

NEURODEGENERATION

Lewy body dementia promotion by air pollutants

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INTRODUCTION: Lewy body dementia (LBD), comprising dementia with Lewy bodies (DLB) and Parkinson's disease (PD) with dementia (PDD), is a devastating and increasingly prevalent neurodegenerative disorder. Ambient PM_{2.5} is a recognized broad dementia risk factor; however, its specific role in initiating LBD, particularly its distinct pathological trajectory versus PD without dementia, remains unaddressed. This study systematically investigates this link.

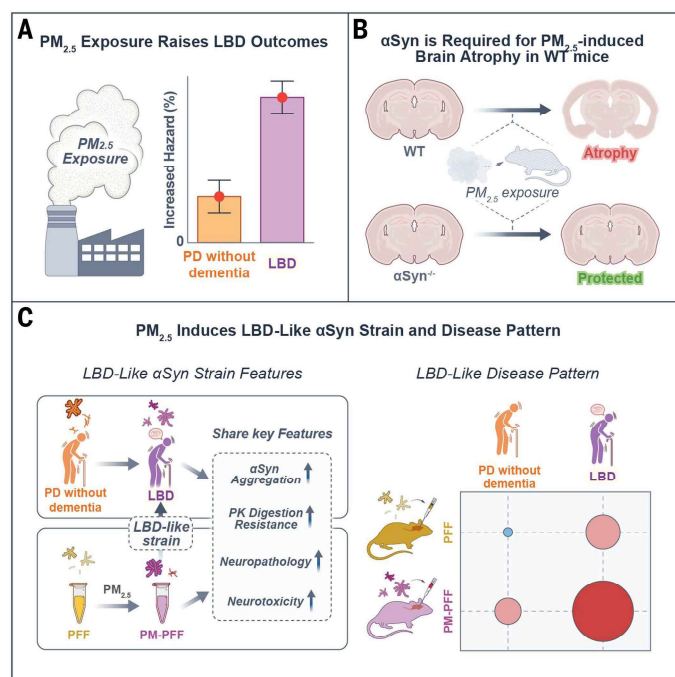
RATIONALE: Pathologic α -synuclein (α Syn) is the defining neuropathological hallmark of LBD. A leading hypothesis posits that environmental neurotoxins, such as fine particulate matter (PM_{2.5}), could trigger initial α Syn misfolding and propagation into the brain. However, epidemiological relationships between PM_{2.5} exposure and LBD versus PD subtypes lacked large-scale substantiation. Whether PM_{2.5} can induce α Syn to form pathogenic strains that drive LBD's specific clinical and pathological signatures remains unclear. Elucidating this environmental-molecular nexus is key to unravelling LBD pathogenesis and identifying targeted interventions. Our study aimed to dissect these fundamental mechanisms.

RESULTS: Convergent, multimodal evidence from large-scale human epidemiology, molecular, cellular, animal, and patient studies demonstrated a robust PM_{2.5}-LBD link.

First, analysis of >56 million US Medicare beneficiaries revealed that chronic PM_{2.5} exposure was significantly associated with first hospitalizations for α -synucleinopathies. A key finding was that the link between PM_{2.5} exposure and hospitalization risk was stronger for LBD (PDD and DLB) patients than for those with PD without dementia, implying a preferential vulnerability or pathogenic mechanism in LBD.

Second, we demonstrated an essential role of α Syn in PM_{2.5}-related neurological disorders. Chronic PM_{2.5} exposure in wild-type (WT) mice induced brain atrophy, cognitive deficits, and widespread α Syn pathology in the brain and peripheral organs (gut, lungs) as well as concomitant tau pathology. Genetic ablation of α Syn conferred strong protection against these PM_{2.5}-induced detrimental effects, clearly establishing α Syn as an important mediator of this environmental neurotoxicity.

Third, we found that PM_{2.5} from diverse global sources (US, China, and Europe) induced **conformational change in α Syn preformed fibrils (PFFs)**, inducing a distinct α Syn strain (PM-PFF). PM-PFF remained stable across passages and, compared with PFF, exhibited LBD-like pathogenic features, including accelerated aggregation, degradation resistance, enhanced propagation, and increased neurotoxicity, mimicking α Syn strains found in LBD. When inoculated into humanized α Syn mice, **this PM-PFF strain preferentially induced cognitive impairments, contrasting with the primarily motor deficits induced by PFF**. Consistently, brain transcriptomic analyses revealed that both chronic PM_{2.5} exposure and PM-PFF inoculation in humanized α Syn mice elicited **gene expression signatures that mirrored those of LBD (PDD and DLB) but not those of PD without dementia, underscoring an LBD-specific pathogenic axis**.



PM_{2.5} promotes LBD by inducing a distinct α Syn strain. (A) PM_{2.5} exposure is associated with a higher relative risk of LBD compared to PD without dementia. (B) Chronic PM_{2.5} exposure leads to brain atrophy in WT mice, an effect abolished in α Syn-knockout (α Syn^{-/-}) mice. (C) Mechanistically, PM_{2.5} triggers an LBD-like α Syn strain and elicits a corresponding transcriptomic profile characteristic of LBD pathology.

CONCLUSION: This study provides evidence linking PM_{2.5} exposure to LBD. The neurotoxic effects of **PM_{2.5} appear to be mediated by α Syn**, with exposure generating a pathogenic strain (PM-PFF) that shares key properties with α Syn strains in human LBD. In mice, this strain induced cognitive deficits and transcriptomic changes resembling those in LBD patients, distinct from those in PD without dementia. These findings identify an environmental mechanism contributing to LBD pathogenesis and underscores the role of α Syn. The PM_{2.5}-induced strain represents a potential target for therapeutic intervention. Collectively, these results emphasize the importance of further research into air pollution's role in neurodegenerative diseases and its implications for public health strategies. □

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NEURODEGENERATION

Lewy body dementia promotion by air pollutants

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Evidence links air pollution to dementia, yet its role in Lewy body dementia (LBD) remains unclear. In this work, we showed in a cohort of 56.5 million individuals across the United States that fine particulate matter (PM_{2.5}) exposure raises LBD risk. Mechanistically, we found that PM_{2.5} exposure led to brain atrophy in wild-type mice, an effect not seen in α -synuclein (α Syn)-deficient mice. PM_{2.5} exposure generated a highly pathogenic α Syn strain, PM_{2.5}-induced preformed fibril (PM-PFF), with enhanced proteinase K resistance and neurotoxicity, resembling α Syn LBD strains. PM_{2.5} samples from China, the United States, and Europe consistently induced proteinase-resistant α Syn strains and in vivo pathology. Transcriptomic analyses revealed shared responses between PM_{2.5}-exposed mice and LBD patients, underscoring PM_{2.5}'s role in LBD and stressing the need for interventions to reduce air pollution and its associated neurological disease burden.

Emerging evidence suggests that urban and roadside air pollution are contributing factors to dementia (1). Higher annual mean concentrations of fine particulate matter (PM_{2.5}) in the US are associated with an increased risk of first hospital admissions for Alzheimer's disease (AD) and related dementia incidence (2–4). Lewy body dementia (LBD), the second most common form of dementia, is characterized by the aggregation of α -synuclein (α Syn) and includes dementia with lewy bodies (DLB) and Parkinson's disease (PD) with dementia (PDD) (5–8). The link between air pollution and LBD is unknown.

In LBD and related α -synucleinopathies (diseases characterized by abnormal aggregation of α Syn), one of the most pivotal discoveries is the prion-like behavior of α Syn, which reflects the presence of

distinct α Syn strains across different α -synucleinopathies (9, 10). These strains drive the spread of α Syn pathology and contribute to subsequent behavioral impairments (11–18). Emerging data also suggest that environmental factors can modify α Syn strains, potentially worsening or mitigating disease progression (18–21).

α Syn strains appear to progress from PD without dementia to PDD in both cross-sectional and longitudinal cohorts (22, 23). We propose that air pollutants, particularly PM_{2.5}, contribute to the development of LBD by promoting the formation of LBD-like α Syn strains. To test this hypothesis, we combined epidemiological evidence with the multimodal analyses of PM_{2.5}-induced α Syn strains derived from mouse models, comparing these with the α Syn strain amplified from the cerebrospinal fluid (CSF) of LBD patients. Additionally, we examined transcriptomic responses in PM_{2.5}-exposed and PM_{2.5}-induced α Syn strain-inoculated mouse brains, comparing these results with previously published data from LBD brain tissues (24). This comprehensive approach aims to clarify the mechanisms by which PM_{2.5} exposure may promote LBD and support interventions that reduce PM_{2.5} exposure.

Study design, population, and data collection in epidemiological study

To examine the relationship between PM_{2.5} exposure and the occurrence of α -synucleinopathies resulting in hospital admissions, we conducted a longitudinal cohort study. Our study population was a longitudinal open cohort of Medicare fee-for-service beneficiaries aged 65 years or older in the US from 1 January 2000 to 21 December 2014, which we identified using Medicare Part A claims data. People are eligible to enter Medicare after they turn 65 years of age, and for each beneficiary, follow-up started on 1 January 2000 or 1 January of the year following entry into the Medicare program until their first hospital admission with one of four dedicated diagnosis code sets, each corresponding to a predefined outcome (see materials and methods), death, or the end of the study period, whichever came first. In this study, PD includes both PD without dementia and PDD. Additionally, PD without dementia specifically refers to patients who have not progressed to PDD. Four α -synucleinopathy-related outcomes considered were first hospital admissions for PD, PD without dementia, PDD, and DLB. We obtained the Medicare inpatient hospital claims from the Medicare Provider and Analysis Review files, which include one record per hospital admission. We extracted the primary or secondary diagnoses in hospital admissions for each beneficiary based on International Classification of Diseases (ICD) codes (detailed in the materials and methods). We also extracted age, sex, race, postal code (i.e., ZIP code) of residence, and Medicaid eligibility for each beneficiary in each follow-up year. Medicaid eligibility is a proxy for individual-level socioeconomic status, where a Medicare beneficiary eligible for Medicaid is likely to have a lower socioeconomic status. Table S1 provides descriptive information on the study cohort. This epidemiological study was conducted under a protocol approved by the Columbia University Mailman School of Public Health Human Subjects Committee.

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The cohort included more than 56.5 million individuals residing in 34,824 ZIP codes, with a mean entry age of 70.1 years (SD = 7.2 years). The total follow-up time ranged from 406.7 to 409.3 million person-years for four α -synucleinopathy-related outcomes. The number of first hospital admissions was 0.31 million for DLB, 0.39 million for PDD, and 0.73 million for PD without dementia, with 1.14 million for PD by the end of follow-up. The interquartile range (IQR) for an annual average $PM_{2.5}$ during the study period was $4.14 \mu g/m^3$.

Geographical distribution of $PM_{2.5}$ and α -synucleinopathies

As shown on the US map in Fig. 1A, the mean annual $PM_{2.5}$ concentration during the study period was $9.7 \mu g/m^3$ (IQR $4.14 \mu g/m^3$). $PM_{2.5}$ concentrations were generally higher in the eastern US than in the western US, although certain areas in California exhibited the country's highest concentrations. Figure 1B illustrates the occurrence of first hospital admissions for the four α -synucleinopathies diagnoses per 100,000 Medicare beneficiaries across the contiguous US, indicating geographical similarities to the distribution of $PM_{2.5}$.

Associations between $PM_{2.5}$ exposure and risk of α -synucleinopathies

Motivated by the geographical similarities between $PM_{2.5}$ and α -synucleinopathy diagnoses, we performed an epidemiological study

adjusting for spatiotemporal, socioeconomic, behavioral, and meteorological covariates (see materials and methods). As shown in Fig. 1C, long-term exposure to $PM_{2.5}$ was associated with increased risk for first hospital admissions with all four α -synucleinopathy diagnoses. In the full cohort, we observed a hazard ratio (HR) of 1.10 [95% confidence interval (CI) (1.09, 1.10)] for PD admissions, consistent with our previously published results (3), and an HR of 1.07 [95% CI (1.07, 1.08)] for PD without dementia per IQR increase in annual $PM_{2.5}$ concentrations. For LBD outcomes, we found a higher risk with an HR of 1.17 [95% CI (1.16, 1.18)] for PDD and an HR of 1.12 [95% CI (1.11, 1.13)] for DLB admissions. Overall, the risk increases were more pronounced for LBD (PDD and DLB) than PD or PD without dementia, highlighting a greater adverse effect of $PM_{2.5}$ exposure on LBD admissions.

Analysis of different $PM_{2.5}$ exposure windows

Figure 1D illustrates the relationships between α -synucleinopathy outcomes and $PM_{2.5}$ concentrations across different exposure windows. $PM_{2.5}$ exposure was assigned to patients based on time-varying averages over the 10- and 5-year periods preceding their first hospital admission with an α -synucleinopathy diagnosis (10-Year and 5-Year Moving Average). Alternatively, $PM_{2.5}$ exposure was assigned using annual $PM_{2.5}$ concentrations from 10 and 5 years before the first hospital admission (10-Year and 5-Year Lagged). Overall, we observed

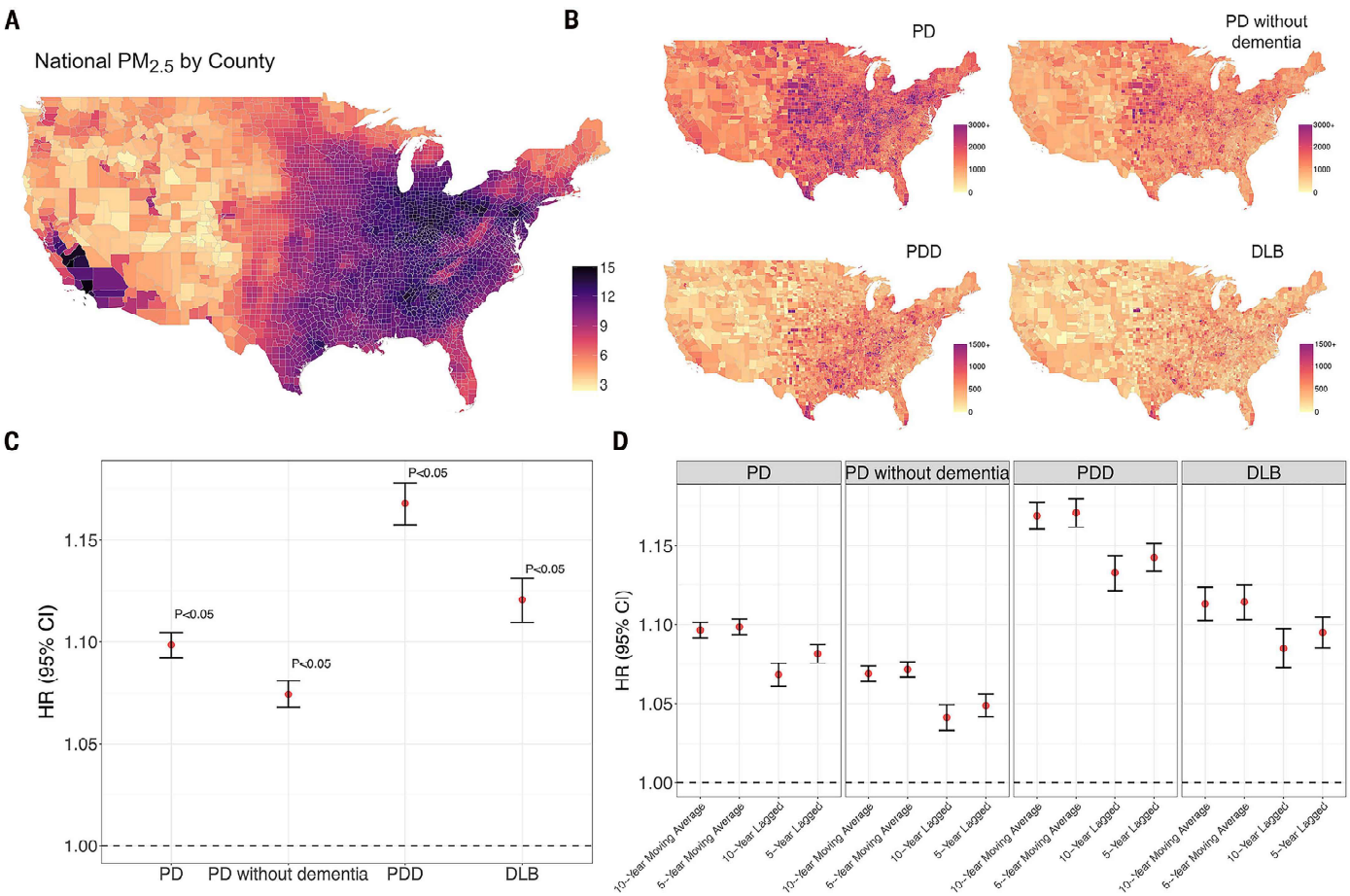


Fig. 1. Correlation between $PM_{2.5}$ exposure with LBD and PD outcomes. (A) Nationwide $PM_{2.5}$ concentrations across the contiguous US from 2000 to 2014. (B) Occurrences of first hospital admissions for four α -synucleinopathies across the contiguous US from 2000 to 2014, per 100,000 Medicare fee-for-service beneficiaries. (C) HRs and 95% CIs for long-term $PM_{2.5}$ exposure and first hospital admissions for four α -synucleinopathies. HRs were calculated using Cox proportional hazard models and adjusted for socioeconomic factors, behavioral risk factors, meteorological variables, geographic region, and year. CIs are represented by the error bars. (D) HRs and 95% CIs for long-term $PM_{2.5}$ exposure and first hospital admissions for four α -synucleinopathies across different exposure windows. Ten- and 5-year moving averages refer to time-varying averages over the 10- and 5-year periods preceding the hospital admission. Ten- and 5-year lagged refers to annual $PM_{2.5}$ concentrations from 10 and 5 years before the hospital admission.

positive associations between PM_{2.5} exposure and the risk of first hospital admission for all four α -synucleinopathies across various exposure windows. The use of multiyear moving average exposures yielded consistent results compared with those based on more recent annual PM_{2.5} exposures, shown in Fig. 1C. By contrast, relying on lagged exposure from many years ago resulted in less pronounced, yet still significant ($P < 0.05$), positive associations.

Together, these findings underscore that PM_{2.5} exposure is one of the environmental risk factors associated with increased hospital admissions for the LBD, including PDD and DLB. Hospital admissions serve as a proxy for neurodegeneration reaching a severe disease stage and may indicate accelerated disease aggravation. We also conducted an extensive set of sensitivity analyses to show the robustness of the observed associations (see supplementary materials and table S2).

Genetic depletion of α Syn prevents PM_{2.5}-induced brain atrophy and neurodegenerative pathology

Building on these epidemiological findings that demonstrate a strong association between PM_{2.5} exposure and LBD, we sought to investigate the underlying mechanisms through controlled animal studies. To explore the causal mechanisms of the association between PM_{2.5} and LBD and model the delayed onset of neurodegeneration, a long-term PM_{2.5} exposure paradigm was conducted using wild-type (WT) mice followed by nest-building tests at 4, 6, and 8 months after exposure. No deficits in fine motor function or emotional behavior were observed (fig. S1A) (25–27). However, by 10 months after exposure, clear impairment emerged, suggesting that prolonged exposure is required to induce behavioral deficits (fig. S1A). Similarly, phosphorylated serine-129 (pS129)-positive α Syn pathology was minimal at 2 months after exposure but showed substantial accumulation by 10 months, reinforcing a time-dependent association between chronic PM_{2.5} exposure and progressive LBD-like pathology (fig. S1, B and C).

Brain atrophy is a hallmark of dementia, including LBD, characterized by gray matter reduction in the cortical and hippocampal regions from neurodegeneration (25, 28–35). To investigate the effects of PM_{2.5} on brain structure, WT mice were exposed nasally to PM_{2.5} every other day for 10 months (details in materials and methods) (Fig. 2, A and B). Compared with phosphate-buffered saline (PBS)-treated controls, the WT mice exposed to PM_{2.5} exhibited brain atrophy, evidenced by an enlargement of the posterior lateral ventricle (LV) and a reduction in the medial temporal lobe (MTL) and hippocampus (Hip) areas (Fig. 2, C to F). α Syn-knockout (α Syn^{−/−}) mice were protected from this PM_{2.5}-induced brain atrophy, showing no changes in these brain regions (Fig. 2, C to F).

Additionally, increased tau hyperphosphorylation (p-tau217, p-tau181, p-tau202/205) (fig. S2), microglial activation (fig. S3) (36–38), astroglial activation (fig. S4) (39–41), elevated oxidative stress (fig. S5) (42–44), a reduced percentage of cortex myelination (fig. S6) (45, 46), increased DNA double-strand breaks (fig. S7) (47–49), and DNA fragmentation (Fig. 2, G and H) (50, 51) were observed in PM_{2.5}-exposed WT mice. These pathological changes were mitigated in PM_{2.5}-exposed α Syn^{−/−} mice (Fig. 2, G and H, and fig. S2 to S7). No amyloid- β accumulation was detected in our study (fig. S8). These results highlight the critical role of α Syn in mediating PM_{2.5}-induced pathology and neurodegeneration.

α Syn^{−/−} mice exhibit resilience to PM_{2.5}-induced cognitive decline

To assess the behavioral impact of PM_{2.5} exposure, open field testing was performed. No differences were observed in activity and the time spent in the center area (Cen) versus the center plus peripheral (Cen+Per) area across the four groups—WT-PBS, α Syn^{−/−}-PBS, WT-PM_{2.5}, and α Syn^{−/−}-PM_{2.5} (fig. S9A)—indicating that 10-month PM_{2.5} exposure did not cause a change in activities among the different groups of animals (11, 52). Next, spatial recognition memory using the

Y-maze was evaluated. WT mice exposed to PM_{2.5} spent less time in the newly discovered arms, indicating impaired spatial recognition memory compared with that of the WT-PBS group (53, 54). By contrast, α Syn^{−/−} mice exposed to PM_{2.5} did not show cognitive deficits relative to the α Syn^{−/−}-PBS group (fig. S9B). To further evaluate memory and cognitive function, the novel object recognition (NOR) test was performed (55, 56). Although no differences were observed during the training phase among the four groups, WT mice exposed to PM_{2.5} exhibited a reduction in the recognition index (percentage) compared with that of the WT-PBS group (fig. S9C). Similarly, α Syn^{−/−} mice showed no differences in recognition index, regardless of PM_{2.5} exposure (fig. S9C). Collectively, these findings suggest that PM_{2.5} exposure induces cognitive decline in WT mice, whereas α Syn^{−/−} mice are protected from these PM_{2.5}-induced deficits.

Mapping of α Syn pathology in the brain and peripheral organs of nontransgenic mice following PM_{2.5} exposure

To investigate the effects of PM_{2.5} exposure on α Syn pathology, pS129 α Syn immunoreactivity in both the brain and peripheral organs of WT mice was examined. In the brain of WT mice, we observed pS129-positive α Syn pathology in key regions, such as the Cornu Ammonis 1 region, dentate gyrus, and parietal cortex (PaC), compared with that in PBS-treated controls (fig. S10). In addition to the brain, we examined α Syn pathology in the gastrointestinal (GI) tract and the lung. In the GI tract, PM_{2.5} exposure induced pS129-positive α Syn pathology in the stomach, duodenum, jejunum, ileum, and colon (fig. S11, A to F). In the lung, PM_{2.5} exposure also led to pS129-positive α Syn pathology (fig. S11, A and G). By contrast, α Syn^{−/−} mice exposed to PM_{2.5} exhibited minimal pS129 α Syn signal in both the brain, GI tract, and the lung (fig. S10 and S11).

PM_{2.5} exposure induces a proteinase-resistant α Syn strain in vivo, contributing to cognitive decline in hA53T mice

Environmental factors can influence the formation of distinct α Syn strains, potentially leading to diverse disease trajectories (18–21). Building on these findings and the role of α Syn in PM_{2.5}-induced deficits, we aimed to determine whether exposure of α Syn to PM_{2.5} could induce a distinct α Syn strain.

Because WT mice do not naturally form α Syn aggregates during the aging process, we used human A53T mutant (hA53T) transgenic mice, which are prone to developing α Syn aggregates and associated pathology as they age. This model allowed us to compare the α Syn strain formed due to natural aging with those induced by PM_{2.5} exposure.

PM_{2.5} was nasally administered every other day to hA53T mice (57–59) over a period of 5 months (fig. S12A). Substantial α Syn pathology was observed in multiple brain regions of PM_{2.5}-exposed hA53T (PM_{2.5}-hA53T) mice compared with that in the PBS-hA53T control group (fig. S12B). Brain regions exhibiting elevated pS129-positive α Syn pathology included the olfactory bulb, prefrontal cortex, PaC, piriform cortex, Hip, hypothalamus, and brainstem but not the midbrain (fig. S12, C and D).

To determine whether ambient PM_{2.5} from different geographic regions could yield similar results, samples of PM_{2.5} were collected from three distinct geographical locations: Shaanxi, China (PM_{2.5}-1); Georgia, US (PM_{2.5}-2); and Prague, Czech Republic (PM_{2.5}-3). Table S3 shows a comparison of PM_{2.5} samples collected from different locations in this study. Nasal administration of the PM_{2.5} samples from the three different geographical locales to hA53T transgenic mice for 2 months induced pS129-positive α Syn pathology that was similar between the three locales (fig. S13).

To investigate whether PM_{2.5} can cause the formation of a different α Syn strain, we performed a seeding amplification assay (SAA) using the TX-100-insoluble fractions of brain lysates from PM_{2.5}-hA53T mice (Fig. 3A), followed by proteinase K (PK) digestion (18, 19) and dot blot analysis. We used aged (12-month-old) symptomatic hA53T mice as the

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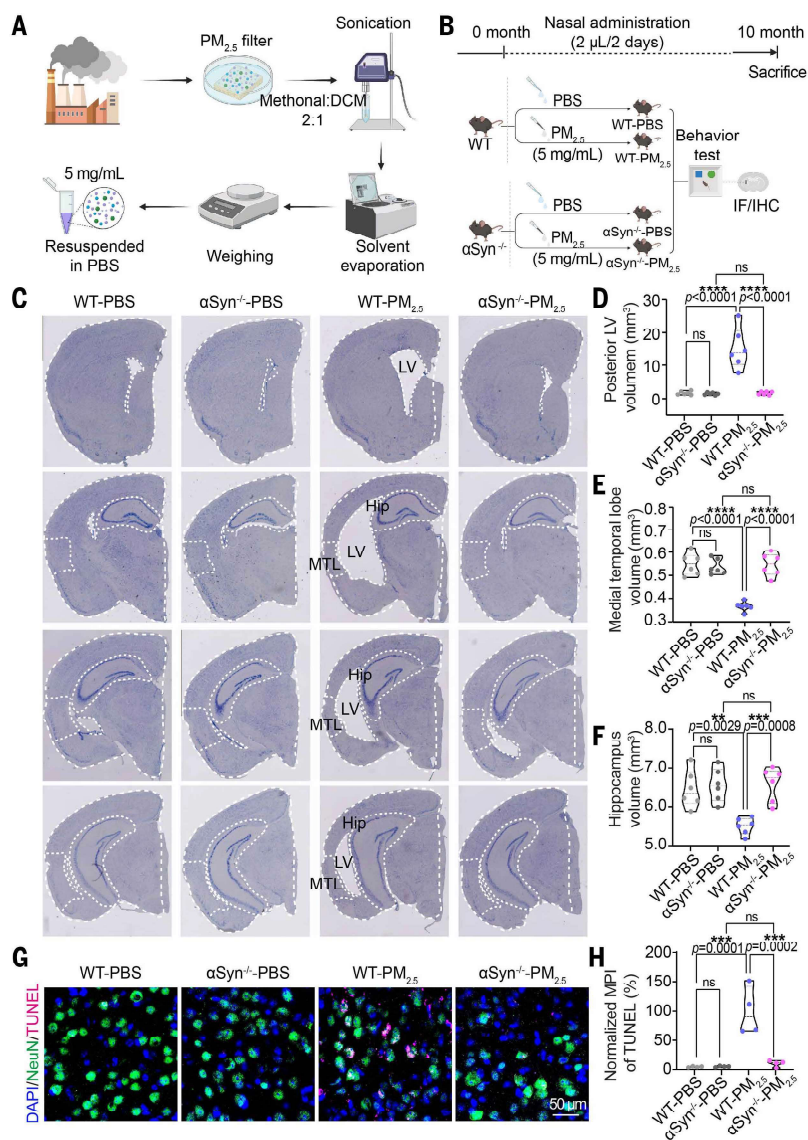


Fig. 2. αSyn depletion prevents PM_{2.5}-induced brain atrophy and cell death. (A) PM_{2.5} extraction and preparation method. DCM, dichloromethane. (B) In vivo experiment timeline of nasal PM_{2.5} administration to WT and αSyn^{-/-} mice. (C) Nissl staining of 12-month-old mouse brains after 10-month PM_{2.5} exposure. (D to F) Volume measurements of (D) posterior LV, (E) MTL, and (F) Hip areas ($n = 6$). (G) Representative fluorescent images showing terminal deoxynucleotidyl transferase-mediated deoxyuridine triphosphate nick end labeling (TUNEL; red) and NeuN (green) staining in the cortex of WT and αSyn^{-/-} mice after exposure to either PBS or PM_{2.5}. DAPI, 4',6-diamidino-2-phenylindole. (H) Quantification of normalized TUNEL+ cells in the cortex of WT and αSyn^{-/-} mice after exposure to either PBS or PM_{2.5} ($n = 4$). Normalized statistics: Data are presented as violin plots showing all individual data points. Statistical significance was determined by using one-way ANOVA with Tukey's correction. ** $P < 0.01$; *** $P < 0.001$; **** $P < 0.0001$; ns, not significant.

control (Fig. 3A). After centrifugation [100,000 rotations per minute (rpm), 1 hour], we collected the amplified αSyn aggregates samples from the pellet and resuspended in PBS and sonicated to generate preformed fibril (PFF) using a prior protocol (12). The amplified αSyn strain from PM_{2.5}-hA53T mice showed higher Thioflavin T (ThT) fluorescence compared with that of aged hA53T mice (Fig. 3B), and dot blot results indicated that the αSyn strain from PM_{2.5}-hA53T mice was more resistant to PK digestion than the strain from the aged hA53T mice (Fig. 3, C and D). After 5 months of PM_{2.5} exposure, the hA53T mice exhibited cognitive and psychiatric impairments, as demonstrated

by poor performance in the NOR test (fig. S14A), the Y-maze test (fig. S14B), and nest-building behavior (fig. S14C). Motor dysfunction was also observed in the PM_{2.5}-hA53T mice (fig. S14D).

Molecular evidence of PM_{2.5}-induced αSyn strain (PM-PFF) formation and distinct cellular response in vitro compared with PFF

Building on the observation that, in hA53T mice, exposure to PM_{2.5} induce a distinct αSyn strain that leads to cognitive deficits, we determined whether PM_{2.5} could directly induce recombinant human αSyn misfolding into a αSyn strain that was comparable to that generated in hA53T mice exposed to PM_{2.5}. Accordingly, recombinant human WT αSyn monomers were exposed to 5% PM_{2.5}-1, PM_{2.5}-2, and PM_{2.5}-3 (w/w) to generate PM_{2.5}-αSyn preformed fibrils PM1-PFF, PM2-PFF, and PM3-PFF, respectively, as well as control PFF using a prior protocol (12) (Fig. 3E). Thioflavin T (ThT) fluorescence assays revealed that PM_{2.5} accelerated αSyn aggregation after 7 days of agitation at 37°C (Fig. 3F and fig. S15A). Dot blot results indicated that the PM-PFF were more resistant to PK digestion than the PFF (Fig. 3, G and H, and fig. S15, B and C). Given the similar properties of PM_{2.5} from all three regions, we used PM_{2.5}-1 for subsequent experiments (unless otherwise specified, hereafter, PM_{2.5} refers to PM_{2.5}-1). Circular dichroism (CD) spectra showed a peak at 218 nm, indicating increased β-sheet structure formation with higher PM_{2.5} concentrations (fig. S16, A and B).

Because different αSyn strains can drive different cellular responses and strain-specific α-synucleinopathies (9, 60, 61), the cellular responses to the PM-PFF strain were compared to those to the control PFF. Primary mouse cortical neurons were exposed to PM-PFF and control PFF (5 μg/mL), and pS129 immunoreactivity was evaluated 10 days after treatment. Immunostaining showed that the PM-PFF strain caused a strong elevation of pS129 immunoreactivity that was approximately twofold greater than neurons treated with the control PFF strain (Fig. 3I and fig. S17A). Neurons treated with PM_{2.5} alone showed minimal pS129 signal (Fig. 3I and fig. S17A), indicating that the increased pS129 signal was specifically induced by the PM-PFF strain and not by PM_{2.5}. Neurotoxicity was evaluated by quantifying NeuN immunostaining, as previously described (12, 17). Exposure to control PFF for 21 days resulted in ~50% neuronal cell death, whereas the PM-PFF strain induced higher neurotoxicity (~70%) (Fig. 3J and fig. S17B). PM_{2.5} alone did not cause neurotoxicity in primary neuronal cultures compared with the PBS control (Fig. 3J and fig. S17B).

These results taken together indicate that PM_{2.5} promotes αSyn aggregation that leads to the formation of a propagative and neurotoxic strain. Moreover, PM_{2.5} alone does not induce pS129-positive αSyn pathology or neurotoxicity in primary neuronal cultures, nor does it cause neurodegeneration in αSyn knockout mice.

Differential effects of PM-PFF and PFF inoculation on cognitive and motor functions in humanized WT αSyn Mice

We next investigated whether PM-PFF can directly induce cognitive deficits in mice. Given that cross-seeded aggregation of human and mouse αSyn is bidirectionally restricted (62), we utilized the humanized WT αSyn (hWT) mice (strain: 010710) (15, 63, 64), in which endogenous mouse αSyn expression is replaced by human αSyn. As

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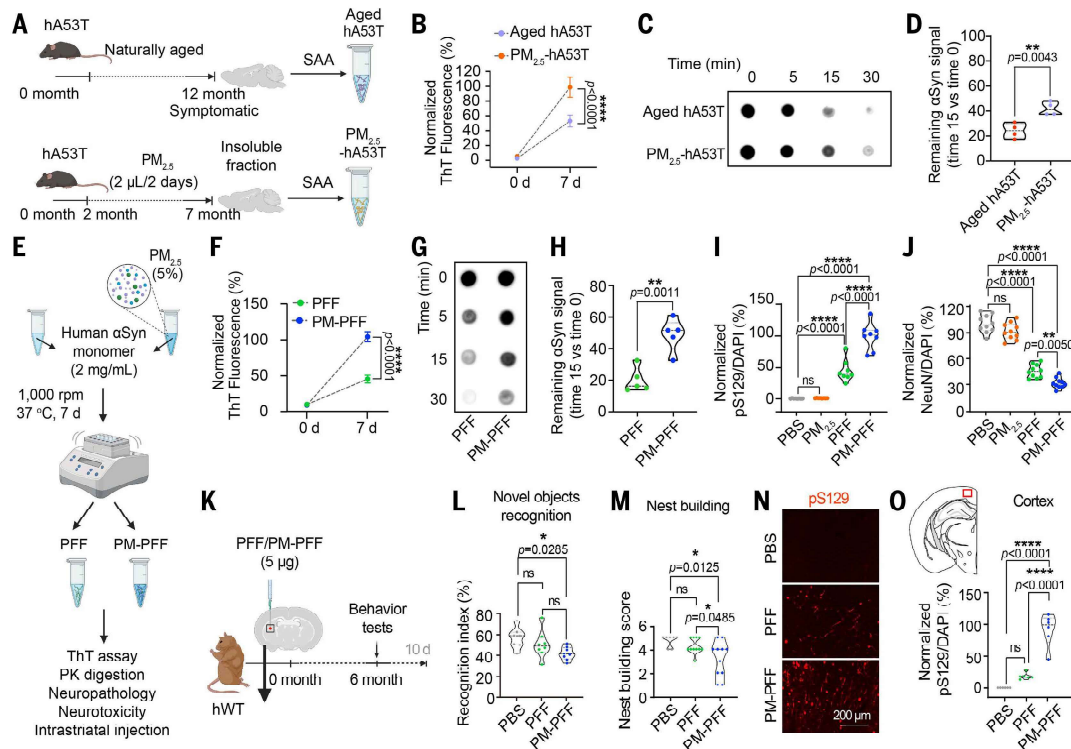


Fig. 3. PM_{2.5} exposure induces a proteinase-resistant, highly pathogenic α Syn strain with enhanced neuropathology, neurotoxicity, and dementia-inducing potential. (A) Insoluble fraction extraction schematic: 5-month-old PM_{2.5}-exposed hA53T (PM_{2.5}-hA53T) mice versus naturally aging symptomatic hA53T (aged hA53T) mice. (B) ThT–maximum fluorescence intensity (mfi) of seeded α Syn: PM_{2.5}-hA53T versus aged hA53T insoluble fractions in SAA. (C) Dot blot of remaining α Syn after PK digestion (0, 5, 15, 30 min) of PM_{2.5}-hA53T and aged hA53T insoluble fractions. (D) Quantification of remaining α Syn at 15 versus 0 min PK digestion in PM_{2.5}-hA53T versus aged hA53T groups. (E) PM-PFF and PFF generation schematic. (F) ThT-mfi of PM-PFF versus PFF. (G) Dot blot of remaining α Syn after PK digestion (0, 5, 15, 30 min) of PFF and PM-PFF insoluble fractions. (H) Quantification of remaining α Syn at 15 versus 0 min PK digestion in PFF versus PM-PFF groups. (I) pS129-positive neuropathology in primary cortical neurons; $n = 8$. (J) Neurotoxicity (NeuN staining) in primary cortical neurons; $n = 10$. (K) In vivo protocol: Striatal PM-PFF or PFF injection in 2-month-old hWT mice. Behavior was assessed at 6 months of age, then euthanasia and staining ensued. (L and M) Novel object recognition (L) and nest building (M) scores of PM-PFF and PFF injected mice at 6 months; 7 PBS, 8 PM-PFF, and 8 PFF mice in the NOR test; 7 PBS, 11 PFF, and 11 PM-PFF mice in the nest-building test. (N and O) Fluorescent images (N) and quantification (O) of cortical pS129 signals at 6 months after injection (PBS, PFF, PM-PFF). [(D), (H), (I), (J), (L), (M), and (O)] Data are presented as violin plots showing all individual data points. Statistics: [(B), (D), (F), and (H)] Data is shown as mean $\pm$ SEM, and Student's t test was performed. [(I), (J), (L), (M), and (O)] Statistical significance was determined by using one-way ANOVA with Tukey's correction. * $P < 0.05$; ** $P < 0.01$; **** $P < 0.0001$; ns, not significant.

illustrated in Fig. 3K, stereotaxic injections of PM-PFF and PFF were administered into the dorsal striatum of 2- to 3-month-old hWT mice. In the α Syn spreading model, PBS was chosen as the negative control based on extensive previous studies in which PBS served as the vehicle control for PFF and demonstrated high reproducibility (12, 17, 18, 65–67). Afterwards, a series of behavioral tests and immunostaining were performed to evaluate cognitive and motor functions as well as the distribution of pS129-positive α Syn pathology.

Behavioral tests revealed that PM-PFF-inoculated mice exhibited a reduction in the recognition index during the NOR test compared with that of the PBS groups, whereas PFF-inoculated mice exhibited no difference from PBS controls (Fig. 3L). Additionally, PM-PFF-inoculated mice left more unused nestlet material than both PFF and PBS controls, resulting in lower Nest building scores (Fig. 3M). There was no difference between PFF and PBS groups (Fig. 3M) (25–27). There were no differences observed in activity and the time spent in the center area (fig. S18A). These results suggest that PM-PFF induces more pronounced cognitive deficits than PFF.

Motor function was assessed by using the pole test, which is a sensitive indicator of dopaminergic function (68). In line with previous studies (16–18) and compared with PBS controls, PFF inoculation caused substantial motor deficits, including increased time to turn and total time to reach the base (fig. S18B). By contrast, PFF inoculation

resulted in more pronounced motor dysfunction compared to PM-PFF (fig. S18B).

To investigate the link between neuropathology and behavioral deficits, we assessed neurodegeneration of dopaminergic neurons in the substantia nigra (SN) using anti-tyrosine hydroxylase and Nissl staining. Both PM-PFF and PFF induced dopaminergic neuronal loss (fig. S19, A to C). However, compared with the PM-PFF group, the PFF group exhibited motor impairment in the pole test (fig. S18B), potentially owing to the greater dopamine cell loss induced by PFF (fig. S18B). Moreover, PM-PFF inoculation resulted in a higher accumulation of pS129-positive α Syn pathology in the cortex compared with that induced by PFF (Fig. 3N and O). In the SN, PFF induced substantial pS129-positive α Syn pathology, whereas PM-PFF caused less pS129 signal than PFF (fig. S19, D and E).

PM_{2.5}-induced α Syn strains exhibit passage stability and mimic key features of LBD α Syn strains

To determine whether the PM-PFF strain exhibits passage stability and shares characteristics with LBD α Syn strains, we compared the biophysical, biochemical, pS129 α Syn immunoreactivity, and neurotoxic properties of α Syn strains derived from LBD ($n = 5$ PDD and 2 DLB), PD without dementia ($n = 5$), and healthy control (HC) ($n = 5$) individuals versus those of PM_{2.5}-induced α Syn second-passage strains (PM-PFF^{2nd})

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(Fig. 4A). LBD α Syn strains displayed higher ThT fluorescence compared with that of PD without dementia strains (Fig. 4B), and PM-PFF^{2nd} similarly showed higher ThT fluorescence than that of the second-passage PFF strains (PFF^{2nd}) (Fig. 4C), suggesting a stronger fibrillar structure in PM-PFF^{2nd} that parallels the properties of LBD strains.

Next, LBD α Syn strains demonstrated greater PK resistance than PD without dementia strains (Fig. 4, D and E), and PM-PFF^{2nd} mirrored this with higher PK resistance than PFF^{2nd} (Fig. 4, F and G), indicating that PM-induced strains adopt a more protease-resistant conformation similar to that of LBD-derived strains. Additionally, LBD α Syn strains induced more pronounced pS129 α Syn immunoreactivity compared with that of PD without dementia strains (Fig. 4, H and I), and PM-PFF^{2nd} caused more severe pS129-positive α Syn pathology than PFF^{2nd} (Fig. 4, J and K).

Lastly, in terms of neurotoxicity, LBD α Syn strains caused greater neurotoxicity in primary cortical neurons compared with that from PD without dementia strains (Fig. 4, L and M), and PM-PFF^{2nd} proved to be more neurotoxic than PFF^{2nd} (Fig. 4, N and O), aligning with the toxic properties seen in LBD strains. Together, these findings strongly suggest that PM-PFF exhibits passage stability and shares critical pathogenic features with LBD α Syn strains.

Transcriptomic responses to PM_{2.5} exposure and PM-PFF inoculation in hWT mice and LBD postmortem brains

To evaluate the trajectory of transcriptomic responses induced by PM_{2.5} exposure and PM-PFF inoculation as well as their resemblance to those observed in LBD compared with those from PD without dementia, we performed RNA sequencing (RNA-seq) gene expression profiling in PM_{2.5}-exposed and PM-PFF-inoculated hWT mice. We selected the anterior cingulate cortex (ACC) to ensure consistency in comparisons between these experimental groups and the disease patterns observed in patients (24). Mice were divided into five groups, each exposed for 2 months under the following conditions: (i) PBS (control), (ii) PM_{2.5}, (iii) PFF, (iv) PM-PFF, and (v) PM-PFF inoculation followed by 7 weeks of PM_{2.5} nasal administration, beginning one week after injection (PM-PFF with PM_{2.5} exposure, 8 weeks total after injection). This fifth group, PM-PFF with PM_{2.5} exposure, intended to model real-world conditions, where patients with PM_{2.5}-induced α Syn seeds were exposed to PM_{2.5}.

Principal component analysis (PCA) of the gene expression data revealed a clear separation between control samples and those treated under the various conditions (Fig. 5A). Differential gene expression

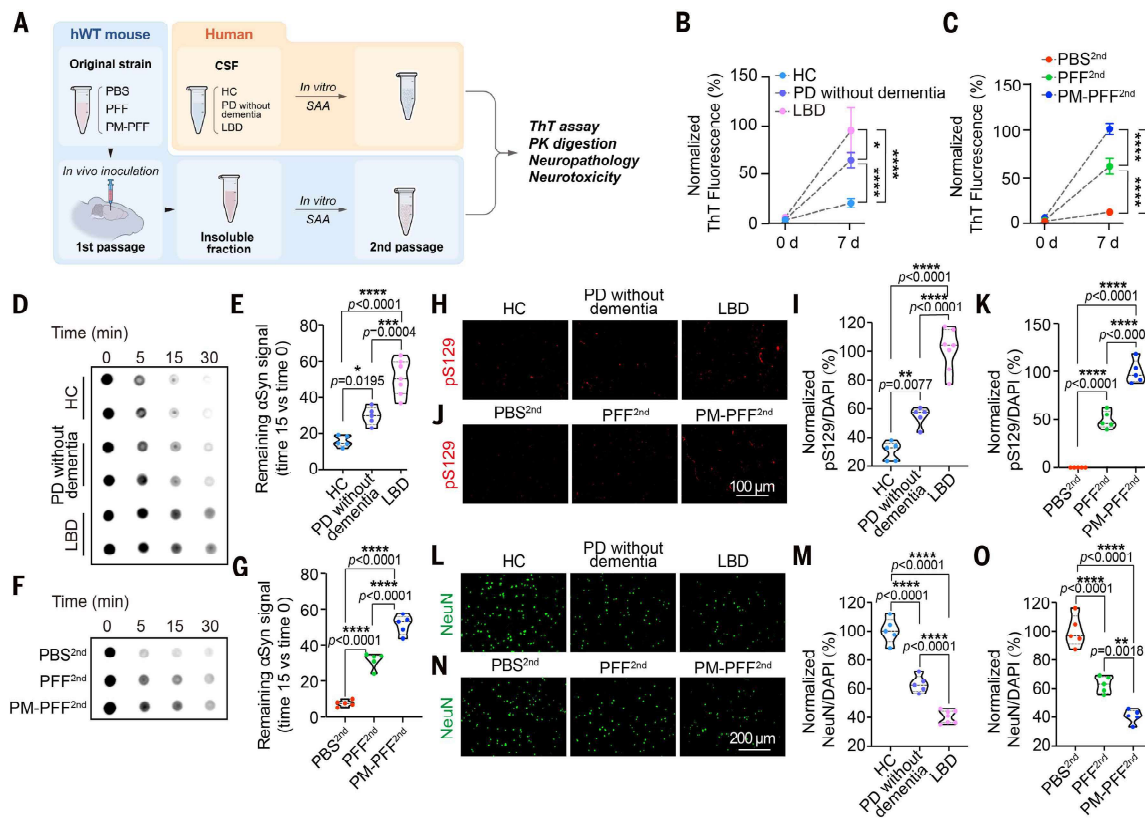


Fig. 4. PM_{2.5}-induced α Syn strain shares key pathological features with LBD patient-derived strain and maintains these features across passages. (A) Schematic of SAA comparing features of LBD patient CSF samples [$n = 7$ LBD (5 PDD, 2 DLB), 5 PD without dementia, and 5 HC] and PM_{2.5}-related mouse brain lysate samples (hWT mice inoculated with PM-PFF, PFF, or PBS; $n = 5$) using biophysical, biochemical, and cellular assays. Second-passage samples (PM-PFF^{2nd}, PFF^{2nd}, PBS^{2nd}) were derived from first-passage inoculations. (B) ThT maximum fluorescence intensity (mfi) of LBD α Syn strain versus PD without dementia and HC. (C) ThT maximum fluorescence intensity (mfi) of PM-PFF^{2nd} versus PFF^{2nd} and PBS^{2nd}. (D) Dot blot of remaining α Syn after PK digestion (0, 5, 15, and 30 min) of LBD, PD without dementia, and HC groups. (E) Quantification of remaining α Syn at 15 versus 0 min PK digestion in LBD α Syn strain versus PD without dementia and HC groups. (F) Dot blot of remaining α Syn after PK digestion (0, 5, 15, and 30 min) of PBS^{2nd}, PFF^{2nd}, and PM-PFF^{2nd} groups. (G) Quantification of remaining α Syn at 15 versus 0 min PK digestion in PM-PFF^{2nd} versus PFF^{2nd} and PBS^{2nd} groups. (H and I) pS129-positive pathology in primary cortical neurons treated with α Syn strains derived from HC, PD without dementia, and LBD (H), with corresponding quantification (I). (J and K) pS129-positive pathology in primary cortical neurons treated with PBS^{2nd}, PFF^{2nd}, and PM-PFF^{2nd} (J), with corresponding quantification (K). (L and M) Neurotoxicity in primary cortical neurons treated with α Syn strains from HC, PD without dementia, and LBD (L), with corresponding quantification (M). (N and O) Neurotoxicity in primary cortical neurons treated with PBS^{2nd}, PFF^{2nd}, PM-PFF^{2nd} (N), with corresponding quantification (O). Statistics: [(B) and (C)] Data is represented as mean $\pm$ SEM; statistical significance was determined by using one-way ANOVA with Tukey's correction with data at day 7. [(E), (G), (I), (K), (M), and (O)] Data are presented as violin plots showing all individual data points. Statistical significance was determined by using one-way ANOVA with Tukey's correction. * $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$; **** $P < 0.0001$.

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analysis identified similar numbers of differentially expressed genes (DEGs) for PM-PFF ($n = 1222$) and PM_{2.5} ($n = 1205$), followed by PM-PFF with PM_{2.5} exposure ($n = 639$), with the fewest DEGs observed in the PFF condition ($n = 109$) (fig. S20A and table S5). Comparison of DEGs across conditions revealed many distinct and overlapping DEGs (fig. S20B). For example, of the 1205 DEGs identified in the PM_{2.5} condition, 582 were specific to PM_{2.5}, whereas 323 were shared with PM-PFF.

Gene set enrichment analysis (GSEA) further revealed the greatest number of dysregulated gene sets in the PM_{2.5} condition ($n = 365$), followed by PM-PFF with PM_{2.5} exposure ($n = 271$) and PM-PFF ($n = 266$), whereas the PFF condition displayed the fewest dysregulated gene sets ($n = 13$) (table S5). Consistent with the DEGs results, both distinct and shared dysregulated gene sets were observed across conditions (fig. S20C), suggesting that these exposures may perturb both distinct and overlapping biological pathways. For example, of the 365 dysregulated gene sets in the PM_{2.5} condition, 144 were specific to PM_{2.5}, including 11 down-regulated pathways related to cell division, whereas 116 gene sets were shared with both PM-PFF and PM-PFF with PM_{2.5} exposure, all of which were up-regulated and related to immune system pathways.

PM_{2.5} exposure induced gene expression changes in mice resemble those observed in LBD patients

Gene expression changes induced by each experimental condition in mice were compared with those observed in the anterior cingulate

cortex of human individuals with DLB, PDD, and PD without dementia (Fig. 5, B to D). In Fig. 5B, Spearman correlations of log₂(fold change) values of gene expression and the percentages of genes with concordant directional changes are presented for each comparison. For PM_{2.5}-exposed mice, we found the strongest correlation with PDD (correlation coefficient, $r = 0.35$, $P = 1.7 \times 10^{-4}$), followed by a weaker but still significant correlation with DLB ($r = 0.18$, $P = 2.4 \times 10^{-4}$), and no significant correlation with PD without dementia ($r = 0.08$, $P = 0.61$) (Fig. 5C). Additionally, the percentage of genes that changed in the same direction was 67% for PDD ($P = 3.7 \times 10^{-4}$) and 56% for DLB ($P = 0.02$), both of which were significantly higher than the 50% expected by chance. This pattern of gene expression correlation aligns with our epidemiological findings, suggesting that PM_{2.5} exposure has the greatest impact on PDD, followed by DLB, with the smallest effect on PD without dementia.

Gene expression changes induced by PM-PFF in mice more closely mimic LBD patients than those induced by PFF

For gene expression changes induced by PFF-injected mice, we observed weak correlations with both DLB ($r = 0.2$, $P = 0.0028$) and PDD ($r = 0.24$, $P = 0.051$) and no significant correlation with PD without dementia ($r = -0.18$, $P = 0.34$). By contrast, gene expression changes induced by PM-PFF injection showed much stronger correlations with both DLB ($r = 0.37$, $P = 1.3 \times 10^{-15}$) and PDD ($r = 0.46$, $P = 1.2 \times 10^{-6}$), whereas no significant correlation was found with PD without dementia ($r = 0.059$, $P = 0.69$) (Fig. 5, B and D). Furthermore, the percentage

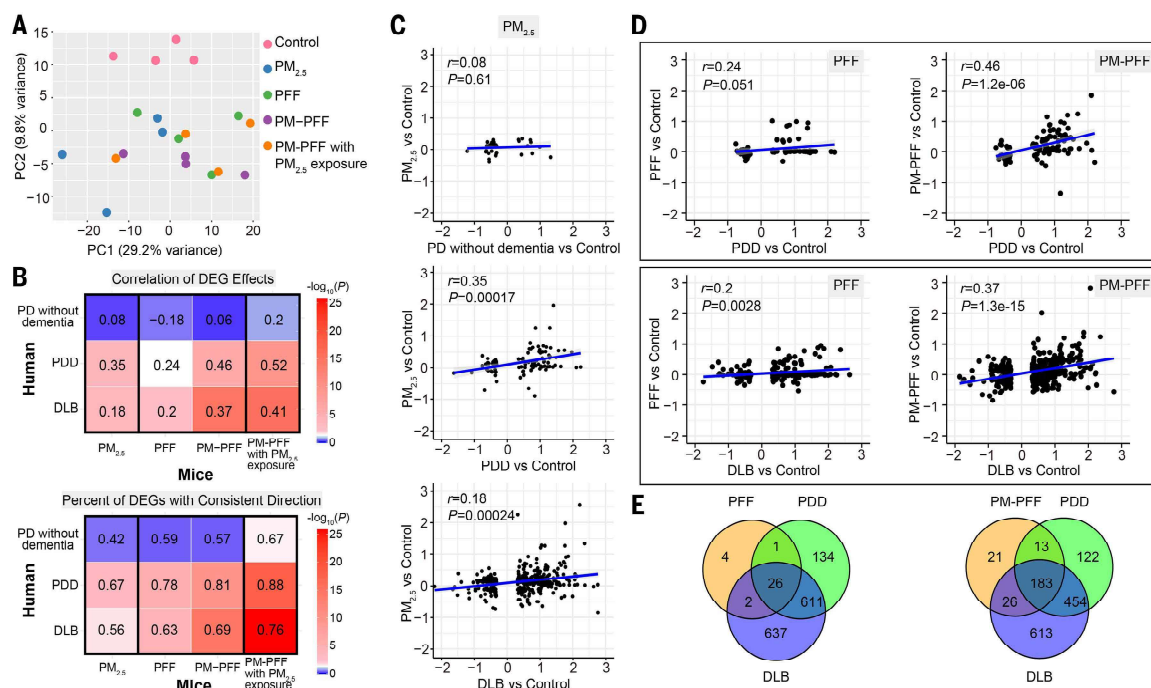


Fig. 5. PM_{2.5} exposure-induced gene expression changes in mice resemble those observed in LBD patients. (A) PCA of gene expression profiles shows clear separation between control samples and those exposed to four conditions: PM_{2.5}, PFF, PM-PFF, and PM-PFF with PM_{2.5} exposure. PM, nasal administration of PM_{2.5} to hWT mice for 2 months; PFF, striatal injection of PFF into hWT mice, followed by 2 months of observation; PM-PFF, striatal injection of PM-PFF into hWT mice, followed by 2 months of observation; PM-PFF with PM_{2.5} exposure, striatal injection of PM-PFF into hWT mice, followed 1 week later by nasal administration of PM_{2.5} for 7 weeks (8 weeks total after injection). (B) Tables comparing DEG signatures between human diseases (DLB, PD without dementia, and PDD) and mouse conditions (PM_{2.5}, PFF, PM-PFF, and PM-PFF with PM_{2.5} exposure). The upper table illustrates the correlation of DEG effect sizes between mice and humans, whereas the lower table shows the proportion of DEGs with consistent direction in effects. Color gradients represent significance levels as $-\log_{10}(P)$, with white color indicating nominal significance ($P = 0.05$). (C) Scatter plot showing the correlation between DEG effect sizes in PM_{2.5}-exposed mice and those observed in PD without dementia, PDD, and DLB patients. Each point represents a gene, with the x axis indicating DEGs effects in humans, and the y axis indicating DEG effects in mice. The shaded area around the blue regression line represents the 95% CI. (D) Scatter plot showing the correlation of DEG effect sizes between PFF- or PM-PFF-injected mice and those observed in DLB and PDD patients. (E) Venn diagram showing the overlap of dysregulated gene sets among PFF- or PM-PFF-injected mice and DLB and PDD patients.

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of genes with concordant directional changes under PM-PFF was 81% for PDD ($P = 1.6 \times 10^{-10}$) and 69% for DLB ($P = 3.7 \times 10^{-15}$), both higher than the 50% expected by chance (Fig. 5B). This stronger correlation with PM-PFF-induced gene expression changes compared with those induced by PFF suggests that PM-PFF more closely resembles the transcriptomic patterns seen in LBD patients. This aligns with our previous findings that PM-PFF exhibits similar features to LBD-derived α Syn strains in terms of biophysical, biochemical, neurotoxic, and pS129-positive α Syn pathology. The similarity in gene expression profiles induced by PM-PFF further validates that PM-PFF functions as an LBD-like α Syn strain, providing additional support for the role of environmental factors, such as PM_{2.5}, in the development of LBD.

Additionally, the PM-PFF with PM_{2.5} exposure condition exhibited the highest correlation and the largest proportion of genes with consistent directional changes for both PDD and DLB (Fig. 5B). This condition closely mimics real-world scenarios, where individuals with PM_{2.5}-induced α Syn seeds are continually exposed to PM_{2.5}, leading to progressive disease pathology. Taken together, these findings suggest a powerful link between PM_{2.5} exposure, the formation of LBD-like α Syn strains, and the development of LBD, highlighting the role of environmental factors in disease progression.

Dysregulation of immune-related pathways underlies both PM-PFF-inoculated mice and LBD patients

To further investigate the biological mechanisms underlying the shared gene expression signatures between PM-PFF-inoculated mice and LBD patients (PDD and DLB), we conducted GSEA with a set of 14,066 homologous genes common to both species (table S6). In PFF-inoculated mice, 33 significant gene sets were identified [false discovery rate (FDR) < 0.05], 29 of which overlapped with gene sets identified in PDD or DLB (Fig. 5E and fig. S21). By contrast, PM-PFF-inoculated mice exhibited a much broader effect on pathways, with 243 significant gene sets (FDR < 0.05), 222 of which overlapped with those in both PDD or DLB (Fig. 5E). These 222 overlapping gene sets were clustered into several major groups (fig. S22), most of which were up-regulated and primarily related to immune system processes. Comparative analysis of enriched pathways between PM_{2.5}- or PM-PFF with PM_{2.5}-exposed mice and LBD patients revealed similar immune-related processes underlying both mouse models and LBD patients (figs. S23 and S24). These results suggest that dysregulation of immune-related pathways plays a central role in the pathogenesis of LBD, further supporting the hypothesis that environmental factors, such as PM_{2.5}, may contribute to LBD development by potentially triggering immune system disturbances similar to those observed in individuals with LBD.

Conclusions

In this study, we explored the role of PM_{2.5} air pollution in promoting LBD and identified an LBD-like PM-PFF strain. Our epidemiological analysis established an association between PM_{2.5} exposure and LBD outcomes, particularly in the context of PDD and DLB. By using transgenic and humanized α Syn mouse models, we demonstrated that PM_{2.5} exposure induces LBD-like pathology, including pS129-positive α Syn aggregation, neurodegeneration, brain atrophy, and cognitive decline.

A key finding of this study is the identification of the PM-PFF strain, which shares biophysical, biochemical, and neuropathological features with α Syn strains derived from LBD patients. Transcriptomic analyses further revealed that gene expression changes induced by PM-PFF in mice closely resemble those observed in individuals with LBD more than those induced by PFF alone. This strong alignment between the PM-PFF strain and LBD-associated gene expression profiles strengthens the conclusion that the PM-PFF strain represents an LBD-like α Syn strain, potentially linking PM_{2.5} exposure to LBD pathogenesis.

Moreover, depletion of α Syn mitigated the pathological and cognitive deficits induced by PM_{2.5} exposure, underscoring the central role of α Syn in PM-induced neurodegeneration. Although our study

confirms α Syn's key role in this process, the absence of a pronounced cognitive difference between WT and α Syn^{-/-} mice under PM_{2.5} exposure suggests that longer observation periods may be necessary for PM_{2.5} exposure-induced deficits. Additionally, other prion-like proteinopathies, such as tau and amyloid- β , may contribute to PM_{2.5} exposure-induced deficits.

Recent studies have demonstrated a strong association between PM_{2.5} exposure and neurodegenerative diseases, highlighting mechanisms including α Syn aggregation, neuroinflammation, and gut-brain axis disruption. However, these studies primarily focused on the links between PM_{2.5} and either AD or PD (69–72). These findings reinforce the role of PM_{2.5} in AD and PD pathogenesis; our study further expands this understanding by emphasizing the impact of PM_{2.5} exposure on α -synucleinopathy-associated dementia, including PDD and DLB.

Limitations of the study

Despite these findings, the following limitations should be noted in the context of an epidemiological study. First, our analysis used first hospital admissions as outcomes, which can only be interpreted as increased need for inpatient care and accelerated disease aggravation associated with higher PM_{2.5} exposure. Hospital admission data did not allow us to examine the relationship between PM_{2.5} and true disease onset or incidence. Furthermore, hospital admission records may miss some cases of disease aggravation and misclassify certain non- α -synucleinopathy outcomes. However, they capture a substantial number of α -synucleinopathy cases progressing to a severe disease stage, as indicated by clinical studies on LBD and PD hospitalizations (73, 74). Second, using ICD codes in Medicare records to identify disease outcomes is subject to outcome misclassifications, which could either over- or underestimate the number of outcomes in the study population (75–77). The large scale of this analysis prevents us from reviewing and applying consensus diagnostic criteria to individuals' clinical or medical records. However, we presented a single outcome combining all first hospital admissions with α Syn-related disorders (including PD without dementia and LBD) and used multiple criteria defined by different sets of ICD codes to identify PD without dementia and LBD outcomes. The consistency across results from multiple sensitivity analyses showed the robust relationship between PM_{2.5} exposure and the aggravation of α -synucleinopathies. Third, determining the exposure window during which air pollution increases the risk of hospital admissions for α -synucleinopathies is challenging. However, through analyses that used different exposure windows, we found consistent associations between PM_{2.5} and the risk of hospital admissions for all four α -synucleinopathies, regardless of the chosen window. Fourth, exposure measurement error could potentially affect effect estimates. In this study, PM_{2.5} exposure was estimated from a well-validated ensemble prediction model (78). Although the model demonstrated excellent overall accuracy, its performance varied across different US regions, partly owing to the limited number of monitoring sites. To this end, in a region-specific analysis of four geographic US regions—Northeast, South, Midwest, and West—the results were generally consistent across regions. Yet, in the Northeast, we observed a strong association with PD outcomes but a substantially weaker association with DLB outcomes, warranting further investigation. Furthermore, ZIP code-level PM_{2.5} exposure may not fully represent accurate residential address or personal exposures of each beneficiary. Several studies have used personal exposure measurements to correct exposure measurement error in studies of comparable populations (79, 80). Empirical evidence indicates that assigning larger-scale ambient air pollution exposure to individuals typically biases results toward the null, consistent with theoretical analyses based on nondifferential measurement error (81). However, real-world scenarios may involve both nondifferential and differential measurement error. The use of ZIP code- and personal-level PM_{2.5} exposure involves trade-offs. When exposure estimates are not at the individual level, they are less prone

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to confounding biases from personal factors that are difficult to control, such as individual-level socioeconomic and behavioral risk factors (82). Fifth, nearly one-fifth of Medicare beneficiaries changed their residential ZIP codes at least once between 2000 and 2014. Because we updated exposure data for each beneficiary every year, their movement did not affect our exposure assessment (83). To this end, a sensitivity analysis of Medicare beneficiaries who did not move throughout the follow-up period (referred to as nonmovers) showed results largely consistent with the main analysis, with only a slight attenuation in effect sizes, suggesting that residential mobility during the study did not substantially alter the observed associations between PM_{2.5} exposure and α -synucleinopathies. Acknowledging the limitations of the epidemiological study, we do not interpret its results as confirmatory or causal; rather, they serve as the key foundation for the subsequent laboratory study.

In addition to the epidemiological study limitations, there are also inherent limitations in our laboratory study. We cannot conclude whether PM_{2.5} exposure preferentially influences the trajectory of DLB or PDD, as this may involve complex interactions between specific PM_{2.5} species and genetic factors. Key distinguishing features of DLB, such as autonomic dysfunction and rapid eye movement sleep behavior disorder, may also manifest in PM_{2.5}-exposed mice, which warrants further evaluation in future studies. Regardless, we applied nasal administration rather than whole-body exposure for PM_{2.5}. We acknowledge that nasal administration differs from inhalation, as it delivers a high dose over a short period rather than continuous low-dose exposure, and the exposure route and subsequent systemic distribution vary slightly. However, because of the large sample requirements and high material loss associated with whole-body exposure, we opted for nasal administration in this study. To ensure rigor, the PM_{2.5} dose used in our study was precisely calculated (see materials and methods) and is comparable to inhalation exposure in polluted urban environments. Furthermore, previous research (84) has shown that, at equivalent doses, initial lung burdens of nanoparticles were similar between instillation and inhalation, though instillation led to greater short-term retention. In the future, our research aims to explore chronic whole-body exposure models for a more accurate representation of real-world exposure.

Overall, these findings establish a mechanistic link between PM_{2.5} exposure and the development of LBD, with the PM-PFF strain emerging as a potential environmental intervention target. Further investigation into specific PM_{2.5} chemical components and their distinct effects on neurodegenerative diseases is warranted, given the spatial and temporal variation in PM_{2.5} chemical composition across the US (85). A more comprehensive integration of medical records, gene-environment interactions, and human epidemiological and neurobiological studies would enhance our understanding of how environmental pollutants contribute not only to the progression but also to the onset of LBD and related disorders.

Materials and methods

Data procedures for epidemiological studies

We used ICD codes to identify patients who had a first admission with primary or secondary diagnoses corresponding to DLB (ICD-9: 331.82; ICD-10: G31.83) and PD (ICD-9: 332.0, 332.1; ICD-10: G20, G21.11, G21.19, G21.3, G21.4, G21.8, G21.9) in hospital admissions among US Medicare beneficiaries during the study period of 2000–2014. Given that the US officially transitioned to ICD-10 on October 1, 2015, most diagnoses recorded during the study period were coded using the ICD-9 categorization scheme. For the four α -synucleinopathy related outcomes considered, PD and DLB diagnoses were given to patients who had a first hospital admission with a diagnosis of PD and DLB, respectively. PDD diagnosis was given to patients with a prior diagnosis of PD and who had a first hospital admission with a dementia diagnosis (ICD-9: 294.10, 294.11; ICD-10: F02.80, F02.81) at least one

year after the PD diagnosis in the follow-up years. PD-without dementia patients are defined as patients who had a first hospital admission with a PD diagnosis during the study period yet without identifying any dementia diagnosis during their entire follow-up period. Various sensitivity analyses were performed to assess the robustness of the findings to different uses of ICD codes, including: (i) excluding secondary parkinsonism diagnoses from PD diagnosis; (ii) combining PD without dementia and LBD diagnoses into a single category for α Syn-related disorder diagnosis; and (iii) restricting the analysis to dementia patients who had to have a primary diagnosis of PD or DLB and a secondary diagnosis of dementia in one admission.

We obtained daily PM_{2.5} concentrations at a high spatiotemporal resolution using a 1-km² grid network across the contiguous US and a well-validated ensemble-based prediction model (58). This model used ensemble-learning approaches to combining three machine learning models: a random forest regression, a gradient boosting machine, and an artificial neural network. These machine learning algorithms used more than 100 predictor variables from satellite data, land-use information, weather variables, and output from chemical transport model simulations. The ensemble-based model was trained and calibrated using daily PM_{2.5} concentrations from 2,156 monitoring sites in the US Environmental Protection Agency's (EPA's) Air Quality System database and the IMPROVE monitoring network. It achieved an average cross-validated R² of 0.86 for daily PM_{2.5} predictions and 0.89 for annual predictions, with performance ranging from 0.77 in mountainous regions of the USA to 0.92 in the eastern Midwest, demonstrating excellent prediction performance.

Residential addresses are not available for Medicare enrollees, only residential ZIP Codes. For each standard ZIP Codes, we used zonal statistics to calculate the daily average PM_{2.5} concentration based on all 1-km² grid cell predictions within the ZIP Codes via aggregations. More specifically, we first overlaid the ZIP Codes boundaries to the 1-km² grid cells and then averaged the predictions at 1-km² grid cells whose centroids fall within the boundary of that ZIP Codes (59). For P.O. Box-only ZIP Codes, the average PM_{2.5} concentrations were calculated by linking to the predictions from the nearest 1-km² grid cell. Based on these results, we estimated the annual ZIP Code average and assigned the ZIP code-wide annual PM_{2.5} concentration means to Medicare beneficiaries according to the ZIP Code of residence and calendar year. PM_{2.5} exposure was assigned to patients for each follow-up year using various exposure windows, based on the time-varying average PM_{2.5} concentrations within the specified window preceding their first hospital admission with a α -synucleinopathy diagnosis. In the US, the mean population per ZIP Code is approximately 7500. Each postal code can cover a small area in cities but can be larger in rural areas. The median land area of a ZIP Code is around 92 km².

We collected neighborhood-level socioeconomic status and behavior risk factors, available at county- or ZIP Code tabulation areas (ZCTA)-level, which have both been associated with ambient air pollution and implicated in neurological health. These variables derived from the Behavioral Risk Factor Surveillance System from 2000 to 2014, the 2000 and 2010 US Census, and the American Community Survey for each year from 2005 to 2014. Specifically, we included (i) two county-level behavior risk variables: average body mass index and smoking rate; (ii) eight ZIP Code-level socioeconomic status and demographic variables: proportion of Hispanic residents, proportion of Black residents, median household income, median home value, proportion of residents in poverty, proportion of residents with a high school diploma, population density, and proportion of residents that own their house; and (iii) four ZIP Code-level meteorological variables: the summer (June to September) and winter (December to February) averages of maximum daily temperatures and relative humidity. We obtained ZIP Code-level meteorological variables using area-weighted aggregations based on daily temperature and humidity data on 4-km² gridded

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rasters from Gridmet via Google Earth Engine. We also considered two indicator variables indicating (i) the four geographic regions of the US (Northeast, South, Midwest, and West) and (ii) calendar years to adjust for residual spatial and temporal confounding, respectively.

Statistical analysis

We applied Cox-equivalent reparameterized Poisson models for each of the four outcomes with parallel computing. The Poisson re-parameterization, although mathematically equivalent to conventional Cox proportional hazards models (86), addresses the computational challenges faced by the conventional time-varying Cox proportional hazards model in such large data (3). Specifically, we fit a stratified quasi-Poisson model to estimate associations between the stratified rates of first hospital admissions with diagnosis codes of neurodegenerative disorder and time-varying annual mean PM_{2.5} concentrations. The dependent variable was the count of outcome-related hospital admissions in each follow-up year, calendar year, and postal code location within strata specified by individual characteristics, using the corresponding total person-time of Medicare-fee-for-service beneficiaries as the offset. By stratifying on individual characteristics—sex, race, Medicaid eligibility, and age at study entry in 5-year categories—we allowed for flexible strata-specific baseline rates. To account for correlated observations from patients within the same ZIP Code across years, we applied an m-out-n bootstrap method using ZIP Code units to calculate CIs.

To adjust for potential confounding, we included area-level social economic, behavior risk factors, and meteorological variables in our analyses. To account for potential residual confounding by spatial and temporal trends, we included indicator variables for region and calendar years. The Anderson-Gill model was used to model time-varying covariates and address left truncation (87). This approach ensures that individuals contribute risk time only after entering and before exiting the open cohort, effectively handling lefts truncation due to individuals must survive until age 65 to become eligible for Medicare.

PM_{2.5} sampling

Fine particulate matter (PM_{2.5}) samples for this study were collected from three locations across Asia, North America, and Europe, representing typical PM_{2.5} exposure in urban environments. A comparison of these samples is presented in table S3.

For atmospheric PM_{2.5} collected from China (PM_{2.5}-1), samples were obtained from March 2011 to February 2013 in Baoji, Shaanxi, China. The site is to the east of Baoji city and next to a commercial center where there is heavy traffic, but no industries are nearby. Other possible sources include open and residential biomass burning, and coal combustion processes for residential heating and energy generation. The sampler was set up 10 m above the ground on the rooftop of the Baoji Municipal Environmental Protection Bureau. PM_{2.5} samples were collected with mini-volume samplers (Airmetrics, Oregon, USA) with a flow rate of 5 L min⁻¹ for 24 hours. The sampling was conducted every 6 days and a total number of 64 samples were collected. The PM_{2.5} samples were collected on 47-mm quartz fiber filters (Whatman QM/A, Maidstone, UK), that were pre-combusted at 900°C for 3 hours. To minimize the evaporation of volatile components, each loaded sample filter was placed in a clean polystyrene petri dish and stored in a refrigerator at <4°C prior to analysis.

Additional atmospheric PM_{2.5} samples (PM_{2.5}-2) were collected in the US, from the South Dekalb (SDK) site located in Atlanta, GA (33.6878°N, 84.2905°W). The SDK site is operated by the Georgia Environmental Protection Division (EPD) (88), and serves as a Southeastern US urban background site in the Atmospheric Science and Chemistry mEasurement NeTwork (ASCENT). This site is heavily forested with surrounding residential properties. However, it can be influenced by local traffic (Interstate I-285) and episodically biomass burning events. A major airport is located ~10 km to the southwest of the site. A total of two weeks

of sampling was conducted from 9 to 22 February 2024. PM_{2.5} filter samples were collected over a one-week period on 47-mm PTFE filter (Teflo, Pall, USA) using a mini-volume sampler (URG-2000-30EH, URG, USA). The flow rate of the mini-volume sampler was 16.7 lpm.

The standard atmospheric PM_{2.5} were purchased from Sigma-Aldrich (NIST2786, St. Louis, MO, USA; PM_{2.5}-3), which was prepared from atmospheric PM_{2.5} collected from the air intake filtration system of a large exhibition center in Prague, Czech Republic in 2005. The collected total suspended particulates were resuspended, and a cyclone was used to remove coarse particles. This atmospheric PM_{2.5} was certificated as Standard Reference Material by National Institute of Standard & Technology (NIST) in July 2021. The NIST2786 standard material was previously characterized for mass fractions of selected organic and inorganic constituents (89).

The filter membranes were cut into small pieces and sonicated in methanol: dichloromethane (2:1) for 20 min at 25% amplitude with 0.5-s pulse on/off cycle (Branson Digital Sonifier SFX 250, Danbury, CT, USA) to obtain an extract of total PM_{2.5}. Subsequently, the liquid containing PM_{2.5} was placed in a Savant SpeedVac Vacuum Concentrator (Thermo Fisher Scientific, Grand Island, NY, USA) to evaporate the solvent. Maintain the sample under vacuum at 60°C for 2 hours to obtain the dried total PM_{2.5}. The mass of the PM_{2.5} is determined by measuring the difference in mass between the empty centrifuge tube and the tube containing the dried sample. The resulting sample was resuspended in Endotoxin-Free Dulbecco's PBS (TMS-012-A, Sigma-Aldrich, St. Louis, MO, USA) at a final concentration of 5 mg/mL and stored at -20°C. Suspensions were sonicated for 30 s before use.

The PM_{2.5} used in Fig. S13 and S15 are PM_{2.5}-1, PM_{2.5}-2, and PM_{2.5}-3, whereas for the other figures, unless otherwise specified, PM_{2.5}-1 was used.

Animal procedures

The following mouse strains (*Mus musculus*) were used: The C57BL/6 wildtype mice (strain 000664), hWT α Syn mice (strain 010710), hA53T transgenic mice (strain 006823), and α Syn^{-/-} mice (strain 003692) were obtained from The Jackson Laboratory. App^{NL-G-F}/MAPT dKI (Strain Name: B6.Cg-Mapt<tm1.1(MAPT)Tcs>App<tm3(NL-G-F)Tcs>) mice were provided by Dr. Takaomi Saido (90–92). Animals were housed in ventilated cages with unlimited access to food and water. All the procedures were approved by the Johns Hopkins Animal Care and Use Committee and carried out following the guidelines from NIH for Care and Use of Experimental Animals.

Intranasal treatment with PM_{2.5}

The mouse was gently restrained by the scruff, positioning it in a supine state with the head slightly tilted backward. A pipette was then used to slowly administer 2 μ L of PM_{2.5} suspension (5mg/mL in PBS) into the nostrils once every two days, whereas the mouse was kept in the supine position until the PM_{2.5} was absorbed. According to the high-resolution PM_{2.5} exposure dataset used in epidemiological studies, the average concentration of PM_{2.5} in the contiguous US is 9.7 μ g/m³. Adult mice, with a characteristic minute ventilation rate of 11–36 ml min⁻¹, inhale 0.15–0.5 μ g of PM_{2.5} per day at this exposure amount (93). The dosage of PM_{2.5} administered intranasally to the mice corresponds to an inhalation exposure of 100–300 μ g/m³ PM_{2.5}, a concentration one order of magnitude higher than the US average, but still atmospherically relevant during pollution events, such as urban haze episodes (94) and wildfires (94, 95). We acknowledge that nasal instillation delivers a high dose over a short period, differing from continuous inhalation exposure at a lower dose rate. A previous study (84) suggested that, at equivalent doses, initial lung burdens of nanoparticles were similar between instillation and inhalation, though instillation led to greater short-term retention. Nevertheless, the nasal instillation method was adopted in this study as it requires a lower amount of material, enabling us to examine the effects of authentic fine particulate matter rather than engineered nanoparticles.

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Stereotaxic injection of PFF and PM-PFF: Two- to 3-month-old hWT α Syn mice (FVB; 129S6-Sncat^{tm1Nbm} Tg (SNCA)1Nbm/J, Strain: 010710), obtained from The Jackson Laboratory (Bar Harbor, ME, USA), were used to identify the distinct propagation patterns of PFF and PM-PFF. Mice were deeply anesthetized with a ketamine mixture (100 mg/kg) and then secured on a stereotaxic apparatus. Unilateral injections of either PFF (10 μ g) or PM-PFF (10 μ g) were administered into the striatum at the following coordinates: anterior-posterior (AP), +0.2 mm; medial-lateral (ML), +2.0 mm; dorsal-ventral (DV), +2.8 mm (relative to the bregma). Mice injected with PBS served as the control group. The injections were performed using a 2 μ L syringe (Hamilton, Reno, NV, USA) at a rate of 0.2 μ L/min, and the needle was left in place for 10 min after injection to ensure complete absorption of the solution. The needle was then withdrawn at a rate of 0.2 mm/min. Postoperative monitoring and care were provided to the mice. Behavioral tests were conducted 6 months after surgery. All mice were euthanized, and tissues were collected for biochemical and histological analyses. Notably, for biochemical analyses, tissues were frozen and stored at -80°C. For histological analyses, mice were perfused with PBS and 4% PFA and transferred to 30% sucrose for cryoprotection (14, 17, 96).

Immunohistochemistry, immunofluorescence, mapping of α Syn pathology, and volumetric analysis

Immunohistochemistry (IHC) and immunofluorescence (IF) staining were performed on 30 μ m thick serial brain sections. The primary antibodies and their working dilutions were detailed in Table S8. For IHC studies, the blocked sections were incubated with primary antibodies against phosphorylated p- α Syn or tyrosine hydroxylase, followed by incubation with biotin conjugated anti-mouse/anti-rabbit antibodies (Vector Laboratories, Burlingame, CA, USA), Avidin-Biotin Complex (ABC)-HRP Detection Kit (Vector Laboratories, Burlingame, CA, USA), and ImmPACT® DAB Substrate Kit (SK-4105, Vector Laboratories, Burlingame, CA, USA). The sections were then counterstained with Nissl (0.09% Thionin), dehydrated in graded alcohols and xylene, then mounted with DPX (06522, Sigma-Aldrich, St. Louis, MO, USA). IHC images were captured using an AxioCam Mrc camera connected to an Observer. Z1 microscope (Zeiss, Oberkochen, Germany). For IF staining, the sections were blocked in 10% goat serum for two hours before being transferred to primary antibodies and incubated overnight at 4°C. After washing with PBST, the sections were incubated at room temperature (RT) for four hours with appropriate secondary antibodies conjugated to Alexa-Fluor 488, 568, or 647, along with Hoechst. Following washes with PBST, the sections were mounted. IF images were acquired using a Keyence Microscope (BZ-X710, Itasca, IL, USA) and a confocal scanning microscope (LSM880, Zeiss, Dublin, CA, USA). All images were analyzed and quantified using the Fiji distribution package of ImageJ. The mapping of pS129 was performed by capturing images at 4x magnification using a Keyence microscope and subsequently stitching these images together to obtain whole brain images. The distribution of pS129 was then plotted based on the average distribution across 4 samples for each group. These sections corresponded at approximate +4.28, +2.68, +0.86, -0.58, -1.34, -2.06, -2.54, -3.28, -5.52, and -7.64 relative to Bregma. For volumetric analysis, every 10 coronal brain section (300 μ m between sections) starting rostrally at bregma +0.14 mm to bregma -2.92 mm was mounted for each mouse. All mounted sections were stained with 0.09% Thionin at RT for 20 minutes, then washed in ultrapure water, formic acid, 80%, 90%, 100%, 100% ethanol, xylene, xylene for 10 minutes. The sections were finally mounted with DPX. The stained slices were imaged with the Keyence. The volume was calculated using the following formula: volume = (sum of area) $\times$ 0.3 mm. For hippocampus, quantification started from bregma -1.22 mm and ended at bregma -2.92 mm. For posterior lateral ventricle, quantification started from bregma 0.14 mm and ended at bregma -2.92 mm. For entorhinal cortex, quantification started at bregma -2.3 mm and ended at bregma -2.92 mm. Sholl

analysis was manually performed for analyzing the morphology of microglia (36–38).

α Syn purification and PFF and PM-PFF preparation

The purification process for recombinant human α Syn monomers was carried out as described in previous studies. In brief, pRK172- α Syn plasmid was transduced in BL21 (DE3) cells and cultured overnight at 37°C. This culture was then scaled up in LB broth containing ampicillin and centrifuged to collect *Escherichia coli* pellets. For lysis, the pellets were resuspended in osmotic shock buffer and homogenized, followed by osmotic shock and centrifugation to remove cell debris. The clear supernatant was then dialyzed against buffer to remove impurities. α Syn monomers were purified using fast protein liquid chromatography on an anion exchange column, collecting fractions that contain the target protein. Subsequently, bacterial endotoxins were removed from the purified α Syn monomers using the ToxinEraser Endotoxin Removal Kit (L00338, GenScript Biotech Corp., Piscataway NJ, USA). The α Syn monomer solution was centrifuged at 12,000 rpm for 20 min at 4°C to remove aggregates, and the supernatant was transferred to a new Eppendorf tube. The α Syn monomers were dissolved in PBS at a concentration of 2 mg/mL and incubated at 37°C while stirring at 1,000 rpm for 7 days to generate PFF. The fibrils were sonicated for 30 s (0.5-s pulse on/off cycle) at 20% amplitude before use. PM-PFF was prepared as described above by adding 5% PM_{2.5} in α Syn fibrillization reaction. All the α Syn monomer, PFF and PM-PFF were kept at -80°C. The purity was assessed using Coomassie brilliant blue staining and immunoblot (14, 17, 96).

Behavioral analysis

Behavioral analyses were performed 10 days prior to the euthanasia of mice to assess behavioral deficits induced by PFF, PM-PFF, and PM_{2.5} exposure. Tests conducted included the pole test, open field, nest building, grip strength, Y-maze, and novel object recognition. Sample sizes were determined based on previously published studies using similar experimental paradigms. To minimize bias, animals were administered by experimenters who were blinded to the treatments and randomly assigned to groups. Mice that developed infections due to treatment and required euthanasia prior to the experimental endpoint were excluded from analysis.

Pole test: In the pole test, a metal rod, 75 cm in length and 9 mm in diameter, wrapped in adhesive gauze, was utilized. The rod was cleaned with 70% ethanol before and after each test. Mice were placed 7.5 cm from the top of the pole with heads upward. On the first day, mice were induced to turn and descend to the bottom of the pole 3 times; on the second day, unguided training was conducted 3 times; on the third day, the time required for turns and the total time to reach the bottom were recorded for 3 times. The maximum cutoff time for ending the experiment was set at 2 min. Both turnaround time and total time were reported (13, 14, 16, 17, 96).

Open field: For the open field test, an apparatus consisting of a cubic plastic box (40 cm $\times$ 40 cm $\times$ 40 cm), divided into 36 equal areas (6.6 cm $\times$ 6.6 cm), was used. The field was subdivided into central and peripheral areas, with the central area comprising four central squares (2 $\times$ 2). Prior to testing, mice were placed in the apparatus room to acclimatize for about 30 min. Then, the mice were allowed to freely explore the box for 30 min. The field was cleaned with 70% ethanol between each test. A tracking system (PAS software) monitored the mice's trajectories, recording the beam breaks as an assessment of locomotor activity. Counts occurring in the center served as an anti-anxiety index (13, 52, 53, 59).

Nest building: The nesting test was conducted using a standard method. Mice were required to use orofacial and forelimb movements, such as pulling nesting material apart with forelimbs and teeth and

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incorporating shredded material into their bedding. Briefly, mice were individually placed in a cage containing a new 2.5 g nestlet (5 cm × 5 cm, Johns Hopkins Medical Research Animal Resources Center, Baltimore, MD, USA). Nest building scores were evaluated after 16 hours (13, 25–27).

Grip strength: Grip strength testing, an indicator of neurodegenerative disease progression, was performed by placing a grid-equipped dynamometer on a table. Mice were gently held by the tail with their forelimbs or all limbs on the grip strength grid. The mice were gently pulled downward, and the maximum reading displayed by the dynamometer was recorded (13, 14, 16, 17, 96).

Y-maze: The Y-maze was used to assess the spatial memory of mice. The Y-shaped maze consisted of three symmetric arms, each 40 cm long, 10 cm wide, and 15 cm high, with adjacent arms forming a 120-degree angle. During the training phase, one arm (novel arm) was blocked with a removable barrier, allowing mice to freely explore from the starting arm to familiar arm for 8 min. After training, mice were returned to their home cages. Two hours later, the test was conducted by removing the barrier, and mice were again placed in the starting arm to freely explore all three arms. The Y-maze was cleaned with 70% ethanol between successive tests. The Any-Maze software recorded and analyzed the time spent in the novel arm, total distance moved, and alternation count (13, 53, 54).

Novel object recognition: The novel object recognition test was conducted following previously reported methods. The apparatus, an opaque polyethylene plastic box (45 cm wide × 45 cm deep × 50 cm high) was used. Initially, all mice were placed in the box without any objects for five minutes. Two identical objects (Object A) were then placed in the box, and mice were allowed to explore for five minutes. The time spent by the mice on each object was recorded during the training session. One hour after training, one Object A was replaced with a new Object B, identical in material and size but different in shape. Mice were then placed in the box to explore for five minutes, and the time spent on Object A or B was recorded (defined as the short-term test phase). The box and objects were cleaned with 70% ethanol after each trial. The video tracking system (ANY-Maze software) recorded the mice's behaviors, considering sniffing, biting, or facing the objects as exploratory activities. Data were defined as the percentage of new object performance = time spent on new Object B / (time on Object A + time on new Object B) × 100 (13, 55, 56).

Amplification of pathogenic α Syn with seeding amplification assay (SAA)

The amplification of α Syn strains from mouse brain homogenates were performed using SAA method by referring to previous work (23). The SAA equipment included a microplate horn (431MPX), a sound enclosure (432MP), and a thermoelectric cooler (4900) purchased from Qsonica (Qsonica, Newtown, CT, USA). Briefly, recombinant α Syn monomers were centrifuged at 100,000 g for 30 min at 4°C to remove any preformed aggregates before use. The α Syn was then diluted in SAA buffer (1% Triton X-100 in PBS) and 100 μ L was transferred to PCR tubes containing an appropriate amount of silicon beads ($d = 1.0$ mm, 11079110z, BioSpec Products, Bartlesville, OK, USA), with 10 μ L of insoluble brain homogenate or CSF samples from LBD patients (5 PDD and 2 DLB), PD without dementia patients ($n = 5$) or health control (HC, $n = 5$) added as a seed. The final concentration of α Syn was 0.5 mg/mL. After mixing, the samples were subjected to sonication (amplitude: 5; 40 s sonication followed by incubation at 37°C for 29 min and 20 s). The amplification monitored by measuring the ThT fluorescence.

ThT fluorescence assay

A 5 μ L aliquot of the sample was added into 55 μ L ThT solution (20 μ M). Subsequently, the mixture was dispensed in triplicate into a 384-well black/clear bottom plate (P6491, Sigma-Aldrich, St. Louis, MO, USA).

The fluorescence was measured using a microplate reader (Varioskan LUX microplate reader, Thermo Fisher Scientific, Grand Island, NY, USA) with excitation/emission at 450/485 nm (23).

CD spectroscopy measurements

The far-UV CD spectra of PFF and PM-PFF were recorded using a spectrophotometer (Aviv 420, Aviv Biomedical, Lakewood, NJ, USA) in a 1 mm path length cuvette. The scanning range was set from 190 to 250 nm at 25°C, with a scan speed of 50 nm/min, data interval of 1 nm, and bandwidth of 2 nm. The average of three scans was taken for all spectra. Noise in the signal was reduced using Origin software to smooth the CD data (97).

PK digestion, dot blot, and silver staining

The SAA amplified samples (8 μ g) or PFF (8 μ g) were mixed with 1 μ L PK (0.1 mg/mL) and PBS to achieve a final volume of 20 μ L. The mixture was incubated in a water bath at 37°C for various time points (0, 5, 15, and 30 min) and the digestion was terminated by the addition of 2 μ L of PMSF (40 mM). For dot blot assay, 2 μ L of the PK-digested samples were loaded onto the nitrocellulose membrane (1620112, Bio-Rad, Hercules, CA, USA) and blocked with 5% milk (1706404XTU, Bio-Rad, Hercules, CA, USA) in TBST for one hour at RT. The membrane was then incubated with mouse anti- α Syn monoclonal antibody (mAb) (1:2000, 610787, BD Biosciences, Franklin Lakes, NJ, USA) at 4°C overnight. After washing with TBST (four times, 10 min for each) the membrane was incubated with anti-mouse IgG-HRP (1:5000, 31430, Thermo Fisher Scientific, Grand Island, NY, USA) at RT for one hour. Following additional TBST washes, the chemiluminescent signal was developed using SuperSignal West Pico Plus chemiluminescent substrate (34096, Thermo Fisher Scientific, Grand Island, NY, USA). All images were processed using an Amersham Image 600 (GE Healthcare Life Sciences, Chicago, IL, USA) (23).

Primary neuronal culture and PFF and PM-PFF transduction

CD1 mice were obtained from the Jackson Laboratory (Bar Harbor, ME, USA). Primary cortical neurons were extracted from the cortex of E15.5 embryos, with careful removal of the meninges and hippocampus. The dissected tissues were then digested in 0.25% trypsin-EDTA at 37°C for 15 min in a water bath. Gently pipetting into a single-cell suspension, then passed through a 40 μ m nylon mesh. The single-cell suspension was seeded on tissue culture plates pre-coated with poly-L-lysine and cultured in Neurobasal medium supplemented with B27, 0.5 mM L-glutamine, penicillin and streptomycin. The inhibitor 5-Fluoro-2'-deoxyuridine (1 mM) was added 3 days after seeding. After culturing in vitro for 7 days, primary neurons were treated with sonicated PFF/PM-PFF at a final concentration of 5 μ g/mL, incubating for another 10 or 21 days before pathological or toxicity assay (14, 17, 96).

Human RNA-seq data processing

We obtained raw FASTQ files from a previous study (24) that performed bulk RNA sequencing of anterior cingulate cortex samples from 6 PDD, 6 DLB, 7 PD patients, and 6 non-neurological control samples. We processed the FASTQ files using the SPEAQueasy (98) RNA-seq pipeline, which integrates several bioinformatics tools to convert raw FASTQ files into ready-to-use R objects for differential gene expression analysis. In brief, reads were initially quality checked with FastQC (24, 99) v0.11.8, followed by trimming with Trimmomatic (100) v0.39 when necessary. The quality-checked reads were then aligned to the human reference genome (hg38/GRCh38) using HISAT2 (101) v2.2.1. Finally, gene-level expression was quantified using featureCounts (102) based on GENCODE release 25 annotations.

Mouse RNA-seq

RNA was extracted from the anterior cingulate cortex of mice treated under each condition, with four replicates per condition. 2-month-old

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hWT α Syn mice (FVB; 129S6-Snca^{tm1Nbm} Tg (SNCA)1Nbm/J, Strain: 010710), obtained from The Jackson Laboratory (Bar Harbor, ME, USA), were used for RNA sequencing experiments. The mice were divided into five groups: the PBS group (intranasal administration of PBS), the PM_{2.5} group (intranasal administration of PM_{2.5}), the PFF group (PFF injection), the PM-PFF group (PM-PFF injection), and the PM-PFF with PM_{2.5} exposure group (PM-PFF injection followed by intranasal PM_{2.5} administration one week later). All treatments were administered for a duration of 2 months. Sequencing libraries were prepared using the RNeasy Lipid Tissue Mini Kit, following the manufacturer's protocol. The RNA-seq data were processed using the same SPEAQueasy RNA-seq pipeline, with reads aligned to the mouse genome (mm10) and gene-level expression quantified based on GENCODE release M25. For PCA of mouse RNA-seq profiles, lowly expressed genes were first filtered out using the filterByExpr function from the edgeR (103) package. The filtered data were then normalized using the trimmed mean of M-values (TMM) method, implemented in the calcNormFactors function. PCA was performed on the mouse RNA-seq data using the top 500 most variable genes, determined by variation of expression concentrations measured as log₂ normalized counts per million (CPM) across samples.

Differential gene expression analysis

Differential gene expression analysis for both human and mouse RNA-seq datasets was conducted using the DESeq2 (104) package. We retained genes with at least 10 reads in at least 6 samples for the human dataset and in at least 4 samples for the mouse dataset. For the human RNA-seq data, we adjusted for potential confounders in the regression model, including sex, age at death, postmortem interval (PMI), and RNA integrity number (RIN). We only included condition status for the mouse data in the regression model to detect group difference of gene expression. To enhance visualization and ranking of genes, we applied the apeglm method (105) for effect size (Log₂FC) shrinkage implemented in DESeq2.

Gene set enrichment analysis

GSEA was conducted using the clusterProfiler (106) package, focusing on gene sets from Gene Ontology (GO) related to biological processes. We set the minimum gene set size (minGSSize) to 20 and the maximum gene set size (maxGSSize) to 500. The input for GSEA was a ranked gene list derived from the shrunken effect sizes obtained with DESeq2. The R package 'aPEAR' (107) was used to identify clusters of similar gene sets detected by GSEA, utilizing the default parameters of the "enrichmentNetwork" function for gene sets clustering and network visualization.

Comparison of transcriptional responses in mice and human patients

We compared the transcriptional responses in mice under each condition to those in human patients with PDD, PD without dementia, and DLB. Following a previously published approach (108), comparison was limited to genes that showed differential expression in humans, defined by a *p*-value < 0.05 and an absolute effect size (log₂FC) greater than 1.2. To ensure a sufficient number of genes for cross-species comparison, we included mouse genes with only nominal evidence of differential expression (*p*-value < 0.05) without restricting the magnitude of effect sizes. The strength of correlation was assessed using Spearman correlation. We applied a binomial test to assess the statistical significance of the percentage of genes with consistent directional effects between mice and humans, assuming an expected 50% consistency by chance.

Quantification and statistical analysis

All data (except epidemiological and transcriptomic data) were analyzed using GraphPad Prism 8. Statistics Data are presented as the mean $\pm$ standard error of the mean or presented as violin plots showing all individual data points. Representative morphological images

were obtained from at least three experiments with similar results. Statistical significance was assessed via a *t* test or one-way analysis of variance (ANOVA) test followed by indicated post-hoc multiple comparison analysis. Assessments with *P* < 0.05 were considered significant.

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SUPPLEMENTARY MATERIALS

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Figs. S1 to S24; Tables S1 to S8

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