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Skin advanced glycation end-products do not predict pulmonary function trajectories in adults from the ILERVAS cohort

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Advanced glycation end-products (AGEs) activate specific receptors (RAGE) promoting inflammation and oxidative stress. The lungs, with high RAGE expression, may be particularly susceptible to AGE-related injury. This study assessed whether baseline skin AGE levels, measured by skin autofluorescence (SAF), predict pulmonary function decline in middle-aged adults with cardiovascular risk factors. This ancillary analysis of the ILERVAS cohort included adults aged 45–70 years with cardiovascular risk factors but without diabetes or chronic kidney disease. Baseline data included demographics, lifestyle, and fasting blood tests. SAF was measured using AGE Reader™, and spirometry performed at baseline and after a median follow-up of 4 years. Associations between baseline SAF and annual declines in FEV_1, FVC, and FEV_1/FVC were analysed using adjusted models and generalized additive models, stratified by smoking status. Among 658 participants (median age 56 years, 48% female), median baseline SAF was 1.90 AU [1.60; 2.20]. Baseline lung function was preserved, with median FEV_1, FVC and FEV_1/FVC of 2795 mL [2270; 3,341], 3,525 mL [2870; 4300], and 78.6% [74.4; 82.8]. Annual declines were − 81.9 mL [− 120.6; − 43.3] for FEV_1, − 99.6 mL [− 159.3; − 37.9] for FVC, and − 0.04% [− 0.85; 0.70] for FEV_1/FVC. No significant associations were found between SAF and spirometry changes. Results were consistent across smoking subgroups. Baseline skin AGE levels did not predict pulmonary function decline over four years in middle-aged adults with cardiovascular risk factors. While SAF reflects cumulative AGE exposure, it has limited prognostic value for lung function in this population.

Keywords Advanced glycation end-products (AGEs), Skin autofluorescence (SAF), Lung function decline, Cardiovascular risk

Advanced glycation end-products (AGEs) are a diverse group of molecules formed through the non-enzymatic glycation of proteins, lipids, and nucleic acids[1]. These can originate endogenously from physiological or pathological conditions such as oxidative stress, inflammation, or hyperglycemia in diabetes[2,3]. Alternatively, exogenous sources include an inadequate diet[4] and toxic habits like smoking[5]. While intracellular AGEs can accumulate and damage organelles such as mitochondria and the endoplasmic reticulum[6], extracellular AGEs

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circulate in the bloodstream before renal excretion[7] or accumulate in the extracellular matrix of tissues, impairing proteins like laminin, elastin, and collagen[6,8]. The overall accumulation of AGEs can result from the interplay of diet and habits, the aging process, and concurrent conditions like diabetes, which leads to endogenous overproduction, and chronic kidney disease (CKD), where accumulation is due to increased synthesis or decreased excretion resulting from impaired glomerular filtration or tubular function[9].

Extracellular AGEs can bind to pro-inflammatory cell membrane receptors for advanced glycated end products (RAGEs), a multi-ligand protein. This binding triggers a cascade involving the activation of nuclear factor-kB (NF-kB), leading to oxidative stress, inflammation, cellular damage, and apoptosis[7].

Although AGEs can be assessed in different biological fluids and tissues, the measurement of skin AGEs by means of autofluorescence (SAF) is considered and easy-to-measure and reliable indicator of the body's overall AGEs burden[10]. The burden of skin AGEs reflects both endogenous production and exogenous intake, and it has been correlated with lifestyle factors such as diet, smoking, and physical activity in individuals without diabetes or CKD[11–14].

RAGEs are widely distributed throughout the body, but their expression is particularly high in the lungs[15], suggesting a significant role in this organ. Indeed, AGEs and RAGEs, and their interaction, are implicated in the pathophysiology of lung conditions such as idiopathic pulmonary fibrosis[16] and chronic obstructive pulmonary disease (COPD)[17,18]. Given this established role in advanced lung pathology, it is crucial to determine if systemic AGE accumulation also drives the initial acceleration of lung function decline in at-risk individuals, potentially serving as an early prognostic marker before the onset of overt pulmonary disease. Numerous cross-sectional studies have reported an association between skin AGEs burden and impaired pulmonary function in both diabetic and non-diabetic subjects[19–21]. However, there is a notable absence of prospective studies in middle-aged adults without diabetes or CKD that assess the prognostic value of skin AGEs in relation to changes in lung function over time. Therefore, our objective was to prospectively evaluate the relationship between baseline skin AGEs burden and the observed lung function decline in four years of follow-up in a middle-aged adult population free from diabetes and CKD.

Methods

This is an ancillary study of the ILERVAS study (ClinTrials.gov Identifier NCT03228459)[22], in which the recruitment criteria were subjects aged between 45 to 70 years old, no history of cardiovascular disease and at least one cardiovascular risk factor such as dyslipidemia, hypertension, obesity (BMI ≥ 30 kg/m^2), smoking habit or having a first relative with premature cardiovascular disease. Those with a prior diagnosis of diabetes or with a glycated hemoglobin ≥ 6.5% and those with CKD, defined as a Glomerular filtration rate GFR < 60 ml/min/1.73 m^2 calculated through the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula (CKD-EPI), were excluded. The subjects included for the present study were recruited between 2016 and 2018. All of them underwent a baseline clinical assessment recording sociodemographic variables such as age and gender, anthropometric variables such as weight, height, body mass index (BMI) and abdominal perimeter (in centimeters). Smoking was collected as the current smoking status (never, former, current) and current pack-years. The 14-item Mediterranean Diet Adherence Screener (MEDAS), developed in the PREDIMED trial[23], was used to estimate the adherence to Mediterranean diet. Physical activity was assessed using the Spanish version of the International Physical Activity Questionnaire-Short Form (IPAQ-SF)[24]. This self-report tool collected data on the frequency and duration (at least 10 min) of walking, moderate-intensity, and vigorous-intensity activities performed in the last seven days, alongside daily sitting time. Total energy expenditure was calculated in MET-minutes per week by multiplying activity duration by assigned MET values: 3.3 for walking, 4.0 for moderate, and 8.0 for vigorous activities.

Fasting blood capillary test

A baseline fasting capillary blood test, using the REFLOTRON Plus system, was performed to measure biological variables such as creatinine, urate and total cholesterol. The GFR was calculated based on the creatinine results, using the (CKD-EPI) formula. Glycated hemoglobin was obtained from capillary blood test, through the COBAS B 101® Roche system.

Skin autofluorescence

Skin AGEs were measured in the right forearm by using a desktop device (AGE Reader™, DiagnOptics Technologies, Groningen, Netherlands) that measure AGEs concentration through its fluorescent properties, which has been validated by comparing its results with the gold standard technique, the skin biopsy[25,26]. To carry out the measures in the forearm, skin with sweat, tattoos, lotions or visible abnormalities was avoided. Subjects with dark skin color were excluded. The absolute value of the measures was expressed in arbitrary units (AU). In addition, according to the age of the participants, a qualitative scale was implemented to categorize the results of the measures in normal or high SAF values.

Pulmonary function test

Pulmonary function test, were performed by trained and certified pulmonary experts according to Spanish guidelines[27], at baseline and at four years of follow-up using a portable ultrasonic spirometer (Datospir©; Sibelmed, Barcelona, Spain). Through this test the forced expiratory volume at one second (FEV_1), Forced vital capacity (FVC) and the ratio FEV_1/FVC were measured in milliliters and expressed as percentages of the predicted values[28]. The bronchodilator test wasn't preformed in the assessment. The definition of the airway obstruction was based on international guidelines[29].

Ethical aspects

The ILERVAS project protocol was approved by the Ethics Committee of the Arnau de Vilanova University Hospital (First visit: CEIC-1410, 19/12/2014; Follow-up: CEIC-2015, 20/12/2018), and all participants provided informed consent. All research was performed following the relevant guidelines and regulations, and in accordance with the Declaration of Helsinki.

Statistical analysis

Descriptive statistics were used to summarize the main characteristics of the study population. Continuous variables are reported as median [interquartile range; 25th–75th percentiles] and categorical variables are presented as frequencies and percentages.

Group comparisons, including those stratified by smoking status, were performed using the chi-square test or Fisher's exact test for categorical variables, and the Mann–Whitney U test for continuous variables.

Spirometry parameters were analyzed at baseline and after a median of 4 years of follow-up. Yearly changes were calculated by dividing the absolute change between visits by the follow-up duration in years.

To evaluate the association between baseline skin advanced glycation end-products (AGEs) and the yearly change in pulmonary function test, adjusted generalized additive models (GAMs) and multivariate regression analysis were fitted. GAMs, using the mgcv package in R, allowed to explore for flexible modeling of potential nonlinear relationships. All models were adjusted for age, sex, weight, height, smoking status (never, former, current), pack-years, estimated glomerular filtration rate (GFR), glycated hemoglobin (HbA1c), mediterranean diet score, and physical activity level assessed by the IPAQ.

Analyses were repeated stratified by smoking status to assess potential effect modification. To assess the potential impact of weight changes on lung function, a sensitivity analysis was performed including the change in BMI (ΔBMI) between baseline and follow-up as a covariate in the multivariate models. Additionally, cross-sectional associations between baseline skin AGEs and baseline spirometry measures were examined using the adjusted variables previously mentioned.

Given the low proportion of missing data, all analyses were performed using complete case analysis.

Statistical analyses were conducted using R version 4.4 (R Foundation for Statistical Computing, Vienna, Austria), and a two-sided p-value < 0.05 was considered statistically significant.

Results

A total of 658 subjects were included in the study. The main characteristics of the patients are shown in Table 1. Briefly, these are middle-aged patients with a median age 56 [interquartile range: 52.0; 61.8] years, 51.7% males, mainly with overweigh and with a significant burden of comorbidity related to cardiovascular risk factors. Regarding habits, 29.3% of subjects were active smokers, most of them have low adherence to Mediterranean diet (94.5%) and with a tendency towards a sedentary lifestyle, 67.5% perform low level of physical activity based on the IPAQ questionnaire results. Only 2.74% of patients had a personal history of COPD. The median baseline SAF was 1.90 AU [1.60; 2.20].

The baseline results of the pulmonary function test of the study population and the yearly change of the results during the follow-up with a median of 4.02 [3.98; 4.12] years are shown in Table 2**.** Briefly, baseline spirometry showed mostly preserved lung function, with median FEV_1, FVC and FEV_1/FVC of 2,795 mL [2,270; 3,341], 3,525 mL [2,870; 4,300], and 78.6% [74.4; 82.8], respectively. The annual changes in lung function were -81.9 mL [-120.6; -43.3] for FEV_1, -99.6 mL [-159.3; -37.9] for FVC, and -0.04% [-0.85; 0.70] for FEV_1/FVC.

When assessing the relationship between baseline skin AGEs results and the annual outcome of the pulmonary function test, no significant associations were found for any resulting variable of the spirometry, FEV_1, FVC and the ratio FEV_1/FVC, either assessed in milliliters or percentage, after adjusting for confounding variables such as age, height, gender, weight, smoking status (never, former or current smoker), pack-years of smoking, GFR, glycated hemoglobin, mediterranean diet and physical activity assessed through MEDAS and IPAQ questionnaires, respectively (Fig. 1 ***and*** Fig. 2). In addition, no significant association was found when the assessment was performed by stratifying for smoking habit, current smokers and non-smokers (either never or former smokers) and adjusting for age, height, gender, weight, pack-years of smoking, GFR, glycated hemoglobin and additionally adjusted for smoking habit (non-smokers or former smokers) in the non-smokers group (Table 3 and Fig. 3). Cross-sectional analyses assessing the association between baseline skin AGEs and baseline pulmonary function did not achieve statistical significance (supplementary material Figure S1). Finally, sensitivity analyses adjusting for changes in BMI over the follow-up period (ΔBMI) confirmed the main findings, showing no significant association between baseline SAF and lung function decline ($p > 0.05$ for all parameters, results not shown).

Discussion

To our knowledge, this is the first prospective study to investigate the relationship between skin AGEs, assessed via SAF, and longitudinal changes in pulmonary function in a middle-aged adult population without diabetes or CKD. While previous research has primarily relied on cross-sectional designs[19–21,30], our study uniquely contributes to the field by evaluating the predictive value of baseline skin AGEs burden over a four-year follow-up period. Interestingly, our findings did not reveal any significant associations between baseline SAF levels and annual changes in spirometric parameters, including FEV_1, FVC, and the FEV_1/FVC ratio, whether expressed in absolute terms or as percentages. This lack of association is particularly striking given that the observed median FEV_1 decline (– 81.9 mL/year) was above the 30–40 mL/year decline typically associated with physiological aging[31]. These negative findings persisted after adjusting for a comprehensive range of potential confounders, including demographic, metabolic, renal, and lifestyle factors. Additionally, stratified analyses by smoking status

	All	N
	N = 658	
Age	56.0 [52.0;61.8]	658
Sex		658
Male	340 (51.7%)	
Female	318 (48.3%)	
Comorbidities		
Hypertension	254 (38.6%)	658
Obesity	177 (26.9%)	658
Dyslipidaemia	328 (49.8%)	658
Family history of CVD	60 (9.12%)	658
COPD	18 (2.74%)	658
Weight (kg)	76.6 [66.8;86.4]	658
Height (cm)	164 [157;172]	658
BMI	28.2 [25.5;31.4]	658
Waist circumference (cm)	100 [93.0;108]	658
Smoking habit		658
Non-smoker	229 (34.8%)	
Former smoker	236 (35.9%)	
Current smoker	193 (29.3%)	
Pack-years of smoking	19.0 [9.57;30.4]	427
Mediterranean diet adherence:		649
Low adherence (< 10)	613 (94.5%)	
High adherence (10 +)	36 (5.55%)	
IPAQ		652
Low level of physical activity	440 (67.5%)	
Moderate level of physical activity	188 (28.8%)	
High level of physical activity	24 (3.68%)	
Laboratory		
Uric acid (mg/dL)	5.36 [4.51;6.39]	658
Creatinine (mg/dL)	0.76 [0.65;0.88]	658
Glomerular filtration rate, CKD-EPI (mL/min/1.73m^2)	96.2 [87.5;103]	658
Total cholesterol (mg/dL)	202 [179;229]	658
Glycated haemoglobin (HbA1c) (%)	5.50 [5.30;5.70]	658
< 5.7	461 (70.1%)	
5.7–6.4	197 (29.9%)	
Skin autofluorescence measure of advanced glycation end-products (AU)	1.90 [1.60;2.20]	658

Table 1. Main characteristics of the study population. Reported values are median [25th percentile; 75th percentile] and N (%). CVD, cardiovascular disease; COPD, chronic obstructive pulmonary disease; BMI, body mass index; IPAQ, international physical activity questionnaire; AU, arbitrary units.

	Baseline	Yearly change
	N = 658	N = 658
FVC (ml)	3525 [2870;4300]	− 99.60 [− 159.26; − 37.87]
FVC (%)	98.8 [88.3;109]	− 2.16 [− 3.88; − 0.47]
FEV_1 (ml)	2795 [2270;3410]	− 81.87 [− 120.61; − 43.29]
FEV_1 (%)	98.5 [86.9;109]	− 2.09 [− 3.76; − 0.69]
FEV_1/FVC	78.6 [74.4;82.8]	− 0.04 [− 0.85; 0.70]

Table 2. Baseline pulmonary function test results and annualized changes over four years of follow-up. Reported values are median [25th percentile; 75th percentile]. FEV_1, force expiratory volume in one second; FVC, forced vital capacity. Median follow-up time between visits is 4.02 years.

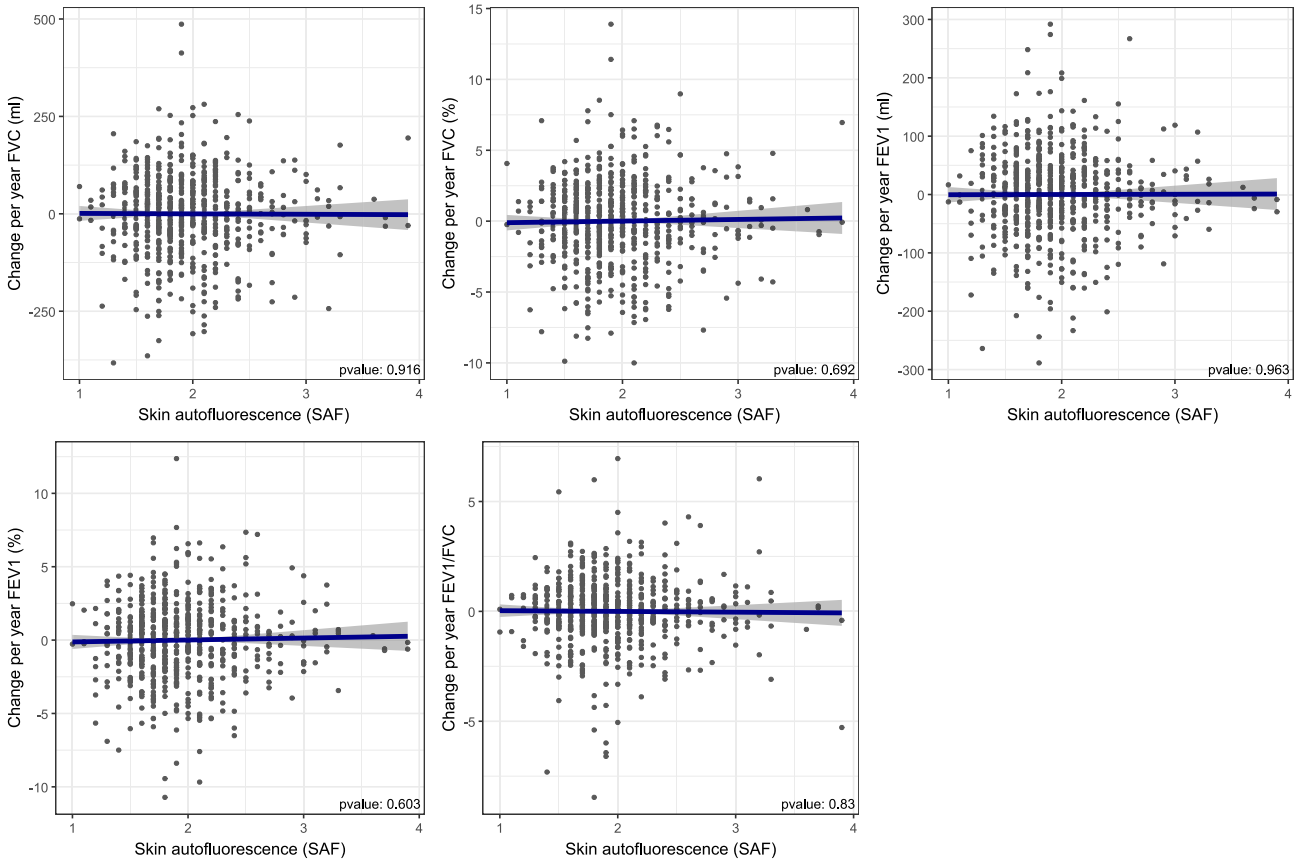


Fig. 1. Association between baseline skin AGE levels and annual change in pulmonary function parameters over four years. Spline from generalized additive models adjusted for age, sex, weight, height, smoking habit, pack-years, GFR, glycated hemoglobin (HbA1c), mediterranean diet and physical activity assessed through MEDAS and IPAQ questionnaires, respectively. AGEs, advanced glycation end-products; GFR, glomerular filtration rate (CKD-EPI (ml/min/1.73m^2)); MEDAS, Mediterranean diet adherence screener; IPAQ, international physical activity questionnaire.

also failed to demonstrate any significant associations. These findings suggest that, in this specific population, skin AGEs burden may not serve as a reliable predictor of pulmonary function decline, contrasting with its previously reported prognostic value in cardiovascular outcomes[32].

Although we know that skin AGEs accumulate in the extracellular matrix by binding to long-lived proteins such as collagen —particularly in collagen-rich tissues like the skin[33]— and may reflect a history of endogenous overproduction or exogenous intake, our prospective findings do not support their predictive value for pulmonary function decline over time. This is particularly relevant given the high expression of RAGE in the lungs[15], which has led to the hypothesis that systemic AGE accumulation could have parallel deleterious effects on lung tissue. However, it is important to characterize the nature of the lung function loss observed in our cohort to interpret these results correctly. The decline in FEV_1 (– 81.9 mL/year) was paralleled by a similar decline in FVC (– 99.6 mL/year), resulting in a stable FEV_1/FVC ratio (– 0.04% change). This pattern indicates a rapid decline with preserved ratio, suggestive of a restrictive ventilatory defect or PRISm (Preserved Ratio Impaired Spirometry), rather than the classic obstructive pattern seen in COPD. This phenotype is frequently observed in populations with high cardiovascular risk and obesity (median BMI 28.2 kg/m^2 in our cohort)[34]. Importantly, our sensitivity analysis adjusting for BMI changes (ΔBMI) during follow-up confirmed that skin AGEs did not predict this decline. Furthermore, previous work in this same cohort has demonstrated that obesity indices (including BMI and visceral adiposity) are not directly associated with skin AGE accumulation[35]. This suggests that the mechanisms driving this specific pattern of lung loss, likely related to metabolic or mechanical factors, are distinct from the AGE-driven airway remodelling typically described in obstructive lung disease.

Several factors may explain this lack of association. First, skin AGEs levels may not accurately reflect AGEs accumulation in other tissues, including the lungs. For instance, in COPD patients, AGEs have been shown to accumulate differently in skin, plasma, and bronchial biopsies[36]. Second, we lacked data on soluble RAGE (sRAGE) levels, which are molecules generated either by proteolytic cleavage of cell membrane RAGE (cRAGE) or by endogenous cellular secretion of a splice variant (esRAGE) that is an isolated form of the extracellular domain of RAGE[37]. The sRAGE play a protective role by neutralizing circulating AGEs, preventing their binding to cell membrane RAGE by acting as a decoy receptors. Prior studies have shown that lower sRAGE levels are associated with greater declines in FEV_1/FVC[38] and FEV_1[39], while higher levels are linked to preserved lung

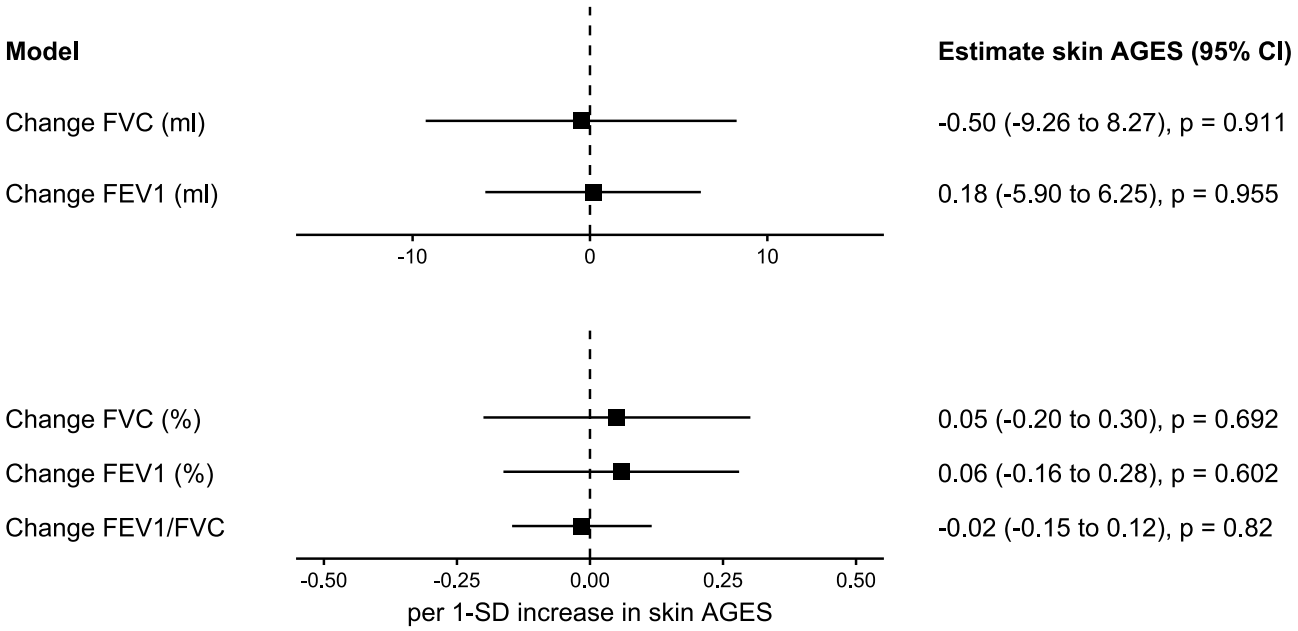


Fig. 2. Annual change in pulmonary function parameters per one standard deviation increase in baseline skin AGE levels. Multivariate regression analysis adjusted for age, sex, weight, height, smoking habit, pack-years, GFR, glycated hemoglobin (HbA1c), mediterranean diet and physical activity assessed through MEDAS and IPAQ questionnaires, respectively. AGEs, advanced glycation end-products; GFR, glomerular filtration rate (CKD-EPI (ml/min/1.73m^2)); MEDAS, Mediterranean diet adherence screener; IPAQ, international physical activity questionnaire; FEV_1, force expiratory volume in one second; FVC, forced vital capacity; 95%CI, 95% confidence interval; 1-SD, one standard deviation.

	Non-current smokers	Current smokers	
	N = 465	N = 193	*P* value
Age	57.0 [53.0;63.0]	54.0 [50.0;59.0]	< 0.001
Sex			0.007
Male	224 (48.2%)	116 (60.1%)	
Female	241 (51.8%)	77 (39.9%)	
Weight (kg)	77.3 [68.1;87.0]	74.1 [64.0;84.1]	0.012
Height (cm)	162 [156;171]	166 [160;172]	< 0.001
Smoking habit			< 0.001
Non-smoker	229 (49.2%)	0 (0.00%)	
Former smoker	236 (50.8%)	0 (0.00%)	
Current smoker	0 (0.00%)	193 (100%)	
Pack-years of smoking	0.25 [0.00;13.0]	24.5 [15.1;34.5]	< 0.001
GFR	95.5 [86.1;102]	98.2 [90.0;104]	0.004
Glycated hemoglobin (HbA1c) (%)	5.50 [5.30;5.70]	5.40 [5.20;5.60]	0.002
Mediterranean diet adherence:			0.733
Low adherence (< 10)	434 (94.8%)	179 (93.7%)	
High adherence (10 +)	24 (5.24%)	12 (6.28%)	
IPAQ			0.038
Low level of physical activity	297 (64.6%)	143 (74.5%)	
Moderate level of physical activity	146 (31.7%)	42 (21.9%)	
High level of physical activity	17 (3.70%)	7 (3.65%)	

Table 3. Main characteristics of the study population according to smoking status. Reported values are median [25th percentile; 75th percentile] and N (%). FR, glomerular filtration rate (CKD-EPI (ml/min/1.73m^2)); IPAQ, international physical activity questionnaire.

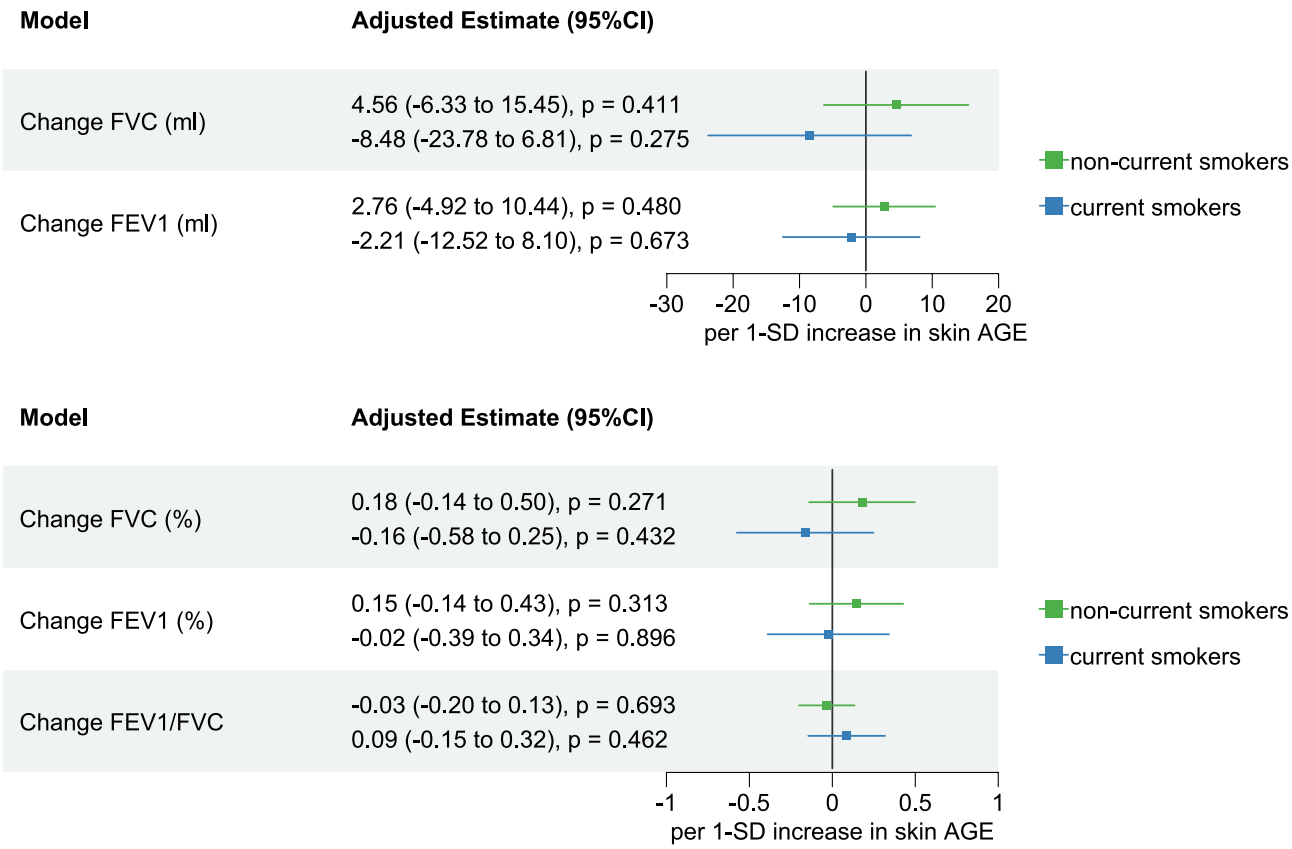


Fig. 3. Association between baseline skin AGE levels and annual change in pulmonary function parameters, stratified by smoking status. Multivariate regression analysis adjusted for age, sex, weight, height, pack-years, GFR, glycated hemoglobin (HbA1c). Non-smoking group additionally adjusted for smoking habit (non-smokers and former smokers). AGEs, advanced glycation end-products; GFR, glomerular filtration rate (CKD-EPI (ml/min/1.73m^2)); FEV_1, force expiratory volume in one second; FVC, forced vital capacity; 95%CI, 95% confidence interval; 1-SD, one standard deviation.

function[40]. In addition, a genetic variability in sRAGE production and RAGE polymorphisms may also influence individual susceptibility[41–43]. Finally, it is possible that AGEs play a more prominent role in lung function decline only after structural damage has already occurred, rather than in the early stages of impairment.

In contrast to several previous cross-sectional studies that reported significant associations between higher skin AGE burden and lower pulmonary function —specifically reduced FEV_1[19,21,30], FVC[19,21], FEV_1/FVC ratio[20], and DLCO[19]— the secondary cross-sectional analysis that we present in the online supplement did not find any statistically significant associations regardless of trends towards some weak associations. These discrepancies may be attributed to key differences in study design and population characteristics. Many of the earlier studies included older individuals[20,30], patients with diabetes[19,21,30], or had larger sample sizes[19,21,30], which could have influenced the strength and direction of observed associations. In contrast, our study focused on a relatively younger, healthier population, rigorously excluding individuals with diabetes or CKD and adjusting for a wide range of potential confounders, including lifestyle and metabolic variables. Indeed, the median baseline SAF of our cohort (1.90 AU, median age 56) was lower than age-matched reference values from general populations, such as the Spanish EVasCu study (mean 2.07–2.21 AU for the 50–59 age group)[44] and the Dutch Lifelines Cohort (predicted 2.05–2.11 AU for a 56-year-old)[45], likely reflecting our strict exclusion of individuals with diabetes or CKD. These methodological distinctions may explain the divergence in findings and highlight the importance of population context when interpreting the clinical relevance of skin AGEs measurements.

To date, this is the first study assessing prospectively the clinical implications of skin AGEs burden for the pulmonary function test outcome, at 4-year of follow-up, in a cohort of middle-aged adult population. This novel longitudinal approach represents a key strength of the study. However, several limitations should be acknowledged. First, the sample size, while sufficient for the primary analysis, may have limited the statistical power to detect more subtle associations. Second, bronchodilator testing was not performed, which limits the ability to differentiate between reversible and fixed airflow limitation. Therefore, while we can assess functional decline, we cannot confirm the presence of fixed obstructive airway disease (COPD). However, previous research indicates that the exclusion of post-bronchodilator spirometry typically leads to an overestimation of COPD prevalence by capturing obstructive lung disease in general[46], suggesting that our analysis is unlikely to have missed significant pathology due to under-diagnosis. Third, we lacked data on certain biomarkers, such as plasma C-reactive protein, circulating AGEs, and sRAGE levels, which could have provided additional insight into systemic inflammation and AGEs-related mechanisms. Nonetheless, the

analysis was adjusted for a broad range of relevant variables, including validated questionnaires assessing adherence to the Mediterranean diet and physical activity. Finally, we did not assess changes in skin AGE burden over time. Longitudinal measurements could have identified individuals with persistently elevated AGE levels (whether due to sustained endogenous overproduction or continued exogenous intake) who may be at greater risk for pulmonary function decline. Future studies incorporating repeated SAF assessments and biomarker profiling may help clarify these dynamics.

In this prospective study, we conducted the first longitudinal evaluation of the predictive value of skin AGEs for pulmonary function decline. Contrary to findings from previous cross-sectional studies, we observed that baseline skin AGEs levels, quantified by SAF, were not associated to changes in spirometric parameters over a four-year follow-up in a middle-aged adult cohort with a high burden of cardiovascular risk factors but without diabetes or significant kidney dysfunction. While SAF remains a valuable indicator of cumulative tissue AGE accumulation, our results suggest its limited utility as a prognostic tool for lung function decline in this specific population. Future research should focus on assessing longitudinal changes in skin AGE burden, incorporate systemic AGE biomarkers, and investigate whether the role of AGEs in pulmonary impairment becomes more prominent in later stages of lung disease.

Data availability

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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Declarations

Competing interests

The authors declare no competing interests.

Ethics approval and consent to participate

This is an ancillary study of the ILERVAS study (ClinTrials.gov Identifier NCT03228459), approved by the Ethics Committee of the Arnau de Vilanova University Hospital (First visit: CEIC-1410, 19/12/2014; Follow-up: CEIC-2015, 20/12/2018), and all participants provided informed consent.

Consent for publication

None of this manuscripts' results have been presented or published elsewhere.

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