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Phenotypic age acceleration through a lens of intersectional inequalities in the German National Cohort (NAKO)

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ABSTRACT

Purpose: Biological aging differences are linked to sociodemographic characteristics, but how intersecting social dimensions shape these differences remains unclear. Integrating aging biology and intersectionality theory, we examined the joint influence of multiple social determinants on phenotypic age acceleration (biological vs. chronological age).
Methods: Using data from 173,925 participants in the German NAKO study, we calculated phenotypic age acceleration based on blood-based biomarkers and created 72 intersectional social strata based on sociodemographic factors. We assessed differences across strata using intersectional Multilevel Analysis of Individual Heterogeneity and Discriminatory Accuracy (I-MAIHDA).
Results: All intersectional strata displayed phenotypic age deceleration (biologically younger than chronological age). The advantage was smallest among men without migration background, living alone and with low socioeconomic status. Substantial discriminatory accuracy (7.13%) revealed intersectional inequalities, predominantly driven by additive effects. Modest interaction effects indicated increased risk for individuals with migration background not living alone and medium/high socioeconomic status and those without migration background living alone with medium/low socioeconomic status.
Conclusions: Our findings suggest that intersectional strata shape biological aging beyond chronological age, potentially through cumulative physiological effects of chronic psychosocial stress. Future epidemiological research should explore the mechanisms linking intersecting social dimensions and biological aging, designing intersectionally-informed targeted interventions.

Introduction

Normal aging is a universal process involving biological, psychological and social changes that unfold gradually over time [1]. However, aging is far from uniform, as individuals may face age-related consequences at different rates due to variations in biological processes

List of abbreviations and acronyms: NAKO, German National Cohort Nationale Kohorte; I-MAIHDA, Intersectional Multilevel Analysis of Individual Heterogeneity and Discriminatory Accuracy; PhenoAge, Phenotypic Age; PhenoAgeAccel, Phenotypic Age Acceleration; SES, Socioeconomic Status; DNAm, DNA methylation; GCE, General Contextual Effect; DA, Discriminatory Accuracy; AUC, Area Under the Curve; BioAge, Biological Age; VPC, Variance Partition Coefficient; ICC, Intraclass Correlation Coefficient; PCV, Proportional Change in Variance.

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and social exposures [2,3]. Chronological age, while a critical risk factor for aging-related morbidity and mortality, fails to capture heterogeneity in biological aging. Individuals of the same chronological age can differ substantially in age-related diseases and overall health [4,5], shaped by social and environmental factors [6,7]. Adverse exposures, health behaviours and life-course events can drive biological changes that accelerate aging processes, suggesting the need for a holistic bio-psychosocial approach that identifies which psycho-social factors shape biological aging [8,9].

Biological aging refers to progressive deterioration of health and increasing mortality that occurs with advancing age [10,11]. Biological age is a strong predictor of future health and survival, reflecting the body's capacity to respond to internal and external stressors. Since it varies widely among individuals, several models have been developed to estimate biological age. Epigenetic clocks based on DNA methylation (DNAm) are robust predictors [12], but their requirement of large-scale molecular data limits their feasibility for widespread clinical practice. In contrast, serum biomarker-based models such as Biological Age (BioAge) [4] and Phenotypic Age (PhenoAge) [13] offer accessible and efficient alternatives. These well-validated clocks rely on routinely collected clinical biomarkers, enabling cost-effective estimation without additional data collection or complex analyses. Since they include lifestyle factors, these models are strongly associated with aging-related morbidity and mortality, making them valuable tools for studying biological age and its divergence from chronological age—often referred to as biological age acceleration [14–16].

A growing body of research underscores the impact of social determinants on biological aging, with stratified associations across sociodemographic factors such as sex/gender, race/ethnicity and socioeconomic status (SES) [17–20]. Emerging from critical Black feminist scholarship, intersectionality theory conceptualizes how interlocking systems of power and oppression (e.g., sexism, racism, classism) shape lived experiences across social identities [21]. It provides a valuable lens to understand how overlapping social determinants are mutually constituted and jointly shape aging processes and health outcomes through structural discrimination and power imbalances [21,22]. These intersecting (dis)advantages may lead to numerous risk factors among marginalized groups, such as increased allostatic load resulting from chronic psychosocial stress exposures [23,24]. From a bio-psychosocial perspective, intersecting social disadvantages may become biologically embedded through cumulative physiological dysregulation related to chronic psychosocial stress and discrimination exposure [23,24]. Resulting biological imprints can intensify over time, contributing to unequal aging trajectories [25]. Despite its relevance, intersectionality remains overlooked in the study of biological aging and its social stratification [26].

Although biological age measures consistently show socioeconomic and racial/ethnic gradients indicative of accelerated aging [17], most research focused on single social determinants. This fragmented approach fails to capture the "double cumulative disadvantage" across intersectional social identities and life-course processes. Multilevel Analysis of Individual Heterogeneity and Discriminatory Accuracy (MAIHDA) is a theory-neutral multilevel framework developed to decompose group-level variance beyond average differences [27,28]. Initially applied to geographical and institutional contexts [29,30], MAIHDA has been extended to intersectional analyses in epidemiology (I-MAIHDA) [31,32]. By clustering individuals within intersectional social strata defined by combinations of social characteristics, I-MAIHDA allows efficient partitioning of outcome variance with better scalability and parsimony [32]. Therefore, avoiding the “tyranny of the averages” (i.e., attribution of the same average value to all members of a certain stratum) [33]. I-MAIHDA reduces the risk of reinforcing stereotypes or stigmatizing certain strata [34,35], and its methodological flexibility offers a promising approach for investigating whether intersecting social inequalities are linked to distinct biological aging outcomes. Despite being welcomed as the new gold standard for social epidemiology [28,36], I-MAIHDA has not yet been applied to study differences in biological age acceleration.

The present study investigates differences in phenotypic age acceleration across intersectional social strata. Additionally, we aim to identify strata where intersectional interactions are associated with accelerated biological aging. As a secondary analysis, we examine an alternative operationalization of PhenoAge to explicitly assess the contribution of chronological age to biological age acceleration and its intersectional patterning.

Materials and methods

Data and sample

The German National Cohort (NAKO) is a prospective population-based cohort study comprising over 204,000 participants randomly sampled from local population registries and recruited through 18 study sites across 13 German states (Table S1) [37]. Eligible individuals were aged 20–69 years, provided written informed consent and were sufficiently healthy to participate in on-site assessments. Participants aged $>$ 40 years were oversampled, and baseline data collection took place between 2014 and 2019. While not all German states had study sites, a population-based recruiting strategy was designed to capture diversity across regions. Further details on the sampling frame, geographic coverage and representativeness of the data are published elsewhere [38]. The study received ethics approval from all centres and was conducted in accordance with the ethical standards from the Declaration of Helsinki. After excluding participants with missing data in any of the strata-defining variables (sex/gender, migration background, education, living alone, or income, see Table S1) and those with insufficient blood biomarkers for imputing PhenoAgeAccel ($<$ four out of nine biomarkers), our final sample included 173,925 participants. Given the importance of chronological age, all analyses were conducted across the full adult age range to capture cumulative life-course processes and avoid loss of statistical power across intersectional strata.

Outcome variables

Based on Morgan Levine’s algorithm [13], for our primary analysis we calculated PhenoAge with nine biomarkers (albumin, creatinine, glucose, natural log-transformed C-reactive protein (CRP), lymphocyte percent, mean cell volume, red blood cell distribution width, alkaline phosphatase and white blood cell count) and the chronological age. Since not all individuals had the nine biomarkers (missing percentages in Table S1), we carried out multiple imputations of missing values. We used 58 out of the 61 available NAKO blood biomarkers as auxiliary variables in the imputation, since the fully conditional approach demands the maximum available number of lab biomarkers [39]. After imputation, we calculated PhenoAge [13] with the following formula:

$$PhenoAge = 141.502 + \frac{\ln\left\{ -0.00553 \cdot \frac{(-1.51714)\cdot \exp(xb)}{0.0076927} \right\}}{0.090165}$$

where $xb = -19.907 - 0.0336 \times \text{Albumin} + 0.0095 \times \text{Creatinine} + 0.1953 \times \text{Glucose} + 0.0954 \times \ln(\text{CRP}) - 0.0120 \times \text{Lymphocyte percent} + 0.0268 \times \text{Mean cell volume} + 0.3306 \times \text{Red blood cell distribution width} + 0.00188 \times \text{Alkaline phosphatase} + 0.0554 \times \text{White blood cell count} + 0.0804 \times \text{Chronological age}$.

Finally, we calculated PhenoAgeAccel as the residuals from regressing PhenoAge on chronological age. Positive values imply accelerated aging, whereas negative values reflect decelerated aging. Although including chronological age in both the algorithm and residualization may compromise interpretability, this is standard practice within the literature to isolate deviations from expected biological aging. In the primary analysis, we applied Levine’s operationalization to preserve the intended interpretation of PhenoAgeAccel and its original

calibration including chronological age as a risk component. We acknowledge this formulation entails a degree of conceptual ambiguity; nevertheless, we retain it as a pragmatically accepted approach to ensure comparability with existing studies. In a secondary analysis, we calculated PhenoAge based on biomarkers only without chronological age and then regressed it on chronological age to obtain PhenoAgeAccel_clean (Supplementary Table S4, Table S5, Figure S4, Figure S5). Although formal normality tests (Shapiro-Wilk) were statistically significant given the large sample, visual inspection of the Q-Q plots (Figures S2 and S3) indicated approximate normality, suggesting that the outcome meets the assumptions for multilevel modelling.

Explanatory variables

We used four socio-demographic variables to create intersectional strata, based on social determinants that potentially stratify health outcomes [40]. *Sex/gender* was categorized as female/male. *Migration background* was self-reported and classified as yes/no based on participants' and their parents' nationality and country of birth, without distinguishing reason of migration. *Living alone* was measured via the number of household inhabitants and coded as yes/no. *Education* level was self-reported and coded as low (primary school), medium (secondary school), or high (university or higher education). *Household income* was captured by the question "What is the average monthly income in your household?" and was coded as low (<€2150/month), medium (€2150–€4250/month), or high (>€4250/month), according to < 80%, 80%-100% or > 120% of the median net equivalent income suggested by the German Federal Statistical Office [41]. We created 72 unique intersectional strata through all possible combinations of sex/gender (2 categories), migration background (2 categories), living alone (2 categories), education (3 categories) and income (3 categories) (2x2x2x3x3 =72) [32].

Statistical analysis

We performed an I-MAIHDA for PhenoAgeAccel with respondents (level 1) nested within intersectional social strata (level 2) defined by individual characteristics [28]. I-MAIHDA involves fitting two sequential multilevel models: first, an unadjusted null model (Model 1) with a random effect for the intersectional strata, which allows to decompose the variance and calculate the discriminatory accuracy through the Variance Partition Coefficient (VPC) [32]. The VPC is a measurement of General Contextual Effect (GCE) that estimates the between-strata variance in PhenoAgeAccel compared to the total variance (including between-individuals). Although it can measure discriminatory accuracy (DA), this is only acceptable under the assumption of similarly sized strata. For continuous outcomes as PhenoAgeAccel, we use the exploratory approach of visualizing the outcome distribution across strata using ridge plots (Figure S1), where less overlap implies higher contextual DA. DA could not be directly quantified using area under the curve (AUC)-based measures without dichotomizing PhenoAgeAccel, which would be theoretically and empirically inappropriate for a continuous biological aging outcome. Second, we fitted a model adding the stratum-defining variables as main fixed effects (Model 2). We recalculated the VPC and, to quantify the between-strata variance attributable to the additive main effects, we calculated the proportional change in variance (PCV). A PCV of 100% indicates full variance explanation by additive effects, while values < 100% imply unexplained variance attributable to intersectional interaction effects [31]. Finally, we examined strata-level residuals and their 95% credible intervals (CI) to partition the variance into additive and interaction effects, the latter capturing the unique contribution of intersectional interactions. Strata with two-sided 95% CI not including 0 would have statistically significant interaction effects, either hazardous (>0, higher PhenoAgeAccel than expected from main effects only) or protective (<0, lower PhenoAgeAccel than expected from main effects only). Further methodological details about I-MAIHDA are provided in a recent tutorial [32]. We determined statistical significance with a two-tailed p-value < 0.05 for regression coefficients. Analyses were conducted in R (version 4.4.2) [42], with descriptive statistics calculated with the "CompareGroups" package. Bayesian regression models were fitted using Markov Chain Monte Carlo (MCMC) with the "brms" package (version 2.22), and stratum-level estimates are given with 95% CI.

Results

Table 1 shows the characteristics of the sample, which was balanced regarding sex/gender. Most respondents did not have a migration background (83.9%) or did not live alone (80.3%). The majority of the sample (44.8%) had a medium income (2150€ - 4250€) and medium (41.9%) or high (55.5%) education level. Overall, women had lower income levels than men. The average blood biomarker levels were similar across sex/gender. The average PhenoAge and PhenoAgeAccel were 44.1 years and −6.1 years respectively, entailing a younger biological age compared to the chronological age. This phenomenon was even more pronounced among women (-6.9 years compared to −5.4 years for men). The overall negative PhenoAgeAccel reflects specific calibration effects of the NHANES cohort [13], compared to the relatively healthy NAKO sample. Additionally, this shows that PhenoAge was calibrated to capture deviations in mortality risk and health span rather than accurately predict chronological age. In fact, biological age measures with high age-prediction accuracy often fail to detect significant age accelerations, whereas risk-oriented algorithms such as PhenoAge work better for health-related deviations [43]. Most of the 72 strata had sufficient sample size for analysis (Table S2 and Table S3) [44], with 59 strata (81.9%) having $N > 50$ and 40 strata (55.6%) having $N > 500$. However, a few strata had $N < 50$ (18.0%).

Figure 1 shows the predicted PhenoAgeAccel for each intersectional stratum from I-MAIHDA Model 1. One stratum — women with a migration background, living alone, low education and high income — had no observations. While all 71 non-empty strata displayed negative PhenoAgeAccel, substantial between-strata heterogeneity was observed. The lowest deceleration (PhenoAgeAccel = −2.43) occurred in men without a migration background, living alone, with low education and low income, while the highest (PhenoAgeAccel = −7.19) occurred in women without a migration background, not living alone, with high education and high income. These findings suggest intersectional inequalities in PhenoAgeAccel across strata (maximum difference = 4.76 years). Table 2 presents results from I-MAIHDA models, including the average effects of strata-defining variables and between-strata variance measures. The VPC in Model 1 indicated that 7.13% of the PhenoAgeAccel variance was explained at the strata level. This represents substantial clustering [31], aligned with the heterogeneity in Figure 1. Adding strata-defining variables as fixed effects (Model 2) reduced the VPC to 0.21%. A PCV of 97.29% indicated that most between-strata PhenoAgeAccel differences were due to additive effects, with only 2.71% explained by intersectional interaction effects.

In the secondary analysis without chronological age in the algorithm, the average PhenoAgeAccel_clean was closer to zero (-5.40 years), while the maximum difference across strata was 10.13 years (highest −11.16; lowest 0.14) (Figure S4). Between-strata variance was slightly reduced in Model 1 (VPC = 5.71%) compared to the primary analysis (Table S4). However, a larger proportion of unexplained variance remained after adding the fixed effects in Model 2 (VPC = 2.1%), resulting in a substantially lower PCV of 64.7%. A greater number of strata exhibited statistically significant intersectional interaction effects (Table S5, Figure S5), indicating the importance of chronological age.

Figure 2 presents the strata-level residuals from I-MAIHDA Model 2, with most residuals including 0 in their CIs. Only five residuals were significantly different from 0, implying interaction effects (Table 3): four strata had hazardous intersectional interactions (positive residuals indicating higher PhenoAgeAccel than expected from the main effects),

Table 1
Descriptive statistics of the study sample, by sex.

Variable	Total (N = 173,925)	Female (N = 86,647)	Male (N = 87,278)	p-value	N
Age	50.2 (12.3)	50.1 (12.3)	50.4 (12.3)	< 0.001	173,925
Migration background				0.385	173,925
Yes	27,999(16.1%)	14,016 (16.2%)	13,983 (16.0%)		
No	145,926 (83.9%)	72,631 (83.8%)	73,295 (84.0%)		
Living alone				< 0.001	173,925
Yes	34,346 (19.7%)	18,368 (21.2%)	15,978 (18.3%)		
No	139,579 (80.3%)	68,279 (78.8%)	71,300 (81.7%)		
Education				< 0.001	173,925
High	96,529 (55.5%)	43,757 (50.5%)	52,772 (60.4%)		
Medium	72,875 (41.9%)	40,117 (46.3%)	32,758 (37.6%)		
Low	4521 (2.6%)	2773 (3.2%)	1748 (2.0%)		
Income level				< 0.001	173,925
> 4250€	45,905 (26.4%)	19,473 (22.5%)	26,432 (30.3%)		
2150€ - 4250€	77,968 (44.8%)	38,794 (44.8%)	39,174 (44.9%)		
< 2150€	50,052 (28.8%)	28,380 (32.8%)	21,672 (24.8%)		
Systolic blood pressure (mm HG)	127 (10.1)	122 (9.2)	131 (9.0)	< 0.001	173,633
Albumin (g/l)	42.0 (2.0)	41.0 (4.1)	42.0 (1.2)	< 0.001	98,982
Creatinine (μmol/l)	72.0 (9.0)	64.0 (6.3)	80.0 (8.0)	< 0.001	166,751
Glucose (mmol/l)	5.20 (0.6)	5.10 (0.4)	5.30 (0.5)	< 0.001	164,494
C-reactive protein (mg/l)	1.02 (0.6)	1.10 (0.7)	0.96 (0.4)	0.001	104,557
Lymphocytes (%)	28.8 (4.7)	29.2 (4.9)	28.5 (5.2)	0.001	32,667
Mean erythrocyte volume (fl)	89.7 (2.8)	90.0 (2.7)	89.5 (3.1)	0.001	70,680
Erythrocyte distribution (%)	13.2 (0.8)	13.2 (0.7)	13.2 (0.5)	0.001	41,850
Alkaline phosphatase (μkatal/l)	1.20 (0.2)	1.10 (0.1)	1.20 (0.2)	< 0.001	88,907
Leukocytes (Gpt/l)	6.12 (1.2)	6.24 (1.3)	6.02 (1.1)	< 0.001	160,982
PhenoAge	44.1 (9.6)	43.9 (9.3)	44.4 (9.7)	< 0.001	173,925
PhenoAgeAccel	-6.1 (2.6)	-6.9 (2.4)	-5.4 (2.3)	< 0.001	173,925

while one stratum had protective intersectional interactions (negative residual indicating lower than expected PhenoAgeAccel). Hazardous interaction effects were observed in four strata: (1) women without a migration background, living alone, with low education and low income; (2) men with a migration background, not living alone, with high education and medium income; (3) men without a migration background, not living alone, with medium education and low income; and (4) women with a migration background, not living alone, with high education and medium income. The only stratum with protective interaction effects was comprised by men without a migration background, living alone, with high education and medium income.

Discussion

In the current study we used data from 173,925 participants in NAKO to apply the I-MAIHDA framework and explore intersectional differences in biological aging, quantified through PhenoAgeAccel. We found substantial between-strata inequalities in accelerated biological aging, with a maximum difference of 4.76 years in PhenoAgeAccel. The majority of between-strata variance was due to additive effects, indicating that individual factors like sex/gender, migration background, living alone, education and income independently contributed to differences in biological aging acceleration. However, the presence of interaction effects for certain strata (e.g., women living alone with low education and low income, or men not living alone with medium-high education and medium-low income) suggests that specific combinations of social determinants amplify or mitigate the risk of accelerated aging. Our findings underscore the role of cumulative and intersecting social disadvantages in shaping biopsychosocial pathways associated with differences in the aging process.

Our secondary analysis provides important insights into the role of chronological age in biological age acceleration. Recalculating PhenoAge without chronological age showed that a substantial part of the PhenoAgeAccel variance reflects the age-related calibration from the original algorithm. This is consistent with its design as a risk-oriented measure for disease and mortality prediction rather than precise age estimation. The persistence of similar (yet attenuated) overall intersectional patterns, and more strata with interaction effects, indicate that social stratification in biological aging is not driven by including chronological age. Instead, chronological age absorbs part of the non-additive intersectional heterogeneity, suggesting that intersecting social positions shape biological aging trajectories beyond chronological age alone.

Our findings align with previous research showing socioeconomic and race/ethnicity gradients in biological aging [13,17,45], with an average higher PhenoAgeAccel among individuals with low education, low/medium income and a migration background. However, most studies relied on single-axis frameworks that fail to capture the cumulative and interacting effects of multiple social determinants. By employing MAIHDA with an intersectional lens, we extend this literature and identify strata-specific interaction effects, such as increased age acceleration among women without a migration background, living alone, with low education and low income, or men not living alone and with higher education and lower income. These intersectional positions often entail financial pressures, limited access to care resources and adverse health behaviours, which collectively disrupt physiological processes and accelerate the aging process [46,47]. This underscores how privilege and structural disadvantage intersect to amplify aging disparities, a nuance often missed in traditional approaches [48].

Accelerated biological aging likely reflects a combination of physiological and psychosocial processes [49]. Chronic stress arising from structural inequalities and discrimination is a plausible pathway linking social disadvantage to accelerated biological aging through mechanisms such as inflammation, dysregulated allostasis and cellular damage [50–52]. We found the highest PhenoAgeAccel among individuals in multiply disadvantaged positions (e.g., women without a migration background, living alone, with low education and low income). These subgroups may face greater social-environmental challenges alongside fewer psychosocial resources, potentially contributing to prolonged stress exposure and reduced coping capacities [53]. Conversely, lower PhenoAgeAccel observed in more advantaged strata (men without a migration background, living alone, with high-education and medium-income) could reflect protective factors associated with social privilege, including access to healthcare, healthier lifestyles and stronger social support [54].

The social hallmarks of aging are deeply intertwined with

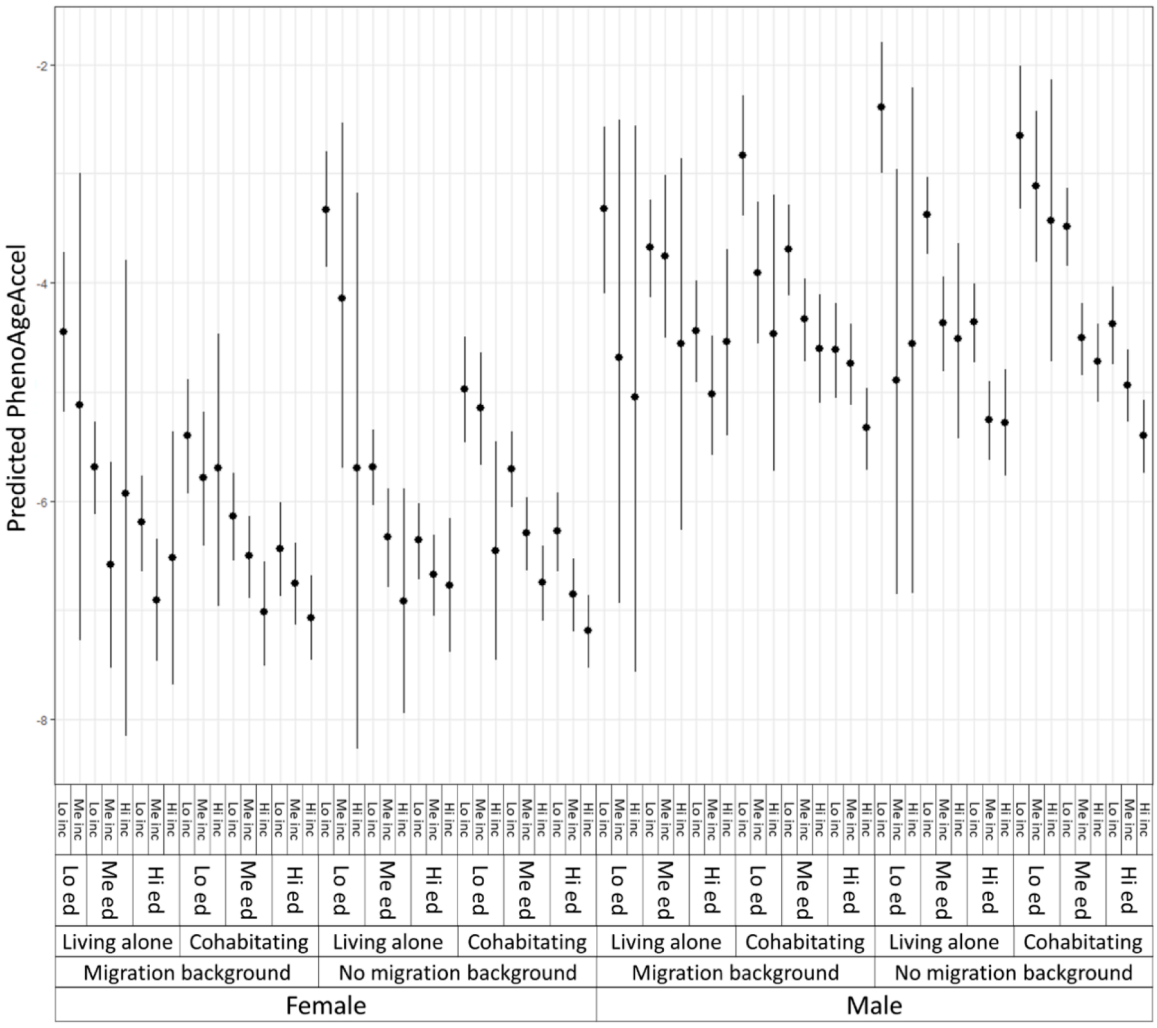

Fig. 1. Predicted phenotypic age acceleration (PhenoAgeAccel) for each intersectional stratum, obtained from I-MAIHDA model 1.

individuals' social positions and access to resources [2], shaping biological aging trajectories. Our study incorporates an intersectional approach against this background, yet future research should explore how intersecting hallmarks affect age-related outcomes. Integrating biopsychosocial and intersectional approaches may help improve understanding of aging disparities and inform more targeted public health interventions.

Our study has several strengths such as the use of a large, nationally representative cohort, the extensive availability of serum biomarkers for a large sample and the application of I-MAIHDA to rigorously assess intersectional effects. However, findings should be interpreted under several limitations. First, the cross-sectional design of the study and correlational nature of I-MAIHDA limit causal inferences. Longitudinal and interventional studies are needed to establish temporal relationships between social stratification and biological aging. Second, while PhenoAge is a validated measure of biological aging, it does not fully capture all clinical dimensions of the aging processes, such as cognitive decline or frailty. Future research should incorporate functioning limitations for a more comprehensive view on the social stratification of aging. Third, information on migration background was limited, preventing differentiation by time since or reasons for migration. Fourth, unmeasured factors that may influence both social position (SES) and biological aging (early-life conditions, genetic susceptibility) could contribute to residual confounding. Additionally, the presence of small intersectional strata ($N < 50$) may affect the precision and stability of strata-level estimates, potentially weakening the reliability of residuals and interaction effects. Hence, findings for small strata should be interpreted cautiously and not generalized beyond the observed sample. Finally, relying on self-reported data for SES variables may introduce reporting bias. Nonetheless, the NAKO study was rigorously planned and carried out with a randomly selected, multi-centre cohort, hence it is plausible to assume minimal reporting bias.

Identifying intersectional disparities in biological aging underscores the importance of addressing cumulative social inequalities in epidemiologic research and intervention design. Our findings suggest that interventions should prioritize improved care and social resource allocation in disadvantaged populations to promote psychosocial resilience and mitigate accelerated aging. Policies promoting equitable access to healthcare, income support programs and anti-discrimination measures may mitigate the accelerated aging observed in high-risk strata. Additionally, public health initiatives could incorporate culturally tailored stress management and mental health programs to address the unique challenges faced by migrant populations.

From a methodological perspective, our study highlights the importance of integrating intersectionality into quantitative aging research. Using I-MAIHDA allowed us to quantify both additive and interaction effects of social determinants, providing a more nuanced understanding of health inequalities. Future research should expand intersectional analyses to additional social determinants linked to biological aging, such as occupational class, ethnicity or neighbourhood deprivation [18,55,56].

Table 2
Results from I-MAIHDA models on PhenoAgeAccel (N = 173,925).

	Model 1	Model 2
Variable	**Estimate (95% CI)**	**Estimate (95% CI)**
FIXED EFFECTS		
Intercept	-5.14 (-5.46, −4.81)***	-4.64 (-4.88, −4.40)***
Sex		
Male		Reference
Female		-2.00 (-2.14, −1.86)***
Migration background		
No		Reference
Yes		-0.11 (-0.25, −0.03)***
Living alone		
No		Reference
Yes		0.15 (0.00, 0.32)**
Education		
High		Reference
Medium		1.05 (0.84, 1.27)***
Low		1.63 (1.41, 1.84)***
Income level		
> 4250€		Reference
2150€ - 4250€		0.62 (0.46, 0.78)***
< 2150€		0.94 (0.75, 1.13)***
RANDOM EFFECTS		
Within-strata variance	22.87	22.87
Between-strata variance	1.75	0.05
VPC	7.17%	0.21%
PCV	-	97.32%

*p < 0.05; **p < 0.01; ***p < 0.001.
Note: PhenoAgeAccel, phenotypic age acceleration; CI, Confidence Interval; VPC, Variance Partition Coefficient; PCV, Proportional Change in Variance.

Conclusions

Our study demonstrates the intersectional stratification of biological aging, emphasizing the need for a biopsychosocial approach to address aging-related health disparities. These findings highlight the urgency of addressing social inequalities to mitigate accelerated aging and promote health equity across diverse populations. We demonstrate the utility of applying an intersectionality-informed framework in epidemiologic research, which helps to identify subgroups at higher risk to inform the development of tailored population-level actions.

Ethics approval

The NAKO was approved by the ethical review committees of all participating NAKO study centres. Informed consent was obtained from all participants.

Contributions

EAP, PG and GF conceived the study. EAP and PG carried out the data application process. HR and EAP performed the statistical analysis and EAP drafted the manuscript. EAP, JLOS, GF and PG contributed to results interpretation. All authors critically revised the manuscript and approved the final version.

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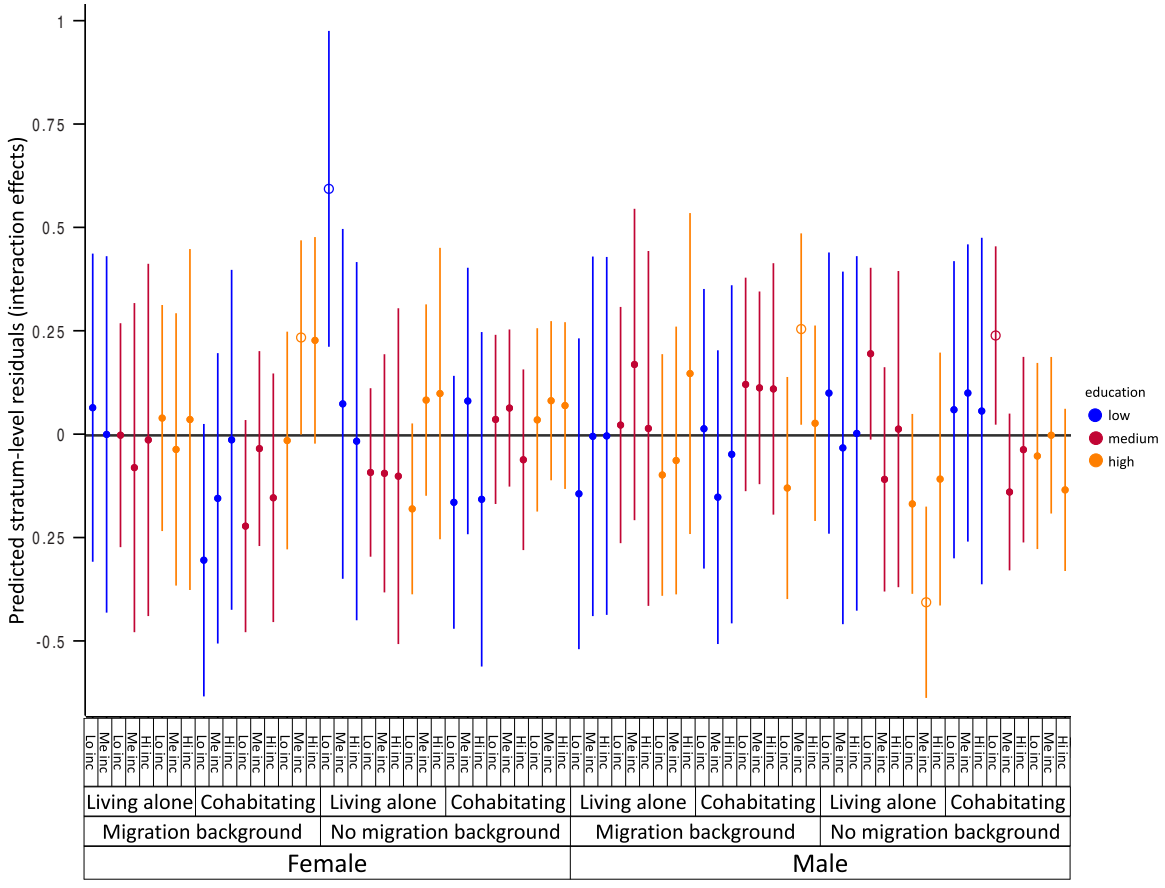

Fig. 2. Strata-level residuals for each intersectional stratum, obtained from I-MAIHDA model 2. Open circles indicate residuals significantly different from zero.

Table 3
Composition of the significant strata-level residuals obtained from I-MAIHDA model 2.

	Sex		Migration background		Living alone		Education			Income			
Stratum	Female	Male	Yes	No	Yes	No	Low	Me.	High	Low	Me.	High	Residual (95% CI)
12111													0.60 (0.21, 0.98)
21232													0.26 (0.03, 0.49)
22221													0.24 (0.03, 0.46)
11232													0.24 (0.00, 0.47)
22132													-0.40 (-0.63, -0.17)

Note: stratum ID are coded for each digit as follows: Sex: 1 = Female, 2 = Male, Migration background: 1 = Yes, 2 = No, Living alone: 1 = Yes, 2 = No, Education: 1 = Low, 2 = Medium, 3 = High, Income: 1 = Low, 2 = Medium, 3 = High; Me. = Medium education.

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CRediT authorship contribution statement

Enrique Alonso-Perez: Writing – original draft, Methodology, Data curation, Conceptualization. **Paul Gellert:** Writing – review & editing, Project administration, Methodology, Data curation, Conceptualization. **Henrik Rudolf:** Visualization, Software, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Julie Lorraine O'Sullivan:** Writing – review & editing, Methodology. **Georg Fuellen:** Writing – review & editing, Conceptualization.

Declaration of Competing Interest

The authors have no competing interest to declare.

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Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.annepidem.2026.110075.

Data availability statement

The dataset used in the current study is not publicly available due to privacy concerns, but they can be obtained for free upon request via the NAKO transfer hub: https://transfer.nako.de/transfer/index.

References

[1] Harman D. Aging: overview. Ann N Y Acad Sci 2001;928(1):1–21.
[2] Crimmins EM. Social hallmarks of aging: suggestions for geroscience research. Ageing Res Rev 2020;63:101136.
[3] Dziechciaz M, Filip R. Biological psychological and social determinants of old age: bio-psycho-social aspects of human aging. Ann Agric Environ Med 2014;21(4).
[4] Crimmins EM, Thyagarajan B, Kim JK, Weir D, Faul J. Quest for a summary measure of biological age: the health and retirement study. Geroscience 2021;43:395–408.
[5] Waziry R, Gras L, Sedaghat S, et al. Quantification of biological age as a determinant of age-related diseases in the Rotterdam Study: a structural equation modeling approach. Eur J Epidemiol 2019;34:793–9.
[6] Franceschi C, Garagnani P, Morsiani C, et al. The continuum of aging and age-related diseases: common mechanisms but different rates. Front Med 2018;5:61.
[7] Fulop T, Larbi A, Witkowski JM, et al. Aging, frailty and age-related diseases. Biogerontology 2010;11:547–63.
[8] Blane D, Kelly-Irving M, d'Errico A, Bartley M, Montgomery S. Social-biological transitions: how does the social become biological? Longitud Life Course Stud 2013;4(2):136–46.
[9] Oblak L, van der Zaag J, Higgins-Chen AT, Levine ME, Boks MP. A systematic review of biological, social and environmental factors associated with epigenetic clock acceleration. Ageing Res Rev 2021;69:101348.
[10] Levine ME. Modeling the rate of senescence: can estimated biological age predict mortality more accurately than chronological age? J Gerontol Ser A Biomed Sci Med Sci 2013;68(6):667–74.
[11] Shaaban CE, Rosano C, Zhu X, et al. Discordant biological and chronological age: implications for cognitive decline and frailty. J Gerontol Ser A 2023;78(11):2152–61.
[12] George A, Hardy R, Fernandez JC, Kelly Y, Maddock J. Life course socioeconomic position and DNA methylation age acceleration in mid-life. J Epidemiol Community Health 2021;75(11):1084–90.
[13] Levine ME, Lu AT, Quach A, et al. An epigenetic biomarker of aging for lifespan and healthspan. Aging (Albany NY) 2018;10(4):573–91.
[14] Chen L, Zhao Y, Liu F, et al. Biological aging mediates the associations between urinary metals and osteoarthritis among U.S. adults. BMC Med 2022;20(1).
[15] Liu Z, Kuo P-L, Horvath S, Crimmins E, Ferrucci L, Levine M. A new aging measure captures morbidity and mortality risk across diverse subpopulations from NHANES IV: a cohort study. PLoS Med 2018;15(12):e1002718.
[16] Zhang R, Wu M, Zhang W, et al. Association between life's essential 8 and biological ageing among US adults. J Transl Med 2023;21(1).
[17] Crimmins EM, Klopack ET, Kim JK. Generations of epigenetic clocks and their links to socioeconomic status in the Health and Retirement Study. Epigenomics 2024;16(14):1031–42.
[18] Farina MP, Kim JK, Crimmins EM. Racial/ethnic differences in biological aging and their life course socioeconomic determinants: The 2016 Health and Retirement Study. J Aging Health 2023;35(3-4):209–20.
[19] Graf GH, Crowe CL, Kothari M, et al. Testing Black-White disparities in biological aging among older adults in the United States: analysis of DNA-methylation and blood-chemistry methods. Am J Epidemiol 2022;191(4):613–25.
[20] Horvath S, Gurven M, Levine ME, et al. An epigenetic clock analysis of race/ethnicity, sex, and coronary heart disease. Genome Biol 2016;17:1–23.
[21] Crenshaw K. Mapping the margins: Intersectionality, identity politics, and violence against women of color. Stan L Rev 1990;43:1241.
[22] Cuevas AG, Cole SW, Belsky DW, McSorley A-M, Shon JM, Chang VW. Multi-discrimination exposure and biological aging: Results from the midlife in the United States study. Brain Behav & ImmunHealth 2024:100774.
[23] Guidi J, Lucente M, Sonino N, Fava GA. Allostatic load and its impact on health: a systematic review. Psychother Psychosom 2020;90(1):11–27.
[24] Stabellini N, Cullen J, Bittencourt MS, et al. Allostatic load/chronic stress and cardiovascular outcomes in patients diagnosed with breast, lung, or colorectal cancer. J Am Heart Assoc 2024;13(14):e033295.

[25] Holman D, Salway S, Bell A. Mapping intersectional inequalities in biomarkers of healthy ageing and chronic disease in older English adults. Sci Rep 2020;10(1).
[26] Thomas Tobin CS, Gutiérrez Á, Farmer HR, Erving CL, Hargrove TW. Intersectional approaches to minority aging research. Curr Epidemiol Rep 2023;10(1):33–43.
[27] Evans CR, Williams DR, Onnela J-P, Subramanian SV. A multilevel approach to modeling health inequalities at the intersection of multiple social identities. Soc Sci & Med 2018;203:64–73.
[28] Merlo J. Multilevel analysis of individual heterogeneity and discriminatory accuracy (MAIHDA) within an intersectional framework. Soc Sci Med 2018;203:74–80.
[29] Merlo J. Invited commentary: multilevel analysis of individual heterogeneity—a fundamental critique of the current probabilistic risk factor epidemiology. Am J Epidemiol 2014;180(2):208–12.
[30] Merlo J, Ohlsson H, Lynch KF, Chaix B, Subramanian S. Individual and collective bodies: using measures of variance and association in contextual epidemiology. J Epidemiol & Community Health 2009;63(12):1043–8.
[31] Axelsson Fisk S, Mulinari S, Wemrell M, Leckie G, Perez Vicente R, Merlo J. Chronic Obstructive Pulmonary Disease in Sweden: An intersectional multilevel analysis of individual heterogeneity and discriminatory accuracy. SSM Popul Health 2018;4:334–46.
[32] Evans CR, Leckie G, Subramanian SV, Bell A, Merlo J. A tutorial for conducting intersectional multilevel analysis of individual heterogeneity and discriminatory accuracy (MAIHDA). SSM Popul Health 2024;26:101664.
[33] Merlo J, Wagner P. The tyranny of the averages and the indiscriminate use of risk factors in public health: a call for revolution. Eur J Epidemiol 2013;28(1):148.
[34] Goldstein H, Browne W, Rasbash J. Partitioning variation in multilevel models. Underst Stat Stat Issues Psychol Educ Soc Sci 2002;1(4):223–31.
[35] Merlo J, Yang M, Chaix B, Lynch J, Råstam L. A brief conceptual tutorial on multilevel analysis in social epidemiology: investigating contextual phenomena in different groups of people. J Epidemiol & Community Health 2005;59(9):729–36.
[36] Evans CR, Borrell LN, Bell A, Holman D, Subramanian SV, Leckie G. Clarifications on the intersectional MAIHDA approach: A conceptual guide and response to Wilkes and Karimi (2024). Soc Sci & Med 2024;350:116898.
[37] NAKO Consortium GNC. The German National Cohort: aims, study design and organization. Eur J Epidemiol 2014;29(5):371–82.
[38] Peters A, de GNCChndgn, Peters A, et al. Framework and baseline examination of the German National Cohort (NAKO). Eur J Epidemiol 2022;37(10):1107–24.
[39] Lee KJ, Carlin JB. Multiple imputation for missing data: fully conditional specification versus multivariate normal imputation. Am J Epidemiol 2010;171(5):624–32.
[40] O'Neill J, Tabish H, Welch V, et al. Applying an equity lens to interventions: using PROGRESS ensures consideration of socially stratifying factors to illuminate inequities in health. J Clin Epidemiol 2014;67(1):56–64.
[41] Bundesregierung D. Lebenslagen in Deutschland: Sechste Armuts- und Reichtumsbericht der Bundesregierung. In: Soziales. BfAu, ed2021.
[42] R. Core Team. Team R: A language and environment for statistical computing. R Foundation for Statistical, 2020. *Computing, Vienna, Austria URL https://www R-project org*. 2024.
[43] Nardini C, Di Lena P. Predictive power of epigenetic age–opportunities and cautions. Epigenomics 2024;17(2):75–7.
[44] Nieves CI, Borrell LN, Evans CR, Jones HE, Huynh M. The application of intersectional multilevel analysis of individual heterogeneity and discriminatory accuracy (MAIHDA) to examine birthweight inequities in New York City. Health & Place 2023;81:103029.
[45] Krieger N, Testa C, Chen JT, et al. Epigenetic Aging and Racialized, Economic, and Environmental Injustice. JAMA Netw Open 2024;7(7):e2421832.
[46] Schrempft S, Belsky D, Draganski B, et al. Associations between life course socioeconomic conditions and the Pace of Aging. J Gerontol Ser A Biol Sci Med Sci 2021.
[47] Simons R, Lei M, Beach S, et al. Economic hardship and biological weathering: The epigenetics of aging in a U.S. sample of black women. Soc Sci & Med 2016;150:192–200.
[48] Stepanikova I, Oates G. Perceived Discrimination and Privilege in Health Care: The Role of Socioeconomic Status and Race. Am J Prev Med 2017;52. 1S1.
[49] Han L, Verhoeven J, Tyrka A, et al. Accelerating research on biological aging and mental health: Current challenges and future directions. Psychoneuroendocrinology 2019;106:293–311.
[50] Gao X, Gào X, Zhang Y, Holleczek B, Schöttker B, Brenner H. Oxidative stress and epigenetic mortality risk score: associations with all-cause mortality among elderly people. Eur J Epidemiol 2019;34:451–62.
[51] Pearlin LI, Schieman S, Fazio EM, Meersman SC. Stress, health, and the life course: Some conceptual perspectives. J Health Soc Behav 2005;46(2):205–19.
[52] Polsky LR, Rentscher KE, Carroll JE. Stress-induced biological aging: A review and guide for research priorities. Brain Behav Immun 2022;104:97–109.
[53] Kristenson M, Eriksen H, Sluiter J, Starke D, Ursin H. Psychobiological mechanisms of socioeconomic differences in health. Soc Sci & Med 2004;58(8):1511–22.
[54] Holz N, Tost H, Meyer-Lindenberg A. Resilience and the brain: a key role for regulatory circuits linked to social stress and support. Mol Psychiatry 2019;25:379–96.
[55] Andrasfay T, Kim JK, Ailshire JA, Crimmins E. Aging on the job? The association between occupational characteristics and accelerated biological aging. J Gerontol Ser B 2023;78(7):1236–45.
[56] Lawrence KG, Kresovich JK, O'Brien KM, et al. Association of neighborhood deprivation with epigenetic aging using 4 clock metrics. JAMA Netw Open 2020;3(11). e2024329-e2024329.