Is parental longevity associated with the cardiovascular risk and the successful ageing of their offspring? Results from the multinational MEDIS study

Stefanos Tyrovolas[1,2], Evangelos Polychronopoulos[2], Anargiros Mariolis[3], Suzanne Piscopo[4], Giuseppe Valacchi[5], Kornilia Makri[6], Akis Zeimbekis[7], Dimitra Tyrovola[2], Vassiliki Bountziouka[2], Efthimios Gotsis[2], George Metallinos[2], Josep-Antoni Tur[8], Antonia Matalas[2], Christos Lionis[6], Josep Maria Haro[1], Demosthenes Panagiotakos[2]

[1]Parc Sanitari Sant Joan de Déu, Fundació Sant Joan de Déu, CIBERSAM, Universitat de Barcelona, Barcelona, Spain; [2]Department of Nutrition and Dietetics, School of Health Science and Education, Harokopio University, Athens, Greece; [3]Health Center of Aeropolis, General Hospital of Sparta, Aeropolis, Greece; [4] Nutrition, Family and Consumer Studies Office, Faculty of Education, University of Malta, Msida, Republic of Malta; [5]Department of Life Sciences and Biotechnology, University of Ferrara, Ferrara, Italy; [6]Clinic of Social and Family Medicine, School of Medicine, University of Crete, Heraklion, Greece; [7]Health Center of Kalloni, General Hospital of Mitilini, Mitilini, Greece; [8]Research Group on Community Nutrition and Oxidative Stress, Universitat de les Illes Balears & CIBERobn, Guillem Colom Bldg, Campus, E-07122 Palma de Mallorca, Spain

Address for Correspondence
Prof. Demosthenes B. Panagiotakos
46 Paleon Polemiston St., Glyfada, 166 74, Attica, Greece
Tel. +30210-9603116 & Fax. +30210-9600719 E-mail: dbpanag@hua.gr

Running headline : Parental longevity and offspring's health

Abstract

The aim of the present study was to evaluate the role of parental longevity and parental cardiovascular disease (CVD) history, in CVD risk and successful ageing of a random sample of older adults living in the Mediterranean basin and who participated in the MEDIS (MEDiterranean ISlands) study. During 2005-2011, 2663 elders were voluntarily enrolled. A multidimensional successful ageing index consisting of 10 components was used. Paternal and maternal longevity was defined as those older participants of whom both parents lived above the age of 90 years. The burden of CVD related factors (CVD RFs) was calculated as the total score of four major CVD RFs (range 0-4). After adjustment, parental longevity was inversely associated with the burden of CVD RFs (p=0.04). Moreover, parental longevity was positively associated with the older adults' successful ageing score [b-coefficient (95% CI): 0.38 (0.06 to 0.71)]. Parent's long-living was revealed as an important factor for successful ageing and for reduced CVD risk, suggesting that further research is needed in the genetic pre-disposition of longevity.

Keywords: parental longevity; successful ageing; cardiovascular disease; older adults, Mediterranean basin

Introduction

The principals of longevity, and healthy and successful ageing remain among the major challenges of public health[1]. Until now, many studies have proposed that longevity follows a familial pathways[2] and could be inherited. According to researchers, a complex phenotype is accompanying the 'long-livers' and more particularly the centenarians, as a result of their improved capacity to physiologically adapt throughout the various life stages[3,4]. Specifically, long-liver groups, like the centenarians, are characterized by delayed onset of cardiovascular disease (CVD), certain cancers, dementia, as well as cognitive and functional impairment.[5-9]. Following the healthy status of their long-liver parents their offspring's are experiencing a similar long-living pathway. Previous findings indicate that long-livers' offspring's are having lower risk for CVD events and CVD related factors (CVD RFs) (i.e. hypertension, diabetes mellitus, etc.)[10,11] and thus have a significant survival advantage[12-14].

In parallel, it is well known that cardiovascular health encompasses both familial (genetic) components as well as environmental factors[15-17]. Various studies have indicated the role of maternal and paternal CVD history on the CVD health status of their offspring[16-17]. Previous studies suggest that parental long-living is beneficially related to their offspring's health status; however the adjustment for parental clinical history is sparse[18]. Clearly the process of longevity is quite complex and is associated with a variety of factors, not only with physical health. Successful ageing is a concept which is considered as a low probability of disease and disability, high cognitive and physical capacity, active participation throughout various social activities and represents the aforementioned complexity in the longevity process[19-20]. Until now, to the best of our

knowledge, there is a lack of epidemiological evidence on the role of parental longevity and CVD history in successful ageing.

Given the complexity of the human longevity and ageing pathway, together with the lack of data among Mediterranean populations, the aim of the present study was to evaluate the role of parental longevity and parental CVD history, in CVD risk and successful ageing of a random sample of older adults living in the Mediterranean basin and who participated in the MEDIS (MEDiterranean ISlands) study. The MEDIS study sample encompasses 2 of the already reported high life expectancy areas in the world (i.e. the islands of Ikaria and Sardinia). In addition, the selected older Mediterranean population has rarely been studied in the last 4 decades; a fact that makes this survey of major importance, as it included two of the islands (i.e. Corfu and Crete) where Ancel Keys and his colleagues from the Seven Countries Study first observed the basic components of longevity[21].

Methods

The MEDIS study sample

During 2005-2011, a population-based, multi-national, convenience sampling was performed to voluntarily enroll older people from 21 Mediterranean islands (the target sample size was 300 people from the Republic of Cyprus, 250 from Malta and 150 from each of the other islands/areas): Republic of Cyprus (n=300), Malta (n=250), Sardinia (n=60), Sicily (n=50), Mallorca and Menorca (n=111) and the Greek islands of Lesvos (n=142), Samothrace (n=100), Cephalonia (n=115), Crete (n=131), Corfu (n=149), Limnos (n=150), Ikaria (n=76), Syros (n=151), Naxos (n=145), Zakynthos (n=103),

Salamina (n=147), Kassos (n=52), Rhodes and Karpathos (n=149), Tinos (n=129), as well as from the rural region of Mani (n=153) (a southern Greek peninsula). According to the study protocol, individuals were not eligible for inclusion if they resided in assisted-living centers, had a clinical history of CVD or cancer, or had lived away from the island or region for a considerable period of time during their lives (i.e. >5 years); these exclusion criteria were applied because the study aimed to assess lifestyle habits that were not subject to modifications due to existing chronic health conditions or by environmental factors, other than living milieu. A group of health scientists (physicians, dietitians, nutritionists and nurses) with experience in field investigation collected the required information using a quantitative questionnaire and standard procedures.

The study followed the ethical considerations provided by the World Medical Association (52nd WMA General Assembly, Edinburgh, Scotland, October 2000). The Institutional Ethics Board of Harokopio University approved the design and procedures of the study (reference No. 16/19-12-2006). Participants were informed about the aims and procedures of the study and gave their consent prior to being interviewed.

Evaluation of clinical characteristics

All of the measurements carried out in the different study centres were standardized and the questionnaires used were translated in all cohort languages following the World Health Organization (WHO) translation guidelines for tools' assessment.[22] Weight, height and waist circumference were measured using a standard protocol; body mass index (BMI) was calculated as the ratio of weight by height squared (kg/m^2). Overweight was defined as BMI between 25 and 29.9 Kg/m^2 and obesity was defined as BMI > 29.9

Kg/m^2. Diabetes mellitus (type 2) was determined by fasting plasma glucose tests and was analyzed in accordance with the American Diabetes Association diagnostic criteria (glycated haemoglobin A1C $\geq$6.5% or fasting blood glucose levels greater than 125 mg/dl or 2-h plasma glucose >200 mg/dl during an oral glucose tolerance test-OGTT- or a random plasma glucose >200 mg/dl, or by a prior diagnosis of diabetes). Participants who had blood pressure levels ≥140/90 mmHg or used antihypertensive medications were classified as hypertensive. Fasting blood lipid levels [high density lipoprotein (HDL-) and low density lipoprotein (LDL-) cholesterol and triglycerides)] were also recorded and hypercholesterolemia was defined as total serum cholesterol levels >200 mg/dL, or the use of lipid-lowering agents according to the National Cholesterol Education Program-Adult Treatment Panel III (NCEP ATPIII) guidelines.[23]

Parental longevity was defined as those older participants of whom both parents were long-livers, beyond the age of 90 years. Moreover, maternal and paternal history of diabetes type II, hypertension and hypercholesterolemia were recorded. No information on maternal and paternal history of obesity was collected. A cumulative paternal and maternal "CVD history index" was developed, summing the 3 health-specific, binary variables mentioned before (a score of 1 was given for each additional related factor: hypertension, hypercholesterolemia, diabetes type II, so theoretical range was 0-3). Further classification was applied. Specifically, those with score 0 were classified with no maternal and paternal CVD history, while those with score 1 to 3 were grouped as having maternal and paternal CVD history.

Evaluation of dietary habits, socio-demographic and other lifestyle characteristics of

the participants

Dietary habits were assessed through a semi-quantitative, validated and reproducible food-frequency questionnaire.[24] Furthermore, consumption of various alcoholic beverages (i.e. wine, beer, whiskey, vodka, and the traditional ouzo, tsipouro and retsina) was measured in terms of wineglasses per day, adjusted for ethanol intake (e.g. one 100 ml glass of wine was considered to have 12% ethanol) and classified for the present analyses, into 0 for no alcohol consumption, 1 for alcohol consumption of at least 1 glass/week. To evaluate the level of adherence to the Mediterranean diet, the MedDietScore (theoretical range 0-55) was used.[25]

Basic socio-demographic characteristics, such as age, gender, years of schooling, financial status, as well as lifestyle characteristics, such as smoking habits and physical activity status, were recorded. Regarding financial status, the participants were asked to report their mean income during the previous three years using a four-point scale (low, inadequate to cover daily expenses = 1, medium, trying hard to cover daily expenses = 2, good, adequate to cover daily expenses = 3, very good, very adequate to cover daily expenses = 4). This scale was decided upon because of the variety of the populations studied, as well as the common difficulty of accessing exact financial data. The participants who were in the upper category were classified as participants with high financial status, while all the others were classified as low and medium financial status (high vs. low-medium financial status). Current smokers were defined as smokers at the time of the interview. Former smokers were defined as those who had previously smoked, but had not done so for a year or more. The remaining participants were defined as occasional or non-current smokers. Physical activity was evaluated in metabolic

equivalent of task (MET) -minutes per week, using the shortened, and validated Greek version of the self-reported International Physical Activity Questionnaire (IPAQ)[26] translated in all the cohort´s languages. As minimally active or "health-enhancing physical activity (HEPA) active" were classified individuals who reported at least 3 MET-minutes per week. Furthermore, the weekly frequency of physical activity was recorded. Symptoms of depression during the previous month were assessed using the validated Greek version (also translated in all the cohort´s languages) of the shortened, self-report Geriatric Depression Scale (GDS) (range 0-20).[27] Moreover, in order to evaluate the older adults' social participation, the weekly frequency of their social activities with their family, their friends as well as their yearly frequency of excursions were recorded.

Further details about the MEDIS study protocol may be found elsewhere.[28]

Evaluated outcomes

Following the multi-dimensional approach to successful ageing already reported by several experts[29] and the MEDIS study group,[20] 10 components (i.e. education, financial status, physical activity, BMI, GDS score, participation in social activities with friends, with family, yearly excursions, CVD RFs score and MedDietScore) were incorporated for the measurement of successful ageing. The composed successful ageing index was represented as the cumulative score of the 10 components (theoretical range 0-10); specifically, individual ratings (from 0 to 1) in each of the 10 components were assigned, according to their positive or negative (i.e. reverse scoring) influence on successful ageing, according to the current literature.[20]

Moreover, a cumulative score indicating the overall burden of CVD RFs of the

older participants, was calculated (a score of 1 was given for each additional risk factor: hypertension, hypercholesterolemia, diabetes and obesity, so the theoretical range was 0-4).

Statistical analysis

Continuous variables are presented as mean ± standard deviation (SD) and categorical variables as frequencies. Comparisons of continuous variables between groups of study were performed using the independent samples t-test (for the normally distributed variables), or the Mann-Whitney U-test and the Kruskall-Wallis test (for the skewed variables). Associations between categorical variables were tested using the chi-square test. Nested multiple logistic regression models were applied to estimate, for an off-spring, the odds of having overall CVD RF 'morbidity index' (0-2 related factors vs. 3-4 related factors), taking into account other participants' characteristics (i.e. age, sex, education and financial status, living alone, former smoking habits, physical activity, adherence to the Mediterranean diet, alcohol consumption, parental longevity, maternal and paternal CVD history). Nested linear regression models were also applied in order to further evaluate the association between various factors, that were potentially associated with the odds of having overall 3-4 CVD factors, (i.e. socio-demographic, bio-clinical, lifestyle factors, parental longevity, maternal and paternal CVD history) and the level of successful ageing. Colinearity was tested using the Variance Inflation Factor criterion (VIF; values >4 suggested colinearity between independent variables and one of them was excluded from the model). The assumption of homoscedasticity was tested by plotting the scatter plot of standardised residuals over the predicted score values. Results from linear regression models are presented as b-coefficients and their 95% Confidence

Intervals. No correction for multiple comparisons testing was performed, because the tested hypotheses were independent. All reported *p*-values were based on two-sided tests. SPSS software (version 20) was used for all calculations (IBM Statistics, Greece).

Results

Among the MEDIS sample, paternal longevity (father lived ≥90 years) was 9% and maternal longevity (mother lived ≥90 years) was 12%. When the 7 geographical areas of the participants were taken into account (West Mediterranean, Ionian, Aegean, Saronikos islands, Crete island, Mani, and Cyprus Republic), the inhabitants of the Republic of Cyprus had the highest prevalence of paternal and maternal longevity (i.e. 19 and 22%) while the participants living in the islands of West Mediterranean (Malta, Sardinia, Sicily, Balearic islands) had the lowest paternal longevity (i.e. 4%) and Saronikos islands had the lowest maternal longevity (i.e. 5%) ($p<0.001$). Parental longevity regarding the 7 geographical areas is presented in ***Table 1***. When rural and urban areas were compared, a significant difference emerged with regard to the proportion of older adults exhibiting paternal longevity (both mother and father lived ≥age of 90 years) (6 vs. 5%, $p=0.008$). Moreover, older adults living in urban areas had a higher burden of parental CVD history as opposed to those living in rural areas (i.e. 52 vs. 37%, $p<0.001$).

[Table 1]

Analytical demographic, behavioral, clinical and lifestyle characteristics of the sample by parental (i.e. maternal, paternal and parental) CVD history are summarized in ***Table 2.*** Compared with older adults with no parental CVD history, those with parental CVD history, had a higher prevalence of hypertension ($p<0.001$), diabetes type II

($p<0.001$), hypercholesterolemia ($p<0.001$), a higher burden of CVD RF ($p<0.001$) and were classified within high financial status ($p<0.002$). No consistent differences were observed, however, between the groups with regard to their BMI level, smoking habits, living alone, alcohol consumption, adherence to the Mediterranean diet, physical activity and successful ageing.

[Table 2]

Age, gender, education and high financial status, living alone, physical activity, smoking habits, alcohol consumption and adherence to the Mediterranean diet, adjusted logistic regression analysis showed that older adults with parental longevity were 0.4-times less likely to have an increased burden of CVD RF, as opposed to those with no parental longevity (95%CI 0.16 to 0.98) (*model 1*). The latter model was further adjusted for maternal and paternal CVD history. When these factors were taken into account parental longevity was not associated any more with the burden of CVD RFs among the older adults (*model 2*). Moreover, in this model the habit of consuming alcohol appears to offer some protection against the accumulation of factors associated with CVD.

[Table 3]

The above mediating association among parental longevity and parental CVD history was further tested throughout the wider concept of successful ageing. Specifically, after adjusting for age, gender, smoking habits and alcohol consumption, parental longevity was positively associated with the successful ageing score [b-coefficient (95% CI): 0.38 (0.06 to 0.71)] of islanders (*model 1*). However, when paternal and maternal

CVD history was taken into account, the association of parental longevity with the older adults' successful ageing score disappeared (*model 2*).

[Table 4]

Discussion

The present study revealed that parental longevity was inversely associated with their offspring's burden of CVD risk, irrespective of age, gender, education and high financial status, living alone, physical activity, smoking habits, alcohol consumption and adherence to the Mediterranean diet. In addition, a positive association among parental longevity and the older adult's successful ageing level was reported. However, the latter findings became non-significant when paternal and maternal CVD RF history was considered in the analysis. The confounding role of paternal and maternal CVD history on the relationship between parental longevity and older adult's burden of CVD RF and successful ageing status could imply that it is not only the possible inherited factor of longevity that promotes successful ageing and CVD health, but also the burden of parental CVD RFs. All of the aforementioned relationships, especially among elderly Mediterranean populations, have rarely been studied.

Despite the lack of previous findings regarding parental longevity and CVD health and successful ageing among Mediterranean populations, a number of studies have previously reported that long-livers offspring's also enjoy a ¨healthy¨ longer life. More specifically, that the offspring of long-livers have lower risk for CVD, as well as various CVD RFs (i.e. hypertension, diabetes mellitus, etc)[10, 11]. Within our data analysis, a

number of components as well as parental longevity and their offspring's burden of CVD RFs were explored to reveal the positive role of parental longevity on their offspring's CVD health (*model 1*). According to several researchers, the aforementioned favorable association could be the result of specific disease genes prevalent in long-livers. Various types of allele genes have been proposed.[30-32]. Furthermore, the role of genes in minimizing the "speed" of ageing and offering protection against age-related diseases could be an additional possible explanation[33]. Recently the role of different pathways (gender, etc.) in ageing and longevity, have been reported[34]. Throughout the multivariate analysis, being female was associated with higher CVD morbidity. The latter finding is in accordance with previous results where females were living longer with higher burden of disease compared with males[35].

Research findings, however, lend support to the existence of genetic determinants for various CVD RFs such as diabetes mellitus, metabolic syndrome and others[16-17]. Various epidemiologic results suggest that parental, and in general familial aggregation of CVD events, is an additional strong determinant[36]. Although several international organizations[23] include parental CVD history as an independent factor in the assessment of CVD health, until now, it is rarely considered in the analysis of previous studies[18]. For the first time, this study extends the analysis by including the maternal and parental CVD history (*model 2*), to show that the beneficial effect of parental longevity on offspring's CVD health thus disappears. This finding indicates that the above mentioned positive contribution of parental longevity could be mediated to those offspring's who have an increased maternal and paternal burden of CVD RFs.

It has been suggested that the process of long-living reflects complex interrelations among multi-dimensional factors, which are represented throughout the successful ageing concept[20]. Successful ageing has been associated with lower mortality rates and better health outcomes[29]. The analysis of the MEDIS data revealed a beneficial effect of parental longevity on their offspring's successful ageing. However this association was not significant any more after the inclusion of parental CVD RF history (*model 2*). Until now, despite the sound evidence supporting the beneficial effect of parental longevity on various health indicators[18], the information about its role in the level of successful ageing is sparse. Genomics, metabolomics[37], epigenetics[38], have been proposed as potential longevity pathways and could beneficially contribute to the favorable level of successful ageing. Taking into account the aforementioned, the offspring of long-livers seem to have a better successful ageing status, and a reduced risk for CVD age-related morbidities than the offspring of non-long-lived parents. This possible familial longevity and CVD health pathway raises some concerns about the need for early prevention measures in order to promote healthy long-living, specifically among the offspring of non-long-lived parents and of parents with increased CVD morbidity. However, further studies are needed in the genetic pre-disposition of longevity, successful ageing and the role of parental burden of CVD RFs.

Strengths and limitations

The present study has several strengths. It is one of the few to evaluate the association of various factors (clinical, socio-demographic and lifestyle), parental longevity and CVD history of a large sample of 'healthy', independently-living older

people in the Mediterranean basin. Among the limitations, is the fact that this is a cross-sectional study limits the potential for aetiological conclusions. Estimation of successful ageing and of total CVD risk among elders is a difficult task[20,39]. The cumulative successful ageing index, as well as the CVD scores that were used here by simply adding the presence of the common determinants of the individuals may not accurately estimate the successful ageing status and the CVD risk of these individuals. Also, in this study there was the potential of recall bias, particularly in the assessment of parental CVD history.

Conclusions

Parental longevity seems to constitute an important factor of successful ageing and CVD health of Mediterranean older adults. Our results suggest that older adults with long-lived parents retain a healthier CVD profile in their later life; a fact that further enhances the familial pathway of longevity and successful ageing. However, further studies are needed to better address this interesting question on the role of hereditary in CVD health and successful ageing.

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Conflict of Interests

None declared

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Table 1. Parental longevity (both long-lived parents) among different geographical areas of the MEDIS study.

Geographical areas	Parental Longevity
Aegean Islands (%)*	4
Island of Crete (%)	2
Ionian Islands (%)*	4
Republic of Cyprus (%)	7
West Mediterranean Islands (%)*	2
Saronikos Islands (%)*	2
South Peloponnesus (%)*	7

* Aegean area includes the islands of: Lesvos, Samothrace, Limnos, Ikaria, Syros, Naxos, Kassos, Rhodes and Karpathos and Tinos. Ionian area includes the islands of: Cephalonia, Corfu and Zakynthos; West Mediterranean area includes the islands of: Malta, Sardinia, Sicily, Mallorca and Menorca; Saronikos area are includes the island of: Salamina; South Peloponnesus area includes the rural area of Mani.

Table 2. Demographic, behavioral and lifestyle characteristics of the Multi-national MEDIS sample, by parental CVD history.

	No Maternal CVD history (n=905)	Maternal CVD history (n=305)	P	No Paternal CVD history (n=803)	Paternal CVD history (n=407)	P	No Parental CVD history (n=654)	Parental CVD history (n=553)	P
Age	74.5±74	72.9±6.9	0.001	74.7±7.4	72.9±6.9	<0.001	75.2±7.5	72.8±6.9	<0.001
Sex (male %)	48	49	0.70	51	41	0.001	52	43	0.001
BMI (kg/m^2)	29.0±11.0	28.7±4.6	0.72	28.8±11.4	29.2±4.8	0.53	28.9±12	28.9±5.0	0.99
Education (years of schooling)	6.4±4.0	7.2±4.1	0.10	6.5±4.2	6.8±3.9	0.35	6.4±4.2	6.8±3.9	0.18
High financial status (%)	15	17	0.43	11	25	<0.001	11	20	0.002
Living alone (%)	26	22	0.19	24	28	0.14	24	28	0.44
Former smoking habits (%)	37	35	0.80	38	33	0.22	40	32	0.06
Physical activity (%)	65	47	0.50	48	80	0.16	49	72	0.30
MedDietScore (0-55)	33.4±4.6	32.9±4.6	0.16	33.5±4.5	33.0±4.7	0.21	33.5±4.7	33.1±4.7	0.25
Alcohol consumption (%)	47	50	0.28	47	49	0.51	45	50	0.09
Hypertension (%)	59	70	0.001	55	74	<0.001	54	71	<0.001
Diabetes Mellitus (%)	22	35	<0.001	22	31	0.001	20	32	<0.001
Hypercholesterolemia (%)	49	64	<0.001	45	68	<0.001	42	65	<0.001
CVD risk score (0-4)	1.6±1.1	2.0±1.1	<0.001	1.5±1.1	2.1±1.1	<0.001	1.5±1.1	2.0±1.1	<0.001
Successful ageing index (0-10)	2.5±1.3	2.6±1.4	0.80	2.5±1.3	2.7±1.4	0.05	2.5±1.3	2.6±1.4	0.75

Table 3. Results from nested multiple logistic regression models performed to evaluate the association of various socio-demographic, bio-clinical, lifestyle characteristics and parental longevity as well as CVD history of the multi-national MEDIS study participants in relation to the overall CVD RF 'morbidity index'+ (0-2 related factors vs. 3-4 related factors).

	Model 1		***Model 2***	
	OR	(95%CI)	OR	(95%CI)
Paternal Longevity (yes vs. no)	0.40*	(0.16; 0.98)	0.88	(0.21; 3.64)
Age (per 1 year)	0.96**	(0.94; 0.98)	0.99	(0.96; 1.03)
Sex (men vs. women)	0.52**	(0.33; 0.82)	0.53*	(0.28; 1.00)
Education status (years of school)	0.93**	(0.88; 0.98)	0.95	(0.88-1.03)
High financial status (yes vs. no)	0.83	(0.52; 1.32)	0.53	(0.24; 1.16)
Living alone (yes vs. no)	0.81	(0.56; 1.16)	0.74	(0.41; 1.23)
Physical activity (yes vs. no)	1.05	(0.74; 1.49)	0.92	(0.55; 1.54)
MedDietScore (change per unit)	1.01	(0.97; 1.06)	1.03	(0.96; 1.11)
Former smoking (yes vs. no)	1.12*	(1.05; 1.20)	1.85	(0.93; 3.67)
Alcohol consumption (yes vs. no)	0.66*	(0.46; 0.95)	0.55*	(0.32; 0.93)
Maternal CVD history (yes vs. no)	-	-	0.79	(0.45; 1.39)
Paternal CVD history (yes vs. no)	-	-	1.98*	(1.19; 3.29)

Abbreviations: OR: odds ratio, CI: confidence interval, CVD RF 'morbidity index': score one was given for each additional risk factor: hypertension, hypercholesterolemia, diabetes and obesity, theoretical range 0-4).

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

Table 4. Results from nested linear regression models performed to evaluate the association of socio-demographic, lifestyle characteristics, parental longevity and CVD history, that were found to be previously associated with participants' CVD related factors, in relation to the level successful ageing.

	Model 1		***Model 2***	
	b-coefficient	(95%CI)	b-coefficient	(95%CI)
Parental longevity (yes vs. no)	0.38*	(0.06; 0.71)	0.58	(-0.10; 1.26)
Age (per 1 year)	-0.08	(-0.02; -0.002)	-0.01	(-0.03; 0.008)
Sex (males vs. females)	0.53***	(0.34; 0.71)	0.72***	(0.40; 1.04)
Living alone (yes vs. no)	-0.17*	(-0.33; -0.008)	-0.19	(-0.47; 0.08)
Former smoking habits (yes vs. no)	0.13	(-0.06; 0.32)	0.21	(-0.10; 0.53)
Alcohol consumption (yes vs. no)	0.49***	(0.34; 0.64)	0.60***	(0.35; 0.86)
Maternal CVD history (yes vs. no)	-	-	-0.04	(-0.31; 0.21)
Paternal CVD history (yes vs. no)	-	-	0.25	(-0.02; 0.54)

Abbreviations: CI: confidence interval.

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