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# An Evidence-Weighted Framework for Multifactorial Analysis of Gut Microbiome Effects on Skin Aging

**PD Sawant**

*G5 Solutions, Melbourne*

***Correspondence authors**

**PD Sawant,**
G5 Solutions, Melbourne.

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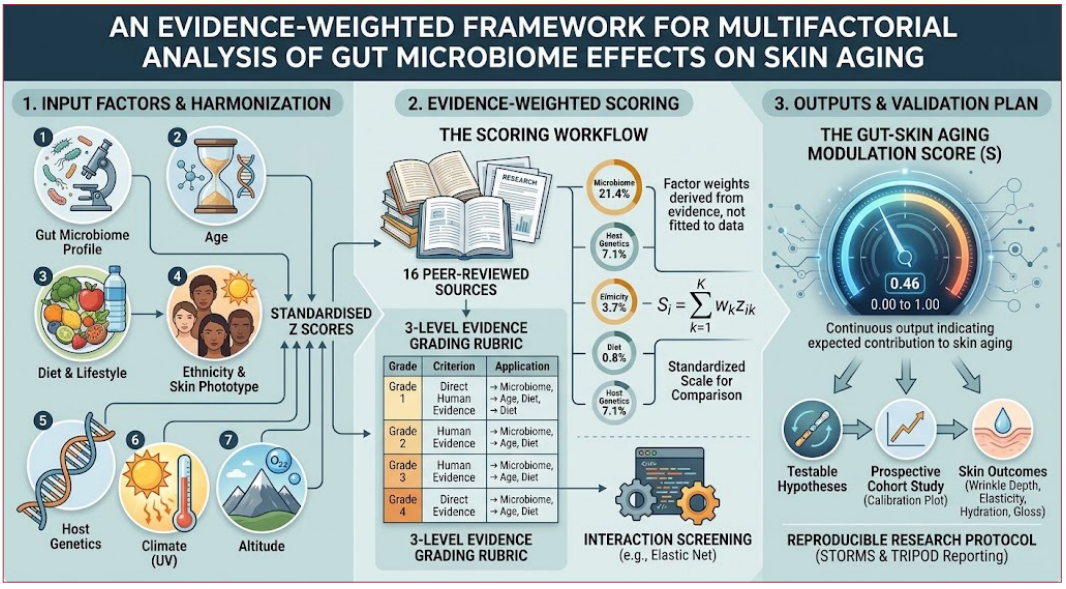
## Abstract

***Background:*** *Skin aging reflects intrinsic processes and environmental exposure, and the gut microbiome has been proposed as a remote modifier acting through immune, metabolic and barrier pathways. The microbiome is itself shaped by age, diet, ethnicity, host genetics and environment, so studies that examine one factor at a time risk confounded interpretation.*

***Objective:*** *This article proposes a conceptual framework, the Gut-Skin Aging Modulation Score, that places gut microbiome composition, chronological age, diet and lifestyle, ethnicity and skin phototype, host genetics, climate and altitude on one standardised scale. Method: Each factor is converted to a z score against a reference cohort and combined with weights derived from a three level evidence grade applied to peer reviewed sources. A five stage workflow covers factor harmonisation, evidence weighted scoring, interaction screening with elastic net* ***regres****sion under false discovery rate control at q = 0.01 and variance inflation diagnostics, outcome mapping, and reporting under the STORMS and TRIPOD checklists. Validation approach: No skin outcome results are reported. A prospective multisite cohort is specified with a planning sample of 606 participants, which gives power of 0.80 at a two sided alpha of 0.01 for an assumed correlation of 0.15. A Monte Carlo analysis of 10,000 synthetic individuals across all 2,187 combinations of one level grade shifts found that the rank order of scores was largely preserved (Spearman correlation 0.88 to 1.00), whereas tertile assignment changed for a median of 14% of individuals. Conclusion: The score is stable in ranking but less stable in tier assignment, so continuous reporting is advised. It is a proposal and not a validated tool, and its usefulness depends on the prospective testing described here.*

**Keywords :** gut-skin axis; skin aging; gut microbiome; evidence-weighted scoring; ethnicity; altitude; inflammaging; short-chain fatty acids; Monte Carlo sensitivity analysis

## Graphical Abstract



## Highlights

- The framework combines seven determinants of gut-skin axis effects on skin aging in one standardized score.
- Factor weights are derived systematically from three-level evidence grading rubric rather than being statistically fitted to data.
- A Monte Carlo analysis shows that score ranks are stable and tier assignment is less stable when grades shift by one level.
- Host genetics, climate and altitude carry the lowest weights because direct evidence linking them to skin aging through the gut is limited.
- This article proposes the use of structured frameworks and simulation workflows to uncover critical parameter relationships, laying a valuable foundation for the future development of personalized nutricosmetic and dermatological products, potentially optimizing clinical trials or reducing and avoiding animal studies to comply with various FDA regulations.

## Introduction

Skin aging develops through intrinsic pathways, including genetics, generation of reactive oxygen species and hormonal change, and through extrinsic pathways dominated by photoageing [1]. The visible result differs between populations. In skin of color, clinical signs of photoaging are reported to appear 10 to 20 years later than in age matched white skin, which suggests that pigmentation and structure alter the effect of a given exposure [2]. Pollution and sunlight add to the burden by driving oxidative stress, which is linked to skin disease and to aging [3]. An independent review describes reactive oxygen species as regulators of ultraviolet induced photodamage, including exogenous aging [4].

Attention has turned to the gut as a remote regulator of these processes. Reviews describe a bidirectional connection between gut and skin in which the gut microbiome is linked to keratinization, to cutaneous immune responses, and to acne, atopic dermatitis and psoriasis [5]. For aging specifically, a recent review argues that aging can perturb the gut microbiome, which in turn accentuates inflammaging by promoting the accumulation of senescent cells, and that probiotics, prebiotics and postbiotics have been associated with better hydration, fewer wrinkles and strengthened barrier integrity [6]. Inflammaging is described as chronic, sterile, low grade inflammation sustained in part by nutrients and gut microbiota [7]. Short chain fatty acids produced by gut bacteria can activate G protein coupled receptors and inhibit histone deacetylases [8], which offers a plausible route from the gut to a distant tissue.

The difficulty is that the gut microbiome is shaped by many of the same factors that shape skin aging. Its composition changes across the life course, with identifiable transition points between infant, adult and elderly profiles in a Japanese cross sectional sample spanning newborns to centenarians [9]. Among 2,084 participants of the HELIUS study living in one Dutch city, individuals tended to share gut microbiota characteristics with others of the same ethnic background, with the Dutch showing the greatest alpha diversity and South Asian Surinamese the smallest [10]. Age, ethnicity, diet and environment therefore act on both the proposed exposure, which is the microbiome, and the outcome, which is skin aging. A study that adjusts for one of them and ignores the others cannot separate a gut effect from a shared cause.

Altitude and climate illustrate the problem. Altitude has been examined in gut microbiome studies, but the sources reviewed here contain no skin endpoint for it, and climate enters the skin literature mainly through ultraviolet exposure [3], [4]. This article therefore treats both as hypotheses and assigns them low weights, as Sections 2.3 and 4 explain.

Existing work treats these determinants in separate literatures. It does not offer a shared scoring structure that lets a reader see, for a given person or population, which determinants are expected to dominate and how strong the supporting evidence is for each. Without such a structure, multifactorial claims about the gut-skin axis remain difficult to compare and difficult to test.

This article proposes a conceptual, literature based framework that places seven determinants on one standardised scale and ties every weight to a stated evidence grade. Machine learning is proposed only for screening interactions and for refining the score once prospective data exist. No skin outcome results are reported. A sensitivity analysis of the weighting rule on synthetic data is reported and labelled as such. Section 2 summarises three source studies, Section 3 gives three equations and their basis, Section 4 sets out five stages, and Sections 5 to 7 cover implementation, discussion and an illustrative application.

## Background

The framework rests on three source studies, each chosen because it supplies exact values for one part of the model: skin outcomes, the balance between genetics and environment, and altitude. Other sources enter in Sections 1, 3 and 5.

## Oral Microbial Intervention and Skin Outcomes

A randomised, double blind, placebo controlled trial of Lactobacillus plantarum HY7714 enrolled 110 volunteers aged 41 to 59 years who had dry skin and wrinkles [11]. Participants received 1 × 1010 CFU per day or placebo for 12 weeks, and hydration, wrinkles, gloss and elasticity were measured every 4 weeks. Wrinkle depth was reduced and gloss improved by week 12 in the probiotic group. Elasticity in that group improved by 13.17% after 4 weeks ($p < 0.05$ versus controls) and by 21.73% after 12 weeks ($p < 0.01$). The authors describe the findings as preliminary confirmation of an anti-aging benefit. The reported endpoints are skin measures, and they supply the outcome vocabulary used in Section 5.

## Host Genetics and Environment

Genotype and microbiome data from 1,046 healthy individuals of several ancestral origins who shared a relatively common environment were analysed together [12]. The gut microbiome

showed no statistically significant association with genetic ancestry, host genetics had a minor role, and genetically unrelated people who shared a household had similar microbiomes. More than 20% of inter-person variability was associated with diet, drugs and anthropometric measurements. A twin study of more than 1,000 fecal samples, including 416 twin pairs, reached a different emphasis, because the abundance of many taxa was influenced by host genetics [13]. The two designs differ. The reading adopted here is that genetics shapes particular taxa while environment dominates overall composition, and this reading is the basis for the low genetics weight in Section 4.

## Altitude and the Gut

A longitudinal study of 610 healthy young men at three locations in China, grouped by altitude, duration of residence and ethnicity, found that Han Chinese participants moving from low to high altitude developed gut microbiota that converged toward that of Tibetan populations and reversed on return [14]. Prevotella copri was the most enriched taxon in both groups at high altitude, and 41 plasma metabolites, including lactic acid, sphingosine-1-phosphate, taurine and inositol, were elevated in Han participants after ascent. An earlier comparison at 3600 m found Prevotella enrichment in Tibetans and Bacteroides enrichment in Han residents, and Tibetan herders at 4800 m had a flora enriched in butyrate-producing bacteria relative to rural Tibetans at 3600 m [15]. Both studies report gut and plasma outcomes. Neither reports a skin outcome, so any route from altitude to skin aging through the gut remains hypothetical.

## Theoretical Foundations

The framework uses three equations, and the basis of each is stated. Equation (1) forms the score for person i from K standardised factors.

$$S_i = \Sigma_{k=1}^{K} w_k z_{ik} \quad (1)$$

Where, $z_{ik}$ is the standardised value of factor *k* for person i, and wk is its weight.

Each factor is oriented so that a higher value means a greater expected contribution to skin aging, and standardisation expresses each factor in reference cohort standard deviations, which allows variables with different units to be added. A weighted sum of this form is how polygenic risk scores are built, by summing genotype counts weighted by effect size estimates [16]. Only the form is borrowed here, and the weights have a different origin.

$$wk = gk / \Sigma_{j=1}^{K} g_j \quad (2)$$

The evidence grade gk takes the value 1, 2 or 3 according to the rubric in Table 3. Rating evidence by explicit grades follows the principle of the GRADE approach, which rates the quality of evidence in a transparent system [17]. This article adapts that principle to three levels. Converting grades into proportional weights is a proposal of this article and has no precedent in the cited sources, which is why Section 5.3 tests its sensitivity.

$$Y_i = \beta_0 + \beta_1 S_i + \varepsilon_i \quad (3)$$

In the prospective cohort, a skin aging outcome $Y_i$, such as elasticity or wrinkle depth, is regressed on the score. The slope $\beta_1$ is unknown, its sign is not assumed, and no value is reported.

Regressing observed values on predicted values and inspecting the slope is a recognised calibration check for prediction models [18]. Together the equations separate how factors combine, how evidence sets the weights, and whether the score predicts skin outcomes, which Equation (3) poses and leaves open.

The framework has five stages. Targets given below are proposed design targets and are not results.

Harmonisation (Stage 1) defines the seven factors and their measured variables. Gut microbiome composition is represented by Shannon alpha diversity and by the relative abundance of short chain fatty acid producing taxa from 16S rRNA or shotgun sequencing, with the sign reversed so that a deficit scores high. Age is recorded in years, and diet and lifestyle with a validated food frequency questionnaire. Ethnicity is self reported, with genetic ancestry added where available, together with Fitzpatrick phototype. Host genetics is represented by family history of early skin aging or by a polygenic score where one exists. Climate is the mean annual ultraviolet index at the residence, and altitude is metres above sea level. Reference cohort means and standard deviations are stored with the weights file so that any later user can reproduce each z score. The named metric is variable completeness, with a proposed target of at least 90% per factor.

Weighting (Stage 2) assigns each factor an evidence grade of 1, 2 or 3 using the rubric in Table 3, and converts the grades to weights with Equation (2). Table 1 lists the resulting proposed weights. Because the weights depend entirely on the grades, this stage includes the perturbation analysis in Section 5.3. The named metric is rank stability, defined as the Spearman correlation between baseline scores and scores under shifted grades, with a proposed target of at least 0.90 in at least 95% of all grade shift combinations.

Screening (Stage 3) uses machine learning only to ask whether the additive score misses structure. Elastic net regression [19] with ten fold cross validation screens the 21 pairwise interaction terms among the seven main effects. Main effects are centred before products are formed. Every retained interaction term is then tested in the final model, and the 21 p values are adjusted with the Benjamini-Hochberg procedure [20] at a false discovery rate of q = 0.01. Variance inflation factors are computed for all main effects and retained terms, and a value of 5 or more flags a term for review. Because fixed variance inflation thresholds are rules of thumb that can mislead [21], a flag triggers inspection of coefficient standard errors and does not by itself remove a term. The random seed, folds and penalty grid are recorded, with the elastic net mixing parameter set on a grid from 0.1 to 1.0 in steps of 0.1. The named metric

is selection stability across 100 bootstrap resamples, with a proposed target of at least 0.80 for any retained term.

Mapping (Stage 4) relates the score to skin outcomes through Equation (3) in a prospective cohort. Outcomes follow the measurements used in the probiotic trial in Section 2.1, namely wrinkle depth, elasticity, hydration and gloss [11]. Follow up is proposed at 12 weeks to match the trial interval. An external cohort that played no part in weighting or screening is held out for calibration [18]. The named metric is the calibration slope in that cohort, with a proposed target between 0.90 and 1.10.

Reporting (Stage 5) documents the study with the STORMS checklist for microbiome studies [22] and the TRIPOD checklist for prediction models [23], and versions the weights as new evidence appears. The named metric is checklist completion, with a proposed target of all 17 STORMS items and all 22 TRIPOD items.

**Table 1:** Proposed factors, evidence grades and weights (proposed, not fitted to data). Weight equals grade divided by 14, rounded to three decimals.

| Factor | Measured variable | Grade | Weight | Principal basis |
|---|---|---|---|---|
| Gut microbiome composition (deficit) | Shannon diversity; abundance of SCFA producers | 3 | 0.214 | [5], [6], [8], [11] |
| Chronological age | Years | 3 | 0.214 | [1], [7], [9] |
| Diet and lifestyle | Food frequency questionnaire | 3 | 0.214 | [8], [12] |
| Ethnicity and skin phototype | Self report; Fitzpatrick type | 2 | 0.143 | [2], [10] |
| Host genetics | Family history; polygenic score if available | 1 | 0.071 | [12], [13] |
| Climate (UV exposure) | Mean annual UV index at residence | 1 | 0.071 | [1], [3], [4] |
| Altitude | Metres above sea level | 1 | 0.071 | [14], [15] |

## Implementation and Validation

### Data Preparation

Raw sequence data are processed with a documented pipeline whose software versions are recorded, and sequencing batch identifiers are retained as covariates. Each factor is standardised against a reference cohort drawn from the same population as the study sample, because a z score computed against a foreign cohort would embed that cohort's ethnicity and diet. Missing values are reported by factor, and a factor with more than 10% missing data is handled by multiple imputation with a complete case analysis as a sensitivity check. The orientation of every factor is fixed before analysis begins. Data governance for the prospective cohort requires approval from an institutional human research ethics committee before recruitment, written informed consent, pseudonymised identifiers with the linkage key held separately, encrypted storage with role based access, a data access committee for external requests, deposit of sequence data in a controlled access repository, and a retention period set by the ethics approval.

### Analysis Protocol

The primary analysis estimates β1 in Equation (iii) with outcomes measured at baseline and after follow up. Covariates not already in the score, such as sex and menopausal status, are prespecified because hormonal change is an intrinsic pathway of skin aging [1]. Interaction screening in Stage 3 runs on a training partition, and only retained terms are carried to the test partition. The primary hypothesis test uses a two sided alpha of 0.01, interaction tests are controlled at a false discovery rate of $q = 0.01$, and outcome assessors are blinded to the score. All thresholds are fixed in a registered protocol.

### Validation

Sample size follows from the primary test of β1. The planning assumption is a correlation of 0.15 between the score and an outcome, a small to moderate association chosen for planning and not taken from a cited source. For a two sided alpha of 0.01 and power of 0.80, which corresponds to a type II error of 0.20, the Fisher z approximation gives 515 participants. Allowing 15% attrition, the planning sample is 606. If the true correlation is 0.10, 1,164 participants are needed (1,369 with attrition), and if it is 0.20, 288 (338 with attrition). Interaction tests and the external calibration cohort need larger samples, to be set by simulation once pilot variances exist.

Validation proceeds in three layers. Bootstrap resampling estimates optimism in calibration. External validation uses a cohort recruited at different altitudes and climates, which also tests the two lowest weighted hypotheses directly. A comparison of calibration under evidence grade weights, equal weights and fitted weights shows whether fitting becomes worthwhile. No outcome result is reported in this article.

Because the grades are subjective, the sensitivity of the weighting rule was examined by Monte Carlo simulation. Ten thousand synthetic individuals were generated with seven independent standard normal factor values and a fixed random seed (20261010). Each of the 2,187 combinations of shifting every grade by minus one, zero or plus one level, bounded between 1 and 3, was applied, and the perturbed score was compared with the baseline score by Spearman correlation and by agreement of tertile assignment. Table 2 gives the single factor shifts. Across all combinations the Spearman correlation had a minimum of 0.883, a median of 0.967 and a fifth percentile of 0.921, and it was at least 0.90 in 2,176 of 2,187 combinations (99.5%). Tertile agreement had a minimum of 0.730, a median of 0.857 and a fifth percentile of 0.781, and no more than 0.51% of individuals moved by two tiers. When the factors were given a pairwise correlation of 0.3, the minimum Spearman correlation rose to 0.967 and the median tertile agreement to 0.923. These values describe the scoring rule under assumed inputs and say nothing about accuracy against

skin outcomes. They support a limited conclusion: rank order is preserved under one level grade shifts, whereas tier membership is not, with a median of 14.3% of individuals changing tier.

**Table 2:** Monte Carlo perturbation matrix for single factor grade shifts. Synthetic data, 10,000 individuals, independent factors. At bound means the grade cannot move beyond 1 or 3, so the score is unchanged.

| Factor | Baseline grade | Shift -1: Spearman | Shift -1: tertile agreement | Shift +1: Spearman | Shift +1: tertile agreement |
|---|---|---|---|---|---|
| Gut microbiome | 3 | 0.986 | 0.909 | at bound | at bound |
| Age | 3 | 0.986 | 0.908 | at bound | at bound |
| Diet and lifestyle | 3 | 0.986 | 0.907 | at bound | at bound |
| Ethnicity and phototype | 2 | 0.984 | 0.903 | 0.987 | 0.911 |
| Host genetics | 1 | at bound | at bound | 0.985 | 0.906 |
| Climate (UV) | 1 | at bound | at bound | 0.985 | 0.902 |
| Altitude | 1 | at bound | at bound | 0.985 | 0.907 |

## Retrieval Scoring

Sources are retrieved and graded before any weight is computed. Table 3 gives the rubric. A source is admitted only if its article page resolves to the stated record. The grade attaches to the evidence a source offers for the factor's modification of the gut-skin pathway and not to the factor's effect on skin aging in general. Each grade is recorded with a one line justification that points to the supporting passage.

**Table 3:** Evidence grading rubric used for retrieval scoring.

| Grade | Criterion | Applications |
|---|---|---|
| 3 | Direct human evidence from a randomised trial or large cohort, supported by an independent mechanistic or review source | Microbiome [11] with [5], [6], [8]; age [9] with [7]; diet [12] with [8] |
| 2 | Direct human cohort or review evidence of a population difference, without a described gut to skin mechanism | Ethnicity and phototype [2], [10] |
| 1 | Indirect or conflicting evidence, or evidence for the gut without any skin endpoint | Genetics [12], [13]; altitude [14], [15]; climate [1], [3], [4] |

## Reproducibility Checklist

1. Register the protocol, including weights, thresholds and analysis plan, before data collection.
2. Archive the grading sheet, source list, reference cohort statistics and weights file with a version date.
3. Record software versions, random seeds (20261010 for the simulation), cross validation folds and the penalty grid.
4. Deposit analysis code, including the Monte Carlo script, and a data dictionary in a public repository.
5. Complete the STORMS and TRIPOD checklists and submit them with the manuscript.
6. Report every prespecified metric, including those that miss their targets.

## Discussion

### Advantages

The position taken here is that an evidence graded additive score is a better starting point for this field than a fitted model, because the available data cannot support fitting. None of the sources reviewed measures gut composition, ethnicity, altitude and skin aging in the same people, and a model fitted to partial data would encode the quirks of those data. The grade to weight rule is crude but explicit and auditable, and the simulation shows that ranking is not sensitive to a one level change in any single grade.

### Interpretability

Because Equation (1) is additive, each factor's contribution is the product of its weight and its z score, which a reader can verify by hand, as Section 7.2 shows. Additivity is the least presumptuous assumption when evidence of interaction is absent, and Stage 3 exists to test it.

### Limitations

The framework cannot establish the causal direction between the microbiome and skin aging. Aging can perturb the gut microbiome [6], and inflammaging is sustained in part by gut microbiota [7], so a cross sectional link between a microbiome deficit and a poor skin outcome is compatible with causation in either direction. Longitudinal sampling with repeated skin measures, or an interventional design such as that in Section 2.1 [11], would separate the directions.

The additive score cannot represent non additive effects at the weighting stage. Ethnicity may modify the effect of diet on the microbiome, and age may modify the effect of altitude, but Equation (i) gives each factor a single slope. Stage 3 can detect such terms only in cohorts large enough to estimate pairwise interactions with acceptable stability, so a multisite cohort with a sample size set by simulation would be needed.

The three level grade is a coarse ordinal scale, and the simulation shows the consequence. Rank order is preserved, yet a median of 14.3% of synthetic individuals, and up to 27%, change tertile under one level shifts, so tier assignment near a cut-off can reflect a grading choice alone. The simulation assumed independent factors, and correlation among real factors reduced the effect in the correlated scenario without removing it. Pooled effect sizes from a formal meta-analysis would replace grades once enough comparable studies exist, and continuous reporting of the score is advised until then.

It is uncertain whether altitude or climate act on skin aging through the gut at all. The altitude studies report gut and plasma outcomes only [14], [15], and the skin literature treats climate through ultraviolet exposure [1], [4]. A cohort that measures gut composition and skin biophysical outcomes at several altitudes would address the question.

## Broader Context

Ethnicity enters the score as a proxy and not as a biological category. In the HELIUS data, ethnic groups differed in microbiota while sharing a city [10], and genetic ancestry did not explain microbiome differences in a separate cohort [12], which points toward shared diet and household environment as the likely carriers. The framework should therefore not be read as ranking populations. Reference [3] is authored by the present author and supports only the statement on oxidative stress, which an independent review [4] also supports. The intended use is to prompt stratified study designs, so that an intervention effect such as that in [11] can be examined across levels of the factors in Table 1.

## Illustrative Application Scenario

### Corpus

The corpus is the set of peer reviewed sources in the reference list, together with a hypothetical reference cohort that is described only to define z scores. The reference cohort is not real, and no data from it are reported. Two hypothetical individuals, labelled Person A and Person B, are used to show the arithmetic. All values for them are synthetic and illustrative, chosen within the plausible range of a standardised score, and none is measured.

### Stage by Stage Application

In Stage 1, seven standardised values are assigned to each person. In Stage 2, the weights from Table 1 apply. Stage 3 is not run because it requires a real dataset, and in Stage 4 only the score is computed and no outcome is predicted. Stage 5 is represented by Table 4, which records every input. Person A has a microbiome deficit and moderate ultraviolet exposure, which gives a score of 0.46 despite a younger age. Person B has an older age and a higher genetic value but a favorable microbiome and diet, which gives 0.32. The numbers show how the weights shape the contribution of each factor. They are not predictions about any person.

**Table 4:** Synthetic, illustrative worked example. Values are not measured data.

| Factor | Weight | z (A) | Contribution (A) | z (B) | Contribution (B) |
|---|---|---|---|---|---|
| Gut microbiome deficit | 0.214 | +1.0 | 0.214 | -0.5 | -0.107 |
| Age | 0.214 | +0.5 | 0.107 | +1.5 | 0.321 |
| Diet and lifestyle | 0.214 | +0.5 | 0.107 | -0.5 | -0.107 |
| Ethnicity and phototype | 0.143 | 0.0 | 0.000 | +0.5 | 0.071 |
| Host genetics | 0.071 | 0.0 | 0.000 | +1.0 | 0.071 |
| Climate (UV) | 0.071 | +0.5 | 0.036 | 0.0 | 0.000 |
| Altitude | 0.071 | 0.0 | 0.000 | +1.0 | 0.071 |
| Score S, Equation (1) | | | 0.46 | | 0.32 |

### Trade-off Table

**Table 5:** Qualitative comparison of scoring approaches.

| Approach | Interpretability | Data Requirement | Overfitting Risk | Dependence on Evidence Grades |
|---|---|---|---|---|
| Evidence-weighted additive score (proposed) | High, each contribution can be checked by hand | Low, a reference cohort for z scores | Low | High, weights change if grades change |
| Fitted multivariable model | Moderate, interactions are harder to read | High, joint measurement of all factors | Moderate to high | None |
| Machine learning on all factors | Low to moderate without added explanation tools | Very high | High without external validation | None |
| Single microbiome biomarker | High | Moderate | Low | Not applicable, other factors ignored |

The proposed score accepts a poorer fit in exchange for transparency and a low data demand, which is the right trade while joint datasets do not exist. Once they do, the fitted model becomes the stronger comparator, and the comparison of calibration under three weighting schemes in Section 5.3 is designed to show when that point has been reached.

This article proposes the use of structured frameworks and simulation workflows to uncover critical parameter relationships, laying a valuable foundation for future personalized nutricosmetic and dermatological product development, potentially optimizing clinical trials or reducing or avoiding animal trials in the future validations.

## Conclusion

A single standardised score is proposed to organise the evidence on how gut microbiome composition, age, diet, ethnicity and phototype, host genetics, climate and altitude may jointly shape skin aging. The contribution is structural: seven determinants, three equations with stated bases, and five stages, with every weight tied to a stated evidence grade and every target declared in advance. The scope is limited to proposal. No skin outcome results or accuracy figures are reported, and the synthetic values used in the simulation and the worked example are labelled as such. Host genetics, climate and altitude carry the lowest weights because the sources reviewed provide little direct evidence for them. Reproducibility rests on a registered protocol, an archived grading sheet, reference cohort statistics and weights file, recorded software versions, seeds and folds, public analysis code including the simulation script, and complete STORMS and TRIPOD reporting. The framework may help the development of personalized treatments of aging.

## Declarations

Conflict of interest: The author declares no competing financial interests.


## Funding

This work received no external funding.


## Ethics

The work used no human participants, human tissue, personal data or animals, so ethics approval was not required.

## Data availability

All values come from the cited sources. The synthetic values in Tables 2 and 4 were produced by a simulation.

## Author contributions

PD Sawant conceptualized the framework, verified the sources, created and reviewed the simulation created using Claude Sonnet 5.5.

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