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The influence of air pollution exposure on the short- and long-term health benefits associated with active mobility: A systematic review

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Abstract

Active mobility (AM), defined as walking and cycling for transportation, can improve health through increasing regular physical activity. However, these health improvements could be outweighed by harm from inhaling traffic-related air pollutants during AM participation. The interaction of AM and air pollutants on health is complex physiologically, manifesting as acute changes in health indicators that may lead to poor long-term health consequences. The aim of this study was to systematically review the current evidence of effect modification by air pollution (AP) on associations between AM and health indicators. Studies were included if they examined associations between AM and health indicators being modified by AP or, conversely, associations between AP and health indicators being modified by AM. Thirty-three studies met eligibility criteria. The main AP indicators studied were particulate matter, ultrafine particles, and nitrogen oxides. Most health indicators studied were grouped into cardiovascular and respiratory indicators. There is evidence of a reduction by AP, mainly ultrafine particles and $PM_{2.5}$, in the short-term health benefits of AM. Multiple studies suggest that long-term health benefits of AM are not negatively associated with levels of the single traffic-related pollutant NO_2. However, other studies reveal reduced long-term health benefits of AM in areas affected by high levels of pollutant mixtures. We recommend that future studies adopt consistent and rigorous study designs and include reporting of interaction testing, to advance understanding of the complex relationships between AM, AP, and health indicators.

Keywords: traffic-related air pollution, active mobility, short-term exposure, long-term exposure, effect modification, health outcomes

Introduction

Active mobility (AM), defined as walking or cycling for transportation, contributes to overall daily physical activity levels (Audrey et al., 2014) and offers numerous short- and long-term health benefits. Short-term benefits include lowered blood pressure and improved lung function, cardiorespiratory fitness and body composition (Matt et al., 2016; Nordengen et al., 2019; Peruzzi et al., 2020). Long-term benefits include lowered risks of cardiovascular disease, some types of cancer, type 2 diabetes and all-cause mortality (Celis-Morales et al., 2017; Dinu et al., 2019; Fan et al., 2019; Kelly et al., 2014). AM also has environmental benefits, including reducing carbon emissions and the broader negative whole-of-life cycle impacts of petrol combustion (Brand et al., 2021; de Nazelle et al., 2010; Frank et al., 2010; Scheepers et al., 2014).

People using AM in traffic micro-environments can experience a higher uptake of air pollution (AP) than people using other commuting modes, even after accounting for AM-related elevated inhalation rates (Cepeda et al., 2017) because they are unable to physically separate themselves from traffic emissions. Although commuters may spend a small amount of their day in transportation, their exposure to traffic-related AP can be high, especially at peak times and in congested (high-traffic) areas (Godec et al., 2021; Perez et al., 2013). Research suggests that at the individual level, a high intake of AP while performing AM in traffic could off-set the health benefits of AM. In fact, both respiratory and cardiovascular short-term indicators associated with AM have been negatively impacted by UFP, PM2.5 and PM10 (Cole-Hunter et al., 2016; Kubesch et al., 2015a; Kubesch et al., 2015b; Matt et al., 2016).

Ambient AP is the leading environmental risk factor for health. It is generated mainly from combustion emissions from traffic, household, and industry. The major air pollutants of concern, which include particulate matter (PM), carbon monoxide (CO), and oxides of nitrogen (NO_x/NO_2), vary in their risks to human health (Curtis et al., 2006). The size of PM affects their toxicity potential; smaller (such as ultrafine, UFP) particles can penetrate deeper into the respiratory system and transport a higher amount of adsorbed pollutants due to their relatively larger surface area, compared to larger particles (Deng et al., 2019; Kwon et al., 2020). Fine PM with an aerodynamic diameter less than 2.5 µm ($PM_{2.5}$) is the sixth leading risk factor for mortality globally (Murray et al., 2020). Different methods have yielded annual estimates from 4.1 to 8.9 million deaths worldwide attributed to ambient long-term exposure to $PM_{2.5}$ (Burnett et al., 2018; Cohen et al., 2017; Murray et al., 2020). The short-term negative effects of $PM_{2.5}$ include respiratory, cardiovascular and metabolic diseases and adverse reproductive outcomes (Brunekreef et al., 2009; Eze et al., 2015; Sarkodie et al., 2019; Stieb et al., 2009). CO and NO_2 have adverse effects on respiratory and cardiovascular health, whereas CO has been linked with congenital cardiac defects and NO_2 with cancer (Curtis et al., 2006). Although it is broadly agreed that there is no safe level of AP, the World Health Organization (2021) has released new guidelines for reducing the major AP concentration levels as new evidence suggests increased health risks at even low AP levels.

There is evidence that promotion of AM within cities benefits both the environment and human health by reducing vehicle emissions and increasing physical activity levels (Nieuwenhuijsen, 2016). Although the independent associations between health indicators and both AP and AM have been extensively examined, no systematic review has explored the joint effects of AP and AM on health indicators. One mapping review and three systematic reviews synthesized the joint effects of AP and physical activity on a range of health indicators (DeFlorio-Barker et al., 2020; Madureira et al., 2019; Qin et al., 2019; Tainio et al., 2021). The reviews included studies of physical activity of varying types and intensities, including walking and cycling for leisure or transport. As these reviews did not aim to address the specific influence of AP on the health benefits of AM, the literature on whether the health benefits of AM are modified by AP has not been summarized. The aim of this study was to synthesize the evidence of effect modification by single air pollutants and high-versus-low air pollution sites on the short- and long-term associations between walking and cycling for transportation and health indicators.

Methods

This systematic review was registered on PROSPERO (date: 12th June, 2020; ID: CRD42020156720), the international database of prospective systematic reviews. The review was conducted according to the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) (Moher et al., 2009).

Study selection criteria

Studies were included if they examined associations between AM and one or more health indicators and the modification effect of AP, or if they examined associations between AP and one or more health indicators and the modification effect of AM. To be included, studies must have been conducted with generally healthy adult populations (aged ≥18 years), have included at least one level of AP in an outdoor urban environment under real-world conditions (e.g., non-filtered and non-concentrated ambient air) and have used an observational or an experimental design. Studies were excluded if they examined only populations at-risk or with illness; were conducted indoors only, such as in a laboratory; analyzed genetic pathways; used animal or cell-based experimental models; or required participants to engage in walking or cycling at intensities atypical for AM (e.g., high-intensity, maximal, or incremental intensities). Articles written either in English or Spanish were eligible.

Search strategy

We conducted literature searches in four electronic databases known for their extensive coverage of public health and environmental science areas: Web of Science, Scopus, Embase and PubMed. The overall search process is detailed in a PRISMA flowchart (Figure 1). We used consistent keywords across databases, and the search strategy was adapted according to each database. A comprehensive list of keywords was divided into two groups. The first group included general concepts of AP exposure and multiple combinations of air pollutants. The second group included combinations of AM keywords including walking and cycling. Keywords within each group were combined using the Boolean operator “OR” and resulting searches were combined using “AND” to include references containing keywords from both groups. Our full search strategy is included in Supplement A Tables S2-S6. We searched for articles published since inception of each database until 28 September, 2021.

The first author (DCP) downloaded and managed search results using Endnote X9.2 (Clarivate Analytics, Philadelphia, PA, 2018). First, DCP manually reviewed the titles of the selected articles. Then, he employed smart groups, Endnote’s function that allows for searching a specific topic among references, to quickly identify references containing exclusion-criteria-relevant keywords in the title (see Supplement A Tables S2-S5 for keywords). When any of these keywords were in a title, he examined the abstract to confirm that the reference was to be excluded. Next, DCP and a second screener (either a post-doctoral research assistant or the third author [MH]) independently screened the titles and abstracts of the remaining articles against inclusion and exclusion criteria. The second author [TCH] was consulted for resolving general uncertainty in eligibility, and the last author [KCH] compared the list of articles that each of the two screeners suggested should be included in the review. Any discrepancies in this suggestion were solved through discussion with the two screeners. DCP then downloaded the full texts of the final pool of included articles, and KCH reviewed a random 10% of these articles to verify them against the inclusion and exclusion criteria. Finally, DCP examined the reference lists of the included articles to identify articles to screen for potential inclusion in the review.

Data extraction and synthesis

An electronic data extraction form was designed in Epidat v4.6.0.0 (The EpiData Association, Odense, Denmark) to collect results and methodological information from the included references: author, year, location, population details, epidemiological study design, sample characteristics, AM measures, AP measures, health indicators, and interaction findings.

Data synthesis was performed narratively using summary tables. For ease of comparison, a novel exposure contrast metric was calculated per health indicator as the relative difference in the $PM_{2.5}$ concentration between the lowest and the highest AP sites. We used $PM_{2.5}$ as the reference because this pollutant was widely examined across studies and has the most weight of evidence for health impacts.

Effect modification assessment

We grouped studies into three categories (Group A, B, and C) based on the analytical approaches that authors used to report effect modification. In Group A studies, the presence or absence of effect modification was determined by the p-value of an interaction term between AM and AP variables, therefore providing direct evidence of effect modification. When the interaction term was statistically significant ($p<0.05$), the association between AM and a particular health outcome was considered to be modified by AP exposure. Therefore, we use the term “significant” throughout this document to refer to statistical significance of an original finding, which we determine as a p-value less than 0.05. Group B studies reported whether the effects of AP exposure on health indicators statistically differed between or within sites of low and high AP. Group C studies reported whether associations between single pollutants and health indicators differed between people using AM and people using other commuting modes. Findings from Group B and Group C studies, therefore, indirectly suggested effect modification by AP exposure.

AM can be intentionally simulated for research purposes under specific traffic-related air pollution (TRAP) scenarios. Group A and Group B studies were designed to emulate AM in real-world TRAP exposure environments, including scripted and staged exercise studies. In summary, these studies can be defined as:

- Unscripted study: Participants walk or cycle on their usual routes to go to and from places in real-world conditions.
- Scripted study: Participants walk or cycle, emulating AM, on hypothesis-driven routes commonly used for AM; usually these routes are chosen by the researchers because they provide either low- or high-TRAP exposure.
- Staged exercise study: Participants follow a protocol on a stationary bicycle that combines periods of moderate-intensity cycling and periods of rest, emulating AM. Both active and rest periods are performed in outdoor areas of both low- and high-TRAP exposure.

Risk of bias assessment

We conducted a risk of bias (RoB) assessment of the included studies following guidelines of the Handbook for Conducting Systematic Reviews for Health Effects Evaluations (Office of Health Assessment and Translation [OHAT], 2019). The OHAT tool assesses the risk of selection, confounding, attrition/exclusion, detection/measurement, reporting, and 'other' biases to internal validity in observational and experimental studies. For our purposes, the detection/measurement criterion was split into measurement of AP, AM, and health indicators to examine each of these separately. For each type of bias, a study receives a rating of 'definitively low RoB'; 'probably low RoB'; 'probably high RoB', which includes studies for which insufficient information is provided to make a determination; and 'definitely high RoB'. Overall scores are not constructed for individual studies. The first and last author (DCP and KCH) used OHAT to independently rate each study, and the second and third authors (TCH and MH) contributed to the resolution of rating disagreements. We acknowledge that directly assessing effect modification by AP was not the purpose of many included studies; therefore, detection of RoB in this review reflected the purpose of this review but not necessarily the aims of the included studies (details in Supplement B).

Results

Description of included studies

Our literature search identified 5725 articles (Figure 1). After 2395 duplicates were removed, titles and abstracts of 3330 articles were independently screened by the two screeners. This process yielded 156 potential articles for inclusion. After review of the full texts of these articles, 28 articles were deemed eligible. From the reference lists of these articles, an additional five articles were found to meet eligibility criteria. All 33 eligible articles, summarized in Table 1, were written in English.

Of the eligible studies, 18 used a crossover design (55%); six were cross-sectional (18%); eight were cohort (24%); and one was quasi-experimental (3%). Most studies were conducted in European countries (61%). Four (12%) were conducted in the USA, three in China (9%), three (9%) in Canada, two (6%) in Taiwan, and one each (3%) in Chile and Australia. Most studies (97%) included men and women, although 55% included fewer females than males.

Studies were grouped into short- or long-term studies based on the timeframe used to investigate health effects. These timeframes ranged from hours and days (short-term) to one year or longer (long-term). Twenty-three studies (70%) examined short-term health indicators, and 10 (30%) examined long-term health outcomes. The median number of participants per study was 32 (range: 5 to 135) in the short-term studies and 43,308 (range: 181 to 234,124) in the long-term studies. The median proportion of females was 34% in the short-term studies and 51% in the long-term studies. In the short-term studies, the average age of participants ranged from 21 to 65 years with a median of 34 years, and in the long-term studies the average age ranged from 37 to 69 years with a median of 56 years.

The most studied pollutants were $PM_{2.5}$ (n=25, 75%), PM_{10} (n=19, 58%) and UFP (n=17, 52%). Air quality conditions varied substantially between studies; hence, the terms high and low TRAP sites refer only to relative, not absolute, levels within studies, not between studies. In the short-term studies, the most studied pollutant was $PM_{2.5}$ (n=20, 61%), with concentrations ranging from 2 to 72 $\mu g/m^3$ at designated low-TRAP sites and from 5 to 83 $\mu g/m^3$ at designated high-TRAP sites. The relative difference in $PM_{2.5}$ concentration between low-TRAP sites and high-TRAP sites for Group A and B short-term studies was 63% and 50%, respectively. In the long-term studies, the most studied pollutant was NO_2 (n=7, 70%), with a mean concentration of 29 $\mu g/m^3$ and a range of 17 to 50 $\mu g/m^3$.

In the 12 Group A studies, effect modification was assessed by the presence or absence of a significant interaction between walking or cycling and either single pollutants or TRAP site (Table 2). Four of these studies (33%) examined short-term health indicators, and the remaining eight (67%) examined long-term health indicators. Four studies (33%) (Cole-Hunter et al., 2016; Kubesch et al., 2015a; Kubesch et al., 2015b; Matt et al., 2016) used data from the 'TAPAS' research project; hence, they shared the same (staged) study design. In the TAPAS project (de Nazelle et al., 2010), participants were randomly allocated into four 2-hour exposure scenarios that combined two TRAP scenarios, a low- and a high-TRAP site, and two physical activity scenarios, rest and cycling (four intervals of 15-min of intermittent cycling on a stationary bike alternating with 15-min intervals of rest). Another three studies (25%) (Andersen et al., 2015; Fisher et al., 2016; Kubesch et al., 2018), examining predictors of long-term health indicators, used data from the Danish Diet, Cancer, and Health cohort (Tjønneland et al., 2007) to explore associations between healthy lifestyle factors and cardiovascular and cancer diseases. Outdoor nitrogen dioxide (NO_2) was used as a proxy measure of TRAP at a participant's residential address. Participants reported frequency of cycling and walking as part of a larger questionnaire.

Authors of the 13 Group B studies reported significant changes in health indicators from baseline to follow-up at each of two to three TRAP sites and significant differences between TRAP sites in these changes (Supplement A Table S1). These studies focused on people cycling (8 studies) and/or walking (5 studies) along pre-established routes. Twelve studies (92%) examined short-term health indicators, and one examined long-term health indicators.

Authors of the eight Group C studies presented the effects of AP on health indicators by commuting mode. Five studies (63%) examined short-term health indicators, and one (13%) examined long-term health indicators. Authors of two studies (25%) (Zuurbier et al., 2011a; Zuurbier et al., 2011b) analyzed data from the TRAVEL project (Zuurbier et al., 2009). For this study participants followed pre-established routes for 2 hours per day and travelled by bicycle, car, or bus on different days. Individual exposure to UFPs, $PM_{2.5}$, PM_{10} and soot, a pollutant formed during the incomplete combustion of hydrocarbons, was continuously monitored along the commuter route for each sampling day, and blood-based markers were collected from participants before and after their daily commute. Authors of three other studies (38%) examined the short-term effects of single pollutants on health indicators among pedestrians, cyclists and users of cars, buses, or trains, while a fourth study examined the long-term health effects of a walking program in two cities with different AP levels.

A meta-analysis was determined to be inappropriate due to the heterogeneity of outcomes and exposures.

Short-term cardiovascular, respiratory, and other health indicators

Effect modification by AP on the associations between cycling or walking and short-term health indicators were explored in 23 studies.

Blood pressure

Collectively, authors examined four blood pressure (BP) indicators in their studies: systolic BP, diastolic BP, pulse pressure and mean arterial pressure. An increase in any of these indicators suggests a detrimental impact on health over time, particularly on cardiovascular health.

Authors of one Group A study analyzed the effects of AP on BP as part of the TAPAS project (Kubesch et al., 2015a). BP was measured at baseline, once during each exposure, and at multiple timepoints afterwards. The significance of an interaction term was tested between intermittent cycling and seven measures of AP: TRAP site and six single pollutants. Mean $PM_{2.5}$ was 63% lower at the low-TRAP site than at the high-TRAP site. Two air pollutants modified the association between cycling and one of two BP indicators examined: in pooled analysis, PM_{10} and PM_{Coarse} significantly modified the association between intermittent cycling and systolic BP.

Authors of two Group B studies (Mirowsky et al., 2015; Sinharay et al., 2018) analyzed the effects of TRAP site on associations between walking and BP. Average $PM_{2.5}$ (mean or median) was 58% lower at the low-TRAP sites than at the high-TRAP sites. TRAP site modified the association between walking and two of four BP indicators examined in one study: there was a decrease in systolic BP from baseline to 24 hours after walking at the high-TRAP site and an increase in systolic BP after walking at the low- and medium-TRAP sites (Mirowsky et al., 2015). This difference between sites was significant. In the other study (Sinharay et al., 2018), systolic BP significantly increased from baseline to 1 hour after walking at both TRAP sites.

Authors of one Group C study (Chuang et al., 2020) examined associations between individual exposure to $PM_{2.5}$ and BP among commuters. BP was measured four times during the exposure. The mean $PM_{2.5}$ for pedestrians without a mask, pedestrians with a mask, and train, car, bus and scooter users was 42, 43, 21, 26, 34 and 53 $\mu g/m^3$, respectively, and systolic BP was significantly increased during the exposure in most commuting modes with the largest effects observed in pedestrians.

In summary, together these four studies provide direct and indirect evidence that exposure to PM and high AP sites can reduce the benefits from AM on systolic, but not diastolic, BP.

Heart rate variability

Collectively, authors examined five heart rate variability (HRV) indicators in their studies: the standard deviation of normal-to-normal intervals (SDNN); the root mean square of successive differences in adjacent normal-to-normal intervals (RMSSD); low frequency power (LF), high frequency power (HF), and the low and high frequency power ratio (LFHFR). A decrease in the time-domain HRV indicators (SDNN and RMSSD) suggests a decrease in vagal tone of the heart and consequently a detrimental effect in the body's ability to cope with stress. The frequency-domain HRV indicators (LF, HF, and LFHFR) reflect the parasympathetic and sympathetic balance of the heart. A decrease in HF suggests an increase in the parasympathetic activity and the body's relaxation and recovery status, therefore a positive health effect. The meaning of changes in LF and LFHFR are still debated amongst the research community. LF has been linked to sympathetic activity, whereas LFHFR has been linked to the balance between sympathetic and parasympathetic activity of the heart. Health effects from changes on LF remain unclear. An increase in LFHFR indicates sympathetic dominance, preparing the body for a "fight or flight" state, which could be an acute positive effect but alternatively, could suggest a negative health effect if the exposure to the toxin or danger is prolonged.

Authors of one Group A study (Cole-Hunter et al., 2016) examined the effect of AP on HRV as part of the TAPAS project. The authors analyzed effect modification by single air pollutants ($PM_{2.5}$, UFP and BC) on associations between cycling and HRV indicators separately for each TRAP site by testing the significance of an interaction term between cycling and each air pollutant in their modelling. Mean $PM_{2.5}$ was 76% lower at the low-TRAP site than at the high-TRAP site. UFP and BC significantly modified associations between cycling and time-domain HRV indicators (SDNN and RMSSD) at each TRAP site. All three air pollutants significantly modified associations between cycling and two of three frequency-domain HRV indicators (HF and LF, not LFHFR) at the high-TRAP site only.

Authors of three Group B studies examined associations between HRV and either walking at three TRAP sites (Mirowsky et al., 2015), cycling at two TRAP sites and in an indoor setting (Weichenthal et al., 2011), or walking at two TRAP sites (Roe et al., 2020). Mean $PM_{2.5}$ was 42% lower at the low-TRAP sites than at the high-TRAP sites. In one study (Mirowsky et al., 2015), the authors analyzed percent change from baseline to immediately after and 24 hours after each exposure. From baseline to immediately after walking there was a decrease in HF at the high-TRAP site and an increase at the low- and medium-TRAP sites. The difference between sites was significant. In the second study (Weichenthal et al., 2011), the authors analyzed percent change from baseline to immediately after and 1 to 3 hours after each exposure. A decrease in HF from baseline to 3 hours after cycling at the high-TRAP site was significantly different from the change observed after cycling indoors. An increase in LFHFR from baseline to 1 and 2 hours after cycling at the low-TRAP site was significantly different from the change seen after cycling indoors. The specific changes observed after cycling indoors were not reported. In the third study (Roe et al., 2020), the authors reported that RMSSD was significantly lower while walking at the high-TRAP site than while walking at the low-TRAP site.

Authors of three Group C studies (Hampel et al., 2014; Liu et al., 2015; Nyhan et al., 2014) examined associations between single air pollutants ($PM_{2.5}$, PM_{10}, VOCs, UFP and/or CO) and HRV among commuters. Nyhan et al. (2014) examined associations between both PM_{10} and $PM_{2.5}$ and HRV indicators for three commuting modes: walking, cycling and public transport. Mean $PM_{2.5}$ for cyclists, pedestrians, and public transport users was 37, 28 and 21 µg/m^3, respectively. Decreases in SDNN and RMSSD from baseline to during exposure that were associated with increases in PM_{10} and $PM_{2.5}$ were significantly greater in cyclists and pedestrians than in bus users. Liu et al. (2015) examined associations between $PM_{2.5}$, PM_{10} and total VOCs with HRV indicators separately for pedestrians, car drivers, bus riders, and train users. Mean $PM_{2.5}$ was highest among pedestrians (42 µg/m^3) and lowest among train users (22 µg/m^3). A decrease in SDNN and RMSSD from baseline to during exposure was associated with significantly increased exposures to $PM_{2.5}$, PM_{10} and total VOCs levels among all commuting modes, with the largest effects observed in pedestrians. Hampel et al. (2014) examined associations of $PM_{2.5}$, UFP and CO with HRV separately for pedestrians, cyclists, and car drivers. The authors calculated HRV indicators from participants' time exposed to TRAP. Mean $PM_{2.5}$ while cycling and walking at the TRAP site was 7 µg/m^3 and at the non-TRAP site was 15 µg/m^3. Cycling and walking at the TRAP site were associated with decreased SDNN and increased HF and LF from baseline to 30 minutes after exposure. These changes were significantly different from the changes observed after walking or cycling at the non-TRAP site.

In summary, together these seven studies provide direct and indirect evidence that high AP sites and some pollutants, namely $PM_{2.5}$, PM_{10}, UFP, black carbon and volatile organic compounds, can reduce the positive benefits of AM on HRV.

Blood-based markers

Collectively, authors examined 17 blood-based markers in their studies, including acute changes in blood cells and blood markers. An increase in the count of white blood cells (neutrophils, lymphocytes, eosinophils, basophils, monocytes, macrophages) suggests an increased immune response to protect from infections and assist allergic responses, a positive health response. An increase in hematocrit over the course of the study may reflect a decrease in blood volume, as would happen with dehydration, which suggests a negative health response. An increase in a range of interleukins, C-reactive protein (CRP), tumor necrosis factor alpha (TNF-alpha), soluble intercellular adhesion molecule (sICAM), and serum amyloid A suggests an increased inflammatory and immune response in the body, an acute positive health response. An increase in cortisol suggests an increase in the body's stress response, an acute positive health response. An increase in the activated partial thromboplastin time suggests reduced coagulation function, an acute negative health response.

Authors of one Group A study from the TAPAS project (Kubesch et al., 2015b) examined associations between AP and 12 blood-based markers: seven blood cell type counts and five inflammation markers. For each blood-based marker, the authors examined the significance of an interaction term between cycling and seven measures of AP, including TRAP site and six single pollutants. Mean $PM_{2.5}$ was 63% lower at the low-TRAP site than at the high-TRAP site. $PM_{2.5}$ and PM_{10} significantly modified the association between cycling and neutrophil counts. UFP significantly modified the association between cycling and both interleukin-8 and hematocrit. TRAP site also significantly modified the association between cycling and hematocrit.

Authors of two Group B studies examined associations between cycling at two TRAP sites and blood cells counts (Cole-Hunter et al., 2013; Jacobs et al., 2010). Three other studies examined associations between walking at three TRAP sites (Mirowsky et al., 2015) or cycling at two TRAP sites (Cole et al., 2018; Jacobs et al., 2010) and proinflammatory blood markers. Mean $PM_{2.5}$ was 66% lower at the low-TRAP sites than at the high-TRAP sites. Significant findings were found in only two of the studies. In one study (Jacobs et al., 2010), the number and percentage of neutrophils significantly increased from baseline to 30 minutes after cycling at the high-TRAP site but not at the low-TRAP site, with a significantly greater increase in the percentage of neutrophils after cycling at the high-TRAP site than at the low-TRAP site. In the other study (Mirowsky et al., 2015), an increase in concentration of soluble intercellular adhesion molecule from baseline to 24 hours after walking was significantly greater at the low-TRAP site than at the high-TRAP site.

Authors of two Group C studies examined associations between blood-based markers and $PM_{2.5}$, PM_{10}, UFP, soot and black carbon among people using active and non-active commuting modes. Nwokoro et al. (2012) examined associations between black carbon exposure and six proinflammatory markers during commuting trips separately for cyclists, pedestrians and public transport users. Only one of six proinflammatory markers, TNF-alpha, was significantly higher in cyclists than in pedestrians and public transport users. Zuurbier et al. (2011a) examined associations between $PM_{2.5}$, PM_{10}, UFP and soot with 20 blood-based markers among people commuting by bicycle, car or bus as part of the TRAVEL study. Mean $PM_{2.5}$ for cyclists, car, and bus users were 69, 81 and 66 $\mu g/m^3$, respectively. A decrease in the percentage of neutrophils from baseline to 6 hours after exposure was associated with significantly increased exposure to UFP in cyclists but not in car or bus users. An increase from baseline to 6 hours after exposure in activated partial thromboplastin time was associated with significantly increased $PM_{2.5}$ and PM_{10} in cyclists but not in car and bus users.

In summary, together these five studies provide direct and indirect evidence that exposure to high levels of $PM_{2.5}$, PM_{10} or UFP, as well as using AM at high AP sites, can reduce the benefits of AM, most notably cycling, on some blood-based markers of inflammation and coagulation.

Lung function and airway inflammation

Collectively, authors examined nine lung function and one airway inflammation indicators in their studies: forced vital capacity (FVC); forced expiratory volume (FEV_1); the ratio between FVC and FEV_1 (FEV_1/FVC ratio); forced mid-expiratory flow ($FEF_{25-75\%}$); peak expiratory flow (PEF); maximal mid-expiratory flow (MMEF); maximal expiratory flows at 25%, 50% and 75% of FVC (MEF 25, MEF 50, MEF 75); and fractional exhaled nitric oxide (FeNO). An increase in any of these indicators, except for FeNO, suggests a positive impact on pulmonary health. An increase in FeNO level suggests the presence of airway inflammation, a negative impact on pulmonary health.

In further analyses from the TAPAS project, authors of two Group A studies examined associations between AP and indicators of lung function (Kubesch et al., 2015b; Matt et al.,

2016) and/or an indicator of airway inflammation (FeNO) (Kubesch et al., 2015b). The significance of an interaction term between cycling and measures of AP was tested, which included TRAP site and six (Kubesch et al., 2015b) or seven (Matt et al., 2016) single pollutants. Mean $PM_{2.5}$ was 57% lower at the low-TRAP sites than at the high-TRAP sites. In one study (Matt et al., 2016), TRAP site, $PM_{2.5}$, PM_{10} and PM_{Coarse} significantly modified the association between cycling and one of five indicator of lung function, PEF, which is a proxy for airway limitation, immediately after each exposure. $PM_{2.5}$ and PM_{10} also significantly modified the association between cycling and another indicator of lung function, the FEV_1/FVC ratio, after exposure (pooled timepoints) in one study (Kubesch et al., 2015b) but not in the other study (Matt et al., 2016). Kubesch et al. (2015b) also found that UFP levels significantly modified the association between cycling and FeNO after exposure.

Authors of seven Group B studies examined associations between lung function indicators and either walking or cycling at two TRAP sites (Cole et al., 2018; Cole-Hunter et al., 2013; Jarjour et al., 2013; Moshammer et al., 2019; Park et al., 2017; Sinharay et al., 2018; Weichenthal et al., 2011). Authors of two other studies (Jacobs et al., 2010; Weichenthal et al., 2011) examined the association between cycling at two TRAP sites and one indicator of airway inflammation. In these studies, mean $PM_{2.5}$ was 69% lower at the low-TRAP sites than at the high-TRAP sites. Authors of three studies examined FVC. In the first study (Sinharay et al., 2018), FVC increased significantly from baseline to 1 and 3 hours after walking at a low-TRAP site but not at a high-TRAP site. The increase in FVC from baseline to 3 hours after walking was significantly greater at the low-TRAP site than at the high-TRAP site. In the second study (Park et al., 2017), FVC increased significantly from baseline to immediately after cycling at a low-TRAP site, whereas it decreased significantly at a high-TRAP site. There was an increase in FVC from baseline to immediately after cycling at the low-TRAP site and a decrease at the high-TRAP site. The difference between sites was significant. In the third study (Moshammer et al., 2019), FVC decreased from baseline to 24 hours after walking at a high-TRAP site, a significantly greater amount of change than observed at a low-TRAP site.

Authors of two studies examined FEV. In the first study (Sinharay et al., 2018), FEV increased significantly from baseline to one point during a walk and 1, 3, 4, and 24 hours after the walk at a low-TRAP site but not at a high-TRAP site, with the exception that FEV increased significantly from baseline to 1 hour after walking at the high-TRAP site. The increase in FEV from baseline to 3, 4 and 24 hours after walking was significantly greater at the low-TRAP site than at the high-TRAP site. In the second study (Park et al., 2017), FEV increased significantly from baseline to immediately after cycling at a low-TRAP site and decreased (but not significantly) at a high-TRAP site. This difference between sites was significant.

Authors of one study examined PEF (Moshammer et al., 2019). PEF increased from baseline to immediately and 1 hour after walking at a high-TRAP site, a significantly greater amount of change than observed at a low-TRAP site.

Authors of two studies examined FeNO. In the first study (Jacobs et al., 2010), FeNO decreased significantly from baseline to 30 minutes after cycling at a high-TRAP site but not at a low-TRAP site. In the second study (Weichenthal et al., 2011), FeNO decreased from baseline to immediately after cycling at a low-TRAP site, a significantly greater amount of change than observed after cycling indoors.

One Group C study examined associations between UFP and both lung function and airway inflammatory indicators among people commuting by bicycle, car or bus as part of the TRAVEL study (Zuurbier et al., 2011b). Mean $PM_{2.5}$ was 69 $\mu g/m^3$ for cyclists, 81 $\mu g/m^3$ for car users and 66 $\mu g/m^3$ for bus riders. From baseline to 6 hours after exposure, PEF increased among cyclists and decreased among car and bus users. Airway resistance increased among cyclists but increased more among car and bus users. Conversely, FeNO decreased among cyclists and increase among car and bus users. These between-group differences were significant.

In summary, seven of these ten studies provide direct and indirect evidence that engaging in AM at sites with high levels of $PM_{2.5}$, PM_{10}, and PM_{Coarse} or high AP can reduce the benefits from AM for FVC, FEV1 FEV1/FVC ratio and PEF. In addition, the studies provide direct and indirect evidence that UFP and sites with high AP can reduce the benefits of cycling for transportation on airway inflammation.

Other health indicators

Arterial stiffness

Authors of one Group B study analyzed the effect of TRAP site on associations between walking and arterial stiffness indicators: pulse wave velocity and the augmentation index (Sinharay et al., 2018). A decrease in these indicators suggests reductions in arterial stiffness, which has a positive impact on health. Mean $PM_{2.5}$ was 56% lower at the low-TRAP site than at the high-TRAP site. Pulse wave velocity significantly decreased from baseline to 1 hour after walking at the low-TRAP site but not at the high-TRAP site. From baseline to 24 hours, pulse wave velocity increased after walking at the high-TRAP but decreased at the low-TRAP site; this difference between sites was statistically significant. The augmentation index significantly decreased from baseline to 1, 3, 4 and 24 hours after walking at the low-TRAP site and decreased, but not significantly, at the high-TRAP site. The decrease at the low-TRAP site was significantly greater than the decrease at the high-TRAP site. From baseline to 24 hours, the augmentation index increased after walking at the high-TRAP but decreased at the low-TRAP site; this difference between sites was statistically significant.

Endothelial function

Authors of one Group B study analyzed the effect of TRAP site on the association between cycling and the reactive hyperemia index, a measure of endothelial function (Cole et al., 2018). An increase in the reactive hyperemia index suggests improved endothelial function. Mean $PM_{2.5}$ was 21% lower at the low-TRAP site than at the high-TRAP site. From baseline to 30 minutes after cycling, the reactive hyperemia index increased at the low-TRAP site and decreased at the high-TRAP site; this difference between sites was statistically significant.

Respiratory symptoms

Authors of two Group B studies analyzed the effect of TRAP site on associations between walking (Sinharay et al., 2018) or cycling (Cole-Hunter et al., 2013) and self-reported respiratory symptoms. $PM_{2.5}$ levels were measured for one of the studies (Sinharay et al., 2018). In that study mean $PM_{2.5}$ was 56% lower at the low-TRAP site than at the high-TRAP site, and odds ratios of having worse respiratory symptoms after walking at a TRAP site than at baseline were not significant for either TRAP site. In the other study (Cole-Hunter et al., 2013), scores on two of 10 measures of respiratory symptoms, which were the measures that assessed offensive odors and dust/soot, were significantly higher immediately after cycling than at baseline in participants who had cycled at a low- or a high-TRAP site; however, immediately after cycling these symptoms were significantly higher in those who had cycled at the high-TRAP site than in those who had cycled at the low-TRAP site. Immediately after cycling, scores on another of the 10 measures, which assessed nose and throat irritation, were significantly higher in participants who had cycled at the high TRAP site than in those who had cycled at the low-TRAP site. Three hours after cycling, dust/soot scores were significantly lower in participants who had cycled at the low-TRAP site than in those who had cycled at the high-TRAP site.

Mood and reaction time

Authors of one Group B study examined the effect of TRAP site on associations between walking and both reaction time and indicators of mood (Roe et al., 2020). A decrease in reaction time suggests a positive impact on cognitive functioning whereas an increase in mood indicators suggests improved psychological well-being. Mean $PM_{2.5}$ was 16% higher at a low-TRAP site than at a high-TRAP site. An increase in hedonic tone, an indicator of mood, from baseline to immediately after exposure was significantly greater after walking at the low-TRAP site than after walking at the high-TRAP site. There were no statistically significant differences between TRAP sites in reaction time.

Oxidative stress through DNA damage

The authors of two Group B studies and one Group C study analyzed the effects of TRAP site (Vinzents et al., 2005) or $PM_{2.5}$ (Chuang et al., 2020) on markers of oxidative stress. An increase in these markers suggests an adverse health impact. The first study (Vinzents et al., 2005) showed significantly higher levels of DNA damage (formamidopyrimidine DNA glycosylase [FPG] sensitive sites) immediately after cycling at a high-TRAP site than after cycling indoors. In the second study (Chuang et al., 2020) the association between $PM_{2.5}$ and urinary 8-hydroxy-20-deoxyguanosine (8-OHdG) was observed among commuters walking (wearing a mask or not) or using a car, bus, train, or scooter. An increase in 8-OhdG concentration from baseline to immediately after exposure was significantly associated with increased $PM_{2.5}$ levels among all commuting modes, with the largest effects observed in pedestrians without masks and scooter users.

Neuronal function

The authors of one Group B study analyzed the effects of TRAP site on the association between cycling and brain-derived neurotrophic factor (BDNF), a measure of neuronal function (Bos et al., 2011). An increase in BDNF suggests a protective effect on brain health. Mean $PM_{2.5}$ was 92% lower at the low-TRAP site (indoors) than at the high-TRAP site. BDNF significantly increased from baseline to 30 minutes after cycling indoors but did not change after cycling at the high-TRAP site.

Summary of short-term study findings about ‘other health indicators’

These studies provide indirect evidence that using AM at sites with high AP can reduce the benefits of AM on pulse wave velocity and augmentation index, measures of arterial stiffness (1 of 1 study); reactive hyperemia index, a measure of endothelial function (1 of 1 study); self-reported offensive odors, dust/soot, and nose and throat irritation (1 of 2 studies); hedonic tone, an indicator of mood (1 of 1 study); FPG-sensitive sites and urinary 8-OhdG, markers of oxidative stress (2 of 3 studies); and BDNF, a measure of neuronal function (1 of 1 study).

Long-term cardiovascular, respiratory, and other health outcomes

Authors of 10 studies explored effect modification by AP on associations between cycling or walking and long-term health outcomes. The analyses conducted for three studies (Andersen et al., 2015; Fisher et al., 2016; Kubesch et al., 2018) used data from the Danish Cohort, while two studies (Raza et al., 2021, 2021b) used data from the Västerbotten Intervention Program, a Swedish cohort study designed to reduce cardiovascular risk at the population level. Three Chinese studies used observational designs (Lin et al., 2021; Liu et al., 2020; Tao et al., 2019). Another study (Molina-Sotomayor et al., 2019) was a quasi-experimental study of participants living in two Chilean cities with different annual AP concentrations. The authors of the final study used data from the UK Biobank Cohort to explore associations between AP, commuting modes and health indicators (Wong et al., 2021).

Mortality

Authors of two Group A studies (Andersen et al., 2015; Lin et al., 2021) examined the effect of AP on associations between AM and mortality. In the first study (Andersen et al., 2015) the authors examined effect modification by NO_2 on associations between cycling or walking and all- and cause-specific mortality over a mean of 13 years. The significance of an interaction term between cycling or walking and NO_2 exposure was used to test effect modification. Mean NO_2 was 17 μg/m^3. NO_2 exposure did not significantly modify the association between cycling or walking and any mortality outcome. In the second study (Lin et al., 2021), authors examined effect modification by $PM_{2.5}$ on associations between walking or cycling and all-cause mortality over a median of 6 years. The significance of an interaction term between commuting mode and $PM_{2.5}$ level was used to test effect modification. Mean $PM_{2.5}$ was 67 μg/m^3. $PM_{2.5}$ significantly modified the association between AM and all-cause mortality.

Chronic cardiovascular disease

Authors of four Group A studies examined the effect of AP on associations between walking or cycling and morbidity outcomes: cardiovascular disease (Lin et al., 2021), myocardial infarction (Kubesch et al., 2018), stroke and coronary heart disease (Raza et al., 2021, 2021b). Participants were followed for 6 to 17 years. Mean NO_2 was 18 μg/m^3, and $PM_{2.5}$ levels ranged from 5 to 67 μg/m^3. The authors tested whether different NO_2, $PM_{2.5}$ and PM_{10} levels modified associations between cycling or walking and morbidity outcomes by including an interaction term in the modelling. No associations were significantly modified by the three pollutants.

Chronic respiratory diseases

Authors of two Group A studies examined the effect of NO_2 on associations between walking or cycling and respiratory diseases: lung cancer (Wong et al., 2021), asthma and COPD (Fisher et al., 2016). Participants were followed for 7 to 16 years, and NO_2 levels ranged from 18 to 28 μg/m^3. The authors found no significant effect modification by NO_2 levels on the association between cycling or walking and respiratory diseases.

Obesity

Authors of one Group A study examined associations between overall and abdominal obesity and specific pollutants among six commuting modes to work including walking and cycling (Liu et al., 2020). One-year mean concentrations of $PM_{2.5}$, PM_{10}, SO_2, CO, NO_2 and O_3, were obtained from fixed monitoring stations nearest to participants' workplaces. The global one-year mean $PM_{2.5}$ was 74 $\mu g/m^3$. The authors tested whether each pollutant modified associations between cycling or walking and obesity by including an interaction term in the modelling. PM_{10} significantly modified associations between both walking and cycling and abdominal obesity. SO_2 significantly modified the association between walking and overall obesity. No other pollutant modified these associations.

Other long-term chronic health outcomes

Cognitive impairment and cardiorespiratory fitness

Authors of one Group B study (Molina-Sotomayor et al., 2019) examined the effects of a 2-year walking program on cognitive impairment and cardiorespiratory fitness among older adults living in two cities with different AP levels. The 3-year mean $PM_{2.5}$ was 54% lower in the low-AP city than in the high-AP city. From baseline to the end of the program, cognitive impairment and cardiorespiratory fitness improved significantly among active participants of both cities, with significantly greater improvements in cardiorespiratory fitness observed among those living in the less polluted city. Both outcomes significantly worsened among sedentary participants of both cities, with significantly larger effects among residents of the more polluted city.

Dyslipidemia and serum lipid concentrations

Authors of one Group C study examined associations between commuting modes to work, including walking and cycling, with dyslipidemia and five indicators of serum lipid concentrations (Tao et al., 2019). One-year mean concentrations of $PM_{2.5}$, PM_{10}, NO_2, SO_2, CO and O_3, were obtained from monitoring stations in participants' districts before a health screen. The global one-year mean $PM_{2.5}$ level was 77 $\mu g/m^3$. Compared with car and taxi use, cycling was associated with reduced odds of the six dyslipidemia indicators. Walking was associated with reduced odds of three of the indicators, and both cycling and walking were associated with reductions in all indicators of serum lipid concentrations. There was no evidence that air pollutants were confounding the associations and all of the studied associations remained significant after adjustment for air pollutants.

Summary of long-term study findings

Long-term studies providing direct evidence of effect modification suggest that high NO_2 levels do not attenuate the reductions in risk of all- and cause-specific mortality from AM (4 of 4 studies). However, the evidence suggests that $PM_{2.5}$ may attenuate the reductions in risk of all-cause mortality linked to AM (1 of 1 study) and PM_{10} and SO_2 may attenuate the reductions in risk of obesity from AM (1 of 1 study). Studies providing indirect evidence of effect modification suggest that the reduction in dyslipidemia risk from AM is not lessened when the presence of specific air pollutants are accounted for (1 of 1 study) and sites with high AP may attenuate the reductions in risk of cognitive impairment and cardiorespiratory fitness from AM (1 of 1 study).

Risk of bias assessment

Details about the RoB assessment are provided in Supplement B. In short, all Group A studies were rated either 'definitely low' or 'probably low' RoB for selection, measurement of health indicators and reporting. Most of these studies were rated as 'probably low' RoB for confounding (n=7, 58%) and either 'definitely low' or 'probably low' RoB for attrition/exclusion (n=10, 83%). Most were rated as 'probably high' RoB for measurement of AM and AP and for 'other' biases (n=8, 67%). The main RoB due to measurement, seen in long-term studies, was the reliance on self-report instruments that were not well-validated to capture AM because regular, objective measurement was not feasible over long periods and the use of data from monitoring stations to capture AP exposure because individual AP exposure was not possible to capture. 'Other' potential biases were inadequate power to test for interaction effects and failure to adjust analyses for multiple comparison testing.

Most Group B studies were rated as 'definitely low' RoB for measurement of AP (n=11, 85%), AM (n=7, 54%), and health indicators (n=12, 92%), and for selective reporting bias (n=12, 92%). Most were rated either 'definitely low' or 'probably low' RoB for attrition/exclusion (n=9, 69%). Most were rated as 'probably high' RoB or had insufficient information for selection (n=7, 54%), confounding (n=7, 54%) and 'other' biases (n=12, 92%). The main RoB from selection, seen in cross-over studies, was the failure to randomly allocate the order of exposure to different TRAP sites. The main RoB due to confounding was the use of a wash-out period between exposures that was likely insufficient to prevent carry-over effects. The main 'other' RoB was failure to adjust analyses for multiple comparison testing.

All Group C studies were rated as 'definitely low' RoB for measurement of health indicators and for selective reporting bias. Most were rated as 'definitely low' RoB for measurement of AP (n=7, 88%), 'probably low' RoB for confounding (n=6, 75%), and either 'definitely low' or 'probably low' RoB for attrition/exclusion (n=5, 63%). Most were rated as 'probably high' RoB or had insufficient information for selection (n=7, 88%), measurement of AM (n=6, 75%) or 'other' biases (n=5, 63%). The main RoB from selection was due to insufficient information on recruitment and participation rates being reported in the article to rate the RoB from selection. The main RoB from measurement of AM was the lack of standardization or control of AM intensity and, less often, duration of AM. The main 'other' RoB was failure to adjust analyses for multiple comparison testing.

A RoB for all studies that examined individual pollutants was potential confounding by pollutants not included in analysis. To address this, correlations between individual pollutants were explored in 14 studies: in 13 of 23 (57%) short-term studies (Cole-Hunter et al., 2013; Cole-Hunter et al., 2016; Cole et al., 2018; Kubesch et al., 2015a; Kubesch et al., 2015b; Liu et al., 2015; Liu et al., 2020; Matt et al., 2016; Mirowsky et al., 2015; Moshammer et al., 2019; Nyhan et al., 2014; Weichenthal et al., 2011; Zuurbier et al., 2011a) and in 1 of 10 long-term studies (Andersen et al., 2015). When high correlations among pollutants were found in short-term studies, $PM_{2.5}$ was usually selected as the only pollutant for subsequent analyses, which may have led to its overrepresentation in this review. The one long-term study examined the correlation between $PM_{2.5}$ and NO_2. Due to a higher correlation between these pollutants, only NO_2 was included in subsequent analyses.

Discussion

This review systematically summarized and synthesized the statistical evidence of effect modification by AP on short- and long-term associations between AM and health indicators. Despite this being a practical question of both public and environmental health importance and the subject of a substantial amount of research, to the best of our knowledge, this has not been done previously. Some systematic reviews, however, have examined the combined effects of AP and physical activity more generally on health indicators showing, in general, mixed evidence that high levels of AP reduce some of the health benefits of physical activity (DeFlorio-Barker et al., 2020; Madureira et al., 2019; Qin et al., 2019).

Effect modification is a complex statistical phenomenon, and we identified three analytical approaches that researchers used in 33 articles to examine effect modification by AP. Grouping together studies with the same approaches, 12 studies (Group A) provided direct evidence of effect modification by testing the significance of an interaction term between AM and either single pollutants or sites of low or high TRAP. Thirteen other studies (Group B) provided suggestive, or indirect, evidence of effect modification as their findings differed according to sites of low or high TRAP. Eight additional studies (Group C) provided suggestive, or indirect, evidence of effect modification by observing differences according to commuting mode. Group A studies provide the best quality of evidence and the most rigorous test of effect modification (Kestenbaum, 2019). These studies consistently reported p-values for the interaction term in their modelling, but they frequently did not report the direction or magnitude (effect size) of effect modification.

Four of the 12 Group A studies examined whether short-term cardiovascular and respiratory benefits of cycling (emulating AM) were attenuated by AP. In general, we found little evidence among these studies of these health benefits being reduced by AP. However, some health benefits, such as improvement in HRV, were greatly reduced in the presence of high levels of specific pollutants. Smaller reductions in health benefits were found in the AM-associated improvements in BP, blood-based markers and lung function. $PM_{2.5}$ and UFP were the pollutants most strongly associated with reductions in these health benefits. There was no evidence of any adverse effect by NO_x. Our OHAT assessment suggests these studies had low RoB although they were prone to ‘other’ RoB due to small sample sizes and lack of adjustment for multiple comparisons testing.

Findings from Groups B and C studies support these findings from Group A studies and suggest that the short-term health benefits of walking, as well as cycling, that emulate AM in type or intensity are reduced in areas of high AP. Our findings support those of recent systematic reviews (DeFlorio-Barker et al., 2020; Madureira et al., 2019; Qin et al., 2019) that showed that the health benefits of physical activity, including cardiovascular, and to lesser extent respiratory, are reduced when performed in areas of high AP levels. As such, our findings augment the existing evidence base showing that, at real-world AP levels, some short-term cardiovascular and respiratory benefits of cycling and walking (emulating AM) may be reduced with $PM_{2.5}$ and UFP exposure and in areas with overall high AP levels. However, our OHAT assessment suggests that these studies may be at high risk of selection, confounding, attrition/exclusion, measurement of AM behaviour and 'other' biases.

We also examined whether the long-term health benefits of walking and cycling that emulate AM are reduced by high AP levels; NO_2, a proxy for traffic emissions; and $PM_{2.5}$. In four long-term Group A studies, authors found the benefits of cycling and walking for cardiovascular and respiratory diseases and mortality (all-cause or cause-specific) were not reduced by higher NO_2 levels. In one of three Group A studies examining $PM_{2.5}$, authors found that AM-associated reductions in risks of all-cause mortality were lessened in the presence of higher $PM_{2.5}$. These findings suggest that $PM_{2.5}$ may have a stronger effect than NO_2 on the association between AM and these outcomes. These findings are supported by the best quality of evidence as they derive from Group A studies, which had lower RoB than other studies. However, there were notable areas in which long-term Group A studies were susceptible to bias. First, they tended to use self-report instruments, often not validated, to measure important confounders and AM. Thus, they were at high risk of introducing confounding and measurement of AM biases. Second, they relied on proxy measures of AP because they were unable to capture individual AP exposure. As a result, their measurement of AP was at high risk of introducing bias. Group B and C studies provided further evidence of effect modification by AP on the association between AM and long-term health outcomes. They too were prone to confounding bias because they tended to use unvalidated self-report instruments to measure important confounders and prone to measurement of AP bias because they were unable to capture individual AP exposure.

Acknowledging potential sources of bias, these results generally indicate that AM offers some long-term health benefits that may be reduced in highly polluted areas, by specific pollutants or using non-AM commuting modes. In contrast, findings from observational studies of physical activity behavior more generally suggest that long-term cardiovascular (Elliott et al., 2020; Kim et al., 2020; Sun et al., 2020), inflammatory (Zhang et al., 2018), and respiratory (Guo et al., 2020) benefits associated with physical activity are not reduced by AP exposure. Overall, our review shows mixed findings, with long-term Group A studies providing direct evidence that the health benefits of AM are not reduced by NO_2 levels and little evidence of reduction in health benefits by $PM_{2.5}$ and SO_2.

Implications

Our review found large variations in outcomes and in how and when AP and AM were measured across studies, which precluded meta-analysis. In addition, we found the sample sizes of the short-term studies were likely to be insufficient to detect statistically significant effect modification by AP. For certain experimental designs, the sample size required for testing interactions must be four times more than the size required for detecting an overall treatment effect (Brookes et al., 2004; Durand et al., 2013). Furthermore, our results showed a clear imbalance in the proportion of male and female participants, most notably in short-term studies, and few studies examined the health effects separately for men and women. Hence, generalizability of some findings to females is not clear. Based on our findings, we make eight recommendations to progress research in this field.

First, we recommend that future studies aiming to unravel effect modification by AP on the short- and long-term associations between AM and health indicators report statistical evidence of effect modification. We suggest that models include the independent AM and AP variables and the cross-product (interaction term) of these two in the same model, where the interaction term includes at least two levels of AM (e.g., walking or cycling) and two levels of AP (e.g., high and low) or continuous measures. We further recommend that reports of effect modification include statistical testing outcomes such as p-values; the coefficients for AM, AP and the interaction term; and the confidence intervals around these coefficients.

Second, we recommend that cross-over studies randomly allocate the order of AP exposure to prevent selection bias. Cross-over studies account for time-dependent confounders by design (Pope III & Burnett, 2007), but an insufficient washout period led to confounding bias in more than a half of the studies included in our review. Therefore, we recommend including a washout period sufficient to prevent confounding bias.

Third, we recommend that short-term studies use sample sizes sufficient to statistically test for effect modification and to decrease the possibility of false negative findings, especially in studies directly attempting to conduct effect modification analysis. We also suggest these studies account for multiple comparisons testing.

Fourth, we recommend that studies examine gender-specific effects to explore differential effects of AM and AP on health indicators.

Fifth, we recommend increasing consistency in experimental study design. For making comparisons across studies, we recommend increasing the consistency in the timepoints at which health indicators are measured across experimental studies. Within each of the three study groupings in this review, the large heterogeneity of timepoints used and the small number of studies examining the same health indicator made comparisons between studies within each grouping impractical. To improve the synthesis of evidence, we recommend that short-term studies measure health indicators hourly before, during (when possible), and after exposure using the same data collection timepoints.

Sixth, we recommend improving AM protocols and measurement. In experimental designs, we recommend AM protocols that reflect real-world conditions, such as commuting routes with different AP levels and intermittency in travel speed due to traffic control measures (e.g., intersections). We also recommend adjusting for duration and intensity of AM because inhalation of AP will be influenced by exertion and fluctuations in exertion over time. For assessing AM intensity, we recommend the use of established measures (e.g., heart rate monitors). In observational studies, we recommend the use of well-established, well-validated measures of AM, such as the International Physical Activity Questionnaire - IPAQ (Craig et al., 2003).

Seventh, we recommend improving the consistency in the measurement of AP. Pollutants in short-term studies have typically been measured along routes with real-world AP levels and at fixed near-traffic locations. These locations have higher AP concentrations and less variability relative to other locations and routes, and such differences in concentrations between locations may induce physiological responses that manifest in changes in health indicators. We suggest that in short-term studies AP levels reflect personal, real-world AP exposures, ideally along routes, and the measurement of AP levels at fixed near-traffic locations is avoided when possible. We also recommend the reporting of differences in pollutant levels between traffic sites.

Last, we recommend that all studies that have the capacity to measure individual pollutants assess correlations among the pollutants to determine if some pollutants should be included as confounders in analysis. To better understand the effects of the complex mixture of air pollutants within the atmosphere, the application of multi-pollutant models should be preferred over single-pollutant models. We acknowledge, however, that despite technological advancements and high-resolution modeling, most long-term observational studies are not yet able to quantify individual AP exposure and to account for variation in transport mode for the same journey (e.g., commuting by train some days and by cycling on other days) and multimodal trips (e.g., cycling from home to a train station and taking a train for the rest of the journey). Greater consistencies across studies will increase generalizability and allow for future meta-analyses, to inform public policy by delivering clearer messages guiding the promotion of AM while protecting health in different AP scenarios.

Strengths and limitations

One strength of this review is that effect modification was not limited to a short-term timeframe (study period of hours and days) as seen in previous systematic reviews in the field. Another strength is that our review was exhaustive, including studies published since database inception and using an extensive list of relevant keywords among multiple databases, minimizing the number of excluded relevant articles.

The main limitation of this review is that the included studies were highly heterogeneous in health indicators and measurement of AM and AP exposure. Although some studies measured the same health indicators, they did not make these measurements at the same timepoints during and after the exposure period, which severely limited comparisons between studies, even within the same grouping, and made a meta-analysis impractical.

Conclusions

This study synthesized the evidence of effect modification by AP on the associations between AM and health indicators. There was some evidence of a reduction by AP, mainly UFP and $PM_{2.5}$, on the short-term health benefits conferred by AM. There was more consistent evidence that health benefits conferred by AM persisted despite the likely harms of exposure to the principally traffic-related pollutant NO_2. Synthesized evidence further suggests a reduction in some long-term health benefits in highly polluted areas (not specific for one pollutant) and in non-active commuting modes. Caution should be used when interpreting these findings because each finding is limited to only a few studies that were not consistent in design, AP measurement, or health indicators examined. As research in this field has great potential to communicate important public health advice for AM users and promoters within cities (generally polluted environments), we urge researchers to work collaboratively to enhance the rigor of their collective efforts and deliver reliable and practical (evidence-based) answers to these questions.

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Figure legend.

Figure 1: PRISMA flowchart: Identification of studies via databases