Association of GFR, Fiber-Rich Regimen and Metabolic Syndrome With Elevated C-Reactive Protein Levels: Results of a Multicenter National Survey

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Abstract- The present study investigates the association of cardiovascular risk factors such as metabolic syndrome (MetS), fiber-rich regimen, and Glomerular Filtration Rate (GFR) with elevated high-sensitivity C-reactive protein (hsCRP) levels. We designed a cross-sectional study based on data of the third National Survey of non-communicable diseases (SuRFNCD-2007); among 2125, Iranian adults (1168 women) aged 25-64 years. Demographic and anthropometric characteristics were collected. Biochemical assessments, were determined on venous blood samples. Quantitative highly sensitive CRP was measured via enzyme-linked immunoassay. Elevated CRP was defined as values above 3 mg/l. Metabolic syndrome was defined according to the ATP III (Adult Treatment Panel III report, 2005). GFR was calculated with the MDRD formula. Multivariable logistic regression accompanied by complex sample survey analysis, including stratified weighting, were recruited. The fiber-rich regimen was determined by the daily consumption of more than five units of vegetables or fruits. Mean age of the population was 39.4±4.5 years. Adjusted odds ratios for prediction of high CRP pertaining to High LDL, Low Physical activity, BUN, MetS ATP III, Declined GFR (per 30 units reduction), optimal Fiber intake, and Current Smoking were calculated. Corresponding values with 95 % CI were 1.36 (1.04-1.85), 1.31(1.11-4.20), 1.04(1.04-1.12), 1.47 (1.04-2.09), 1.22 (1.11-3.36), 0.84 (0.87-1.48), 1.74 (0.39-1.38), respectively. We figured out that MetS, declined GFR in early stages of CKD, and low physical activity were related to high inflammatory state, while fiber-rich regimen decreased the likelihood of high CRP in smokers.

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Introduction

Multiple studies ranging from basic experimental pieces of evidence to population-based researches have revealed that CHD is, in large part, a systemic inflammatory process. Furthermore, Inflammation contributes to all stages of atherosclerosis, which plays a key role in the pathophysiology of CHD, and thus circulating factors related to inflammation may be novel predictors of cardiovascular events (1-4). C-reactive protein influences different pro-inflammatory pathways and serves as an indicator of low-grade inflammation. Although derived predominantly from the liver, it has been found in atherosclerotic plaques, too. This finding probably reflects that the plaque is vulnerable to rupture. It also has a potential predictive value for cardiovascular risk, especially in apparently healthy individuals (intermediate-risk category) (1,5-7).

Metabolic syndrome (MetS) comprises a constellation of cardiovascular risk equivalents associated with an increased risk of developing cardiovascular diseases and type 2 diabetes mellitus, Furthermore, inflammation has been proposed to be a major pathophysiological factor for the development of MetS and insulin resistance. In the

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same way, the association of hsCRP and MetS has been investigated in different settings, repeatedly (8-11). In spite of the pieces of evidence mentioned above, inflammatory markers explained only a small part of the association between the metabolic syndrome and CHD mortality in one study (2).

Materials and Methods

A total of 2125 adults (957 men and 1168 women) aged 25-64 years have been selected for the analysis. We have used the Database of the third national surveillance of risk factors of non-communicable diseases (SuRFNCD), carried out in 2007. Details of the survey have been described elsewhere (12). In brief, a cluster sampling scheme was employed to randomly select a representative sample of adults aged 25-64 years. Each cluster consisted of two men and two women from each age category (5-year strata). The number of clusters was proportionate to the urban/rural population size in each province, for example, 51 clusters (1020 subjects) from Tehran (the largest province) and 2 clusters (40 subjects) from Ilam (The smallest province). Trained healthcare professionals carried out interviews and physical examinations at the participants' households. Standardized questionnaires were applied in order to collect general health characteristics and demographic information. According to a predetermined schedule, the quality of records was rechecked. Physical examination and collection of blood samples were performed in the second and third steps of the plan, respectively. All of the participants were included through a standard and clear process of informed consent. Common ethical considerations for both SuRFNCD-2007 and the present study received the approval of the National Center for Disease Control and declaration of Helsinki.

Anthropometric indices were measured in light clothing and with no footwear. A portable calibrated electronic weighing scale, and portable measuring inflexible bars were used for this purpose. Waist circumference (WC) was measured using constant tension tape at the end of a normal expiration, with arms relaxed at the sides, at the midpoint between the lower margin of the rib cage and the highest point of the hip on the mid-axillary line. The body mass index (BMI, in kg/m^2) was calculated according to the Quetelet formula. A Calibrated sphygmomanometer (Omron M7, HEM-780-E, Tokyo, Japan) was used to determine participants' blood pressure at 5-min intervals. The mean value of three measurements was recorded as systolic and diastolic blood pressures. The assessment of physical activity was performed by the second version of the Global Physical Activity Questionnaire (GPAQ) and is described extensively elsewhere.

After overnight fasting for 10-12 hours, Blood samples were taken according to the standard protocol. Ten milliliters of Venous blood was taken in sitting position, collected in four tubes, centrifuged immediately, and transferred under cold chain condition to the Central Reference Laboratory of Ministry of Health of Iran (Tehran, Iran). Fasting plasma glucose (FPG), total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), and triglycerides (TG) were measured.

Quantitative CRP concentrations in serum were measured using high-sensitivity enzyme-linked immunosorbent assay (The quantitative CRP kit, Parsazmun, Karaj, Iran), with an intra-assay coefficient of variation of 2.6%.

Revised ATP III (2005) criteria were used to define metabolic syndrome (13). According to the current NCEP-ATP III criteria, the definition of the metabolic syndrome is established with the presence of any three of the following five traits: (1). Abdominal obesity, defined as waist circumference in men >102 cm (40 in) and in women >88 cm (35 in) (2). Serum triglycerides ≥150 mg/dL (1.7 mmol/L) or drug treatment for elevated triglycerides (3).Serum HDL cholesterol <40 mg/dL (1 mmol/L) in men and <50 mg/dL (1.3 mmol/L) in women or drug treatment for low HDL-C. (4).Blood pressure ≥130/85 mmHg or drug treatment for elevated blood pressure (5). Fasting plasma glucose (FPG) ≥100 mg/dL (5.6 mmol/L) or drug treatment for elevated blood glucose.

STEPs schedule released by WHO was the cornerstone of measuring daily fiber consumption in participants. One standard serving was equal to 80 grams (translated into different units of cups according to the type of vegetable and standard cup measures available in the country. An optimal or fiber-rich diet was defined as the consumption of five or more units per day. CRP values above 3 mg/l were considered high. We also used the Framingham risk score in order to estimate the 10-year risk of coronary heart disease in subjects (14). GFR was calculated via the MDRD equation (15).

Complex sample survey analysis was carried out using SPSS 18 for windows (Chicago, IL) and STATA SE 12 (Texas 77845 USA). Data were weighted for sex, age (5-year strata), and residential area (urban/rural within 30 provinces), according to the population of Iran based on the national census, 2006. Continuous variables are expressed as mean±standard deviation (SD). A *P* of

less than 0.05 for a two-tailed test was considered statistically significant. Since the hs-CRP concentrations were skewed rightward, we found that the log transformation of values would give a better fit to the normal distribution. Partial correlation coefficients were calculated between quantitative CRP and features of metabolic syndrome after adjustment for different variables. Independent t-test and $\chi 2$ analysis were applied to compare continuous and categorical variables, respectively. Multivariable logistic regression analyses were performed to ascertain the independent correlations between various components of MetS and log-transformed hs-CRP. To demonstrate the standard use of blood test results in clinical practice, primary analyses were performed without covariate adjustment. During secondary analyses, we carried out multiple adjustments of Possible confounders (e.g., sex, age, smoking, LDL-C, insulin resistance, BMI, WC, leptin, physical activity). The odds ratio (OR) with a 95% confidence interval (CI) was calculated for each SD increment in hs-CRP. We repeated the analyses after the exclusion of 165 subjects with hs-CRP levels ≥10 (mg/l) in order to decrease the impact of probable active inflammatory or infectious conditions. Then, the results were compared to each other. This analysis was also applied to assess the difference in the Framingham risk score (FRS) among the groups with and without metabolic syndrome and quartiles of hs-CRP.

Results

A total of 2125 adults aged 25-64 years were enrolled after excluding subjects with missing data in questionnaires (n=113), pregnant women (n=28), and individuals who refused to give blood samples (n=106). Having thorough records of data (without missing values) in three major domains of the study (*i.e.*, questionnaire variables, laboratory measurements, and physical examination) was essential to meet the criteria of eligibility. The pattern of subjects with missing data (especially hs-CRP and other biochemical data) was completely at random, so the representativeness of the sample was not compromised. Table 1 shows an overview of the general characteristics of the study population with respect to categories of metabolic syndrome (MetS).

Table 1. Baseline clinical and laboratory characteristics of the study participants.

Variables		Total (n=2125)	N*	MetS-ATP3		*P*
				No (n=1270)	Yes (n=855)	
Age (year)		39.4 ± 4.5 (39.2 ,39.6)	2125	37.0 ± 6.3 (36.6, 37.3)	44. ± 9.5 (43.4, 44.6)	0.000
Sex	**Male**	49.6% (48.7, 50.5)	957	53.7% (656) (51.9, 55.5)	41.9% (301) (39.0, 44.8)	0.000
PA	**Low**	28.8% (26.8, 30.8)	641	26.9% (24.5, 29.5)	32.2% (29.0, 35.6)	0.08
	Moderate	35.5% (33.5, 37.6)	750	35.9% (33.4, 38.5)	34.8% (31.4, 38.3)	0.603
	High	35.7% (33.6, 37.9)	734	37.2% (34.5, 40.0)	33.0% (29.7, 36.5)	0.047
BMI * (kg/m2)		26.64 ±5.07 (26.43 , 26.86)	2125	25.00 ± 4.23 (24.77, 25.23)	29.74 ± 4.77 (29.42, 30.06)	0.000
WC* (cm)		88.85 ± 12.79 (88.30, 89.39)	2125	84.02 ± 10.63 (83.44, 84.61)	97.95 ± 11.62 (97.17, 98.73)	0.000
FPG(mg/dl) *		92.4 ± 25.8 (91.3 , 93.5)	2125	85.79 ± 13.88 (85.02, 86.55)	104.73 ± 40.08 (102.04, 107.42)	0.000
SBP (mmHg)*		123.3 ±15.2 (122.6 , 123.9)	2125	118.19 ± 12.75 (117.49, 118.89)	132.81 ± 18.36 (131.58, 134.04)	0.000
DBP (mmHg)*		80.5 ±10.5 (80.1 , 80.9)	2125	77.26 ± 9.18 (76.75, 77.76)	86.63 ± 11.07 (85.89, 87.38)	0.000
TG (mg/dl)		143.9 ±70.1 (140.9,146.9)	2125	115.60 ± 53.65 (112.64, 118.55)	197.26 ± 79.29 (191.93, 202.58)	0.000
HDL-C(mg/dl)		37.0 ±10.0 (36.6 ,37.5)	2125	38.97 ± 9.77 (38.43, 39.51)	33.39 ± 8.14 (32.84, 33.94)	0.000
LDL-C (mg/dl)		130.4 ±31.8 (129.0 ,131.7)	2125	125.51 ± 31.96 (123.75, 127.27)	139.56 ± 33.39 (137.32, 141.80)	0.000
TC(mg/dl)		196.3 ±36.7 (194.7 ,197.8)	2125	187.64 ± 36.43 (185.64, 189.65)	212.50 ± 37.66 (209.97, 215.02)	0.000
Leptin(ng/ml)		7.48 ± 5.82 (7.24 ,7.73)	2125	6.29 ± 4.94 (6.02, 6.56)	9.73 ± 7.70 (9.22, 10.25)	0.000
Fasting plasma Insulin(µU/ml)		9.81 ± 6.87 (9.52 ,10.10)	2125	8.86 ± 5.25 (8.57, 9.15)	11.60 ± 9.36 (10.97, 12.23)	0.000
GFR (ml/min/1.73 BSA)		94 ± 15.80 (89.52 ,98.40)	2125	97 ± 16.80 (84.52 ,101.40)	91 ± 8.50 (86.54 ,108.30)	0.65

Cont. Table 1

Smoking	**Non-smoker**	86.3% (84.8, 87.6)	1857	86.6% (1097) (84.7, 88.2)	85.7% (760) (83.2, 88.0)	0.534
	Ex-smoker	3.8% (3.2, 4.5)	86	2.8% (43) (2.1, 3.6)	5.8% (43) (4.7, 7.2)	0.502
	Current smoker	9.9% (8.7, 11.2)	182	10.7% (130) (9.2%, 12.4)	8.4% (52) (6.5, 10.9)	0.545
hs-CRP (mg/L)		5.53 ±2.84 (5.41, 5.65)	2125	5.44 ± 2.80 (5.28, 5.59)	5.72 ± 2.91 (5.52, 5.91)	0.026
Log CRP		0.66 ± 0.30 (0.65 ,0.68)	2125	0.65 ± 0.31 (0.64, 0.67)	0.68 ± 0.26 (0.67, 0.70)	0.020
10 YFRS (% ±SD)		7.10 ± 4.89 (6.90, 7.31)	2125	4.55 ± 3.36 (4.36, 4.73)	11.92 ± 9.23 (11.30, 12.54)	0.000

Continuous and categorical variables are expressed as Mean± standard deviation (95 % CI) and percentage (95 % CI), respectively

We have analyzed the relationships coexisting between different predictors of high CRP in multivariate regression analysis in the context of weighted complex sample models. The results of the summarized models were shown in Table 2. Metabolic syndrome maintained clinical impact on elevated CRP with a modest statistical significance despite smoking and fiber-rich diet. Age, sex, and area of residence were structural variables, which comprised the weighted plan file pertaining to complex sample analysis. Further adjustments for BMI, insulin resistance, leptin level, and total cardiovascular risk (Framingham risk calculation) were considered in serial models 1a, 1b, and 1c. Moreover, we demonstrated that the exclusion of 165 patients with extremely high values (hsCRP >10) led to similar results verifying the association of MetS and CRP. We have also calculated the odds ratio of MetS for elevated logarithmic CRP, as illustrated in Table 3.

Table 2. Multivariate regression models for evaluation of predictors of high CRP (≥3 mg/L)

Predictors		**OR 1 (95% CI**						**OR 2**	***P***
		1a	***P***	**1b**	***P***	**1c**	***P***	**(95% CI)¶**	
High LDL	**≥ 130 Vs. < 130**	1.40 (1.04-1.88)	0.026	1.37 (1.04-1.88)	0.027	1.36 (1.04- 1.85)	0.026	1.39 (1.05- 1.84)	0.021
Low Physical activity	**(+) Vs. (-)**	2.68 (1.25- 5.42)	0.000 **	2.24 (1.16- 4.56)	0.003	1.31 (1.11- 4.20)	0.012	1.64 (1.09- 5.16)	0.01
BUN	**Units of change :10**	1.08 (1.04- 1.12)	0.000	1.06 (1.04- 1.12)	0.000	1.04 (1.04- 1.12)	0.000	1.08 (1.04- 1.12)	0.000
MetS. ATPIII	**(+) Vs. (-)**	1.46 (1.03- 2.06)	0.034	1.48 (1.04- 2.10)	0.029	1.47 (1.04- 2.09)	0.029	1.44 (1.05 – 2.18)	0.033
Declined GFR (ml/min/1.73 BSA)	**Per 30 units decrease**	1.37 (1.24- 5.54)	0.003	1.34 (1.12- 4.51)	0.018	1.22 (1.11- 3.36)	0.002	1.44 (1.21- 6.11)	0.011
Fiber index (Veg-Fruit per day)	**> 5 units Vs. < 5 units**	0.84 (0.87- 1.48)	0.09	0.82 (0.46- 1.52)	0.56	--	--	--	--
Current Smoking	**(+) Vs. (-)**	1.74 (0.39- 1.38)	0.34	--	--	--	--	--	--

¶OR 1 and OR 2 show the Odds ratio values calculated in 2 stages respectively before and after exclusion of CRP values above 10 mg/L. (0.000 **): refers to significant P-values smaller than 0.0001. In model 1a, the ORs were adjusted for age, sex and area of residence. In model 1b, ORs were adjusted for covariates in model 1a plus BMI. In model 1c, adjustments are performed for covariates of 1b plus Insulin resistance (HOMA index), leptin level, and total cardiovascular risk (Framingham risk calculation). Adjustments of OR2 were identical to model 1c

Table 3. Multivariate regression models prediction of high CRP (≥3 mg/L) among subgroups of current smokers versus others (non-smokers and former smokers)

Variables in subgroup		**subgroups**	**Odds ratios (95 % CI)**	***P***
Low PA	**(+) Vs. (-)**	Current smokers	3.47 (1.62 , 7.42)	0.002
		Others	2.96 (1.34, 5.63)	0.013
Fiber consumption index	**> 5 units Vs. < 5 units**	Current smokers	0.10 (0.04 , 0.21)	0.000 *
		Others	1.14 (0.85, 1.43)	0.14
MetS. ATP III	**(+) Vs. (-)**	Current smokers	6.11 (2.14 , 17.44)	0.001
		Others	1.36 (1.05, 4.91)	0.036
Diabetes	**(+) Vs. (-)**	Current smokers	8.27 (2.14 , 31.8)	0.003
		Others	0.76 (0.36,3.68)	0.63
BUN	**:Per 10 units increse**	Current smokers	1.15 (1.04 , 1.28)	0.009
		Others	1.21 (1.07,3.16)	0.000
GFR (ml/min/1.73 BSA)	**Per 30 units decrease**	Current smokers	1.44 (1.23 , 3.55)	0.016
		Others	1.27 (1.04, 2.11)	0.01

Odds ratios with 95 % confidence intervals. All values are adjusted for age, sex, and residential area. Low PA stands for low physical activity, and GFR represents the renal function. It was calculated via MDRD equation

The ratio emerged 1.28 (1.07-2.95) with *P*=0.017. Other results were also similar using Log CRP since we did not report the whole results again. Since there was only one common significant interaction in the mentioned models between smoking and metabolic syndrome, we conducted subgroup analysis. However, the interaction of fiber index and GFR tended to statistical significance (*P*=0.045) as well as diabetes and smoking (*P*=0.041). In a subgroup of non-diabetics, smokers were more likely to have a high CRP by an odds ratio of 1.48 (1.13-3.29). The association of MetS and high CRP persisted among current smokers. A robust protective effect was addressed by the optimal fiber index as a new finding in this subgroup (90% reduction in high CRP odds).

Discussion

C- reactive protein is recognized as a valuable marker of inflammation, which in turn serves as an emerging indicator of increased cardiovascular risk, especially in the category of intermediate-risk patients. Various mechanisms have delineated the links between elevated CRP and cardiovascular outcomes. Activation of the complement cascade, blunting of endothelial vasoreactivity, monocyte recruitment, localization in atherosclerotic plaques of the intima, induction of PAI-1 expression, and production of tissue factor may play a role. Besides, CRP attenuates nitric oxide (NO) synthesis along with mediating LDL uptake in macrophages, LDL oxidation, and induced production of adhesion molecules. C-reactive protein contributes to the development and establishment of atherosclerosis, plaque instability, and rupture via several mechanisms. Whether acting as a causative factor or playing the role of a bystander has remained uncertain. In this regard, some investigations have highlighted weak prognostic implications of CRP reduction as a therapeutic option. In other words, they have claimed doubts owing to the dual-target effect as observed in the treatment of patients with high LDL and increased CRP in the JUPITER trial. Thus, we could not discriminate against the attributable influence of lowering LDL from declined inflammation (CRP) following statin therapy. Furthermore, there was no control group composed of low LDL with concomitant normal CRP. Moreover, measurement errors, different etiologies such as malignant disorders, infections, and rheumatologic causes may lead to confounding results. However experts still recommend applying CRP measurement in risk stratification of patients in order to guide treatment (1,3,16). A large body of evidence supports the presence of independent associations between traditional risk factors of coronary artery disease and inflammatory biomarkers. With this in mind, mentioned correlations underscore common or coexisting pathophysiologic pathways. In other words, some of the conventional factors such as obesity, metabolic syndrome, insulin resistance, smoking, and low physical activity may result in cardiovascular events through increasing inflammation. We had previously found higher levels of baseline CRP in healthy Iranian adults (17). Given this fact, substantial role of the genetic heterogeneity should be signified. Hence, we evaluated potential relations of different risk factors with high CRP in apparently healthy Iranian adults. A wide spectrum of ethnic groups was collected in the primary study sample from all provinces of Iran. Proportional stratification based on sex, age, and area of residence portends an appropriate representative sample.

We found that metabolic syndrome, low physical activity and low fiber consumption were associated with a greater chance of inflammatory state even after the exclusion of extreme CRP values (values above 10 mg/L might signify the presence of other inflammatory disorders like infections). In addition, taking a fiber-sufficient regimen provided considerable protective effects against inflammation only for smokers. We failed to demonstrate its benefit in the other subgroups as well as the whole sample. Herein, a constellation of poor lifestyle features was related to greater odds of inflammation. Statements regarding the association of MetS and high CRP were in line with most of the prior studies (10,18-25). On the other hand, the results of a few studies have raised doubts (26). We have compared the results, including the present study in Figure1. The clinical relevance of MetS in our results was comparable to that of previous reports. Fiber-rich regimens may decline CRP levels as observed here in smokers, which was consistent with some investigations (27,28). Controversy surrounds the efficacy, amounts of fiber, different ingredients, supplements, interactions, measurement biases, and frequency of meals (29). However, decreased probability of inflammation in our study derived via optimal fiber intake confirms the utility of a simple tool. In other words, at least five units of vegetables or fruits may contain little benefits in the general adult population. A noteworthy yield was considerable interaction of smoking and fiber-rich regimen. Another weak interaction was also observed between the fiber index and GFR. Subgroup analysis revealed a considerable association of optimal vegetable-

fruits intake and high CRP in current smokers. This prominent benefit might denote precipitation of antioxidant effects of fibers in the context of the high burden of inflammation. On the contrary, the impact of smoking on the inflammatory state was not significant, which was concordant with several reports (21,22). However, in the subgroup of non-diabetics, smokers were more likely to have high CRP. Current smokers had similar levels of CRP as compared with non-smokers (5.28 vs. 5.60, *P*:0.21), while average CRP in former smokers (4.61) was significantly lower than those of the other groups were.

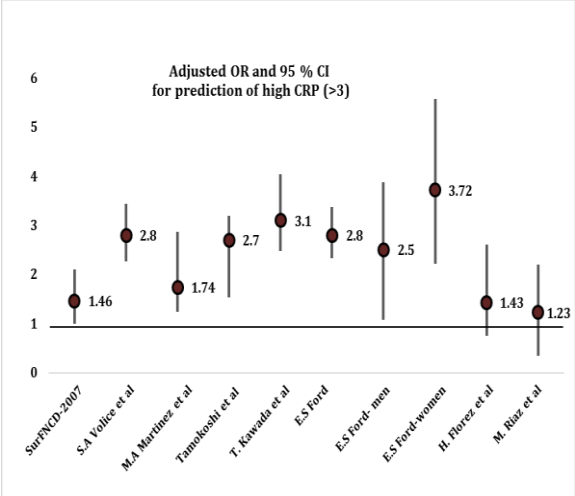

Figure 1. Adjusted OR and 95 % CI for prediction of high CRP (>3). SurFNCD-2007 refers to the results of the present study

Renal impairment of mild to moderate intensity (none of the patients had GFR <30 ml/min or symptomatic chronic kidney disease) was a modest independent predictor of inflammation. Thus, we should pay more attention to subclinical stages of CKD concerning the silent inflammatory state, which may initiate concurrent atherosclerosis.

The retrospective design of the study restricts an absolute conclusion about causality. The definition of metabolic syndrome was based on ATP-III, whereas IDF criteria might be more compatible in Iranians, particularly using optimal standardized cutoffs for waist circumference. Nevertheless, similar results were found with IDF, which has not been presented here. Although we have compared current smokers versus other subtending non-smokers and former smokers in subgroup analysis, a heterogeneous composite resulted. In fact, Mean CRP levels were greater in non-smokers than that of former smokers making a conflict. Former smokers in our study had the least CRP means while they often stand in the middle (more than nonsmokers do but under current smokers) in other publications. Although we performed repeated the analysis after the exclusion of extremely elevated values, a single measurement of CRP compromises the reliability. Furthermore, changes in CRP maintain greater accuracy and relevance with the likelihood of cardiovascular risk.

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