The Inverse Relationship between Cardiorespiratory Fitness and Intima-Media Thickness with Prehypertensive Middle-Aged Women

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Individuals with prehypertension have a greater risk of developing hypertension and cardiovascular disease than those with normal blood pressure. Good cardiorespiratory fitness has been associated with a reduced risk for cardiovascular diseases, but whether it is related to slower progression of early atherosclerosis is unclear. We evaluated 442 women, aged 40-60 years, with resting systolic blood pressure 120-139 mmHg and diastolic blood pressure 80-89 mmHg, defined as prehypertension in cross-sectional study. Blood glucose, blood lipids and carotid intima-media thickness (CIMT) were measured at rest. Cardiorespiratory fitness (VO_2peak) was measured by respiratory gas exchange during a treadmill exercise test. Participants were divided into three cardiorespiratory fitness levels: low, moderate, and high. The prevalence of subclinical carotid atherosclerosis was defined as a mean carotid intima-media thickness greater than the 75th percentile. After adjustment for various confounders, a high cardiorespiratory fitness level was associated with significantly lower SBP, DBP and CIMT compared with low and moderate fitness ($p < 0.05$). After adjustment for established risk factors, high and moderate fitness were each associated with significantly lower odds ratios for carotid atherosclerosis 0.74 (95% CI 0.45-0.92) and 0.70 (95% CI 0.46-0.95), respectively, compared with low fitness. Our results indicate that good cardiorespiratory fitness is associated with a slower progression of early atherosclerosis in middle-aged women. These findings are important, because they emphasize that middle-aged women can be evaluated for cardiorespiratory fitness to estimate their future risk for atherosclerotic vascular diseases.

Keywords: cardiorespiratory fitness; carotid atherosclerosis; exercise testing; prehypertension; women's health
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Introduction

Hypertension causes left ventricular hypertrophy, cardiac insufficiency, chronic renal insufficiency, arteriosclerosis, cerebral infarction, peripheral arterial disease, and other target organ damage, and is one of the major risk factors for cardiovascular disease (Gray et al. 2011; Mozaffarian et al. 2015).

The seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC-7) defined prehypertension as a systolic blood pressure (SBP) from 120 to 139 mmHg and/or a diastolic blood pressure (DBP) from 80 to 89 mmHg. This criterion is based on a finding that the risk for cerebral infarction and coronary artery disease doubles for every 20 mmHg increase in SBP/DBP, starting from an initial pressure of 115/75 mmHg (Chobanian et al. 2003). The Strong Heart Study has reported that the four-year incidence of hypertension at the prehypertension stage is 38% (De Marco et al. 2009). The Framingham Heart Study has reported that prehypertensive patients have double the risk for progression to hypertension compared with those who have normal BP (Vasan et al. 2001). In addition, an 18-year-long large-scale longitudinal study in the United States has reported that prehypertension is an independent risk factor for major cardiovascular diseases (Liszka et al. 2005).

Carotid artery intima-media thickness (CIMT) is an index for evaluating the structural degeneration of arteries. An increase in CIMT is related not only to the risk for atherosclerotic diseases including coronary artery disease, and cardiovascular and cerebrovascular diseases but also to high mortality; therefore, delaying an increase in CIMT is important for disease prevention (O'Leary et al. 1999; Crouse et al. 2004; Kablak-Ziembicka et al. 2008).

Previous studies reported that hypertension is directly related to an increase in CIMT, and that it accelerates this increase (Pasha et al. 2011). In addition, decreased arterial

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elasticity, increased CIMT and increased development of atherosclerosis were observed in the prehypertension group (Ninomiya et al. 2007). Therefore, hypertension increases the risk, not only for cardiovascular diseases, but also for cerebrovascular diseases (Hsia et al. 2007; De Marco et al. 2009).

Cardiorespiratory fitness (CRF) is a well-known marker for the risk of cardiovascular diseases: mortality rates are higher for patients with low CRF than for those with relatively high CRF (Berry et al. 2011; Sui et al. 2007). There was a strong inverse association between CRF and CIMT that when the CRF is increased, the CIMT value becomes decreased (Scholl et al 2015). Lakka et al. (2001) reported that good cardiorespiratory is associated with slower progression of early atherosclerosis in middle-age men. Jae et al. (2007), in their study of middle-aged patients with hypertension, have reported that people with low fitness are at relatively high risk for arteriosclerosis caused by increased CIMT, emphasizing the importance of CRF in hypertensive patients. Given the association of hypertension with CRF and an increase in CIMT, reviewing the association between CRF and CIMT in prehypertensive patients is important for preventing arteriosclerosis. However, only a few studies have investigated the association between prehypertension and CRF, and they focused mostly on male patients.

In this study, we hypothesized that CIMT might be related to CRF level in middle-aged, prehypertensive women. Therefore, the purpose of this study was to investigate the relationship between CRF measured in terms of peak oxygen uptake (VO_2peak) and CIMT in middle-aged, prehypertensive women. We also investigated to compare the differences in blood pressure, serum lipid, and CIMT according to the level of CRF measurement at prehypertensive stage.

Methods

Participants

The subjects who underwent a general health examination at Samsung Medical Center Health Medical Center in S. Korea between March 2015 and December 2016, were eligible for this cross-sectional study. These general health examinations: used for the prevention and/or early detection of disease, consisted of a general physical examination, anthropometric measurements, BP, electrocardiography, blood analysis, carotid ultrasound, and an exercise stress test with concurrent metabolic gas analysis. All testing was completed at once. Informed consent was obtained from all patients before health screening and the study was approved by the Samsung medical center institutional review board. From a total sample of 1,273 women, we excluded women with symptom of angina, abnormal electro cardio graphic, changes during exercise stress testing or diagnosis of cardiovascular disease (coronary heart disease, stroke) (n = 57). In addition, we excluded the previous history of hypertension, use of antihypertensive medication (n = 254). Finally, our analysis sample subjects were selected within 442 women (age 40-60 years), with prehypertension.

Laboratory tests included total cholesterol, triglycerides, high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C) and fasting glucose. Blood samples were collected following a 12-h overnight fast and were analyzed by the hospital's clinical laboratory.

Blood pressure measurement

SBP and DBP were measured in the supine position using a digital BP monitor (Dinamap PRO 100, Milwaukee, USA) during quiet rest. Participants rested for at least 5 minutes before the measurements. Brachial BP measurements were repeated until two values within 5 mmHg of each other were obtained. The prehypertensive group was defined as those with SBP 120-139 mmHg and DBP 80-89 mmHg, according to the BP classification of the JNC-7 report (Chobanian et al. 2003).

Assessment of cardiorespiratory fitness

CRF was measured directly in terms of VO_2peak during maximal or symptom-limited treadmill testing (Quinton 4500; Cardiac Science Corp., Bothel, Washington, USA). VO_2peak analysis was based on dynamic breath-by-breath measurements using a JARGER system (VIASYS Healthcare, Hoecherg, Germany). Exercise heart rate (HR) was recorded continuously and exercise BP was assessed at the end of each stage and at peak exercise. VO_2peak was defined as the highest value for the plateau in oxygen uptake and was indexed by body weight (mL/kg per minute). Subjects were divided into three CRF groups: low, moderate, and high. The least fit 20% in each group were classified as having low fitness, the next 40% as moderate fitness, and the top 40% as high fitness, as previously reported (Blair et al. 1996; Lee et al. 1999). The women who has normal range of BP response has the average of VO2peak (27.7 ± 5.4 mL/kg/min), and the other women who has prehypertension has the average of VO2peak (27.2 ± 4.8 mL/kg/min) which means there are no significant different each groups.

Carotid atherosclerosis

Carotid artery ultrasound imaging was performed using a high-resolution B-mode ultrasound system (Logiq 7, GE Medical System, USA) with a 5-13 MHz linear array transducer. Both the right and left common carotid artery, the carotid bifurcation, and the internal carotid artery were measured by an experienced ultrasonography technician who was unaware of the subject's clinical information. With the subject in a supine position, each segment of the carotid arteries was imaged in both the transverse and longitudinal planes. The CIMT was defined as the distance between the leading edge of the lumen-intima interface and the leading edge of the media-adventitia interface of the far wall of the carotid artery. All measurements were made at end diastole. The CIMT of the common carotid artery was determined from an average of five measurements of a 10-mm segment (separated by 2 mm intervals) obtained 2 cm proximally to the carotid bifurcation. The CIMT of the internal carotid artery was measured in the proximal 1 cm. The overall maximum CIMT was defined as the mean of the maximum intima-media thickness and averaged for the left and right sides. The prevalence of subclinical atherosclerosis was defined as a mean CIMT more than the seventy-fifth percentile for each age group (Lester et al. 2009).

Statistical analysis

Data are expressed as mean ± SD for continuous variables and as number (percent) for categorical variables. Differences among the three CRF levels in cardiovascular risk factors related to BP, dyslipidemia and CIMT were examined by one-way analysis of variance. Tukey post-hoc analyses were used to test for differences between CRF level groups. To determine the associations between prehypertension, CIMT, and fitness, odds ratios (OR) and 95% confidence intervals (CI) were calculated using multivariate logistic regression models, after adjustment for age, body mass index (BMI), LDL-C, and resting HR. Statistical significance was set at $p < 0.05$, and analyses were performed using SPSS 21.0 (SPSS Inc., Chicago, IL, USA).

Results

Table 1 lists the characteristics of the participants stratified by fitness level. The VO_2peak values corresponding with the fitness categories were as follows: low fitness, 21.4 ± 2.7 mL/kg/min (n = 115); moderate fitness 26.8 ± 2.5 mL/kg/min (n = 175); and high fitness, 32.0 ± 2.6 mL/kg/min (n = 152). The women in the low-fitness group had higher BMI, SBP, DBP, and maximum BP compared to moderately and highly fit women ($p < 0.05$).

For LDL-C, the low-fitness group had the highest value and the high-fitness group had the lowest value, resulting in a significant difference between the three groups ($p < 0.05$). The value of CIMT was also greatest in the low-fitness group and smallest in the high-fitness group, with a significant difference between the groups ($p < 0.05$).

Fig. 1 shows comparisons of the mean CIMT values according to fitness levels. Compared with the low-fitness

Table 1. Characteristics of women according to cardiorespiratory fitness (CRF) categories.

Variable	Fitness Level[a]		
	Low fitness	Moderate fitness	High fitness
	n = 115	n = 175	n = 152
Age (years)	48.9 ± 5.7	49.2 ± 6.1	48.0 ± 6.7
BMI (kg/m^2)	26.0 ± 1.8	24.3 ± 2.5[b]	24.1 ± 2.0[d]
Smokers (%)	6.3	4.1[b]	4.3[d]
Resting SBP (mmHg)	131.9 ± 6.5	128.2 ± 6.7[b]	127.5 ± 5.8[d]
Resting DBP (mmHg)	80.5 ± 4.2	77.0 ± 6.5[b]	77.2 ± 7.0[d]
Total cholesterol (mg/dL)	189.0 ± 9.2	194.3 ± 10.7	190.6 ± 8.7
HDL-C (mg/dL)	50.4 ± 4.7	48.1 ± 4.4	49.2 ± 4.5
LDL-C (mg/dL)	135.8 ± 10.5	127.1 ± 14.8[b,c]	115.4 ± 13.2[d]
Triglycerides (mg/dL)	151.3 ± 65.6	153.5 ± 72.3	152.5 ± 70.9
Glucose (mg/dL)	105.4 ± 19.6	104.5 ± 25.7	104.9 ± 22.3
WBC count (×10^9 cells/l)	6.3 ± 1.4	6.2 ± 1.5	6.3 ± 1.5
Fibrinogen (mg/dL)	325.5 ± 72.4	324.7 ± 75.1	325.8 ± 74.3
Resting HR (bpm)	66.5 ± 8.2	65.3 ± 9.3	65.5 ± 9.1
Maximal HR (bpm)	150.3 ± 14.8	152.5 ± 15.1	150.5 ± 15.8
Maximal SBP (mg/dL)	195.2 ± 25.0	184.3 ± 24.2[b]	178.9 ± 27.5[c]
CIMT (mm)	0.74 ± 0.05	0.67 ± 0.06[b,c]	0.65 ± 0.05[d]
VO_2peak (mL/kg/min)	21.4 ± 2.7	26.8 ± 2.5[b,c]	32.0 ± 2.6[d]

Data are mean ± SD. BMI, body mass index; CIMT, carotid artery intima-media thickness; HDL-C, high-density lipoprotein cholesterol; HR, heart rate; LDL-C, low-density lipoprotein cholesterol; SBP/DBP, systolic/diastolic blood pressure; WBC, white blood cell count.

[a]According to VO_2max, the least fit 20% were classified as low fitness, the next 40% as moderate fitness, and the top 40% as high fitness.

[b]Denotes significant difference ($p < 0.05$) between moderate and low CRF groups.

[c]Denotes significant differences ($p < 0.05$) between moderate and high CRF groups.

[d]Denotes significant difference ($p < 0.05$) between high and low CRF groups.

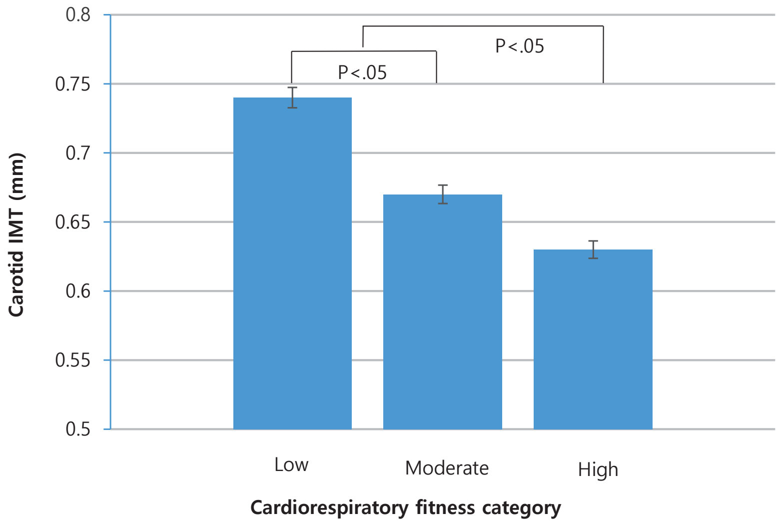

Fig. 1. Carotid artery intima-media thickness (CIMT) in relation to fitness level.

Table 2. Logistic regression odds ratios (95% confidence interval) for carotid atherosclerosis in relation to cardiorespiratory fitness.

Variable	Low fitness	Moderate fitness	High fitness	p-value
	n = 115	n = 175	n = 152	
Prevalence n (per 100 persons)	27.1 (23.5)	28.1 (16.0)	15.8 (10.3)	
Unadjusted OR (95% CI)	1 (reference)	0.69 (0.53-0.84)	0.64 (0.48-0.86)	< 0.001
Adjusted OR (95% CI)	1 (reference)	0.74 (0.45-0.92)	0.70 (0.46-0.95)	< 0.001

Adjusted for age, body mass index, systolic blood pressure, low-density lipoprotein cholesterol, white blood cell count, fibrinogen, heart rate, and glucose.

group (0.76 ± 0.15 mm), CIMT was reduced in the moderate- and high-fitness groups (0.67 ± 0.16 and 0.65 ± 0.15 mm; $p < 0.001$).

Table 2 shows the logistic regression analysis according to fitness group. In an unadjusted model, subjects with high fitness were 36% less likely (OR, 0.64; 95 % CI, 0.48-0.86) to have carotid atherosclerosis (CIMT > 75^{th} percentile) than subjects in the low-fitness group ($p < 0.001$). After adjustment for established risk factors (age, BMI, LDL-C, white blood cell count, SBP, DBP, fibrinogen, HR, glucose) high and moderate fitness were each associated with significantly lower odds of having carotid atherosclerosis: 0.74 (95% CI 0.45-0.92) and 0.70 (95% CI 0.46-0.95), respectively, compared with low fitness.

Discussion

In this study, CIMT measured using carotid artery ultrasound imaging in middle-aged prehypertensive women significantly increased as CRF decreased ($p < 0.001$), indicating that physical strength may be an important factor that can lower the risk of cardiovascular diseases in middle-aged, prehypertensive women.

JNC-7 implicated aging, diabetes, high BMI, smoking, hypercholesterolemia, past history of myocardial infarction, cardiac insufficiency, and cerebral infarction as risk factors for cardiovascular diseases. However, it was noted that the association between myocardial infarction and cardiovascular diseases can be explained in only 50% of patients with coronary artery disease (Hennekens 1998). Therefore, studies have begun to focus, not only on the classical risk factors for cardiovascular diseases, but also on structural and functional damage to blood vessels.

In previous studies of blood vessel damage that occurs during the prehypertensive stage, aortic elasticity measured by echocardiography was reduced to similar degrees in young adults with prehypertension and those with hypertension (Celik et al. 2006). In addition, aortic dilation assessed by magnetic resonance imaging and intravascular ultrasound was significantly reduced in the prehypertensive group (Toikka et al. 2002). In the prehypertensive group, increased CIMT, new development of atherosclerosis, and reduced diastolic function were observed (Ninomiya et al. 2007). In addition, a longitudinal study of prehypertensive patients found that they were at high risk for cardiovascular diseases and stroke (Liszka et al. 2005; De Marco et al. 2009).

In the present study, CIMT was significantly elevated among middle-aged prehypertensive women. This finding is consistent with that of Pasha et al. (2011), who compared CIMT among patients with various levels of BP, and found higher CIMT among hypertensive patients, even after the measurements had been adjusted for other variables. The results of rabbit aortic wall have been reported that changes in the level of pressure applied to arterial walls induce lipoprotein oxidation, which leads to arterial stiffness (Meyer et al. 1996). In addition, the clinical study of cardiovascular disease-free adults has total antioxidant capacity decreases and levels of oxidized lipoprotein increase as BP increases (Chrysohoou et al. 2007). Such an imbalance between lipoprotein oxidation and anti-oxidation causes the carotid arteries to stiffen (Demirbag et al. 2006). These findings suggest that hypertension can affect blood vessels and increase CIMT.

Maximal oxygen intake, which is a measure of CRF, is associated with the risk for premature death due to ischemic heart disease, cardiovascular disease, and stroke (Sieverdes et al. 2010; Berry et al. 2011). CRF has recently been reported to be associated with CIMT. Gando et al. (2011) divided 771 healthy adults aged 18-80 years into two groups (fit and unfit), and compared their CIMT. They reported significantly low values of CIMT in subjects with high CRF (Gando et al. 2011). Scholl et al. (2015) reported that 7,300 middle-aged German subjects had been analyzed the result that Cardiorespiratory fitness is a major determinant of common CIMT. Improved CRF does slightly, but not completely, abolish the adverse consequences of cardiovascular disease risk factors on common CIMT. Jae et al. (2007) also investigated the relationship between CRF and arteriosclerosis caused by increased CIMT in 2,532 middle-aged, hypertensive men. They found that subjects with low levels of maximal oxygen intake were at higher risk for arteriosclerosis than those with higher levels of maximal oxygen intake.

In the present study, patients were divided into three groups according to their CRF for comparison of BP and serum lipids. Significant differences in BP, LDL-C, and CIMT were found according to CRF. With regard to the differences in CIMT according to the level of CRF, the group with the lowest oxygen intake had the highest CIMT, while the group with highest oxygen intake had the lowest CIMT. Therefore, low CRF contributed to an increase in CIMT in middle-aged prehypertensive women.

The cardioprotective mechanisms of cardiorespiratory fitness are likely multifactorial. As demonstrated by previous studies, increased physical activity and fitness level have been improved to prevent overall cardiovascular risk (Bauer et al. 2009; Scholl et al. 2015). In this study, the cardiovascular risk profile is also indicated that the risk factor is lower in the higher fitness group. In addition, the important cardioprotective mechanism may be through an inverse relationship with vascular inflammation. In several cohort studies, there are significant reductions in markers of inflammation from higher fitness group (Abramson and Vaccarino 2002; Church et al. 2002)

We acknowledge several methodological limitation of our study. Give the cross sectional design, we were also unable to determine causality. Our sample included only women, so we are unable to determine whether this association extends to women. We also did not control for diet status, including alcohol consumption. The effect of alcohol consumption or other dietary factors may potentially confound the relationship between cardiorespiratory fitness and carotid atherosclerosis. Also, future studies are needed to prospectively evaluate this association in population sample.

In conclusion, the present study compared the relationship between CIMT, a predictive factor for cardiovascular diseases, and CRF in middle-aged prehypertensive women. A significant inverse relationship was found between CIMT and high CRF in middle-aged, hypertensive women. BP was positively correlated with CIMT. Therefore, by maintaining stable levels of BP, and high levels of oxygen intake through regular exercise, middle-aged women may be able to delay an increase in CIMT, and prevent cardiovascular diseases. Therefore, by maintaining stable levels of BP, and high levels of oxygen intake through regular exercise, middle-aged women may be able to delay an increase in CIMT, and prevent cardiovascular diseases.

References

Abramson, J.L. & Vaccarino, V. (2002) Relationship between physical activity and inflammation among apparently healthy middle-aged and older US adults. *Arch. Intern. Med.*, **162**, 1286-1292.

Bauer, M., Mohlenkamp, S., Lehmann, N., Schmermund, A., Roggenbuck, U., Moebus, S., Stang, A., Mann, K., Jöckel, K.H. & Erbel, R. (2009) The effect of age and risk factors on coronary and carotid artery atherosclerotic burden in males: results of the Heinz Nixdorf recall study. *Atherosclerosis*, **205**, 595-602.

Berry, J.D., Willis, B., Gupta, S., Barlow, C.E., Lakoski S.G., Khera, A., Rohatgi, A., de Lemos, J.A., Haskell, W. & Lloyd-Jones, D.M. (2011) Lifetime risks for cardiovascular disease mortality by cardiorespiratory fitness levels measured at ages 45, 55, and 65 years in men: the cooper center longitudinal study. *J. Am. Coll. Cardio.*, **57**, 1604-1610.

Blair, S.N., Kampert, J.B., Kohl, H.W. 3rd, Barlow, C.E., Macera, C.A., Paffenbarger, R.S. Jr. & Gibbons, L.W. (1996) Influences of cardiorespiratory fitness and other precursors on cardiovascular disease and all-cause mortality in men and women. *JAMA*, **276**, 205-210.

Celik, T., Iyisoy, A., Kursaklioglu, H., Cagdas Yuksel, U., Kilic, S., Kutsi Kabul, H. & Genc, C. (2006) Impaired aortic elastic properties in young patients with prehypertension. *Blood Press Monit.*, **11**, 251-255.

Chobanian, A.V., Bakris, G., Black, H.R., Cushman, W.C., Green, L.A., Izzo, J.R. Jr., Jones, D.W., Materson, B.J., Oparil, S., Wright, J.T. Jr. & Roccella, E.J. (2003) The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: the JNC 7 report. *JAMA*, **289**, 2560-2572.

Chrysohoou, C., Panagiotakos, D.B., Pitsavos C., Skoumas, J., Economou, M., Papadimitriou, L. & Stefandis, C. (2007) The association between pre-hypertension status and oxidative stress markers related to atherosclerotic disease: the ATTICA study. *Atherosclerosis*, **192**, 169-176.

Church, T.S., Barlow, C.E., Earnest, C.P., Kampert, J.B., Priest, E.L. & Blair, S.N. (2002) Associations between cardiorespiratory fitness and C-reactive protein in men. *Arterioscler. Thromb. Vasc. Biol*., **22**, 1869-1876.

Crouse, J.R. 3rd, Grobbee, D.E., O'Leary, D.H., Bots, M.L., Evans, G.W., Palmer, M.K., Riley, W.A. & Raichlen, J.S. (2004) Measuring effects on intima-media thickness: an evaluation of rosuvastatin in subclinical atherosclerosis: the rationale and methodology of theMETEORstudy. *Cardiovasc. Drugs Ther.*, **18**, 231-238.

De Marco, M., de Simone, G., Roman, M.J., Chinali, M., Lee, E.T., Russell, M., Howard, B.V. & Devereux, R.B. (2009) Cardiovascular and metabolic predictors of progression of prehypertension into hypertension: the Strong Heart Study. *Hypertension*, **54**, 974-980.

Demirbag, R., Yilmaz, R., Kunt, A.S., Gur, M., Ulucay, A. & Unlu, D. (2006) Relationship between plasma total antioxidant capacity and thoracic aortic intima-media thickness. *Echocardiography*, **23**, 183-188.

Gando, Y., Yamamoto, K., Kawano, H., Murakami, H., Ohmori, Y., Kawakami, R., Sanada, K., Higuchi, M., Tabata, I. & Miyachi, M. (2011) Attenuated age-related carotid arterial remodeling in adults with a high level of cardiorespiratory fitness. *J. Atheroscler. Thromb.*, **18**, 248-254.

Gray, L., Lee, I.M., Sesso, H.D. & Batty, G.D. (2011) Blood pressurein early adulthood, hypertension in middle age, and future cardiovascular disease mortality: HAHS (harvard alumni health study). *J. Am. Coll. Cardiol*., **8**, 2396-2403.

Hennekens, C.H. (1998) Increasing burden of cardiovascular disease: current knowledge and future directions for research on risk factors. *Circulation*, **97**, 1095-1102.

Hsia, J., Margolis, K.L., Eaton, C.B., Wenger, N.K., Allison, M., Wu, L., LaCroix, A.Z. & Black, H.R. (2007) Prehypertension and cardiovascular disease risk in the Women's Health Initiative. *Circulation*, **115**, 855-860.

Jae, S.Y., Carnethon, M.R., Heffernan, K.S., Choi, Y.H., Lee, M.K. & Fernhall, B. (2007) Association between cardiorespiratory fitness and prevalence of carotid atherosclerosis among men with hypertension. *Am. Heart J*., **153**, 1001-1005.

Kablak-Ziembicka, A., Przewlocki, T., Tracz, W., Pieniazek, P., Musialek, P., Sokolowski, A., Drwila, R. & Rzeznik, D. (2008) Carotid intima-media thickness in pre- and postmenopausal women with suspected coronary artery disease. *Heart Vessels*, **23**, 295-300.

Lakka, T.A., Laukkanen, J.A., Rauramaa, R., Salonen, R., Lakka, H.M., Kaplan, G.A. & Salonen, J.T. (2001) Cardiorespiratory fitness and the progression of carotid atherosclerosis in middle-aged men. *Ann. Intern. Med*., **134**, 12-20.

Lee, C.D., Blair, S.N. & Jackson, A.S. (1999) Cardiorespiratory fitness, body composition, and all-cause and cardiovascular disease mortality in men. *Am. J. Clin. Nutr*., **69**, 373-380.

Lester, S.J., Eleid, M.F., Khandheria, B.K. & Hurst, R.T. (2009) Carotid intima-media thickness and coronary artery calcium score as indications of subclinical atherosclerosis. *Mayo Clin. Proc.*, **84**, 229-233.

Liszka, H.A., Mainous, A.G. 3rd, King, D.E., Everett, C.J. & Egan, B.M. (2005) Prehypertension and cardiovascular morbidity. *Ann. Fam. Med*., **3**, 294-299.

Meyer, G., Merval, R. & Tedgui, A. (1996) Effects of pressure-induced stretch and convection on low-density lipoprotein and albumin uptake in the rabbit aortic wall. *Circ. Res*., **79**, 532-540.

Mozaffarian, D., Benjamin, E.J., Go, A.S., Arnett, D.K., Blaha, M.J., Cushman, M., de Ferranti, S., Després, J.P., Fullerton, H.J., Howard, V.J., Huffman, M.D., Judd, S.E., Kissela, B.M., Lackland, D.T., Lichtman, J.H., et al. (2015) Heart disease and stroke statistics-2015 update: a report from the American Heart Association. *Circulation*, **131**, e29-322.

Ninomiya, T., Kubo, M., Doi, Y., Tanizaki, Y., Tsuruya, K., Sueishi, K., Tsuneyoshi, M., Iida, M. & Kiyohara, Y. (2007) Prehypertension increases the risk for renal arteriosclerosis in autopsies: the Hisayama Study. *J. Am. Soc. Nephrol.*, **18**, 2135-2142.

O'Leary, D.H., Polak, J.F., Kronmal, R.A., Manolio, T.A., Burke, G.L. & Wolfson, S.K. Jr. (1999) Carotid-artery intima and media thickness as a risk factor for myocardial infarction and stroke in older adults. *N. Engl. J. Med.*, **340**,14-22.

Pasha, S.M., Wiria, A.E., Wammes, L.J., Smit, J.W., Partono, F., Supali, T., Yazdanbakhsh, M. & Tamsma, J.T. (2011) Blood pressure class and carotid artery intima-media thickness in a population at the secondary epidemiological transition. *J. Hypertens.*, **29**, 2194-2200.

Scholl, J., Bots, M.L. & Peters, S.A. (2015) Contribution of cardiorespiratory fitness, relative to traditional cardiovascular disease risk factors, to common carotid intima-media thickness. *J. Intern. Med*., **277**, 439-446.

Sieverdes, J.C., Sui, X., Lee, D.C., Church, T.S., McClain, A., Hand, G.A. & Blair, S.N. (2010) Physical activity, cardiorespiratory fitness and the incidence of type 2 diabetes in a prospective study of men. *Brit. J. Sports Med.*, **44**, 238-244.

Sui, X., LaMonte, M.J., Laditka, J., Hardin, J.W., Chase, N., Hooker, S.P. & Blair, S.N. (2007) Cardiorespiratory fitness and adiposity as mortality predictors in older adults. *JAMA*, **298**, 2507-2516.

Toikka, J.O., Niemi, P., Ahotupa, M., Niinikoski, H., Ronnemaa, T. & Viikari, J.S. (2002) Decreasedlarge artery distensibility in borderline hypertension is related to increased in vivo low-density lipoprotein oxidation. *Scand. J. Clin. Lab. Invest.*, **62**, 301-306.

Vasan, R.S., Larson, M.G., Leip, E.P., Kannel, W.B. & Levy, D. (2001) Assessment of frequency of progression to hypertension in non-hypertensive participants in the Framingham Heart Study: a cohort study. *Lancet*, **358**, 1682-1686.