

The relation between healthy lifestyle changes and decrease in systemic inflammation in patients with stable cardiovascular disease



C.C. van 't Klooster^a, Y. van der Graaf^b, P.M. Ridker^{c,d,e}, J. Westerink^a, J. Hjortnaes^{f,g}, I. Sluijs^b, F.W. Asselbergs^{h,i,j}, M.L. Bots^b, L.J. Kappelle^k, F.L.J. Visseren^{a,**}, On behalf of the UCC-SMART study group

^a Department of Vascular Medicine, University Medical Center Utrecht (UMCU), Utrecht University, Utrecht, the Netherlands

^b Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht (UMCU), University Utrecht, Utrecht, Netherlands

^c Division of Preventive Medicine, Brigham and Women's Hospital, Boston, USA

^d Division of Cardiology, Brigham and Women's Hospital, Boston, USA

^e Department of Epidemiology, Harvard T.H. Chan School of Public Health, Boston, USA

^f Department of Cardiothoracic Surgery, University Medical Center Utrecht (UMCU), Utrecht University, Utrecht, the Netherlands

^g Regenerative Medicine Center Utrecht, University Medical Center Utrecht (UMCU), Utrecht University, Utrecht, the Netherlands

^h Department of Cardiology, Division Heart & Lungs, University Medical Center Utrecht (UMCU), Utrecht University, Utrecht, the Netherlands

ⁱ Institute of Cardiovascular Science, Faculty of Population Health Sciences, University College London, London, United Kingdom

^j Health Data Research UK and Institute of Health Informatics, University College London, London, United Kingdom

^k Department of Neurology, University Medical Center Utrecht (UMCU), Utrecht University, Utrecht, the Netherlands

HIGHLIGHTS

- In patients with established cardiovascular disease (CVD), lifestyle improvements are related to a decrease in C-reactive protein (CRP).
- These lifestyle improvements are smoking cessation, physical activity increase, and weight loss.
- Multiple lifestyle changes are related to the most decrease in CRP concentration.
- Lifestyle changes might reduce CVD risk partly through lowering systemic inflammation.

ARTICLE INFO

Keywords:

Patients with stable cardiovascular disease
Lifestyle changes
Low-grade inflammation
C-reactive protein

ABSTRACT

Background and aims: Pharmacological lowering of inflammation has proven effective in reducing recurrent cardiovascular event rates. Aim of the current study is to evaluate lifestyle changes (smoking cessation, weight loss, physical activity level increase, alcohol moderation, and a summary lifestyle improvement score) in relation to change in plasma C-reactive protein (CRP) concentration in patients with established cardiovascular disease. **Methods:** In total, 1794 patients from the UCC-SMART cohort with stable cardiovascular disease and CRP levels ≤ 10 mg/L, who returned for a follow-up study visit after median 9.9 years (IQR 5.4–10.8), were included. The relation between changes in smoking status, weight, physical activity, alcohol consumption, a summary lifestyle improvement score and change in plasma CRP concentration was evaluated with linear regression analyses. **Results:** Smoking cessation was related to a 0.40 mg/L decline in CRP concentration (β -coefficient -0.40 ; 95%CI $-0.73, -0.07$). Weight loss (per 1SD = 6.4 kg) and increase in physical activity (per 1SD = 48 MET hours per week) were related to a decrease in CRP concentration (β -coefficients -0.25 ; 95%CI $-0.33, -0.16$ and -0.09 ; 95%CI $-0.17, -0.01$ per SD). Change in alcohol consumption was not related to CRP difference. Every point higher in the summary lifestyle improvement score was related to a decrease in CRP concentration of 0.17 mg/L (β -coefficient -0.17 ; 95%CI $-0.26, -0.07$). **Conclusions:** Smoking cessation, increase in physical activity, and weight loss are related to a decrease in CRP concentration in patients with stable cardiovascular disease. Patients with the highest summary lifestyle

* Corresponding author. Department of Vascular Medicine, University Medical Centre Utrecht, PO Box 85500, 3508 GA, Utrecht, the Netherlands.
E-mail address: f.l.j.visseren@umcutrecht.nl (F.L.J. Visseren).

<https://doi.org/10.1016/j.atherosclerosis.2020.03.022>

Received 6 January 2020; Received in revised form 27 February 2020; Accepted 26 March 2020

Available online 06 April 2020

0021-9150/ © 2020 The Authors. Published by Elsevier B.V. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

improvement score have the most decrease in CRP concentration. These results may indicate that healthy lifestyle changes contribute to lowering systemic inflammation, potentially leading to a lower cardiovascular risk in patients with established cardiovascular disease.

1. Introduction

Systemic low-grade inflammation plays a role in the development of atherothrombotic disease by initiating plaque formation, as well as stimulating plaque progression and transformation to vulnerable plaques that are more prone to erosion or rupture [1]. Epidemiological evidence further supports the role of low-grade inflammation in the development of lung cancer [2–4]. Pharmacological lowering of systemic inflammation, at least with an interleukin (IL)-1 β antagonist, has recently been shown to reduce incidence rates of both cardiovascular events and lung cancer [2,5].

C-reactive protein (CRP), an acute phase protein, is part of the IL-1 β , IL-6 inflammatory pathway [6], and plasma CRP concentrations ≤ 10 mg/L reflect systemic low-grade inflammation [7]. Several medical conditions, as well as lifestyle factors including smoking [8], abdominal obesity [9], physical activity [10], and alcohol intake [11], influence systemic inflammation. Mechanisms include promotion of local pulmonary inflammation due to cigarette smoke by recruitment of natural killer cells and neutrophils from the microcirculation to the lungs [12], leading to a systemic inflammatory response by secretion of pro-inflammatory mediators [13]. Adipose tissue production of pro-inflammatory cytokines such as tumour necrosis factor-alpha (TNF- α), and IL-6 is increased as the visceral adipose tissue compartment expands [14]. Regular physical activity reduces systemic low-grade inflammation through three potential mechanisms including reduction of visceral adipose tissue, increased production of anti-inflammatory cytokines from contracting skeletal muscles, and reduced production of inflammatory cytokines by monocytes [15]. Chronic excessive alcohol use leads to increased production of pro-inflammatory cytokines due to alcoholic liver injury [16], whereas light to moderate alcohol use compared to no alcohol is thought to reduce inflammation through ethanol-induced inhibition of pro-inflammatory cytokine and chemokine production, such as IL-6 and TNF, by circulating monocytes [17,18].

Despite these associations, the effect of lifestyle improvements on reducing low-grade inflammation in patients with cardiovascular disease remains controversial. Although weight loss and physical activity have been shown to reduce CRP levels [19–21], conflicting results are reported for effects of smoking cessation, diet, and alcohol consumption [22–27]. The aim of the current study is to examine the association between lifestyle behaviors and systemic low-grade inflammation at baseline, as well as the relation between lifestyle changes (including smoking cessation, weight loss, physical activity level increase, alcohol moderation, and a summary lifestyle improvement score) and change in systemic low-grade inflammation, measured by CRP plasma concentrations, in a cohort of patients with established cardiovascular disease.

2. Patients and methods

2.1. Study population

Participants originated from the Utrecht Cardiovascular Cohort-Second Manifestations of ARterial disease (UCC-SMART) cohort, an ongoing prospective cohort study that started in 1996. The UCC-SMART cohort includes 18 to 79 year-old patients referred to the University Medical Center (UMC) in Utrecht, the Netherlands. Study design and rationale have been described in detail previously [28]. From 2006 onwards, patients with at least 4 years of follow-up were invited for reassessment of baseline measurements (UCC-SMART-2 cohort). Yearly,

approximately 350 consecutive patients of the original UCC-SMART-cohort were invited by mail, achieving a recruitment efficacy of 58% (Supplemental Fig. S1). Baseline characteristics of patients with a second visit compared to patients with a baseline visit only are shown in Supplemental Table S1. The study complies with the Declaration of Helsinki, was approved by the University Medical Center's Ethics Committee, and all patients provided written informed consent. For the current study, patients with established cardiovascular disease at baseline, who returned for second measurements, and with CRP levels ≤ 10 mg/L at both visits, were included (N = 1794). Established cardiovascular disease was defined as cerebrovascular disease (transient ischemic attack, cerebral infarction, amaurosis fugax, retinal infarction, history of carotid surgery), coronary artery disease (angina pectoris, myocardial infarction, coronary revascularization), peripheral artery disease (symptomatic and documented obstruction of distal arteries, revascularization of the leg, amputation), or an aneurysm of the abdominal aorta (distal aortic anteroposterior diameter ≥ 3 cm, history of AAA surgery). Participants with CRP levels > 10 mg/L were excluded (N = 217), as CRP levels > 10 mg/L are commonly associated with an acute inflammatory response [7]. Time between visit and vascular event was at least two months (both baseline and follow-up measurement). Advice on lifestyle improvements was given according to general clinical practice, lifestyle interventions were not part of this observational cohort study.

2.2. Measurements at baseline and follow-up visit

The same data was acquired at baseline and follow-up visit following a standardized protocol. Information on smoking status (never, former, or current, and number of pack-years) and alcohol consumption (no alcohol, < 1 , 1–10, 11–20, 21–30, or > 30 units per week) was obtained by a questionnaire. Weight was measured on traditional scales. A previously validated questionnaire suitable for ranking subjects [29] was used for measuring physical activity, with one additional question on the intensity of sports activity. Number of hours per week reported by patients for sports, walking, cycling, and gardening, was multiplied by a specific metabolic equivalent of task (MET) derived from the Compendium of Physical activity [30], resulting in a number of MET hours per week per activity. The total amount of physical activity was the sum of the MET hours per week of all activities. Work-related physical activity (categories; sedentary occupation, standing occupation, manual labor, or heavy manual labor) and retirement status were additionally recorded. Information on dietary habits was not available.

2.3. Lifestyle changes and summary lifestyle improvement score

Achievement of lifestyle goals regarding smoking, weight, physical activity, and alcohol consumption according to cardiovascular disease prevention guidelines [31] was assessed at baseline and follow-up. Change in continuous lifestyle variables (weight, physical activity, and number of pack-years), as well as CRP, was determined by the difference between follow-up and first measurement. Changes in categorical variables were defined as smoking cessation (compared to continuing smoking), smoking start (compared to continued non-smoking), alcohol use change from heavy to moderate or no alcohol use (compared to continued heavy users), and alcohol use change from no alcohol to moderate (compared to continued none use). For the creation of a summary lifestyle improvement score, summing up the changes in the four lifestyle components, each lifestyle factor was graded; -1 for

deterioration (e.g. started smoking or gained weight ($> 1SD$)), 0 for no change (e.g. remained former smoker, similar alcohol use, weight and physical activity change within 1SD), and 1 for improvement (e.g. quit smoking or lost weight ($> 1SD$)). The sum of the grades of the four lifestyle characteristics formed the summary lifestyle improvement score with a minimum of -4 and a maximum of 4 , and was calculated for each individual patient.

2.4. Registration of events during follow-up

From the first visit onwards, patients received biannual questionnaires obtaining information on incident cardiovascular disease, bleeding events, diabetes mellitus, and end stage renal disease. Upon an affirmative answer, additional information was gathered through hospital or general practitioner's data. An endpoint committee of three physicians independently judged all clinical events, and conflicting decisions were discussed. Detailed information on definitions and number of endpoints is described in [Supplemental Table S2](#).

2.5. Data analyses

Missing data for smoking status ($< 0.3\%$), alcohol use ($< 1\%$), weight ($< 0.5\%$), CRP ($< 1.6\%$), use of lipid lowering and platelet inhibitory medication ($< 0.3\%$), and physical activity ($< 16\%$) were singly imputed by bootstrapping and predictive mean matching, based on multiple regression using both baseline and follow-up visit measurements as well as outcome data (aregImpute function in R, Hmisc package). With regard to the high percentage of missing physical activity data, a sensitivity analysis was performed with only complete

cases regarding physical activity.

For descriptive statistics, a baseline table, histogram for the distribution of difference in CRP concentration and cross tables of CRP differences per lifestyle characteristic were created. Cross-sectional analyses at baseline were performed first for all lifestyle factors by linear regression analyses with CRP concentration at baseline as the dependent variable and lifestyle factors (smoking status, alcohol use, body mass index (BMI), and physical activity at baseline) as independent variables. To investigate the relation between lifestyle changes and change in CRP concentration, linear regression analyses were performed. Difference in CRP was taken as the dependent variable, and each change in lifestyle as independent variable. Continuous independent variables (weight change and physical activity change) were assessed per SD increase. For the categorical independent variables, continuous smokers, continuous heavy alcohol users, and continuous non alcohol users were taken as the reference category. Baseline CRP was added to the models, as the magnitude of the difference in CRP level might depend on baseline concentration. To adjust for potential confounding, age and sex, and additionally change in use of lipid lowering (including change in statin use) or antiplatelet medication, smoking status change, weight change, physical activity change, and alcohol use change (if not determinant of interest) were added to the models. Exploratory models were evaluated with addition of educational level, retirement between visits, change in work-related physical activity, estimated glomerular filtration rate (eGFR) change, systolic blood pressure change, diabetes at baseline, diabetes acquired during follow-up, and low density lipoprotein cholesterol (LDL-c) change were assessed, as well as additional adjustment for the use of hormone replacement therapy at baseline in women, or other anti-

Table 1

Patient characteristics at the first and follow-up study visit.

Population, n = 1794	First visit	Follow-up visit ^a	Mean difference between visits ^b
Male, n (%)	1409 (79%)	1409 (79%)	NA
Age (years) ^c	57 ± 9	66 ± 9	9 ± 3
Cerebrovascular disease, n (%)	447 (25%)	485 (27%)	NA
Coronary heart disease, n (%)	1181 (66%)	1242 (69%)	NA
Peripheral vascular disease, n (%)	274 (15%)	323 (18%)	NA
Diabetes mellitus, n (%)	220 (12%)	370 (21%)	NA
Metabolic syndrome, n (%) ^d	848 (47%)	953 (53%)	NA
Current smoking, n (%)	520 (29%)	310 (17%)	NA
Former smoking, n (%)	933 (52%)	1156 (64%)	NA
Number of pack-years ^c	15 (3–30)	19 (4–34)	3 ± 7
Alcohol use (> 10 units per week), n (%)	595 (33%)	490 (27%)	NA
Physical exercise (MET hours/week) ^c	43 (25–71)	44 (25–72)	1 ± 48
Medication			
Lipid lowering medication, n (%)	1204 (67%)	1485 (83%)	NA
Blood pressure lowering medication, n (%)	1310 (73%)	1385 (77%)	NA
Anti-platelet therapy, n (%)	1385 (77%)	1446 (81%)	NA
Anti-coagulants, n (%)	137 (8%)	192 (11%)	NA
Other anti-inflammatory medication, n (%) ^e	51 (3%)	117 (7%)	NA
Physical examination			
Body Mass Index (kg/m ²) ^c	27 ± 4	27 ± 4	0.6 ± 2
Weight (kg) ^c	82 ± 13	83 ± 14	0.9 ± 6
Waist circumference (cm) ^c	95 ± 11	98 ± 12	3.6 ± 7
Systolic blood pressure (mmHg) ^c	139 ± 20	140 ± 17	0.5 ± 21
Diastolic blood pressure (mmHg) ^c	82 ± 11	80 ± 10	-2.2 ± 13
Laboratory measurements			
Hs-CRP (mg/L) ^c	1.5 (0.8–3.1)	1.4 (0.7–2.7)	-0.2 ± 2.2
Triglycerides (mmol/L) ^c	1.4 (1.0–2.0)	1.2 (0.9–1.8)	-0.2 ± 0.9
HDL cholesterol (mmol/L) ^c	1.2 (1.0–1.4)	1.2 (1.0–1.5)	0.05 ± 0.3
LDL cholesterol (mmol/L) ^c	2.8 (2.2–3.5)	2.4 (2.0–3.0)	-0.3 ± 1.1
eGFR (CKD-EPI, mL/min/1.73m ²) ^{c,f}	79 ± 15	75 ± 17	-4 ± 11

^a Median time between visits 9.9 years (IQR 5.4–10.8 years).

^b Individual differences between visits, only for continuous variables.

^c Data are mean ± SD or median (interquartile range).

^d Metabolic syndrome was defined according to the National Cholesterol Education Program Adult Treatment Panel III definition [40].

^e Other anti-inflammatory medications: non-steroidal anti-inflammatory drugs (NSAIDs), COX-2 inhibitors, colchicine, corticosteroids, and immunosuppressive medication (including methotrexate).

^f Kidney function was estimated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula [41].

inflammatory medication (including non-steroidal anti-inflammatory drugs (NSAIDs), COX2 inhibitors, corticosteroids, and immunosuppressive medication).

The relation between multiple lifestyle changes and change in CRP concentration was evaluated by plotting mean difference (standard error of the mean (SEM)) of CRP versus the summary lifestyle improvement score, for all patients and stratified for CRP concentration at baseline (the median CRP level at baseline of 1.5 mg/L was chosen as cut-off value). Furthermore, linear regression was performed with the summary lifestyle improvement score as a continuous independent variable and CRP difference as dependent variable, adjusted for age, sex, CRP at baseline, and change in use of lipid lowering or antiplatelet medication.

2.6. Additional analyses and assumptions of linear regression

Potential effect modification by time since smoking status was tested by adding an interaction term to the model. Estimated marginal means of CRP concentration were calculated for never smokers and patients who quit smoking during follow-up, adjusted for age, sex, change in other lifestyle factors, and lipid lowering and antiplatelet medication. To evaluate potential effects of incident cancer (N = 105) or cardiovascular disease (N = 126) during the follow-up period on the relation between lifestyle changes and change in CRP, a sensitivity analysis was performed by excluding these patients.

Assumptions of linear regression; linearity between independent variable and outcome, normality of residuals, and homogeneity of variance were assessed visually and no violations were observed.

3. Results

3.1. Baseline characteristics

In total, 1794 patients with clinically manifest cardiovascular disease and CRP levels ≤ 10 mg/L were included. Mostly males were included (79%), due to the specific study population of patients with established CVD. Median time between the first and follow-up study visit was 9.9 years (interquartile range (IQR) 5.4–10.8 years). Patient characteristics for the first and follow-up visit are shown in Table 1. Median CRP concentration was 1.5 mg/L (IQR 0.8–3.1) at baseline and 1.4 mg/L (IQR 0.7–2.7) at follow-up, and CRP levels were fairly stable with a mean difference of -0.18 mg/L (SEM 0.05) between the first and follow-up study visits (Supplemental Fig. S2).

3.2. Change in lifestyle between baseline and follow-up

At baseline and follow-up only 5% and 4% of the patients had achieved all four lifestyle goals for smoking, physical activity, BMI, and alcohol intake, even though slight improvements were observed for smoking and BMI (Supplemental Table S2). The majority of the patients did not change their lifestyle habits during follow-up, regarding smoking, physical activity, weight, and alcohol use (Supplemental Table S3). At baseline, 520 (29%) patients were current smokers. During follow-up, 261 patients quit smoking whereas 51 patients started smoking. Most patients had a stable weight comparing baseline and follow-up (N = 1327 (74%)), and the majority of patients had a stable level of physical activity (N = 1364 (76%)). Although most patients did not change their alcohol intake (N = 1493 (83%)), 203 patients moderated alcohol use from more than 10 units to fewer than 10 per week (Table 2).

3.3. Relation between lifestyle changes and change in CRP concentration

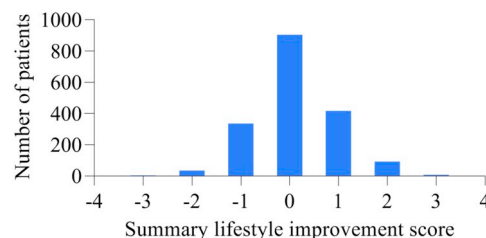
Cross-sectional analyses at baseline showed that smoking status and BMI were associated with CRP concentration at baseline. Alcohol consumption and physical activity were not associated with baseline CRP

Table 2

Change in lifestyle factors between baseline and follow-up visit, separate and combined in the summary lifestyle improvement score.

	-1	Score	1
		0	
Smoking status change ^a	51 (3%)	1482 (83%)	261 (15%)
Weight change ^b	291 (16%)	1327 (74%)	176 (10%)
Physical activity level change ^c	212 (12%)	1364 (76%)	218 (12%)
Alcohol use change ^d	98 (6%)	1493 (83%)	203 (11%)

Number of patients per summary lifestyle improvement score



^a Smoking status change: started smoking (-1), no change (remained non-smoker or current smoker) (0), or quit smoking (1).

^b Weight change: > 1SD (=6.4 kg) higher (-1), within 1SD (0), > 1SD lower (1).

^c Physical activity change: > 1SD (=48 METh/w) lower (-1), within 1SD (0), > 1SD higher (1).

^d Alcohol use change: From ≤ 10 to > 10 units per week (-1), similar (0), from > 10 to ≤ 10 units per week (1).

concentration (Supplemental Fig. S3).

Smoking cessation was related to a 0.40 mg/L decline in CRP concentration (β -coefficient -0.40 ; 95%CI $-0.73,-0.07$) (Fig. 1). No effect modification was observed by time since smoking cessation (p -value for interaction 0.97). Estimated marginal means of CRP level for participants who quit smoking during follow-up and for never smokers were 2.24 mg/L (95%CI 1.95,2.53) and 1.87 mg/L (95%CI 1.59,2.15) respectively. With regard to physical activity, for every SD increase in MET hours per week, CRP was 0.09 mg/L lower (β -coefficient -0.09 ; 95%CI $-0.17,-0.01$) (Fig. 1). Similar results were observed after excluding patients with missing data on physical activity at the follow-up visit (β -coefficient -0.13 ; 95%CI $-0.22,-0.04$). Weight loss was related to a decrease in CRP concentration; per SD weight loss the CRP concentration decreased with 0.25 mg/L (β -coefficient -0.25 ; 95%CI $-0.33,-0.16$) (Fig. 1). Change from heavy to moderate alcohol use was not related to CRP concentration (β -coefficient -0.22 ; 95%CI $-0.52,0.09$), and no relation was observed between change from no alcohol to moderate alcohol use and change in CRP level (β -coefficient -0.08 ; 95%CI $-0.54,0.38$) (Fig. 1). Additional adjustment for use of hormone replacement therapy at baseline in women, diabetes mellitus at baseline, educational level, retirement between visits, change in work-related physical activity, or change in eGFR, systolic blood pressure, the presence of diabetes mellitus, LDL-c, and anti-inflammatory medication use did not change results.

Analyses repeated after exclusion of patients with incident cardiovascular disease (n = 126) or any type of cancer, except for non-melanoma skin cancer (n = 105) between the two visits showed similar results.

3.4. Relation between summary lifestyle improvement score and change in CRP concentration

Patients with the highest summary lifestyle improvement scores (≥ 2) (N = 99 (6%)) on average had the most decline in CRP concentration or, after stratification by baseline CRP concentration, the most favorable trend in CRP level (Fig. 2). A linear relation was

Figure 1. Relation between lifestyle changes and change in CRP concentration

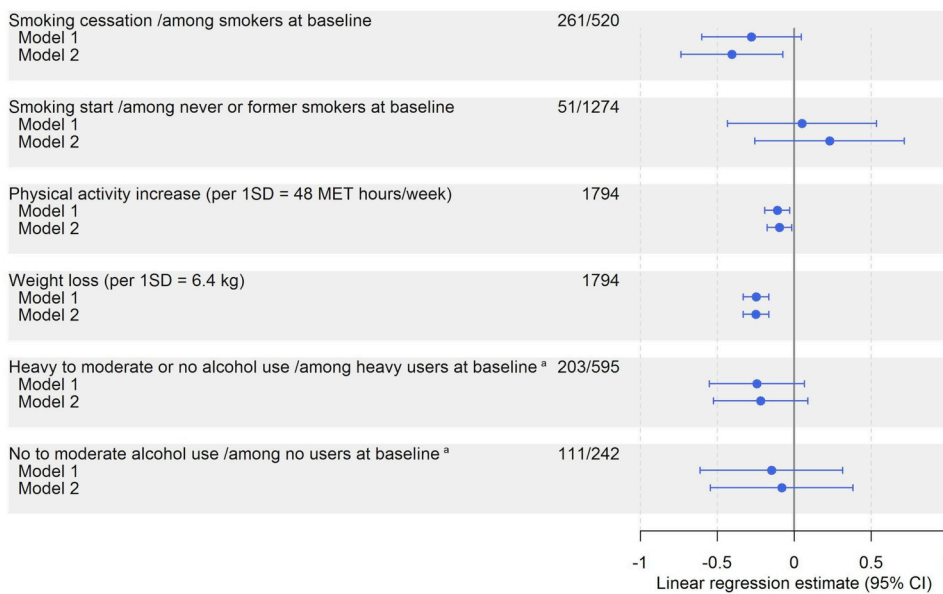
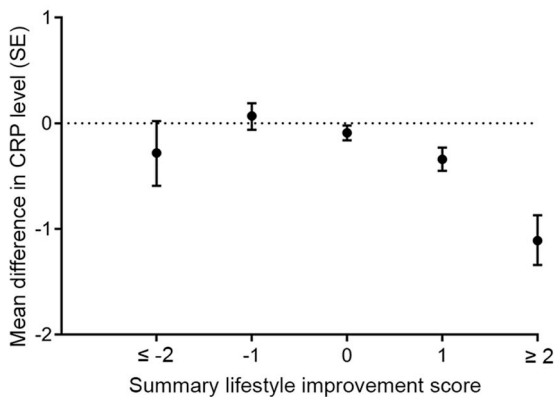


Fig. 1. Relation between lifestyle changes and change in CRP concentration.

Model 1: adjusted for age, sex, and CRP concentration at baseline. Model 2: additionally adjusted for difference in smoking status, physical activity level, weight, alcohol use (if not determinant of interest), and change in lipid lowering and antiplatelet therapy.

^a Heavy alcohol use: > 10 units per week; moderate alcohol use: > 0–10 units per week.

(A) All patients



observed between summary lifestyle improvement score and CRP difference, when adjusted for baseline CRP, age, sex, and change in lipid lowering and antiplatelet medication. Every point higher was related to a decrease in CRP concentration of 0.17 mg/L (β -coefficient -0.17 ; 95%CI $-0.26, -0.07$). As no relation was observed between alcohol consumption and CRP, an additional analysis was performed for the summary lifestyle improvement score without incorporation of alcohol use, showing similar results.

4. Discussion

In the present study, it is shown that lifestyle factors smoking and body mass index are associated with systemic low-grade systemic inflammation at baseline and that smoking cessation, increase in physical activity, and weight loss are related to a decrease in CRP plasma concentration in patients with established cardiovascular disease. Alcohol use and change in alcohol use were not associated with CRP plasma concentration. Every point higher in the summary lifestyle improvement score, a combination of changes in lifestyle factors, was related to a further decrease in CRP concentration.

Results of the present study support the notion that lifestyle factors and lifestyle changes are related to low-grade systemic inflammation, potentially explaining part of the beneficial effects of lifestyle changes on reduction of cardiovascular risk. Results for weight loss and physical activity increase are in line with previous studies in population based cohorts and trial populations for lifestyle interventions [19,20]. Inconsistencies were observed for smoking cessation and alcohol consumption [22–24]. Smoking cessation was not related to change in CRP after one year in a longitudinal smoking cessation trial with 1504 participants [24], or to change in CRP after an average of 3.4 years (range 1.0–10 years) in 975 smokers at baseline [22]. However, smoking cessation was accompanied by an increase in waist circumference [24], which may have counterbalanced CRP lowering effects of smoking cessation, and was not apparently taken into account in the analyses [22,24]. In the current study, smoking cessation was not related to CRP difference in crude analysis, only after adjustment for weight change, the relation became apparent. Moderate alcohol intake compared to no alcohol use was previously related to lower CRP

(B) Stratified for CRP at baseline

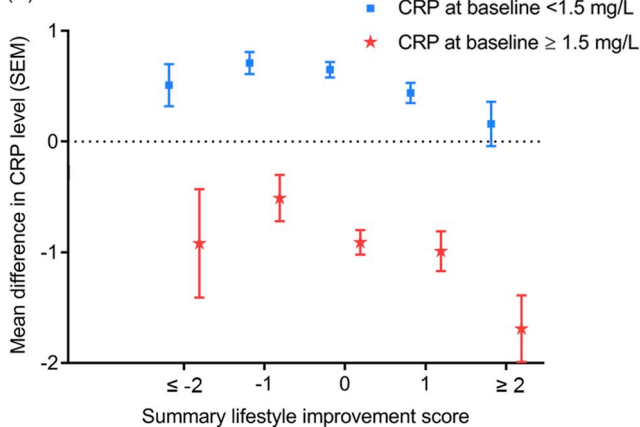


Fig. 2. Relation between summary lifestyle improvement score and change in CRP concentration.

Change in CRP level is the difference between follow-up visit and baseline.

concentrations in cross-sectional or trajectory analyses in population based studies [11,23] and in a subgroup of patients with a history of cardiovascular disease ($N = 1154$) [32]. In patients who consumed fewer than 7 drinks per week [32] or less than 20 g of ethanol (corresponding to 0.5 L beer) daily [11] CRP concentration was lowest. In the current study, moderate alcohol intake (> 0 –10 drinks per week) was not related to CRP concentration, implying that the upper limit of moderate alcohol use might be fewer than 10 drinks per week to have a beneficial effect on CRP concentration. Dietary information was not available in the present study. The relation between diet composition and CRP is uncertain; in a trial randomizing patients to a dietary regiment type, weight loss was the main driver of lowering CRP levels, irrespective of diet composition [25], whereas a cross-sectional observational study found a relation between dietary glycemic load and CRP independent of BMI [26].

The Canakinumab Antiinflammatory Thrombosis Outcome Study (CANTOS) trial showed that targeting inflammation by canakinumab, an IL-1 β inhibitor, lowered CRP levels and reduced the risk of recurrent CVD [5]. Furthermore, the Colchicine Cardiovascular Outcomes Trial (COLCOT) showed that lowering inflammation with colchicine in patients after a recent myocardial infarction reduced the risk of ischemic cardiovascular events [33]. CRP was lower in the colchicine group, although not statistically significant, and inflammation markers were only determined in a small and selected subgroup of patients [33]. No influence on CRP levels nor incident cardiovascular disease by methotrexate was observed in the Cardiovascular Inflammation Reduction Trial (CIRT) [34]. The combined results of these trials, illustrate the involvement of the IL-1 β , IL-6, CRP pathway in pathophysiology of atherothrombosis and lead to the hypothesis that cardiovascular disease risk reduction could be dependent on the targeted inflammatory pathway [6,34]. Since smoking cessation, weight loss, and increased physical activity showed a beneficial effect on CRP concentration, mechanisms by which lifestyle interventions lead to a decreased risk of recurrent cardiovascular disease might include reduction of low-grade systemic inflammation. Similarly, low-grade inflammation is considered a stimulating factor in lung cancer development [2–4], and smoking cessation might lead to a decreased risk of lung cancer compared to continuous smokers [35], partially through a reduction of low-grade inflammation. The effect of other lifestyle factors on lung cancer risk in smokers, such as weight and physical activity, is unclear [36,37].

The relation between lifestyle changes and decrease in CRP concentration in patients with cardiovascular disease is important for clinical practice, as a healthy lifestyle is an important part of secondary prevention [38]. A previous cross-sectional study suggested that 38% of patients with coronary artery disease and high inflammatory burden could achieve CRP levels lower than 2 mg/L after assumed lifestyle optimisation [39]. However, in the current study, reflecting real life, most patients did not manage to optimize lifestyle. Therefore, patients might benefit from further encouragement or assistance with improving lifestyle habits. Patients with a CRP concentration of ≥ 1.5 mg/L at baseline and the most lifestyle improvements (summary lifestyle improvement score of 2 or 3) had a mean difference in CRP concentration of -1.69 mg/L (SEM 0.30). In the CANTOS trial, including cardiovascular patients with a CRP concentration of ≥ 2 mg/L at baseline, canakinumab 150 mg lowered median CRP levels by 2.3 mg/L after 48 months follow-up (median 4.3 mg/L at baseline and 2.0 mg/L at follow-up), compared to a decrease of 0.5 mg/L in the placebo group [5]. Although this is a short term pharmacological intervention, these results suggest that patients with established cardiovascular disease potentially benefit from specific anti-inflammatory therapy, on top of healthy lifestyle changes, to lower cardiovascular risk.

Strengths of the study include the large study population of patients with cardiovascular disease and the repeated measurement of lifestyle factors and CRP concentration. Potential limitations should be considered and include the reported lifestyle habits by questionnaires at two time points (baseline and follow-up), which might not be

representative of the complete follow-up period. However, lifestyle habits and CRP concentration are measured simultaneously, and CRP concentration will therefore be representative for lifestyle habits of the preceding weeks. The long duration between baseline and follow-up visit potentially limits clinical importance of lifestyle goals achievement. Social desirability bias could have influenced participants' answers concerning physical activity, smoking, and alcohol consumption, leading to an underestimation of the relation with CRP concentration. Furthermore, the selection of patients who returned for follow-up measurements could lead to selection bias. The questionnaire to quantify physical activity is previously validated [29], but not specifically for change in physical activity level. Furthermore, validation showed that the questionnaire is suitable for ranking subjects rather than calculating absolute energy expenditure [29], and might be less suited for determining individual achievement of guideline recommended physical activity goals. Absence of elaborate information on daily alcohol intake (rather than weekly), may have influenced the results for alcohol consumption and CRP, and the relatively small number of patients changing from no to moderate alcohol intake ($N = 111$) could have limited precision. Unmeasured confounders, including diet, hormone replacement therapy at follow-up for women, additional comorbidities, or medication compliance could have influenced the results of the study. However, by studying the relation between difference in lifestyle and difference in CRP concentration within participants, effects of unmeasured confounding are potentially limited. Given the observational study design, firm conclusions on causality should be made with caution as residual confounding cannot be ruled out.

In conclusion, smoking cessation, increase in physical activity, and weight loss are related to a decrease in CRP concentration in patients with stable cardiovascular disease. Patients with the highest summary lifestyle improvement score have the most decrease in CRP concentration. These results may indicate that healthy lifestyle changes contribute to lower systemic inflammation, potentially leading to a lower cardiovascular risk in patients with stable cardiovascular disease.

Financial support

The UCC-SMART study was financially supported by a grant of the University Medical Center Utrecht. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

CRedit authorship contribution statement

C.C. van 't Klooster: Conceptualization, Methodology, Formal analysis, Investigation, Writing - original draft, Writing - review & editing. **Y. van der Graaf:** Conceptualization, Methodology, Investigation, Supervision, Writing - review & editing. **P.M. Ridker:** Conceptualization, Writing - review & editing. **J. Westerink:** Methodology, Investigation, Writing - review & editing. **J. Hjortnaes:** Writing - review & editing. **I. Sluijs:** Methodology, Writing - review & editing. **F.W. Asselbergs:** Investigation, Writing - review & editing. **M.L. Bots:** Investigation, Writing - review & editing. **L.J. Kappelle:** Investigation, Writing - review & editing. **F.L.J. Visseren:** Conceptualization, Methodology, Investigation, Supervision, Writing - review & editing.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

P.M. Ridker, has received investigator initiated research grants from Kowa, Novartis, Pfizer, AstraZeneca, NHLBI, NCI. Dr Ridker has served as a consultant to Corvidia, Inflammazone, Novartis, Amgen, Merck,

and Civi Bio. Dr Ridker is listed as co-inventor on patents related to the use of inflammatory biomarkers in CVD and diabetes that are no longer active. F.W. Asselbergs reports grants from UCL Hospitals NIHR Biomedical Research Centre, outside the submitted work. The other authors have nothing to declare.

Acknowledgements

We gratefully acknowledge the contribution of the research nurses; R. van Petersen (data-manager); B. van Dinther (study manager) and the members of the Utrecht Cardiovascular Cohort-Second Manifestations of ARterial disease-Studygroup (UCC-SMART-Studygroup): F.W. Asselbergs and H.M. Nathoe, Department of Cardiology; G.J. de Borst, Department of Vascular Surgery; M.L. Bots and M.I. Geerlings, Julius Center for health Sciences and Primary Care; M.H. Emmelot, Department of Geriatrics; P.A. de Jong and T. Leiner, Department of Radiology; A.T. Lely, Department of Obstetrics & Gynecology; N.P. van der Kaaij, Department of Cardiothoracic Surgery; L.J. Kappelle and Y.M. Ruigrok, Department of Neurology; M.C. Verhaar, Department of Nephrology, F.L.J. Visseren (chair) and J. Westerink, Department of Vascular Medicine, University Medical Center Utrecht and Utrecht University.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.atherosclerosis.2020.03.022>.

References

- [1] G.K. Hansson, Inflammation, atherosclerosis, and coronary artery disease, *N. Engl. J. Med.* 352 (16) (2005) 1685–1695.
- [2] P.M. Ridker, J.G. MacFadyen, T. Thuren, et al., Effect of interleukin-1beta inhibition with canakinumab on incident lung cancer in patients with atherosclerosis: exploratory results from a randomised, double-blind, placebo-controlled trial, *Lancet* 390 (10105) (2017) 1833–1842.
- [3] K.H. Allin, S.E. Bojesen, B.G. Nordestgaard, Inflammatory biomarkers and risk of cancer in 84,000 individuals from the general population, *Int. J. Canc.* 139 (7) (2016) 1493–1500.
- [4] C.C. van 't Klooster, J. Hjortnaes, Y. van der Graaf, F.W. Asselbergs, J. Westerink, J.G.J.V. Aerts, F.L.J. Visseren, The relation between systemic inflammation and incident cancer in patients with stable cardiovascular disease, *Eur. Heart J.* 40 (48) (2019) 3901–3909.
- [5] P.M. Ridker, B.M. Everett, T. Thuren, et al., Antiinflammatory therapy with canakinumab for atherosclerotic disease, *N. Engl. J. Med.* 377 (12) (2017) 1119–1131.
- [6] P.M. Ridker, From C-reactive protein to interleukin-6 to interleukin-1: moving upstream to identify novel targets for atheroprotection, *Circ. Res.* 118 (1) (2016) 145–156.
- [7] T.A. Pearson, G.A. Mensah, R.W. Alexander, et al., Markers of inflammation and cardiovascular disease: application to clinical and public health practice: a statement for healthcare professionals from the Centers for Disease Control and Prevention and the American Heart Association, *Circulation* 107 (3) (2003) 499–511.
- [8] S.G. Wannamethee, G.D. Lowe, A.G. Shaper, A. Rumley, L. Lennon, P.H. Whincup, Associations between cigarette smoking, pipe/cigar smoking, and smoking cessation, and haemostatic and inflammatory markers for cardiovascular disease, *Eur. Heart J.* 26 (17) (2005) 1765–1773.
- [9] D.R. Faber, Y. van der Graaf, J. Westerink, F.L. Visseren, Increased visceral adipose tissue mass is associated with increased C-reactive protein in patients with manifest vascular diseases, *Atherosclerosis* 212 (1) (2010) 274–280.
- [10] E.S. Ford, Does exercise reduce inflammation? Physical activity and C-reactive protein among U.S. adults, *Epidemiology* 13 (5) (2002) 561–568.
- [11] A. Imhof, M. Woodward, A. Doering, et al., Overall alcohol intake, beer, wine, and systemic markers of inflammation in western Europe: results from three MONICA samples (Augsburg, Glasgow, Lille), *Eur. Heart J.* 25 (23) (2004) 2092–2100.
- [12] M.R. Stampfli, G.P. Anderson, How cigarette smoke skews immune responses to promote infection, lung disease and cancer, *Nat. Rev. Immunol.* 9 (5) (2009) 377–384.
- [13] E.J. Oudijk, J.W. Lammers, L. Koenderman, Systemic inflammation in chronic obstructive pulmonary disease, *Eur. Respir. J. Suppl.* 46 (2003) 5s–13s.
- [14] G.R. Hajer, T.W. van Haefen, F.L. Visseren, Adipose tissue dysfunction in obesity, diabetes, and vascular diseases, *Eur. Heart J.* 29 (24) (2008) 2959–2971.
- [15] M. Gleeson, N.C. Bishop, D.J. Stensel, M.R. Lindley, S.S. Mastana, M.A. Nimmo, The anti-inflammatory effects of exercise: mechanisms and implications for the prevention and treatment of disease, *Nat. Rev. Immunol.* 11 (9) (2011) 607–615.
- [16] H. Tilg, A.M. Diehl, Cytokines in alcoholic and nonalcoholic steatohepatitis, *N. Engl. J. Med.* 343 (20) (2000) 1467–1476.
- [17] G. Szabo, P. Mandrekar, D. Catalano, Inhibition of superantigen-induced T cell proliferation and monocyte IL-1 beta, TNF-alpha, and IL-6 production by acute ethanol treatment, *J. Leukoc. Biol.* 58 (3) (1995) 342–350.
- [18] J.J. Galligan, R.L. Smathers, C.T. Shearn, et al., Oxidative stress and the ER stress response in a murine model for early-stage alcoholic liver disease, *J. Toxicol.* 2012 (2012) 207594.
- [19] R.A. Fernandes, R.M. Ritti-Dias, P.B. Balagopal, et al., Self-initiated physical activity is associated with high sensitivity C-reactive protein: a longitudinal study in 5,030 adults, *Atherosclerosis* 273 (2018) 131–135.
- [20] E. Selvin, N.P. Paynter, T.P. Erlinger, The effect of weight loss on C-reactive protein: a systematic review, *Arch. Intern. Med.* 167 (1) (2007) 31–39.
- [21] J.L. Abramson, V. Vaccarino, Relationship between physical activity and inflammation among apparently healthy middle-aged and older US adults, *Arch. Intern. Med.* 162 (11) (2002) 1286–1292.
- [22] S. Gallus, A. Lugo, P. Suatoni, et al., Effect of tobacco smoking cessation on C-reactive protein levels in a cohort of low-dose computed tomography screening participants, *Sci. Rep.* 8 (1) (2018) 12908.
- [23] S. Bell, G. Mehta, K. Moore, A. Britton, Ten-year alcohol consumption typologies and trajectories of C-reactive protein, interleukin-6 and interleukin-1 receptor antagonist over the following 12 years: a prospective cohort study, *J. Intern. Med.* 281 (1) (2017) 75–85.
- [24] A. Asthana, H.M. Johnson, M.E. Piper, M.C. Fiore, T.B. Baker, J.H. Stein, Effects of smoking intensity and cessation on inflammatory markers in a large cohort of active smokers, *Am. Heart J.* 160 (3) (2010) 458–463.
- [25] J.M. Nicklas, F.M. Sacks, S.R. Smith, et al., Effect of dietary composition of weight loss diets on high-sensitivity c-reactive protein: the Randomized POUNDS LOST trial, *Obesity* 21 (4) (2013) 681–689.
- [26] S. Liu, J.E. Manson, J.E. Buring, M.J. Stampfer, W.C. Willett, P.M. Ridker, Relation between a diet with a high glycemic load and plasma concentrations of high-sensitivity C-reactive protein in middle-aged women, *Am. J. Clin. Nutr.* 75 (3) (2002) 492–498.
- [27] P. Marques-Vidal, M. Bochud, F. Bastardot, et al., Associations between alcohol consumption and selected cytokines in a Swiss population-based sample (CoLaus study), *Atherosclerosis* 222 (1) (2012) 245–250.
- [28] P.C. Simons, A. Algra, M.F. van de Laak, D.E. Grobbee, Y. van der Graaf, Second manifestations of ARterial disease (SMART) study: rationale and design, *Eur. J. Epidemiol.* 15 (9) (1999) 773–781.
- [29] M.A. Pols, P.H. Peeters, M.C. Ocke, N. Slimani, H.B. Bueno-de-Mesquita, H.J. Collette, Estimation of reproducibility and relative validity of the questions included in the EPIC Physical Activity Questionnaire, *Int. J. Epidemiol.* 26 (Suppl 1) (1997) S181–S189.
- [30] B.E. Ainsworth, W.L. Haskell, M.C. Whitt, et al., Compendium of physical activities: an update of activity codes and MET intensities, *Med. Sci. Sports Exerc.* 32 (9 Suppl) (2000) S498–S504.
- [31] M.F. Piepoli, A.W. Hoes, S. Agewall, et al., European guidelines on cardiovascular disease prevention in clinical practice: the sixth joint task force of the European society of Cardiology and other societies on cardiovascular disease prevention in clinical practice (constituted by representatives of 10 societies and by invited experts) Developed with the special contribution of the European association for cardiovascular prevention & rehabilitation (EACPR), *Eur. Heart J.* 37 (29) (2016) 2315–2381 2016.
- [32] M.A. Albert, R.J. Glynn, P.M. Ridker, Alcohol consumption and plasma concentration of C-reactive protein, *Circulation* 107 (3) (2003) 443–447.
- [33] J.C. Tardif, S. Kouz, D.D. Waters, et al., Efficacy and safety of low-dose colchicine after myocardial infarction, *N. Engl. J. Med.* 381 (26) (2019) 2497–2505.
- [34] P.M. Ridker, B.M. Everett, A. Pradhan, et al., Low-Dose methotrexate for the prevention of atherosclerotic events, *N. Engl. J. Med.* 380 (8) (2019) 752–762.
- [35] S.A. Khuder, A.B. Mutgi, Effect of smoking cessation on major histologic types of lung cancer, *Chest* 120 (5) (2001) 1577–1583.
- [36] K.B. Borch, E. Weiderpass, T. Braaten, M.S. Hansen, I. Licaj, Risk of lung cancer and physical activity by smoking status and body mass index, the Norwegian Women and Cancer Study, *Eur. J. Epidemiol.* 34 (5) (2019) 489–498.
- [37] P. Duan, C. Hu, C. Quan, et al., Body mass index and risk of lung cancer: systematic review and dose-response meta-analysis, *Sci. Rep.* 5 (2015) 16938.
- [38] S.C. Smith Jr., E.J. Benjamin, R.O. Bonow, et al., AHA/ACC secondary prevention and risk reduction therapy for patients with coronary and other atherosclerotic vascular diseases: 2011 update: a guideline from the American heart association and American college of Cardiology foundation, *Circulation* 124 (22) (2011) 2458–2473.
- [39] C. Blaum, F.J. Brunner, F. Kroger, et al., Modifiable lifestyle risk factors and C-reactive protein in patients with coronary artery disease: implications for an anti-inflammatory treatment target population, *Eur J Prev Cardiol* 2047487319885458 (2019).
- [40] S.M. Grundy, J.I. Cleeman, S.R. Daniels, et al., Diagnosis and management of the metabolic syndrome: an American heart association/national heart, lung, and blood institute scientific statement, *Circulation* 112 (17) (2005) 2735–2752.
- [41] A.S. Levey, L.A. Stevens, C.H. Schmid, et al., A new equation to estimate glomerular filtration rate, *Ann. Intern. Med.* 150 (9) (2009) 604–612.