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ORIGINAL ARTICLE

C-reactive protein predicts endocortical expansion but not fracture in older men: the prospective STRAMBO study

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Abstract

Summary In older men, higher high-sensitivity C-reactive protein (hsCRP) concentrations were associated with faster prospectively assessed endocortical expansion (distal radius, distal tibia) and slightly higher cortical bone loss at distal tibia, but not with the fracture risk. High hsCRP level has a limited impact on bone decline in older men.

Purpose Data on the link of the high-sensitivity C-reactive protein (hsCRP) with bone loss and fracture risk are discordant. We studied the association of the hsCRP with the prospectively assessed decrease in areal bone mineral density (aBMD), bone microarchitecture decline, and fracture risk in older men.

Methods At baseline, hsCRP was measured in 823 men aged 60–88. Areal BMD and bone microarchitecture (distal radius, distal tibia) were assessed by dual-energy X-ray absorptiometry and high-resolution peripheral QCT, respectively, at baseline and after 4 and 8 years. Data on incident fractures were collected for 8 years.

Results Higher hsCRP concentration was associated with faster increase in aBMD at the whole body and lumbar spine, but not other sites. Higher hsCRP levels were associated with faster decrease in cortical area and more rapid increase in trabecular area at the distal radius (0.048 mm^2/year/SD, $p < 0.05$) and distal tibia (0.123 mm^2/year/SD, $p < 0.001$). At the distal tibia, high hsCRP level was associated with greater decrease in total and cortical volumetric BMD (vBMD) and in failure load. The hsCRP levels were not associated with the fracture risk, even after accounting for competing risk of death.

Conclusion Higher hsCRP levels were associated with greater endocortical expansion at the distal radius and tibia. Higher hsCRP was associated with slightly faster decrease in total and cortical vBMD and failure load at distal tibia, but not with the fracture risk. Thus, high hsCRP levels are associated with faster cortical bone loss, but not with fracture risk in older men.

Keywords Bone loss · Bone microarchitecture · C-reactive protein · Fracture risk · Men

Introduction

Osteoporosis in men is characterized by low areal bone mineral density (aBMD) measured by DXA and poor bone microarchitecture [1]. Low aBMD is associated with high fracture risk [2, 3]; however, it poorly identifies men at high fracture risk [3]. Thus, it is necessary to explore other indices of bone fragility in men.

C-reactive protein (CRP) is an acute phase protein and inflammation marker [4]. Its synthesis is induced by pro-inflammatory cytokines stimulating bone resorption (interleukin-6, interleukin-1β, tumor necrosis fac**tor α). Blood CRP levels may reflect their effect on bone** [5]**. Chronic inflammatory diseases are** associated with high levels of these cytokines, low aBMD, rapid bone loss, and high fracture risk [6].

Low-grade inflammation may also lead to the development of osteoporosis [7]. However, in this condition, CRP level must be assayed by the high sensitivity CRP (hsCRP) assay [8]. Higher hsCRP levels were associated with higher risk of nontraumatic vertebral and hip fracture in men from the Bruneck study, higher risk of non-vertebral fracture in men from the Tromsø cohort, and with higher risk of clinical vertebral fracture in the MrOS Sweden cohort [9–11]. By contrast, hsCRP did not predict fractures in the MrOS cohort

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(hip, clinical vertebral, non-spine) or in the Cardiovascular Health Study (hip, pelvis, humerus, distal forearm) [12, 13]. However, high hsCRP levels are associated with higher mortality [14]. Thus, the analysis of the fracture risk could be biased by over-mortality of subjects with high hsCRP level.

Moreover, the morphological basis underlying possible association between CRP and fracture is not clear. Data on the link between CRP and aBMD are inconsistent [15, 16]. In men, high hsCRP levels were associated with low aBMD in some [11, 17], but not other cohorts [13, 16, 18]. Bone microarchitecture contributes to the fracture prediction, but the link between hsCRP and bone microarchitecture was weak and limited to trabecular bone microarchitecture in elderly men [18]. High hsCRP was associated with rapid bone loss in inflammatory diseases [19], but data were inconsistent in general population [20, 21]. However, they were obtained in small groups and during short follow-up periods. This link is important because accelerated bone loss is a risk factor for fracture independent of aBMD in men and women [22].

Therefore, our objective is to study the relationship of the hsCRP levels with the subsequent bone loss and with microarchitecture deterioration at the level of radius and tibia, as well as with the prospectively assessed fracture risk in older men followed prospectively for 8 years.

Subjects and methods

Cohort

The STRAMBO study is a single-center, prospective study, focused on fracture prediction by bone microarchitecture measures in men [18]. It was approved by the local ethics committee and performed in agreement with the Helsinki statement (1975, 1983) as collaboration between INSERM (National Institute of Health and Medical Research) and Mutuelle des Travailleurs de la Région Lyonnaise (MTRL). Invitations were sent to a randomly selected sample of clients of MTRL living in Greater Lyon. Between 2006 and 2008, we recruited 1169 men aged 20 to 87 years. Men who were able to give their informed consent, to answer questions, and to participate in diagnostic tests were included. This analysis includes 823 men aged ≥ 60, who had hsCRP measurements at baseline and were followed prospectively for up to 8 years.

High-sensitivity C-reactive protein (hsCRP)

Non-fasting blood were collected at 1:00 p.m. and stored at − 80 °C. Serum hsCRP was measured by immunoturbidimetric latex CRP assay (Roche Diagnostics, Mannheim, Germany). Detection limit was 0.15 mg/L [18]. Intra-assay and inter-assay coefficients of variation (CV) were < 10%. The median in 115 men aged 20–35 years was 0.75 mg/L (interquartile range: 0.47; 1.58) [18].

Dual energy X-ray absorptiometry (DXA)

Areal BMD (aBMD) was measured at baseline and then after 4 and 8 years, at lumbar spine, total hip, whole body, and non-dominant distal radius, using a Hologic Discovery A (Hologic, Bedford, MA). Its stability was assessed by the spine phantom measured daily (CV = 0.35%). The in vivo CV was 1.1–1.2%. Body composition was assessed at baseline [23]. Relative appendicular lean muscle mass index (RALM) was calculated as the sum of lean mass of four limbs divided by (body height)^2.

High-resolution peripheral quantitative computed tomography (HRpQCT)

Bone microarchitecture was assessed at the distal non-dominant radius and at distal right tibia using HR-pQCT (XtremeCT, Scanco Medical, Brüttisellin, Switzerland) with a isotropic voxel of 82 µm. A scout view was used to define the reference line at the endplates of radius and tibia. A 3D stack of 110 slices was acquired, starting at 9.5 mm and 22.5 mm from the reference line for radius and tibia. Total volumetric bone density (Tt.vBMD) is the average vBMD in the entire volume of interest (VOI). VOI is separated into trabecular and cortical compartments by a threshold-based algorithm. Cortical area (Ct.Ar) is the average cross-sectional area (CSA) of cortical bone in all slices. Cortical thickness (Ct.Th^d) is the mean cortical volume divided by the outer bone surface [24]. Cortical vBMD (Ct.vBMD) is the mean density. Trabecular area (Tb.Ar) is the mean CSA of the trabecular cavity in all slices. Trabecular vBMD (Tb.vBMD) is the mean density. Trabeculae were identified by the mid-axis transformation. Derived trabecular separation (Tb.Sp^d) and thickness (Tb.Th^d) were calculated using the derived trabecular bone volume fraction (Tb.BV/TV^d). Intra-individual distribution of trabeculae (Tb.1/N.SD^d) is the standard deviation of distances between the mid-axes and reflects the trabecular network heterogeneity. Quality control was performed daily using a phantom containing hydroxyapatite rods. CV for phantom densities was 0.05–0.9% (short term) and 0.5–1.7% (long term). CVs for reproducibility of microarchitectural variables in vivo were 0.7–4.5% [21]. Scans were obtained at baseline and then after 4 and 8 years. Scans were graded for motion artefacts from a scale of 1 (no motion) to 5 (sever streaking artefacts) [25]. Scans with a motion score of ≥ 4 were excluded. The motion scores of 1–3 were considered good quality. Scans overlapping < 85% with scan(s) of same participant was also excluded.

Finite element analysis

Micro finite element (μFE) analysis was performed on the unregistered segmented HR-pQCT images to determine reaction force and estimated failure load of the whole bone. Linear models were generated by the voxel-by-voxel approach, with a Poisson's ratio of 0.3, and a homogeneous Young's modulus of 6829 GPa was assigned as bone tissue properties [26]. The model boundary conditions were an axial compression with 1% compressive strain, and resultant reaction force of the bone was measured. Failure load was estimated using a yield criterion of 2% critical volume and 0.7% critical strain [27]. The μFE models were solved using a conjugate gradient approach with a convergence criterion of 1×10^{-6} (FAIM v8.0, Numerics88 Solutions Ltd., Canada) on the University of Calgary's high-performance computing cluster.

Incident fractures

Information on incident fractures was collected as described previously [28]. We retained low-trauma non-spine fractures (fall from a standing position or less) reported during the follow-up visit or in the yearly questionnaires and confirmed by health professional (medical report, X-ray). Lateral single-energy scans of the spine (Th4 to L4) were obtained in the dorsal decubitus position using a DXA device equipped with rotating C-arm. Scans were performed in all men present at each visit (baseline, 4 and 8 years). An incident spine fracture was diagnosed based on visual analysis (endplate fracture) and/or a decrease in any of the vertebral heights by > 15% versus the previous scan [28]. The vertebrae not correctly visible were considered non-fractured.

Covariates

Men replied to a reviewer-assisted epidemiological questionnaire. Smoking was assessed as a current smoker vs. non-smoker. Alcohol intake was calculated as the average amount of alcohol consumed weekly. Current leisure physical activity comprised the time spent walking or sport activity. Self-reported occupational physical activity was classified as low, medium, high, or very high. Comorbidities (ischemic heart disease, hypertension, diabetes mellitus, stroke, Parkinson's disease, chronic obstructive pulmonary disease, rheumatoid arthritis, cancer) were self-reported (yes/no) and not further ascertained. Weight and height were measured in light clothes without shoes. Grip strength was measured 3 times at the dominant hand by a hand dynamometer (Martin Vigorimeter, Germany). Clinical tests were performed and the score of lower limb physical function was calculated as previously described.

Mortality

Data on the date of death was obtained from proxies or physician indicated by the participant at the moment of the recruitment.

Biochemical measurements

Testosterone, 17β-estradiol (17β-E2), and sex hormone-binding globulin (SHBG) were measured as previously described [23]. Calculated free testosterone (cFT) and bioavailable 17β-E2 (bio-17β-E2) were calculated [23]. 25-Hydroxycholecalciferol (25OHD) and parathyroid hormone (PTH) were measured as previously described [23]. Glomerular filtration rate (GFR) was estimated with the Chronic Kidney Disease Epidemiology Collaboration Eq. [29].

Statistical analysis

The analyses were performed using R-3.6.3 software (R Foundation for Statistical Computing, Austria; https://www.r-project.org). Correlations were assessed using Pearson's correlation coefficient. Comparisons were performed by analysis of covariance (ANCOVA) for continuous variable without and with age adjustment. Chi-square test or Fisher's exact test was used for class variables. The evolution of bone microarchitecture was explored using linear mixed effect models. Bivariate analysis explored the association between independent variables and each bone index with a simple linear regression and α risk of 10%. Selection of the variables was based on previously published data, biological plausibility, and the analysis of the link between bone microarchitectural variables and potential confounders. Model assumptions were checked by histograms and quantile–quantile plots of residuals. Quality of statistical model for a given set of variables was assessed with the coefficient of determination. Conditions for validity of fixed effect models have been verified graphically. Random coefficient models were added to characterize individual trajectories to allow individual prediction. Percentage changes were assessed using log-transformed variables. All final models were adjusted for age, BMI, bio-17β-E2, PTH, and GFR. In addition, the models for distal radius (DXA, HR-pQCT) were adjusted for grip strength and those for distal tibia, hip, lumbar spine, and whole body for the score of lower limb physical function. Interactions between the variables were checked. The analyses in various classes identified post hoc the level of 1 mg/L as the most discriminating threshold. Fracture-free survival related to HR-pQCT indices was analyzed by the Cox model

after checking the assumption of proportional hazards using the Schoenfeld residues. Follow-up time was censored at the first fracture, death, last news, or 8 years after baseline, whichever came first. The link between hsCRP and fracture risk was assessed by a multivariable model adjusted for age, BMI, prior falls and fractures, and femoral neck aBMD. As hsCRP may be associated with increased mortality, men with higher hsCRP may develop fewer fractures because of higher competing risk of mortality. The Fine and Gray model was integrated into multivariable models to calculate HR (95% CI), allowing for competing mortality risks [30].

Results

Associations between hsCRP and other variables at baseline

The median hsCRP was 1.67 mg/L (interquartile range: 0.87; 3.28). 240 men (29%) had hsCRP ≤ 1 mg/L, 354 (43%) had hsCRP 1–3 mg/L, 100 (12%) had hsCRP 3–5 mg/L, and 129 (16%) men had hsCRP > 5 mg/L. The hsCRP concentrations correlated positively with age, weight, and BMI, but negatively with height (Table 1). After adjustment for age and weight, higher hsCRP correlated with less time spent outdoors, lower grip strength, and lower RALM. Higher hsCRP correlated with lower testosterone (total, cFT) and higher total and bio-17β-E2 levels. These correlations persisted after adjustment for age and weight. Higher hsCRP correlated with higher PTH and lower GFR; however, both associations became non-significant after adjusting for age and weight.

After adjustment for age and weight, ever smokers (current, former) had higher hsCRP levels vs. the never-smokers (Table 2). Higher occupational physical activity and prior fractures were associated with higher hsCRP. Men who self-reported prior stroke, Parkinson's disease, diabetes mellitus treated with oral medications, COPD, or cancer had higher hsCRP concentrations. All the differences remained significant after adjustment for age and weight.

Associations between baseline hsCRP and bone loss assessed by DXA

Among 823 men who had the hsCRP assay, 820, 646, and 492 had good quality DXA scans at baseline, 4, and 8 years, respectively, for least one skeletal site. The causes of attrition were death (61 and 168), poor health status (32 and 126), relocation (3 and 7), second hip prosthesis (4 and 3), or poor quality of the scans. Men who were lost to follow-up before the last visit were older (76.5 versus 70.2 years, $p < 0.001$) and had higher hsCRP levels (median: 2.10 versus 1.44 mg/L, $p < 0.001$, after adjustment for age: $p = 0.005$).

Table 1 Correlation coefficients between hsCRP and continuous variables adjusted for age and weight

hsCRP	Simple correlation coefficient			Partial correlation coefficient		
	r	95% CI	*p*-value**	*r*	95% CI	*p*-value**
Age	0.183	0.116–0.249	< 0.001			
Weight	0.190	0.123–0.256	< 0.001	0.212	0.145–0.276	< 0.001
Height	− 0.102	− 0.171 to − 0.033	< 0.005	− 0.170	− 0.237 to − 0.101	< 0.005
BMI	0.269	0.204–0.331	< 0.001	0.259	0.195–0.322	< 0.001
Alcohol intake	0.062	− 0.008–0.130	0.08	0.062	− 0.008 to 0.131	0.08
Leisure ph. act.*	− 0.031	− 0.100–0.038	0.37	− 0.010	− 0.071 to 0.067	0.95
Time outdoors*	− 0.178	− 0.244 to − 0.111	< 0.001	− 0.126	− 0.193 to − 0.058	< 0.001
RALM	0.025	− 0.045 to 0.095	0.48	− 0.090	− 0.159 to − 0.020	< 0.05
Grip strength	− 0.174	− 0.240 to − 0.106	< 0.001	− 0.118	− 0.185 to − 0.050	< 0.001
Testosterone	− 0.169	− 0.234 to − 0.100	< 0.001	− 0.101	− 0.170 to − 0.033	< 0.005
cFT	− 0.184	− 0.250 to − 0.117	< 0.001	− 0.094	− 0.161 to − 0.025	< 0.015
17β-estradiol	0.249	0.183–0.312	< 0.001	0.256	0.190–0.319	< 0.001
Bio-17β-estradiol	0.246	0.180–0.310	< 0.001	0.267	0.201–0.329	< 0.001
25OHD	− 0.050	− 0.008–0.019	0.15	0.010	− 0.058 to 0.080	0.76
PTH	0.085	0.016–0.153	< 0.05	0.036	− 0.033 to 0.105	0.30
GFR	− 0.119	− 0.186 to − 0.050	< 0.001	− 0.025	− 0.093 to 0.044	0.48

Linear correlation coefficients were calculated using Pearson's coefficient except for leisure physical activity and time spent outdoors (*), for which Spearman's correlation coefficient was used for the simple correlation and log-transformed variables were used for partial correlation. **: adjusted for age and weight except weight, which is adjusted only for age

RALM, relative appendicular lean mass; *cFT*, calculated free testosterone; *25OHD*, 25-hydroxyvitamin D; *PTH*, parathyroid hormone; *GFR*, glomerular filtration rate

Table 2 Comparison of the hsCRP concentration across categorical variables

Variable	Category	Number	Median [q1; q3]	*p**	*p***
Ever smoker	Yes	559	1.81 [0.96; 3.62]	< 0.001	< 0.001
	No	264	1.33 [0.71; 2.64]		
Occupational physical activity	Weak	173	1.36 [0.68; 2.71]	< 0.001	< 0.001
	Moderate	242	1.78 [0.88; 3.29]		
	High	234	1.56 [0.88; 3.56]		
	Very high	174	1.81 [1.03; 3.59]		
Prevalent fracture	Yes	169	2.10 [1.09; 4.83]	< 0.001	< 0.001
	No	654	1.59 [0.84; 3.03]		
Ischemic heart disease	Yes	131	1.91 [0.90; 3.56]	0.20	0.24
	No	692	1.61 [0.85; 3.25]		
Prior stroke	Yes	32	2.14 [1.16; 4.17]	< 0.05	< 0.01
	No	791	1.62 [0.86; 3.25]		
Parkinson's disease	Yes	15	2.31 [0.81; 5.25]	0.06	< 0.05
	No	808	1.62 [0.86; 3.27]		
Diabetes mellitus	Insulin	15	1.58 [0.75; 2.70]	< 0.005	< 0.001
	Oral agents	83	2.34 [0.96; 3.85]		
	No	725	1.61 [0.86; 3.19]		
Chronic obstructive pulmonary disease	Yes	51	2.44 [1.52; 4.12]	< 0.001	< 0.001
	No	772	1.59 [0.84; 3.27]		
Cancer	Yes	108	1.98 [0.95; 3.28]	< 0.05	< 0.05
	No	715	1.60 [0.85; 3.27]		
ACE inhibitors	Yes	119	2.21 [1.20; 5.01]	< 0.001	< 0.001
	No	704	1.57 [0.83; 3.06]		
Calcium channel blockers	Yes	127	2.12 [1.11; 4.84]	< 0.001	< 0.001
	No	696	1.57 [0.84; 3.18]		

p*: unadjusted comparisons performed using Kruskal–Wallis test; p**: comparisons adjusted for age and weight performed on the log-transformed hsCRP concentration using analysis of covariance

Higher hsCRP concentrations were associated with more rapid increase in aBMD at lumbar spine and whole body (Table 3). The increase in aBMD was faster in men with hsCRP > 1 mg/L versus men who had lower hsCRP levels. The associations between hsCRP concentrations and bone loss at the hip and distal radius were not significant regardless of the statistical model.

Association between hsCRP and changes in bone microarchitecture at distal radius

Among 823 men who had the hsCRP assay, 789 (96%), 640 (81%), and 446 (57%) had good quality HR-pQCT scans at baseline, 4, and 8 years, respectively, for least one skeletal site. After adjustment for confounders, higher hsCRP levels were associated with faster decrease in Ct.Ar and $Ct.Th^d$ (absolute values) and more rapid increase in Tb.Ar (Table 4). In men with hsCRP > 1 mg/L, Ct.Ar, $Ct.Th^d$, and Tt.vBMD (absolute values) decreased and Tb.Ar increased faster vs. men with hsCRP ≤ 1 mg/L. Serum hsCRP did not correlate with changes in trabecular measures and in the μFEA estimates of bone strength.

Association between hsCRP and changes in bone microarchitecture at distal tibia

After adjustment for confounders, higher hsCRP levels were associated with faster decrease in Ct.Ar, $Ct.Th^d$, and Ct.vBMD as well as faster increase in Tb.Ar (Table 5). In men with hsCRP > 1 mg/L, Ct.Ar, $Ct.Th^d$, Ct.vBMD, and Tt.vBMD decreased and Tb.Ar increased more rapidly versus men with hsCRP ≤ 1 mg/L (Fig. 1). Higher hsCRP levels were associated with a faster decrease in failure load and with a non-significant trend to faster decline in reaction force. By contrast, hsCRP levels did not correlate with changes in trabecular indices.

hsCRP and fracture risk

During the follow-up, 102 men had at least one incident fracture (spine fractures in 47 men, non-spine fractures in 62 men). After adjustment for the confounders, higher hsCRP levels were not associated with the risk of fracture (Table 6). After adjustment for age, BMI, and comorbidities, higher hsCRP was associated with higher risk of death (HR = 1.21

Table 3 Association between baseline hsCRP concentration and change in areal BMD measured by DXA

hsCRP	Change in the HR-pQCT measures per 1 SD (β ± SEE)		Comparison of the changes in the HR-pQCT measures			
			Unadjusted		Adjusted[#]	
	Unadjusted	Adjusted[#]	< 1 mg/L	> 1 mg/L	< 1 mg/L	> 1 mg/L
Areal bone mineral density (mg/cm³/year)						
Lumbar spine	1.168 ± 0.316[d]	1.117 ± 0.319[d]	3.364 ± 0.491	5.621 ± 0.606[d]	3.373 ± 0.492	5.631 ± 0.607[d]
Femoral neck	− 0.058 ± 0.022	− 0.028 ± 0.022	− 2.571 ± 0.340	− 2.936 ± 0.420	− 2.583 ± 0.340	− 2.936 ± 0.420
Trochanter	0.203 ± 0.194	0.249 ± 0.195	2.160 ± 0.305	2.192 ± 0.377	2.172 ± 0.304	2.179 ± 0.376
Total hip	0.083 ± 0.209	0.105 ± 0.211	− 2.572 ± 0.328	− 2.665 ± 0.406	− 2.582 ± 0.328	− 2.660 ± 0.406
Whole body	0.728 ± 0.280[b]	0.765 ± 0.282[b]	0.981 ± 0.436	2.908 ± 0.537[d]	0.962 ± 0.436	2.901 ± 0.537[d]
1/3 distal R	0.278 ± 0.157	0.260 ± 0.158	− 2.203 ± 0.245	− 2.212 ± 0.302	− 2.206 ± 0.145	− 1.946 ± 0.157
Mid-distal R	0.087 ± 0.136	0.075 ± 0.136	− 3.469 ± 0.212	− 3.675 ± 0.261	− 3.625 ± 0.125	− 3.551 ± 0.136
Ultra-distal R	0.102 ± 0.122	0.091 ± 0.122	− 2.932 ± 0.189	− 3.039 ± 0.233	− 3.013 ± 0.112	− 2.922 ± 0.122
Areal bone mineral density (%/year)						
Lumbar spine	0.100 ± 0.029[d]	0.100 ± 0.029[d]	0.284 ± 0.045	0.491 ± 0.055[d]	0.285 ± 0.045	0.492 ± 0.056[d]
Femoral neck	0.001 ± 0.029	0.007 ± 0.029	− 0.378 ± 0.045	− 0.409 ± 0.056	− 0.380 ± 0.045	− 0.409 ± 0.056
Trochanter	0.039 ± 0.028	0.047 ± 0.028	− 0.348 ± 0.044	− 0.329 ± 0.055	− 0.350 ± 0.044	− 0.329 ± 0.054
Total hip	0.015 ± 0.024	0.018 ± 0.024	− 0.306 ± 0.037	− 0.306 ± 0.046	− 0.308 ± 0.037	− 0.305 ± 0.046
Whole body	0.060 ± 0.024[a]	0.064 ± 0.024[b]	0.075 ± 0.037	0.234 ± 0.045[d]	0.074 ± 0.037	0.234 ± 0.045[d]
1/3 distal R	0.038 ± 0.022	0.035 ± 0.022	− 0.304 ± 0.035	− 0.317 ± 0.043	− 0.313 ± 0.020	− 0.277 ± 0.022
Mid-distal R	0.013 ± 0.024	0.010 ± 0.024	− 0.572 ± 0.038	− 0.624 ± 0.047	− 0.611 ± 0.023	− 0.600 ± 0.025
Ultra-distal R	0.026 ± 0.029	0.023 ± 0.029	− 0.679 ± 0.046	− 0.713 ± 0.056	− 0.704 ± 0.027	− 0.681 ± 0.029

Data presented as the average change in aBMD per SD increase in log-transformed hsCRP or in each group; *R*, radius

[a] $p < 0.05$, [b] $p < 0.01$, [c] $p < 0.005$, [d] $p < 0.001$

Models were adjusted for age, BMI, bio-17β-estradiol, parathyroid hormone, and glomerular filtration rate

as well as for grip strength (radius) and for the score of lower limb physical function (hip, lumbar spine, and whole body)

Table 4 Association between baseline hsCRP concentration and change in bone microarchitecture indices at distal radius

hsCRP	Change in the HR-pQCT measures per 1 SD (β ± SEE)		Comparison of the changes in the HR-pQCT measures			
			Unadjusted		Adjusted[#]	
	Unadjusted	Adjusted[#]	< 1 mg/L	> 1 mg/L	< 1 mg/L	> 1 mg/L
Absolute values						
Tt.vBMD	−0.133 ± 0.080	−0.137 ± 0.080	−1.114 ± 0.128	−1.442 ± 0.158[a]	−1.122 ± 0.128	−1.455 ± 0.158[a]
Ct.Ar	−0.063 ± 0.030[a]	−0.066 ± 0.030[a]	−0.567 ± 0.049	−0.721 ± 0.061[a]	−0.572 ± 0.049	−0.729 ± 0.061[b]
Ct.Th[d]	−0.792 ± 0.357[a]	−0.819 ± 0.357[a]	−7.138 ± 0.576	−8.836 ± 0.711[a]	−7.185 ± 0.576	−8.915 ± 0.712[a]
Ct.vBMD	−0.201 ± 0.152	−0.216 ± 0.152	−3.472 ± 0.245	−3.895 ± 0.302	−3.496 ± 0.245	−3.943 ± 0.302
Tb.Ar	0.051 ± 0.041[a]	0.051 ± 0.024[a]	0.372 ± 0.039	0.493 ± 0.049[a]	0.372 ± 0.039	0.494 ± 0.049[a]
Tb.vBMD	−0.011 ± 0.041	−0.012 ± 0.041	0.142 ± 0.065	0.056 ± 0.081	0.139 ± 0.065	0.051 ± 0.081
Tb.N	0.172 ± 0.898	0.062 ± 0.898	2.857 ± 1.453	3.451 ± 1.790	2.733 ± 1.454	2.115 ± 1.791
Tb.Th[d]	−0.010 ± 0.008	−0.090 ± 0.080	−0.361 ± 0.600	−0.405 ± 0.740	−0.418 ± 0.601	−0.504 ± 0.741
Tb.Sp[d]	0.004 ± 0.003	0.003 ± 0.002	−0.446 ± 0.400	−0.363 ± 0.494	−0.414 ± 0.401	−0.322 ± 0.495
Tb.1/N.SD[d]	0.288 ± 0.206	0.301 ± 0.208	0.390 ± 0.336	0.633 ± 0.414	0.420 ± 0.336	0.678 ± 0.415
Reaction force	2.36 ± 2.71	2.08 ± 2.71	−32.48 ± 4.38	–32.15 ± 5.41	−32.94 ± 4.38	−39.94 ± 5.41
Failure load	1.00 ± 1.28	0.87 ± 1.28	−15.96 ± 2.08	−16.06 ± 2.56	−16.17 ± 2.08	−16.42 ± 2.56
Percentage values (%/year)						
Tt.vBMD	−0.035 ± 0.031	−0.036 ± 0.031	−0.432 ± 0.050	−0.533 ± 0.062	−0.436 ± 0.050	−0.539 ± 0.062
Ct.Ar	−0.109 ± 0.074	−0.116 ± 0.074	−1.211 ± 0.120	−1.515 ± 0.148[a]	−1.225 ± 0.120	−1.540 ± 0.148[a]
Ct.Th[d]	−0.045 ± 0.023[a]	−0.047 ± 0.023[a]	−0.444 ± 0.036	−0.546 ± 0.045[a]	−0.447 ± 0.036	−0.551 ± 0.045[a]
Ct.vBMD	−0.026 ± 0.022	−0.029 ± 0.022	−0.456 ± 0.035	−0.517 ± 0.043	−0.460 ± 0.035	−0.525 ± 0.043
Tb.Ar	0.019 ± 0.008[a]	0.019 ± 0.008[a]	0.121 ± 0.013	0.164 ± 0.016[b]	0.121 ± 0.013	0.164 ± 0.016[b]
Tb.vBMD	0.008 ± 0.028	0.004 ± 0.028	0.041 ± 0.045	0.007 ± 0.056	0.039 ± 0.045	0.004 ± 0.056
Tb.N	0.005 ± 0.049	0.003 ± 0.049	0.126 ± 0.079	0.104 ± 0.097	0.119 ± 0.079	0.096 ± 0.097
Tb.Th[d]	0.025 ± 0.047	0.019 ± 0.047	−0.070 ± 0.076	−0.049 ± 0.094	−0.077 ± 0.076	−0.062 ± 0.094
Tb.Sp[d]	−0.005 ± 0.050	−0.003 ± 0.050	−0.133 ± 0.081	−0.108 ± 0.100	−0.127 ± 0.081	−0.100 ± 0.099
Tb.1/N.SD[d]	0.110 ± 0.072	0.109 ± 0.075	0.046 ± 0.118	0.160 ± 0.146	0.057 ± 0.118	0.176 ± 0.146
Reaction force	0.040 ± 0.058	0.035 ± 0.058	−0.677 ± 0.093	−0.694 ± 0.115	−0.690 ± 0.093	−0.713 ± 0.115
Failure load	0.031 ± 0.053	0.027 ± 0.053	−0.633 ± 0.084	−0.656 ± 0.105	−0.645 ± 0.084	−0.673 ± 0.105

[a] $p < 0.05$, [b] $p < 0.01$, [c] $p < 0.005$, [d] $p < 0.001$

[#] Adjusted for age, BMI, bio-17β-estradiol, parathyroid hormone, glomerular filtration rate, and grip strength

Tt.vBMD, total volumetric bone mineral density (vBMD) (mg/cm^3/yr); *Ct.Ar*, cortical area (mm^2/yr); *Ct.Th*^{d}, cortical thickness (μm/yr); *Ct.vBMD*, cortical vBMD (mg/cm^3/yr); *Tb.Ar*, trabecular area (mm^2/yr); *Tb.vBMD*, trabecular vBMD (mg/cm^3/yr); *Tb.N*, trabecular number (1/mm/yr × 10^3); *Tb.Th*^{d}, trabecular thickness (μm/yr); *Tb.Sp*^{d}, trabecular separation (μm/yr); *Tb.1/N.SD*^{d}, trabecular spacing standard deviation (trabecular distribution) (μm/yr); reaction force (N/yr); failure load (N/yr)

per SD, 95% CI: 1.05–1.40, $p < 0.01$). However, the association between hsCRP and fracture risk did not change after adjustment for competing risk of mortality. The results were similar for other cut-offs of the hsCRP concentrations. The results were similar for spine and non-spine fractures.

Discussion

In a cohort of older men followed prospectively for 8 years, higher hsCRP levels were associated with more rapid endocortical expansion and cortical thinning. The decrease in bone strength estimated by μFEA was observed at the distal tibia, a load-bearing site. High hsCRP levels were not associated with the bone loss assessed by DXA or with the fracture risk.

In our cohort, hsCRP level correlated positively with age and BMI. After adjustment for age, high hsCRP level was associated with smoking, low testosterone, and lower grip strength. Men with poor health (morbidities, treatments) had higher hsCRP levels. Our data are consistent with the concept of "inflammaging," ageing-related chronic subclinical inflammation characterized by high secretion of inflammatory cytokines and high activity of T lymphocytes [7, 13]. The inflammatory cytokines stimulate bone resorption and may contribute to the bone loss. Higher hsCRP levels may reflect activated inflammatory status and higher levels of

Table 5 Association between baseline hsCRP concentration and change in bone microarchitecture indices at distal tibia

hsCRP	Change in the HR-pQCT measures per 1 SD (β ± SEE)		Comparison of the changes in the HR-pQCT measures			
			Unadjusted		Adjusted[#]	
	Unadjusted	Adjusted[#]	< 1 mg/L	> 1 mg/L	< 1 mg/L	> 1 mg/L
Absolute values						
Tt.vBMD	−0.061 ± 0.058	−0.056 ± 0.058	−0.681 ± 0.091	−0.983 ± 0.113[b]	−0.685 ± 0.091	−0.986 ± 0.113[b]
Ct.Ar	−0.152 ± 0.056[b]	−0.152 ± 0.056[b]	−0.873 ± 0.088	−1.195 ± 0.109[c]	−0.878 ± 0.088	−1.203 ± 0.109[c]
Ct.Th[d]	−1.043 ± 0.485[a]	−1.026 ± 0.484[a]	−8.025 ± 0.769	−11.001 ± 0.956[c]	−8.071 ± 0.767	−11.063 ± 0.953[c]
Ct.vBMD	−0.376 ± 0.142[b]	−0.387 ± 0.142[b]	−3.453 ± 0.223	−4.018 ± 0.276[a]	−3.471 ± 0.222	−4.055 ± 0.276[a]
Tb.Ar	0.129 ± 0.030[d]	0.122 ± 0.030[d]	0.156 ± 0.049	0.366 ± 0.060[d]	0.156 ± 0.049	0.362 ± 0.059[d]
Tb.vBMD	0.023 ± 0.032	0.026 ± 0.032	0.336 ± 0.039	0.341 ± 0.049	0.335 ± 0.039	0.342 ± 0.049
Tb.N	1.376 ± 0.909	1.455 ± 0.909	4.421 ± 1.458	6.279 ± 1.809	4.376 ± 1.456	6.177 ± 1.808
Tb.Th[d]	−0.015 ± 0.042	−0.020 ± 0.042	−0.036 ± 0.066	−0.044 ± 0.082	−0.042 ± 0.066	−0.056 ± 0.082
Tb.Sp[d]	−0.349 ± 0.261	−0.365 ± 0.261	−1.334 ± 0.419	−1.738 ± 0.205	−1.321 ± 0.418	−1.724 ± 0.159
Tb.1/N.SD[d]	−0.122 ± 0.164	−0.193 ± 0.159	−0.273 ± 0.264	−0.641 ± 0.328	−0.268 ± 0.254	−0.673 ± 0.316
Reaction force	−8.43 ± 4.32	–8.24 ± 4.31	−59.74 ± 6.90	−76.10 ± 8.55	−60.05 ± 6.87	−76.46 ± 8.52
Failure load	−3.91 ± 1.93[a]	−3.85 ± 1.93[a]	−30.27 ± 3.08	−38.63 ± 3.83[a]	−30.27 ± 3.08	−38.77 ± 3.83[a]
Percentage values						
Tt.vBMD	−0.017 ± 0.023	−0.014 ± 0.023	−0.273 ± 0.037	−0.372 ± 0.045[a]	−0.275 ± 0.036	−0.373 ± 0.045[a]
Ct.Ar	−0.133 ± 0.065[a]	−0.143 ± 0.065[a]	−0.839 ± 0.104	−1.143 ± 0.129[a]	−0.848 ± 0.103	−1.159 ± 0.128[a]
Ct.Th[d]	−0.057 ± 0.026[a]	−0.056 ± 0.026[a]	−0.405 ± 0.042	−0.556 ± 0.052[c]	−0.408 ± 0.042	−0.560 ± 0.052[c]
Ct.vBMD	−0.049 ± 0.020[a]	−0.051 ± 0.020[a]	−0.438 ± 0.032	−0.513 ± 0.040	−0.441 ± 0.032	−0.519 ± 0.039[a]
Tb.Ar	0.015 ± 0.005[c]	0.014 ± 0.005[c]	0.015 ± 0.008	0.050 ± 0.009[d]	0.015 ± 0.008	0.049 ± 0.009[d]
Tb.vBMD	0.024 ± 0.016	0.027 ± 0.016	0.184 ± 0.026	0.197 ± 0.032	0.183 ± 0.026	0.198 ± 0.032
Tb.N	0.048 ± 0.032	0.047 ± 0.032	0.157 ± 0.052	0.216 ± 0.064	0.155 ± 0.052	0.212 ± 0.064
Tb.Th[d]	−0.018 ± 0.050	−0.025 ± 0.050	−0.060 ± 0.080	−0.077 ± 0.100	−0.067 ± 0.080	−0.093 ± 0.100
Tb.Sp[d]	−0.075 ± 0.051	−0.076 ± 0.051	−0.279 ± 0.082	−0.368–0.102	−0.276 ± 0.082	−0.363 ± 0.102
Tb.1/N.SD[d]	−0.078 ± 0.058	−0.083 ± 0.058	−0.191 ± 0.092	−0.314 ± 0.115	−0.189 ± 0.092	−0.312 ± 0.115
Reaction force	−0.065 ± 0.035	−0.062 ± 0.034	−0.469 ± 0.055	−0.584 ± 0.069	−0.473 ± 0.055	−0.587 ± 0.068
Failure load	−0.061 ± 0.031[a]	−0.069 ± 0.032[a]	−0.466 ± 0.050	−0.589 ± 0.062[a]	−0.470 ± 0.049	−0.592 ± 0.061[a]

[a] $p < 0.05$, [b] $p < 0.01$, [c] $p < 0.005$, [d] $p < 0.001$

[#] Adjusted for age, BMI, bio-17β-estradiol, parathyroid hormone, glomerular filtration rate, and the score of lower limb physical function

Tt.vBMD, total volumetric bone mineral density (vBMD) (mg/cm^3/yr); *Ct.Ar*, cortical area (mm^2/yr); *Ct.Th*^{d}, cortical thickness (μm/yr); *Ct.vBMD*, cortical vBMD (mg/cm^3/yr); *Tb.Ar*, trabecular area (mm^2/yr); *Tb.vBMD*, trabecular vBMD (mg/cm^3/yr); *Tb.N*, trabecular number (1/mm/yr × 10^3); *Tb.Th*^{d}, trabecular thickness (μm/yr); *Tb.Sp*^{d}, trabecular separation (μm/yr); *Tb.1/N.SD*^{d}, trabecular spacing standard deviation (trabecular distribution) (μm/yr); reaction force (N/yr); failure load (N/yr)

proinflammatory cytokines and of derivatives of reactive oxygen metabolites [31, 32].

Data on the association between hsCRP levels and aBMD loss are discordant, but mostly non-significant [16, 20, 21, 33]. Elderly women with persistently elevated hsCRP concentration had faster aBMD loss at the hip [20]. In late postmenopausal women, greater increase in hsCRP level was associated with more rapid bone loss [33]. In our cohort, hsCRP was not associated with the bone loss at the hip or distal radius. By contrast, higher hsCRP was associated with greater aBMD gain at the lumbar spine and whole body. This increase is not straightforward. However, higher hsCRP level may be associated with greater weight gain or development of osteoarthritis which result in bone gain [34, 35].

We have previously shown that in elderly men, higher hsCRP concentration was associated with poor trabecular bone status (lower Tb.N, higher TB.1/N.SD[d]) at distal radius [18]. Thus, high hsCRP levels may be associated with higher bone resorption which is not matched by a similar increase in bone formation. Prospective data on the link between bone structural decline and inflammation are scarce. In patients with rheumatoid arthritis or ankylosing spondylitis, severe disease (assessed by hsCRP or clinical score) was associated with faster prospectively assessed bone loss [19, 36]. Potential mechanisms include stimulatory effect of inflammatory cytokines on bone resorption on the endocortical surface. Interestingly, this endocortical bone loss may be partly offset by periosteal apposition as suggested by higher outer

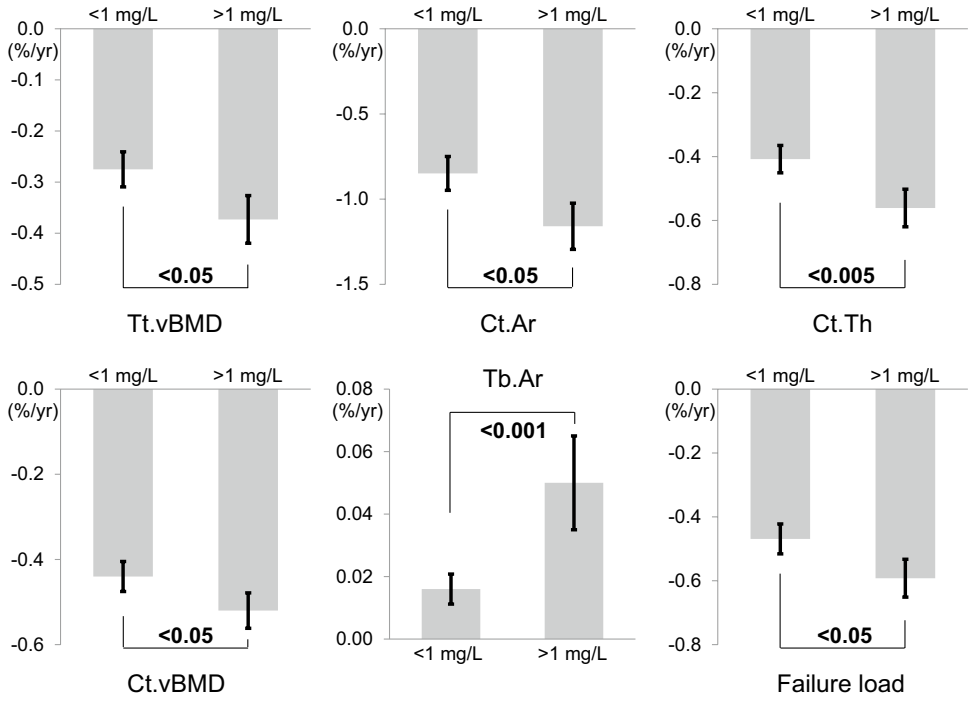

Fig. 1 Comparison of the bone microarchitecture measures at the distal tibia in men with hsCRP concentration > 1 mg/L vs. < 1 mg/L: Tt.vBMD, total volumetric bone mineral density (vBMD); Ct.Ar, cortical area; Ct.Th, cortical thickness; Ct.vBMD, cortical vBMD; Tb.Ar, trabecular area; failure load. The model adjusted for age, BMI, bio-17β-estradiol, parathyroid hormone, glomerular filtration rate, and the score of lower limb physical function

Table 6 Association between baseline hsCRP concentration and fracture risk over 8 years

Fractures	Fracture incidence (*n*/*N*, %)	Incidence (/1000 p-yrs)	Model	Per 1 SD increase		> 1 mg/L vs. ≤ 1 mg/L	
				HR (95% CI)	*p*	HR (95% CI)	*p*
All	102/823 (12.4%)	18.09	Unadjusted	1.13 (0.94–1.37)	0.20	1.30 (0.83–2.03)	0.25
			Adjusted*	1.04 (0.95–1.28)	0.70	1.09 (0.68–1.73)	0.72
Additionally adjusted for competing risk of death				*1.01 (0.82–1.24)*	*0.92*	*1.07 (0.67–1.71)*	*0.77*
Spine	47/823 (7.1%)	10.49	Unadjusted	1.13 (0.86–1.50)	0.38	1.54 (0.78–3.04)	0.21
			Adjusted*	1.15 (0.87–1.53)	0.32	1.51 (0.75–3.06)	0.25
Additionally adjusted for competing risk of death				*1.14 (0.86–1.51)*	*0.37*	*1.43 (0.71–2.89)*	*0.32*
Non-spine	62/823 (7.5%)	10.74	Unadjusted	1.21 (0.95–1.54)	0.13	1.38 (0.77–2.48)	0.28
			Adjusted*	1.06 (0.81–1.39)	0.65	1.06 (0.58–1.95)	0.85
Additionally adjusted for competing risk of death				*1.03 (0.79–1.34)*	*0.81*	*1.06 (0.58–1.94)*	*0.86*

*Adjusted for age, BMI, femoral neck aBMD, prior falls, and fractures

perimeter of bones in patients with rheumatoid arthritis [37]. Moreover, sirtuin 1 (SIRT1), NAD + -dependent deacetylase, may inhibit osteoclastogenesis and induce osteoblast differentiation [38]. Inflammation is associated with low SIRT1 level which may contribute to the progressive bone loss [39]. Proinflammatory cytokines disrupt osteocyte function and increase the secretion of RANKL (stimulating bone resorption) and of sclerostin (inhibiting bone formation) [40]. These mechanisms of the inflammation-related bone decline are consistent with our findings.

In our study, high hsCRP was not associated with fracture risk after adjustment for confounders including aBMD, prior falls, and fractures. Previously, high hsCRP levels were not associated with higher fracture risk in older men (and in the mixed cohorts) or this association was weak and limited to some skeletal sites (e.g., spine) [10–13, 16, 41, 42]. By contrast, higher hsCRP levels were associated with higher fracture risk in the models poorly controlled for confounders such as aBMD or prior falls [9, 43]. Higher hsCRP level was associated with higher risk of non-vertebral fracture in women from the Tromsø study, higher risk of nontrauma fracture in women from the Bruneck study, and with the higher risk of limb or vertebral fracture in elderly women from the Muramatsu study [9, 11, 44]. By contrast, hsCRP levels were not associated with the risk of fracture (major osteoporotic, hip) in elderly women from the OPRA study [20]. However, women have lower aBMD and their bone may be more sensitive to the inflammation-induced bone

loss, because estrogen deficit activates the Th17 proinflammatory cytokines. Moreover, fracture risk was higher in subjects with long-term (or recurrent) active inflammation and higher hsCRP levels, e.g., in patients with rheumatoid arthritis [6]. Fracture risk was also increased in individuals who had elevated levels of several inflammatory markers simultaneously [13]. These data show that active inflammatory status can be associated with increased fracture risk. By contrast, in older men aged 60–87 years from cohort, hsCRP levels were low (median: 1.67 mg/L) and only 16% of men has hsCRP > 5 mg/L. Thus, we could be unable to detect a mild increase in fracture risk related to the low-grade ageing-related inflammatory syndrome.

Our study has limitations. It is a single-center cohort composed of home-dwelling Caucasian men. Our results may not be extrapolated to women or other ethnic groups. We had one hsCRP value per man and we could not differentiate between chronic stable and acute inflammation. However, men refused to come when they had an acute disease; thus, few high hsCRP levels are supposed to be associated with acute inflammation. Blood was collected in the non-fasting status in early afternoon; however, there is no diurnal variation of serum hsCRP in humans [45]. The attrition rate was high. Men who were lost to follow-up were older and had higher hsCRP levels (also when adjusted for age). Men who were lost to follow-up could have faster bone loss and higher fracture risk. It shows that we underestimate the rate of bone loss, fracture incidence, and also the strength of the links between variables. $Ct.Th^{d}$ and $Tb.Th^{d}$ were calculated, not measured. The assessment of cortical bone may be erroneous in the oldest men with thin cortex. Bone microarchitecture assessment may be inaccurate because of the partial volume effect. HR-pQCT cannot detect age-related microdamage, posttranslational protein modification, or mineral imperfection. µFEA assesses bone compression, not other deformations [46]. Endocortical trabecularization leads to inclusion of remnants of internal cortical layer into the trabecular bone and results in underestimation of trabecular bone loss and overestimation of cortical bone loss. Dichotomization cortical/trabecular is to be interpreted cautiously. Microradiographic analyses performed in the bones collected *post mortem* in elderly women show no clear-cut endocortical edge, but gradual transition between the compartments [47, 48]. Perforations of subendocortical cortical pores lead to overestimation of endocortical expansion as well as to underestimation of the rise in cortical porosity and of the decrease in Ct.vBMD [47, 48]. We checked self-reported non-spine fractures, but false negatives are possible. Incident spine fractures were assessed only in men who returned for follow-up visits and had DXA. Medical records of the participants were not scrutinized. It may underestimate the number of incident spine fractures, especially because older and sicker men, who did not return, could have higher spine fracture incidence. Prior non-spine fractures, falls, and morbidities were self-reported and not checked. In an observational study, residual confounding is possible.

Overall, in a cohort of older men followed prospectively for 8 years, high hsCRP was associated with greater endocortical expansion at distal radius and distal tibia. Higher hsCRP level was also associated with more rapid decrease in Tt.vBMD, Ct.vBMD, and failure load at distal tibia and with a greater increase in aBMD at the lumbar spine and whole body. After adjustment for potential confounders including the competing risk of death, higher hsCRP was not associated with the fracture risk. Thus, ageing-related low-grade inflammatory syndrome may results in slightly greater bone loss, probably mainly at the endocortical surface. However, bone loss is not generalized and its impact on bone strength is minor. Thus, in our cohort, higher hsCRP level does not seem to be a major predictor of bone decline and fragility in older men. However, given the loss to follow-up of the oldest men with the highest hsCRP concentrations, we could have underestimated the existing links. Thus, further studies are necessary to explore this topic.

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Declarations

Conflict of interest NonE.

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