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This study was part of Beijing Osteoporosis with Neurological Disorders in Epigenetic Changes Study (BONE)

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BONE study is a community-based and ambispective cohort study of clinical and subclinical osteoporosis with neurological disorders disease. Between 2017 and 2018, BONE study enrolled 2,000 adults aged 55-102 from six communities in Beijing district (Mu dan yuan community, Ji men li community, Xiao nan zhuang community, Lan qi ying community, Jiu xian qiao community, Chang chun jie community).

Statistical Analysis Plan

Baseline characteristics of the participants were described using the mean (standard deviation [SD]) for continuous variables and proportions for categorical variables stratified by the presence or absence of CCI progression. We constructed Cox proportional hazards models to evaluate the association between CCI progression risk and the variables age, BioAge, PhenoAge, BioAge Accel, and PhenoAge Accel as continuous variables, as well as BioAge Accel > 0 and PhenoAge Accel > 0 as categorical variables. Additionally, age was included as an adjustment factor in the latter four models, and all models were further adjusted for the covariates described in the previous section.

To evaluate and compare the predictive effectiveness of chronological age and biological ages for CCI progression risk, we calculated the Akaike Information Criterion (AIC), Bayesian Information Criterion (BIC), Concordance Index (C-index), and Time-dependent Area Under the Curve (Time-dependent AUC) for the constructed models. The likelihood ratio test (LRT) was used to compare the goodness-of-fit of models including biological ages versus models using only chronological age.

To assess the robustness of the results, we conducted the following additional analyses. First, Fine and Gray's competing risks model was employed as a sensitivity analysis, treating death as a competing risk to evaluate the association between BAs, BAAs, and the risk of CCI progression. Second, restricted cubic spline modeling was applied in Cox regression to explore nonlinear relationships between BioAge Accel, PhenoAge Accel, and CCI progression, with the optimal number of knots determined by AIC and BIC values.

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Latent class mixed models were applied to identify distinct trajectories of comorbidities from 2017 to 2024, using the R package lcmm (version 1.7.8). This method allows for the identification of heterogeneous subpopulations with distinct comorbidity progression patterns within an overall population. Five candidate models with 1-5 latent classes were initially built, incorporating fixed effects for time and random intercepts and slopes. Model performance was evaluated within the maximum-likelihood framework based on the Bayesian Information Criterion (BIC) and Akaike Information Criterion (AIC), with the lower values indicating better fit. Classification quality was assessed by ensuring average posterior probabilities greater than 0.7 and a minimum class size of 5% 40. The optimal model with three distinct comorbidity trajectories was selected according to these criteria. Participants were assigned to the class with the highest posterior probability.

Residential greenspace exposure within 300-m and 1000-m buffers was calculated for each trajectory class. Differences in greenspace percentages across trajectory classes were assessed using the Kruskal-Wallis test. Baseline demographic, socioeconomic, and lifestyle characteristics across comorbidity trajectory classes were summarized, and differences were assessed using chi-squared tests. Associations between residential greenspace exposure and comorbidity trajectories were analyzed using multinomial logistic regression models 41, adjusting for potential confounders. Model validity was further evaluated using likelihood ratio tests, Pseudo R2 , and multicollinearity diagnostics. Subgroup analyses were conducted stratified by demographic,

socioeconomic, and lifestyle characteristics were conducted to explore potential effect modification. All statistical tests were two-sided, and $p < 0.05$ was considered statistically significant.