Immunity & Ageing

RESEARCH

Open Access

The relationship between biological aging and psoriasis: evidence from three observational studies

Zheng Lin[1†], Hong-fei Wang[1†], Lu-yan Yu[1†], Jia Chen[1], Cheng-cheng Kong[2], Bin Zhang[2], Xuan Wu[1], Hao-nan Wang[1], Yi Cao[1*] and Ping Lin[2*]

Abstract

Background The relationship between psoriasis and aging remains unclear. Biological age is considered as a tool for strong association with aging, but there is a lack of reports on the relationship between biological age and psoriasis. Therefore, this study aimed to explore the relationship between biological age and psoriasis.

Methods Patients with psoriasis and non-psoriasis were recruited from National Health and Nutrition Examination Survey (NHANES) (12,973 cases), Medical Information Mart for Intensive Care (MIMIC-IV) (558 cases) and The First Clinical Medical College of Zhejiang Chinese Medical University (206 cases). Biological age was calculated using Klemera-Doubal method age (KDM-age) and phenotypic age (PhenoAge). Linear regression and logistic regression were used to explore the association between psoriasis and biological age advance. Cox regression was used to investigate the association between biological age advance and mortality. Finally, biological age advance was used to predict the death of psoriasis patients.

Results In NHANES, linear regression showed that psoriasis led to a 0.54 advance in PhenoAge (Adjust Beta: 0.54, 95CI: 0.12–0.97, $p=0.018$). The KDM-age advance due to psoriasis was not statistically significant ($p=0.754$). Using data from China, we came to the new conclusion that for every unit rise in Psoriasis Area and Severity Index, PhenoAge advance rose by 0.12 (Beta: 0.12, 95CI: 0.01–0.22, $p=0.031$). Using NHANES data, cox regression shows for every unit rise in PhenoAge advance patients had an 8% rise in mortality (Adjust hazard ratio: 1.08, 95CI: 1.04–1.12, $p<0.001$). Using MIMIC-IV, logistic regression showed a 13% increase in mortality within 28 days of admission for every 1 unit rise in PhenoAge advance (odds ratio: 1.13, 95CI: 1.09–1.18, $P<0.001$). Finally, we used PhenoAge advance to predict death, with an AUC of 0.71 in the NHANES, an ACU of 0.79 for predicting death within 1 years in the general ward of MIMIC-IV. In the ICU of MIMIC-IV, the AUC for predicting death within 28 days was 0.71.

Conclusion Psoriasis leads to accelerated biological aging in patients, which is associated with the severity of psoriasis and more comorbidities. In addition, PhenoAge has the potential to monitor the health status of patients with psoriasis.

Keywords Psoriasis, Biological age, Phenotypic age, Aging, NHANES, MIMIC-IV

†Zheng Lin, Hong-fei Wang and Lu-yan Yu contributed equally to this work.

*Correspondence:
Yi Cao
caoyi1965@163.com
Ping Lin
Yjlp1@163.com

Background

Psoriasis is an immune-mediated genetic disorder characterized by scaly skin lesions [1], affects approximately 0.14%-1.99% of the global population [2]. Compared to the general population, patients with psoriasis are at increased risk for immune and metabolic comorbidities including cardiovascular disease, diabetes mellitus, metabolic dysfunction-associated steatotic liver disease and inflammatory bowel disease [3–5]. A survey based on the United States population noted that psoriasis was associated with an increased risk of all-cause mortality (hazard ratio (HR): 1.99, 95% CI: 1.01–3.93, $p=0.047$) [6]. It has been noted that the risk of cardiovascular death is 19% higher in patients with psoriasis than in the general population [7], and the risk of cancer death is 22% higher in patients with severe psoriasis than in the general population [8]. All this evidence suggests that psoriasis may lead to a reduction in life expectancy. Therefore, accurately identifying the risk factors that contribute to reduced life expectancy in patients with psoriasis and precise testing the health status of patients with psoriasis are critical to improving the disease burden of psoriasis.

Aging is a complex process at the biological level, characterized by the cumulative effects of various molecular and cellular damages over time [9]. The process of biological aging occurs at different rates between individuals with the same chronological age, making biological age a better indicator of human health compared to actual age [10]. Biological age is now widely used to quantify biological aging to study risk factors that alter the rate of aging and to predict age-related outcomes [11]. Studies have shown that increasing biological age is associated with an increased risk of a variety of adverse outcomes (e.g., cancer, depression, autoimmune disease, and death) [12–14]. Psoriasis is a disease based on an immune disorder [15], and immune senescence is widely recognized as an important component of biological aging [16]. Chronic inflammation in psoriasis may lead to changes in markers of aging. Therefore, biological age may be a better indicator than chronological age of the biological aging burden of psoriasis. Using biological age, we can explore in depth whether psoriasis leads to accelerated biological aging. In addition, current psoriasis assessment tools are based on skin lesion scores and quality of life scores, and there is a lack of tools for overall assessment of the health status of psoriasis patients [17]. Biological age reflects the overall health status of patients to some extent, we therefore believe that biological age has the potential to be a health detection tool for psoriasis patients.

Commonly used biological ages constructed on the basis of clinical indicators include the Klemera-Doubal method age (KDM-age) and phenotypic age (PhenoAge) [14, 18]. KDM-age models biological age as an average biological state associated with a specific actual age in a reference population, which assumes that the biological age increases linearly over time. PhenoAge models biological age as an average biological state associated with a specific level of mortality risk in a reference population, which assumes that the biological age increases exponentially over time. These approaches combine information from biomarkers of multiorgan system integrity and have shown consistent evidence in studies predicting mortality and aging-related morbidity.

Based on the current literature, the relationship between psoriasis and biological aging remains unclear. A case–control study with a sample size of 40 people showed no association between psoriasis and biological age accelerated [19]. A case–control study with a sample of 70 people showed that female with psoriasis had a higher epigenetic age than healthy controls [20]. We believe that the contradictory results may be due to the small sample size of the current studies, which leads to the randomness of the conclusions. Therefore, the aim of this study was using multiple large databases to provide high-quality evidence on the relationship between biological aging and psoriasis.

The significance of our study is twofold: first, to demonstrate the disease burden of psoriasis from a biological aging perspective, which has been less frequently mentioned in previous studies. Second, if the biological age physical examination accurately reflects the health status of psoriasis patients, then targeting early proactive interventions in psoriasis patients with accelerated biological age advance may become a more individualized treatment option.

Our study was divided into three parts: firstly, we compared the differences in biological age advance between the psoriasis population and the general population based on data from National Health and Nutrition Examination Survey (NHANES) and validated the findings using patients recruited from The First Clinical Medical College of Zhejiang Chinese Medical University; secondly, we investigated the relationship between biological age advance and short- and long-term mortality of psoriasis patients based on follow-up data from NHANES and Medical Information Mart for Intensive Care-IV (MIMIC-IV); finally, we attempted to predict all-cause death in psoriasis patients using biological age advance.

Materials and methods

Study design and population

In this study, we collected data on biological age and death in psoriasis patients and non-psoriasis patients from the NHANES, MIMIC and The First Clinical Medical College of Zhejiang Chinese Medical University. The research process can be seen in Fig. 1.

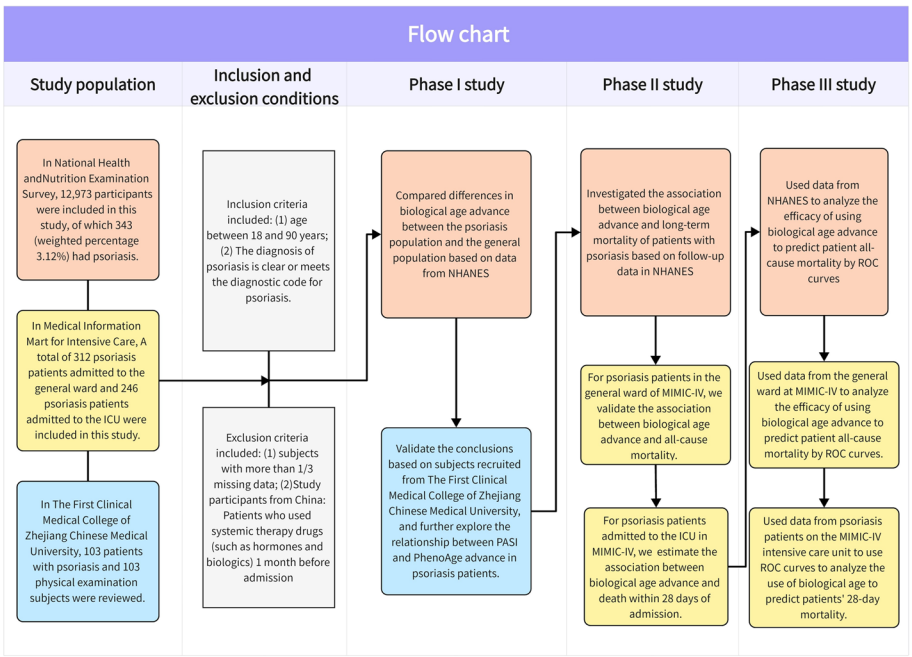

Fig. 1 Flow chart

NHANES is an ongoing U.S. national cross-sectional survey that collects health-related information from the U.S. civilian population every two years. Participants are interviewed at home and then invited to a mobile screening center to undergo a variety of tests and provide blood samples. Open data can be accessed from the https://www.cdc.gov/nchs/nhanes. A total of 31,007 NHANES subjects from three cycles, 2003–2004, 2005–2006, and 2009–2010, participated in this study. Inclusion criteria included (1) age between 20 and 90 years. Exclusion criteria included: (1) subjects with more than 1/3 missing data; (2) subjects who did not answer the question "Have medical personnel ever told you that you have PSO" or "Has a doctor or other health care professional ever told you that you have PSO". All NHANES protocols were approved by the NCHS Research Ethics Review Board (Protocol #98- 12, Continuation of Protocol #2005–06, Continuation of Protocol #2011–23, http://www.cdc.gov/nchs/nhanes/irba98.htm) and informed consent was obtained at participant enrollment.

MIMIC is an NIH-funded medical database that collects information on a large number of hospitalized patients, and publicly available data can be found at https://mimic.mit.edu. This study utilized data from the publicly available MIMIC-IV. A total of 312 psoriasis patients admitted to the general ward and 246 psoriasis patients admitted to the intensive care unit were included in this study. Inclusion criteria included: (1) age between 18 and 90 years; (2) fulfilment of the diagnostic code for psoriasis. Exclusion criteria included: (1) subjects with more than 1/3 missing data. For compliance, author Zheng Lin obtained a Collaborative Institutional Training Initiative (CITI) (record ID: 13,501,620) and the necessary permissions to use the MIMIC-IV database. The database includes comprehensive information on each patient's length of stay, laboratory tests, medication administration, and vital signs. To protect patient privacy, all personal information is de-identified and random codes are used instead of patient identifiers. Therefore, this section does not require patient consent or ethical approval.

In this study, 103 patients with psoriasis and 103 physical examination subjects who attended our hospital from January 2020 to January 2021 were reviewed from The First Clinical Medical College of Zhejiang Chinese Medical University. Inclusion criteria included (1) age between 18 and 90 years old; (2) meeting the diagnosis of psoriasis or confirming the absence of psoriasis. Exclusion criteria included (1) subjects with more than 1/3 missing data; (2) Patients who used systemic therapy drugs (such as hormones and biologics) 1 month before admission. The protocol was approved by the Ethics Review Committee of The First Clinical Medical College of Zhejiang Chinese Medical University. Since we only reviewed the existing database, the Ethics Committee exempted patients from informed consent (2024-KLS-683–01).

Evaluation of psoriasis

Among NHANES participants, if participants answered yes to the questions "Have medical personnel ever told you that you have psoriasis" or "Has a doctor or other health care professional ever told you that you have psoriasis", the participant was considered to have psoriasis.

In MIMIC-IV, patients are considered to have psoriasis if their disease codes include psoriasis (10-L40), psoriasis vulgaris (10-L400), arthropathic psoriasis (10-L405, 10-L4050), psoriatic arthritis (9–6960), generalised pustular psoriasis (10-L401), psoriasis punctata (10-L404), distal interphalangeal psoriasis arthropathy (10-L4051), disfiguring psoriatic arthritis (10-L4052), and other psoriatic arthropathies (10-L4059), then one would be considered to have psoriasis.

Patients recruited from The First Clinical Medical College of Zhejiang Chinese Medical University were diagnosed by experienced dermatologists based on typical lesions and dermoscopy, with reference to the diagnostic criteria of the Chinese Psoriasis Guidelines [21]. The specific criteria were as follows: typical lesions: lesions of infiltrative erythema covered with white or silvery-white scales with wax droplets, membranous phenomena, and punctate hemorrhages; dermoscopy: uniformly distributed punctate and spherical blood vessels on a red background with diffuse white scales. At more than 50×magnification, these punctate and spherical vessels appear as clusters of capillaries.

Evaluation of covariates

Among NHANES participants, we collected the following covariates, including age, gender (male and female), race/ethnicity (Mexican American, Other Hispanic, Non-Hispanic White, Non-Hispanic Black, Other Race), educational attainment, income (whether greater than $20,000), average level of physical activity, body mass index (BMI), history of smoking, alcohol use, diabetes, hypertension, kidney disease, liver disease, thyroid disease, history of heart disease, history of cancer, dietary inflammatory index (DII). Participants who responded affirmatively to the question "Smoked at least 100 cigarettes in lifetime" were considered to have a history of smoking. Participants who answered "yes" to the question "more than 12 drinks per year" were considered to have a history of alcohol consumption. Comorbidities were assessed by self-report, such as participants who answered "yes" to the question "Your doctor told you that you have diabetes" were considered to have diabetes. DII was calculated using the Dietindex package in R [22]. NHANES participants' mortality were obtained from the National Death Index, available from https://www.cdc.gov/nchs/ndi.

Among MIMIC-IV study participants, we collected the following covariates, including age, gender (male and female), race/ethnicity (Asian, Black, Hispanic, unknown, White), history of myocardial infarction, congestive heart failure, peripheral vascular disease, cerebrovascular disease, chronic lung disease, rheumatic disease, cancer, liver disease, and diabetes. All comorbidities were retrieved by the corresponding disease code. MIMIC-IV was linked to the Social Security system to obtain the date of the patient's out-of-hospital death, so the mortality of MIMIC-IV's study participants was obtained through records in MIMIC-IV.

The following covariates were collected from patients attending The First Clinical Medical College of Zhejiang Chinese Medical University, including age, gender (male and female), BMI, smoking history, alcohol use, diabetes mellitus, hypertension, and Psoriasis Area and Severity Index (PASI). All past medical history was obtained through patient self-report and PASI was used to comprehensively assess psoriasis severity. PASI was calculated by calculating the scores of four zones: head and neck, trunk, upper limbs and lower limbs, the sum of which is the PASI, with higher scores suggesting higher psoriasis severity [17]. The specific formula is PASI = 0.1 × BSA (percentage of damaged surface in each body part) x E (including grade of color, thickness, scales, and erythema) x S (score for four specific body parts).

Calculation of biological age

In this study, two classical algorithms were used to quantify biological aging: the KDM-age and the PhenoAge [14, 18]. KDM-age: calculated from clinical indices such as alkaline phosphatase, albumin, glycosylated haemoglobin, total cholesterol, systolic blood pressure, creatinine, C-reactive protein, and blood urea nitrogen concentrations. PhenoAge: calculated from alkaline phosphatase, albumin, glucose, creatinine, C reactive protein concentration, erythrocyte distribution width, lymphocyte percentage, mean cell volume, and white blood cell count. Four points should be noted in particular: 1. Systolic blood pressure in the NHANES data was taken as the mean of two measurements; 2. Systolic blood pressure in the MIMIC-IV general ward data was not openly available due to database limitations, so systolic blood pressure was excluded from the modelling and calculation of the KDM-age in this group of patients; 3. Serum data in all MIMIC-IV patients were taken from the first day of examination on admission to the ward, and if there were multiple examinations, the mean value was taken; 4. At The First Clinical Medical College of Zhejiang Chinese Medical University, all serological indicators were collected according to the following criteria: Venous blood was collected from the anterior elbow vein after all

subjects fasted for 1 night (minimum 8 h) and analyzed in the central laboratory according to standard laboratory procedures.

Quantifying Patient Biological Aging Using the BioAge package in R [23], available from https://github.com/dayoonkwon/BioAge. This package implements a method for modelling to calculate biological aging using NHANES III (1988—1994) data and allows for projection of the model to NHANES IV (1999—2018) or other datasets. KDM-age advance or PhenoAge advance is defined as the difference in age calculated by KDM-age or PhenoAge difference calculated relative to the actual age at the time of the biomarker measurement. Biological age advance acceleration was defined as KDM-age advance greater than 0 or PhenoAge advance greater than 0.

Statistical analysis

Before the data were analyzed, we performed some processing of the data. After excluding study participants with more than 30% of missing variables, there were still some missing values in NHANES and MIMIC-IV, and to solve this problem, we used random forest regression to estimate the missing data. Study participants from The First Clinical Medical College of Zhejiang Chinese Medical University had good completeness and did not need to fill in. For ease of calculation, categorical variables were handled as follows: gender was coded as male 1 and female 0; dichotomous variables (smoking history, drinking history, etc.) were coded with 1 for yes and 0 for no.

All variables were first subjected to univariate analysis of variance, with normal continuous data expressed as mean ± standard deviation, skewed continuous data expressed as median (upper quartile, lower quartile), and categorical parameters expressed as n (percentage). Continuous data were tested for normality using Shapiro's test and histograms, with $p < 0.05$ considered normal. Continuous normal data were tested using the t-test, continuous skewed data were tested using the Wilcoxon M-W test, and non-parametric data were tested using the Pearson chi-square test, with $p < 0.05$ being considered a statistically significant difference. All data in this paper were analyzed using R version 4.4.2 (R Foundation for Statistical Computing, Vienna, Austria) for data analysis.

Given the complexity of the NHANES sampling design and in accordance with the NHANES analytical and reporting guidelines, this study weighted the participant samples from 2003–2006 and 2009–2010 to ensure national representation.

In the first part of the study, we compared differences in biological age advance between the psoriasis population and the general population based on data from NHANES. For NHANES study participants: 1. we used weighted linear regression to estimate the beta of increased biological age due to psoriasis and weighted logistic regression to estimate the odds ratio of psoriasis leading to biological age advance acceleration; 2. we assessed the linear relationship between biological age advance and risk of psoriasis by restricted cubic spline regression; 3. correlation tests were performed to reveal serum markers that were strongly associated with biological age advance in patients with psoriasis. Subsequently, we used logistic regression and linear regression to validate the conclusions based on subjects recruited from The First Clinical Medical College of Zhejiang Chinese Medical University, and used linear regression and restricted cubic spline analysis to further explore the relationship between PASI and PhenoAge advance in psoriasis patients.

In the second part of the study, we investigated the association between biological age advance and short- and long-term mortality of patients with psoriasis based on follow-up data in NHANES and MIMIC-IV. For the psoriasis cohort in NHANES, Kaplan–Meier (KM) curves and weighted cox regression were used to explain the association between biological age advance and all-cause mortality. For psoriasis patients in the general ward of MIMIC-IV, we used KM curves and cox regression to validate the association between biological age advance and all-cause mortality. For psoriasis patients admitted to the ICU in MIMIC-IV, we used logistic regression to estimate the association between biological age advance and death within 28 days of admission.

In the third part of the study, we used data from NHANES and the general ward at MIMIC-IV, analyze the efficacy of using biological age advance to predict patient all-cause mortality by ROC curves. In addition, we used data from psoriasis patients on the MIMIC-IV intensive care unit to use ROC curves to analyze the use of biological age to predict patients' 28-day mortality in advance of admission. All predictions were evaluated using accuracy, precision, recall, specificity, area under the curve (AUC) and confusion matrix.

Based on all regression models developed by NHANES participants, Model 1 did not adjust for any variables, Model 2 adjusted for age, gender, race/ethnicity, education, income, average physical activity level, BMI, history of smoking, history of alcohol use, and Model 3 which was based on Model 2 adjusted for diabetes mellitus, hypertension, renal disease, liver disease, thyroid disease, history of cardiac disease, and history of cancer. In addition, all regression models were analyzed in subgroups according to gender, age (> 30), whether or not they smoked, hypertension, and cancer. For the regression models based on participants from The First Clinical Medical College of Zhejiang Chinese Medical University, model 1 was not adjusted for any variables, and model

2 was adjusted for age, sex, body mass index, smoking, alcohol consumption, diabetes and hypertension. Based on regression models developed by MIMIC-IV participants, model 1 was not adjusted for any variables, and model 2 was adjusted for age, sex, race/ethnicity, history of myocardial infarction, congestive heart failure, peripheral vascular disease, cerebrovascular disease, chronic lung disease, rheumatic disease, cancer, liver disease, and diabetes. The cutoff value for biological age advance to predict patient all-cause mortality was implemented through the cutoff package in R. This R package enables the calculation of cutoff values that balance sensitivity and specificity.

Results

Baseline information

Of the 31,007 participants recruited to NHANES in 2003–2006 and 2009–2010, 14,349 (46.27%) participants in the study had missing psoriasis status data, and 3,685 (11.88%) of the remaining patients had more than 30% of the missing data. A final 12,973 participants were included in this study, of which 343 (weighted percentage 3.12%) had psoriasis. The mean age of all NHANES participants included was 41 years, 51% participants were female (Table 1). The mean age of the 103 patients with psoriasis recruited at The First Clinical Medical College of Zhejiang Chinese Medical University was 45 years, 35% participants were female (Table 2). The mean age of the 312 psoriasis patients admitted to the general ward of the MIMIC-IV were 60 years, 46% participants were female (Table 3). The mean age of the 246 patients with psoriasis admitted to the intensive care unit of the MIMIC-IV were 60 years, 42% participants were female (Table 4). When examining baseline comparisons of participants, we found that patients with psoriasis were older, had a higher BMI, were more likely to smoke, and had a greater risk of having high blood pressure, heart disease, and cancer.

Comparison of baseline and aging markers in patients with psoriasis between the NHANES, MIMIC and China cohorts can be seen in supplementary tables 1–2. After pair-to-pair comparison, we found that the heterogeneity between NHANES and China cohorts was small, while the heterogeneity between MIMIC and the above two cohorts was large.

Differences of biological age advance between psoriasis populations and the general population

PhenoAge advance was more accelerated in patients with psoriasis compared to the general population in NHANES ($p=0.001$), while KDM-Age advance did not differ between the two ($p=0.754$). Patients judged to have PhenoAge advance acceleration accounted for 46.6% of patients with psoriasis compared to 37% in the general population, a statistically significant difference ($p<0.001$). There was no significant difference in the proportion of patients with psoriasis and the general population in determining KDM-Age advance acceleration ($p=0.280$) (Table 1).

In weighted linear regression (Fig. 2 A, B, C), model 3 showed that after adjusting for demographic variables and comorbidities, psoriasis caused PhenoAge advance accelerated 0.54 years (Adjust Beta (AB): 0.54, 95CI: 0.12–0.97, $p=0.018$). This feature was significant in the subgroups of female (AB: 0.83, 95CI: 0.16–1.51, $p=0.021$), age > 30 years (AB: 0.60, 95CI: 0.11–1.09, $p=0.023$). No statistically significant in KDM-Age advance due to psoriasis was seen compared to the general population (AB: -0.07, 95CI: -0.91–0.77, $p=0.871$).

In weighted logistic regression (Fig. 2 D, E, F), model 3 showed an 0.41-fold increase in the probability that psoriasis would lead to PhenoAge advance acceleration (adjusted odds ratio (AOR): 1.41, 95CI: 1.09–1.82, $p=0.011$). This feature was more pronounced in female (AOR: 1.71, 95CI: 1.28–2.28, $p=0.001$), those older than 30 years (AOR: 1.51, 95CI: 1.13–2.03, $p=0.007$), smokers (AOR: 1.45, 95CI: 1.06–1.98, $p=0.021$), and those with hypertension (AOR: 1.7, 95CI: 1.06–2.72, $P=0.028$), and cancer patients (AOR: 2.12, 95CI: 1.17–3.83, $P=0.015$). The probability of KDM-Age advance acceleration due to psoriasis was not statistically significant compared to the general population (AOR: 1.15, 95CI: 0.85–1.56, $P=0.349$).

In a restricted cubic spline regression (Fig. 3), we found that, with or without adjustment, the association between PhenoAge advance and risk of psoriasis was monotonically increasing when the PhenoAge advance was greater than 0.

Correlation analysis showed (Fig. 4) that the three serum indicators most associated with PhenoAge advance in psoriasis patients were red blood cell distribution width (cor = 0.74), C-reactive protein (cor = 0.52), and white blood cell count (cor = 0.47).

In the study subjects recruited from The First Clinical Medical College of Zhejiang Chinese Medical University, patients with psoriasis had a more accelerated PhenoAge advance ($p<0.001$), and those judged to have accelerated PhenoAge accounted for 55% of psoriasis patients, compared to 23% of the general population, a difference that was statistically significant ($p<0.001$). In linear regression (Fig. 5 A), adjusted to show that after adjusting for demographic variables and comorbidities, psoriasis resulted in 1.97 years of PhenoAge advance acceleration (Beta: 1.97, 95CI: 0.54–3.39, $p=0.007$). In logistic regression (Fig. 5 B), after adjustment, psoriasis resulted in a 3.07-fold increase in the probability that PhenoAge advance

Table 1 Characteristics of adults in National Health and Nutrition Examination Survey 2003–2006 and 2009–2010

Variables	Non-psoriasis, $n = 12,630$ (weighted[&] % = 96.88)	Psoriasis, $n = 343$ (weighted[&] % = 3.12)	*p*-value
Gender			0.786
Male	6060 (48.8)	163 (49.6)	
Female	6570 (51.2)	180 (50.4)	
Age	41.50 ± 14.67	44.30 ± 14.11	< 0.001**
Race/ethnicity			< 0.001**
Mexican American	2570 (9.3)	33 (3.5)	
Other Hispanic	896 (4.5)	21 (2.9)	
Non-Hispanic White	5836 (67.7)	230 (82.4)	
Non-Hispanic Black	2664 (12.1)	44 (6.7)	
Other Race—Including Multi-Racial	664 (6.4)	15 (4.5)	
Education			0.694
Did not graduate high school	3141 (16.6)	71 (14.8)	
High school graduate	3314 (25.1)	84 (23.2)	
Did not graduate college	3731 (32.6)	107 (35.0)	
College graduate	2444 (25.7)	81 (26.9)	
Annual household income			0.821
< $20,000	2480 (13.5)	77 (13.9)	
≥ $20,000	10,150 (86.5)	266 (86.1)	
BMI	28.41 ± 6.71	29.99 ± 7.07	< 0.001**
Smoking			< 0.001**
Yes	5520 (45.4)	202 (59.6)	
No	7110 (55.6)	141 (40.4)	
Drinking			0.345
Yes	9291 (78.0)	270 (80.8)	
No	3339 (22.0)	73 (19.2)	
Average physical activity level			0.679
Vigorous work activity	2837 (24.7)	80 (26.1)	
Moderate to low intensity work activities	9793 (75.3)	263 (73.9)	
Diabetes			0.446
Yes	1210 (7.6)	42 (8.9)	
No	11,420 (92.4)	301 (91.1)	
Hypertension			0.001**
Yes	3302 (23.9)	134 (34.1)	
No	9328 (76.1)	209 (65.9)	
Kidney disease			0.147
Yes	261 (1.5)	11 (2.6)	
No	12,369 (98.5)	332 (97.4)	
Liver disease			0.336
Yes	373 (3.0)	16 (3.8)	
No	12,257 (97.0)	327 (96.2)	
Thyroid disease			0.456
Yes	960 (8.4)	34 (9.9)	
No	11,670 (91.6)	309 (90.1)	
Heart disease,			0.005**
Yes	630 (4.0)	40 (7.2)	
No	12,000 (96.0)	303 (92.8)	
Cancer			< 0.001**
Yes	786 (6.4)	45 (12.7)	
No	11,844 (93.6)	298 (87.3)	

Table 1 (continued)

Variables	Non-psoriasis, $n=12,630$ (weighted[&] %=96.88)	Psoriasis, $n=343$ (weighted[&] %=3.12)	*p*-value
Systolic blood pressure (mmHg)	119.75 ± 15.57	120.84 ± 15.65	0.157
Albumin (g/dL)	4.28 ± 0.34	4.23 ± 0.35	0.023*
Alkaline phosphatase (U/L)	67.66 ± 22.59	68.76 ± 22.80	0.352
Total cholesterol (mg/dL)	197.44 ± 41.33	201.40 ± 40.43	0.118
Serum glucose (mg/dL)	5.30 ± 1.60	5.26 ± 1.38	0.690
Creatinine (mg/dL)	0.88 ± 0.30	0.90 ± 0.18	0.073
Blood urea nitrogen (mg/dL)	12.19 ± 4.64	12.73 ± 4.99	0.019*
Uric acid (mg/dL)	5.35 ± 1.37	5.46 ± 1.34	0.121
C-reactive protein (mg/dL)	0.38 ± 0.75	0.47 ± 0.92	0.112
Glycohemoglobin (%)	5.47 ± 0.82	5.48 ± 0.77	0.831
White blood cell count (1000 cells/uL)	7.29 ± 2.14	7.43 ± 2.05	0.204
Lymphocyte (%)	30.38 ± 7.83	29.09 ± 7.67	0.017*
Red cell distribution width (%)	12.66 ± 1.08	12.86 ± 1.24	0.004**
Mean cell volume (fL)	89.81 ± 5.20	90.19 ± 5.84	0.329
DII	0.97 ± 1.51	0.93 ± 1.55	0.717
PhenoAge	41.06 ± 15.18	44.64 ± 14.99	< 0.001**
PhenoAge advance	-0.44 ± 4.38	0.34 ± 4.83	0.001**
PhenoAge advance acceleration			< 0.001**
Yes	5271 (37.0)	173 (46.6)	
No	7359 (63.0)	170 (53.4)	
KDM-Age	39.28 ± 15.26	42.23 ± 14.52	< 0.001**
KDM-Age advance	-2.22 ± 8.64	-2.08 ± 7.58	0.754
KDM-Age advance acceleration			0.280
Yes	4766 (34.7)	129 (38.0)	
No	7866 (65.3)	214 (62.0)	

Values that are statistically significant (two-side *P* value < 0.05) are indicated by *; Values that are statistically significant (two-side *P* value < 0.01) are indicated by **; *BMI* Body mass index (calculated as kg/m2); *NHANES* National Health and Nutrition Examination Survey; &Weighted percentage was calculated using NHANES survey design parameters, *DII* Dietary inflammation index, *HEI2015* Healthy eating index, *KDM-Age* Klemera-Doubal method age

would be accelerated earlier (OR: 4.07, 95CI: 2.02–8.5, $p<0.001$). In addition, we found (Fig. 5A) that linear regression showed an 0.12 rise in PhenoAge advance in psoriasis patients for each unit rise in PASI (Beta: 0.12, 95CI: 0.01–0.22, $p=0.031$). In the restricted cubic spline regression (Fig. 5 C), we found a monotonically increasing association between PhenoAge advance and PASI when PhenoAge advance was greater than 0, with or without adjustment.

Relationship between biological age and short- and long-term mortality of patients with psoriasis

For the psoriasis population in NHANES, based on univariate analysis (Table 5), we found that psoriasis patients who died within a median follow-up time of 10.83 years (interquartile range (IQR): 9.75–14.67) were older, had a higher BMI, a higher proportion of smokers, and had a higher risk of suffering from hypertension, diabetes mellitus, liver disease, heart disease, and cancer than surviving psoriasis patients. The KM curve shows that (Fig. 6) that survival was significantly lower in psoriasis patients with PhenoAge advance acceleration than in other psoriasis patients ($P<0.001$). Weighted cox regression analysis (model3) showed (Fig. 7) that for every 1 unit (year) rise in PhenoAge advance, all-cause mortality during the follow-up period increased by 8% in patients (AHR: 1.08, 95CI: 1.04–1.12, $P<0.001$). This feature was more pronounced in those who older than 50 years (AHR: 1.15, 95CI: 1.09–1.21, $P<0.001$), smoked (AHR: 1.11, 95CI: 1.05–1.16, $P<0.001$), hypertensive patients (AHR: 1.13, 95CI: 1.07–1.19, $P<0.001$) and cancer patients (AHR: 1.44, 95CI: 1.17–1.72, $P=0.009$). Meanwhile, PhenoAge advance acceleration resulted in a 2.67-fold increase in all-cause mortality during follow-up (AHR: 3.67, 95CI: 2.95–4.4, $P<0.001$), a feature that was more pronounced in males (AHR: 6.08, 95CI: 4.9–7.25, $P=0.003$), those older than 50 years (AHR: 6.31, 95CI: 5.43–7.2, $P<0.001$), smokers (AHR: 3.41, 95CI: 2.54–4.28, $P=0.006$), hypertensive patients (AHR: 3.99, 95CI: 3.12–4.86, $P=0.002$) and cancer patients (AHR: 11.23, 95CI: 9.42–13.04,

Table 2 Characteristics of adults in the First Clinical Medical College of Zhejiang Chinese Medical University

Variables	Non-psoriasis ($n=103$)	Psoriasis ($n=103$)	*p*
Gender			0.368
Male	74 (72)	67 (65)	
Female	29 (28)	36 (35)	
Age	59 (49, 65)	45 (34, 55.5)	< 0.001
BMI	24.32 (22.51, 26.85)	24.96 (22.66, 27.56)	0.386
Smoking			0.485
Yes	23 (22)	18 (17)	
No	80 (78)	85 (83)	
Drinking			0.01
Yes	19 (18)	6 (6)	
No	84 (82)	97 (94)	
Diabetes			0.064
Yes	12 (12)	23 (22)	
No	91 (88)	80 (78)	
Hypertension			0.077
Yes	13 (13)	23 (22)	
No	90 (87)	80 (78)	
Albumin (g/dL)	4.05 (3.8, 4.32)	3.94 (3.68, 4.22)	0.018
Alkaline phosphatase (U/L)	73 (61, 85)	74 (64, 89)	0.353
Creatinine (mg/dL)	0.8 ± 0.19	0.72 ± 0.14	0.001
Serum glucose (mg/dL)	4.96 (4.44, 5.45)	4.99 (4.52, 5.52)	0.409
C-reactive protein (mg/dL)	0.1 (0.1, 0.18)	0.14 (0.1, 0.45)	0.024
White blood cell count (1000 cells/uL)	5.71 (4.86, 6.61)	6.4 (5.05, 7.55)	0.02
Lymphocyte (%)	31.63 ± 7.48	27.89 ± 8.88	0.001
Red cell distribution width (%)	13 (12.65, 13.5)	13.2 (12.75, 13.75)	0.196
Mean cell volume (fL)	91.3 (89.05, 93.75)	90.1 (86.45, 92.65)	0.015
PhenoAge	58.01 (48.08, 62.91)	45.83 (35.96, 56.96)	< 0.001
PhenoAge advance	-2.03 (-3.2, -0.05)	0.78 (-1.4, 3.21)	< 0.001
PhenoAge advance accelerate			< 0.001
Yes	24 (23)	57 (55)	
No	79 (77)	46 (45)	

Values that are statistically significant (two-side *P* value < 0.05) are indicated by *; Values that are statistically significant (two-side *P* value < 0.01) are indicated by **; *BMI* Body mass index (calculated as kg/m2)

$P=0.009$). Restricted triple spline analysis (Fig. 8) showed a monotonically increasing relationship between risk of death and PhenoAge advance in psoriasis patients, with or without adjustment. In contrast, no statistically significant associations were seen between KDM-Age advance (AHR: 1.01, 95CI: 0.98–1.04, $P=0.42$) and KDM-Age advance acceleration (AHR: 1.79, 95CI: 0.96–2.61, $P=0.116$) and death in psoriasis patients (Fig. 7).

For the psoriasis population in the general ward of MIMIC-IV, based on univariate analysis (Table 3), we found that patients with psoriasis who died within a follow-up time of 1 year were older and had a higher risk of suffering from cancer, liver disease, and diabetes mellitus. The KM curves showed (Fig. 9) that psoriasis patients in the first 50% of the PhenoAge advance had significantly lower survival than the other psoriasis patients ($P<0.001$). Cox regression analysis showed (Fig. 10 A,B) that, after adjustment, for every 1-unit (year) rise in PhenoAge advance, the all-cause mortality rate of patients during the follow-up period increased by 7% (HR: 1.07, 95CI: 1.04–1.1, $P<0.001$). Meanwhile, PhenoAge advance of the first 50% resulted in an 8.6-fold increase in the risk of all-cause mortality during follow-up in patients with psoriasis (HR: 9.6, 95CI: 8.39–10.81, $P<0.001$). KDM-Age advance was adjusted to show that for every 1-unit increase in KDM-Age advance (year), the all-cause mortality rate during follow-up increased by 1% in patients (HR: 1, 95CI: 1.00–1.01, $P<0.001$). KDM-Age advance acceleration did not show a significant outcome with all-cause mortality (HR: 1.76, 95CI: 0.91–2.61, $P=0.191$).

Table 3 Baseline characteristics and death information of patients with psoriasis from general ward in Medical Information Mart for Intensive Care—IV

Variables	The viable psoriasis individuals, *n* = 271 (86.9%)	The deceased psoriasis individuals, *n* = 41 (13.14%)	*p*
Gender			0.957
Male	147 (54)	23 (56)	
Female	124 (46)	18 (44)	
Age	59.22 ± 14.45	70.83 ± 12.58	< 0.001**
Race			0.493
Asian	8 (3)	2 (5)	
Black	10 (4)	3 (7)	
Hispanic	12 (4)	2 (5)	
Unknown	9 (3)	0 (0)	
White	232 (86)	34 (83)	
Albumin (g/dL)	4.1 (3.74, 4.4)	3.4 (3.03, 3.6)	< 0.001**
Alkaline phosphatase (U/L)	81.23 (64, 99.61)	99.5 (81, 141.16)	< 0.001**
Total cholesterol (mg/dL)	177.42 (155.65, 198.29)	153.14 (138.59, 166.15)	< 0.001**
Serum glucose (mg/dL)	6.02 (5.41, 6.89)	6.84 (6.12, 8.77)	< 0.001**
Creatinine (mg/dL)	0.89 (0.74, 1.09)	1.09 (0.78, 1.34)	0.015*
Blood urea nitrogen (mg/dL)	15.66 (12.37, 20.2)	23.47 (14.99, 30.41)	< 0.001**
Uric acid (mg/dL)	5.57 (5.13, 6.16)	5.59 (4.96, 6.13)	0.956
C-reactive protein (mg/dL)	1.96 (0.56, 4.77)	4.06 (2.63, 6.31)	< 0.001**
Glycohemoglobin (%)	5.76 (5.53, 6.18)	5.91 (5.77, 6.85)	0.026*
White blood cell count (1000 cells/uL)	7.95 (6.54, 9.82)	7.95 (6.46, 9.55)	0.66
Lymphocyte (%)	21 (15.14, 27.15)	16.75 (11.6, 24.33)	0.074
Red cell distribution width (%)	13.9 (13.18, 15.1)	15.82 (14.75, 16.91)	< 0.001**
Mean cell volume (fL)	91.58 (88.31, 94.49)	93.85 (89.76, 102.78)	0.006**
Myocardial infarct			0.331
Yes	20 (7)	1 (2)	
No	251 (93)	40 (98)	
Congestive heart failure			0.307
Yes	31 (11)	7 (17)	
No	240 (89)	34 (83)	
Peripheral vascular disease			0.509
Yes	18 (7)	4 (10)	
No	253 (93)	37 (90)	
Cerebrovascular disease			0.643
Yes	9 (3)	2 (5)	
No	262 (97)	39 (95)	
Chronic pulmory disease			0.288
Yes	56 (21)	5 (12)	
No	215 (79)	36 (88)	
Rheumatic disease			0.399
Yes	29 (11)	2 (5)	
No	242 (89)	39 (95)	
Malignt cancer			0.002**
Yes	16 (6)	9 (22)	
No	255 (94)	32 (78)	
Liver disease			0.005**
Yes	23 (8)	10 (24)	
No	248 (92)	31 (76)	
Diabetes			0.036*

Table 3 (continued)

Variables	The viable psoriasis individuals, *n* = 271 (86.9%)	The deceased psoriasis individuals, *n* = 41 (13.14%)	*p*
Yes	61 (23)	16 (39)	
No	210 (77)	25 (61)	
PhenoAge	69.49 ± 17.86	89.89 ± 13.22	< 0.001**
PhenoAge advance	8.54 (3.66, 14.87)	16.76 (12.82, 22.08)	< 0.001**
PhenoAge advance top 50 percent			< 0.002**
Yes	118 (44)	38 (93)	
No	153 (56)	3 (7)	
KDM-Age	67.28 (45.21, 110.57)	134.41 (74.81, 215.81)	< 0.001**
KDM-Age advance	10.72 (-10.39, 43.27)	56.22 (3.2, 135.55)	< 0.001**
KDM-Age advance acceleration			0.051
Yes	165 (61)	32 (78)	
No	106 (39)	9 (22)	

Values that are statistically significant (two-side *P* value < 0.05) are indicated by *; Values that are statistically significant (two-side *P* value < 0.01) are indicated by **; *KDM-Age* Klemera-Doubal method age

For the psoriasis population in the MIMIC-IV intensive care unit, based on univariate analysis (Table 4), we found that patients with psoriasis who died within 28 days of admission were older and at higher risk of having peripheral vascular disease. Logistic regression analysis showed (Fig. 10 C,D) that for every 1 unit (year) rise in PhenoAge advance, patients had a 13% increase in all-cause mortality within 28 days of admission (OR: 1.13, 95CI: 1.09–1.18, $p < 0.001$). Meanwhile PhenoAge advance of the first 50% resulted in a 4.3-fold increase in the risk of all-cause mortality within 28 days of admission in patients with psoriasis (OR: 5.37, 95CI: 1.95–8.79, $P = 0.002$). Logistic regression analysis showed that for every 1-unit (year) increase in KDM-Age advance, all-cause mortality within 28 days of admission in patients increase 2% (OR: 1.02, 95CI: 1.02–1.04, $P < 0.001$), and KDM-Age advance accelerated did not show a significant outcome with all-cause mortality within 28 days of admission in patients (OR: 2.98, 95CI: 1.03–9.6, $P = 0.054$).

Predicting short- and long-term prognosis in psoriasis patients using biological aging

For the psoriasis population in NHANES (Fig. 11 A), the AUC for prediction of death within the median follow-up time using PhenoAge advance was 0.71, with an accuracy of 0.66, a precision of 0.26, a recall of 0.71, a specificity of 0.65, and a calculated cutoff value of 1. The AUC for prediction of death within the median follow-up time using KDM-Age advance was 0.52, accuracy was 0.20, precision was 0.12, recall was 0.71, specificity was 0.11, and the calculated cut-off value was -10 (Table 6).

For the psoriasis population in the general ward of the MIMIC-IV (Fig. 11 B), the AUC for prediction of death within the follow-up time using PhenoAge advance was 0.79, with an accuracy of 0.66, a precision of 0.26, a recall of 0.88, and a specificity of 0.63, and a calculated cut-off value of 11. The AUC for the prediction of death within the follow-up time using KDM-Age advance was 0.67, accuracy was 0.69, precision was 0.24, recall was 0.61, specificity was 0.71, and the calculated cut-off value was 36 (Table 6).

For the psoriasis population in the MIMIC-IV intensive care unit (Fig. 11 C), the AUC for prediction of death within 28 days of admission to the ICU using PhenoAge advance was 0.71, with an accuracy of 0.37, a precision of 0.06, a recall of 0.91, and a specificity of 0.34, and a calculated cut-off value of 11. The AUC for prediction of ICU admission within 28 days of death using KDM-Age advance was 0.71, with an accuracy of 0.59, a precision of 0.08, a recall of 0.73, and a specificity of 0.58 (Table 6). All predicted confusion matrices can be seen in Table 7.

Discussion

This is the first study to use NHANES and MIMIC-IV to explore the relationship between biological aging and psoriasis. The results of the first part of our study were very interesting that psoriasis was an independent risk factor for PhenoAge advance acceleration in the NHANES cohort. However, psoriasis did not lead to KDM-Age advance acceleration. Restricted cubic spline analysis also showed a robust relationship between PhenoAge advance and psoriasis. Data from The First Clinical Medical College of Zhejiang Chinese Medical University corroborated the findings obtained in NHANES and suggested a strong association between psoriasis severity and PhenoAge advance. In addition, we

Table 4 Baseline characteristics and death information of patients with psoriasis from intensive care unit in Medical Information Mart for Intensive Care—IV

Variables	The viable psoriasis individuals, $n = 235$ (95.53%)	The psoriasis patients died within 28 days of admission to the icu, $n = 11$ (4.47%)	*p*
Gender			0.124
Male	133 (57)	9 (82)	
Female	102 (43)	2 (18)	
Age	60.24 ± 13.76	70.73 ± 14.4	0.038*
Race			0.407
Asian	1 (0)	0 (0)	
Black	13 (6)	0 (0)	
Hispanic	4 (2)	0 (0)	
Unknown	38 (16)	4 (36)	
White	179 (76)	7 (64)	
Albumin (g/dL)	3.62 (3.25, 4.05)	2.85 (2.61, 3.61)	0.02*
Alkaline phosphatase (U/L)	86.44 (70.25, 115.47)	103 (75.3, 169.79)	0.186
Total cholesterol (mg/dL)	162.05 (144.29, 183.92)	130 (113.92, 150.39)	< 0.001**
Serum glucose (mg/dL)	6.53 (5.87, 7.88)	6.79 (6.62, 7.13)	0.395
Creatinine (mg/dL)	0.96 (0.76, 1.25)	1.55 (1.14, 2.28)	0.002**
Blood urea nitrogen (mg/dL)	19.32 (13.79, 27.04)	36.4 (23.5, 45.4)	0.001**
Uric acid (mg/dL)	6.21 (5.7, 7.35)	6.91 (6.64, 8.19)	0.02*
C-reactive protein (mg/dL)	3.81 (1.51, 6.78)	6.56 (3.39, 9.74)	0.058
Glycohemoglobin (%)	5.84 (5.58, 6.64)	5.66 (5.56, 5.87)	0.14
White blood cell count (1000 cells/uL)	9.28 (7.48, 11.78)	11.73 (9.18, 14.21)	0.053
Lymphocyte (%)	17.6 (12.52, 23.23)	9.68 (3.67, 15.52)	0.006**
Red cell distribution width (%)	14.74 (13.82, 16.23)	16.74 (15.51, 17.06)	0.032*
Mean cell volume (fL)	92.33 (88.71, 95.61)	93.14 (89.33, 100.42)	0.43
Myocardial infarct			0.372
Yes	35 (15)	0 (0)	
No	200 (85)	11 (100)	
Congestive heart failure			0.514
Yes	71 (30)	2 (18)	
No	164 (70)	9 (82)	
Peripheral vascular disease			0.015*
Yes	10 (4)	3 (27)	
No	225 (96)	8 (73)	
Cerebrovascular disease			1
Yes	19 (8)	1 (9)	
No	216 (92)	10 (91)	
Chronic pulmory disease			1
Yes	46 (20)	2 (18)	
No	189 (80)	9 (82)	
Rheumatic disease			0.507
Yes	14 (6)	1 (9)	
No	221 (94)	10 (91)	
Malignt cancer			0.457
Yes	12 (5)	1 (9)	
No	223 (95)	10 (91)	
Liver disease			0.113
Yes	40 (17)	4 (36)	
No	195 (83)	7 (64)	
Diabetes			0.208

Table 4 (continued)

Variables	The viable psoriasis individuals, *n* = 235 (95.53%)	The psoriasis patients died within 28 days of admission to the icu, *n* = 11 (4.47%)	*p*
Yes	98 (42)	2 (18)	
No	137 (58)	9 (82)	
PhenoAge	76.91 ± 16.21	98.05 ± 15.6	0.001**
PhenoAge advance	14.86 (8.76, 22.61)	20.83 (13.74, 36.55)	0.021*
PhenoAge advance top 50 percent			0.217
Yes	115 (49)	8 (73)	
No	120 (51)	3 (27)	
KDM-Age	97.66 (70.77, 175.98)	97.66 (70.77, 175.98)	0.002**
KDM-Age advance	41.88 (6.73, 107.25)	41.88 (6.73, 107.25)	0.008**
KDM-Age advance acceleration			0.207
Yes	115 (49)	8 (73)	
No	121 (51)	3 (27)	

Values that are statistically significant (two-side *P* value < 0.05) are indicated by *; Values that are statistically significant (two-side *P* value < 0.01) are indicated by **; *icu* intensive care unit, *KDM-Age* Klemera-Doubal method age

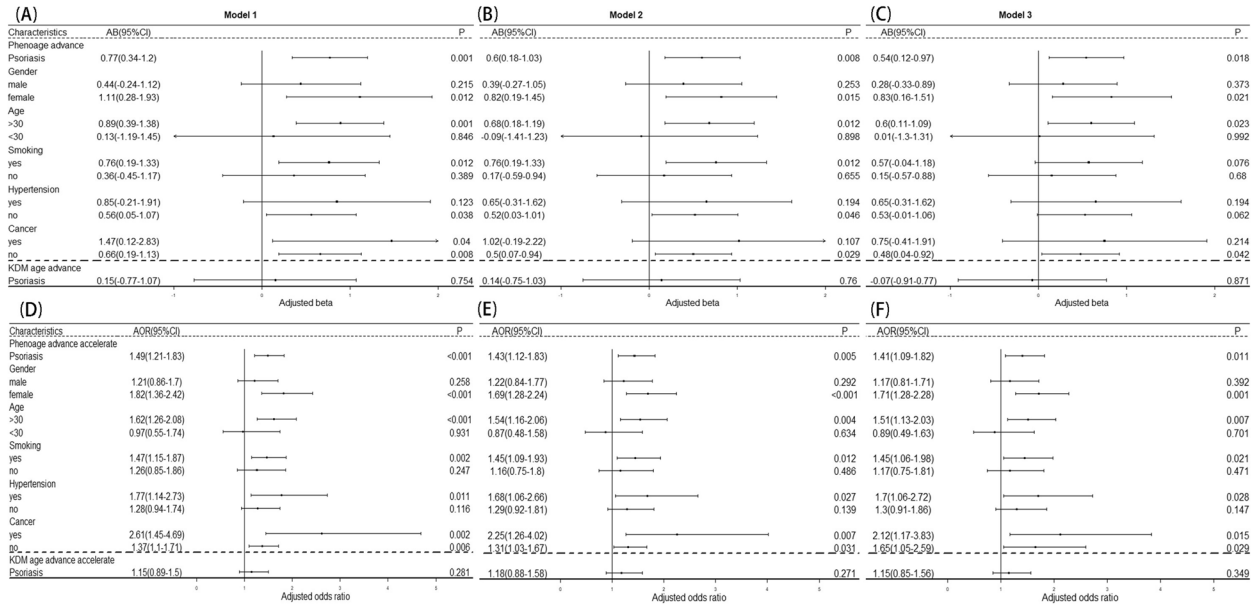

Fig. 2 Association between biological age advance and psoriasis in NHANES. **A**, **B**, **C** is weighted linear regression. **D**, **E**, **F** is weighted logistic regression

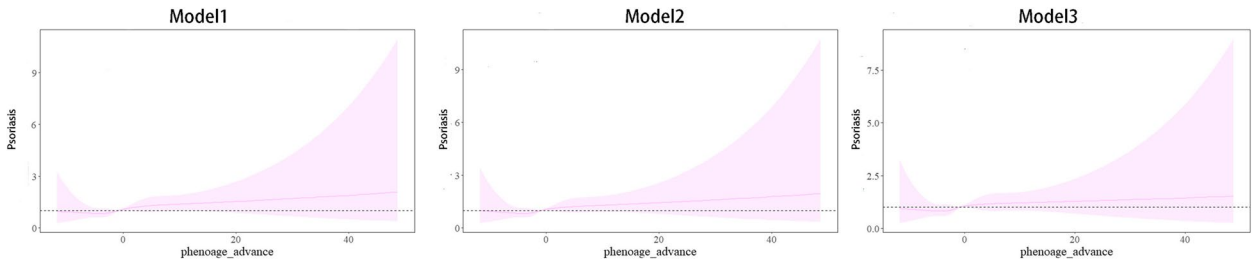

Fig. 3 Restricted cubic spline between PhenoAge advance and psoriasis in NHANES

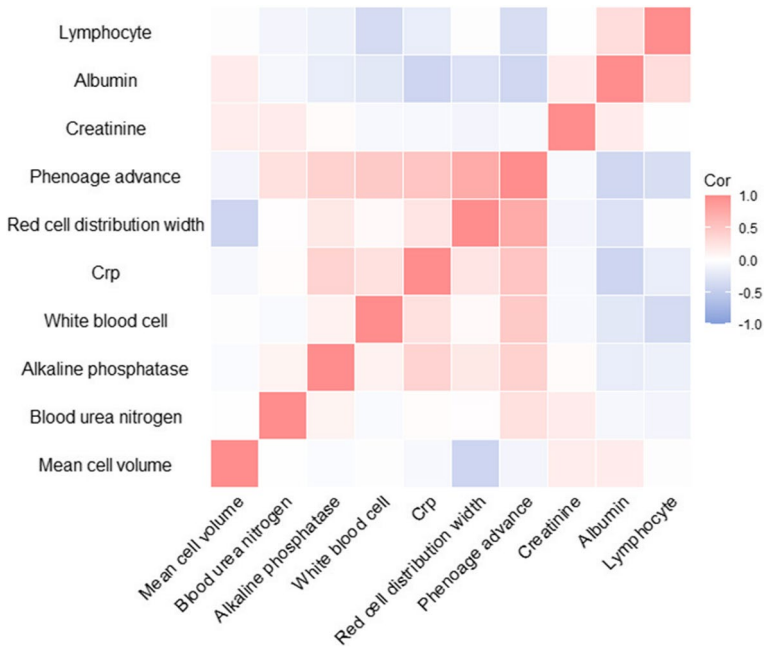

Fig. 4 Correlation heat maps of variables associated with PhenoAge advance in psoriasis patients in NHANES

found that PhenoAge advance accelerated more rapidly in psoriasis patients of advanced age and with comorbidities than in the general psoriasis population. Taken together, we believe that rational management of psoriasis and control of comorbidities are important therapeutic directions to extend the life span of patients with psoriasis.

In the second part of the study, for the NHANES cohort, our study showed that for every unit (year) rise in PhenoAge advance, patients experienced an 8% increase in all-cause mortality during follow-up. This was similarly demonstrated in the MIMIC-IV general ward cohort. In contrast, the results were not significant in KDM-Age. In the MIMIC-IV intensive care unit cohort, the association between PhenoAge advance and patient death within 28 days of admission remained significant. In contrast, the results were not significant in KDM-Age. Our study demonstrates for the first time a strong association between PhenoAge advance and short- and long-term prognosis in patients with psoriasis. It also reaffirms our previous view that PhenoAge is a better indicator of patients' vital health status than KDM-Age in psoriasis patients.

Although the link between PhenoAge advance and short- and long-term prognosis in psoriasis patients has been demonstrated, we still wanted to develop more of PhenoAge's potential, which is why we conducted our third part of study. In this study, we demonstrated that the use of PhenoAge advance can predict short- and long-term prognosis in psoriasis patients. Notably, PhenoAge advance showed higher recall and lower accuracy for either near-term prognosis or distant prognosis of patients with psoriasis, suggesting that PhenoAge advance can only be used as a reference option for predicting near-term prognosis or distant prognosis. The specific clinical application process can be seen in Fig. 12. To sum up, in the outpatient follow-up population, psoriasis patients with PhenoAge greater than 1 are very likely to have disease progression, and detailed examination to clarify the etiology is recommended for such patients. As for patients admitted to the general ward or ICU, those with a premature rise in PhenoAge advance greater than 11 may have a worse prognosis and require more aggressive drug and surgical treatment. In particular, one paper suggests that all possible therapies targeting non-specific restoration of the immune system could be counterproductive, given that the complex physiological phenotypes exhibited during immune aging in the body are the result of synergistic and antagonistic changes in multiple pathways [24]. Therefore, for psoriasis patients with accelerated biological aging, it may be important to consider the use of biologics for specific treatment.

In our study, PhenoAge was more significantly associated with psoriasis than KDM-Age. This may be due to the fact that PhenoAge incorporates more metrics on immune senescence, including red blood cell distribution width, white blood cell count, lymphocyte percentage, and mean cell volume, thus better reflecting

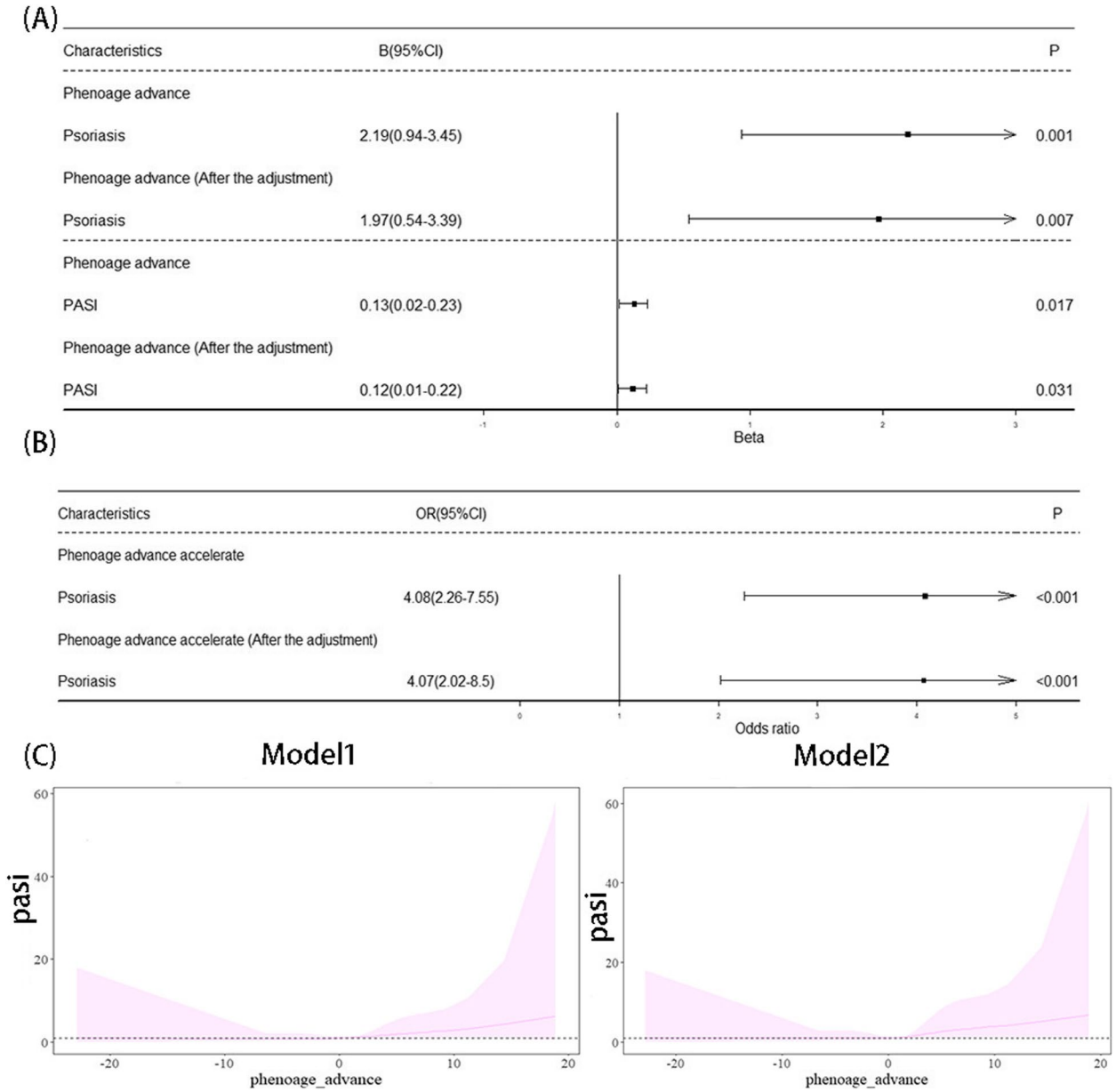

Fig. 5 Association between biological age advance and psoriasis in China population. **A** is linear regression. **B** is logistic regression. **C** is restricted cubic spline between PhenoAge advance and PASI

the state of immune senescence [25]. After correlation testing, the results showed that red blood cell distribution width and leukocyte count contributed the top two PhenoAge advance in psoriasis patients, which proves our view. Besides, compared with other DNA methylation epigenetic clocks, PhenoAge more sensitive to disease progression and death but less robust to represent chronological age [26]. The possible reason is that their modeling principles are different. Horvath and Hannum's clocks are trained on chronological age, while PhenoAge is specifically designed to predict biological age and death risk through combined training of biomarkers, so the two types of clocks are called chronological age trained clocks or death clocks, respectively [27]. In addition, PhenoAge is calculated based on clinical biomarkers, it is more easily changing parameter in terms of weeks or even days compared to the other epigenetic clock which changes in matter of months.

In this study, there was greater heterogeneity between MIMIC and the other two cohorts. The possible reason is

Table 5 Baseline characteristics and death information of patients with psoriasis in National Health and Nutrition Examination Survey 2003–2006 and 2009–2010

Variables	The viable psoriasis individuals, $n=291$ (weighted[&] %$=88.13$)	The deceased psoriasis individuals, $n=58$ (weighted[&] %$=11.87$)	*p*-value
Gender			0.903
Male	130 (49.2)	28 (48.1)	
Female	155 (50.8)	24 (51.9)	
Age	42.79 ± 12.86	57.73 ± 14.84	< 0.001**
Race/ethnicity			0.270
Mexican American	28 (3.5)	4 (2.9)	
Other Hispanic	21 (3.3)	0 (0)	
Non-Hispanic White	185 (82.3)	42 (87.7)	
Non-Hispanic Black	41 (7.4)	3 (2.4)	
Other Race—Including Multi-Racial	10 (3.5)	3 (7.0)	
Education			0.088
Did not graduate high school	58 (13.6)	13 (25.2)	
High school graduate	68 (23.3)	15 (24.3)	
Did not graduate college	85 (34.0)	18 (39.6)	
College graduate	74 (29.0)	6 (10.8)	
Annual household income			0.005**
< $20,000	56 (12.1)	21 (28.5)	
≥ $20,000	229 (87.9)	31 (71.5)	
BMI	29.71 ± 6.94	32.85 ± 7.39	0.016*
Smoking			0.014*
Yes	160 (57.7)	42 (80.3)	
No	125 (42.3)	10 (19.7)	
Drinking			0.664
Yes	220 (80.2)	44 (83.2)	
No	65 (19.8)	8 (16.8)	
Average physical activity level			0.064
Vigorous work activity	76 (28.4)	4 (11.6)	
Moderate to low intensity work activities	209 (71.6)	48 (88.4)	
Diabetes			< 0.001**
Yes	24 (6.1)	18 (30.7)	
No	261 (93.9)	34 (69.3)	
Hypertension			< 0.001**
Yes	92 (29.3)	42 (73)	
No	193 (70.7)	10 (27)	
Kidney disease			0.565
Yes	7 (2.5)	4 (3.6)	
No	278 (97.5)	48 (96.4)	
Liver disease			0.006**
Yes	10 (2.4)	6 (14.1)	
No	275 (97.6)	46 (85.9)	
Thyroid disease			0.514
Yes	27 (9.6)	7 (12.9)	
No	258 (90.4)	45 (87.1)	
Heart disease,			< 0.001**
Yes	20 (4.4)	20 (28.3)	
No	265 (95.6)	32 (71.7)	
Cancer			0.004**
Yes	29 (10.0)	16 (33.8)	

Table 5 (continued)

Variables	The viable psoriasis individuals, *n* = 291 (weighted[&] % = 88.13)	The deceased psoriasis individuals, *n* = 58 (weighted[&] % = 11.87)	*p*-value
No	256 (90.0)	36 (66.2)	
Systolic blood pressure (mmHg)	120.54 ± 15.62	123.90 ± 16.06	0.296
Albumin (g/dL)	4.25 ± 0.34	4.05 ± 0.29	0.001**
Alkaline phosphatase (U/L)	67.76 ± 22.37	74.84 ± 23.29	0.061
Total cholesterol (mg/dL)	201.00 ± 40.06	207.99 ± 42.92	0.272
Serum glucose (mg/dL)	5.11 ± 0.89	6.49 ± 2.93	0.009**
Creatinine (mg/dL)	0.89 ± 0.18	0.95 ± 0.23	0.083
Blood urea nitrogen (mg/dL)	12.41 ± 4.63	15.34 ± 6.76	0.005**
Uric acid (mg/dL)	5.37 ± 1.32	6.09 ± 1.40	< 0.001**
C-reactive protein (mg/dL)	0.46 ± 0.86	0.63 ± 1.32	0.259
Glycohemoglobin (%)	5.40 ± 0.61	6.05 ± 1.41	0.014*
White blood cell count (1000 cells/uL)	7.37 ± 1.99	8.18 ± 2.30	0.078
Lymphocyte (%)	29.51 ± 7.58	25.04 ± 7.02	< 0.001**
Red cell distribution width (%)	12.79 ± 1.21	13.48 ± 1.32	0.011*
Mean cell volume (fL)	89.98 ± 5.90	91.54 ± 5.44	0.098
DII	0.88 ± 1.53	1.49 ± 1.50	0.015*
HEI2015	53.56 ± 11.05	49.77 ± 7.84	0.005*
PhenoAge	42.68 ± 13.04	61.76 ± 16.31	< 0.001**
PhenoAge advance	-0.12 ± 4.46	4.03 ± 5.85	< 0.001**
PhenoAge advance acceleration			0.005**
Yes	132 (43.3)	40 (73.2)	
No	153 (56.7)	12 (26.8)	
KDM-Age	40.55 ± 12.61	57.06 ± 17.82	< 0.001**
KDM-Age advance	-2.24 ± 6.46	-0.67 ± 13.41	0.386
KDM-Age advance acceleration			0.165
Yes	107 (37.3)	21 (46.4)	
No	178 (42.7)	31 (53.6)	
Underlying Leading Cause of Death			/
Diseases of heart	/	10 (21.8)	
Malignant neoplasms	/	20 (34.7)	
Chronic lower respiratory diseases	/	2 (2.6)	
Accidents (unintentional injuries)	/	1 (2.6)	
Cerebrovascular diseases	/	1 (1.4)	
Diabetes mellitus	/	2 (3.3)	
Influenza and pneumonia	/	2 (1.6)	
All other causes	/	14 (31.9)	
Multiple Cause of Death			/
Diabetes	/	8 (17.9)	
Hypertension	/	10 (17.9)	

Values that are statistically significant (two-side *P* value < 0.05) are indicated by *; Values that are statistically significant (two-side *P* value < 0.01) are indicated by **; *BMI* Body mass index (calculated as kg/m2), *NHANES* National Health and Nutrition Examination Survey; &Weighted percentage was calculated using NHANES survey design parameters, DII, dietary inflammation index; HEI2015, healthy eating index; KDM-Age, Klemera-Doubal method age

that the study object included in NHANES is the general population, the study object included in China is hospitalized patients, and the study object included in MIMIC is severe patients. It is common sense to assume that patients in intensive care units and inpatient units are sicker, which may lead to changes in markers of aging.

The possible mechanisms of psoriasis and biological aging are as follows. Firstly, immune senescence caused by psoriasis is the basis of accelerated biological senescence. Our study suggests that the three serum markers most associated with PhenoAge advance in psoriasis patients are red blood cell distribution width, C-reactive

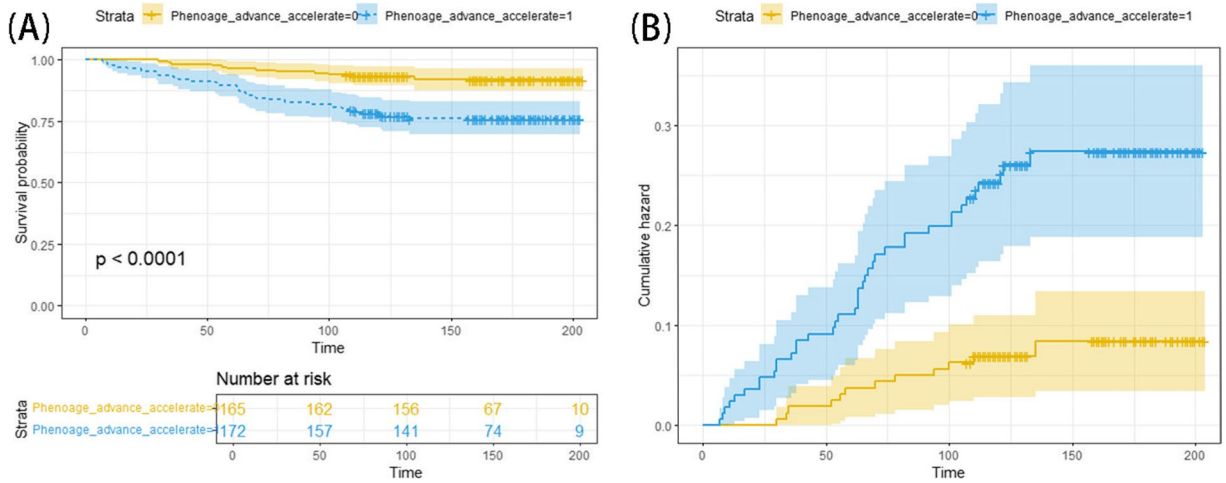

Fig. 6 Kaplan–Meier curve of psoriasis population in NHANES (according to PhenoAge advance accelerate)

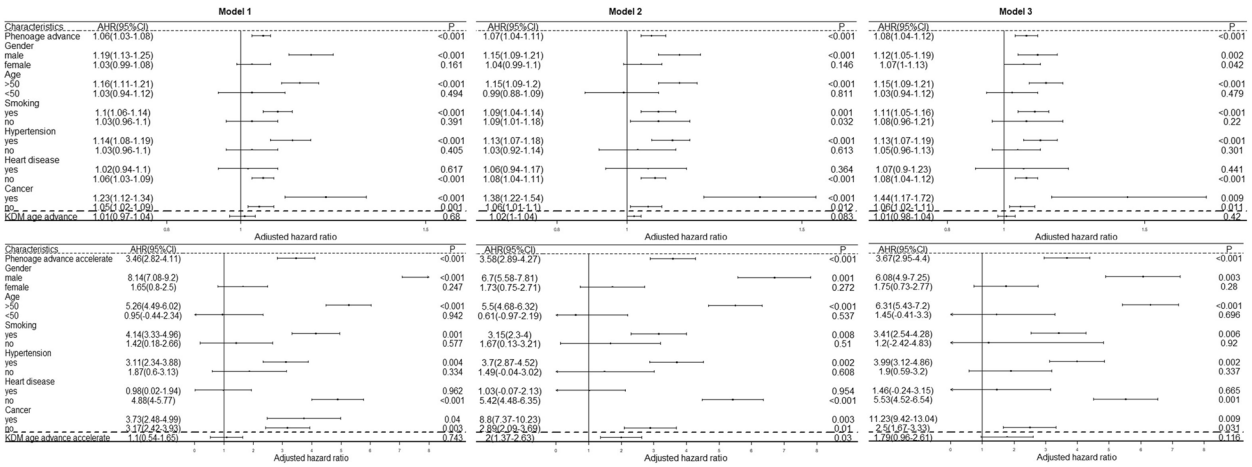

Fig. 7 Association between biological aging and mortality in patients with psoriasis in NHANES

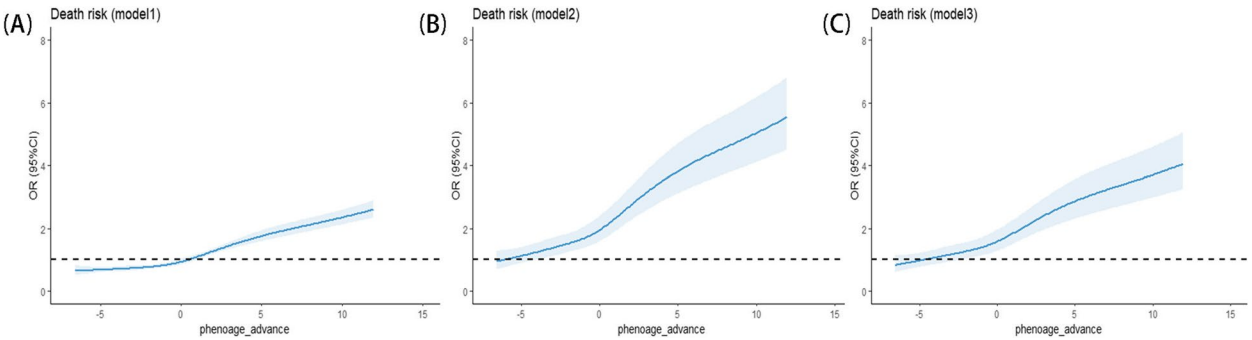

Fig. 8 Restricted cubic spline between PhenoAge advance and mortality in NHANES

protein, and white blood cell count. These three suggest that immunity and inflammation are the most important causes of biological aging in psoriasis patients. In the microenvironment of psoriasis patients, with the abnormal activation of interleukin 23/interleukin 17 pathway, inflammatory factors such as C-reactive protein and

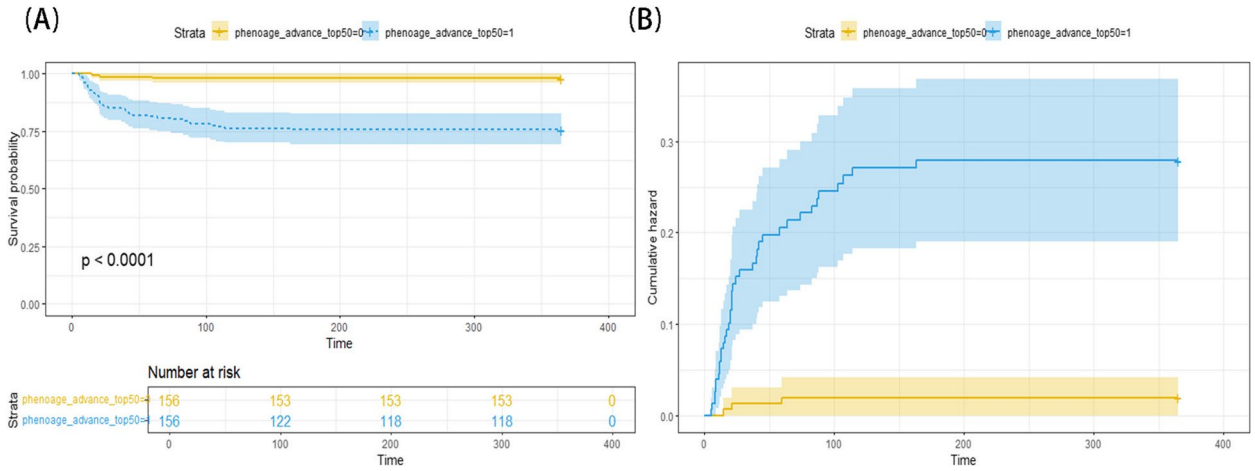

Fig. 9 Kaplan–Meier curve of psoriasis population in MIMIC (according to PhenoAge advance top 50%)

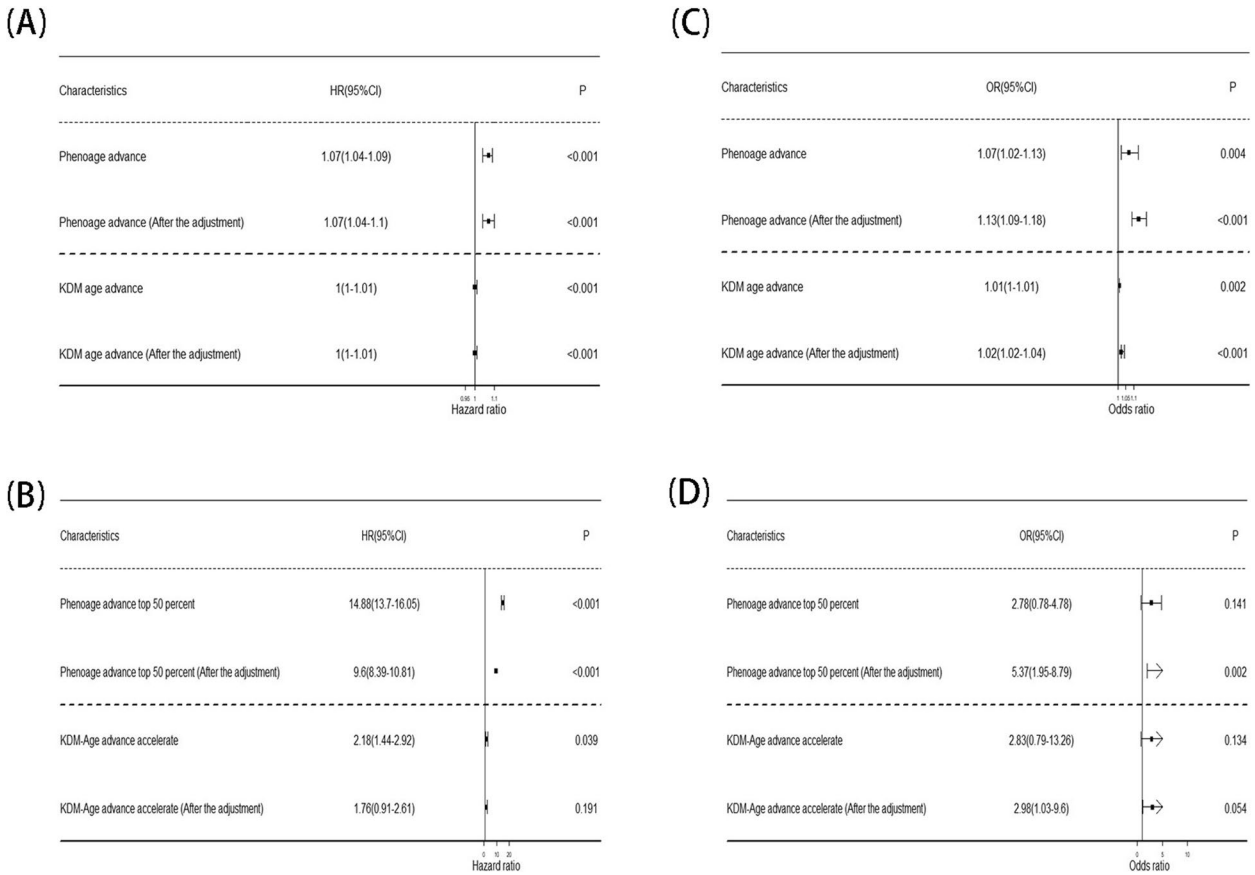

Fig. 10 Association between biological aging and mortality in patients with psoriasis in MIMIC

tumor necrosis factor alpha are up-regulated [28]. In the inflammatory environment, specific abnormalities in immune cell function occur, including reduced phagocytosis, abnormal adhesion chemotaxis, and increased apoptosis [29–32]. Importantly, their ability to clear senescent cells is reduced, leading to accelerated biological senescence [33]. At the same time, immune senescence can further enhance the inflammatory response. Senescent immune cells exhibit a unique aging-related secretory phenotype, secreting a large number of soluble

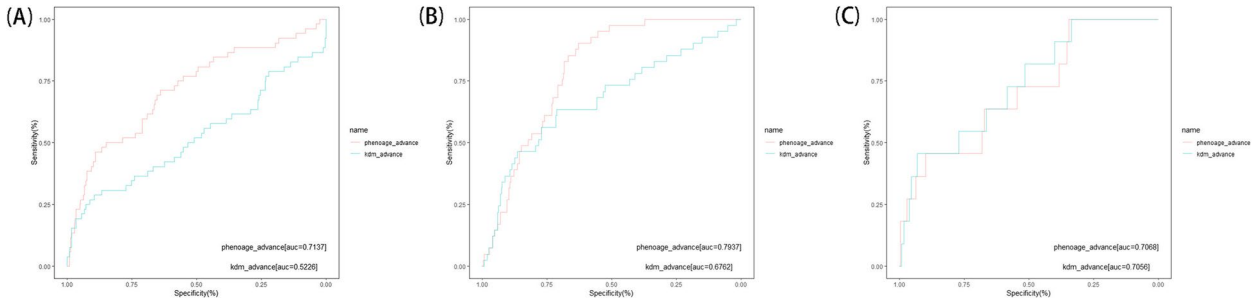

Fig. 11 ROC curve for biological age prediction of mortality. **A**—NHANES. **B**—MIMIC's general ward. **C**—MIMIC's ICU

Table 6 Performance of biological age in predicting short-and long-term outcomes in patients with psoriasis

	Variable	Accuracy	Precision	Recall	Specificity	Cutoff
NHANES group (*n* = 343)[a]	PhenoAge advance	0.66	0.26	0.71	0.65	1.00
	KDM-Age advance	0.20	0.12	0.71	0.11	-10.00
MIMIC general ward group (*n* = 312)[b]	PhenoAge advance	0.66	0.26	0.88	0.63	11.00
	KDM-Age advance	0.69	0.24	0.61	0.71	36.00
MIMIC icu group (*n* = 246)[c]	PhenoAge advance	0.37	0.06	0.91	0.34	11.00
	KDM-Age advance	0.59	0.08	0.73	0.58	60.00

FN False negatives, *FP* False positives, *TN* True negatives, *TP* True positives, *Accuracy* (TP + TN)/(TP + TN + FP + FN), *Precision* TP/(TP + FP), *Recall* TP/(TP + FN), *Specificity* TN/(TN + FP), *NHANES* National Health And Nutrition Examination Survey, *MIMIC* Medical Information Mart for Intensive Care

[a] The outcome measure in the NHANES group was death during follow-up

[b] The outcome measure for MIMIC general ward group was death during follow-up

[c] The outcome measure for MIMIC icu group was death within 28 years of admission to icu

Table 7 Confusion matrix of biological age in predicting short—and long-term outcomes in patients with psoriasis

	Variable	TN	FN	FP	TP
NHANES group (*n* = 343)[a]	PhenoAge advance	188	15	103	37
	KDM-Age advance	31	15	260	37
MIMIC general ward group (*n* = 312)[b]	PhenoAge advance	170	5	101	36
	KDM-Age advance	193	16	78	25
MIMIC icu group (*n* = 246)[c]	PhenoAge advance	81	1	154	10
	KDM-Age advance	137	3	98	8

FN False negatives, *FP* False positives, *TN* True negatives, *TP* True positives

FN False negatives, *FP* False positives, *TN* True negatives, *TP* True positives, *Accuracy* (TP + TN)/(TP + TN + FP + FN), *Precision* TP/(TP + FP); Recall = TP/(TP + FN), *Specificity* TN/(TN + FP), *NHANES* National Health And Nutrition Examination Survey, *MIMIC* Medical Information Mart for Intensive Care

[a] The outcome measure in the NHANES group was death during follow-up

[b] The outcome measure for MIMIC general ward group was death during follow-up

[c] The outcome measure for MIMIC icu group was death within 28 years of admission to icu

factors, including interleukin and tumor necrosis factor, leading to an inflammatory phenotype [34, 35].

Secondly, the results of subgroup analyses in our study suggest that metabolic comorbidities of psoriasis may be an important cause of accelerated aging in psoriasis patients. Accelerated cellular senescence is an important disease feature in diabetes and cardiovascular disease [36]. Many studies have defined psoriasis as an immune-metabolic disease [37]. A similar genetic background, chronic inflammation, immune regulation and oxidative stress underlie the pathogenesis of metabolic comorbidities in psoriasis [38]. Based on current research, the main mechanisms leading to accelerated cellular senescence in metabolic diseases are still attributed to chronic inflammation and oxidative stress [39]. For instance, interleukin 1β can induce insulin resistance

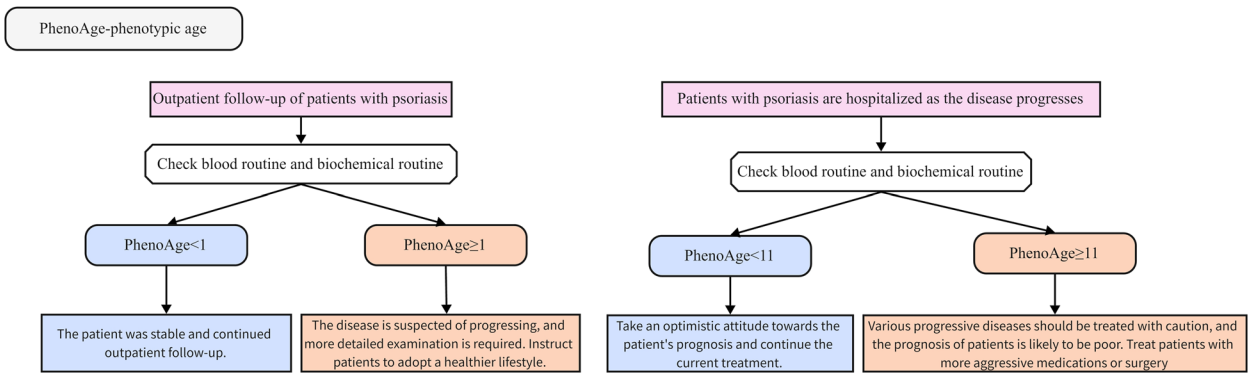

Fig. 12 A vision for including PhenoAge in the management of clinical psoriasis patients

by activating the p38 mitogen-activated protein kinase pathway, and TNF-α contributes to the development of diabetes by inhibiting insulin receptor-mediated insulin resistance [40, 41]. Interleukin 17 induces hypertension by reducing nitric oxide produced by the endothelium, and interleukin 17 mediated endothelial dysfunction can be normalized by interleukin 17 neutralizing antibodies [42].

Finally, as a disease with significant genetic predisposition, the biological aging it causes may be related to genes and heredity. Of the limited number of studies, one mendelian randomization study shows that psoriasis was associated with a genetic susceptibility to telomere shortening [43]. An epigenome-based study revealed that Abnormal DNA methylation of some genes can be controlled by genetic factors and also mediate risk variation for psoriasis [44], and Abnormal DNA methylation is widely believed to be associated with biological aging [45]. However, based on the current literature, the relationship between genetic susceptibility to psoriasis and biological aging remains unclear.

This study has a number of limitations. First, as cross-sectional analyses, the ability to establish clear causal relationships is inherently limited. Also, due to the limitations of the NHANES database, we were only able to diagnose psoriasis based on patients' self-reports. Such diagnostic criteria lack specificity. Besides, Due to the difference in follow-up time and large heterogeneity between the NHANES and MIMIC cohorts, our study of using PhenoAge to predict long-term and short-term mortality in patients with psoriasis has not been cross-validated externally. Finally, due to the lack of data on medication, this study did not consider the effect of therapeutic drugs received by participants in NHANES and MIMIC-IV on serum markers in patients with psoriasis, which may affect the reliability of the conclusions.

Nonetheless, our study has some strengths, the biggest being that all conclusions have been validated with data from at least two sources, which makes our conclusions relatively reliable.

Conclusion

This study provides new insights into the relationship between biological aging and psoriasis. Psoriasis leads to biological aging accelerated, which correlates with the severity of psoriasis as well as comorbidities. This shows the disease burden of psoriasis in the perspective of aging and suggests the importance of managing psoriasis appropriately and controlling comorbidities. In addition, PhenoAge advance was strongly associated with life expectancy in psoriasis patients, and PhenoAge advance can predict short-term prognosis and long-term prognosis of psoriasis patients to some extent. Therefore, aggressive early intervention in psoriasis patients with accelerated biological aging has the potential to become a more personalized treatment option.

Abbreviations

NHANES	National Health and Nutrition Examination Survey
MIMIC	Medical Information Mart for Intensive Care
KDM-age	Klemera-Doubal method age
PhenoAge	Phenotypic age
HR	Hazard ratio
KM	Kaplan-Meier
BMI	Body mass index
PASI	Psoriasis Area and Severity Index
CITI	Collaborative Institutional Training Initiative
AUC	Area under the curve
AB	Adjust Beta
AOR	Adjusted odds ratio
IQR	Interquartile range

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12979-025-00500-4.

Supplementary Material 1.

Acknowledgements

Thank you to all study participants in this study, and to the data investigators and stewards of National Health and Nutrition Examination Survey and Medical Information Mart for Intensive Care.

Authors' contributions

Zheng Lin: conceptualization, methodology, software, formal analysis, data curation, writing. Hong-fei Wang: conceptualization, data curation, writing.

Lu-yan Yu: investigation, data curation, writing. Jia chen: validation, data curation. Cheng-cheng Kong: validation, conceptualization. Bin Zhang: investigation. Xuan Wu: recruitment of subjects. Hao-nan Wang: recruitment of subjects. Yi Cao: conceptualization, data curation. Ping Lin: supervision, project administration, funding acquisition. All authors have read and agreed to the published version of the manuscript.

Funding
This study of this article was supported by the national and provincial joint project (GZY-ZJ-KJ-23088) and Hangzhou medical science and technology project (ZD20220005).

Data availability
NHANES (National Health and Nutrition Examination Survey) is an ongoing U.S. national cross-sectional survey that collects health-related information from the U.S. civilian population every two years. Open data can be accessed from the https://www.cdc.gov/nchs/nhanes.
MIMIC (Medical Information Mart for Intensive Care) is an NIH-funded medical database that collects information on a large number of hospitalized patients, and publicly available data can be found at https://mimic.mit.edu.
The datasets generated during and/or analyzed during the program carried out in The First Clinical Medical College of Zhejiang Chinese Medical University are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
All NHANES protocols were approved by the NCHS Research Ethics Review Board (Protocol #98- 12, Continuation of Protocol #2005–06, Continuation of Protocol #2011–23, http://www.cdc.gov/nchs/nhanes/irba98.htm) and informed consent was obtained at participant enrollment.
For compliance, author Zheng Lin obtained a Collaborative Institutional Training Initiative (CITI) (record ID: 13501620) and the necessary permissions to use the MIMIC-IV database. The database includes comprehensive information on each patient's length of stay, laboratory tests, medication administration, and vital signs. To protect patient privacy, all personal information is de-identified and random codes are used instead of patient identifiers. Therefore, this section does not require patient consent or ethical approval.
The research program carried out in The First Clinical Medical College of Zhejiang Chinese Medical University was approved by the Ethics Review Committee of The First Clinical Medical College of Zhejiang Chinese Medical University. Since we only reviewed the existing database, the Ethics Committee exempted patients from informed consent (2024-KLS-683–01).

Consent for publication
This manuscript does not contain personal information about any of the study participants.

Competing interests
The authors declare no competing interests.

Author details
[1]Dermatology Department, The First Clinical Medical College, Zhejiang Chinese Medical University, Post and Circuit Road, Shangcheng District, Hangzhou, ZheJiang 310006, China. [2]Geriatric department, The Third Hospital of Hangzhou, Zhejiang Chinese Medical University, Xi Hu Avenue, Shangchenq Distinct, Hangzhou, ZheJiang 310009, China.

Received: 4 January 2025 Accepted: 31 January 2025
Published online: 11 February 2025

References

1. Griffiths CEM, Armstrong AW, Gudjonsson JE, Barker J. Psoriasis Lancet. 2021;397(10281):1301–15.
2. Parisi R, Iskandar IYK, Kontopantelis E, Augustin M, Griffiths CEM, Ashcroft DM, et al. National, regional, and worldwide epidemiology of psoriasis: systematic analysis and modelling study. BMJ. 2020;369:m1590.
3. Egeberg A, Mallbris L, Warren RB, Bachelez H, Gislason GH, Hansen PR, et al. Association between psoriasis and inflammatory bowel disease: a Danish nationwide cohort study. Br J Dermatol. 2016;175(3):487–92.
4. Takeshita J, Grewal S, Langan SM, Mehta NN, Ogdie A, Van Voorhees AS, et al. Psoriasis and comorbid diseases: Epidemiology. J Am Acad Dermatol. 2017;76(3):377–90.
5. Lin Z, Shi YY, Yu LY, Ma CX, Pan SY, Dou Y, et al. Metabolic dysfunction associated steatotic liver disease in patients with plaque psoriasis: a case-control study and serological comparison. Front Med (Lausanne). 2024;11:1400741.
6. Semenov YR, Herbosa CM, Rogers AT, Huang A, Kwatra SG, Cohen B, et al. Psoriasis and mortality in the United States: Data from the National Health and Nutrition Examination Survey. J Am Acad Dermatol. 2021;85(2):396–403.
7. Horreau C, Pouplard C, Brenaut E, Barnetche T, Misery L, Cribier B, et al. Cardiovascular morbidity and mortality in psoriasis and psoriatic arthritis: a systematic literature review. J Eur Acad Dermatol Venereol. 2013;27(Suppl 3):12–29.
8. Trafford AM, Parisi R, Kontopantelis E, Griffiths CEM, Ashcroft DM. Association of Psoriasis With the Risk of Developing or Dying of Cancer: A Systematic Review and Meta-analysis. JAMA Dermatol. 2019;155(12):1390–403.
9. Kennedy BK, Berger SL, Brunet A, Campisi J, Cuervo AM, Epel ES, et al. Geroscience: linking aging to chronic disease. Cell. 2014;159(4):709–13.
10. Earls JC, Rappaport N, Heath L, Wilmanski T, Magis AT, Schork NJ, et al. Multi-Omic Biological Age Estimation and Its Correlation With Wellness and Disease Phenotypes: A Longitudinal Study of 3,558 Individuals. J Gerontol A Biol Sci Med Sci. 2019;74(Suppl_1):S52-S60.
11. 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.
12. Gao X, Geng T, Jiang M, Huang N, Zheng Y, Belsky DW, et al. Accelerated biological aging and risk of depression and anxiety: evidence from 424,299 UK Biobank participants. Nat Commun. 2023;14(1):2277.
13. Chen L, Wu B, Mo L, Chen H, Zhao Y, Tan T, et al. Associations between biological ageing and the risk of, genetic susceptibility to, and life expectancy associated with rheumatoid arthritis: a secondary analysis of two observational studies. Lancet Healthy Longev. 2024;5(1):e45–55.
14. Mak JKL, McMurran CE, Kuja-Halkola R, Hall P, Czene K, Jylhava J, et al. Clinical biomarker-based biological aging and risk of cancer in the UK Biobank. Br J Cancer. 2023;129(1):94–103.
15. Lanna C, Mancini M, Gaziano R, Cannizzaro MV, Galluzzo M, Talamonti M, et al. Skin immunity and its dysregulation in psoriasis. Cell Cycle. 2019;18(20):2581–9.
16. Boots AM, Maier AB, Stinissen P, Masson P, Lories RJ, De Keyser F. The influence of ageing on the development and management of rheumatoid arthritis. Nat Rev Rheumatol. 2013;9(10):604–13.
17. Mattei PL, Corey KC, Kimball AB. Psoriasis Area Severity Index (PASI) and the Dermatology Life Quality Index (DLQI): the correlation between disease severity and psychological burden in patients treated with biological therapies. J Eur Acad Dermatol Venereol. 2014;28(3):333–7.
18. Klemera P, Doubal S. A new approach to the concept and computation of biological age. Mech Ageing Dev. 2006;127(3):240–8.
19. Macit B, Ragi SD, Moseley I, Molino J, McGeary JE, Horvath S, et al. A case-control study: epigenetic age acceleration in psoriasis. Arch Dermatol Res. 2024;316(7):340.
20. Borsky P, Chmelarova M, Fiala Z, Hamakova K, Palicka V, Krejsek J, et al. Aging in psoriasis vulgaris: female patients are epigenetically older than healthy controls. Immun Ageing. 2021;18(1):10.
21. Committee on Psoriasis CSoD. Guideline for the diagnosis and treatment of psoriasis in China(2023 edition) . Chin J Dermatol. 2023;56(07):573–625.
22. Zhan JJ, Hodge RA, Dunlop AL, Lee MM, Bui L, Liang D, et al. Dietaryindex: a user-friendly and versatile R package for standardizing dietary pattern analysis in epidemiological and clinical studies. Am J Clin Nutr. 2024;120(5):1165–74.
23. Kwon D, Belsky DW. A toolkit for quantification of biological age from blood chemistry and organ function test data: BioAge. Geroscience. 2021;43(6):2795–808.
24. Liu Z, Liang Q, Ren Y, Guo C, Ge X, Wang L, et al. Immunosenescence: molecular mechanisms and diseases. Signal Transduct Target Ther. 2023;8(1):200.

25. Levine ME. Modeling the rate of senescence: can estimated biological age predict mortality more accurately than chronological age? J Gerontol A Biol Sci Med Sci. 2013;68(6):667–74.
26. Levine ME, Lu AT, Quach A, Chen BH, Assimes TL, Bandinelli S, et al. An epigenetic biomarker of aging for lifespan and healthspan. Aging (Albany NY). 2018;10(4):573–91.
27. Duan R, Fu Q, Sun Y, Li Q. Epigenetic clock: A promising biomarker and practical tool in aging. Ageing Res Rev. 2022;81:101743.
28. Guo J, Zhang H, Lin W, Lu L, Su J, Chen X. Signaling pathways and targeted therapies for psoriasis. Signal Transduct Target Ther. 2023;8(1):437.
29. Dubey M, Nagarkoti S, Awasthi D, Singh AK, Chandra T, Kumaravelu J, et al. Nitric oxide-mediated apoptosis of neutrophils through caspase-8 and caspase-3-dependent mechanism. Cell Death Dis. 2016;7(9):e2348.
30. Niwa Y, Kasama T, Miyachi Y, Kanoh T. Neutrophil chemotaxis, phagocytosis and parameters of reactive oxygen species in human aging: cross-sectional and longitudinal studies. Life Sci. 1989;44(22):1655–64.
31. Liles WC, Kiener PA, Ledbetter JA, Aruffo A, Klebanoff SJ. Differential expression of Fas (CD95) and Fas ligand on normal human phagocytes: implications for the regulation of apoptosis in neutrophils. J Exp Med. 1996;184(2):429–40.
32. Fulop T, Larbi A, Dupuis G, Le Page A, Frost EH, Cohen AA, et al. Immunosenescence and Inflamm-Aging As Two Sides of the Same Coin: Friends or Foes? Front Immunol. 2017;8:1960.
33. Pawelec G. Age and immunity: What is "immunosenescence"? Exp Gerontol. 2018;105:4–9.
34. Bruunsgaard H, Andersen-Ranberg K, Hjelmborg J, Pedersen BK, Jeune B. Elevated levels of tumor necrosis factor alpha and mortality in centenarians. Am J Med. 2003;115(4):278–83.
35. Puzianowska-Kuznicka M, Owczarz M, Wieczorowska-Tobis K, Nadrowski P, Chudek J, Slusarczyk P, et al. Interleukin-6 and C-reactive protein, successful aging, and mortality: the PolSenior study. Immun Ageing. 2016;13:21.
36. Palmer AK, Gustafson B, Kirkland JL, Smith U. Cellular senescence: at the nexus between ageing and diabetes. Diabetologia. 2019;62(10):1835–41.
37. Armstrong AW, Read C. Pathophysiology, Clinical Presentation, and Treatment of Psoriasis: A Review. JAMA. 2020;323(19):1945–60.
38. Greenberg R, Goldsmith T, Zeltser D, Shapira I, Berliner S, Rogowski O, et al. Comorbidities in patients with palmoplantar plaque psoriasis. J Am Acad Dermatol. 2021;84(3):639–43.
39. Shakeri H, Lemmens K, Gevaert AB, De Meyer GRY, Segers VFM. Cellular senescence links aging and diabetes in cardiovascular disease. Am J Physiol Heart Circ Physiol. 2018;315(3):H448–62.
40. Buerger C, Richter B, Woth K, Salgo R, Malisiewicz B, Diehl S, et al. Interleukin-1beta interferes with epidermal homeostasis through induction of insulin resistance: implications for psoriasis pathogenesis. J Invest Dermatol. 2012;132(9):2206–14.
41. Rohm TV, Meier DT, Olefsky JM, Donath MY. Inflammation in obesity, diabetes, and related disorders. Immunity. 2022;55(1):31–55.
42. Karbach S, Croxford AL, Oelze M, Schuler R, Minwegen D, Wegner J, et al. Interleukin 17 drives vascular inflammation, endothelial dysfunction, and arterial hypertension in psoriasis-like skin disease. Arterioscler Thromb Vasc Biol. 2014;34(12):2658–68.
43. Cao Z, Li Y, Wu J. Causal linkage of psoriasis with ageing: Mendelian randomization and enrichment analysis towards telomere length and psoriasis. Postgrad Med J. 2024. https://doi.org/10.1093/postmj/qgae115.
44. Zhou F, Shen C, Xu J, Gao J, Zheng X, Ko R, et al. Epigenome-wide association data implicates DNA methylation-mediated genetic risk in psoriasis. Clin Epigenetics. 2016;8:131.
45. Horvath S, Raj K. DNA methylation-based biomarkers and the epigenetic clock theory of ageing. Nat Rev Genet. 2018;19(6):371–84.

Publisher's Note