REVIEW ARTICLE

Association of cardiovascular risk factors, behaviours, short stature and longevity.

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abstract

Cardiovascular risk factors (CVRFs) and behaviours interact during adulthood with the sad privilege of being the first cause of disability and death.

CVRFs interact positively with additive effects such as of hypercholesterolaemia and high blood pressure and the risk derived from the simultaneous exposure is greater than would be expected by the simple addition of the corresponding factors.

During the last century, life expectancy increased rapidly in Europe as well as in other parts of the world.

Life expectancy is a health indicator of a given population, while the term longevity simply means an average life expectancy.

Comparative studies between Japan and some western countries clearly reveal the difference in longevity of its inhabitants.

High stature could be assessed as a late risk factor too.

Introduction

It is known that atherosclerosis is a slow, progressive disease that starts in childhood and usually manifests itself clinically much later, as it has been demonstrated by several authors [1-7], including genetic predisposition, the environment, harmful behaviours and cardiovascular risk factors (CVRFs) that produce a disease initially asymptomatic.

Identify and treat CVRFs in childhood and adolescence would be the most important value of Cardiovascular Prevention.

Long-lived patients who are still autonomous may hypothetically have protective factors and/or fewer CVRFs which afford a better quality of life.

The decline in mortality in the Japanese people is undoubtedly influenced in the general improvement of health consideration of a number of factors such as diet, work, social relations, primary health care, public health services, the economy, among others as the short stature among Okinawans who have the highest prevalence of centenarians in the world (33.6/100000 inhabitants).

Cardiovascular risk factors

The role of RFs on cardiovascular morbidity and mortality may be influenced by age [8], male gender [9], and by ethnic or geographic factors. [10]

Age is a prognostic factor of great importance, already recognized by Benjamìn Gompertz (insurance actuary) in 1825, and is the most powerful independent RF for the prognosis of death and atherosclerosis disease. It is the most powerful risk factor for hypertension, and cardiovascular death. [11]

Male sex is associated with greater cardiovascular complications.

The association between high blood pressure and cardiovascular disease and mortality has been the subject of numerous observational studies.

From a long time ago it has been demonstrated that arterial hypertension is also a major RF in the elderly. [12] [13] [14]

Patients with a history of hypertension have at least six times greater risk of heart failure than those individuals without that a history. [15]

No specific guidelines exist for hypertension management for this particular elderly population.

Numerous observational studies have confirmed the predictive role and existence of a causal relationship between hypercholesterolaemia and coronary heart disease. (for example: Framingham Heart study, MRFIT study).

Hypercholesterolaemia is one of the main modifiable CVRFs.

Also, cholesterol chemically is an alcohol; hypercholesterolaemia induces a decreasing in the chromatic vision, the higher visual function, located in the areas 17, 18 and 19 of the cerebral cortex. [16]

Hypercholesterolaemia was correlated with dizziness by the action on the labyrinth as a neurotoxic effect. [17]

Evidence exists that hypercholesterolaemia is a risk factor for the neuronal aging. The findings in elderly Finnish men suggested that high serum cholesterol concentration was an independent risk factor for Alzheimer's disease.

The National Cholesterol Education Project sets no upper age limit for lipid screening; however, it recommends "caution in proceeding to drug therapy in the elderly" for primary prevention. Some authors question the utility of cholesterol as a significant risk factor for heart disease mortality in elderly people.

Unfortunately, little direct evidence exists about the benefits or burdens of screening and

treating octogenarians with high serum lipids.

The epidemic of type 2 diabetes (DM) is clearly linked to increasing rates of overweight and obesity in the U.S. population, but projections by the Centers for Disease Control and Prevention suggest that even if diabetes incidence rates level off, the prevalence of diabetes will double in the next 20 years, in part due to the aging of the population. [18]

The results of the observations revealed a significant association between obesity and diabetes after accounting for genetic factors. [19]

Data from the Framingham study indicate that diabetic patients are at a higher risk of developing heart failure than non-diabetics.

Cardiovascular mortality is double in males and quadruple in diabetic women. Diabetes is also a risk factor for sudden death.

During the past decades, the prevalence of overweight and obesity in the Western world has increased by 30-50%, leading to what has been described as a global epidemic. Obesity is often associated with co-morbidities such as hypertension, diabetes, atherogenic dyslipidemia, and chronic inflammation, thereby constituting an important risk factor for cardiovascular disease and mortality. [20] [21]

According to US Life Expectancy Statistics obesity decreases the average life span of males and females, 4.9 and 4.1 years, respectively.

Uric acid, despite being a major antioxidant protecting tissues against the toxic effects of oxygen radicals in the human plasma, both correlates and predicts development of obesity, hypertension, and cardiovascular disease, conditions associated with oxidative stress. [22]

A significant association between lower serum uric acid levels in long-lived individuals and their offspring has been observed. [23]

RFs interact positively, such that cardiovascular risk derived from the simultaneous exposure to several RFs is greater than would be expected by the simple addition of the corresponding factors. [24]

When other factors such as diet were analyzed the authors found a significant association between the consumption of mono and polyunsaturated fats and a lower incidence of cardiovascular diseases, suggesting that the dietary patterns of the Southern European countries, with a low intake of saturated fat and a high intake of fruits and vegetables, was a decisive factor in lower cardiovascular mortality. [25]

Numerous studies have been made showing the benefits of adherence to a "healthy diet" in reducing cardiovascular disease, data have been collected from more than 12 cross-sectional studies such as: Monica Project

[26], Cardia study [27], Dash diet [28], OmniHeart [29], among others.

Dr. Raymond Pearl of the University of Johns Hopkins, USA, in 1938, published a paper showing that smokers live less than non-smokers.

The negative effects of smoking are well-documented.

Tobacco smoking is incompatible with successful aging and compromises life expectancy even in extreme longevity. [30]

The alcohol intake and survival is controversial. A meta-analysis of 143 papers describing the relative drinking of alcohol and cognition found that moderate drinking seems to reduce the risk of dementia and cognitive decline in older subjects. [31]

The World Health Organization has repeatedly confirmed the importance of regular physical activity in old age, in an attempt to preserve functional ability as much as possible.

The most important variable in lifestyle is physical activity, it is also a very important

predictor of mortality and may actually be a superior predictor of mortality than the individual's body mass index (BMI).

Adults aged 65 years and older gain substantial health benefits from regular physical activity, and these benefits continue to occur throughout their lives. [32]

It has recently been reported that even a small amount of regular exercise can have a true impact on longevity.

Favorable attitudes, emotions, personality characteristics, and self-rated health have been associated with successful aging in late life.

Psychological factors may exert protective effects on mental health outcomes in advanced age. [33]

Elderly people who are optimistic have lived 7.6 years on average more than those with a negative mindset. [34]

In genetic studies the relationship between elongation of telomeres and longevity is controversial. [35] [36] [37]

In human leucocytes has been shown that the length of telomeres decreases with age and the shortening is associated with age-related illnesses such as cardiovascular disease.

For several decades investigators have been trying to determine whether the body size is associated with risk for cardiovascular disease.

Short/height stature is controversial about longevity.

Several studies observed an increased risk for coronary disease in shorter men. [38] [39] [40] [41] [42]

Another studies have observed an inverse association between height and risk for coronary disease. [43]

The search published in Plos One Medical Magazine, began in 1965 was conducted in between Kuakini Honolulu Heart Program and Kuakini Honolulu-Asia Aging Study, Hawaii, a 60-year long research on a sample of 8,006 Americans men of Japanese origin born between 1900 and 1919; about 1,200 of these men have reached an age of between 90 and 100 years and about 250 are still alive.

AFRICA study

(AFRICA: Acronyms in Spanish of Association of coronary risk factors in old age) [44]

This is a multicenter crosss-sectional study developed in Argentina in old age patients was carried out in order to know the prevalence of behavioural, and the presence or absence of CVRFs and their association.

Data were collected on 322 individuals aged 90 years or more, 47% of whom had a family history of longevity, probably due to some genetic component.

In our series we found a ratio man/woman of 2.8 similar to the general population aged ≥90 years.

The majority of patients ate meals comprising mainly fruit, milk and vegetables every day and half of the participants drank a moderate amount of red wine.

On average, their BMI was normal and they regularly took some form of physical activity.

The age of the menopause for the long-lived women was 48 years.

Frequently, type 2 DM was associated with obesity. No subject had insulin-dependent DM was found.

Interestingly, considering the onset of arterial hypertension started at the high average age of 72 years, it might be due to arteriosclerosis rather than to essential hypertension, a possibility that would be supported by the lack of participants in the study whose hypertension had started before the age of 50 years, time in which there were no angiotensin converting enzyme inhibitors or angiotensin receptors blockers therapy. May be, for the same reason, we detected no association between obesity and

hypertension, unlike that seen in children, adolescents and adults. According to these data essential hypertension would label a malignant disease.

Few were found to be current smokers (3.8%) and even fewer individuals had two or three concurrent CVRFs:

HBP	**HC**	**11%**
Diabetes +	**BMI < 25**	**4%**
Diabetes +	**BMI 25-30**	**7%**
Diabetes +	**BMI > 30**	**25%**
HBP +	**Quintile highest of obesity**	**0%**
HC +	**Quintile highest of obesity**	**0%**

HBP +	**HC +**	**Smoking**	**0.4%**
HBP +	**HC +**	**Diabetes**	**0.8%**
HBP +	**HC +**	**Male gender**	**2.4%**
HBP +	**HC +**	**sedentary lifestyle**	**4.3%**

Note: HBP: high blood pressure; HC: hypercholesterolaemia; BMI: Body mass index.

Short/high stature and longevity.

In a retrospective cross-sectional study, data were collected from 1510 hypertensive patients consecutively who were assisted at the hypertension research centre (Foggia, Italy) in the last 5 years. Female/male 896/614, each gender divided into three groups of age: 60-69/70-79/80-89 years old (average age: female 64/74/83; male: 64/74/83).

The population registered over 90 years old were women 12 and men 3, scarce amount to obtain a statistical value.

All patients enrolled in the study had not cardiovascular, endocrine, renal and metabolic decompensated diseases.

The prevalence of women was highest in each decades (60-69/70-79/80-89), and in turn, they are shorter stature than men (13.5/13.3/13.2 cm) with a statistically significant difference ($p < 0.0001$).

From 60 to 80 years, the ratio of women to men increases from 1.3 to 1.8.

Although hormones are assumed to explain this advantage, they may play only a partial role.

The total population decreases in each decade, affirming that age is the most potent cardiovascular risk factor.

The stature and body weight, in relation to the increase of age, they were lower with a statistically significant difference in each age group.

The BMI decreases poorly in each group, but a significant difference was found in both genders between 70 and 80 years.

The systolic blood pressure increases every decade, in all groups, with a significant difference only between 60 and 70 years old, both gender.

The diastolic blood pressure decrease every decade, in all groups, without statistically significant difference. Table 1

Interestingly, in each group of age, both genders, comparing the patients who were in the lowest quintile of height respect to the highest quintile, the BMI were always more higher, but statistically significant difference only in both groups of 60 years. Table 2

This could mean that the association of high stature and obesity would be a delayed CVRF.

We can observed that the height of our patients over 80 years of age was 149 cm among women and 162.2 cm among men, both lower than the average height population.

Table 1

FEMALE	N	Height	Weight	BMI	SBP	DBP	HR
60 yrs	**439**	**154.5**	**74.7**	**31.4**	**134.1**	**79.4**	**70.6**
70 yrs	**333**	**152.2**	**72.6**	**31.3**	**140.1**	**77.4**	**70.3**
80 yrs	**124**	**149.0**	**66.2**	**29.9**	**144.2**	**76.3**	**71.3**
MALE							
60 yrs	**346**	**168.0**	**83.9**	**29.7**	**132.6**	**80.4**	**68.8**
70 yrs	**197**	**165.5**	**79.7**	**29.1**	**137.1**	**77.6**	**67.6**
80 yrs	**71**	**162.2**	**72.7**	**27.6**	**138.1**	**75.2**	**69.9**

BMI: body mass index. SBP: systolic blood pressure. DBP: diastolic BP. HR: heart rate.

Table 2

		FEMALE			MALE		
Decade	**Height**	**Low Q**	**HighQ**	**p**	**Low Q**	**HighQ**	**p**
60	**BMI**	**32.5**	**29.0**	**0.0002**	**30.7**	**28.6**	**0.01**
70	**BMI**	**32.0**	**30.6**	**0.1**	**29.9**	**29.2**	**0.5**
80	**BMI**	**30.2**	**26.6**	**0.07**	**28.2**	**27.0**	**0.5**

Q: quintile

Summary

Atherosclerosis develops depending on hereditary characteristics and exposure to CVRFs, environmental factors and lifestyle.

Age and male gender are very strong predictors of cardiovascular events.

The low prevalence of simple RF or its associations in an individual may result in an improved quality of life.

In addition to arterial harm, we could hypothesize that hypercholesterolaemia can produce a possible damage of nervous system higher than we know.

Hypertension associated to hyper-cholesterolaemia were as harmful as the smoking habit.

Diet healthy and regular physical activity they are beneficial. Today, there is stronger evidence

that increasing adherence to the Mediterranean Diet is associated with lower blood pressure.

The alcohol intake is controversial, varies according to the quantity, the time of consumption and the response of the individual.

Obesity, frequently associated to hypertension, during childhood, adolescence, and adult population, is always a very major problem by health.

DM is a strong RF for macro and microvascular disease.

Ethnic, geographic, and socio-economic factors should be considered.

Psychological attitude and methodical lifestyle should not be to excluded when evaluating longevity.

People of short stature could live longer. The tall population could live longer if it is not obese.

In hypertensive patients the high stature could be a late CVRF, it is worst when associated with higher BMI and increases age.

Being bipedal is the price we must pay for, or by the association of all CVRFs?

The control of the several CVRFs in the population by means of cardiovascular prevention programs is one of the aims of public health and health care systems, and it may contribute to longer life expectancy and a better quality of life.

Bibliography

[1] The Fifth Report of the Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure (JNC V). Arch Intern Med 1993;153:154-83.

[2] Task Force on Blood Pressure Control in Children. Report of the Second Task Force on Blood Pressure Control in Children - 1987. Pediatrics 1987;79:1-25.

[3] Pesonen E, Norio R, Hirvonen J, Karkola K, Kuusela V, Laaksonen H, et al. Intimal thickening in the coronary arteries of infants and children as an indicator of risk factors for coronary heart disease. Eur Heart J 1990;11:53-60.

[4] Newman III WP, Freedman DS, Voors AW, Srinivasan SR, Cresanta JL, Berenson GS, et al. Relation of serum lipoprotein levels and systolic blood pressure to early atherosclerosis: The Bogalusa Heart Study. N Engl J Med 1986;314:138-44.

[5] PDAY Research Group. Relationship of atherosclerosis in young men to serum lipoprotein cholesterol concentration and smoking: a preliminary report from the Pathological Determinants of Atherosclerosis in Youth (PDAY) Research Group JAMA 1990;264:3018-24.

[6] Mahoney LT, Burns TL, Stanford W, Thompson BH, Witt JD, Rost CA, et al. Coronary risk factors measured in childhood and young adult life are associated with coronary artery calcification in young adults: The Muscatine Study. J Am Coll Cardiol 1996;27:277-84.

[7] Muhonen LE, Burns TL, Nelson RP, Lauer RM. Coronary risk factors in adolescents related to their knowledge of familial coronary heart disease and hypercholesterolemia: The Muscatine Study. Paediatrics 1994;93:4

[8] Krumholz HM, Seeman TE, Merrill SS et al. Lack of association between cholesterol and coronary heart disease mortality and morbidity an all-cause mortality in persons older than 70 years. JAMA 1994;272:1335-40.

[9] Thomas F, Guize L, Bean K, Benetos A. Combined effects of pulse pressure and heart rate on cardiovascular mortality. J Hypertens 2001;19:863-9.

[10] WHO-MONICA Project. Geographical variation in the major risk factors of coronary heart disease in men and women aged 35-64 years. Wld Hlth Stat Q 1988;41:115-40.. Wld Hlth Stat Q 1998;41:115-40.

[11] Elliott W. Management of hypertension in the very elderly patient. Hypertension, 2004; 44: 800–804.

[12] McMahon R, Peto R, Cuttler J, et al. Blood pressure, stroke and coronary heart disease. Part 1. Prolonged differences in blood pressure: prospective observational studies corrected for the regression dilution bias. Lancet 1990;335:765-74.

[13] Kannel WB. Blood pressure as a cardiovascular risk factor: prevention and treatment. JAMA 1996;275:1571-6.

[14] Kannel WB, Gordon T. Evaluation of cardiovascular risk in the elderly: The

Framingham study. Bull N Y Acad Med 1978;54:573-91.

[15] Kannel WB, Castelli WP, McNamara PM, McKee PA, Feinleib M. Role of blood pressure in the development of congestive heart failure. The Framingham Study. N Engl J Med 1972;287:781-787.

[16] Alcalá Malavé A, Morell M, Rius F. Chromatic computerized analysis is an early indicator of cardiovascular risk associated with hypercholesterolemia. Rev Esp Cardiol 2001; 54: (1417-1425).

[17] Hypercholesterolemia and possible neurotoxic effect. Paterno, CA et al. 1° World Congress of Clinical Lipidology. Budapest, Hungary. December 2012.

[18] Boyle JP, Thompson TJ, Gregg EW, Barke r LE, Williamson DF.

Projection of the year 2050 burden of diabetes in the US adult population: dynamic modeling of incidence, mortality, and prediabetes prevalence. Popul Health Metr 2010;8:29.

[19] P, Pedersen NL, Gustafson Y, Michaëlsson K, Nordström A. Risks of myocardial infarction, death, and diabetes in identical twin pairs with different boy mass indexes. JAMA Intern Med 2016;176(10):1522-1529.

[20] Melanson KJ, McInnis KJ, Rippe JM et L. Obesity and cardiovascular disease risk: research update. Cardiol Rev 2001;9:202-7.

[21] Alexander JK. Obesity and coronary heart disease.Am J Med Sci 2001;321:215-24.

[22**]** Cutler RG. Urate and ascorbate: their possible roles as antioxidants in determining longevity of mammalian species. *Arch Gerontol Geriatr 1984;3(4):321-48.*

[23] Lai JYC, Atzmon G, , Melamed ML, Hostetter TH, Crandall JP, Barzilai N, Bitzer M. Family History of Exceptional Longevity is associated with lower serum uric acid levels in Ashkenazy Jews. J Am Geriatr Soc 2012,60(4):745-50.

[24] Plaza Pérez I, Villar Álvarez F, Mata López P, Pérez Jiménez F, Maiquez Galán A, Banegas Banegas JR. Control of cholesterolemia in Spain 2000. An instrument for cardiovascular prevention. Rev Esp Cardiol. 2000;53:815-37.

[25] Menotti A, Keys A, Kromhout D, Nissinen A, Blackburn H, Fidanza F, et al. Twenty-five-year mortality from coronary heart disease and its prediction in five cohorts of middle-aged men in Finland, The Netherlands, and Italy. Prev Med 1990;19:270-8.

[26] Myocardial Infarction and Coronary Deaths in the World Health Organization Monica Project. Registration Procedures, Event Rates, and Case-Fatality Rates in 38 Populations From 28 Countries in Four Continents. Circulation 1994;90:583-612.

[27] Liu K, Daviglus ML, Loria CM, Colangelo LA, Spring B, Moller AC, and Donald M. Healthy lifestyle through young adulthood and the presence of low cardiovascular disease risk profile in middle-age: The Coronary Artery Risk Development in (Young) adults (CARDIA) study. Circulation 2012;125:996-1004.

[28] Appel U, Brands MW, Daniels SR, Karanja N, Elmer PJ, Sacks FM. Dietary approaches to prevent and treat hypertension: s scientific statement from the American Heart Hypertension. Hypertension 2006;47:296-308.

[29] Appel U, Sacks FM, Carey VJ, Obarzanek E, Swain JF, Miller ER 3rd, Conlin PR, Erlinger TP, Rosner BA, Laranjo NM, Charleston J, McCarron P, Bishop LM. OmniHeart Collaborative Research Group. Effects of protein, monounsatured fat, and carbohydrate intake on blood pressure and serum lipids. Results of the OmniHeart randomized trial. JAMA 2005;294:2455-64.

[30] Tafaro L, Cicconetti P, Tedeschi G, Baratta A, Ursino R, Ettorre E, and Marigliano V. Smoking and longevity: an incompatible binomial?
V. Smoking and longevity: an incompatible binomial? *Archives of gerontology and geriatrics* 2004 *Supplement*, (9), 425-430.

[31] Neafsey EJ, Collins MA. Moderate alcohol consumption and cognitive risk. Neuropsychiatric Disease and Treatment 2011;7:465-84.

[32] Chodzko-Zajko WJ (Co-Chair), Proctor DN (Co-Chair), Fiatarone Singh MA, Minson CT, Nigg CR, Salem GJ, and Skinner JS. Journal of the American College of Sports Medicine 2010;March,01:1510-1530.

[33] Kato K, Zweig R, Schechter CB, Barzilai N, Atzmon G. Positive attitude toward life, emotional expression, self-rated health, and depressive symptoms among centenarians and near-centenarians. Aging and Mental Health, 2016;20(9):930-9.

[34] Levy B, Slade MD, Kunkel SR, Kasl SV. Longevity increased by positive self-perceptions of aging. Journal of Personality and Social Psychology 2002;2:261-270.

[35] Atzmon G, Cho M,Cawthon RM, Budagov T, Katz M, Yang X, Siegel G, Bergman A, Huffman DM, Schechter CB, Wright WE, Shay JW, Barzilai N, Govindaraju DR, and Suh Y. Evolution in Health and Medicine Sackler Colloquium: Genetic variation in human telomerase is associated with telomere length in Ashkenazi centenarians. PNAS, 107(1):1710-1717, 2010.

[36] Gierman HJ, Fortney K, Roach JC, Coles NS, Li H, Glusman G, Markov GJ, Smith JD, Hood L, Coles LS, Kim SK. Whole-Genome Sequencing of the World's Oldest People. PLoS One 2014; 9(11):e112430

[37] Rajpathak SN, Liu J, Ben-David O, Reddy S, Atzmon G, Crandall J, Barzilai N. Lifestyle Factors of People with Exceptional longevity. J Am Geriatr Soc 2011;59(8):1509-12.

[38] Gertler MM, Garn SM, White PD. Young candidates for coronary heart disease. JAMA 1951;147:621-5.

[39] Paffenbarger RS, Wolf PA, Notkin J, Thorne MC. Chronic disease in former college students, I: early precursors of fatal coronary heart disease. Am J Epidemiol 1996;83:314-28.

[40] Morris JN, Kagan A, Pattison DC, Gardner M, Raffle PAB. Incidence and prediction of ischaemic heart disease in London busmen. Lancet 1966;2:553-59.

[41] Marmot MG, Rose G, Shipley RM, Hamilton PJS. Employment grade and coronary

heart disease in British civil servants. J Epidemiol Commun Health 1979;32:244-9.

[42] Herbert PR, Rich-Edwards JW, Manson JE, Ridker PM, Cook NR, O'Connor GT, Baring JE, Henneckens CH. Height and incidence of cardiovascular disease in male physicians. Circulation 1993;88:1437-43.

[43] Kannam J, Levy D, Larson M, Wilson PWF. Short stature was not associated with increased risk for all-cause or cardiovascular mortality in either sex. It was associated with increased risk for myocardial infarction in women but not in men. Circulation 1994;90:2241-47.

[44] Paterno, CA et al. Association of Coronary Risk Factors in Old Age (*Asociaciòn de Factores de RIesgo Coronario en la Ancianidad*). AFRICA study. Rev Esp Cardiol 2006;59(6):628-31.

