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The Inverse Way to Study the Relationship of Diet with Health and Disease

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Abstract

To study the relationship of dietary score versus age at death (AD) in an extinct cohort at 61 years of follow-up, based on an "inverse" procedure. Data from the Italian Rural Areas (IRA) of the Seven Countries Study of Cardiovascular Diseases, made up of 1712 middle-aged men followed for 61 years, were used. The "direct" approach means applying a dietary score to each subject of a cohort and, by means of a model, estimating the probabilities of events for different dietary score levels. The "inverse" approach, instead, compares the levels of the dietary score, separately, in subjects with an event versus those without it. In the "direct" approach, the factor scores from a Principal Components Analysis of 19 food groups were divided into 3 tertiles (more or less healthy than the central tertile), and the levels of AD were estimated and compared across the 3 dietary classes. In the "inverse" approach, the events were divided into 3 groups of different severity (that is different levels of AD) and the actual consumed food groups were computed for each of the 3 classes. Findings compared across the 3 AD classes of the "inverse" approach did not show substantial contradictions with the "direct" approach results, but only some differences with the "direct" approach that selects more statistically significant food groups than the “inverse” one. Plant foods, olive oil, and fish favored higher levels of AD in both approaches, while butter intake had an adverse effect. Mean levels of AD across 3 AD classes were 61.5, 75.1, and 87.2 years, and there were clearly significant trends in consumption of these critical food groups. Two approaches, i.e., “direct” and “inverse,” to study the relationship between dietary score and AD yielded similar findings, forming a reciprocal confirmation.

Keywords
Age at death; food groups; nutrients; dietary score; direct and inverse approaches

1. Introduction

This is not an analysis focused on predicting age at death as a function of dietary food groups and/or other determinants. The purpose is only to see whether using dietary food groups with a numerical approach different from the traditional one yields similar findings. Age at death is simply used as the endpoint chosen for this purpose.

In the traditional way to search for a diet, a dietary score, or similar tools consisted of defining a diet from the available data and then seeing whether it is associated with good or bad outcomes of any kind of events in the study population, a procedure that we arbitrarily call the “direct” approach. The definition of a dietary score can be made *a priori*, that is, defining its composition using the available food groups and/or nutrients, on the basis of the opinions of the investigators, or *a posteriori*, assigning this task to computer procedures and models that take this decision on the basis of statistical interplays and procedures, largely independent from the investigators’ opinions. Then, the selected diet is statistically associated with the cohort events using predictive models to determine whether the diet, or subclasses of the diet, are related to the occurrence of events and/or with different probabilities.

Actually, it has been shown that *a priori* and *a posteriori* procedures perform in similar ways [1], although the latter is used very rarely. These have been the traditional approaches that have identified several diets or dietary scores, such as the Mediterranean Diet [2] and several others. The number of these proposals is rather large. We may just mention some of them as examples, like the WHO diet proposal [3], the Mediterranean diet pyramid [4], the Healthy Eating Index [5], the DASH dietary rules against hypertension [6], some major Greek scores [7, 8], the Mediterranean Adequacy Index [9], two reports from the EPIC project [10, 11], the NIH-AARP Diet [12], an Italian *a-posteriori* index [13], the Alternative Healthy Eating Index [14], and many more. In a review of *a priori* Mediterranean scores, 30 were mentioned and commented on [15]. All these dietary scores, following various statistical approaches and variables, such as the length of follow-up, have shown their ability to predict all-cause mortality risk, often indicating that a diet rich in vegetables and fish is protective. In contrast, a diet rich in animal foods and sugar products does increase the risk. Clearly, many other papers adopting different choices reported the role of dietary habits in relation to all-cause mortality, although none reached the cohort's extinction. Actually, the literature is full of contributions of this type, and mention of many others would be redundant and useless, because describing their accomplishments has nothing to do with the main purpose of the present analysis, which deals only with technical issues.

We were stimulated to try a different approach, that is, an "inverse" approach, to validate the conclusions of studies conducted with the "direct" approach. This means to identify, in a population study, a subgroup of individuals who, after a sizable period of time, were exempt from a defined endpoint or carrying the disease or anyhow in a better or worse shape than others in terms of disease or death, and to describe their diet based on actual food groups used by people with versus those without events or with different ones.

Both "direct" and "inverse" approaches require the availability of dietary analysis at baseline and of events at the end of follow-up. The difference is the direction of the study, i.e. in the "direct" approach the diet goes to search for events, while in the "inverse" approach" the procedure goes the other so that the events go back to search for their original diets (Figure 1). Reviewing randomly some major studies of this type, we had the impression that such an "inverse" approach was not previously considered systematically, although it is quite difficult to assure that this is true.

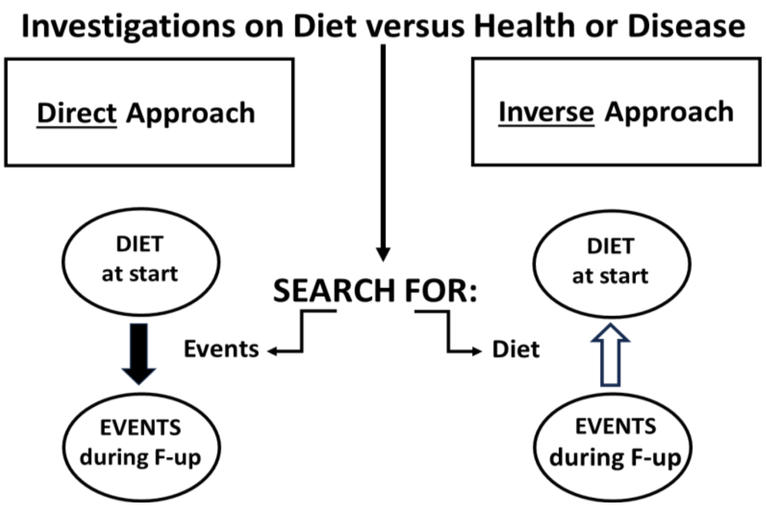

Figure 1 Structure of direct and inverse approach in studying diet versus health and disease.

2. Materials and Methods

2.1 Population and Measurements

We used data from the Italian Rural Areas (IRA) of the Seven Countries Study, first measured in 1960, when the baseline examination was made on 1712 middle-aged men (aged 40-59) out of 1735 listed in the roster of two rural municipalities, with an entry participation rate of 98.7% [16]. The entry examination included the measurement of many risk factors and personal characteristics, as reported elsewhere [16]. All measurement techniques underwent strict standardization procedures, and several variables were excluded because they were not suitable for standardization at that time.

In the early phases of the study, a dietary survey was conducted, based on dietary history using an *ad-hoc* questionnaire administered by trained and supervised nutritionists. These data allowed us to identify 19 food groups. and to estimate the amounts of several nutrients on the basis of local food tables [17]. The list of food groups used here is a minor, more specific variant of previous analyses, since we could split the generic oils intake into olive oil and seed oils.

Using the 19 food groups, a dietary score was computed using the *a posteriori* procedure of Principal Components Analysis (PCA) and dividing the resulting individual factor scores into 3 tertiles. Based on their food group content and a series of preliminary predictive analyses, the 3 classes were arbitrarily called Non-Healthy Diet, Intermediate Diet, and Healthy Diet. Since we used 19 instead of 18 food groups, this score was slightly different from those computed and analyzed in previous contributions. Details can be found in older publications [18-20].

Follow-up for mortality and survival was almost complete after 61 years, when the cohort was practically extinct. In fact, among 1712 men examined at entry, there were 1708 deaths (99.8%), 3 survivors, and 1 lost to follow-up after 50 years.

As an endpoint for analytical purposes, we selected age at death (AD) instead of all-cause mortality because the cohort was practically extinct. AD is an old demographic metric that has been recently re-evaluated [21, 22], whose use in cohort studies is proper only if the cohort is extinct or nearly extinct. It has some similarities with life expectancy, but it is represented by a unique number summarizing the lifelong experience of health and disease.

2.2 Statistical Analysis

The 19 food groups of baseline examination were adjusted for 1000 calories and presented in Table 1 in a descriptive fashion.

Table 1 Baseline mean levels of variables used for the analysis in the study population. Food groups and nutrient nutrients' intake expressed in grams per 1000 Kcal.

	FOOD GROUPS				
	Mean	**SD**	**Median**	**25th and 75th percentile**	
Bread	120.8	60.0	113.5	87.4	144.2
Cereals	41.6	19.7	38.5	30.0	48.0
Potatoes	8.4	8.6	7.2	3.1	10.5
Vegetables	19.1	17.6	16.0	8.6	23.9
Legumes	1.5	4.4	0.7	0	1.6
Fruit	64.9	55.7	56.4	22.1	90.8
Sugar	4.6	4.6	4.1	0	6.4
Olive oil	10.6	8.3	9.6	5.4	14.8
Seed oil	3.2	6.2	0	0	4.2
Meat	40.8	25.1	37.0	24.6	51.2
Fish	7.6	7.2	6.6	3.6	9.7
Eggs	6.1	7.3	4.9	0.9	7.6
Butter	4.1	5.4	2.3	2.3	6.6
Margarine	3.5	5.5	0	0	5.7
Milk (solid component)	4.2	5.8	1.9	0	6.8
Cheese	5.0	7.4	3.7	1.1	5.8
Pastries	4.4	8.1	2.2	0	5.6
Alcohol	26.9	18.4	24.3	16.6	32.3
Sugar beverages (solid component)	0.2	0.9	0	0	0
Energy, Kcal	2941	642	2935	2584	3232

SD: standard deviation.

For the "direct" approach, a multiple linear regression (MLR) model was solved with AD as the endpoint and 3 tertiles of factor scores as covariates. AD was attributed also to the 3 survivors and to the subject lost to follow-up when he was aged 91 years, adopting the last age when seen alive. The MLR estimated differences in AD across the 3 arbitrary factor-score (tertile) classes, and the levels of food groups within these tertiles could be computed. This approach was basically probabilistic. For the so-called "inverse" approach, AD, in its role of endpoint, was arbitrarily divided into 3 age classes: class 1 (41 to 69 years with N = 578); class 2 (70 to 79 years with N = 555); class 3 (80 to 106 years with N = 579). Incidentally, the size of the 3 classes almost corresponded to 3 tertile classes of AD. Then, the actual mean baseline levels of 19 food groups, expressed in grams per 1000 calories, were distributed into the 3 classes of AD. Comparisons across the 3 classes were made using ANOVA. This approach was basically descriptive. Using the 7 significant food groups identified in the "inverse" approach, another PCA analysis was computed, and the distribution of food groups into 3 classes of AD was reported. Finally, two MLR models were produced with AD as the endpoint and, separately, with the factor score derived from the 19 food groups used in the "direct" approach as a covariate versus the one derived from the 7 food groups found significant in the "inverse" approach.

3. Results

3.1 Baseline Characteristics

Baseline dietary habits are described in Table 1, which includes the mean levels of 19 food groups. These figures are, more or less, those expected in a Mediterranean rural population in the 1960's, with relatively high levels of carbohydrates (roughly 45% of total energy), plant food and olive oil, low levels of fat and SAFA, plus quite high levels of MUFA and PUFA (nutrient data not reported in detail). Alcohol intake was almost entirely from red wine and accounted for around 20% of energy.

3.2 Direct Approach

The MLR of the "direct" approach (Table 2) shows that, when solving the model as a function of dietary score, there is a gradient of AD across the 3 dietary score classes. There is a clear advantage for subjects in the upper dietary score class, with AD in the upper class being more than 4 years higher than in the reference class. Then, comparisons between a healthy and a non-healthy diet showed large and significant differences across most food groups, in a direction that justifies the names adopted for the 3 tertile distributions. Altogether, 15 of 19 food groups provided significant ANOVA (including trends) across the 3 classes of factor score. A major difference is related to olive oil intake, which is much higher in the healthy diet group. At the same time, unexpected findings are a slightly higher intake of cheese and sugar in the healthy diet class. Mean levels of the dietary factor score were distributed across 3 tertiles, with increasing values from class 1 to class 3.

Table 2 Direct approach. Multiple linear regression (MLR) of age at death (AD) as a function of 3 tertiles of dietary factor score, resulting in the mean AD, food groups intake distributed in tertiles of factor score. All food groups are expressed in grams per 1000 Kcal.

	MLR of age at death as a function of 3 tertiles of dietary factor score			
	Coefficient	**95% CI**	**p value**	**Age at death**
Intercept	72.17	----	**----**	----
Dietary score tertile 1	Reference	----	**----**	72.2
Dietary score tertile 2	2.86	1.53 4.19	**<0.0001**	75.0
Dietary score tertile 3	4.44	3.11 5.77	**<0.0001**	76.4
p value	----	----	**----**	**<0.0001 (ANOVA)**
	FOOD GROUPS IN TERTILES OF DIETARY FACTOR SCORE			
	Tertile 1 Non-healthy Diet	**Tertile 2 Intermediate diet**	**Tertile 3 Healthy diet**	**P of ANOVA**
Bread	113.2	119.3	128.8	**<0.0001 (*)**
Cereals	41.1	39.4	44.2	**0.0002 (*)**
Potatoes	8.7	7.8	8.7	0.1389
Vegetables	16.1	18.0	23.0	**<0.0001 (*)**
Legumes	1.7	1.5	1.3	0.1661
Fruit	64.2	56.9	73.8	**<0.0001 (*)**
Sugar	4.6	4.1	5.3	**<0.0001**
Olive oil	3.8	9.5	18.5	**<0.0001**
Seed oil	8.9	0.7	0.2	**<0.0001 (*)**
Meat	43.1	37.7	41.5	**0.0010**
Fish	6.8	6.8	9.2	**<0.0001 (*)**
Eggs	5.9	6.1	5.9	0.8931
Butter	5.8	3.6	2.8	**<0.0001 (*)**
Margarine	2.3	3.5	4.7	**<0.0001 (*)**
Milk (solid component)	4.7	3.8	4.1	**0.0219**
Cheese	4.6	4.4	4.7	**0.0004 (*)**
Pastries	12.7	11.2	13.6	0.1869
Alcohol	30.8	26.4	23.5	**<0.0001 (*)**
Sugar beverages (solid component)	0.10	0.10	0.34	**<0.0001 (*)**
Energy, Kcal	2975	3075	2771	**<0.0001**
Dietary factor score	-1.0479	0.1329	0.9153	**<0.0001**

CI: confidence intervals. (*) Significant also for the trend.

3.3 Inverse Approach

In the "inverse" approach, we started with 3 arbitrary AD classes whose average levels spanned about 25 years. The actual shape of dietary habits (Table 3) shows that men in the highest AD class had food group intake in line with those in the upper tertile of the general population, characterized by higher levels of plant foods, olive oil, fish, margarine, and lower levels of butter. However, only 7 food groups were found to be significant across the 3 classes in the "inverse" approach analysis, but, in general, similar trends can be seen in other food groups' intake across the 3 AD groups. Overall energy intake, instead, was not substantially different across the same groups. All comparisons reported in Table 2 and Table 3 were statistically significant, also for trends, increasing in this way their value, showing a dose-response shape.

Table 3 Inverse approach. Mean age at death (AD) in 3 arbitrary AD classes, actual levels of dietary habits in 3 AD classes, and mean dietary factor score in 3 AD classes. Food groups expressed in grams per 1000 Kcal.

	MEAN AGE AT DEATH in 3 arbitrary classes			
	41-69 years	**70-79 years**	**80-106 years**	**P of ANOVA**
Mean age at death years	61.5	75.1	87.2	**<0.0001 (*)**
N	578	555	579	----
Food groups				----
Bread	112.2	122.7	127.6	**<0.0001 (*)**
Cereals	39.7	42.5	42.7	**0.0142 (*)**
Potatoes	8.0	8.5	8.7	0.3456
Vegetables	16.6	19.5	21.1	**<0.0001 (*)**
Legumes	1.5	1.6	1.3	0.3288
Fruit	63.6	64.9	66.5	0.6849
Sugar	4.4	4.8	4.6	0.4034
Olive oil	9.6	11.1	11.2	**0.0007 (*)**
Seed oil	3.5	3.2	3.0	0.3625
Meat	40.3	40.6	41.3	0.7826
Fish	7.0	7.5	8.3	**0.0160 (*)**
Eggs	5.5	6.3	6.1	0.1084
Butter	4.5	4.0	3.7	**0.0378 (*)**
Margarine	3.0	3.5	3.9	**0.0214 (*)**
Milk (solid component)	4.2	4.0	4.3	0.5616
Cheese	4.7	5.0	5.3	0.4696
Pastries	13.6	11.7	12.2	0.3340
Alcohol	28.1	26.9	25.7	0.09326
Sugar beverages	0.2	0.2	0.1	0.2470
Energy, Kcal	2960	2947	2915	0.4682

(*) Significant also for the trend.

3.4 Other Analyses

Using the 7 significant food groups identified above in the "inverse" approach, we ran another version of the "direct" approach, solving a new PCA analysis that was associated with a spread of food groups in tertiles of factor scores definitely larger than in the previous case based on all 19 food groups (Table 4). This represents another version of a "direct" approach, suggesting that preselected food groups provide definite good discrimination in their association with AD.

Table 4 Distribution of food groups in 3 tertile classes of factor score derived from another PCA computed on the 7 food groups that were significant in the "inverse approach" analysis reported in Table 3. Food groups in grams per 1000 Kcal.

	Tertiles of factor score			
	1	**2**	**3**	**P of ANOVA**
Bread	85.8	124.0	162.6	**<0.0001 (*)**
Cereals	31.9	40.5	52.4	**<0.0001 (*)**
Vegetables	9.9	16.3	31.0	**<0.0001 (*)**
Olive oil	5.8	10.6	15.5	**<0.0001 (*)**
Fish	4.2	6.8	11.9	**<0.0001 (*)**
Butter	6.6	3.9	1.8	**<0.0001 (*)**
Margarine	0.5	2.2	7.8	**<0.0001 (*)**
Age at death, years	72.9	74.6	76.3	**<0.0001 (*)**

(*) Significant also for the trend.

Finally, two MLR models were produced with AD as end-point –as predictor- the factor score derived from the initial model with 19 food groups and -separately- the one derived from the one considering the 7 food groups that were significant in the "inverse approach". They were not reported in detail, but we compared them using the linear coefficients of observed versus estimated AD of the two approaches. They were slightly greater for the 19 food groups model but not significantly different from the model with the 7 food groups (p of difference = 0.3703). This was an indirect proof of the similarity of the two approaches.

4. Discussion

This analysis had technical purposes, and the meaning focused on the attempt to see whether a numerical approach, different from the traditional one in studying the relationship of diet with disease, may reach similar conclusions. The concept of a "direct" dietary approach means adopting the characteristics of a dietary pattern and applying them to a given population, with the (probabilistic) aim of determining whether they may predict different risk levels for a given morbidity or other events. The "inverse" dietary approach, on the opposite side, starts from a population sample and measures the dietary characteristics among groups carrying or not carrying a given morbidity or outcome. In the latter case, the approach is descriptive and not probabilistic.

The material of this analysis was already largely exploited in terms of "direct approach" [18-21]. For example, a contribution in 2022 [20] provided a multiple linear regression with AD as the endpoint and including as predictors the same ("direct") dietary score plus 32 other variables, including social data, traditional risk factors, behavioral lifestyle habits, clinical signs, and several major prevalent diseases. The dietary score, subdivided into 3 tertiles, showed strong predictive power in the presence of many potential confounders, but without multicollinearity. The study population in this analysis is highly specific, as it is limited to middle-aged men from rural Italy in the 1960s and excludes women. From this point of view, it is unknown whether the conclusions would extend to women, different age groups, different cultural and socio-economic situations, and nowadays lifestyles. The cohort size was also quite limited, though partly compensated for by the extremely long follow-up, which reached extinction and therefore allowed coverage of the entire life span of AD. We do not claim any particular utility of this analysis, since it started as an attempt to answer a curiosity dealing with a methodological problem. The analysis seems unique since we could not find in the current literature other analyses using AD as an endpoint in an extinct population sample.

In general, our impression is that the "inverse" approach and its relationships with the "direct" one should not depend on the characteristics mentioned above, but this must be confirmed by further analyses. In addition, using larger denominators of the study population, it might be possible to replicate this analysis using a single disease as an endpoint, if it represents a great proportion of morbid/fatal events. Among other further tests, it would be interesting to replicate the comparison of "direct" versus "inverse" approaches using artificially created data files.

Findings of the procedure defined as "direct" approach show nothing new compared with previous analyses of the same material, except the beneficial role of olive oil that could be tested here for the first time since we were able to dissociate it from seed oils. Distributing the several dietary variables into 3 AD classes was the job of the "inverse" procedure, which offered a new vision of the problem. Out of 19 food groups, 15 were significantly different across the 3 tertiles of factor score in the "direct" approach, while only 7 of them did so in the 3 AD classes by the "inverse" approach. It should be again clarified that the "direct" approach needs the construction of a dietary score. Still, there is no difference between the *a priori* and *a posteriori* procedures; the only difference is the greater difficulty in using the latter. Moreover, these two procedures likely do not interfere with the "direct" versus the "inverse" approaches analyzed in the present contribution.

Apparently, there are no contradictions between these approaches, but the "inverse" approach seems more selective despite the use of the same data, simply handled and distributed in a different way. The "direct" approach is, in fact, based on probabilistic procedures, while the "inverse" one is more oriented towards a descriptive procedure. From a different perspective, at least in our experience, the "direct" approach is more sensible since it selects more variables (food groups). In comparison, the "inverse" approach is more specific, selecting fewer variables with large weights in association with the events, which points to the core of the problem. The most evident example concerns the beneficial intake of olive oil, which is clearly greater in the "inverse" than in the "direct" approach. Nevertheless, some of the differences could be attributed to the interference of the arbitrary definition of the 3 levels of dietary habits based on the PCA factor score subdivided into equal-numerical groups derived from its rank distribution, and to the arbitrary classification of AD into 3 classes in the "inverse" approach. Actually, the latter derives from the common way of classifying a person's age, as adult (41-69 years), old (70-79 years), and old-old (80-104 years). Only after that, we discovered that the 3 classes had a rather similar size, almost corresponding to the 3 tertiles of the distribution, a condition that may represent an advantage.

Actually, the "direct" approach creates a predictive model that can be applied to other populations. In contrast, the "inverse" approach simply describes some facts, namely the characteristics of the dietary habits of individuals who carry or do not carry an event. As a consequence, its major role is to confirm the value of the traditional "direct" approach. This "inverse" approach cannot be compared with other similar experiences, as they are simply absent in the current literature. For the moment, we can only say that it tends to confirm the findings of the traditional "direct" approach, clearly viewed from an opposite point of view.

The idea to run the "inverse" approach partly comes from areas such as engineering, statistics, and mathematics, where an "inverse problem" is an inference or estimation problem [23, 24]. The data are finite in number and contain errors, and the unknown typically is infinite-dimensional, as it is in nonparametric regression. The data are only indirectly related to the unknown, an additional complication in an "inverse problem". Although the optimal determination of a model from a finite data set which generalizes Backus-Gilbert theory for nonlinear effects may enable to evaluate to what degree the reconstructed model resembles the true model [24], so far, a simple and clear procedure to compare the performance of the performed approaches, "direct" versus "inverse", was not found and much more work is needed to find an acceptable solution. This extends to the present analysis in the sense that a formal comparison between our "direct" versus "inverse" approaches cannot be adequately performed.

5. Conclusions

The innovative "inverse" procedure proposed here for showing the relationship between a dietary habit and an event (AD in this case) produced findings comparable with the traditional procedure obtained by a "direct" approach, despite some small differences. More work is needed to demonstrate its real value. For the moment, we preliminarily conclude that the "inverse" approach could serve as a confirmatory procedure. It is too soon to say whether other important advantages exist. Testing on larger, more diverse population samples is needed to confirm their apparent roles. However, using AD as an endpoint will likely be much more difficult, as studies examining cohort extinction are extremely rare. However, large groups of coherent morbid conditions might be enough for the purpose, and certainly other disciplines from engineering, statistics, and mathematics may contribute to formal comparisons and individualization of optimal pre-test conditions for useful reciprocal applications.

Author Contributions

A.M. and P.E.P. contributed to the conception, design, work analysis, interpretation of data, draft of the manuscript, final approval and agreed to be accountable for all aspects of work ensuring integrity and accuracy.

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Competing Interests

The authors have declared that no competing interests exist.

Data Availability Statement

The data used in this analysis derive from the Italian Areas of the Seven Countries Study. Due to internal rules, the data and computing codes are not publicly available, although the institution presently responsible of data may evaluate specific requests for dedicated analyses.

AI-Assisted Technologies Statement

Authors declare that they did not use generative artificial intelligence or any AI-assisted tools in the writing process of the paper.

Informed consent

Baseline measurements were taken before the era of the initial Helsinki Declaration and approval was implied in participation, while verbal or written consent was obtained for the collection of field examinations and follow-up data along with explicit authorizations to publish scientific results provided the participants names were unidentifiable. The original blank copy (in Italian) and the translation in English of the informed consent may be provided on administrative request.

Additional Materials

The following additional materials are uploaded at the page of this paper.

1. Informed consent.

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