Biological Age Acceleration and Cardiovascular Disease: A Survey of Predictive Biomarkers

Abstract

This survey paper explores the concept of biological age acceleration and its implications for cardiovascular disease (CVD) risk, emphasizing the significance of predictive biomarkers in enhancing risk stratification and personalized healthcare strategies. Biological age acceleration, distinct from chronological age, reflects the physiological state of an individual and is linked to increased risks of age-related diseases, including CVD. Key findings highlight the utility of DNA methylation age estimators, such as DNAm GrimAge, as robust predictors of disease incidence and mortality risk. The integration of BrainAge and MetaboAge scores enhances predictive capabilities, demonstrating the potential of combined biomarker approaches. Advanced computational techniques, including deep learning models, further refine biomarker-based assessments, particularly in quantifying accelerated aging in smokers. The survey underscores the importance of integrating molecular and clinical data for comprehensive risk assessment and the value of personalized lifestyle interventions in reducing CVD risk. Additionally, it suggests that shared treatment strategies targeting aging may benefit age-related diseases. The paper calls for further research to refine and validate biomarkers, integrate multi-omics data, and develop innovative therapeutic interventions to mitigate the adverse effects of biological age acceleration, ultimately improving cardiovascular health outcomes. These advancements underscore the potential for extending healthspan and enhancing quality of life through targeted, personalized healthcare strategies.

1 Introduction

1.1 Significance of Biological Age Acceleration

Biological age acceleration is pivotal for understanding individual health outcomes and disease progression, particularly in cardiovascular disease (CVD). In contrast to chronological age, which merely tracks time, biological age reflects an individual's physiological state, influenced by genetic, environmental, and lifestyle factors [1]. This distinction is crucial, as individuals of the same chronological age can exhibit marked differences in health status, especially with advancing age [2]. The significance of biological age acceleration is underscored by its association with CVD, a leading global cause of death, projected to claim 23.6 million lives by 2030 [3].

Epigenetic clocks, which leverage DNA methylation data to estimate biological age, have emerged as reliable biomarkers for aging. These biomarkers are vital for elucidating mechanisms of age-related diseases, including CVD, by linking epigenetic alterations to disease susceptibility and progression [4]. Chronic inflammation, or inflammaging, is a significant contributor to age-related diseases and cardiovascular health, highlighting the importance of understanding biological age acceleration. The progressive dysfunction of the aging adaptive immune system, particularly in CD4+ T cells, exacerbates chronic inflammation and the aging phenotype, emphasizing the interplay between immune function and biological age acceleration [5].

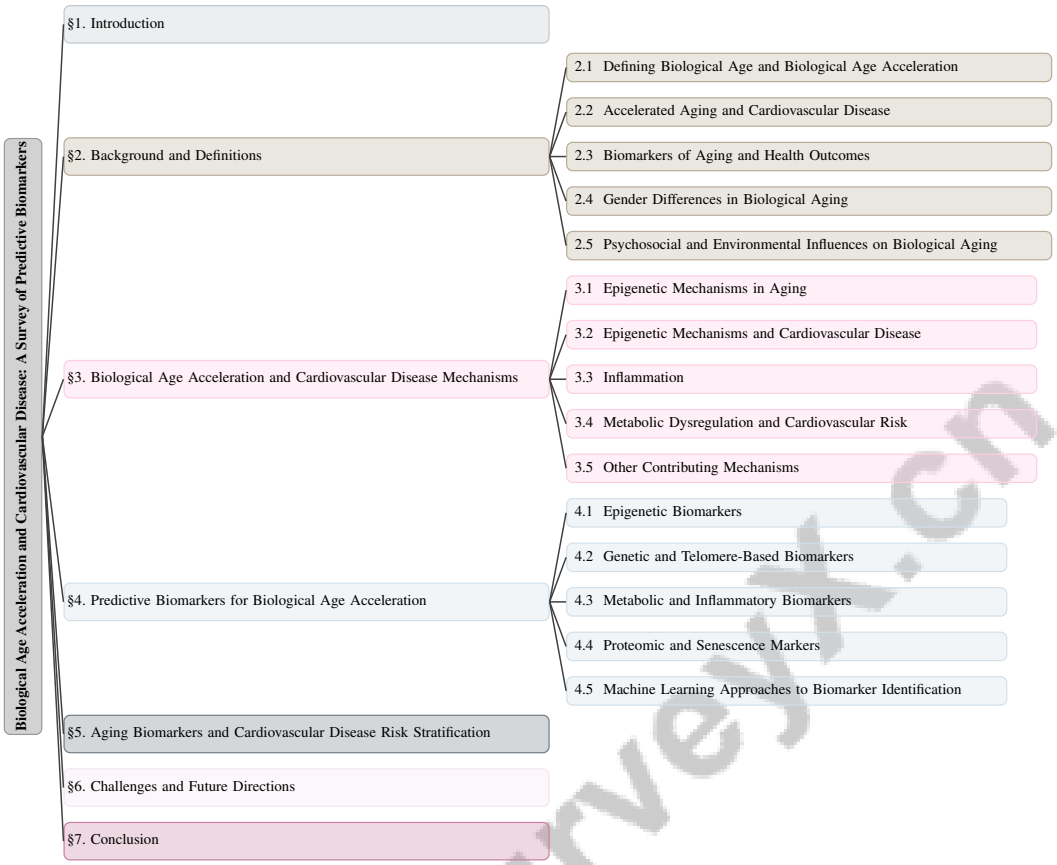


Figure 1: chapter structure

Metabolic dysregulation, such as insulin resistance, further heightens cardiovascular risk, necessitating advanced predictive models that integrate biological age markers for effective risk stratification [6]. Estimating biological age from diverse physiological and molecular data, including neuroimaging, is crucial for improving clinical assessments and interventions, although current models often overlook uncertainty, leading to confounding results.

The investigation of biological age scores, which synthesize multiple biomarkers, offers a comprehensive approach to understanding aging and its health implications. These scores address the limitations of chronological age in predicting health outcomes and informing personalized treatment strategies [7]. Additionally, studies on hemodynamic changes in microgravity, as observed in astronauts, provide insights into the implications of biological age acceleration for cardiovascular health on Earth [8].

Enhancing our understanding of biological age acceleration is essential for developing effective strategies to tackle health challenges posed by accelerated aging, including predictive modeling, optimized disease management, and extending healthspan through targeted interventions. Furthermore, endothelial dysfunction, a critical event in sepsis pathogenesis, is interlinked with aging and chronic diseases such as CVD, underscoring the broader implications of biological age acceleration [9].

1.2 Objective of the Paper

This survey aims to synthesize current research on biological age acceleration, particularly its implications for cardiovascular disease (CVD). It seeks to elucidate the complex biological processes underlying aging, focusing on biomarkers used in biological age models and their effectiveness [10]. The paper evaluates DNA methylation clocks as robust aging biomarkers, addressing their out-of-sample performance and utility in predicting age-associated health risks [11]. Additionally, it highlights the role of physical activity in modulating aging processes, comparing biological and chronological ages to assess aging rates in the elderly [12].

The survey further explores the integration of machine learning models in predicting myocardial infarction, enhancing healthcare strategies for CVD prevention [13]. It addresses the inadequacy of existing risk assessment tools and proposes novel methods, such as the "immune score," leveraging routine blood test data for improved risk stratification [14]. Moreover, the survey investigates how environmental, lifestyle, and health factors influence biological aging, as measured by DNA methylation age, contributing to a nuanced understanding of aging dynamics [15].

By examining methodological approaches in biological age research, the survey aims to address the critical need for accurate global health data, facilitating reliable assessments and comparisons of health trends across regions [16]. Through these objectives, the survey aspires to enhance the predictive capabilities of biological age models, ultimately improving cardiovascular risk stratification and personalized healthcare interventions.

1.3 Structure of the Survey

This survey is structured to provide a comprehensive examination of the relationship between biological age acceleration and cardiovascular disease (CVD). It begins with an **Introduction** that contextualizes the importance of biological age acceleration in relation to CVD, outlines the objectives, and discusses current research limitations. Following this, the **Background and Definitions** section provides foundational definitions and explores the connection between accelerated aging and CVD, introducing biomarkers and their significance in health outcomes.

The survey then delves into **Biological Age Acceleration and Cardiovascular Disease Mechanisms**, examining biological processes and pathways linking accelerated aging to CVD, including epigenetic mechanisms, inflammation, oxidative stress, endothelial dysfunction, and metabolic dysregulation, supported by relevant studies. The subsequent section, **Predictive Biomarkers for Biological Age Acceleration**, identifies and evaluates various biomarkers, categorizing them by biological origin and measurement methods, focusing on their predictive utility.

Further investigation into **Aging Biomarkers and Cardiovascular Disease Risk Stratification** discusses how these biomarkers can enhance risk assessment and their potential clinical applications. The penultimate section, **Challenges and Future Directions**, critically assesses current research limitations and proposes future directions, including novel biomarkers and therapeutic interventions. The paper concludes with a **Conclusion** that synthesizes key findings and emphasizes the need for further research to refine and validate predictive and aging biomarkers.

1.4 Limitations and Need for Further Investigation

Research on biological age acceleration and its implications for cardiovascular disease (CVD) faces several limitations that warrant further investigation. A significant challenge is the inadequate performance of existing CVD risk prediction models, which often rely on a limited number of conventional risk factors and fail to capture the complex interactions among diverse predictors [7]. This limitation is exacerbated by traditional methods' inability to effectively classify heart disease due to data complexity and current diagnostic approaches' constraints [3].

Additionally, existing methods inadequately address uncertainty in individual biological age predictions, focusing more on model parameters than on subject-specific outcomes [4]. The reliance on specific cohorts and datasets restricts the generalizability of findings, as these may not represent the broader population [17]. The model's performance is further limited by the scarcity of secondary care data, highlighting the need for more diverse datasets to enhance generalizability [6].

The complexity of inflammatory processes and the multifactorial nature of aging present additional challenges for developing targeted interventions [18]. Gaps in understanding the precise molecular pathways and interactions among aging hallmarks complicate the development of effective interventions [5]. Moreover, a focus on high-income countries limits the applicability of findings to low- and middle-income regions, particularly regarding conditions like sepsis [9].

Addressing these limitations requires targeted research initiatives that incorporate diverse sample sizes and develop comprehensive predictive models. Enhanced longitudinal analyses and standardized methodologies are essential for improving the reliability and generalizability of findings, ultimately advancing cardiovascular risk stratification and intervention strategies. Furthermore, the lack of established methods for evaluating the calibration of multistate models in clinical prediction underscores

the need for improved alignment between estimated risks and observed event rates [19].The following sections are organized as shown in Figure 1.

2 Background and Definitions

2.1 Defining Biological Age and Biological Age Acceleration

Biological age is a comprehensive measure of an individual's physiological state, integrating genetic, environmental, and lifestyle factors, offering a more nuanced understanding of health and disease susceptibility compared to chronological age [15]. DNA methylation levels, particularly those assessed through Horvath and Hannum epigenetic clocks, are pivotal in quantifying biological age, providing insight into aging processes via tissue-specific methylation changes [20]. Biological age acceleration occurs when biological age advances faster than chronological age, often due to systemic molecular imbalances, leading to increased risks of age-related diseases like cardiovascular conditions [21, 22]. Estimating biological age from organ-specific data, such as MRI-derived body composition metrics, highlights the complexity of biological age acceleration and the need for precise measurements [23]. The integration of advanced techniques like neuroimaging and metabolomics enhances the predictive potential of biological age markers, aiding in disease risk evaluation and intervention customization [17, 15].

2.2 Accelerated Aging and Cardiovascular Disease

Accelerated aging is intricately linked to heightened cardiovascular disease (CVD) risk, driven by physiological and molecular changes such as inflammaging—chronic low-grade inflammation that increases vulnerability to age-related diseases [18]. This persistent inflammatory state often results in endothelial dysfunction, characterized by impaired vascular function and increased chronic disease risk [9]. Aging also affects the immune system, particularly T cell aging, reducing immune functionality and elevating disease susceptibility [5]. Major CVD risk factors, including hypertension and diabetes, are exacerbated by accelerated aging [24]. Cardiovascular deconditioning during long-term spaceflight, which mirrors accelerated aging effects, reinforces the systemic nature of aging's physiological impacts [8]. The interplay between metabolic dysfunctions, such as insulin resistance, and epigenetic changes complicates CVD pathogenesis in accelerated aging contexts. Developing accurate CVD predictive models is challenged by data limitations and comorbidity interactions. Advanced Bayesian modeling and annotated electronic medical records underscore the importance of diverse data integration for capturing CVD risk dynamics and enhancing predictive accuracy [25, 26, 27, 28].

2.3 Biomarkers of Aging and Health Outcomes

Biomarkers are crucial for assessing aging processes and health outcomes, offering insights beyond chronological age. These indicators, encompassing molecular, cellular, and physiological measures, provide a comprehensive understanding of biological age and disease risk [2]. Epigenetic biomarkers, particularly DNA methylation clocks, are notable for their precision in estimating biological age through tissue-specific methylation patterns. The integration of diverse biomarkers, such as miRNAs and gut microbiota-derived biomolecules, highlights the multifaceted nature of aging and its health impacts. These biomarkers interact with host systems via epigenetic mechanisms, reflecting biological aging complexity. Advanced imaging techniques, like convolutional neural networks applied to MRI data, reveal brain-predicted age as a reliable brain aging biomarker, accommodating prediction uncertainty [29]. Electronic health records (EHRs) offer rich longitudinal data for cardiovascular risk prediction, illustrating the potential of clinical data and biomarker analysis integration [6]. Sophisticated machine learning models enhance risk stratification by incorporating diverse risk factors and complex interactions [7]. U-learning approaches, utilizing combinatory multi-subsampling for ensemble predictions and confidence intervals, exemplify innovative methods for refining continuous outcome predictions [4]. High-resolution neuroelectric measures from extensive datasets improve biomarker-based assessment accuracy in resting and task conditions [17], underscoring biomarkers' significance in refining health outcome predictions and enhancing risk stratification.

2.4 Gender Differences in Biological Aging

Biological aging processes exhibit significant gender differences, impacting healthspan and lifespan [30]. These disparities manifest in physiological and molecular aspects influencing age-related disease risks, particularly cardiovascular disease (CVD). Men and women display distinct aging patterns in hormonal regulation, immune function, and metabolic processes, affecting disease susceptibility and progression. Hormonal differences, notably estrogen's protective effects in premenopausal women, are crucial in modulating cardiovascular risk by enhancing endothelial function, optimizing lipid metabolism, and regulating inflammatory processes, leading to lower CVD incidence during reproductive years. Maternal factors, such as high-fat diets, link to long-term diabetes, hypertension, and CVD risks in offspring, emphasizing balanced diets for cardiovascular health maintenance [31, 32]. Post-menopause estrogen decline correlates with increased CVD risk, illustrating hormonal changes' complex interplay with cardiovascular health. Gender differences in immune aging are evident, with women generally exhibiting robust immune responses and slower immune system decline than men, influencing aging rates and disease outcomes. Effective immune responses are critical for mitigating age-related diseases like CVD and cancer, with research indicating aging-associated immune efficiency decline exacerbating susceptibility [33, 34]. T cell aging and immune signaling pathway alterations further emphasize gender-specific factors' importance in aging research. Metabolic differences also impact gender-related biological aging disparities, with men typically experiencing higher metabolic disorder rates, such as insulin resistance and obesity—critical CVD risk factors. While women often have lower biological ages and longer lifespans, they may experience greater frailty and poorer health in later years, revealing sex, metabolism, and aging-related health outcomes' complex interplay [35, 30, 36, 37]. These disparities arise from genetic and lifestyle factors, necessitating tailored risk assessment and intervention strategies considering gender-specific aging dynamics. Understanding gender differences in biological aging is vital for developing effective CVD risk mitigation strategies and improving health outcomes. By integrating gender-specific biomarkers and risk factors into predictive models, researchers can enhance cardiovascular risk stratification accuracy, facilitating personalized healthcare interventions tailored to distinct aging profiles and health needs, as demonstrated by advancements in personalized medicine and machine learning techniques [25, 38, 39, 7].

2.5 Psychosocial and Environmental Influences on Biological Aging

Psychosocial and environmental factors significantly affect biological aging, influencing aging rates and age-related disease susceptibility. A major challenge is the historical male bias in research sampling, limiting understanding of sex-specific biological aging mechanisms and implications [30]. Addressing this gap requires diverse sample integration to elucidate psychosocial stressors' differential impacts across genders. Childhood trauma critically affects psychological and neurobiological processes, increasing psychopathology vulnerability and potentially accelerating biological aging [40]. Early-life stress's long-term effects underscore early interventions and support systems' importance in mitigating adverse health trajectory impacts. Environmental factors, including lifestyle and gut microbiota composition, play pivotal aging process roles. Inflammaging, marked by chronic low-grade inflammation, is influenced by gut microbiota, modulating immune responses and metabolic processes [41]. These interactions highlight maintaining a balanced microbiome through diet and lifestyle modifications to promote healthy aging. The survey emphasizes a multidisciplinary approach to understanding complex interactions between psychosocial stress, epigenetic modifications, and health outcomes [35]. This perspective is crucial for developing targeted interventions addressing biological aging's multifactorial nature, incorporating insights from epidemiology, psychology, and molecular biology. Environmental and lifestyle factors, such as physical activity, nutrition, and pollutant exposure, profoundly affect aging [34]. These factors can exacerbate or mitigate biological age acceleration effects, underscoring public health strategies promoting healthy living environments and lifestyles.

3 Biological Age Acceleration and Cardiovascular Disease Mechanisms

The interplay between biological age acceleration and cardiovascular disease (CVD) involves complex mechanisms, prominently featuring epigenetic modifications. These modifications bridge aging processes with cardiovascular health by influencing molecular pathways that manifest in accelerated biological aging within cardiovascular contexts. Figure 2 illustrates the hierarchical structure of

these mechanisms, highlighting primary categories such as epigenetic mechanisms, inflammation and oxidative stress, metabolic dysregulation, and other contributing factors. Each category is further divided into subcategories, detailing key concepts like DNA methylation, chronic inflammation, insulin resistance, and psychosocial factors. This comprehensive overview underscores the intricate interactions that influence cardiovascular health, thereby enhancing our understanding of the relationship between biological age acceleration and CVD.

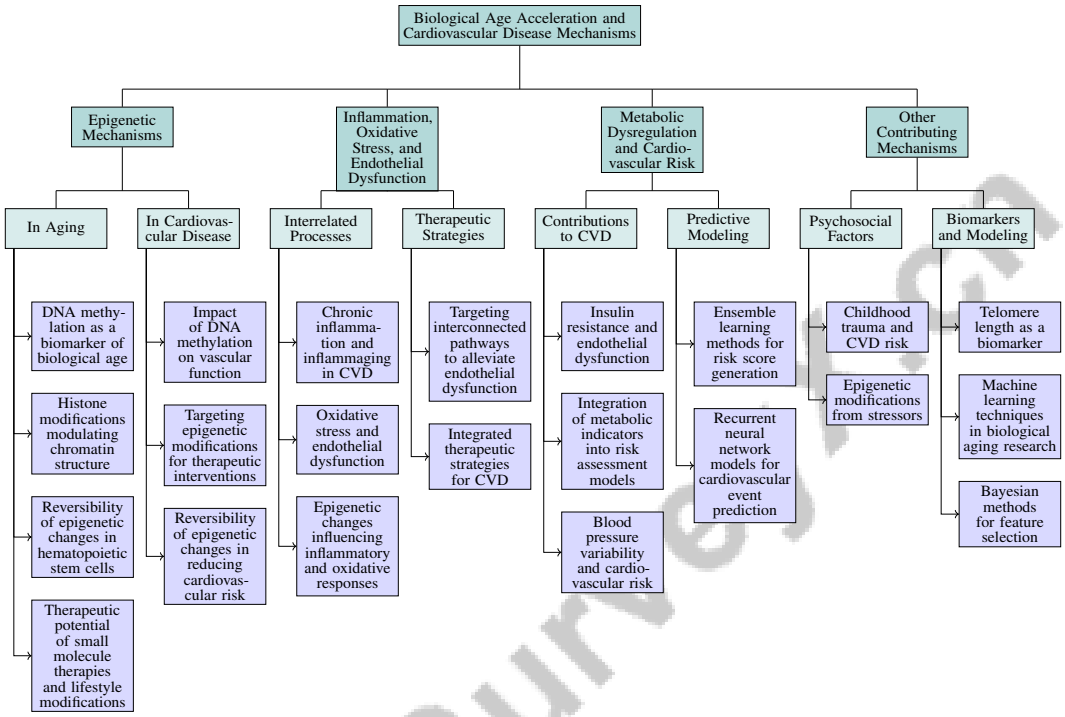


Figure 2: This figure illustrates the hierarchical structure of biological age acceleration and cardiovascular disease mechanisms, highlighting primary categories such as epigenetic mechanisms, inflammation and oxidative stress, metabolic dysregulation, and other contributing mechanisms. Each category is further divided into subcategories, detailing key concepts like DNA methylation, chronic inflammation, insulin resistance, and psychosocial factors, providing a comprehensive overview of the complex interactions influencing cardiovascular health.

3.1 Epigenetic Mechanisms in Aging

Epigenetic mechanisms, including DNA methylation, histone modifications, and non-coding RNA interactions, are pivotal in regulating gene expression, significantly impacting aging. DNA methylation is a robust biomarker of biological age, closely associated with mortality risk and age-related diseases, such as CVD [11]. Histone modifications also modulate chromatin structure, influencing gene expression profiles linked to aging [5]. These modifications maintain genomic stability and cellular homeostasis, crucial for cardiovascular health. The heterochromatin loss model emphasizes alterations in chromatin organization, highlighting the interplay between genetic and environmental factors in aging [8].

Epigenetic changes in hematopoietic stem cells suggest reversibility, offering therapeutic potential for mitigating age-related decline in stem cell function and improving cardiovascular outcomes. Advanced modeling techniques, such as logistic mixed-effects models with t-SNE and GMM, enhance understanding of phenotypic variability in cardiovascular health [7]. Brain age predictions based on interpretable features reflect epigenetic alterations, linking cognitive decline and cardiovascular risks [4].

Recent research highlights the role of epigenetic modifications in maintaining cellular homeostasis and their contribution to age-related diseases, revealing potential therapeutic targets [33, 42, 43]. Interventions manipulating epigenetic mechanisms, such as small molecule therapies and lifestyle

modifications, are being explored to mitigate aging effects and improve health outcomes in older populations. Ongoing clinical trials assess these approaches' safety and efficacy, paving the way for innovative strategies against age-related health issues.

As shown in Figure 3, this figure illustrates the primary epigenetic mechanisms in aging, highlighting DNA methylation, histone modifications, and non-coding RNA interactions. Each mechanism is linked to specific aspects of aging, such as DNA methylation serving as a biomarker of biological age and its impact on cardiovascular diseases, histone modifications influencing chromatin structure and gene expression, and non-coding RNAs playing roles in gene regulation and potential therapeutic applications. The intricate interplay between these epigenetic modifications and age-related diseases, particularly cardiovascular conditions, is evident. The figures depict miRNA-induced changes in histone modifications and chromatin accessibility, illustrating miRNAs' multifaceted roles in altering gene expression and chromatin dynamics. Additionally, the comparative analysis of cellular aging and cancerogenesis emphasizes key genetic elements' roles in these processes, providing insight into how normal cellular functions can be disrupted, leading to age-related pathologies and cancer [42, 33].

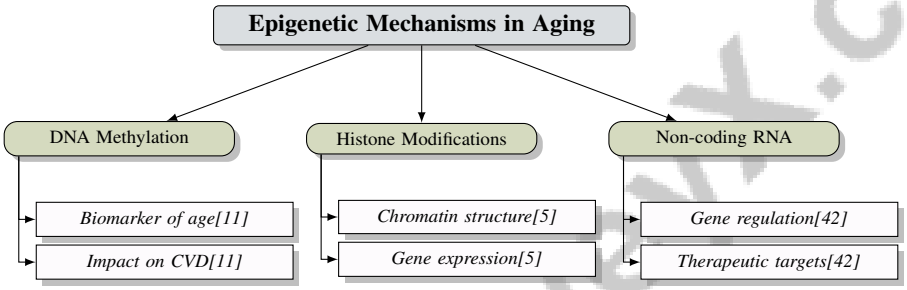


Figure 3: This figure illustrates the primary epigenetic mechanisms in aging, highlighting DNA methylation, histone modifications, and non-coding RNA interactions. Each mechanism is linked to specific aspects of aging, such as DNA methylation serving as a biomarker of biological age and its impact on cardiovascular diseases, histone modifications influencing chromatin structure and gene expression, and non-coding RNAs playing roles in gene regulation and potential therapeutic applications.

3.2 Epigenetic Mechanisms and Cardiovascular Disease

Epigenetic changes, particularly in DNA methylation, significantly contribute to CVD pathogenesis within accelerated aging. These modifications regulate gene expression, impacting vascular function and CVD development [42]. The relationship between epigenetic alterations and aging underscores their influence on genomic instability, telomere attrition, and cellular senescence [22].

Targeting epigenetic modifications offers therapeutic potential for age-related diseases, including CVD. Understanding these molecular mechanisms can lead to novel interventions to mitigate their effects [44]. The reversibility of certain epigenetic changes presents promising avenues for interventions aimed at decelerating biological age acceleration and reducing cardiovascular risk.

Epigenetic changes impact endothelial function, inflammation, and metabolic pathways, critical in CVD. Modulating CVD pathways through epigenetic mechanisms reveals the interaction between genetic and environmental factors in disease risk. Targeted epigenetic therapies, including small molecule treatments and lifestyle modifications, promise to enhance cardiovascular health outcomes by potentially reversing aging effects [25, 26, 43].

3.3 Inflammation, Oxidative Stress, and Endothelial Dysfunction

Inflammation, oxidative stress, and endothelial dysfunction are interrelated processes crucial to CVD pathogenesis. Immune system deregulation leads to chronic inflammation, or inflammaging, pivotal in age-related diseases, including CVD [45]. This chronic state accelerates vascular aging and endothelial dysfunction [41].

Endothelial dysfunction, a precursor to atherosclerosis, impairs endothelial cells' ability to regulate vascular functions. Oxidative stress, resulting from ROS production imbalance, damages cellular com-

ponents, impairing endothelial function and promoting a pro-inflammatory environment conducive to CVD progression [9].

Epigenetic changes, such as histone and telomere alterations, correlate with aging phenotypes and longevity [46]. These modifications influence gene expression patterns regulating inflammatory and oxidative responses, impacting cardiovascular health. Targeting these modifications may restore hematopoietic stem cell function and mitigate age-related endothelial dysfunction [47].

The molecular mechanisms underlying chronic inflammation and oxidative stress highlight CVD pathogenesis's complexity and the need for integrated therapeutic strategies. Targeting interconnected pathways may develop interventions to alleviate endothelial dysfunction and reduce cardiovascular risk, improving health outcomes in aging populations [18].

3.4 Metabolic Dysregulation and Cardiovascular Risk

Metabolic dysregulation significantly contributes to cardiovascular risk, especially in accelerated aging. Insulin resistance promotes dyslipidemia and endothelial dysfunction, key pathways leading to CVD [36]. The interplay between metabolic changes and immune function is evident in immunosenescence, where age-related metabolic alterations exacerbate cardiovascular risk [48].

Advanced modeling techniques, such as convolutional operations on time-series data, classify CVD risk by extracting features from patient records, enhancing cardiovascular outcome predictions [49]. Integrating metabolic indicators into risk assessment models improves cardiovascular prediction accuracy.

Biological age assessment through DNA methylation age and leukocyte telomere length offers insights into metabolic health and physical functioning associations, as shown in monozygotic twin studies [50]. These biomarkers provide a nuanced understanding of metabolic dysregulation's impact on cardiovascular risk in accelerated aging.

Blood pressure variability, influenced by anti-hypertensive treatments, significantly affects cardiovascular risk. While treatments lower average SBP, they may increase SBP variability, associated with heightened CVD risk [51]. This highlights managing metabolic and cardiovascular health complexity in aging populations.

Ensemble learning methods, like XGBoost, handle unbalanced data and generate explainable risk scores for conditions like T2DM, illustrating metabolic disorders' intricate relationship with cardiovascular risk [52]. Analyzing common blood markers, including CBC, provides essential insights into metabolic dysregulation and health risk assessments [14].

Integrating recurrent neural network models, such as MT-GRU, analyzing longitudinal EHR data, advances cardiovascular event prediction across multiple time horizons [6]. Incorporating metabolic factors into comprehensive risk assessment frameworks enhances cardiovascular risk stratification in accelerated aging, contributing to personalized healthcare strategies to mitigate cardiovascular risk.

3.5 Other Contributing Mechanisms

Beyond primary pathways, other biological mechanisms contribute to CVD in biological age acceleration. Childhood trauma accelerates biological aging by influencing social information processing and emotional regulation, increasing CVD risk [40]. These stressors result in lasting epigenetic modifications, affecting long-term health outcomes and emphasizing psychosocial factors' importance in aging research [35].

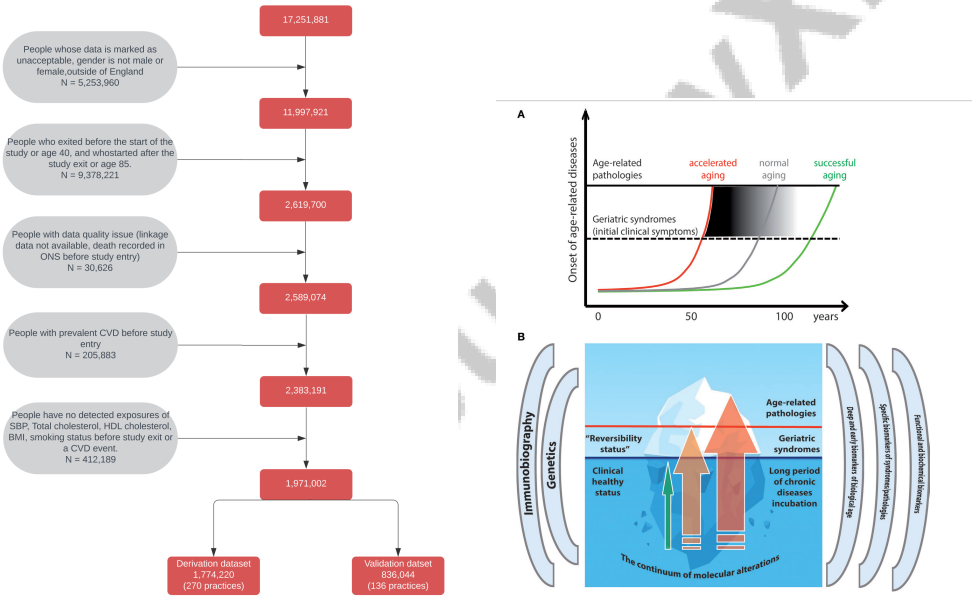
Telomere length (TL) is a recognized biomarker of cellular senescence and aging, with shorter telomeres linked to elevated CVD risk [53]. While TL has limitations in capturing aging's complexity, it remains crucial in a comprehensive aging research framework [54]. Heterochromatin, essential for genome protection and gene regulation, plays a role in CVD pathogenesis; structural alterations lead to genomic instability and modified gene expression in accelerated aging [55].

Machine learning techniques promise biological aging research by identifying complex patterns among biomarkers, enhancing biological age estimation and risk stratification accuracy. Applying deep learning to blood biochemistry and cell count data exemplifies innovative methodologies for quantifying accelerated aging and health implications [56]. Integrating BrainAge and MetaboAge

scores provides a holistic understanding of aging, capturing neurological and metabolic dimensions of biological age [57].

Bayesian methods, like BSGS-D, enhance feature selection in complex datasets, resulting in robust models for predicting health outcomes [27]. Integrating structured biological information into analytical frameworks, as in sparse CCA, provides insights into complex biomarker-aging relationships [58]. DunedinPoAm utilizes longitudinal data to identify methylation changes correlating with biological decline, offering a reliable aging measure [59]. Levine et al.'s method uses clinical measures to identify CpGs correlating with biological aging, enhancing aging-related outcome predictions [60]. Despite challenges in large-scale omics data analysis, these innovations enhance understanding of biological mechanisms in patient populations.

Advanced methodologies, including Bayesian hierarchical factor analysis and longitudinal inverse classification, enhance understanding of CVD's multifaceted biological processes in biological age acceleration. These approaches identify nontraditional risk factors, like genetic variants and gene pathways, facilitating personalized lifestyle recommendations to reduce CVD risk. Comprehensive analysis of clinical, demographic, and multi-omics data paves the way for improved risk assessment and targeted intervention strategies, leading to more effective CVD prevention and management [25, 26, 10].



(a) ERROR!!![61] (b) ERROR!!![34]

Figure 4: Examples of Other Contributing Mechanisms

As shown in Figure 4, exploring biological age acceleration and cardiovascular disease requires considering various contributing mechanisms beyond primary risk factors. The depicted figure aims to visually represent complex interactions and pathways contributing to cardiovascular disease, highlighting the need for a comprehensive understanding of how biological age acceleration influences cardiovascular health. By examining these mechanisms, researchers gain insights into potential intervention points and strategies for mitigating cardiovascular risk associated with accelerated biological aging [61, 34].

4 Predictive Biomarkers for Biological Age Acceleration

4.1 Epigenetic Biomarkers

Epigenetic biomarkers are critical in elucidating the molecular mechanisms driving biological age acceleration and its associated diseases. DNA methylation patterns, especially those identified

Benchmark	Size	Domain	Task Format	Metric
DNAmAge[21]	43	Epigenetics	Biological Age Assessment	DNAmAge
TAME[62]	8	Geroscience	Biomarker Selection	Accuracy, Responsiveness
DL-CPH[38]	2,164,872	Epidemiology	Risk Prediction	R-squared, Harrell's C
CVD-RFAC[28]	9,678	Cardiovascular Disease	Risk Factor Annotation	F1-measure, Precision
PAG[63]	7,243	Prostate Cancer	Risk Assessment	AUC
BA-MA[57]	11,826	Aging	Mortality Prediction	Mean Absolute Error, Hazard Ratio
AgeGuess[64]	200,000	Aging Research	Age Estimation	Accuracy, Points
GrimAge[65]	490	Clinical Gerontology	Predictive Modeling	Hazard Ratio, Odds Ratio

Table 1: This table presents a comprehensive overview of various benchmarks utilized in the assessment of epigenetic biomarkers and their applications in biological age estimation, risk prediction, and disease modeling. It details the size, domain, task format, and evaluation metrics of each benchmark, providing insight into their relevance and utility in geroscience and aging research.

by epigenetic clocks like DNAm PhenoAge, correlate strongly with health outcomes and mortality, enhancing biological age assessments [21]. These biomarkers present potential pathways for interventions aimed at monitoring age-related changes. Table 1 offers a detailed examination of representative benchmarks in the field of epigenetic biomarkers, highlighting their significance in advancing biological age assessments and identifying disease-related risk factors.

Advancements in epigenome editing suggest that age-related epigenetic alterations are potentially reversible, which is significant for diseases like cardiovascular disease (CVD) [66]. Deep learning frameworks, such as Age-Net, refine biological age estimation from imaging data, identifying individuals at risk of accelerated aging [67]. Machine learning models like the Greedy Dual-Stream Model (GDSM) enhance predictive accuracy by capturing comprehensive brain features, even with limited data [68]. The U-learning method provides robust prediction inference in high-dimensional contexts, offering tailored confidence intervals for individual predictions [4].

The uniCATE method estimates the univariate conditional average treatment effect (CATE) for each biomarker, facilitating the identification of predictive biomarkers [69]. This approach highlights biomarkers predictive of biological age acceleration and responsive to interventions, offering insights into potential therapeutic targets.

Lifestyle interventions, particularly personalized cardiovascular disease risk reduction strategies, show promise in mitigating age-related dysfunction, especially in renal aging contexts [25]. These findings underscore the importance of incorporating lifestyle factors into predictive models, paving the way for personalized health management and prevention strategies. Structured methodologies enable researchers to pinpoint genes and metabolites influencing the aging process, underscoring the critical role of epigenetic biomarkers in predicting biological age acceleration and identifying therapeutic avenues.

4.2 Genetic and Telomere-Based Biomarkers

Genetic and telomere-based biomarkers are pivotal in studying biological age acceleration, providing insights into the molecular underpinnings of aging and its health implications. Telomeres, the protective caps on chromosome ends, are vital for genomic stability and cellular replicative capacity. Shorter telomere length (TL) is a well-established biomarker of cellular aging, correlating with increased risks of age-related diseases, particularly CVD [53]. TL attrition is influenced by genetic and environmental factors, making it a significant indicator of biological age acceleration [54].

Genetic variations, such as single nucleotide polymorphisms (SNPs), contribute to telomere length variability and aging processes, offering a genetic basis for differences in aging trajectories among individuals [55]. Integrating genetic data with telomere measures provides a comprehensive framework for assessing biological age and predicting health outcomes.

Advancements in machine learning and computational biology have enhanced the analysis of complex genetic data, facilitating the identification of novel genetic biomarkers linked to biological age acceleration [70]. These technologies enable exploration of interactions between genetic factors and other biomarkers, such as telomere length, enhancing biological age prediction accuracy. The

application of deep learning models to genetic and telomere data exemplifies the potential for developing personalized risk profiles and intervention strategies [71].

Integrating genetic and telomere-based biomarkers into predictive models of biological age acceleration holds promise for advancing personalized healthcare. By identifying individuals at risk of accelerated aging through advanced biological markers, researchers can develop targeted interventions to reduce age-related health risks, enhance healthspan, and potentially extend lifespan. These biomarkers illuminate the biological aging process and correlate with diverse health outcomes, enabling a more personalized approach to health management in aging populations [62, 72, 56, 60]. Developing comprehensive biomarker panels incorporating genetic and telomere measures marks a significant advancement in aging research, providing new insights into the complexities of biological aging.

4.3 Metabolic and Inflammatory Biomarkers

Method Name	Biomarker Evaluation	Intervention Strategies	Predictive Modeling
PPLasso[73]	-	-	Predictive Biomarkers
I-Rand[74]	Metabolic Biomarkers	Dietary Interventions	Predictive Modeling
EPB-POF[75]	Baseline Viral Load	Lifestyle Modifications	Predictive Biomarkers

Table 2: Overview of methodologies for evaluating biomarkers and their application in intervention strategies and predictive modeling related to cardiovascular disease (CVD) risk. The table highlights the use of PPLasso, I-Rand, and EPB-POF methods, each focusing on distinct aspects such as metabolic biomarkers, dietary interventions, and predictive modeling to enhance cardiovascular risk assessment.

Metabolic and inflammatory biomarkers are crucial for understanding the interactions contributing to cardiovascular disease (CVD) risk, especially in the context of biological age acceleration. Insulin resistance, a hallmark of metabolic dysregulation, is closely linked to increased cardiovascular risk, with recent therapeutic strategies prioritizing its reduction over traditional CVD symptom management [36].

Identifying and analyzing predictive biomarkers is essential for effective risk stratification. Advanced methodologies like PPLasso effectively decorrelate biomarkers, overcoming limitations of traditional methods such as Lasso in high-dimensional settings [73]. This approach enhances biomarker evaluation reliability, aiding in identifying critical metabolic and inflammatory indicators contributing to CVD risk.

As illustrated in Figure 5, the categorization of metabolic and inflammatory biomarkers related to CVD risk highlights key components such as insulin resistance, predictive biomarkers, and lifestyle interventions. The figure emphasizes the importance of strategies like the PPLasso method and lifestyle modifications in managing CVD risk, reinforcing the narrative that effective intervention relies on a comprehensive understanding of these relationships. Additionally, Table 2 provides a comprehensive overview of advanced methodologies used for biomarker evaluation, intervention strategies, and predictive modeling in the context of cardiovascular disease risk assessment.

Physical activity influences biological age, with physiological indicators like heart rate reserve and blood pressure serving as biomarkers [12]. Incorporating exercise, dietary changes, and relaxation techniques into intervention protocols has shown potential in modulating biological age and lowering cardiovascular risk [21]. These findings highlight the significance of lifestyle modifications in managing metabolic and inflammatory processes linked to CVD.

Dietary interventions, such as low-carbohydrate diets, have been assessed for their efficacy in mitigating risks associated with type-2 diabetes and CVD [74]. These strategies target metabolic pathways, providing promising avenues for reducing cardiovascular risk in individuals with accelerated biological aging.

Integrating baseline biomarkers, such as viral load and CD4 cell count, into predictive models offers a more robust framework for evaluating cardiovascular risk compared to traditional approaches [75]. This comprehensive assessment of metabolic and inflammatory biomarkers enhances the ability to forecast CVD risk, contributing to more effective and personalized healthcare strategies aimed at improving cardiovascular outcomes.

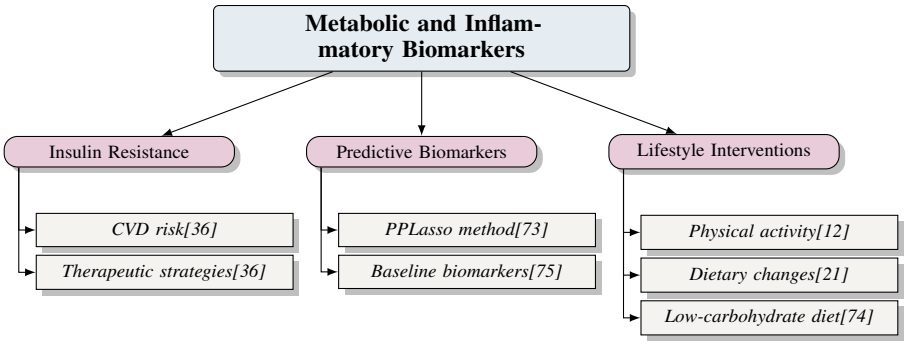


Figure 5: This figure illustrates the categorization of metabolic and inflammatory biomarkers related to cardiovascular disease (CVD) risk, highlighting insulin resistance, predictive biomarkers, and lifestyle interventions. Key strategies and methodologies, such as the PPLasso method and lifestyle modifications, are emphasized for their roles in managing CVD risk.

4.4 Proteomic and Senescence Markers

Proteomic and senescence markers offer valuable insights into the biological processes underlying age acceleration, particularly concerning cardiovascular disease (CVD) risk. Proteomic markers, derived from analyzing protein expression patterns, provide a detailed view of cellular processes and their alterations with aging, identifying molecular signatures associated with biological age acceleration and potential therapeutic targets [21].

Senescence markers reflect cellular aging states characterized by irreversible growth arrest and the secretion of pro-inflammatory cytokines, collectively termed the senescence-associated secretory phenotype (SASP). This phenotype drives chronic inflammation, a key contributor to age-related diseases, including CVD [41]. The accumulation of senescent cells impairs tissue function and increases disease susceptibility, necessitating strategies to mitigate their effects [5].

Recent advances in proteomics have facilitated the identification of specific protein profiles correlating with biological age, elucidating pathways involved in age-related decline. High-throughput proteomic technologies enable the discovery of novel biomarkers that enhance biological age acceleration prediction and associated health risks [70]. These proteomic signatures provide a comprehensive framework for understanding protein interactions and their roles in aging processes.

Integrating senescence markers into predictive models of biological age acceleration advances personalized healthcare. By identifying individuals at risk of accelerated aging, these markers can inform targeted interventions to reduce the burden of age-related diseases and extend healthspan. The development of comprehensive biomarker panels that integrate both proteomic data and senescence markers signifies a pivotal advancement in aging research. This innovative approach enhances quantitative assessments of biological age and aging mechanisms, opening new pathways for exploring interconnected age-related diseases, ultimately contributing to strategies aimed at extending healthspan and improving physiological function in aging populations [72, 60].

4.5 Machine Learning Approaches to Biomarker Identification

Method Name	Methodological Sophistication	Data Integration	Predictive Accuracy
WSF[3]	Weighted Score Fusion	Multiple Classifiers Integration	Improved Prediction Accuracy
SMOG[76]	-	-	Hierarchical Structures
MT-GRU[6]	Attention Mechanisms	Diverse Ehr Data	Improve Predictions
BPA[2]	Machine Learning Techniques	Integrate Neuroimaging Data	Gaussian Process Regression
uniCATE[69]	Nonparametric Inference Procedure	-	Better Accuracy

Table 3: Overview of machine learning methods for biomarker identification, highlighting their methodological sophistication, data integration capabilities, and predictive accuracy. The table compares various approaches, including Weighted Score Fusion, Structural Modeling using Overlapped Group, and multi-task gated recurrent unit models, among others, showcasing their unique contributions to improving predictive performance in biomarker discovery.

Machine learning (ML) approaches have transformed the identification and validation of predictive biomarkers, employing sophisticated methodologies that surpass traditional analytical techniques. Table 3 provides a comprehensive comparison of different machine learning methodologies employed in the identification and validation of predictive biomarkers, emphasizing their methodological sophistication, data integration strategies, and predictive accuracy. An explainable XGBoost-based ensemble learning approach exemplifies this advancement by combining multiple models to enhance predictive performance, improving the identification of biomarkers associated with cardiovascular disease (CVD) risk [52]. This method underscores ML's potential in refining predictive models by leveraging various classifiers for greater accuracy [3].

The Structural Modeling using Overlapped Group (SMOG) method, a generalized penalized regression technique, enforces hierarchical structures between prognostic and predictive effects, facilitating high-dimensional data analysis and enhancing biomarker identification robustness [76]. This approach highlights the importance of incorporating hierarchical structures in ML models to improve accuracy and reliability in biomarker validation.

Advanced ML techniques, such as multi-task gated recurrent unit (MT-GRU) models, utilize attention mechanisms to predict cardiovascular events by analyzing diverse electronic health record (EHR) data, demonstrating ML's utility in managing complex datasets and improving cardiovascular risk stratification [6]. These models exemplify the integration of ML techniques with clinical data to enhance health outcome predictions.

Machine learning applications in predicting brain age from neuroimaging data, as demonstrated by the BrainAge framework, provide insights into neurological aging processes and their correlations with various health outcomes [2]. This approach underscores ML's potential in identifying biomarkers linked to brain age and accelerated aging, offering a framework for understanding complex interactions between neurological and cardiovascular health.

The uniCATE method introduces a flexible nonparametric inference procedure that is double-robust and asymptotically linear, enabling valid inference about biomarker importance [69]. This innovation facilitates the discovery of biomarkers predictive of biological age acceleration and responsive to interventions, offering insights into potential therapeutic targets.

Future research could explore integrating additional lifestyle factors and environmental exposures to enhance ML models' predictive capabilities, providing a more comprehensive approach to biomarker identification and validation. Recent advancements in ML techniques are revolutionizing aging research by offering methodologies for quantifying biological age and understanding age-related diseases' underlying mechanisms. These ML approaches, particularly when integrated with high-throughput omics data, enable developing sophisticated 'aging clocks' that can identify novel biomarkers of biological aging. This progress enhances our ability to measure and monitor aging at a molecular level, opening new avenues for addressing the complexities of biological age acceleration and ultimately aiming to improve healthspan and combat age-associated diseases [77, 72, 70, 10].

5 Aging Biomarkers and Cardiovascular Disease Risk Stratification

The role of aging biomarkers in cardiovascular disease (CVD) risk assessment has gained significant attention, emphasizing the need for a comprehensive understanding of these markers in refining risk stratification. This section explores advancements in predictive models that integrate aging biomarkers, enhancing the precision and personalization of cardiovascular risk evaluations. By incorporating both traditional clinical parameters and innovative biomarkers, these models improve the accuracy of cardiovascular risk assessments.

5.1 Advanced Predictive Models

Advanced predictive models incorporating aging biomarkers have profoundly improved cardiovascular risk assessments, offering nuanced insights into individual health trajectories. The Phenotypic Age metric, derived from NHANES IV data, exemplifies the integration of clinical parameters with aging biomarkers, showing strong associations with mortality risk over a 12.6-year follow-up of 11,432 adults [78]. Epigenetic markers like DNAm PhenoAge have further refined mortality risk assessments, outperforming previous DNAm age measures in predictive accuracy [60].

Methodologies such as the ABAP method utilize aging biomarkers from 3D MR imaging to enhance cardiovascular risk assessments by capturing complex interactions between aging and cardiovascular health [79]. Machine learning techniques, including CNN approaches, offer superior performance in mortality risk predictions, leveraging wearable devices for real-time health risk monitoring [77]. AutoPrognosis, developed for the UK Biobank, integrates multiple biomarkers and computational techniques to improve CVD risk prediction, particularly in underserved subgroups [7].

Incorporating socioeconomic factors, such as education level, into predictive models enhances risk stratification. Low education is an independent predictor of accelerated biological aging, highlighting the need to include modifiable risk factors in comprehensive assessments [37]. These models, leveraging AI and machine learning, identify novel risk factors and enhance prediction accuracy, aiding early CVD detection and improving patient outcomes [62, 7, 56].

5.2 Personalized Risk Assessment and Treatment

Biomarkers have revolutionized personalized risk assessment and treatment strategies in CVD management. By creating dynamic and individualized risk profiles, healthcare providers can surpass traditional static methods, enhancing the precision of risk stratification and treatment planning. The 2-stage landmarking model exemplifies this by adapting personalized risk profiles over time [61].

Biomarkers such as DNA methylation patterns, telomere length, and proteomic signatures offer insights into aging and disease progression, facilitating tailored interventions to mitigate CVD risk. Advanced molecular diagnostics support precise treatment selection, and recent empirical Bayes techniques improve biomarker screening accuracy, minimizing false discovery rates [80, 69].

Machine learning models enhance personalized risk assessment by integrating diverse biomarker data with clinical and lifestyle factors. These models dynamically adjust CVD risk predictions based on real-time data, enabling timely, evidence-based interventions [61, 25, 69, 6]. Wearable devices provide continuous monitoring, offering actionable data to guide treatment decisions.

Personalized treatment strategies informed by biomarker data improve CVD management outcomes. By aligning interventions with individual needs and risk factors, healthcare providers can enhance treatment efficacy, facilitate lifestyle recommendations, and optimize preventative care strategies [25, 61, 39, 28].

5.3 Biomarkers in Clinical Applications

The integration of biomarkers in clinical practice revolutionizes CVD management by enabling personalized approaches to diagnosis, risk assessment, and treatment. Utilizing genetic insights and nontraditional risk factors, such as genetic variants and multi-omics data, clinicians can develop tailored interventions [25, 26, 28]. Biomarkers like DNA methylation patterns, telomere length, and proteomic signatures inform targeted interventions, enhancing treatment efficacy and prevention measures.

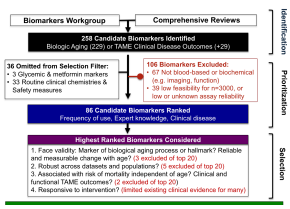
Predictive biomarkers facilitate early identification of individuals at elevated CVD risk, allowing timely interventions to mitigate disease progression. DNA methylation clocks assess biological age and predict age-related health risks, enabling personalized lifestyle modifications and pharmacological interventions [25, 56].

Advancements in machine learning and computational biology improve biomarker integration, enabling predictive models that stratify patient populations based on treatment responses. Techniques like PPLasso and empirical Bayes approaches enhance biomarker screening, while machine learning algorithms like XGBoost refine treatment strategies [73, 13, 75, 80, 69]. Wearable devices offer real-time monitoring, informing clinical decision-making and treatment adjustments.

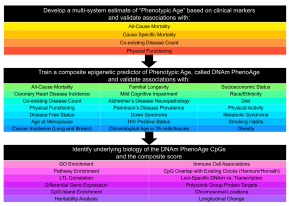
Biomarkers extend beyond risk assessment to monitor treatment efficacy and identify potential adverse effects. Systematic monitoring of biomarker fluctuations aids in assessing therapeutic interventions, identifying patient sub-populations likely to benefit from specific treatments, and minimizing false discovery rates in biomarker identification [81, 75, 80, 69, 56].

Biomarker integration in clinical applications marks a significant advancement in CVD management, enabling tailored prevention and treatment strategies based on genetic, clinical, and demographic

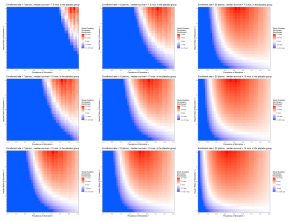
profiles. This personalized approach enhances risk assessment accuracy, facilitates targeted lifestyle recommendations, and improves patient outcomes [25, 26, 61, 28].



(a) Identification, Prioritization, and Selection of Biomarkers for Clinical Trials[62]



(b) ERROR!!![60]



(c) The image shows a series of heatmaps representing the hazard ratio of biomarker + versus biomarker - for different enrollment rates and median survival times in a placebo group.[82]

Figure 6: Examples of Biomarkers in Clinical Applications

Figure 6 illustrates the importance of aging biomarkers in CVD risk stratification and clinical applications. Biomarkers serve as essential tools in clinical trials, providing insights into disease progression and therapeutic efficacy. The first image details a systematic approach to identifying and selecting biomarkers for clinical trials. The second image, marked as an error, highlights potential challenges in biomarker research. The third image uses heatmaps to represent hazard ratios of biomarker-positive versus biomarker-negative subjects, emphasizing the importance of understanding biomarker prevalence and its impact on clinical outcomes [62, 60, 82].

5.4 Socioeconomic and Lifestyle Factors

Socioeconomic and lifestyle factors significantly influence the effectiveness of biomarker-based CVD risk stratification and prevention efforts. These factors include income, education, occupation, diet, physical activity, and stress management, all impacting health outcomes and intervention responses [24].

Socioeconomic status (SES) affects health disparities, access to healthcare, and the ability to maintain healthy behaviors. Lower SES is linked to higher CVD risk due to poor nutrition, sedentary lifestyles, and chronic stress, which accelerate CVD progression [31, 24, 83, 37, 28]. Integrating SES into biomarker-based models ensures tailored interventions for different population groups.

Modifiable lifestyle factors, such as diet, exercise, and smoking, are critical in influencing cardiovascular health. Regular physical activity and a balanced diet improve cardiovascular biomarkers, reducing CVD risk and promoting health [25, 31, 61, 83, 28].

Stress management and mental health significantly impact cardiovascular outcomes. Psychosocial stress exacerbates CVD progression, influencing prognosis. Effective stress management is crucial for preventing CVD in high-risk individuals [38, 31, 35, 83, 28]. Interventions addressing stress through mindfulness, therapy, and support improve biomarker profiles and risk stratification efforts.

6 Challenges and Future Directions

6.1 Methodological Challenges

Research on biological age acceleration and cardiovascular disease (CVD) faces several methodological hurdles that affect the precision of health outcome assessments. A key issue is the inadequacy of traditional ROC curves, which do not effectively incorporate covariate data, potentially leading to misleading diagnostic evaluations [84]. Moreover, methods like the immune score that rely on reference ranges can introduce errors, as these ranges may not account for individual variability in blood parameters [14].

Integrating diverse data sources—genetic, epigenetic, and clinical—into predictive models is fraught with challenges regarding interpretability and scalability. Although powerful, the complexity of

advanced models can obscure insights into underlying biological processes [3]. Single-cell research is essential to establish causal links between DNA damage and epigenetic changes [44].

Current studies are often limited by dataset size discrepancies and confounding factors, which can compromise the robustness of findings [20]. The prevalence of risk factors like hypertension and diabetes, along with insufficient public awareness and healthcare resources, complicates the development of comprehensive predictive models [24]. Additionally, existing benchmarks often lack the capability to measure neuroelectric currents in white matter, resulting in an incomplete understanding of individual brain function differences [17].

Predictive uncertainty in current methods can lead to inaccurate age estimations, particularly in critical decision-making scenarios [23]. Non-random missing health data and variability in study quality introduce biases that can skew research outcomes [15]. Furthermore, the computational complexity of certain methods, such as Risk-stratify, can be considerable, depending on dataset size and covariate numbers, complicating the research process [39].

To address these challenges, innovative research strategies that incorporate diverse data sources, advanced computational techniques, and inclusive study designs are essential. Overcoming these methodological obstacles will enhance the precision and reliability of biological age assessments, improving the understanding of biological age acceleration and its implications for cardiovascular health, ultimately guiding interventions targeting age-related diseases and optimizing healthspan [77, 72, 85, 56, 10].

6.2 Promising Research Directions

Future research should focus on integrating multi-omics data to refine aging clocks and target specific tissues or cellular functions, thereby deepening the understanding of biological aging and its causal mechanisms. Expanding studies to include diverse cohorts and additional predictive markers, such as genetic and environmental factors, will enhance insights into comorbidities like obstructive sleep apnea and CVD. Developing novel biomarkers and refining existing methods are crucial for advancing clinical applications of biological age models across varied populations [18].

Research should elucidate interconnections among the hallmarks of aging and explore therapeutic strategies to mitigate T cell aging and its effects on the immune system [5]. Longitudinal studies assessing socioeconomic status changes and their impact on biological aging, along with interventions aimed at reducing disadvantages, present promising avenues. Moreover, examining targeted interventions to increase physical activity among elderly populations and assessing the psychological impacts of exercise are essential for developing comprehensive strategies to counter biological age acceleration.

Integrating additional datasets and advanced modeling techniques will enhance prediction accuracy in cardiovascular disease risk assessment [6]. Future research could explore fusion approaches for other diseases and develop user-friendly applications for clinicians [3]. Expanding the range of biomarkers included in algorithms and validating tools like the BioAge package across diverse populations will improve their applicability in clinical trials targeting aging. Optimizing algorithms for larger datasets and exploring applications in other medical domains for risk stratification will contribute to more robust predictive models [7].

Refining the DDPMC model and exploring additional covariates for validation represent promising directions. Future research will also focus on comparing the proposed VI-based BCNN method with other Bayesian approximations, such as dropout-based methods, to enhance uncertainty estimation [19]. By addressing these research directions, the scientific community can develop innovative strategies to mitigate biological age acceleration's adverse effects, ultimately improving cardiovascular health outcomes [4].

Additionally, future research could refine models to incorporate more biological factors and explore their implications in multicellular organisms. Developing AROC estimators based on direct ROC regression methodologies and utilizing penalized splines to enhance model flexibility are also promising avenues [84]. Expanding datasets to include a broader range of conditions affecting biological age and refining the immune score by incorporating additional analytes could enhance predictive capabilities. Larger, more homogeneous studies and new epigenetic clocks are necessary to provide insights into biological aging [17]. Identifying specific microbial taxa promoting healthy aging and

interventions to restore gut microbiota balance could offer novel therapeutic strategies. Targeting specific epigenetic marks for reversing age-related decline and exploring the scalability of interventions across diverse populations are essential for optimizing therapeutic efficacy. Improving calibration of uncertainty estimates and investigating alternative strategies for uncertainty quantification will enhance predictive accuracy in future research. Finally, larger datasets and exploration of underlying mechanisms of age-related changes in DNA methylation across tissues could yield further insights into the aging process.

6.3 Innovative Therapeutic Interventions

Innovative therapeutic interventions targeting biological age acceleration hold significant promise in reducing cardiovascular disease (CVD) risk. By integrating evolutionary theory with genomic tools, researchers can better understand gene-environment (GxE) interactions and develop health interventions for non-communicable diseases (NCDs), including CVD [86]. This approach highlights the potential of combining evolutionary insights with genomic technologies to inform therapeutic strategies.

Emerging technologies, such as advanced sequencing methods, offer the potential to develop new generations of DNA methylation clocks with improved performance and robustness [11]. These advancements could yield more precise biomarkers for biological age, facilitating the identification of individuals at risk of accelerated aging and enabling targeted interventions to mitigate CVD risk. Additionally, applying automated slice and patch selection methods in brain age estimation models could enhance scalability and applicability across larger, multi-site datasets, refining predictive accuracy and therapeutic targeting [68].

Incorporating countermeasures into models of cardiovascular deconditioning, particularly under varying gravity conditions, underscores the importance of exploring novel interventions that address systemic aging effects [8]. These countermeasures could inform therapies aimed at enhancing cardiovascular resilience and reducing biological age acceleration's impact.

Insights into the hallmarks of aging, especially the decline in T cell function, could lead to therapeutic strategies aimed at enhancing immune function in the elderly [5]. By targeting specific pathways involved in immune aging, these interventions have the potential to improve cardiovascular health and extend healthspan.

The application of Bayesian nonparametric methods for estimating covariate-adjusted ROC curves exemplifies the potential for improving diagnostic accuracy and tailoring therapeutic interventions to individual risk profiles [84]. Leveraging these advanced analytical techniques can refine risk stratification and optimize treatment strategies for individuals with accelerated biological aging.

These innovative therapeutic interventions represent a significant advancement in managing biological age acceleration and its associated health risks. By synthesizing knowledge from evolutionary biology, genomics, and sophisticated computational techniques, researchers can create tailored interventions that address both traditional and nontraditional cardiovascular disease (CVD) risk factors, providing personalized lifestyle recommendations. These strategies aim to significantly reduce CVD risk and improve health outcomes for aging populations, particularly through predictive models that integrate multi-omics data and individual patient characteristics, enhancing personalized medicine initiatives [25, 26].

7 Conclusion

This survey underscores the critical importance of biological age acceleration in evaluating cardiovascular disease (CVD) risk, focusing on the role of predictive biomarkers in enhancing risk stratification and personalizing healthcare interventions. The findings demonstrate the effectiveness of DNA methylation age estimators, such as DNAm GrimAge, as strong indicators of disease onset and mortality risk, independent of chronological age. The inclusion of BrainAge and MetaboAge scores offers additional perspectives on biological aging, thereby improving the predictive accuracy for mortality outcomes and supporting the efficacy of combined biomarker strategies. The use of deep learning models to measure accelerated aging, particularly in smokers, highlights the potential of sophisticated computational methods to refine biomarker-based evaluations.

The integration of molecular and clinical data in risk assessment is emphasized, advocating for holistic approaches that utilize a wide range of data sources. Personalized lifestyle recommendations, guided by longitudinal inverse classification techniques, have proven effective in significantly reducing CVD risk, underscoring the benefits of customized interventions. Moreover, the continuum between aging and age-related diseases (ARDs) implies that shared therapeutic strategies targeting aging could offer substantial benefits. The discovery of specific epigenetic markers linked to immune aging presents opportunities for developing new biomarkers for age-related diseases.

As biological age advances, the balance between gut microbiota and the host weakens, resulting in dysbiosis and potential health issues. This highlights the need for continued research to refine and validate biomarkers, incorporate multi-omics data, and explore innovative therapeutic strategies to counteract the adverse effects of biological age acceleration. Progress in predicting study durations for biomarker-driven clinical trials could enhance trial design and efficiency, contributing to the development of effective interventions. Addressing these research avenues will empower the scientific community to create innovative solutions to mitigate the negative impacts of biological age acceleration, ultimately enhancing cardiovascular health outcomes.

References

[1] M Bateson and C Poirier. Can biomarkers of biological age be used to assess cumulative lifetime experience? *Animal Welfare*, 28(1):41–56, 2019.

[2] James H Cole, Stuart J Ritchie, Mark E Bastin, Valdés Hernández, S Muñoz Maniega, Natalie Royle, Janie Corley, Alison Pattie, Sarah E Harris, Qian Zhang, et al. Brain age predicts mortality. *Molecular psychiatry*, 23(5):1385–1392, 2018.

[3] Hafsa Binte Kibria and Abdul Matin. The severity prediction of the binary and multi-class cardiovascular disease – a machine learning-based fusion approach, 2022.

[4] Zhe Fei and Yi Li. U-learning for prediction inference via combinatory multi-subsampling: With applications to lasso and neural networks, 2024.

[5] Maria Mittelbrunn and Guido Kroemer. Hallmarks of t cell aging. *Nature immunology*, 22(6):687–698, 2021.

[6] Fernando Andreotti, Frank S. Heldt, Basel Abu-Jamous, Ming Li, Avelino Javer, Oliver Carr, Stojan Jovanovic, Nadezda Lipunova, Benjamin Irving, Rabia T. Khan, and Robert Dürichen. Prediction of the onset of cardiovascular diseases from electronic health records using multi-task gated recurrent units, 2020.

[7] Ahmed M Alaa, Thomas Bolton, Emanuele Di Angelantonio, James HF Rudd, and Mihaela Van der Schaar. Cardiovascular disease risk prediction using automated machine learning: A prospective study of 423,604 uk biobank participants. *PloS one*, 14(5):e0213653, 2019.

[8] Caterina Gallo, Luca Ridolfi, and Stefania Scarsoglio. Cardiovascular deconditioning during long-term spaceflight through multiscale modeling, 2020.

[9] Jesus F Bermejo-Martin, Marta Martín-Fernandez, Cristina López-Mestanza, Patricia Duque, and Raquel Almansa. Shared features of endothelial dysfunction between sepsis and its preceding risk factors (aging and chronic disease), 2018.

[10] Zhe Li, Weiguang Zhang, Yuting Duan, Yue Niu, Yizhi Chen, Xiaomin Liu, Zheyi Dong, Ying Zheng, Xizhao Chen, Zhe Feng, et al. Progress in biological age research. *Frontiers in public health*, 11:1074274, 2023.

[11] Dmitriy I. Podolskiy and Vadim N. Gladyshev. Dna methylation markers to assess biological age, 2018.

[12] Olena Andrieieva, Anna Hakman, Vitalii Kashuba, Maryna Vasylenko, Kostiantyn Patsaliuk, Andrii Koshura, and Iryna Istyniuk. Effects of physical activity on aging processes in elderly persons. 2019.

[13] Jonayet Miah, Duc M Ca, Md Abu Sayed, Ehsanur Rashid Lipu, Fuad Mahmud, and S M Yasir Arafat. Improving cardiovascular disease prediction through comparative analysis of machine learning models: A case study on myocardial infarction, 2023.

[14] Santiago Hernández-Orozco, Abicumaran Uthamacumaran, Francisco Hernández-Quiroz, Kourosh Saeb-Parsy, and Hector Zenil. A neuro-symbolic ai approach to personal health risk assessment and immune age characterisation using common blood markers, 2024.

[15] Joanne Ryan, Jo Wrigglesworth, Jun Loong, Peter D Fransquet, and Robyn L Woods. A systematic review and meta-analysis of environmental, lifestyle, and health factors associated with dna methylation age. *The Journals of Gerontology: Series A*, 75(3):481–494, 2020.

[16] Mariel M. Finucane, Christopher J. Paciorek, Goodarz Danaei, and Majid Ezzati. Bayesian estimation of population-level trends in measures of health status, 2014.

[17] Don Krieger, Paul Shepard, and David O. Okonkwo. Normative atlases of neuroelectric brain activity and connectivity from a large human cohort, 2018.

[18] Claudio Franceschi, Paolo Garagnani, Giovanni Vitale, Miriam Capri, and Stefano Salvioli. Inflammaging and 'garb-aging'. *Trends in Endocrinology & Metabolism*, 28(3):199–212, 2017.

[19] Alexander Pate, Matthew Sperrin, Richard D. Riley, Niels Peek, Tjeerd Van Staa, Jamie C. Sergeant, Mamas A. Mamas, Gregory Y. H. Lip, Martin O Flaherty, Michael Barrowman, Iain Buchan, and Glen P. Martin. Calibration plots for multistate risk predictions models: an overview and simulation comparing novel approaches, 2023.

[20] Roderick C Slieker, Caroline L Relton, Tom R Gaunt, P Eline Slagboom, and Bastiaan T Heijmans. Age-related dna methylation changes are tissue-specific with elovl2 promoter methylation as exception. *Epigenetics & chromatin*, 11:1–11, 2018.

[21] Kara N Fitzgerald, Romilly Hodges, Douglas Hanes, Emily Stack, David Cheishvili, Moshe Szyf, Janine Henkel, Melissa W Twedt, Despina Giannopoulou, Josette Herdell, et al. Potential reversal of epigenetic age using a diet and lifestyle intervention: a pilot randomized clinical trial. *Aging (albany NY)*, 13(7):9419, 2021.

[22] Vasily V Ashapkin, Lyudmila I Kutueva, and Boris F Vanyushin. Aging as an epigenetic phenomenon. *Current genomics*, 18(5):385–407, 2017.

[23] Taro Langner, Fredrik K. Gustafsson, Benny Avelin, Robin Strand, Håkan Ahlström, and Joel Kullberg. Uncertainty-aware body composition analysis with deep regression ensembles on uk biobank mri, 2021.

[24] Special article.

[25] Michael T. Lash and W. Nick Street. Personalized cardiovascular disease risk mitigation via longitudinal inverse classification, 2020.

[26] Thierry Chekouo and Sandra E. Safo. Bayesian integrative analysis and prediction with application to atherosclerosis cardiovascular disease, 2020.

[27] Mirajul Islam, Michael J. Daniels, Zeynab Aghabazaz, and Juned Siddique. Bayesian feature selection in joint models with application to a cardiovascular disease cohort study, 2024.

[28] Jia Su, Bin He, Yi Guan, Jingchi Jiang, and Jinfeng Yang. Developing a cardiovascular disease risk factor annotated corpus of chinese electronic medical records, 2017.

[29] Tim Hahn, Jan Ernsting, Nils R. Winter, Vincent Holstein, Ramona Leenings, Marie Beisemann, Lukas Fisch, Kelvin Sarink, Daniel Emden, Nils Opel, Ronny Redlich, Jonathan Repple, Dominik Grotegerd, Susanne Meinert, Jochen G. Hirsch, Thoralf Niendorf, Beate Endemann, Fabian Bamberg, Thomas Kröncke, Robin Bülow, Henry Völzke, Oyunbileg von Stackelberg, Ramona Felizitas Sowade, Lale Umutlu, Börge Schmidt, Svenja Caspers, German National Cohort Study Center Consortium, Harald Kugel, Tilo Kircher, Benjamin Risse, Christian Gaser, James H. Cole, Udo Dannlowski, and Klaus Berger. An uncertainty-aware, shareable and transparent neural network architecture for brain-age modeling, 2021.

[30] Sara Hägg and Juulia Jylhävä. Sex differences in biological aging with a focus on human studies. *elife*, 10:e63425, 2021.

[31] Eman M Alissa and Gordon A Ferns. Dietary fruits and vegetables and cardiovascular diseases risk. *Critical reviews in food science and nutrition*, 57(9):1950–1962, 2017.

[32] Cheryl A. Hawkes, Victoria Goss, Elina Zotova, Tual Monfort, Anthony Postle, Sumeet Mahajan, James A. R. Nicoll, Roy O. Weller, and Roxana O. Carare. Impact of maternal high fat on neurovascular unit of adult offspring, 2024.

[33] Christina Pagiatakis, Elettra Musolino, Rosalba Gornati, Giovanni Bernardini, and Roberto Papait. Epigenetics of aging and disease: a brief overview. *Aging clinical and experimental research*, 33:737–745, 2021.

[34] Claudio Franceschi, Paolo Garagnani, Cristina Morsiani, Maria Conte, Aurelia Santoro, Andrea Grignolio, Daniela Monti, Miriam Capri, and Stefano Salvioli. The continuum of aging and age-related diseases: common mechanisms but different rates. *Frontiers in medicine*, 5:61, 2018.

[35] Helena Palma-Gudiel, Lourdes Fañanás, Steve Horvath, and Anthony S Zannas. Psychosocial stress and epigenetic aging. *International review of neurobiology*, 150:107–128, 2020.

[36] Valeska Ormazabal, Soumyalekshmi Nair, Omar Elfeky, Claudio Aguayo, Carlos Salomon, and Felipe A Zuñiga. Association between insulin resistance and the development of cardiovascular disease. *Cardiovascular diabetology*, 17:1–14, 2018.

[37] Giovanni Fiorito, Cathal McCrory, Oliver Robinson, Cristian Carmeli, Carolina Ochoa Rosales, Yan Zhang, Elena Colicino, Pierre-Antoine Dugue, Fanny Artaud, Gareth J Mckay, et al. Socioeconomic position, lifestyle habits and biomarkers of epigenetic aging: a multi-cohort analysis. *Aging (Albany NY)*, 11(7):2045, 2019.

[38] Sebastiano Barbieri, Suneela Mehta, Billy Wu, Chrianna Bharat, Katrina Poppe, Louisa Jorm, and Rod Jackson. Predicting cardiovascular risk from national administrative databases using a combined survival analysis and deep learning approach, 2020.

[39] Kartik Ahuja and Mihaela van der Schaar. Risk-stratify: Confident stratification of patients based on risk, 2018.

[40] Katie A McLaughlin, Natalie L Colich, Alexandra M Rodman, and David G Weissman. Mechanisms linking childhood trauma exposure and psychopathology: a transdiagnostic model of risk and resilience. *BMC medicine*, 18:1–11, 2020.

[41] Claudio Franceschi, Paolo Garagnani, Paolo Parini, Cristina Giuliani, and Aurelia Santoro. Inflammaging: a new immune–metabolic viewpoint for age-related diseases. *Nature Reviews Endocrinology*, 14(10):576–590, 2018.

[42] Dominik Saul and Robyn Laura Kosinsky. Epigenetics of aging and aging-associated diseases. *International journal of molecular sciences*, 22(1):401, 2021.

[43] Kang Wang, Huicong Liu, Qinchao Hu, Lingna Wang, Jiaqing Liu, Zikai Zheng, Weiqi Zhang, Jie Ren, Fangfang Zhu, and Guang-Hui Liu. Epigenetic regulation of aging: implications for interventions of aging and diseases. *Signal transduction and targeted therapy*, 7(1):374, 2022.

[44] Carolina Soto-Palma, Laura J Niedernhofer, Christopher D Faulk, Xiao Dong, et al. Epigenetics, dna damage, and aging. *The Journal of clinical investigation*, 132(16), 2022.

[45] Daehwan Kim, Dobri D Kiprov, Connor Luellen, Michael Lieb, Chao Liu, Etsuko Watanabe, Xiaoyue Mei, Kaitlin Cassaleto, Joel Kramer, Michael J Conboy, et al. Old plasma dilution reduces human biological age: a clinical study. *Geroscience*, 44(6):2701–2720, 2022.

[46] Shufei Song and F Brad Johnson. Epigenetic mechanisms impacting aging: a focus on histone levels and telomeres. *Genes*, 9(4):201, 2018.

[47] Ashley Kramer and Grant A Challen. The epigenetic basis of hematopoietic stem cell aging. In *Seminars in hematology*, volume 54, pages 19–24. Elsevier, 2017.

[48] Zaoqu Liu, Qimeng Liang, Yuqing Ren, Chunguang Guo, Xiaoyong Ge, Libo Wang, Quan Cheng, Peng Luo, Yi Zhang, and Xinwei Han. Immunosenescence: molecular mechanisms and diseases. *Signal transduction and targeted therapy*, 8(1):200, 2023.

[49] Yuxiang Hu, Jinxin Hu, Ting Xu, Bo Zhang, Jiajie Yuan, and Haozhang Deng. Research on early warning model of cardiovascular disease based on computer deep learning, 2024.

[50] Elina Sillanpää, Eija K Laakkonen, Elina Vaara, Taina Rantanen, Vuokko Kovanen, Sarianna Sipilä, Jaakko Kaprio, and Miina Ollikainen. Biological clocks and physical functioning in monozygotic female twins. *BMC geriatrics*, 18:1–7, 2018.

[51] Sandra Keizer, Zhuozhao Zhan, Vasan S. Ramachandran, and Edwin R. van den Heuvel. Joint modeling with time-dependent treatment and heteroskedasticity: Bayesian analysis with application to the framingham heart study, 2023.

[52] Maria Athanasiou, Konstantina Sfrintzeri, Konstantia Zarkogianni, Anastasia C. Thanopoulou, and Konstantina S. Nikita. An explainable xgboost-based approach towards assessing the risk of cardiovascular disease in patients with type 2 diabetes mellitus, 2020.

[53] Alexander Vaiserman and Dmytro Krasnienkov. Telomere length as a marker of biological age: state-of-the-art, open issues, and future perspectives. *Frontiers in genetics*, 11:630186, 2021.

[54] Waylon J Hastings, David M Almeida, and Idan Shalev. Conceptual and analytical overlap between allostatic load and systemic biological aging measures: analyses from the national survey of midlife development in the united states. *The Journals of Gerontology: Series A*, 77(6):1179–1188, 2022.

[55] Jong-Hyuk Lee, Edward W Kim, Deborah L Croteau, and Vilhelm A Bohr. Heterochromatin: an epigenetic point of view in aging. *Experimental & molecular medicine*, 52(9):1466–1474, 2020.

[56] Open.

[57] Pedro Mateus, Swier Garst, Jing Yu, Davy Cats, Alexander G. J. Harms, Mahlet Birhanu, Marian Beekman, P. Eline Slagboom, Marcel Reinders, Jeroen van der Grond, Andre Dekker, Jacobus F. A. Jansen, Magdalena Beran, Miranda T. Schram, Pieter Jelle Visser, Justine Moonen, Mohsen Ghanbari, Gennady Roshchupkin, Dina Vojinovic, Inigo Bermejo, Hailiang Mei, and Esther E. Bron. Mri-based and metabolomics-based age scores act synergetically for mortality prediction shown by multi-cohort federated learning, 2024.

[58] Sandra E. Safo, Shuzhao Li, and Qi Long. Integrative analysis of transcriptomic and metabolomic data via sparse canonical correlation analysis with incorporation of biological information, 2016.

[59] Daniel W Belsky, Avshalom Caspi, Louise Arseneault, Andrea Baccarelli, David L Corcoran, Xu Gao, Eiliss Hannon, Hona Lee Harrington, Line JH Rasmussen, Renate Houts, et al. Quantification of the pace of biological aging in humans through a blood test, the dunedinpoam dna methylation algorithm. *elife*, 9:e54870, 2020.

[60] Morgan E Levine, Ake T Lu, Austin Quach, Brian H Chen, Themistocles L Assimes, Stefania Bandinelli, Lifang Hou, Andrea A Baccarelli, James D Stewart, Yun Li, et al. An epigenetic biomarker of aging for lifespan and healthspan. *Aging (albany NY)*, 10(4):573, 2018.

[61] Francesca Gasperoni, Christopher H. Jackson, Angela M. Wood, Michael J. Sweeting, Paul J. Newcombe, David Stevens, and Jessica K. Barrett. Optimal risk-assessment scheduling for primary prevention of cardiovascular disease, 2023.

[62] Jamie N Justice, Luigi Ferrucci, Anne B Newman, Vanita R Aroda, Judy L Bahnson, Jasmin Divers, Mark A Espeland, Santica Marcovina, Michael N Pollak, Stephen B Kritchevsky, et al. A framework for selection of blood-based biomarkers for geroscience-guided clinical trials: report from the tame biomarkers workgroup. *Geroscience*, 40:419–436, 2018.

[63] Alvaro Fernandez-Quilez, Tobias Nordström, Fredrik Jäderling, Svein Reidar Kjosavik, and Martin Eklund. Prostate age gap (pag): An mri surrogate marker of aging for prostate cancer detection, 2023.

[64] J. A. Barthold Jones, U. W. Nash, J. Vieillefont, K. Christensen, D. Misevic, and U. K. Steiner. The ageguess database: an open online resource on chronological and perceived ages of people aged 3-100, 2018.

[65] Cathal McCrory, Giovanni Fiorito, Belinda Hernandez, Silvia Polidoro, Aisling M O'Halloran, Ann Hever, Cliona Ni Cheallaigh, Ake T Lu, Steve Horvath, Paolo Vineis, et al. Grimage outperforms other epigenetic clocks in the prediction of age-related clinical phenotypes and all-cause mortality. *The Journals of Gerontology: Series A*, 76(5):741–749, 2021.

[66] Karim Armanious, Sherif Abdulatif, Wenbin Shi, Shashank Salian, Thomas Küstner, Daniel Weiskopf, Tobias Hepp, Sergios Gatidis, and Bin Yang. Age-net: An mri-based iterative framework for brain biological age estimation. *IEEE Transactions on Medical Imaging*, 40(7):1778–1791, 2021.

[67] Karim Armanious, Sherif Abdulatif, Wenbin Shi, Tobias Hepp, Sergios Gatidis, and Bin Yang. Uncertainty-based biological age estimation of brain mri scans, 2021.

[68] Iman Kianian and Hedieh Sajedi. Brain age estimation with a greedy dual-stream model for limited datasets, 2024.

[69] Philippe Boileau, Nina Ting Qi, Mark J. van der Laan, Sandrine Dudoit, and Ning Leng. A flexible approach for predictive biomarker discovery, 2022.

[70] Zhaonian Zhang, Richard Jiang, Danny Crookes, and Paul Chazot. Machine learning-based biological ageing estimation technologies: A survey, 2022.

[71] Saurabh Sihag, Gonzalo Mateos, Corey McMillan, and Alejandro Ribeiro. Predicting brain age using transferable covariance neural networks, 2022.

[72] Jarod Rutledge, Hamilton Oh, and Tony Wyss-Coray. Measuring biological age using omics data. *Nature Reviews Genetics*, 23(12):715–727, 2022.

[73] Wencan Zhu, Céline Lévy-Leduc, and Nils Ternès. Identification of prognostic and predictive biomarkers in high-dimensional data with pplasso, 2022.

[74] Xiaowu Dai, Saad Mouti, Marjorie Lima do Vale, Sumantra Ray, Jeffrey Bohn, and Lisa Goldberg. A resampling approach for causal inference on novel two-point time-series with application to identify risk factors for type-2 diabetes and cardiovascular disease, 2023.

[75] Zhiwei Zhang, Lei Nie, Guoxing Soon, and Aiyi Liu. The use of covariates and random effects in evaluating predictive biomarkers under a potential outcome framework, 2015.

[76] Chong Ma, Wenxuan Deng, Shuangge Ma, Ray Liu, and Kevin Galinsky. Structural modeling using overlapped group penalties for discovering predictive biomarkers for subgroup analysis, 2019.

[77] Timothy V Pyrkov, Konstantin Slipensky, Mikhail Barg, Alexey Kondrashin, Boris Zhurov, Alexander Zenin, Mikhail Pyatnitskiy, Leonid Menshikov, Sergei Markov, and Peter O Fedichev. Extracting biological age from biomedical data via deep learning: too much of a good thing? *Scientific reports*, 8(1):5210, 2018.

[78] Zuyun Liu, Pei-Lun Kuo, Steve Horvath, Eileen Crimmins, Luigi Ferrucci, and Morgan Levine. A new aging measure captures morbidity and mortality risk across diverse subpopulations from nhanes iv: a cohort study. *PLoS medicine*, 15(12):e1002718, 2018.

[79] Sophie Starck, Yadunandan Vivekanand Kini, Jessica Johanna Maria Ritter, Rickmer Braren, Daniel Rueckert, and Tamara Mueller. Atlas-based interpretable age prediction in whole-body mr images, 2024.

[80] Shonosuke Sugasawa and Hisashi Noma. Efficient screening of predictive biomarkers for individual treatment selection, 2020.

[81] Chinyereugo M Umemneku-Chikere, Lorna Wheaton, Heather Poad, Devleena Ray, Ilse Cuevas Andrade, Sam Khan, Paul Tappenden, Keith R Abrams, Rhiannon K Owen, and Sylwia Bujkiewicz. Individual participant data from digital sources informed and improved precision in the evaluation of predictive biomarkers in bayesian network meta-analysis, 2023.

[82] Hong Zhang, Jie Pu, Shibing Deng, Satrajit Roychoudhury, Haitao Chu, and Douglas Robinson. Study duration prediction for clinical trials with time-to-event endpoints using mixture distributions accounting for heterogeneous population, 2023.

[83] Mika Kivimäki and Andrew Steptoe. Effects of stress on the development and progression of cardiovascular disease. *Nature Reviews Cardiology*, 15(4):215–229, 2018.

[84] Vanda Inacio de Carvalho and Maria Xose Rodriguez-Alvarez. Bayesian nonparametric inference for the covariate-adjusted roc curve, 2018.

[85] Qian Zhang, Costanza L Vallerga, Rosie M Walker, Tian Lin, Anjali K Henders, Grant W Montgomery, Ji He, Dongsheng Fan, Javed Fowdar, Martin Kennedy, et al. Improved precision of epigenetic clock estimates across tissues and its implication for biological ageing. *Genome medicine*, 11:1–11, 2019.

[86] Amanda J. Lea, Andrew G. Clark, Andrew W. Dahl, Orrin Devinsky, Angela R. Garcia, Christopher D. Golden, Joseph Kamau, Thomas S. Kraft, Yvonne A. L. Lim, Dino Martins, Donald Mogoi, Paivi Pajukanta, George Perry, Herman Pontzer, Benjamin C. Trumble, Samuel S. Urlacher, Vivek V. Venkataraman, Ian J. Wallace, Michael Gurven, Daniel Lieberman, and Julien F. Ayroles. Evolutionary mismatch and the role of gxe interactions in human disease, 2023.

Disclaimer:

SurveyX is an AI-powered system designed to automate the generation of surveys. While it aims to produce high-quality, coherent, and comprehensive surveys with accurate citations, the final output is derived from the AI's synthesis of pre-processed materials, which may contain limitations or inaccuracies. As such, the generated content should not be used for academic publication or formal submissions and must be independently reviewed and verified. The developers of SurveyX do not assume responsibility for any errors or consequences arising from the use of the generated surveys.