ARTICLE

Relative Contribution of Intrinsic vs Extrinsic Factors to Skin Aging as Determined by a Validated Skin Age Score

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Objective: To assess the relative contribution of intrinsic aging vs lifestyle factors to facial skin age.

Design: Prospective analysis of a cohort.

Setting: Skin research institute.

Study Subjects: A cohort of 361 white women (age range, 18-80 years) with apparently healthy skin.

Measurements: Visual and tactile assessment of facial skin features.

Results: Twenty-four skin characteristics were used to build a skin age score (SAS). The relationship between the SAS and chronological age followed a linear model with 2 plateaus—1 before age 30 years and 1 after age 71 years. An analysis was performed to determine whether certain lifestyle habits known to have effects on skin aging were related to the discrepancies between chronological age and the SAS. Significant effects were identified for phototype, body mass index, menopausal status, degree of lifetime sun exposure, and number of years of cigarette smoking. However, these factors accounted for only 10% of the discrepancies. Moreover, most skin characteristics used reflected changes understood to represent intrinsic aging rather than photodamage or other extrinsic factors.

Conclusions: An SAS can be generated from multiple discrete signs evaluated on facial skin and is an informative tool for quantifying skin aging. The SAS is influenced by factors already recognized to affect the aging phenotypes; however, factors related to the rate of intrinsic aging, presumably genetic in character, seem to play a larger role than previously suspected.

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SKIN AGING is a continuous process that affects skin function and appearance. However, not everybody ages at the same speed. It is generally agreed that certain individuals look "old for their age" or "young for their age." Intrinsic, environmental, and lifestyle factors contribute to the pace of skin aging.[1-3] Chronic sun exposure has been identified as one of the most important environmental injuries leading to acceleration and aggravation of skin aging.[4] However, premature aging of the skin is also observed in several hereditary disorders and has been associated with defined defects of single genes that code either for structural proteins or for enzymes involved in repair of DNA damage.[5-7] In addition, polymorphisms in certain genes, most notably those encoding the melanocortin 1 receptor, have been shown to result in increased susceptibility to UV radiation[8,9] and thereby might also affect the aging process.

To determine the relative contributions of the different determinants of skin aging, it is desirable to generate an objective measure of skin aging in a given individual for comparison with others of the same chronological age. Such determination of whether skin aging in this individual is either accelerated or slowed down would facilitate the identification of factors, genetic and environmental, that account for the observed variability in the rate of aging.

The challenge, therefore, classic in the realm of geriatrics and gerontology,[10] is to estimate a "biological" age that reflects appearance, performance, and functional capacity better than chronological age.[10-12] Typically, the methodological approach consists of selecting a set of markers that correlates strongly with chronological age, the underlying assumption being that these markers are the most accurate indicators of the individual aging process. Research into biomarkers of aging has used a variety of mathematical methods ranging from

multiple regression equations to principal component analyses to factor analysis.[13-17] Descriptors of the skin status have been taken into account only crudely in the few previous studies of biological age.[15-18]

Although aging of the skin, similar to aging of other organ systems, remains poorly understood, considerable progress has been made in the past 15 years in describing the specific component features of aged and photoaged skin.[1-4,19] Many of these features were first articulated in an effort to measure sometimes subtle but nevertheless important changes in appearance as the result of sun protection or use of topical antiaging therapies.[20-22] Several features were found to correlate well with global assessment of skin appearance by investigators and patients and to reflect histologic improvements at the light microscopic and electron microscopic levels.[23] From this work and perhaps from an increasing public awareness that habitual sun exposure contributes to "premature aging," there evolved an understanding that chronic photodamage (adverse effects of UV irradiation) accounted for a large portion of perceived aging changes in skin,[2-4] despite a paucity of data to support this belief.

Skin aging is usually assessed either by examination of individual skin features, that is, wrinkles, slackening, and pigment irregularities,[1-3] or by global evaluation of appearance.[19] In the present study, we produced a global indicator for skin aging based on individual assessment of a wide range of visual and tactile skin characteristics initially grouped by features of presumed common etiology (eg, sagging or wrinkles). Then, a method that allowed accounting for the underlying structure of data was applied.[24] Using this approach, which is widely used in behavioral sciences,[25,26] we produced a series of partial scores corresponding to each feature and a global score that describes skin aging overall.

METHODS

STUDY POPULATION

A study was conducted between November 2, 1998, and March 30, 1999, on 361 white women aged 18 to 80 years (mean ± SD age, 43.5 ± 15.8 years) living in the Île-de-France region (Paris and its suburbs) with apparently healthy skin who had not applied skin care or makeup products the evening before and the morning of the study. Clinical evaluation was performed in controlled environmental conditions (room temperature, 22.9°C ± 0.3°C; relative humidity, 48.4% ± 2.4%) after 30 minutes of acclimatization.

Sixty-two skin characteristics were assessed on the face using ordinal scales by an investigator trained in the clinical assessment of healthy skin. Furthermore, individual data known to have an effect on skin aging were collected: chronological age, onset of menopause, self-assessment of lifetime sun exposure using a 4-level scale (none, mild, moderate, or severe), and reactivity of the skin to sun exposure using Fitzpatrick's 4-level phototype classification (always burn and never tan, usually burn and tan with difficulty, sometimes mild burn and tan about the average, or rarely burn and tan with ease). The distribution of skin phototype[27] was as follows: type I, 7%; type II, 31%; type III, 49%; and type IV, 13%. The distribution in class of body mass index (BMI) (calculated as weight in kilograms divided by the square of height in meters) was 7% for underweight individuals (BMI $\leq$ 18.5), 68% for normal weight individuals (18.5 $<$ BMI $<$ 25.0), 19% for overweight individuals (25.0 $\leq$ BMI $\leq$ 29.9), and 6% for obese individuals (BMI $>$ 30.0).[28] Smoking for smokers or former smokers was categorized according to the number of years of cigarette smoking.[29]

STATISTICAL ANALYSIS

Statistical analysis was conducted in 3 steps using statistical software (SAS release 6.12; SAS Institute Inc, Cary, NC)[30]: (1) selection and grouping of characteristics according to the different features of skin aging, (2) score development, and (3) modeling of the link with chronological age and identification of factors affecting the skin age score (SAS).

Selection and Grouping of Characteristics

To keep only variables that had a linear link with age, the relationship between age and skin characteristics was studied: the distribution of skin characteristics by 10-year age ranges was examined using the χ^2 test (FREQ procedure, option CHISQ). Only variables with a significant link were retained for further analysis. A typology of these variables was made to group the remaining characteristics according to each feature of presumed common etiology (eg, wrinkles or pigmentation irregularities). The correlation matrix of the characteristics was calculated using the Kendall τ-b correlation (CORR procedure), and then this matrix was used to group the characteristics (VARCLUS procedure, option MAXEIGEN). Then, the internal consistency of these groups was checked using the Cronbach α coefficient (FREQ procedure, option ALPHA). Finally, a first-order confirmatory factor analysis was performed to test the restitution by these groups of variability between skin characteristics and to identify redundant variables to eliminate these variables (CALIS procedure).[24,31]

Score Development

A second-order confirmatory factor analysis was then used, on the basis of the groups of characteristics obtained in the previous stage, to build a series of partial scores corresponding to each of these groups, together with a global score to describe skin aging overall (CALIS procedure).[31] The global score was eventually modified to be expressed in years: the score was calculated for each individual, and its distribution was modified so that the average and the distribution of individual values around the average were identical to those for the chronological age of the sample (STANDARD procedure). Finally, to directly calculate these scores using the individual category value of each characteristic, a series of formulas was developed (REG procedure).

Of 62 skin characteristics assessed by clinical examination of the faces of 361 women, only 33 showed significant links with chronological age. Confirmatory factor analysis allowed exclusion of redundant characteristics and those with no linear link with age. Finally, 24 characteristics, which were split into 6 groups by presumed common etiology (**Figure 1**), were used to obtain a global score quantifying facial skin aging. Figure 1 summarizes the basic concepts of second-order confirmatory factor analysis. The formulas for practicable calculation of these scores are available from the authors on request.

Modeling of the Link With Age and Identification of Factors Affecting the SAS

A model was first constructed to describe the relationship between the SAS and chronological age. Then, individual SASs predicted by the model were calculated (NLIN procedure). Finally, factors reported to play a determining role in skin aging

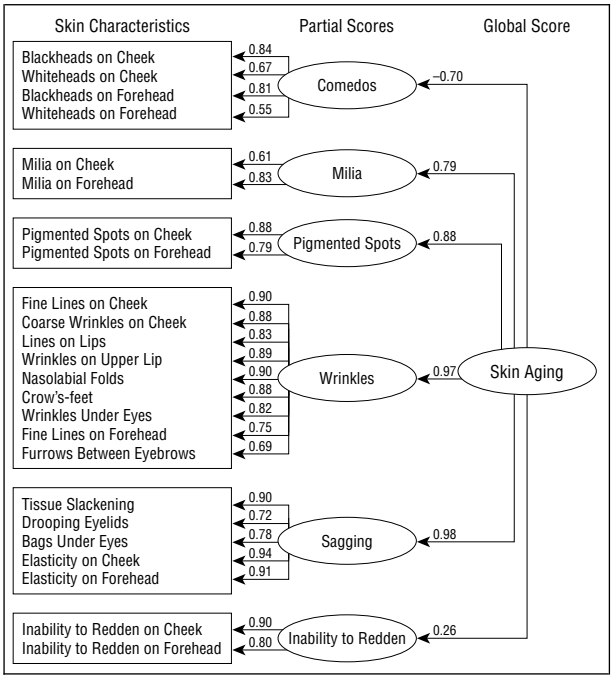

Figure 1. Second-order confirmatory factor analysis model used for development of partial and global skin aging scores. Correlation coefficients are indicated above the arrows. Correlations between each group of characteristics and corresponding partial scores, together with correlations between partial scores and the global score, were estimated using the CALIS procedure. Each partial score was then estimated as a weighted average for its centered-reduced characteristics, with weights corresponding to the correlations. The global score was obtained in the same manner, from the reduced partial scores. The formulas used for calculation of these scores are available on request.

(smoking and sun exposure[1-3,32]), as well as the potential interactions between these factors, were tested in a multiple regression model (GLM procedure, option SOLUTION) using the following ratio:

(SAS − Predicted Skin Age)/Predicted Skin Age

Photographs of the faces of selected women were taken using a medical imaging camera (Canfield Clinical Systems, Fairfield, NJ) under standardized conditions to illustrate individuals with SASs greater or less than their chronological age.

RESULTS

PREVALENCE OF AGING SIGNS IN WOMEN OF DIFFERENT AGES

The prevalence and severity of the selected characteristics increased with age, except for those related to acne, which decreased with age, as expected (**Table**). Unexpectedly, however, many of the signs showed a sharp increase in prevalence (from absent to slight) between the groups aged 30 to 39 and 40 to 49 years. Severity of these signs generally increased from slight to marked 2 to 3 decades later in most participants. These signs seemed to be best ascribed to intrinsic aging, largely consisting of "expression lines" such as furrows between the eyebrows ("frown lines") and fine lines on the forehead, the 2 earliest signs of aging, affecting most women before age 30 years. In contrast, signs most clearly ascribable to photoaging ("pigmented spots," ie, lentigines) first affected most women 2 to 3 decades later.

Also of interest was the high prevalence of open and closed comedos indicative of low-grade acne, even in this population from which individuals diagnosed as having at least the inflammatory form of this disease had been excluded. The prevalence of comedos fell below 50% only after age 50 years, and approximately one third of women in the 50- to 59-year-old age group were still affected with lesions, presumably abating only after menopause.

THE SAS INCREASES LINEARLY WITH CHRONOLOGICAL AGE

The relationship between the SAS and chronological age followed a linear model ("predicted skin age"), with a slope of 1.06 ($r=0.88$; $P<.001$) and 2 plateaus—1 before age 30 years and 1 after age 71 years (**Figure 2**). That means that between ages 31 and 71 years, on average, skin age progresses linearly and corresponds almost exactly to chronological age. In contrast, before age 30 years, any physiological age–associated changes in the skin are subclinical and are not reflected in the appearance, whereas older than 71 years, the 3-level scales used to rate most of the characteristics lost their discriminatory capacity, that is, the aging-associated characteristics were present in virtually all women in that age group.

IDENTIFICATION OF FACTORS AFFECTING THE SAS

Significant effects affecting the SAS were identified for the following self-reported factors either independently, such as for phototype, or as interactions between factors, such as for corpulence (a function of height and weight) and menopausal status, as well as for lifetime sun exposure and smoking habits. The SAS was generally less than chronological age for dark phototypes (III and IV) and greater for light phototypes (I and II) ($P<.008$). Similarly, the SAS was less than chronological age for overweight or obese premenopausal women (BMI>25), greater for overweight or obese postmenopausal women (BMI>25), and even greater for nonoverweight women regardless of menopausal status (BMI<25) ($P<.002$). As expected, the SAS was generally less than chronological age for women not severely exposed to the sun, regardless of their smoking habits; greater for women severely exposed to the sun who smoked or had previously smoked for less than 15 years; and far greater for women severely exposed to the sun who smoked for more than 15 years ($P<.03$). The multiple regression model explaining in more detail the discrepancies between the SAS and predicted skin age can be obtained on request from the authors. However, these factors explained only part of the individual deviations from the predicted age (approximately 10% of the variance, multiple correlation coefficient $r=0.30$; $P<.001$).

Photographs of 4 women, 2 with an SAS less than their chronological age (**Figure 3**A and C) and 2 with an SAS greater than their chronological age (Figure 3B and D) are shown to illustrate the visible signs summarized by the SAS. The SAS does not measure "attractiveness" per se of either the skin or the individual.

Frequency of Visual and Tactile Skin Characteristics According to Age Groups*

Skin Characteristic	Characteristics Categories	Age Group, y					
		18-29 (n = 84)	30-39 (n = 77)	40-49 (n = 87)	50-59 (n = 41)	60-69 (n = 36)	70-80 (n = 36)
Blackheads (cheek)	1 = Absent	10	13	44	66†	92	89
	2 = Hardly visible	58	53	51	32†	3	8
	3 = Visible	32	34	6	2†	6	3
Blackheads (forehead)	1 = Absent	13	10	32	61†	89	89
	2 = Hardly visible	54	60	55	37†	6	3
	3 = Visible	33	30	13	2†	5	8
Whiteheads (cheek)§	2 = Present	68	70	44†	29	6	11
Whiteheads (forehead)§	2 = Present	69	66	59	41†	31	16
Milia (cheek)§	2 = Present	0	0	6	22	37	49
Milia (forehead)§	2 = Present	0	3	11	37	69‡	68
Pigmented spots (cheek)	1 = Absent	100	99	54	22‡	11	8
	2 = A few	0	1	46	78‡	83	89
	3 = Many	0	0	0	0‡	6	3
Pigmented spots (forehead)	1 = Absent	100	97	83	56	23‡	19
	2 = A few	0	3	17	44	74‡	78
	3 = Many	0	0	0	0	3‡	3
Fine lines (cheek)	1 = Absent	100	82	21‡	7	0	0
	2 = A few	0	18	76‡	73	53	33
	3 = Many	0	0	3‡	20	47	67
Fine lines (forehead)	1 = Absent	79	46‡	19	2	0	0
	2 = A few	21	49‡	67	66	31	33
	3 = Many	0	5‡	14	31	69	67
Coarse wrinkles (cheek)	1 = Absent	100	82	23‡	5	0	0
	2 = Slight	0	18	76‡	88	69	50
	3 = Very marked	0	0	1‡	7	31	50
Furrows between eyebrows	1 = Absent	71	29‡	10	10	6	0
	2 = Slight	29	71‡	82	82	42	42
	3 = Very marked	0	0‡	8	8	53	58
Lines on lips	1 = Absent	99	97	75	20‡	0	0
	2 = A few	1	3	25	78‡	94	61
	3 = Many	0	0	0	2‡	6	39
Wrinkles on upper lip	1 = Absent	100	95	46‡	2	0	0
	2 = A few	0	5	53‡	85	47	25
	3 = Many	0	0	1‡	12	53	75
Nasolabial folds	1 = Absent	98	68	15‡	0	0	0
	2 = Slight	2	31	80‡	56	19	3
	3 = Very marked	0	1	5‡	44	81	97
Tissue slackening	1 = Absent	100	95	49‡	2	3	0
	2 = Slight	0	5	51‡	93	55	25
	3 = Very marked	0	0	0‡	5	42	75
Drooping eyelids	1 = Absent	96	77	36‡	15	17	8
	2 = Slight	4	23	61‡	66	47	39
	3 = Very marked	0	0	3‡	19	36	53
Bags under eyes	1 = Absent	98	75	28‡	5	3	0
	2 = Slight	2	24	65‡	78	58	33
	3 = Very marked	0	1	7‡	17	39	67
Crow's-feet	1 = Absent	100	83	26‡	2	6	3
	2 = Slight	0	17	70‡	71	31	25
	3 = Very marked	0	0	3‡	27	64	72
Wrinkles under eyes	1 = Absent	92	49‡	6	0	3	0
	2 = Slight	8	49‡	83	59	39	28
	3 = Very marked	0	1‡	11	41	58	72
Elasticity (cheek)	1 = Supple	99	91	30‡	0	0	0
	2 = In-between	1	9	68‡	85	64	28
	3 = Flaccid	0	0	2‡	15	36	72
Elasticity (forehead)	1 = Supple	100	91	46‡	7	0	0
	2 = In-between	0	8	53‡	81	78	33
	3 = Flaccid	0	1	1‡	12	22	67
Inability to redden when pinched (cheek)§	2 = Present	2	3	13	7	11	27
Inability to redden when pinched (forehead)§	2 = Present	2	6	9	12	11	24

*Data are given as percentages.
†Fifty percent or less of individuals show presence of the respective skin characteristic to be negatively linked with age.
‡Fifty percent or more of individuals show presence of the respective skin characteristic to be positively linked with age.
§Percentages for category 1 = absent are 100% minus those given for category 2 = present.

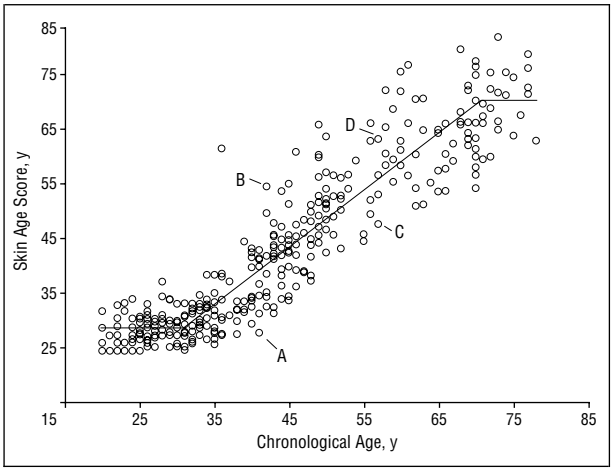

Figure 2. Relationship between the skin age score and chronological age. Each individual is represented by an open circle. Skin age predicted by the model appears as a straight line (r=0.88; P<.001) between age 31 years (upper limit for the first plateau) and age 71 years (lower limit for the second plateau). A to D indicate individuals whose photographs are depicted in Figure 3.

COMMENT

Estimations of age are constantly performed either consciously or unconsciously during social interaction. This type of age estimate relies on a global impression, taking into account not only biological factors, such as age-associated changes in the skin, but also posture and the shape of the face.[33,34] Regarding skin, it is widely believed that besides the intrinsic aging process, chronic sun exposure accelerates and modulates the aging process.[1-3] Certain genetic defects exemplified by Werner syndrome[5,35] or cutis laxa[6] greatly accelerate or aggravate selected features of aging, suggesting that the wide range of normal aging rates may result from polymorphisms in as yet unidentified human "longevity genes."[36,37] To identify such genetic factors and as yet unknown environmental effects, it would be desirable to objectively evaluate the degree of skin aging in given individuals compared with others of the same chronological age and to develop a tool to judge whether the aging process is more or less advanced.

An initial approach to biological age assessment was multiple regression analysis.[15,16] However, this method was criticized in part because it distorts the individual biological age at the regression edges. This distortion is due to the intrinsic mathematical property of linear regression that overestimates biological age for younger individuals and underestimates it for older ones. A second approach, principal component analysis, which produces linear functions of observed aging variables[13] and offers the advantage of relying on a correlation matrix and not on a predefined model, was more appropriate than regression analysis. A much more sophisticated approach was taken by Itoh[16] and Nakamura,[14] who used factor analysis methods, in which the fundamental concept is that unobservable "factors" underlie the observed variables. Factor analysis can successfully model and explain a data set only when the observed variables can be linearly related to a few unobservable factors,[38] and this requirement was met in the present study.

The concept of a global biological age has been criticized because different organs may age at different rates,[12] although few previous studies included skin descriptors.[15-18] In the present study, we focused on facial skin to develop an organ-specific age indicator. Our model pertains only to the skin, and no attempt was made to relate SASs to other aspects of aging in the study participants.

Consistent with earlier findings,[39,40] the SAS identifies an effect of skin phototype on dyspigmentation and development of facial wrinkles. In addition, our finding that BMI affects the SAS is in agreement with the recent study by Purba et al,[18] who found a negative correlation between BMI and the presence of wrinkles on sun-exposed areas. In general, the relationship between corpulence and less wrinkled "younger" skin is not intuitive. It is difficult to imagine wrinkles being simply "stretched out" over abundant subcutaneous fat, and it is tempting instead to consider that the fat may be acting metabolically to increase local estrogen levels,[41,42] thereby affecting the skin aging processes. Finally, our finding that excessive sun exposure together with heavy smoking strongly increases the SAS, whereas heavy smoking without excessive sun exposure lacks such effect, agrees with the finding of Yin et al,[32] who reported that smoking and sun exposure contribute independently to wrinkle formation but that tobacco smoking in combination with extensive sun exposure has a multiplicative effect.

The first of 3 unexpected findings in our analysis was the very high prevalence of comedos, affecting approximately 90% of individuals aged 18 to 39 years, despite the fact that inflammatory acne was an exclusion criteria for the study. Only after age 50 years were most participants judged to be free of these findings, lending support to the public perception that adult acne is common, at least among women. Also of note, while contributing significantly to the SAS, lowering it relative to chronological age, these findings cannot be considered to have improved the participants' appearance.

Second, of the visual skin signs that contributed significantly to the SAS, few have an apparent causal relationship with chronic photodamage, and the one most clearly attributable to sun exposure (pigmented spots presumably representing lentigines) was of relatively late onset and could hardly be viewed as "accelerating" the aging process. On the contrary, the development of "expression lines" and the general slackening of the skin, manifested for example by prominent nasolabial folds and "drooping" or redundant eyelids, tended to become prevalent in the fourth and fifth decades of life, marking the transition from young (unblemished or "perfect") skin to aged skin.

Third, the analysis revealed a sharp rise in prevalence for most age-associated skin signs between 30- to 39- and 40- to 49-year-old women, suggesting that the dread popularly attributed to the 40th birthday may have an objective basis.

Finally, if not unexpectedly, the analysis revealed large differences in SASs for women of the same chronological age, in the range of 25 to 30 years spread across all individuals older than 40 years. Individuals with an SAS

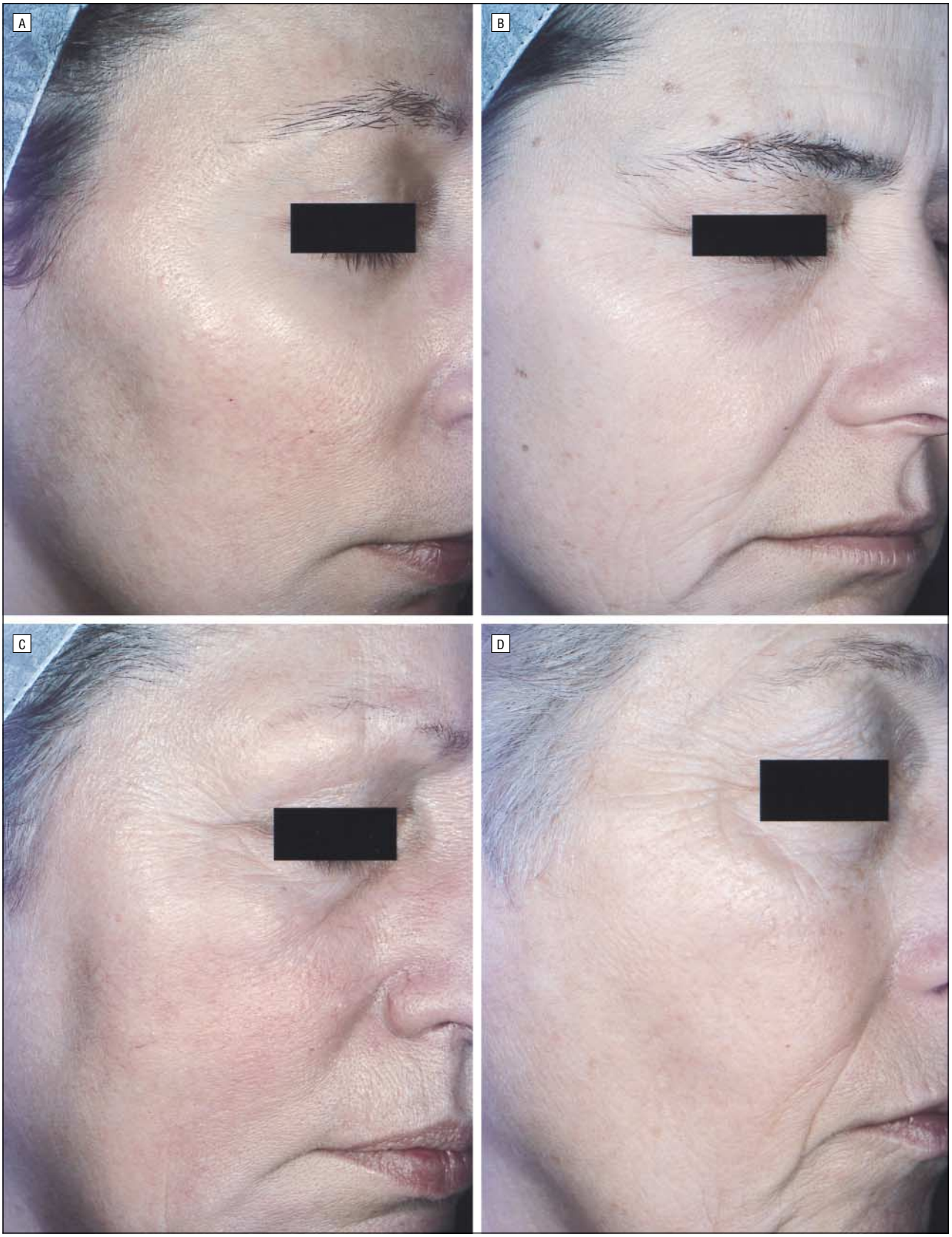

Figure 3. Photographs of women with a skin age score (SAS) less than their chronological age (A and C) and greater than their chronological age (B and D). A, A 41-year-old woman with an SAS of 28 and skin phototype IV. She used tobacco for 20 years and had moderate lifetime sun exposure. She was not experiencing menopause, and her body mass index (BMI, calculated as weight in kilograms divided by the square of height in meters) was 21. B, A 42-year-old woman with an SAS of 55 and skin phototype IV. She smoked for 10 years and had severe lifetime sun exposure. She was not experiencing menopause, and her BMI was 21. C, A 57-year-old woman with an SAS of 49 and skin phototype IV. She was a nonsmoker, but her lifetime sun exposure was severe. She was experiencing menopause, and her BMI was 27 (overweight). D, A 57-year-old woman with an SAS of 64 and skin phototype III. She was a nonsmoker, but her lifetime sun exposure was severe. She was experiencing menopause, and her BMI was 24.

either 10 years greater or 10 years less than their actual age were common. This broad variability among 361 women of relatively homogeneous genetic background, all residents of the same geographic area sharing relatively similar lifestyles, suggests that subtle genetic or environmental factors, likely both, play large roles in the rate of skin aging. Indeed, given that age-associated changes are often far less under basal conditions than under stress,[43] it is likely that the present approach of using exclusively noninvasive measures under carefully standardized nonstressful conditions minimized the age differences that might be measured in such a population.

Taken as a whole, these results support the idea that an SAS constructed by the method described herein is a simple and informative tool that might be used for epidemiologic studies, for longitudinal follow-up after antiaging procedures or treatments, and to guide the search for genetic polymorphisms underlying the observed variability in the rate of skin aging. Because recognized environmental, lifestyle, and biological factors explained only approximately 10% of the discrepancies between the SAS and chronological age, it is indeed warranted to search for such additional factors contributing to aging. Identifying individuals who show advanced or retarded skin aging, who might then be targeted for more detailed analysis, seems to be one useful approach.

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REFERENCES

1. Yaar M, Gilchrest BA. Aging versus photoaging: postulated mechanisms and effectors. *J Investig Dermatol Symp Proc.* 1998;3:47-51.
2. Yaar M, Gilchrest BA. Skin aging: postulated mechanisms and consequent changes in structure and function. *Clin Geriatr Med.* 2001;17:617-630.
3. Lavker R. Cutaneous aging: chronologic versus photoaging. In: Gilchrest B, ed. *Photodamage.* Cambridge, Mass: Blackwell Science; 1995:123-125.
4. Kligman LH, Kligman AM. Photoaging. In: Fitzpatrick TB, ed. *Dermatology in General Medicine.* New York, NY: McGraw-Hill Co; 1986:1470-1475.
5. Furuichi Y. Premature aging and predisposition to cancers caused by mutations in RecQ family helicases. *Ann N Y Acad Sci.* 2001;928:121-131.
6. Milewicz DM, Urban Z, Boyd C. Genetic disorders of the elastic fiber system. *Matrix Biol.* 2000;19:471-480.
7. Pesce K, Rothe MJ. The premature aging syndromes. *Clin Dermatol.* 1996;14: 161-170.
8. Flanagan N, Ray AJ, Todd C, Birch-Machin MA, Rees JL. The relation between melanocortin 1 receptor genotype and experimentally assessed ultraviolet radiation sensitivity. *J Invest Dermatol.* 2001;117:1314-1317.
9. Healy E, Flanagan N, Ray AJ, et al. Melanocortin-1-receptor gene and sun sensitivity in individuals without red hair. *Lancet.* 2000;355:1072-1073.
10. Dean W, Morgan RF. In defense of the concept of biological aging measurement: current status. *Arch Gerontol Geriatr.* 1988;7:191-210.
11. Borkan GA, Bachman SS, Norris AH. Comparison of visually estimated age with physiological predicted age as indicators of rates of aging. *Soc Sci Med.* 1982; 16:197-204.
12. Bulpitt CJ. Assessing biological age: practicality? *Gerontology.* 1995;41:315-321.
13. Nakamura E, Miyao K, Oseki T. Assessment of biological age by principal component analysis. *Mech Ageing Dev.* 1988;46:1-18.
14. Nakamura E. A study on the basic nature of human biological aging process based upon a hierarchical factor solution of the age-related physiological variables. *Mech Ageing Dev.* 1991;60:153-170.
15. Bulpitt CJ, Shipley MJ, Broughton PM, et al. The assessment of biological age: a report from the Department of Environment Study. *Aging (Milano).* 1994;6: 181-191.
16. Itoh MA. Assessment of aging by multivariate analyses. *Osaka City Med J.* 1979; 28:169-190.
17. Guinot C, Malvy D, Tenenhaus M, et al. Assessment of skin aging with principal component analysis. *J Eur Acad Dermatol Venereol.* 1998;11(suppl 2):S261-S262.
18. Purba MB, Kouris-Blazos A, Wattanapenpaiboon N, et al. Can skin wrinkling in a site that has received limited sun exposure be used as a marker of health status and biological age? *Age Ageing.* 2001;30:227-234.
19. Larnier C, Ortonne JP, Venot A, et al. Evaluation of cutaneous photodamage using a photographic scale. *Br J Dermatol.* 1994;130:167-173.
20. Stiller MJ, Bartolone J, Stern R, et al. Topical 8% glycolic acid and 8% L-lactic acid creams for the treatment of photodamaged skin. *Arch Dermatol.* 1996;132: 631-636.
21. Weiss JS, Ellis CN, Headington JT, Tincoff T, Hamilton TA, Voorhees JJ. Topical tretinoin improves photoaged skin: a double-blind vehicle-controlled study. *JAMA.* 1988;259:527-532.
22. Armstrong RB, Lesiewicz J, Harvey G, Lee LF, Spoehr KT, Zultak M. Clinical panel assessment of photodamaged skin treated with isotretinoin using photographs. *Arch Dermatol.* 1992;128:352-356.
23. Ditre CM, Griffin TD, Murphy GF, et al. Effects of alpha-hydroxy acids on photoaged skin: a pilot clinical, histologic, and ultrastructural study. *J Am Acad Dermatol.* 1996;34:187-195.
24. D'Agostino RB, Russel HK. Confirmatory factor analysis. In: Armitage P, Colton T, eds. *Encyclopedia of Biostatistics.* Chichester, England: John Wiley & Sons Ltd; 1998:897-898.
25. Arnau RB, Thompson B. Second-order confirmatory factor analysis of the WAIS-III, Wechsler Adult Intelligence Scale. *Assessment.* 2000;7:237-246.
26. Engelsen BK, Hagtvet KA. The dimensionality of the 12-item version of the Eating Attitudes Test: confirmatory factor analyses. *Scand J Psychol.* 1999;40:293-300.
27. Fitzpatrick TB. The validity and practicality of sun reactive skin types I through VI. *Arch Dermatol.* 1988;124:869-871.
28. World Health Organization. *Physical Status: The Use and Interpretation of Anthropometry.* Geneva, Switzerland: World Health Organization; 1995.
29. Petos R, Doll R. Keynote address: the control of lung cancer. In: Mizell M, Correa P, eds. *Lung Cancer: Causes and Prevention.* New York: Springer-Verlag NY Inc; 1984:1-9.
30. SAS Institute Inc. *SAS STAT User's Guide, Version 6.* 4th ed. Cary, NC: SAS Institute Inc; 1989.
31. Hatcher L. *A Step by Step Approach to Using the SAS System for Factor Analysis and Structural Equation Modeling.* Cary, NC: SAS Institute Inc; 1994.
32. Yin L, Morita A, Tsuji T. Skin aging induced by ultraviolet exposure and tobacco smoking: evidence from epidemiological and molecular studies. *Photodermatol Photoimmunol Photomed.* 2001;17:178-183.
33. George PA, Hole GJ. Factors influencing the accuracy of age estimates of unfamilar faces. *Perception.* 1995;24:1059-1073.
34. George PA, Hole GJ. The influence of feature-based information in the age processing of unfamiliar faces. *Perception.* 1998;27:295-312.
35. Yu CE, Oshima J, Fu YH, et al. Positional cloning of the Werner's syndrome gene. *Science.* 1996;12:258-262.
36. Guarente L, Kenyon C. Genetic pathways that regulate ageing in model organisms. *Nature.* 2000;9:255-262.
37. Vijg J, Van Orsouw N. Searching for genetic determinants of human aging and longevity: opportunities and challenges. *Mech Ageing Dev.* 2002;123:195-205.
38. Jolliffe IT. Factor analysis: overview. In: Armitage P, Colton T, eds. *Encyclopedia of Biostatistics.* Chichester, England: John Wiley & Sons Ltd; 1998:1474-1482.
39. Nagashima H, Hanada K, Hashimoto I. Correlation of skin phototype with facial wrinkle formation. *Photodermatol Photoimmunol Photomed.* 1999;15:2-6.
40. Gilchrest BA. The variable face of photoaging: influence of skin type. *Cosmet Toiletries.* 1992;107:41-42.
41. Cohen PG. The hypogonadal-obesity cycle: role of aromatase in modulating the testosterone-estradiol shunt: a major factor in the genesis of morbid obesity. *Med Hypotheses.* 1999;52:49-51.
42. Wardlaw GM. Putting body weight and osteoporosis into perspective. *Am J Clin Nutr.* 1996;63(suppl):433S-436S.
43. Ghadially R, Brown BE, Sequeira-Martin SM, Feingold KR, Elias PM. The aged epidermal permeability barrier: structural, functional, and lipid biochemical abnormalities in humans and a senescent murine model. *J Clin Invest.* 1995;95: 2281-2290.