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Review

Exercise Under Particulate Matter Exposure: Neurotrophic Responses and Functional Brain Outcomes

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Abstract

Whether particulate matter (PM) exposure modifies the brain-related benefits of exercise remains unresolved. This focused narrative review examined exercise-related neurotrophic responses, centred on brain-derived neurotrophic factor (BDNF), alongside cognitive and brain outcomes under particulate or traffic-related pollution. PubMed and Web of Science Core Collection were searched, and 37 reports, comprising 33 main and four indirect reports, were synthesised by biological outcome level and response pattern. Circulating BDNF responses were heterogeneous; vascular endothelial growth factor (VEGF) and insulin-like growth factor 1 (IGF-1) provided complementary peripheral evidence. Human experiments and population studies reported attenuation in selected cognitive, dementia and imaging contrasts, alongside retained favourable activity associations, uncertain modification and potential activity-related buffering. Central molecular evidence from inhalation experiments was limited; selected animal improvements arose after intravenous particle administration or in an airway-instillation model with cerebral ischaemia/reperfusion, constraining translation to exercise during ambient inhalation. Differences in comparators, interaction scales and exposure measurement, together with potentially overlapping cohorts, limited inference. Neurotrophic and functional findings should be interpreted in relation to the measured outcome and study comparison: a change in peripheral BDNF alone does not establish brain benefit under PM exposure. The evidence supports neither a uniform loss of exercise benefit nor a general concentration threshold for reversal to harm. Studies measuring neurotrophic markers and central or functional outcomes together, with activity-specific exposure and exercise-intensity assessment and appropriate exposure-by-exercise comparisons, are needed to test how these responses relate.

Keywords: air pollution; particulate matter; exercise; physical activity; brain-derived neurotrophic factor; neurotrophic responses; cognition; brain health

Check for updates

Academic Editor: Anil Namdeo

Received: 2 September 2026
Revised: 29 October 2026
Accepted: 29 October 2026
Published: 31 October 2026

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1. Introduction

1.1. Particulate Matter and Brain Health

Particulate matter (PM) is a heterogeneous mixture characterised by particle size, chemical composition, source and concentration, with regional and seasonal variation in composition limiting comparisons of exposure based on particle mass alone [1]. Its relationship with brain health must also be considered in the context of exposure route and timing. Earlier reviews brought physical activity and air pollution into a common brain-health framework and assessed acute health responses to exercising in polluted air [2,3].

Inhalation experiments without exercise have identified changes in memory, brain inflammation and blood–brain barrier (BBB) function after particulate or vehicle-exhaust exposure [4,5]. Reviews of epidemiological evidence have linked air pollution with poorer cognitive performance and cognitive decline [6], and $PM_{2.5}$ with a broader range of neurological outcomes, including stroke and dementia [7]. A more recent meta-analysis reported associations of long-term $PM_{2.5}$ and black carbon/$PM_{2.5}$ absorbance exposure with incident dementia, although between-study heterogeneity was substantial [8].

In the 1946 British Birth Cohort, higher midlife exposure to selected pollutants was associated with poorer later-life cognition and differences in hippocampal or ventricular volume [9]. Air pollution and physical inactivity were both identified as potentially modifiable dementia risk factors in the 2020 Lancet Commission report [10]. These findings motivate examining their joint associations, but do not determine whether exercise-related brain responses are attenuated, retained or otherwise modified under exposure.

1.2. Exercise, Neurotrophic Signalling, and Peripheral BDNF

Experimental evidence supports a role for brain-derived neurotrophic factor (BDNF) in exercise-related synaptic plasticity and learning [11]. In healthy participants, a meta-analysis of randomised controlled trials reported average increases in circulating BDNF after acute exercise and longer-term training, although responses varied across studies [12]. These findings support examining whether pollution modifies exercise-related neurotrophic responses, without assuming that an increase must occur in every protocol. This review centres on BDNF, with vascular endothelial growth factor (VEGF) and insulin-like growth factor 1 (IGF-1) as secondary markers. Their biological relevance does not make circulating concentrations interchangeable with central molecular or functional outcomes. Platelet release and sample processing further require serum and plasma BDNF to be distinguished [13,14].

1.3. Rationale and Aims of the Review

Acute exercise experiments, longer training interventions, population studies and animal models address different questions and measure outcomes ranging from circulating growth factors to hippocampal gene expression, cognition, brain imaging and barrier-associated markers. Their comparison requires attention to both the biological outcome and the contrast supported by the design.

This focused narrative review has four aims. First, it synthesises exercise-related BDNF responses under particulate or traffic-related pollution, with VEGF and IGF-1 as complementary growth-factor outcomes. Second, it distinguishes peripheral, central and functional outcomes and organises their reported patterns as attenuation, retention, potential amplification or uncertain modification. Third, it examines the evidence linking neurotrophic responses to central and functional outcomes, distinguishing within-study comparisons from cross-study contrasts. Fourth, it evaluates how study design, exposure timing and route, particle composition, activity measurement and population context constrain interpretation and identify priorities for further research.

2. Review Scope and Evidence Identification

2.1. Review Design and Objective

This focused narrative review examines how particulate and traffic-related pollution may modify exercise- or physical activity-related neurotrophic and brain outcomes. Its purpose is to identify response patterns and the conditions under which they can be interpreted across heterogeneous human and animal studies. Reporting was guided by the Scale for the Assessment of Narrative Review Articles (SANRA) [15]. Evidence was

synthesised narratively, with biological outcome level, exposure characteristics and study design providing the organising framework.

2.2. Literature Search and Selection

PubMed and Web of Science Core Collection were searched, with the final searches conducted on 13 October 2026. The search strategy combined three concept blocks using AND, with related terms within each block linked by OR: (1) particulate or traffic-related pollution, including particulate matter, ultrafine particles, diesel exhaust and black carbon; (2) exercise, physical activity and training; and (3) neurotrophic, cognitive, brain and cerebrovascular outcomes. PubMed expressions combined Medical Subject Headings with title/abstract terms; Web of Science searches used the Topic field. Database-specific expressions are provided in Supplementary Methods S1. No publication-year, language or document-type filters were applied.

The database searches yielded 1798 records, comprising 1386 from Web of Science and 412 from PubMed; 265 duplicates were removed. From the remaining 1533 records, 53 publications that jointly addressed exercise or physical activity and particulate or traffic-related air pollution and reported neurotrophic or brain-related outcomes were selected as candidates. One author assessed all 53 candidate publications against the eligibility criteria, and a second author verified the selection decisions. Ultimately, 33 reports were included in the main evidence synthesis and four as indirect evidence. Of the remaining candidates, nine were retained as contextual literature and seven were excluded because their publication type or exposure scope did not meet the eligibility criteria, or their relevance to the core review question was limited.

2.3. Eligibility and Evidence Organisation

For the main synthesis, eligible primary reports were peer-reviewed human experimental or observational studies or animal experiments that jointly examined exercise or physical activity and particulate or traffic-related pollution and reported a relevant neurotrophic, cognitive, neurodevelopmental, brain, cerebrovascular, blood–brain barrier or neural-injury outcome. No age or health-status restrictions were imposed. BDNF was the principal neurotrophic marker; VEGF and IGF-1 were secondary growth-factor outcomes. Selection was independent of result direction, statistical significance and authorship. Reviews, protocols and conference abstracts were not counted as primary reports.

Eligible comparisons included exercise across exposure conditions, pollution associations stratified by activity, joint exposure–activity categories, and formal interaction analyses. An interaction test was not required for inclusion; the comparison structure determined the inference supported. The main synthesis comprised human exercise comparisons, human observational or panel analyses, and animal experiments. Four reports were considered separately as indirect evidence: two compared exercise in complex natural and built environments without isolating a particle-specific cognitive contrast, and two used outdoor time as an activity proxy in developmental analyses with differing exposure and activity assessment periods.

Studies limited to pulmonary or systemic inflammatory and oxidative outcomes, studies using exercise only to increase ventilation or physical activity only as a covariate, and non-exercise mechanistic studies contributed contextual evidence where relevant. Exposures limited to gaseous pollutants or tobacco smoke were outside the core particulate/traffic-related scope. These contextual sources were not added to the 37 synthesis reports.

2.4. Data Extraction and Narrative Synthesis

Study-level records captured design and sample characteristics; pollution source, metric, route and timing; activity type, intensity or volume and assessment method; outcome and sampling compartment; comparator structure; reported estimates and uncertainty; and potential cohort overlap. Qualitative appraisal considered design suitability, measurement directness, confounding and precision, together with study-specific limitations such as multiplicity, missing data or reporting inconsistencies. These considerations informed interpretation of individual findings rather than a single numerical quality score. Exposure metrics and administration routes are summarised in Table 1. Table 2 provides a concise overview of outcome level, reported pattern and comparison basis. Supplementary Table S1 retains detailed exposure/activity conditions, samples, estimates and qualifications for each included report.

Findings were synthesised along two axes: biological outcome level (peripheral biomarkers, central molecular or structural outcomes, and cognitive or functional outcomes) and response pattern (attenuated, retained, potentially amplified, or uncertain exercise-related responses). A retained response denotes an exercise-related response observed under pollution exposure, without implying equivalence to a lower-exposure condition. Patterns were interpreted within the available comparison, considering effect magnitude and precision where reported; they were not used to tally statistically significant findings. A non-significant result did not establish equivalence or absence of an effect. Differences between subgroup p values did not establish effect modification [16]; formal interaction estimates, joint-category associations and within-stratum results were distinguished, as were additive and multiplicative interaction scales.

Interpretation retained distinctions between measured or modelled pollution and exposure proxies, and between inhalation, airway instillation and intravenous administration. Intravenous experiments informed responses to direct systemic administration, not protection during ambient inhalation. Designs lacking the comparisons needed to assess effect modification were not treated as direct tests of a pollution-by-exercise interaction. Peripheral biomarkers were not equated with central neuroplasticity or blood–brain barrier permeability, and group-level agreement between biomarkers and cognition was not taken as evidence of mediation or surrogate validity. Reports sharing a cohort were treated as related analyses rather than independent replications; their sample sizes were not summed. The same eligibility and appraisal principles were applied to studies co-authored by the review authors.

Table 1. Exposure metrics, administration routes and limits of dose comparison.

Metric or Route	Study Context	Comparison Boundary
Airborne mass $\mu g/m^3$	20-min roadside/filtered-air cycling; 50-km traffic-pollution/filtered-air trial [17,18].	Sampled-air concentration, not uptake. Inhaled-mass estimation also requires individual ventilation and duration.
Ventilation L/min	90-min cycling: 47.8 polluted/47.3 filtered; both HR-estimated [19].	Estimated, not directly measured. Combined estimation errors preclude exact between-study dose equivalence.
Particle number particles/cm^3	Human counter range: 0.02–1 µm; rat soot-particle size: 5–115 nm [20,21].	Not interchangeable with $\mu g/m^3$. Retain detector range, particle size and composition.
Residential exposure Long-term context	PM mass, $PM_{2.5}$ absorbance or components; habitual activity and brain/cognitive outcomes [22,23].	Not personal exercise dose. Absorbance and component concentrations are distinct from total $PM_{2.5}$ mass.

Table 1. *Cont.*

Metric or Route	Study Context	Comparison Boundary
Intratracheal instillation Bolus → airway	Particulate suspension before cerebral ischaemia/reperfusion, following preventive wheel exercise [24].	Body-mass-normalised bolus, not continuous inhalation. Ambient-concentration conversion requires additional dosimetric assumptions.
Intravenous administration Injection → bloodstream	Repeated particulate administration with treadmill or resistance training in mice [25,26].	Bypasses respiratory deposition and exercise-driven inhaled-dose increases; tests administered systemic exposure.

Note: With constant concentration and ventilation, estimated inhaled mass = concentration × minute ventilation × duration (compatible units). Inhaled mass is not deposited mass or brain dose. Deposition depends on particle and breathing characteristics; ultrafine-carbon findings do not define a universal deposition fraction [27]. HR, heart rate; PM, particulate matter.

Table 2. Study-level overview of exercise and brain outcomes under particle exposure.

Study, Design and Sample	Outcome Level and Main Pattern	Comparison and Qualification
A Human Exercise Studies · 8 Reports		
Molina-Sotomayor et al. (2019) [28] Two-city, two-year walking comparison; 181 older women.	Cognition; cardiorespiratory fitness. MMSE improved in both active groups; fitness gains were smaller with higher $PM_{2.5}$.	Group comparisons; no factorial interaction established. City differences may confound the contrast.
Liu et al. (2023) [29] Randomised parallel trial; 93 participants; filtered/unfiltered air, HIIT/MICT/stretching.	Cognition; prefrontal haemodynamics. Higher $PM_{2.5}$ attenuated the HIIT-versus-stretching Stroop contrast; haemodynamics varied by channel/task.	Formal interaction; HIIT–MICT interaction differences and a harm threshold were not established.
Molina-Sotomayor et al. (2020) [30] Two-city, 24-month resistance training; 157 older women.	Cognition; circulating IGF-1. MMSE gains were larger at lower $PM_{2.5}$; IGF-1 increased within both active groups.	No factorial interaction reported; post-test IGF-1 omnibus comparison was inconclusive. City confounding and attrition.
Cassilhas et al. (2022) [31] Randomised four-group trial; 48 older adults; indoor/outdoor exercise.	Cognition; serum BDNF. Exercise-by-site interactions favoured indoor exercise for cognitive tests and BDNF.	Formal site interaction; exercise modality co-varied. PM-specific effects and BDNF mediation remain unestablished.
Bos et al. (2013) [20] Non-randomised urban/rural training; 34 enrolled, 24 analysed.	Cognition; serum BDNF. Rural training favoured Stroop performance; BDNF changes were statistically uncertain.	Time-by-site interaction for Stroop; age imbalance, attrition and other site differences limit attribution.
Silveira et al. (2022) [18] Chamber crossover; ten male cyclists, blood analyses in nine; 50-km cycling.	Plasma BDNF; exercise performance. BDNF post/pre ratio was larger in polluted than filtered air.	Paired condition contrast; cognition unmeasured. Greater peripheral response does not establish adaptation.
Bos et al. (2011) [17] Within-person cycling comparison; 35 analysed; roadside/filtered air.	Serum BDNF. BDNF increased under filtered air; the roadside increase was statistically uncertain.	Within-condition tests; no change-score contrast or condition-by-time test reported. Different significance does not establish modification.
Pasqua et al. (2020) [19] Chamber crossover; ten men; 90-min cycling in polluted/filtered air.	Serum VEGF; systemic responses. VEGF was higher at 90 min under polluted air, with higher IL-6/blood pressure.	Time-point contrast; no established condition-by-time interaction. Cognition unmeasured.

Table 2. *Cont.*

Study, Design and Sample	Outcome Level and Main Pattern	Comparison and Qualification
B Observational human studies · 21 reports		
Zhang et al. (2022) [32] Repeated panel; 90 young adults; personal $PM_{2.5}$ and accelerometer MVPA.	Cognition: Stroop. MVPA was associated with faster responses across exposure levels.	Formal linear interaction was inconclusive; numerically stronger high-pollution associations do not establish amplification.
Zhang and Xu (2026) [33] UK Biobank cohort; 96,661 participants; accelerometer PA.	Incident AD/vascular dementia. A selected $PM_{2.5}$ interaction suggested attenuation for AD; most interactions were inconclusive.	Multiplicative interactions; unadjusted multiple comparisons. Interaction HRs do not indicate harm from activity itself.
Das and Ayalon (2026) [34] LASI cross-sectional analysis; 31,902 older adults; household-combustion proxy.	Cognition. Overall PA-by-pollution interaction was inconclusive; a three-way interaction suggested sex differences.	Formal three-way interaction is not a women-only two-way test; mixed activity measure and exposure proxy.
Furlong et al. (2022) [22] UK Biobank cross-sectional MRI; 8600 participants; accelerometer vigorous PA.	Brain structure: white-matter hyperintensities. Favourable activity associations weakened with higher NO_2 and $PM_{2.5}$ absorbance.	FDR-adjusted interactions; pollutant/outcome-specific. Absorbance is not PM mass; longitudinal changes were not measured.
Gui et al. (2020) [35] Cross-sectional children; parent ratings 5028, computerised tests 522; $PM_{2.5}/PM_{10}$.	Working memory; inhibitory control. Higher PM was associated with poorer performance; MVPA modification was uncertain.	Effect-modification tests; reported activity and residential exposure. Non-significance does not establish equivalent associations.
Li et al. (2024) [36] Fuyang cross-sectional study; 3937 older adults; residential PM, reported PA.	Cognition: MMSE. Activity associations suggested attenuation at higher PM.	Exploratory interaction criterion $p < 0.20$; all interaction p-values exceeded 0.05. Significance-loss concentrations are not harm thresholds.
Hong et al. (2025) [37] Kidney-transplant evaluation cohort; baseline cognition in 2073 patients.	Cognition: 3MS; dementia follow-up. Adverse $PM_{2.5}$–3MS associations were stronger at low leisure PA.	Formal cognitive-score interaction; dementia modification untested with only 29 events. Clinical-population scope.
Zhu and Zou (2025) [38] CHARLS 2018 cross-sectional study; middle-aged/older adults; regional PM, reported PA.	Cognition. Adverse $PM_{2.5}$ associations were weaker at higher PA in instrumental-variable models.	Formal interaction; association directions differed from ordinary least-squares models. Instrument assumptions constrain interpretation.
Liu et al. (2023) [23] CFPS repeated analysis; 108,099 observations; residential $PM_{2.5}$/components, reported PA.	Verbal/mathematics scores. Favourable activity associations persisted but weakened at higher $PM_{2.5}$.	Formal interactions; observations are not unique participants. Activity frequency/duration do not measure intensity.
Yu et al. (2026) [39] CHARLS five-wave analysis; 12,196 participants; city $PM_{2.5}$/components, reported PA.	Cognition; mental status; memory. Supplementary results supported buffering for mental status; other cognitive interactions were uncertain.	Formal interactions; abstract and supplementary estimates disagree. Interpretation is endpoint-specific.
Tuffier et al. (2024) [40] Danish Nurse prospective cohort; 1409 dementia cases; reported leisure activity.	Incident dementia. $PM_{2.5}/NO_2$ associations were weaker at higher activity levels.	Likelihood-ratio interaction tests; road-noise adjusted. Female occupational cohort and self-reported activity limit generalisability.
Zhang et al. (2024) [41] UK Biobank prospective cohort; 155,828 older adults; reported PA.	AD; all-cause/vascular dementia. $PM_{2.5}$-by-low-activity additive interaction supported for AD only.	Additive and multiplicative tests; AD multiplicative modification remained uncertain. Results cannot be transferred across scales or outcomes.

Table 2. *Cont.*

Study, Design and Sample	Outcome Level and Main Pattern	Comparison and Qualification
B Observational human studies · 21 reports		
Ran et al. (2021) [42] Hong Kong Elderly Health Centres cohort; 57,775 older adults; reported PA.	Incident dementia. Higher activity was associated with lower dementia risk across $PM_{2.5}$ levels.	Additive/multiplicative interaction evidence was inconclusive; retained associations do not establish equivalent effects.
Küçükali et al. (2025) [43] NICOLA longitudinal cohort; 2836 participants; residential $PM_{2.5}$, reported MVPA.	MMSE decline. High-$PM_{2.5}$/low-activity effect modification remained uncertain on both scales.	Additive and multiplicative confidence intervals included null values; cut-point sensitivity leaves modification uncertain.
Song et al. (2022) [44] Repeated panel; 34 retirees; fixed-site $PM_{2.5}$/components, reported activity.	Serum NfL/BDNF. $PM_{2.5}$–NfL association was stronger at lower activity; BDNF modification was uncertain.	Between-group significance indicated for NfL; test method unclear. Small, unequal activity strata.
Raichlen et al. (2022) [45] UK Biobank prospective cohort; 35,562 older adults; accelerometer activity.	Incident all-cause dementia. Inverse activity associations weakened at higher $PM_{2.5}$/absorbance.	Multiplicative interactions; high-exposure activity HRs remained below 1 with intervals including 1. Harm reversal not demonstrated.
Lee et al. (2022) [46] KoGES Ansan–Ansung cross-sectional assessment; 4175 adults; $PM_{2.5}$/PM_{10}, reported exercise.	Cognition: K-MMSE. Adverse PM associations were stronger in non-exercisers.	Interaction analyses supported modification; cross-sectional cognition does not measure decline, and exercise categories do not resolve intensity.
Tan et al. (2021) [47] Chinese Veteran cross-sectional study; 7040 men; residential PM, daily activity.	Prevalent dementia. $PM_{2.5}$–dementia association was stronger among active participants.	Formal between-stratum difference; endpoint-specific. This contrast should not be extended to MCI or other pollutants.
Zhang et al. (2023) [48] CLHLS cross-sectional study; 9839 older adults; road-distance proxy, reported exercise.	Cognitive impairment. Selected exercise–distance combinations had lower odds than non-exercise/near-road residence.	Common-reference joint categories; no established interaction or particle-specific effect. Road distance captures multiple environmental attributes.
Fu et al. (2025) [49] Zhejiang prospective cohort; 10,055 older adults; mixture score, leisure exercise.	Incident AD. Pollution-score–AD associations were stronger among exercisers.	Multiplicative interaction; this does not establish harm from exercise itself. Mixture scores cannot define $PM_{2.5}$ thresholds.
Deng et al. (2021) [50] CLHLS prospective cohort; 4161 older adults; cooking-fuel proxy, reported exercise.	Cognitive decline/impairment. Biomass-associated decline was weaker among exercisers; impairment modification remained uncertain.	Outcome-specific interaction tests; fuel type is a household-pollution proxy, not measured PM dose.
C Animal experiments · 4 reports		
Cho and Roh (2025) [25] Randomised four-group experiment; 40 male mice; intravenous PM_{10}-like material; eight-week treadmill training.	Peripheral serum biomarkers. With exercise, IGF-1, BDNF and VEGF were higher versus PM alone; S100B/NSE remained elevated versus controls.	Pairwise contrasts; no factorial interaction test reported or direct BBB permeability measurement.
Bos et al. (2012) [21] Randomised 2 × 2 experiment; 24 male rats; 90-min soot UFP inhalation with running/rest.	Central: hippocampal BDNF mRNA. Versus ambient-air rest: higher after ambient-air exercise; UFP-plus-exercise contrast uncertain.	No factorial interaction test reported; comparison-wise significance does not establish attenuation.

Table 2. *Cont.*

Study, Design and Sample	Outcome Level and Main Pattern	Comparison and Qualification
C Animal experiments · 4 reports		
Cho and Roh (2026) [26] Four-group experiment; 48 male mice; intravenous PM_{10}-like material; eight-week HFD ladder training.	Peripheral serum biomarkers. Versus exposed sedentary HFD mice: BDNF/VEGF higher, S100B lower; NSE contrast uncertain.	No PM-free exercise comparator for PM × exercise interaction; BBB permeability unmeasured.
Sun et al. (2025) [24] Six-group experiment; male mice, typically 3–5/endpoint; intratracheal particles plus cerebral ischaemia/reperfusion; preventive wheel exercise.	Behaviour and brain tissue. Selected behavioural, brain-injury and tight-junction-protein outcomes improved, strongest with six-week exercise.	No PM-free exercised ischaemia/reperfusion comparator; no full interaction or direct BBB permeability measurement.
D Indirect evidence · 4 reports		
Han (2021) [51] Four-group comparison; 116 university students; 15-min natural/built-environment walking/jogging; station $PM_{2.5}$/PM_{10}.	Cognition: spatial-span and digit-span attention. PM measures showed no clear attention associations.	No PM × activity coefficient reported; environmental contrasts cannot isolate particle effects.
Sun et al. (2023) [52] Shanghai–Minhang Birth Cohort; 512 pairs (503 stratified); prenatal $PM_{2.5}$/components; outdoor activity at age six.	Cognition: full-scale IQ, verbal comprehension, perceptual reasoning. $PM_{2.5}$ interactions uncertain; selected component interactions supported for verbal comprehension.	Formal interaction analyses; non-concurrent exposure/activity and unmeasured activity intensity.
Deng et al. (2025) [53] Shenzhen Birth Cohort; 1547 pairs; prenatal/postnatal $PM_{2.5}$/components; outdoor-time proxy.	Neurodevelopment: five ASQ-3 domains through 24 months. $PM_{2.5}$/component-by-activity-proxy interactions remained uncertain.	Formal interaction analyses; outdoor time does not measure infant exercise intensity or dose.
Roe et al. (2020) [54] Counterbalanced crossover pilot; 11 older adults recruited; 20-min green/built walks; portable $PM_{2.5}$.	Cognition: simple reaction time. Reaction-time differences between routes were uncertain.	PM-by-environment models assessed heart-rate variability, not cognition; green-route PM was not consistently lower.

Note: A–C comprise 33 main reports; D comprises four indirect reports. Reports may share cohorts and should not be treated as independent replications. "Uncertain" indicates limited statistical support or precision, not evidence of absence or equivalence. Detailed study characteristics and findings are provided in Supplementary Table S1. 3MS, Modified Mini-Mental State Examination; AD, Alzheimer's disease; ASQ-3, Ages and Stages Questionnaires, third edition; BBB, blood–brain barrier; BDNF, brain-derived neurotrophic factor; CFPS, China Family Panel Studies; CHARLS, China Health and Retirement Longitudinal Study; CLHLS, Chinese Longitudinal Healthy Longevity Survey; FDR, false discovery rate; HFD, high-fat diet; HIIT, high-intensity interval training; HR, hazard ratio; IGF-1, insulin-like growth factor 1; IL-6, interleukin-6; IQ, intelligence quotient; K-MMSE, Korean Mini-Mental State Examination; KoGES, Korean Genome and Epidemiology Study; LASI, Longitudinal Ageing Study in India; MCI, mild cognitive impairment; MICT, moderate-intensity continuous training; MMSE, Mini-Mental State Examination; MRI, magnetic resonance imaging; mRNA, messenger RNA; MVPA, moderate-to-vigorous physical activity; NfL, neurofilament light chain; NICOLA, Northern Ireland Cohort for the Longitudinal Study of Ageing; NO_2, nitrogen dioxide; NSE, neuron-specific enolase; PA, physical activity; PM, particulate matter; S100B, S100 calcium-binding protein B; UFP, ultrafine particles; VEGF, vascular endothelial growth factor.

3. Biological Framework

3.1. Neurotrophic Markers and Biological Outcome Level

BDNF provides a mechanistic anchor because hippocampal BDNF blockade prevented exercise-related gains in spatial learning and associated synaptic-plasticity signalling in rodents [11]. Experiments blocking peripheral VEGF or brain entry of circulating IGF-1 likewise support their involvement in exercise-induced hippocampal neurogenesis [55,56]. These findings establish biological plausibility, but do not validate blood concentrations as surrogates for neural or cognitive responses to exercise under PM exposure.

Peripheral BDNF has potential biological relevance, but its interpretation depends on species, sample matrix and study design. Positive associations with hippocampal BDNF have been reported for whole blood in rats and plasma in pigs [57]. These cross-sectional animal findings do not establish that exercise-induced changes in human serum or plasma track central responses under PM exposure. Human platelets store and release BDNF [13]; clotting duration and temperature affect serum measurements [58], while centrifugation strategy influences plasma concentrations [14]. Thus, serum and plasma should remain distinct, and neither an increase nor a non-significant change alone establishes enhanced or suppressed central plasticity. Peripheral growth factors, central molecular measures, brain structure or haemodynamics, and cognitive performance are consequently treated as separate outcome levels.

3.2. Exposure Route and Inhaled Versus Deposited Dose

Exposure route determines the biological processes modelled. Inhalation involves respiratory deposition; intratracheal instillation delivers an airway bolus, whereas intravenous injection bypasses airway deposition and the exercise-related increase in inhaled dose [21,24–26]. Responses to these routes cannot be treated as equivalent evidence for exercising in ambient pollution.

Exercise increases ventilation and can alter particle deposition. In a controlled study of ultrafine carbon particles, deposition fraction increased during moderate exercise [27]; this does not establish a universal fraction for other particles or breathing conditions. Where concentration and ventilation are approximated as constant, their product with exposure duration estimates inhaled particle mass. Heart-rate-based ventilation estimates also depend on the calibration used, with substantial differences between individual and population-average predictions [59]. These estimates do not measure deposited or brain dose, or establish exact dose matching across studies. Table 1 distinguishes exposure metrics and administration routes and explains why reported concentrations or reconstructed inhaled masses cannot establish equivalent deposited or brain doses across studies.

3.3. Mechanistic Links and Analytical Framework

Several pathways may connect inhaled pollution with brain outcomes. Mechanistic reviews identify systemic inflammatory signalling, microglial responses and oxidative stress as plausible contributors to neural injury [60], alongside changes in neurotransmission and synaptic plasticity that may differ by exposure and cognitive domain [61]. In rats, inhaled isotope-labelled ultrafine carbon particles produced persistent enrichment in the olfactory bulb, consistent with olfactory translocation. This finding supports a possible route of entry but does not quantify its contribution to human brain exposure [62].

In male mice, prolonged $PM_{2.5}$ inhalation impaired spatial learning and memory alongside increased hippocampal inflammatory gene expression and reduced dendritic spine density or branching [63]. Other inhalation experiments demonstrated oxidative and inflammatory changes after traffic-related PM_1 exposure [4] and increased tracer-measured BBB permeability with altered tight-junction proteins in vehicle-exhaust-exposed ApoE-

deficient mice [5]. These findings provide mechanistic context, but neither establish a common pathway across models nor demonstrate that exercise modifies these processes.

The synthesis therefore relates response patterns to the endpoint measured and the comparison supported by each design. Concordant group changes in biomarkers and cognition do not demonstrate mediation. Likewise, circulating S100B and neuron-specific enolase (NSE), or brain tight-junction-protein expression, are distinguished from direct BBB permeability measurements [24–26]. This framework permits evaluation of retained, attenuated or potentially amplified responses without assuming a common mechanism across outcome levels. Table 3 maps the outcome domains and provides mechanistic examples of why a circulating response cannot automatically be interpreted as a change in brain plasticity, BBB permeability or cognition. Figure 1 illustrates how outcome level, response pattern and study design shape interpretation in selected human studies across long-term and acute or short-term exposure contexts.

Table 3. Outcome domains and boundaries of inference.

Outcome Domain	Measure and Examples	What the Measure Does Not Establish
Circulating growth factors	Blood-compartment concentrations or changes: serum/plasma BDNF; VEGF; IGF-1 [17–19,30].	Serum ≠ plasma: platelet release, clotting and centrifugation affect BDNF [13,14]. Blood concentrations do not quantify brain entry; blocking circulating IGF-1 entry prevented exercise-induced hippocampal neurogenesis in rodents [56].
Circulating injury/ barrier markers	Peripheral profiles: serum S100B, NSE and NfL [25,26,44].	Not BBB tracer passage. Lower S100B or a non-significant NSE contrast alone does not establish restored permeability or central protection [25,26].
Central molecular/ barrier measures	Tissue expression or injury/barrier responses: hippocampal BDNF mRNA; cerebral tight-junction proteins; brain water [21,24].	mRNA ≠ protein abundance or cognitive benefit. Junction proteins/brain water ≠ direct BBB permeability. Intestinal FITC-dextran tests gut permeability [21,24].
Brain structure/ haemodynamics	Structural or task-linked signals: MRI white matter hyperintensity volume; prefrontal fNIRS [22,29].	MRI and fNIRS assess different constructs. fNIRS is not a behavioural cognitive test; haemodynamic associations alone do not establish cognitive mediation [29].
Cognitive/ behavioural/ clinical	Function, disease or development: Stroop/MMSE; animal mazes; incident dementia; ASQ-3 screening [24,29,30,42,53].	Constructs and time scales differ. Short-term task gains ≠ dementia prevention; ASQ-3 is a screen. Concordant biomarker/cognitive group contrasts ≠ mediation [31].

Note: Examples illustrate interpretation rather than summarise effect direction. Platelet and IGF-1 transport experiments provide background mechanistic evidence. Exercise performance or estimated aerobic capacity alone is not treated as a brain-health endpoint. Here, ≠ indicates non-equivalence or insufficient evidence for inference, not absence of a relationship. ASQ-3, Ages and Stages Questionnaires, third edition; BBB, blood–brain barrier; BDNF, brain-derived neurotrophic factor; FITC, fluorescein isothiocyanate; fNIRS, functional near-infrared spectroscopy; IGF-1, insulin-like growth factor 1; MMSE, Mini-Mental State Examination; MRI, magnetic resonance imaging; mRNA, messenger RNA; NfL, neurofilament light chain; NSE, neuron-specific enolase; S100B, S100 calcium-binding protein B; VEGF, vascular endothelial growth factor.

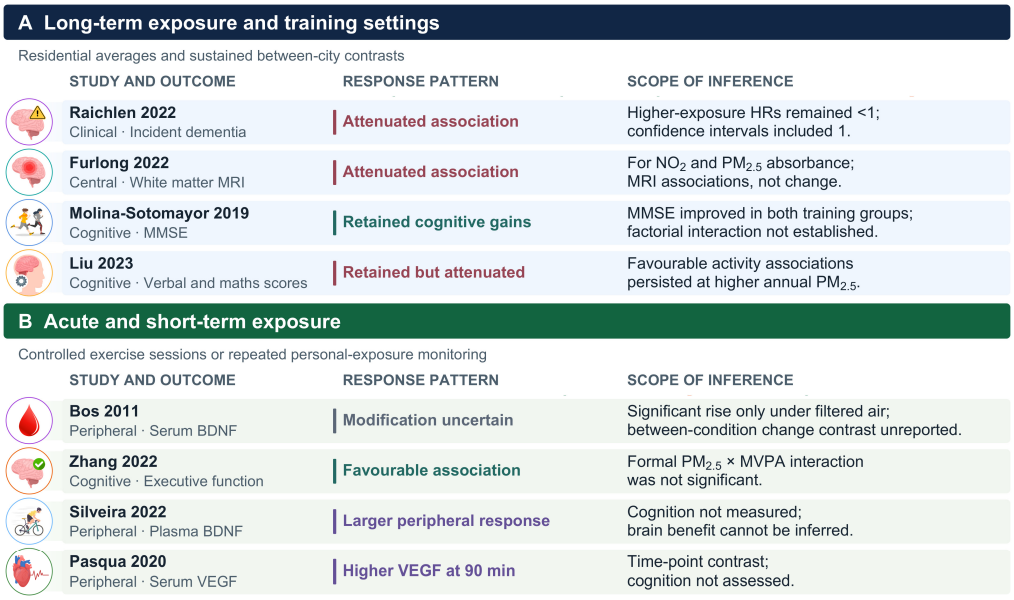


Figure 1. Exposure context, biological outcome level and interpretation in selected human studies. (**A**) Long-term exposure and training settings: Raichlen et al. (2022) [45], Furlong et al. (2022) [22], Molina-Sotomayor et al. (2019) [28], and Liu et al. (2023) [23]. (**B**) Acute or short-term exposure: Bos et al. (2011) [17], Zhang et al. (2022) [32], Silveira et al. (2022) [18], and Pasqua et al. (2020) [19]. Response patterns should be interpreted together with the biological outcome level and the contrast supported by each study; no common concentration scale, dose–response relationship or safety threshold is implied. Retained responses do not establish equivalence with cleaner air, and larger peripheral responses do not establish greater brain benefit. BDNF, brain-derived neurotrophic factor; HR, hazard ratio; MMSE, Mini-Mental State Examination; MRI, magnetic resonance imaging; MVPA, moderate-to-vigorous physical activity; VEGF, vascular endothelial growth factor. Study summaries are provided in Table 2; full details are in Supplementary Table S1.

4. Evidence Synthesis

4.1. Peripheral Responses in Human Studies

Acute exercise studies show heterogeneous peripheral responses to polluted air. Serum BDNF increased significantly only after filtered-air cycling in the roadside comparison by Bos et al.; however, neither a condition × time test nor a between-condition change contrast was reported, so this pattern does not establish suppression of the exercise response [17]. Conversely, Silveira et al. observed a larger plasma BDNF post/pre-exercise ratio during a 50-km cycling trial under traffic-related pollution than filtered air (3.3 versus 1.3; $p = 0.048$). Cognition was not assessed [18]. Serum VEGF was also higher under polluted air at 90 min of moderate cycling, alongside inflammatory and blood-pressure responses; this peripheral vascular signal cannot be interpreted as evidence of enhanced central neuroplasticity [19].

Longer interventions do not show uniformly concordant biomarker and cognitive responses. In the 12-week urban/rural study, the Stroop time × site interaction was significant, whereas serum BDNF changes were non-significant in both groups [20]. In contrast, the four-group indoor/outdoor trial reported exercise × site interactions favouring indoor exercise for both serum BDNF and cognitive outcomes. These concordant group differences do not establish BDNF-mediated improvement, particularly because site and exercise modality co-varied [31]. In the two-city resistance-training study, IGF-1 increased within both active groups, although the post-training omnibus comparison across groups was non-significant ($p = 0.322$). These analyses address different contrasts and should not be reduced to either a uniform benefit or a null effect [30]. These findings support interpreting circulating growth factors and cognitive responses as distinct outcomes.

A small repeated panel of retirees added a peripheral neural-injury signal: the $PM_{2.5}$–serum neurofilament light-chain association was stronger at lower activity, whereas no statistically significant activity-group difference was reported for BDNF. Unequal activity strata and an unclear between-group test method limit this potential buffering interpretation [44].

4.2. Central and Peripheral Outcomes in Animal Models

Direct central molecular evidence remains limited. After 90-min soot-UFP inhalation or ambient-air exposure with running or rest, hippocampal BDNF mRNA was higher in the ambient-air exercise group than the ambient-air rest group at 24 h; the UFP-plus-exercise group did not differ significantly from ambient-air rest. This pattern suggests attenuation, but no factorial interaction was reported. It therefore does not establish that UFP exposure abolished an exercise effect, and gene expression alone cannot determine the corresponding protein or cognitive response [21].

Behavioural and brain-tissue improvements were reported in mice receiving wheel exercise before intratracheal particle instillation and cerebral ischaemia/reperfusion, with the strongest pattern after six weeks of exercise. This supports benefit within the combined exposure–disease model, rather than protection during ambient inhalation in healthy animals. The absence of a PM-free exercised ischaemia/reperfusion group precludes a full PM × exercise interaction estimate. Moreover, brain tight-junction proteins and injury measures provide barrier-associated evidence, not a direct tracer measurement of BBB permeability [24].

Intravenous models further separate circulating growth-factor responses from injury-marker responses. Treadmill training with PM increased serum IGF-1, BDNF and VEGF relative to PM alone, while S100B and NSE remained elevated relative to control [25]. Under high-fat-diet and PM exposure, resistance training increased BDNF and VEGF and reduced S100B, whereas the NSE contrast was non-significant [26]. These findings support selected peripheral biomarker improvements, not directly measured BBB restoration. The treadmill study reported one-way group comparisons; the resistance-training design lacked a PM-free exercise group. Consequently, neither establishes a full factorial interaction, and systemic particle administration cannot reproduce ventilation-dependent inhalation exposure [25,26].

4.3. Cognitive Responses in Exercise Interventions

A randomised trial of 93 participants provided acute evidence of exposure-related attenuation. $PM_{2.5}$ × high-intensity interval training (HIIT) coefficients for congruent and incongruent Stroop reaction time were 2.231 and 3.305 ms per $\mu g/m^3$, respectively, with both confidence intervals excluding zero. These estimates support attenuation of the HIIT contrast with stretching as exposure increased. The corresponding moderate-intensity continuous training (MICT) confidence intervals included zero, but this does not establish that HIIT and MICT interaction coefficients differed. Prefrontal haemodynamic findings were channel- and task-specific and do not independently establish the mechanism of the cognitive response [29].

Training studies indicate that cognitive improvement can persist in more polluted settings, with variable magnitude across outcomes. Mini-Mental State Examination (MMSE) scores improved in both active groups after progressive walking; resistance training likewise produced gains in both cities, with greater improvement in the lower-pollution setting. Neither study established a factorial pollution × exercise interaction [28,30]. The urban/rural Stroop interaction and the indoor/outdoor trial's cognitive interactions provide more direct statistical evidence of differing responses across settings. However, age

imbalance and attrition in the former, and co-variation of site and exercise modality in the latter, limit attribution specifically to particles [20,31].

4.4. Population Evidence

Observational studies provide evidence that particulate exposure can weaken activity-related associations with cognition or dementia, although this pattern is not uniform. UK Biobank analyses using accelerometry reported attenuation of inverse activity–dementia associations at higher $PM_{2.5}$ or $PM_{2.5}$ absorbance; the activity estimates in the highest exposure categories did not demonstrate a reversal to harm [45]. A subsequent subtype analysis identified attenuation for a selected Alzheimer's disease contrast, but most interactions were non-significant and multiple comparisons were unadjusted [33]. Across 108,099 repeated observations in three China Family Panel Studies waves, favourable associations of activity with combined verbal and mathematics scores also weakened as $PM_{2.5}$ increased, while remaining evident at higher exposure [23].

Retained favourable associations and uncertain modification qualify an attenuation-centred interpretation. In older Hong Kong adults, greater activity was associated with lower dementia risk without clear additive or multiplicative interaction with $PM_{2.5}$ [42]. In the young-adult panel, activity was associated with faster Stroop responses, but the formally tested linear interaction was non-significant; numerically stronger associations under higher pollution did not establish amplification [32]. A childhood study likewise reported no significant modification by activity, while both additive and multiplicative interaction intervals in the Northern Ireland cohort included their null values [35,43]. The Fuyang analysis suggested attenuation using an exploratory $p < 0.20$ criterion, with all three PM interaction p-values exceeding 0.05 [36]. These findings preserve uncertainty; non-significance does not establish equivalent effects.

Activity-related buffering was also reported, with its interpretation tied to the outcome and model. Pollution associations were weaker at higher activity levels for incident dementia in Danish nurses and for cross-sectional cognitive scores in KoGES [40,46]. Among kidney-transplant candidates, low activity strengthened the association of $PM_{2.5}$ with baseline cognitive scores; effect modification for dementia was not tested, and only 29 dementia events occurred [37]. Household biomass use showed a similar activity-related difference for cognitive decline, but the interaction for incident cognitive impairment remained uncertain [50]. CHARLS findings require additional qualification: the cross-sectional buffering signal arose from an instrumental-variable model, with association directions differing across models, whereas the longitudinal analysis supported interaction for the mental-status component but not overall cognition or episodic memory [38,39]. Disagreement between the abstract and supplementary results limits confidence in the reported buffering effect [39].

The interaction scale and comparison also affect the synthesis. In UK Biobank, $PM_{2.5}$ and low activity showed additive interaction for Alzheimer's disease, while multiplicative interaction remained uncertain and neither scale supported modification for all-cause or vascular dementia [41]. In LASI, a significant activity × household-pollution × sex term indicated sex variation in the joint association, despite a non-significant overall two-way interaction [34]. Conversely, pollution associations were stronger among active participants for prevalent dementia in Chinese veterans and incident Alzheimer's disease in the Zhejiang cohort [47,49]. Such contrasts concern the association with pollution within activity strata and do not by themselves establish harm from exercise. Finally, lower cognitive-impairment odds in selected exercise–road-distance categories did not establish an exercise-by-distance interaction, because the reported comparisons used a common reference group [48].

Structural imaging provides a distinct outcome level. In UK Biobank, vigorous activity interacted with residential NO_2 and $PM_{2.5}$ absorbance on white matter hyperintensity volume after correction for multiple testing. The favourable activity association was attenuated at higher exposure [22]. This finding concerns a cross-sectional MRI phenotype rather than measured cognitive decline or a training-induced change. It also cannot be transferred directly to $PM_{2.5}$ mass, because absorbance represents a different exposure metric. The analysis therefore adds structural evidence to a literature otherwise dominated by cognitive scores and diagnoses.

4.5. Indirect Evidence

The indirect reports broaden the developmental and environmental context while addressing different questions from concurrent exercise under measured particulate exposure. The Shanghai–Minhang cohort examined prenatal $PM_{2.5}$ in relation to intelligence at six years, with outdoor activity assessed in childhood. $PM_{2.5}$-specific interaction tests were non-significant, although selected constituent interactions were reported for verbal comprehension [52]. The Shenzhen cohort likewise found no significant outdoor-time interaction across five developmental domains for prenatal or postnatal $PM_{2.5}$ and its components [53]. Outdoor time does not quantify exercise intensity or dose, and prenatal exposure precedes the activity assessment. Environmental walking or jogging comparisons also varied multiple route characteristics alongside pollution [51,54]. Neither comparison established a particle-specific cognitive effect; the older-adult pilot's PM-by-environment analysis concerned heart-rate variability rather than cognition [54]. They therefore contribute contextual and null findings without isolating particle-specific protection from physical activity.

5. Sources of Heterogeneity

5.1. Exposure Composition and Timing

Particle mass, component concentrations, $PM_{2.5}$ absorbance and composite pollution scores describe different exposure contrasts. Black carbon can provide an additional indicator of combustion-related particles beyond total PM mass [64]. Component analyses and studies of combustion-related markers support reporting exposure composition, but coefficients with different measurement scales and correlated co-pollutants cannot be interpreted as universal toxicity ratios [23,39]. Likewise, a household-fuel category or distance from a major road cannot identify a particle-specific effect [48,50].

Exposure timing also changes the question being answered. Session-level concentrations address responses during or after a defined bout, whereas residential annual averages describe longer-term exposure contexts. Indoor–outdoor and city comparisons additionally combine air quality with environmental differences. Traffic noise is another relevant co-exposure: the Danish Nurse Cohort incorporated it in the analysis, whereas its separation from particle effects was not uniform across the evidence base. These differences limit attribution of cross-study contrasts to a single pollutant or exposure duration [28,29,31,40].

5.2. Activity Measurement and Population Context

Prescribed exercise, accelerometer-derived activity, self-reported activity volume and a yes/no exercise category are not interchangeable doses. Frequency or duration cannot resolve intensity when intensity was unmeasured [23,33]. Fitness, exercise protocols and exposure conditions differed across the small chamber studies, so the larger BDNF response in recreationally trained cyclists does not demonstrate physiological adaptation to pollution [18,19]. Age, sex and metabolic health remain plausible modifiers, but differences between studies or populations require direct interaction tests before they can

be attributed to these characteristics. The sex-related result in LASI and the high-fat-diet mouse experiment illustrate the importance of the exact comparison available [26,34].

5.3. Comparator Structure and Statistical Interpretation

A larger pollution association among active participants and a weaker activity association at higher pollution are related forms of effect modification, but neither alone establishes that activity becomes harmful [49]. Joint categories compared with a common reference answer a different question from a within-exposure exercise contrast [48]. Interpretation therefore depends on the specified comparator, outcome scale and uncertainty interval. Additive interaction can be present without statistically supported multiplicative interaction, and different within-stratum *p* values do not establish either [16,41,65]. Preserving these distinctions explains part of the apparent disagreement between studies without assigning every difference to biological heterogeneity.

6. Implications for Brain Health

6.1. Linking Biological Outcome Levels

The central interpretive finding is that a change in peripheral BDNF alone cannot establish a brain-health benefit under PM exposure. Increased circulating BDNF can coexist across the literature with attenuated cognitive associations, but the studies differ in population, exposure, exercise and timing. These contrasts generate a hypothesis about cross-level discordance; they do not demonstrate that biological outcome level determines the direction of an interaction. Within-study concordance in BDNF and cognitive group contrasts is more informative, although concordant group means still do not establish mediation or validate an individual-level surrogate. Paired measurements should therefore be interpreted as distinct outcomes until their temporal and statistical relationships have been tested [18,20,23,31].

6.2. Limits of Quantitative Translation

The evidence does not identify a general $PM_{2.5}$ concentration at which exercise-related brain benefit reverses to harm. The approximately 33 $\mu g/m^3$ division in the acute cognitive trial was a sample-mean split, not an estimated change point [29]. Loss of statistical significance within an exposure stratum likewise does not establish loss of benefit or a safety boundary [36,45]. Activity–pollution trade-offs derived from observational coefficients cannot specify an exercise dose that compensates for exposure [23,39]. These estimates can describe study-specific contrasts and inform hypotheses; their use as concentration limits or exercise prescriptions would require direct validation. Table 4 distinguishes quantitative evidence for study-specific contrasts from the additional evidence needed to define an exposure threshold or compensatory activity dose.

Table 4. Quantitative findings and limits of translation.

Outcome and Study	Reported Estimate	Interpretation and Limit
Stroop reaction time Acute HIIT trial [29]	$PM_{2.5}$ × HIIT versus stretching: Congruent β 2.231 (95% CI 0.523–3.938) Incongruent β 3.305 (0.791–5.819) Unit: ms per $\mu g/m^3$	HIIT reaction-time advantage weakened as $PM_{2.5}$ increased. ≈33 $\mu g/m^3$ was the sample mean, not an estimated benefit-to-harm change point.
Cognitive score CFPS repeated observations [23]	$PM_{2.5}$ × activity frequency: β −0.005 (95% CI −0.006 to −0.003) $PM_{2.5}$ × duration: β −0.002 (−0.003 to −0.001)	Favourable activity associations persisted but weakened. Frequency/duration ≠ intensity. Coefficient ratios do not establish a compensatory activity dose.

Table 4. *Cont.*

Outcome and Study	Reported Estimate	Interpretation and Limit
Incident dementia UK Biobank [45]	$PM_{2.5}$ × activity interaction: HR 1.33 (95% CI 1.13–1.57) Activity HR, lowest $PM_{2.5}$ tertile: 0.66 (0.49–0.91) Highest tertile: 0.88 (0.68–1.14) Scaling: activity 1 SD; pollution 1 IQR	Inverse activity association attenuated. Interaction HR ≠ activity HR. No concentration threshold estimated; an activity CI including 1 does not demonstrate reversal to harm.
White matter hyperintensity volume UK Biobank MRI [22]	NO_2 × vigorous activity; $PM_{2.5}$ absorbance × vigorous activity: FDR-adjusted interaction $p = 0.037$	Favourable associations attenuated at higher exposure. Cross-sectional MRI does not establish a $PM_{2.5}$ mass threshold; absorbance ≠ particle mass.
Alzheimer's disease UK Biobank [41]	$PM_{2.5}$ × low activity (<600 vs. ≥600 MET-min/week): Additive RERI 0.330 (95% CI 0.012–0.648) Multiplicative interaction $p = 0.067$	Additive modification supported for Alzheimer's disease only. Neither scale supported all-cause/vascular dementia modification; no common dementia threshold established.
Cognitive components CHARLS [39]	Table S3: $PM_{2.5}$ × log-transformed activity volume Mental status: β 0.000630 (95% CI 0.0002–0.0010), $p = 0.0021$ Overall cognition: $p = 0.07$ Episodic memory: $p = 0.59$	Mental-status buffering supported; other outcomes uncertain. Abstract–supplement discrepancies lower confidence; no validated daily dose to offset pollution effects.

Note: Estimates are study-specific and use different outcome and activity scales; they are not directly comparable across rows. For CFPS, $PM_{2.5}$ is expressed in μg/m^3, activity frequency in occasions/week and duration in hours/week. The null value is 0 for β and RERI and 1 for an HR. Here, ≠ indicates non-equivalence, not absence of a relationship. CFPS, China Family Panel Studies; CHARLS, China Health and Retirement Longitudinal Study; CI, confidence interval; FDR, false discovery rate; HIIT, high-intensity interval training; HR, hazard ratio; IQR, interquartile range; MET, metabolic equivalent; MRI, magnetic resonance imaging; NO_2, nitrogen dioxide; PM, particulate matter; RERI, relative excess risk due to interaction; SD, standard deviation; β, regression coefficient.

7. Limitations and Research Priorities

7.1. Limits of the Assembled Evidence

This focused narrative review searched two databases and documented literature selection decisions, but some relevant publications may not have been included because of the search scope and eligibility criteria. Verification of selection decisions did not constitute independent duplicate screening. Measurement limitations and reporting inconsistencies constrained some finding-specific appraisals, while diverse exposure metrics, comparator structures and biological outcomes limited direct quantitative comparison across studies [35,39].

Small controlled-exposure samples and attrition constrain precision, while differences in training protocols and settings complicate comparisons. In observational analyses, residential exposure estimates and reported activity may not capture exposure during exercise. Cross-sectional associations cannot resolve temporal ordering, and prospective designs remain susceptible to residual confounding. These design limitations restrict causal interpretation even when an interaction estimate is statistically significant [18,20,22,23].

Reports are not necessarily independent samples. Analyses from UK Biobank, CHARLS and CLHLS may include overlapping participants; participant-level overlap was not quantified. Supplementary Table S1 records the cohort sources, and sample sizes were not summed across reports.

Two of the four animal reports were co-authored by the present authors and used intravenous exposure with peripheral outcomes. Their findings were subject to the same selection and interpretive criteria and cannot establish central protection during ambient inhalation. The remaining animal reports provide hippocampal gene-expression comparisons after acute inhalation exposure and a preventive-exercise instillation model with cerebral ischaemia/reperfusion, leaving chronic central protection under environmentally relevant inhalation unresolved [21,24–26].

7.2. Priorities for Discriminating Between Explanations

The next experiments should measure BDNF and complementary growth factors alongside central or cognitive outcomes within the same protocol, retain appropriate exposed and unexposed exercise comparators, and measure exposure during activity [18,31]. Measured ventilation and clearly distinguished inhaled and deposited doses would strengthen dose interpretation. Repeated sampling can test whether apparent disagreement reflects sampling time; randomising exercise intensity while controlling exposure and accounting for baseline fitness would better isolate intensity effects. Inhalation experiments are needed to test the exposure-route generalisability of intravenous findings, while paired peripheral and central measurements can test whether biomarker changes correspond to brain outcomes. Including both sexes would broaden the populations represented in these experiments [21,24–26]. Component-resolved human studies should address correlated co-pollutants and relevant environmental factors, including noise.

Analyses should prespecify the primary endpoint, comparator, interaction scale and multiplicity strategy, and report effect estimates with uncertainty rather than relying on subgroup significance [16,65]. Candidate modifiers such as age, sex, metabolic status and training history require adequately powered direct tests. A proposed concentration change point or compensatory activity dose should be estimated with uncertainty and validated in independent data before quantitative guidance is considered. Table 5 translates these interpretive issues into proposed reporting priorities for future studies.

Table 5. Proposed reporting priorities.

Domain	Report	Why It Matters
Exposure	Metric and units; source and composition; averaging window; measured/modelled/proxy exposure; spatial resolution; animal route and dose.	Session concentrations and residential averages differ. Instillation and intravenous dosing are not equivalent to ambient inhalation [23–25,29].
Co-exposures/ setting	Gaseous pollutants; traffic noise; environmental contrasts; adjustment variables; filtration efficiency for each pollutant.	Traffic noise, study site and exercise modality can accompany pollution differences [31,40].
Activity/ ventilation	Activity type, frequency, duration and intensity; units and assessment method; measured or estimated ventilation and method; inhaled/deposited dose distinction.	Frequency does not establish intensity. Inhaled mass is not deposited/brain dose or proof of dose matching [23,27].
Biospecimen/ sampling	Sample matrix; clotting and centrifugation; storage; assay and detection limit; sampling time relative to exposure and exercise.	Platelet release and processing influence measured BDNF; matrix and sampling details aid interpretation [13,14].
Outcome/linkage	Endpoint, units and time; biological level; barrier markers versus permeability; outcomes measured together in the same participants/ animals.	Peripheral elevation does not establish central protection; concordant group contrasts do not establish mediation or surrogate validity [24,25,31].

Table 5. *Cont.*

Domain	Report	Why It Matters
Population/ provenance	Age and sex; training/metabolic status; prior exposure if assessed; species/strain; cohort and recruitment period; analysis sample and overlap.	Population differences require direct tests. Shared-cohort reports may include overlapping participants and are not necessarily independent [33,34,41].
Design/ comparators	Group definitions; exposure–activity combinations; reference categories; allocation; exposure/activity/outcome timing; contrast underlying each estimate.	Within-exposure or joint-category contrasts are not full interaction tests. Nonconcurrent exposure and activity require distinct temporal interpretation [26,48,52].
Analysis/ translation	Prespecified endpoints and contrasts; interaction scale; multiplicity strategy; estimates and uncertainty; missing data; threshold estimation and independent validation.	Subgroup *p*-value differences do not establish interaction. Additive/multiplicative conclusions may differ; a sample mean is not a safety threshold [16,29,41,65].

Note: These priorities are proposed from the present synthesis and should be applied according to study design; they are not a validated reporting checklist. BDNF, brain-derived neurotrophic factor.

8. Conclusions

Neurotrophic responses and functional brain outcomes associated with exercise under PM exposure show heterogeneous patterns across studies. Circulating BDNF responses vary, with VEGF and IGF-1 providing complementary growth-factor evidence; selected cognitive, dementia and imaging comparisons show attenuation alongside retained favourable activity associations and potential buffering. These findings support interpreting neurotrophic responses in relation to the biological outcome level, exposure context and comparison supported by each study. A change in peripheral BDNF alone cannot establish brain benefit, and cognitive or imaging findings do not by themselves demonstrate a BDNF-mediated mechanism.

Animal experiments provide mechanistic leads whose relevance depends on the exposure route and model. The evidence does not identify a general PM concentration at which exercise-related brain benefit reverses to harm or an activity dose that compensates for pollution exposure. A priority is to measure BDNF, complementary growth factors and central or functional outcomes together while assessing actual exposure during exercise and exercise intensity, with appropriate exposure-by-exercise comparisons. This approach can test whether neurotrophic changes accompany functional benefit and under which exposure and exercise conditions those relationships hold.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/atmos17111077/s1, Supplementary Methods S1: Database search strategies; Supplementary Table S1: Detailed study characteristics and findings.

Author Contributions: Conceptualization, H.-T.R.; methodology, S.-Y.C. and H.-T.R.; writing—original draft preparation, S.-Y.C. and H.-T.R.; writing—review and editing, S.-Y.C. and H.-T.R.; project administration, H.-T.R.; funding acquisition, H.-T.R. All authors have read and agreed to the published version of the manuscript.

Funding: This work was supported by the Ministry of Education of the Republic of Korea and the National Research Foundation of Korea (NRF-2025S1A5A2A01009403).

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: No new data were created or analysed in this study. Data sharing is not applicable to this article.

Conflicts of Interest: The authors declare no financial conflicts of interest. Both authors were co-authors of two primary reports included in the main synthesis [25,26]. The potential implications of this authorship overlap are addressed in Section 7.1.

Abbreviations

The following abbreviations are used in this manuscript:

BBB	blood–brain barrier
BDNF	brain-derived neurotrophic factor
CHARLS	China Health and Retirement Longitudinal Study
CLHLS	Chinese Longitudinal Healthy Longevity Survey
HIIT	high-intensity interval training
IGF-1	insulin-like growth factor-1
KoGES	Korean Genome and Epidemiology Study
LASI	Longitudinal Ageing Study in India
MICT	moderate-intensity continuous training
MMSE	Mini-Mental State Examination
mRNA	messenger RNA
MRI	magnetic resonance imaging
NO_2	nitrogen dioxide
NSE	neuron-specific enolase
PM	particulate matter
$PM_{2.5}$	particulate matter with an aerodynamic diameter $\leq$ 2.5 μm
S100B	S100 calcium-binding protein B
SANRA	Scale for the Assessment of Narrative Review Articles
UFP	ultrafine particles
VEGF	vascular endothelial growth factor

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