CARDIOVASCULAR DISEASE (CVD)
Plasma/Serum Lycopene and Disease Risk

Disease type	First Author	Study Title and Complete Citation	Date	Abstract	Study Type	G.Tom +, N, -	P.Tom +, N, -	F.Tom +, N, -	Lyco +, N, -	Other +, N, -
Heart	D'Odorico A,	High plasma levels of alpha- and beta-carotene are associated with a lower risk of atherosclerosis: results from the Bruneck study. D'Odorico A, Martines D, Kiechl S, Egger G, Oberhollenzer F, Bonvicini P, Sturniolo GC, Naccarato R, Willeit J. Atherosclerosis. 2000 Nov;153(1):231-9.	2000	BACKGROUND AND PURPOSE: A large number of studies have contributed to the hypothesis that carotenoids, vitamins A and E are protective against atherosclerosis by acting as antioxidants. The aim of this study was to assess the relationship between plasma levels of carotenoids (alpha- and beta- carotene, lutein, lycopene, zeaxanthin, beta-cryptoxanthin), vitamins A and E, and atherosclerosis in the carotid and femoral arteries. METHODS: This prospective and cross sectional study involved a randomly selected population sample of 392 men and women aged 45-65 years. Carotid and femoral artery atherosclerosis was assessed by high-resolution duplex ultrasound. RESULTS: alpha- and beta- carotene plasma levels were inversely associated with the prevalence of atherosclerosis in the carotid and femoral arteries (P=0.004) and with the 5-year incidence of atherosclerotic lesions in the carotid arteries (P=0.04). These findings were obtained after adjustment for other cardiovascular risk factors (sex, age, LDL (low density lipoproteins), ferritin, systolic blood pressure, smoking, categories of alcohol consumption, social status, C-reactive	PC, CS				N Atherosclerosis risk including 5 year athero lesion	

				protein). Atherosclerosis risk gradually decreased with increasing plasma alpha- and beta-carotene concentrations (P=0.004). No associations were found between vitamin A and E plasma levels and atherosclerosis. CONCLUSIONS: This study provides further epidemiological evidence of a protective role of high alpha- and beta-carotene in early atherogenesis.						
Heart	Farwell WR	The relationship between total plasma carotenoids and risk factors for chronic disease among middle-aged and older men. Farwell WR, Michael Gaziano J, Norkus EP, Sesso HD. Br J Nutr. 2008 Oct;100(4):883-9. Epub 2008 Mar 12.	2008	Individual plasma carotenoids have been associated with various chronic diseases but little is known about the relationship between total plasma carotenoids and risk factors for chronic diseases. In the Physicians' Health Study, we examined 492 men free of CVD and cancer for the relationship between total plasma carotenoids (the sum of alpha-carotene, beta-carotene, lycopene, zeaxanthin, lutein and beta-cryptoxanthin) and a wide variety of factors that predict chronic disease. Multivariate linear and logistic regression was performed to calculate parameter estimates (95% CI) and OR (95% CI) for total plasma carotenoids. In linear regression models, BMI, hypertension, alcohol intake and plasma levels of each lipid parameter and a-tocopherol significantly predicted levels of total plasma carotenoids. Upon adjustment for multiple chronic disease risk factors, the OR for levels of total plasma carotenoids greater than or equal to the median (> or=1.301 micromol/l) was statistically significant for current smoking (OR 0.21; 95% CI 0.06, 0.77), weekly alcohol ingestion (OR 2.30; 95% CI 1.06, 4.99), daily alcohol ingestion (OR 2.46; 95% CI 1.29, 4.67), each 100 mg/l increase in total cholesterol (OR 0.73; 95% CI 0.58, 0.91), LDL-cholesterol	CS					N plasma [carotenoids] not related to lifestyle/clinical risk factors

				(OR 1.48; 95% CI 1.17, 1.89) and HDL-cholesterol (OR 1.58; 95% CI 1.26, 1.99), each 100 mg/ml increase in intercellular adhesion molecule-1 (OR 0.70; 95% CI 0.53, 0.93) and each 10 micromol/l increase in alpha-tocopherol (OR 1.33; 95% CI 1.12, 1.57), using logistic regression. Few lifestyle and clinical risk factors appear to be related to levels of total plasma arotenoids; however, levels of biomarkers such as plasma lipids and alpha-tocopherol may be strongly related.						
Heart	Guardiola M	The apolipoprotein A5 (APOA5) gene predisposes Caucasian children to elevated triglycerides and vitamin E (Four Provinces Study). Guardiola M, Ribalta J, Gómez-Coronado D, Lasunción MA, de Oya M, Garcés C Atherosclerosis. 2010 Oct;212(2):543-7. Epub 2010 Jul 15.	2010	OBJECTIVE: Apolipoprotein A-V plays an important role in lipid metabolism regulation, particularly modulating triglyceride levels, as has been shown by many association studies in adults. The aim of this study was to analyse the effect of APOA5 on lipid profiles and fat-soluble vitamins (due to its strong relationship with triglyceride metabolism) in children. METHODS: We determined polymorphisms -1131T>C and S19W in the APOA5 gene in 964 6-8-year-old participants of the 4P study and analysed the influence of the APOA5 gene on plasma lipid levels (total cholesterol, LDL cholesterol, HDL cholesterol and triglycerides), apolipolipoproteins (apo A-I and apo B) and fat-soluble antioxidant vitamin (α-tocopherol, γ-tocopherol, lycopene, α-carotene, β-carotene and retinol) levels. RESULTS: The allele frequencies of both polymorphisms were comparable to those described in adult Caucasian populations (0.08 and 0.07 for -1131T>C and S19W, respectively). Boys carrying the -1131C allele have a 12% increase in circulating triglyceride levels (p=0.016) and a 7% decrease in HDL phospholipid	CS				N	Children Lipids

				levels (p=0.016). Linked to its effect on triglycerides, boys with the -1131C allele also have a 5% increase in plasma a-tocopherol levels (p=0.032). This effect was not observed in female participants. Boys carrying the rare allele for the S19W polymorphism have a 4% increase in circulating cholesterol levels (p=0.045), whereas girls have a 9% increase in circulating triglyceride levels (p=0.029). Linked to its effect on triglycerides, female carriers of the rare allele for S19W also have a 6% increase in a-tocopherol levels (p=0.009). CONCLUSION: In children, the effect of APOA5 gene variants on triglyceride levels is related to gender, and because of the strong relationship between lipid metabolism and fat-soluble antioxidant vitamins, it also involves a significant elevation in a-tocopherol concentrations.						
Heart	Klipstein-Grobusch K	Serum carotenoids and atherosclerosis. The Rotterdam Study. Klipstein-Grobusch K, Launer LJ, Geleijnse JM, Boeing H, Hofman A, Witteman JC. Atherosclerosis. 2000 Jan;148(1):49-56.	2000	High circulating levels of carotenoids have been thought to exhibit a protective function in the development of atherosclerosis. We investigated whether aortic atherosclerosis was associated with lower levels of the major serum carotenoids in alpha-carotene, beta-carotene, beta-cryptoxanthin, lutein, lycopene, and zeaxanthin-in a subsample of the elderly population of the Rotterdam Study. Aortic atherosclerosis was assessed by presence of calcified plaques of the abdominal aorta. The case-control analysis comprised 108 subjects with aortic atherosclerosis and controls. In an age- and sex-adjusted logistic regression model, serum lycopene was inversely associated with the risk of atherosclerosis. The odds ratio for the highest compared to the lowest quartile of serum lycopene	CC				N Elderly ~~~~~ (-) Smoker	

				was 0.55 (95% CI 0.25-1.22; p(trend)=0.13). Multivariate adjustment did not appreciably alter these results. Stratification by smoking status indicated that the inverse association between lycopene and aortic calcification was most evident in current and former smokers (OR=0.35; 95% CI 0.13-0.94; p(trend)=0.04). No association with atherosclerosis was observed for quartiles of serum concentrations of alpha-carotene, beta-carotene, lutein, and zeaxanthin. In conclusion, this study provides evidence for a modest inverse association between levels of serum lycopene and presence of atherosclerosis, the association being most pronounced in current and former smokers. Our findings suggest that lycopene may play a protective role in the development of atherosclerosis.						
Heart: Acute Coronary Events	Rissanen TH	Low serum lycopene concentration is associated with an excess incidence of acute coronary events and stroke: the Kuopio Ischaemic Heart Disease Risk Factor Study. Rissanen TH, Voutilainen S, Nyyssönen K, Lakka TA, Sivenius J, Salonen R, Kaplan GA, Salonen JT. Br J Nutr. 2001 Jun;85(6):749-54.	2001	A number of epidemiological studies have shown an association between beta-carotene and the risk of cardiovascular diseases, whereas only a few studies are available concerning the association of lycopene with the risk of coronary events, and no studies have been undertaken concerning lycopene and stroke. Thus, we tested the hypothesis that low serum levels of lycopene are associated with increased risk of acute coronary events and stroke in middle-aged men previously free of CHD and stroke. The subjects were 725 men aged 46-64 years examined in 1991-3 in the Kuopio Ischaemic Heart Disease Risk Factor Study. Forty-one men had either a fatal or a non-fatal acute coronary event or a stroke by December 1997. In a Cox' proportional hazard's model adjusting for examination years, age, systolic blood pressure and three	PC				(-) Acute coronary events	

				nutritional factors (serum folate, beta-carotene and plasma vitamin C), men in the lowest quarter of serum lycopene levels (< or =0.07 micromol/l) had a 3.3-fold (95 % CI 1.7, 6.4, risk of acute coronary events or stroke compared with the others. Our study suggests that a low serum level of lycopene is associated with an increased risk of atherosclerotic vascular events in middle-aged men previously free of CHD and stroke.						
Heart: BP	John JH	Effects of fruit and vegetable consumption on plasma antioxidant concentrations and blood pressure: a randomised controlled trial. John JH, Ziebland S, Yudkin P, Roe LS, Neil HA; Oxford Fruit and Vegetable Study Group. Lancet. 2002 Jun 8;359(9322):1969-74.	2002	BACKGROUND: High dietary intakes of fruit and vegetables are associated with reduced risks of cancer and cardiovascular disease. Short-term intensive dietary interventions in selected populations increase fruit and vegetable intake, raise plasma antioxidant concentrations, and lower blood pressure, but long-term effects of interventions in the general population are not certain. We assessed the effect of an intervention to increase fruit and vegetable consumption on plasma concentrations of antioxidant vitamins, daily fruit and vegetable intake, and blood pressure. METHODS: We undertook a 6-month, randomised, controlled trial of a brief negotiation method to encourage an increase in consumption of fruit and vegetables to at least five daily portions. We included 690 healthy participants aged 25-64 years recruited from a primary-care health centre. FINDINGS: Plasma concentrations of alpha-carotene, beta-carotene, lutein, beta-cryptoxanthin, and ascorbic acid increased by more in the intervention group than in	RCT				N	

				controls (significance of between-group differences ranged from p=0.032 to 0.0002). Groups did not differ for changes in lycopene, retinol, alpha-tocopherol, gamma-tocopherol, or total cholesterol concentrations. Self-reported fruit and vegetable intake increased by a mean 1.4 (SD 1.7) portions in the intervention group and by 0.1 (1.3) portion in the control group (between-group difference=1.4, 95% CI 1.2-1.6; p<0.0001). Systolic blood pressure fell more in the intervention group than in controls (difference=4.0 mm Hg, 2.0-6.0; p<0.0001), as did diastolic blood pressure (1.5 mm Hg, 0.2-2.7; p=0.02). INTERPRETATION: The effects of the intervention on fruit and vegetable consumption, plasma antioxidants, and blood pressure would be expected to reduce cardiovascular disease in the general population. Comment in: Lancet. 2002 Nov 30;360(9347):1785-6; author reply 1786. Lancet. 2002 Nov 30;360(9347):1786.						
Heart: BP	Hozawa A	Circulating carotenoid concentrations and incident hypertension: the Coronary Artery Risk Development in Young Adults (CARDIA) study. Hozawa A, Jacobs DR Jr, Steffes MW, Gross MD, Steffen LM, Lee DH.	2009	BACKGROUND: Several epidemiological studies have demonstrated that carotenoid concentrations relate inversely to cardiovascular disease incidence. Thus, we examined the association of circulating carotenoids with hypertension, a major macrovascular disease risk factor. METHODS: Black and White men and women in the Coronary Artery Risk Development in Young Adults Study, aged 18-30 years at recruitment (1985-1986) from four US cities, were investigated over 20 years. At years 0, 7, and 15, we determined the relationships of the sum of four serum carotenoids	PC				N	BP

		J Hypertens. 2009 Feb;27(2):237-42.		(alpha-carotene, beta-carotene, lutein/zeaxanthin, cryptoxanthin) and of lycopene with incident hypertension using proportional hazards regression models. RESULTS: In 4412 participants, year 0 sum of four carotenoids was significantly inversely associated with 20-year hypertension incidence after adjustment for baseline systolic blood pressure and other confounding factors (relative hazard per SD increase of sum of four carotenoids: 0.91; 95% confidence interval = 0.84-0.99). The inverse relationships persisted in time-dependent models updating year 0 sum of four carotenoids with year 7 and year 15 values (relative hazard per SD increase of sum of four carotenoids: 0.84; 95% confidence interval = 0.77-0.92). Lycopene was unrelated to hypertension in any model. CONCLUSION: Those individuals with higher concentrations of sum of carotenoids, not including lycopene, generally had lower risk for future hypertension.						
Heart: BP and lipids	Ried K	Protective effect of lycopene on serum cholesterol and blood pressure: Meta-analyses of intervention trials. Ried K, Fakler P. Maturitas. 2011 Apr;68(4):299-310. Epub 2010 Dec 15.	2011	BACKGROUND: Cardiovascular disease is associated with oxidative stress, inflammatory processes, and vascular dysfunction. Lycopene, a carotenoid found in tomatoes, is an antioxidant with a protective effect on lipid peroxidation and anti-atherosclerotic capacity. This review summarises current evidence on the effect of lycopene on serum lipid concentrations and blood pressure. METHODS: We searched the PubMed and Cochrane databases for intervention studies between 1955 and September	Meta-Analysis				(-) BP (4 studies) ~~~~~ (-) TC, LDL, Lipids (12 studies) lyco supp ≥25 mg/d ↓LDL 10%	

				2010 investigating the effect of lycopene on blood lipids or blood pressure for a minimum duration of 2 weeks. We conducted meta-analyses using a random effect model of all studies fitting the inclusion criteria. Additionally, we conducted subgroup meta-analysis of serum lipid concentrations by lycopene dosage and subgroup meta-analysis by baseline blood pressure. RESULTS: Twelve studies (13 trial arms) meeting the inclusion criteria investigated the effect of lycopene on serum lipids, and four studies examined its effect on blood pressure. Meta-analysis on serum lipids revealed a significant cholesterol-lowering effect of lycopene for total serum cholesterol (mean change±SE: -7.55±6.15mg/dl; p=0.02) and low-density-lipoprotein (LDL) cholesterol (mean change±SE: -10.35±5.64mg/dl, p=0.0003) in the subgroup of trials using lycopene dosages of ≥25mg daily, whereas subgroup meta-analysis of trials using lower lycopene dosages was not significant. Meta-analysis of the effect of lycopene on systolic blood pressure of all trials suggested a significant blood pressure reducing effect (mean systolic blood pressure change±SE: -5.60±5.26mm Hg, p=0.04). CONCLUSIONS: Our meta-analysis suggests that lycopene taken in doses ≥25mg daily is effective in reducing LDL cholesterol by about 10% which is comparable to the effect of low doses of statins in patient with slightly elevated cholesterol levels. More research is needed to confirm suggested beneficial effects on total serum cholesterol and systolic blood pressure.					~~~~~ N <25 mg/d	

Heart: CIMT	Riccioni G	Circulating plasma antioxidants, inflammatory markers and asymptomatic carotid atherosclerosis in end-stage renal disease patients: a case control study. Riccioni G, D Orazio N, Scotti L, Petruzzelli R, Latino A, Bucciarelli V, Pennelli A, Cicolini G, Di Ilio E, Bucciarelli T. Int J Immunopathol Pharmacol. 2010 Jan-Mar;23(1):327-34.	2010	Few studies have been conducted on the relationship between antioxidant plasma vitamin concentrations, inflammatory markers and carotid atherosclerosis with inconclusive results in endstage renal disease (ESRD) patients. A case-control study was performed to investigate the relationship between plasma antioxidant concentrations, inflammatory markers, and carotid intima-media thickness (CIMT) in healthy subjects and in patients undergoing hemodialysis (HD). We enrolled 40 subjects (20 healthy, 20 with ESRD) asymptomatic for carotid atherosclerosis. After carotid ultrasound investigation (CUI), medical history data, physical examination, venous blood samples were collected. These were analyzed for concentrations of antioxidant vitamins (A, E), carotenoids (lycopene, beta-carotene), inflammatory markers (C-reactive protein, fibrinogen), and lipid profile. Low concentrations of vitamin A, vitamin E, lycopene, and beta-carotene were significantly associated with carotid atherosclerosis in patients with ESRD (p less than 0.001). In addition, high concentration of low density lipoprotein cholesterol and total cholesterol (p less than 0.01), C-reactive protein and fibrinogen (p less than 0.001) were also associated with carotid atherosclerosis, while other laboratory parameters considered (high density lipoprotein cholesterol and triglycerides) were not significantly associated with carotid atherosclerosis. A regular intake of foods rich in antioxidant vitamins with low fat concentrations may slow the progression of atherosclerotic process in this group of patients.	CC				(-)	

Heart: endothelial function and MetS	Yeo HY	Association of serum lycopene and brachial-ankle pulse wave velocity with metabolic syndrome. Yeo HY, Kim OY, Lim HH, Kim JY, Lee JH. Metabolism. 2011 Apr;60(4):537-43. Epub 2010 Jun 26.	2011	Metabolic syndrome (MetS) is known to inversely correlate with antioxidant status. Recently, it has been reported that MetS is associated with arterial stiffness, a composite risk factor for early therosclerosis. In addition, our recent study for healthy women showed an inverse relationship between arterial stiffness and circulating lycopene. Therefore, this study aimed to investigate the interrelationship between arterial stiffness, antioxidant status, and the risk of MetS. Korean men (N = 299) were subgrouped according to the number of MetS risk factors (RF 0, RF 1-2, RF ≥ 3). Anthropometric parameters, brachial-ankle pulse wave velocity (baPWV; a marker of arterial stiffness), antioxidants (lycopene, β-carotene, α-tocopherol), lipid profiles, glucose, insulin, and oxidative stress (low-density lipoprotein [LDL] particle size, oxidized LDL) were measured. Corresponding to the number of MetS RF, baPWV (1306 ± 17, 1364 ± 16, and 1420 ± 33 cm/s; P < .001) and insulin resistance (1.5 ± 0.1, 1.9 ± 0.1, and 2.7 ± 0.2; P < .001) gradually increased after adjustment for age, body mass index, smoking, and drinking, whereas serum lycopene among antioxidants and LDL particle size gradually decreased (0.036 ± 0.001, 0.031 ± 0.001, and 0.028 ± 0.001 mmol/L; P = .004 and 23.9 ± 0.1, 23.7 ± 0.1, and 23.3 ± 0.1 nm; P < .001, respectively). Brachial-ankle pulse wave velocity inversely correlated with serum lycopene after adjustment for the above confounders, blood pressure, insulin resistance, and oxidative stress (r = -0.136, P < .05). Oxidative stress markers also significantly correlated with baPWV as well as serum lycopene. Study subjects were divided into 2 groups by the median level of serum lycopene. When serum lycopene was lower than median level (≤ 0.0294	CS				(-) Arterial stiffness and Oxidation (-) Arterial stiffness more pronounced in MetS with low PL	

				mmol/L), baPWV was significantly higher in MetS subjects than non-MetS subjects (1436 ± 41 vs 1367 ± 23 cm/s) after adjustment for age, body mass index, smoking, drinking, and oxidative stress (P = .041). However, when serum lycopene levels were high, no statistically significant difference was observed between the 2 subject groups (1386 ± 36 vs 1326 ± 13 cm/s). In conclusion, our result shows the interrelationship between circulating lycopene, baPWV, and MetS. In addition, much enhanced baPWV in MetS may be associated with lower lycopene concentration.						
Heart: endothelial function, oxidation and inflammation	Kim OY	Independent inverse relationship between serum lycopene concentration and arterial stiffness. Kim OY, Yoe HY, Kim HJ, Park JY, Kim JY, Lee SH, Lee JH, Lee KP, Jang Y, Lee JH. Atherosclerosis. 2010 Feb;208(2):581-6. Epub 2009 Aug 13.	2010	OBJECTIVE: Emerging evidence suggests a role of lycopene in the primary prevention of cardiovascular disease. This study aimed to investigate the association of serum lycopene concentration with brachial-ankle pulse wave velocity (baPWV), a marker of arterial stiffness and markers of oxidative stress and inflammation. METHODS: healthy women (n=264, 31-75 yrs) were classified into tertiles according to serum lycopene concentration. Multivariate linear regression analyses were used to assess the relationship between serum lycopene and baPWV. RESULTS: Subjects in middle tertile (T2) and upper tertile (T3) had lower baPWV (1263+/-23 and 1265+/-14 cm/s vs. 1338+/-21 cm/s; p=0.009) and lower oxidized LDL (oxLDL) (53+/-3 and 55+/-3 U/L vs. 66+/-3 U/L; p<0.001) than those in lower tertile (T1). Subjects in T3 showed higher LDL particle size (24.3+/-0.08 nm vs. 24.0+/-0.07 nm, p=0.005) and lower C-reactive protein (hs-CRP) (0.80+/-0.25mg/dL vs. 1.27+/-0.24 mg/dL, p=0.015), compared with those in T1.	CS				(-) Arterial stiffness OxLDL CRP	

				Logistic regression analysis showed that baPWV decreased with the increment of lycopene concentration; log baPWV decreased by 0.21 cm/s (95% CI -0.168;-0.045, p=0.001) per unit change in lycopene. After adjustment for age, BMI, smoking, drinking, menopause and blood pressure, the estimated effect was attenuated by 35%, but remained statistically significant [-0.13 cm/s (95% CI -0.112;-0.018, p=0.006)]. Further adjustment for beta-carotene, alpha-tocopherol, oxLDL, LDL particle size, and hs-CRP increased the strength of the association [beta=-0.221 (95% CI -0.215;-0.012, p=0.029)]. CONCLUSION: This study supports the presence of an independent inverse relationship between circulating lycopene and baPWV. Additionally, reduced oxidative modification of LDL may be one of mediators on the mechanisms how lycopene reduces arterial stiffness.						
Heart: IMT	Rissanen T	Lycopene, atherosclerosis, and coronary heart disease. Rissanen T, Voutilainen S, Nyyssonen K, Salonen JT. Exp Biol Med (Maywood). 2002 Nov;227(10):900-7.	2002	Diets rich in fruits and vegetables containing carotenoids have been of interest because of their potential health benefit against chronic diseases such as cardiovascular diseases (CVD) and cancer. Interest particularly in lycopene is growing rapidly following the recent publication of epidemiological studies that have associated high lycopene levels with reductions in CVD incidence. Two studies were conducted. In the first one, we examined the role of lycopene as a risk-lowering factor with regard to acute coronary events and stroke in the prospective Kuopio Ischemic Heart Disease Risk Factor (KIHD) Study. The subjects were 725 middle-aged men free of coronary heart disease and stroke at the study baseline. In a Cox's proportional hazards' model adjusting for covariates,	CS and PC				(-) (-)men IMT	

				men in the lowest quartile of serum levels of lycopene had a 3.3-fold (P < 0.001) risk of the acute coronary event or stroke as compared with others. In the second study, we assessed the association between plasma concentration of lycopene and intima-media thickness of the common carotid artery wall (CCA-IMT) in a cross-sectional analysis of the Antioxidant Supplementation in the Atherosclerosis Prevention (ASAP) study data in 520 asymptomatic men and women. In a covariance analysis adjusting for common cardiovascular risk factors, low plasma levels of lycopene were associated with an 18% increase of IMT in men as compared with men in whom plasma levels were higher than median (P = 0.003 for difference). In women, the difference did not remain significant after the adjustments. On the basis of these works, it is evident that the circulating levels of lycopene play some role with regard to cardiovascular health in Finland, at least in men. We conclude that circulating levels of lycopene, a biomarker of tomato-rich food, may play a role in early stages of atherogenesis and may have clinical and public health relevance.						
Heart: IMT	Rissanen T	Lycopene, atherosclerosis, and coronary heart disease. Rissanen T, Voutilainen S, Nyyssonen K, Salonen JT. Exp Biol Med (Maywood). 2002 Nov;227(10):900-7.	2002	Diets rich in fruits and vegetables containing carotenoids have been of interest because of their potential health benefit against chronic diseases such as cardiovascular diseases (CVD) and cancer. Interest particularly in lycopene is growing rapidly following the recent publication of epidemiological studies that have associated high lycopene levels with reductions in CVD incidence. Two studies were conducted. In the first one, we examined the role of lycopene as a risk-lowering factor with regard to acute coronary events and stroke in the	PC and CS				(-) IMT	

				prospective Kuopio Ischemic Heart Disease Risk Factor (KIHD) Study. The subjects were 725 middle-aged men free of coronary heart disease and stroke at the study baseline. In a Cox's proportional hazards' model adjusting for covariates, men in the lowest quartile of serum levels of lycopene had a 3.3-fold (P < 0.001) risk of the acute coronary event or stroke as compared with others. In the second study, we assessed the association between plasma concentration of lycopene and intima-media thickness of the common carotid artery wall (CCA-IMT) in a cross-sectional analysis of the Antioxidant Supplementation in the Atherosclerosis Prevention (ASAP) study data in 520 asymptomatic men and women. In a covariance analysis adjusting for common cardiovascular risk factors, low plasma levels of lycopene were associated with an 18% increase of IMT in men as compared with men in whom plasma levels were higher than median (P = 0.003 for difference). In women, the difference did not remain significant after the adjustments. On the basis of these works, it is evident that the circulating levels of lycopene play some role with regard to cardiovascular health in Finland, at least in men. We conclude that circulating levels of lycopene, a biomarker of tomato-rich food, may play a role in early stages of atherogenesis and may have clinical and public health relevance.						
Heart: IMT	Rissanen T	Serum lycopene concentrations and carotid atherosclerosis: the Kuopio Ischaemic Heart Disease Risk Factor	2003	BACKGROUND: Interest in lycopene is growing rapidly following the recent publication of epidemiologic studies in which high circulating lycopene concentrations were associated with reductions in cardiovascular disease. Lycopene is one of the major carotenoids	CS				(-) IMT	

		Study. Rissanen TH, Voutilainen S, Nyyssonen K, Salonen R, Kaplan GA, Salonen JT. Am J Clin Nutr. 2003 Jan;77(1):133-8.		in the Western diet and is probably one of the protective factors in a vegetable-rich diet. OBJECTIVE: We studied the hypothesis that the intima-media thickness of the common carotid artery (CCA-IMT) would be greater in men with low serum lycopene concentrations. DESIGN: We investigated the relation between serum lycopene concentration and CCA-IMT in 1028 middle-aged men (aged 46-64 y) in eastern Finland who were participants in the Kuopio Ischaemic Heart Disease Risk Factor study and who were examined in 1991-1993. The subjects were classified into quarters according to serum lycopene concentration. RESULTS: In a covariance analysis with adjustment for covariates, the men in the lowest quarter of serum lycopene concentration had a significantly higher mean CCA-IMT and maximal CCA-IMT (P = 0.005 and P = 0.001 for the difference, respectively) than did the other men. The mean and maximal CCA-IMT increased linearly across the quarters of serum lycopene concentration. CONCLUSIONS: A low serum lycopene concentration is associated with a higher CCA-IMT in middle-aged men from eastern Finland. This finding suggests that the serum lycopene concentration may play a role in the early stages of atherosclerosis. Increased thickness of the intima-media has been shown to predict coronary events; thus, lycopene intakes and serum concentrations may have clinical and public health relevance.						

Heart: IMT	Dwyer JH	Progression of carotid intima-media thickness and plasma antioxidants: the Los Angeles Atherosclerosis Study. Dwyer JH, Paul-Labrador MJ, Fan J, Shircore AM, Merz CN, Dwyer KM. Arterioscler Thromb Vasc Biol. 2004 Feb;24(2):313-9. Epub 2003 Dec 1.	2004	OBJECTIVE: Recent epidemiologic and animal model data suggest that oxygenated carotenoids are protective against early atherosclerosis. We assessed the association between atherosclerotic progression, measured by carotid intima-media thickness (IMT), and plasma levels of oxygenated and hydrocarbon carotenoids, tocopherols, retinol, and ascorbic acid. METHODS AND RESULTS: Participants were from an occupational cohort of 573 middle-aged women and men who were free of symptomatic cardiovascular disease at baseline. Ultrasound examination of the common carotid arteries, lipid level determination, and risk factor assessment were performed at baseline and 18-month follow-up. Plasma levels of antioxidants were determined at baseline only. Change in IMT was related to baseline plasma antioxidant levels in regression models controlling for covariates. In models adjusted for age, sex, and smoking status, 18-month change in IMT was significantly inversely related to the 3 measured oxygenated carotenoids (lutein, beta-cryptoxanthin, zeaxanthin; P<0.02 for all) and one hydrocarbon carotenoid, alpha-carotene (P=0.003). After adjusting for additional cardiac risk factors and potential confounders, including high-sensitivity C-reactive protein, these associations remained significant (P<0.05). CONCLUSIONS: These findings suggest that higher levels of plasma oxygenated carotenoids (lutein, zeaxanthin, beta-cryptoxanthin) and alpha-carotene may be protective against early atherosclerosis	PC				N	
Heart: IMT	Karppi J	Plasma carotenoids are	2011	Background. studies have suggested that high plasma concentrations of	CS				(-) IMT	

		related to intima - media thickness of the carotid artery wall in men from eastern Finland. Karppi J, Kurl S, Laukkanen JA, Rissanen TH, Kauhanen J. J Intern Med. 2011 Nov;270(5):478-85. doi: 10.1111/j.1365-2796.2011.02401.x. Epub 2011 Jun 8.		carotenoids may slow the development of early atherosclerosis, but results have been inconclusive. We examined the effect of carotenoids on early atherosclerosis in a Methods. population-based study. The association between plasma carotenoid concentrations and intima-media thickness of the common carotid artery (CCA-IMT) was years) in Eastern Finland. They investigated in 1212 elderly men (aged 61-80 were examined by B-mode ultrasound todetect early signs of carotid atherosclerosis, and plasma concentrations of carotenoids were measured by Men in the lowest quartile of high-performance liquid chromatography. Results. CCA-IMT had significantly higher concentrations of plasma β-cryptoxanthin, lycopene and a-carotene than men in the highest quartile(P for the differences: 0.043, 0.045 and 0.046, respectively), after adjustment for age, examination year, body mass index, smoking, alcohol intake, years of education, symptomatic coronary heart disease (CHD) or CHD history, diabetes, low-density lipoprotein cholesterol, medications and season. The concentrations of plasma β-cryptoxanthin, lycopene and a-carotene decreased linearly with increasing The results of this study suggest that high plasma CCA-IMT. Conclusions. concentrations of β-cryptoxanthin, lycopene and a-carotene may be associated with decreased carotid atherosclerosis in elderly men from eastern Finland.						

Heart: IMT, inflammation	Riccioni G	Plasma antioxidants and asymptomatic carotid atherosclerotic disease. Riccioni G, Bucciarelli T, D'Orazio N, Palumbo N, di Ilio E, Corradi F, Pennelli A, Bazzano LA. Ann Nutr Metab. 2008;53(2):86-90. Epub 2008 Oct 21. Compound (MeSH Keyword),.	2008	BACKGROUND: Atherosclerosis remains clinically mute for a long time and frequently manifests itself with an acute cardiovascular event. The possibility of detecting this disease in a subclinical phase and reducing or reversing its progression is an issue of relevance. Published studies on the association between antioxidant vitamins and carotenoids and carotid intima-media thickness (CIMT) have been inconclusive. METHODS: We enrolled 220 consecutive, asymptomatic participants. After carotid ultrasound investigation, a medical history was taken, a physical examination was performed and venous blood samples were collected. Venous blood samples were analyzed for concentrations of antioxidant vitamins and carotenoids. RESULTS: Low concentrations of vitamin A ($p < 0.01$), vitamin E ($p < 0.001$), lycopene ($p < 0.01$) and beta-carotene ($p < 0.001$) were significantly associated with carotid atherosclerosis (CIMT > or = 0.8 mm). In addition, marginally higher body mass index, plasma haemoglobin and high-density lipoprotein cholesterol were also associated with carotid atherosclerosis, while other laboratory parameters considered in this study (total cholesterol, low-density lipoprotein cholesterol, triglycerides and C-reactive protein) were not significantly associated with carotid atherosclerosis. CONCLUSIONS: Low plasma concentrations of antioxidant vitamins (A, E, beta-carotene) and lycopene were associated with early carotid atherosclerotic lesions as measured by CIMT. Regular intake of foods rich in lycopene and antioxidant vitamins may slow the progression of atherosclerosis.	CS				(-)/N (-) ↓ [lyco] = ↑ athero lesions (IMT) ~~~~~ N CRP Lipids	N CRP TG LDL TC

Heart: inflam & endothelial fxn	Rowley K	Inflammation and vascular endothelial activation in an Aboriginal population: relationships to coronary disease risk factors and nutritional markers. Rowley K, Walker KZ, Cohen J, Jenkins AJ, O'Neal D, Su Q, Best JD, O'Dea K. Med J Aust. 2003 May 19;178(10):495-500.	2003	OBJECTIVE: To describe the levels of inflammation and vascular endothelial activation in an Aboriginal community, and the relationship of these factors to coronary heart disease (CHD) risk factors and markers of nutritional quality. DESIGN AND PARTICIPANTS: A cross-sectional survey of 95 women and 76 men participating in a chronic-disease prevention program. SETTING: A remote Aboriginal community in Western Australia in 1996. MAIN OUTCOME MEASURES: Concentrations of markers of inflammation (C-reactive protein [CRP]) and vascular endothelial activation (soluble E-selectin [sE-selectin]); presence of metabolic syndrome; concentrations of diet-derived antioxidants. RESULTS: Participants exhibited very high plasma concentrations of CRP (mean, 5.4 mg/L; 95% CI, 4.6-6.3 mg/L) and sE-selectin (mean, 119 ng/mL; 95% CI, 111-128 ng/mL). Both CRP and sE-selectin concentrations were significantly higher in the presence of the metabolic syndrome. There were significant inverse linear relationships between concentrations of CRP and plasma concentrations of the antioxidants lycopene, beta-carotene, cryptoxanthin and retinol. Even stronger inverse associations were evident between concentrations of sE-selectin and lycopene, beta-carotene, cryptoxanthin and lutein. CONCLUSIONS: Vascular inflammation and endothelial activation may be important mediators of elevated CHD risk in Aboriginal people. Inadequate	CS				(-) CRP sE-selectin	

				nutrition and physical inactivity may contribute to this process.						
Heart: inflam & endothelial fxn	van Herpen-Broekmans WM	Serum carotenoids and vitamins in relation to markers of endothelial function and inflammation. Van Herpen-Broekmans WM, Klopping-Ketelaars IA, Bots ML, Kluft C, Princen H, Hendriks HF, Tijburg LB, van Poppel G, Kardinaal AF. Eur J Epidemiol. 2004;19(10):915-21.	2004	BACKGROUND: Endothelial cell dysfunction may be related to an increase in cellular oxidative stress. Carotenoids and vitamins could have an antioxidant-mediated tempering influence on endothelial function and inflammation, thereby reducing the risk of atherosclerosis. METHODS: We measured serum carotenoids, alpha-tocopherol and Vitamin C concentrations in 379 subjects sampled from the general population. High-sensitive C-reactive protein (CRP), fibrinogen (Fbg) and leukocytes were measured as markers of inflammation. Furthermore, soluble intercellular adhesion molecule-1 (sICAM-1) and flow-mediated vasodilation (FMD; n= 165) were measured as markers of endothelial function. Relationships between serum carotenoids and vitamins and markers of endothelial function and inflammation were analysed after adjustment for confounding. RESULTS: In the total study group, lutein and lycopene were inversely related to sICAM-1 with regression-coefficients of -0.38+/-0.19 (p = 0.04) and -0.16+/-0.08 (p = 0.04) per 1 micromol/l, respectively. beta-Carotene was inverse related to leukocytes (-0.23+/-0.07; p = 0.007) and CRP (-1.09+/-0.30; p = 0.0003) per 1 micromol/l. Vitamin C was inverse related to CRP (-0.01+/-0.005; p = 0.04) per 1 micromol/l, whereas alpha-tocopherol was positively related to CRP (0.03+/-0.01; p = 0.02) per 1 micro/l. Zeaxanthin was	CS				(-)/N	

				inversely related to FMD (31.2+/-15.3; p = 0.04) per 1 micromol/l. CONCLUSION: The inverse relations between carotenoids, Vitamin C and sICAM-1, CRP and leukocytes may help to explain the possible protective effect of carotenoids and Vitamin C on atherosclerosis through an influence on inflammatory processes and endothelial function.						
Heart: inflammation	Lidebjer C	Low plasma levels of oxygenated carotenoids in patients with coronary artery disease. Lidebjer C, Leanderson P, Ernerudh J, Jonasson L. Nutr Metab Cardiovasc Dis. 2007 Jul;17(6):448-56.	2007	BACKGROUND AND AIMS: Low circulating levels of carotenoids have been associated with cardiovascular disease. The distribution of different carotenoids in blood may have an impact on the cardioprotective capacity. The aim of the present study was to determine the plasma levels of 6 major carotenoids in patients with coronary artery disease (CAD) and relate the findings to clinical, metabolic and immune parameters. METHODS AND RESULTS: Plasma levels of oxygenated carotenoids (lutein, zeaxanthin, beta-cryptoxanthin) and hydrocarbon carotenoids (alpha-carotene, beta-carotene, lycopene) were determined in 39 patients with acute coronary syndrome, 50 patients with stable CAD and 50 controls. Serological assays for inflammatory activity and flow cytometrical analysis of lymphocyte subsets were performed. Both patient groups had significantly lower plasma levels of oxygenated carotenoids, in particular lutein+zeaxanthin, compared to controls. Low levels of oxygenated carotenoids were associated with smoking, high body mass index (BMI), low high density lipoprotein (HDL) cholesterol and, to a	CC				N	

				minor degree, inflammatory activity. Plasma levels of lutein+zeaxanthin were independently associated with the proportions of natural killer (NK) cells, but not with other lymphocytes, in blood. CONCLUSION: Among carotenoids, lutein+zeaxanthin and beta-cryptoxanthin were significantly reduced in CAD patients independent of clinical setting. The levels were correlated to a number of established cardiovascular risk factors. In addition, the relationship between NK cells and lutein+zeaxanthin may indicate a particular role for certain carotenoids in the immunological scenario of CAD.						
Heart: lipids and oxidation	Barona J	A Mediterranean-style low-glycemic-load diet increases plasma carotenoids and decreases LDL oxidation in women with metabolic syndrome. Barona J, Jones JJ, Kopec RE, Comperatore M, Andersen C, Schwartz SJ, Lerman RH, Fernandez ML. J Nutr Biochem. 2011 Jul 18. [Epub ahead of print]	2011	Thirty-five women with metabolic syndrome and high plasma low-density lipoprotein (LDL) cholesterol (≥100 mg/dl) participated in a dietary intervention consisting of a Mediterranean-style low-glycemic-load diet for 12 weeks. Participants were randomly allocated to consume diet only (n=15) or diet plus a medical food containing soy protein and plant sterols (n=20). Plasma concentrations of carotenoids, lipoprotein subfractions and oxidized LDL (OxLDL) were measured. Independent of treatment, women had a significant increase in plasma lutein (P<.0001) and β-carotene (P<.0001), while plasma lycopene was reduced (P<.05) after 12 weeks. Low-density lipoprotein cholesterol was reduced from 138±35 to 114±33 mg/dl (P<.0001). In addition, decreases were observed in the atherogenic subfractions: large very low-density lipoprotein (P<.05), small LDL (P<.00001) and medium high-density lipoprotein (P<.05). Oxidized LDL was significantly reduced by 12% in both groups (P<.01). Changes in OxLDL were	Interv				N	

				inversely correlated with plasma lutein (r=-.478, P<.0001). The data indicate that women complied with the dietary regimen by increasing fruits and vegetable intake. Decreased consumption of high-glycemic foods frequently co-consumed with lycopene-rich tomato sauce such as pasta and pizza may be responsible for the lowering of this carotenoid in plasma after 12 weeks. These results also suggest that plasma lutein concentrations may protect against oxidative stress by reducing the concentrations of OxLDL						
Heart: MI	Street DA	Serum antioxidants and myocardial infarction. Are low levels of carotenoids and alpha-tocopherol risk factors for myocardial infarction? Street DA, Comstock GW, Salkeld RM, Schüep W, Klag MJ. Circulation. 1994 Sep;90(3):1154-61.	1994	BACKGROUND: In vitro, animal and epidemiological studies suggest that lipoprotein oxidation may play an important role in atherosclerosis. Antioxidants may protect against lipoprotein oxidation and in that way inhibit atherosclerosis and its clinical sequelae. To investigate this possibility, we examined the association between levels of several antioxidants and myocardial infarction using serum specimens collected 7 to 14 years before the onset of myocardial infarction. METHODS AND RESULTS: A nested case-control design was used. Cases and control subjects were selected from the 25,802 persons who had donated 15 mL of blood in 1974 for a serum bank. Cases comprised 123 persons with a subsequent first diagnosis of myocardial infarction who ranged from 23 through 58 years of age in 1974 and who had had their first diagnosis of myocardial infarction during 1981 to 1988. Two groups of control subjects matched to the cases for sex and age were selected from donors to the serum bank, one from those with hospital admissions during the same period and the other from the total group	CC nested				N MI	

				of donors. Sera were assayed for four carotenoids (beta-carotene, lycopene, lutein, and zeaxanthin), alpha-tocopherol, and cholesterol. Because associations with these serum nutrients showed similar trends whether based on hospital or community controls, the two control groups were combined. There was a significantly increasing risk for subsequent myocardial infarction with decreasing levels of beta-carotene in 1974 (P value for trend, .02) and a suggestive trend with decreasing levels of lutein (P = .09). When the results were stratified by smoking status, the excess risk of myocardialinfarction associated with low serum levels of carotenoids was limited to smokers. A protective association with higher levels of alpha-tocopherol was suggested only among persons with high levels of serum cholesterol. CONCLUSIONS: Low serum levels of carotenoids were associated with an increased risk of subsequent myocardial infarction among smokers.						
Heart: MI	Kohlmeier L	Lycopene and myocardial infarction risk in the EURAMIC Study. Kohlmeier L, Kark JD, Gomez-Gracia E, Martin BC, Steck SE, Kardinaal AF, Ringstad J, Thamm M, Masaev V, Riemersma R, Martin-Moreno JM, Huttunen JK, Kok FJ.	1997	A multicenter case-control study was conducted to evaluate the relations between antioxidant status assessed by biomarkers and acute myocardial infarction. Incidence cases and frequency matched controls were recruited from 10 European countries to maximize the variance in exposure within the study. Adipose tissue needle aspiration biopsies were taken shortly after the infarction and analyzed for levels of carotenoids and tocopherols. An examination of colinearity including all covariates and the three carotenoids, alpha-carotene, beta-carotene, and lycopene, showed that the variables were sufficiently independent to model	CC				(-) MI and Adipose tissue lyco	Adipose tissue biopsy

		Am J Epidemiol. 1997 Oct 15;146(8):618-26.		simultaneously. When examined singularly, each of the carotenoids appeared to be protective. Upon simultaneous analyses of the carotenoids, however, using conditional logistic regression models that controlled for age, body mass index, socioeconomic status, smoking, hypertension, and maternal and paternal history of disease, lycopene remained independently protective, with an odds ratio of 0.52 for the contrast of the 10th and 90th percentiles (95% confidence interval 0.33-0.82, p = 0.005). The associations for alpha- and beta-carotene were largely eliminated. We conclude that lycopene, or some substance highly correlated which is in a common food source, may contribute to the protective effect of vegetable consumption on myocardial infarction risk.						
Heart: MI	Ruiz Rejón F	Plasma status of retinol, alpha- and gamma-tocopherols, and main carotenoids to first myocardial infarction: case control and follow-up study. Ruiz Rejón F, Martín-Peña G, Granado F, Ruiz-Galiana J, Blanco I, Olmedilla B. Nutrition. 2002 Jan;18(1):26-31.	2002	OBJECTIVE: Epidemiologic studies have suggested that dietary intake and plasma concentrations of antioxidants have an inverse relation with coronary heart disease. To test whether fat-soluble antioxidants can play a role against the occurrence of myocardial infarction (MI), we measured plasma levels of retinol, tocopherols, and individual carotenoids in MI patients. METHODS: A case-control and follow-up study of patients in the Móstoles area (Madrid, Spain). One hundred six patients (62 after 1 y) and 104 control subjects participated in the study. Blood samples were collected after overnight fast or during the first 24 h of MI onset for biochemical profiles of retinol, alpha- and gamma-tocopherols, and carotenoid by means of a quality-	CC				N MI	

				controlled high-performance liquid chromatography. RESULTS: During the acute phase after MI onset, plasma levels of retinol, gamma-tocopherol, and xanthophylls (lutein/zeaxanthin and beta-cryptoxanthin) decreased, whereas alpha-tocopherol, alpha-carotene, beta-carotene, and lycopene showed levels similar to those of control subjects. Logistic regression analysis showed low concentrations of gamma-tocopherol (and retinol) in plasma as the only statistically significant factor associated with MI, after adjusting for traditional risk factors. However, 1 y later, the MI patients showed a general improvement in plasma lipids and fat-soluble antioxidant status, and none of the analytes was associated with MI. CONCLUSIONS: The decreased plasma status of retinol, gamma-tocopherol, and xanthophylls during the acute phase of MI normalized the year after the MI event, suggesting that most subjects had followed an overall healthier lifestyle and dietary pattern. The results also raise concerns on the usefulness of these plasma compounds as specific, relevant, and predictive markers in relation to coronary heart disease						
Heart: MI	Hak AE	Plasma carotenoids and tocopherols and risk of myocardial infarction in a low-risk population of US male physicians. Hak AE, Stampfer	2003	BACKGROUND: Increased intake of carotenoids and vitamin E may protect against myocardial infarction (MI). However, prospective data on blood levels of carotenoids other than beta-carotene and vitamin E (tocopherol) and risk of MI are sparse. METHODS AND RESULTS: We conducted a prospective, nested case-control analysis	CC nested				N MI	

		MJ, Campos H, Sesso HD, Gaziano JM, Willett W, Ma J. Circulation. 2003 Aug 19;108(7):802-7. Epub 2003 Aug 4.		among male physicians without prior history of cardiovascular disease who were followed for up to 13 years in the Physicians' Health Study. Samples from 531 physicians diagnosed with MI were analyzed together with samples from paired control subjects, matched for age and smoking, for 5 major carotenoids (alpha- and beta-carotene, beta-cryptoxanthin, lutein, and lycopene), retinol, and alpha- and gamma-tocopherol. Overall, we found no evidence for a protective effect against MI for higher baseline plasma levels of retinol or any of the carotenoids measured. Among current and former smokers but not among never-smokers, higher baseline plasma levels of beta-carotene tended to be associated with lower risk (P for interaction=0.02). Men with higher plasma levels of gamma-tocopherol tended to have an increased risk of MI (P for trend=0.01). CONCLUSIONS: These prospective data do not support an overall protective relation between plasma carotenoids or tocopherols and future MI risk among men without a history of prior cardiovascular disease.						
Heart: mortality	Shardell MD	Low-serum carotenoid concentrations and carotenoid interactions predict mortality in US adults: the Third National Health and Nutrition Examination Survey. Shardell MD, Alley DE, Hicks GE, El-	2011	Evidence regarding the health benefits of carotenoids is controversial. Effects of serum carotenoids and their interactions on mortality have not been examined in a representative sample of US adults. The objective was to examine whether serum carotenoid concentrations predict mortality among US adults. The study consisted of adults aged ≥20 years enrolled in the Third National Health and Nutrition Examination Survey, 1988 to 1994, with measured serum carotenoids and mortality follow-up through 2006 (N = 13,293). Outcomes were all-cause,	CS				(-) All causes of mortality ~~~~~ N CVD	

		Kamary SS, Miller RR, Semba RD, Ferrucci L. Nutr Res. 2011 Mar;31(3):178-89		cardiovascular disease, and cancer mortality. In adjusted Cox proportional hazards models, participants in the lowest total carotenoid quartile (<1.01 μmol/L) had significantly higher all-cause mortality (mortality rate ratio, 1.38; 95% confidence interval, 1.15-1.65; P = .005) than those in the highest total carotenoid quartile (>1.75 μmol/L). For a-carotene, the highest quartile (>0.11 μmol/L) had the lowest all-cause mortality rates (P < .001). For lycopene, the middle 2 quartiles (0.29-0.58 μmol/L) had the lowest all-cause mortality rates (P = .047). Analyses with continuous carotenoids confirmed associations of serum total carotenoids,a-carotene, and lycopene with all-cause mortality (P < .001). In a random survival forest analysis, very low lycopene was the carotenoid most strongly predictive of all-cause mortality, followed by very low total carotenoids. a-Carotene/β-cryptoxanthin, a-carotene/lutein+zeaxanthin and lycopene/lutein+zeaxanthin interactions were significantly related to all-cause mortality (P < .05). Low a-carotene was the only carotenoid associated with cardiovascular disease mortality (P = .002). No carotenoids were significantly associated with cancer mortality. Very low serum total carotenoid, a-carotene, and lycopene concentrations may be risk factors for mortality, but carotenoids show interaction effects on mortality. Interventions of balanced carotenoid combinations are needed for confirmation.						
Heart: oxidation	Rao AV	Effect of diet and smoking on serum lycopene and lipid peroxidation. Rao AV, Agarwal S.	1998	Lycopene, a naturally present carotenoid in tomatoes and other fruits, has been proposed to have antioxidant and potential anticarcinogenic properties in recent studies. This study was conducted to investigate the effect of diet and smoking on serum lycopene and lipid	Interv				(-)	smokers vs non-smokers

		Nutr Res, 1998;18:713–21.		peroxidation expressed as thiobarbituric acid reactive substances (TBARS) in 20 healthy human subjects. A reduction of 50% in the serum lycopene levels and an increase of 25% in TBARS was observed when subjects were maintained on a lycopene-free diet. Serum lycopene levels were also reduced by 25% following a meal compared to the fasting levels. Serum lycopene levels of habitual smokers were compared with non-smokers. Although the levels were not significantly different between the two groups, serum lycopene levels fell by 40% with a 40% increase in TBARS in smokers following smoking three cigarette. This study showed that the levels of serum lycopene were influenced significantly as a result of oxidative stress in the form of diet induced metabolism and smoking, suggesting in vivo antioxidant properties of lycopene.						
Heart: oxidation	Sesso HD	Plasma lycopene, other carotenoids, and retinol and the risk of cardiovascular disease in women. Sesso HD, Buring JE, Norkus EP, Gaziano JM. Am J Clin Nutr. 2004 Jan;79(1):47-53.	2004	BACKGROUND: Growing evidence suggests that lycopene has significant in vitro antioxidant potential. Lycopene has rarely been tested in prospective studies for its role in cardiovascular disease (CVD) prevention. OBJECTIVE: We examined the association between plasma lycopene and the risk of CVD in middle-aged and elderly women. DESIGN: A prospective, nested, case-control study was conducted in 39 876 women initially free of CVD and cancer in the Women's Health Study. Baseline blood samples were collected from 28 345 (71%) of the women. During a mean of 4.8 y of f ollow-up, we identified 483 CVD cases and 483 control subjects matched by age, smoking status, and follow-up time. Plasma lycopene, other carotenoids, retinol, and total cholesterol were measured. RESULTS: In analyses	CC nested				(-)W	Ox

				matched for age and smoking, with adjustment for plasma cholesterol, the relative risks (RRs) and 95% CIs of CVD in increasing quartiles of plasma lycopene were 1.00 (referent), 0.78 (95% CI: 0.55, 1.11), 0.56 (0.39, 0.82), and 0.62 (0.43, 0.90). In multivariate models, the RRs were 1.00 (referent), 0.94 (0.60, 1.49), 0.62 (0.39, 1.00), and 0.67 (0.41, 1.11); those in the upper compared with the lower half of plasma lycopene had an RR of 0.66 (0.47, 0.95). For CVD, exclusive of angina, women in the upper 3 quartiles had a significant multivariate 50% risk reduction compared with those in the lowest quartile. The stepwise addition of individual plasma carotenoids did not affect the RRs. CONCLUSIONS: Higher plasma lycopene concentrations are associated with a lower risk of CVD in women. These findings require confirmation in other cohorts, and the determinants of plasma lycopene concentrations need to be better understood.						
Heart: oxidation	Sesso HD	Plasma lycopene, other carotenoids, and retinol and the risk of cardiovascular disease in men. Sesso HD, Buring JE, Norkus EP, Gaziano JM. Am J Clin Nutr. 2005 May;81(5):990-7.	2005	BACKGROUND: Emerging evidence suggests a possible role of lycopene in the primary prevention of cardiovascular disease (CVD). OBJECTIVE: We examined whether plasma lycopene concentrations in the Physicians' Health Study were associated with CVD in a prospective, nested, case-control design. DESIGN: Baseline blood samples were collected starting in 1996. During a mean follow-up of 2.1 y, we identified 499 cases of CVD (confirmed myocardial infarction, stroke, CVD death, or revascularization procedures) and an equal number of men free of CVD and matched for age (x: 69.7 y), follow-up	CC nested				NM	Ox

				time, and smoking status. We collected self-reported coronary disease risk factors and measured plasma carotenoids, retinol, lipids, and C-reactive protein. RESULTS: In matched analyses with additional adjustment for plasma total cholesterol and randomized treatment, the relative risks (RRs) of CVD for men in the lowest to highest quartiles of plasma lycopene were 1.00 (reference), 0.92, 1.04, and 0.95 (P for linear trend = 0.93). With multivariate adjustment, the RRs of total CVD were 1.00 (reference), 1.08, 0.94, and 1.03 (P for linear trend = 0.98). For important vascular events (241 cases), excluding revascularization procedures, the multivariate RRs remained nonsignificant (P for linear trend = 0.50). Adding plasma carotenoids, lipids, or C-reactive protein to multivariate models had a minimal effect on the RRs of total CVD for plasma lycopene. Compared with lycopene, higher concentrations of plasma lutein/zeaxanthin and retinol suggested a moderate increase in CVD risk, whereas no association was found for beta-cryptoxanthin, alpha-carotene, and beta-carotene. CONCLUSIONS: Higher plasma lycopene concentrations were not associated with the risk of CVD in this study of older men. Further evaluation in diverse populations is necessary.						
Heart: oxidation	Paterson E	Supplementation with fruit and vegetable soups and beverages increases plasma carotenoid concentrations but does not alter markers of	2006	This study was aimed at determining whether an increase of 5 portions of fruits and vegetables in the form of soups and beverages has a beneficial effect on markers of oxidative stress and cardiovascular disease risk factors. The study was a single blind, randomized, controlled, crossover dietary intervention study. After a 2-wk run-in period with fish	RCT				N	

		oxidative stress or cardiovascular risk factors. Paterson E, Gordon MH, Niwat C, George TW, Parr L, Waroonphan S, Lovegrove JA. J Nutr. 2006 Nov;136(11):2849-55.		oil supplementation, which continued throughout the dietary intervention to increase oxidative stress, the volunteers consumed carotenoid-rich or control vegetable soups and beverages for 4 wk. After a 10-wk wash-out period, the volunteers repeated the above protocol, consuming the other intervention foods. Both test and control interventions significantly increased the % energy from carbohydrates and decreased dietary protein and vitamin B-12 intakes. Compared with the control treatment, consumption of the carotenoid-rich soups and beverages increased dietary carotenoids, vitamin C, alpha-tocopherol, potassium, and folate, and the plasma concentrations of alpha-carotene (362%), beta-carotene (250%) and lycopene (31%) ($P < 0.01$) and decreased the plasma homocysteine concentration by 8.8% ($P < 0.01$). The reduction in plasma homocysteine correlated weakly with the increase in dietary folate during the test intervention ($r = -0.35$, $P = 0.04$). The plasma antioxidant status and markers of oxidative stress were not affected by treatment. Consumption of fruit and vegetable soups and beverages makes a useful contribution to meeting dietary recommendations for fruit and vegetable consumption.						
Heart: oxidation	Shin MJ	Plasma levels of leptin are associated with the plasma levels of LDL conjugated dienes in children. Shin MJ, Park E. Ann Nutr Metab. 2007;51(1):1-6. Epub 2007 Jan 24.	2007	BACKGROUND: Plasma leptin has been suggested to be involved in the proatherogenic process by increasing oxidative stress. We investigated the relationship between leptin and plasma conjugated diene formation, a measure of LDL oxidation in vivo in schoolchildren. METHODS: We measured blood lipid profiles, plasma antioxidant vitamins, leptin and diene conjugation in LDL of	CS				(-) ↑ LDLox (CD assay) with ↓ plasma [lyco] inverse relationship in OB children	

				118 Korean children (35 overweight-obese vs. 83 normal weight children). RESULTS: The overweight-obese children showed significantly higher levels of leptin ($p < 0.0001$), conjugated dienes ($p = 0.02$), total cholesterol ($p < 0.05$), triglyceride ($p < 0.005$) and LDL cholesterol ($p < 0.01$) and a significantly lower level of plasma lycopene ($p < 0.0001$) compared with the normal weight children. When all the subjects were classified into the three groups by tertiles of leptin levels, significant differences in circulating conjugated dienes ($p < 0.05$), lipid-corrected lycopene ($p < 0.05$), total cholesterol ($p < 0.05$), triglyceride ($p < 0.05$) and LDL cholesterol ($p < 0.05$) were found among the three groups. CONCLUSION: Our results showed that leptin was positively associated with the LDL conjugated diene formation, which might be related to the proatherogenic process in schoolchildren.						
Heart: oxidation	Watters JL	Associations of antioxidant nutrients and oxidative DNA damage in healthy African-American and White adults. Watters JL, Satia JA, Kupper LL, Swenberg JA, Schroeder JC, Switzer BR. Cancer Epidemiol Biomarkers Prev. 2007 Jul;16(7):1428-36.	2007	High antioxidant intake has been shown to reduce cancer risk and may also mitigate the effects of oxidative DNA damage, which is hypothesized to be causally linked to carcinogenesis. This study examined potential racial differences in (a) dietary intakes and plasma concentrations of vitamin C, vitamin E, and carotenoids and oxidative DNA damage and (b) associations between plasma antioxidants and oxidative DNA damage. Data were from a cross-sectional study of 164 generally healthy nonsmoking African-Americans and Whites in North Carolina, ages 20 to 45 years, equally distributed by race and sex. Participants completed a demographic and health questionnaire, four 24-h dietary recalls, and a dietary	CS				(-) ↓ oxDNA damage	

				supplement inventory; had height and weight measured; and provided a semifasting blood sample. African-Americans had statistically significantly lower plasma concentrations of vitamin E, alpha-carotene, beta-carotene, and lutein + zeaxanthin than Whites, as well as lower self-reported intake of most antioxidants. Levels of oxidative DNA damage, measured using the alkaline comet assay, were lower in African-Americans than Whites. An inverse association between lycopene and oxidative DNA damage (r = -0.20; P = 0.03) was found in the combined study population after adjusting for sex, age, body mass index, passive smoke exposure, physical activity, education, income, and alcohol intake. There was also a positive association of vitamin E with oxidative DNA damage in the total population (r = 0.21; P = 0.02) and in African-American men (r = 0.63; P = 0.01) after adjusting for covariates. This study is among the first to examine these associations in a sample of healthy adults with an adequate representation of African-Americans.						
Heart: oxidation	Martínez-Tomás R	Effect of the consumption of a fruit and vegetable soup with high in vitro carotenoid bioaccessibility on serum carotenoid concentrations and markers of oxidative stress in young men. Martínez-Tomás R, Larqué E, González-Silvera D, Sánchez-Campillo M,	2011	AIM: To evaluate the effect of the daily intake of a fruit & vegetable soup with high in vitro bioaccessibility of carotenoids on β-carotene and lycopene serum concentrations. METHODS: Fourteen healthy young men (24 ± 1 years) received 300 mL/day of a carrot, tomato, and broccoli soup, containing 3.9 mg β-carotene and 4 mg lycopene, for 4 weeks followed by a 4-week washout period. The serum carotenoid response and oxidative markers were analyzed after 3 and	Interv				(-) on 1 marker of ocidative strerss, but not specific to lycopene	

		Burgos MI, Wellner A, Parra S, Bialek L, Alminger M, Pérez-Llamas F. Eur J Nutr. 2011 Jun 7. [Epub ahead of print]		4 weeks of soup consumption and after a 4-week washout. RESULTS: The in vitro bioaccessibility of β-carotene and lycopene was 55 and 43%, respectively, in the soup. Serum β-carotene concentrations were significantly higher than baseline (0.33 ± 0.05 μmol/L) after 3 weeks (0.69 ± 0.06 μmol/L) and 4 weeks (0.78 ± 0.10 μmol/L) of soup consumption ($P < 0.001$). Serum lycopene was also significantly higher compared with baseline levels (0.26 ± 0.08-0.56 ± 0.04 μmol/L and 0.60 ± 0.04 μmol/L, after 3 and 4 weeks, respectively) ($P < 0.001$). Although the highest concentration of both carotenoids was found after 4 weeks, the levels were not statistically different from the levels at 3 weeks. A 4-week washout significantly decreased serum carotenoid concentrations, although only β-carotene returned to baseline. Glutathione peroxidase (GPx) increased significantly after soup supplementation compared with baseline, while superoxide dismutase was significantly lower only after 3 weeks. Glutathione reductase, lipid, protein, and DNA oxidative markers remained unchanged. CONCLUSIONS: The soup contributed to increasing the concentration of each carotenoid by more than 100% after 3 and 4 weeks of consumption, the maximum increase being observed after 4 weeks. Oxidative markers did not show any variation except for GPx. Serum lycopene half-life was longer than that of β-carotene, which may be important for studies evaluating both carotenoids.						

Heart: oxidation, inflammation	Wang L	Associations of plasma carotenoids with risk factors and biomarkers related to cardiovascular disease in middle-aged and older women. Wang L, Gaziano JM, Norkus EP, Buring JE, Sesso HD. Am J Clin Nutr. 2008 Sep;88(3):747-54.	2008	BACKGROUND: Cardiovascular disease (CVD) risk factors may potentially influence plasma concentrations of carotenoids. However, data on the association of plasma carotenoids with CVD related biomarkers are only limited. OBJECTIVE: We examined the cross-sectional association of plasma carotenoids with blood lipids, glycated hemoglobin (Hb A(1c)), and C-reactive protein (CRP) in middle-aged and older women initially free of CVD and cancer. DESIGN: Participants from 3 nested case-control studies in the Women's Health Study were pooled. Baseline plasma carotenoids, including alpha-carotene, beta-carotene, beta-cryptoxanthin, lycopene, and lutein-zeaxanthin, blood lipids, Hb A(1c), and CRP were available for 2895 women. RESULTS: Women who were current smokers or obese had lower plasma concentrations of most carotenoids expect for lycopene. After adjusting for age, race, lifestyle factors, clinical factors, plasma total cholesterol, and dietary carotenoids, an increase of 30 mg/dL in LDL cholesterol was associated with a 17% increase in alpha-carotene, a 16% increase in beta-carotene, and an 8.5% increase in lycopene; an increase of 10 mg/dL in HDL cholesterol was associated with a 5.3% decrease in lycopene; an increase of 0.3% in Hb A(1c) was associated with a 1.4% increase in lycopene; and an increase of 2 mg/L in CRP was associated with a 1.3% decrease in beta-carotene (all P < 0.01). CONCLUSIONS: In middle-aged and older women free of CVD and cancer, plasma carotenoids were associated with	CS				(+) ↑ lyco:↑ LDL ↑ HbA(1c):↑ lyco ↓ HDL:↓lyco ~~~~~ N lyco:BW and CRP	HDL Hb A(1c)

				smoking, obesity, LDL cholesterol, HDL cholesterol, Hb A(1c), and CRP. The associations differ among individual carotenoids, possibly reflecting metabolic effects of lifestyle and physiologic factors on plasma carotenoids, and may partially explain the inverse association of plasma carotenoids with CVD outcomes observed in epidemiologic studies.						
Heart: oxidation, inflammation, endothelial	Hozawa A	Relationships of circulating carotenoid concentrations with several markers of inflammation, oxidative stress, and endothelial dysfunction: the Coronary Artery Risk Development in Young Adults (CARDIA)/Young Adult Longitudinal Trends in Antioxidants (YALTA) study. Hozawa A, Jacobs DR Jr, Steffes MW, Gross MD, Steffen LM, Lee DH. Clin Chem. 2007 Mar;53(3):447-55. Epub 2007 Jan 18.	2007	BACKGROUND: Serum carotenoid concentrations relate inversely to cardiovascular disease incidence. To clarify the effect of carotenoids on atherosclerotic risk factors, we examined the association of circulating carotenoids with inflammation, oxidative stress, endothelial dysfunction, and smoking. METHODS: Black and white men and women in the Coronary Artery Risk Development in Young Adults study, ages 18 to 30 years at recruitment (1985-1986) from 4 US cities, were investigated over 15 years. We included 2048 to 4580 participants in analyses of the sum of serum alpha-carotene, beta-carotene, zeaxanthin/lutein, and beta-cryptoxanthin concentrations and of lycopene at year 0 and at year 7. RESULTS: The year 0 sum of 4 carotenoids was inversely associated (all P <0.05) with year 0 leukocyte count (slope per sum carotenoid SD, -0.17); year 7 fibrinogen (slope, -0.10); year 7 and year 15 C-reactive protein (slope, -0.12 and -0.09); and year 15 F(2)-isoprostanes (slope, -13.0), soluble P-selectin (slope, -0.48), and soluble intercellular adhesion molecule-1 (sICAM1; slope, -5.1). Leukocyte counts and sICAM1 and F(2)-isoprostane concentrations had stronger associations in smokers than in nonsmokers, and	PC				(-)/N	N CRP P-selectin isoPros ~~~~ (-) ICAM

				sICAM1 concentrations were higher in the highest carotenoid quartile in smokers than in the lowest carotenoid quartile in nonsmokers. Superoxide dismutase was positively associated with the sum of 4 carotenoids (slope, 0.12; P <0.01). Lycopene was inversely associated only with sICAM1. The year 7 carotenoid associations with these markers were mostly similar to those at year 0. CONCLUSIONS: Circulating serum carotenoids were associated, some interactively with smoking, in apparently beneficial directions with markers of inflammation, oxidative stress, and endothelial dysfunction.						
Heart: oxidation, inflammation, endothelial	Kim OY	Independent inverse relationship between serum lycopene concentration and arterial stiffness. Kim OY, Yoe HY, Kim HJ, Park JY, Kim JY, Lee SH, Lee JH, Lee KP, Jang Y, Lee JH Atherosclerosis. 2009 Aug 13. [Epub ahead of print]	2009	OBJECTIVE: Emerging evidence suggests a role of lycopene in the primary prevention of cardiovascular disease. This study aimed to investigate the association of serum lycopene concentration with brachial-ankle pulse wave velocity (baPWV), a marker of arterial stiffness and markers of oxidative stress and inflammation. METHODS: healthy women (n=264, 31-75 yrs) were classified into tertiles according to serum lycopene concentration. Multivariate linear regression analyses were used to assess the relationship between serum lycopene and baPWV. RESULTS: Subjects in middle tertile (T2) and upper tertile (T3) had lower baPWV (1263+/-23 and 1265+/-14cm/s vs. 1338+/-21cm/s; p=0.009) and lower oxidized LDL (oxLDL) (53+/-3 and 55+/-3U/L vs. 66+/-3U/L; p<0.001) than those in lowertile (T1). Subjects in T3 showed higher LDL particle size (24.3+/-0.08nm vs. 24.0+/-	CS				(-)	CRP baPWV size LDL LDLox

				0.07nm, p=0.005) and lower C-reactive protein (hs-CRP) (0.80+/-0.25mg/dL vs. 1.27+/-0.24mg/dL, p=0.015), compared with those in T1. Logistic regression analysis showed that baPWV decreased with the increment of lycopene concentration; log baPWV decreased by 0.21cm/s (95% CI -0.168;-0.045, p=0.001) per unit change in lycopene. After adjustment for age, BMI, smoking, drinking, menopause and blood pressure, the estimated effect was attenuated by 35%, but remained statistically significant [-0.13cm/s (95% CI -0.112;-0.018, p=0.006)]. Further adjustment for beta-carotene, alpha-tocopherol, oxLDL, LDL particle size, and hs-CRP increased the strength of the association [beta=-0.221 (95% CI -0.215;-0.012, p=0.029)]. CONCLUSION: This study supports the presence of an independent inverse relationship between circulating lycopene and baPWV. Additionally, reduced oxidative modification of LDL may be one of mediators on the mechanisms how lycopene reduces arterial stiffness.						
Heart: stroke	Ito Y	Cardiovascular disease mortality and serum carotenoid levels: a Japanese population-based follow-up study. Ito Y, Kurata M, Suzuki K, Hamajima N, Hishida H, Aoki K. J Epidemiol. 2006 Jul;16(4):154-60.	2006	BACKGROUND: Some observational epidemiologic studies suggest that dietary and serum carotenoids are associated with reduced cardiovascular disease mortality. METHODS: Three thousand and sixty-one subjects (1,190 males and 1,871 females), aged 39 to 80 years, were recruited from residents of Hokkaido, Japan who had attended comprehensive health check-up programs from 1988 through 1995. Serum levels of alpha-carotene, beta-carotene, and lycopene were separately determined by high-performance liquid	PC				(-)/N CVD (-) stoke N	mortality stroke and heart dis

				chromatography. Serum levels of total carotene consisted of the sum of alpha-carotene, beta-carotene, and lycopene levels. Each serum level of alpha-carotene, beta-carotene, lycopene, total carotene, triglyceride, and alanine transaminase (ALT) activity was transformed logarithmically. The hazard ratios of serum alpha- and beta-carotenes, lycopene, and total carotene values were estimated by the Cox proportional hazard model after adjusting for sex, age, and other potential confounding factors. RESULTS: During the 11.9-year follow-up period, 80 deaths (49 males and 31 females) from cardiovascular disease, 40 deaths from heart disease, and 37 deaths from stroke were identified among the cohort subjects. High serum values of carotenoids such as alpha- and beta-carotenes, and lycopene were found to be significantly associated with low hazard ratios for cardiovascular disease mortality. However, a significant inverse association between high serum lycopene value and the risk for stroke mortality was not always observed. CONCLUSIONS: High serum levels of total carotene, comprising alpha- and beta-carotenes and lycopene, may reduce the risk for cardiovascular disease mortality among the Japanese population.						