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Association between Frailty and Senescence from National Health and Nutrition Examination Survey (NHANES): A Cross-Sectional Study

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Abstract

Background: Aging is an inevitable phenomenon of biological processes, and frailty, one of its key symptoms, usually reflects a decline in the body's functional and adaptive capacity. In this study, we aimed to investigate the association between Frailty Index (FI) and phenotypic age using quantitative measures. Herein, a cross-sectional study in a U.S. population reinforces current clinical knowledge that frailty promotes accelerated aging in phenotypic age.

Methods: In this cross-sectional study, data from the National Health and Nutrition Examination Survey (NHANES) were utilized, encompassing 11,918 participants aged 20 years and older. The analyses employed multiple logistic regression and Restricted Cubic Splines (RCS). Additionally, subgroup analyses stratified by covariates were performed.

Results: This study included 11,918 adult participants with complete data. After adjusting for all confounding factors, a significant positive correlation was observed between FI and phenotypic age 2.04 (1.89, 2.18), indicating that for every 0.1 increase in FI score, the phenotypic age increased by 2.04 years. Further subgroup analysis demonstrated that this association was significant only in some subgroups.

Conclusion: We observed a correlation between FI and the accelerated aging represented by phenotypic age. Our findings warrant further confirmation in future, more extensive prospective studies.

Keywords: Frailty index; Aing; Phenotypic age; Logistic regression model; Cross-sectional study

Introduction

The world's older population continues to proliferate, with the population aged 65 years and over projected to rise from 10 percent in 2022 to 16 percent in 2050. This trend raises important health concerns and will be accompanied by a significant increase in socio-economic pressures due to rapidly increasing life expectancy. The rapid increase in the elderly population poses serious health challenges and is expected to impose a significant socio-economic burden. With accelerated aging, there is a greater susceptibility to a range of non-communicable diseases, such as diabetes, renal failure, arthritis, Alzheimer's disease, Parkinson's disease, and malignant tumors, which require continuous monitoring and management [1]. Although actual age is an easy way of reflecting aging, the rate varies, and differences in the rate of aging among individuals manifest in differences in vulnerability to death and disease [2,3]. In addition, inter-individual variability in cognitive function and health status increases with age. Therefore, some things could be improved by using actual age to reflect the level of aging. In previous studies, biological and phenotypic age were better predictors of mortality, age related diseases, number of co-morbidities, and decline in physical functioning relative to actual age [4]. Several previous studies have demonstrated that weakened physical functioning promotes aging of the body and thus accelerates the acceleration of epigenetic age.

Frailty is a common geriatric syndrome characterized by age-related declines in multiple organ systems' physiologic reserve and function, leading to increased susceptibility to stressors. Frailty is more prevalent not only in older adults but also in patients with chronic diseases. It may lead to an increased risk of various adverse health outcomes (e.g., stroke, Alzheimer's disease, and malignancy), which in turn increases healthcare costs and economic burden [5-7]. In recent years, several frailty assessment tools have emerged, of which the most widely used in community populations are the Frailty Phenotype (FP) and the Frailty Index (FI). Compared with FP, FI is a continuous variable that may have better discriminatory power in identifying adults with low levels of frailty and assessing their risk for adverse health outcomes. Thus, further clarification of the causal relationship between FI and apparent age would help identify those experiencing accelerated aging. This would provide valuable information for utilizing a simple proxy such as the FI for risk assessment, guiding disease prevention, and ultimately preventing premature death.

Therefore, the present study aimed to assess the correlation between FI and phenotypic age based on the U.S. NHANES database.

Literature Review

Study description

The National Center for Health Statistics (NCHS) conducted the National Health and Nutrition Examination Survey (NHANES), a nationwide, population-based, cross-sectional study investigating nutrition and health status in the United States. The study utilized a complex multistage stratified probability sampling method on a biannual cycle to ensure that the samples collected represented the U.S. population. The NHANES research designs and data are publicly accessible on the website www.cdc.gov/nchs/nhanes/, allowing the public to access detailed information regarding the study's methodology and findings.

Study population

Data from the NHANES 1999-2018 survey period were used in this study because complete data from the FI related factors, phenotypic age, and typical medical condition questionnaires were available, which were critical to the analysis. Initially, 101,317 participants participated in the study. To ensure the validity of the analysis, specific exclusions were made: The phenotypic age of the participants (n=62,269), poverty income ratio missing data (n=3,054), education (n=35), body mass index (n=520), education level (n=9), smoking (n=9,762), hypertension (n=11), diabetes mellitus (n=1007), fasting glucose (n=12,718), and fasting triglycerides (n=23) were also excluded. After applying these exclusion criteria, 11,918 eligible participants aged 20 years and older remained for the final analysis.

Definition of FI

Mitnitski, et al. developed FI based on the Canadian Study of Health and Aging (CSHA) [8]. FI is the proportion of individual cumulative defects in the included indicators. The defects included can be symptoms, signs, functional disorders laboratory abnormalities, etc., and must meet five conditions:

- They must be related to health status, excluding age-related traits (such as gray hair).
- The defect rate increases with age.
- The defects cannot be saturated prematurely, such as presbyopic, which is common in people aged 55, so they should not be included.
- The defects included should cover as many organ systems as possible.
- The constituent indexes of FI may be different in different studies, and the number of FI constituent indexes is more important than the content of FI constituent indexes.

Still, the constituent variables should be consistent when comparing FI in the same population longitudinally. The more variables included in FI, the more robust the estimate. We calculated FI based on the article by Mitnitski and Hakeem FF [9,10].

Definition of phenotypic age

Using biological age to measure the aging process of individuals can make up for the deficiency that chronological age cannot explain the difference in health levels among individuals of the same age. Horvath's team set out to develop new epigenetic clocks-DNAm PhenoAge and DNAm GrimAge [11]. Levine, et al., used the phenotypic age described above to further regress DNA methylation levels to obtain DNAm PhenoAge. DNAm PhenoAge was highly correlated with aging (r=0.65-0.89) and outperformed the Horvath clock and Hannum clock in predicting disease and death risk using a variety of tissue and cell samples [12]. Phenotypic age was calculated based on Levine's method, which uses chronological order to determine phenotypic age and nine biomarkers: Albumin, creatinine, glucose, C-reactive protein, lymphocyte percentage, mean cell volume, red blood cell distribution width, alkaline phosphatase, and white blood cell count [13].

Covariate selection

The choice of covariates in this study included sex (male/female), age (years), Poverty Income Ratio (PIR), race, detailed measurements of all variables (Mexican American/non-Hispanic white/non-Hispanic black/other), education level (less high school, high school, or college graduate), Body Mass Index (BMI, kg/m^2), smoking data (yes/no), hypertension (yes/no), diabetes (yes/no), fasting triglycerides (mg/dL), and fasting glucose (mg/dL) are www.cdc.gov/nchs/nhanes/publicly available at www.example.com.

Statistical analysis

This study reported Categorical parameters as proportions, while continuous variables were summarized as means with Standard Deviation (SD). Statistical tests appropriate for each variable type were used to assess participant differences. Weighted student t-test for continuous variables and weighted chi-square test for categorical variables.

Three multiple linear regression models were constructed to investigate the relationship between FI and phenotypic age.

Model I: No adjustment for covariates.

Model II: Adjusted for gender, race, and age.

Model III: Adjusted for age, race, gender, education level, PIR, smoking, BMI, diabetes, hypertension, fasting glucose, and fasting triglyceride status.

Restricted Cubic Splines (RCS) were used to model the association between FI and phenotypic age to account for potential non-linear relationships. In addition, the relationship between FI and phenotypic age was examined in subgroups defined by stratified variables such as age, race, education level, smoking, body mass index, diabetes mellitus, and hypertension. Statistical analysis was performed using R version 4.1.13. At the same time, the enhances R package and webpage were used to extract exposure, outcomes, and covariates. A significance level of $p<0.05$ was considered statistically significant to assess the association between FI and phenotypic age outcome.

Results

Baseline characteristics of participants

The study showed 11,918 participants aged 20 and older, with a mean FI of 0.14 and a mean phenotypic age of 46.53. 5899 women and 6019 men were included, and there were significant differences between the two groups except for age, race, and hypertension. However, enrolled males had higher FI and phenotypic age than females.

Association between FI and phenotypic age

The study presents the hazard ratios from the logistic regression model that assessed the association between FI and accelerated aging. Model I, without adjustment for covariates, suggested a positive association between FI and phenotypic age acceleration (95% CI: 9.80, 10.50). The study adjusted for a weaker correlation (95% CI: 3.08, 3.40) for demographic variables (age, sex, and race) in model II. The fully adjusted model III, which further controlled for all covariates, showed that the association remained significant (95% CI: 1.89, 2.18). We further grouped the FI into quartiles and adjusted for all covariates, demonstrating a significant increase in phenotypic age in the Q3 (95% CI: 0.07, 0.15) and Q4 (95% CI: 0.38, 0.46) populations compared to the Q1 population, but not in the Q2 population (95% CI: -0.01, 0.06).

In addition, a smooth curve fit was used to examine the non-linear relationship between FI and phenotypic age acceleration. The results confirm no nonlinear relationship between the two groups, in the Navigator. The restricted cubic spline curve shows an accelerating trend in phenotypic age with increasing FI.

Subgroup analysis

In our study, we conducted additional subgroup analyses to investigate the relationship between FI and phenotypic age within specific subgroups. The findings revealed a significant correlation between FI and phenotypic age exclusively in particular subgroups, namely age ≥ 60, gender, smoking, prevalence of hypertension, and high BMI. The results of these subgroup analyses are depicted visually illustrating the stratified analyses and demonstrating the variation in the relationship between FI and phenotypic age across different subgroups.

Discussion

Among 11,918 U.S. adults included in this study, we found a significant positive association between frailty and accelerated aging. When biological aging was measured using phenotypic age, higher FI was positively associated with higher phenotypic age and remained nearly consistent across partial subgroups. This study used a large, nationally representative sample and provided valuable insights into the relationship between frailty and aging in the U.S. population.

Frailty is a prevalent syndrome of old age that is strongly associated with disability, mortality, and hospitalization [14-16]. However, the underlying mechanisms of the frailty still need to be better understood [17-20]. In recent years, researchers have generally recognized the link between frailty and a wide range of diseases. A meta-analysis conducted by Yang Peng, covering 56 observational studies of 1,852,951 individuals, showed that frailty was not only associated with a significant increase in all-cause mortality (HR 2.40; 95% CI 2.17-2.65) but was also associated with a significant increase in adult caused cardiovascular disease (HR 2.64; 95% CI 2.20-3.17), cancer (HR 1.97; 95% CI 1.50-2.57) and respiratory disease (HR 4.91; 95% CI 2.97-8.12) were strong predictors of cause-specific mortality in adults. In 2011, Rockwood et al. used data from the Canadian National Population Health Survey to validate that the FI had good predictive validity across the full age range of adults. Meanwhile, a Mendelian randomization analysis based on summary GWAS data suggested that the FI was causally associated with depression, Alzheimer's disease, and stroke at the genetic level. The China chronic disease prospective study further demonstrated that the FI can effectively predict the risk of all-cause and multi-cause mortality in the population. Although studies continue to support the use of epigenetic age as a proxy for biological age, such as its association with frailty, Alzheimer's disease, cancer, and cardiovascular disease, some studies have failed to find an association between the epigenetic clock and frailty. A cohort study by Maria Giulia Bacalini based on an Italian population suggests that there may not be a correlation between frailty indices and epigenetic age among older adults. However, this may be influenced by small study sample sizes, inconsistent measures of frailty, differences in groups or covariates, and confounding factors such as metabolic disorders like hypertension and hyperlipidemia.

The study of frailty assessment has become a recent focus in population health. However, in academia, there still needs to be a unified definition of frailty. To address this issue, Song et al. proposed a conceptualized definition, considering frailty as an accumulative process of individual health loss in older adults, encompassing various aspects such as disease, disability measurements, and cognitive and functional decline. According to this comprehensive definition, the degree of frailty in an individual is directly proportional to the accumulation of health deficits manifested in various symptoms, such as diseases and disabilities. To quantify the degree of individual frailty, the FI comes into play. This index effectively measures the proportion of unhealthy indicators among all health measurement indicators for an individual, with a range of 0 to 1, where a score of 1 indicates severe frailty and a score of 0 indicates no presence of any diseases. In previous studies, the FI has not only served as an indicator for predicting the risk of mortality but has also proven to be a good measure for health assessment, demonstrating good validity and reliability. Frailty is considered an early manifestation of aging and, simultaneously, a vital risk factor for many chronic diseases, including neurodegenerative diseases, metabolic syndrome, cardiovascular diseases and malignant tumors. Therefore, the positive correlation mechanism between frailty and biological aging is complex and extensive.

The mechanism underlying the positive correlation between weakness and physiological aging is complex and extensive. Aging itself results from various factors, including heredity and

the environment. It is widely recognized that accelerating biological aging leads to more and earlier adverse consequences, while delaying biological aging helps prevent these consequences to some extent. Previous studies have revealed that aging characteristics are overexpressed in various tissues or samples during the processes accompanying the organism's decline. These features encompass genomic instability, epigenetic alterations, defective protein deposition, impaired mitochondrial function, cellular senescence, stem cell failure, and inflammatory states. While these changes occur in all individuals as they age, they are particularly pronounced in the frail. A meta-analysis by Bader AA, et al., involving nine observational studies, concluded that frailty prevalence is higher in Middle Eastern countries. Demographic studies of these countries confirm that their populations are aging rapidly, emphasizing the correlation between weakness and senescence. Interestingly, the frailty characterized by the FI is not only highly significant in older populations but also includes pathological conditions associated with accelerated biological aging in younger subject samples, even across different biological species, such as HIV/AIDS and autoimmune/inflammatory diseases. In terms of mechanistic studies, interleukins, inflammation, carnitine, the vitamin E pathway, and disorders of mitochondrial metabolism have been identified as factors associated with the underlying mechanisms of aging and frailty. Previous studies have shown that down-regulation of IL-6 signaling is associated with a reduced risk of frailty, while IL-6 knockout inhibits the accumulation of aging-associated proteins. This suggests that interleukin-6 may be one of the pathogenic mechanisms of frailty and accelerated aging. In the future, multi-omics technology development is expected to entirely reveal the developmental mechanism between weakness and aging.

Our study reveals a positive linear correlation between FI and phenotypic age acceleration in a representative sample of U.S. adults. This study is one of the most extensive investigations into these two variables' relationships. Linear and nonlinear statistical analyses provided reliable and informative results for the correlation between phenotypic age-represented senescence and frailty indices. However, it is essential to recognize some limitations of the study. First, because the study utilized a cross-sectional design, it was impossible to establish a causal relationship between FI and phenotypic age. To address this issue, it is suggested that future multi-group Mendelian randomization studies based on GWAS, transcriptomics, and proteomics be conducted further to explore the potential causal relationship between the two. This approach will provide more valuable insights. Second, considering that NHANES is based on a sample of the non-institutionalized population in the United States, the generalizability of the study results may be affected by geographic and population differences. Also, NHANES is primarily a cross-sectional study and lacks long-term follow-up data, which may limit understanding of changes in frailty indices and phenotypic age over time. Therefore, longitudinal study designs are emphasized to better understand the relationships between variables. Third, NHANES may not cover all factors that may influence FI and phenotypic age, such as genetic and lifestyle factors. These omitted variables could potentially impact study conclusions. Finally, respondents in different age groups in the NHANES sample may have other physical and social characteristics, which may confound the FI and phenotypic age analysis. Overall, it was emphasized that more prospective cohort studies and randomized controlled clinical trials are needed in the future to validate the results of the current study and to explore in depth the potential mechanisms underlying the association between FI and phenotypic age. Despite some limitations, the study provided valuable insights into the relationship between frailty and aging. Addressing these limitations, will contribute to a better understanding of this association and support the development of preventive and therapeutic strategies for diseases associated with aging.

Conclusion

In summary, our findings suggest a significant association between FI and accelerated phenotypic age, *i.e.,* as the FI increases, the phenotypic age of individuals also tends to increase. This finding was validated across multiple models and at different adjustment levels, reinforcing this association's reliability. This has important clinical and research implications for our understanding of the mechanisms of aging and for guiding the development of interventions. Effectively identifying these individuals with accelerated aging will help prevent premature death and extend healthy life expectancy. Future studies can further delve into the biological mechanisms underlying the association between FI and phenotypic age to provide deeper understanding and guidance.

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Data Availability

All materials utilized to conduct this research are openly posted and accessible through references within the manuscript.

Competing Interests

The authors declare that they have no competing interests.

Ethics Approval

The study analysed data downloaded from the National Health and Nutrition Examination Survey public database. The National Center for Health Statistics Ethics Review Committee granted ethics approval. The methods involved in this study were conducted by relevant guidelines and regulations (Declaration of Helsinki). All individuals provided written informed consent before participating in the study. Details are available at https: // www. cdc. gov/nchs/nhanes/irba 98. htm. The current study was deemed exempt from further review because the data used are identified and publicly accessible.

Research Involving Human Participants

This article contains no research with human subjects conducted by any of the authors.

Informed Consent

Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

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