Xu *et al. Alzheimer's Research & Therapy* (2024) 16:245
https://doi.org/10.1186/s13195-024-01611-8

Alzheimer's Research & Therapy

RESEARCH Open Access

Facial aging, cognitive impairment, and dementia risk

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Abstract

Background Facial aging, cognitive impairment, and dementia are all age-related conditions. However, the temporal relation between facial age and future risk of dementia was not systematically examined.

Objectives To investigate the relationship between facial age (both subjective/perceived and objective) and cognitive impairment and/or dementia risk.

Methods The study included 195,329 participants (age ≥ 60 y) from the UK Biobank (UKB) with self-perceived facial age and 612 participants from the Nutrition and Health of Aging Population in China Project (NHAPC) study (age ≥ 56 y) with objective assessment of facial age. Cox proportional hazards model was used to prospectively examine the hazard ratios (HRs) and their 95% confidence intervals (CIs) of self-perceived facial age and dementia risk in the UKB, adjusting for age, sex, education, *APOE* ε4 allele, and other potential confounders. Linear and logistic regressions were performed to examine the cross-sectional association between facial age (perceived and objective) and cognitive impairment in the UKB and NHAPC, with potential confounders adjusted.

Results During a median follow-up of 12.3 years, 5659 dementia cases were identified in the UKB. The fully-adjusted HRs comparing high vs. low perceived facial age were 1.61 (95% CI, 1.33 ~ 1.96) for dementia (*P*-trend ≤ 0.001). Subjective facial age and cognitive impairment was also observed in the UKB. In the NHAPC, facial age, as assessed by three objective wrinkle parameters, was associated with higher odds of cognitive impairment (*P*-trend < 0.05). Specifically, the fully-adjusted OR for cognitive impairment comparing the highest versus the lowest quartiles of crow's feet wrinkles number was 2.48 (95% CI, 1.06 ~ 5.78).

Conclusions High facial age was associated with cognitive impairment, dementia and its subtypes after adjusting for conventional risk factors for dementia. Facial aging may be an indicator of cognitive decline and dementia risk in older adults, which can aid in the early diagnosis and management of age-related conditions.

Keywords Facial age, Dementia, Cognitive impairment

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Introduction

Aging is associated with a decrease in organ function across the body, potentially resulting in cognitive impairment and skin aging. The skin is an organ with a complex network of nerve endings, receptors, and immune cells. Facial aging, a prominent manifestation of this process, is characterized by features such as wrinkling, loss of elasticity, laxity, and a rough-textured appearance [1, 2]. Previous studies indicated that the skin and neurodevelopment shared a developmental origin and genetic susceptibility variants [3], suggesting potential connections between the skin and nervous system. Further, facial skin is unique in its neural crest origin whereas skin at other body sites develops from mesoderm [4]. Some research also showed that lifestyle factors that contributed to skin aging, such as over-exposure to the sun and smoking, could also unfavorably impact cognitive function and dementia risk [5]. Consistent with this notion, previous studies observed the association between perceived age and cognitive functioning [6–8]. However, the temporal relation between facial age and dementia was not systematically examined in these studies. Furthermore, due to the lack of follow-up data for dementia and objective facial measurements, and limited sample size of these studies, further evidence is needed.

We thus examined whether self-perceived facial age was prospectively associated with dementia risk, independent of conventional dementia risk factors in a large-scale UK cohort. We further took advantage of both perceived facial age assessed by a naïve panel of volunteers and objective facial parameters in a Chinese population to study the cross-sectional association between facial age and cognitive impairment.

Methods

Study population

The UK Biobank (UKB) obtained ethical approval from the North West Multi-centre Research Ethics Committee (REC reference: 16/NW/0274) to conduct a large, prospective cohort study with over 500,000 participants aged between 40 and 69 years at baseline, recruited during 2006–2010. All participants provided informed consent through an electronic signature at the outset of the study. More information regarding the UKB can be found at https://www.ukbiobank.ac.uk. For this analysis, 195,329 participants aged 60 y or older, free of dementia at baseline, were included, with exclusions made for those who withdrew from the study, had missing information on facial age, or chose *Do not know* or *Prefer not to answer* related to this question (Figure S1).

We also included participants with objective facial age data from the Nutrition and Health of Aging Population in China Project (NHAPC), a community-based study designed to evaluate the effects of genetic and environmental factors and their interaction on age-related chronic diseases [9]. Briefly, in 2011, 675 out of 866 Shanghai participants, who had not undergone cosmetic surgery, took part in the DXA scan and consented to facial photographs and measurements [10]. The current analysis further excluded 63 participants with unavailable skin measurements and missing data on perceived age, leaving 612 individuals (258 men and 354 women; aged 63 years old on average) (Figure S2). The study protocol was approved by the Institutional Review Board of the Shanghai Institute for Nutritional Sciences, and all participants provided written informed consent.

Assessment of facial age

In the UKB, the definition of self-perceived facial age was derived from the single-choice question (field ID 1757) - *Do people say that you look younger than you are, older than you are, about your age, do not know, and prefer not to answer?* Participants were provided with choices of *Younger than you are*; *Older than you are*; *About your age*; *Do not know*; *Prefer not to answer*. Only those participants who chose *Younger than you are*, *Older than you are*, and *About your age* were included in the analysis.

In the NHAPC, each participant had their photograph taken using a VISIA® CR booth (Canfield, OH, USA), which was connected to a computer system running the Canfield Mirror software, wich was validated previously [11, 12]. Photographs were taken from both the front and a side (45° angle) view. All participants underwent an equilibration period of a least one hour prior to the photograph, with makeup removed using a facial wipe at least 15–20 min prior to the measurements. The images were then presented to a panel of 50 naïve assessors from Shanghai, aged between 20 and 60 years old, who were asked: *How old do you think this person looks*. The mean age estimate for each participant was taken as their perceived age. Previous studies validated that naïve assessors could be used to generate reproducible age assessments, and that gender, age, and expertise of the assessors had little impact when large numbers of assessors were involved [11, 12]. We also included objective facial age indicators, including wrinkles and lines in certain areas (Crow's feet area and cheek area) and instrumental measurements for skin (methods in Supplement 1). In brief, objective facial age was assessed through MATLAB-based image analysis of wrinkles and hyperpigmentation, along with instrumental measurements of skin hydration, transepidermal water loss (TEWL), and elasticity using devices like the Corneometer®, DermaLab®, and Cutometer®.

Covariates assessment

During the baseline assessment, covariates from UKB included demographic data such as age at baseline

(continuous), sex (men; women), ethnicity (white British; others), and education (College or University degree; A levels or equivalent; O levels or equivalent; none of the above); BMI category (<25.0; 25.0-29.9; ≥30.0 kg/m^2); at least one *APOE* ε4 allele (no, yes, missing); CRP (continuous); lifestyle factors including smoking status (current; former; never), alcohol drinker intake (current; previous; never), regular physical activity (no; yes; others), depressive symptoms (no; yes), time spent outdoors in the summer (tertiles), use of sun/UV protection (never/rarely; sometimes; most of the time; always; do not go out in sunshine) and dietary intake; family history of AD (no; yes); and previous diseases, such as cancer at baseline (no; yes), CVD at baseline (no; yes), hypertension at baseline (no; yes), and type 2 diabetes at baseline (no; yes). We further derived chronic disease score and lifestyle score (methods in Supplement 1, Table S2). Details of covariates used in the UKB and NHAPC were shown in the methods in Supplement 1.

Identification of primary outcome – dementia

Dementia cases were detected from the UKB using mainly hospital inpatient records and death registry data for dementia, and classified based on the ICD coding system (Table S1). Our analysis also included the identification of dementia subtypes, including Alzheimer's disease (AD), vascular dementia (VaD), and other and unspecified dementia cases (Table S1). The accuracy of codes for identifying persons with dementia and dementia subtypes by hospital admissions and mortality data in combination was validated in a subset of participants (around 17,000) through clinical expert adjudication according to full-text medical record, with positive predictive values of 84.5% for total dementia, 71.4% for AD, and 43.8% for VaD [13].

Identification of secondary outcome – cognitive function

Between 2014 and 2015, participants in the UKB who completed the baseline assessment (between 2006 and 2010) were invited via e-mail to participate in a web-based questionnaire. The questionnaire included web-based versions of two widely recognized cognitive tasks: the Trail-Making Test A/B (TMTA and TMTB), which measured processing speed and speed/executive function, respectively, and the Digit Symbol Substitution Test (DSST), which measured executive function. We used DSST, TMTA, and TMTB as the main endpoints, and further selected reaction time, and fluid intelligence as subordinate endpoints from the UKB cognitive battery validated by previous study [14, 15] (Table S3). Reaction time and fluid intelligence were measured at baseline (2006–2010), and then selectively reassessed in a subset of participants at subsequent intervals: during the first repeat assessment (2012-13), imaging visit (initiated in 2014), and the first repeat imaging visit (initiated in 2019). The analytical samples for each cognitive outcome varied due to the availability of data from participants (methods in Supplement 1).

For the NHAPC, cognitive function was measured in 2011 with the Chinese version of the Mini-Mental State Examination (MMSE), validated and widely used in prior studies [16, 17]. The MMSE is a 30-point questionnaire used extensively in clinical and research settings to measure global cognitive function and participants with a total score of ≤24 were defined as having cognitive impairment [16, 17].

Statistical analysis

Person-time was calculated from baseline to the occurrence of study outcomes in the UKB, death from any non-dementia cause, or the end of follow-up (September 30, 2021 (England), July 31, 2021 (Scotland), and February 28, 2018 (Wales))—whichever came first. Death from any non-dementia cause, as obtained from the death registry data, was treated as a censoring event. Cox proportional hazards models were applied to examine the associations of facial age with risk of dementia. The results were reported as hazard ratios (HRs) with 95% confidence intervals (CIs), adjusting for the covariates in the full model: age at entry, sex, ethnicity, smoking status, BMI category, alcohol drinker status, education, regular physical activity, family history of AD, at least one *APOE* ε4 allele, cancer, CVD, hypertension, type 2 diabetes, CRP, depressive symptoms, time spent outdoors in the summer, and use of sun/UV protection. Three variables (e.g., regular physical activity, at least one *APOE* ε4 allele, and depressive symptoms; all categorial variable) had missing rate≥5%, we assigned missing data to an independent category for each variable; otherwise, missing data were coded with median values for continuous variables or mode values for categorical variables. Detailed information on missing covariates could be seen in Table S4.

We assigned 1 for *Younger than your age*, 2 for *About your age*, and 3 for *Older than your age* within the category of facial age to test for linear trends. We assessed the proportional hazard assumption of all models and no significant violations were found by Schoenfeld residuals. Both linear regression model and mixed model were used to examine the association between facial age and cognitive function outcomes in UKB (methods in Supplement 1).

For the cognitive function outcome, we first examined the association between facial age and primary cognitive tests (DSST, TMTA, and TMTB) or secondary cognitive tests (reaction time and fluid intelligence score) from the UKB via linear regression model, adjusting for the aforementioned covariates in the full model. To take advantage of repeated assessment of subordinate cognitive

tests (reaction time and fluid intelligence score) among a subset (around 10%) of participants with corresponding cognitive test from the UKB, we further used a linear mixed model with unstructured covariance by setting individual ID as a random intercept, a random slope for instance time (years), and facial age measures × instance time as an interaction term besides other covariates adjusted in the full model as fixed effect to examine the annual change of reaction time or fluid intelligence score according to baseline facial age.

We used logistic regression models to calculate the adjusted odds ratios (ORs) and 95% CIs for cognitive impairment across perceived facial age and objective skin measurements in NHAPC. When examining the effect of perceived facial age, the independent variable was defined as the difference between perceived facial age and chronological age. The objective skin measurements were divided into categorical variables based on quartiles and *P* for trend tests were performed by treating quartiles as continuous variables in the regression models. All of the models adjusted for the same covariates in the full model (methods in Supplement 1).

Stratified analyses were performed in the UKB for all the covariates in the full model. We employed a likelihood-ratio test to assess the statistical significance of interactions, comparing models with and without cross-product terms between facial age and the stratifying variables. The false discovery rate (FDR) was applied in multiple testing in the stratified analysis [18].

To test the robustness of our results, we conducted several sensitivity analyses: (1) a lag analysis by excluding dementia cases with onset during the first 5 years of follow-up to account for the potential reverse causation; (2) exclusion of cancer and CVD at baseline to reduce the influence of chronic diseases on dementia risk; (3) exclusion of neurological conditions (ICD10, G00-G99; e.g., Parkinson's disease) at baseline to minimize diagnostic bias; (4) further adjustments for the overall health rating to minimize the confounding; (5) exclusion of participants within the lowest 10th percentile of the two cognitive tests (reaction time and fluid intelligence score), who might be at risk of mild cognitive impairment, to minimize the potential reversal causality; (6) using the Fine and Gray competing risk model to account for the competing events regarding death from non-dementia causes; and (7) further adjustments for the traumatic brain injury and hearing impairment. We also employed multiple imputations with chained equations to estimate missing values for covariates, thereby assessing the impact of missing data on our analysis. All statistical analyses were performed using R version 3.6.3. A two-sided $P<0.05$ was considered to be statistically significant.

Results

Characteristics of the participants

Among the UKB participants, the mean age was 64.1±2.86 y and 52.5% were women. Those who chose *Older than your age* tended to be men, current smokers, less likely to do regular physical activity, and had higher prevalence of depressive symptom and comorbidities compared with those who chose *Younger than your age* (Table 1). The mean age of participants in the NHAPC was 63.0±5.53 y (57.8% women) and 23.4% of participants were identified with cognitive impairment by MMSE. Demographic characteristics according to perceived age were shown in Table S5.

Perceived facial age and dementia

During a median follow-up of 12.3 years, 5659 dementia cases and 19,301 deaths from non-dementia cause were identified. Compared with those who chose *Younger than your age* regarding the facial age question, the fully-adjusted hazard ratios for participants who chose *Older than your age* were 1.61 (95% CI, 1.33 ~ 1.96) for dementia, 1.23 (95% CI, 0.87 ~ 1.75) for AD, 1.55 (95% CI, 1.06 ~ 2.28) for VaD, and 1.74 (95% CI, 1.40 ~ 2.18) for other and unspecified dementia in the full model (all *P*-trend ≤ 0.001) (Table 2). The associations persisted in the subgroup analysis by sex, education, lifestyle factors, comorbidities, *APOE* ε4 allele, and family history of AD (*P*-interaction > 0.05 for all after FDR correction), except for BMI, AD-PRS, and time spent in the summer (Table S6). Stratified analyses suggested that the associations were more pronounced in people whose BMI was over 30 kg/m^2, who spent more time outdoors in summer, and who had higher polygenic risk scores for AD (*P*-interaction < 0.05 after FDR correction). The sensitivity analyses showed consistent results (Table S7-S9).

Perceived facial age and cognitive function in the UKB

The primary cognitive measurement was the DSST, which was available for 42,639 participants. These participants were better educated than participants who did not complete the DSST (Table S10). The difference in the DSST score was −0.69 (95% CI, -1.12 ~ -0.26) comparing two extreme perceived facial age groups, after adjusting for all covariates in the full model (*P*-trend < 0.001) (Table 3). Similar significant findings were found for the TMTA and TMTB outcomes (executive function/processing tests) (Table 3). The difference in the reaction time was 15.5 (95% CI, 10.5 ~ 20.6) comparing two extreme perceived facial age groups, after adjusting for all covariates in the full model (*P*-trend < 0.001) (Table 3). Among the participants with repeated information, people who chose *About your age* had 1.95 (95% CI, 0.50 to 2.40) milliseconds longer per increasing year than people who chose *Younger than your age* (Table S11). We did not

Table 1 Baseline characteristics of participants according to facial age status

	Younger than your age (*N* = 147,835)	About your age (*N* = 45,242)	Older than your age (*N* = 2252)	Overall (*N* = 195,329)	*P* value
Age					
Mean (SD)	64.1 (2.89)	64.1 (2.76)	63.7 (2.70)	64.1 (2.86)	< 0.001
White British, n (%)	134,979 (91.3)	42,065 (93.0)	1970 (87.5)	179,014 (91.6)	< 0.001
Women, n (%)	80,288 (54.3)	21,621 (47.8)	661 (29.4)	102,570 (52.5)	< 0.001
Smoking					< 0.001
Current	11,255 (7.6)	4148 (9.2)	349 (15.5)	15,752 (8.1)	
Past	61,164 (41.4)	19,107 (42.2)	1013 (45.0)	81,284 (41.6)	
Never	75,416 (51.0)	21,987 (48.6)	890(39.5)	98,293 (50.4)	
Education level					< 0.001
College or University degree	38,696 (26.2)	11,283 (24.9)	576 (25.6)	50,555 (25.9)	
A levels or equivalent	34,496 (23.3)	10,266 (22.7)	485 (21.5)	45,247 (23.2)	
O levels or equivalent	34,603 (23.4)	9931 (22.0)	427 (19.0)	44,961 (23.0)	
None of the above; NA	40,040 (27.1)	13,762 (30.4)	764 (33.9)	54,566 (27.9)	
Alcohol intake					< 0.001
Current	135,927 (91.9)	40,986 (90.6)	1910 (84.8)	178,823 (91.5)	
Previous	5271 (3.6)	1887 (4.2)	161 (7.1)	7319 (3.7)	
Never	6637 (4.5)	2369 (5.2)	181 (8.0)	9187 (4.7%)	
Regular physical activity[a]					< 0.001
No	40,723 (27.5)	14,102 (31.2)	836 (37.1)	55,661 (28.5)	
Yes	83,702 (56.6)	23,951 (52.9)	1009 (44.8)	108,662 (55.6)	
Missing	23,410 (15.8)	7189 (15.9)	407 (18.1)	31,006 (15.9)	
Positive family history of AD, n (%)	22,271 (15.1)	6849 (15.1)	314 (13.9)	29,434 (15.1)	0.301
Time spent outdoors summer, hour	4.23 (2.30)	4.18 (2.29)	4.07 (2.52)	4.21 (2.30)	< 0.001
Depressive symptoms[b]					< 0.001
No	133,690 (90.4)	40,712 (90.0)	1862 (82.7)	176,264 (90.2)	
Yes	5613 (3.8)	1722 (3.8)	191 (8.5)	7526 (3.9)	
Missing	8532 (5.8)	2808 (6.2)	199 (8.8)	11,539 (5.9)	
At least one *APOE* ε4 allele					< 0.001
No	87,887 (59.4)	26,465 (58.5)	1258 (55.9)	115,610 (59.2)	
Yes	34,532 (23.4)	10,478 (23.2)	531 (23.6)	45,541 (23.3)	
Missing	25,416 (17.2)	8299 (18.3)	463 (20.6)	34,178 (17.5)	
BMI, kg/m^2	27.5 (4.45)	27.8 (4.65)	28.3 (5.20)	27.6 (4.51)	< 0.001
Cancer at baseline, n (%)	15,179 (10.3)	5991 (13.2)	493 (21.9)	21,663 (11.1)	0.016
CVD at baseline, n (%)	20,408 (13.8)	6467 (14.3)	333 (14.8)	27,208 (13.9)	< 0.001
T2DM at baseline, n (%)	9340 (6.3)	3191 (7.1)	252 (11.2)	12,783 (6.5)	< 0.001
Hypertension at baseline, n (%)	58,362 (39.5)	19,155 (42.3)	1133 (50.3)	78,650 (40.3)	< 0.001
CRP, mg/L	2.69 (4.38)	2.91 (4.92)	3.18 (5.03)	2.75 (4.52)	< 0.001
Use of sun/UV protection					< 0.001
never/rarely	15,005 (10.1)	4981 (11.0)	432 (19.2)	20,418 (10.5)	
sometimes	49,651 (33.6)	16,275 (36.0)	792 (35.1)	66,718 (34.2)	
most of the time	49,975 (33.8)	15,225 (33.7)	615 (27.3)	65,815 (33.7)	
always	32,354 (21.9)	8445 (18.7)	378 (16.8)	41,177 (21.1)	
do not go out in sunshine	850 (0.6)	316 (0.7)	35 (1.6)	1201 (0.6)	

Abbreviations SD = standard deviation; NA = not applicable; BMI = body mass index; CVD = cardiovascular disease; T2DM = type 2 diabetes mellitus; CRP = C-reactive protein. Values are means (SD) for continuous variables or percentages for categorical variables (the sum may not equal 100 due to rounding)

[a] Regular physical activity was identified as at least 150 min/week of moderate activity or 75 min/week of vigorous activity (or equivalent combination)

[b] Depressive symptom was identified by the Patient Health Questionaire-2 (PHQ-2); a score of 3 or more was indicative of possible depressive symptoms

Table 2 Hazard ratio and 95% confident intervals for dementia and its subtypes, according to the facial age status

	Cases/person years	Model 1[a]	*P* value	Model 2[b]	*P* value
Dementia					
younger than your age (ref.)	4088/1,760,025	1 (ref.)		1 (ref.)	
about age	1466/530,949	1.21(1.14 ~ 1.28)	< 0.001	1.16(1.09 ~ 1.23)	< 0.001
older than your age	105/25,424	1.97(1.62 ~ 2.39)	< 0.001	1.61(1.33 ~ 1.96)	< 0.001
P trend			< 0.001		< 0.001
Alzheimer's Disease					
younger than your age (ref.)	1762/1,765,141	1 (ref.)		1 (ref.)	
about age	635/532,763	1.22(1.11 ~ 1.34)	< 0.001	1.19(1.09 ~ 1.31)	< 0.001
older than your age	32/25,592	1.43(1.01 ~ 2.04)	0.04	1.23(0.87 ~ 1.75)	0.24
P trend			< 0.001		< 0.001
Vascular Dementia					
younger than your age (ref.)	951/1,767,045	1 (ref.)		1 (ref.)	
about age	358/533,458	1.26(1.11 ~ 1.42)	< 0.001	1.17(1.04 ~ 1.33)	0.01
older than your age	27/25,601	2.12(1.45 ~ 3.12)	< 0.001	1.55(1.06 ~ 2.28)	0.03
P trend			< 0.001		0.001
Other and unspecified dementia					
younger than your age (ref.)	2862/1,763,301	1 (ref.)		1 (ref.)	
about age	1034/532,190	1.21(1.13 ~ 1.30)	< 0.001	1.16(1.08 ~ 1.25)	< 0.001
older than your age	81/25,506	2.16(1.73 ~ 2.69)	< 0.001	1.74(1.40 ~ 2.18)	< 0.001
P trend			< 0.001		< 0.001

[a] Model 1 was adjusted for age (years), and sex (women; men)

[b] Model 2 was additionally adjusted for ethnicity (white British; others), smoking status (current; former; never), body mass index category (< 25.0; 25.0-29.9; ≥30.0 kg/m^2), alcohol intake (current; previous; never), education (College or University degree; A levels or equivalent; O levels or equivalent; None of the above), regular physical activity (no; yes; others), family history of AD (no; yes), at least one *APOE* ε4 allele (no, yes, missing), cancer at baseline (no; yes), CVD at baseline (no; yes), hypertension at baseline (no; yes), type 2 diabetes at baseline (no; yes), C-reactive protein, depressive symptom (no; yes), time spent outdoors in the summer (tertiles) and use of sun/UV protection (never/rarely; sometimes; most of the time; always; do not go out in sunshine) on the basis of the covariates adjusted in the Model 1

find the cross-sectional association between facial age and fluid intelligence score.

Facial age and cognitive impairment in the NHAPC

Consistent with the result of the UKB data, we observed a significant positive association of the difference between perceived facial age and chronologic age with odds of cognitive impairment (adjusted OR for 1 year difference = 1.10; 95% CI, 1.01 ~ 1.19) in the NHAPC population. Regarding objective skin measurements, the facial wrinkle in the crow's feet area was significantly associated with cognitive impairment. The adjusted OR for cognitive impairment comparing the highest versus the lowest quartiles of crow's feet wrinkles number was 2.48 (95% CI, 1.06 ~ 5.78) (*P*-trend < 0.05) (Table 4). Higher intensity of crow's feet wrinkles and higher contrast of crow's feet wrinkles were also significantly associated with higher odds of cognitive impairment (both *P*-trend < 0.05) (Table 4). We found the same result in the analysis stratified by sex (Table S12).

Discussion

We found that high perceived facial age was associated with high risk of cognitive impairment and incident dementia, including AD, VaD, and other and unspecified dementia, independent of conventional risk factors of dementia. We further used the NHAPC as our validation cohort which provided evidence to support this observation by using objective measurement of facial age.

Our findings on facial age and risk of cognitive impairment and dementia were consistent with previous studies [7, 8]. The construct validity regarding perceived facial age assessed by a panel of assessors was substantiated in previous study [11]. Subsequent studies have extensively employed perceived facial age via this method to examine its significant correlation with skin characteristics [12], health status, age-related morbidities (for example, osteoporosis, hearing loss, cataracts, and so on) [8], and mortality [6]. A systematic review suggested that perceived facial age, including evaluations of facial wrinkling face-to-face, or photoaging alongside perceived age derived from standardized criteria or objective photographic analyses, could be as a useful predictor for a range of functional and molecular aging phenotypes, overall mortality, and comorbidities such as cardiovascular, pulmonary, and osseous conditions [19]. However, most studies were limited with follow-up time and sample size to identify dementia, and used perceived facial age, which was a crude measure and prone to misclassification, especially in studies limited with sample size. Our result therefore prospectively examined the temporal relation between self-reported perceived facial age and future dementia risk, together with these earlier studies, further strengthening the notion that facial age

Table 3 Association of facial age with cognitive test performance in the UK Biobank

		Full model[a]	*P* value
Main endpoints	Digit symbol substitution test (No. correct) (*n* = 42,639)		
	younger than your age (ref.)	1 (ref.)	
	about age	-0.15(-0.26~-0.05)	0.01
	older than your age	-0.69(-1.12~-0.26)	< 0.001
	P trend		< 0.001
	Trail making test A (time, seconds) (*n* = 36,181)		
	younger than your age (ref.)	1 (ref.)	
	about age	1.12(0.71 ~ 1.52)	< 0.001
	older than your age	0.83(-0.82 ~ 2.48)	0.32
	P trend		< 0.001
	Trail making test B (time, seconds) (*n* = 42,639)		
	younger than your age (ref.)	1 (ref.)	
	about age	1.35(0.68 ~ 2.03)	< 0.001
	older than your age	1.50(-1.25 ~ 4.25)	0.29
	P trend		< 0.001
Subordinate endpoints	Reaction time (time, milliseconds) (*n* = 193,178)		
	younger than your age (ref.)	0 (ref.)	
	about age	8.15 (6.88 ~ 9.42)	< 0.001
	older than your age	15.5 (10.5 ~ 20.6)	< 0.001
	P trend		< 0.001
	Fluid Intelligence score (*n* = 16,068)		
	younger than your age (ref.)	0 (ref.)	
	about age	-0.01 (-0.08 ~ 0.06)	0.28
	older than your age	-0.08 (-0.40 ~ 0.24)	0.46
	P trend		0.71

[a] Full model was adjusted for age (years), sex (women; men), smoking status (current; former; never), ethnicity (white British; others), body mass index category (< 25.0; 25.0-29.9; ≥30.0 kg/m^2), alcohol intake (current; previous; never), education (College or University degree; A levels or equivalent; O levels or equivalent; None of the above), regular physical activity (no; yes; others), family history of AD (no; yes), at least one *APOE* ε4 allele (no, yes, missing), cancer at baseline (no; yes), cardiovascular diseases at baseline (no; yes), hypertension at baseline (no; yes), type 2 diabetes at baseline (no; yes), C-reactive protein, depressive symptom (no; yes), time spent outdoors in the summer (tertiles) and use of sun/UV protection (never/rarely; sometimes; most of the time; always; do not go out in sunshine)

Table 4 Odds ratio and 95% confidence interval of cognitive impairment according to objective skin variables in the NHAPC study[a]

Skin variables		Odds ratio for cognitive impairment					
		Q1	Q2	Q3	Q4	*P*-trend	FDR *P*-trend
Crow's feet area	Wrinkle intensity	1 (ref.)	1.26 (0.61, 2.60)	1.90 (0.90, 3.99)	2.09 (0.91, 4.80)	0.04	0.15
	Total number of wrinkles and lines	1 (ref.)	1.43 (0.72, 2.86)	2.07 (1.02, 4.19)	2.48 (1.06, 5.78)	0.02	0.10
	Line wrinkle contrast weighted average	1 (ref.)	1.15 (0.56, 2.38)	2.47 (1.23, 4.97)	2.13 (0.97, 4.68)	0.01	0.10
Cheek area	Wrinkle intensity	1 (ref.)	0.69 (0.34, 1.39)	1.35 (0.65, 2.75)	0.88 (0.41, 1.88)	0.75	0.73
	Total number of wrinkles and lines	1 (ref.)	0.77 (0.39, 1.53)	1.09 (0.54, 2.21)	1.01 (0.47, 2.16)	0.70	0.73
	Line wrinkle contrast weighted average	1 (ref.)	0.82 (0.43, 1.55)	1.09 (0.57, 2.09)	0.70 (0.35, 1.42)	0.53	0.69
Instrumental measurements [b]	TEWL	1 (ref.)	1.23 (0.64, 2.34)	0.91 (0.45, 1.86)	1.75 (0.75, 4.06)	0.39	0.61
	R2	1 (ref.)	1.20 (0.57, 2.56)	1.74 (0.84, 3.58)	1.32 (0.63, 2.77)	0.37	0.61
	R6	1 (ref.)	1.16 (0.59, 2.27)	0.73 (0.37, 1.45)	0.89 (0.43, 1.83)	0.42	0.61
	Skin hydration and skin barrier function	1 (ref.)	0.95 (0.53, 1.70)	0.51 (0.26, 1.00)	0.66 (0.33, 1.32)	0.09	0.22

Abbreviations TEWL = transepidermal water loss, R2: ratio of total reversible recovery, R6: ratio of elastic deformation and inelastic deformation

[a] Adjusted for age, sex (men; women), education level (primary school or below; middle school; college or above), current smoker (no; yes), current drinker (no; yes), physical activity (high, moderate, or low), cardiovascular diseases history (no; yes), cancer history (no; yes), hypertension (no; yes), diabetes history (no; yes), body mass index (BMI, < 18.5;18.5–24.0; ≥24.0 kg/m^2), C-reactive protein (CRP, quartiles), depressive symptom (no; yes), sun exposure (< 0.5; 0.5-2; 2–4; ≥ 4 h/d), and sun screen (never; occasionally; often)

[b] TEWL was measured to assess the rate of water loss through the skin, an indication of barrier function, a lower value indicating better skin health. Skin hydration was the measurement of the outer layer of the epidermis (stratum corneum), a higher value is an indicator of better skin barrier function. Skin elasticity was measured by two parameters, and the ratio of total reversible recovery (R2) and the ratio of elastic deformation and inelastic deformation (R6) were the indicators of gross elasticity, the closer to 1 the more elastic

(both subjective/perceived or objective) could be a useful indicator or research tool that could uncover a significant aging-dementia link from the public health perspective, providing insight into the influence of biological mechanisms and risk factors on tissue aging. Moreover, the associations between facial age and AD or VaD remained significantly, and were relatively comparable effect sizes with well-estiblished risk factors (e.g., hearing loss, air pollution, physical inactivity, and use of alcohol and smoking; HRs for dementia ranged from 1.1 to 1.9, based on a recently published review [20]. Given advances in artificial intelligence (AI) for predicting perceived facial age from images that was demonstrated to be the marker of biological age [21], the potential of perceived facial age as a diagnostic tool is noteworthy. The application of facial age could facilitate large-scale cohort study and early detection of dementia through mass screenings or health programs, although its clinical value remains to be established.

GWAS studies on self-reported facial age within UKB identified variants related to cell signaling pathways (e.g., *NEK6* and *SMAD2* subnetworks) and pigmentation (e.g., *MC1R* gene), suggesting perceived age might be a proxy trait for age-related diseases [22, 23]. Previous study also reported genetic correlations with perceived facial age assessed from front and side facial images by a panel of assessors, revealing that *MC1R* gene variants, critical in pigmentation, are significantly linked to how old individuals appear, independent of wrinkling, skin color, or sun exposure, with the *MC1R* variant's influence potentially aging individuals' appearance by up to two years [24]. Thus, although the self-perceived facial age in the UKB was subjective and likely a variable phenotype across participants, evidence emerged that analyzing a large number of participants allowed for the detection of certain biological aspects of aging.

Among specific objective measurements, we found that wrinkles in the crow's feet area appeared to have stronger association, relative to other skin features (e.g., xerosis and slackness), with cognitive impairment. Previous studies had reported that wrinkles in the crow's feet area increased with chronological age, and this area was considered the most representative site to evaluate wrinkles [12, 25]. Mayes AE et al., found stronger relationships of perceived facial age with wrinkles and hyperpigmentation compared with skin hydration and TEWL in women, providing evidence that wrinkles may be an important indicator of facial aging for older adults [12]. However, Umeda-Kameyama et al., found that lower half of faces showed better discrimination in dementia by AI than upper half of faces with neutral expression in Japanese participants [26].

Overall, facial aging and cognitive impairment are both complex processes influenced by a variety of biological, genetic, and environmental factors (smoking, sun exposure, and low socioeconomic status) [27, 28]. Participants from prior study exhibited a notably stronger correlation between MMSE and perceived age than with chronological age [7]. Previous animal studies suggested that skin aging induced by ultraviolet could affect neuroimmune system, microglial dysfunction and cognitive impairment [29]. Telomere status could be another underlying pathway in the association between facial age and dementia [30].

Among stratified analysis, the association might be more pronounced in people who had high BMI, spent more time outdoors in summer and had higher AD polygenic risk score. Unstable BMI and excess sunlight exposure are associated with a higher risk of facial aging [31] and dementia [32, 33]. The association between facial age and dementia was prominent in the participants who were more susceptible to AD risk. However, we cannot exclude the possibility of chance finding. Further studies are needed to replicate our observations. Regarding different cognitive domains, we observed a significant association between facial age and poor executive function, slow processing speed but not intelligence. This could be due to ceiling effects, considering participants in the UKB were more likely to be white British, well-educated, women, and from more affluent areas where rates of smoking and alcohol drinking were lower compared to the general UK population, which could cause healthy volunteer bias [34]. Participants who finished the DSST test tended to be higher-educated than those who did not.

The main strengths of the analysis included large sample size, considerate facial age features, both global and domain-specific cognitive function measurements and prospective design, and validation in an independent cohort with objective measurement. This study had several limitations. Firstly, the definition of facial age collected from the questionnaire was subjective which would introduce misclassification and might attenuate the association towards none, although the NHAPC study utilized both perceived facial age validated by previous study [11] and objective facial morphology measurements and yielded similar results. Secondly, dementia and dementia subtypes identified through hospitalization and mortality data could be underestimated, though research confirmed high level of concordances between dementia or AD identified from hospital data and death registry and diagnosis from clinical expert adjudication of the medical record [13]. Notably, the majority of total dementia cases, which were non-AD and non-VaD (most were unspecified dementia), account for more than 50%, and together with the observed overlap among these subtypes (AD, VaD, and unspecified dementia), suggesting a misclassification bias concerning dementia subtypes.

This concern extended to the ascertainment of different subtypes of dementia and we should focuse on total dementia when interpreting the results. Thirdly, the reversal causality could not be ruled out because of the cross-sectional study design of the NHAPC study, and the fact that participants with mild cognitive dysfunction in the UKB were not excluded. Furthermore, for the NHAPC, given the relatively small sample size (n=612) and the nature of our study as a supplementary validation to the UKB, we opted not to apply rigorous multiple testing corrections to avoid overly conservative results; however, we acknowledged that this decision might impact the interpretation of significance, and future research with larger sample sizes should implement such corrections to validate our findings. However, participants tended to be healthier and have higher health consciousness [34] and further adjustment for sunscreen use and the overall self-rating health score and excluding those with low cognitive test scores at the baseline did not change results materially, suggesting that the potential impact of reversal causality could be low-to-modest. Finally, although considerate confounders were adjusted in the model, there might still be other unmeasured factors, such as aesthetic procedure or regular skin treatments, which could lead to residual confounding.

Conclusions

Among people at older ages, low self-perceived facial age was prospectively associated with lower risk of dementia in the UKB. Additionally, objective skin features and perceived age based on assessors were also cross-sectionally associated with cognitive impairment in the NHAPC. Facial age (both subjective/perceived and objective) could serve as an indicator and applied into screening strategies for identifying and treating risk population of cognitive decline or dementia in early intervention for older adults. Further investigations regarding objective facial age or facial skin parameters and dementia risk are warranted and new tools in early detection of dementia through faces should be developed.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s13195-024-01611-8.

Supplementary Material 1

Acknowledgements

The authors are thankful to the participants and staff of the UK Biobank and the Nutrition and Health of Aging Population in China study for their valuable contributions. This research has been conducted using the UK Biobank resource under application number 96083.

Author contributions

LS, XL, and XG had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. XX and GJ contributed equally. LS, XL, and XG are joint corresponding authors. All authors reviewed and revised the manuscript and approved the final submitted version and had final responsibility for the decision of submission. LS, XL and XG were the guarantors. The corresponding author (XG) attests that all listed authors have met authorship criteria and that no others meeting the criteria have been omitted. Concept and design: All authors. Acquisition, analysis, or interpretation of data: XX and GJ Drafting the manuscript: XX Review: DAG, XG, YL, XC, YL, YG, YM, JW, SW Statistical analysis: XX Supervision: LS, XL, and XG.

Funding

This study was supported by grants from Strategic Priority CAS Project (XDB38010300), Shanghai Municipal Science and Technology Major Project (2017SHZDZX01), the National Natural Science Foundation of China (81970684), and the Startup grant at Fudan University (JIF201036Y).

Data availability

The NHAPC datasets used in the current study are not publicly available due to ethics restrictions, but are available from the corresponding author on reasonable request. UK Biobank data are available online at http://www.ukbiobank.ac.uk. Local IRB approval was not necessary for analyzing data from UK Biobank study because the data were received de-identified.

Declarations

Ethical approval

The North West Multi-centre Research Ethics Committee granted UK Biobank its ethical approval (REC reference: 11/NW/03820). Before being included in the study, all participants gave written informed consent before enrollment in the study, which was conducted in accordance with the principles of the Declaration of Helsinki. The NHAPC study was approved by the Institutional Review Board of the Institute for Nutritional Sciences, Chinese Academy of Sciences.

Data sharing statement

The NHAPC datasets used in the current study are not publicly available due to ethics restrictions, but are available from the corresponding author on reasonable request. UK Biobank data are available online at http://www.ukbiobank.ac.uk. Local IRB approval was not necessary for analyzing data from UK Biobank study because the data were received de-identified.

Role of the funders/sponsor

The funding agencies had no role in study design, data collection and analysis, the decision to publish, or preparation of the manuscript.

Competing interests

Authors DAG and XLG are employed by Unilever and were involved in the design of NHAPC and reviewed this manuscript; they were not involved in the UK biobank design. All other authors declare no competing interests.

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Received: 11 July 2024 / Accepted: 28 October 2024
Published online: 06 November 2024

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