CONSTRUCTION OF BIOLOGICAL AGE EQUATION FOR ASIANS: A KNHANES 2010 STUDY

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Abstract

Background

The recent four decades have brought to fruition a profusion of research methods allowing for an in-depth look at aging processes in an animal realm. However, due to ethical constraints methods applicable to the study of invertebrate and mammals, another then homo sapiens, are inadmissible for the study of a human being. This incited search for other methods allowing for a comprehensive understanding of physiological processes associated with aging in humans.

Methods

The study sample was extracted from the Korea National Health and Nutrition Examination Surveys conducted in the year 2010 that encompasses the set of physiologically critical biomarkers defining Health-Related Quality of Life. Original data were submitted to an extensive data multi-step cleaning process consisting of rejection from the study subjects younger than 40 and older than 80 years of age and women who had had been pregnant during the examination process and outlier detection and cleaning procedure. This was followed by principal component analysis; a data reduction method employed as a means of elucidation of factors delineating the aging process in an Asian population. The resulting variables were implemented in the construction of a mathematical formula defining a biological age.

Results

In broad terms, the biological age of South Koreans is defined by a pulmonary examination, blood examination, urine test, blood pressure, and dyslipidemia screenings.

Conclusions

Maintaining salutary life habits, including a well-balanced diet, upholding proper functioning of kidneys may prevent detrimental changes associated with aging, and in consequence extend longevity.

Key words: **biological aging; principal component analysis; South Korean; health related quality of life.**

Background

From the time immemorial longevity has been a tantalizing purport for humanity. However, perpetual life is inescapably associated with age-induced diseases; a vivid description of such a phenomenon is portrayed in a visit to Luggnagg, Gulliver's Travels, part III [1].

Notwithstanding endless search for a means of extending "normal" lifespan, including early nefarious attempts [2], only the recent three decades have furnished humanity with a vista of tools allowing for a significant extension of a lifespan.

An extensive literature search of a "lifespan" term in Pubmed brings a plethora of publications ramifying into two distinct research models: (1) invertebrate; Caenorhabditis elegans and Drosophila melanogaster, and (2) vertebrate; Mus musculus and Homo sapiens. Although current experimental techniques allow us to interfere with the lifespan on a molecular level, ethical constraints forbid us from such a study on a human model. Thus, the only alternative is a large-scale epidemiological study.

Longevity defined as a chronological age (CA), i.e., the amount of time gone since birth, is, de facto, defined by a biological age (BA) [3]; the entity rendered by an interplay of an array of physiological parameters defining Health-Related Quality of Life (HRQoL). The latter term can be circumscribed using a mathematical model, in which a variety of health-related biomarkers determined by age-induced functional and physiological vicissitudes are employed as independent variables.

The early study employed a multiple regression [4] for assessment of BA. However, Hochschild et al., [5] contemplated this approach as inappropriate due to, among others, multicollinearity. This observation brought a vista of other math-

ematical methods that may be employed for assessment of BA, among which principal component analysis (PCA) [6] is the most frequently used. Even though the application of PCA allowed overcoming the majority of problems encountered in multiple regression models, formulation of an epitome for BA is obstructed by a clinical and biological efficacy of biomarkers employed in the construction of BA.

The facts above perspicuously indicate that a sound and robust mathematical model of BA, applicable to different ethnic groups, must be based on a concoction of a reliable mathematical procedure, and feasible clinical biomarkers; these can be derived from large-scale epidemiological databases, *vide* Korea National Health and Nutrition Examination Surveys (KNHANES).

This study is an attempt to elucidate a mathematical equation describing the biological aging of the South Korean population employing principal component analysis and physiological parameters encompassed in KNHANES screening commenced during 2010.

Patients and methods

Data Collection

The study sample was derived from the KNHANES conducted in the year 2010. The KNHANES is a cross-sectional and nationally representative survey conducted by the Korea Centers for Disease Control and Prevention, South Korea, and consists of a health interview and nutrition and health examination survey. The original KNHANES 2010-database comprises 8,958 subjects; 4,115 men and 4,843 women. All the data are available upon request from the division of Health and Nutrition Survey, Korea CDC (http://knhanes.cdc.go.kr/). The use of the KNHANES data employed in this research was approved by the Korea Centers for Disease Control and Prevention authorities.

Data cleaning

Data-cleaning was a multi-step procedure: (a) rejection from the study subjects younger than 40 and older than 80 years of age, (b) rejection from the study women who had had been pregnant during the examination process, and (c) outlier detection and cleaning.

Outliers were defined using an algorithm proposed earlier [7], which employs a Box-Cox transformation. Thus, data points less or equal to Q1 -1.5•IQR or greater than or equal to Q3 + 1.5•IQR were rejected from the study; Q1, Q3- first and third quartile, IQR- interquartile range. To assure the homogeneity of the study sample data cleaning was performed for all consecutive ages.

Employing the reasoning of Masoro and coworkers [8], physiological tests were stratified into seven groups: (1) blood pressure (BP), (2) anthropometric measurements, (3) blood examination: diabetes screening; dyslipidemia screening, liver function screening, anemia screening, kidney function test, and normal blood test, (4) urine test, (5) pulmonary examination, (6) osteoporosis test, and (7) body-fat test. The complete set of primary variables defining a biological age used in this study is presented in Table 1.

Statistical analysis

A statistical analysis was a four-step computational procedure: (1) correlation analysis; to remove nugatory parameters variables listed in Table 1 were scrutinized against a correlation with age; those for which the correlation with age was less than 0.1 at P-value ≤ 0.05 or a correlation was greater than 0.1 and P-value > 0.05 were rejected from the further analysis; (2) redundancy analysis; variable elucidated in the first step was rejected if its cross-correlation with another variable was greater or equal to 0.9 at P-value ≤ 0.01; to avoid rejection of clinically important data, the output of this procedure was scrutinized against the knowledge of the researchers, (3) BA was calculated using PCA approach by a means of the approach analogous to this proposed by Abdul-Wahab et al. [9]. Statistically significant principal components (PCs) were selected using a scree plot. The position of a „big gap" or an „elbow" defined the number of PCs employed in the further analysis, and (4) assessment of BA using multiple regression analysis employing variables carrying the highest loadings for a given PC.

Underestimation of means for BA for the upper and lower ends of the regression curve results in a systemic error representing itself as overestimation of BA's means for lower and upper ends of the regression curve. Therefore, a correction procedure proposed by Dubina et al., [10] given by the following equation was employed: , yi is a chronological age of an individual, y is the mean value for the whole study sample, and b is the correlation coefficient between chronological age and BA.

Results

Basic characteristic of the study sample

A data cleaning procedure resulted in a substantial decrease of the size of the sample from 8,958 subjects encompassed by the original KNHANES dataset to 4,363 subjects encompassing 1,956 men and 2,407 women. The reference range, i.e., 2.5^{th} and 97.5^{th} percentiles of the studied parameters for all subjects and stratified by gender are shown in Table 1.

Correlations and principal component analysis

Utilization of the outlined statistical approach resulted in elicitation of six principal components accounting for 68% of the total variance in the sample comprising men and women, and eight principal components, accounting for 79% and 80% of the total variance in samples comprising men or women, respectively.

Construction of a biological age equation and a corrected equation

A naïve application of a stepwise regression resulted in equations describing biological aging in South Koreans (BA), and South Korean men (BA_m), and women (BA_w) (eqns. 1, 2, and 3, respectively):

Yet, as stated in the methods section, a naïve application of linear regression for construction of BA results in a systemic error. Application of a correction procedure yields the corresponding set of equations for the whole South Korean population, and South Korean men and women (Eq 4, 5, and 6, respectively);

Discussion

In this study, we constructed an equation defining the biological age of Asians for the whole South Koreans population, South Korean men, and women. Our study concept follows earlier recommendations accentuating that biological age ought to be defined by a vista of clinically significant physiological parameters [11]. Thus, a coalescence of a principal component analysis and a marker selection based on an advanced data reduction procedure, strengthen by an extensive literature analysis, allowed us to construct an equation describing biological aging. The resulting equation may be used as a guide for the selection of appropriate means of preventing aging and/or maintaining healthy aging. An analysis of Eq. 4 shows that five biomarkers define biological age in an Asian population: FEV1, WC, UCR, FPG, and VD.

The discussion presented henceforth supports both clinical viability and biological soundness of this equation. In brief, FEV1 decreases linearly with age after 40 years of age and defines a biological age of lungs [12], WC is a marker of obesity and morbidity across different ethnic groups [13] and strongly correlates with age, UCR steadily decreases as a function of age in both men and women [14, 15], FPG is a marker of aging and general health status; Yates et al., [16] reports a clear cross-correlation between fasting plasma glucose and aging rendered by a steady decline in pancreatic beta cell function, VD is a marker of aging and aging driven morbidity [17].

Biological age in Korean men, equation 5, is defined by FEV1, RBC, SBP, FPG, FEV1/FVC. Although, a review of these parameters in the context of equation 5 alone, and the context of equations 4 and 6, distinctly indicates that pulmonary function plays a profound role in the aging process, an intuitive analysis of this equation suggests that pulmonary function should positively, not negatively, correlate with a chronological age. It is even more surprising when taking into account that FEV1 positively correlates with VO_{2max} [18]. Nevertheless, an extensive analysis of analogous studies [6, 19] reveals this paradox as a standard feature of all so far derived equations defining biological aging and up-to-date there is no clear explanation of this singularity.

Blood pressure (BP) is a determinant of aging present in equations 5 and 6, SBP in the former and DBP in the latter. The presence of this parameter in equations defining biological aging is not surprising when taking into account a distinct, clear cross-correlation between BP and aging [14, 20].

The biological viability of an RBC, the term present in equation 5, is justified by its a clear-cut gradual decrease in RBC along an increase in chronological age [21]. Additionally, an amalgam of this observation with the results of the study on anemia in the elderly [22] implies that RBC is a high-risk marker for a variety of age-associated chronic diseases.

There is also perspicuous literature derived a correlation between UCR, present eq. 4, and USG, present in Eq. 6, indicating the interchangeability of both parameters [23]. It is because both parameters refer to an age-dependent failure of a renal function [24], which in turn strongly correlates with morbidity and mortality in aging societies [25]. USG is also directly coupled with BUN levels; a parameter that's clinical viability is supported by the study indicating BUN as (1) a prominent marker for post-discharge mortality in patients hospitalized for heart failure independently of the renal function level [26] and (2) an extrusive marker of aging in women [27].

However, the presence of FEV1/FVC in equations 5 and six is, accordingly to the recent evidence [28], more of a mathematical than gerontological nature.

Conclusions

Advances in computational sciences elicited a multitude of approaches allowing for the numerical definition of HRQoL and biological age [4, 5, 10, 19, 29-32]. In this study, we employed a well-established mathematical method for the elucidation of a set of physiological parameters defining biological age. The chosen methodology allowed for the elucidation of biological determinants whose modulation may allow to extend longevity.

The weak point of this study is ignoring parameters defining mental/cognitive changes associated with aging. However,

List of abbreviations

Alkaline phosphatase activity	ALP
Total muscle mass except for the head	Ln
Blood urea nitrogen concentration	BUN
Body mass index	BMI
Fasting plasma glucose	QFPG
Ferritin concentration	FRT
Forced expiratory volume in 1 second /Height2	FEV1/HT2
Forced expiratory volume in 1 second	FEV1
Forced expiratory volume in 1 second/forced vital capacity	FEV1/FVC
Forced expiratory volume in 1 second/forced vital capacity/ Height2	FEV1/FVC/H2
Forced vital capacity	FVC
Forced vital capacity / Height2	FVC/H2
Glutamic oxaloacetic transaminase activity	GOT
Height	HT
Hematocrit	HCT
Hemoglobin concentration	Hb
High-density lipoprotein cholesterol concentration	HDL-C
Insulin level	INS
Low-density lipoprotein cholesterol concentration	LDL-C
Mean corpuscular hemoglobin	MCH
Mean corpuscular volume	MCV
Pyruvate transaminase activity	GPT
Red blood cell count	RBC
Serum creatinine concentration	SC
Total cholesterol concentration	TC
Total fat except for the head	Ft
Triglycerides concentration	TG
Uric acid pH	UApH
Urinary creatinine concentration	UCR
Urine cotinine concentration	UCOT
Urine specific gravity	USG
Vitamin D concentration	VD
Waist circumference	WC
White blood cell count	WBC
Whole body bone mineral content	BMC
Whole body bone mineral density	BMD

due to technical reasons-the lack of psychological parameters in the database-we were not able to incorporate these parameters into the primary model. Nevertheless, some of the employed variables, for example, WC, are defined by and define the mental status [13].

Nevertheless, we showed that a kidneys health condition, which has its reflection in levels of BP, BUN, UCR, and USG, and pulmonary health are the key factors distinctly influencing biological age. Thus, we managed, using a mathematic equation, to prove that salutary life habits, such as a well-balanced diet [33] combined with physical exercises [34] should prevent detrimental changes in the parameters above, and extend longevity and improve HRQoL.

Competing Interests: None

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References

1. Swift J.: *Gulliver's travels.* New York, NY: Barnes & Noble Classics; 2008.
2. Infessura S.: *Diario della città di Roma di Stefano Infessura scribasenato, Nuova edizione edn. Roma* ,: Forzani e c.; 1890.
3. Ingram D. K.: *Toward the behavioral assessment of biological aging in the laboratory mouse: concepts, terminology, and objectives.* Experimental aging research 1983, 9(4):225–238.
4. Furukawa T., Inoue M., Kajiya F., Inada H., Takasugi S.: *Assessment of biological age by multiple regression analysis.* Journal of gerontology 1975, 30(4):422–434.
5. Hochschild R.: *Can an index of aging be constructed for evaluating treatments to retard aging rates? A 2,462-person study.* Journal of gerontology 1990, 45(6): B187–214.
6. Ueno L. M., Yamashita Y., Moritani T., Nakamura E.: *Biomarkers of aging in women and .the rate of longitudinal changes.* Journal of physiological anthropology and applied human science 2003, 22(1): 37–46.
7. Horn P. S., Feng L., Li Y., Pesce A. J.: *Effect of outliers and nonhealthy individuals on reference interval estimation.* Clin Chem 2001, 47(12):2137–2145.
8. Masoro E. J.: *Physiological system markers of aging.* Experimental gerontology 1988, 23(4-5): 391–97.
9. Abdul-Wahab S. A., Bakheit C. S., Al-Alawi S. M.: *Principal component and multiple regression analysis in modelling*

of ground-level ozone and factors affecting its concentrations. Environ Modell Softw 2005, 20(10):1263–1271.
10. Dubina T. L., Mints A. Y., Zhuk E. V.: *Biological age and its estimation. III. Introduction of a correction to the multiple regression model of biological age and assessment of biological age in cross-sectional and longitudinal studies.* Experimental gerontology 1984, 19(2):133–143.
11. Sprott R. L.: *Biomarkers of aging and disease: introduction and definitions.* Experiment al gerontology 2010, 45(1): 2–4.
12. Yamaguchi K.: *[A new method for evaluating lung age].* Nihon Kokyuki Gakkai zasshi = the journal of the Japanese Respiratory Society 2011, 49(9): 713–716.
13. Zhao G., Ford E. S., Li C., Tsai J., Dhingra S., Balluz L. S.: *Waist circumference, abdominal obesity, and depression among overweight and obese U.S. adults: National Health and Nutrition Examination Survey 2005-2006.* BMC psychiatry 2011, 11: 130.
14. Hosoya T., Toshima R., Icida K., Tabe A., Sakai O.: *Changes in renal function with aging among Japanese.* Internal medicine 1995, 34(6): 520–527.
15. Moriguchi J., Ezaki T., Tsukahara T., Fukui Y., Ukai H., Okamoto S., Shimbo S., Sakurai H., Ikeda M.: *Decreases in urine specific gravity and urinary creatinine in elderly women*. International archives of occupational and environmental health 2005, 78(6): 438–445.
16. Yates A. P., Laing I.: *Age-related increase in haemoglobin A1c and fasting plasma glucose is accompanied by a decrease in beta cell function without change in insulin sensitivity: evidence from a cross-sectional study of hospital personnel.* Diabetic medicine : a journal of the British Diabetic Association 2002, 19(3): 254–258.
17. Tuohimaa P.: *Vitamin D and aging.* The Journal of steroid biochemistry and molecular biology 2009, 114(1-2): 78–84.
18. Babb T. G., Long K. A., Rodarte J. R.: *The relationship between maximal expiratory flow and increases of maximal exercise capacity with exercise training.* Am J Resp Crit Care 1997, 156(1): 116–121.
19. Park J., Cho B., Kwon H., Lee C.: *Developing a biological age assessment equation using principal component analysis and clinical biomarkers of aging in Korean men.* Archives of gerontology and geriatrics 2009, 49(1): 7–12.
20. Pinto E.: Bl*ood pressure and ageing.* Postgraduate medical journal 2007, 83(976): 109–114.
21. Kubota K., Shirakura T., Orui T, Muratani M., Maki T., Tamura J., Morita T.: *[Changes in the blood cell counts with aging].* Nihon Ronen Igakkai zasshi Japanese journal of geriatrics 1991, 28(4): 509–514.
22. Guralnik J. M., Ershler W. B., Schrier S. L., Picozzi V. J.: A*nemia in the elderly: a public health crisis in hematology*. Hematology / the Education Program of the American Society of Hematology American Society of Hematology Education Program 2005: 528–532.
23. Haddow J. E., Knight G. J., Palomaki G. E., Neveux L. M., Chilmonczyk B. A.: *Replacing creatinine measurements with specific gravity values to adjust urine cotinine concentrations.* Clin Chem 1994, 40(4): 562–564.
24. Schmitt R., Cantley L. G.: *The impact of aging on kidney repair.* American journal of physiology Renal physiology 2008, 294(6): F1265–1272.
25. Vanholder R, Massy Z, Argiles A, Spasovski G, Verbeke F, Lameire N, European Uremic Toxin Work G: *Chronic kidney disease as cause of cardiovascular morbidity and mortality.* Nephrology, dialysis, transplantation : official publication of the European Dialysis and Transplant Association – European Renal Association 2005, 20(6): 1048–1056.
26. Filippatos G., Rossi J., Lloyd-Jones D. M., Stough W. G., Ouyang J., Shin D. D, O'Connor C., Adams K. F., Orlandi C., Gheorghiade M.: *Prognostic value of blood urea nitrogen in patients hospitalized with worsening heart failure: insights from the Acute and Chronic Therapeutic Impact of a Vasopressin Antagonist in Chronic Heart Failure (ACTIV in CHF) study.* Journal of cardiac failure 2007, 13(5): 360–364.
27. Yoshida K.: *[The effects of aging on renal function test].* Nihon Sanka Fujinka Gakkai zasshi 1994, 46(12): 1311–1314.
28. Golczewski T., Lubinski W., Chcialowski A.: *A mathematical reason for FEV1/FVC dependence on age.* Respiratory research 2012, 13: 57.
29. Kimura M., Mizuta C., Yamada Y., Okayama Y., Nakamura E.: *Constructing an index of physical fitness age for Japanese elderly based on 7-year longitudinal data: sex differences in estimated physical fitness age.* Age 2012, 34(1): 203–214.
30. Ludwig F. C., Smoke M. E.: *The measurement of biological age.* Experimental aging research 1980, 6(6): 497–522.
31. Hofecker G., Skalicky M., Kment A., Niedermuller H.: M*odels of the biological age of the rat. I. A factor model of age parameters.* Mechanisms of ageing and development 1980, 14(3-4): 345–359.
32. Heikkinen E., Kiiskinen A., Kayhty B., Rimpela M., Vuori I.: *Assessment of biological age. Methodological study in two finnish populations.* Gerontologia 1974, 20(1): 33–43.
33. Ford D. W., Jensen G. L., Hartman T. J., Wray L., Smiciklas-Wright H.: *Association Between Dietary Quality and Mortality in Older Adults: A Review of the Epidemiological Evidence.* Journal of Nutrition in Gerontology and Geriatrics 2013, 32(2): 85–105.
34. Venturelli M., Schena F., Richardson R. S.: *The role of exercise capacity in the health and longevity of centenarians.* Maturitas 2012, 73(2): 115–120.