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ORIGINAL ARTICLE

Does high sensitive CRP improve cardiovascular risk prediction in metabolic syndrome among the aged?

MARIKA SALMINEN[1,2,3], MARIKKA KUOPPAMÄKI[1,4], TERO VAHLBERG[5], ISMO RÄIHÄ[1,6], KERTTU IRJALA[7] & SIRKKA-LIISA KIVELÄ[1,8]

[1]*Institute of Clinical Medicine, Family Medicine, University of Turku, Turku, Finland,* [2]*Härkätie Health Centre, Lieto, Finland,* [3]*Primary Health Care Unit, Hospital District of Southwest Finland and Satakunta, Turku and Pori, Finland,* [4]*Naantali Health Centre, Naantali, Finland,* [5]*Institute of Clinical Medicine, Biostatistics, University of Turku, Turku, Finland,* [6]*Department of Internal Medicine, Turku City Hospital, Turku, Finland,* [7]*Mehiläinen, Turku, Finland, and* [8]*Faculty of Pharmacy, Division of Social Pharmacy, University of Helsinki, Helsinki, Finland*

Abstract

Objectives. To analyze whether an elevated level of high hsCRP has an additive effect on metabolic syndrome (MetS) in predicting future cardiovascular events (CVEs) as well as on all-cause mortality among the aged subjects. *Design.* A prospective, population-based study with a 9-year follow-up. The study population consisted of persons aged 64 and above in 1998–99 without vascular disease and CRP less than 10 mg/l at baseline (n = 733). Adjusted hazard ratios (HRs) and their 95% confidence intervals (CIs) for CVEs and all-cause mortality predicted by baseline MetS (defined by both International Diabetes Federation (IDF) and World Health Organization (WHO)) and hsCRP-level were estimated. *Results*. During the 9-year follow-up, a total of 142 CVEs and 206 deaths occurred. After multivariable adjustment, no significant interactions were found between hsCRP and MetS in CVEs (IDF: p = 0.828; WHO: p = 0.572) or in all-cause mortality (IDF: p = 0.113; WHO: p = 0.374). HsCRP was not associated with the occurrence of CVEs (IDF: HR = 1.10, 95% CI = 0.92–1.32, p = 0.281; WHO: HR = 1.10, 95% CI = 0.93–1.32, p = 0.247) or with all-cause mortality (IDF: HR = 1.12, 95% CI = 0.97–1.29, p = 0.134; WHO: HR = 1.11, 95% CI = 0.96–1.28, p = 0.146). *Conclusions*. It seems that hsCRP does not give any extra value in evaluation of CVE risk or all-cause mortality of older subjects with MetS.

Key words: *aged, cardiovascular, high-sensitivity C-reactive protein, metabolic syndrome, mortality*

Introduction

Low-grade inflammation is characteristic for metabolic syndrome (MetS). C-reactive protein (CRP), the best characterized biomarker of inflammation, has been shown to be an independent predictor of future cardiovascular events (CVEs) (1). On contrast of several other biomarkers that also reflect biological aspects of inflammation, hsCRP measurement is inexpensive, standardized, widely available, and it has a decade-to-decade variation similar to that of cholesterol (2).

Several studies have confirmed significant correlation between the CRP level and components of MetS among adults (3–5). Thus, MetS is a proinflammatory state characterized by increased CRP levels (1). It has been proposed that hsCRP may give additive prognostic value at all levels of MetS (2). On the other hand, according to a study conducted among the aged (≥ 65 years of age), MetS was associated with low-grade systemic inflammation, and the association was mainly supported by a strong independent correlation between waist circumference (WC) and high hsCRP level (6).

The potential interrelationships between CRP and incident CVEs in adult populations (middle-aged or persons aged < 65 years mainly) have been evaluated in several prospective studies (7–11). In a large-scale population cohort study of 6345 apparently healthy women, hsCRP was found to be a useful biomarker in risk for incident vascular disease and

Correspondence: Marika Salminen, Family Medicine, Lemminkäisenkatu 1, FI-20014 University of Turku, Finland. Tel: + 358 2 333 8419. Fax: + 359 2 333 8439. E-mail: majosa@utu.fi

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diabetes (9). Also among 5245 middle-aged men, hsCRP level predicted development of type 2 diabetes independently with established risk factors (7). In some studies, hsCRP has found to have an additive effect on MetS in predicting future CVEs. In the Nurses' Health Study and the Health Professionals Follow-up Study, MetS was a strong predictor of coronary heart disease in both men and women, but the predictive effect of CRP was additive only in men (8). Among middle-aged men with MetS, hsCRP enhanced risk prediction of coronary heart disease and diabetes (10). In the retrospective study of Takeno et al. (11), the effect of CRP was additive to MetS in predicting future major adverse cardiac events in patients with acute myocardial infarction. However, among older adults hsCRP has found to be associated with mortality (12–14), but not with incident CVEs (12).

The purpose of this study was to analyze whether an elevated level of hsCRP has an additive effect on MetS in predicting future CVEs as well as all-cause mortality among aged subjects (≥64 years of age) free of CVDs at baseline.

Material and methods

This study is a part of the longitudinal, epidemiological study carried out in the municipality of Lieto in Southwest Finland (15,16). The longitudinal study was designed to describe the prevalence, risk factors and prognosis of cardiovascular, respiratory, and other common diseases in an unselected Finnish population aged 64 years and over. All persons born in or prior to 1933 (N = 1529) were asked to participate in the baseline examinations which were carried out between March 1998 and September 1999. Of those eligible, 63 died before they were examined, and 273 refused or did not respond, leaving 1260 (82.4%) participants, 533 men and 727 women (16). The sample for the current study consisted of 733 (66.7%) persons with no vascular disease (ICD-10 Diagnostic codes I20–I25, I50, I61, I63, I64, I66, I69.1, I69.3, and I69.4), with data of MetS and confounding factors and CRP less than 10 mg/l at the baseline. They were followed up for 9 years in order to determine the incidence of CVEs as well as all-cause mortality as described later.

Clinical chemistry parameters

Blood samples were drawn after an overnight fast at the Health Centre, and they were analyzed in the Central Laboratory of Turku University Hospital. A high-sensitive CRP assay was made with immunonephelometric method (Behring BNA, Germany). Detailed information on blood specimens are given elsewhere (17,18).

Measurements

Weight and height were measured, and body mass index (BMI), measured as kilograms per square meter, was calculated. Blood pressure was measured in a sitting position using the standard cuff method and a mercury sphygmomanometer. Systolic blood pressure was determined by the Korotkoff phase 1 and diastolic blood pressure by the Korotkoff phase 4 or 5. Two values were recorded with 2 mm Hg accuracy and with 5 minutes apart and the mean value was used.

Diabetes was defined based on a diagnosis (E10–E14) in the medical records, and/or treatment with antidiabetic agents (ATC code A10), and/or fasting serum glucose level greater than or equal to 7 mmol/l measured during the baseline examination in 1998–1999 (19).

Confounding factors

Gender, age, smoking status, and frequency of physical exercises were used as confounding factors. Data on smoking (1. nonsmoker, 2. ex-smoker, and 3. current smoker) and the frequency of taking exercises (1. 1–7 days a week, 2. less than once a week—not at all) were collected by interview.

Definition of metabolic syndrome

To determine subjects with MetS, the modified definition of the International Diabetes Federation (IDF) (20,21) and World Health Organization (WHO) were used (19). According to the modified criteria of IDF, MetS was defined as BMI over 30 kg/m^2 plus two factors out of the following four ones: 1. raised triglycerides (≥1.7 mmol/l) or specific treatment for this lipid abnormality (C10AB), 2. low HDL-cholesterol (≤1.03 mmol/l for men; ≤1.29 mmol/l for women) or specific treatment for this lipid abnormality (C10AC), 3. raised blood pressure (systolic ≥130 mm Hg or diastolic ≥85 mm Hg) or treatment of previously diagnosed hypertension (C02, 03, 07–09), 4. elevated fasting plasma glucose (≥5.6 mmol/l) or previously diagnosed type 2 diabetes. In our study, WC was not measured, and therefore, we used modified criteria of IDF where BMI greater than or equal to 30 kg/m^2 was used to assume central obesity (according to the definition by IDF, if BMI is over 30 kg/m^2, central obesity can be assumed and WC does not need to be measured) (20,21). MetS was defined according to the WHO criteria as glucose intolerance, IGT or diabetes and/or insulin resistance together with two or more of the following factors: blood pressure (≥140/90 mmHg), raised plasma triglyserides (≥1.7 mmol/l) and/or low

HDL-cholesterol (<0.9 mmol/l for men and <1.0 mmol/l for women), obesity (waist–hip ratio >90 cm for men and >85 cm for women and/or BMI >30 kg/m^2), microalbuminuria (urinary albumin excretion rate ≥ 20 μg/min or albumin creatinine ratio ≥ 30 mg/g) (19).

The incidence of cardiovascular events and all-cause mortality during the follow-up period

The primary endpoints were chosen so that the cases could be obtained reliably from Finnish official registers. Nonfatal and fatal events were identified by obtaining data from the Finnish Hospital Discharge Register provided by the National Institute for Health and Welfare. Fatal events were also identified by obtaining data from the Finnish Cause of Death Registry (Statistics Finland). The data from the registers were acquired by using the unique personal identification numbers.

All CVEs were defined on the basis of International Classification of Diseases, 10th revision (ICD-10). All CVEs consisted of nonfatal coronary heart disease events (I20–23) (nonfatal myocardial infarction or angina pectoris) and surgical procedures for coronary by-pass surgery or angioplasty (codes FNA, FNB, FNC, FND, FNE, FN1AT, FN1BT, FN1YT, FNF, and FNG). Fatal coronary events (deaths due to ischemic heart disease) were defined by ICD-10 codes I20–25. Cerebrovascular events included ICD-10 codes I61, I63, I64, I69, I69.1, I69.3, I69.4, and I69.8. Also deaths due to hypertensive disease, heart failure, atherosclerosis, or peripheral arterial disease (with ICD-10 codes I10–I15, I50, I70, and I71) were included. All events (nonfatal and fatal) before the beginning of January 2008 were obtained.

Data from all participants who had died before the beginning of January 2008 were obtained from the official Finnish Cause of Death Registry using their unique personal identification numbers.

Ethics

The study was conducted according to the guidelines of the Declaration of Helsinki. The Ethics Committee of the Hospital District of Southwest Finland approved the study protocol. Participants gave their informed consent.

Statistical analyses

At baseline, differences between subjects with MetS and without MetS were tested by the Chi-squared test, Fisher's exact test or two-sample *t*-test. The normalities of distributions were checked graphically using histograms. Because of the skewed distributions, triglyceride levels were log-transformed and glucose values were square (x^2)-transformed for statistical analyses.

Hazard ratios (HRs) and their 95% confidence intervals for incidence of CVEs and all-cause mortality were calculated using Cox proportional hazard models. Proportional hazards assumption was tested using Martingale residuals**.** The follow-up periods were calculated from the baseline measurements to the end of the follow-up period of 9 years or to the incidence of CVEs or to the death of the person. The interaction between hsCRP and MetS was included in Cox regression models. Analyses were adjusted for confounding factors: age, gender, smoking status, and frequency of exercise. P-values less than 0.05 were considered statistically significant. All statistical analyses were performed using SAS System for Windows, version 9.1 (SAS Institute Inc., Cary, NC, USA).

Results

Baseline characteristics

The mean age of participants ($n=733$) was 72.0 (standard deviation: 6.0) years. Altogether, 133 (18.1%) and 139 (19.0%) persons fulfilled the criteria of MetS according to IDF and WHO criteria, respectively. Baseline characteristics of subjects with or without MetS according to two different criteria are shown in Table I.

High-sensitivity C-reactive protein and metabolic syndrome

Levels of hsCRP were significantly higher among those with MetS than among those without it. These results were not dependent on the definition of MetS (Table II).

Cardiovascular events

During the 9-year follow-up of the total sample of 733 subjects, 142 CVEs occurred. After multivariable adjustment, there was no significant interaction between hsCRP and MetS when MetS was defined either by the criteria of IDF ($p=0.828$) or that of WHO ($p=0.572$). HsCRP was not associated with the incidence of CVEs (Table III). CVEs were more common in subjects with MetS compared to those not having MetS defined by either of the two criteria.

All-cause mortality

During the 9-year follow-up 206 deaths occurred. The main causes of death were cardiovascular

Table I. Baseline characteristics of all participants (n = 733) with metabolic syndrome (MetS) or without it as defined by International Diabetes federation (IDF) and World Health Organization (WHO) criteria.

	IDF			WHO[b]		
	MetS (n = 133) n (%)	No MetS (n = 600) n (%)	P-value[a]	MetS (n = 139) n (%)	No MetS (n = 593) n (%)	P-value[a]
Gender						
Men	45 (34)	261 (44)		62 (45)	243 (41)	
Women	88 (66)	339 (57)	0.042	77 (55)	350 (59)	.446
Marital status						
Married/living together	77 (58)	369 (62)		83 (60)	362 (61)	
Living alone	13 (10)	81 (14)		13 (9)	81 (14)	
Widowed	43 (32)	150 (25)	0.163	43 (31)	150 (25)	.221
Education						
More than basic	5 (4)	31 (5)		6 (4)	30 (5)	
Basic[c]	8 (6)	29 (5)		6 (4)	31 (5)	
Less than basic	120 (90)	540 (90)	0.691	127 (91)	532 (90)	.841
Previous occupation						
Service sector/administration/teaching	46 (35)	188 (32)		40 (29)	193 (33)	
Manufacturing industry/construction	44 (33)	217 (37)		57 (41)	204 (35)	
Agriculture	35 (27)	159 (27)		37 (27)	157 (27)	
Homemaker	7 (5)	28 (5)	0.867	5 (4)	30 (5)	.506
Smoking						
Nonsmokers	94 (71)	411 (69)		89 (64)	415 (70)	
Ex-smokers	33 (25)	142 (24)		43 (31)	132 (22)	
Current smokers	6 (5)	47 (8)	0.407	7 (5)	46 (8)	.072
Frequency of exercise						
1–7 days a week	85 (64)	474 (79)		96 (69)	462 (78)	
Less than once a week—not at all	48 (36)	126 (21)	< 0.001	43 (31)	131 (22)	.035
	Mean (SD)	Mean (SD)		Mean (SD)	Mean (SD)	
Age	71.6 (5.5)	72.4 (6.3)	0.178	73.0 (6.4)	72.1 (6.1)	.117
HDL-cholesterol	1.3 (0.3)	1.5 (0.4)	< 0.001	1.3 (0.3)	1.5 (0.4)	<.001
LDL-cholesterol	3.8 (0.9)	3.7 (1.0)	0.178	3.6 (0.9)	3.7 (1.0)	.289
Triglyceride	1.8 (0.8)	1.4 (0.7)	< 0.001	2.0 (0.9)	1.3 (0.6)	<.001
Glucose	6.7 (1.9)	5.8 (1.3)	< 0.001	7.6 (2.2)	5.5 (0.8)	<.001
Systolic blood pressure	163 (20)	157 (21)	0.001	164 (21)	157 (21)	<.001
Diastolic blood pressure	85 (11)	82 (10)	0.009	85 (12)	82 (10)	.011
Body mass index	33.4 (2.9)	25.8 (3.5)	< 0.001	30.1 (4.7)	26.4 (4.1)	<.001

[a]Chi-squared test or Fisher's exact test for categorized variables and Student's t-test for continuous variables.
[b]Missing data for one subject.
[c]Six years of elementary school.

diseases (n = 128), neoplasms (n = 33), diseases of respiratory system (n = 10), diseases of digestive system (n = 7), and diseases of nervous system (n = 6). After multivariable adjustment, there was no significant interaction between hsCRP and MetS by either criteria (IDF: p = 0.113; WHO: p = .374). Neither hsCRP nor MetS was associated with all-cause mortality.

Discussion

In this population-based, 9-year follow-up study of aged Finns living in Southwest Finland, levels of hsCRP were higher among those with MetS than among those not having MetS, but hsCRP level had no additive effect on MetS in predicting CVEs or all-cause mortality. MetS, however, predicted CVEs in elderly persons with no previous cardiovascular disease.

The results of our study, indicating that hsCRP levels were significantly higher in aged subjects with MetS compared with those without MetS, are similar to the results of previous studies. Several studies, conducted among adult populations, have confirmed significant correlation between CRP levels and components of MetS (3–5,8,10,11). We have found only one previous study about the relationship between increased CRP plasma levels and MetS in an aged population (≥ 65 years). In this study, MetS was defined by the NCEP-ATP III-AHA/NHLBI criteria. MetS was associated with low-grade systemic inflammation, and the association was mainly supported by a strong independent correlation between WC and high hsCRP levels. The risk of

Table II. Difference in level of high-sensitivity C-reactive protein (hsCRP) among subjects with MetS and without it as defined by International Diabetes federation (IDF) and World Health Organization (WHO) criteria (n = 733).

	MetS	No MetS	
	Median **(IQR)** Mean (SD)	Median **(IQR)** Mean (SD)	P-value[a]
IDF	n = 133	n = 600	
hsCRP	2.1 **(1.2–4.1)** 2.9 (2.1)	1.4 **(0.7–3.0)** 2.2 (2.1)	<.001
WHO[b]	n = 139	n = 593	
hsCRP	2.3 **(1.2–4.3)** 2.9 (2.2)	1.4 **(0.7–2.9)** 2.2 (2.1)	<.001

IQR, Interquartile range; SD, Standard deviation.
[a]Two-sample t-test.
[b]Missing data for 1 subject.

having high hsCRP which is increased from the first to the third tertile of WC indicated a possible dose–effect relationship. This suggests that even in older age groups, visceral accumulation of adipose tissue might become "pathological" when exceeding a certain threshold (6).

According to our results, adding hsCRP as a clinical criterion to MetS, as proposed by Ridker et al. (9), does not give any additive value in predicting CVEs or all-cause mortality in an aged population with MetS. Several previous prospective studies evaluating interrelationships between CRP, MetS, and incident CVEs have shown that hsCRP adds appreciable information beyond MetS to predict future CVEs in the middle-aged subjects (aged mainly less than 65 years of age) (8,10,11). In addition, in an analysis comprising individual data from 52 prospective cohort studies, adding information on CRP to the standard risk factors used to predict the risk of a first CVE (20). The main cause for the contradictory results between our study and earlier studies is probably the older age of the participants in our study. It is possible that, in older age groups, low-grade inflammation is not in a central role in the development of atherosclerotic changes as it is in younger age groups. Other possible causes for contradictory results may be the use of different cardiovascular endpoints and the use of diverse cardiovascular endpoint definitions in different studies. The results of our study are more consistent with the results of the Cardiovascular Health Study (CHS) All Stars (12,14). According to CHS All Stars CRP is associated with mortality (12,14) but not with CVEs (12) among the older adults (aged at least 65 years). In addition, although the increase in CRP was significantly associated with increased risk of mortality, this association was no longer significant when final biomarker level was included in model indicating that change in level over time is less predictive of mortality than final level of inflammation biomarkers (12). One must notice that there were several major differences between the CHS All Stars and our study, for example, in our study, also MetS was included in the analyses, because both MetS and hsCRP have clearly shown to be associated with incident CVEs at least among middle-aged population. Our primary

Table III. Adjusted hazard ratios (HR) and their 95% confidence intervals (CI) (in parentheses) of metabolic syndrome (MetS) (as defined by International Diabetes federation (IDF) and World Health Organization (WHO)) and high-sensitivity C-reactive protein (hsCRP) for all vascular events and all-cause mortality during the 9-year follow-up (n = 733).

	All vascular events			All-cause mortality		
MetS defined by IDF	n (%)	HR (95% CI)	P-value	n (%)	HR (95% CI)	P-value
Model 1[a]						
Yes (n = 133)	35 (26)	1.57 (1.05–2.35)	0.028	35 (26)	1.05 (0.72–1.53)	.809
No (n = 600)	107 (18)	1		171 (22)	1	
hsCRP		1.10 (0.92–1.32)	0.281		1.12 (0.97–1.29)	.134
Model 2[a]						
MetS defined by WHO[b]						
Yes (n = 139)	41 (30)	1.81 (1.25–2.62)	0.002	47 (34)	1.28 (0.92–2.62)	.141
No (n = 593)	100 (17)	1		159 (27)	1	
hsCRP		1.10 (0.93–1.32)	0.247		1.11 (0.96–1.28)	.146

[a]MetS and hsCRP were entered into the Models 1 and 2. HRs were adjusted for age, gender, smoking status, and frequency of exercise.
[b]Missing data for one subject.

interest was to find out whether an elevated level of hsCRP has an additive effect on MetS in predicting future CVEs among aged subjects free of CVDs at baseline. The results of our study indicate that the risk of incident CVEs is mostly predicted by the risk factor cluster of MetS. Although the levels of hsCRP were higher among those with MetS compared with those not having MetS, hsCRP does not seem to offer any additional benefit in the prediction of CVE risk among the elderly population free from CVDs at baseline.

The original IDF definition of MetS was not used in our study due to the lack of WC measurement. We used BMI as the sole measure of obesity which may have affected the results. Central obesity assessed by WC has been considered as a pivotal and essential component of MetS in the new definition of IDF. However, if BMI is over 30 kg/m^2, central obesity can be assumed and WC is not needed to be measured (21,22). Using BMI instead of WC may have led to an underestimation of the prevalence of MetS in our study, because there may have been subjects fulfilling the criterion of central obesity (WC 94 cm in men and 80 cm in women) among those whose BMI was less than 30 kg/m^2. Age-related physiological changes have a marked impact on body composition, including a decline in lean body mass and total body water in parallel with an increase in fat mass (23,24). Due to these changes, indices of central fat distribution, primarily WC, appear to have a greater prognostic value than BMI for characterizing obesity and associated health risks in the aged (25).

We excluded participants with CRP 10 mg/l and greater at the baseline in order to avoid distortion of the biomarker´s relation to CVEs and mortality by transient increases associated with acute illnesses (26). The other strengths of this study are the population-based design with the very high participation rate and the long follow-up time. Almost the entire aged population living in Lieto municipality participated. BMI measurements relied on clinical anthropometric assessment. The primary endpoints were chosen so that the cases could be obtained reliably from Finnish official registers. Nonfatal and fatal events were identified by obtaining data from the Finnish Hospital Discharge Register provided by the National Institute for Health and Welfare. This register covers all hospitals in Finland and gives population-level data on admissions, hospital days, hospital types, and diseases which caused hospitalization. Hospitals are obliged to maintain medical records about their patients. Fatal events were also identified by obtaining data from the Finnish Cause of Death Registry (Statistics Finland). Incidence rates were adjusted for several confounding variables at baseline.

In conclusion, our findings suggest that although levels of hsCRP are higher among those with MetS than among those not having MetS, hsCRP level does not predict CVEs among the aged with no previous vascular disease. Neiher MetS nor hsCRP predicted all-cause mortality. It seems that hsCRP does not give any additive value in screening of CVE risk or predicting mortality in aged subjects with MetS.

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References

1. Devaraj S, Singh U, Jialal I. Human C-reactive protein and the metabolic syndrome. Curr Opin Lipidol. 2009;20:182–9.
2. Ridker PM, Wilson PWF, Grundy SM. Should C-reactive protein be added to metabolic syndrome and to assessment of global cardiovascular risk? Circulation. 2004;109:2818–25.
3. Festa A, D'Agostino R Jr, Howard G, Mykkänen L, Tracy RP, Haffner SM. Chronic subclinical inflammation as part of insulin resistance syndrome: the insulin resistance atherosclerosis study (IRAS). Circulation. 2000;102:42–7.
4. Yudkin JS, Juhan-Vague I, Hawe E, Humphries SE, di Minno G, Margaglione M, et al. Low-grade inflammation may play role in the etiology of the metabolic syndrome in patients with coronary heart disease: the HIFMECH Study. Metabolism. 2004;53:852–7.
5. Vu JD, Vu JB, Pio JR, Malik S, Franklin SS, Chen RS, Wong ND. Impact of C-reactive protein on the likelihood of peripheral arterial disease in United States adult with the metabolic syndrome, diabetes mellitus, and preexisting cardiovascular disease. Am J Cardiol. 2005;96:655–8.
6. Zuliani G, Volpato S, Galvani M, Blè A, Bandinelli S, Corsi AM, et al. Elevated C-reactive protein levels and metabolic syndrome in the elderly: the role of central obesity data from the InChianti study. Atherosclerosis. 2009;203:626–32.
7. Freeman DJ, Norrie J, Caslake MJ, Gaw A, Ford I, Lowe GD, et al. C-reactive protein is an independent predictor of risk for the development of diabetes in the West of Scotland Coronary Prevention Study. Diabetes. 2002;51:1596–1600.
8. Pischon T, Hu FB, Rexrode KM, Girman CJ, Manson JE, Rimm EB. Inflammation, the metabolic syndrome, and the risk of coronary heart disease in women and men. Atherosclerosis. 2008;197:392–9.
9. Ridker PM, Pare G, Parker A, Zee RY, Danik JS, Buring JE, et al. Loci related to metabolic-syndrome pathways including LERP, HNF1A, IL6R, and GCKR associate with plasma

C-reactive protein: the Women's Genome Health Study. Am J Human Gen. 2008;82:1185–92.
10. Sattar N, Gaw A, Scherbakova O, Ford I, O'Reilly DS, Haffner SM, et al. Metabolic syndrome with and without C-reactive protein as a predictor of coronary heart disease and diabetes in the West of Scotland Coronary Prevention Study. Circulation. 2003;108:414–9.
11. Takeno M, Yasuda S, Otsuka Y, Morii I, Kawamura A, Yano K, Miyazaki S. Impact of metabolic syndrome on the long-term survival of patients with acute myocardial infarction – potential association with C-reactive protein. Circ J. 2008; 72:415–9.
12. Jenny NS, French B, Arnold AM, Strotmeyer ES, Cushman M, Chaves PHM, et al. Long-term assessment of inflammation and healthy aging in late life: the Cardiovascular Health Study All Stars. J Gerontol. 2012;67:970–6.
13. Wassel CL, Barrett-Connor E, Laughlin GA. Association of circulating C-reactive protein and interleukin-6 with longevity into 80s and 90s: The Rancho Bernardo Study. J Clin Endocrinol Metab. 2010;95:4748–55.
14. Kizer JR, Arnold AM, Jenny NS, Cushman M, Strotmeyer ES, Ives DG, et al. Longitudinal changes in adiponectin and inflammatory markers and relation to survival in the oldest old: The Cardiovascular Health Study All Stars Study. J Gerontol. 2011;66A:1100–7.
15. Isoaho R, Puolijoki H, Huhti E, Kivelä SL, Laippala P, Tala E. Prevalence of chronic obstructive pulmonary disease in elderly Finns. Respir Med. 1994;88:571–80.
16. Löppönen M, Räihä I, Isoaho R, Vahlberg T, Kivelä SL. Diagnosing cognitive impairment and dementia in primary health care – a more active approach is needed. Age Ageing. 2003;32: 606–12.
17. Takala TI, Suominen P, Isoaho R, Kivelä SL, Löppönen M, Peltola O, et al. Iron-replete reference intervals to increase sensitivity of hematologic and iron status laboratory tests in the elderly. Clin Chem. 2002;48:1586–9.
18. Loikas S, Löppönen M, Suominen P, Møller J, Irjala K, Isoaho R, et al. RIA for serum holo-transcobalamin: Method evaluation in the clinical laboratory and reference interval. Clin Chem. 2003;49:455–62.
19. World Health Organization. Definition, Diagnosis and Classification of Diabetes Mellitus and its Complications. Report of a WHO Consultation, Part 1: Diagnosis and Classification of Diabetes Mellitus. Geneva: World Health Organization; 1999.
20. The Emerging Risk Factors Collaboration; Kaptoge S, Di Angelantonio E, Pennells L, Wood AM, White IR, Gao P, et al. C-reactive protein, fibrinogen, and cardiovascular disease prediction. N Eng J Med 2012;367:1310–20.
21. Alberti K, Zimmet P, Shaw F for the IDF Epidemiology Task Force Consensus Group. The metabolic syndrome – a new worldwide definition. Lancet 2005;366:1059–62.
22. Zimmet P, Magliano D, Matsuzawa Y, Alberti G, Shaw J. The metabolic syndrome: a global health problem and a new definition. J Atheroscler Thromb. 2005;12:295–300.
23. Baumgartner RN, Stauber PM, McHugh D, Koehler KM, Garry PJ. Cross-sectional age differences in body composition in persons 60 + years of age. J Gerontol Series A Biol Sci Med Sci. 1995;50:M307–16.
24. Bales CW, Ritchie CS. Sarcopenia, weight loss, and nutritional frailty in the elderly. Annual Rev Nutr. 2002;22:309–23.
25. Seidell JC, Visscher TL. Body weight and weight change and their health implications for the elderly. Eur J Clin Nutr. 2000;54:S33–9.
26. Pearson TA, Mensah GA, Alexander RW, Anderson JL, Cannon RO, Criqui M, et al. Markers of inflammation and cardiovascular disease: application to clinical and public health care. Circulation. 2003;107:499–511.