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The retinal age gap-particulate hypothesis: environmental exposure as a latent contributor to deep learning-based retinal age prediction

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Abstract

Deep learning models applied to retinal fundus photographs and optical coherence tomography (OCT) can predict chronological age with remarkable accuracy. The discrepancy between predicted and chronological age is termed the "retinal age gap", and it is associated with mortality and multiple systemic diseases. However, the biological and physical correlates underlying these predictions remain incompletely understood. We propose that cumulative environmental particulate exposure—including microplastics, nanoplastics, and other airborne or ingested particulates—may contribute as a previously unrecognized component of the retinal age signal captured by deep learning models. Specifically, we hypothesize that particulate-associated retinal features may constitute one of several feature classes utilized by these models. Such features potentially manifest as hyperreflective foci on OCT or as tiny discrete foci on fundus imaging. We outline seven falsifiable predictions spanning epidemiology, imaging analysis, experimental manipulation, and post-mortem validation. Importantly, this framework does not posit that particulate burden is the primary determinant of retinal age. Rather, it may act as a latent and cumulative exposure signal embedded within a multifactorial aging phenotype. If supported, this hypothesis would expand the interpretability of retinal age models and position retinal imaging as a potential tool for studying long-term environmental exposure. This work is intended as a testable framework to guide empirical investigation rather than a definitive explanatory model.

Key words: retinal age gap; hyperreflective foci; microplastics.

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The triumph and mystery of retinal age gap

In 2018, researchers demonstrated that deep learning models could predict chronological age from retinal fundus photographs with a mean absolute error of approximately 3.5 years.[1] Subsequent studies refined these models, achieving errors as low as 2.8 years,[2] and extended the finding to multiple populations and imaging platforms.[3-5]

More striking than age prediction itself is what the retinal age gap predicts. A larger gap means a retina that looks older than its chronological age. This larger gap has been associated with increased risk of all-cause mortality, cardiovascular mortality, incident stroke, Parkinson's disease, dementia, and chronic kidney disease.[2,5-8] These associations persist after adjusting for traditional risk factors, suggesting that retinal age gap captures something fundamental about systemic health.

Despite robust predictive performance, the specific image features driving these models remain incompletely characterized. Current evidence suggests contributions from vascular morphology, neuroretinal structure, and global texture patterns.[1,7,9] However, these features do not fully explain the breadth of predictive associations observed, which suggests that additional latent signals may exist.

The emerging evidence for retinal particulates

Parallel to this work, an entirely separate literature has been developing. Environmental scientists and toxicologists have documented the ubiquity of microplastics and nanoplastics in the human environment.[10] These particles have been detected in human blood,[11] placenta,[12] lungs,[13] and gastrointestinal tract.[14]

Recent studies have extended these findings to ocular tissues. In 2024, researchers identified microplastics in human vitreous humor samples from 49 patients, detecting 1,745 plastic particles including nylon, PVC, and polystyrene.[15] A 2025 study confirmed the presence of multiple polymer types in *post-mortem* human retinal tissue.[16] Animal models have demonstrated that ingested nanoparticles can penetrate the blood-retina barrier within hours,[17] and toxicological studies have documented oxidative stress, apoptosis, and mitochondrial dysfunction in retinal cells exposed to plastics.[18-20]

While the presence of particulates in retinal tissue is increasingly supported, their detectability using standard clinical imaging modalities remains uncertain and represents a key unresolved question. On retinal imaging, researchers have proposed that tiny discrete foci (TDF) in fundus photography and hyperreflective foci (HRF) in optical coherence tomography (OCT) may represent exogenous particles.[21] These foci may demonstrate temporal per-

sistence and spatial stability, distinguishing them from more transient inflammatory cells.[22] Scoping reviews have noted that HRF can occur even in clinically healthy eyes.[23] This observation raises the question of what these foci actually represent.

The missed connection

These two literatures have developed independently. Retinal age researchers have not considered particulates as a potential contributor to their models, and environmental ophthalmologists have not engaged with deep learning age prediction. These two domains -retinal age prediction and environmental particulate biology- have not been systematically integrated. This manuscript proposes a conceptual bridge, though we explicitly acknowledge the current lack of direct empirical linkage between these domains.

The retinal age gap-particulate hypothesis: formal statement

We hypothesize that deep learning models for retinal age prediction may partially capture cumulative environmental particulate exposure. This exposure represents one component within a broader, multifactorial feature space (Figure 1).

This hypothesis does not assert that particulate burden is the dominant driver of retinal age predictions. Rather, the hypothesis posits three claims. First, environmental particulates may accumulate in retinal tissue over time. Second, such accumulation may produce direct or indirect imaging signatures. Third, these signatures may be detectable by deep learning models as part of complex feature representations. Thus, the retinal age gap may reflect a composite signal that incorporates intrinsic aging, systemic health, and environmental exposure.

Evaluation of the hypothesis

Mechanistic considerations

Table 1 illustrates how environmental microplastics could plausibly be visualized in retinal imaging, moving from global pollution to potential AI-assisted detection.

The particle-to-pixel challenge

A central constraint of this hypothesis is the resolution limit of retinal imaging. Because many particulates exist below the resolution threshold of fundus photography and OCT, direct visualization of individual particles is unlikely. The hypothesis therefore relies on three indirect mechanisms: particle aggregation into detectable clusters, secondary biological responses (such as microglial activation and retinal pigmented epithelium changes), and emergent texture patterns that deep learning models could detect. These mechanisms remain speculative and require empirical validation.

Non-specificity of hyperreflective foci

Hyperreflective foci are known to arise from multiple processes, including lipid deposition, inflammation, and cellular migration. Any attribution to particulate matter must therefore be established through differential validation rather than assumed.

Competing explanations

Established contributors to retinal age prediction include vascular morphology, neurodegenerative changes, and global image tex-

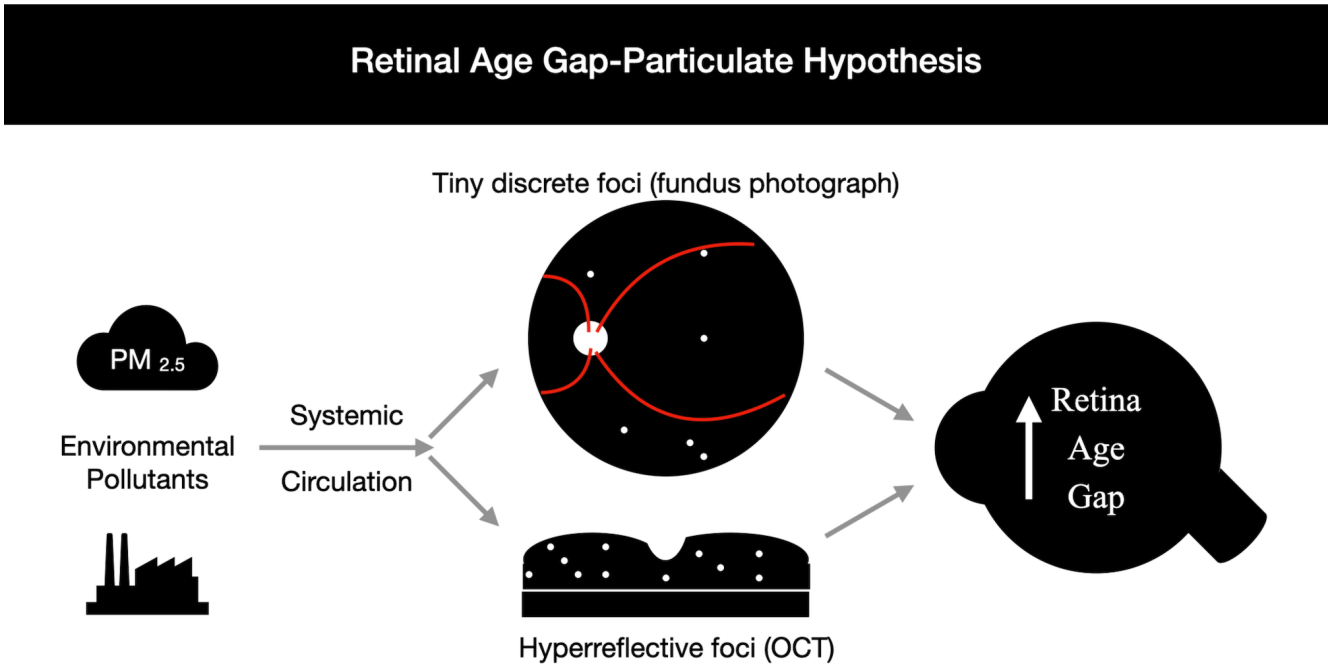

Figure 1. Retinal age gap-particulate hypothesis illustrating environmental pollutants, appearing as tiny discrete foci in fundus photography and as hyperreflective foci in retinal optical coherence tomography.

ture. The present hypothesis should be interpreted as complementary to these mechanisms rather than as a replacement for them.

Hypothesis testing

Testable predictions: a roadmap to falsifiability

Seven falsifiable predictions are proposed, organized across epidemiological association (Predictions 1-4), imaging analysis (Predictions 5-6), and *post-mortem* validation (Prediction 7). Each prediction includes explicit falsification criteria.

Prediction 1: geographic variation

If the retinal age gap reflects particulate exposure, then the mean retinal age gap should vary systematically with geographic pollution levels after controlling for chronological age. Populations in high-particulate environments such as urban centers, industrial regions, and areas with high PM2.5 concentrations should show an accelerated retinal age gap compared to low-exposure populations.

Proposed test: re-analyze existing retinal age datasets (UK Biobank, AREDS, Singapore Epidemiology of Eye Disease) with geocoded exposure data from air quality monitoring stations or satellite-based PM2.5 estimates. Compare retinal age gap distributions across exposure quintiles.

Falsification condition: no association between geographic exposure gradients and retinal age gap after controlling for socioeconomic and demographic confounders.

Prediction 2: occupational variation

Occupations with known high particulate exposure -miners, construction workers, welders, foundry workers, traffic police, urban outdoor workers- should show systematically higher retinal age gap than age-matched controls from low-exposure occupations.

Proposed test: cohort studies with occupational histories and existing fundus images. The UK Biobank includes occupational data; similar cohorts exist in Scandinavia with linked occupational exposure matrices.

Falsification condition: no occupational exposure gradient in retinal age gap after controlling for smoking, socioeconomic status, and geographic location.

Prediction 3: temporal trends following exposure change

If particulates accumulate over time, retinal age gap should increase with exposure duration. Longitudinal studies should show that individuals who move from low- to high-pollution areas accelerate their retinal age gap trajectory compared to those who remain in low-exposure areas. Conversely, migration from high- to low-exposure areas should attenuate or slow retinal age gap acceleration.

Proposed test: longitudinal retinal imaging datasets with migration history. The UK Biobank is currently adding longitudinal imaging; existing clinical cohorts with repeated fundus photography could be linked to residential history.

Falsification condition: no detectable change in retinal age gap trajectory following residential moves across pollution gradients.

Prediction 4: exposure-intervention effects

If exposure drives retinal age gap, then interventions that reduce exposure should slow or reverse retinal age gap acceleration. Clean air initiatives, occupational protective equipment, residential relocation to low-pollution areas, or high-efficiency particulate air (HEPA) filtration should produce detectable changes in retinal age gap trajectory over time.

Proposed test: Longitudinal studies before/after policy interventions (e.g., clean air zones, coal plant retirements) or individual interventions (e.g., HEPA filter installation in homes). Compare retinal age gap trajectories in intervention *vs* control populations.

Falsification condition: No detectable effect of exposure-reduction interventions on retinal age gap trajectory over 3-5 year follow-up.

Prediction 5: spatial correspondence of predictive features and foci

The specific image features most predictive of the retinal age gap should localize to regions where particulate foci are most common. These features can be identified by explainable AI techniques

Table 1. Evidence chain for retinal age gap-particulate hypothesis.

Step	Process	Evidence	Reference
1	Environmental release	Plastic pollution is documented globally, with microplastics found in oceans, soil, and air	Manhas *et al*.[24]
2	Human exposure	Inhalation and ingestion of microplastics have been documented in food, water, and air	Ziani *et al*.[25]
3	Systemic distribution	Microplastic particles have been detected in human blood samples	Leonard *et al*.[11]
4	Blood-retina barrier penetration	Animal models show microplastics can cross the blood-retina barrier within hours	Zheng *et al*.[17]
5	Retinal accumulation	Human post-mortem tissue studies confirm microplastic presence in the retina	Zhang *et al*.[16]
6	Appearance as hyperreflective foci and tiny discrete foci	Literature proposes microplastics may appear as hyperreflective foci (OCT) and tiny discrete foci (fundus photography)	Tan[21]
7	Visibility on fundus photography and OCT	Detectability depends on particle size and clustering; optics literature shows resolution limits for small features	Tan[21]
8	Detection by deep learning models	Deep learning models are sensitive to texture, pattern, and local features, enabling detection of subtle signals	Zang *et al*.[26]

such as saliency maps, Gradient-weighted Class Activation Mapping, and SHapley Additive exPlanations. The relevant regions include perivascular areas, the retinal pigmented epithelium layer, the macula, and areas with visible hyperreflective foci on corresponding OCT or tiny discrete foci on corresponding fundus photographs.

Proposed test: apply feature visualization methods to existing retinal age gap models. In eyes with both fundus photography and OCT, correlate saliency maps with manual counts of hyperreflective foci and tiny discrete foci. Test whether regions highlighted by the model contain more foci than randomly selected regions.

Falsification condition: saliency maps show no spatial correspondence with foci locations; highlighted regions are randomly distributed relative to foci.

Prediction 6: foci removal attenuates prediction accuracy

If particulate foci drive retinal age gap predictions, then digitally removing or masking these foci from fundus images and OCT should produce three effects. First, it should decrease retinal age gap prediction accuracy. Second, it should attenuate the association between retinal age gap and mortality. Third, it should shift predicted ages toward chronological age, especially in high-exposure individuals.

Proposed test: collaborate with a deep learning group to perform in-painting or masking experiments. Train or fine-tune models on images with foci manually or algorithmically removed. Compare prediction accuracy and retinal age gap distributions before and after removal.

Falsification condition: removing foci has no detectable effect on prediction accuracy or on the association between retinal age gap and mortality.

Prediction 7: post-mortem validation

In eyes with fundus photographs and OCT taken before death, post-mortem retinal tissue analysis should show that particulate burden -measured by pyrolysis-gas chromatography-mass spectrometry, laser directed infrared spectroscopy, or electron microscopy- correlates with: i) pre-mortem retinal age gap; ii) number of visible foci on fundus photography and OCT; and iii) regional density of foci corresponding to regions highlighted by saliency maps.

Proposed test: collaborate with eye banks and analytical chemistry labs. Collect eyes from donors with available antemortem fundus photographs and OCTs. Measure particulate burden in dissected retinal layers. Correlate with retinal age gap predictions and manual foci counts.

Falsification condition: no correlation between measured particulate burden and either retinal age gap or visible foci count.

Distinguishing particulate-associated foci from inflammatory signals: a deep learning architecture proposal

To test Prediction 5 (spatial correspondence) and Prediction 6 (foci removal), any empirical investigation must first solve a methodological challenge: how to differentiate particulate-associated foci from inflammatory or lipid-derived hyperreflective foci. We propose several algorithmic approaches to address this challenge, each leveraging different aspects of available data and computational techniques.

Multi-task learning architecture

A multi-task deep learning framework offers one promising approach. Such a framework could simultaneously predict three outputs: the retinal age gap, the count and morphology of foci, and an inflammatory signature. This inflammatory signature would be derived from known inflammatory biomarkers, which might include the presence of cotton wool spots, microglial activation patterns on OCT, or concurrent systemic inflammatory markers where available. By training the model to perform multiple related tasks simultaneously, the representation learning layer may learn to disentangle particulate signals from inflammatory ones. This strategy is analogous to multi-task models that jointly predict multiple cardiovascular risk factors from fundus images.[1]

Contrastive learning with physical priors

A second approach involves contrastive learning trained on synthetic data. Researchers could generate synthetic foci based on known physical properties of microplastics, including typical size distributions (usually 1 to 100 micrometers), refractive indices (polystyrene at approximately 1.59 and PVC at approximately 1.54, compared with retinal tissue at approximately 1.36), and expected clustering patterns. The contrastive learning framework would then distinguish these synthetic foci from real inflammatory foci that have been annotated by retinal specialists. This approach allows the model to learn embeddings that separate the two classes without requiring pixel-level labels.[22] Physical priors can be encoded through differentiable renderers that simulate particulate appearance under OCT physics, such as Monte Carlo ray tracing for backscatter intensity.

Temporal persistence modeling

The literature has proposed that exogenous particulates may demonstrate temporal persistence and spatial stability compared with transient inflammatory cells.[22] This distinguishing feature opens the door to temporal persistence modeling. A recurrent or transformer-based architecture operating on longitudinal imaging could learn temporal signatures that differentiate the two classes. Specifically, particulate-associated foci would show low temporal variance and spatial consistency, whereas inflammatory foci would wax, wane, or migrate over time. This approach requires longitudinal datasets, which are increasingly available through resources such as the UK Biobank's repeated imaging protocol.

Attention-based feature attribution

Explainable AI techniques can also contribute to this discrimination task. Attention maps from Vision Transformers (ViTs) or layer-wise relevance propagation (LRP) from convolutional networks can reveal whether a model attends to foci with particulate-like features-such as discrete, hyperreflective, and perivascular appearance- or to diffuse inflammatory patterns.[27-28] Researchers could validate a model's discriminative capacity by comparing attention distributions across images from populations with known particulate exposure (for example, occupational cohorts) against images from populations with known inflammatory conditions (such as uveitis or diabetic retinopathy).

Validation strategy

We propose a three-tiered validation strategy for these algorithms. First, synthetic datasets with known ground-truth particulate locations would provide controlled testing conditions. Second, ani-

mal models comparing controlled particulate exposure against induced inflammation would offer biological validation. Third, human post-mortem tissue correlation (Prediction 7) would serve as the ultimate reference standard, because chemical confirmation of particle identity can validate algorithmic classifications against ground truth.

Falsification condition: the hypothesis assumes that particulates produce a distinguishable imaging signature. This assumption would be falsified if models cannot achieve above-chance discrimination in validation datasets where ground-truth labels come from post-mortem chemical analysis or controlled animal experiments.

Bayesian hypothesis generation: a prospective framework

Bayesian Hypothesis Generation (BHG) formalizes the evaluation of novel hypotheses under uncertainty.[29] BHG requires specifying a prior, identifying pre-existing observations, and estimating likelihoods under competing hypotheses. When applied to the retinal age gap-particulate hypothesis, BHG reveals a critical finding. The pre-existing observations required for retrospective evaluation do not yet exist because the hypothesis is genuinely novel. No published studies have examined geographic variation in the retinal age gap with pollution exposure, occupational exposure gradients, spatial correspondence between saliency maps and hyperreflective foci, or post-mortem correlation of particulate burden with antemortem retinal age gap.

This hypothesis is best understood as a structured, pre-empirical framework rather than a quantitatively validated model. While Bayesian reasoning can conceptually guide hypothesis evaluation, precise numerical priors and likelihoods are not currently empirically grounded.

Accordingly, we adopt a qualitative interpretation. The prior plausibility is low-to-moderate due to novelty and limited direct evidence. The hypothesis gains strength only through convergent validation across independent predictions.

Discussion

These implications, if confirmed, are contingent on empirical validation. Readers should interpret them as potential outcomes rather than definitive conclusions.

For retinal age research

Confirmation of this hypothesis would improve the interpretability of retinal age models and recontextualize their findings. Specifically, the retinal age gap may predict mortality partly because particulate exposure itself predicts mortality. Models can now be refined to distinguish particulate burden from true aging processes, potentially improving both prediction and explanation.

For environmental health

Confirmation would also introduce environmental exposure as a measurable component of retinal imaging. Fundus photography and OCT would become population-scale tools for environmental exposure monitoring, meaning that every routine eye exam could contribute data to environmental surveillance. Retrospective analysis of existing cohorts -the UK Biobank alone contains fundus images from >80,000 individuals- can reveal historical exposure patterns and their health consequences. Countries with national eye screening programs such as diabetic retinopathy screening in the UK and Singapore, already have *de facto* environmental monitoring infrastructures in place.

For clinical medicine

Patients with accelerated retinal age gap can be counseled about environmental exposures. Interventions would shift from purely lifestyle measures such as diet, exercise, and smoking cessation, to also include environmental measures like air filtration, occupational protection, and residential location choices.

For public policy

If retinal age gap correlates with pollution, it provides a direct, visual, population-level metric for policy evaluation. Clean air initiatives can be assessed by their impact on retinal age gap distributions. Regulatory decisions about industrial emissions, vehicle standards, and urban planning gain a new evidentiary basis. The retina would literally become a window into the success or failure of environmental policy.

For aging research

The concept of biological age must be reconsidered. Much of what we call aging may actually be accumulated environmental damage. If the retinal age gap is partially attributable to pollution, then anti-aging interventions must include environmental remediation. Under this framework, the boundary between aging and exposure blurs considerably.

Limitations and alternative explanations

Resolution limits

Fundus photography and OCT cannot resolve individual nanoparticles. The hypothesis therefore requires that particulate accumulation produces detectable patterns through clustering, aggregation, or secondary tissue effects. If particulate foci are truly sub-resolution and produce no detectable statistical signature, the hypothesis fails. This outcome would constitute a genuine falsification condition.

Confounding

Retinal age also reflects vascular changes, neuronal loss, drusen accumulation, and other true aging processes.[3,9] The hypothesis proposes that particulates contribute to the retinal age gap, not that they explain the entire phenomenon. Teasing apart these contributions will require the multi-prediction approach outlined above.

Causality *vs* correlation

Even if particulate burden correlates with retinal age, causation remains to be established. Particulate exposure correlates with

socioeconomic status, smoking, occupation, and geographic location—all of which may independently affect retinal aging. The proposed tests (occupational variation, migration studies, intervention effects) are designed to address this, but causal inference will require multiple converging lines of evidence. Failure of post-mortem correlation or masking experiments would substantially weaken the hypothesis.

Particle heterogeneity

Microplastics are only one class of environmental particulates. The hypothesis applies broadly to inhaled or ingested particulates of all types, including combustion products, mineral dusts, and industrial emissions. Disentangling the effects of different particle types will require detailed chemical characterization alongside imaging.

Call for collaboration

Testing this hypothesis requires collaboration across disciplines that rarely interact. We invite deep learning researchers to apply explainable AI methods to existing models and test whether saliency maps localize to foci-like features. We invite environmental epidemiologists to link retinal age datasets with geocoded exposure data and occupational histories. We invite analytical chemists to measure particulate burden in post-mortem eyes that have available antemortem images. We invite ophthalmologists to characterize particulate foci in living patients and correlate these findings with retinal age gap predictions. We invite toxicologists to investigate whether specific particle types produce characteristic imaging signatures. Finally, we invite public health researchers to design studies that evaluate policy interventions through retinal age gap monitoring.

The datasets largely exist, and the methods are established. What has been missing is the hypothesis connecting them, which this paper now provides. We offer it to the research community for empirical testing, refinement, or falsification.

Conclusions

We present a testable hypothesis that environmental particulate exposure may contribute to the retinal age signal detected by deep learning models. This framework is explicitly provisional and intended to stimulate empirical investigation.

This work does not resolve the interpretability of retinal age prediction. Instead, it reframes retinal age prediction as a multidimensional problem that incorporates biological, systemic, and environmental components. The validity of this hypothesis will depend on rigorous experimental and epidemiological testing.

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