ESC European Society of Cardiology

European Heart Journal - Cardiovascular Imaging (2025) **26**, 1664–1672
https://doi.org/10.1093/ehjci/jeaf217

ORIGINAL PAPER

Association between inflammatory biomarkers, chronic stress, and pericoronary adipose tissue attenuation obtained with coronary CT

Tobia Albertini[1†], Marc Dörner[2,3†], Andreas A. Giannopoulos[1], Roland von Känel [2], Dominik C. Benz [1], Nidaa Mikail[1,4], Daniel de Wilde[1], Clarissa D. Voegel[5], Tina M. Binz[5], Philipp A. Kaufmann [1], Catherine Gebhard[1,4,6], Ronny R. Buechel [1], and Aju P. Pazhenkottil [1,2]*

[1]Cardiac Imaging, Department of Nuclear Medicine, University Hospital Zurich, University of Zurich, Zurich 8091, Switzerland; [2]Department of Consultation-Liaison-Psychiatry and Psychosomatic Medicine, University Hospital Zurich, University of Zurich, Zurich 8091, Switzerland; [3]German Center for Neurodegenerative Diseases (DZNE) within the Helmholtz Association, Magdeburg 39120, Germany; [4]Center for Molecular Cardiology, University of Zurich, Schlieren 8952, Switzerland; [5]Center for Forensic Hair Analytics, Zurich Institute of Forensic Medicine, University of Zurich, Zurich 8006, Switzerland; and [6]Department of Cardiology, Inselspital, Bern University Hospital, University of Bern, Bern 3010, Switzerland

Received 21 May 2025; revised 27 June 2025; accepted 9 July 2025; online publish-ahead-of-print 31 August 2025

See the editorial comment for this article 'Eat, stress, inflame: examining the link between chronic stress, coronary inflammation and plaque', by N.N. Mannakkara and J.R. Weir-McCall, https://doi.org/10.1093/ehjci/jeaf223.

Aims

Pericoronary adipose tissue (PCAT) attenuation is a novel imaging biomarker of coronary inflammation associated with an increased risk of coronary artery disease (CAD). However, no studies have examined the relationship between chronic stress and PCAT. This study aimed to evaluate the intersection between chronic stress, inflammatory biomarkers, coronary plaque features, and PCAT attenuation.

Methods and results

A total of 98 participants without known CAD were included. PCAT attenuation, total plaque volume (TPV) quantification, and vulnerable plaque features were assessed by coronary CT angiography and chronic stress was measured by hair cortisol concentration (HCC) and vital exhaustion questionnaire. Regression models were used to analyse associations of PCAT with the inflammatory biomarkers interleukin-6 (IL-6) and tumour necrosis factor-α (TNF-α), TPV, vulnerable plaque features, and coronary stenosis. Moderating analyses were performed to test whether chronic stress modulated the association between inflammatory biomarkers and PCAT attenuation. PCAT attenuation was significantly associated with IL-6 (mean difference 1.05, 95% CI 0.21–1.89, $P = 0.014$), TNF-α (mean difference 0.60, 95% CI 0.06–1.13, $P = 0.027$), and a greater TPV (mean difference 3.51, 95% CI 0.02–7.00, $P = 0.048$), but not vulnerable plaque features or coronary stenosis. HCC (interaction term −0.12, 95% CI −0.22 to −0.02, $P = 0.019$) and vital exhaustion (interaction term 0.13, 95% CI 0.01–0.25, $P = 0.024$) moderated the relationship between IL-6, but not TNF-α, and PCAT attenuation.

Conclusion

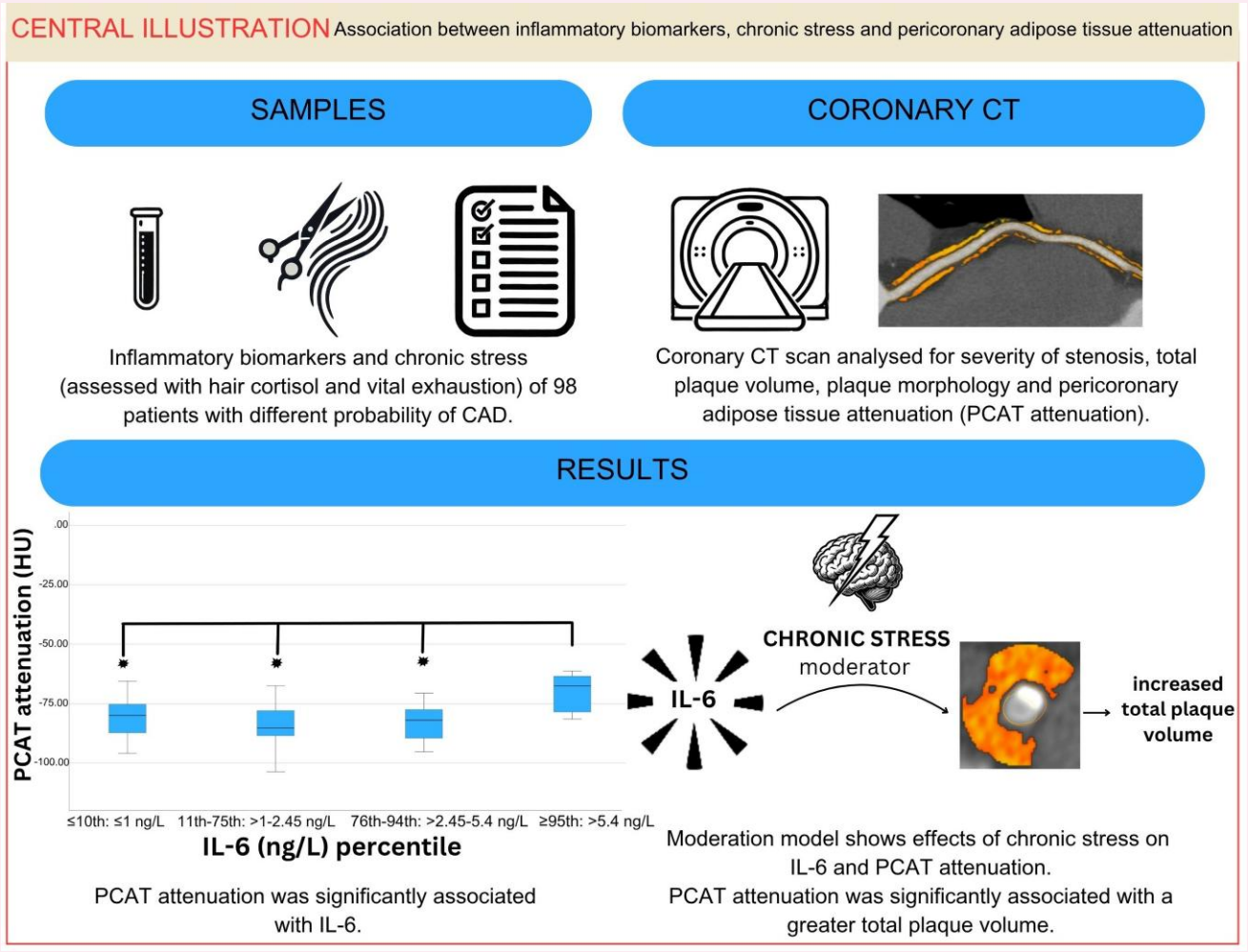
This study suggests that circulating inflammatory biomarkers are associated with PCAT attenuation, which was further correlated with TPV. Chronic stress may moderate the relationship between inflammatory cytokines and PCAT attenuation.

* Corresponding author. E-mail: aju.pazhenkottil@usz.ch
† These authors contributed equally (first authorship) to this work.

© The Author(s) 2025. Published by Oxford University Press on behalf of the European Society of Cardiology.
This is an Open Access article distributed under the terms of the Creative Commons Attribution-NonCommercial License (https://creativecommons.org/licenses/by-nc/4.0/), which permits non-commercial re-use, distribution, and reproduction in any medium, provided the original work is properly cited. For commercial re-use, please contact reprints@oup.com for reprints and translation rights for reprints. All other permissions can be obtained through our RightsLink service via the Permissions link on the article page on our site—for further information please contact journals.permissions@oup.com.

Downloaded from https://academic.oup.com/ehjcimaging/article/26/10/1664/8233038 by Deutsches Zentrum fuer Neurodegenerative Erkrankungen user on 29 October 2025

Graphical Abstract



Keywords pericoronary adipose tissue attenuation • interleukin-6 • chronic stress • hair cortisol • vital exhaustion • coronary artery disease

Introduction

Coronary artery disease (CAD) has been shown to be the leading cause of death worldwide. Although the prognosis of patients suffering from CAD could be substantially improved through preventive and therapeutic measures over the last decades, the risk of developing CAD remains high. This is mainly due to the major risk factors associated with CAD, such as smoking, diabetes, dyslipidaemia, or arterial hypertension.[1]

On a pathophysiological level, endothelial injury, abnormal lipid metabolism, and haemodynamic damage together with flow-mediated inflammatory changes in the endothelium are the main contributors to atherosclerosis development.[2] Atherosclerosis as a main feature of CAD is inflammatory in nature, progressive and finally leads to plaque formation in vessels via complex pathophysiological pathways. In fact, circulating levels of inflammatory cytokines, such as tumour necrosis factor-α (TNF-α) and interleukin-6 (IL-6), are associated with CAD risk independent of conventional risk factors.[3]

Several studies suggested that the pericoronary adipose tissue (PCAT) may be linked to the coronary artery wall by regulating vascular biology via paracrine cross-talk signals and thus may play a pivotal role in the development of CAD.[4] The phenotypic changes in PCAT can be traced by coronary computed tomography angiography (CCTA), as measured by the PCAT attenuation. Recently, PCAT attenuation has been proposed as a novel imaging biomarker of coronary inflammation.[5] Indeed, an elevated PCAT attenuation was indicative of CAD, associated with vulnerable plaque features and stenosis severity, and a higher risk of cardiac death.[5–7]

Chronic emotional stress has been found to promote systemic inflammation and endothelial dysfunction.[8] Vital exhaustion has been suggested as a state of excessive psychophysical fatigue and is considered a form of adaptation to prolonged distress.[9,10] Prior studies indicated that vital exhaustion may be linked to an increased risk of cardiovascular disease,[10] augmented lipid metabolism,[11] and higher levels of inflammatory cytokines.[12] Another recent study suggested that hair cortisol concentration (HCC), a biological marker of chronic stress exposure, may be a significant predictor of coronary atherosclerosis.[13] This raises the question whether chronic stress may influence the PCAT and its density, the PCAT attenuation. Of note, there has been so far no study that examined the association of chronic stress with the PCAT, despite the potential clinical implications.

Downloaded from https://academic.oup.com/ehjcimaging/article/26/10/1664/8233038 by Deutsches Zentrum fuer Neurodegenerative Erkrankungen user on 29 October 2025

Thus, our interests were three-fold: first, we evaluated the association between pro-inflammatory cytokines, chronic stress, and the PCAT attenuation in patients with suspected CAD. A second aim was to analyse the potential repercussions of an elevated PCAT attenuation, such as coronary stenosis, total plaque volume (TPV), or vulnerable plaque features. Third, as chronic stress facilitates systemic inflammation,[8] we aimed to assess the moderating effects of HCC and vital exhaustion on PCAT attenuation, plaque burden, and pro-inflammatory cytokines.

Methods

Setting and sample

We retrospectively analysed data from a prospective study cohort, including 98 patients without known CAD and with a very low to moderate pre-test probability (PTP) of CAD. These were referred by their treating physicians for a CCTA at the Department of Nuclear Medicine, University Hospital Zurich, between January 2020 and December 2023 to exclude CAD. Inclusion criteria were age ≥ 18 years, written informed consent and sufficient German language skills. Patients were excluded if they had a history of coronary artery stenting, coronary artery bypass grafting, or an implanted cardiac device. Additionally, patients with diabetes and those who had a history of smoking within the past five years were excluded. The study was approved by the Cantonal Ethics Committee of Zurich (BASEC no. 2019–00251, and BASEC no. 2023-00935).

Measurements

CAD risk factors and PTP of CAD

Besides sociodemographic variables, such as age and sex, we assessed risk factors of CAD: dyslipidaemia and arterial hypertension (diagnoses were obtained from the patients' medical records). A positive family history of heart disease was defined as a diagnosis of cardiovascular disease in a first-rank male relative under the age of 55, and in a first-rank female relative under the age of 65. Smoking status was declared by the patient and verified on the day of their CCTA scan. Furthermore, present medication was documented.

The European Society of Cardiology (ESC) guidelines of 2024 had been applied to determine PTP of CAD.[14,15] 57 (58.2%) of our participants fulfilled criteria for very low (≤5%), 26 (26.5%) for low (>5–15%), and 15 (15.3%) for moderate (>15–50%) PTP. The indication for CCTA was determined by the referring physicians based on previous tests, such as resting or exercise electrocardiogram (ECG), resting echocardiography, or due to limiting symptoms including typical and atypical angina pectoris, palpitations, or dyspnoea.[14,15]

Quantitative analysis of HCC, IL-6, and TNF-α

Hair samples were collected from the back of each participant's head. To assess the direction of hair growth, each hair sample was aligned, tied with thread, and secured with tape at the scalp end. Consequently, hair samples were washed, cut into snippets, and extracted for 4 h in 1 mL methanol in the ultrasonic bath. Afterwards, a fully automated supported liquid extraction with ethyl acetate on a Biotage Extrahera (Uppsala, Sweden) workstation was performed. A liquid chromatography-tandem mass spectrometry method was used for the quantification of cortisol. Concentrations were calculated in pg/mg using the Sciex OS software (version 3.3, Sciex, Germany). This method has been fully validated according to international guidelines and provides information on systemic cortisol exposure over the past months.[16] Laboratory chemical analysis of IL-6 (ng/L) and TNF-α (pg/mL) was conducted according to standard clinical practice.

Maastricht vital exhaustion questionnaire short version

To assess vital exhaustion on the day of the CCTA, the short version of the Maastricht Vital Exhaustion Questionnaire (MVEQ) was used.[9] It consists of nine items which are self-rated with 0 (no), 1 (do not know), or 2 (yes), resulting in a total score ranging between 0 and 18 points. Higher scores indicate greater levels of vital exhaustion.

CCTA protocol

All patients underwent a CCTA scan on a 256-slice CT scanner (CT Revolution, GE Healthcare, Waukesha, WI, USA) with prospective ECG triggering.[17] The standard protocol included intravenous metoprolol (Beloc Zok, AstraZeneca, London, UK) application if the heart rate was > 65 beats per minute, unless contraindicated. All patients received a 2.5 mg sub-lingual dose of isosorbide dinitrate (Isoket, Schwarz Pharma, Monheim, Germany) 3–5 min before image acquisition. Tube voltage (100–120 kilovolt peak), the tube current (180–550 milliampere) as well as contrast agent volume (Visipaque 320, 320 mg J/mL, GE Healthcare) were adapted to body mass index as previously described.[18]

CCTA plaque analysis

CCTA scans were analysed by readers with several years of experience in cardiac imaging, using semi-automated plaque analysis software (QAngio CT, Research Edition, Version 3.2.14.4, Medis Medical Imaging Systems, Leiden, The Netherlands). Readers were blinded to sociodemographic and clinical characteristics of the participants. Stenosis severity of the coronary arteries was assessed in multi-planar reformatted images reconstructed in short-axis and long-axis view. The presence of CAD was defined as obstructive (at least 50% stenosis) and non-obstructive CAD according to the Coronary Artery Disease-Reporting and Data System (CAD-RADS).[19] Coronary plaques were visually categorized into non-calcified or calcified plaques. Automated contouring of the inner lumen and outer wall of each vessel was conducted, and manual adjustments were applied whenever clear deviations were detected. TPV (both calcified and non-calcified plaques) was determined by subtracting the inner lumen volume from the volume comprising the whole vessel, including the outer wall (*Figure 1*).

Plaque morphology was described using the following high risk plaque features as previously defined[20]: positive remodelling, low attenuation plaque, spotty calcification, and the napkin-ring sign.

PCAT attenuation analysis

The PCAT was defined as the tissue moving radially outward from the outer vessel wall, and analysed with an established software (see section 'CCTA plaque analysis'). Our investigation focused on the proximal 10–50 mm of the right coronary artery (RCA), as did previous studies.[4,5] To avoid aortic wall interference, we excluded 10 mm from the RCA ostium.[4,5] All voxels with values between −190 and −30 Hounsfield units (HU) were identified as PCAT. The PCAT attenuation was determined by averaging the HU values of the PCAT, which is located within a radial distance from the outer vessel wall equal to the average diameter of the respective vessel (*Figure 1*).[4,5]

Statistical procedures

IBM SPSS Statistics for Windows, Version 29 (Armonk, NY: IBM Corp) was used for statistical analysis. Mean values, standard deviation, and relative and absolute distributions were calculated to describe patient characteristics. A one-way ANOVA was used to compare normally distributed continuous variables and boxplot values, and a χ^2 or Fisher's exact test to compare categorical variables. To investigate associations between pro-inflammatory cytokines (IL-6 and TNF-α) as independent variables and the PCAT attenuation as dependent variable, we conducted a multi-variable linear regression analysis. Another multi-variable linear regression analysis was applied to explore potential clinical sequelae of an elevated PCAT attenuation as independent variable and the TPV, calcified plaque volume, or the total number of vulnerable plaque features as dependent variables. An ordinal logistic regression model was performed to examine associations of the

Downloaded from https://academic.oup.com/ehjcimaging/article/26/10/1664/8233038 by Deutsches Zentrum fuer Neurodegenerative Erkrankungen user on 29 October 2025

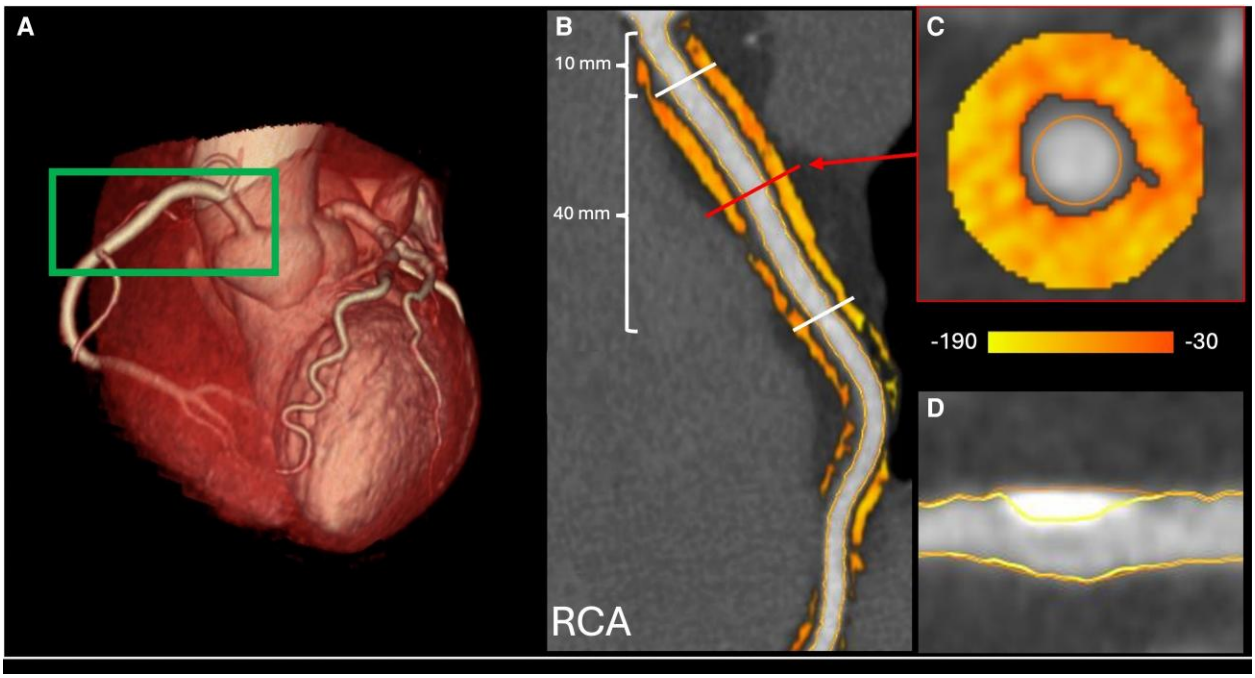


Figure 1 Coronary computed tomography angiography (CCTA) analysis. (*A*) CCTA reconstruction and demonstration of the right coronary artery (RCA, rectangle). (*B* and *C*) The proximal 10-50 mm of the RCA were analysed, shown here in a curved multi-planar reconstruction (*B*) and axial section (*C*) with visualization of pericoronary adipose tissue (PCAT) attenuation in the corresponding colour map (−190 to −30 Hounsfield units). (*C* and *D*) Highlight the contour of the inner lumen and outer vessel wall. Total plaque volume (TPV) was defined as volume between the two lines. D illustrates a calcified plaque.

PCAT attenuation as independent variable with the presence of CAD (no CAD, non-obstructive CAD, and obstructive CAD) as dependent variable. At last, we applied the PROCESS regression path analysis modelling tool for SPSS to test moderating synergistic effects of chronic stress (HCC in pg/mg or short version of the MVEQ total score) on pro-inflammatory cytokines (IL-6 or TNF-α) as independent and the PCAT attenuation as dependent variable, and, in a second step, on the PCAT attenuation as independent and the TPV as dependent variable. All models were adjusted for age, sex, arterial hypertension, dyslipidaemia, past smoking (never vs. smoking history more than 5 years ago), a positive family history of heart disease, and also for chronic stress (HCC and vital exhaustion total score). Collinearity statistics did not demonstrate any issues of multi-collinearity, unless otherwise noted. Significance level (two-sided *P*-value) was set at $P < 0.05$.

Results

Sample

Sociodemographic and clinical characteristics of the study sample are illustrated in *Table 1*. Participants with obstructive CAD and non-obstructive CAD were significantly older and more frequently had arterial hypertension compared with those without CAD. Males had a significantly higher prevalence of obstructive CAD than women. The TPV and the calcified plaque volume, as well as positive remodelling, napkin-ring signs, spotty calcifications, and the number of high risk plaque features were significantly higher in participants with obstructive CAD compared with those with non-obstructive CAD and those without CAD. The remaining variables did not differ significantly.

On the day of the examination, 30 participants (30.6%) were receiving Angiotensin-converting enzyme (ACE) inhibitors or Angiotensin II receptor blockers (ARB), 11 (11.2%) were on antiplatelet treatment such as acetylsalicylic acid, and 17 (17.3%) were taking statins.

Associations between IL-6, TNF-α, PCAT attenuation, and chronic stress

In *Table 2*, the results of the multi-variable linear regression analyses exploring associations of IL-6 and TNF-α, as well as chronic stress, with the PCAT attenuation are demonstrated. The pro-inflammatory cytokines (IL-6 and TNF-α) were analysed separately due to collinearity. Participants with higher IL-6 and TNF-α values were more likely to show an elevated PCAT attenuation of the RCA. However, chronic stress did not indicate any direct effect on the PCAT attenuation. *Figure 2* illustrates differences between IL-6 or TNF-α groups categorized into percentiles and the PCAT attenuation. The ≥95th percentile IL-6 group demonstrated significantly higher PCAT attenuation values when compared with each of the other IL-6 groups ($P = 0.004$). Furthermore, the ≥95th percentile TNF-α group had significantly higher PCAT attenuation values than the 10th ($P = 0.027$) and 11th to 75th percentile group ($P = 0.035$). Another multi-variable linear regression analysis tested effects of medication on the PCAT attenuation, but did not identify significant associations (see Supplementary data online, *Table S1*).

Associations between PCAT attenuation, chronic stress, CAD, plaque volume, and morphology

A separate multi-variable linear regression analysis was applied, using the TPV as dependent, and the PCAT attenuation of the RCA as the

Downloaded from https://academic.oup.com/ehjcimaging/article/26/10/1664/8233038 by Deutsches Zentrum fuer Neurodegenerative Erkrankungen user on 29 October 2025

Table 1 Overview of the study sample

	Total sample ($n = 98$)	Obstructive CAD ($n = 22$)	Non-obstructive CAD ($n = 22$)	No CAD ($n = 54$)	*P*-value ($P < 0.05$)
Male Sex, *n* (%)	54 (55.1)	18 (81.8)	14 (63.6)	22 (40.7)	**0.003**
Age (y), mean (SD)	57.9 (11.8)	66.0 (11.3)	61.3 (9.9)	53.2 (10.4)	**<0.001**
Dyslipidaemia, *n* (%)	31 (31.6)	7 (31.8)	8 (36.4)	16 (29.6)	0.849
Arterial hypertension, *n* (%)	34 (34.7)	12 (54.5)	11 (50.0)	11 (20.4)	**0.004**
Family history of cardiac disease, *n* (%)	31 (31.6)	6 (27.3)	7 (31.8)	18 (33.3)	0.875
Past smoker, *n* (%)	27 (27.6)	8 (36.4)	5 (22.7)	14 (25.9)	0.553
PCAT attenuation RCA (HU), mean (SD)	−80.5 (9.0)	−77.4 (9.9)	−81.3 (6.1)	−81.4 (9.5)	0.195
TPV (mm^3), mean (SD)	74.0 (180.8)	280.4 (294.6)	39.9 (63.5)	3.2 (7.5)	**<0.001**
Calcified plaque volume (mm^3), mean (SD)	37.0 (96.3)	144.8 (157.5)	16.3 (35.9)	0.5 (2.1)	**<0.001**
Positive remodelling, *n* (%)	26 (26.5)	19 (86.3)	7 (31.8)	0 (0)	**<0.001**
Low attenuation plaque, *n* (%)	0 (0)	0 (0)	0 (0)	0 (0)	/
Napkin-ring sign, *n* (%)	5 (5.1)	5 (22.7)	0 (0)	0 (0)	**<0.001**
Spotty calcifications, *n* (%)	9 (9.2)	7 (31.8)	2 (9.1)	0 (0)	**<0.001**
Number of high risk plaque features, mean (SD)	0.8 (1.5)	3.1 (1.9)	0.3 (0.5)	0 (0)	**<0.001**
IL-6 (ng/L), mean (SD)	2.1 (2.3)	2.7 (3.0)	1.8 (1.1)	2.0 (2.4)	0.501
TNF-α (pg/mL), mean (SD)	7.2 (3.6)	7.5 (2.8)	7.3 (1.7)	7.1 (4.4)	0.909
HCC (pg/mg), mean (SD)	6.7 (6.5)	6.9 (6.5)	7.4 (7.1)	6.3 (6.4)	0.769
Vital exhaustion (MVEQ total score), mean (SD)	5.9 (5.0)	6.0 (4.9)	5.7 (4.6)	5.8 (5.2)	0.979

n, number; y, years; SD, standard deviation; PCAT, pericoronary adipose tissue; RCA, right coronary artery; HU, Hounsfield units; TPV, total plaque volume; CAD, coronary artery disease; IL-6, interleukin-6; TNF-α, tumour necrosis factor-α; HCC, hair cortisol concentration; MVEQ, Maastricht vital exhaustion questionnaire. Significant *P*-values are marked bold.

Table 2 Multi-variable linear regression for the PCAT attenuation as dependent variable

	Model I		Model II	
Variables	**Mean difference (95% CI)**	***P*-value**	**Mean difference (95% CI)**	***P*-value**
Male sex	1.94 (−1.90 to 5.78)	0.319	2.02 (−1.84 to 5.89)	0.301
Age	0.01 (−0.14 to 0.18)	0.846	0.05 (−0.11 to 0.22)	0.510
Dyslipidaemia	1.79 (−2.41 to 6.00)	0.398	1.37 (−2.80 to 5.55)	0.514
Arterial hypertension	−0.28 (−4.39 to 3.83)	0.893	−0.42 (−4.62 to 3.76)	0.840
Family history of cardiac disease	−3.69 (−7.82 to 0.42)	0.078	−3.40 (−7.52 to 0.72)	0.105
Past smoker	1.86 (−2.20 to 5.93)	0.366	0.94 (−3.11 to 5.01)	0.644
HCC (pg/mg)	−0.10 (−0.39 to 0.17)	0.452	−0.12 (−0.40 to 0.16)	0.406
Vital exhaustion (MVEQ total score)	0.13 (−0.25 to 0.52)	0.489	0.17 (−0.21 to 0.57)	0.371
IL-6 (ng/L)	1.05 (0.21 to 1.89)	**0.014**		
TNF-α (pg/mL)			0.60 (0.06 to 1.13)	**0.027**

CI, confidence interval. Significant *P*-values are marked bold.

independent variable. An increased PCAT attenuation was significantly associated with a greater TPV [mean difference 3.51, 95% confidence interval (CI) 0.02 to 7.00, $P = 0.048$]. Yet, there were no significant direct effects of chronic stress (HCC: mean difference −0.12, 95% CI −5.13 to 4.89, $P = 0.962$; vital exhaustion: mean difference 5.43, 95% CI −1.49 to 12.35, $P = 0.122$) on TPV. Moreover, there was no significant association between the calcified plaque volume as dependent, and the PCAT attenuation as the independent variable (mean difference 1.73, 95% CI −0.13 to 3.60, $P = 0.068$).

The number of high risk plaque features as a dependent variable did not indicate any significant associations with the PCAT attenuation (mean difference 0.01, 95% CI −0.02 to 0.04, $P = 0.429$), or chronic stress (HCC: mean difference 0.03, 95% CI −0.01 to 0.07, $P = 0.209$; vital exhaustion: mean difference 0.04, 95% CI −0.01 to 0.10, $P =$

Downloaded from https://academic.oup.com/ehjcimaging/article/26/10/1664/8233038 by Deutsches Zentrum fuer Neurodegenerative Erkrankungen user on 29 October 2025

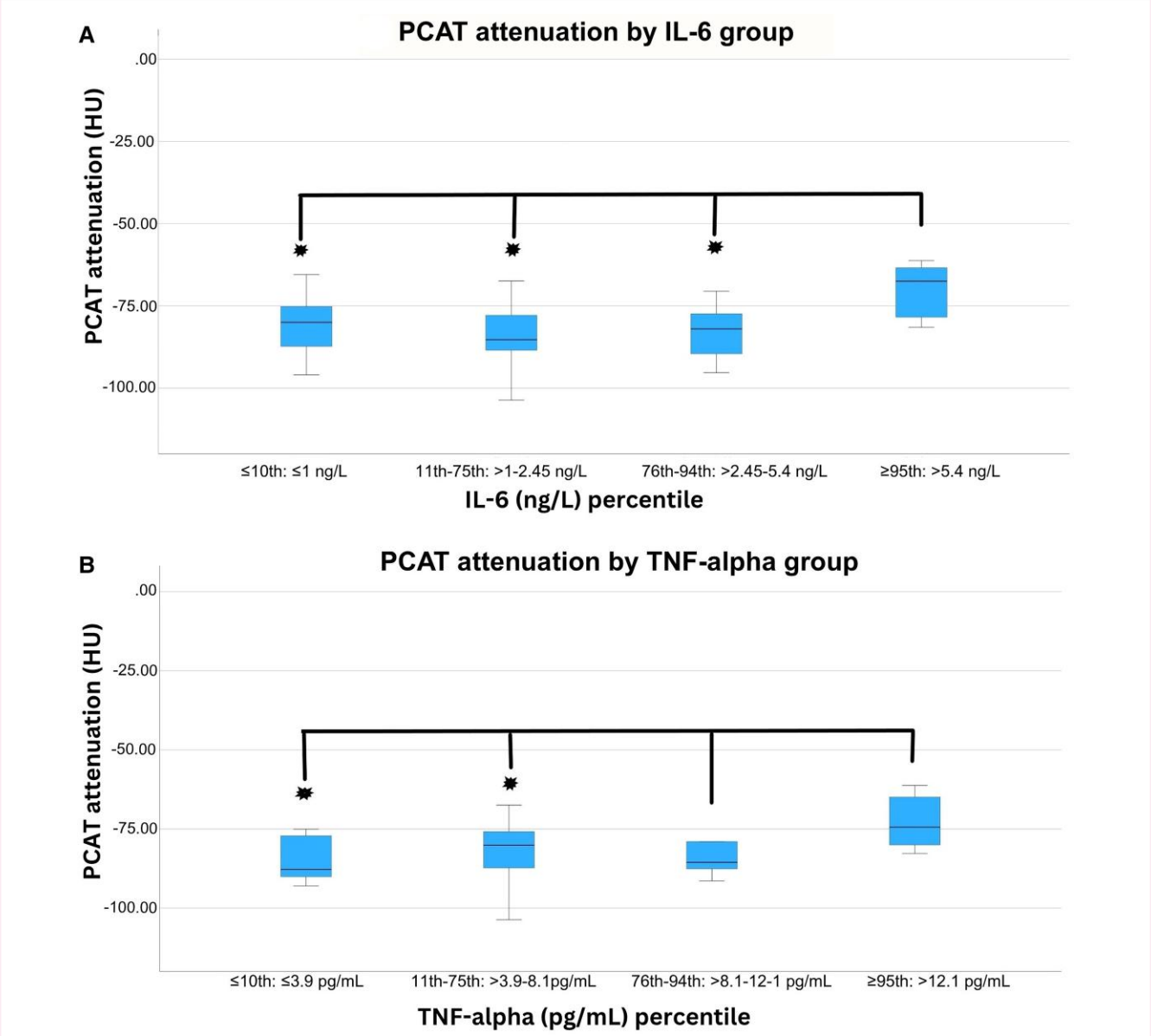


Figure 2 Boxplots of IL-6 and TNF-α groups regarding PCAT attenuation. (*A*) Boxplots illustrating PCAT attenuation by different Interleukin-6 (IL-6) groups categorized into <10th (≤1 ng/L), 11th to 75th (>1–2.45 ng/L), 76th to 94th (>2.45–5.4 ng/L), and ≥95th percentile (>5.4 ng/L). (*B*) Boxplots illustrating PCAT attenuation by different tumour necrosis factor-α (TNF-α) groups categorized into <10th (≤3.9 pg/mL), 11th to 75th (>3.9–8.1 pg/mL), 76th to 94th (>8.1–12.1 pg/mL), and ≥95th percentile (>12.1 pg/mL). Asterisks show significant differences when compared with the ≥95th percentile.

0.167). Additionally, the PCAT attenuation was not linked to positive remodelling in CCTA as dependent variable (mean difference 0.01, 95% CI −0.01 to 0.04, $P = 0.393$).

An ordinary logistic regression analysis examining associations between the PCAT attenuation as independent and the presence of CAD as dependent variable did not reach statistical significance [odds ratio (OR) 1.03, 95% CI 0.97 to 1.09, $P = 0.300$]. Chronic stress as another independent variable did also not suggest any significant association with the presence of CAD (HCC: OR 1.06, 95% CI 0.98 to 1.14, $P = 0.115$; vital exhaustion: OR 1.09, 95% CI 0.97 to 1.21, $P = 0.123$).

Moderation effects of chronic stress on IL-6, TNF-α, and the PCAT attenuation

A moderation analysis suggested significant effect sizes of HCC as moderator with synergistic effects on IL-6 and the PCAT attenuation (*Table 3* and *Figure 3*). The model was statistically significant and explained a variance of 20% ($P = 0.003$, adjusted $R^2 = 0.20$). In contrast, HCC did not moderate the relationship between TNF-α and the PCAT attenuation. Greater vital exhaustion, as measured by the MVEQ score, had a significant synergistic effect on IL-6 as independent and the PCAT attenuation as dependent variable (*Table 3*; model summary: $P = 0.004$, adjusted $R^2 = 0.20$). However, there was no significant

Downloaded from https://academic.oup.com/ehjcimaging/article/26/10/1664/8233038 by Deutsches Zentrum fuer Neurodegenerative Erkrankungen user on 29 October 2025

Table 3 Interaction terms for chronic stress on IL-6, TNF-α, the PCAT attenuation, and TPV

	Model I	
Variables	**Interaction term (95% CI)**	***P*-value**
HCC × IL-6 -> PCAT attenuation	−0.12 (−0.22 to −0.02)	**0.019**
HCC × TNF-α -> PCAT attenuation	−0.05 (−0.15 to 0.04)	0.272
Vital exhaustion × IL-6 -> PCAT attenuation	0.13 (0.01 to 0.25)	**0.024**
Vital exhaustion × TNF-α -> PCAT attenuation	0.06 (−0.03 to 0.16)	0.197
HCC × PCAT attenuation -> TPV	−0.43 (−1.21 to 0.35)	0.277
Vital exhaustion × PCAT attenuation -> TPV	0.53 (−0.67 to 1.73)	0.382

CI, confidence interval. Significant *P*-values are marked bold.

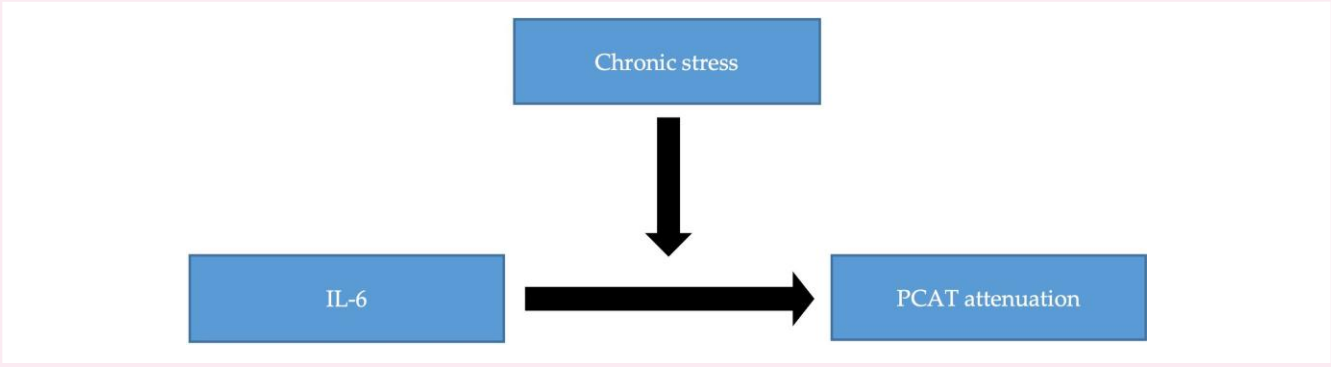


Figure 3 Moderation model. Effects of chronic stress on IL-6 and the PCAT attenuation. IL-6 was the independent variable, the PCAT attenuation the dependent variable, and hair cortisol concentration (pg/mg) or vital exhaustion the moderator.

moderation effect of vital exhaustion on TNF-α and the PCAT attenuation. In a second moderation analysis that explored moderation effects of chronic stress on the PCAT attenuation and TPV, no significant interaction terms could be identified (*Table 3*).

Discussion

In this cross-sectional study, higher circulating levels of the pro-inflammatory cytokines IL-6 and TNF-α were significantly linked to an elevated PCAT attenuation of the RCA in patients without known CAD. Furthermore, an increased PCAT attenuation was associated with a greater TPV. Interestingly, chronic stress, as assessed by hair cortisol concentration and vital exhaustion, demonstrated synergistic moderating effects on IL-6 and the PCAT attenuation.

The identified relationship between IL-6, TNF-α, and the PCAT attenuation confirms previous findings.[4] Cytokines expressed from atherosclerotic plaques or by the inflamed vascular wall could lead to adipocyte dedifferentiation and further secretion of chemokines in PCAT, and consequently an accelerated development of perivascular inflammation.[21] On the other hand, the PCAT may release pro-inflammatory cytokines, including IL-6 and TNF-α, in response to pre-hypertensive increases in blood pressure. Then, these cytokines cause vascular dysfunction and stiffness, as well as oxidative stress, all of which are pivotal in the development of atherosclerosis and CAD.[22] Additionally, the observation of a greater TPV in patients with an elevated PCAT attenuation had also been suggested by past studies, in which the PCAT attenuation predicted the degree of stenosis of the coronary arteries, and even an increased risk of cardiac death.[5,6] In contrast to these findings, the present study did not demonstrate significant associations of an elevated PCAT attenuation with the presence of obstructive CAD or vulnerable plaque features. The current findings suggest that inflammation-related changes in PCAT may precede overt obstructive CAD, highlighting their potential role in early disease stages, particularly in this study with relatively healthy participants.

A novel finding of this study is the moderating effect of chronic stress on the PCAT attenuation and its associated pro-inflammatory cytokine IL-6. This is in line with results of other studies that suggested a relationship between HCC or vital exhaustion and coronary atherosclerosis, cardiovascular disease, augmented lipid metabolism, and increased levels of cytokines.[10–13] It is known that chronic stress leads to the activation of the hypothalamus-pituitary-adrenal axis and consequently to raised concentrations of cortisol.[13] Then, the persistent exposure to cortisol may result in glucocorticoid resistance, a reduced capability of cortisol to inhibit pro-inflammatory cytokine production and to induce anti-inflammatory cytokine expression.[23] Finally, the excessive secretion of cortisol that leads to a pro-inflammatory state may initiate the development of cardiovascular disease risk factors and accelerate the advancement of atherosclerotic plaques.[24] Moreover, a recent study revealed that stress-related neural activity assessed by amygdalar activity may be significantly correlated with PCAT attenuation and high risk plaque features in patients with CAD.[25] This aligns with our findings, highlighting the critical pathway linking stress to inflammation and PCAT attenuation. Yet, it remains unclear why chronic stress demonstrated significant moderating effects on PCAT attenuation and IL-6, but not TNF-α. This might be explained by the relatively small sample size. A previous study that investigated the relationship of PCAT

Downloaded from https://academic.oup.com/ehjcimaging/article/26/10/1664/8233038 by Deutsches Zentrum fuer Neurodegenerative Erkrankungen user on 29 October 2025

attenuation with serum levels of inflammatory markers concluded that circulating biomarkers, such as IL-6 and TNF-α, might be useful in detecting systemic and coronary inflammation. However, its serum levels might be often influenced by other systemic or non-cardiac infections.[26] This could be a possible confounder, and it is still not known how chronic stress interacts with IL-6 and TNF-α, and PCAT attenuation.

It is well known that vascular inflammation drives atherogenesis and can trigger acute coronary syndromes, even in the absence of obstructive CAD. Identifying and treating patients with inflamed coronary arteries, with or without atherosclerotic plaques, particularly in the absence of obstructive CAD, presents a major unmet need in preventive medicine. The PCAT attenuation may provide a useful estimate of coronary artery inflammation. This approach may transform CCTA from a test to triage patients with obstructive CAD to further intervention into a prevention tool that guides management for all patients undergoing CCTA. Our finding of significant moderating effects of chronic stress on pro-inflammatory cytokines and PCAT, but not on TPV, might emphasize the need to also target coronary inflammation and not only coronary atherosclerosis. Evidence from clinical trials suggests that anti-inflammatory treatments, such as statins, colchicine, or anti-interleukin-1β reduce cardiovascular events. Given the potential unwanted actions of anti-inflammatory treatments, targeting treatments specifically to patients with coronary artery inflammation could improve the allocation of the anti-inflammatory treatments more precisely than systemic markers, such as C-reactive protein assays.[27] In our study, use of ACE inhibitors/ARB, antiplatelet treatment, or statins, did not indicate any association with PCAT attenuation. Yet, this medication was not applied to treat coronary inflammation, and thus, further studies are warranted to elucidate this question.

Among our 98 participants, only 22 subjects showed signs of an obstructive CAD. Thus, the PCAT attenuation may have an additional value in subjects without (obstructive) CAD, suggesting in this case a potential effective primary prevention of CAD based on anti-inflammatory agents and stress reduction. These results may be even more intriguing when bearing in mind the current ESC guidelines for the management of chronic coronary syndromes of 2024,[15] when in patients with a very low PTP of <5% any further diagnostic testing should be usually deferred.

This study has several limitations. First, it was cross-sectional and longitudinal studies are needed to infer statements of causality. Second, this study was conducted at a single centre, which may restrict generalizability. Furthermore, mostly participants with a very low to low PTP of CAD were included, and thus patients with more severe levels of inflammation may have been excluded from the present study. This could also explain why, rather, participants with highest levels of IL-6 and TNF-α demonstrated an elevated PCAT, and why overall IL-6 and TNF-α levels were relatively low. Yet, this might lead to a certain bias in our findings, which should be taken into account. Additionally, this study considered the PCAT attenuation of the RCA, as did many other studies, since the analysis in that vessel is technically more robust.[4,5] However, future studies should strive to include the other coronary arteries. Moreover, ideally the TPV should be indexed to the lumen volume to reduce the impact of sex and body size on the plaque volume, which is another limitation of this study.

Conclusion

The current study confirms the PCAT attenuation as novel inflammatory imaging biomarker, which seems to be correlated with pro-inflammatory cytokines and TPV, and moderated by chronic stress. These findings may imply that PCAT attenuation presents a modifiable risk parameter for the development of atherosclerotic plaques and cardiovascular disease. PCAT attenuation could be used as a specific marker of vascular inflammation to test the effects of novel therapeutics and psychosocial interventions.

Supplementary data

Supplementary data are available at *European Heart Journal - Cardiovascular Imaging* online.

Acknowledgements

The authors express their gratitude to Anja Zabel and all the nuclear medicine technicians for their excellent technical support.

Author contributions

Tobia Albertini (Conceptualization and design, Literature research, Data analysis and interpretation, Writing—creating figures, Writing—Original Draft Preparation, Writing—Review and Editing), Marc Dörner (Conceptualization and design, Literature research, Data analysis and interpretation, Writing—creating figures, Writing—creating Tables, Writing—Original Draft Preparation, Writing—Review and Editing), Andreas A. Giannopoulos (Conceptualization and design, Writing—Review and Editing), Roland von Känel (Conceptualization and design, Writing—Review and Editing), Dominik C. Benz (Conceptualization and design, Writing—Review and Editing), Nidaa Mikail (Conceptualization and design, Writing—Review and Editing), Daniel de Wilde (Conceptualization and design, Writing—Review and Editing), Clarissa D. Voegel (Conceptualization and design, Writing—Review and Editing), Tina M. Binz (Conceptualization and design, Writing—Review and Editing), Philipp A. Kaufmann (Conceptualization and design, Writing—Review and Editing), Catherine Gebhard (Conceptualization and design, Writing—Review and Editing), Ronny R. Buechel (Conceptualization and design, Writing—Review and Editing), and Aju Pazhenkottil (Conceptualization and design, Literature research, Writing—Review and Editing). All authors have read and agreed to the published version of the manuscript.

Consent: Informed consent was obtained from all subjects involved in the study.

Funding

A.P.P. received grant support from the Swiss Heart Foundation (Project no. FF22097) related to this study.

Conflict of interest: The University Hospital Zurich holds a research agreement with GE Healthcare.

Data availability

The data underlying this article will be shared on reasonable request to the corresponding author.

References

1. Malakar AK, Choudhury D, Halder B, Paul P, Uddin A, Chakraborty S. A review on coronary artery disease, its risk factors, and therapeutics. *J Cell Physiol* 2019;**234**:16812–23.
2. Sagris M, Antonopoulos AS, Simantiris S, Oikonomou E, Siasos G, Tsioufis K *et al.* Pericoronary fat attenuation index-a new imaging biomarker and its diagnostic and prognostic utility: a systematic review and meta-analysis. *Eur Heart J Cardiovasc Imaging* 2022;**23**:e526–e536.
3. Kaptoge S, Seshasai SRK, Gao P, Freitag DF, Butterworth AS, Borglykke A *et al.* Inflammatory cytokines and risk of coronary heart disease: new prospective study and updated meta-analysis. *Eur Heart J* 2014;**35**:578–89.
4. Antoniades C, Tousoulis D, Vavlukis M, Fleming I, Duncker DJ, Eringa E *et al.* Perivascular adipose tissue as a source of therapeutic targets and clinical biomarkers. *Eur Heart J*. 2023;**44**:3827–3844.

Downloaded from https://academic.oup.com/ehjcimaging/article/26/10/1664/8233038 by Deutsches Zentrum fuer Neurodegenerative Erkrankungen user on 29 October 2025

5. Oikonomou EK, Marwan M, Desai MY, Mancio J, Alashi A, Centeno EH *et al.* Non-invasive detection of coronary inflammation using computed tomography and prediction of residual cardiovascular risk (the CRISP study): a post-hoc analysis of prospective outcome data. *Lancet* 2018;**392**:929–39.
6. Zhang R, Ju Z, Li Y, Gao Y, Gu H, Wang X. Pericoronary fat attenuation index is associated with plaque parameters and stenosis severity in patients with acute coronary syndrome: a cross-sectional study. *J Thorac Dis* 2022;**14**:4865–76.
7. Chan K, Wahome E, Tsiachristas A, Antonopoulos AS, Patel P, Lyasheva M *et al.* Inflammatory risk and cardiovascular events in patients without obstructive coronary artery disease: the ORFAN multicentre, longitudinal cohort study. *Lancet* 2024;**403**:2606–18.
8. Wirtz PH, von Känel R. Psychological stress, inflammation, and coronary heart disease. *Curr Cardiol Rep* 2017;**19**:111.
9. Spinoni M, Zagaria A, Violani C, Grano C. The short version of the Italian Maastricht vital exhaustion questionnaire (MVEG): psychometric properties and relationships with anxiety, depression, and stress in a community sample of older adults. *J Clin Psychol Med Settings* 2024;**31**:628–37.
10. Cohen R, Bavishi C, Haider S, Thankachen J, Rozanski A. Meta-analysis of relation of vital exhaustion to cardiovascular disease events. *Am J Cardiol* 2017;**119**:1211–6.
11. Igna CV, Julkunen J, Vanhanen H. Vital exhaustion, depressive symptoms and serum triglyceride levels in high-risk middle-aged men. *Psychiatry Res* 2011;**187**:363–9.
12. Hoekstra T, Barbosa-Leiker C, Twisk JWR. Vital exhaustion and markers of low-grade inflammation in healthy adults: the Amsterdam and health longitudinal study. *Stress Health* 2013;**29**:392–400.
13. Nafisa A, Wattoo FH, Qayyum M, Gulfraz M. The association between chronic stress, hair cortisol, and angiographically documented coronary atherosclerosis, a case-control study. *Stress* 2021;**24**:1008–15.
14. Knuuti J, Wijns W, Saraste A, Capodanno D, Barbato E, Funck-Brentano C *et al.* 2019 ESC guidelines for the diagnosis and management of chronic coronary syndromes. *Eur Heart J* 2019;**41**:407–77.
15. Vrints C, Andreotti F, Koskinas KC, Rossello X, Adamo M, Ainslie J *et al.* 2024 ESC guidelines for the management of chronic coronary syndromes. *Eur Heart J* 2024;**45**:3415–537.
16. Voegel CD, Baumgartner MR, Kraemer T, Wüst S, Binz TM. Simultaneous quantification of steroid hormones and endocannabinoids (ECs) in human hair using an automated supported liquid extraction (SLE) and LC-MS/MS - Insights into EC baseline values and correlation to steroid concentrations. *Talanta*. 2021;**222**:121499.
17. Abbara S, Blanke P, Maroules CD, Cheezum M, Choi AD, Han BK *et al.* SCCT guidelines for the performance and acquisition of coronary computed tomographic angiography: a report of the society of cardiovascular computed tomography guidelines committee: endorsed by the north American society for cardiovascular imaging (NASCI). *J Cardiovasc Comput Tomogr* 2016;**10**:435–49.
18. Benz DC, Gräni C, Moch BH, Mikulicic F, Vontobel J, Fuchs TA *et al.* Minimized radiation and contrast agent exposure for coronary computed tomography angiography: first clinical experience on a latest generation 256-slice scanner. *Acad Radiol* 2016;**23**:1008–14.
19. Cury RC, Leipsic J, Abbara S, Achenbach S, Berman D, Bittencourt M *et al.* CAD-RADS 2.0–2022 coronary artery disease-reporting and data system. *J Cardiovasc Comput Tomogr* 2022;**16**:536–57.
20. Williams MC, Moss AJ, Dweck M, Adamson PD, Alam S, Hunter A *et al.* Coronary artery plaque characteristics associated with adverse outcomes in the SCOT-HEART study. *J Am Coll Cardiol* 2019;**73**:291–301.
21. Wu H, Ghosh S, Perrard XD, Feng L, Garcia GE, Perrard JL. T-cell accumulation and regulated on activation, normal T cell expressed and secreted upregulation in adipose tissue in obesity. *Circulation* 2007;**115**:1029–38.
22. Drummond GR, Vinh A, Guzik TJ, Sobey CG. Immune mechanisms of hypertension. *Nat Rev Immunol* 2019;**19**:517–32.
23. Staufenbiel SM, Penninx BWJH, Spijker AT, Elzinga BM, van Rossum EFC. Hair cortisol, stress exposure, and mental health in humans: a systematic review. *Psychoneuroendocrinology* 2013;**38**:1220–35.
24. Tian R, Hou G, Li D, Yuan TF. A possible change process of inflammatory cytokines in the prolonged chronic stress and its ultimate implications for health. *ScientificWorldJournal.* 2014;**2014**:780616.
25. Dai N, Tang X, Weng X, Cai H, Zhuang J, Yang G *et al.* Stress-related neural activity associates with coronary plaque vulnerability and subsequent cardiovascular events. *JACC Cardiovasc Imaging* 2023;**16**:1404–15.
26. Goeller M, Achenbach S, Herrmann N, Bittner DO, Kilian T, Dey D *et al.* Pericoronary adipose tissue CT attenuation and its association with serum levels of atherosclerosis-relevant inflammatory mediators, coronary calcification and major adverse cardiac events. *J Cardiovasc Comput Tomogr* 2021;**15**:449–54.
27. Visseren FLJ, Mach F, Smulders YM, Carballo D, Koskinas KC, Bäck M *et al.* 2021 ESC guidelines on cardiovascular disease prevention in clinical practice: developed by the task force for cardiovascular disease prevention in clinical practice with representatives of the European Society of Cardiology and 12 medical societies with the special contribution of the European association of preventive cardiology (EAPC). *Eur Heart J* 2021;**42**:3227–337.

Downloaded from https://academic.oup.com/ehjcimaging/article/26/10/1664/8233038 by Deutsches Zentrum fuer Neurodegenerative Erkrankungen user on 29 October 2025