Journal of Medicine and Medical Sciences Vol.14 (5) pp. 1-11, October,2023
Available online https://www.interesjournals.org/medicine-medical-sciences.html

Research Article

Indicators of Aging: Evidence from Association Analysis of Self-Management Abilities and Blood Biomarkers

Amita Sharma[1], Willem J. M. I. Verbeke[2*]

[1]Department of Operations Research and Quantitative Analysis, Institute of Agri-Business Management, Swami Keshwanand Rajasthan Agricultural University, Bikaner, India

[2]Erasmus University, Rotterdam, Netherlands

[*]Corresponding Author's E-mail**:** willemverbekew@gmail.com

Received: 05-Sep-2023, Manuscript No. jmms-23-110516; **Editor assigned**: 08-Sep-2023, PreQC No. jmms-23-110516 (PQ); **Reviewe**d: 25-Sep-2023, QC No. jmms-23-110516; **Revised**: 03-Oct-2023, Manuscript No. jmms-23-110516 (R); **Published**: 11-Oct-2023, DOI: 10.14303/2141-9477.2023.56

Abstract

Self-management abilities are described as a general ability to manage one's own aging process. In this paper we study whether biomarkers extracted from blood are associated with self-management abilities. We explore the confounding effects of age and gender on a sample of Dutch citizens (N=9431) provided by the Lifelines Cohort Study Biobank, focusing on two age groups: 18–64 years and above 65 years. We built logistic models linking the total self-management abilities score and biomarkers data. All models had R-squared values of less than 3% and were significant (p-value<0.05). We found that the high-density lipoprotein level was significant in all models, and basophilic, eosinophilic, erythrocytes, leukocytes, and neutrophilic granulocytes, all related to the human immune system, were also significant in one or two models. This indicates that the immune system plays a role in affecting the total self-management abilities score. We also uncovered confounding effects in age and gender variables indicating heightened health risks for elderly females.

Keywords: Self-management abilities scale, Biomarkers, Logistic regression, Molecular aging, Gender

Abbreviations: SMA: Self-Management Ability; SMAS-30: Self-Management Ability Scale 30; Total SMAS: Total Self-Management Ability Scale; AIC: Akaike Information Criterion; BIC: Bayesian Information Criterion; GAM: Generalized Additive Model; BA: Basophilic Granulocytes; EO: Eosinophil Granulocytes; ER: Erythrocytes, HT: Hematocrit; HB: Hemoglobin; LY: Lymphocytes; MO: Monocytes; GR: Neutrophil Granulocytes; TR: Thrombocytes; BALB: Albumin; CHO: Cholesterol; CA: Calcium; UZ: Uric Acid; GGT: Gamma-Glutamyl Transferase; BKR: Creatinine; TGL: Triglycerides; K: Potassium; NA: Sodium; LDL: Low Density Lipoprotein; UR: Ureum; ALT: Alanine Aminotransferase; AST: Aspartate Aminotransferase; AF: Alkaline Phosphate; X.LE: Leucocytes; HBAC: Glycated Hemoglobin (HbA1c); GLU: Blood Glucose; FOS: Phosphorus; HDL: high-density lipoproteins; M_unadjusted: logistic model not adjusted for age and gender; M_age: Logistic model adjusted for age, M_gender: logistic model adjusted for gender and M_age_gender: Logistic model adjusted for both age and gender.

INTRODUCTION

The worldwide population is aging (World Health Organization, 2021) and a significant portion of this population will put a strain on the economy and the sustainability of public finance due to the greater incidence of aging-related diseases. In the Netherlands, the demand for care is increasing with the rising numbers of elderly people. It is estimated that approximately 70 percent of people aged 65 and older will suffer at least one chronic disease (Zorgvoorbeter.nl, 2022). This aging has led to 'grey pressure' on the economy in that the potential working population is shrinking within the aging population (Zorgvoorbeter.nl, 2022). To reduce healthcare costs, governments and insurance companies are putting the emphasis on motivating elderly people to engage in healthy aging-based activities, such as lifestyle interventions (RIVM: Focus Lifestyle Changes, 2022), early diagnosis of biological aging (e.g., Lara, et al., 2015), frailty detection in the elderly (Saedi, et al., 2019) and patients securing self-management of chronic illness (Steverink, et al., 2005).

As people grow older the risk of failing to manage resources rises because as the majority of people leave the workforce, they lose touch with important external resources: their habitual social structure, social status and meaningful roles in life (Hobfoll, 2002; Steverink, et al., 2005). Hence, they might suffer downward spirals of resource loss. For example, loss of social status may cause depression which undermines the energy needed to undertake care of one's physical health or to seek thriving new social environments (e.g., Steverink, et al., 2005). Consequently, aging comes with an even greater reliance on direct or internal resources, meaning the ability to respond to challenges or develop the self-management skills to attain new external resources (e.g., Baltes and Baltes, 1990). These factors make it worthwhile to focus research on self-management abilities (SMA), which are commonly defined as "managing direct resources in such a way that (aspects of) physical and social well-being are achieved, maintained, and restored when lost" (Schuurmans, et al., 2005, p. 2216). Indeed, a study conducted in the Netherlands found that a person's score on the SMA scale (SMAS) was negatively associated with poor health (Cramm, et al., 2014).

In this era of Geroscience, "which strives to understand how aging enables chronic diseases and seeks to develop novel multi-disease preventative and therapeutic approaches" (Kennedy, et al., 2014, p. 709; Geroscience, NIH), we focus on whether specific molecular biomarkers associated with the SMAS could indicate an intrinsic capacity (Salinas-Rodriguez, et al., 2022) that might initiate healthy ageing processes or promote the development of biologically based treatment efforts (e.g., Page, et al., 2018). As per our literature survey, no previous study has been done to explore the link between biomarkers and SMAS.

We especially explore age as a confounder because although aging comes with a progressive loss of physiological integrity, the rate of loss can be controlled (e.g., Jylhava, et al., 2017; Lopez-Otin, et al., 2013). Because elderly females are prone to develop mental health problems later in life (e.g., Sialino, et al., 2021) we also explore the confounding effect of age and gender combined, besides gender alone as confounder.

MATERIALS AND METHODS

Subjects

Data were collected from the Lifelines Cohort Study Biobank in Groningen, the Netherlands. This large-scale collection makes biological data and samples available for epidemiological research, following a standard application procedure. Every five years, participants in the age range 18–88 years visit one of the Lifelines Cohort Study Biobank sites for a physical examination.

Sample size

The sample comprises of 5543 females and 3888 males in three major age groups: Under 18, 18–64, and over 64 years. We combined the first two age groups, focusing on 18–64 (N=8598) years and over 65 (N=833) years.

SMAS measures

The self-management abilities scale is an instrument to measure a set of abilities that help a person do daily activities. It is related to six subscales:

- Taking initiative and
- Investment behavior (active motivation);
- Self-efficacy beliefs and

- Positive frame of mind (cognitive abilities); and Multifunctionality of resources and
- Resource variety (resource-combining abilities) (Steverink, 2005; Schuurmans, et al., 2005).

This paper labels the compilation of all SMAS dimensions as the TotalSMAS score.

The SMAS-30 scale consists of 30 Likert scale items. Ten SMAS items are measured on a 6-point Likert scale and 20 SMAS items are measured on a 5-point Likert scale (Steverink, et al., 2009). From the 30 SMAS items, six SMAS were calculated according to the methodology suggested by Lifelines. After obtaining six SMAS subscales scores, we calculated the total SMAS score. **Figure 1** shows the distribution of subscales and total SMAS scores.

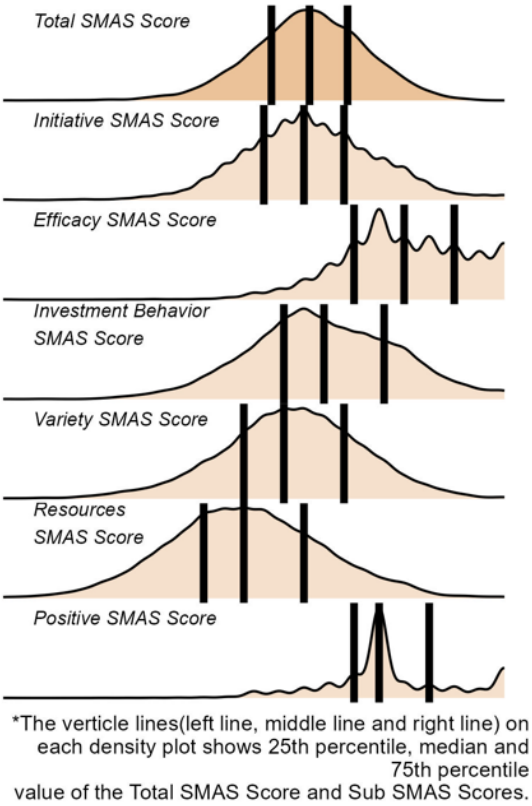

Figure 1. Density plot of SMAS scores.

Table 1. Summary statistics of SMA subscale scores and total SMAS scores.

SMAS scales	Mean	Median	Quartile 1	Quartile 2	Minimum	Maximum	Standard deviation
Taking initiative	61.43	60	52	68	0	100	13.66
Investment behavior	63.84	64	56	76	0	100	14.93
Self-efficacy beliefs	80.17	80	70	90	0	100	13.01
Positive frame of mind	77.05	75	70	85	0	100	13.24
Resources	48.52	48	40	60	0	100	15.74
Variety in resources	57.48	56	48	68	0	100	14.38
Total SMAS	64.75	65	58.17	71.83	0	100	10.44

The distribution of the six subscales, and the total SMAS score was near to normal. Hence, we did not transform the variables.

Biomarkers

From Lifelines we selected 28 biomarkers extracted from blood taken while the donor was fasting:

- **Cardiac markers:** HDL: High-Density Lipoproteins; CHO: Cholesterol; LDL: Low Density Lipoproteins; TGL: Triglycerides
- **Immune system markers:** BA: Basophilic Granulocytes; EO: Eosinophil; Granulocyte, ER: Erythrocytes; X. LE: Leucocytes; GR: Neutrophil Granulocytes; TR: Thrombocytes; LY: Lymphocytes; MO: Monocytes.
- **Hepatic markers:** GGT: Gamma-Glutamyl Transferase; BALB: Albumin; ALT: Alanine

Aminotransferase; AST: Aspartate Aminotransferase; AF: Alkaline Phosphate; HBAC: Glycated Hemoglobin (HbA1c).

- **Renal markers:** UZ: Uric Acid; UR: Ureum; BKR: Creatinine.
- **Pancreatic markers:** LY: Lymphocytes; GLU: Blood Glucose.
- **Mineral markers:** NA: Sodium; FOS: Phosphorus; CA: Calcium and finally
- **HT:** Hematocrit, a marker for red blood cell count.

The basic information and summary statistics of each biomarker variable is given. The distribution of each biomarker was near to normal. Hence, we did not transform the variables. Data analysis comprised multiple techniques.

First, we carried out a basic exploration to understand the patterns in the data and decide on the next steps of analysis. The definition of each variable of the data in Annexure A corresponds to the details provided by Lifelines. Annexure B shows the descriptions of the SMAS-30 items used to measure self-management abilities. **Figure 2** presents the age and gender-wise distribution of the total SMAS score.

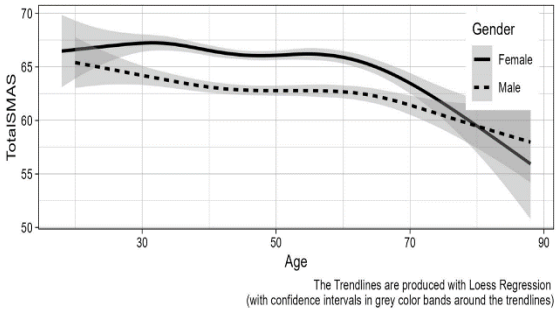

Figure 2. Age and gender wise distribution of total SMAS score.

In **Figure 2**, we can see that the total SMAS score of female subjects higher than the TotalSMAS score of male subjects up to age 75. This follows almost the same trend throughout the lifespan. The TotalSMAS score starts decreasing between ages 55 and 60 for both female and male subjects. The trend lines in **Figure 2** are generated by the Generalized Additive Model (GAM) method. After age 75, the TotalSMAS score decreases faster in females than in males.

To understand the relationship between biomarkers and the total SMAS score, we checked the correlation among the biomarkers **(Figure 3)**.

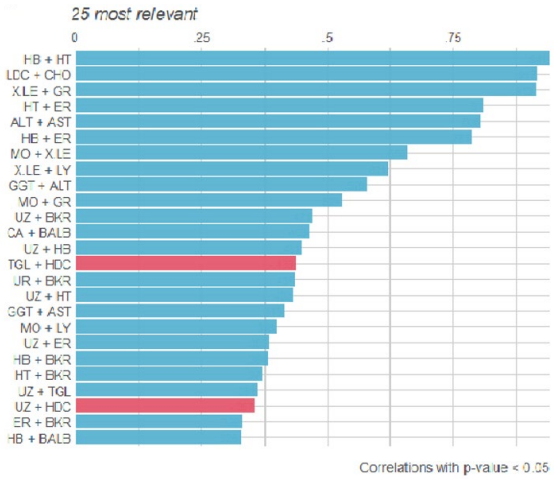

Figure 3. Ranked cross-correlations.

Three pairs of correlations were greater than 0.90 (HB+HT, LDL+CHO and X. LE+GR). There were two pairs of biomarkers with significant negative correlation- TGL+HDC (-0.438) and UZ+HDC (-0.357). In our study, the TotalSMAS score is a continuous decision variable. The mean, median, minimum and maximum values of the TotalSMAS score were 64, 75, 65, 10, and 100, respectively. The median was used to divide the population into equal halves. Thereby we created a binary variable "y" by setting the label=1 to subjects with a total SMAS score of less than or equal to 65 and the label=0 to subjects with a total SMAS score of more than 65.

We built a logistic regression model to predict whether a subject will have a low total SMAS score (less than or equal to 65) or a high total SMAS score (more than 65). To fine-tune the model, we selected the best model based on minimum AIC and BIC criteria from the set of models obtained by stepwise regression through backward and forward elimination. Only significant biomarker variables at a 0.05 significance level were retained in our model.

A final logistic regression unadjusted for gender and age confounders was obtained to determine the effect of biomarkers on the likelihood that the subject will have a total SMAS score ≤ 65 versus a total SMAS score>65. The logistic regression model was statistically significant, χ^2 (6, N=9431)=148.69, p<0.0001. The model explained 2.3% (Negelkerke R^2) of the variance in the TotalSMAS score and correctly classified 57.7% of cases.

However, we cannot use this model for prediction as it has a very low R^2 value (2.3%) but it can be used to understand the relationship of the biomarkers with variance in the total SMAS score because regression

output has significant regression coefficients related to biomarkers–UR (1.043), NA (1.031), HDL (0.644), GGT (1.003), GR (1.050), FOS (0.567), and CHO (1.048) **(Figure 4)**. The regression coefficients are expressed after exponentiation as a norm while interpreting the logistic regression output.

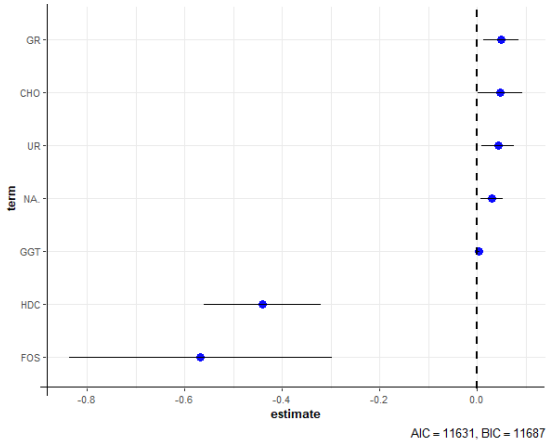

Figure 4. Logistic model: total SMAS ~biomarkers without adjusting age and gender.

Further, we introduced the effects of confounders in data analysis. Due to the presence of confounders, the regression model output may change. Biomarkers of age and gender are potential confounders. We found that age and gender were independently associated with total SMAS scores so they could be confounding factors. The age and TotalSMAS score were negatively correlated, r (9429)=-0.734, p<0.05 (**Figure 5**). Patil (2021) also studied the association of TotalSMAS scores with age through a mosaic plot and the χ^2 test. According to two sample tests between gender and biomarkers, there were significant differences in mean AF, BA, CA, ER, GLU, HDL, LDL, NA, UR, ALT, BALB, CHO, GR, HT, TGL, UZ, AST, BKR, EO, GGT, HB, K, MO, and TR for male and female subjects. The biomarkers LY and X.LE did not differ significantly between male and female subjects.

RESULTS

The first finding is that there is a decreasing trend in the total SMAS score as age increases.

After age 70, the total SMAS score rapidly decreases, and the decrease in the total SMAS score of females is more rapid than for male counterparts.

Next, in the mosaic plots, a low total SMAS score (below or equal to 65) is represented by 1 and a high total SMAS score (above 65) is represented by 0.

The age variable is represented by two age groups (age ≤ 64 and 64<age). We observed an increase in the number of observations of low total SMAS scores in the older age group (64<age). A χ^2 test of independence was performed to examine the relation between age group and total SMAS score.

The association between these variables was found significant, $\chi^2(1, N=9431) = 44.60$, p<0.05 **(Figures 5 and 6)**. The result of χ^2 test of independence shows that there is a significant association between age group and total SMAS score.

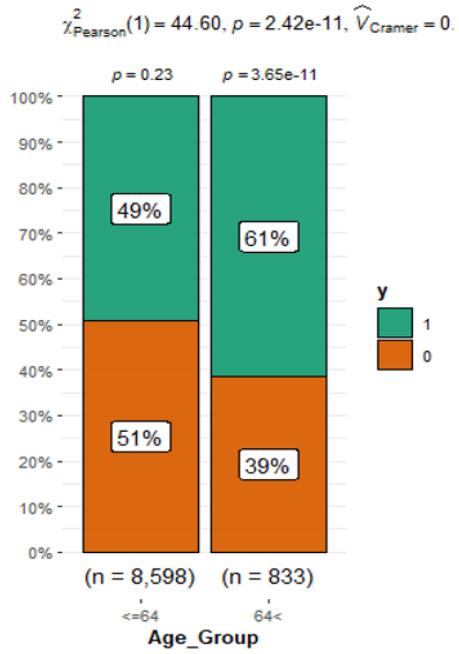

Figure 5. Age *vs.* total SMAS.

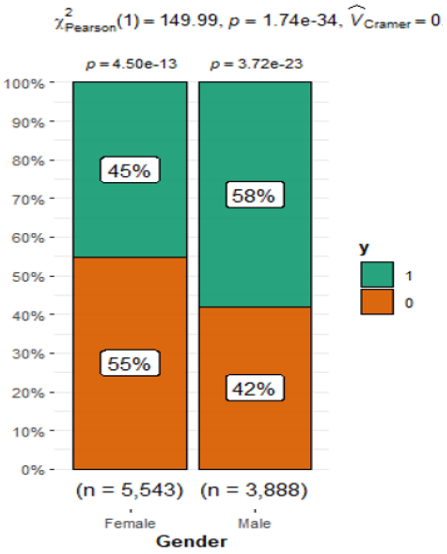

Figure 6. Gender *vs.* total SMAS.

Similarly, we studied the association between gender and total SMAS score. The mosaic plot between gender and total SMAS score categories showed the association between the two variables. Females have a higher proportion of low total SMAS scores than their male counterparts.

A χ^2 test of independence was performed to examine the relation between gender and TotalSMAS score. The association between these variables was found significant, $\chi^2(1, N=9431)=149.99$, $p<0.05$ **(Figure 6)**. The result of χ^2 test of independence shows that there is a significant association between gender and total SMAS score.

We observed that all 27 biomarkers have a significant correlation with age. The biomarkers UR, CHO, LDL, GLU, NA, AF, UZ, K, BKR, HT, HDL, CA, GGT, TGL, AST, BA, HB, ALT, EO, and MO are positively associated.

The biomarker UR has the highest positive correlation with age ($r=0.34$, $p<0.05$). The biomarkers ER, LY, X.LE, TR, GR, and BALB were negatively associated with age.

The biomarker BALB has the highest negative correlation with age ($r=-0.17$, $p<0.05$). These results confirm that age is an influential confounder variable **(Figure 7)**.

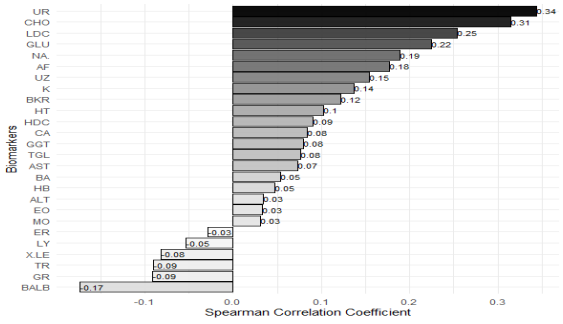

Figure 7. Age *vs.* biomarkers correlations.

Gender is a binary variable; therefore, we need to check whether there is a significant difference in the mean of a biomarker for male and female subjects. From the two sample tests between gender and biomarkers, there was a significant difference in the means of AF, BA, CA, ER, GLU, HDL, LDL, NA, UR, ALT, BALB, CHO, GR, HT, TGL, UZ, AST, BKR, EO, GGT, HB, K, MO, and TR for male and female subjects at significance level 0.05. The biomarkers LY and X. LE showed no significant difference in the means of male and female subjects. In two sample tests between age groups (age ≤ 64 and age>64) and biomarkers, we found AF, CA, GLU, LDL, NA, UR, BALB, CHO, FOS, GR, HT, LY, TGL, UZ, AST, BKR, EO, GGT, HB, K, MO, TR, and X. LE biomarkers have significant association with age groups at significance level 0.05. The biomarkers BA, ER, HDL and ALT had no significant association with age groups.

We built three logistic models adjusted per confounder: M_age: adjusted for age, M_gender: adjusted for gender, and M_age_gender: adjusted for both age and gender. Table 2 shows four logistic models, including the first unadjusted model (M_unadjusted) with regression coefficients so that we can easily compare the differences in confounding effects **(Figures 8-10)**.

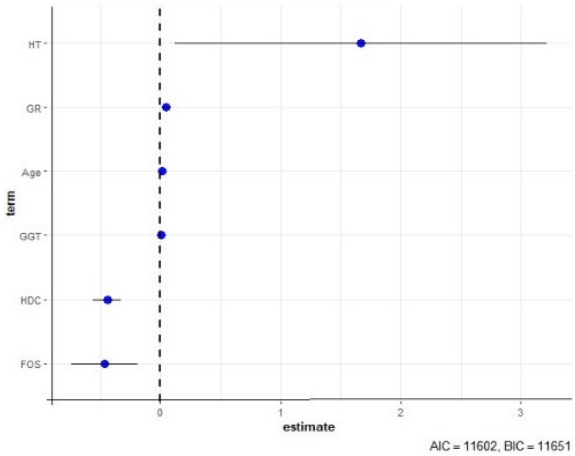

Figure 8. Logistic model: Total SMAS~biomarkers with adjusting age.

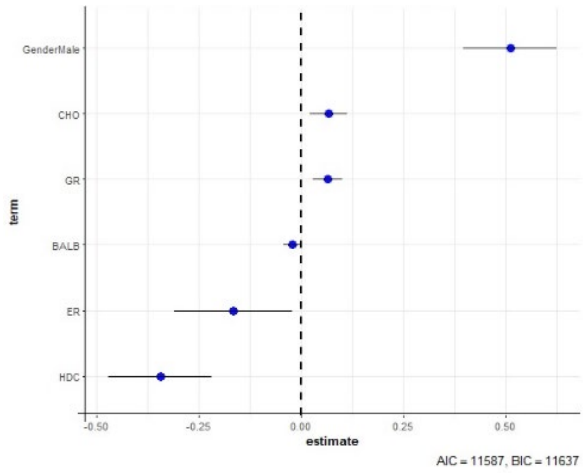

Figure 9. Logistic model: Total SMAS~biomarkers with adjusting gender.

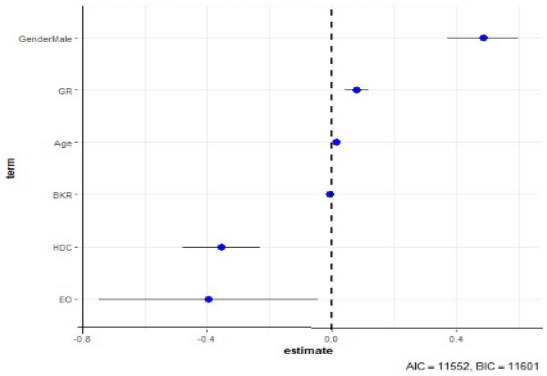

Figure 10. Logistic model: Total SMAS~biomarkers with adjusting age and gender.

Table 2 shows the biomarker variables and their corresponding exponential value of regression coefficients for each model. Two biomarkers, HDL and GR, show statistical significance in all four models (M_unadjusted, M_age, M_gender, and M_age_gender). As the HDL regression coefficient changed by 9.97% (less than 10%), we can conclude that the association between the total SMAS score and HDL is not confounded by gender. The regression coefficient of biomarker GR changed by 3.10% (under 10%) so, we can conclude that the relationship between total SMAS score and GR is not confounded by age or gender. The biomarker FOS regression coefficient shifts to 10.84% (slightly more than 10%) so, we can interpret that the association between total SMAS score and FOS is confounded by age. The biomarker CHO regression coefficient changed by 1.95% (lower than 10%) so, we can conclude that the association between total SMAS score and CHO is not confounded by gender. The biomarker GGT regression coefficient changed by 0.049% (less than 10%) so, we can conclude that the association between the total SMAS score and GGR is not confounded by age.

Table 2. Logistic models with biomarkers and exponential regression coefficients

Biomarkers	M_unadjusted	M_age	M_gender	M_age_gender
UR	1.0433			
NA	1.03095			
HDL	0.64425	0.6418	0.7085	0.7014
GGT	1.0029	1.0024		
GR	1.0503	1.0485	1.0667	1.0829
FOS	0.5671	0.6286		
CHO	1.0484		1.0688	
HT		5.3035		
BALB			0.9777	
ER			4.7645	
BKR				0.9952
EO				0.6737

Further, we also compared confounding effects by stratifying the sample by gender **(Figures 11 and 12)**. We divided the sample into observations of male subjects and observations of female subjects and developed logistic regression models again.

Compared to the logistic models built from the complete sample, the separate logistic models based on male and female samples have much lower AIC and BIC values. This makes them quite different and a much better option for study than the four models built on the complete sample.

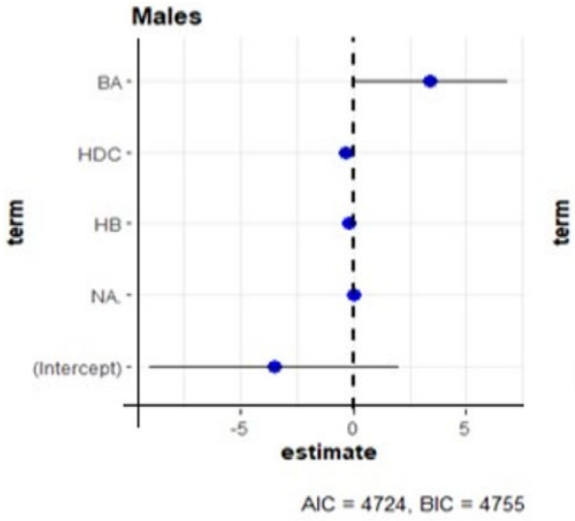

Figure 11. Logistics regression: total SMAS~biomarkers.

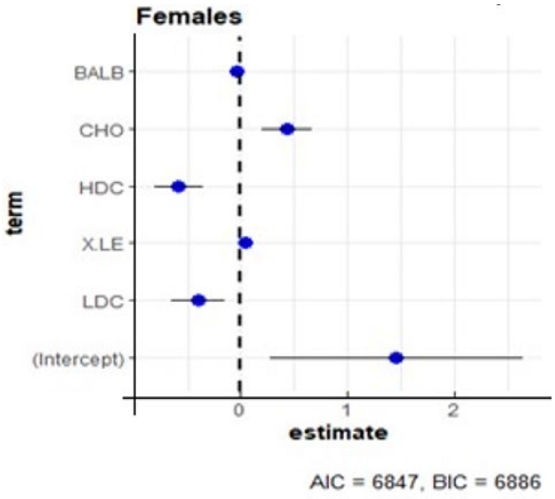

Figure 12. Logistics model: Total SMAS~biomarkers.

DISCUSSION

In line with the Geoscience mission, which seeks to improve current multi-disease preventative and therapeutic approaches as people age (Gerosciences, NIH), this study sought to investigate how SMAS scores correlate with relevant biomarkers extracted from blood, made available by the Lifelines Biobank in the Netherlands. Blood-derived biomarkers were selected as substance because running blood sample tests is quick and low cost, needs no biopsy and thus can be a prolific, economically feasible diagnostic method (e.g., Ferrucci, et al., 2019). This study used the SMAS adopted from Steverink, et al., (2009), made available by Lifelines.

Please note, we focused on the ability of elderly people to engage in self-management activities in general (an internal resource or intrinsic capacity) which could potentially provide them with external resources and prevent avoid their engaging in negative resource spirals, which can bring about several mental and physiological diseases. SMAS is often associated with other internal resources such as resiliency (e.g., Luo, et al., 2019), coping and adaptation (e.g., Avdulu, et al., 2016) and self-efficacy (e.g., Bodenheimer, et al., 2002).

We built logistic regression models for the confounders age and gender separately and together, adjusting for male participants and female participants. The biomarkers HDL, UR, NA, GGT, GR, FOS, CHO, HT, BALB, ER, BKR, EO, BA, LDL, and X.LE had significant regression coefficients. These biomarkers are known to be significantly related to the biological aging of five crucial organs in humans and are used frequently in clinical practice settings (Bae, et al., 2013 for a good overview). The variable significant in all six models was HDL. This biomarker is a lipoprotein considered to be good at removing cholesterol from the bloodstream. As well as HDL, CHO and HT are known to be associated with cardiac age. From the set of significant biomarkers, BA, EO, ER, X.LE, and GR are related to the innate functioning of the human immune system and are also known to be affected by age (Lawton, 2020). The biomarkers NA and FOS are essential minerals that play key roles in cell and neuron metabolism. GGT and BALB are related to hepatic age, and UR and BKR are related to renal age.

The total SMAS score starts decreasing between the ages of 55 and 60 for both female and male subjects but females score higher on SMA than males, which might indicate higher resiliency. After the age of 75 however, the Total SMAS score decreases more rapidly in females than in males. Apparently, the female 'disadvantage', as Sialino, et al., (2021) put it, only occurs at an older age as females lack the internal resources that might in turn prevent depression (see also Maji, 2018). Note that especially HDL (cardiac age), GR, EO (immune functioning) and BKR (renal age) are significant markers for self-management ability in aging females.

We did not focus on how SMAS might help an elderly person to cope with chronic illnesses, such as depression, diabetes or anxiety, which occur frequently in older age (Grady and Gough, 2014). We conceived SMAS as a phenotype, excluding the occurrence of possible diagnoses of chronic illness (e.g., Avdulu, et al., 2016).

This might explain why our regressions show low variances of SMAS, which can be expected from using molecular biomarkers, and from the fact that we used total SMAS scores instead of the subdimensions of SMAS. Indeed, all models had R-squared values of <3% and were significant (p-value<0.05). In other words, the biomarkers found in this study do not explain high variances in healthy people.

The predictive biomarkers uncovered in the study are commonly found as biological age predictors (e.g., Lopez, et al., 2013; Bae, et al., 2013; Ferucci, et al., 2019), biomarkers for frailty (e.g., Saedi, et al., 2019) and in studies on healthy aging (e.g., Lara, et al., 2015). Self-management abilities and healthy aging (not suffering chronic disease) have bidirectional relationships but an investigation

focused on this aspect was beyond the scope of this study (e.g., Lara, et al., 2015).

LIMITATIONS AND FUTURE SCOPE

When studying confounding effects, sample selection should be randomized. Given that our study was based on secondary data provided by Lifelines, we could not control the sampling method so randomization might not have occurred. Chance is another source of potential error in a study based on a sample. The influence of chance can be minimized by using larger samples to reduce the error emanating from the sample size; a sample larger than 300 is considered an acceptable size. The size of our sample is 9431, which is well above acceptable and thus limits error due to chance. One limitation of the research work is the relatively small number of cases belonging to the specific class of interest within the sample size of 9431. With only 833 cases representing the over or equal to +65 years' age group, there is a risk of insufficient representation and limited generalizability for this particular group. The imbalanced class distribution further compounds the issue, potentially introducing bias and impacting the accuracy of statistical analyses. Additionally, the small sample size of the specific class may limit the statistical power of the study, hindering meaningful subgroup analysis and potentially leading to type II errors. It is important to acknowledge these limitations and emphasize the need for future research with larger, more balanced datasets to enhance representation and improve the validity of findings. Another source of error is bias, which is actually a systematic error in the design or execution of the studies. There are four types of bias that may be found in a study: Selection bias, performance bias, measurement bias, and attrition bias. We cannot entirely rule out the existence of bias in this study.

Confounding is another type of systematic error that can occur in epidemiologic studies. If an extraneous third variable, called a confounder (Alexander et al., 2015) is present, it can distort either over- or underestimate the observed association between exposure and health outcomes. The distortion introduced by a confounding factor can be large and can even change the apparent direction of an effect. It can, however, be adjusted for in the factor analysis.

The handbook of clinical neurology lists body mass index, smoking status, age at onset of illness, socioeconomic status, educational status, and extent of support network as common confounders. Life events are also potential confounders (Seeman, et. al., 2019). It is well understood in epidemiology that proper care must be taken to control for confounders to avoid making incorrect inferences. This is because unintended differences between the cases and controls in the sample can give rise to spurious associations (Iles and Barrett, 2011).

We built a binary logistic model for our study. Future work could be directed at building nonlinear models (e.g., Klemera and Doubal, 2006). There is also the possibility that biomarkers do not affect the Total SMAS score in a standalone manner but rather in groupings that indicate co-morbidity, thus forming composite biomarker predictions (e.g., Khan, et al., 2017; Levine, 2013).

CONCLUSION

In future research, principal component analysis and structured equation modelling might find a better explanation for the relationship between biomarkers and total SMAS score.

STATEMENTS AND DECLARATIONS

The authors declare that they have no known competing financial interests or personal relationships that may have influenced the work reported in this paper.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

This data this research paper used is the proprietary asset of lifelines biobanks, which has its own ethics compliance committee that abides by ethics guidelines issued by the Dutch authority. We did not require ethics approval as we used secondary data collected by Lifelines Biobanks.

CONSENT TO PUBLISH

This research paper does not use Images, Figures, or Tables from other publications.

AVAILABILITY OF DATA AND MATERIALS

Lifelines biobanks provided data through a secure server on a fee basis. It does not allow downloads of patient-sensitive data for sharing in public. Lifelines biobanks will provide access to the data for reviewers on request.

FUNDING

This research received no grants from funding agencies in the public, commercial, or not-for-profit sectors.

AUTHORS' CONTRIBUTIONS

The authors confirm their contributions to the paper as follows:
WV: Study concept, design, data sourcing.
AS: Analysis, interpretation of results and manuscript preparation.
WV: Review of findings and approval of the final draft.

ACKNOWLEDGEMENTS

We thank Lifelines Biobank and its staff members for data-related services and support.

REFERENCES

1. Alexander LK, Lopes B, Ricchetti-Masterson K, Yeatts KB (2015). Confounding bias. Part I. UNC Gillings School of Global Public Health.
2. Baltes MM, PB Baltes (2014). The psychology of control and aging (psychology revivals). Psychology Press, 452.
3. Clark NM, Becker MH, Janz NK, Lorig, K, Rakowski W, et al. (1991). Self-management of chronic disease by older adults: a review and questions for research. J Ag H. 3: 3-27.
4. Cramm JM, Twisk J, Nieboer AP (2014). Self-management abilities and frailty are important for healthy aging among community-dwelling older people; a cross-sectional study. BMC Ger. 14:1-5.
5. Gao W, Ping S, Liu X (2020). Gender differences in depression, anxiety, and stress among college students: a longitudinal study from China. J Affect Dis. 263: 292-300.
6. Geroscience: National Institute of Aging (2014) Geroscience: The intersection of basic aging biology, chronic disease, and health.
7. Gershon RC, Wagster MV Hendrie HC, Fox NA, et al. (2013). NIH toolbox for assessment of neurological and behavioral function. Neurology. 80: 2-6.
8. Grady PA, Gough LL. (2014). Self-management: a comprehensive approach to management of chronic conditions. Am J Pub Health. 104:25-31.
9. Iles MM, Barrett JH. (2011). Single-locus tests of association for population-based studies. In Anal Compl Disea Assoc Stud. 109-122.
10. Kennedy Brian K, Shelley L Berger, Anne Brunet, Judith Campisi, Ana Maria Cuervo, et al. (2014). Geroscience: linking aging to chronic disease. Cell. 159: 709-713.
11. Khan SS, Singer BD, and Vaughan DE. (2017). Molecular and physiological manifestations and measurement of aging in humans. Ag Cell 16:624-633.
12. Klemera P, Doubal S. (2006). A new approach to the concept and computation of biological age. Mech Ageing Dev. 127:240-248.
13. Lama MAQ. (2011). The relation of depression and anxiety in academic achievement among group of university students. Int J Psych Couns. 3:96-100.
14. Lara J, Cooper R, Nissan J, Ginty AT, Khaw K, et al. (2015). A proposed panel of biomarkers of healthy ageing. BMC Med. 13: 1-8.
15. Lara J, Godfrey A, Evans E, Heaven B, Brown LJ, et al. (2013). Towards measurement of the Healthy Ageing Phenotype in lifestyle-based intervention studies. Maturitas 76: 189-199.
16. Lawton G (2020). You're only as young as your immune system. New Sci. 245: 44-48.
17. Levine M (2013). Modeling the rate of senescence: Can estimated biological age

predict mortality more accurately than chronological age? J Gerontol A Biol Sci Med Sci. 68:667-674.
18. Liu Y, Zhang N, Bao G, Huang Y, Ji B, et al. (2019). Predictors of depressive symptoms in college students: A systematic review and meta-analysis of cohort studies. J Aff Dis. 244:196-208.
19. Lorig K, and Holman H (2003). Self-management education: history, definition, outcomes, and mechanisms. Ann Beh Med. 26:1-7.
20. Maji S. (2018). Society and 'good woman': A critical review of gender difference in depression. Int J Soc Psychi. 64: 396-405.
21. Norum KR (2005). World Health Organization's Global Strategy on diet, physical activity and health: the process behind the scenes. Scan J Nutr. 49:83-88.
22. Page GG, Corwin EJ, Dorsey SG, Redeker NS, McCloskey DJ, et al. (2018). Biomarkers as common data elements for symptom and self-management science. J Nurs Schol. 50: 276-286.
23. Patil I (2021). Visualizations with statistical details: The 'ggstatsplot' approach. JOS Softw. 6:3167.
24. RIVM: Focus Lifestyle Changes (2022). The majority of Dutch people want to focus on a healthy lifestyle.
25. Saedi AA, Feehan J, Phu S, Duque G (2019). Current and emerging biomarkers of frailty in the elderly. Clin Int Ag. 14: 389-398.
26. Sialino LD, van Oostrom SH, Wijnhoven HA, Picavet S, Verschuren WM, V, et al. (2021). Sex differences in mental health among older adults: investigating time trends and possible risk groups with regard to age, educational level and ethnicity. Ag Ment H. 25: 2355-2364.
27. Scheffer MM, Menting J, and Boeije HR (2021). Self-management of social well-being in a cross-sectional study among community-dwelling older adults: The added value of digital participation. BMC Ger. 21:1-7.
28. Schuurmans H, Steverink N, Frieswijk N, Buunk BP, Slaets JP, et al. (2005). How to measure self-management abilities in older people by self-report. The development of the SMAS-30. Qual O Life Res. 14:2215-2228.
29. Seeman MV, Becker RE, Greig NH (2019). Geriatric pharmacotherapy: appraising new drugs for neurologic disorders in older patients. Handb Clin Neurol. 167: 3-18.
30. Steverink N, Lindenberg S, Slaets JP. (2005). How to understand and improve older people's self-management of wellbeing. Eur J Age. 2:235-244.
31. Steverink N (2009). Self-Management Ability Scale: SMAS-30/version 2. Background, manual and scoring.
32. Theeke L, Carpenter RD, Mallow J, Theeke E (2019). Gender differences in loneliness, anger, depression, self-management ability and biomarkers of chronic illness in chronically ill mid-life adults in Appalachia. App Nurs Res. 45:55-62.
33. Trappenburg J, Jonkman N, Jaarsma T, van Os-Medendorp H, Kort H, (2013). Self-management: one size does not fit all. Pat Ed Coun. 9: 134-137.
34. World Health Organization (2021). Ageing and health.
35. World Health Organization (2021). UN Decade of Healthy Ageing.