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Original Research Article

Early sport practice is related to lower prevalence of cardiovascular and metabolic outcomes in adults independently of overweight and current physical activity

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ABSTRACT

Background and objective: Early sport practice prevents development of diseases in children/adolescents, but still unclear its effect over health in adulthood. Therefore, the purpose of this study was to analyze the association between sport practice in early life and chronic diseases in adulthood.

Materials and methods: A retrospective population-based survey carried out in eight Brazilian cities with adults of both genders. Throughout a multistage random process 2720 adults (1096 male and 1624 female) were selected and interviewed. Type 2 diabetes mellitus and arterial hypertension were assessed in a face-to-face interview through a self-report, which was necessarily based on previous medical diagnosis. Early sport practice was assessed in childhood (7–10 years old) and adolescence (11–17 years old). Current physical activity and body mass index were assessed in adulthood throughout a face-to-face interview.

Results: Type 2 diabetes mellitus and arterial hypertension were identified in 8.1% (95% CI, 7.1–9.2) and 23.5% (95% CI, 21.9–25.1) of the sample, respectively. Early sport practice during childhood and adolescence was associated with lower occurrence of arterial hypertension (OR, 0.49; 95% CI, 0.33–0.73) and type 2 diabetes (OR, 0.46; 95% CI, 0.24–0.88) in adulthood.

Conclusions: Independently of obesity and current physical activity, early sport practice in early life was positively associated with lower occurrence of chronic diseases in adulthood.

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1. Introduction

Obesity is an important public health problem affecting all ages and socioeconomic groups elevating greatly the incidence of cardio-metabolic disorders [1]. A sub clinic state of oxidative stress and inflammation are the hallmark of adiposity leading to increased reactive-oxygen species (ROS) production, as well as a decreased bioavailability of nitric oxide (NO) [2,3]. These alterations can affect deep vascular function and increase the risk for cardio-metabolic diseases (atherosclerosis, arterial hypertension and type 2 diabetes mellitus) and increased risk of premature death [4].

Both arterial hypertension and diabetes mellitus have been associated with severe cardiovascular complication such as stroke, myocardial infarction and coronary artery disease [5,6]. Indeed, a great effort has been made to minimize the high rate of fatal and non-fatal clinical outcomes as consequence of both disorders by international public health organizations [7]. Regarding arterial hypertension, evidences have shown that antihypertensive therapy reduces the complications of high blood pressure. However, only 71% of all hypertensive patients are under treatment and a half of those do not have it controlled [8]. Moreover, diabetic patients have a 2- to 4-fold higher incidence of coronary artery disease than non-diabetic subjects [9].

Conversely, lifestyle changing is the primary action in the health care policies to prevent type 2 diabetes mellitus, cardiovascular diseases, atherosclerosis and cancer [10,11]. Indeed, evidences have shown that the health-promoting effects of physical activity practice are associated with improvement in redox status by increasing antioxidant status and nitric oxide bioavailability to the tissues [12-16]. Moreover, a plethora of studies, employing questionnaires or by applying exercise test, have associated physical inactivity/low fitness levels with increased incidence of cardio-metabolic diseases in childhood, adolescence or in adulthood [17-19].

On the other hand, there is absence of data investigating the effect of sport practice performed in early life (from childhood to adolescence) on the prevention of arterial hypertension and type 2 diabetes mellitus [20], as well as, if this possible protective effect is mediated by body composition modifications and maintenance of physical activity practice in later life. Previous epidemiological study with 1436 adults showed a significant association between lower occurrence of arterial hypertension/type 2 diabetes mellitus and increased physical activity practice during childhood and adolescence [21]. However, the authors did not analyze if this early physical activity effect is either dependent or independent of the current physical activity performed in adulthood.

Therefore, the present study was conducted to evaluate in a population-based study the relationship between engagement in sport practice in early life and the occurrence of both disorders arterial hypertension and type 2 diabetes mellitus in adulthood. We have hypothesized that early sport practice is related to unhealthy outcomes independently of current physical activity performed in leisure time.

2. Materials and methods

2.1. Sample

The present study was approved by the Ethical Committee of the Institute of Bioscience of the Sao Paulo State University (UNESP) and all the participants provided a written informed consent in accordance to the policies of Review Board.

This survey was carried out in the São Paulo state, the more industrialized Brazilian State, from March of 2009 to June of 2010. Eight cities located in various geographical regions of the state (capital, east, west, north, south, center and coast) and with similar human development index (ranging from 0.777 to 0.871) were selected to the survey. A minimum sample size of 2274 subjects was estimated considering the prevalence of arterial hypertension and type 2 diabetes mellitus of 25.7% [21] (at least 2274 subjects) and 8.9% [21] (at least 1071 subjects), error of 2.2%, significance of 5% ($z = 1.96$), design effect of 1.5 and additional of 20% to predict losses. In the urban area of each city, a multistage random process was carried out. In the initial stage, the cities were stratified into five geographical regions (east, west, north, south and center), and within these regions, districts were randomly selected. Afterwards, streets and avenues were randomly within of the districts. In the second stage, three or four houses were randomly selected in each selected street/avenue. All adults found at house were considered eligible for face-to-face interview. The final sample size was composed by 2720 adults that agreed to participate and fulfilled the three inclusion criteria: (i) age ≥ 18 -years-old, (ii) no chronic orthopedic complication (osteoporosis and osteomyelitis), and (iii) living for at least 2 years in the current home.

2.2. Body mass index determination

Body weight (kg) and height (m) were self-reported and body mass index (BMI) was calculated as body weight divided by the height squared and expressed as kg/m^2 . After that, BMI was stratified according to the World Health Organization classification (normal weight: $\text{BMI} < 25 \text{ kg/m}^2$; overweight: $\text{BMI} \geq 25$ and $< 29.9 \text{ kg/m}^2$; obesity: $\text{BMI} \geq 30 \text{ kg/m}^2$) [22].

2.3. Diagnosis of arterial hypertension and type 2 diabetes mellitus

The presence of both diseases arterial hypertension and type 2 diabetes mellitus was assessed in a face-to-face interview through a self-report, which was necessarily based on previous medical diagnosis. Additionally, subjects who did not report the presence of both arterial hypertension and type 2 diabetes mellitus, but antihypertensive or hypoglycemic therapies were characterized as hypertensive or diabetic. Previous information indicated high reliability in this self-report method in our sample (2 weeks of interval, with kappa statistic [κ] of 1.00).

2.4. Covariates

City, age, gender, schooling and BMI were treated as covariates. Age was structured as categorical variable, as well

as schooling in years (1–4 years; 5–8 years; 9–11 years; ≥ 12 years). During the fieldwork, 33 subjects did not indicated their body weight, and therefore, the analysis for the nutritional status were carried out with 2687 subjects. As previously reported [21], high scores for BMI's reliability (intraclass correlation [ICC] = 0.99; $P = 0.001$). The agreement level for obesity presence was also high ($\kappa = 0.86$; $P = 0.001$).

2.5. Current physical activity

Current physical activity level was assessed by questionnaire [23], in which the subject was defined as physically active if performed any sport activity (walking, run, dance and activities in fitness clubs also were considered) of moderate to vigorous intensity, by ≥ 180 min/week, for at least 4 months before the interview.

2.6. Early sport practice

Physical activity performed in the childhood and adolescence was assessed through two questions [21]: (i) "Outside school, have you been engaged in any organized/supervised sport activities in clubs for at least 1 year from 7 to 10 years-old?" and (ii) "Outside school, have you been engaged in any organized/supervised sport activities in clubs for at least 1 year from 11 to 17 years-old?" Other physical activities such as modalities of dance were also included.

2.7. Statistical analysis

Categorical data were expressed as rates and compared by chi-square test (Yates' correction has been used in 2×2 contingency tables). In the univariate model, the chi-square test analyzed associations and those ones with significance level of $P \leq 20\%$ were selected to compound the multivariate model. Thus, in the multivariate model for binary logistic regression (odds ratio [OR] and 95% confidence interval [95% CI]), the potential confounders (city, age, gender, schooling and nutritional status) were inserted simultaneously to adjust the OR values. Significance level (P) was previously set at 5% and the statistical software BioEstat (version 5.0) was used in all analysis.

3. Results

In the overall sample, the mean age was 46.3 years (95% CI, 45.6–47.1). Women represented 59.7% ($n = 1624$) of the studied population and this proportion was similar in all analyzed cities ($P = 0.411$). Obesity was identified in 15.1% (95% CI, 13.8–16.5) of the sample and this rate was similar in both genders ($P = 0.383$) and was also similar in all analyzed cities ($P = 0.094$).

The prevalence of arterial hypertension and type 2 diabetes mellitus were 23.5% (95% CI, 21.9–25.1) and 8.1% (95% CI, 7.1–9.2) of the sample, respectively. Women presented higher prevalence of arterial hypertension ($P = 0.006$) whereas the prevalence of type 2 diabetes mellitus was similar for men (8.1%) and women (8.3%) ($P = 0.960$). Analyzing the influence of BMI, schooling and age on the prevalence of arterial hypertension and type 2 diabetes mellitus, we found a positive

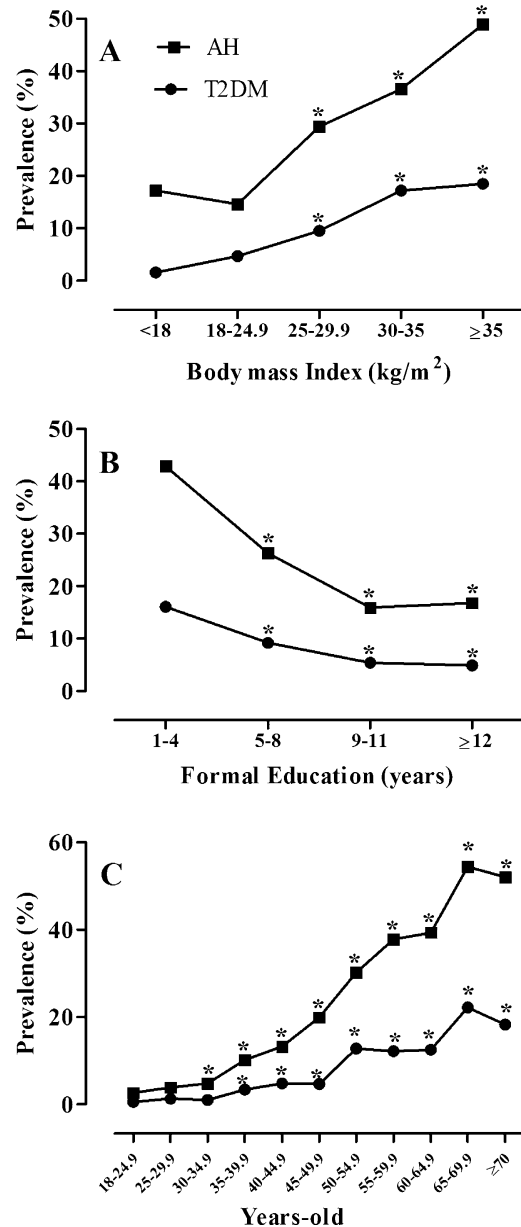


Fig. 1 – Occurrence of chronic diseases according to nutritional status (panel A), formal education (panel B) and aging (panel C) in Brazilian adults. * $P < 5\%$ denotes statistical difference compared to the groups: 18–24.9 kg/m² (panel A), 1–4 years of schooling (panel B) and 18–24.9 years-old (panel C).

relationship between an increase in BMI and aging with high prevalence of arterial hypertension and type 2 diabetes mellitus. On the other hand, the highest formal education was negatively associated with the prevalence of both disorders (Fig. 1, panels A, B and C).

Early sport practice in both childhood and adolescence was associated with lower occurrence of type 2 diabetes mellitus in adult with normal weight (OR, 0.23; 95% CI, 0.10–0.53), overweight (OR, 0.32; 95% CI, 0.16–0.65) and obesity (OR, 0.39; 95% CI, 0.18–0.83). Similar results were observed for arterial hypertension (Table 1).

Table 1 – Early sport practice and the occurrence of arterial hypertension and type 2 diabetes mellitus, according to nutritional status.

Early sport practice	Arterial hypertension		Type 2 diabetes mellitus	
	N (%)	OR _{crude} (95% CI)	N (%)	OR _{crude} (95% CI)
Normal weight				
None	162 (21.7)	1.00	51 (6.8)	1.00
Child-or-adol	24 (9.9)	0.39 (0.25–0.62)	7 (2.9)	0.40 (0.18–0.90)
Both	20 (4.9)	0.18 (0.11–0.30)	7 (1.7)	0.23 (0.10–0.53)
Chi-square (P-value)	0.001		0.001	
Overweight				
None	194 (37.7)	1.00	63 (12.2)	1.00
Child-or-adol	26 (20.2)	0.41 (0.26–0.66)	08 (6.2)	0.47 (0.22–1.01)
Both	37 (16.2)	0.31 (0.21–0.47)	10 (4.4)	0.32 (0.16–0.65)
Chi-square (P value)	0.001		0.001	
Obesity				
None	121 (44.8)	1.00	58 (21.5)	1.00
Child-or-adol	13 (29.5)	0.51 (0.25–1.03)	04 (9.1)	0.36 (0.12–1.06)
Both	26 (28.3)	0.48 (0.29–0.81)	09 (9.8)	0.39 (0.18–0.83)
Chi-square (P value)	0.003		0.005	

OR = odds ratio; 95% CI = 95% confidence interval; Chil-or-adol = sport practice in either childhood or adolescence.

Similarly, independently of potential confounders (including current leisure physical activity and nutritional status), early sport practice during childhood and adolescence was associated with lower occurrence of arterial hypertension (OR, 0.49; 95% CI, 0.33–0.73) (Fig. 2, panels A and B) and type 2 diabetes mellitus (OR, 0.46; 95% CI, 0.24–0.88) (Fig. 3, panels A and B).

4. Discussion

In the present survey, we found the highest prevalence of arterial hypertension and type 2 diabetes mellitus in subjects with the highest BMI, as well as in the elderly. Regarding to BMI, releasing of a large amount of cytokines into the blood circulation by the adipocytes has been linked to greater

prevalence in cardiovascular and endocrine-metabolic disorders [24,25]. Indeed, the pro-inflammatory and pro-oxidant effects of some adipocytokines are strongly associated with endothelium dysfunction that is considered to be involved in the genesis of the arterial hypertension. Additionally, increased intramuscular fat mass has been associated with insulin resistance [25–27]. Thus, altogether could explain the adverse effects of adiposity on the cardio-metabolic disease prevalence (Table 2).

Interestingly, normal, overweight and obese adults who were physically active in early life showed lower prevalence of arterial hypertension as compared to sedentary adults in early life showing the importance of physical activity in controlling arterial blood pressure independent of weight loss. Indeed, previous studies have shown that shear stress induced by physical exercise is a powerful stimulus to activate nitric oxide

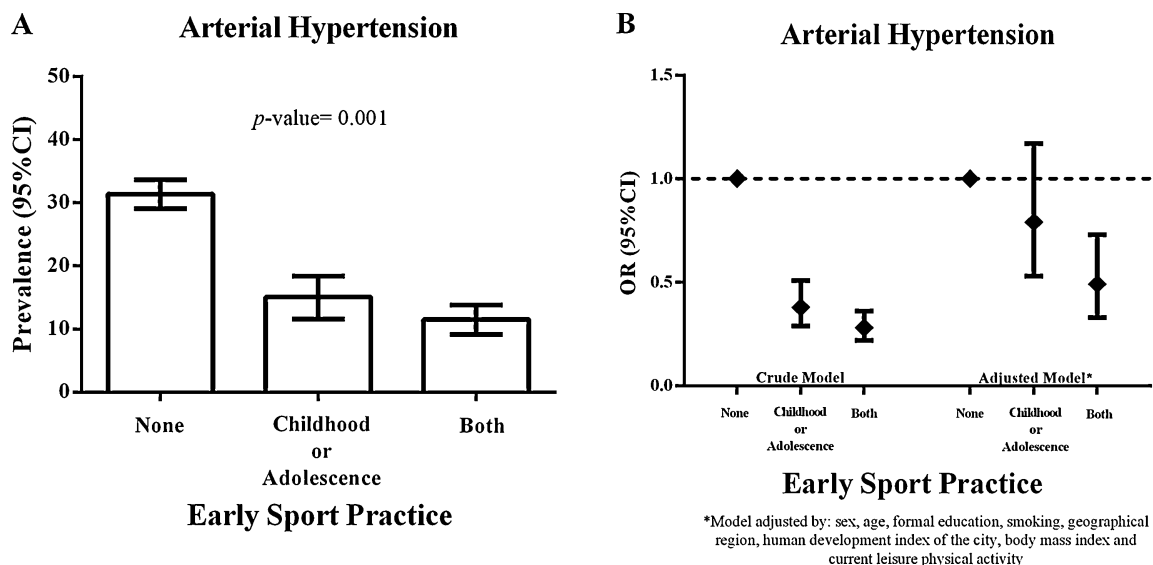


Fig. 2 – Multivariate association between early sport practice and occurrence of arterial hypertension in adulthood (panels A and B).

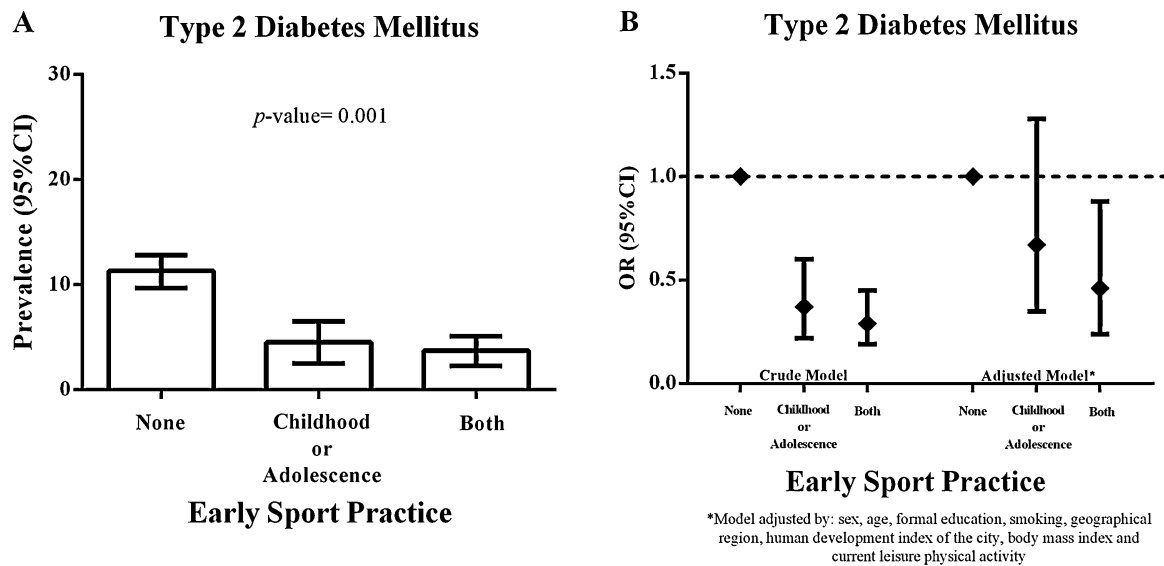


Fig. 3 – Multivariate association between early sport practice and occurrence of type 2 diabetes mellitus in adulthood (panels A and B).

production and/or to increase its bioavailability to the tissues [14,16], even without changes in body fatness [28]. Therefore, in the present study in a population-based study sport practice in early life constituted a variable associated with lower arterial hypertension in adulthood independently of weight status.

In this study, early sport practice was also related to lower type 2 diabetes mellitus prevalence, independently of important risk factors, such as obesity [29,30] and physical inactivity. The health-promoting effect of physical activity on diabetes mellitus is associated with increased glucose uptake mainly in skeletal muscle, regulating thus the dysglycemia. The mechanist event of this beneficial effect is attributed to muscle contraction during physical activity, which in turn activates the AMP-activated protein kinase, promoting the translocation of the GLUT-4 to plasma membrane and consequently glucose uptake in an insulin-independent manner [31]. Agreeing with

this, previous epidemiological and clinical studies have reported effective control of type 2 diabetes mellitus through physical exercise practice [21,32,33], which is mainly mediated by its effect on weight loss [21].

On the other hand, our findings are particularly relevant because obesity and type 2 diabetes mellitus are strongly related (increased production of the inflammatory mediators and ROS generation) and, as was true to arterial hypertension too, early sport practice was associated with lower occurrence of both diseases, independently of overweight/obesity and current physical activity. With this in mind, an alternative hypothesis was elaborated to explain how the early physical activity can prevent diseases without classical pathways, such as maintenance of physical activity in later life and weight loss.

Over the last years, genetics have been widely investigated because many diseases have genetic origins, including

Table 2 – Multivariate association between early sport practice and occurrence of health outcomes in adulthood.

Independent variable	Chi-square test % (95% CI)	Binary logistic regression	
		OR _{crude} (95% CI)	OR _{adjusted} (95% CI) ^a
Outcome: arterial hypertension			
Early sport practice			
None	31.4 (29.1–33.7)	1.00	1.00
Child-or-adol	15.1 (11.6–18.4)	0.38 (0.29–0.51)	0.79 (0.53–1.17)
Both	11.5 (9.2–13.8)	0.28 (0.22–0.36)	0.49 (0.33–0.73)
Chi-square (P value)	0.001		
Outcome: type 2 diabetes mellitus			
Early sport practice			
None	11.3 (9.7–12.8)	1.00	1.00
Child-or-adol	4.5 (2.5–6.5)	0.37 (0.22–0.60)	0.67 (0.35–1.28)
Both	3.7 (2.3–5.1)	0.29 (0.19–0.45)	0.46 (0.24–0.88)
Chi-square (P value)	0.001		

OR = odds ratio; 95% CI = 95% confidence interval; Chil-or-adol = sport practice in either childhood or adolescence.

^a Model adjusted by sex, age, formal education, smoking, geographical region, human development index of the city, body mass index and current leisure physical activity.

metabolic and cardiovascular diseases (commonly linked to the over/under expression of specific genes [methylation]). Indeed, modifications in the expression of some genes have been related to the adoption of behavioral variables (such as smoking, diets and physical inactivity) and this process happens throughout life [34-36]. However, early life constitutes a more sensitive period in human life, in which this methylation rate could be more susceptible to be changed [37]. Recent studies have suggested that, during this sensitive period, modifications in the methylation of some genes generated by stress agents (such as unhealthy behaviors) have higher likelihood to be maintained in later life [36,37]. Agreeing with this, White et al. [38] identified that tracking of physical activity from childhood to adulthood is related to lower values of global methylation.

With this in mind, if confirmed this new insight about prevention of diseases in adulthood through the early physical activity; is dramatically underestimated the current relevance attributed to engagement in sport activities during pediatric ages in the maintenance of health throughout life.

The multistage random process used, as well measures of reliability/reproducibility are relevant markers of external and internal validity of the data, respectively. On the other hand, some limitations have to be recognized such as absence of the data regarding intensity and time per week of the sport activities performed in early ages. Moreover, self-report of the diseases is a notorious weakness in this survey (although, the observed prevalence and its associations with independent variables corroborate with previous studies).

5. Conclusions

In summary, our results show that maintenance of sport practice throughout childhood and adolescence was positively associated with lower occurrence of arterial hypertension in adulthood. Moreover, the preventive effect of the early sport practice was extended to overweight/obese people and happened independently of the current physical activity.

Conflict of interest

The authors declare that there is no conflict of interest.

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REFERENCES

- [1] Galgani J, Ravussin E. Energy metabolism, fuel selection and body weight regulation. *Int J Obes (Lond)* 2008;32:S109-19.
- [2] De Caterina R, Massaro M, Scoditti E, Annunziata Carluccio M. Pharmacological modulation of vascular inflammation in atherothrombosis. *Ann N Y Acad Sci* 2010;1207:23-31.
- [3] Packard RR, Libby P. Inflammation in atherosclerosis: from vascular biology to biomarker discovery and risk prediction. *Clin Chem* 2008;54:24-38.
- [4] Pischon T, Boeing H, Hoffmann K, Bergmann M, Schulze MB, Overvad K, et al. General and abdominal adiposity and risk of death in Europe. *N Engl J Med* 2008;359:2105-20.
- [5] Cade WT. Diabetes-related microvascular and macrovascular diseases in the physical therapy setting. *Phys Ther* 2008;88:1322-35.
- [6] Gupta AK, McGlone M, Greenway FL, Johnson WD. Prehypertension in disease-free adults: a marker for an adverse cardiometabolic risk profile. *Hypertens Res* 2010;33:905-10.
- [7] Sehestedt T, Hansen TW, Li Y, Richart T, Boggia J, Kikuya M, et al. Are blood pressure and diabetes additive or synergistic risk factors? Outcome in 8494 subjects randomly recruited from 10 populations. *Hypertens Res* 2011;34:714-21.
- [8] Roger VL, Go AS, Lloyd-Jones DM, Benjamin EJ, Berry JD, Borden WB, et al. Executive summary: heart disease and stroke statistics - 2012 update: a report from the American Heart Association. *Circulation* 2012;125:188-97.
- [9] Janghorbani M, Van Dam RM, Willett WC, Hu FB. Systematic review of type 1 and type 2 diabetes mellitus and risk of fracture. *Am J Epidemiol* 2007;166:495-505.
- [10] Guh DP, Zhang W, Bansback N, Amarsi Z, Birmingham CL, Anis AH. The incidence of co-morbidities related to obesity and overweight: a systematic review and meta-analysis. *BMC Public Health* 2009;9:88.
- [11] Sone H, Akanuma H, Fukuda T. Oxygenomics in environmental stress. *Redox Rep* 2010;15:98-114.
- [12] de Moraes C, Davel AP, Rossoni LV, Antunes E, Zanesco A. Exercise training improves relaxation response and SOD-1 expression in aortic and mesenteric rings from high caloric diet-fed rats. *BMC Physiol* 2008;8:12.
- [13] Ignarro LJ, Balestrieri ML, Napoli C. Nutrition, physical activity, and cardiovascular disease: an update. *Cardiovasc Res* 2007;73:326-40.
- [14] Sponton CH, Rezende TM, Mallagrino PA, Franco-Penteado CF, Bezerra MA, Zanesco A. Women with TT genotype for eNOS gene are more responsive in lowering blood pressure in response to exercise. *Eur J Cardiovasc Prev Rehabil* 2010;17:676-81.
- [15] Teixeira-Lemos E, Nunes S, Teixeira F, Reis F. Regular physical exercise training assists in preventing type 2 diabetes development: focus on its antioxidant and anti-inflammatory properties. *Cardiovasc Diabetol* 2011;10:12.
- [16] Zanesco A, Antunes E. Effects of exercise training on the cardiovascular system: pharmacological approaches. *Pharmacol Ther* 2007;114:307-17.
- [17] Church T. Exercise in obesity, metabolic syndrome, and diabetes. *Prog Cardiovasc Dis* 2011;53:412-8.
- [18] Fagard RH. Exercise therapy in hypertensive cardiovascular disease. *Prog Cardiovasc Dis* 2011;53:404-11.
- [19] Thompson D, Karpe F, Lafontan M, Frayn K. Physical activity and exercise in the regulation of human adipose tissue physiology. *Physiol Rev* 2012;92:157-91.
- [20] Kemper HC, Twisk JW, van Mechelen W. Changes in aerobic fitness in boys and girls over a period of 25 years: data from the Amsterdam Growth And Health Longitudinal Study revisited and extended. *Pediatr Exerc Sci* 2013;25:524-35.
- [21] Fernandes RA, Zanesco A. Early physical activity promotes lower prevalence of chronic diseases in adults. *Hypertens Res* 2010;33:926-31.
- [22] World Health Organization. Obesity, preventing and managing the global epidemic: report of the who

- consultation on obesity. Geneva: World Health Organization; 1998, Available at: http://www.who.int/nutrition/publications/obesity_executive_summary.pdf [accessed 13.04.07].
- [23] Baecke JA, Burema J, Frijters JE. A short questionnaire for the measurement of habitual physical activity in epidemiological studies. *Am J Clin Nutr* 1982;36:936-42.
- [24] Angermayr L, Melchart D, Linde K. Multifactorial lifestyle interventions in the primary and secondary prevention of cardiovascular disease and type 2 diabetes mellitus – a systematic review of randomized controlled trials. *Ann Behav Med* 2010;40:49-64.
- [25] Ikeoka D, Mader JK, Pieber TR. Adipose tissue, inflammation and cardiovascular disease. *Rev Assoc Med Bras* 2010;56:116-21.
- [26] Huang PL. eNOS, metabolic syndrome and cardiovascular disease. *Trends Endocrinol Metab* 2009;20:295-302.
- [27] Mlinar B, Marc J, Janez A, Pfeifer M. Molecular mechanisms of insulin resistance and associated diseases. *Clin Chim Acta* 2007;375:20-35.
- [28] Zaros PR, Pires CE, Bacci Jr M, Moraes C, Zanesco A. Effect of 6-months of physical exercise on the nitrate/nitrite levels in hypertensive postmenopausal women. *BMC Womens Health* 2009;9:17.
- [29] Eizirik DL, Colli ML, Ortis F. The role of inflammation in insulinitis and beta-cell loss in type 1 diabetes. *Nat Rev Endocrinol* 2009;5:219-26.
- [30] Schalkwijk CG, Stehouwer CD. Vascular complications in diabetes mellitus: the role of endothelial dysfunction. *Clin Sci (Lond)* 2005;109:143-59.
- [31] Nagata D, Hirata Y. The role of AMP-activated protein kinase in the cardiovascular system. *Hypertens Res* 2010;33:22-8.
- [32] Balducci S, Zanuso S, Nicolucci A, Fernando F, Cavallo S, Cardelli P, et al. Anti-inflammatory effect of exercise training in subjects with type 2 diabetes and the metabolic syndrome is dependent on exercise modalities and independent of weight loss. *Nutr Metab Cardiovasc Dis* 2010;20:608-17.
- [33] Fatone C, Guescini M, Balducci S, Battistoni S, Settequattrini A, Pippi R, et al. Two weekly sessions of combined aerobic and resistance exercise are sufficient to provide beneficial effects in subjects with type 2 diabetes mellitus and metabolic syndrome. *J Endocrinol Invest* 2010;33(7):489-95.
- [34] Alegria-Torres JA, Baccarelli A, Bollati V. Epigenetics and lifestyle. *Epigenomics* 2011;3(3):267-77.
- [35] Elliott HR, Tillin T, McArdle WL, Ho K, Duggirala A, Frayling TM, et al. Differences in smoking associated DNA methylation patterns in South Asians and Europeans. *Clin Epigenetics* 2014;6(1):4.
- [36] Waterland RA, Michels KB. Epigenetic epidemiology of the developmental origins hypothesis. *Annu Rev Nutr* 2007;27:363-88.
- [37] Nagy C1, Turecki G. Sensitive periods in epigenetics: bringing us closer to complex behavioral phenotypes. *Epigenomics* 2012;4(4):445-57.
- [38] White AJ, Sandler DP, Bolick SC, Xu Z, Taylor JA, DeRoo LA. Recreational and household physical activity at different time points and DNA global methylation. *Eur J Cancer* 2013;49(9):2199-206.