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Review article

Co-exposure to air pollution and noise from traffic and their association with cognitive impairment in adults. Systematic review

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ABSTRACT

Background: Both air pollution (AP) and traffic noise are known as being independently associated with adverse cognitive outcomes. Although traffic is known to be a common source of both types of exposures, there is limited evidence on how these exposures interact and mutually confound cognitive function.
Objective: Investigate how long-term AP and traffic noise are interrelated in their association with and effect on cognitive impairment, with a specific focus on possible effect modification (EM)/interaction and mutual confounding.
Methods: All English-language studies meeting the eligibility criteria were considered. We included all studies on MEDLINE, Web of Science, and LUDOK database of Swiss TPH published until April 17, 2024. The quality of evidence was evaluated according to the Office of Health Assessment and Translation (OHAT) system.
Results: Nineteen studies on the long-term effects of co-exposure to AP and traffic noise on cognitive function were identified. All studies showed moderate external validity. The overall confidence in the evidence was low to moderate. Effect estimates remained stable after mutual adjustment for AP and noise across most cognitive outcomes. This pattern was consistent for both exposures. Three studies with high exposure levels reported evidence of EM and interaction, while two studies with lower exposure levels observed no interactions.
Conclusion: Studies analysing co-exposures require more transparent reporting of changes in effect estimates before and after adjustment, as well as an additional examination for possible EM and interaction.

1. Introduction

Currently, negative independent effects of either air pollution (AP) or noise on health have been well researched, however less attention exists about the effects of their combination as in traffic (WHO Europe, 2019; World Health Organization, 2021). The growing rates of traffic and urbanization require an examination of their interrelation. Short-term exposures to AP and noise can lead to health issues such as altered heart rate variability (Huang et al., 2013), psychological stress (Tao et al., 2021), and sleep disturbances (Ayta, 2024; Basner and McGuire, 2018). In the long term, an important adverse health effect of AP and noise is a decline in cognitive function. This decline is particularly problematic in aging populations, because it is related to an increased risk of mortality and associated with neurodegenerative diseases, such as dementia (Batty et al., 2007).

Systematic reviews and meta-analyses have investigated the association between long-term AP exposure and cognition based on epidemiological studies with longitudinal and cross-sectional designs. Delgado-Saborit et al. (2021) reviewed 69 studies examining the general effects of AP on cognition and found consistent evidence that chronic AP exposure is linked to reduced global cognition, reduced performance in specific cognitive domains, and white matter volume reduction (Delgado-Saborit et al., 2021). Thompson et al. (2023) conducted a systematic review of 68 studies and a meta-analysis of 14 studies that analysed different pollutants. They found that in people aged 40 and older, NO_2 was associated with lower general cognition. In the same age group, $PM_{2.5}$ was associated with lower general cognition, verbal fluency, and executive function (Thompson et al., 2023). Similarly, McLachlan et al. (2023) demonstrated that, in adults aged 50 and older, declines in cognitive and executive function, memory, and language were most strongly correlated with greater exposure to $PM_{2.5}$ and PM_{10}, and to a lesser extent, NO_2, based on a systematic review and

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meta-analysis of 26 longitudinal studies (McLachlan et al., 2023). Reviews by Wilker et al. (2023), McLachlan et al. (2023), and Tuffier et al. (2024) identified $PM_{2.5}$ as a potential risk factor for dementia. With more limited data, these reviews also identified NO_2 and NO as potential risk factors (McLachlan et al., 2023; Tuffier et al., 2024; Wilker, 2023).

The relationship between long-term noise exposure and cognitive function has been explored in two meta-analyses and systematic reviews. In a systematic review of 48 studies, Thompson et al. (2022) found an association between environmental noise exposure and cognitive impairment in middle-to-older adults. The evidence was deemed high quality using the Office of Health Assessment and Translation (OHAT) Risk of Bias Rating Tool. In their meta-analysis of three studies, they found higher odds of cognitive impairment in people over 45 years old with higher residential noise exposure compared to those with lower exposure (Thompson et al., 2022). Meng et al. (2022) explored the association between chronic noise exposure, including noise from traffic, community environments, and occupational sources, and the risk of dementia. They conducted a systematic review including 11 studies, nine were eligible for a dose-response meta-analysis. They found a positive linear association between an increment in noise exposure and overall dementia risk (Meng et al., 2022).

Both AP and noise share the same source – traffic, which suggests that they have a common or confounding effect on health outcomes. Minimizing biases in observational studies is crucial for the validity and robustness of statistical inferences (Sterrantino, 2024). Two epidemiological concepts that describe the interrelation between variables in the context of exposure-outcome relationships are effect modification (EM) and interaction. Often considered as a single concept, they both describe how an independent variable's effect on a dependant variable is influenced by another variable. EM describes how the impact of a single intervention differs across levels of a second variable. Interaction, on the other hand, refers to the combined effects of two interventions (Bours, 2023; VanderWeele, 2009a) (see Supplement (S.) B for further explanations).

Most studies investigating the interrelation between AP and traffic noise have focused on cardiovascular outcomes. Three reviews mostly suggested that the association between exposure and outcome is independent of the other exposure (Eminson et al., 2023; Stansfeld, 2015; Tétreault et al., 2013). A systematic review by Chandra et al. (2022) includes a section on air and noise pollution and cognitive dysfunction in older adults. However, it lacks in-depth analysis and it does not exclusively include studies of both exposures (Chandra et al., 2022).

Existing reviews that examine co-exposure to AP and noise often lack key methodological components of a systematic review, such as a formal risk of bias assessment. Moreover, they typically do not follow established systematic review protocols, limiting the reproducibility and reliability of their findings. A new systematic review is warranted to address this methodological gap by rigorously evaluating the evidence on traffic-related co-exposure to AP and noise and its association with cognitive outcomes. In addition, several recent epidemiological studies assessing both exposures simultaneously have not yet been included in any systematic synthesis, underscoring the need for an updated and comprehensive review. Therefore, the type of interrelation between AP and noise in their effect on cognition and associated neurodegenerative diseases is still unclear. This leads to the open question whether confounding or EM/interaction occurs between these two exposures. It is unclear to what extend the association of one exposure is affected by the other, and if so, in which direction (positive or negative joint effect). Clarifying their interrelation could facilitate and standardise statistical calculations, thereby providing a better understanding of their mode of action.

Thus, this systematic review aimed to investigate the interrelation between long-term AP and traffic noise in their association with cognitive outcomes and associated neurodegenerative diseases in adults. It does not take into account studies about cognitive development in children or studies analysing other sources of noise. We compared the statistical models and adjustment sets used in different studies to account for co-exposure. We explored the magnitude of confounding by investigating estimates before and after adjusting for the other exposure. Finally, we analysed EM and interaction in the effects of AP and noise on cognitive outcomes and associated neurodegenerative diseases.

2. Methods

This systematic review was guided by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses 2020 (PRISMA) 27-item checklist (Page et al., 2021). The Participants, Exposure, Comparator, Outcomes, and Study Design (PECOS) statement for this research is as follows:

P: Adults.

E: Long-term co-exposure to traffic air pollutants and noise.

C: Different levels of long-term exposure, persons less exposed (continuously or in high/low exposure groups).

O: Cognitive function, cognitive decline, and incidence of cognitive impairment or associated neurodegenerative disease such as dementia (morbidity and mortality)

S: Epidemiological observational studies quantifying the exposure-outcome relationship at the individual level (non-experimental).

2.1. Eligibility criteria

All studies published in English in the MEDLINE, Web of Science, and LUDOK (by Swiss TPH) databases until April 17, 2024 with all types of designs except for ecological studies were considered. The inclusion and exclusion criteria can be found in Table 1.

2.2. Information sources

Search websites were the databases MEDLINE (PubMed), Web of Science, and LUDOK database (by Swiss TPH). Additionally, we searched for related articles through MEDLINE and Google Scholar and manually scanned the reference lists of 11 reviews about either AP or noise to identify included studies. All relevant studies were available through institutional access.

2.3. Search strategy

The search took place from 11/03/24–17/04/24 until saturation. The search consisted of four concepts with more extensive entry terms: traffic, cognition, AP, and noise. To limit irrelevant results (>95 000 hits), "traffic" and "cognition" were combined using the AND operator. AP and noise were combined using the OR operator (traffic AND cognition AND (AP OR noise)). The search terms were checked by the second reviewer. Duplicates were removed using Endnote (X8), a reference management software program. The search strategy and details can be found in the supplementary materials. Selection process, title, abstract, and full text screening were conducted by one author. The primary selection was based on the title and abstract to determine if the study included traffic, cognition, and one exposure. Since most of the studies found were about either AP or noise (AP OR noise), all relevant articles were opened in full text to identify articles with co-exposure. In studies with AP as primary exposure, the full text was searched for the term "noise"; in studies with noise as the primary exposure, the full text was searched for the term "air pollut" and other terms. The suitability of the identified co-exposure studies was discussed with a second author. The final selection was based on the full text according to the inclusion criteria. Excluded studies, with justifications, are listed in the supplementary material (S. B Table 3).

2.4. Risk of bias in individual studies and certainty assessment

Risk of bias was evaluated using the OHAT method. It entails six

Table 1
Inclusion and Exclusion criteria to determine study eligibility (ICD-11 codes from the WHO version 2025-1, where applicable).

	Inclusion Criteria	Exclusion Criteria
Population	General adult population 18+, countries of all income levels, urban and rural	Populations exposed exclusively indoors or occupational
Exposure	Long-term (months to years) traffic-related AP and traffic noise investigated together in the same article Traffic AP Pollutants: particulate matter ($PM_{2.5}$, PM_{10}, PM_{coarse}), nitrogen oxides (NO_x, NO_2), ozone, carbon monoxide Road traffic noise Estimated daily environmental noise exposure (e.g. day-evening-night noise level (L_{den}), equivalent continuous sound level (LA_{eq}), nighttime noise (L_{night})	Short-term exposures (minutes to months), any other kind of noise except road traffic, only one exposure, green spaces, traffic accidents, indoor or household AP, other air pollutants as carbon dioxide, volatile organic compounds, sulfur dioxide, lead/airborne metals, polycyclic aromatic hydrocarbons, indirect measures such as distance to or traffic density at nearest major roads
Comparators	Exposure to lower levels of AP and noise in the same or in a referent population	
Outcomes	Cognitive function and dysfunction ratings on a continuous scale (intelligence and IQ, task-measured, attention, working memory, executive function, memory and learning, reaction time, processing speed), structural brain imaging measuring brain degeneration, functional neuroimaging measuring brain function, morbidity and mortality from neurodegenerative diseases such as dementia (6D80-6D83), Parkinson (8A00), Multiple sclerosis (8A40)	Neurodevelopmental and neuropsychological disorders (e.g. depression (6A7Z), anxiety (MB24.3)), stroke (8B20), annoyance, quality of life, self-reported health, sleep, medication, polyneuropathy (8C0Z), sensory function (VW10-1Z), motoneuron diseases
Study design and publication type	Human studies including observational studies, cross-sectional studies, case-control studies, longitudinal studies (prospective, retrospective); Peer-reviewed academic publications in English published until April 2024; Studies reporting a quantitative measure of association and a measure of precision	Non-epidemiological (e.g. controlled experimental exposures in a lab); Qualitative studies, studies reporting only unadjusted results, and clear evidence of an analytical error; Studies without individual level data (e.g. ecological study); Studies where no original data were analysed, reviews, or methodological papers; Genome-wide association study (GWAS) and all other -omics studies; Nonhuman studies (in vivo, in vitro, other); Grey literature, conference abstracts or papers, notes, editorials, letters, and unpublished data, reports without methods section

domains to, which are evaluated with ten risk-of-bias questions. We selected eight of these questions as appropriate for the review, given the observational design of the included studies. Each question has four response options, as well as the option to judge the direction of bias (OHAT, 2019). For each question, we defined specific criteria (Supplement B Table 4). We only judged the direction of bias in items rated with the response options "probably high risk of bias" or "definitely high risk of bias" and only when they were deemed relevant. For transparency, the online tool hawcproject.org was used, which can be visited for detailed information (Hawc Project, 2024). External validity (not included in OHAT) was assessed using four items: population representativeness, time period, and similarity of exposure and outcome measures (SupplementS. B Table 5). Next, we rated confidence in the body of evidence as suggested by the Grading of Recommendations, Assessment, Development, and Evaluations (GRADE) framework (within the OHAT approach (BMJ Best Practice, 2024). The studies were clustered into four groups according to key features of their study design and measured outcomes. The following steps were taken: 1. Rating of initial confidence by key features of the study design, 2. Consideration of factors decreasing confidence, 3. Consideration of factors increasing confidence, 4. Assessment of confidence in the body of evidence (OHAT, 2019) (S. B Tables 6 and 7).

2.5. Effect estimates

For the interrelation between AP and/or noise and cognition, the effect estimates used were odds ratios with 95 % confidence intervals in case-control or cross-sectional studies. For the interrelation between AP and/or noise and mortality/morbidity, the effect estimate was the hazard ratio with 95 % confidence intervals in cohort studies. Depending on the type of outcome, different statistical models exist for adjustment, such as linear regression, logistic regression, or Cox proportional hazard regression. EM was analysed using regression models with interaction terms or stratified analyses for separate subgroups, depending on the outcome. This allowed comparison between groups exposed to high or low levels of AP and noise. To detect confounding, the common change-in-estimate criterion was used, in which confounders are defined as variables that modify the unadjusted exposure-outcome effect by a certain percentage (Lee, 2014). Within each study, the effect estimates of the statistical model, including both exposures (multi-pollutant model) were subtracted from the effect estimates of the model excluding one exposure (single-pollutant model). A change was considered statistically significant if the confidence intervals did not overlap 1.0. Changes-in-estimate of at least 0.1 were converted into percentages. According to common epidemiologic convention, a relevant change in estimate was defined as a difference $\geq$0.1/$\geq$10 % of the estimate with one exposure (Maldonado and Greenland, 1993). Due to the heterogeneity of the data, no confidence intervals for changes in estimates were calculated. The change in noise model estimates adjusted for AP was compared to the change in estimates of AP model estimates adjusted for noise.

2.6. Data synthesis

This study adheres to the Guidelines for Accurate and Transparent Health Estimates Reporting (GATHER) (Stevens et al., 2016) and to the PRISMA reporting guidelines (Page et al., 2021). Due to the heterogeneity of data, such as differences in exposure measurement and variability of air pollutants across the included studies, a meta-analysis was not feasible. Numbers were rounded to two decimal places.

3. Results

We identified 3602 records from three databases and reference list searches. After screening, 34 records were assessed for eligibility. The reasons for exclusion were missing data for co-exposure despite the measurement of both AP and noise (e.g., examining AP and noise separately) adjusting AP or noise together with other factors, short-term exposures, and data duplicates (Supplement B Table 3). Finally, 19 studies were included in the review, which examined 78 exposure-outcome relationships (Fig. 1). Of these studies, 16 originate from Europe and three from North America. Fifteen studies had a longitudinal design, and four had a cross-sectional study design. Fourteen studies assessed only confounding, two studies assessed confounding and interaction (Andersson et al., 2018; Tzivian et al., 2016b), two studies

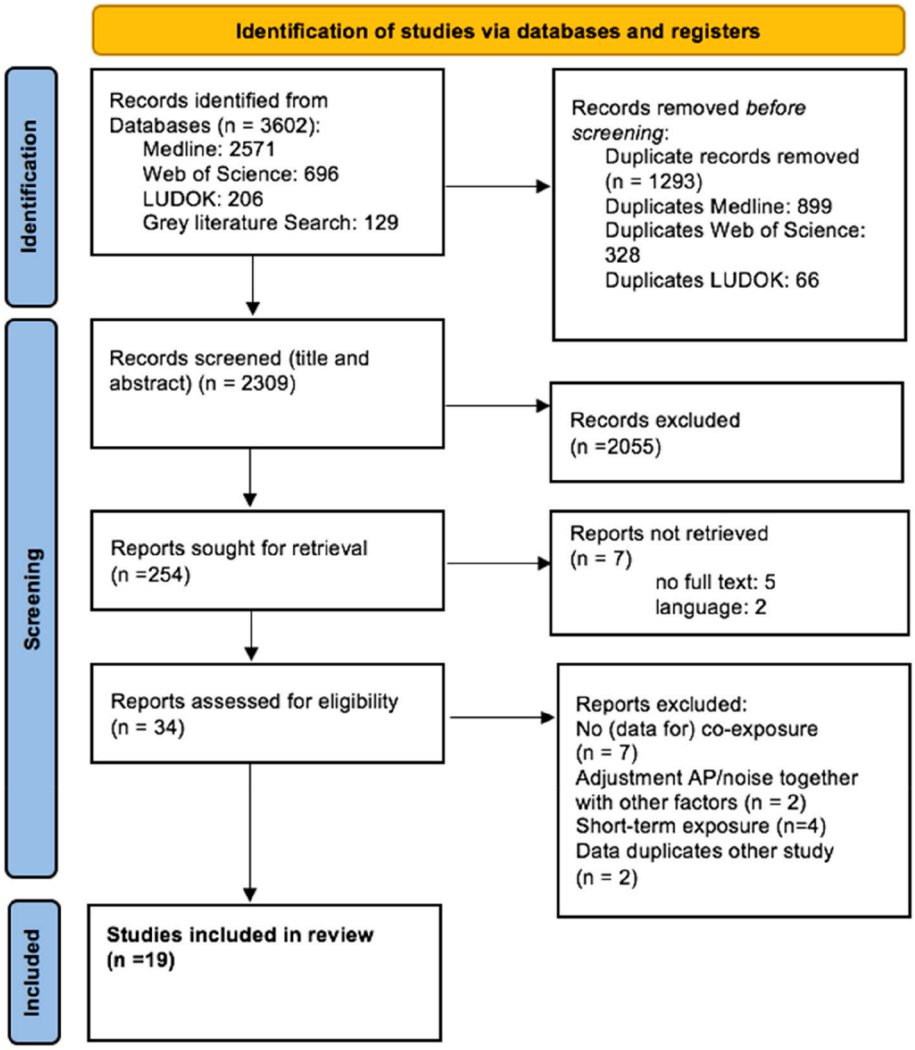

Fig. 1. PRISMA flow chart for study selection.

assessed confounding and EM (Tzivian et al., 2016b; Yu et al., 2023), and two studies assessed interaction and EM (Tzivian et al., 2017; Wu et al., 2024).

To estimate exposure to AP and noise, both exposures were modeled at the participants' home addresses in all included studies. The mean outdoor traffic noise level was between 31 and 69 dB(A) (L_{den} or L_{night}). Noise dichotomization in low and high noise groups was between 45 dB (A)-65dB(A) in studies analysing EM or interaction. All air pollutants exceeded WHO guidelines for $PM_{2.5}$, PM_{10}, and NO except for $PM_{2.5}$ in Yuchi et al. (2020) (World Health Organization, 2021). The correlation between AP and noise ranged from Spearman's p = 0.15 (Andersson et al., 2018) to Pearson's r = 0.61 (Cole-Hunter et al., 2022). Lucht et al. (2022) were the only researchers to provide correlations between indoor L_{den} and indoor L_{night} (modeled from outdoor noise) and AP, besides outdoor noise and AP. Cognitive function was measured using multidimensional cognitive function testing such as CERAD-Plus in seven studies. The assessment of morbidity and mortality from dementia was based on register data in five studies and on clinical dementia assessment in four studies. The assessment of morbidity and mortality from Parkinson disease was based on questionnaires and registry data. Neuro-imaging, such as functional Magnetic Resonance Imaging (MRI) or structural MRI, was used in five studies. Several studies combined these assessment methods. All studies adjusted for personal factors, 16 for lifestyle factors, 11 for environmental factors, and eight for health-related factors (Table 2, Supplement A Table 1).

All studies raised concerns about a risk of bias, which were in OHAT domains with "probably high risk of bias" or "definitely high risk of bias" (S. B Fig. 2). The main concerns about bias were.

- Selection bias (n = 6): For example, in the study by Mac Domhnaill et al. (2021), data on AP was only available for a subsample in Dublin that was not representative of the full sample.
- Confounding (n = 6): For example, missing data about the study population such as lifestyle data (Cantuaria et al., 2021) or adjusting for AP and noise together with other variables in the same model (Glaubitz et al., 2022).
- Attrition bias (n = 4): Drop-out of participants with cognitive impairment.
- Detection bias of the exposure (n = 15): Insufficient noise modelling techniques that do not adequately reflect individual indoor noise levels and susceptibility lead to exposure bias in almost all studies. For instance, high noise levels may cause behaviour changes, such as closing windows, which reduces exposure not only to noise but also of air pollutants. Considering air pollutants, studies rely on spatially or temporally aggregated data, which might not fully cover individual-level exposure variations and overlook short-term peaks.
- Detection bias of the outcome (n = 5): Imprecision of register-based dementia diagnoses.

Table 2
Study characteristics and effect estimate changes in two-exposure models.

Study	Study design, Sample size, Location	AP exposure	Noise exposure	Outcome	Model, covariates	%Changes in estimates as a result of relationships
Andersson et al. (2018)	LS, N = 1721, Sweden	NO_x: Concentrations per quartile: 1st < 9 μg/m3 2nd 9 μg/m3 - <17 μg/m3 3rd 17 μg/m3 - <26 μg/m3 4th ≥ 26 μg/m3	LA_{eq} 24 h: Dichotomization on 55 dB(A): N = 102 (6 %) with LA_{eq} > 55 dB(A)	Incidence of dementia	Cox proportional hazard; P, L, H; Adding an interaction term between noise and NO_x	Adjusting noise for NO_x: ΔHR = −0.11, 10 %
Cantuaria et al. (2021)	LS, N = 1 938 994, Denmark	Mean (SD) 10 year mean air pollution exposure (μg/m^3): $PM_{2.5}$: <55 dB(A): 15.2; ≥55 dB(A):15.9; NO_2: <55 dB(A): 16.5; ≥55 dB(A): 21.3	L_{den}: road traffic: L_{denmax} = 55.3 dB(A), L_{denmin} = 44.3 dB(A) railway noise: L_{denmax} = 51.6 dB(A), L_{denmin} = 44.7 dB(A)	Incidence of dementia	Cox proportional hazard; P, E	Adjustment of the Road and Railway L_{denmax} for $PM_{2.5}$ and NO_2: ΔHR (95 % CI): Road, L_{denmax} in dB(A): 45–50: 0 * 50–55: −0.01* 55–60: −0.03* 60–65: −0.04* ≥65: −0.12*, 10 % Railway, L_{den} max in dB (A) 40–45: −0.01* 45–50: −0.01 * 50–55: −0.03* 55–60: −0.03* ≥60: −0.03*
Carey et al. (2018)	LS, N = 130 978, Greater London, England	NO_2: 37.1 ± 5.7 μg/m^3 $PM_{2.5}$: 15.7 ± 0.8 μg/m^3 $PM_{2.5}$ (traffic):1.4 ± 0.5 μg/m^3 O_3: 38.0 ± 3.9 μg/m^3	L_{night}: 52.1 ± 4.6 dB (A)	Incidence of dementia	Cox proportional hazard; P, L, H	AP adjusted for noise: NO_2: ΔHR = 0.01, $PM_{2.5}$: ΔHR = 0.01, $PM_{2.5}$ traffic: ΔHR = 0 Noise adjusted for AP (NO_2): ΔHR = 0.01
Cole-Hunter et al. (2022)	LS, N = 22 858, Denmark	$PM_{2.5}$ (μg/m3) mean: 20.6 ± 3.8 range: 6-48 NO_2 (μg/m3) mean: 13.2 ± 7.7, range: 3-81	L_{den} mean: 52.8 ± 7.9 dB(A), range: 8–79 dB(A)	Incidence of dementia	Cox proportional hazard; P, L, E	Noise adjusted for AP: $PM_{2.5}$: 5-year: ΔHR = 0.03 23-year: ΔHR = 0.02 NO_2: 5-year: ΔHR = 0.14, 13 % 23-year: ΔHR = 0.18, 17 %
Fuks et al. (2019)	LS, N = 288, Ruhr area vs. rural Münsterland, Germany	PM_{10} (μg/m3), mean ± SD: 28.0 ± 2.3 NO_2 (μg/m3), mean ± SD: 32.2 ± 7.4	L_{den} dB(A), mean ± SD: 55.9 ± 7.7 L_{den} ≥ 50 dB(A): 74.70 % L_{night} dB(A), mean ± SD: 47.2 ± 7.4 L_{night} ≥ 50 dB(A): 35.40 %	Multidimensional cognitive function testing	Logistic regression, P, L, H	Noise adjusted for AP: ΔHR = −0.18, 7 %, ΔHR = −0.24, 23 %, ΔHR = 0.18, 11 %, ΔHR = −0.04
Glaubitz et al. (2022)	LS, N = 574, Ruhr area, Germany	PM_{10} (μg/m^3): 27.52 ± 1.81 $PM_{2.5}$ (μg/m^3): 18.26 ± 1.04 $PM_{2.5abs}$ (x 10^{-5}/m): 1.54 ± 0.32 NO_2 (μg/m^3): 29.54 ± 4.44	L_{den} dB(A): 52.98 ± 8.76 L_{night} dB(A): 44.07 ± 8.44	Functional brain organization of seven established brain networks assed with resting state fMRI; to assess brain function, determination of the degree of segregation	Multiple linear regression, P, L, E	Noise adjusted for AP = AP adjusted for noise = (No quantitative comparison possible)
Klompmaker et al., 2021	LS, N = 10 481 566, Netherlands	NO_2 (μg/m^3), median (IQR): 26.3 (8.3) $PM_{2.5}$ (μg/m^3), median (IQR): 16.8 (1.4) BC (10^{-5}/m), median (IQR): 1.3 (0.3) PM_{10}, PM_{coarse} National LUR models: PM_{10} (μg/m^3),	Road traffic noise (L_{den}, dB(A)), median (IQR): 53.5 (7.5) Rail-traffic noise (L_{den}, dB(A)) median (IQR): 30.7 (9.4)	Neurodegenerative disease mortality [including Dementia, motor neuron disease, Parkinson's Disease, AD, Multiple sclerosis	Cox proportional hazard; P, E	AP adjusted for noise: NO_2: 1.016–0.992 ΔHR = 0.024 $PM_{2.5}$: 1.018–1.009 ΔHR = 0.009 Noise adjusted for AP: NO_2: ΔHR = −0.004 $PM_{2.5}$: ΔHR = −0.004

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Table 2 (*continued*)

Study	Study design, Sample size, Location	AP exposure	Noise exposure	Outcome	Model, covariates	%Changes in estimates as a result of relationships
		median (IQR): 24.5 (1.3) PM_{coarse} (μg/m^3), median (IQR): 8.1 (0.8)				
Lomme et al. (2023)	LS, EPIC-NL: N = 35 106 controls and 168 PD; AMIGO: N = 14 747 controls and 67 PD, Netherlands	NO_2 (μg/m^3): EPIC-NL 25.2 ± 6.16 controls, 26.6 ± 5.48 PD, AMIGO 22.1 ± 5.59 controls, 23.0 ± 5.99 PD NO_x (μg/m^3): EPIC-NL 37.9 ± 11.3 controls, 40.5 ± 10.7 PD, AMIGO 31.8 ± 9.80 controls, 33.5 ± 11.2 PD $PM_{2.5abs}$ (10-5m^{-1}): EPIC-NL 1.36 ± 0.21 controls, 1.38 ± 0.20 PD, AMIGO 1.21 ± 0.20 controls, 1.25 ± 0.22 PD PM_{coarse} (μg/m^3): EPIC-NL 8.54 ± 0.91 controls, 8.62 ± 0.86 PD, AMIGO 8.17 ± 0.66 controls, 8.32 ± 0.78 PD $PM_{2.5}$ (μg/m^3): EPIC-NL 16.8 ± 0.56 controls, 16.9 ± 0.60 PD, AMIGO 16.5 ± 0.67 controls, 16.7 ± 0.75 PD PM_{10} (μg/m^3): EPIC-NL 25.4 ± 1.45 controls, 25.5 ± 1.42 PD, AMIGO 24.5 ± 0.93 controls, 24.7 ± 1.10 PD UFP (particl./cm^3): EPIC-NL 11.1 ± 2.36 controls, 11.4 ± 2.32 PD, AMIGO 9.45 ± 2.04 controls, 9.48 ± 1.67 PD	L_{den} dB(A) EPIC-NL 55.7 ± 4.65 controls, 57.1 ± 4.62 PD AMIGO 53.1 ± 5.82 controls, 54.5 ± 5.43 PD	PD incidence	Logistic regression; P, L	AP adjusted for noise: NO_2:ΔHR = −0.35, 24 %; NO_x: ΔHR = −0.46*, 22 % Noise adjusted for AP: NO_2:ΔHR = −0.13*, 8 % NO_x: ΔHR = −0.17, 10 % $PM_{2.5}$: ΔHR = −0.04* PM_{coarse}: ΔHR = −0.13*, 8 % PM_{10}: ΔHR = −0.13*, 8 % $PM_{2.5\ abs}$: ΔHR = −0.1*, 6 % UFP: ΔHR = 0*
Lucht et al. (2022)	LS, N = 579, Ruhr Area, Germany	PM_{10} (μg/m^3): 27.5 ± 1.8 $PM_{2.5}$ (μg/m^3): 18.2 ± 1.0 $PM_{2.5abs}$ (0.0001/m: 1.5 ± 0.4 NO_2 (μg/m^3): 29.5 ± 4.6	Outdoor L_{den} dB(A): 53.4 ± 8.4 Outdoor L_{night} dB(A): 44.4 ± 8.3 Indoor L_{den} dB(A): 35.1 ± 12.5 Indoor L_{night} dB(A): 27.3 ± 13.8	Structural MRI brain images	Linear regression, P, L	Noise adjusted for A = AP adjusted for noise = (No quantitative comparison possible)
Mac Domhnaill et al., 2021	CS, N = 1706, Dublin and Cork, Ireland	NO_2 (μg/m^3): 15.6 ± 3.9	Night-time noise L_{night} dB(A): 51.4 ± 5.1	Multidimensional cognitive function testing	Linear regression, P, L, H, E	Adjusting AP for noise: Δ dy/dx (95 % CI) (L_{night} and NO_2)-NO_2: Second quintile: 0.098 Third quintile: −0.11, 52 % Forth quintile: 0.46, 122 % Highest quintile: 0.457, 96 % (L_{night} and $PM_{2.5}$)-

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Table 2 (*continued*)

Study	Study design, Sample size, Location	AP exposure	Noise exposure	Outcome	Model, covariates	%Changes in estimates as a result of relationships
						$PM_{2.5}$: Second quintile: 0.052 Third quintile: −0.11, 50 % Forth quintile: 0.34, 112 % Highest quintile: 0.068, 30 % (L_{night} and PM_{10})-PM_{10}: Second quintile: 0.037 Third quintile: −0.144, 82 % Forth quintile: 0.377, 115 % Highest quintile: 0.104, 42 %
Nussbaum et al. (2020)	LS, N = 615, Ruhr Area, Germany	PM_{10} (μg/m^3): 27.5 ± 1.8 $PM_{2.5}$ (μg/m^3): 18.3 ± 1.0 $PM_{2.5abs}$ (0.0001/m): 1.5 ± 0.3 NO_x (μg/m^3): 49.3 ± 11.3 NO_2 (μg/m^3): 29.6 ± 4.7	L_{night} dB(A): 44.0 ± 8.5 L_{den} dB(A): 52.9 ± 8.7	Multidimensional cognitive function testing, functional MRI brain images	Multiple linear regression, P, L, E	Noise adjusted for AP = AP adjusted for noise = (No quantitative comparison possible)
Ogurtsova et al. (2023)	LS, N = 2554, Ruhr area, Germany	PM_{10} (μg/m^3): 27.4 (2) $PM_{2.5}$ (μg/m^3): 18.2 (1.4) $PM_{2.5abs}$ (0.0001/m): 1.51 (0.34) NO_2 (μg/m^3):29.3 (5.9)	L_{night} 10 dB(A) median (IQR): 4.3 (1.3)	Multidimensional cognitive function testing	Linear regression, P, L	Noise adjusted for AP = (No quantitative comparison possible)
Tzivian et al., 2016a	CS, N = 4050, Ruhr area, Germany	$PM_{2.5}$ (μg/m^3): 18.39 ± 1.05 $PM_{2.5abs}$(10^{-5}/m): 1.58 ± 0.35 PM_{coarse} (μg/m^3): 10.13 ± 1.53 PM_{10} (μg/m^3): 27.74 ± 1.84 NO_2 (μg/m^3): 30.12 ± 4.85 NO_x (μg/m^3): 50.47 ± 11.70	L_{den} dB(A): 53.74 ± 9.49 L_{night} dB(A): 44.88 ± 9.17	Multidimensional cognitive function testing	Linear and logistic regression, P, L, H, E	$PM_{2.5}$ and other AP ($PM_{2.5abs}$, PM_{coarse}, PM_{10}, NO_2, NO_x) adjusted for L_{den}/L_{night} = L_{den}/L_{night} adjusted for $PM_{2.5}$ and other AP ($PM_{2.5abs}$, PM_{coarse}, PM_{10}, NO_2, NO_x): ↑ (No quantitative comparison possible)
Tzivian et al. (2016b)	CS, N = 2050, Ruhr area, Germany	$PM_{2.5}$ (μg/m^3): 18.39 ± 1.05 $PM_{2.5abs}$ (10^{-5}/m): 1.58 ± 0.35 PM_{coarse} (μg/m^3): 10.13 ± 1.53 PM_{10} (μg/m^3): 27.74 ± 1.84 NO_2 (μg/m^3): 30.12 ± 4.85 NO_x (μg/m^3): 50.47 ± 11.70	L_{den} dB(A): 53.74 ± 9.49 L_{night} dB(A): 44.88 ± 9.17	Multidimensional cognitive function testing	Multiple regression, P, L, H, E, Effect modification: product terms of AP (dichotomous) × noise; AP × noise (dichotomous)	$PM_{2.5}$ adjusted for L_{den}/L_{night}: ↓ L_{den} adjusted for $PM_{2.5}$ = (No quantitative comparison possible) EM: ΔOR = 0.2, 18 %
Tzivian et al. (2017)	CS, N = 3885, Ruhr area, Germany	$PM_{2.5}$ (μg/m^3): 18.39 ± 1.05 $PM_{2.5abs}$(10^{-5}/m): 1.58 ± 0.35 PM $_{coarse}$ (μg/m^3): 10.17 ± 1.42 PM_{10} (μg/m^3): 27.74 ± 1.84 NO_2 (μg/m^3): 30.10 ± 4.84 NO_x (μg/m^3): 50.43 ± 11.61	L_{den} dB(A): 53.84 ± 9.23 L_{night} dB(A): 44.96 ± 8.98	Multidimensional cognitive function testing	Multiple linear regression, P, L, E, Effect modification: multiplicative interaction terms, categories of differently exposed groups	Δbeta = −0.32, 200 %; −0.52 (D) -–0.06 (Additive Effect (sum B + C)) = −0.46

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Table 2 (*continued*)

Study	Study design, Sample size, Location	AP exposure	Noise exposure	Outcome	Model, covariates	%Changes in estimates as a result of relationships
Wu et al. (2024)	LS, N = 2594, Stockholm, Sweden	Traffic related $PM_{2.5}$ ≥ 8.7 μg/m3: n = 1000 (38.6 %)	Aircraft dB(A) L_{den} mean: 45.0, Road traffic dB(A) L_{den} mean: 64.1, Railway dB(A) L_{den} mean: 43.7	Multidimensional cognitive function testing	Effect modification: Including interaction terms in the models, Wald test to calculate p-values for interaction; P, L, H, E	Aircraft noise β (95 % CI): $PM_{2.5}$ <8.7 μg/m3: −0.008 (−0.014, −0.001), p for interaction = 0.740, ≥8.7 μg/m3: −0.006 (−0.015, 0.004); Road traffic noise β (95 %CI): $PM_{2.5}$ <8.7 μg/m3: −0.002 (−0.006, 0.002), p for interaction = 0.058, ≥8.7 μg/m3: −0.006 (−0.001, 0.012); Railway noise β (95 % CI): $PM_{2.5}$ <8.7 μg/m3: 0.002 (−0.003, 0.008), p for interaction = 0.813, ≥8.7 μg/m3: −0.003 (−0.003, 0.010)
Yu et al. (2020)	LS, N = 1 612, Sacramento Valley, USA	Traffic-related NO_x, ppb, mean (SD): 2.6 (2.2)	24hr Average Noise, dB(A), mean (SD): 69 (8.9) Nighttime (10PM - 7AM) Noise, dB(A), mean (SD): 60 (8.9)	Multidimensional cognitive function testing, structural MRI	Cox proportional hazards, P, L, E	Noise adjusted for AP: ΔHR = −0.1, 8 %
Yu et al. (2023)	LS, N = 1 612, Sacramento Valley, USA	NO_2 exposure at baseline (ppb, mean ± SD): 28.6 ± 6.0 O_3 exposure at baseline (ppb, mean ± SD): 46.6 ± 11.0 $PM_{2.5}$ exposure at baseline (μg/m^3, mean ± SD): 12.8 ± 1.4	24-h noise at baseline (dB(A), mean ± SD): 68.5 ± 8.9	Multidimensional cognitive function testing, structural MRI	Cox proportional hazards, P, L, Effect modification: interaction term	Adjusting AP for noise: (NO_2 + noise) - NO_2: Dementia/CIND, ΔHR = −0.06 Dementia, ΔHR = −0.05 ($PM_{2.5}$ + noise) – $PM_{2.5}$: Dementia/CIND, ΔHR = −0.04 Dementia, ΔHR = −0.08 (O_3 + noise) - O_3: Dementia/CIND, ΔHR = 0 Dementia, ΔHR = 0.01 EM: NO_2: Dementia/CIND: 24-h noise <65 dB(A), HR (95 % CI): 0.76 (0.52, 1.11); 24-h noise ≥65 dB(A) (95 % CI): 1.28 (0.97, 1.69); p_{inter} = 0.02; Dementia: 24-h noise <65 dB(A), HR (95 % CI): 0.80 (0.50, 1.29); 24-h noise ≥65 dB(A) (95 % CI): 1.15 (0.79, 1.67); p_{inter} = 0.21 $PM_{2.5}$ Dementia/CIND: 24-h noise <65 dB(A), HR (95 % CI): 0.94 (0.71, 1.23); 24-h noise ≥65 dB(A) (95 % CI): 1.10 (0.84, 1.44); p_{inter} = 0.38; Dementia: 24-h noise <65 dB(A), HR (95 % CI): 0.96 (0.69, 1.33); 24-h noise ≥65 dB(A) (95 % CI): 1.57 (1.11, 2.21); p_{inter}

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Table 2 (*continued*)

Study	Study design, Sample size, Location	AP exposure	Noise exposure	Outcome	Model, covariates	%Changes in estimates as a result of relationships
						= 0.03 O_3 Dementia/CIND: 24-h noise <65 dB(A), HR (95 % CI): 1.02 (0.83, 1.26); 24-h noise ≥65 dB(A) (95 % CI): 1.00 (0.83, 1.21); p_{inter} = 0.92; Dementia: 24-h noise <65 dB(A), HR (95 % CI): 0.93 (0.69, 1.25); 24-h noise ≥65 dB(A) (95 % CI): 1.13 (0.89, 1.43); p_{inter} = 0.30
Yuchi et al. (2020)	LS, N = 2 500 000, Vancouver, Canada	$PM_{2.5}$ (μg/m^3), medium (IQR) NAD: 4.1 (1.5); PD: 4.1 (1.7) Black carbon (μg/m^3) medium (IQR) NAD: 1.1 (1.2); PD: 1.1 (1.3) NO_2 (ppb) medium (IQR) NAD: 31.1 (9.2); PD: 31.3 (9.2) NO (ppb) medium (IQR) NAD: 29.5 (12.1); PD: 29.7 (13.7)	Noise (L_{den} dB(A)) medium (IQR) NAD: 60.8 (6.0); PD: 60.8 (5.6)	Incident cases of NAD, AD, PD and MS	Cox proportional hazard, P, H	Adjusting AP for noise: ($PM_{2.5}$ (μg/m^3) + Noise) – PM2.5: NAD: ΔHR = 0, PD: ΔHR = −0.01, AD: ΔHR = 0.01, MS: ΔHR = 0.15, 12 % (Black carbon (μg/m^3) + Noise) – BC: NAD: ΔHR = 0, PD: ΔHR = −0.01, AD: ΔHR = −0.11, 11 % MS: ΔHR = 0.02 (NO_2 (ppb) + Noise)-NO2: NAD: ΔHR = −0.01, PD: ΔHR = −0.03, AD: ΔHR = −0.07, MS: ΔHR = 0.04 (NO (ppb) + Noise)-NO: NAD: ΔHR = −0.01, PD: ΔHR = −0.02, AD: ΔHR = −0.07, MS: ΔHR = 0.03 Adjusting noise for AP: ($PM_{2.5}$ (μg/m^3) + Noise) – noise NAD: ΔHR = 0.01, PD: ΔHR = 0.07, AD: ΔHR = −0.08, MS: ΔHR = 0.48, 52 % (Black carbon (μg/m^3) + Noise) -noise NAD: ΔHR = 0, PD: ΔHR = 0.01, AD: ΔHR = −0.08, MS: ΔHR = 0.03 (NO_2 (ppb) + Noise) -noise NAD: ΔHR = 0, PD: ΔHR = 0.08, AD: ΔHR = −0.22, 22 % MS: ΔHR = 0.14, 15 % (NO (ppb) + Noise) – noise: NAD: ΔHR = −0.02, PD: ΔHR = 0, AD: ΔHR = −0.15, 15 % MS: ΔHR = −0.04

LS = longitudinal study; CS = cross-sectional study; EM = effect modification; AP = air pollution; AD = Alzheimer's Disease, PD= Parkinson's Disease; MS = Multiple Sclerosis; NAD= Non-Alzheimer's Disease; CIND = cognitive impairment not dementia; MRI = Magnetic Resonance Imaging.
PM = Particulate Matter; UFP = Ultra Fine Particles; NO = Nitrogen Monoxide; NO_2 = Nitrogen Dioxide; NO_x = Nitrogen Oxides; O_3 = Ozone; abs = absorbance.
P—personal factors, including age, sex, socioeconomic status (SES), income, marital status, ethnicity, education level, country or region of origin, occupational status, Index of Multiple Deprivation decile, and annoyance.
L—lifestyle factors, including (passive) smoking, drinking, (outdoor) exercise, body mass index (BMI), waist-hip ratio, diet, social connectedness, and activities of daily living.

H—health-related factors, including general health status, comorbidity, diabetes, stroke, depression, hypertension, Apolioprotein E (ApoE4), ischaemic heart disease, heart failure, LDL cholesterol level, intake of statin medication, and intake of anti-hypertensive medication.
E—environmental factors, including indoor air pollution, calendar year, proportion of high quality green space, neighbourhood SES, urbanization, municipality-level average income, unemployment rate of the region and of the neighbourhood, percentage non-Western immigrants of the region and of the neighbourhood, residential density, environmental tobacco smoke, and city of residence.
* = Confidence intervals indicate significant change.

- Selective reporting (n = 8): Studies measured both exposures but did not provide data or calculations for adjustment, especially when findings were insignificant.
- Other (n = 1): Average marginal effects as population-level estimate (Mac Domhnaill et al., 2021).

3.1. Adjustment analysis to assess mutual confounding between AP and noise

Of the studies using two-exposure models, 15 adjusted the noise model for AP, 11 adjusted the AP model for noise, and nine adjusted both models for the other exposure. For most outcomes, the effect estimates changed by under 10 % (>−10 % – <10 %) before and after controlling for the other exposure.

Of the 15 studies that adjusted noise models for AP, four studies (Cole-Hunter et al., 2022; Fuks et al., 2019; Tzivian et al., 2016; Yuchi et al., 2020) found that effect estimates changed by at least 10 %, with a maximal ΔHR = 52 % in Yuchi et al. (2020) for $PM_{2.5}$ and L_{den} in people with multiple sclerosis. Conversely, six studies found changes in effect estimates of 10 % or less (≤−10 %) after adjustment (Andersson et al., 2018; Cantuaria et al., 2021; Fuks et al., 2019; Lomme et al., 2023; Yu et al., 2020; Yuchi et al., 2020) with a maximal change of ΔHR = −23 % in Fuks et al. (2019) for PM_{10}/NO_2 and L_{night}. Effect estimates remained stable in 12 studies (change > −10 % – <10 %).

Regarding AP models adjusted for noise, out of the overall 11 studies, the effect estimates changed by ≥ 10 % in two studies (Mac Domhnaill et al., 2021; Yuchi et al., 2020) with maximal change of Average Marginal Effect = 122 % in Mac Domhnaill et al. (2021) for NO_2 and L_{night}. In the opposite direction, effect estimates changed ≤ −10 % in four studies (Lomme et al., 2023; Mac Domhnaill et al., 2021; Tzivian et al., 2016b; Yuchi et al., 2020) with maximal effect estimates change ΔHR = −24 % in Lomme et al. (2023) for NO_2 and L_{den}. Effect estimates remained relatively stable in eight studies (>−10 % – <10 %) (Tables 2 and 3, S. A Table 2).

3.2. Effect modification and interaction between AP and noise

Five studies conducted analyses to account for EM or interaction. Three of these studies found evidence for EM of AP by noise, meaning how noise levels (low or high) modify the effect of AP on cognitive function. Tzivian et al. (2016b) found stronger associations between $PM_{2.5}$ and mild cognitive impairment (MCI) in participants with high noise exposure (OR = 1.30 (95 % CI: 1.01, 1.67)) than in participants with low noise exposure (OR MCI = 1.10 (95 % CI: 0.93, 1.29)) without significant interaction (p_{inter} = 0.28). Similarly, Tzivian et al. (2017) observed a stronger association between $PM_{2.5}$, PM_{coarse} and PM_{10} and cognitive function in participants with high noise exposure compared to those with low noise exposure. No such EM was observed for $PM_{2.5abs}$, NO_2 and NO_x. The interaction between noise and $PM_{2.5}$ was significant (p_{inter} = 0.04). Yu et al. (2023) found higher incidence of dementia/-cognitive impairment without dementia (CIND) and dementia in participants exposed to NO_2 or $PM_{2.5}$ and high noise compared to low noise. A significant interaction occurred in both the dementia/CIND group exposed to NO_2 and high noise (p_{inter} = 0.02) as well as in the dementia group exposed to $PM_{2.5}$ and high noise (p_{inter} = 0.03). However, two Swedish studies by Wu et al. (2024) and Andersson et al. (2018) did not find any significant interactions between AP and noise. Andersson et al. did not provide any data or calculations.

Table 3
Change in effect estimates after adjusting noise models for AP or AP models for noise.

	≥10 % change effect estimates ↑	=	≤ −10 % change effect estimates ↓
Noise model adjusted for AP	Cole-Hunter et al., 2022 (NO_2), Fuks et al., 2019, Tzivian et al., 2016a (from figure) Yuchi et al. (2020)	Cantuaria et al., 2021 (railway)[a], Carey et al., 2018 (all pollutants), Cole-Hunter et al., 2022 ($PM_{2.5}$), Fuks et al., 2019, Glaubitz et al., 2022, Klompmaker et al., 2021, Lomme et al., 2023, Lucht et al., 2022, Nussbaum et al., 2020 ($PM_{2.5}$ and L_{night}) Ogurtsova et al., 2023, Tzivian et al., 2016b, Yuchi et al. (2020)	Andersson et al., 2018 (NO_x), Cantuaria et al., 2021 (road)[a], Fuks et al., 2019, Lomme et al., 2023, Yu et al., 2020, Yuchi et al. (2020)
AP model adjusted for noise	Mac Domhnaill et al., 2021 (forth and highest quintile), Yuchi et al. (2020)	Carey et al., 2018 (NO_2), Glaubitz et al., 2022, Klompmaker et al., 2021, Lucht et al., 2022, Nussbaum et al., 2020 ($PM_{2.5}$ and L_{night}), Tzivian et al., 2016a, Yu et al., 2023, Yuchi et al. (2020)	Lomme et al., 2023,[a], Mac Domhnaill et al., 2021 (third quintile), Tzivian et al., 2016b, Yuchi et al. (2020)

[a] = Confidence intervals indicate significant change.

Further, Tzivian et al. (2017) and Wu et al. (2024) examined how $PM_{2.5}$ levels (low or high) modify the effect of noise exposure on cognitive function. Participants exposed to low level of $PM_{2.5}$ and noise had an additively calculated cognitive score (global cognitive score (GCS)) increase of β = 0.31 [−0.19; 0.80] per 10 dB(A). Participants exposed to high level of $PM_{2.5}$ and noise had a GCS decrease of β = −0.37 [−0.70; −0.03] per 10 dB(A) in Tzivian et al. (2017). Contrary, in Wu et al. (2024) no EM by $PM_{2.5}$ was observed.

Tzivian et al. (2017) also conducted a division into four groups to differentiate between participants exposed to both high AP and high noise, compared to those with only one high exposure (high AP and low noise or high noise and low AP). They found a stronger negative association in participants with double high exposure compared to the sum of the high AP or high noise category for all air pollutants. For example, the theoretically calculated additive effect of high AP and high L_{den} group was β = −0.06 [−0.53; 0.40], while the obtained association in the high $PM_{2.5}$ and high L_{den} group was β = −0.52 [−0.81; −0.23] (Table 4, Supplement A Table 2, Supplement B Table 8).

4. Discussion

This systematic review analysed the effects of simultaneous exposure to AP and traffic noise on cognitive impairment in adults, based on 19 studies published until April 2024. Minimal mutual confounding was found between AP and noise, as effect estimates remained stable before and after adjustments. Evidence of EM was observed in studies with high-exposure levels. Participants exposed to high levels of both AP and

noise had worse cognitive outcomes; one study reporting an over-additive effect. Significant interactions were mainly found in high-exposure cases, where combined exposure to both AP and noise resulted in greater cognitive decline than exposure to either factor alone.

4.1. Discussion of the results

4.1.1. Confidence in mutual confounding, EM and interaction of the results

The majority of the included studies adjusted the main exposure of interest for the other exposures. Before and after adjustment, the effect estimates for most cognitive outcomes remained stable, though there were some exceptions. Due to the large number of stable outcomes (change in effect estimates of less than 10 % after adjustment) and the absence of factors decreasing confidence, such as indirectness or imprecision, we have moderate confidence in the absence of confounding between AP and noise (S. B Table 6). However, the precision of effect estimates was mixed in this group with stable outcomes, which could have downgraded the confidence in the evidence. Overall, we still decided to keep the category moderate evidence for this group with stable outcomes. For the outcomes of the 16 studies with changes of at least 10 % after adjustment for the other exposure, we have low confidence due to unexplained inconsistency and imprecision. These included studies reporting changes of at least 10 % in either direction (Fuks et al., 2019; Mac Domhnaill et al., 2021; Yuchi et al., 2020) or studies in which the magnitude of change depended on the level of exposure (Cantuaria et al., 2021; Mac Domhnaill et al., 2021). This partly observed pattern in which the magnitude of confounding changes depending on the level of exposure demands further examination. In Cantuaria et al. (2021), the difference between noise models adjusted for $PM_{2.5}$ and noise models not adjusted for $PM_{2.5}$ arises only in the highest noise group ($L_{denmax} \geq 65$ dB(A) ($\Delta HR = 10$ %). Similarly, in Mac Domhnaill et al. (2021), the difference between AP models adjusted for noise and unadjusted AP models is greatest in the peak NO_2, $PM_{2.5}$ and PM_{10} exposure quintiles. These two studies were the only ones presenting effect estimates according to exposure level.

Concerning EM and interaction, we only analysed five studies, which is why these results are preliminary. Of those studies, three focused on the interrelation between AP and noise, and we found moderate evidence for EM and interaction. Despite the small number of studies analysing EM and interaction, confidence was rated moderate due to the magnitude of the effects, whereas confidence in the two Swedish studies not finding EM and interaction was rated low. They were downgraded due to indirectness in Andersson et al. (2018). Regarding indirectness and external validity, the question arises whether the cognitive effects of co-exposure of AP and noise in these studies can be applied to other populations. A sufficient exposure level is required to assess a cognitive detrimental effect, and this level varies depending on factors such as age. Studies with participants exposed to higher noise levels showed a more significant negative effect than studies with low exposure. Therefore, the detection of EM and interaction may depend on the grouping. Andersson et al. (2018) divided participants into the high and low noise groups at 55 dB(A) and found no interaction, whereas Yu et al. (2023) separated at 65 dB(A) and found significant interaction and EM. Another limitation, present not only in Andersson et al. (2018) but also in studies such as Fuks et al. (2019), was the limited number of participants in each noise stratum, resulting in limited statistical power. In the study by Andersson et al. (2018), only 6 % of the population (N = 102) was exposed to noise levels ≥55 dB(A) and the study by Fuks et al. (2019) included a population of only N = 288. Even more power would be required to conduct interaction analysis. Based on the results of this review, we hypothesize that the pathway through which AP and noise co-exposure affects cognition may depend on the level of exposure.

Table 4
Effect modification by air pollution and noise in high exposed groups.

Effect modification by noise (high noise compared to low noise)	$PM_{2.5}$: OR MCI = 0.2, 18 % [a] β GCS = −0.32, 200 % [b] HR Dementia/CIND = 0.16, 17 % [c] HR Dementia = 0.61, 64 % [c] NO_2: HR Dementia/CIND = 0.52, 68 % [c] HR Dementia = 0.35, 44 % [c] O_3: HR Dementia/CIND = −0.02, 2 % [c] HR Dementia = 0.20, 22 % [c]
Effect modification by AP (high AP compared to low AP)	$PM_{2.5}$: β = −0.06 per 10 dB(A), 19 % [b] Aircraft noise β (95 %CI): $PM_{2.5}$ <8.7 μg/m^3: −0.008 (−0.014, −0.001), p_{inter} = 0.740, ≥8.7 μg/m^3: −0.006 (−0.015, 0.004);[d] Road traffic noise β (95 %CI): $PM_{2.5}$ <8.7 μg/m^3: −0.002 (−0.006, 0.002), p_{inter} = 0.058, ≥8.7 μg/m^3: −0.006 (−0.001, 0.012); [d] Railway noise β (95 %CI): $PM_{2.5}$ <8.7 μg/m^3: 0.002 (−0.003, 0.008), p_{inter} = 0.813, ≥8.7 μg/m^3: −0.003 (−0.003, 0.010) [d]
Effect modification by AP and noise (high AP and high noise compared to low AP and low noise)	$PM_{2.5}$: β = −0.52 [-0.81; −0.23], 52 % [b]

Andersson et al., 2018: no interaction (no data).
AP: Air pollution, OR: Odds ratio, HR: Hazard ratio, MCI: mild cognitive impairment, GCS: global cognitive score, CIND: cognitive impairment no dementia.
[a] Tzivian et al., 2016b.
[b] Tzivian et al., 2017.
[c] Yu et al., 2023.
[d] Wu et al., 2024.

4.1.2. Mutual confounding between AP and noise in studies beyond this review

The results of the review should be compared with those of other studies analysing confounding between AP and noise on their effect on cognition. Tuffier et al. (2024) published after the end of the systematic search period and were therefore not included. They examined the association between long-term exposure to AP and road traffic noise and the incidence of dementia in a Danish nurse cohort. They found an association of AP and dementia that was independent of traffic noise, and the effect estimates changed by a maximum of 5 % after adjustment for AP and noise. Conversely, the association between traffic noise and dementia weakened once AP was considered, suggesting a degree of confounding by AP (Tuffier et al., 2024). Similar to Tuffier et al., Cullen et al. (2018) found an association between AP and dementia independent of traffic noise. They conducted cross-sectional and longitudinal analyses of outdoor AP exposure and cognitive function in the UK Biobank, which was also excluded from the systematic review because noise was only adjusted in combination with other variables. They analysed the association between AP and baseline cognitive function (cross-sectional) as well as the association between AP and change in cognitive function (longitudinal). In both analyses, the results were similar when noise was added to the models. Likewise, Weuve et al. (2021) found that long-term community noise in the US was associated with higher odds of MCI, AD, and worse cognitive performance, independent of exposure to traffic-related AP (Weuve et al., 2021). However, the size of effect measure change cannot be determined in the studies by Cullen et al. and Weuve et al. because AP (in Weuve et al., 2021) and noise (in Cullen et al., 2018) were only adjusted in combination with all other variables in one model. Thus, these two studies do not answer the question of

whether confounding exists since we cannot determine whether confounding between AP and noise truly does not exist or has been adjusted for.

4.1.3. EM and interaction between AP and noise in studies beyond this review

The results of this review align with the those of Eminson et al. (2023), who discovered that noise had the greatest impact on cardiovascular outcomes at higher AP exposure levels, though it was not statistically significant. Few other studies not included in this review, analysed EM in the association between environmental factors and cognition. Weuve et al. (2021) found that the estimated association between community noise and dementia or cognition did not substantially vary by AP exposure, particularly NO_x exposure. The mean noise level was 56.2 dB(A) and the mean NO_x level was 40.8 ppb. Their study was not included in the review because Weuve et al. focused on community-noise rather than traffic noise. Li et al. (2023) analysed the relationship between residential distance to major traffic roads and dementia incidence and brain structure measures. They identified NO_2 and $PM_{2.5}$ as the two main mediators linking residential distance to dementia and brain structure measures. Contrary, no significant mediation was observed for noise pollution (Li et al., 2023). Thomson (2019) found evidence of mediation of the longitudinal associations between AP and increased risk of dementia by brain size (Thompson et al., 2025).

4.2. From epidemiology to biology: underlying effects of co-exposure

4.2.1. Mediation

The concept of mediation refers to how causal effects occur by relating to their underlying biological processes. Mediation involves an exposure variable influencing an intermediate variable (the mediator), which then impacts the outcome (Bours, 2023). It is crucial to consider that the observational studies included in this review do not support causal conclusions. However, exploring potential biological mediation effects could offer insights into why effect modification and interactions between AP and noise might arise.

4.2.2. The biological mechanisms of AP and noise in their effect on the brain

Air pollutants can enter the brain directly through the olfactory bulb, resulting in direct effects on the nervous system. Alternatively, air pollutants can cause systemic effects via the bloodstream, indirectly affecting the brain when passing the blood-brain barrier. This direct and indirect absorption can trigger various neurological disorders by causing inflammation of the nervous system, oxidative stress, protein aggregation, activation of microglial cells, and cerebral vascular-barrier disorders (Kim et al., 2020). A recent review showed that neuroinflammation and glucocorticoid signalling are the main pathways in $PM_{2.5}$ and ultrafine particle induced neurotoxicity (Qin et al., 2024).

Noise also triggers physiological responses through direct and indirect pathways. The direct pathway involves the effects of high sound level, while the indirect pathway involves cognitive and emotional responses to a stimulus. Both pathways overlap in generating stress responses (Hahad et al., 2022). Numerous studies examining the biological mechanisms of noise at the molecular level suggest that the negative effects of noise on brain health are primarily driven by reactive oxygen species, oxidative stress, inflammatory pathways, altered neurotransmitter levels, and by epigenetic modification (Arjunan & Rajan, 2020; Hahad et al., 2022; Münzel et al., 2018). Emerging genetic evidence suggests that inflammatory factors mediate the link between AP and noise-related diseases (Ma et al., 2024).

4.2.3. Interaction between AP and noise through their combined effect on the inflammasome

Inflammasomes have been linked to various inflammatory conditions. Inflammasomes are receptors of the innate immune system that detect infectious microbes and host-derived molecules, triggering inflammation and controlling the activation of caspase-1 (Guo et al., 2015). Both AP and noise trigger the inflammasome. Thus, inflammation can be regarded as the mediator between AP and noise exposure and the outcome of cognition (Fig. 2). New research provides first genetic evidence linking AP and noise to neurological diseases, with inflammatory factors acting as dual mediators in these associations (Ma et al., 2024). Based on the results of this review we propose that higher levels of AP and noise exposure might be associated with higher inflammation, mutually enforcing each other at a certain point. In environmental epidemiology, when one exposure is routinely adjusted for by the other exposure to account for confounding factors, the mutual reinforcement of inflammation processes by AP and noise through the inflammasome may be overlooked, resulting in an underestimation of their detrimental health effects.

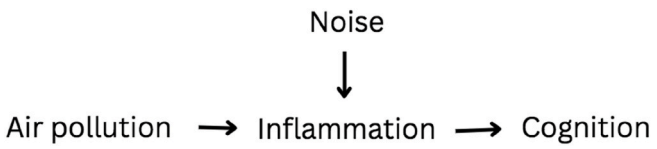

Fig. 2. Interaction between AP and noise through their combined effect on inflammation and the inflammasome. This causal diagram show that by influencing the mediator inflammation, noise has an effect on the magnitude and/or direction of the indirect (mediated) effect of air pollution on cognition. Noise interacts with the effect of air pollution. Thus, the mediated effect of air pollution on cognition depends on the effect of noise on cognition, and vice versa (Bours, 2023).

4.3. From biology back to epidemiology: general limitations of co-exposure research

4.3.1. Measuring the effects of exposures on inflammation

The entirety of an individual's external and internal exposures throughout their lifetime, from birth to death is encompassed in the exposome. In other words, external exposures and their associated biochemical changes within the body accumulate progressively with age. This results in altered health risks. When physiological aging occurs alongside AP and noise exposure, inflammation and oxidative stress promote each other, resulting in unhealthy aging (Hahad et al., 2021; Pandics et al., 2023). Most older adults experience this so called inflammaging, a condition marked by increased levels of inflammatory markers in the blood. This significantly heightens the risk of chronic illness, disability, frailty, and early mortality (Ferrucci and Fabbri, 2018).

Although molecular mechanisms indicate synergisms between AP and noise exposure on cognition, epidemiological evidence from this review cannot yet support this. If epidemiological research could demonstrate a positive joint effect of AP and noise, this effect would most probably appear in older adults who have experienced prolonged exposure and possess genetic or personal vulnerabilities to cognitive decline—not in younger individuals. Since cognitive decline results from individual susceptibility and exposure throughout one's lifetime, cross-sectional studies measuring cognitive decline may only yield meaningful results if the measured exposure adequately reflects the lifelong exposure or exposure during a vulnerable period, such as the state of MCI.

4.3.2. Limitations of statistical control and interaction analysis

Statistical control differs fundamentally from experimental control since it only addresses measured confounding factors, which can introduce biases through inappropriate control (Christenfeld et al., 2004). Problems include residual confounding due to mismeasurement, in which imperfectly measured factors may still explain associations, as well as assumptions about linear relationships between confounders and outcomes (Christenfeld et al., 2004). For example, even if AP has been

controlled for, it may have been mismeasured and could still explain the association between noise and cognitive decline. In general, AP epidemiology is susceptible to confounding and errors in exposure measurement (Sheppard et al., 2012). Similarly, measurement uncertainty exists in noise assessment, e.g., due to the inaccuracy of the georeferencing process (Gómez et al., 2020). Additionally, differences between crude and adjusted effect sizes may result from noncollapsibility rather than confounding. However, this may be negligible when variables do not consistently affect each other (Bliss et al., 2012; Greenland and Robins, 2009; Schuster et al., 2021).

Also, interpreting whether an interaction is meaningful or not, demands consideration of confounding. When assessing mechanistic interactions, it is necessary to control for confounding of the relationship between both factors and the outcome (VanderWeele and Knol, 2014). Although mechanistic interactions between AP and noise exposure are important for both understanding their causes and informing policy, the statistical power of these interactions is limited and measurement error is a major concern (Corraini et al., 2017; Weuve et al., 2021). Additionally, heterogeneities in study populations, including variations in exposure ranges, the types of exposures assessed, and co-exposures, can result in different interaction estimates, even if all estimates are unbiased (Weuve et al., 2021). Thus, the interaction effects of multiple pollutants can be unreliable unless the interactions are particularly strong or abundant data is available (Bellavia et al., 2019).

4.3.3. Challenges of multi-pollutant mixture data

Besides interaction, which has been discussed in this review in-depth, multi-pollutant mixture data exhibits several other characteristics and challenges. Mixture data is characterized by high dimensionality, multicollinearity, and nonlinear effects. The most significant statistical challenge in the study of multi-pollutant mixtures is multicollinearity. It can be induced when analysing correlated pollutants with similar sources, exposure pathways, and/or metabolic processes simultaneously (Yu et al., 2022). In this review, we compared the cognitive effects of only one air pollutant from a single-pollutant model to the cognitive combined effect of a multipollutant model analysing the same single air pollutant in combination with noise or vice versa. However, if air pollutants are correlated, they might also confound each other and analysing each air pollutant separately might overestimate its effect. Moreover, single-pollutant models do not reflect real world conditions since people are exposed to mixtures. Advanced statistical tools that use machine learning, such as Bayesian kernel machine regression, could be helpful to analyse multi-pollutant mixture data (Yu et al., 2022).

4.4. Strengths and limitations of this review

This review provides first insights into a current yet understudied topic, contributing to the field of AP and noise research. It emphasizes the importance of critically evaluating the results of adjustments and conducting additional analyses to identify EM or interactions. This review's approach to identifying confounding factors using the change-of-estimates method can also be applied to analysing other co-exposures and mixtures. Adhering to the PRISMA guidelines, the review followed the conventions for transparent reporting. The OHAT tool was used to systematically and standardly assess studies. It was adopted as a guiding framework, as recommended by Boogaard et al. (2023), rather than as a strict tool for excluding biased studies.

Nevertheless, this review has several limitations. Although we conducted extensive literature research, relevant studies may have been missed due to human error or search engine algorithms. Using the search term "traffic" and linking it with the operator "AND" to other terms might have excluded studies covering broader noise concepts, such as community noise (e.g., Weuve et al., 2021). However, without the "traffic" restriction, the search results would have been unmanageable. No studies conducted in low- and middle-income countries were included, which may be due to underlying structural inequities that hinder publication and dissemination. Although we used a standardized approach for quality appraisal, we may have over- or underestimated the effects of bias on the results because we based the rating on our experience and only on documents published in journals.

According to epidemiological convention, the threshold for meaningful confounding of effect estimates was set at $\geq$10 %, but it can be questioned whether this threshold truly defines meaningful confounding. The change-in-estimate test yields the best results when the threshold for determining significant differences between crude and adjusted estimates is set at 10 % (Maldonado and Greenland, 1993). Bliss et al. (2012, 2013) showed that the change-in-estimate method is highly sensitive in logistic regression but yields false positives if a third variable is associated with exposure but not the outcome. Since AP and noise are both associated with the outcome in our review, false positives are unlikely—but this may not apply to Cox models, which were used in some included studies. Eminson et al. (2023) argued that confounding by AP in noise-cardiovascular studies requires pre-/post-adjustment associations. They note that changes in non-significant estimates may lack meaning. We prioritized effect size changes (to assess magnitude) and assumed large changes could mask interactions, but excluded significance tests due to their limited value in observational research.

Finally, this review is limited by the small number of included studies and their heterogeneity, since most of them were not designed to detect interrelationships, but rather to control for confounding factors. The studies used highly variable adjustment sets and analysed additional exposures, such as surrounding green space in Klompmaker et al. (2021), or outcomes, such as annoyance in Fuks et al. (2019). Due to the heterogeneity of the statistical models (linear versus Cox regression), the analysis of interactions was performed either on an additive or multiplicative scale in the studies included. This limited the comparability of the joint effects of AP and noise in this review.

4.5. Implications for research and policy

No only more, but more thorough research is necessary to properly understand the effects and interrelations of AP and noise. Although numerous studies have assessed the effects of AP or noise on health, only few included both exposures, and even fewer published related data. This might be because controlling for more variables reduces the precision of the results (Alexander et al., 2015). Nevertheless, we suggest that authors measure co-exposures and provide information about the statistical calculations performed and their implications for outcomes. If this information is not relevant to the main text, it should be included in the supplementary material. When hypothesizing that the adverse effects of AP or noise on cognition are most observable at moderate to high levels (Weuve et al., 2021), it is necessary to analyse effect measures according to exposure level, as in Cantúria et al. (2021) and Mac Domhnaill et al. (2021). This allows one to draw more comprehensive conclusions about confounding mechanisms. Given the biological processes involved, treating AP and noise merely as confounders may be inadequate. Instead, further analysis of EM and interaction effects should be undertaken. In terms of interaction, researchers are supposed to clearly differentiation between interaction on an additive and on a multiplicative scale to better characterise joint effects between AP and noise. To conduct these analyses and allow for a greater variability of exposure levels, studies with higher statistical power are necessary. Therefore, data sets from different population cohorts could be standardized and connected. Adjustment could be made more transparent by grouping variables into different domains, such as personal, lifestyle, health, and environment, and by indicating whether the variables were measured at the individual level. In mixtures research, especially when combining studies from two fields with distinct approaches, a more homogeneous approach in observational studies could facilitate work in reviews and meta-analyses. Further variables, such as temperature with special consideration for heat waves, should be taken into account. There is epidemiological evidence of a positive joint effect between AP and heat (Zhou et al., 2023), as well as evidence from mice indicating a shared pathway of noise and heat in their negative impact on cognition

(Sun et al., 2021). Research from low- and middle-income countries, which have different exposure clusters than Europe and North America, would contribute to a more comprehensive understanding. A case-control study of deaf or hearing-impaired people could allow for a comparison of the effects of AP and noise exposure on the hearing population versus AP exposure only on deaf or hearing-impaired people.

However, considering the inflammatory process and individual susceptibility to environmental stressors, focusing on a pre-set outcome such as cognition might lead to an underestimation of the effect since participants with genetic susceptibility, such as the ApoE gene, are at risk of developing dementia. Participants who develop a different condition, such as cardiovascular disease, would remain undetected. One possible solution is to use blood biomarkers to detect biological age (Bortz et al., 2023). Using blood biomarkers would shift the focus from detecting impairment and diseases in the elderly to lifelong exposure starting with young participants. Since younger participants usually spend less time at home than older adults, an alternative to exposure modelling at home would be to measure noise with smartphones (Padilla-Ortiz et al., 2023) or AP with miniaturized monitors (Borghi et al., 2017). This approach would better capture individual-level exposure variations. A citizen science approach could foster public engagement and awareness of traffic exposure.

In terms of methodology, the OHAT tool provided a valuable framework. However, a beginner would benefit from a less complicated handbook. The online tool hawcproject.org has facilitated the process. Thus, we recommend increasing its visibility and accessibility. It would have been helpful within the tool to group the risk of bias questions according to their significance for the research question.

The interrelation between AP and noise has implications for health and urban policy. A possible positive joint effect implies a higher urgency to reduce traffic, especially cars with combustion engines. A key intervention would be to reduce traffic flow by creating traffic-restricted living areas, such as neighbourhoods, city centres, schools, and other workplaces or places of leisure. This was implemented for example in the Barcelona Superblock model with initial health indicator improvements shortly after implementation (Nieuwenhuijsen et al., 2024). Besides, policies should empower high-risk populations. People with lower socioeconomic status are at risk of living in areas with high traffic exposure, which could further exacerbate their health and health inequity. Protection is also possible through mitigation, e.g., providing noise-insulated housing and informing residents about avoiding opening windows during rush-hour. More awareness is needed of the indirect public costs of traffic through morbidity and healthcare expenses which may be even higher than the sum of the costs of each exposure. Health impact assessments, such as the software tool for health risk assessment of AP developed by WHO Europe "AirQ+" (WHO Europe, 2024) may need to consider noise exposure simultaneously. In settings where intervention on the primary exposure of interest (e.g., AP) is not possible, intervention on another exposure (e.g., noise) might still have an effect if both factors interact. Recent research indicates that a modest reduction in AP can substantially improve health and equity, even in populations with low exposure (Chen et al., 2025). Thus, implementing stricter European Union AP exposure limits would be beneficial, as would developing a collective understanding that reducing combustion vehicle traffic serves both environmental and public health interests. Citizens need to be informed about the possible detrimental cognitive effects of synergies and become more involved in claiming their human right to clean air (Climate & Clean Air Coalition, 2022). Cross-sectional collaborations between public health, environmental health, and urban or traffic planning specialists are needed to promote healthy environments.

5. Conclusion

This review found no consistent evidence of meaningful mutual confounding between traffic-derived AP and noise in their effects on cognition in adults. However, there may still be EM or interaction between the two exposures, especially among highly exposed groups. As urbanization increases, more and more people worldwide are exposed to mixtures of various environmental stressors. Thus, future research should 1) measure both exposures and present effect estimates according to exposure level; 2) have sufficient power to perform analyses for EM and interaction, with a clear statistical protocol, data, and code; 3) follow standardised adjustment guidelines; 4) and consider alternative ways how to measure the interrelation between exposures and their effect on the inflammasome and exposome. Given the increasing prevalence of cognitive diseases in aging populations and the potential interaction between AP and noise on cognitive function, reducing and mitigating traffic is urgent.

CRediT authorship contribution statement

C. Hildt: Writing – original draft, Visualization, Project administration, Methodology, Investigation, Formal analysis, Data curation. **L. Tzivian:** Writing – review & editing, Validation, Supervision, Methodology, Conceptualization. **K. Ogurtsova:** Writing – review & editing, Validation, Supervision. **B. Hoffmann:** Writing – review & editing, Validation, Supervision, Project administration, Methodology, Conceptualization.

Declaration of generative AI and AI-assisted technologies in the writing process

During the preparation of this work the author used LeChat free/Mistral AI in order to paraphrase sentences. After using this tool/service, the authors reviewed and edited the content as needed and take full responsibility for the content of the published article.

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Appendix A. Supplementary data

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Data availability

Data will be made available on request.

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