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Disentangling Brain Aging: A Multimodal Biomarker Framework to Separate Intrinsic Aging, Lifestyle Effects, and Neuropathology

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Abstract

Brain age prediction models estimate biological brain age from neuroimaging data, with the Brain Age Gap (BAG), the discrepancy between predicted and chronological age, widely used as a biomarker of accelerated or delayed aging. However, BAG tacitly pathologizes normal biological and socio-behavioral variation by conflating aging, lifestyle, and disease. To address this limitation, we propose a Multimodal Disentanglement Framework (MDF) that decomposes BAG into three orthogonal components: 1) intrinsic biological aging, 2) lifestyle-modulated brain changes, and 3) pathology-associated deviation. Using multimodal MRI and rich phenotypic data from 12,340 participants in the UK Biobank, we trained a hierarchical deep learning architecture to isolate these components. Our results show that lifestyle factors explain 38% of BAG variance, while only 12% is attributable to future neuropathology. Crucially, the pathology-specific component significantly outperforms standard BAG in predicting all-cause mortality (HR = 1.82 vs. 1.41) and incident Alzheimer's disease (AUC = 0.84 vs. 0.71). These findings challenge the assumption that BAG reflects "pure" biological aging and underscore the ethical necessity of disentangling modifiable from pathological drivers in brain biomarker research.

Keywords

Brain Age Prediction, Biological Aging, Disentangled Representation Learning, Lifestyle Confounding, Neuroethics, Multimodal Neuroimaging

1. Introduction

Brain age prediction has become a cornerstone of computational neuroscience, offering a data-driven proxy for brain health by comparing an individual's neuroimaging profile to population-level age trajectories [1]-[3]. The resulting Brain Age Gap (BAG), defined as predicted age minus chronological age, is interpreted as evidence of accelerated (positive BAG) or decelerated (negative BAG) brain aging [4]. BAG correlates with mortality [5], cognitive decline [6], and psychiatric and neurological disorders [7], motivating its use in both research and clinical screening.

Yet, as Heinrichs [7] critically observes, this framework tacitly pathologizes deviations from a normative "healthy aging" trajectory, often without explicit justification. Standard models are typically trained on ostensibly "healthy" controls, implicitly defining any deviation, including those driven by education, socioeconomic status, or physical activity, as abnormal [8] [9]. These risks are associated with misattributing socially mediated brain differences to irreversible biological decline.

Moreover, BAG lacks specificity: it aggregates diverse biological, environmental, and pathological influences into a single scalar [10]. Recent work shows that lifestyle factors such as smoking, BMI, and exercise significantly shift BAG [11] [12], while others demonstrate that BAG captures early signs of Alzheimer's pathology [13]. Without disentangling these sources, BAG cannot reliably distinguish between reversible lifestyle effects and irreversible neuropathology.

To resolve this, we introduce the Multimodal Disentanglement Framework (MDF), a novel deep learning architecture that explicitly separates BAG into three interpretable components:

- **Intrinsic aging:** age-related changes independent of lifestyle or disease.
- **Lifestyle-modulated aging:** brain changes linked to modifiable behaviors.
- **Pathology deviation:** residual anomalies predictive of future clinical outcomes.

Using data from the UK Biobank, we validate MDF against longitudinal health outcomes and demonstrate its superiority over standard BAG in both predictive accuracy and ethical interpretability.

2. Materials and Methods

2.1. Participants

We began with the full UK Biobank imaging cohort (N = 40,366 participants with baseline brain MRI as of 2023). From this pool, we applied the following sequential exclusion criteria:

1) Prevalent neurological or major psychiatric disorder (self-reported or hospital-recorded): dementia, Parkinson's, stroke, multiple sclerosis, schizophrenia, or bipolar disorder (n = 2812).

2) Incomplete multimodal MRI: missing T1-weighted, diffusion MRI (dMRI), or resting-state fMRI (n = 18,437).

3) Poor imaging quality: motion artifacts or preprocessing failures in T1 (n =

1204), dMRI (n = 2103), or fMRI (n = 1987); total unique exclusions = 3109.

4) Missing key covariates: incomplete data on education, physical activity, smoking, alcohol use, or BMI (n = 1283).

5) Insufficient follow-up: <2 years for mortality or incident disease (n = 315).

The final analytic sample comprised 12,340 participants (mean age = 63.2 years ± 7.1 years; 54% female). Compared to the full UK Biobank imaging cohort, our sample was slightly younger (63.2 vs. 64.8 years) and had higher education levels (42% vs. 36% university degree), but comparable prevalence of hypertension (38% vs. 40%) and mortality rates (standardized mortality ratio = 0.96), supporting generalizability for aging-related outcomes.

2.2. Data Preprocessing

- T1 MRI: Processed with FreeSurfer v7.2 for cortical thickness and subcortical volumes.
- dMRI: Tract-based spatial statistics (TBSS) for fractional anisotropy (FA) and mean diffusivity (MD).
- fMRI: Preprocessed with fMRIPrep; functional connectivity matrices computed using the Schaefer 200-parcel atlas.
- Lifestyle composite: Derived from PCA of smoking, alcohol use, physical activity, education, and BMI.

2.3. Multimodal Disentanglement Framework (MDF)

MDF consists of:

- Shared encoder: A multimodal transformer with 6 layers, 8 attention heads, and a hidden dimension of 512, fusing 142 cortical thicknesses, 42 subcortical volumes, 48 TBSS metrics, and 19,900 fMRI connectivity edges.
- Three disentangled decoders (3-layer MLPs with ReLU activation).
- Intrinsic branch: Trained on participants in the top 10% of lifestyle health (approximating a "resilient aging" reference group [12]). Sensitivity analyses using the top 5%, 15%, and 20% showed stable pathology AUC for Alzheimer's disease (0.82 - 0.85; See Supplementary Data).
- Lifestyle branch: Predicts lifestyle composite score from imaging features.
- Pathology branch: Trained only on orthogonal residuals after regressing out both chronological age and lifestyle score via least squares—ensuring statistical independence and preventing information leakage.

Total brain age is reconstructed as:

$$\hat{A}_{\text{total}} = \hat{A}_{\text{intrinsic}} + \hat{A}_{\text{lifestyle}} + \hat{A}_{\text{pathology}} \quad (1)$$

2.4. Evaluation

- Prediction accuracy: MAE and R^2 from 5-fold stratified cross-validation.
- Variance decomposition: % of BAG variance explained by each component.
- Clinical validity: Cox regression for mortality; ROC-AUC for 5-year incident

Alzheimer's disease (AD) and stroke.

- External validation: Attempted in ADNI (N = 842); limited by protocol differences and sparse lifestyle data (see Section 5).

3. Results

3.1. Model Performance

The Multimodal Disentanglement Framework (MDF) achieved the lowest mean absolute error (MAE = 2.87 years) and highest explained variance (R^2 = 0.89) as shown in Table 1, outperforming both unimodal (T1-only) and standard multimodal baselines. The improvement over T1-only models (ΔMAE = −1.05 years) underscores the value of integrating structural, microstructural, and functional connectivity data. Notably, while standard multimodal BAG reduced error by 0.77 years relative to T1, MDF yielded an additional 0.28 year reduction, demonstrating that architectural innovations, specifically, disentangled representation learning contribute meaningfully beyond mere data fusion. This suggests that explicitly modeling orthogonal biological processes enhances predictive fidelity, likely by reducing interference between confounding signals.

Table 1. Age prediction performance across models.

Model	MAE (Years)	R^2
Standard BAG (T1)	3.92	0.78
Multimodal BAG	3.15	0.85
MDF (Proposed)	2.87	0.89

3.2. Variance Decomposition

Variance decomposition reveals that lifestyle factors account for 38% of total BAG variance, nearly as much as intrinsic aging (42%) (Table 2). This finding directly challenges the common assumption that BAG primarily reflects biological senescence. The lifestyle composite (derived from physical activity, education, smoking, alcohol, and BMI) showed strong negative correlations with BAG ($r = -0.51$, $p < 0.001$), indicating that healthier behaviors are associated with younger-appearing brains. In contrast, the pathology component trained to predict future clinical events explained only 12% of BAG variance, highlighting that most "accelerated aging" in standard models is non-pathological. The residual 8% may reflect measurement noise, genetic factors, or unmeasured environmental exposures.

Table 2. Sources of BAG variability in the full cohort.

Component	% Variance in Bag
Intrinsic Aging	42%
Lifestyle Factors	38%
Pathology Deviation	12%
Unexplained	8%

3.3. Clinical Predictive Validity

When predicting all-cause mortality over a median follow-up of 8.2 years, the MDF pathology component yielded a hazard ratio (HR) of 1.82 per 5-year increase, significantly higher than standard BAG (HR = 1.41; $p < 0.001$ for difference in C-statistics) (Table 3). Similarly, for incident Alzheimer's disease within 5 years, the pathology-specific score achieved an AUC of 0.84, outperforming standard BAG ($\Delta AUC = +0.13$, $p = 3 \times 10^{-6}$). This gain in specificity arises because MDF isolates deviations orthogonal to both age and lifestyle, thereby enriching for true neuropathological signal. For stroke prediction, the improvement was more modest but still significant (AUC increased from 0.63 to 0.76), suggesting that cerebrovascular pathology is partially captured by the disentangled framework.

Table 3. Predictive performance for clinical outcomes (adjusted for age, sex, and scanner).

Outcome	Standard BAG (HR/AUC)	MDF Pathology Component (HR/AUC)
All-Cause Mortality	HR = 1.41 ($p < 0.001$)	HR = 1.82 ($p < 0.001$)
Incident Alzheimer's	AUC = 0.71	AUC = 0.84
Incident Stroke	AUC = 0.63	AUC = 0.76

Importantly, the lifestyle component showed no significant association with mortality or dementia after adjusting for baseline health status (HR = 1.04, $p = 0.21$), confirming that its contribution to BAG is largely non-pathological. This supports the interpretation that lifestyle-driven BAG reflects adaptive or modifiable brain states, not irreversible decline.

3.4. Interpretation

Our results directly address Heinrichs' [7] concern that BAG tacitly pathologizes normal variation. The finding that lifestyle accounts for 38% of BAG variance while pathology contributes only 12% demonstrates that apparent "accelerated aging" in standard models often reflects modifiable, socially patterned differences, not disease. This challenges normative assumptions that equate deviation from a "healthy" ideal with pathology and supports a more ethically grounded interpretation of brain biomarkers.

3.5. Sensitivity and Robustness Analyses

- Cross-scanner consistency: MAE range = 2.84 - 2.91.
- Age-stratified effects: Lifestyle explained 45% of BAG variance in midlife (45 - 64 years) vs. 29% in older adults (65 - 80 years).
- Collider bias: Our sample consists of individuals who survived to imaging age (45 - 80), potentially underrepresenting severe pathology and attenuating effect sizes, a common limitation in aging cohorts.

4. Discussion

Our findings validate MDF as a scientifically rigorous and ethically responsible alternative to standard BAG. By disentangling lifestyle from pathology, we avoid the tacit pathologization critiqued by Heinrichs (2023) and enable actionable, non-stigmatizing interpretations (e.g., "your brain age is elevated due to low exercise").

We integrate four recent advances:

- Wittens *et al.* [14] demonstrated that heavy alcohol use significantly increases BPAD, confirming that BAG captures modifiable behavioral effects.
- Zhang *et al.* [15] showed that smoking cessation, moderate alcohol use, and physical activity significantly slow BAG progression, especially in high-risk individuals.
- Nguyen *et al.* [16] introduced Brain Structure Ages (BSA), estimating age at the regional level to improve multi-disease classification, complementing our disentanglement by localizing pathology.
- Zwilling *et al.* [17] identified a nutrient biomarker profile (omega-3 fatty acids, carotenoids, vitamin E) associated with delayed brain aging, reinforcing that BAG is modifiable through diet.

Unlike these studies, which treat lifestyle as a confound, MDF explicitly models lifestyle as a target signal, enabling positive behavioral framing and personalized intervention.

Furthermore, Sihag *et al.* [18] recently proposed a graph signal processing framework that interprets BAG as a residual of healthy aging, enabling anatomically explainable biomarkers for neurodegeneration, aligning with our pathology branch's design.

5. Limitations

- External validation: Attempted in ADNI (N = 842) but limited by protocol differences and sparse lifestyle data, highlighting challenges in cross-cohort generalizability.
- Collider bias: Conditioning on survival may attenuate pathology associations.
- Molecular validation: Pathology branch trained on clinical endpoints, not amyloid/tau biomarkers.

6. Conclusion

Brain age prediction need not conflate aging with pathology. MDF provides a framework that separates intrinsic aging, lifestyle, and disease, enabling targeted interventions, reducing unwarranted medicalization, and advancing a nuanced understanding of brain health across the lifespan.

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Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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Supplementary Data

Table S1. Effect sizes and confidence intervals for BAG component associations with clinical outcomes.

Outcome	Component	B (SE)	95% CI	P-Value	Cohen's F^2
Mortality	Standard BAG	0.082 (0.012)	[0.059, 0.105]	<0.001	0.031
	MDF Pathology	0.141 (0.015)	[0.112, 0.170]	<0.001	0.068
	MDF Lifestyle	0.011 (0.009)	[−0.007, 0.029]	0.23	0.001
Incident AD	Standard BAG	0.067 (0.018)	[0.032, 0.102]	<0.001	0.025
	MDF Pathology	0.129 (0.021)	[0.088, 0.170]	<0.001	0.059
	MDF Lifestyle	0.008 (0.013)	[−0.017, 0.033]	0.53	<0.001

1) β = standardized regression coefficient from Cox (mortality) or logistic (AD) models, adjusted for age, sex, scanner, and education; 2) Cohen's f^2: effect size for regression models (f^2 ≥ 0.02 = small, ≥0.15 = medium, ≥0.35 = large); 3) SE = standard error; CI = confidence interval.

Table S2. Variance partitioning of brain age gap by age group.

Age Group	Intrinsic (%)	Lifestyle (%)	Pathology (%)	Unexplained (%)
45 - 54	35	45	10	10
55 - 64	40	40	11	9
65 - 74	46	33	13	8
75 - 80	52	29	14	5

Lifestyle explains the largest share of BAG variance in midlife (45 - 64), while intrinsic aging dominates in older adults (75+), suggesting lifestyle effects plateau with age.

Table S3. Sensitivity to lifestyle decile cut-off.

Top Percentile	Pathology AUC (Alzheimer's)
5%	0.82
10%	0.84
15%	0.83
20%	0.85

Supplementary Statistical Details

1. Model Validation

- Cross-validation: 5-fold stratified CV (by age and sex); MAE reported as mean ± SD across folds: 2.87 years ± 0.09 years.
- Calibration: Observed vs. predicted age showed slope = 0.98 (95% CI: 0.96 - 1.00), intercept = 0.7 years ($R^2 = 0.89$).

2. Survival Analysis

Cox proportional hazards assumptions verified via Schoenfeld residuals (all $p > 0.10$).

3. Harrell's C-Index

- Standard BAG: 0.64.
- MDF Pathology: 0.71.
- $\Delta C = +0.07$, $p < 0.001$ (DeLong test).

4. ROC Analysis

- AUC comparison (DeLong test).
- AD: $\Delta AUC = 0.13$, $p = 3 \times 10^{-6}$.
- Stroke: $\Delta AUC = 0.13$, $p = 1 \times 10^{-4}$.

5. Sensitivity Analysis

- Excluding participants with BMI > 35 or smoking history.
- Lifestyle variance ↓ to 31%.
- Pathology AUC for AD remained stable (0.83 vs. 0.84).

6. Data and Code Availability

Code: https://github.com/brain-age-mdf
Data: UK Biobank https://www.ukbiobank.ac.uk

7. Preprocessing Pipeline

Publicly available via OpenNeuro.