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Association of accelerated biological aging and frailty with the risk of severe infection: a prospective study in the UK Biobank

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ABSTRACT

Background: Infectious diseases contribute substantially to morbidity and mortality among aging populations, yet the impact of biological aging on severe infection risk remains unclear.
Methods: Cox proportional hazards models estimated hazard ratios (HRs) and 95 % confidence intervals (CIs) for associations of accelerated biological aging (measured by KDM-BA and PhenoAge) and frailty index (FI) with overall and type-specific severe infections. Life expectancy differences by biological aging status were assessed. Bivariate response surface models evaluated combined effects of FI and two biological age acceleration indicators on severe infections.
Results: KDM-BA acceleration (HR: 1.18; 95 % CI: 1.16 to 1.19) and PhenoAge acceleration (HR: 1.27; 95 % CI: 1.25 to 1.29) were associated with increased severe infection risk. Higher FI levels showed progressively greater risk, with HRs (95 % CIs) of 1.40 (1.38 to 1.43), 2.01 (1.96 to 2.06), 2.64 (2.53 to 2.76) and 3.37 (2.96 to 3.83) for FI categories 0.1 -< 0.2, 0.2 -< 0.3, 0.3 -< 0.4, and ≥ 0.4 versus FI < 0.1. Associations varied by infection type: KDM-BA acceleration and PhenoAge acceleration showed the strongest associations with respiratory infections, whereas the frailty index was most associated with digestive infections. Significant combined effects of FI and biological age accelerations further increased risk. Biologically younger individuals had longer life expectancy: +1.59 years (95 % CI: 1.40 to 1.77) for KDM-BA acceleration and +2.2 years (95 % CI: 2.00 to 2.40) for PhenoAge acceleration.
Conclusion: Accelerated biological aging and frailty were significantly associated with increased risks of overall and type-specific severe infections. These findings suggest that integrating biological aging assessments into routine healthcare could improve infection risk stratification and guide targeted prevention strategies.

1. Introduction

Infectious diseases accounted for 32 % of the top ten global causes of death in 2021, [1] reflecting the significant impact of infectious diseases on global health. Studies have indicated that severe infections were associated with major cardiovascular disease events, [2] lung cancer risk, [3] and dementia incidence [4–6] Aging is considered a significant risk factor for severe infections [7] It is a complex biological process characterized by a gradual decline in structure and functional integrity [8] Research has indicated a significant association between frailty phenotypes and severe infections, with frailty, being a manifestation of aging, further exacerbating the risk of infections [9,10] The decline in immune function during aging leads to systemic inflammatory responses [7,11] This alteration in the immune system increases susceptibility to infectious diseases [12] Previous studies have suggested that accelerated biological aging may increase the probability and severity of COVID-19 infection [13,14] However, current epidemiological evidence regarding the relationship between multidimensional biological aging and a

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broader definition of severe infections remains insufficient, warranting further investigation into their interrelationship.

Biological age (BA) incorporates a variety of biomarkers that reflect an individual's physiological status and the associated risks of disease and death related to age, [15] and provides a more accurate assessment of human aging. Several methods for measuring BA have been validated and tested [16] Among those, algorithms that integrate the information of standard clinical parameters are considered highly accurate in predicting morbidity and mortality [17] We used the Klemera-Doubal method Biological Age (KDM-BA) and PhenoAge algorithms to calculate biological age of each individual. The KDM method primarily assesses cardiopulmonary function and metabolism, while the PhenoAge algorithm focuses on changes in immune function and metabolism. KDM-BA acceleration, and PhenoAge acceleration are calculated by regressing BA on chronological age [15] Additionally, we considered an alternative indicator of biological aging, [18,19] frailty, which is a physiological syndrome characterized by the accelerated loss of physiological reserves during aging [20] The two most commonly used measures of frailty are the frailty phenotype (FP)[21] and the frailty index (FI) [22] We utilized the frailty index, which represents the accumulation of health deficits and serves as a predictive indicator for broader health outcomes beyond chronological age (CA) [23] Understanding the relationships among biological aging, severe infections, and infection subtypes may contribute to the development of more precise public health policies. This includes tailoring healthcare intensity according to different levels of biological aging to help mitigate the risk of severe infections in population [9]

We conducted a prospective analysis of over 300,000 UK Biobank participants to systematically assess associations of two accelerated biological aging markers and the frailty index (FI) with the risk of severe infections and specific types. We further examined how accelerated biological aging and frailty influence life expectancy. We applied bivariate response surface models to assess the combined effects of frailty index and each of the two biological age acceleration indicators separately.

2. Methods

2.1. Study population

The UK Biobank is a population-based prospective study that recruited over 500,000 participants aged 37 to 73 years from England, Wales and Scotland between 2006 and 2010. Participants were required to provide health-related information through verbal interviews, touchscreen questionnaires, physical measures, and biological samples [24,25]

Initially, 502,250 participants with available data were included. We excluded those who withdrew consent ($n = 87$), had severe infections at baseline ($n = 43{,}523$) or had missing data on KDM-BA or PhenoAge biomarkers ($n = 150{,}562$). We also excluded participants with 10 or more items which were used to construct FI missing (more than 20 %). A total of 307,136 participants were included in our study (Supplementary Figure 1). This study was approved by the Northwest Multicenter Research Ethics Committee (11/NW/0382), and informed consent was obtained from all participants (application number: 98,410).

2.2. Assessment of biological age and biological age acceleration

We used two widely validated and applied methods, KDM-BA[26] and PhenoAge, [27] both based on clinical and blood chemistry metrics. Details of the calculation are available in the supplementary material. The clinical and blood biochemical markers, along with their corresponding UK Biobank data fields, are listed in Supplementary Table 1. Because biological age was calculated by deterministic functions, and imputing missing biomarkers would change the construct and distribution of biological age. Thus, we removed data entries with missing values prior to analysis [28,29]

To quantify the difference between participants' BA and chronological age, we calculated biological age acceleration (BA acceleration) values. These values were defined as residuals from regressing KDM-BA and PhenoAge on chronological age. Both KDM-BA acceleration and PhenoAge acceleration were categorized into two groups: biologically older (values > 0) and biologically younger (values ≤ 0). A positive value indicates accelerated aging, where biological age exceeds chronological age, while a negative value suggests slower aging, where biological age is lower than expected.

2.3. Frailty index

The frailty index (FI) was defined as the proportion of accumulated deficits. The standard procedure for constructing a frailty index was established in 2008 [30] The FI was constructed using 49 self-reported items covering multiple health domains (Supplementary Table 2) [31] The FI score was calculated as the sum of an individual's deficits divided by the total number of deficits used to construct the FI, yielding a score ranging from 0 to 1, where 0 indicates no deficits and 1 represents the most severe deficit. Consistent with standard FI construction guidance, [32,33] participants with 10 or more missing items required for FI construction (> 20 %) were excluded. For those with 1–9 missing items, we used multiple imputation (MI) by chained equations ($m = 5$) to avoid unnecessary loss of information and potential bias associated with complete-case deletion of FI items [31,34] Based on a previous study, [31] participants were classified into five categories: FI < 0.10, $0.1 \leq$ FI < 0.2, $0.2 \leq$ FI < 0.3, $0.3 \leq$ FI < 0.4, and FI ≥ 0.4. The FI score was also analyzed as a continuous variable in this study.

2.4. Assessment of outcome

The primary outcome was the occurrence of severe (hospital-treated) infection. The International Classification of Diseases, 10th revision (ICD-10 codes), was used to extract primary diagnoses of infection from hospital discharge records[2,35] (Supplementary Table 3). Severe infections were further classified into four categories[6,36]: respiratory infection, digestive infection, blood or sexually transmitted infection, and central nervous system infection, based on more than 900 ICD-10 codes. Additionally, we also considered life-threatening infectious diseases [37]

2.5. Covariates

This study included multiple covariates based on prior research findings. The covariates included age, sex, ethnicity, body mass index (BMI), Townsend Deprivation Index (TDI), smoking status, alcohol intake frequency and physical activity. Data that were missing on covariates were imputed using multiple imputation by chained equations based on 5 replications [34] The corresponding UKB data fields are listed in Supplementary Table 4.

2.6. Statistical analysis

Baseline characteristics were summarized as means (standard deviations, SD) for continuous variables and counts (proportions) for categorical variables. We utilized Cox proportional hazards regression models to assess the associations of KDM-BA acceleration, PhenoAge acceleration and the frailty index with severe infections risk, yielding hazard ratios (HRs) with their corresponding 95 % confidence intervals (CIs). Two models were analyzed: Model 1 (unadjusted) and Model 2 (adjusted by age, sex, ethnicity, body mass index (BMI), Townsend Deprivation Index (TDI), smoking status, alcohol intake frequency, and physical activity). Residual life expectancy was estimated by calculating the area under the survival curve up to age 100. The years of life gained were determined by calculating the difference between the areas under

two survival curves (e.g., biologically younger vs. biologically older) [38] Proportional hazards survival analyses were performed using the "stpm2" command in Stata to evaluate how accelerated biological aging and frailty influence life expectancy, respectively [39]

To further explore the dose-response relationships of KDM-BA acceleration, PhenoAge acceleration and frailty index (as continuous variables) with the risk of severe infections, we employed a restricted cubic spline (RCS) model. Based on previous studies, subgroup analyses stratified by infection categories were conducted to examine whether infection type influenced the results.

Cox generalized additive models (CGAM) were used to analyze the combined effects of frailty index and biological age acceleration on the risk of severe infections. We used nonparametric bivariate response surface model to visually assess the joint pattern of frailty index and biological age acceleration. The model was used to estimate nonlinear or linear associations between exposures and outcome by using nonparametric plate smoothing functions [40,41] The bivariate exposure-response surface diagrams from the CGAMs were used to visualize interaction of frailty index and biological age acceleration.

Several sensitivity analyses were conducted to assess the robustness of the main findings: (1) excluding participants with missing frailty index components or incomplete covariate data, (2) excluding participants who developed the outcome disease within the first two years after cohort entry, (3) conducting subgroup analyses stratified by sex, (4) conducting subgroup analyses stratified by age, and (5) to account for the competing risk of death, we used Fine and Gray subdistribution hazard model to examine the associations between biological aging and severe infections risk. All statistical analyses were conducted using R (version 4.3.3) and STATA (version 18.0).

3. Results

3.1. Baseline characteristics of participants

The baseline characteristics of UK Biobank participants, stratified by severe infections status, are shown in Supplementary Table 5. A total of 307,136 participants were included in the analysis, among whom 65,364 developed severe infections during a median follow-up of 13.4 years. Compared to participants without severe infections, those who developed severe infections had higher proportions of males, current smokers, and low physical activity. They also exhibited higher mean age, body mass index (BMI), and Townsend Deprivation Index (TDI). Among participants with severe infections, a higher proportion was classified as biologically older by KDM-BA and PhenoAge method (53.9 % for KDM-BA acceleration, 52.8 % for PhenoAge acceleration). Compared to those without severe infections, fewer participants with severe infections had a better frailty status. Mean KDM-BA acceleration, PhenoAge acceleration, and frailty index scores (as continuous variables) were all higher among participants with severe infections than those without (KDM-BA acceleration: mean=0.12, SD=1.04; PhenoAge acceleration: mean=0.19, SD=1.09). Comparison of characteristics between data with imputation and without imputation is shown in Supplementary Table 6.

3.2. Association of biological age accelerations and frailty index with severe infections risk

Survival curves demonstrated significant associations of accelerated biological aging and frailty index with severe infections risk, which were consistent with findings from the adjusted Cox regression models (Table 1 and Fig. 1). In the fully adjusted model, KDM-BA acceleration (aHR=1.12, 95 % CI: 1.11 to 1.13) and PhenoAge acceleration (aHR=1.21, 95 % CI: 1.20 to 1.22) were significantly linked to the increased risk of severe infections. Compared to biologically younger individuals, the risk of severe infections among biologically older individuals increased by 18 % (aHR=1.18, 95 % CI: 1.16 to 1.19 for KDM-BA acceleration) and 27 % (aHR=1.27, 95 % CI: 1.25 to 1.29 for PhenoAge acceleration). A dose-response relationship was observed between FI score and the risk of infection. For every 0.1 increase in FI (10 % increase in frailty), the risk increased by 47 % (aHR=1.47, 95 % CI: 1.45 to 1.48). In the group with the highest frailty index (≥ 0.4), the aHR was 3.37 (95 % CI: 2.96 to 3.83), which was significantly higher than in the reference group (< 0.1). We used restricted cubic splines to explore and visualize the dose-response relationship of KDM-BA acceleration, PhenoAge acceleration and frailty index (as continuous variables) with the risk of severe infections. It revealed the non-linear and positive associations of KDM-BA acceleration, PhenoAge acceleration and frailty index with the risk of severe infections. Both KDM-BA acceleration = 0 and PhenoAge acceleration = 0 served as the threshold, where negative values suggested biologically younger, while positive values indicated biologically older (accelerated aging) and the increased risk of severe infections. A clear dose-response relationship was observed beyond a FI threshold of 0.1, with risk increasing progressively as FI scores increased, as indicated by the rising HR values (Supplementary Figure 2).

Table 1
Association between biological age acceleration, frailty index and morbidity of severe infection.

Exposure	No. of cases/Total no.	Incidence/ 1000 PYs	cHR (95 % CI)	aHR[a] (95 % CI)
KDM-BA acceleration	65,364/ 30,7136	17.43	1.18(1.17 to 1.19)	1.12(1.11 to 1.13)
Category				
Biologically Younger	30,099/ 158,301	15.35	1.00(ref)	1.00(ref)
Biologically Older	35,265/ 148,835	19.71	1.29(1.27 to 1.31)	1.18(1.16 to 1.19)
PhenoAge acceleration	65,364/ 307,136	17.43	1.30(1.29 to 1.31)	1.21(1.20 to 1.22)
Category				
Biologically Younger	30,813/ 168,137	14.67	1.00(ref)	1.00(ref)
Biologically Older	34,551/ 138,999	20.95	1.44(1.42 to 1.46)	1.27(1.25 to 1.29)
Frailty Index Score[b]	65,364/ 307,136	17.43	1.66(1.64 to 1.68)	1.47(1.45 to 1.48)
Category				
<0.1	21,792/ 140,381	12.28	1.00(ref)	1.00(ref)
0.1 to <0.2	29,604/ 128,216	19.10	1.57(1.54 to 1.59)	1.40(1.38 to 1.43)
0.2 to <0.3	11,124/ 32,439	30.58	2.55(2.49 to 2.61)	2.01(1.96 to 2.06)
0.3 to <0.4	2586/5633	44.83	3.76(3.61 to 3.92)	2.64(2.53 to 2.76)
≥0.4	259/467	59.96	5.20(4.58 to 5.92)	3.37(2.96 to 3.83)

[a] Adjusted for age, sex, ethnicity, body mass index (BMI), Townsend Deprivation Index (TDI), smoking status, drinking frequency, physical.
[b] Results are expressed per 0.1 increments on the frailty index (FI) scale (10 % higher frailty).

Table 2 showed the associations between biological aging and the risk of severe infections stratified by infection type. In fully adjusted models, accelerated biological aging and frailty index (FI) were related to the increased risk across all severe infection types. When classified by infection type, KDM-BA acceleration (continuous variable) had the strongest association with increased risk of respiratory infection (aHR=1.26, 95 % CI: 1.24 to 1.28), followed by blood or sexually transmitted infection (aHR=1.23, 95 % CI: 1.09 to 1.39), central nervous system infection (aHR=1.12, 95 % CI: 1.03 to 1.22), and digestive system infection (aHR=1.11, 95 % CI: 1.09 to 1.13). Similarly, PhenoAge acceleration (continuous variable) demonstrated the strongest association with respiratory infection, followed by digestive system infection, central nervous system infection, and blood or sexually

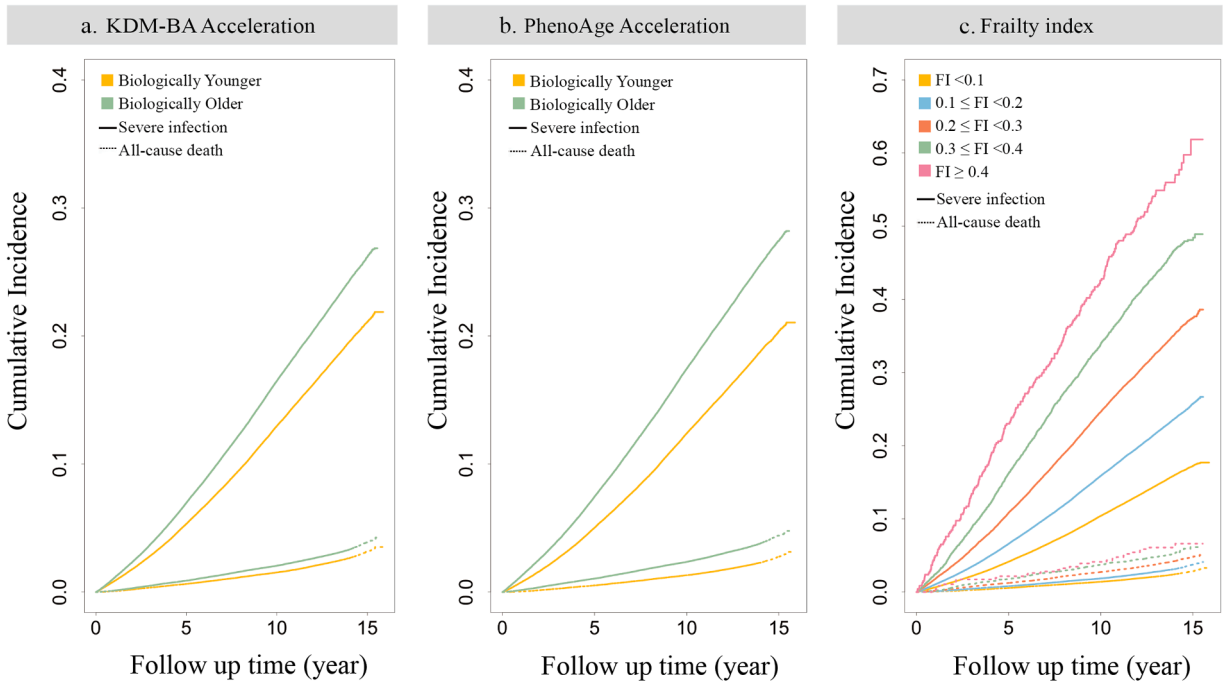

Fig. 1. Cumulative incidence of severe infection and all-cause death stratified by different biological aging metrics.

transmitted infection. A dose-response relationship was observed between FI score and severe infections risk when stratified by infection type. When FI was analyzed as a continuous variable, the strongest association was with digestive system infection, followed by respiratory infection, blood-borne or sexually transmitted infection, and central nervous system infection. For every 0.1 increase in FI (10 % increase in frailty), the risk increased by 61 %, 54 %, 51 %, and 46 %, respectively.

3.3. Life expectancy

Life expectancy analysis indicated that biologically younger individuals aged 45 years or older had significantly longer life expectancy than biologically older ones, and individuals who had lower scores in frailty index tended to have longer life expectancy compared to those with scores over 0.4 (Fig. 2). Among participants at the age of 45 years, compared to biologically older ones, individuals who were biologically younger gained a life expectancy ranging from 1.59 (95 % CI: 1.40 to 1.77, KDM-BA acceleration) years to 2.20 years (95 % CI: 2.00 to 2.40, PhenoAge acceleration). At age 45 years, individuals who had lower scores in frailty index gained a life expectancy ranging from 0.87 years to 3.24 years (0.87, 95 % CI: 0.72 to 1.01 for FI 0.3 to < 0.4; 1.69, 95 % CI: 1.42 to 1.97 for FI 0.2 to < 0.3; 2.49, 95 % CI: 2.09 to 2.88 for FI 0.1 to < 0.2; 3.24, 95 % CI: 2.74 to 3.74 for FI < 0.1) compared to those whose frailty index was over 0.4.

3.4. Bivariate surface models

The bivariate response model indicated significant synergistic effects between frailty index and each of the two biological age accelerations (KDM-BA acceleration and PhenoAge acceleration) ($P < 0.05$; Fig. 3). Fig. 3a shows a monotonic increase in the linear predictor of risk with rising frailty index and KDM-BA acceleration values. The highest predicted risk occurred in individuals with the highest levels of both frailty index and KDM-BA acceleration. A similar combined association was observed for PhenoAge acceleration in Fig. 3b However, the frailty index–PhenoAge acceleration surface exhibited a slightly steeper risk gradient, suggesting that PhenoAge acceleration might have a marginally stronger joint effect with frailty index on the risk of severe infections than KDM-BA acceleration.

3.5. Sensitivity analysis

Sensitivity analyses yielded similar results (Supplementary Tables 7–10). The results of sensitivity analyses confirmed that exclusion of participants with missing data, removal of those infected within the first two years of follow-up, stratification by sex and age, and competing risk did not substantially alter the main findings.

4. Discussion

This large-scale study of over 300,000 UK Biobank participants systematically evaluated the associations between biological aging and severe infections risk. Strong associations were observed between severe infections risk and biological age acceleration, as well as the frailty index. These associations remained significant across different infection types. The bivariate response model results showed the strong combined effects between frailty index and both KDM-BA acceleration and PhenoAge acceleration. Life expectancy results demonstrated that biologically younger individuals exhibited longer life expectancy compared to those who were biologically older, and individuals with lower FI score tended to have a longer life expectancy compared to those whose FI score was over 0.4.

Our study investigated the association between biological aging and a broad spectrum of severe infections using data in a large, general population cohort in the UK Biobank. We employed two biological age acceleration methods (KDM-BA and PhenoAge) along with the frailty index (FI) to characterize biological aging. We observed a significant association between accelerated biological aging and an increased risk of severe infections. Cao et al [42] confirmed an association between accelerated epigenetic aging and the risk of SARS-CoV-2 infection and severe COVID-19 outcomes using five epigenetic clocks and a telomere length estimator. However, these methods measure biological aging at the cellular level and were limited to blood samples from only 232 healthy individuals and 413 COVID-19 patients [43] In contrast, the KDM-BA and PhenoAge methods integrate information from multiple physiological systems and are considered highly accurate predictors of

Table 2
Association of biological age acceleration and frailty index with risk of severe infections stratified by infection type.

Type-specific infection	Exposure	Incidence/ 1000 PYs	cHR (95 %CI)	aHR[a] (95 %CI)
Respiratory infection	KDM-BA acceleration Category[c]	5.78	1.32(1.30 to 1.34)	1.26(1.24 to 1.28)
	Biologically Younger	4.61	1.00(ref)	1.00(ref)
	Biologically Older	7.04	1.53(1.49 to 1.57)	1.41(1.37 to 1.45)
	PhenoAge acceleration Category[c]	5.78	1.49(1.47 to 1.51)	1.34(1.32 to 1.36)
	Biologically Younger	4.27	1.00(ref)	1.00(ref)
	Biologically Older	7.66	1.82(1.77 to 1.86)	1.50(1.46 to 1.54)
	Frailty Index Score[b] Category	5.78	1.82(1.79 to 1.85)	1.54(1.51 to 1.56)
	<0.1	3.74	1.00(ref)	1.00(ref)
	0.1 to <0.2	6.22	1.67(1.62 to 1.73)	1.43(1.38 to 1.47)
	0.2 to <0.3	11.06	3.00(2.89 to 3.12)	2.16(2.08 to 2.25)
	0.3 to <0.4	17.36	4.79(4.51 to 5.10)	2.99(2.80 to 3.19)
	≥0.4	28.37	8.08(6.85 to 9.54)	4.44(3.74 to 5.26)
Digestive infection	KDM-BA acceleration Category[c]	3.63	1.18(1.16 to 1.20)	1.11(1.09 to 1.13)
	Biologically Younger	3.17	1.00(ref)	1.00(ref)
	Biologically Older	4.13	1.31(1.26 to 1.35)	1.15(1.11 to 1.19)
	PhenoAge acceleration Category[c]	3.63	1.29(1.27 to 1.31)	1.23(1.21 to 1.25)
	Biologically Younger	3.10	1.00(ref)	1.00(ref)
	Biologically Older	4.29	1.39(1.35 to 1.44)	1.29(1.25 to 1.34)
	Frailty Index Score[b] Category	3.63	1.80(1.77 to 1.84)	1.61(1.58 to 1.65)
	<0.1	2.30	1.00(ref)	1.00(ref)
	0.1 to <0.2	4.02	1.76(1.69 to 1.83)	1.58(1.52 to 1.65)
	0.2 to <0.3	6.77	2.98(2.84 to 3.12)	2.38(2.27 to 2.51)
	0.3 to <0.4	10.55	4.70(4.34 to 5.09)	3.39(3.12 to 3.69)
	≥0.4	15.30	6.78(5.42 to 8.48)	4.50(3.59 to 5.65)
Blood or sexually transmitted infection	KDM-BA acceleration Category[c]	0.06	1.34(1.19 to 1.51)	1.23(1.09 to 1.39)
	Biologically Younger	0.05	1.00(ref)	1.00(ref)
	Biologically Older	0.07	1.35(1.05 to 1.72)	1.20(0.93 to 1.56)
	PhenoAge acceleration Category[c]	0.06	1.37(1.22 to 1.53)	1.12(0.99 to 1.27)
	Biologically Younger	0.05	1.00(ref)	1.00(ref)
	Biologically Older	0.08	1.60(1.25 to 2.05)	1.16(0.90 to 1.50)
	Frailty Index Score[b] Category	0.06	1.82(1.57 to 2.10)	1.51(1.29 to 1.76)
	<0.1	0.04	1.00(ref)	1.00(ref)
	0.1 to <0.2	0.07	1.58(1.19 to 2.10)	1.41(1.06 to 1.89)
	0.2 to <0.3	0.11	2.59(1.79 to 3.73)	1.86(1.27 to 2.72)
	0.3 to <0.4	0.18	4.07(2.20 to 7.52)	2.27(1.20 to 4.28)
	≥0.4	0.52	12.41 (3.92 to 39.32)	5.63(1.74 to 18.27)
Central nervous system infection	KDM-BA acceleration Category[c]	0.14	1.17(1.08 to 1.27)	1.12(1.03 to 1.22)
	Biologically Younger	0.12	1.00(ref)	1.00(ref)
	Biologically Older	0.17	1.40(1.19 to 1.65)	1.29(1.09 to 1.53)
	PhenoAge acceleration Category[c]	0.14	1.23(1.14 to 1.33)	1.17(1.08 to 1.27)
	Biologically Younger	0.13	1.00(ref)	1.00(ref)
	Biologically Older	0.16	1.25(1.07 to 1.47)	1.14(0.96 to 1.35)
	Frailty Index Score[b] Category	0.14	1.61(1.46 to 1.78)	1.46(1.31 to 1.63)
	<0.1	0.10	1.00(ref)	1.00(ref)
	0.1 to <0.2	0.15	1.52(1.26 to 1.84)	1.39(1.14 to 1.69)
	0.2 to <0.3	0.25	2.45(1.93 to 3.12)	2.03(1.57 to 2.61)
	0.3 to <0.4	0.39	3.88(2.60 to 5.78)	2.95(1.94 to 4.48)
	≥0.4	0.52	6.29(2.07 to 19.12)	4.51(1.45 to 13.99)
Life-threatening infection	KDM-BA acceleration Category[c]	4.81	1.23(1.21 to 1.24)	1.16(1.14 to 1.18)
	Biologically Younger	4.09	1.00(ref)	1.00(ref)
	Biologically Older	5.59	1.37(1.33 to 1.41)	1.24(1.20 to 1.27)
	PhenoAge acceleration Category[c]	4.81	1.41(1.39 to 1.43)	1.28(1.27 to 1.30)
	Biologically Younger	3.78	1.00(ref)	1.00(ref)
	Biologically Older	6.10	1.63(1.59 to 1.68)	1.37(1.33 to 1.41)
	Frailty Index Score[b] Category	4.81	1.69(1.66 to 1.72)	1.43(1.41 to 1.46)
	<0.1	3.32	1.00(ref)	1.00(ref)
	0.1 to <0.2	5.17	1.57(1.52 to 1.62)	1.34(1.30 to 1.39)
	0.2 to <0.3	8.55	2.61(2.50 to 2.72)	1.89(1.81 to 1.98)
	0.3 to <0.4	13.23	4.06(3.78 to 4.36)	2.54(2.36 to 2.74)
	≥0.4	17.19	5.38(4.35 to 6.66)	2.98(2.41 to 3.70)

[a] Adjusted for age, sex, ethnicity, body mass index (BMI), Townsend Deprivation Index (TDI), smoking status, drinking frequency, physical activity.
[b] Results are expressed per 0.1 increments on the frailty index (FI) scale (10 % higher frailty).
[c] KDM-BA acceleration and PhenoAge acceleration were classified into two groups: biologically younger (values ≤0) and biologically older (values >0).

morbidity [17] Beyond SARS-CoV-2, multiple evidence support the association between infection and aging. Chronic viral infections such as HIV and cytomegalovirus (CMV) were associated with accelerated epigenetic aging measured by DNA-methylation clocks, [44,45] even under effective therapy, underscoring that pathogen exposure can imprint aging-like signatures on the host. These observations support the idea that infection and aging biology are intertwined across

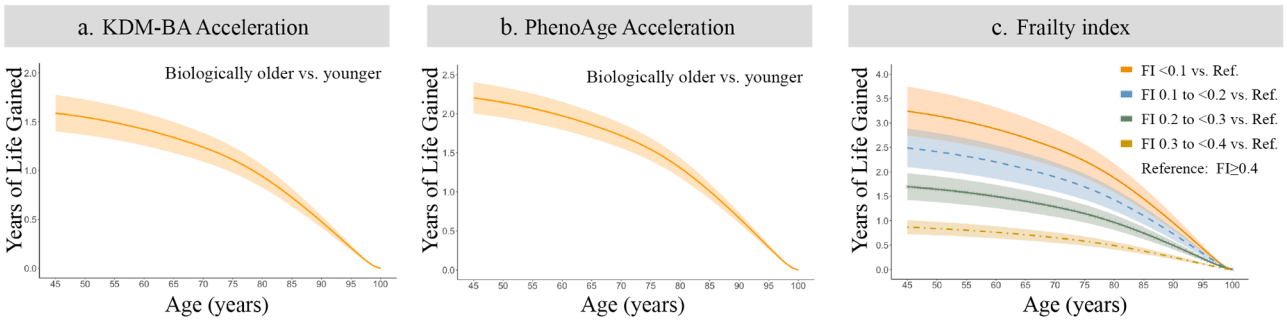

Fig. 2. Estimated years of life gained based on different biological aging measures: KDM-BA acceleration, PhenoAge acceleration, and Frailty Index.

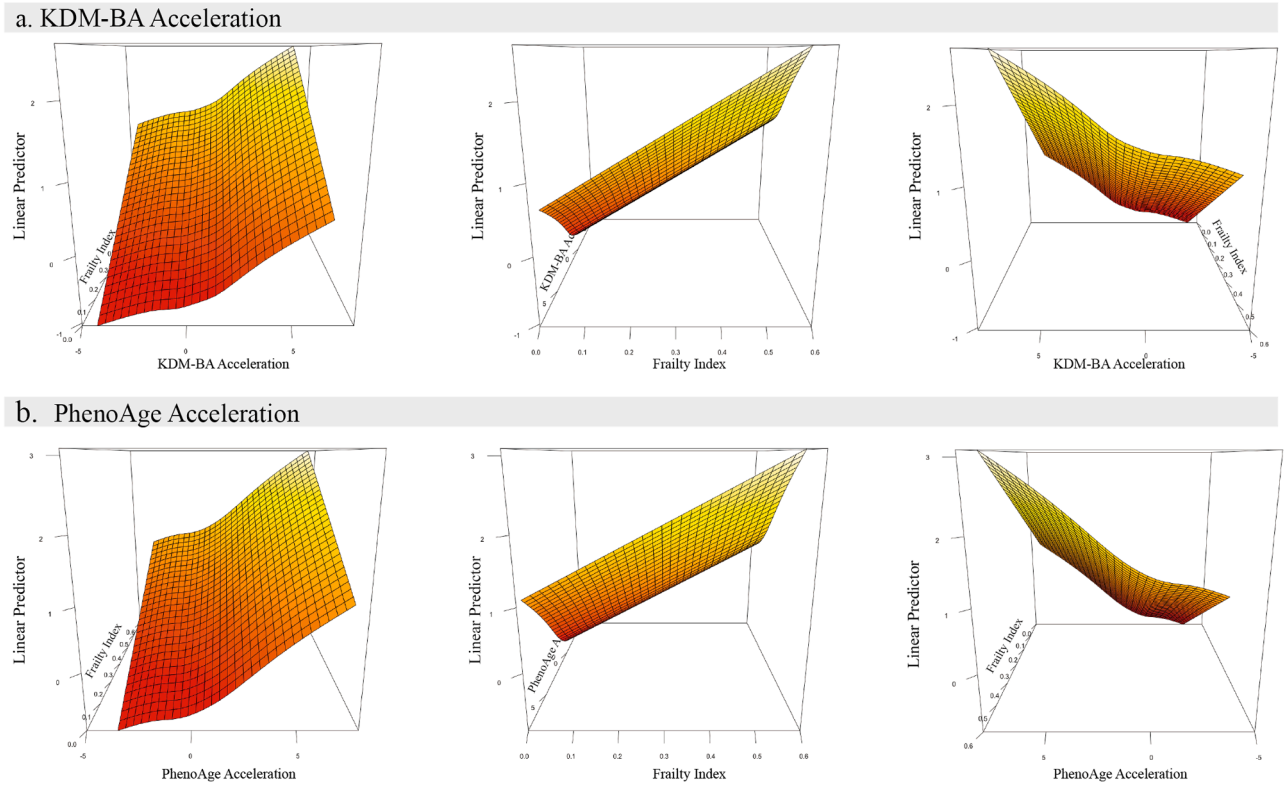

Fig. 3. Different perspectives of exposure-response surface plots of the combined effects of frailty index (FI) and biological age acceleration on severe infection.

pathogens rather than being COVID-specific. Complementing this, individuals who are biologically "older" by shorter leukocyte telomere length have higher risks of infectious-disease hospitalization and infection-related mortality in large population cohorts [46] Together, these data support our framing of aging biology as the exposure that tracks with subsequent severe infection risk as the outcome across diverse etiologies. Alternative biological-aging modalities also capture infection-relevant vulnerability. Xu et al. assessed frailty using the Fried phenotype (FP) in a study of 416,220 UK Biobank participants [9] Their findings indicated a significant association between frailty and increased risk of severe infections, which is consistent with our finding. Although both the FP and FI can accurately predict adverse outcomes, differences exist between these two methods. The FI, based on the principle of accumulated deficits, requires evaluating a broader range of health information. The FP comprises five phenotypic criteria: involuntary weight loss, exhaustion, slow gait speed, poor handgrip strength, and reduced physical activity [47] However, FP assessment of muscle strength and gait speed may be constrained by limited availability of grip-strength devices and practical restrictions, such as space and time. Additionally, as a continuous variable, FI provides better sensitivity for identifying individuals with lower frailty levels, including middle-aged populations [48]

We observed that biological aging and frailty are strongly associated with different infection types. In our study, biological age acceleration showed the strongest association with respiratory infections. This pattern is consistent with prior evidence. A previous study proved that biological aging is significantly associated with decreasing lung function, [49] leading to susceptible to respiratory infections. Aging is also associated with the risk of HIV infection[50] and other types of infection. We also found that frailty index showed the strongest association with digestive infections. Prior work suggested that human gut microbiome is a highly dynamic system and a basis of host health and helps build and maintain the intestinal immune barrier [51] Evidence further indicates that aging-related microbial communities can increase intestinal permeability and drive chronic inflammation, leading to higher levels of frailty-associated pro-inflammatory cytokines [52,53] Norovirus infections often involve older adults with frailty, who are prone to more prolonged clinical courses [54] Previous studies also found association between frailty and respiratory tract-transmitted diseases especially the role that frailty plays in increasing the risk of the development

of influenza and COVID-19 [55,56]

There are some plausible potential mechanisms that may link biological aging to infection based on the previous findings. Aging is driven by the accumulation of genetic and epigenetic damage, inflammation, oxidative stress, and other forms of damage [14] Aging induces a decline in immune function, a process termed immunosenescence. Immunosenescence is primarily characterized by decreased thymic production of naïve T cells accompanied by an accumulation of memory cells. This leads to the reduction in the T cell repertoire and diminished responsiveness to new antigens [11,57,58] During the process, a chronic low-grade inflammatory state which is called inflammaging[7] is linked to immune dysfunction occurs [57,59] As a result of the occurrence of immunosenescence, there is an increasing in the incidence of many age-related diseases, such as infection, cancer and so on. We used KDM-BA and PhenoAge methods to calculate the biological age acceleration, aiming to improve the prediction of aging outcomes. With aging, the immune system undergoes changes, contributing to frailty [60] Existing research suggests that frailty may exacerbate immune changes and contribute to inflammaging [61] The combined effects of immunosenescence and inflammaging increase susceptibility to infectious diseases in older adults [62,63]

Furthermore, we explored associations across a broader spectrum of infection subtypes. Prior studies have mainly focused on specific infection, such as COVID-19 [42] Our study addresses this gap by evaluating 900 infection codes and examining whether the associations alter in different infection types. Our study found that biological aging is strongly connected with the severe infection risk, and the association can be observed when stratified by infection type. The finding suggests that biological aging may act as a universal risk factor influencing multiple types of infections. Additionally, we also found that biologically younger individuals had significantly longer life expectancy than biologically older ones. Similarly, individuals with lower FI scores had longer life expectancy compared to those scoring above 0.4. Therefore, monitoring biological aging and timely implementation of anti-aging interventions may reduce the severe infection risk. Furthermore, bivariate graphs found the significant combined effects between frailty index and both KDM-BA acceleration and PhenoAge acceleration. This finding suggests that these accelerated aging markers are not only independently associated with the risk of severe infections but also exhibit a stronger association with the occurrence of severe infections when interacting with one another. This discovery highlights the significant role of multidimensional biological aging in predicting infection risk, revealing that the interactions between different aging mechanisms may have a cumulative effect on an individual's susceptibility to infections. Therefore, a deeper understanding of the combined effects of these biological aging markers could enhance risk stratification for severe infections and potentially alleviate the burden of aging-related infectious diseases.

To our knowledge, this is the largest cohort study to comprehensively analyze accelerated biological aging, frailty and severe infections, covering over 900 infectious diseases. Furthermore, we applied two well-established clinical BA algorithms, KDM-BA and PhenoAge. The consistency of sensitivity analyses further reinforced the robustness of our findings.

Nevertheless, this study has several limitations. First, we conducted the main analysis based on participants with complete biomarkers. This trade-off avoids redefining biological age acceleration through model-based imputation of biomarkers but may limit generalizability. As for those with 1–9 missing FI items, we used multiple imputation to avoid loss of information and potential bias due to deletion of all missing FI items. We added Supplementary Table 11, which compares baseline characteristics between participants excluded due to missing biological aging measures or $\geq$20 % missing FI items and participants of main analysis. The results show no evidence of systematic differences, alleviating concerns about selection bias. We further conducted a sensitivity analysis using stricter complete-case definitions for FI and covariates and produced similar results. Second, the frailty index was derived from self-reported questionnaire data, which may introduce recall bias. However, it has been proved to be an effective measure of frailty index in the UK Biobank and widely used in previous studies [31,64,65] Third, only baseline information was measured, preventing the assessment of long-term trajectories of accelerated biological aging, frailty, and their associations with severe infections. Future research should focus on life-course methods. Fourth, despite adjusting for a wide range of confounding factors, residual confounding from unmeasured variables, such as genetic factors or medication use, may still exist. Fifth, participants in UK Biobank are volunteers, limiting generalizability to the entire UK population. Further studies should address these limitations through additional research.

5. Conclusion

In conclusion, our study highlights the critical role of accelerated biological aging and frailty in increasing the risk of severe infections. These findings highlight the necessity of incorporating aging biomarkers and frailty assessments into public health strategies and preventive healthcare planning. Further research should explore potential interventions, such as lifestyle modifications and medical treatments, to mitigate the effects of biological aging on infection risk. Longitudinal and intervention-based studies are also needed to further validate and refine these approaches.

List of abbreviations

BA (Biological age), CI (confidence interval), FI (Frailty Index), HR (hazard ratio), KDM-BA (Klemera-Doubal method Biological Age), SD (standard deviation)

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Availability of data and materials

The UK Biobank data can be accessed online at https://www.ukbiobank.ac.uk. Researchers registered with UK Biobank can request access to the database by completing an application.

CRediT authorship contribution statement

Runzhi Bai: Writing – original draft, Visualization, Methodology, Formal analysis, Conceptualization. **Lulu Pan:** Writing – review & editing, Resources, Data curation. **Yifang Huang:** Writing – review & editing, Software, Methodology. **Zixuan Jiang:** Visualization, Software, Data curation. **Jing Wang:** Writing – review & editing, Validation, Software. **Yahang Liu:** Resources, Data curation, Conceptualization. **Chen Huang:** Writing – review & editing, Resources, Data curation. **Xueying Zheng:** Writing – review & editing, Resources, Data curation. **Yongfu Yu:** Resources, Funding acquisition, Data curation. **Qingqing Li:** Writing – review & editing, Supervision, Project administration. **Guoyou Qin:** Resources, Funding acquisition, Data curation.

Declaration of interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence

the work reported in this paper.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.tjfa.2025.100118.

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