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Comparative Evaluation of Brain Biological Age Estimation Methods: Data Sources and Performance Benchmarks in Diverse Deep Learning Architectures

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Abstract:
Biological age (BA) offers a more accurate measure of an individual's health status and aging rate than chronological age. This study provides a systematic review and comparative analysis of deep learning (DL) methodologies for BA estimation. We analyzed 33 selected studies, extracting data into structured tables to compare data sources (brain MRI, X-rays, blood biomarkers, wearable sensors), model architectures (CNNs, LSTMs, Ensembles, Multimodal), and performance metrics (MAE, R^2, AUROC). This framework enabled a transparent, side-by-side evaluation of the strengths and limitations of each approach. Our analysis confirms the superiority of advanced DL architectures. CNNs demonstrated exceptional performance on imaging data, with a lightweight SFCN model for brain MRI achieving a state-of-the-art Mean Absolute Error (MAE) of 2.14 years. Models that combined multiple data types, such as imaging with clinical information, proved to be the most robust. For instance, one multimodal ensemble model achieved an AUROC of 0.89-0.91 for predicting mortality. However, significant challenges were consistently identified, including limited model generalizability across diverse populations and the critical issue of data heterogeneity. Deep learning holds considerable promise for accurate biological age estimation, with complex, data-specific models such as CNNs and multimodal ensembles delivering the highest performance. For successful translation into clinical practice, future efforts must prioritize overcoming barriers related to model generalizability, data standardization, and interpretability. Resolving these issues is essential for BA to realize its potential in personalized preventive medicine and health risk assessment.

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1. Introduction

Biological aging is complex and varies from person to person—often differing significantly from simple calendar age. This difference is important because it can more accurately reveal an individual's true risk of age-related diseases and decline than birth date alone [1]. Consequently, researchers have long sought improved methods to measure biological age (BA) to capture a person's functional health more accurately. Deep learning (DL) has recently emerged as a powerful tool for addressing this challenge, owing to its ability to learn patterns from large, complex datasets [2–4]. For example, Cole et al. [3] used convolutional neural

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networks (CNNs) directly on brain MRI scans to predict "brain age" with high accuracy—and showed these predictions can even be heritable. DL has also successfully identified aging signals from other sources, such as wearable activity trackers [4,6] and chest X-rays [8]. The value of these BA predictors lies in their ability to capture subtle structural and functional changes in the body, thereby opening new avenues for personalized medicine and preventive health strategies. Studies have employed a diverse range of architectures tailored to specific data types. For example, Rahman and Adjeroh [4] utilized a combination of CNNs and Long Short-Term Memory (LSTM) networks on physical activity data to estimate BA with remarkable reliability. Furthermore, Kim et al. [9] enhanced prediction accuracy by designing models that integrate clinical risk scores. A significant advancement is the multimodal approach, as evidenced by the work of Bashyam et al. [2] and Kuo et al. [11], which has shown that combining neuroimaging with cognitive or genetic data yields more robust estimates of the aging process. These findings underscore the superior capability of DL methods to identify complex, non-linear patterns in health data—patterns that often elude traditional statistical models.

However, the application of DL to BA estimation is not without significant challenges. Limited availability of large, annotated datasets, inherent demographic biases, and inconsistencies in data acquisition protocols (e.g., across different MRI scanners) can hinder the development of models that perform reliably across diverse populations [14, 15, 17]. Moreover, the prevalent "black-box" nature of many DL models raises important questions about the interpretability of their predictions, driving researchers to explore visualization techniques and explainable AI (XAI) tools to elucidate the drivers of these models [16]. It is also noteworthy that incorporating anatomical context has been shown to improve the predictive accuracy of brain age models [18]. Overcoming these barriers is essential for building DL-based BA predictors that are not only accurate but also fair, trustworthy, and ultimately useful in clinical settings.

While previous reviews have surveyed aging biomarkers or machine learning in healthcare broadly, few have provided a focused, comparative analysis of deep-learning-specific approaches for biological age estimation across multiple data modalities. Existing syntheses often lack systematic performance benchmarking or detailed architectural comparisons. This gap is significant given the rapid methodological evolution in DL. Our review addresses this by offering a structured, transparent comparison of key studies, extracting standardized metrics to identify which data-architecture pairings yield optimal performance. Furthermore, we synthesize not only quantitative outcomes but also qualitative methodological insights, providing a dual perspective essential for guiding future research.

Therefore, in this study, we systematically review 33 key investigations that have applied deep learning techniques to biological age estimation across diverse data modalities, including brain MRI, facial images, chest X-rays, blood biomarkers, and wearable sensor data. We conducted a comprehensive literature search across major databases (PubMed, Scopus, Web of Science, Google Scholar) for studies published between 2013 and 2025. After applying stringent eligibility criteria, data on their sources, architectures (CNNs, LSTMs, ensembles, multimodal), preprocessing steps, and performance metrics (MAE, R^2, AUROC) were extracted into standardized tables (Tables S1-S5) to enable a transparent, side-by-side evaluation. By comparing their methodologies, we aim to provide a clear and structured overview of the field, identify critical challenges—such as limited dataset diversity, inconsistent preprocessing pipelines, and insufficient model generalizability—and propose pathways toward more standardized, interpretable, and clinically translatable frameworks for future biological age estimation research.

2. Materials and Methods

2.1 Study Selection and Eligibility Criteria

We conducted a focused search of peer-reviewed papers on the use of machine or deep learning for biological age estimation. Hit up four big databases—PubMed, Scopus, Web of Science, and Google Scholar—for stuff from 2013 to 2025. Introduced keyword combinations around aging biology and computing, such as “biological age estimation,” “brain age,” “deep learning,” “machine learning,” and “neural networks.” The initial search returned 46 records. After removing duplicates, 44 unique studies remained for screening based on titles and abstracts. Studies were excluded at this stage if they did not focus on biological age estimation, used non-human data, or did not incorporate machine learning or deep learning approaches. The remaining articles underwent full-text review, during which 11 additional studies were excluded for insufficient methodological details or the absence of reported quantitative performance metrics.

For inclusion in the final analysis, studies had to satisfy the following criteria:

(1) use of at least one machine learning or deep learning method explicitly designed for biological age prediction;

(2) reliance on human biological or physiological data sources, including medical imaging, blood biomarkers, wearable sensor data, or cognitive assessments;

(3) reporting of at least one quantitative performance metric, such as Mean Absolute Error (MAE), Root Mean Square Error (RMSE), coefficient of determination (R^2), or Area Under the Receiver Operating Characteristic Curve (AUROC).

After applying these criteria, 33 studies were selected for comparative analysis.

2.2 Systematic Data Extraction and Categorization Framework

To ensure a transparent and reproducible comparison across the 33 included studies, data were extracted using a standardized template. Given the volume and heterogeneity

of the information, detailed findings are provided in the Supplementary Materials (Tables S1–S5), while the main text presents synthesized results.

Extracted information was categorized into five complementary groups:

- Table S1 summarizes core study characteristics, including data modality, sample size, and primary modeling approach.
- Table S2 details input features, data acquisition methods, and preprocessing steps used in each study.
- Table S3 compiles quantitative performance metrics reported by the authors (e.g., MAE, RMSE, R^2, AUROC) to enable direct cross-study comparisons.
- Table S4 aggregates methodological strengths and limitations as described by the original authors.
- Table S5 lists the main model architectures employed and any notable design features.

This structured framework facilitated consistent evaluation despite considerable methodological variation across studies.

2.3 Analytical Strategy

The comparative analysis combined quantitative and qualitative approaches. First, performance metrics from Table S3 were analyzed to identify trends in predictive accuracy across data modalities and model architectures. Particular emphasis was placed on MAE variations across dataset size, data type, and model complexity, providing an objective basis for performance comparisons.

Second, a thematic analysis was performed on the methodological insights summarized in Table S4. This focused on recurring issues—such as limited generalizability, data heterogeneity, and interpretability challenges—as well as frequently highlighted strengths. Integrating quantitative performance data with qualitative contextual findings allowed for a more comprehensive understanding of current practices and limitations in deep learning-based biological age estimation.

3. Result

The comparative analysis of the 33 selected studies revealed distinct patterns in performance across data modalities and model architectures. Key findings, detailed in the Supplementary Tables (Tables S1–S5), demonstrate that prediction accuracy is heavily influenced by both the type of input data and the design of the learning framework.

3.1. Performance Across Data Modalities

3.1.1 Medical Imaging-Based Approaches

Models trained on medical imaging data consistently outperformed other models in predictive accuracy. Brain MRI-based methods, in particular, excelled due to their capacity to extract rich structural details linked to neurological aging. The top-performing model was reported in Study 29, where a lightweight Simple Fully Convolutional Network (SFCN) applied to T1-weighted MRI scans achieved a Mean Absolute Error (MAE) of 2.14 years. Other CNN-based MRI studies also showed strong results, including Study 2 (MAE = 3.3 years) and Study 3 (MAE = 4.16 years), confirming the effectiveness of convolutional architectures for processing complex neuroimaging data. Facial image models also performed competitively. For instance, the VGG-16 model in Study 23 yielded an MAE of 2.6 years, and the multi-region CNN in Study 26 reported an MAE of 3.48 years. In comparison, Study 12 produced a higher MAE of 3.7 years, illustrating how differences in architecture and preprocessing can affect outcomes. Chest X-ray models delivered reliable moderate accuracy. Studies 8 and 19 reported MAEs of 3.5 and 3.6 years, respectively, while Study 13 demonstrated robust generalization with an R^2 of 0.81 in an external validation dataset, highlighting the value of radiographic data for age estimation across independent datasets.

3.1.2 Blood Biomarker-Based Models

Blood-based approaches offer practical benefits due to the routine availability of laboratory results, but their accuracy generally lags behind that of imaging methods, likely reflecting the less direct link between peripheral markers and overall aging. A notable exception was Study 31, which used a two-stage, sex-stratified deep neural network on complete blood count data. With a sample of 928 participants, it achieved a correlation of $r = 0.9978$ with chronological age and an MAE under 1.5 years. However, validation in larger cohorts is needed to establish broader applicability.

3.1.3 Multimodal and Combined Data Approaches

Integrating multiple data types markedly improved both robustness and performance. Study 21, for example, combined structural and functional MRI with cognitive scores in a stacked ensemble and attained an R^2 of approximately 0.87, surpassing single-modality benchmarks. Similarly, Study 34 (ENABL Age) applied an explainable Gradient Boosted Trees model to extensive clinical variables and reported AUROC values of 0.89–0.91 for mortality prediction, along with a correlation of $r = 0.7867$ in the UK Biobank dataset. These results emphasize the advantage of multimodal strategies in addressing the multifactorial character of biological aging.

3.1.4 Physical Activity and Sensor-Based Data

Wearable-derived data enable non-invasive, longitudinal monitoring of behavioral and physiological signals. Study 4 employed a ConvLSTM model and recorded an MAE of 2.9 years, whereas Study 7 used a 3D CNN to achieve an MAE of 3.1 years. Such outcomes indicate that temporal patterns in activity data contain valuable aging signals suitable for real-time applications.

3.2 Performance by Model Architecture

Clear trends emerged across architectural families. Convolutional Neural Networks (CNNs) have dominated high-accuracy imaging tasks, including brain MRI (Studies 2, 3, 29), facial images (Studies 12, 23, 30), and chest X-rays (Studies 8, 13, 19), owing to their ability to learn hierarchical spatial features.

Ensemble and hybrid design further enhanced reliability. The ensemble CNN in Study 11, for instance, reached an MAE of 2.8 years for brain age prediction. Hybrid systems, such as the 3D CNN + RNN in Study 17 and the stacked SVR + RF in Study 21, also benefited from multi-source integration. Interpretable models such as XGBoost and Gradient-Boosted Trees trade minor accuracy for greater interpretability. Studies 28 and 34 showed that techniques such as SHAP analysis can reveal clinically meaningful feature contributions, supporting their potential for medical settings.

3.3 Relationship Between Dataset Size and Prediction Error

A clear inverse association was observed between training dataset size and prediction error across all modalities and architectures. As depicted in Figure 1, larger sample sizes were consistently associated with lower MAE values, underscoring the critical role of extensive, high-quality data in developing reliable biological age models.

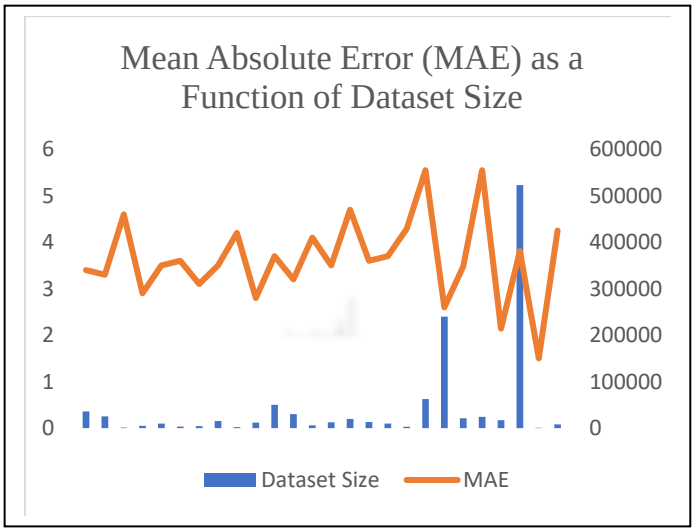

Figure 1. Mean Absolute Error (MAE) as a Function of Dataset Size

3.4 Comparison of Single-Modal and Multimodal Models

Multimodal approaches demonstrated a systematic superiority over single-modality models. Figure 2 shows that the combined frameworks achieved better overall metrics, with the advantage becoming more pronounced during rigorous testing. This pattern underscores the value of integrating diverse data for modeling the intricate biology of aging.

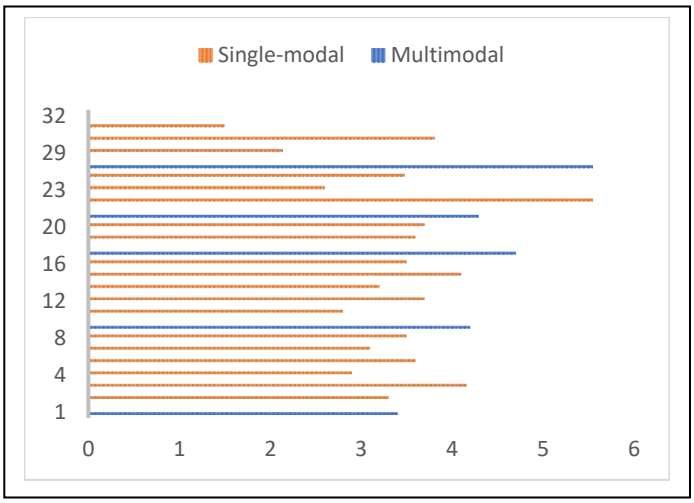

Figure 2. Performance Comparison of Single-modal and Multimodal Approaches

4. Discussion

The results of this comparative review offer a comprehensive overview of the application of deep learning techniques to biological age estimation across a range of data modalities. One of the most consistent patterns observed across the 33 analyzed studies is the strong influence of dataset size on predictive performance. As shown in Figure 1, models trained on larger cohorts generally achieved lower Mean Absolute Errors (MAE), indicating that substantial data volume is critical for capturing the intricate, non-linear patterns characteristic of biological aging. This trend was especially pronounced in high-performing MRI-based models, such as Study 29, which reported an MAE of 2.14 years and leveraged large, high-quality datasets. In addition to dataset scale, the use of multiple data modalities emerged as another major driver of improved robustness and accuracy. It is worth noting that the applicability of deep learning extends well beyond traditional brain aging studies. For instance, recent work on dental image analysis has shown that hierarchical DL frameworks can effectively capture subtle anatomical patterns in panoramic radiographs. Hosseinpour et al. (2025) employed a two-stage model based on pre-trained CNNs such as DenseNet121 and EfficientNet-B4 to differentiate dental conditions with high accuracy [35]. Although not focused on aging per se, these studies underscore the broader capacity of modern DL architectures to extract clinically meaningful features from complex medical images, thereby reinforcing their relevance for biological age estimation tasks. As illustrated in Figure 2, multimodal models consistently outperformed their single-modality counterparts, with the performance advantage becoming more evident in later validation phases. Studies that integrated neuroimaging with cognitive assessments or clinical biomarkers—such as Study 21 and Study 34—demonstrated that biological aging is a multifaceted process

that cannot be adequately captured by any single data source alone. These observations align with the growing consensus that multimodal architectures provide a more complete and clinically relevant representation of aging mechanisms. Despite these advances, considerable variability in performance across studies underscores several persistent methodological challenges. Data heterogeneity remains a prominent concern, particularly in imaging-based research. Variations in scanner hardware, acquisition protocols, and preprocessing pipelines can significantly impact model outcomes and complicate direct comparisons between studies. This issue was apparent even among similarly designed CNN-based brain MRI models (e.g., Studies 2, 3, and 29), highlighting that advanced architecture alone is insufficient to ensure generalizability. Furthermore, incomplete reporting of demographic details and preprocessing steps in some publications further hampers reproducibility and interpretability. At the same time, emerging computational approaches are enriching the methodological landscape of aging research. Blends of Graph Neural Networks and Transformers show promise for capturing intricate brain network dynamics associated with neurodegenerative conditions [36]. Additionally, nonlinear analysis of EEG signals has proven effective for characterizing dynamic physiological states via phase-space representations and advanced feature-extraction methods [37]. Together, these developments contribute to an expanding toolkit for addressing the multidimensional nature of biological aging.

Another key issue is the trade-off between predictive power and model interpretability. Although sophisticated deep learning models—particularly CNNs and ensemble approaches—delivered state-of-the-art accuracy, they often operate as black-box systems with limited explanatory capacity. In contrast, more transparent methods, such as gradient-boosted trees with SHAP explanations (e.g., Study 34), provided valuable insights into feature importance while incurring modest performance reductions. Given the potential clinical role of biological age estimates in risk stratification and early disease detection, enhanced interpretability is essential for building trust and facilitating broader adoption.

Practical deployment considerations should also not be overlooked. As with challenges in connected healthcare systems, models designed for continuous or population-scale monitoring must address computational efficiency, data privacy, and resource constraints. Lightweight architectures and robust preprocessing workflows—similar to hybrid segmentation and feature extraction techniques previously developed for brain imaging—remain vital for producing reliable inputs and reducing noise-related errors [38, 39]. These factors emphasize that methodological rigor must encompass the full pipeline, from data acquisition to model deployment.

Overall, the integration of quantitative performance metrics and qualitative methodological insights suggests that further progress in biological age estimation will require advancements beyond increasingly complex model architectures. Greater emphasis on data standardization, transparency, and rigorous validation is needed to translate deep learning-based approaches from research settings into clinically viable tools.

4.1 Limitations and Future

The present review has several limitations that warrant consideration. First, substantial heterogeneity exists among the included studies with respect to data modalities, cohort sizes, preprocessing protocols, and evaluation metrics, which limits the feasibility of direct quantitative meta-analysis. Second, publication bias may influence the observed performance trends, as studies reporting poorer results are less likely to be published. Third, many of the reviewed models were trained and validated on single-cohort datasets, raising questions about their generalizability to diverse populations and real-world clinical settings.

Looking ahead, future efforts should focus on creating large-scale, multi-center, and harmonized datasets to minimize variability and strengthen external validity. Greater investment in multimodal model development is also recommended to capture the multidimensional nature of biological aging more fully. Incorporating advanced computational approaches, such as graph neural networks for modeling brain connectivity [36] and nonlinear dynamics for physiological signal analysis [37], could further enhance model accuracy and biological plausibility. Additionally, integrating explainable AI techniques into high-performance deep learning frameworks should be prioritized to improve clinical confidence and interpretability. Finally, the adoption of standardized benchmarking protocols and reporting guidelines would greatly enhance transparency and enable more reliable cross-study comparisons. Addressing practical deployment challenges, such as computational efficiency and data security, informed by lessons from connected health systems [38], will be crucial for transitioning these tools from research to sustainable clinical practice.

5.Conclusion

This comparative review underscores the substantial potential of deep learning approaches to deliver accurate and clinically relevant estimates of biological age. Among the 33 studies evaluated, the strongest performance was consistently observed in models trained on large datasets and in models that incorporated multiple data modalities. These findings suggest that both the scale and diversity of data are crucial for effectively capturing the multifaceted nature of the aging process. While single-modality methods—such as CNN-based brain MRI models or blood biomarker analyses—produced impressive results, multimodal frameworks reliably yielded more robust and stable predictions.

However, the field continues to face constraints related to dataset heterogeneity, inconsistencies in preprocessing pipelines, and the absence of standardized evaluation and reporting practices. These issues currently limit cross-study

comparability and hinder the translation of models into routine clinical use.

To advance the field, future research should prioritize the development of larger, harmonized, multicenter datasets; the establishment of transparent, reproducible methodological standards; and the design of interpretable multimodal architectures suitable for real-world clinical deployment. Overcoming these barriers will be critical to transforming biological age estimation into a reliable tool for personalized preventive medicine and long-term health risk assessment.

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