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Neurological and respiratory outcomes of the HIPTox controlled double-blind air pollution exposure trial

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Air pollution, particularly particulate matter (PM), is a well-established risk factor for cardiopulmonary disease, but its impact on brain health remains underexplored. This double-blind clinical trial investigated acute cognitive and respiratory responses to common PM-containing pollutant mixtures. Fifteen healthy volunteers (≥ 50 years, family history of dementia) undertook 60-minute exposures to woodsmoke, diesel exhaust, cooking emissions, limonene secondary organic aerosol (SOA), and clean air (control), separated by ≥2-weeks. Pre- and post-exposure assessments evaluated cognitive and respiratory function. Pollutant source significantly influenced cognition: diesel exhaust and woodsmoke improved processing speed; limonene SOA enhanced working memory compared to cooking emissions; and diesel exhaust may impair executive function. Forced Expiratory Volume in 1 second percentage predicted was lower following woodsmoke and limonene SOA versus clean air. Specific pollutant sources acutely influenced cognition and lung function, with responses varying by source. This approach can guide focused mitigation strategies to protect both respiratory and neurological health.

Air pollution is the leading global environmental risk to health, contributing significantly to mortality worldwide[1]. While its adverse effects on cardiovascular and respiratory systems are well established, there is growing evidence that air pollution is also neurotoxic[2], associated with neuroinflammation, altered brain structure, and accelerated cognitive decline[3]. However, major gaps remain in our understanding of which components of air pollution are most harmful and the mechanisms by which they exert their effects[4].

Long-term exposure to poor air quality has been associated to increased risk of neurodegenerative diseases such as Alzheimer's disease, Parkinson's disease, and multiple sclerosis[5]. Air pollution also appears to impact brain health across the life course with chronic exposures associated with changes to cognitive, educational, and neurodevelopmental outcomes in children[6,7]. We have previously shown that short-term exposures can affect several cognitive domains[8,9], although evidence remains mixed regarding the impact of source specific pollutant mixtures[3].

Air quality guidelines, such as those from the World Health Organization[10], primarily rely on particle mass concentration as the standard metric. As mass concentration refers to the total weight of particles per unit volume of air, this treats all PM as equally harmful[11], overlooking the role of chemical composition. Toxicological studies indicate that composition is critical to toxic potential, yet epidemiological research rarely distinguishes between pollutant sources as they are often highly correlated in modelled exposures. Studying short-term impacts of PM-containing air pollution mixtures on cognitive function offers a unique opportunity to observe differential toxicity *in vivo*, and to demonstrate the connectivity between acute pulmonary and neurological response – the lung-to-brain axis.

Air pollution may affect the brain through two primary pathways: direct interaction of inhaled particles or their chemical constituents with

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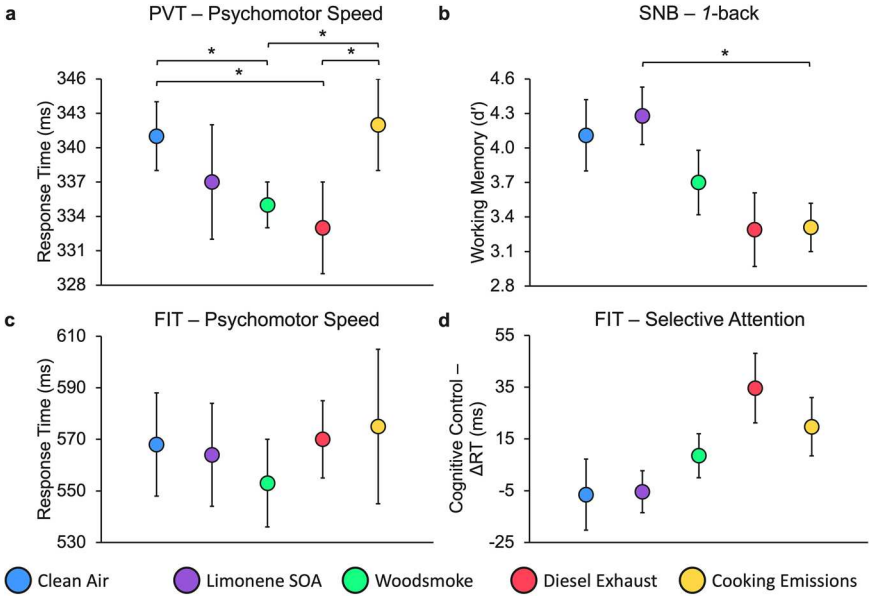

Fig. 1 | Cognitive outcomes. GEE-calculated Estimated Marginal Means for post-exposure outcomes across each exposure session for (**a**) psychomotor speed in the Psychomotor Vigilance Task (PVT); **b** 1-back perception match performance in the Spatial n-back Task (SNB); **c** psychomotor speed in the Face Identification Task (FIT); and (**d**) selective attention (lower indicates improved performance) in the FIT. PVT Psychomotor Speed was significantly quicker following Woodsmoke [$p = 0.026$] and Diesel Exhaust [$p = 0.039$] compared to Clean Air, and Woodsmoke [$p = 0.035$] and Diesel Exhaust [$p = 0.033$] compared to Cooking Emissions [Wald $\chi^2(4) = 180.62$, $p < 0.001$]. This trend did not hold in the FIT [Wald $\chi^2(4) = 7.76$, $p = 0.101$]. Exposure was a significant predictor for 1-back working memory [Wald $\chi^2(4) = 15.79$, $p = 0.003$], with better performance following Limonene SOA compared to Cooking Emissions [$p = 0.019$]. Data points are Estimated Marginal Means for post-exposure cognitive outcomes, accounting for pre-exposure baseline and visit order; vertical lines denote Standard Error. $^*p < 0.05$. $n = 13$ independent human participants (biological replicates), within a fully repeated measures design.

glial cells and neurons, either via translocation along olfactory neurons to the olfactory bulb or via entry across the blood–brain barrier[12]; or indirectly through systemic inflammation and its impact on the brain[13]. Our previous work investigated whether the two hypothesised mechanisms differ in their impact on cognitive function by experimentally blocking the nasal inhalation route. No significant differences were observed, suggesting comparable effects across both pathways[9].

There is a pressing need to respond to emerging evidence of air pollution's impact on brain health across the life course, from early cognitive delays and adverse mental health to increased dementia risk. In the United Kingdom alone, the economic burden of air pollution is estimated at £20 billion annually, based on cardiopulmonary outcomes[14]. The neurological consequences likely add significantly to this cost. Globally, the financial impact of neurodegenerative disease is also staggering. In 2019, dementia cost economies globally 1.3 trillion US dollars, with projections reaching 2.8 trillion as early as 2030[15]. Understanding which components of air pollution drive these effects, and the mechanisms through which they act, is therefore of critical importance to public health and policy.

This single-centre, double-blind human exposure trial investigates the effects of four common air pollutants: SOA from limonene (a common cleaning product ingredient), diesel exhaust, cooking emissions, and woodsmoke, on cognitive function, compared to clean air.

The primary objective of this study is to identify the acute effects of a range of PM-containing air pollution exposures on cognitive function in clinically healthy older adults with a family history of dementia.

The primary endpoint is cognitive impairment following pollutant exposure, assessed through three prespecified measures: (i) change in approach bias, a measure of socio-emotional processing; (ii) reduction in cognitive control, a measure of selective attention; and (iii) reduction in the 2-back discrimination index, a measure of working memory, each compared with clean air exposure.

Secondary endpoints include reductions in psychomotor speed and motor control, other metrics associated with working memory (1-back and 3-back), and reduction of lung function following pollutant exposure, each compared with clean air exposure.

Results

We report the findings from the GEE models and post-hoc comparisons, beginning with cognitive outcomes followed by respiratory measures. All analyses reported here correspond to prespecified endpoints; no data-driven changes to endpoints were made.

Cognitive outcomes

Exposure was a statistically significant predictor of processing speed in the PVT, a prespecified secondary endpoint (Wald $\chi^2(4) = 180.62$, $p < 0.001$). Contrary to our predictions, significant pairwise comparisons revealed that brain processing speed improved, as indicated by lower response times, following exposure to diesel exhaust (Estimated Marginal Mean; EMM = 333 ms, Standard Error; SE = 4) and woodsmoke (EMM = 335 ms, SE = 2) compared to clean air (EMM = 341 ms, SE = 3) and cooking emissions (EMM = 342 ms, SE = 4). See Fig. 1a and Table 1. We suggest that the presence of NO_X in these sources, averaging 258.25ppb (SE = 223.52) in diesel exhaust and 36.60ppb (SE = 36.84) in woodsmoke (see Table 4), might explain the observed effect, given that nitric oxide (NO; a component of NO_X) is a known vasodilator[16]. To explore this, we conducted a one-tailed Spearman's rank-order correlation to assess the relationship between post-exposure response time (RT), across all datapoints regardless of exposure condition, and the average NO concentration during exposure. The analysis showed as a weak statistically significant negative correlation ($\rho = -0.214$, $n = 65$, $p = 0.043$), suggesting that, even without controlling for baseline RT or visit order as in our GEE, our hypothesis has some preliminary support.

Exposure was also a statistically significant predictor on the perception match block (1-back) in the SNB, a prespecified secondary endpoint (Wald $\chi^2(4) = 15.79$, $p = 0.003$). Participants performed better, as indicated by higher d′ scores, following exposure to limonene SOA (EMM = 4.28, SE = 0.25) compared to cooking emissions (EMM = 3.31, SE = 0.21); see Fig. 1b.

Table 1 | Estimated Marginal Means for post-exposure cognitive outcomes, accounting for pre-exposure baseline and visit order

		Exposures					Exposure Main Effect			Pairwise Differences (*p* value)
		Clean Air (CA)	Limonene SOA (LS)	Woodsmoke (WS)	Diesel Exhaust (DE)	Cooking Emissions (CE)	χ^2 value	*α*-value	*p* value	
Executive Function (FIT)	Selective Attention	−6.51 (13.74)	−5.39 (8.11)	8.53 (8.51)	34.62 (13.44)	19.74 (11.26)	6.13	0.025	0.189	
	Psychomotor Speed	568 (20)	564 (20)	553 (17)	570 (15)	575 (30)	7.76	0.025	0.101	
Expression Recognition (ERT)	Discrimination	2.71 (0.16)	2.82 (0.16)	2.97 (0.12)	3.11 (0.16)	3.13 (*0.13*)	4.33	0.025	0.363	
	Approach-Avoidance Bias	−0.01 (0.28)	−0.03 (0.21)	−0.20 (0.18)	0.03 (0.33)	−0.27 (0.25)	1.38	0.025	0.849	
Psychomotor Vigilance (PVT)	Psychomotor Speed	341 (3)	337 (5)	335 (2)	333 (4)	342 (4)	180.62	0.05	<0.001*	DE < CA (0.039) DE < CE (0.033) WS < CA (0.026) WS < CE (0.035)
Motor Control (PPT)	Gross Motor Control	39.91 (0.76)	40.39 (0.76)	40.68 (0.75)	41.17 (0.94)	41.26 (0.49)	3.78	0.025	0.437	
	Fine Motor Control	38.37 (1.66)	39.02 (1.26)	38.19 (0.72)	36.06 (1.74)	36.73 (1.33)	15.00	0.025	0.005*	N/A
Working Memory (SNB)	1-back	4.11 (0.31)	4.28 (0.25)	3.70 (0.28)	3.29 (0.32)	3.31 (0.21)	15.79	0.016	0.003*	LS > CE (0.019)
	2-back	2.77 (0.44)	2.76 (0.35)	2.64 (0.18)	3.20 (0.52)	2.76 (0.35)	11.33	0.016	0.023	
	3-back	1.96 (0.24)	1.82 (0.30)	1.46 (0.19)	1.16 (0.21)	1.70 (0.28)	4.71	0.016	0.318	

Numbers in brackets denote Standard Error.
CA clean air, *LS* limonene SOA, *WS* woodsmoke, *DE* diesel exhaust, and *CE* cooking emissions.
*Indicates significant at corrected alpha level.

No significant differences were observed in the more cognitively demanding 2-back (primary endpoint) or 3-back blocks; see Table 1.

Although not statistically significant, trends in the FIT, an executive function measure, warrant attention. Unlike the PVT, which showed faster response times following exposure to diesel exhaust, no such speed advantage was observed (Fig. 1c). This task requires participants to perceive the stimuli and perform a judgement before responding, suggesting that the observed speed gains may be limited to basic perception-response, as required in the PVT, rather than higher-order cognitive processes. Supporting this, no significant differences were found in the PPT, which directly assesses motor control. Interestingly, participants exposed to diesel exhaust tended to perform worse on the FIT, as indicated by elevated cognitive control (a primary endpoint) values (ΔRT), reflecting reduced selective attention as hypothesised. In contrast, those exposed to clean air showed the best performance on this measure (Fig. 1d). These opposing, non-significant trends suggest that while basic response speed may improve following diesel exhaust exposure, executive functioning could be negatively affected. Whilst exposure was a statistically significant predictor of the secondary endpoint of fine motor control on the PPT (Wald $\chi^2(4) = 15.00$, $p = 0.005$), no significant pairwise comparisons were identified; see Table 1.

Exposure was not a significant predictor of the primary endpoint of the 2-back working memory block on the SNB at the corrected 0.016 α-value (Wald $\chi^2(4) = 11.33$, $p = 0.023$). Exposure was also not a significant predictor of gross motor control (PPT), 3-back working memory block (SNB), expression discrimination (ERT), or approach-avoidance bias (ERT); see Table 1.

In summary, none of the primary cognitive endpoints showed statistically significant effects of exposure. Two prespecified secondary endpoints were significant: processing speed on the PVT, where response times were faster following diesel exhaust and woodsmoke compared to clean air and cooking emissions; and discrimination performance on the 1-back block of the SNB, which was higher following limonene SOA than cooking emissions. All other cognitive outcomes were non-significant.

Respiratory outcomes

Spirometry was used as a safety measure both to screen for underlying airways disease and to ensure that there was no exposure-related bronchospasm as evidenced by a reduction in Forced Expiratory Volume in 1 second (FEV_1). Changes in FEV_1 and FVC were also secondary endpoints.

Although exposure was not a significant predictor of absolute FEV_1, it was a significant predictor of FEV_1 percentage predicted (FEV_1%), a standard parameter for diagnosing clinical airflow obstruction which considers personal physiology, Wald $\chi^2(4) = 14.49$, $p = 0.006$. Pairwise comparisons revealed that airway function, as indicated by FEV_1%, was significantly lower following exposure to woodsmoke (EMM = 101.0%, SE = 1.06) and limonene SOA (EMM = 100.2%, SE = 1.56) compared to clean air (EMM = 103.7%, SE = 0.91); see Fig. 2. While this change is not considered clinically significant[17], it is unexpected given the short (60-min) exposure duration and concentration levels. This may suggest subclinical effects that warrant further attention, particularly in vulnerable populations.

Exposure was a statistically significant predictor of Forced Vital Capacity (FVC) % predicted (Wald $\chi^2(4) = 21.65$, $p < 0.001$). However, significant pairwise comparisons were not identified; see Table 2. Exposure was not a significant predictor of FVC absolute values at the corrected 0.025 *α* value (Wald $\chi^2(4) = 10.38$, $p = 0.035$).

Discussion

This study aimed to assess the comparative impact of source-specific PM-containing pollutant mixtures on cognitive function. The novel methodology involved integrating a controlled exposure paradigm with pre- and post-exposure assessment across multiple distinct pollution sources tested within the same participants. This multi-exposure, within-subject approach enabled direct comparison of acute respiratory and cognitive responses across four real-world pollutant mixtures (and clean air), providing a robust framework for hazard comparison.

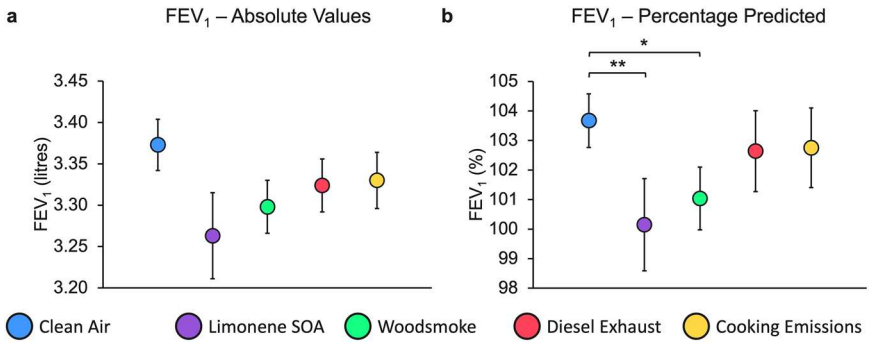

Fig. 2 | Respiratory outcomes. GEE-calculated Estimated Marginal Means for post-exposure outcomes across each exposure session for **a**) forced expiratory volume in one second (FEV_1) absolute values; **b**) FEV_1 expressed as a percentage of what is expected for individual participant age, height, sex, and ethnicity. Exposure was a significant predictor of only FEV_1% predicted [Wald $\chi^2(4) = 14.49$, $p = 0.006$], with pairwise comparisons showing a significant reduction following Limonene SOA [$p < 0.001$] and Woodsmoke [$p = 0.017$] compared to Clean Air. Estimated Marginal Means for post-exposure respiratory outcomes, accounting for pre-exposure baseline and visit order; vertical lines denote Standard Error. *$p < 0.05$; **$p < 0.001$. $n = 13$ independent human participants (biological replicates), within a fully repeated measures design.

Table 2 | Estimated Marginal Means for post-exposure respiratory outcomes, accounting for pre-exposure baseline and visit order

		Exposures					Exposure Main Effect			Pairwise Differences (*p* value)
		Clean Air (CA)	Limonene SOA (LS)	Woodsmoke (WS)	Diesel Exhaust (DE)	Cooking Emissions (CE)	χ^2 value	*α*-value	*p* value	
Forced Expiratory Volume in 1 s (FEV_1)	Absolute value	3.37 (0.03)	3.26 (0.05)	3.30 (0.03)	3.32 (0.03)	3.33 (0.03)	2.53	0.025	0.640	
	Percentage predicted (%)	103.7 (0.9)	100.2 (1.6)	101.0 (1.1)	102.6 (1.4)	102.8 (1.4)	14.49	0.025	0.006*	CA > LS (< 0.001) CA > WS (0.017)
Forced Vital Capacity (FVC)	Absolute value	4.50 (0.10)	4.48 (0.09)	4.44 (0.07)	4.48 (0.11)	4.51 (0.08)	10.38	0.025	0.035	
	Percentage predicted (%)	108.4 (1.5)	107.6 (2.1)	106.2 (1.4)	107.1 (1.6)	108.3 (1.5)	21.65	0.025	<0.001*	N/A

Numbers in brackets denote Standard Error.
CA clean air, *LS* limonene SOA, *WS* woodsmoke, *DE* diesel exhaust, and *CE* cooking emissions.
*Indicates significant at corrected alpha level.

A key outcome of this study was the successful implementation of a repeated measures clinical trial using PM-containing air pollution mixtures as a treatment conditions, using a controlled facility that allowed precise manipulation of pollutant mixtures. Despite the limitations posed by a small sample size, measurable changes in cognitive and respiratory functioning were observed, supporting the sensitivity of the paradigm and demonstrating acute changes in brain function following acute air pollution challenges. Adoption of the repeat exposure paradigm in subsequent studies offers a robust framework for exploring and ranking the hazard of environmental pollutants from defined sources on human health.

In the present study, we observed an improvement in psychomotor speed following exposure to NO_X-containing sources. Whilst the absolute differences in response time were small, statistically significant improvements were detected after diesel exhaust and woodburning exposures were identified compared to clean air. NO_X exposure may be linked to the vasodilatory effect of NO_X component, NO[16]. Evidence in animal studies shows NO exposure increases locomotion, possibly due to changes in striatum neurotransmission[18]. In humans, a study involving 12 healthy participants found that a 90-minute nitrogen dioxide (NO_2) exposure, similar to sitting near a lit gas cooker, significantly increased plasma nitrite and reduced both systolic and diastolic blood pressure[19]. Notably whilst the researchers only measured NO_2, the reduction in blood pressure suggested systemic vasodilation, likely due to the conversion of nitrite to nitric oxide. It is therefore reasonable to suggest that NO may enhance cerebral blood flow supporting faster neural processing and improved immediate perception-response speed. These findings offer a plausible physiological explanation for the cognitive effects observed in our study. Future studies should incorporate direct assessments of cerebrovascular or systemic haemodynamic responses alongside a clean air with NO_X condition to confirm whether NO-mediated vasodilation underlies the observed pattern.

Identifying changes in working memory performance was not expected, given previous research showing no effect of short-term exposure on working memory performance[9]. Surprisingly, participants performed better on the perception-match task (1-back) following exposure to limonene SOA compared to cooking emissions. No significant differences were observed in the more cognitively demanding 2-back or 3-back blocks, highlighting that working memory performance was largely unaffected by exposure. Given the simplicity of the task and the lack of practical significance, this finding may be limited[20].

It was anticipated that participants exposed to clean air would demonstrate superior performance on the executive function task, as this would be in line with previous research[9,21]. While the results trended in this direction, they did not reach statistical significance. This may reasonably be attributed to our sample size, which may constrain detection of the subtle cognitive effects we anticipate result from short exposures. Nonetheless, the observed trend aligns with expectations that cleaner air may be associated with improved executive functioning. Based on the exposure contrast Wald χ^2 value observed in this study (6.13) with 13 participants, we can estimate an

effect size of 0.6867 (Cohen's *w*), assuming the Wald statistic approximates a chi-square distribution. Extrapolating from this using G*Power 3.1[22], a sample size of 29 participants would be needed to achieve 85% power, supporting our protocol power calculation[23].

The observed transient drop in lung volumes, as measured by FEV_1 percentage predicted, following exposure to woodsmoke and limonene SOA, is both unexpected and noteworthy. Although these changes are not considered clinically significant[17], their statistical significance suggests a direct effect on the airway and highlights the sensitivity of these measures in assessing the impact of acute air pollution exposures. This is particularly important given that the lung function measures were originally included for safety monitoring rather than as primary outcomes. The findings underscore the sensitivity of the clinically healthy respiratory system to brief and low-level exposures to certain pollutants and highlight the need for more refined and targeted assessments in future studies. Incorporating more sensitive and specific measures of airway reflexes could provide deeper insight into the physiological mechanisms at play, especially in populations with heightened vulnerability to air pollution.

Despite standardisation of PM concentrations across exposure conditions, participants demonstrated above-chance performance in identifying pollutant exposures based on their odour profile, with particularly high accuracy for woodsmoke and cooking emissions. This may have potentially influenced the cognitive results[24] via expectancy, arousal, and hedonic appraisal. Previous literature suggests that ambient odours, pleasant or unpleasant, can alter mood, alertness, vigilance, perceived stress, and task performance; pleasant scents often enhance attention and positive affect[25–27], whereas unpleasant ones can lower mood, increase irritation, elevate perceived health symptoms, or increase distraction[28–30]. These odour-dependent effects provide a plausible behavioural pathway that may partially account for some observed cognitive patterns independent of pollutant exposure, and critically, the direction of effect appears dependent on perceived pleasantness. To address this, future studies could implement a greater proportion of clean air controls, use active placebo conditions involving inert substances with similar sensory profiles to the target pollutants, and include additional odour-awareness metrics such as intensity and pleasantness of experienced exposure.

In addition, the study design did not permit full randomisation of exposure order, owing to the operational requirements of the exposure chamber and the extended reset periods needed between pollutant conditions. Although participants did not complete the exposures in an identical sequence and visit number was included as a covariate to account for learning and time-related influences, we recognise that these steps cannot entirely remove the possibility of residual practice effects or temporal drift across the study period. Future work should incorporate full randomisation of exposure order wherever possible or adopt counterbalanced designs that better account for possible learning effects and temporal drift.

Despite recruitment challenges, as outlined in the protocol paper[23], we successfully demonstrate the viability of this novel research paradigm investigating multiple pollution exposures within a clinical trial setting. Significant differences were observed even with a relatively small sample of 13 participants, underscoring the sensitivity and potential of the approach. These findings suggest that, with refinement, the paradigm may be well-suited to future studies aiming to explore similar outcomes with limited but well-characterised cohorts. To support this, ongoing Patient and Public Involvement and Engagement (PPIE) activities are examining the motivations behind participant enrolment, engagement, and completion. Feedback on study design, communication, and perceived relevance is being collected to improve future participant experiences. Ethical complexities encountered during the study will also be reported in detail, offering transparency and guidance for future research teams. Together, these efforts aim to strengthen the paradigm's applicability and ensure that future studies are both scientifically robust and participant centred.

In summary, this study describes how repeat exposures of individuals to different policy-relevant PM-containing pollution mixtures can be used to perform a meaningful hazard ranking. Importantly, by demonstrating that multiple source-specific pollutant mixtures can be delivered safely and reproducibly within a chamber-controlled, within-subject clinical trial, this study advances current human exposure research by establishing a scalable and methodologically robust framework that has not previously been applied across this breadth of real-world sources. This study focused specifically on acute cognitive and respiratory effects, to demonstrate the operation of the lung-to-brain axis, in which context the directionality of the observed responses is less important than their temporal equivalence. The improvements in certain cognitive domains, and their potential link to NO, needs further investigation to determine whether it reflects changes in cerebral blood flow. This could be addressed in future studies by including a NO_X-only condition. Studies should also include sensitive pulmonary and respiratory assessments to better capture the effect of short-term exposures on acute respiratory changes. Perhaps the largest challenge will be to implement an effective blinding methodology which does not interfere with pollutant composition, ensuring experimental integrity and minimising unconscious bias.

The ultimate goal of work in this field is to confidently hazard-rank the toxicity of common indoor and outdoor pollution sources, thereby supporting more targeted policy interventions focused on health-relevant pollutants and informing strategies to mitigate pollution-related health risks.

Methods

Study design and participants

This was a single-centre, double-blind study investigating the effects of multiple common indoor and outdoor PM-containing air pollutant sources on the cognitive function of clinically healthy older (≥ 50 years old) adult volunteers with a family history of dementia. While participants did not have a dementia diagnosis, their family history places them at elevated risk of developing dementia. Investigating pollution-related short-term changes in cognitive function in this group offers early insights into how modifiable risk factors, such as pollution exposure, contribute to neurodegenerative disease trajectories. The study followed a repeated measures design in which participants were exposed in sequence to four different air pollutant mixtures, as well as clean air which served as the control or placebo condition. Due to logistical constraints, the exposure sequence order was determined by participant availability rather than randomisation. However, this did not compromise the double-blind design. Cognitive assessments and respiratory function tests were conducted before and 4 hours after each exposure. For the full study protocol, refer to Faherty et al.[23].

The trial was conducted in accordance with the principles of the Declaration of Helsinki, the guidelines for Good Clinical Practice of the International Conference of Harmonisation, and additional local regulations. No significant deviations from the protocol occurred. All participants provided written informed consent before any study-related activities. All procedures were approved by local institutional ethics review boards of participating sites: The Health Research Authority (HRA) Integrated Research Application System (IRAS), ID 314890, and University of Manchester Research Ethics Committee (UREC), ID 2022-14762-25491. All data was collected between May and November 2023. See Supplementary information for the CONSORT (2025)[31] checklist.

The CONSORT diagram (Fig. 3) describes the enrolment, allocation, follow-up, and analysis of the study. 13 participants completed all five visits. The mean age was 59.9 years (standard deviation; SD = 6.6), most were men (8 of 13; 62%), and all identified as White. See Supplementary Table 1 for additional demographic details.

Randomisation and masking

This was a double-blind study in which both trial participants and the researchers or care staff responsible for data collection were blinded to the exposure conditions. The team responsible for administering the exposures and senior investigators were aware of the exposure order. While participants were informed about the four PM-containing pollution exposure

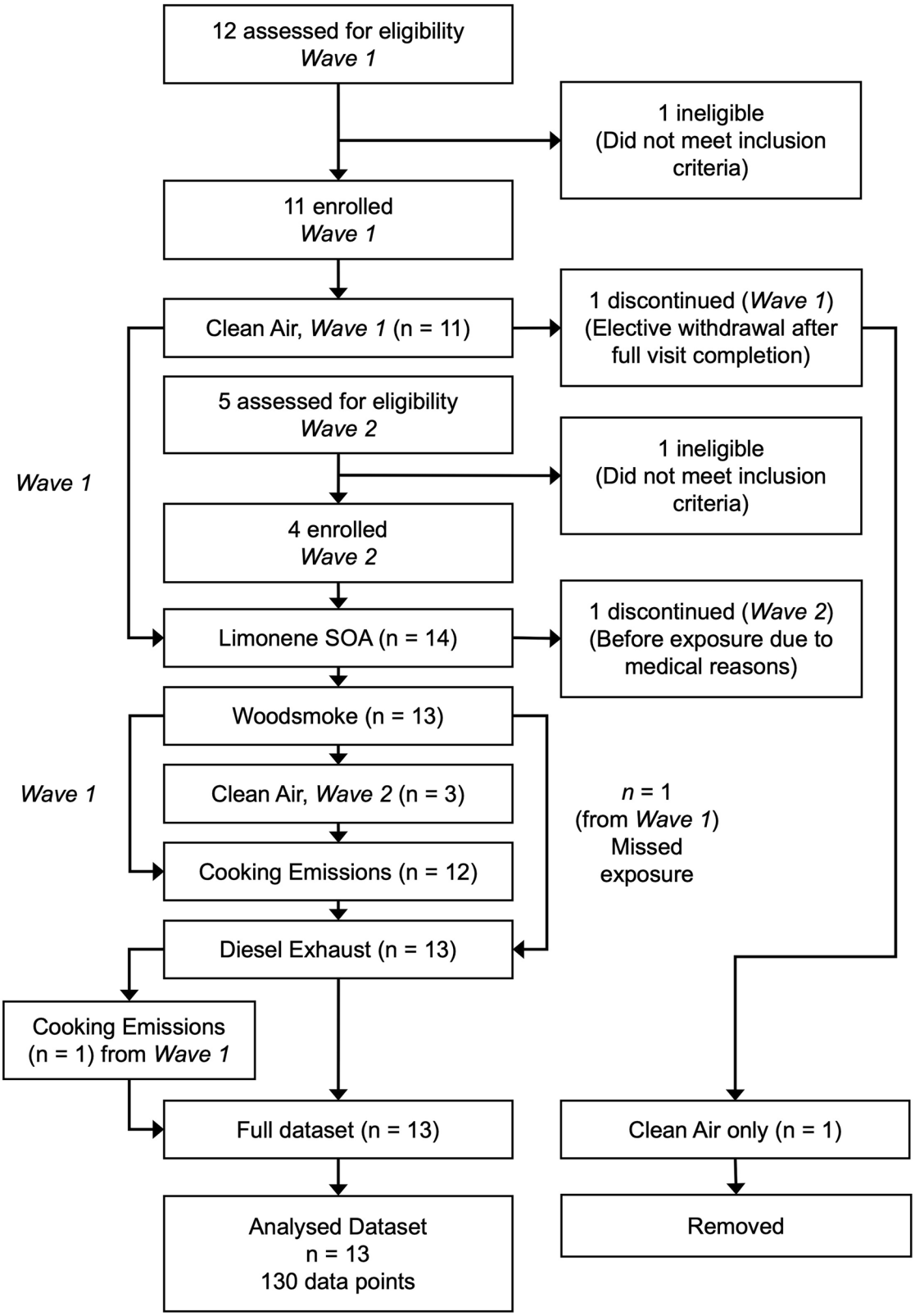

Fig. 3 | HIPTox Human Exposure study CONSORT diagram. See Supplementary Table 1 for characteristics of participants.

mixtures (and clean air), they were unaware of the order in which they received them. After each exposure, the (unblinded) exposure administration team asked participants to identify which of the five conditions they believed they had experienced, along with a confidence rating between 1, 'not at all confident', and 5, 'completely confident'.

A χ^2 goodness-of-fit test was conducted to determine whether participants' reported exposure identifications differed from chance (20% accuracy). The results were statistically significant (χ^2 (4, $n = 13$) = 20.128, $p < 0.001$), indicating that participants were able to identify exposures more accurately than would be expected by random guessing. Across all visits,

Table 3 | Exposure awareness of participants

	Clean Air	Limonene SOA	Woodsmoke	Diesel Exhaust	Cooking Emissions	Total
Number (%) Correct	4 (31%)	5 (38%)	11 (85%)	6 (46%)	13 (100%)	39 (60%)
Average confidence (Correct)	3.00	2.20	4.36	2.50	4.38	–
Number (%) Incorrect	9 (69%)	8 (62%)	2 (15%)	7 (54%)	0 (0%)	26 (40%)
Average confidence (Incorrect)	1.44	2.25	2.50	2.29	–	–

Number and percentage of participants correctly identifying the air pollution exposure; and average confidence of correct and incorrect reports scaled from 1, 'not at all confident', to 5, 'completely confident'.

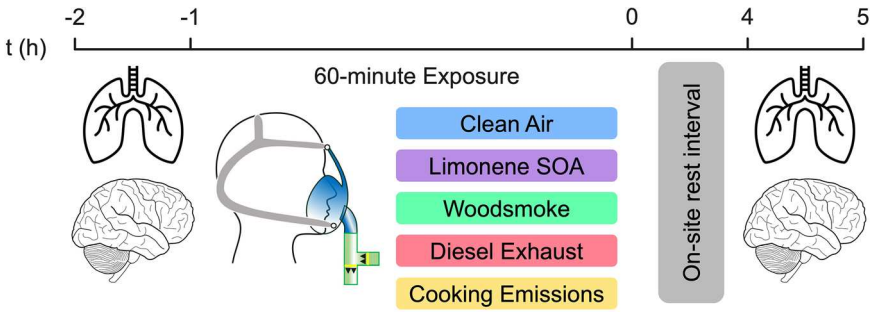

Fig. 4 | Study Procedure. Daily procedure. Symbols indicate spirometry (lungs) and cognitive testing (brain).

Table 4 | 60-minute average Particulate Matter, Nitrogen Oxides, and Nitric Oxide concentrations during each exposure

	Clean Air	Limonene SOA	Woodsmoke	Diesel Exhaust	Cooking Emissions
Particulate Matter (μgm^{-3})	0.02 (0.01)	147.25 (17.71)	148.24 (37.24)	155.44 (10.41)	141.91 (11.69)
Nitrogen Oxides (ppb)	2.67 (2.61)	0.66 (1.88)	36.60 (36.84)	258.25 (223.52)	3.33 (4.01)
Nitric Oxide (ppb)	2.22 (2.42)	0.00 (0.00)	30.54 (30.07)	158.08 (141.78)	2.00 (2.57)

Numbers in brackets indicate standard deviation.

participants correctly identified the condition 39 times and incorrectly 26 times. Examination of the data (Table 3) shows that clean air, limonene SOA, and diesel exhaust were more difficult for participants to identify correctly, and this was mirrored by lower confidence ratings for these. In contrast, participants were both accurate and confident in identifying woodsmoke and cooking emissions.

Notably, whilst participants may have correctly identified the exposure source, they were not told until full study completion as to whether their assumptions were correct. Because of this, no expectancy-driven effects could accumulate across sessions.

Procedures

During screening, participants were fitted for a VariFit™ NIV non-vented mask covering the nose and mouth. Three mask sizes were available, allowing the selection of the most appropriate size for each participant. Participants were asked to confirm comfort and for any obvious leakage during tidal breathing; once confirmed each mask was assigned as their individual mask for all subsequent visits. Masks were thoroughly cleaned and disinfected between visits.

On visit days, participants undertook spirometry and five cognitive tasks prior to a 60-minute exposure to a controlled concentration air pollutant from common sources, as well as a clean air exposure which served as the control condition. During each exposure, participants' individually fitted masks were secured firmly to their face using adjustable head straps. The mask was connected to an aerosol chamber via a short wide-bore plastic tube, and a two-way directional valve ensured inhalation from the chamber and exhalation into the surrounding room. After exposure, participants were monitored for 4 hours post-exposure before repeating spirometry assessments and cognitive tasks. A visual representation of the daily procedure is shown in Fig. 4.

The pollutant mixtures under investigation were selected due to their significant contribution to indoor and outdoor air quality. Diesel exhaust has known cardiopulmonary and emerging neurological effects[32]. Woodsmoke emissions have increased in recent years and are a growing concern in the UK[33]. Cooking emissions are a major source of indoor aerosols, with early evidence suggesting possible neurological impacts[34]. Limonene, a common base ingredient in cleaning products, produces secondary organic aerosols (SOA), a form of indoor air pollution that remains understudied in relation to cognitive health.

Exposures were conducted at the Manchester Aerosol Chamber (MAC) facility, part of the ACTRIS atmospheric simulation chamber network. A $18m^3$ Fluorinated ethylene propylene Teflon bag is housed within a temperature and humidity-controlled enclosure[35]. Exposure conditions were prepared by the exposure team before the participant entered the MAC facility and were continuously monitored, with air quality measured throughout. See Table 4 for average PM, nitrogen oxides (NO_X), and nitric oxide (NO) concentrations across the five conditions. Each pollution source was intentionally standardised to the same PM mass, but no control of the co-emitted gases was attempted, or indeed possible. The authors note that variation in NO_X concentrations reflects the natural fluctuation of real-world combustion emissions[36,37]. Chamber dilution was controlled to PM mass only, and therefore NO_X variability followed the natural PM:NO_X ratio of the source rather than arising from chamber or sampling instability.

During exposure, exhaled air was released into the surrounding room, thereby preventing contamination of the chamber's air mixture. Inhalation occurred through passive breathing only, with no applied positive pressure;

airflow through the mask and tubing was governed solely by participants' normal tidal breathing at ambient atmospheric pressure.

Respiratory outcomes were measured using spirometry, primarily as a safety assessment. Participants performed spirometry until three reproducible measurements of forced expiratory volume in one second (FEV_1) and forced vital capacity (FVC) were obtained, in accordance with American Thoracic Society/European Respiratory Society guidelines[38].

To assess cognitive function, we utilised five tasks: one standardised manual task and four internally developed computer-based tasks as in Faherty et al., 2025[9]. Details are provided below with full methodologies included in the Supplementary Materials and published protocol[23].

Purdue Pegboard Test (PPT): A standardised manual task that assessed fine motor control, specifically hand and finger dexterity in manipulating small objects[39]. Outcomes were gross motor control and fine motor control.

Spatial n-Back Task (SNB): A working memory task involving the spatial location of stimuli. It measured participants' ability to retain and manipulate multiple pieces of spatial information over short periods. Outcomes were 1-back, 2-back, and 3-back discrimination performance (accuracy).

Face Identification Task (FIT): A selective attention task using highly distracting facial stimuli. This task assessed cognitive control, particularly the ability to suppress irrelevant information and maintain focus on task-relevant goals. Outcomes were cognitive control (selective attention) and overall response time.

Expression Recognition Task (ERT): A Go/No-Go task using emotional facial expressions to evaluate socio-emotional cognition. It measured participants' speed and accuracy in identifying facial expressions under time pressure. Outcomes were overall discrimination ability (accuracy) and approach-avoidance bias.

Psychomotor Vigilance Task (PVT): A simple reaction time task that assessed sustained attention and psychomotor speed. It measured how quickly participants responded to visual stimuli over an extended period. The outcome metric was response time.

Statistical analysis

To assess the effects of 60-minute exposures to common air pollutants on cognitive and respiratory outcomes, we used generalised estimating equations (GEE) with an identity link and exchangeable correlation structure. Separate models were run for each cognitive and respiratory outcome to identify which of the exposures were associated with adverse changes, with exposure condition as the primary predictor (clean air as the reference). Models included baseline performance, average baseline across visits, and exposure order as covariates. An interaction term between exposure and baseline was included to test for moderation effects. Participant ID was used to account for within-subject correlations across repeated measures. To safeguard against potential misspecification of the correlation structure, robust standard errors were employed to provide reliable inference.

Because the cognitive tasks in this study index distinct constructs (working memory, selective attention, socio-emotional processing, psychomotor speed, and motor control), each task was treated as its own analytic family for multiple-comparison control. Grouping outcomes into conceptually coherent families and avoiding global corrections across unrelated domains aligns with methodological guidance and helps to limit unnecessary loss of power (inflated Type II error) that can arise from over-broad multiplicity adjustments[40]. Consistent with this approach, separate GEE models were fit for each outcome. Within each cognitive task, multiple outcomes from the same test were corrected using an α/k adjustment (Bonferroni). For instance, the Spatial *n*-back task comprised three dependent measures (1-, 2-, and 3-back discrimination), resulting in an adjusted alpha of $0.05/3 \approx 0.0167$, which we rounded down to 0.016 to be conservative. This approach ensured control of the family-wise error rate within each task while avoiding unnecessary corrections across conceptually unrelated domains.

Following the GEE analyses, post-hoc tests were conducted for each outcome where exposure condition was identified as a significant predictor. Pairwise comparisons were used to examine differences between all exposure conditions, not only relative to clean air, to better understand how the pollution sources differentially impact cognitive and respiratory outcomes.

Data availability

Data supporting the findings of this study are available in the article, its Supplementary information and Source data file. Raw and processed demographic, cognitive, and respiratory data generated in this study and used for analysis have been deposited in the University of Birmingham eData Repository[41]. Cognitive task instructions and MATLAB scripts used for cognitive testing are available on GitHub https://github.com/fahertyt/HIPTox_cognition.

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Author contributions

All authors meet the ICMJE criteria for authorship. G.M. curated the work packages across the HIPTox consortium. I.M., G.M., F.D.P., J.F.H and J.S. had supervisory roles throughout the project. All authors contributed to the study conception and design. T.F., H.B., D.H., A.V., D.J.B., M.D.S. and J.R.H. collected the data. T.F., J.S., I.M., H.B., G.M. and F.D.P. developed the statistical analysis. T.F. and H.B. checked the analysis and verified the underlying data reported in the manuscript. T.F. wrote the initial manuscript and created figures. All authors contributed to manuscript revisions and approved the final version. All authors had full access to all the data in the study and accept responsibility to submit for publication.

Competing interests

The authors declare no competing interests.

Additional information

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