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Cardiometabolic and Inflammatory Biomarkers as Mediators between Educational Attainment and Functioning at the Age of 90 Years

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Running head: SES, biomarkers & functioning in old age

Abstract

Background: Low socioeconomic status (SES) is associated both with poorer functioning and elevated levels of inflammatory and cardiometabolic biomarkers, however knowledge of such relations for the oldest old is limited. Our aim was to study whether education is associated with cardiometabolic (cholesterol levels, BMI and leptin) and inflammatory (CRP, IL-6, IL-1Ra) biomarkers for the 90-year-olds who participated in the Vitality 90+ study. In addition, we investigated whether these biomarkers explain educational inequalities in functioning.

Methods: All persons in Tampere, Finland, who were born in 1909 or 1910, were invited to participate, irrespective of their health status or dwelling place. The sample consisted of 262 participants who went through the home interview and blood tests. The SES indicator used was the highest education, and physical functioning was assessed using the Barthel index. The association of education with individual and combined biomarker scores, and with functioning, was analyzed cross-sectionally applying generalized linear models.

Results: The low- and mid-level-educated participants had greater odds of belonging to the high risk group in cardiometabolic biomarkers than did the high-educated. Differences were statistically significant in three individual biomarkers (HDL-cholesterol, leptin, BMI) and in a cardiometabolic score. There were no educational differences in inflammatory biomarkers. When all biomarkers were combined, they mediated educational differences in functioning on an average of 23%. After controlling for smoking, alcohol use and diseases, biomarkers mediated part of the differences between the mid-level- and high-educated.

Conclusions: High education was associated with better cardiometabolic biomarkers and functioning among the 90-year-olds. In part, educational inequalities in functioning were explained by cardiometabolic biomarkers.

Key words: Health Disparities, Longevity, Biomarkers, Socioeconomic status, Functioning

Introduction

Higher exposure to psychosocial stress, deleterious environments and unhealthy behaviors are considered to be pathways from low socioeconomic status (SES) to poorer health (1). Mechanisms for indicating how SES is transformed into differences in physical health are still poorly known. One pathway, proposed by McEwen and Seeman (2), suggests that perceived stress initiates physiological responses. Cumulative or long-standing exposure to physiological stress mediators (neuroendocrine, cardiovascular, metabolic and immune systems) changes the optimal physiological operating ranges; this can cause dysfunction in organ systems and may lead to various diseases.

Education has influence on the occupation and income. These three common SES indicators have impact on health through different pathways but they show largely similar health patterns. In many studies, low SES is associated with adverse inflammatory and cardiometabolic biomarker readings. Higher levels of C-reactive protein (CRP) and interleukin-6 (IL-6) are reported for 52-79-year-olds who had low SES (3-5). Cardiometabolic biomarkers, lower high-density lipoprotein (HDL) cholesterol, higher body mass index (BMI) and metabolic syndrome are regularly associated with low SES in the middle-aged (6-9). For older people, similar associations are found in some (10, 11), but not all (4, 12), studies. Instead of one biomarker, SES differences in biomarkers are often studied with a combined biomarker measure of allostatic load, a concept that reflects the functioning of several regulatory organ systems (13). The association of SES with the allostatic load measure has been shown to be stronger than its association with individual biomarkers (14-16).

Among older people, SES differences in functioning, measured as physical performance, mobility or activities in daily living, are demonstrated by a number of studies (17-19). There is also a growing body of evidence that shows, respectively, an inverse association between inflammatory (20-24) and cardiometabolic (25-27) biomarkers with functioning. Suggested associations between biomarkers and functioning are direct if, e.g., high BMI burdens muscles and cardiorespiratory systems or IL-6 accelerates the progression of disability. Associations may also be indirect if metabolic alterations influence functioning through cardiovascular consequences or through increased inflammation (28-30).

Studies that disentangle associations between SES, biomarkers and functioning are rare and knowledge, especially regarding the oldest old, is limited. We focused on the indicators of two major physiological regulatory systems, cardiometabolic and inflammatory, both of which, independently, predict the progression of diseases and are potential pathways through which SES contributes to health differences. In addition to more traditional measures, we included BMI as one of the cardiometabolic indicators. Even though BMI is not an ideal measure of body fat among the very old it still predicts morbidity and physical disability in this group (31, 32).

The purpose of this population-based study was to examine (1) whether education is associated with five cardiometabolic biomarkers, BMI, leptin, HDL cholesterol, a ratio of HDL and total cholesterol and triglycerides, and with three inflammatory biomarkers, IL-6, CRP and interleukin-1 receptor antagonist (IL-1Ra) among 90-year-olds and (2) whether the biomarkers mediate differences in functioning between the educational groups.

Methods

Study Population

Data came from the Vitality 90+ study which is a multidisciplinary research project concerning people 90 years old or older living in the city of Tampere, Finland (33). Participants in the present study were derived from the Tampere City Population Register in January 2000. All individuals living in Tampere, born in 1909-1910, irrespective of health status or dwelling place, were invited to participate (n = 535). According to the National Population Register, 66 people died before the study began and another 42 died before being examined, leaving 427 eligible people. During the study, 86 individuals refused to participate referring to poor physical or mental condition and seven could not be reached. Another 45 refused blood tests and took part only in the interviews. The study population initially numbered 289 but the final sample of those who went through the home interview and blood tests dropped to 262 (61% of the eligible population). Interviews and blood tests were carried out at the participant's place of residence. The study protocol was approved by the Ethics Committee of the Pirkanmaa Hospital District and the Ethics Committee of the Tampere Health Center. All participants, or their legal representatives, gave written informed consent.

Education

We used the highest attained education as an indicator of socioeconomic status. Education creates the opportunities for employment and income and has an influence on health even in old age through the resources gained in adulthood (34). Education was categorized into three hierarchic levels: high (at least 9 years), mid-level (4-8 years) and low (less than 4 years).

Biomarkers

Cardiometabolic markers

Blood samples were taken in the morning after an overnight fast. Biomarkers were analyzed from plasma or serum, separated by low-speed centrifugation and stored in aliquots at −80°C. HDL, total cholesterol and triglyceride concentrations were analyzed using a Cobas Integra 700 automatic analyzer (Hoffmann-La Roche Ltd). Leptin, which is a surrogate for body fat and is produced primarily by adipocytes was measured from serum (35). Leptin concentrations were analyzed with a luminex-based multiplex analysis system (Bio-Plex 200 System, BioRad Laboratories, Inc.) BMI was calculated as weight in kilograms divided by height in square meters. The number of missing values was 18 in leptin and 12 in BMI.

Inflammatory markers

The concentrations of IL-6 and IL-1Ra were determined using commercially available enzyme-linked immunosorbent assay kits (Pelikine Compact human IL-6 ELISA kit for IL-6 and Quantikine R&D Systems for IL-1Ra). High sensitivity CRP concentrations were analyzed using a Cobas Integra 700 automatic analyzer. The number of missing values was 4 in IL-6 and 2 in IL-1Ra.

Functional status

The Barthel index, which shows the degree of independence in functioning, was used as a measure of functioning. The individual variables (feeding, bathing, grooming, dressing, bowel and bladder control, toilet use, transfers bed to chair and back, mobility and stair-climbing) each provide 0, 5, 10 or 15 points, resulting in a summed count that varies between 0 and 100 points. The higher the points the greater the independence in functioning. (36).

Covariates

Multivariate analysis was controlled for confounders that are known to be associated with both SES and functioning. Diagnoses of heart disease (I0-50), infectious disease (A00-99 and B00-99), diabetes (E10-14), dementia (F00-03, G30) and arthritis (M15-19) were coded according to the International Classification of Diseases, 10th Revision. When a participant had at least one disease in the respective category, it was coded as 1 disease. The number of diagnoses varied from 0 to 5. Smoking was categorized as i) current, ii) former or iii) never a smoker and alcohol use as i) more than 2 times a week ii) less than 2 times a week iii) rarely iv) never.

Statistical analyses

Participants' biomarker characteristics by gender are described as medians with the interquartile range, stratified by education. Educational differences in biomarker levels were tested with the Kruskal-Wallis Test and pairwise comparisons were studied with the Dunn-Bonferroni test. For all other analyses, results are shown together for men and women because the association between education and biomarkers was highly similar, and, based on interaction terms, there was no reason to stratify analyses by gender.

Binary logistic regression models were applied to calculate the odds ratios of having high risk value in each individual biomarker. High risk was defined as the highest third of the values except for HDL-cholesterol and for the ratio of HDL and total cholesterol; for these, the lowest third signified high risk (Table 1). We decided to use tertiles because it is not clear if the same clinical cut-offs should be applied for the 90+ population as for the general population and there are no agreed clinical thresholds for the inflammatory markers. Also, it is possible that health risks may increase even below the clinical thresholds. All the biomarkers were studied individually and as two scores: cardiometabolic (BMI, leptin, HDL-cholesterol, triglycerides and a ratio of HDL and total cholesterol) and inflammatory (IL-6, CRP and IL-1Ra). Individual biomarkers were coded as 1 when the participant had a high risk value and the number of high risk biomarkers were summed to form two continuous variables ranging from 0-5 and 0-3, respectively.

Table 1. Cut-off points for high risk readings in individual biomarkers.

	Cut-point	Median (interquartile range)
CARDIOMETABOLIC BIOMARKERS		
Body mass index (kg/m^2)	≥ 25.6	24.2 (22.1-26.4)
Leptin (ng/mL)	≥ 16.9	11.7 (5.9-21.8)
High-density lipoprotein (HDL) cholesterol (mmol/L)	≤ 1.20	1.38 (1.11-1.67)
Ratio of HDL and total cholesterol	≤ 0.22	0.25 (0.20-0.31)
Triglycerides (mmol/L)	≥ 1.81	1.44 (1.14-1.99)
INFLAMMATORY BIOMARKERS		
Interleukin-6 (pg/mL)	≥ 3.84	2.64 (1.63-5.07)
C-reactive protein (mg/L)	≥ 2.90	1.70 (0.50-4.20)
Interleukin-1 receptor antagonist (pg/mL)	≥ 444	372 (276-487)

Educational differences in cardiometabolic and inflammatory scores were examined using order logistic regression. Both biomarker scores were categorized into three equal groups: a cardiometabolic score of 0, 1-2 or 3-5 and an inflammatory score of 0, 1 or 2-3 high risk measurements. The parallel lines assumptions were tested and fulfilled.

The associations between functioning and biomarker scores were examined with the Kruskal-Wallis Test. For the analysis, functioning was divided into three categories where summed count 100 points indicated independence in functioning, 61-99 moderate disability, and 0-60 severe disability. The biomarker scores were used as continuous variables. In order to study differences in functioning according to education, a summed count variable was formed of functioning and a negative binomial regression analysis with a log link was applied. The analysis was first adjusted separately for cardiometabolic and inflammatory scores, second for a combined score including both cardiometabolic and inflammatory biomarkers, third for smoking, alcohol use and diseases and finally for a combined biomarker score, smoking, alcohol use and diseases. Percentage reduction was computed as $[(RR_{model\_1} - RR_{model\_2}) / (RR_{model\_1} - 1)] \times 100$. Data were analyzed using SPSS version 20.0 (IBM Statistics).

Results

Out of 262 nonagenarians who participated in the study, 74% were women and 81% community-dwelling. Descriptive biomarker statistics stratified by education are presented in Table 2. For women, differences by education were statistically significant in BMI, leptin and HDL-cholesterol. After the pairwise comparisons, the high-educated had lower levels of leptin than mid-level-educated ($p = 0.03$) and lower BMI than the low-educated ($p = 0.01$). For men, differences were not statistically significant. Overall, women had lower education and higher HDL-cholesterol and leptin readings than did men ($p = 0.03$, 0.04 and <0.001).

Sex-adjusted associations between education and individual biomarkers from binary logistic regression are shown in Figures 1 and 2. An education gradient was seen in BMI, HDL-cholesterol, triglycerides and in the ratio of HDL and total cholesterol but only a few differences were statistically significant: the low-educated had higher BMI than the high-educated (OR 5.76, 95% CI 2.00-16.60) and the mid-level-educated had higher odds of having higher leptin and lower HDL-cholesterol levels than the high-educated (OR 2.75, 95% CI 1.07-7.09 and 2.46, 1.04-5.81).

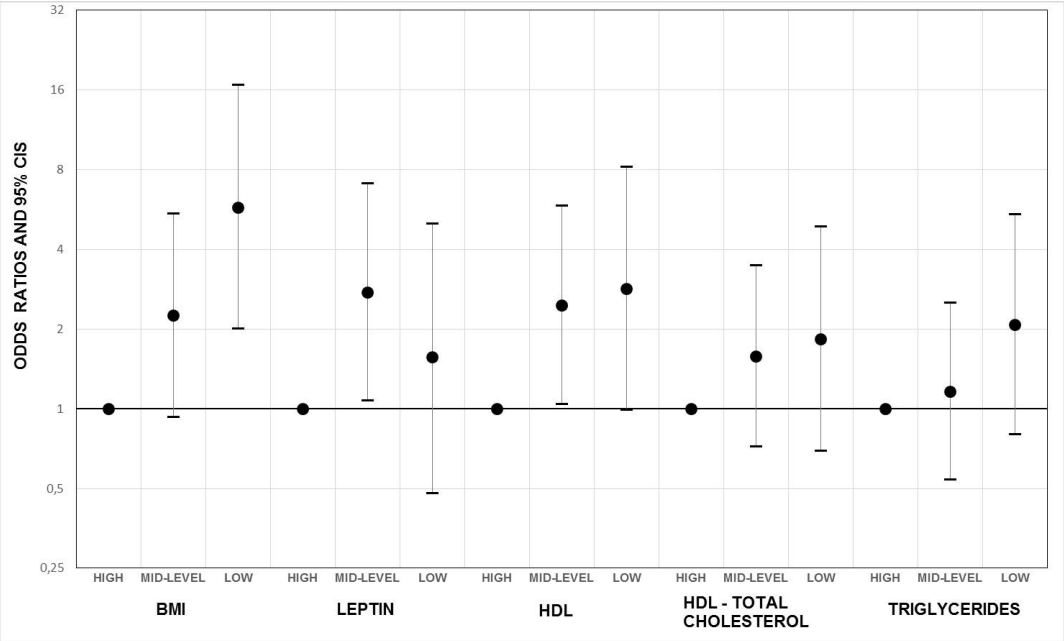

Figure 1. Odds ratios of having high risk readings in cardiometabolic biomarkers according to education. Participants in the vitality 90+ study. Sex-adjusted binary logistic regression models.

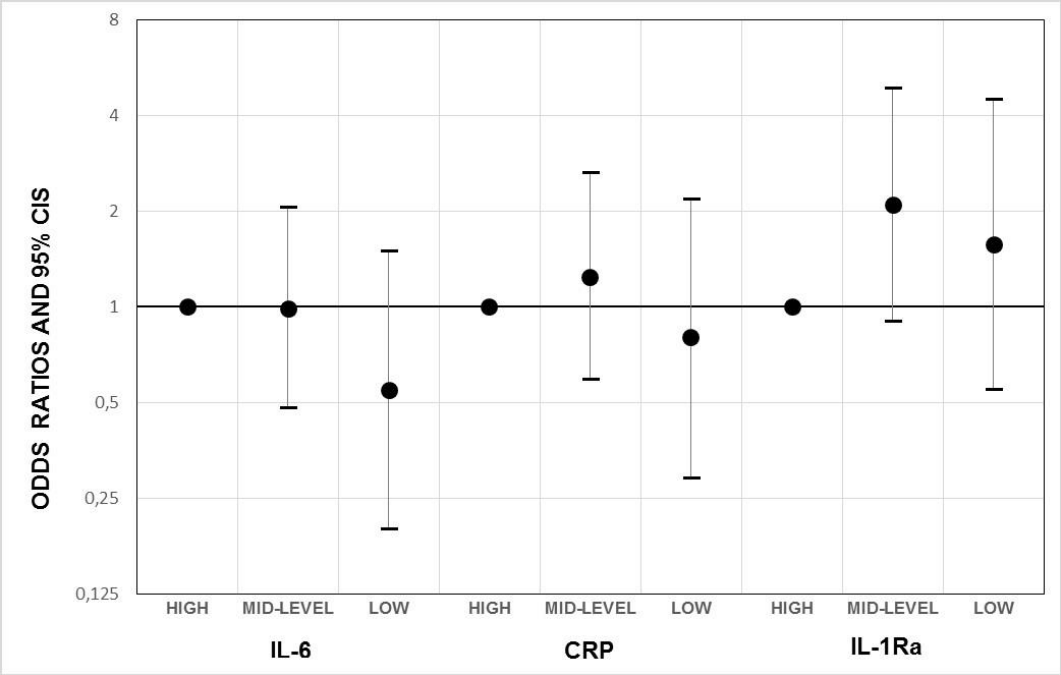

Figure 2. Odds ratios of having high risk readings in inflammatory biomarkers according to education. Participants in the vitality 90+ study. Sex-adjusted binary logistic regression model.

Ordered logistic regression analysis showed that the cardiometabolic score was higher for the mid-level- and low-educated (logit coefficients, 0.84 95% CI 0.14-1.53, 1.10 95% CI 0.20-1.99) than for high-educated (results not shown). There were no significant differences in the inflammatory score according to education. However, a higher inflammatory score was associated with poorer functioning ($p < 0.001$) while in the cardiometabolic score, there seemed to be a similar association, but statistical significance was not reached ($p = 0.08$) (Table 3).

Table 4 shows the association between education and functioning and the potential mediating effect of biomarkers in this association. In the sex-adjusted negative binomial regression model, rate ratios indicated better functioning for the high-educated in comparison to the low- and mid-level-educated (RR 0.92, 95% CI 0.84-1.00 and 0.88, 0.83-0.93). When the cardiometabolic score was added to the model, educational differences in functioning decreased, but the inflammatory score did not reduce the differences. In the model with the combined biomarker score, differences in functioning decreased 13% between the high- and the low-educated and 33% between the high- and mid-level-educated. In the model with smoking, alcohol use and diseases, high-educated still had better functioning than the mid-level-educated. In the final model with smoking, alcohol use, diseases and the combined biomarker score, functioning differences between the educational groups disappeared.

Table 2. Cardiometabolic and inflammatory biomarker levels by education; descriptive statistics are given separately for women and men.

	Education			
	High	Mid-level	Low	*p* Value
WOMEN, N (%)	24 (12)	137 (70)	34 (17)	
CARDIOMETABOLIC BIOMARKERS				
Body mass index, kg/m^2	22.6	23.9	25.3	0.015
	20.5-24.8	22.1-26.3	22.9-28.2	
Leptin, ng/mL	7.3	14.7	12.6	0.032
	5.5-13.6	6.9-30.1	8.1-23.5	
High-density lipoprotein cholesterol,	1.66	1.40	1.36	0.048
(HDL) mmol/L	1.33-1.94	1.10-1.70	1.08-1.69	
Ratio of HDL and total cholesterol	0.28	0.26	0.25	0.301
	0.22-0.34	0.20-0.31	0.19-0.30	
Triglycerides, mmol/L	1.35	1.46	1.73	0.436
	1.14-1.85	1.19-2.01	1.11-2.42	
INFLAMMATORY BIOMARKERS				
Interleukin-6, pg/mL	2.98	2.80	2.36	0.324
	1.69-6.95	1.65-5.30	1.36-4.15	
C-reactive protein, mg/L	1.40	1.70	1.20	0.528
	0.50-5.05	0.50-4.15	0.18-3.53	
Interleukin-1 receptor antagonist, pg/mL	284	402	385	0.134
	243-433	292-516	303-475	
MEN, N (%)	15 (23)	45 (69)	5 (8)	
CARDIOMETABOLIC BIOMARKERS				
Body mass index, kg/m^2	23.9	23.9	26.8	0.055
	21.5-27.4	22.4-26.0	26.1-31.3	
Leptin, ng/mL	4.9	8.3	8.9	0.401
	3.0-13.3	3.6-15.0	6.9-16.1	
High-density lipoprotein cholesterol,	1.32	1.18	1.33	0.333
(HDL) mmol/L	1.16-1.63	1.04-1.53	1.13-1.56	
Ratio of HDL and total cholesterol	0.25	0.25	0.24	0.736
	0.22-0.30	0.20-0.32	0.20-0.26	
Triglycerides, mmol/L	1.24	1.41	1.82	0.525
	0.91-1.86	1.09-1.79	1.14-2.30	
INFLAMMATORY BIOMARKERS				
Interleukin-6, pg/mL	2.46	3.19	1.52	0.081
	1.99-10.90	1.93-5.56	1.42-2.35	
C-reactive protein, mg/L	2.20	2.60	1.30	0.078
	0.30-2.60	1.05-5.70	0.45-2.30	
Interleukin-1 receptor antagonist, pg/mL	348	356	364	0.900
	256-422	261-452	245-698	

Notes: Median and interquartile range, p-values from the Kruskal-Wallis Test.

Table 3. Cardiometabolic and inflammatory scores according to the level of functioning.

	Biomarker scores	
Functioning	Cardiometabolic (N = 235)	Inflammatory (N = 258)
Barthel index points	range 0-5	range 0-3
0-60	1.86	1.63
61-99	1.73	0.90
100	1.33	0.83
p-values Kruskal-Wallis Test	0.08	< 0.001

Table 4. Rate ratios of having good functioning according to education.

	Adjustments for						
	Sex	Sex and cardiometabolic score	Sex and inflammatory score	Sex and combined biomarker score		Sex, smoking, alcohol use and diseases	Sex, smoking, alcohol use, diseases and combined biomarker score
EDUCATION	RR (95% CIs)	RR (95% CIs)	RR (95% CIs)	RR (95% CIs)	% Red. ł	RR (95% CIs)	RR (95% CIs)
High	1.00	1.00	1.00	1.00		1.00	1.00
Mid-level	0.88 (0.83 to 0.93)***	0.91 (0.87 to 0.97)**	0.88 (0.82 to 0.95)***	0.92 (0.87 to 0.97)**	33	0.92 (0.86 to 0.99)*	0.95 (0.89 to 1.02)
Low	0.92 (0.84 to 1.00)*	0.93 (0.85 to 1.01)	0.90 (0.81 to 0.99)*	0.93 (0.85 to 1.01)	13	0.96 (0.87 to 1.05)	0.95 (0.87 to 1.04)

Notes: Negative binomial regression with a log link, rate ratios and their 95% confidence intervals.

* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$.

ł Percentage reduction in rate ratios is from the sex-adjusted model to combined biomarker-adjusted model.

Discussion

In this population-based study on 90-year-olds, higher educational attainment was associated both with beneficial cardiometabolic biomarker levels and better functioning, but an association with inflammatory biomarkers was not clear. In the individual biomarkers, high-educated had lower BMI than low-educated and lower leptin and higher HDL-cholesterol levels than the mid-level-educated. Similar findings are reported for BMI and HDL-cholesterol in the US National Health and Nutrition Examination Survey (15) and in the nationally representative Finnish survey for 65-84-year-olds (10). We are not aware of studies that show associations between low SES with high leptin levels. Higher CRP and IL-6 levels are reported for well-functioning 70-79-year-old community-dwellers in the Health, Aging and Body Composition study (3) and for 52-70-year-old participants in the Framingham Offspring Study (4) who had low SES, but our study showed more vague associations with inflammatory markers. We performed a sensitivity analysis by excluding those who died within a year of the analyses but the result remained the same. It is likely that survival selection occur in the 90+ population which decreases educational inequalities in health.

We found that high-educated had less risk values in the cardiometabolic biomarkers than the other educational groups but this was not seen in the inflammatory score. In the general population, a cumulative burden of inflammatory, metabolic and cardiovascular biomarkers was found to be lower for the higher educated (15), though the same study reported weaker differences for older participants. We did not adjust analyses for the diagnosed diseases when studying educational differences in biomarkers because our chosen biomarkers may also reflect pathology of those diseases.

The inflammatory score was inversely associated with functioning, indicating that those who had more high risk readings had poorer functioning. We also showed that the high-educated had better functioning than the low- and mid-level-educated when measured with the Barthel index.

Finally, we studied whether biomarkers mediated the association between education and functioning. We found that cardiometabolic and inflammatory biomarkers together explained on average 23% of the functioning differences. Further adjustments for smoking, alcohol use and diseases also decreased educational differences in functioning, especially between the high- and low-educated. After adjustments for smoking, alcohol use and diseases, biomarkers had some independent value in mediating functioning differences between the high- and mid-level-educated. In the Health, Aging and Body Composition study, an average of 41% of the educational differences in incident mobility limitation was explained by biomedical factors and the strongest explanatory factors were the BMI and the inflammatory index (11). In the Health and Retirement Study, the high-educated had less risk values in cardiovascular biomarkers than the lower educated in the 53+-year-old population, especially in women, but biomarkers had only a negligible impact on reducing differences in functional limitations (37).

In summary, our results are in line with other studies with respect to educational differences in cardiometabolic biomarkers and their mediating effect on functioning; but, in contrast to some other studies, we found no educational differences in inflammatory biomarkers. Our study differs from the earlier ones in the sense that the participants in this study were very old, had many chronic conditions and no exclusion criteria were used. Low chronic inflammation (inflamm-aging) is found to be characteristic of advanced old age and is related to disability and comorbidities (38, 39). If every participant suffers from a low-grade proinflammatory state, it may hamper the identification of differences between educational groups. Nevertheless, the inflammatory score associated negatively with functioning and earlier studies using the same data have shown that these biomarkers are predictors of mortality (40). Some studies suggest that SES differences in biological risk factors peak in middle age and the biological profile becomes more similar in old age because of the mortality

selection bias (41). Koster and colleagues (2006) reported that low SES is associated with high levels of proinflammatory markers, but participants in that study were well-functioning 70-79-year-olds and the associations were mainly explained by behavior factors, such as smoking, alcohol use and physical activity. In our data, smoking and alcohol use were rare and did not really differ between the educational groups.

We decided to determine the high risk category using tertiles instead of the clinical cut-offs because there are no clinical cut-offs for all of the biomarkers and it is not clear if the thresholds are valid for the oldest old. Yet our high risk thresholds correspond well to other studies; triglycerides and IL-6 (16, 42), HDL-cholesterol (11), CRP (15) and to clinical cut-off values in triglycerides, HDL-cholesterol, a ratio of HDL and total cholesterol, CRP and BMI. Our threshold for BMI was lower than in other studies. Because of the accumulation of body fat and muscle loss, negative health effects may occur at a lower BMI in older people (32). Not much is known about the thresholds for leptin and IL-1Ra for the oldest old, but compared with other studies, our threshold for IL-1Ra seems to be high (42). Studies suggest, that even though clinical cut-offs might not be exceeded, subclinical pathologies could increase adverse health effects (43).

To our understanding, this is the first study that investigates the role of biomarkers as mediators between the education and functioning in the oldest old. The strengths of the study rely on the wide range of information, including biological, behavioral and social data, for the well-defined population-based sample. There were limitations in the study. First, analyses were cross-sectional which means that the association between biomarkers and functioning can be either way. Second, because some individuals refused to participate, referring to poor health status, it is probable that our sample represents the healthier end of the basic population as is the case in most of the studies focusing on the oldest old. Third, the study sample was rather small for the epidemiological analyses but not particularly small given that it provides data on biological measures in the very old population. The vast majority of the participants were women however, the study population corresponded to the general gender distribution in this age group.

The biomarkers we studied, represent two major physiological regulatory systems, cardiometabolic and inflammatory, which independently and together, predict the progression of diseases. They are also potential pathways through which SES influence on health differences (43). This study suggests that part of the educational differences in functioning in the oldest old can be explained by cardiometabolic biomarkers. Life-course studies with social and biological data are needed to better understand the role of biomarkers in the mechanisms that link SES to health.

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