Effects of the inhaled dose of air pollution on health: a systematic review

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Shareable abstract (@ERSpublications)
Research on inhaled dose of air pollution (IDoAP) focuses on respiratory function in healthy adults, ignoring vulnerable groups. O_3-IDoAP is linked to reduced lung function, which is driven by O_3 levels rather than ventilation. https://bit.ly/4lt4TPm

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Abstract

The inhaled dose of air pollution (IDoAP) is an air pollution exposure quantification method that accounts for individuals' amount of inspired air (*i.e.* minute ventilation), and thus for the physical activity practised by individuals. We aimed to summarise the existing literature and identify research gaps on the health effects of IDoAP.

We included original peer-reviewed research in PubMed, Scopus, SPORTDiscus, Embase and Cochrane prior to November 2024 and appraised bias following Cochrane and ROBINS-E tools. Title, abstract and full-text screening, data extraction and bias appraisal were completed in duplicate.

Of 1888 screened studies, 25 studies were included, mostly focusing on healthy adults (21 out of 25 studies), overlooking susceptible populations such as pregnant individuals or those with pre-existing disease. Studies focused primarily on IDoAP of O_3 (IDoAP-O_3) (14 out of 25 studies) and particulate matter <2.5 µm in aerodynamic diameter (IDoAP-$PM_{2.5}$) (13 out of 25 studies), with an exposure duration of up to 24 h. Lung function was the most studied outcome (19 out of 25 studies). Acute exposure to IDoAP-O_3 was associated with reduced lung function: increasing IDoAP-O_3 by 150 µg·m^{-3} led to a decrease in forced expiratory volume in 1 s (FEV_1) of 0.27 L. This was driven by O_3 concentration, while increases in minute ventilation did not affect FEV_1. A number of research gaps were identified. These comprised research on susceptible and vulnerable populations, including residents of low-to-middle-income regions, and people with extreme occupational exposures; air pollutants other than O_3 and $PM_{2.5}$; and outcomes besides respiratory markers. Alternative statistical approaches are also required, such as multi-exposure models.

Our findings support initiatives to generate low-pollution public corridors to keep IDoAP levels as low as possible to maximise health benefits from physical activity.

Introduction

Exposure to air pollution is one of the greatest environmental threats to human health [1, 2]. Air pollutants impair most organs and physiological systems [3], and are responsible for over 12% of deaths and 8% of

disability-adjusted life years worldwide [4]. The noxious effects of air pollution may be even greater when one exercises because of accelerated, deeper breathing, which results in greater volumes of air pollutants being inspired into the lungs and absorbed into the systemic circulation [5–10]. To gain a more comprehensive understanding of the health issues posed by air pollution, a systematic review of the scientific literature on air pollution and health that accounts for individuals' physical activity is needed [11–13].

The inhaled dose of air pollution (IDoAP) is a potentially more precise air pollution exposure quantification method compared to traditionally measured air pollution exposure concentrations, because IDoAP accounts for the volume of air that passes through the lungs. This volume is referred to as minute ventilation ($\dot{V}_E$) and can be calculated as the product of breathing rate and the depth of the breath (tidal volume (V_T)) [14–16]. Consequently, IDoAP can be estimated as the product of the concentration of an air pollutant, $\dot{V}_E$ and the exposure duration. Although no single device exists to date to measure IDoAP, both air pollutant concentrations and $\dot{V}_E$ can be quantified *via* several methods and devices at varying spatiotemporal resolutions [7]. For example, air pollution can be estimated using concentrations captured at the closest fixed-site monitoring stations, by wearable personal monitors or *via* land-use regression or other types of modelling [17]. $\dot{V}_E$ can be estimated using surrogate parameters such as heart rate [7, 14, 17], or by using predetermined reference values corresponding to different physical activity types and intensities [18, 19]. Finally, exposure duration can be monitored using a diary log or time stamps of deployed wearable (air pollution or physical activity) sensors.

Studies on the effects of IDoAP on different organs and physiological systems are emerging but still scarce. To address the question of whether the benefits of physical activity outweigh the risks of air pollution exposure when both occur concomitantly, and to determine whether IDoAP serves as a superior, integrative air pollution exposure quantification method compared to traditional ambient air pollution concentrations in research studies, we conducted a systematic review with the aim to 1) summarise the known health effects of IDoAP by identifying and quantifying studied populations and settings, air pollutants, physiological systems and specific outcomes, and the temporal and spatial resolutions used to estimate IDoAP; 2) compare the estimated IDoAP health effects across different air pollutant concentrations, $\dot{V}_E$ levels and exposure durations, and identify possible patterns or dose-response effects; and 3) contrast the health effects observed using the IDoAP concept *versus* traditional air pollutant concentrations and physical activity levels separately, deploying different statistical approaches. A final output of this systematic review was the identification of research gaps associated with the three aforementioned aims.

Methods

Search strategy and selection criteria

This systematic review followed the Cochrane recommendations [20] and results were reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [21] and the Synthesis without Meta-analysis (SWiM) [22] guidelines for reporting of systematic reviews. All methods were prespecified and detailed in a protocol (https://osf.io/wdnge/).

Articles were included if they fit all of the following criteria: 1) original research articles, either experimental or observational; 2) involved human participants directly, or indirectly by modelling human respiratory systems and/or physical activity; 3) estimated the inhaled dose of nitrogen dioxide (NO_2) (IDoAP-NO_2), ozone (O_3) (IDoAP-O_3), particulate matter (PM) of any size (*i.e.* <2.5 µm in aerodynamic diameter ($PM_{2.5}$) (IDoAP-$PM_{2.5}$) or <10 µm (PM_{10}) (IDoAP-PM_{10})), ultrafine particles (UFP) (IDoAP-UFP), black carbon (BC) (IDoAP-BC) and other PM (IDoAP-Other)); and 4) evaluated the effect of IDoAP on any health system. Studies fulfilling these criteria but reporting results in a way that did not allow the extraction of potential associations were excluded. There were no language or publication year restrictions.

On 2 May 2022, three reviewers (A. Josa-Culleré, I. Rivas and S. Koch) searched PubMed, Scopus, SPORTDiscus, Embase and Cochrane libraries, combining terms related to air pollution (*e.g.* in PubMed: "air pollution/analysis"[MeSH]) with terms linked to inhaled dose (*e.g.* "inhalation exposure/statistics and numerical data"[MeSH]) and additional terms to specify original studies in humans (*e.g.* "((human*) *)) NOT (editorial) NOT (case study) NOT (commentary)"). A second literature search using identical key words and procedures was performed on 1 November 2024. The full search strategy can be found in supplementary table S1.

CADIMA software was used for the selection process [23]. First, duplicates resulting from the various databases were identified and removed. Then, reference selection took place in two sequential screening phases: title and abstract screening (performed by A. Josa-Culleré, I. Rivas and S. Koch in the first search and A. Josa-Culleré and A. Cakmak-Onal in the second search), and full-text screening (A. Josa-Culleré

and A. Cakmak-Onal in both searches). Prior to each phase, a consistency check was performed by screening 15 records and discussing inconsistencies until consensus was reached on the pursued search strategy, and on inclusion and exclusion criteria. Agreement between reviewers was calculated and considered good, with a κ of 0.67. Each screening was performed in duplicate (*i.e.* each record was reviewed twice, once by two reviewers). Disagreements were solved through consultation with a third and/or fourth reviewer (S. Koch, I. Rivas).

A tailored matrix was designed to systematically extract data to address the three research aims. Extracted variables related to general study characteristics (*e.g.* location, study type), studied participants (*e.g.* sample size, age group), settings (*e.g.* cycling, usual activities), estimation method of IDoAP and its temporal resolution, air pollutant concentrations and IDoAP across assessed physiological systems (*e.g.* respiratory, inflammatory), and quantified associations. For quality control, 10 articles were randomly selected and data extracted by all four reviewers (A. Josa-Culleré, A. Cakmak-Onal, I. Rivas and S. Koch), after which data were extracted in duplicate (A. Josa-Culleré, A. Cakmak-Onal). When necessary, an open-source software was used to convert data plots into numerical values (Digitizer V.2.6.8) [24]. The data extracted by the two reviewers were compared by A. Josa-Culleré, and discrepancies were discussed and solved by I. Rivas and S. Koch. The specific extracted data items, including further information on the categories of temporal resolution, are detailed in supplementary section S1.

The risk of bias assessment was performed differently for experimental and observational studies. For experimental studies, we followed the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach for risk of bias evaluation, and assessed the risk of bias for each study and relevant health outcome [25, 26]. For observational studies, we used the Risk Of Bias In Non-randomized Studies - of Exposure (ROBINS-E) tool [27]. It assesses the risk of bias arising from confounding, measurement of the exposure and the outcome, selection of the participants, potential post-exposure interventions, missing data and selection of the reported results [27].

Data analysis

Whenever possible, we sought to obtain the beta coefficient and its 95% confidence interval when regression models were used to quantify the association between IDoAP and the assessed health outcome. If several beta coefficients were reported due to the use of multiple regressions, we preferably extracted the adjusted estimate. If beta coefficients were not provided, we collected the change from baseline (*i.e.* the post-exposure value minus the pre-exposure value of the outcome). In cases where results were reported as per cent change, the absolute change was obtained using the baseline value of the outcome to facilitate between-study comparisons. When measures of variability other than the confidence interval were provided, they were transformed into confidence intervals using the Cochrane recommendations whenever possible [28].

To summarise results about the health effects of IDoAP, we defined two approaches *a priori*. First, we planned to conduct a meta-analysis for every pair of pollutant–outcome where a minimum of five protocols studying the effect of IDoAP of the same pollutant on a health outcome using the same design was available. Second, we identified possible drivers of the reported health effects in response to IDoAP exposure by dissecting IDoAP into its three components (*i.e.* air pollution concentrations, $\dot{V}_E$ levels or exposure duration) for exposure–outcome pairs with at least five studies, irrespective of the study design. Next, we generated four generalised additive models in which the response variable was the change in the respective health outcome, and the explanatory variables were the IDoAP (model 1), the air pollutant concentrations (model 2), the $\dot{V}_E$ levels (model 3), and the exposure durations (model 4). Models 2 and 3 were adjusted by $\dot{V}_E$ and the air pollutant concentration, respectively.

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation or writing of the report.

Results

Of the 1888 original hits, 25 articles were included in this review (figure 1): 13 (52%) field studies and 12 (48%) conducted in a laboratory setting (table 1). In total, 11 studies (44%) were experimental, and 14 (56%) were observational. Because most studies applied several protocols (*e.g.* using different exposure concentrations or different physical activity intensities) and assessed various air pollutants, the 25 studies translated to a total of 101 different study protocols including 43 (43%) for field studies and 58 (57%) for laboratory studies. Of note, two articles originated from the same study but assessed different outcomes. The detailed protocols can be found in supplementary table S2.

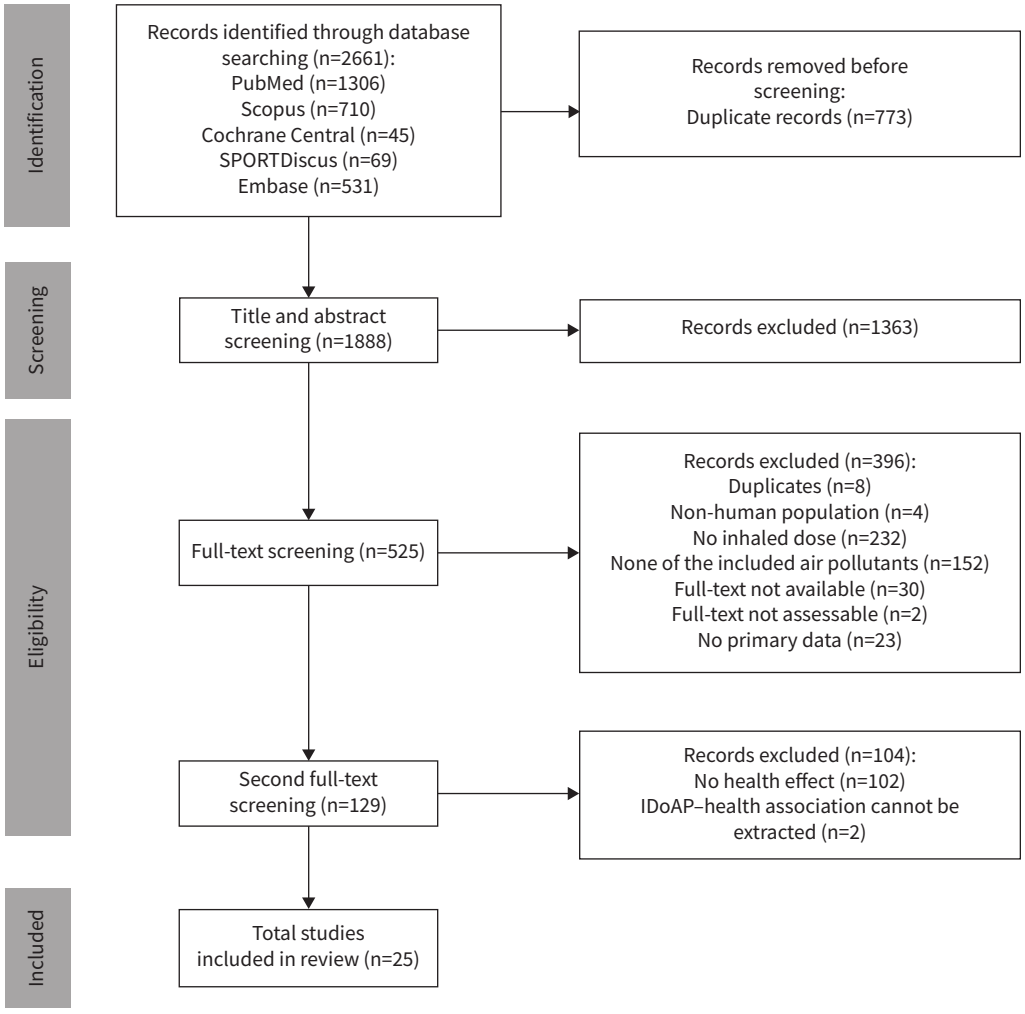

FIGURE 1 Flow diagram of study selection. IDoAP: inhaled dose of air pollution.

Most studies (n=15, 60%) took place in North America, four (16%) in the East Asia and Pacific region, five (20%) in Europe and Central Asia and one (4%) in Latin America; none was carried out in Africa. The overall median (25th–75th percentile) sample size was 20 participants (10–55 participants). All studies focused on healthy individuals: 21 (84%) on adults, three (12%) on adolescents and one (4%) on older adults. None was completed in individuals considered susceptible (*i.e.* those considered to be predisposed to compound harm) or vulnerable (*i.e.* those considered more likely to be exposed to air pollution), *e.g.* pregnant individuals, those diagnosed with a chronic disease or disability, or those who have historically been marginalised [29].

As outlined in table 1, in 11 studies (44%), participants cycled while being exposed to air pollution. Ten studies (40%) consisted of a mix of activities, of which six (24%) included intermittent exercise, mostly consisting of alternations between cycling and resting. Four field studies (16%) used multiple active and passive transport modes such as walking and cycling *versus* being in a car or on a bus. Finally, in five field studies (20%), participants performed their usual day-to-day activities, *e.g.* working or performing household chores. None of the studies compared different exercise types nor included any type of strength training. Further details on the exact applied study protocol including physical activity and/or targeted $\dot{V}_E$ levels are summarised in supplementary table S2.

Both the temporal and spatial resolutions of the air pollution exposure concentrations assessed to estimate IDoAP were considered high due to the deployment of personal monitors with at least hourly measurements in nine out of the 13 field studies, while specific air pollutant concentrations were generated in 11 of the 12 laboratory studies. The temporal resolution to estimate $\dot{V}_E$ was considered high in eight of

TABLE 1 Summary of study characteristics

Study characteristics	All studies	Field studies	Laboratory studies
Studies	25 (100)	13 (52)	12 (48)
Study protocols	101 (100)	43 (43)	58 (58)
Study location			
East Asia and Pacific	4 (16)	3 (23)	1 (8)
Europe and Central Asia	5 (20)	5 (38)	0 (0)
Latin America and Caribbean	1 (4)	1 (8)	0 (0)
North America	15 (60)	4 (31)	11 (92)
Study population			
Children (<12 years)	0 (0)	0 (0)	0 (0)
Adolescents (12–18 years)	3 (12)	2 (15)	1 (8)
Adults (19–64 years)	21 (84)	11 (85)	10 (83)
Seniors (⩾65 years)	1 (4)	0 (0)	1 (8)
Sex			
Both	20 (80)	13 (100)	7 (58)
Only male	4 (16)	0 (0)	4 (33)
Only female	1 (4)	0 (0)	1 (8)
Health status			
Healthy	25 (100)	13 (100)	12 (100)
Respiratory disease	0 (0)	0 (0)	0 (0)
Cardiovascular disease	0 (0)	0 (0)	0 (0)
Other diseases	0 (0)	0 (0)	0 (0)
Settings[#]			
Cycling	11 (44)	3 (23)	8 (67)
Usual activities	5 (20)	5 (39)	0 (0)
Mix:	10 (40)	5 (39)	5 (42)
Intermittent exercise	6 (24)	1 (8)	5 (42)
Multiple transport modes	4 (16)	4 (31)	0 (0)
Other	3 (12)	3 (23)	0 (0)
Temporal resolution of the air pollution exposure estimation			
Low resolution	0 (0)	0 (0)	0 (0)
Medium resolution	4 (16)	4 (31)	0 (0)
High resolution	10 (40)	9 (69)	1 (8)
Laboratory setting	11 (44)	0 (0)	11 (92)
Temporal resolution of the minute ventilation estimation			
Low resolution	1 (4)	1 (8)	0 (0)
Medium resolution	2 (8)	2 (15)	0 (0)
High resolution	8 (32)	8 (62)	0 (0.0)
Very high resolution	14 (56)	2 (15)	12 (100)

Data are presented as n (%). [#]: categories are not mutually exclusive and some studies looked at multiple protocols; therefore, numbers may add up to more than 25.

the 13 field studies, with physical activity intensity having been obtained from personal wearable monitors and subsequent derivations of $\dot{V}_E$ estimates using reference tables maintaining, at the minimum, an hourly resolution. All laboratory studies produced and maintained specific air pollutant concentrations and used very-high-resolution methods to directly measure $\dot{V}_E$ at the mouth with facemasks continuously worn by the participants. Finally, on average field studies covered an exposure duration of 16 h (range 1–24 h), while laboratory studies covered an exposure duration of 2.4 h (range 0.50–6.6 h).

Regarding the assessed air pollutants, in field studies, IDoAP-PM was the most frequently assessed, particularly IDoAP-$PM_{2.5}$ (12 studies, 92%), IDoAP-BC (seven studies, 54%) and IDoAP-PM_{10} (five studies, 38%). In laboratory settings, most studies focused on IDoAP-O_3 (10 studies, 83%) (figure 2).

With regards to assessed body systems, the respiratory system was the most studied in 19 studies. Within the respiratory system, the most frequently assessed outcomes were forced expiratory volume in 1 s (FEV_1) and forced vital capacity (FVC) in 17 studies, while forced expiratory flow at 25% to 75% of vital capacity ($FEF_{25–75\%}$) was assessed in 11 studies. Six field studies (24%) evaluated the effects of IDoAP on the inflammatory system *via* biomarkers such as the fraction of exhaled nitric oxide

Parameter	All studies	Field studies	Laboratory studies
Studies	**25 (100)**	**13 (52)**	**12 (48)**
Air pollutant[#]			
BC	8 (32)	7 (54)	1 (8)
NO_2	3 (12)	2 (15)	1 (8)
O_3	13 (52)	3 (23)	10 (83)
PM_{10}	5 (20)	5 (38)	0 (0)
$PM_{2.5}$	12 (48)	12 (92)	0 (0)
UFP	1 (4)	1 (8)	0 (0)
Health effects[#]			
Respiratory	**19 (76)**	**7 (54)**	**12 (100)**
Lung and respiratory function	19 (76)	7 (54)	12 (67)
Respiratory symptoms	2 (8)	0 (0)	2 (11)
Airway resistance	2 (8)	1 (8)	1 (6)
Inflammatory	**6 (24)**	**6 (46)**	**0 (0)**
Biomarker of inflammation	6 (24)	6 (46)	0 (0)
Coagulation parameters	1 (4)	1 (8)	0 (0)
Haematological parameter	2 (8)	2 (15)	0 (0)
Cardiovascular	**8 (32)**	**5 (38)**	**3 (25)**
Blood pressure	4 (16)	2 (15)	1 (6)
Heart rate status and variability	3 (12)	1 (8)	2 (11)
Other cardiovascular parameters	1 (4)	1 (8)	0 (0)
Mental health effects	**1 (4)**	**1 (8)**	**0 (0)**
Genotoxicity	**1 (4)**	**1 (8)**	**0 (0)**

FIGURE 2 Air pollutant and health effects evaluated in the included studies. Data are presented as n (%). Colours depict the percentage of studies within columns assessing each of the air pollutant and health effects, going from white (0%) to dark green (100%). Bold numbers indicate results for general health systems (*e.g.* respiratory system) in contrast to specific health effects (*e.g.* lung and respiratory function). [#]: categories are not mutually exclusive and some studies looked at multiple air pollutants and/or health effects (*e.g.* one study may look at biomarkers of inflammation, haematological parameters and respiratory symptoms); therefore, numbers may add up to more than 25. BC: black carbon; NO_2: nitrogen dioxide; O_3: ozone; $PM_{2.5}$: particulate matter <2.5 µm in aerodynamic diameter; PM_{10}: particulate matter <10 µm in aerodynamic diameter; UFP: ultrafine particles.

(F_{eNO}) or C-reactive protein. Eight studies (32%) quantified the effects of IDoAP on the cardiovascular system *via* heart rate and blood pressure, one study (4%) assessed IDoAP's effects on mental health, and one study (4%) assessed its genotoxicity. A more detailed overview of what outcomes and pollutants were assessed in field and laboratory studies, including their frequencies, is provided in supplementary table S3.

Of the outcomes, only IDoAP-O_3 exceeded the *a priori* set minimal threshold of five studies for meaningful comparisons of the findings, for its association with FEV_1 (quantified in 60 study protocols), FVC (quantified in 67 study protocols) and $FEF_{25–75\%}$ (quantified in 42 study protocols). Because of the heterogeneity in study design, meta-analysis was not possible. Most studies reported an acute reduction of both FEV_1 and FVC when being physically active while exposed to O_3 (figure 3 and supplementary figure S1A), and this negative effect tended to be more pronounced with higher IDoAP-O_3 levels (figure 3 and supplementary figure S1B). When assessing the effect of each of the three components of IDoAP-O_3 (*i.e.* O_3 concentration, $\dot{V}_E$ and duration of exposure), a higher O_3 concentration related to greater reductions in FEV_1 and FVC (*e.g.* an increase from 0 to 150 $\mu g \cdot m^{-3}$ in O_3 led to a decrease of 0.27 L in FEV_1, respectively), whereas increases in $\dot{V}_E$ or exposure duration were not associated with changes in FEV_1 or FVC (figure 3 and supplementary figure S1C). A similar trend was observed for $FEF_{25–75\%}$ (supplementary figure S2). IDoAP did not seem to be associated with a significant change in NO_2, PM_{10}, $PM_{2.5}$, BC or other PM; however, the number of studies was considerably lower for these pollutants, with one to four protocols per pollutant (supplementary figure S3). Four studies (18 study protocols) looked at the effect of IDoAP-O_3 on breathing frequency and V_T (supplementary figure S4). Overall, increasing IDoAP-O_3 was associated with increased respiratory rate and decreased V_T.

For inflammatory and cardiovascular outcomes, only one of seven study protocols suggested an association between IDoAP-$PM_{2.5}$ and increased F_{eNO} (supplementary figure S5). No study showed an association between IDoAP of any pollutant and C-reactive protein. IDoAP-O_3 but not $PM_{2.5}$ was

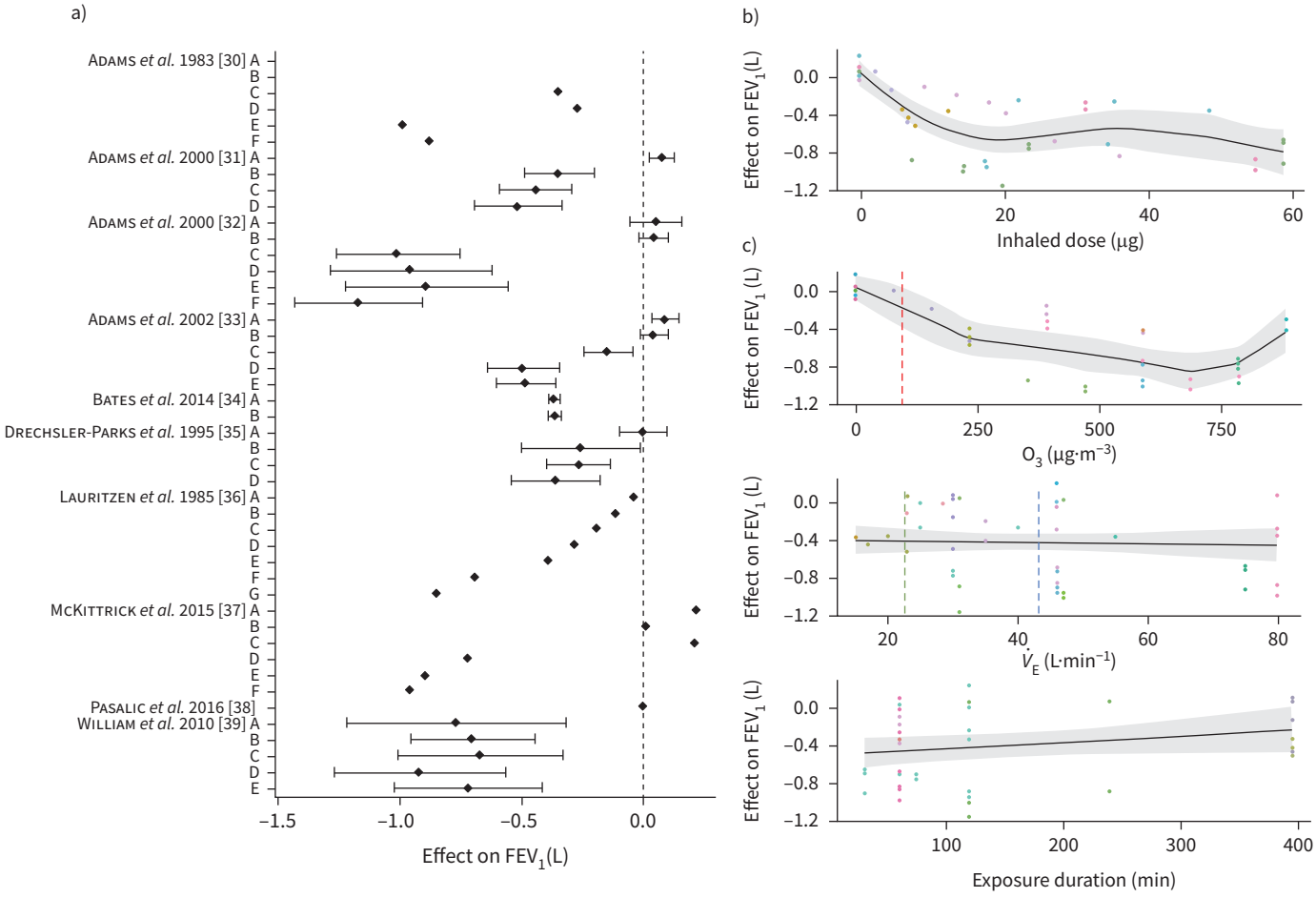

FIGURE 3 Effect of inhaled dose of air pollution and its components for ozone (IDoAP-O_3) on forced expiratory volume in 1 s (FEV_1). a) Change in FEV_1 per study and protocol. Study first author and year are provided, with the letters "A" to "G" referring to different protocols applied within the same study [30–39]. b, c) Effect of IDoAP-O_3 and its components on FEV_1. The colour of the dots refers to the different studies. In c, the vertical dotted lines indicate the maximum daily 8-h mean O_3 concentration recommended by the World Health Organization (WHO) (red) [1] and the minute ventilation ($\dot{V}_E$) estimate used in the WHO/Europe Health Economic Assessment Tool (HEAT) for walking (green) and running (blue) [18].

associated with increased heart rate while exercising. One study protocol looked at the effect of IDoAP-BC on mental health and reported a positive association between IDoAP-BC and symptoms of depression. No other systems such as cognitive or reproductive systems were assessed.

With respect to objective 3, none of the studies reported the estimates of the 1) main or 2) interaction effects of air pollution and physical activity, or of 3) IDoAP on a measured health outcome in the same dataset, making an evaluation of IDoAP as a superior air pollution quantification method impossible.

The overall risk of bias within the 11 experimental studies was considered low in seven studies (supplementary tables S4 and S5). In the remaining five studies, concerns arose mainly due to incomplete information on the randomisation process and potential deviations from the intended interventions. For observational studies, possible selection bias was identified in all 14 studies and was of particular concern in nine studies. In four studies, concerns related to the existence and treatment of missing data were identified together with insufficient information on the method used to estimate IDoAP; in another study the selection of participants was insufficiently described; and in another study the risk of bias arising from potential confounding was considered high.

Discussion

This study systematically reviewed the scientific evidence linking IDoAP with health outcomes. The main findings were 1) peer-reviewed original studies predominantly focused on healthy adults from high-income regions, investigating primarily the association between respiratory outcomes and IDoAP-O_3 in laboratory settings, while field studies primarily focused on IDoAP-PM and respiratory outcomes; 2) the study protocols and methods used to estimate IDoAP were highly heterogeneous; and 3) IDoAP-O_3 was associated with an acute decrease in FEV_1, FVC and $FEF_{25–75\%}$, and these associations were mainly driven by O_3 concentrations rather than $\dot{V}_E$ levels or exposure duration. We could not determine whether IDoAP serves as a more sensitive air pollution quantification method compared to the traditional air pollution concentration and physical activity, each measured as an individual variable, because no study assessed the health effect of air pollution exposure and physical activity applying all the required statistical approaches.

Our review showed that IDoAP research in individuals considered susceptible or vulnerable is lacking (research gap 1, figure 4). Pre-existing health conditions and early and older ages do not only increase susceptibility to air pollution exposure caused by *e.g.* a reduced immune system [40]. These individuals'

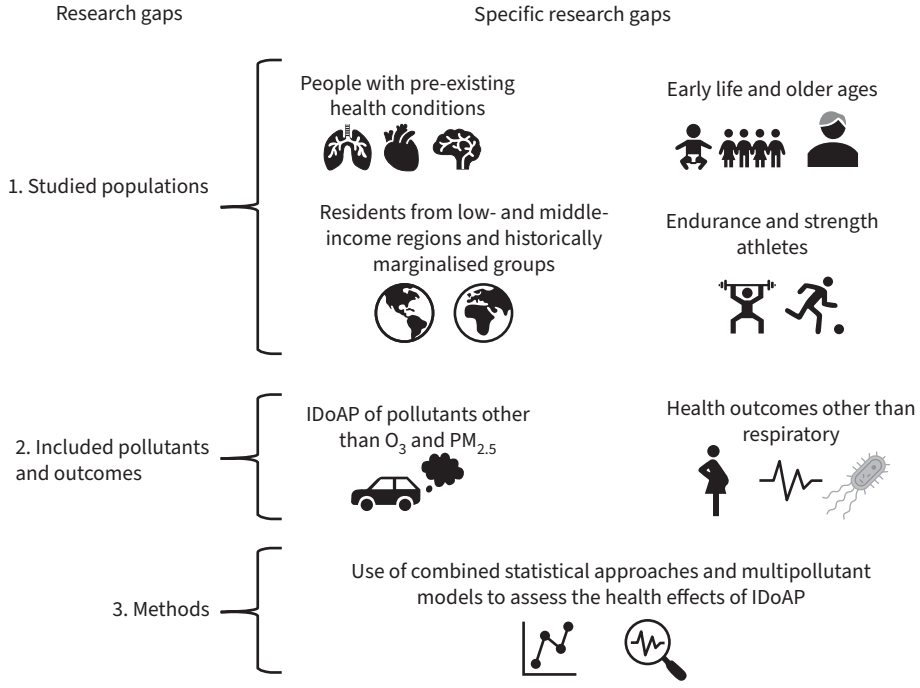

FIGURE 4 Research gaps identified through the systematic review. IDoAP: inhaled dose of air pollution; $PM_{2.5}$: particulate matter <2.5 μm in aerodynamic diameter.

$\dot{V}_E$ levels and respiratory responses to physical activity also differ from those of healthy adults (*i.e.* less efficient breathing strategies); consequently, the effects and underlying mechanisms of IDoAP on these susceptible populations might be bigger and different, respectively, than in healthy adults [41] and may not be detectable using air pollutant concentration alone. A potential explanation for this research gap might be the lack of algorithms to estimate $\dot{V}_E$ specifically in these susceptible groups. These algorithms would permit the estimation of IDoAP *via* surrogate parameters (*e.g.* heart rate) that are cheaper and less complex to measure than directly measuring at the mouth with facemasks, particularly in the real world. Finally, another reason why the IDoAP concept has not yet been studied in these populations might be hesitancy related to the additional challenges and costs in obtaining ethical approval and recruitment.

Another understudied population is athletes, whose long and frequent training sessions may result in a consistently higher IDoAP, with effects not comparable to those of the general population because of their different body composition and increased metabolic and respiratory demands. Further, IDoAP-induced health effects might vary between different exercise types, such as endurance *versus* strength training. Finally, in comparison to higher-income regions, low-to-middle-income regions (LMIRs) have higher air pollution exposure concentrations [42]. Occupational and day-to-day activities of LMIR residents tend to entail higher physical activity levels and longer exposure durations [40, 43]. As a result, traditional air pollution exposure measures that do not account for $\dot{V}_E$ levels or exposure duration may not be appropriate to assess the health effects of these exposures. IDoAP could provide an integrative solution to advance our understanding of the health effects of air pollution exposure in these populations.

IDoAP research on pollutants other than O_3 and $PM_{2.5}$ and on organs besides the lung and the respiratory tract are missing. Further insights into how IDoAP affects other systems, such as cognitive function and mental health, are lacking (research gap 2) but relevant as the demographic shift progresses. In the years to come, the number of individuals affected by age-related physiological and cognitive decline is expected to increase, as are mental health issues. A better understanding of how IDoAP affects such conditions could be relevant for preventive measures. Air pollution is a complex mixture of gases and particles of diverse sizes and compositions, each affecting physiological systems through different pathways [1]. Because available studies used different protocols and varying temporal and spatial resolutions to estimate and report IDoAP, our ability to compare results across studies was hindered. A previous systematic review of 53 randomised controlled trials aiming to determine the effects of air pollution exposure (in lieu of IDoAP) while engaging in physical activity was also hindered in drawing further conclusions due to the inability to meta-analyse the results [44]. In our review, exposure duration across all studies was limited to a maximum of 24 h, reducing the observed window to solely acute and short-term health effects, and overlooking chronic or long-term effects.

Finally, there was a lack of studies focusing on multipollutant rather than on single pollutant inhaled dose models, which would better capture real-life air pollutant mixtures and account for potential confounding between pollutants (research gap 3) [45]. Further, studies did not provide the statistical analyses required to answer the question of whether the IDoAP concept truly serves as a more sensitive method in the detection of health effects compared to the traditional approach of integrating air pollutant concentrations and physical activity levels as separate variables into a single regression model. Addressing this question will require coherent, uniform methods to assess and interpret IDoAP. Our results suggest that, in healthy adults, acute effects in FEV_1, FVC and $FEF_{25–75\%}$ in response to IDoAP-O_3 were mainly driven by the concentration of O_3 rather than by $\dot{V}_E$ levels, and thus the intensity of physical activity. This reduction in FEV_1, FVC and $FEF_{25–75\%}$ in response to IDoAP-O_3 exposure was observed even when O_3 concentrations were below the recommended 2021 World Health Organization (WHO) Air Quality Guidelines [1], and confirms findings of adverse health effects when exposed to concentrations that were previously considered "low" [46–48]. Further, our results align with those of a previous systematic review: despite higher IDoAP when actively commuting (*i.e.* walking or biking), participants' life expectancy was estimated to be greater compared to passive commuters in motorised vehicles [49], suggesting that the benefits of physical activity outweigh the risks of air pollution in a healthy adult population. Similar to our review, the work by Giles *et al*. [50–52] reported no effect modification by exercise intensity in the association between diesel exhaust exposure on various health outcomes. Consequently, to mitigate air pollution risks during physical activity, IDoAP should be kept as low as possible by reducing one's air pollution exposure, *e.g.* by separating oneself in distance or time from air pollution sources such as traffic rush hour, vehicle-dense motorways, construction sites or industrial zones [53].

This systematic review resulted in several implications beyond the identified research gaps (figure 4). From a public health perspective in healthy adults, physical activity, even at moderate or high intensities, should not be discouraged categorically when O_3 concentrations exceed the WHO guidelines. Because none of the

included studies assessed IDoAP at air pollution concentrations and exposure durations comparable to climate disasters such as acute wild fires, it is impossible to extrapolate this finding to extreme air pollution concentrations that can extend over several days, weeks or months. In the years to come, the progressing climate crisis is expected to create hotter environments, thus favouring higher indoor and outdoor air pollution concentrations. Even though our review did not include any studies related to wild fires, likely due to their acute occurrences challenging the quick deployment of research protocols, further research of how IDoAP in acute settings affects the health of individuals living and working in nearby areas would deepen our understanding of how physical activity and air pollution concomitantly affect health. Given that many air pollutants travel far beyond their sources, local measures alone are insufficient to combat this global threat. Therefore, protecting lung and overall health from the effects of IDoAP-O_3 (and other pollutants) requires multisectoral action at local, national and international levels. These efforts should include, among other strategies, the reduction of key O_3 precursors such as NO_x and volatile organic compounds. It also highlights the need to amplify the number of easily accessible low-pollution public corridors for individuals to engage in physical activity, so that health benefits can be maximised in part due to low IDoAP. Because our findings can only be applied to healthy adults, we call for intensified research efforts to study the combined effects of physical activity and air pollution exposure in individuals traditionally identified as susceptible (*e.g.* people with pre-existing conditions) and those who are considered healthy but vulnerable, *e.g.* because of occupational environments, including firefighters or construction workers as well as professional endurance athletes.

A strength of this review was the rigorous, replicable and systematic approach followed throughout, which was of particular importance considering the heterogeneity of the identified studies. However, a shortcoming of our review was the inability to meta-analyse results. As previously mentioned, all included studies were on acute effects of IDoAP, preventing us from drawing conclusions on the long-term health effects of IDoAP, and excluded exposure concentrations and durations of extreme climate disasters or LMIRs, all of which reduces the generalisability of our results. Another limitation is that the use of single-pollutant models in most of the included studies may have led to uncontrolled confounding by other pollutants. Finally, even though not within the aims of this work, a review of the existing methodological approaches to calculate IDoAP and the implications of different estimation processes is still needed to agree on a unified calculation process to enhance comparability across studies and to deepen our understanding of IDoAP on health.

In conclusion, this systematic review identified the following IDoAP research gaps: 1) a lack of studies in susceptible and vulnerable individuals and LMIRs, 2) the narrow scope of studied health outcomes and air pollutants and 3) the need for more comprehensive statistical approaches to be able to assess the potential superiority of the IDoAP approach compared to traditional approaches when studying the combined effects of air pollution exposure during physical activity. IDoAP-O_3 was associated with reduced lung function in healthy adults, an effect that was mainly driven by O_3 concentration rather than exercise intensity. Global and individual-level air pollution exposures, particularly those of O_3, should be reduced and low-pollution public corridors generated for individuals to maximise the health effects from physical activity.

Questions for future research

Future studies on IDoAP should consider the following research gaps:

- Studied populations: no studies included people with pre-existing health conditions, such as respiratory diseases, early life and older ages, people living in LMIRs, and endurance and strength athletes.
- Pollutants and outcomes: there is scarce research on IDoAP for pollutants other than O_3 and $PM_{2.5}$, and for outcomes other than lung function.
- Methods: future studies should aim to combine statistical approaches and use multipollutant models to get a better understanding of the health effects of IDoAP.

Data availability: The data supporting the findings of this review will be made available to interested parties upon reasonable request to the corresponding author.

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acquisition, methodology, visualisation, writing – review and editing. I. Rivas: conceptualisation, data curation, methodology, supervision, visualisation, writing – review and editing. S. Koch: conceptualisation, data curation, methodology, supervision, visualisation, writing – original draft, writing – review and editing.

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