Self-Rated Health is Associated with Elevated C-Reactive Protein Even among Apparently Healthy Individuals

Eran Leshem-Rubinow MD[1]*, Shani Shenhar-Tsarfaty PhD[1]*, Assi Milwidsky MD[2], Sharon Toker PhD[4], Itzhak Shapira MD[1], Shlomo Berliner MD[2], Yael Benyamini PhD[5], Samuel Melamed PhD[4] and Ori Rogowski MD[3]

[1]Department of Cardiology and Departments of Internal Medicine [2]E and [3]C, Tel Aviv Sourasky Medical Center, Tel Aviv, affiliated with Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel

[4]Faculty of Management, and [5]Shapell School of Social Work and Herczeg Institute on Aging, Tel Aviv University, Tel Aviv, Israel

ABSTRACT: **Background:** A single self-rated health (SRH) assessment is associated with clinical outcome and mortality, but the biological process linking SRH with immune status remains incompletely understood.

Objectives: To examine the association between SRH and inflammation in apparently healthy individuals.

Methods: Our analysis included 13,773 apparently healthy individuals attending the Tel Aviv Sourasky Medical Center for periodic health examinations. Estimated marginal means of the inflammation-sensitive biomarkers [i.e., highly sensitive C-reactive protein (hs-CRP) and fibrinogen] for the different SRH groups were calculated and adjusted for multiple potential confounders including risk factors, health behavior, socioeconomic status, and coexistent depression.

Results: The group with the lowest SRH had a significantly higher atherothrombotic profile and significantly higher concentrations of all inflammation-sensitive biomarkers in both genders. Hs-CRP was found to differ significantly between SRH groups in both genders even after gradual adjustments for all potential confounders. Fibrinogen differs significantly according to SRH in males only, with low absolute value differences.

Conclusions: A valid association exists for apparently healthy individuals of both genders between inflammation-sensitive biomarker levels and SRH categories, especially when comparing levels of hs-CRP. Our findings underscore the importance of assessing SRH and treating it like other markers of poor health.

IMAJ 2015; 17: 213–218

KEY WORDS: self-rated health (SRH), inflammation, C-reactive protein (CRP), apparently healthy individuals

For Editorial see page 245

It has been found that subjective health perceived by an individual at a certain time point is associated with various measures of physical, functional and mental health [1] and includes important information not usually obtained in daily clinical practice [2]. All this information can be summarized by a single self-rated health (SRH) item, which typically involves rating one's global health on a scale of five, from poor to excellent. SRH has been found to be an independent predictor of clinical outcome and mortality [3,4], even after adjusting for a variety of health-related measures. Its predictive validity has been reported in a large number of community-based studies [5] in many different countries as well as in studies of patient populations. For example, poor SRH has been associated with increased morbidity and mortality and with adverse outcomes in myocardial infarction [6] and dialysis [7] patients.

The psychobiological mechanisms leading a person to perceive his or her health as poor and the reasons for its independent association with future health and clinical prognosis are not fully understood. One explanation suggests that SRH is more inclusive than the covariates typically used by researchers and clinicians and reflects, among other aspects of health, symptoms of existing diseases as well as those in preclinical stages [6,8]. This explanation is in line with past studies implicating [9,10] the role of the immune system in predicting changes in individuals' health perceptions. Changes in health perception may be reflective of inflammation, characterized by acute-phase reactants and circulating pro-inflammatory cytokines that are interpreted by the brain as a sign of sickness [11], leading to changes in behavior, physical sensations, cognition, and emotions.

Cytokine-induced sickness behavior may be salient to the person and consequently is reflected in his/her SRH [12]. The association between SRH and inflammatory markers has been tested in previous studies, which were mostly based on relatively small samples (< 300 participants) [9,10,13], focused only on older adults [14] or on chronically ill patients [9], and/or did not adjust for both existing diseases and risk factors [15]. The current study examines the association between SRH and inflammation-sensitive biomarker levels in a large sample of apparently healthy women and men in midlife attending a periodic health examination, including adjustments for major diseases and risk factors.

*The first two authors contributed equally to this study

SUBJECTS AND METHODS

We analyzed data collected through the Tel Aviv Sourasky Medical Center Inflammation Survey, a registered databank of the Israel Ministry of Justice [16,17]. This relatively large survey comprises apparently healthy individuals attending this center for periodic health examinations sponsored by their employer as a fringe benefit.

All those who attended the routine health examinations at the Tel Aviv Sourasky Medical Center between September 2002 and September 2010 were invited to participate in the survey. Individuals were recruited while awaiting their turn for medical examination and gave their written consent in accordance with the guidelines of the Institutional Ethics Committee. A total of 17,393 subjects gave their informed consent (10,975 males, 6418 females).

We initially excluded 3030 subjects because of their medical findings, including malignant conditions, immunosuppressive therapy, known inflammatory disease (arthritis, inflammatory bowel disease, psoriasis, etc.), pregnancy, steroidal or non-steroidal treatment (except for aspirin at a dose of ≤ 325 mg/day), and acute infection or invasive procedures (surgery, catheterization, etc.) during the previous 6 months. Additional exclusion criteria included missing data on one of the inflammatory biomarkers (n=166) or regarding self-reported health (n=346). Finally, due to the very small number of individuals who reported poor or very poor health, and in order to eliminate their bias, we further excluded those 78 individuals. Following these exclusions the final sample comprised 13,773 individuals (8851 males and 4922 females) with a mean age of 44 (± 11) years.

LABORATORY METHODS

Analysis of complete blood counts was performed using the Coulter STKS™ (Beckman Coulter, Nyon, Switzerland) electronic cell analyzer. Fibrinogen concentrations were calculated by the method of Clauss [18] and a Sysmex 6000™ (Sysmex Corporation, Hyaga, Japan) autoanalyzer. High sensitivity C-reactive protein (hs-CRP) levels were measured using a Boehring BN II Nephelometer™ (DADE Boehring, Marburg, Germany) [19]. The erythrocyte sedimentation rate (ESR) was calculated using the Westergren method [20].

DEFINITION OF ATHEROTHROMBOTIC RISK

Findings in the routine health checkups were assessed for atherothrombotic risk using various criteria. Risk factors included diabetes mellitus, defined as fasting glucose levels ≥ 126 mg/dl (7.0 mmol/L) or regular intake of insulin or any oral hypoglycemic; hypertension, defined as blood pressure > 140/90 mmHg on two separate measurements or regular intake of antihypertensive drugs; dyslipidemia, defined as low density lipoprotein (LDL) concentration or non-high density lipoprotein (HDL) cholesterol concentration, and individuals displaying elevated triglyceride concentrations above recommended levels according to risk profile defined by the updated ATP III recommendations [21] or the intake of lipid-lowering medications. The definition of metabolic syndrome was based on the NCEP ATP III Criteria [21], with the modified Impaired Fasting Glucose criteria of the American Diabetes Association, as proposed by the updated AHA/NHLBI scientific statement [22]. Smokers were individuals who smoked at least five cigarettes per day, while past smokers had quit smoking at least 30 days prior to examination.

STATISTICAL ANALYSIS

All analyses were performed separately for each gender due to the significant variance in inflammation-sensitive biomarker levels between genders and the different factors influencing these biomarkers within each group. All continuous variables are presented as the mean (standard deviation), and categorical variables as the number (percent) of patients in each group. Hs-CRP levels, ESR and triglyceride concentrations did not have normal distributions in this population. A logarithmic transformation was used to convert them to normal distributions for all statistical purposes, such as regressions and ANCOVA. All hs-CRP, ESR and triglyceride results are thus depicted as back-transformed geometric means and standard deviation. The one-sample Kolmogorov-Smirnov test and Q-Q plots were used to test for normality of distributions.

For continuous variables, one-way analyses of variance (ANOVA) were performed to compare various parameters among different SRH groups, as well as for calculating the significance of trends. For all categorical variables, the chi-square test was used to assess the overall significance of variance among groups.

In order to assess the independent association of SRH with the variability in inflammation-sensitive biomarker levels, we calculated the estimated marginal means of the inflammation-sensitive biomarkers for the different SRH groups and adjusted for various potential confounders using a general linear model of ANCOVA. These potential confounders were variables with either known or suspected influence on inflammatory-sensitive biomarker levels and SRH, and included:

- age
- waist circumference
- cardiovascular risk factors such as diabetes mellitus, history of atherothrombotic event (ischemic heart disease, cerebrovascular event or peripheral arterial disease), hypertension, dyslipidemia and family history of coronary heart disease
- health behaviors, including current and past smoking status, alcohol consumption habits and physical activity intensity
- regular intake of either oral contraceptives or hormone replacement therapy in women
- level of education expressed as number of school years

- level of depression calculated using the Patient Health Questionnaire (PHQ-9) [23].

This questionnaire includes nine questions on signs and symptoms of depression, and the total sum of scores was used in the analyses. In our cohort the internal reliability was high (Cronbach's alpha of 0.78). The SPSS statistical package version 19.0 was used to perform all statistical analyses (SSPS Inc., Chicago, IL, USA).

RESULTS

The anthropometric characteristics, blood pressure values, relevant laboratory studies, inflammation-sensitive biomarker levels, sport activity and alcohol consumption habits of both genders are described in Tables 1 and 2 for males and females, respectively, according to SRH groups. The group with the lowest SRH had a significantly higher atherothrombotic profile, as evident by higher plasma glucose concentrations, LDL and triglyceride concentrations, lower HDL concentration, higher waist and body mass index (BMI), older age, higher measured systolic and diastolic blood pressure, lower physical activity in both genders, and lower alcohol consumption in women. In addition, we noted significantly higher concentrations of all inflammation-sensitive biomarkers in this group in both genders.

Various cardiovascular risk factors for both genders are described in Table 3, and the frequency of relevant drug intake in Table 1. As noted in Table 1, the rates of atherothrombotic diseases and risk factors, including family history, were all higher in the lower SRH group. The percentages of individuals taking cardiovascular medication were also higher in this group, including medications that lower inflammatory biomarkers, such as statins. On the other hand, oral contraceptives were much more prevalent in the higher SRH group, and those medications are known to elevate inflammatory biomarkers.

Since the crude and unadjusted association of inflammation-sensitive biomarkers across the different SRH groups yielded significant results in both genders [Tables 1 and 2], we further investigated the association of these biomarkers in each of the three SRH groups following gradual adjustments for confounders [Table 4]. Our findings show that hs-CRP significantly differs between SRH groups in both genders even after the adjustments to all potential confounders [Table 4]. Fibrinogen differs according to SRH but the difference is significant in males only, with low absolute value (data not shown*). ESR and white blood cell (WBC) count do not sustain significance following adjustment (data not shown*).

Finally, to minimize the potential effect of some of the variables, we repeated the analyses for hs-CRP after further excluding individuals with a history of atherothrombotic event, diabetes mellitus, hypertension, dyslipidemia, or metabolic syndrome, as well as current smokers. This subsample of apparently

*Available from the author on request

Table 1. Mean (SD) of anthropometric variables, laboratory findings and inflammation-sensitive biomarker levels, by SRH group (men)

	SRH	Average	Good	Excellent	ANOVA	
Men	**N**	**909**	**5345**	**2597**	***P* value**	***P* for trend**
Anthropometric profile	Age (years)	47 (11)	45 (11)	40 (11)	‹ 0.001	‹ 0.001
	No. of school years	15.2 (3.0)	15.5 (2.9)	15.4 (2.8)	0.027	0.148
	Waist circumference (cm)	101 (12)	95 (10)	91 (9)	‹ 0.001	‹ 0.001
	BMI (kg/m^2)	29 (5)	27 (4)	26 (3)	‹ 0.001	‹ 0.001
	Systolic BP (mmHg)	128 (16)	125 (15)	122 (13)	‹ 0.001	‹ 0.001
	Diastolic BP (mmHg)	81 (9)	79 (8)	76 (8)	‹ 0.001	‹ 0.001
	Alcohol consumption (units)	1.2 (2.9)	1.3 (2.3)	1.3 (2.2)	0.788	0.521
	Physical activity (hours)	1.4 (2.2)	2.1 (2.6)	3.1 (3.1)	‹ 0.001	‹ 0.001
Lab findings	Plasma glucose levels (mg/dl)	101 (27)	95 (17)	91 (12)	‹ 0.001	‹ 0.001
	HDL cholesterol (mg/dl)	48 (10)	50 (10)	52 (11)	‹ 0.001	‹ 0.001
	LDL cholesterol (mg/dl)	121 (33)	122 (31)	117 (31)	‹ 0.001	0.005
	Triglyceride levels (mg/dl)	130 (2)	115 (2)	97 (2)	‹ 0.001	‹ 0.001
Inflammatory biomarkers	hs-CRP levels (mg/L)	2.0 (2.8)	1.4 (2.8)	1.1 (2.8)	‹ 0.001	‹ 0.001
	Fibrinogen (mg/dl)	299 (62)	286 (57)	270 (54)	‹ 0.001	‹ 0.001
	ESR (sec)	9.3 (2.2)	8.2 (2.1)	7.2 (2.2)	‹ 0.001	‹ 0.001
	WBC (10^3/µl)	7.3 (1.9)	6.8 (1.6)	6.5 (1.5)	‹ 0.001	‹ 0.001

SRH = self-rated health, SD = standard deviation, ANOVA = one-way analysis of variance, BMI = body mass index, BP = blood pressure, HDL = high density lipoprotein, LDL = low density lipoprotein, hs-CRP = high sensitivity C-reactive protein, ESR = erythrocyte sedimentation rate, WBC = white blood cells

Table 2. Mean (SD) of anthropometric variables, laboratory findings and inflammation-sensitive biomarker levels, by SRH group (women)

Women	SRH	Average	Good	Excellent	ANOVA	*P* for trend
	N	**559**	**3232**	**1131**	***P* value**	
Anthropometric profile	Age (years)	48 (10)	45 (10)	41 (11)	‹ 0.001	‹ 0.001
	No. of school years	14.5 (2.9)	15.3 (2.9)	15.6 (2.7)	‹ 0.001	‹ 0.001
	Waist circumference (cm)	88 (13)	82 (12)	78 (10)	‹ 0.001	‹ 0.001
	BMI (kg/m^2)	28 (6)	25 (5)	24 (4)	‹ 0.001	‹ 0.001
	Systolic BP (mmHg)	121 (18)	117 (16)	112 (14)	‹ 0.001	‹ 0.001
	Diastolic BP (mmHg)	76 (9)	74 (8)	72 (7)	‹ 0.001	‹ 0.001
	Alcohol consumption (units)	0.3 (0.9)	0.5 (1.4)	0.7 (1.5)	‹ 0.001	‹ 0.001
	Physical activity (hours)	1.3 (2.5)	1.7 (2.4)	2.5 (2.9)	‹ 0.001	‹ 0.001
Lab findings	Plasma glucose levels (mg/dl)	97 (29)	90 (15)	87 (10)	‹ 0.001	‹ 0.001
	HDL cholesterol (mg/dl)	60 (14)	64 (15)	67 (15)	‹ 0.001	‹ 0.001
	LDL cholesterol (mg/dl)	124 (35)	118 (32)	111(31)	‹ 0.001	‹ 0.001
	Triglyceride levels (mg/dl)	106 (2)	91 (2)	81 (2)	‹ 0.001	‹ 0.001
Inflammatory biomarkers	hs-CRP levels (mg/L)	2.4 (3.3)	1.6 (3.2)	1.4 (3.2)	‹ 0.001	‹ 0.001
	Fibrinogen (mg/dl)	327 (60)	312 (59)	303 (58)	‹ 0.001	‹ 0.001
	ESR (sec)	18.5 (1.8)	16.4 (1.8)	15.4 (1.9)	‹ 0.001	‹ 0.001
	WBC (10^3/µl)	7.0 (1.8)	6.8 (1.7)	6.7 (1.7)	‹ 0.001	‹ 0.001

SD = standard deviation, ANOVA = one-way analysis of variance, BMI = body mass index, BP = blood pressure, HDL = high density lipoprotein, LDL = low density lipoprotein, hs-CRP = high sensitivity C-reactive protein, ESR = erythrocyte sedimentation rate, WBC = white blood cells

Table 3. Number (%) of individuals with history of cardiovascular event and cardiovascular risk factors by SRH group (men and women)

SRH	Average		Good		Excellent		Chi-square
Men (N)	**909**		**5345**		**2597**		***P* value**
History of atherothrombotic event	111	(12.2)	216	(4.0)	31	(1.2)	‹ 0.001
Diabetes mellitus	130	(14.3)	246	(4.6)	39	(1.5)	‹ 0.001
Hypertension	401	(44.1)	1457	(27.3)	384	(14.8)	‹ 0.001
Dyslipidemia	455	(50.1)	1847	(34.6)	473	(18.2)	‹ 0.001
Current smoker	201	(22.3)	920	(17.3)	338	(13.1)	‹ 0.001
Past smoker	266	(29.5)	1455	(27.4)	568	(22.0)	
Family history of CHD	197	(21.7)	798	(14.9)	298	(11.5)	‹ 0.001
Women (N)	**559**		**3232**		**1131**		***P* value**
History of atherothrombotic event	44	(7.9)	85	(2.6)	4	(0.4)	‹ 0.001
Diabetes mellitus	51	(9.1)	101	(3.1)	8	(0.7)	‹ 0.001
Hypertension	165	(29.5)	499	(15.4)	68	(6.0)	‹ 0.001
Dyslipidemia	209	(37.4)	718	(22.2)	120	(10.6)	‹ 0.001
Current smoker	140	(25.2)	607	(18.9)	156	(13.9)	‹ 0.001
Past smoker	103	(18.6)	649	(20.2)	206	(18.4)	
Family history of CHD	118	(21.1)	570	(17.6)	166	(14.7)	0.003

CHD = coronary heart disease

healthy individuals comprised 7686 individuals (4784 males, 2902 females). Significant differences in hs-CRP are evident between the SRH groups even among this healthier group (data not shown*). However, the hs-CRP concentrations are lower and the differences between the SRH groups smaller in this healthier subsample, as compared to the full sample, especially among women.

DISCUSSION

The current study demonstrates an association between inflammation-sensitive biomarker levels and SRH categories among apparently healthy individuals, especially when comparing levels of hs-CRP. This association is valid for both genders and even when tested among those individuals with no known co-morbidities.

These observations are in line with prior publications addressing the issue that perception of subjective health is related to levels of inflammatory cytokines, and that poor SRH is associated with higher levels of cytokines. This correlation between pro-inflammatory cytokines (specifically tumor necrosis factor-alpha and interleukin-1 beta) has been shown by general population surveys to be significant in primary care [24] and in relation to illness (e.g., coronary heart disease), but only in women [9,10]. Those studies assumed that the difference between genders was attributed to differences in self-health judgment between men (reflecting symptoms of function) and women (associated with subjective symptoms and being more sensitive to the overall quantity of their negative feelings) [25]. Accordingly, if SRH is affected by cytokines, the perceived symptoms are expected to be diffuse and subjective in nature. Therefore, the stronger relation between SRH and inflammatory cytokines found in women was considered due to differences in health apprehension between the sexes. On the other hand, the immune characteristics of men are different from those of women, who have a higher prevalence of autoimmune diseases, and it is possible that these differences together with a possible higher immune baseline in women account for the significant correlation between inflammatory response and SRH found in prior research. Our results show a significant association between hs-CRP and SRH among apparently healthy individuals of both genders, validating a previous correlation between SRH and inflammatory biomarkers in women only. A possible explanation for this association among males is the large sample size of our cohort. In addition, our cohort population comprised relatively healthy individuals who were younger than in previous studies regarding SRH in the general population, and we performed multilayer adjustments to clinical and behavioral factors, including depression that was assumed in the past to be the reason for gender differences [24].

We acknowledge several limitations. Our cohort of participants undergoing a periodic health examination may not be

representative of the general population as most were highly educated, white-collar workers who exhibited generally good health-behavior patterns. This could explain the very small number of individuals who reported poor or very poor health. However, our results were significant even after we narrowed the range of SRH answers. We assume that a more heterogeneous cohort would yield even better associations, but this is yet to be explored.

Our study has several strengths, such as the large sample size, the multiple biomarkers used to assess the inflammatory profile, controlling for several well-known antecedents of SRH, and that the analyses were based on apparently healthy persons. In addition, the participants were not aware of their inflammation levels when answering the questionnaire, thus avoiding common method bias.

The findings support the argument that SRH is more inclusive than covariates typically used in epidemiological studies, suggesting that SRH is sensitive both to medical information and to the experience of bodily sensations. These sensations may be affected by inflammatory biomarkers and may explain how SRH predicts morbidity and mortality even when objective disease is absent. Thus, our findings underscore the importance of assessing SRH and addressing it like other markers of poor health. SRH provides an important screening tool for high risk populations [3] as for the general population. Unmasking the biological determinants of the self-perception leading to SRH, along with the biomarkers correlating with it, is most important and should be addressed in future longitudinal research.

Table 4. Estimated marginal mean (95% CI) of hs-CRP according to SRH group (men and women)

	Average	Good	Excellent	*P* value
Men				
Crude	2.05 (1.92–2.19)	1.44 (1.41–1.48)	1.09 (1.05–1.13)	‹ 0.001
Age adjusted	1.96 (1.84–2.10)	1.42 (1.39–1.46)	1.14 (1.09–1.18)	‹ 0.001
Age & waist adjusted	1.65 (1.55–1.76)	1.41 (1.37–1.44)	1.25 (1.20–1.29)	‹ 0.001
Age, waist & renal function adjusted*	1.48 (1.35–1.63)	1.28 (1.17–1.39)	1.17 (1.06–1.28)	‹ 0.001
As above + health behavior†	1.56 (1.41–1.71)	1.37 (1.25–1.50)	1.28 (1.16–1.41)	‹ 0.001
As above + SES (education)	1.55 (1.40–1.70)	1.36 (1.25–1.49)	1.26 (1.15–1.40)	‹ 0.001
Multi-adjusted with PHQ-9	1.44 (1.30–1.60)	1.30 (1.18–1.43)	1.22 (1.10–1.35)	0.001
Women				
Crude	2.46 (2.24–2.71)	1.60 (1.53–1.66)	1.40 (1.30–1.49)	‹ 0.001
Age adjusted	2.47 (2.24–2.71)	1.60 (1.53–1.66)	1.40 (1.30–1.50)	‹ 0.001
Age & waist adjusted	1.96 (1.80–2.15)	1.60 (1.54–1.65)	1.58 (1.48–1.68)	‹ 0.001
Age, waist & renal function adjusted*	1.87 (1.61–2.19)	1.67 (1.45–1.92)	1.71 (1.46–1.99)	0.061
As above + health behavior†	1.77 (1.51–2.07)	1.58 (1.36–1.83)	1.63 (1.39–1.91)	0.062
As above + use of hormones	2.14 (1.83–2.50)	1.88 (1.63–2.17)	1.91 (1.63–2.23)	0.028
As above + SES (education)	2.14 (1.83–2.50)	1.91 (1.65–2.21)	1.95 (1.66–2.29)	0.068
Multi-adjusted with PHQ-9	2.21 (1.88–2.60)	1.93 (1.66–2.24)	1.95 (1.66–2.30)	0.033

*Family history of coronary heart disease, diabetes mellitus, history of atherothrombotic event, hypertension, dyslipidemia

†Current or past smoking status, alcohol consumption, sport intensity

SES = socioeconomic status, PHQ-9 = Patient Health Questionnaire

Correspondence

Dr. A. Milwidsky

Dept. of Internal Medicine C, Tel Aviv Sourasky Medical Center, Tel Aviv 64239, Israel

Phone: (972-3) 697-3705

Fax: (972-3) 697-4988

email: assi_mil@hotmail.com

References

1. Pinquart M. Correlates of subjective health in older adults: a meta-analysis. *Psychol Aging* 2001; 16 (3): 414-26.
2. Benyamini Y, Leventhal EA, Leventhal H. Self-assessments of health: what do people know that predicts their mortality? *Res Aging* 1999; 21 (3): 477-500.
3. Fayers PM, Sprangers MA. Understanding self-rated health. *Lancet* 2002; 359 (9302): 187-8.
4. Haring R, Feng YS, Moock J, et al. Self-perceived quality of life predicts mortality risk better than a multi-biomarker panel, but the combination of both does best. *BMC Med Res Method* 2011; 11: 103.
5. Benyamini Y, Idler EL. Community studies reporting association between self-rated health and mortality: additional studies, 1995-1998. *Res Aging* 1999; 21(3): 392-401.
6. Gerber Y, Benyamini Y, Goldbourt U, Drory Y. Prognostic importance and long-term determinants of self-rated health after initial acute myocardial infarction. *Med Care* 2009; 47 (3): 342-9.
7. Thong MS, Kaptein AA, Benyamini Y, Krediet RT, Boeschoten EW, Dekker FW. Association between a self-rated health question and mortality in young and old dialysis patients: a cohort study. *Am J Kidney Dis* 2008; 52 (1): 111-17.
8. Benyamini Y. Why does self-rated health predict mortality? An update on current knowledge and a research agenda for psychologists [Editorial]. *Psychol Health* 2011; 26 (11): 1407-13.
9. Janszky I, Lekander M, Blom M, Georgiades A, Ahnve S. Self-rated health and vital exhaustion, but not depression, is related to inflammation in women with coronary heart disease. *Brain Behav Immun* 2005; 19 (6): 555-63.
10. Unden AL, Andreasson A, Elofsson S, et al. Inflammatory cytokines, behaviour and age as determinants of self-rated health in women. *Clin Sci (Lond)* 2007; 112 (6): 363-73.
11. Dantzer R. Cytokine-induced sickness behavior: where do we stand? *Brain Behav Immun* 2001; 15 (1): 7-24.
12. Jylhä M. What is self-rated health and why does it predict mortality? Towards a unified conceptual model. *Soc Sci Med* 2009; 69 (3): 307-16.
13. Christian LM, Glaser R, Porter K, Malarkey WB, Beversdorf D, Kiecolt-Glaser JK. Poorer self-rated health is associated with elevated inflammatory markers among older adults. *Psychoneuroendocrinology* 2011; 36: 1495-504.
14. Jylhä M, Volpato S, Guralnik JM. Self-rated health showed a graded association with frequently used biomarkers in a large population sample. *J Clin Epidemiol* 2006; 59 (5): 465-71.
15. Dowd JB, Zajacova A. Does self-rated health mean the same thing across socioeconomic groups? Evidence from biomarker data. *Ann Epidemiol* 2010; 20 (10): 743-9.
16. Rogowski O, Shapira I, Shirom A, Melamed S, Toker S, Berliner S. Heart rate and microinflammation in men: a relevant atherothrombotic link. *Heart* 2007; 93 (8): 940-4.
17. Rogowski O, Shapira I, Peretz H, Berliner S. Glycohaemoglobin as a determinant of increased fibrinogen concentrations and low-grade inflammation in apparently healthy nondiabetic individuals. *Clin Endocrinol (Oxf)* 2008; 68 (2): 182-9.
18. Clauss A. Rapid coagulation methos for fibrinogen determination. *Acta Haematol Basel* 1957; 17: 237-46.

19. Rifai N, Tracy RP, Ridker PM. Clinical efficacy of an automated high-sensitivity C-reactive protein assay. *Clin Chem* 1999; 45 (12): 2136-41.

20. ICSH recommendations for measurement of erythrocyte sedimentation rate. International Council for Standardization in Haematology (Expert Panel on Blood Rheology). *J Clin Pathol* 1993; 46 (3): 198-203.

21. NCEP/ATPIII. Executive Summary of The Third Report of The National Cholesterol Education Program (NCEP) Expert panel on detection, evaluation, and treatment of high blood cholesterol in adults (Adult Treatment Panel III). *JAMA* 2001; 285 (19): 2486-97.

22. Grundy SM, Cleeman JI, Daniels SR, et al. Diagnosis and management of the metabolic syndrome: an American Heart Association/National Heart, Lung, and Blood Institute Scientific Statement. *Circulation* 2005; 112 (17): 2735-52.

23. Kroenke K, Spitzer RL, Williams JB. The PHQ-9: validity of a brief depression severity measure. *J Gen Intern Med* 2001; 16 (9): 606-13.

24. Tanno K, Ohsawa M, Onoda T, et al. Poor self-rated health is significantly associated with elevated C-reactive protein levels in women, but not in men, in the Japanese general population. *J Psychosomat Res* 2012; 73 (3): 225-31.

25. Kumpusalo E, Pekkarinen H, Neittaanmaki L, Penttila I, Halonen P. Identification of health status dimensions in a working-age population. An exploratory study. *Med Care* 1992; 30 (5): 392-9.