REVIEW

Impact of C-Reactive Protein on Disease Risk and Its Relation to Dietary Factors: Literature Review

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Abstract

C-reactive protein (CRP) is one of the acute-phase proteins in inflammation and CRP serum concentrations are therefore of interest. Data for high-sensitivity CRP (hs-CRP) with a low detection limit of approximately 0.04 mg/L have become available over the past decade and research has shown a link between high concentrations of hs-CRP and obesity as well as smoking. Expanded adipose tissue is in fact known to secrete proinflammatory cytokines which enhance hepatic synthesis of CRP. Moderate alcohol consumption and high physical activity have been associated with low levels of hs-CRP, but the evidence in these cases is not conclusive. It has been suggested that hs-CRP is an independent marker of the risk of cardiovascular disease, but the predictive capacity remains controversial. However, many prospective studies have observed increased risk of type 2 diabetes mellitus associated with high concentrations of hs-CRP, independent of obesity and other cardiovascular risk factors. On the other hand, no measurable increase in the risk associated with high levels of hs-CRP was observed with multivariate adjustment in several studies. A number of authors have reported that high concentrations of hs-CRP are associated with increased risks of colorectal and other cancers, but the findings again are inconsistent. Diet and hs-CRP are also of increasing research interest. High intakes of carotenoids and vitamin C, but not of vitamin E, seem to decrease the level of circulating hs-CRP. In addition, high consumption of vegetables and fruit are associated with lower levels of circulating hs-CRP, perhaps by exerting anti-inflammatory effects. Both mechanistic and epidemiologic studies regarding dietary factors and low-grade inflammation are necessary to add to our knowledge of dietary influence on chronic disease development.

Key Words: C-reactive protein - disease risk - diet

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Introduction

Inflammation has recently been implicated in the etiology of atherosclerosis, type 2 diabetes mellitus (DM), and cancer. Inflammation is a normal response to infection and tissue injury, but it may be pathological if the response is excessive or continuous. C-reactive protein (CRP) is one of the acute-phase proteins. CRP was discovered as a substance in the sera of patients with pneumococcal pneumonia which reacted with polysaccharide C of *Streptococcus pneumonia* (Tillett and Francis, 1930). The circulating CRP is synthesized and secreted predominantly by hepatocytes in response to proinflammatory cytokines such as tumor necrosis factor α (TNF-α), interleukin-1 (IL-1), and interleukin-6 (IL-6) (Ablij and Meinders, 2002; Pepys and Hirschfield, 2003). IL-6 enhances the *de novo* synthesis of CRP by up-regulating CRP mRNA transcription, and IL-1β also synergistically regulates the CRP synthesis by enhancing translation. The function of CRP is reviewed extensively elsewhere (Kolb-Bachofen, 1991; Ablij and Meinders, 2002; Pepys and Hirschfield, 2003). CRP binds to endogenous and exogenous ligands such as constituents of microbes, native and modified lipoproteins, necrotic cells, and apoptotic cells. CRP bound to these ligands activates the classical complement pathway, and enhances oposonization and phagocytosis microorganisms and necrotic cells. CRP or homologous proteins have been characterized in diverse species of vertebrae and even in the phylogenetically distant arachnid, *Limulus polyphemus*, horseshoe crab, and the major function is considered to be linked to innate immunity.

Circulating CRP is present in only trace amounts in healthy individuals, and is hardly detectable by the standard clinical tests, which typically have a lower detection limit of 3–8 mg/L (Ridker, 2001). CRP concentrations of recent research interest are in the so-called normal range which can be measured only by the high-sensitivity testing. The lower detection limit for high-sensitivity CRP (hs-CRP) is as low as approximately 0.04 mg/L (Jaye and Waites, 1997). In a study of healthy blood donors (Shine et al., 1981), the median of hs-CRP levels was 0.8 mg/L with a range of 0.07–29 mg/L. Serum amyloid A protein and fibrinogen are acute-phase reactants which also show a temporal profile similar to the change of CRP in acute inflammation. The reasons for the wide use of hs-CRP are stability and availability of robust, automated methods for its measurement (Pearson et al.,

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2003). The intra-assay coefficient of correlation is generally < 10% in the range of 0.3–10 mg/L (Pearson et al., 2003). CRP concentrations show little or no diurnal or seasonal variation (Meier-Ewert et al., 2001; Ockene et al., 2001). Pairwise blood samples drawn from 379 subjects with an mean interval of 12 years showed a correlation coefficient of 0.59 in one study (Danesh et al., 2004). Values of hs-CRP greater than 10 mg/L are probably indicative of subclinical infection or inflammation (Pearson et al., 2003). In this paper, we review current knowledge regarding the relation of hs-CRP to risks of coronary heart disease, type 2 DM, and cancer and also discuss the role of dietary factors as determinants of circulating hs-CRP.

Behavioral Correlates of Circulating hs-CRP

Many studies have shown a strong, positive association between obesity and hs-CRP (Visser et al., 1999; Timpson et al., 2005), and weight loss results in decrease in hs-CRP concentrations (Dietrich and Jialal, 2005; Selvin et al., 2007). A causal link between obesity and CRP is also supported by recent laboratory evidence. Adipocytes and monocyte-derived macrophages in expanded adipose tissue mass secrete proinflammatory cytokines such as TNF-α and IL-6, and thereby enhancing hepatic synthesis of CRP (review: Eckel et al., 2005). Elevation of hs-CRP is also noted in the presence of the metabolic syndrome, a constellation of metabolic abnormalities such as glucose intolerance, hypertriglyceridemia, and hypertension which increases the risk of cardiovascular disease as well as of type 2 DM, with central obesity as a core component (Eckel et al., 2005). CRP levels have been shown to be progressively increased with increase in the number of abnormal metabolic features in different populations (Frohlich et al., 2000; Ridker et al., 2003; Choi et al., 2006).

Smoking is related to increased levels of hs-CRP (Bazzano et al., 2003). This positive association may be a reflection of underlying atherosclerotic lesions or due to systemic or non-vascular local inflammation. It has been shown that circulating hs-CRP is lower in both men and women with moderate alcohol consumption. In a cross-sectional study (Albert et al., 2003), CRP concentrations were lower with increasing levels of alcohol consumption with no further decrease at the highest levels of intake. Exceptionally, alcohol drinking was positively correlated with CRP levels in a cross-sectional study in Russia (Averina et al., 2006). It is notable that alcohol consumption is derived mainly from binge vodka intake in this study population. The investigators in the Russian study also noted that ex-drinkers had higher concentrations of CRP than lifelong non-drinkers of alcohol (Averina et al., 2006). No difference in serum hs-CRP was noted between lifelong non-drinkers and ex-drinkers in another study, however (Volpato et al., 2004).

Albert et al. (2003) noted that decrease in hs-CRP levels associated with moderate alcohol intake was not observed in women receiving hormone replacement therapy (HRT). Women on HRT show higher hs-CRP levels than women not on HRT (Pradhan et al., 2002; Albert et al., 2003; Lakoski et al., 2006), but there is no increase in TNF-α and IL-6 associated with HRT (Pradhan et al., 2002; Eilertsen et al., 2005). Furthermore, the increase in hs-CRP is not seen in transdermal HRT (Lowe et al., 2001; Eilertsen et al., 2005). It is thus thought that the first pass effect of estrogen through oral HRT induces increased hepatic synthesis of CRP (Lowe et al., 2001; Eilertsen et al., 2005).

Lower concentrations of hs-CRP have been reported in individuals with high physical activity (Timpson et al., 2005) and high physical fitness estimated by maximal oxygen uptake (Kuo et al., 2007), but the findings are less consistent (Manns et al., 2003; Fredrikson et al., 2004). An inverse association between physical activity and hs-CRP was totally dependent on obesity in one study (Manns et al., 2003).

Obesity and smoking are undoubtedly related to high concentrations of hs-CRP. Although further studies are needed as to the relation of alcohol and physical activity to hs-CRP, it is obviously necessary to take into consideration these factors in investigating the relation to disease risk as well as dietary determinants of hs-CRP.

Elevated CRP Levels and Disease Risk

Atherosclerotic diseases

Raised concentrations of total and low-density lipoprotein (LDL) cholesterol are an important risk factor for atherosclerotic diseases. It is well recognized that inflammation links to the development and progression of atherosclerosis (Ross, 1999; Pearson et al., 2003; Libby and Ridker, 2004). The initial step is endothelial cell activation, probably triggered by modified LDL, cigarette smoking, hypertension, hyperglycemia, and infectious microorganisms such as *Chlamydia pneumoniae* and herpesviruses. The endothelial activation is characterized by expression of monocyte adhesion molecules and chemotactic factors; the former facilitating monocyte attachment to endothelium, and the latter resulting in migration of monocytes into the intima where differentiation of monocytes to macrophages occurs. Uptake of modified LDL by macrophages results in the formation of foam cells. Lipid-laden macrophages secrete a number of inflammatory cytokines and amplify inflammation in the arterial wall.

Many studies have pointed to a positive relation between plasma hs-CRP and the risk of coronary heart disease. In a meta-analysis of a total of 1,053 coronary events from seven prospective studies, a relative risk of 1.7 (95% confidence interval [CI] 1.4–2.1) was demonstrated for the top versus bottom third of the baseline plasma hs-CRP, estimated to be 2.4 mg/L and 1.0 mg/L, respectively (Danesh et al., 1998). Thus it might be considered that hs-CRP is an independent marker of the risk of cardiovascular disease (Pearson et al., 2003). However, in the Reykjavik Study (Danesh et al., 2004), the largest prospective study regarding hs-CRP and coronary heart sisease, hs-CRP provided little additional predictive value over that given by assessment of major established risk factors including total cholesterol, smoking, body mass index (BMI), and systolic blood pressure. The investigators also noted in a meta-analysis

Table 1. Circulating CRP Levels and Risk of Type 2 Diabetes Mellitus in Prospective Studies

Author and year	Study and follow-up period	No. of cases	Sex	Diagnosis of DM	Comparison[a]	Relative risk		
						Age- & sex-adjusted	Multivariate adjusted[b]	% Decrease
Pradhan et al., 2001	Women's Health Study, US: 4 years	188	F	Self-report confirmed by fasting/nonfasting plasma glucose, symptom and medication.	Q4 vs. Q1	15.7	4.2 (1.5-12.0)	73
Barzilay et al., 2001	CHS, US: 3-4 years	45	Both	Fasting plasma glucose	Q4 vs. Q1	2.03	1.83 (1.24-2.86)	10
Festa et al., 2002	IRAS, US:5.2 years (mean)	144	Both	75-g OGTT	1 SD of ln CRP	1.44	1.17 (0.95-1.43)	19
Freeman et al., 2002	WOSCOPS, Scotland: follow-up years ND	127	M	Fasting plasma glucose	Q5 vs. Q1	6.13	2.46 (1.20-5.04)	60
Han et al., 2002	Mexico City Diabetes Study: 6 years	86	M F	75-g OGTT and medication	T3 vs. T1	ND	0.8 (0.4-2.0) 5.4 (2.2-13.4)	–
Duncan et al., 2003	ARIC Study, US: ca 9 years	581	Both	Fasting/nonfasting plasma glucose, self-reported physician diagnosis, and medication	Q4 vs. Q1	2.76	1.23 (0.74-2.03)	55
Spranger et al., 2003	EPIC-Potsdam Study: 2-3 years	188	Both	Self-reported clinical diabetes	High vs. low	3.5	1.9 (1.2-3.2)	46
Thorand et al., 2003	MONICA Augsburg Study:7.2 years (mean)	101	M	Self-report (95% physician's diagnosis)	Q4 vs. Q1	2.73	1.49 (0.76-2.91)	45
Nakanishi et al., 2003	Japanese Americans in US: 6.5 years (mean)	122	M F	75-g OGTT	Q4 vs. Q1	ND	2.84 (1.09-7.39) 3.11 (1.25-7.75)	–
Hu et al., 2004	Nurses' Health Study, US: 10 years	737	F	Self-report confirmed by fasting/nonfasting plasma glucose, symptom, and medication.	Q5 vs. Q1	7.08	4.36 (2.80-6.80)	38
Laaksonen et al., 2004	KIHD, Finland: 11years	78	M	Fasting plasma glucose or clinical diagnosis	3+ vs<1 mg/L	4.11	2.31 (1.11-4.80)	44
Doi et al., 2005	Hisayama Study, Japan: 9 years (mean)	131	M F	Fasting plasma glucose or medication for DM	T3 vs. T1	3.23 3.35	2.63 (1.23-5.65) 2.25 (1.01-5.01)	19 33
Dehghan et al., 2007	Rotterdam Study, The Netherlands: 9.8 years (mean)	544	Both	Fasting/nonfasting plasma glucose or clinical diagnosis	Q4 vs. Q1	2.83	1.73 (1.29-2.33)	39

ARIC: Atherosclerosis Risk in Communities, CHS: Cardiovascular Health Study, DM: diabetes mellitus, EPIC-Potsdam Study: European Prospective Investigation into Cancer and Nutrition-Potsdam Study, IRAS: Insulin Resistance Atherosclerosis Study, KIHD: Kuopio Ischaemic Heart Disease Risk Factor Study, MONICA: Monitoring of Trends and Determinants in Cardiovascular Disease, ND: not described, OGTT: oral glucose tolerance test, WOSCOPS: West of Scotland Coronary Prevention Study[a] Q5 vs. Q1: the highest versus lowest quintile, Q4 vs. Q1: the highest versus lowest quartile, T3 vs. T1: the highest versus lowest tertile.[b]Adjusted for body mass index and other cardiovascular risk factors in addition to age and sex. Han et al. (2002) did not adjust for body mass index. In parentheses are 95% confidence intervals.

of 22 prospective studies that the pooled relative risk for the top versus bottom third of hs-CRP levels was much lower in studies published since the year 2000 than derived from those published before the year 2000, suggesting publication bias for positive results in earlier studies. In conclusion, elevated hs-CRP may be predictive of future risk of coronary heart disease to some extent, but the predictive capability remains controversial.

There have been *in vitro* studies implicating CRP itself as a proinflammatory and pathogenetic factor in atherogenesis (Li and Fang, 2004). The presence of CRP in atherosclerotic plaques, often colocalized with activated complement complex, may be regarded as evidence for a pathogenic role (Li and Fang, 2004). However, widely used commercial human CRP, a recombinant product in *E. coli*, is contaminated with bacterial lipopolysaccharides and sodium azide (Taylor et al., 2005), which are most likely to have resulted in false results (Pepys, 2005).

Type 2 diabetes mellitus

To date, a total of 13 prospective studies have addressed the relation of circulating hs-CRP and type 2 DM (Table 1). Definition of type 2 DM varied in different studies. Most were based on fasting or nonfasting plasma glucose concentrations using the World Health Organization or the American Diabetes Association criteria; only three studies used the 75-g oral glucose tolerance test; and two studies were based on self-reported physician's diagnosis. With adjustment for demographic factors, a statistically significant increase in the risk of type 2 DM was observed in individuals at the highest level of CRP compared with those with the lowest level in all of the 13 studies except two which included no such data (Han et al., 2002; Nakanishi et al., 2003). The increased risk associated with high hs-CRP levels remained after adjustment for BMI and other cardiovascular risk factors in the majority of the studies. Factors included in the model for statistical adjustment varied slightly. Waist-to-hip ratio was also adjusted for in two studies (Duncan et al., 2003; Spranger et al., 2003), and waist circumference was controlled for in one study (Dehghan et al., 2007). The multivariate adjusted relative risk reported in the Mexican

study was not adjusted for BMI, but the investigators noted that an increased risk observed for women, not men, hardly changed with further adjustment for BMI (Han et al., 2002). On the other hand, no measurable increase in the risk was observed with multivariate adjustment in the Atherosclerosis Risk in Communities Study (Duncan et al., 2003), the Monitoring of Trends and Determinants in Cardiovascular Disease Augsburg Study (Thorand et al., 2003), and the Insulin Resistance Atherosclerosis Study (Festa et al., 2002). Importantly, the increased risk of type 2 DM associated with elevated CRP was substantially attenuated on multivariate analysis controlling for BMI and other factors. Notable are findings showing 45 to 73% decreases in the increased risk after multivariate adjustment (Pradhan et al., 2001; Freeman et al., 2002; Duncan et al., 2003; Spranger et al., 2003; Thorand et al., 2003). The data suggest that high levels of hs-CRP may not be causally related to the development of type 2 DM. High hs-CRP levels are possibly a risk marker linked with obesity. In the Rotterdam Study (Dehghan et al., 2007), however, a specific haplotype of three genetic polymorphisms linked with elevated levels of hs-CRP was associated with an increased risk of type 2 DM; a relative risk of 1.45 (95% CI 1.08–1.96) was reported in the multivariate analysis adjusted for age, sex, BMI, waist circumference, systolic and diastolic blood pressure, and high-density lipoprotein cholesterol. This finding suggests a direct effect of elevated CRP level in the development of type 2 DM. However, the haplotype associated with increased risk of type 2 DM was relatively rare, accounting for only 6%.

Cancer

Chronic inflammation related to certain infections and other causes is linked to increased risk of certain cancers, and malignant cells themselves secrete proinflammatory cytokines which in turn enhance progression (Balkwill and Mantovani, 2001; Coussens and Werb, 2002). Nuclear factor-κB (NF-κB) seems to play a pivotal role in the inflammation-cancer link. Microbial pathogens and tissue necrosis lead to the activation of NF-κB and other transcription factors, and this activation upregulates expression of proinflammatory cytokines, cyclooxygenase-2 enzymes and other molecules enhancing tumor growth and progression (Karin, 2006). It is thus natural to investigate the association between inflammatory markers and cancer risk.

The association with hs-CRP has most frequently been studied for colorectal cancer. In patients undergoing surgery, higher CRP levels were related to a higher risk of recurrence and of dying from colorectal cancer (Nozoe et al., 1998; Miki et al., 2004). Of eight prospective studies (Table 2), four demonstrated 1.4 to 2.9 times increased risks for the highest category of circulating hs-CRP (Erlinger et al., 2004; Il'yasova et al., 2005; Gunter et al., 2006; Otani et al., 2006), while the other half showed no material positive association between hs-CRP and colorectal cancer (Ito et al., 2005; Zhang et al., 2005;

Table 2. Circulating CRP Levels and Risk of Colorectal Cancer in Prospective Studies

Author and year	Study and follow-up period	No. of cases	Sex	Comparison[a]	Relative risk (95%CI)	Adjusted variable[b]
Erlinger et al., 2004	CLUE II Study, US: 11 years	172	Both	Q4 vs. Q1	2.00 (1.16-3.46)	Race and date of blood drawn
Ito et al., 2005	JACC Study, Japan: 4-11 years	141	Both	T3 vs. T1	1.18 (0.68-2.06)	Smoking, BMI, alcohol use, and participating institution
Zhang et al., 2005	Women's Health Study, US:10.8 years (maximum)	169	F	>3 vs. <1 mg/L	0.54 (0.29-1.00)	Smoking, BMI, physical activity, alcoh ol use, family history of colorectal cancer, aspirin use, menopausal status, hormone replacement therapy, multivitamin supplement use, and others; excluding the first 5 years of follow-up.
Il'yasova et al., 2005	HABC Study, US: 5.5 years (mean)	41	Both	1-unit of ln CRP (mg/L)	1.44 (1.03-2.02)	Race and study area.
Gunter et al., 2006	ATBC Study, Finland:14-17 years	130	M	Q4 vs. Q1	2.9 (1.4-6.0)	Smoking, BMI, and aspirin use; excluding cases diagnosed in the first 5 years of follow-up.
Otani et al., 2006	JPHC Study, Japan: 11.5 years	375	Both	Q4 vs. Q1	1.6 (1.1-2.5)	Smoking, BMI, physical activity, alcohol use, family history of colorectal cancer, and others.
Siemes et al., 2006	Rotterdam Study, The Netherlands: 10.2 years (mean)	189	Both	>3 vs. <1 mg/L	0.71 (0.44-1.15)	Smoking, physical activity, NSAID use, TC, hormone use, fruit, selenium, and total energy intake; excluding the first 5 years of follow-up.
Trichopoulos et al., 2006	EPIC Study, Greek: 5-10 years	48	Both	1 SD of CRP (3.2 mg/L)	1.16 (0.78-1.72)	Smoking, BMI, alcohol use, NSAID use, and duration of storage in years; excluding the first one year of follow-up.

ATBC Study: Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study, BMI: body mass index, EPIC Study: European Prospective Investigation into Cancer and Nutrition Study, HABC Study: Health, Aging, and Body Composition Study, JACC Study: Japan Collaborative Cohort Study, JPHC Study: Japan Public Health Center-based Prospective Study, NSAID: nonsteroidal anti-inflammatory drug [a]Q4 vs. Q1: the highest versus lowest quartile, T3 vs. T1: the highest versus lowest tertile.[b]Age and sex were controlled for all studies.

Siemes et al., 2006; Trichopoulos et al., 2006). Incidence of colorectal cancer in the first years of follow-up may cause bias in the association between hs-CRP and colorectal cancer. Four studies examined the relation between hs-CRP and colorectal cancer excluding the first 1–5 years of follow-up (Erlinger et al., 2004; Zhang et al., 2005; Otani et al., 2006; Siemes et al., 2006; Trichopoulos et al., 2006). Although the results were not shown, two other studies also examined the relation excluding the first years of follow-up reportedly with the results unchanged (Erlinger et al., 2004; Otani et al., 2006). Some investigators performed site-specific analysis, but generally found no differential association according to subsites of the colorectum (Erlinger et al., 2004; Ito et al., 2005; Zhang et al., 2005; Otani et al., 2006; Siemes et al., 2006). A statistically significant decrease, rather than increase, in the risk for the comparison of > 3 mg/L versus < 1 mg/L was noted for rectal caner in the Rotterdam Study (Siemes et al., 2006) and for proximal colon cancer in the Women's Health Study (Zhang et al., 2005).

Few studies observed increased risks of lung cancer (Il'yasova et al., 2005; Siemes et al., 2006; Trichopoulos et al., 2006) and of female breast cancer (Siemes et al., 2006) in individuals with high levels of hs-CRP. Three prospective studies examined the association between hs-CRP and cancer of all sites combined; two showed a statistically significant increase in the risk (Il'yasova et al., 2005; Trichopoulos et al., 2006), but no such association was found in another study (Rifai et al., 2002). Overall, based on limited evidence, it is unlikely that elevated levels of hs-CRP are associated with increased risk of colorectal and other cancer.

Dietary Factors and Circulating CRP

Antioxidant vitamins

While inflammatory cells produce reactive oxygen species, oxidative stress *per se* may have proinflammatory effects (Kobayashi et al., 2003; Suzuki et al., 2003; Abramson et al., 2005). Lower hs-CRP levels were observed in relation to high concentrations of serum β-carotene and other carotenoids in the Third National

Table 3. Antioxidant Vitamins and Circulating CRP Levels in Intervention Trials

Author and year	Design and period	Characteristics of subjects	Treatment (amount/day)	No of subjects	Effect on CRP
Devaraj et al., 2000	One-arm/ 3 months	Type 2 DM patients with/ without macrovascular complications and healthy subjects	α-tocopherol (1200 IU)	72	Approx. 25% decreased in three groups of subjects.
Upritchard et al., 2000	4-arm RCT/ 4 weeks	Patients with type 2 DM	Vitamin E (800 IU) Vitamin C (500 mg) Tomato juice (500 ml) Placebo	15 12 12 13	Median change 5.6 to 2.9mg/L (p = 0.004) was observed in vitamin E group, but no change in other groups.
Kaul et al., 2001	One-arm/ 6-8 weeks	Healthy subjects	α-tocopherol (400 IU)	26	Geometric mean changed 1.02 to 1.45 mg/L (p > 0.05).
Church et al., 2003	2-arm RCT/ 6 months	Healthy subjects	Multivitamin[a] Placebo	43 44	Mean change was 0.91 mg/L lower in the treatment (95% CI 0.30-1.52).
Bruunsgaard et al., 2003	2-arm RCT/ 3 years	Healthy subjects	Vitamin E (182 mg) + C (500 mg) Placebo	55 52	Median changes: 1.0 to 1.2 mg/L (p > 0.10) in the treatment and 1.5 to 1.7 mg/L (p > 0.10) in the placebo.
Block et al., 2004	3-arm RCT/ 2 months	Healthy subjects	Vitamin C (515 mg) Antioxidant mixture[b] Placebo	53 49 58	24% decrease (95% CI 6-39) by vitamin C. No measurable decrease in antioxidant mixture and placebo groups.
Ullegaddi et al., 2006	4-arm RCT/ 14 days	Patients with acute ischemic stroke	Vitamin E (727 mg) + C (500 mg) B-group vitamins[c] Vitamins E + C + B No supplementation	24 24 24 24	Significantly lower in the three treatment groups than in the controls.
Leichtle et al., 2006	One-arm/ 9 weeks	Patients with coronary artery disease and healthy subjects	α-tocopherol (100–400 mg)	24	Mean changes were 0.54 to 0.33 mg/L (NS) in healthy subjects and 1.23 to 0.55 mg/L (NS) in patients.
Woollard et al., 2006	One-arm/ 6 weeks	Healthy subjects	α-tocopherol (400 IU)	40	No change regardless of vitamin C status.
Wu JH et al., 2007	3-arm RCT/ 6 weeks	Patients with type 2 DM	α-tocopherol (500 mg) Mixed tocopherol[d)] Placebo	18 19 18	No significant decrease in three groups.

DM: diabetes mellitus, NS: no significant, RCT: randomized controlled trial. [a]Multivitamin was 24-ingredient multivitamin/mineral formula. [b] Antioxidant mixture consisted of 515 mg vitamin C, 371 mg α-tocopherol, 171 mg γ-tocopherol, 252 mg mixed tocotrienols, and 95 mg α-lipoic acid.c) B-group vitamins consisted of 5 mg folic acid, 5 mg vitamin B2, 50 mg vitamin B6, and 0.4 mg vitamin B12.d) Mixed tocopherol consisted of 75 mg α-tocopherol, 315 mg γ-tocopherol, and 110 mg δ-tocopherol.

Health and Nutrition Examination Survey (Ford et al., 2003), in a small Italian study (Valtueña et al., 2007), and in a study of non-smoking healthy subjects and cancer patients combined (McMillan et al., 2002). As regards vitamin C, an inverse association with serum concentrations was observed in the United States (Ford et al., 2003), the Netherlands (van Herpen-Broekmans et al., 2004), and England (Boekholdt et al., 2006; Wannamethee et al., 2006). On the other hand, while some studies reported an inverse correlation for serum concentrations of vitamin E (McMillan et al., 2002) and vitamin E intake (Scheurig et al., 2007), serum concentrations of vitamin E were uncorrelated with hs-CRP levels in others (Ford et al., 2003; van Herpen-Broekmans et al., 2004; Scheurig et al., 2007). Brighenti et al. (2005) reported that hs-CRP levels were progressively lower with increasing levels of total antioxidant capacity of the diet, estimated from dietary intake of vegetables, fruits, and others; the method was validated by three different *in vitro* assays (Pellegrini et al., 2003). In the Malmö Diet and Cancer Study (Fredrikson et al., 2004), a component characterized by high intake of fiber, vitamin C, and β-carotene was associated with low hs-CRP levels. Bertran et al. (2005) failed to find any association with β-carotene, vitamin C, or vitamin E in residents of Catalonian villages.

A total of 10 trials have addressed the effect of antioxidant vitamins on circulating CRP in healthy subjects and patients with type 2 DM or cardiovascular disease (Table 3). The effect of vitamin E was studied most frequently; single effects were examined in six studies (Devaraj and Jialal, 2000; Upritchard et al., 2000; Kaul et al., 2001; Leichtle et al., 2006; Woollard et al., 2006; Wu et al., 2007), and effects in combination with vitamin C in two studies (Bruunsgaard et al., 2003; Ullegaddi et al., 2006). Vitamin C itself is a free radical scavenger, and also can regenerate a reduced form of α-tocopherol from the tocopheroxyl radical which formed by oxidation (Hamilton et al., 2000; Pryor, 2000). Thus the combination of vitamin E and vitamin C may have a greater antioxidant effect than single administration. Relatively high dose of vitamin E seems to result in decrease in hs-CRP in patients with higher hs-CRP levels at baseline (Devaraj and Jialal, 2000; Upritchard et al., 2000; Ullegaddi et al., 2006). Vitamin E at low dose combined with vitamin C did not produce a significant decrease in hs-CRP (Bruunsgaard et al., 2003). Vitamin C of 500 mg/day resulted in a 24% decrease in hs-CRP in healthy subjects in one study (Block et al., 2004), but not in another study of patients with type 2 DM (Upritchard et al., 2000). A statistically significant decrease in hs-CRP was reported in a trial using multivitamin including vitamin E 800 IU and vitamin C 1000 mg per day (Church et al., 2003). Overall, vitamin E does not seem to affect hs-CRP levels materially while carotenoids and vitamin C may contribute to lower levels of hs-CRP.

Vegetables and fruit

Vegetables and fruit are a major dietary source of antioxidant vitamins, and it is naturally interesting whether high consumption of these foods are beneficial with respect to circulating hs-CRP. Two cross-sectional studies compared hs-CRP levels between vegetarians and omnivores. One study reported lower hs-CRP concentrations (geometric means 0.77 vs. 1.30 mg/L, $p < 0.01$) in vegetarians as compared with non-vegetarians (Szeto et al., 2004) whereas the other study found no difference between the two (Mezzano et al., 1999). Subjects were matched by sex and age, but BMI and smoking were not adjusted for in these studies. High consumption of vegetables and fruits are consistently associated with lower concentrations of hs-CRP in men and women living in Massachusetts, the United States (Gao et al., 2004), in the British Regional Heart Study (Wannamethee et al., 2006), and in female teachers in Tehran, Iran (Esmaillzadeh et al., 2006). BMI, smoking, and other covariates were adjusted for in these cross-sectional studies.

In an intervention study of two years in Italy (Esposito et al., 2004), individuals following a Mediterranean-style diet showed a substantial decrease in hs-CRP (1.1 mg/L) while the control group did not experience such a decrease (0.1 mg/L); the difference was statistically significant ($p = 0.01$). In this study, consumptions of vegetables and fruit, nuts, whole grain, and olive oil increased in the Mediterranean diet group compared with the control group. High intake of carotenoid-rich vegetables and fruit (8 servings per day), but not intermediate intake (5 servings per day) resulted in a significant decrease in hs-CRP as compared with low intake (2 servings per day) in a randomized trial in Germany (Watzl et al., 2005).

Although studies are limited in number, the available evidence strongly indicates that high consumption of vegetables and fruit is beneficial in terms of circulating hs-CRP levels.

Dietary patterns

The effect of a single nutrient, food, or food group is difficult to assess in observational studies because foods and nutrients are consumed in combination. A dietary pattern is a comprehensive variable that integrates consumptions of several foods or food groups. This method can overcome problems relating to the close intercorrelation among foods or nutrients (Kant, 2004; Newby and Tucker, 2004). Dietary patterns can be determined by different statistical methods including principal component analysis and reduced rank regression method. Of seven cross-sectional studies regarding dietary pattern and hs-CRP (Table 4), four studies were based on principal component analysis (Fung et al., 2001; Lopez-Garcia et al., 2004; Nettleton et al., 2006; Esmaillzadeh et al., 2007), and three used the reduced rank regression method (Hoffmann et al., 2004; Heidemann et al., 2005; Schulze et al., 2005). Regardless of the statistical method used for define dietary patterns, consistent results have been reported in different studies. Overall, the Western diet pattern characterized by high intake of red and processed meats, sweets, soft drinks, and refined grains is correlated with higher hs-CRP concentrations, whereas the prudent or healthy dietary pattern, characterized by high intake of vegetables, fruit, whole grains, and poultry, is related to lower levels of hs-CRP.

Table 4. Dietary Pattern and Circulating CRP Levels

Author and year	Subjects and country	Method	Main findings
Fung et al., 2001	466 men, health professionals, US	PCA determined 2 dietary patterns based on 42 food groups which derived from approximately 130 items in SQFFQ.	The second pattern (Western diet) was associated with high CRP levels while the first pattern (prudent diet) showed no association.
Hoffmann et al., 2004	200 CAD cases and 255 controls, Germany	RRR based on 49 food groups derived from SQFFQ 146 items	CRP was higher in individuals with higher score of the pattern characterized by high intake of meat, margarine, and poultry, and low intake of vegetables, wine, and whole grain cereals.
Lopez-Garcia et al., 2004	732 women, US	PCA determined 2 dietary patterns based on 37 food groups which derived from 116 items in FFQ.	The first pattern (prudent diet) was associated with low CRP levels, and the second pattern (Western diet) was associated with high CRP levels.
Heidemann et al., 2005	574 men and women, Germany	RRR based on 48 food groups derived from SQFFQ 148 items.	CRP was higher in individuals with lower score of the pattern characterized by high intake of fresh fruit and low intake of high-caloric soft drinks, beer, red meat, poultry, and processed meat, legumes and non-whole grain bread.
Schulze et al., 2005	1350 women, US	RRR based on 39 food groups derived from approximately 130 items in SQFFQ.	CRP was higher in individuals with higher score of the pattern characterized by high intake of soft drinks, refined grains, and processed meats and low intake of wine, coffee, cruciferous vegetables, and yellow vegetables.
Nettleton et al., 2006	5089 men and women, US	PCA determined 4 dietary patterns based on 47 food groups which derived from 120 items in SQFFQ.	The first pattern (fats and processed meats) was associated with high CRP levels, and the fourth pattern (whole grains and fruits) with low CRP levels; the second (vegetables and fish) and the third pattern (beans, tomatoes, and refined grains) showed no association.
Esmaillzadeh et al., 2007	486 women, Iran	PCA determined 3 dietary patterns based on 41 food groups which derived from 168 items in SQFFQ.	The first pattern (healthy) was associated with low CRP levels, the second pattern (Western diet) with high CRP levels, and the third pattern (traditional Iranian diet) showed no association.

CAD: coronary artery disease, FFQ: food frequency questionnaire, PCA: principal component analysis, RRR: reduced rank regression method, SQFFQ: semiquantitative food frequency questionnaire

Other dietary factors

Dietary fiber has been implicated as being protective in atherosclerotic diseases, insulin resistance, and type 2 DM (Salmeron et al., 1997; Liu et al., 1999). Several cross-sectional studies have reported an inverse association of dietary fiber intake with hs-CRP and other inflammatory markers (King et al., 2003; King et al., 2005; Bo et al., 2006; Qi et al., 2006). However, evidence is limited as to whether dietary fiber itself exerts anti-inflammatory effects. Dietary fiber consumption is highly correlated with magnesium intake because both are contained in the same foods. The Pearson correlation coefficient between the two was as high as 0.81 in a study in northern Italy (Bo et al., 2006). In fact, dietary intake and serum concentrations of magnesium were strongly, inversely associated with hs-CRP concentrations (Guerrero-Romero and Rodríguez-Morán, 2002; Song et al., 2005; Bo et al., 2006). Magnesium intake was more strongly associated with hs-CRP than dietary fiber after mutual adjustment (Bo et al., 2006). Magnesium supplementation improves endothelial function in patients with coronary artery disease (Shechter et al., 2000) and insulin sensitivity in patients with type 2 DM (Rodríguez-Morán and Guerrero-Romero, 2003). These findings suggest that magnesium intake is more important in relation to lowered hs-CRP levels than dietary fiber.

Estrogen use increases hs-CRP, as discussed above, and it is of interest whether phytoestrogens such as soy isoflavone are related to hs-CRP or other inflammatory markers. Isoflavone also has an effect of lowering serum LDL cholesterol, and may be protective in atherogenesis (Anderson et al., 1995). Several intervention trials have examined the effect of isoflavone on inflammatory makers including hs-CRP, but resulted in inconsistent results (Jenkins et al., 2002; D'Anna et al., 2005; Hall et al., 2005).

Fish oil or n-3 fatty acids have a wide variety of anti-inflammatory effects (Mori and Beilin, 2004; Calder, 2006). In an early small trial, 18 g of fish-oil concentrate per day was shown to decrease in vitro production of IL-1 and TNF-α by stimulated peripheral-blood mononuclear cells (Endres et al., 1989). Cross-sectional studies have fairly consistently observed that high consumption of fish or n-3 fatty acids is correlated with lower levels of hs-CRP and other biomarkers of inflammation (Pischon et al., 2003; Lopez-Garcia et al., 2004; Zampelas et al., 2005). However, results from intervention studies of fish

oil or n-3 fatty acids are not necessarily consistent (review: Calder, 2006; Fujioka et al., 2006). Further studies are required to drawn a conclusion on this issue.

Summary

High levels of circulating hs-CRP in the so-called normal range have been related to increased risks of atherosclerotic disease and type 2 DM. However, it remains controversial whether the associations of hs-CRP with these diseases are totally independent of obesity and other risk factors. Obesity is highly, positively correlated with circulating hs-CRP because proinflammatory cytokines secreted in expanded adipose tissue enhance the hepatic synthesis of CRP. Smoking is also strongly associated with high concentrations of hs-CRP. Epidemiologic findings are inconsistent regarding the relation of hs-CRP to risks of colorectal cancer and other sites of cancer. Further studies using hs-CRP are warranted so as to elucidate the role of inflammation in the etiology of these seemingly non-inflammatory diseases.

The association of dietary factors with circulating hs-CRP has been of another interest. Although evidence is limited, high consumption of vegetables and fruit as well as high intake of carotenoids and vitamin C has been associated with lower levels of circulating hs-CRP. Several cross-sectional studies have shown that a dietary pattern representing the Western-type diet is associated with increased levels of hs-CRP while a healthy or prudent dietary pattern characterized by high intake of vegetables, fruit, and whole grain is associated with lower concentrations of hs-CRP. High consumption of vegetables and fruit may exert an anti-inflammatory effect. Potentials of magnesium, dietary fiber, and n-3 fatty acids to lower hs-CRP levels warrant further investigation. Both mechanistic and epidemiologic studies regarding dietary factors and low-grade inflammation will add to our knowledge on diet and chronic diseases.

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References

Ablij H, Meinders A (2002). C-reactive protein: history and revival. *Eur J Intern Med*, **13**, 412.

Abramson J L, Hooper W C, Jones D P, et al (2005). Association between novel oxidative stress markers and C-reactive protein among adults without clinical coronary heart disease. *Atherosclerosis*, **178**, 115-21.

Albert M A, Glynn R J, Ridker P M (2003). Alcohol consumption and plasma concentration of C-reactive protein. *Circulation*, **107**, 443-7.

Anderson J W, Johnstone B M, Cook-Newell M E (1995). Meta-analysis of the effects of soy protein intake on serum lipids. *N Engl J Med*, **333**, 276-82.

Averina M, Nilssen O, Arkhipovsky V L, et al (2006). C-reactive protein and alcohol consumption: Is there a U-shaped association? Results from a population-based study in Russia. The Arkhangelsk study. *Atherosclerosis*, **188**, 309-15.

Balkwill F, Mantovani A (2001). Inflammation and cancer: back to Virchow? *Lancet*, **357**, 539-45.

Barzilay J I, Abraham L, Heckbert S R, et al (2001). The relation of markers of inflammation to the development of glucose disorders in the elderly: the Cardiovascular Health Study. *Diabetes*, **50**, 2384-9.

Bazzano L A, He J, Muntner P, et al (2003). Relationship between cigarette smoking and novel risk factors for cardiovascular disease in the United States. *Ann Intern Med*, **138**, 891-7.

Bertran N, Camps J, Fernandez-Ballart J, et al (2005). Diet and lifestyle are associated with serum C-reactive protein concentrations in a population-based study. *J Lab Clin Med*, **145**, 41-6.

Block G, Jensen C, Dietrich M, et al (2004). Plasma C-reactive protein concentrations in active and passive smokers: influence of antioxidant supplementation. *J Am Coll Nutr*, **23**, 141-7.

Bo S, Durazzo M, Guidi S, et al (2006). Dietary magnesium and fiber intakes and inflammatory and metabolic indicators in middle-aged subjects from a population-based cohort. Am *J Clin Nutr*, **84**, 1062-9.

Boekholdt S M, Meuwese M C, Day N E, et al (2006). Plasma concentrations of ascorbic acid and C-reactive protein, and risk of future coronary artery disease, in apparently healthy men and women: the EPIC-Norfolk prospective population study. *Br J Nutr*, **96**, 516-22.

Brighenti F, Valtueña S, Pellegrini N, et al (2005). Total antioxidant capacity of the diet is inversely and independently related to plasma concentration of high-sensitivity C-reactive protein in adult Italian subjects. *Br J Nutr*, **93**, 619-25.

Bruunsgaard H, Poulsen H E, Pedersen B K, et al (2003). Long-term combined supplementations with alpha-tocopherol and vitamin C have no detectable anti-inflammatory effects in healthy men. *J Nutr*, **133**, 1170-3.

Calder P C (2006). n-3 polyunsaturated fatty acids, inflammation, and inflammatory diseases. *Am J Clin Nutr*, **83**, 1505S-19S.

Choi E Y, Park E H, Cheong Y S, et al (2006). Association of C-reactive protein with the metabolic risk factors among young and middle-aged Koreans. *Metabolism*, **55**, 415-21.

Church T S, Earnest C P, Wood K A, Kampert J B (2003). Reduction of C-reactive protein levels through use of a multivitamin. *Am J Med*, **115**, 702-7.

Coussens L M, Werb Z (2002). Inflammation and cancer. *Nature*, **420**, 860-7.

Danesh J, Collins R, Appleby P, et al (1998). Association of fibrinogen, C-reactive protein, albumin, or leukocyte count with coronary heart disease: meta-analyses of prospective studies. *Jama*, **279**, 1477-82.

Danesh J, Wheeler J G, Hirschfield G M, et al (2004). C-reactive protein and other circulating markers of inflammation in the prediction of coronary heart disease. *N Engl J Med*, **350**, 1387-97.

D'Anna R, Baviera G, Corrado F, et al (2005). The effect of the phytoestrogen genistein and hormone replacement therapy on homocysteine and C-reactive protein level in

postmenopausal women. *Acta Obstet Gynecol Scand*, **84**, 474-7.

Dehghan A, Kardys I, de Maat M P, et al (2007). Genetic variation, C-reactive protein levels, and incidence of diabetes. *Diabetes*, **56**, 872-8.

Devaraj S, Jialal I (2000). Alpha tocopherol supplementation decreases serum C-reactive protein and monocyte interleukin-6 levels in normal volunteers and type 2 diabetic patients. *Free Radic Biol Med*, **29**, 790-2.

Dietrich M, Jialal I (2005). The effect of weight loss on a stable biomarker of inflammation, C-reactive protein. *Nutr Rev*, **63**, 22-8.

Doi Y, Kiyohara Y, Kubo M, et al (2005). Elevated C-reactive protein is a predictor of the development of diabetes in a general Japanese population: the Hisayama Study. *Diabetes Care*, **28**, 2497-500.

Duncan B B, Schmidt M I, Pankow J S, et al (2003). Low-grade systemic inflammation and the development of type 2 diabetes: the atherosclerosis risk in communities study. *Diabetes*, **52**, 1799-805.

Eckel R H, Grundy S M, Zimmet P Z (2005). The metabolic syndrome. *Lancet*, **365**, 1415-28.

Eilertsen A L, Hoibraaten E, Os I, et al (2005). The effects of oral and transdermal hormone replacement therapy on C-reactive protein levels and other inflammatory markers in women with high risk of thrombosis. *Maturitas*, **52**, 111-8.

Endres S, Ghorbani R, Kelley V E, et al (1989). The effect of dietary supplementation with n-3 polyunsaturated fatty acids on the synthesis of interleukin-1 and tumor necrosis factor by mononuclear cells. *N Engl J Med*, **320**, 265-71.

Erlinger T P, Platz E A, Rifai N, et al (2004). C-reactive protein and the risk of incident colorectal cancer. *Jama*, **291**, 585-90.

Esmaillzadeh A, Kimiagar M, Mehrabi Y, et al (2006). Fruit and vegetable intakes, C-reactive protein, and the metabolic syndrome. *Am J Clin Nutr*, **84**, 1489-97.

Esmaillzadeh A, Kimiagar M, Mehrabi Y, et al (2007). Dietary Patterns and Markers of Systemic Inflammation among Iranian Women. *J Nutr*, **137**, 992-8.

Festa A, D'Agostino R Jr., Tracy R P, et al (2002). Elevated levels of acute-phase proteins and plasminogen activator inhibitor-1 predict the development of type 2 diabetes: the insulin resistance atherosclerosis study. *Diabetes*, **51**, 1131-7.

Ford E S, Liu S, Mannino D M, et al (2003). C-reactive protein concentration and concentrations of blood vitamins, carotenoids, and selenium among United States adults. Eur J Clin Nutr, **57**, 1157-63.

Fredrikson G N, Hedblad B, Nilsson J A, et al (2004). Association between diet, lifestyle, metabolic cardiovascular risk factors, and plasma C-reactive protein levels. *Metabolism*, **53**, 1436-42.

Freeman D J, Norrie J, Caslake M J, et al (2002). C-reactive protein is an independent predictor of risk for the development of diabetes in the West of Scotland Coronary Prevention Study. *Diabetes*, **51**, 1596-600.

Frohlich M, Imhof A, Berg G, et al (2000). Association between C-reactive protein and features of the metabolic syndrome: a population-based study. *Diabetes Care*, **23**, 1835-9.

Fujioka S, Hamazaki K, Itomura M, et al (2006). The effects of eicosapentaenoic acid-fortified food on inflammatory markers in healthy subjects--A randomized, placebo-controlled, double-blind study. *J Nutr Sci Vitaminol*, **52**, 261-5.

Fung T T, Rimm E B, Spiegelman D, et al (2001). Association between dietary patterns and plasma biomarkers of obesity and cardiovascular disease risk. *Am J Clin Nutr*, **73**, 61-7.

Gao X, Bermudez O I, Tucker K L (2004). Plasma C-reactive protein and homocysteine concentrations are related to frequent fruit and vegetable intake in Hispanic and non-Hispanic white elders. *J Nutr*, **134**, 913-8.

Guerrero-Romero F, Rodríguez-Morán M (2002). Relationship between serum magnesium levels and C-reactive protein concentration, in non-diabetic, non-hypertensive obese subjects. *Int J Obes Relat Metab Disord*, **26**, 469-74.

Gunter M J, Stolzenberg-Solomon R, Cross A J, et al (2006). A prospective study of serum C-reactive protein and colorectal cancer risk in men. *Cancer Res*, **66**, 2483-7.

Hall W L, Vafeiadou K, Hallund J, et al (2005). Soy-isoflavone-enriched foods and inflammatory biomarkers of cardiovascular disease risk in postmenopausal women: interactions with genotype and equol production. *Am J Clin Nutr*, **82**, 1260-8; quiz 1365-6.

Hamilton I M, Gilmore W S, Benzie I F, et al (2000). Interactions between vitamins C and E in human subjects. *Br J Nutr*, **84**, 261-7.

Han T S, Sattar N, Williams K, et al (2002). Prospective study of C-reactive protein in relation to the development of diabetes and metabolic syndrome in the Mexico City Diabetes Study. *Diabetes Care*, **25**, 2016-21.

Heidemann C, Hoffmann K, Spranger J, et al (2005). A dietary pattern protective against type 2 diabetes in the European Prospective Investigation into Cancer and Nutrition (EPIC)--Potsdam Study cohort. *Diabetologia*, **48**, 1126-34.

Hoffmann K, Zyriax B C, Boeing H, et al (2004). A dietary pattern derived to explain biomarker variation is strongly associated with the risk of coronary artery disease. *Am J Clin Nutr*, **80**, 633-40.

Hu F B, Meigs J B, Li T Y, Rifai N, Manson J E (2004). Inflammatory markers and risk of developing type 2 diabetes in women. *Diabetes*, **53**, 693-700.

Il'yasova D, Colbert L H, Harris T B, et al (2005). Circulating levels of inflammatory markers and cancer risk in the health aging and body composition cohort. *Cancer Epidemiol Biomarkers Prev*, **14**, 2413-8.

Ito Y, Suzuki K, Tamakoshi K, et al (2005). Colorectal cancer and serum C-reactive protein levels: a case-control study nested in the JACC Study. *J Epidemiol*, **15 Suppl 2**, S185-9.

Jaye D L, Waites K B (1997). Clinical applications of C-reactive protein in pediatrics. *Pediatr Infect Dis J*, **16**, 735-46; quiz 746-7.

Jenkins D J, Kendall C W, Connelly P W, et al (2002). Effects of high- and low-isoflavone (phytoestrogen) soy foods on inflammatory biomarkers and proinflammatory cytokines in middle-aged men and women. *Metabolism*, **51**, 919-24.

Kant A K (2004). Dietary patterns and health outcomes. *J Am Diet Assoc*, **104**, 615-35.

Karin M (2006). Nuclear factor-kappaB in cancer development and progression. *Nature*, **441**, 431-6.

Kaul N, Devaraj S, Grundy S M, Jialal I (2001). Failure to demonstrate a major anti-inflammatory effect with alpha tocopherol supplementation (400 IU/day) in normal subjects. *Am J Cardiol*, **87**, 1320-3.

King D E, Egan B M, Geesey M E (2003). Relation of dietary fat and fiber to elevation of C-reactive protein. *Am J Cardiol*, **92**, 1335-9.

King D E, Mainous A G 3rd, Egan B M, Woolson R F, Geesey M E (2005). Fiber and C-reactive protein in diabetes, hypertension, and obesity. *Diabetes Care*, **28**, 1487-9.

Kobayashi S, Inoue N, Ohashi Y, et al (2003). Interaction of oxidative stress and inflammatory response in coronary plaque instability: important role of C-reactive protein. *Arterioscler Thromb Vasc Biol*, **23**, 1398-404.

Kolb-Bachofen V (1991). A review on the biological properties

of C-reactive protein. Immunobiology., 183, 133-45.
Kuo H K, Yen C J, Chen J H, Yu Y H, Bean J F (2007). Association of cardiorespiratory fitness and levels of C-reactive protein: data from the National Health and Nutrition Examination Survey 1999-2002. *Int J Cardiol*, **114**, 28-33.
Laaksonen D E, Niskanen L, Nyyssonen K, et al (2004). C-reactive protein and the development of the metabolic syndrome and diabetes in middle-aged men. *Diabetologia*, **47**, 1403-10.
Lakoski S G, Cushman M, Criqui M, et al (2006). Gender and C-reactive protein: data from the Multiethnic Study of Atherosclerosis (MESA) cohort. *Am Heart J*, **152**, 593-8.
Leichtle A, Teupser D, Thiery J (2006). Alpha-tocopherol distribution in lipoproteins and anti-inflammatory effects differ between CHD-patients and healthy subjects. *J Am Coll Nutr*, **25**, 420-8.
Li J J, Fang C H (2004). C-reactive protein is not only an inflammatory marker but also a direct cause of cardiovascular diseases. *Med Hypotheses*, **62**, 499-506.
Libby P, Ridker P M (2004). Inflammation and atherosclerosis: role of C-reactive protein in risk assessment. *Am J Med*, **116 Suppl 6A**, 9S-16S.
Liu S, Stampfer M J, Hu F B, et al (1999). Whole-grain consumption and risk of coronary heart disease: results from the Nurses' Health Study. *Am J Clin Nutr*, **70**, 412-9.
Lopez-Garcia E, Schulze M B, Fung T T, et al (2004). Major dietary patterns are related to plasma concentrations of markers of inflammation and endothelial dysfunction. *Am J Clin Nutr*, **80**, 1029-35.
Lopez-Garcia E, Schulze M B, Manson J E, et al (2004). Consumption of (n-3) fatty acids is related to plasma biomarkers of inflammation and endothelial activation in women. *J Nutr*, **134**, 1806-11.
Lowe G D, Upton M N, Rumley A, et al (2001). Different effects of oral and transdermal hormone replacement therapies on factor IX, APC resistance, t-PA, PAI and C-reactive protein--a cross-sectional population survey. *Thromb Haemost*, **86**, 550-6.
Manns P J, Williams D P, Snow C M, Wander R C (2003). Physical activity, body fat, and serum C-reactive protein in postmenopausal women with and without hormone replacement. *Am J Hum Biol*, **15**, 91-100.
McMillan D C, Talwar D, Sattar N, et al (2002). The relationship between reduced vitamin antioxidant concentrations and the systemic inflammatory response in patients with common solid tumours. *Clin Nutr*, **21**, 161-4.
Meier-Ewert H K, Ridker P M, Rifai N, et al (2001). Absence of diurnal variation of C-reactive protein concentrations in healthy human subjects. *Clin Chem*, **47**, 426-30.
Mezzano D, Munoz X, Martinez C, et al (1999). Vegetarians and cardiovascular risk factors: hemostasis, inflammatory markers and plasma homocysteine. *Thromb Haemost*, **81**, 913-7.
Miki C, Konishi N, Ojima E, et al (2004). C-reactive protein as a prognostic variable that reflects uncontrolled up-regulation of the IL-1-IL-6 network system in colorectal carcinoma. *Dig Dis Sci*, **49**, 970-6.
Mori T A, Beilin L J (2004). Omega-3 fatty acids and inflammation. *Curr Atheroscler Rep*, **6**, 461-7.
Nakanishi S, Yamane K, Kamei N, Okubo M, Kohno N (2003). Elevated C-reactive protein is a risk factor for the development of type 2 diabetes in Japanese Americans. *Diabetes Care*, **26**, 2754-7.
Nettleton J A, Steffen L M, Mayer-Davis E J, et al (2006). Dietary patterns are associated with biochemical markers of inflammation and endothelial activation in the Multi-Ethnic Study of Atherosclerosis (MESA). *Am J Clin Nutr*, **83**, 1369-79.
Newby P K, Tucker K L (2004). Empirically derived eating patterns using factor or cluster analysis: a review. *Nutr Rev*, **62**, 177-203.
Nozoe T, Matsumata T, Kitamura M, Sugimachi K (1998). Significance of preoperative elevation of serum C-reactive protein as an indicator for prognosis in colorectal cancer. *Am J Surg*, **176**, 335-8.
Ockene I S, Matthews C E, Rifai N, et al (2001). Variability and classification accuracy of serial high-sensitivity C-reactive protein measurements in healthy adults. *Clin Chem*, **47**, 444-50.
Otani T, Iwasaki M, Sasazuki S, Inoue M, Tsugane S (2006). Plasma C-reactive protein and risk of colorectal cancer in a nested case-control study: Japan Public Health Center-based prospective study. *Cancer Epidemiol Biomarkers Prev*, **15**, 690-5.
Pearson T A, Mensah G A, Alexander R W, et al (2003). Markers of inflammation and cardiovascular disease: application to clinical and public health practice: A statement for healthcare professionals from the Centers for Disease Control and Prevention and the American Heart Association. *Circulation*, **107**, 499-511.
Pellegrini N, Serafini M, Colombi B, et al (2003). Total antioxidant capacity of plant foods, beverages and oils consumed in Italy assessed by three different in vitro assays. *J Nutr*, **133**, 2812-9.
Pepys M B (2005). CRP or not CRP? That is the question. *Arterioscler Thromb Vasc Biol*, **25**, 1091-4.
Pepys M B, Hirschfield G M (2003). C-reactive protein: a critical update. *J Clin Invest*, **111**, 1805-12.
Pischon T, Hankinson S E, Hotamisligil G S, et al (2003). Habitual dietary intake of n-3 and n-6 fatty acids in relation to inflammatory markers among US men and women. *Circulation*, **108**, 155-60.
Pradhan A D, Manson J E, Rifai N, et al (2001). C-reactive protein, interleukin 6, and risk of developing type 2 diabetes mellitus. *JAMA*, **286**, 327-34.
Pradhan A D, Manson J E, Rossouw J E, et al (2002). Inflammatory biomarkers, hormone replacement therapy, and incident coronary heart disease: prospective analysis from the Women's Health Initiative observational study. *JAMA*, **288**, 980-7.
Pryor W A (2000). Vitamin E and heart disease: basic science to clinical intervention trials. *Free Radic Biol Med*, **28**, 141-64.
Qi L, van Dam R M, Liu S, et al (2006). Whole-grain, bran, and cereal fiber intakes and markers of systemic inflammation in diabetic women. *Diabetes Care*, **29**, 207-11.
Ridker P M (2001). High-sensitivity C-reactive protein: potential adjunct for global risk assessment in the primary prevention of cardiovascular disease. *Circulation*, **103**, 1813-8.
Ridker P M, Buring J E, Cook N R, et al (2003). C-reactive protein, the metabolic syndrome, and risk of incident cardiovascular events: an 8-year follow-up of 14 719 initially healthy American women. *Circulation*, **107**, 391-7.
Rifai N, Buring J E, Lee I M, et al(2002). Is C-reactive protein specific for vascular disease in women? *Ann Intern Med*, **136**, 529-33.
Rodríguez-Morán M, Guerrero-Romero F (2003). Oral magnesium supplementation improves insulin sensitivity and metabolic control in type 2 diabetic subjects: a randomized double-blind controlled trial. *Diabetes Care*, **26**, 1147-52.
Ross R (1999). Atherosclerosis--an inflammatory disease. *N Engl J Med*, **340**, 115-26.
Salmeron J, Manson J E, Stampfer M J, et al (1997). Dietary fiber, glycemic load, and risk of non-insulin-dependent

diabetes mellitus in women. *JAMA*, **277**, 472-7.
Scheurig A C, Thorand B, Fischer B, et al (2007). Association between the intake of vitamins and trace elements from supplements and C-reactive protein: results of the MONICA/KORA Augsburg study. Eur J Clin Nutr.
Schulze M B, Hoffmann K, Manson J E, et al (2005). Dietary pattern, inflammation, and incidence of type 2 diabetes in women. *Am J Clin Nutr*, **82**, 675-84; quiz 714-5.
Selvin E, Paynter N P, Erlinger T P (2007). The effect of weight loss on C-reactive protein: a systematic review. *Arch Intern Med*, **167**, 31-9.
Shechter M, Sharir M, Labrador M J, et al (2000). Oral magnesium therapy improves endothelial function in patients with coronary artery disease. *Circulation*, **102**, 2353-8.
Shine B, de Beer F C, Pepys M B (1981). Solid phase radioimmunoassays for human C-reactive protein. *Clin Chim Acta*, **117**, 13-23.
Siemes C, Visser L E, Coebergh J W, et al (2006). C-reactive protein levels, variation in the C-reactive protein gene, and cancer risk: the Rotterdam Study. *J Clin Oncol*, **24**, 5216-22.
Song Y, Ridker P M, Manson J E, et al (2005). Magnesium intake, C-reactive protein, and the prevalence of metabolic syndrome in middle-aged and older U.S. women. *Diabetes Care*, **28**, 1438-44.
Spranger J, Kroke A, Mohlig M, et al (2003). Inflammatory cytokines and the risk to develop type 2 diabetes: results of the prospective population-based European Prospective Investigation into Cancer and Nutrition (EPIC)-Potsdam Study. *Diabetes*, **52**, 812-7.
Suzuki K, Ito Y, Ochiai J, et al (2003). Relationship between obesity and serum markers of oxidative stress and inflammation in Japanese. *Asian Pac J Cancer Prev*, **4**, 259-66.
Szeto Y T, Kwok T C, Benzie I F (2004). Effects of a long-term vegetarian diet on biomarkers of antioxidant status and cardiovascular disease risk. *Nutrition*, **20**, 863-6.
Taylor K E, Giddings J C, van den Berg C W (2005). C-reactive protein-induced in vitro endothelial cell activation is an artefact caused by azide and lipopolysaccharide. *Arterioscler Thromb Vasc Biol*, **25**, 1225-30.
Thorand B, Lowel H, Schneider A, et al (2003). C-reactive protein as a predictor for incident diabetes mellitus among middle-aged men: results from the MONICA Augsburg cohort study, 1984-1998. *Arch Intern Med*, **163**, 93-9.
Tillett W S, Francis T (1930). Serological reactions in pneumonia with a non-protein somatic fraction of the pneumococcus. *J Exp Med*, **52**, 561-71.
Timpson N J, Lawlor D A, Harbord R M, et al (2005). C-reactive protein and its role in metabolic syndrome: mendelian randomisation study. *Lancet*, **366**, 1954-9.
Trichopoulos D, Psaltopoulou T, Orfanos P, et al (2006). Plasma C-reactive protein and risk of cancer: a prospective study from Greece. *Cancer Epidemiol Biomarkers Prev*, **15**, 381-4.
Ullegaddi R, Powers H J, Gariballa S E (2006). Antioxidant supplementation with or without B-group vitamins after acute ischemic stroke: a randomized controlled trial. JPEN *J Parenter Enteral Nutr*, **30**, 108-14.
Upritchard J E, Sutherland W H, Mann J I (2000). Effect of supplementation with tomato juice, vitamin E, and vitamin C on LDL oxidation and products of inflammatory activity in type 2 diabetes. *Diabetes Care*, **23**, 733-8.
Valtueña S, Del Rio D, Pellegrini N, et al (2007). The total antioxidant capacity of the diet is an independent predictor of plasma beta-carotene. *Eur J Clin Nutr*, **61**, 69-76.
van Herpen-Broekmans W M, Klopping-Ketelaars I A, Bots M L, et al (2004). Serum carotenoids and vitamins in relation to markers of endothelial function and inflammation. *Eur J Epidemiol*, **19**, 915-21.
Visser M, Bouter L M, McQuillan G M, et al (1999). Elevated C-reactive protein levels in overweight and obese adults. *JAMA*, **282**, 2131-5.
Volpato S, Pahor M, Ferrucci L, et al (2004). Relationship of alcohol intake with inflammatory markers and plasminogen activator inhibitor-1 in well-functioning older adults: the Health, Aging, and Body Composition study. *Circulation*, **109**, 607-12.
Wannamethee S G, Lowe G D, Rumley A, Bruckdorfer K R, Whincup P H (2006). Associations of vitamin C status, fruit and vegetable intakes, and markers of inflammation and hemostasis. *Am J Clin Nutr*, **83**, 567-74; quiz 726-7.
Watzl B, Kulling S E, Moseneder J, Barth S W, Bub A (2005). A 4-wk intervention with high intake of carotenoid-rich vegetables and fruit reduces plasma C-reactive protein in healthy, nonsmoking men. *Am J Clin Nutr*, **82**, 1052-8.
Woollard K J, Rayment S J, Bevan R, et al (2006). Alpha-tocopherol supplementation does not affect monocyte endothelial adhesion or C-reactive protein levels but reduces soluble vascular adhesion molecule-1 in the plasma of healthy subjects. *Redox Rep*, **11**, 214-22.
Wu J H, Ward N C, Indrawan A P, et al (2007). Effects of alpha-tocopherol and mixed tocopherol supplementation on markers of oxidative stress and inflammation in type 2 diabetes. *Clin Chem*, **53**, 511-9.
Zampelas A, Panagiotakos D B, Pitsavos C, et al (2005). Fish consumption among healthy adults is associated with decreased levels of inflammatory markers related to cardiovascular disease: the ATTICA study. *J Am Coll Cardiol*, **46**, 120-4.
Zhang S M, Buring J E, Lee I M, Cook N R, Ridker P M (2005). C-reactive protein levels are not associated with increased risk for colorectal cancer in women. *Ann Intern Med*, **142**, 425-32.