission factors from the COPERT model, the underestimated SATURN traffic flows at smaller/lower-level roads, disregarding the impacts of road gradient on vehicle emissions and the impacts of street canyons and influential terrain on air pollution concentrations. Further work in these areas is needed to improve exposure and the associated burden of disease estimates.

Few if any peer-reviewed studies have specifically reported on the contribution of traffic to the overall NO_2/NO_x levels. Yet, the under estimation in the AD model is not new and many studies in the literature document similar trends, showing that ADMS-Urban can underestimate NO_x concentrations by up to 59% (Briant et al., 2013; De Hoogh et al., 2014; Peace et al., 2004).

In the context of the literature and relying on measurements from ESCAPE, we did some further exploration of what the impacts of TRAP, in particular, may be, if these levels were not under estimated. We showed that the impacts could be considerable, taking the estimates from 12% (Table 5) up to 24% (Table 6). This exercise was clearly hypothetical and did not consider the different population-weighted exposures from the different models, but it is likely to give a more realistic picture of the impacts of TRAP exposures on the burden of childhood asthma.

Another limitation relates to the use of exposure estimates averaged over the census tract level. Generally, HIA assessments draw on exposure proxies (for example, census tracts average exposure) that cannot fully capture the actual exposure variability in the population (Mueller, 2017). Exposure variability may be due to the population mobility as it is unknown whether the population studied spend most of their time in their residential census tracts or elsewhere, or due to the high variability in air pollution levels within the same census tracts themselves. This may further lead to exposure misclassification (Nieuwenhuijsen, 2015) and distort estimated health impacts.

Finally, NO_2 was generated by conversion of NO_x levels resulting from the AD model. This is a simplistic procedure which may result in further exposure misclassification as the spatial variability of NO_2 levels due to spatial variability of primary NO_2 sources is concealed.

5. Conclusions

This study provides the first full-chain HIA of TRAP and childhood asthma; using meta-analytic and pollutant-specific exposure-response functions and considering the full-chain from exposure source, through pathways to population health impacts. The burden of childhood asthma attributable to air pollution is poorly documented in the literature. We add to this evidence base demonstrating that between 18% to 38% of all childhood asthma cases in Bradford may be associated with air pollution. We show that this magnitude depends on the pollutant and the exposure assessment method selected. The results of the full-chain model were likely to be an under estimation the impact of air pollution, especially the impacts of TRAP, which might have been significantly underestimated. This under estimation is mainly due to the combination of low vehicle emission factors, not including road gradients and influential terrain elements, overestimated speeds and the exclusion of many minor roads in Bradford. Further work to improve the accuracy and real-world representation of traffic, emission and AD models is needed and will further refine the burden of disease estimates and their utility in policy and decision making.

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Competing financial interests

The authors declare they have no competing interests.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envint.2018.03.008.

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