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Determinants of elevated chemerin as a novel biomarker of immunometabolism: data from a large population-based cohort

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Abstract

Objective: Chemerin is a novel inflammatory biomarker suggested to play a role in the development of metabolic disorders, providing new avenues for treatment and prevention. Little is known about the factors that predispose elevated chemerin concentrations. We therefore aimed to explore a range of lifestyle-associated, dietary, and metabolic factors as potential determinants of elevated chemerin concentrations in asymptomatic adults.

Design: We used cross-sectional data from a random subsample of 2433 participants (1494 women and 939 men) aged 42–58 years of the European Prospective Investigation into Cancer and Nutrition-Potsdam cohort.

Methods: Random forest regression (RFR) was applied to explore the relative importance of 32 variables as statistical predictors of elevated chemerin concentrations overall and by sex. Multivariable-adjusted linear regression was applied to evaluate associations between selected predictors and chemerin concentrations.

Results: Results from RFR suggested BMI, waist circumference, C-reactive protein, fatty liver index, and estimated glomerular filtration rate as the strongest predictors of chemerin concentrations. Additional predictors included sleeping duration, alcohol, red and processed meat, fruits, sugar-sweetened beverages (SSB), vegetables, dairy, and refined grains. Collectively, these factors explained 32.9% variation of circulating chemerin. Multivariable-adjusted analyses revealed linear associations of elevated chemerin with metabolic parameters, obesity, longer sleep, higher intakes of red meat and SSB, and lower intakes of dairy.

Conclusions: These findings come in support of the role of chemerin as a biomarker characterizing inflammatory and metabolic phenotypes in asymptomatic adults. Modifiable dietary and lifestyle-associated determinants of elevated chemerin concentrations require further evaluation in a prospective study setting.

Key Words

- ▶ chemerin
- ▶ inflammation
- ▶ biomarkers
- ▶ lifestyle determinants

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Introduction

Over the past decade, chemerin has been increasingly implicated as a biomarker of immunometabolism, linking low-grade inflammation and metabolic disorders (1). Chemerin was first discovered as a chemokine with strong chemoattractant activity on various immune cells, including macrophages, dendritic cells, and natural killer cells with key roles in both innate and adaptive immunity (2). It was further rediscovered as an adipokine that is expressed in the adipocytes and was shown to be associated with obesity, insulin resistance, inflammation, and fatty liver disease (FLI) (3, 4). Experimental and clinical data suggested that circulating chemerin levels are associated with chronic diseases, such as cardiovascular disease (5) including atherosclerosis (6) and chronic heart failure (7). In addition, chemerin was associated with risk of colorectal cancer (8) and all-cause mortality (9). Thus, chemerin could serve either as an early marker or as an independent predictor of chronic subclinical inflammation. To guide strategies for precision prevention, better understanding of the factors that predispose elevated chemerin concentrations is highly warranted.

The evidence, however, on the potential influence of dietary and lifestyle factors on circulating chemerin has been scant. Several small trials investigated specific interventions for weight loss (hypocaloric diet and increased physical activity) in reducing chemerin levels (10, 11, 12). In addition, a few observational studies explored associations between chemerin and dietary patterns (13), physical activity (14), and selected health behaviors, that is, smoking and alcohol consumption (15). So far, large observational studies that simultaneously evaluate multiple lifestyle factors in relation to chemerin concentrations are lacking.

We therefore aimed to identify main statistical predictors as potentially important determinants of elevated chemerin concentrations among a wide range of lifestyle-associated, dietary, and metabolic factors and to characterize the associations between selected determinants and elevated chemerin concentrations using data from a large population sample within the European Prospective Investigation into Cancer and Nutrition (EPIC)-Potsdam cohort.

Material and methods

Study population

EPIC-Potsdam is a prospective cohort study intended to investigate the role of diet in the development of chronic diseases (16). From 1994 to 1998, 27,548 participants from Potsdam, Germany, and the surrounding geographical area

were recruited. For the current analysis, 2500 participants were randomly selected. After exclusions due to unavailable blood samples, implausible dietary intakes (women: <600 kcal or >3500 kcal; men: <800 kcal or >4200 kcal), or outliers, 2433 participants (1494 women and 939 men) remained eligible for this cross-sectional analysis (see Fig. 1 for flow chart). Detailed information about recruitment procedures has been reported elsewhere (17). The study protocol was approved by the Medical Society of the State of Brandenburg, Germany, and all participants provided written-informed consent prior to enrollment (16).

Data collection

Anthropometric (BMI, waist circumference (WC)) and blood pressure measurements were conducted according to standardized protocols as previously reported (16). Information on socio-demographic characteristics and lifestyle factors, that is, smoking, physical activity, sleeping habits, alcohol consumption, medication, self-reported health satisfaction, and prevalent diseases, were collected using computer-assisted personal interviews. Participants were considered hypertensive at study baseline if they had a systolic blood pressure ≥ 140 mmHg, diastolic blood pressure ≥ 90 mmHg, reported prior diagnosis of hypertension, or current antihypertensive medication use. Habitual dietary intakes of 12 months prior to recruitment were assessed through validated 148-item semi-quantitative food frequency questionnaires (18). The analyses focused on major food groups shown to be associated with metabolic phenotypes and chronic diseases (19), that is, red and processed meat, fish, dairy products, eggs, vegetables, fruits, nuts, legumes, whole grains, refined grains, and sugar-sweetened beverages (SSB). Intake values of food groups and alcohol are presented in grams per day (g/day).

Biomarker measurements

Participants provided 30 mL peripheral venous blood at the examination center during daytime hours, which was processed and subsequently stored in tanks of liquid nitrogen at -196°C or in deep freezers at -80°C until time of analysis. Chemerin was measured in citrate-treated plasma with a commercially available sandwich ELISA (BioVendor, Brno, Czech Republic) at the Institute for Clinical Chemistry and Pathobiochemistry, Otto-von-Guericke University Magdeburg (Magdeburg, Germany). Coefficients of variation reported by the manufacturer

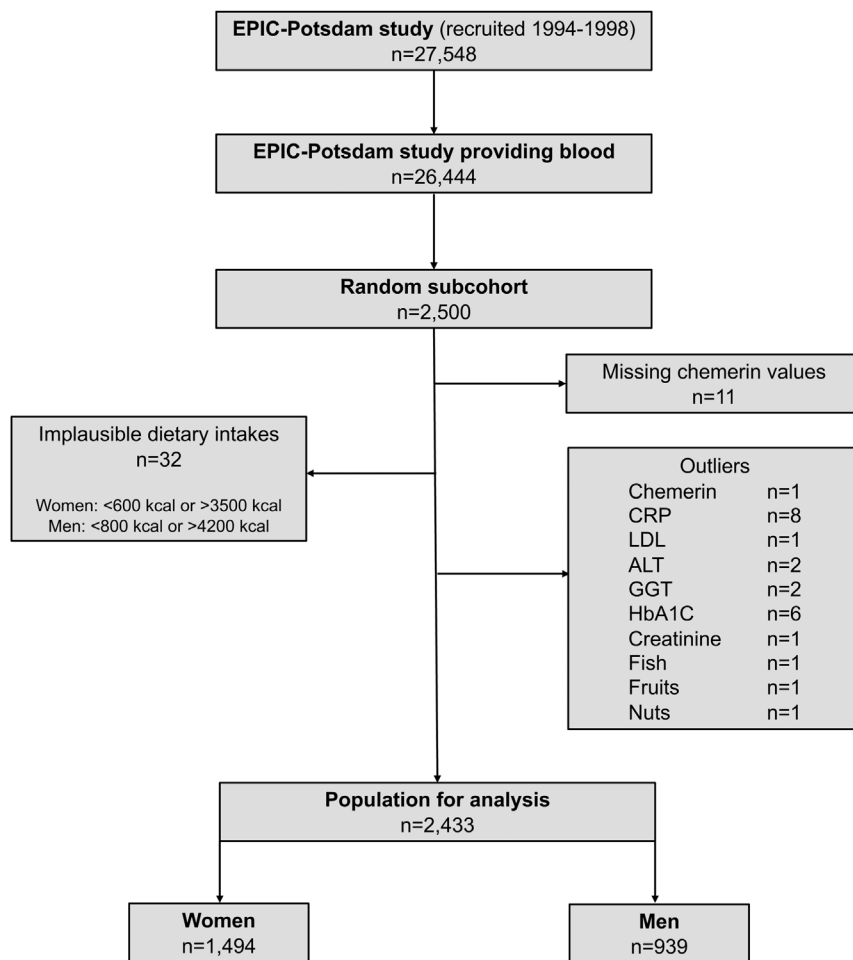


Figure 1
Flow chart of the study population selection including exclusion and removal of outliers.

were 5.1 and 7.0% within assays and 6.9 and 8.3% between assays. Chemerin measurements showed good reproducibility over 4 months (intraclass correlation coefficient assessing intra-individual variation: 0.72 (95% CI: 0.65–0.78)), indicating that one-time chemerin measurements are reasonably representative of the average individual concentration over time (20). Plasma concentrations of cholesterol, triglycerides, HDL-C, high-sensitivity C-reactive protein (hs-CRP), creatinine, γ -glutamyl transferase (GGT), alanine transaminase (ALT), and uric acid were measured at the Department of Internal Medicine, University of Tübingen (Tübingen, Germany) with an automatic ADVIA 1650 analyzer (Siemens Medical Solutions, Erlangen, Germany) in 2007 (21). All biomarker measurements conducted in plasma were corrected for the dilution introduced by citrate volume to improve comparability with concentrations measured in EDTA-plasma reported in the literature (22). LDL-C was calculated using Friedewald’s formula (23). Glomerular filtration rate (eGFR), an indicator of kidney

function, was estimated using measured creatinine concentrations based on the proposed formula by the Chronic Kidney Disease Epidemiology Collaboration (24). The fatty liver index (FLI) was used as a proxy of liver fat accumulation (25). Blood draw, sample handling, and laboratory measurements were conducted by experienced technical personnel and followed manufacturer’s instructions. Missing biomarker entries ($n=444$) were imputed for $n=223$ participants (Supplementary Table 1, see section on [supplementary materials](#) given at the end of this article) using a random forest procedure within the R package 'missForest' (26). Sensitivity analysis without imputation of biomarkers revealed no differences in effect estimates of main analyses (data provided in Supplementary Table 2).

Statistical analysis

In descriptive analysis, the distribution of lifestyle-associated, dietary, and metabolic parameters as medians (interquartile

ranges (IQR) or numbers (percentages) was characterized according to quartiles of chemerin concentrations. Dietary and metabolic variables were modeled as continuous variables along with BMI, WC, recreational sports (hours per week), and sleeping duration (hours of sleep per 24 hours). To reduce the potential effect of multicollinearity between BMI and WC, WC was regressed on BMI to obtain residual WC, which was used in the adjustment models. Alcohol consumption in grams per day was divided by 5 to represent intake per 5 grams. Smoking was modeled as a dichotomized variable (ever smoker vs never smoker). Health satisfaction was modeled as a four-level categorical variable (very dissatisfied to very satisfied). For descriptive analyses, alcohol consumption and sleeping duration were further categorized using predefined cut points (27, 28), and physical activity was dichotomized into inactive vs active.

To determine the best set of determinants (statistical predictors) of elevated chemerin concentrations, random forest regression (RFR) was applied as a machine learning technique suited for evaluation of multiple interrelated predictors (29). An important advantage of RFR is the ability to account for potential non-linear association among predictor and response variables. In this analysis, 1000 regression tree models were generated and combined with up to five unique datapoints in each terminal node. The main predictors among the various predictor variables were explored separately (according to exposure profiles – lifestyle-associated factors, dietary factors and metabolic factors) and conjointly and plotted according to relative statistical importance using the R package 'randomForestSRC' (30). In addition, the explained variance of each individual predictor, a set of predictors selected by RFR, as well as all predictors conjointly were estimated using linear regression analyses.

Since RFR only provides information on the relative statistical importance of predictor variables out of a set of variables, but do not show effect size and direction of associations, multivariable-adjusted linear regression was further applied to allow detailed assessment of the associations. In these analyses, food groups and metabolic (clinical/biochemical) exposure variables were z-score standardized. All models were adjusted for age, sex, BMI, residual WC, physical activity and smoking, educational attainment, prevalent hypertension, prevalent diabetes, prevalent cancer (except for nonmelanoma skin cancer), prevalent cardiovascular disease, and antihypertensive medication. The lifestyle-associated variables were mutually adjusted for the remaining factors, that is, alcohol consumption, health satisfaction, and sleeping duration. The food intake variables were additionally energy-adjusted (per 1000 kcal).

In sensitivity analyses, individuals with the following characteristics were excluded from the analyses or evaluated separately: women ($n=1494$), prevalent cancer (except nonmelanoma skin types), prevalent cardiovascular disease, or prevalent type 2 diabetes ($n=182$), and hs-CRP of 10 mg/L or higher that could reflect acute inflammation ($n=78$) (31). Differences in the associations according to sex were tested on the multiplicative scale based on calculated interaction terms of the respective variables and sex variable. All statistical analyses were performed in SAS (version 9.4, Enterprise Guide 7.1, SAS Institute Inc., Cary, NC, USA) and R (version 3.4.3, R Foundation for Statistical Computing, Vienna, Austria).

Results

Table 1 presents the descriptive characteristics of the study population, overall and stratified by sex. The median (IQR) of chemerin concentration was 147.6 (125.6, 172.4) ng/mL. The participants had a mean (s.d.) age of 50.3 (9.0) years, and their average BMI was 26.1 (4.3) kg/m². Overall, men were more likely to be smokers and showed higher alcohol consumption. The distribution of evaluated lifestyle-associated, dietary, and metabolic factors according to quartiles of chemerin concentrations are presented in Supplementary Table 3. These analyses, among others, revealed a trend of increasing chemerin concentrations with reduced wine consumption, longer sleep duration, higher prevalence of sleeping disorders, level of health dissatisfaction and physical inactivity.

Figure 2 shows the results from RFR depicting the importance of evaluated variables as statistical predictors of chemerin concentrations among the three groups of factors, that is, lifestyle-associated, dietary, and metabolic, as well as all predictors modeled together. Among the lifestyle-associated factors, BMI and WC were selected as the most important predictors of circulating chemerin, followed by sleeping duration and alcohol intake. Among the dietary factors, consumption of red meat and processed meat, fruits, SSB, vegetables, dairy products, and refined grains were selected as main predictors of chemerin concentrations. With regard to metabolic factors, FLL, hs-CRP, and eGFR, followed by triglycerides and creatinine showed highest importance in the prediction of chemerin. In an analysis that evaluated the relative variable importance of all predictors together, hs-CRP was the most important predictor of circulating chemerin, followed by FLL, eGFR, BMI, WC, and triglycerides.

In linear regression analyses, the set of variables selected by RFR explained 32.9% variation of chemerin

concentrations (lifestyle-associated factors including BMI, WC, sports, smoking, alcohol, sleeping duration, and health satisfaction: 18.1%; dietary factors including processed meat, red meat, fish, dairy, eggs, legumes, vegetables, fruits, nuts, whole grains, refined grains, SSB: 1.7%; metabolic factors including hs-CRP, total cholesterol, LDL-C, HDL-C, triglycerides, FLI, ALT, GGT, uric acid, creatinine, eGFR, systolic BP, diastolic BP: 27.7%) (Supplementary Table 4). Overall, the full range of evaluated variables jointly explained 35.4% of chemerin concentrations.

Figure 3 shows results from the multivariable-linear regression analyses that further demonstrate the direction and strength of the associations between chemerin and selected determinants. For example, higher chemerin concentrations were associated with higher BMI (standardized beta = 2.9 (95% CI: 2.6, 3.2) ng/mL) and WC (1.2 (95% CI: 1.0, 1.3) ng/mL), longer sleeping duration (1.3 (95% CI: 0.2, 2.5) ng/mL), higher intakes of red meat and SSB (1.7 (95% CI: 0.5, 3.0) ng/mL and 1.7 (95% CI: 0.4, 2.9) ng/mL, respectively), and lower intakes of dairy (−1.5 (95% CI: −2.8, −0.2) ng/mL).

In analyses stratified by sex, WC, red meat, dairy, FLI, and hs-CRP were selected as main statistical predictors in RFR analysis for both men and women (Fig. 4). Relative to WC, BMI showed high importance in women and less in men. Sleeping duration and intakes of eggs, fruits, and vegetables were further selected as important predictors in the analyses for women, whereas smoking and intake of nuts were selected as important predictors in the analyses for men. Multivariable-adjusted linear regression analyses stratified by sex additionally characterized the suggested differences (Supplementary Table 5). For example, red meat consumption was associated with increasing chemerin concentrations in women only (standardized beta = 1.8 (95% CI: 0.1, 3.5) ng/mL), and the association with FLI was only present in men (3.0 (95% CI: 0.3, 5.6) ng/mL). However, no statistically significant interaction by sex could be seen for the majority of the factors, with the exception of red meat consumption ($P_{\text{interaction}} = 0.02$).

In sensitivity analyses, the observed associations were not substantially altered after excluding participants with any prevalent disease. After excluding participants with elevated hs-CRP (≥ 10 mg/L), the associations with SSB and FLI were attenuated toward null (Supplementary Table 6).

Discussion

In this large population-based study, we explored potential determinants of elevated chemerin concentrations among a wide range of lifestyle-associated, dietary, and

metabolic factors in adult asymptomatic individuals. Our analyses highlighted the importance of BMI, WC, hs-CRP, FLI, and eGFR as main statistical predictors of chemerin concentrations. Systolic and diastolic blood pressure and triglycerides also contributed to the variation of circulating chemerin. Modifiable dietary and lifestyle-associated factors were further suggested to predict chemerin concentrations, albeit to a lesser degree. These included intakes of red and processed meat, SSB, dairy, and sleeping duration. Factors that were associated with increased concentrations of chemerin included physical inactivity and health dissatisfaction. Additional predictors of elevated chemerin concentrations included alcohol consumption and intakes of refined grains, fruits, and vegetables.

This is the first observational study to explore such a wide range of factors covering various phenotypes, including modifiable lifestyle and dietary factors in relation to elevated chemerin concentrations in predominantly healthy adults. Yet, our results notably distinguished inflammatory and metabolic factors as the most important determinants of elevated chemerin concentrations. So far, various lines of research characterized chemerin as a potential player in the development of cardio-metabolic diseases and described its multifaceted functions in the regulation of energy metabolism, adipogenesis, and angiogenesis (32). Systemically elevated chemerin could originate from various sources representing tissue damage or immune activation in different organs with regulatory actions in various inflammatory processes (32). Thus, it may not be surprising that its elevated concentrations coincide with elevated levels of other inflammation markers such as CRP as shown in our data. However, CRP is a non-specific biomarker of inflammation and may also reflect obesity-associated inflammatory phenotype. Indeed, the enlarged adipose tissue is one important source of secretion of pro-inflammatory mediators (33). Chemerin can be also characterized as one of those mediators, as it is predominantly expressed in adipocytes within white adipose tissue, and its association with obesity is well established (4). Chemerin is expressed similarly in human preadipocytes and adipocytes but can also be found in the stroma-vascular fraction, suggesting that the different adipose tissue cell types may contribute to chemerin production (34). In addition, immune cells such as macrophages, dendritic cell subsets, and natural killer cells express CMKLR1 and are chemerin responsive (2). Furthermore, higher chemerin concentrations were associated with larger amounts of visceral adipose tissue (VAT) as compared to lower amounts of subcutaneous adipose tissue (SAT) (4, 35). Interestingly, our data revealed

Table 1 Descriptive characteristics of the study population, overall and by sex. Dietary intake and clinical parameters are expressed as median (IQR).

	Chemerin (ng/mL), median (IQR)	Total, n = 2433	Men, n = 939	Women, n = 1494
Socio-demographic factors				
	Age (years), mean (s.d.)	50.3 (9.0)	52.4 (8.1)	49.0 (9.3)
Education	University degree, n (%)	935 (38.4)	496 (52.8)	439 (29.4)
Health status				
Prevalent condition	Cardiovascular disease and/or hypertension, n (%)	1270 (52.2)	624 (66.5)	646 (43.2)
	Type 2 diabetes and/or cancer, n (%)	249 (10.3)	100 (10.7)	149 (10)
Medication use				
	Antihypertensive, anti-coagulant, lipid-lowering, n (%)	632 (26.0)	291 (31.0)	341 (22.9)
	Aspirin, n (%)	246 (10.1)	89 (9.5)	157 (10.5)
	Anti-diabetic, n (%)	58 (2.4)	36 (3.8)	22 (1.5)
Lifestyle-associated factors				
Obesity measures				
	Body mass index (kg/m ²), mean (s.d.)	26.1 (4.3)	26.8 (3.5)	25.7 (4.6)
	Waist circumference (cm), mean (s.d.)	85.8 (12.8)	94.2 (9.9)	80.6 (11.6)
Physical activity				
	Recreational sports (h/week), median (IQR)	4.5 (2.0, 8.0)	5.5 (2.5, 9.5)	4.0 (2.0, 7.5)
	Inactive, n (%)	596 (24.7)	220 (23.5)	376 (25.4)
Smoking	Ever smoker, n (%)	1290 (53.0)	665 (70.8)	625 (41.8)
Alcohol consumption				
	Intake of consumers (g/day), median (IQR)	8.5 (3.1, 20.1)	18.4 (8.6, 32.5)	5.2 (2.1, 10.6)
	Non-consumers, n (%)	72 (3.0)	32 (3.4)	40 (2.7)
	Light and moderate drinkers (<15 g/day women; <30 g/day men), n (%)	1859 (76.5)	665 (70.8)	1194 (80.0)
	Heavy drinkers (≥15 g/day women; ≥30 g/day men), n (%)	502 (20.6)	242 (25.8)	260 (17.4)
Sleeping duration				
	Short (<7 h/day), n (%)	609 (25.0)	249 (26.5)	360 (24.1)
	Long (>8 h/day), n (%)	303 (12.5)	114 (12.1)	189 (12.6)
Self-reported well-being				
	Health satisfaction – Dissatisfied, n (%)	432 (17.8)	141 (15.0)	291 (19.5)
Dietary factors				
	Processed meat (g/day)	49.8 (31.6, 76.3)	63.4 (45.4, 101.3)	43.0 (25.1, 59.9)
	Red meat (g/day)	36.5 (23.3, 54.7)	47.7 (32.5, 69.8)	31.7 (19.3, 45.5)
	Fish (g/day)	18.4 (9.9, 29.0)	23.0 (11.2, 34.8)	16.4 (9.0, 28.5)
	Dairy (g/day)	170.9 (94.5, 276.7)	148.8 (73.6, 251.8)	191.7 (106.7, 310.5)
	Eggs (g/day)	13.6 (9.0, 21.9)	16.0 (9.0, 25.3)	13.6 (7.8, 20.7)
	Legumes (g/day)	16.5 (9.1, 30.3)	21.6 (11.0, 38.6)	13.9 (8.0, 26.3)
	Vegetables (g/day)	93.1 (66.5, 127.1)	83.1 (59.4, 114.4)	98.9 (71.1, 134.9)
	Fruits (g/day)	122.4 (91.5, 202.3)	107.9 (82.0, 180.9)	140.5 (96.4, 215.6)
	Nuts (g/day)	0.8 (0.4, 4.1)	0.8 (0.4, 4.1)	0.8 (0.4, 4.1)
	Whole grains (g/day)	32.0 (8.7, 75.1)	22.1 (5.5, 63.0)	37.4 (11.3, 82.0)
	Refined grains (g/day)	134.1 (86.3, 190.5)	175.9 (119.8, 231.7)	112.4 (72.5, 160.5)
	Sugar-sweetened beverages (g/day)	1.4 (0.0, 24.7)	5.6 (0.0, 48.3)	0.0 (0.0, 9.7)
Metabolic factors				
Chronic inflammation				
	hs-CRP (µg/mL)	0.8 (0.2, 2.2)	0.7 (0.2, 1.8)	0.9 (0.2, 2.6)
Lipid metabolism				
	Total cholesterol (mmol/L)	5.3 (4.6, 6.0)	5.4 (4.8, 6.1)	5.1 (4.5, 5.9)
	LDL-C (mmol/L)	3.1 (2.5, 3.7)	3.2 (2.7, 3.8)	3.0 (2.4, 3.6)
	HDL-C (mmol/L)	1.4 (1.2, 1.7)	1.3 (1.1, 1.5)	1.5 (1.3, 1.8)
	Triglycerides (mmol/L)	1.2 (0.9, 1.8)	1.6 (1.1, 2.3)	1.1 (0.8, 1.5)
Liver function				
	FLI	0.5 (0.1, 2.1)	1.5 (0.5, 4.1)	0.2 (0.1, 0.8)
	ALT (U/L)	20.0 (15.0, 28.0)	27.0 (20.0, 38.0)	17.0 (14.0, 22.0)
Kidney function				
	GGT (U/L)	18.0 (12.0, 33.0)	28.0 (18.0, 48.0)	14.0 (9.0, 22.0)
	Uric acid (mg/dL)	4.5 (3.7, 5.5)	5.6 (4.8, 6.3)	4.1 (3.4, 4.8)
	Creatinine (mg/dL)	0.8 (0.7, 1.0)	1.0 (0.9, 1.1)	0.8 (0.7, 0.8)
	eGFR (mL/min per 1.73 m ²)	91.1 (79.7, 101.0)	91.0 (80.4, 99.8)	91.1 (79.5, 101.7)
Blood pressure				
	Systolic (mmHg), mean (s.d.)	129.3 (17.6)	135.3 (17.1)	125.6 (16.8)
	Diastolic (mmHg), mean (s.d.)	83.7 (10.6)	86.8 (10.7)	81.7 (10.0)

ALT, alanine aminotransferase; BP, blood pressure; CRP, C-reactive protein; eGFR, estimated glomerular filtration rate; FLI, fatty liver index; g, grams; GGT, gamma-glutamyl transferase; h, hour; hs, high-sensitivity; IQR, interquartile range.

WC as a strong lifestyle-associated predictor of elevated chemerin concentrations in men and women, whereas BMI was shown as a strong predictor in women but not in men. WC is a measure of body fat distribution that is suggested to reflect visceral adiposity. In contrast, BMI is a measure of body composition and does not distinguish body fat and lean muscle mass (36). It is well known that as they age men and women are characterized by differing fat distribution profiles, such that men tend to accumulate fat in VAT whereas in women fat is stored predominantly in SAT depots. VAT is metabolically more active and may better reflect early inflammation-related pathological conditions as compared to SAT. In this context, our data may provide an important insight that chemerin could serve as a biomarker that can depict VAT-associated inflammatory phenotypes in both sexes. Although WC is often used as a proxy measure of VAT and has shown to be

stronger correlated to VAT than BMI (37), it may still not be the best method to estimate visceral fat accumulation (38). Further studies that employ precise assessment of fat compartments would be needed.

Besides adipose tissue, chemerin is also expressed in the liver (32) and kidney (39). In our study, FLI and eGFR were among the most important metabolic predictors of chemerin, followed by triglycerides and creatinine. Also systolic and diastolic blood pressure were selected to contribute to the variation of chemerin. Similar results were previously reported for an association between chemerin and impaired renal function (39, 40) and other metabolic phenotypes that may lead to liver and kidney damage (4, 41, 42). Our findings for blood pressure are supported by mechanistic research on chemerin that has been focused on the vascular system and hypertension (43). Among these, human and animal studies revealed that chemerin

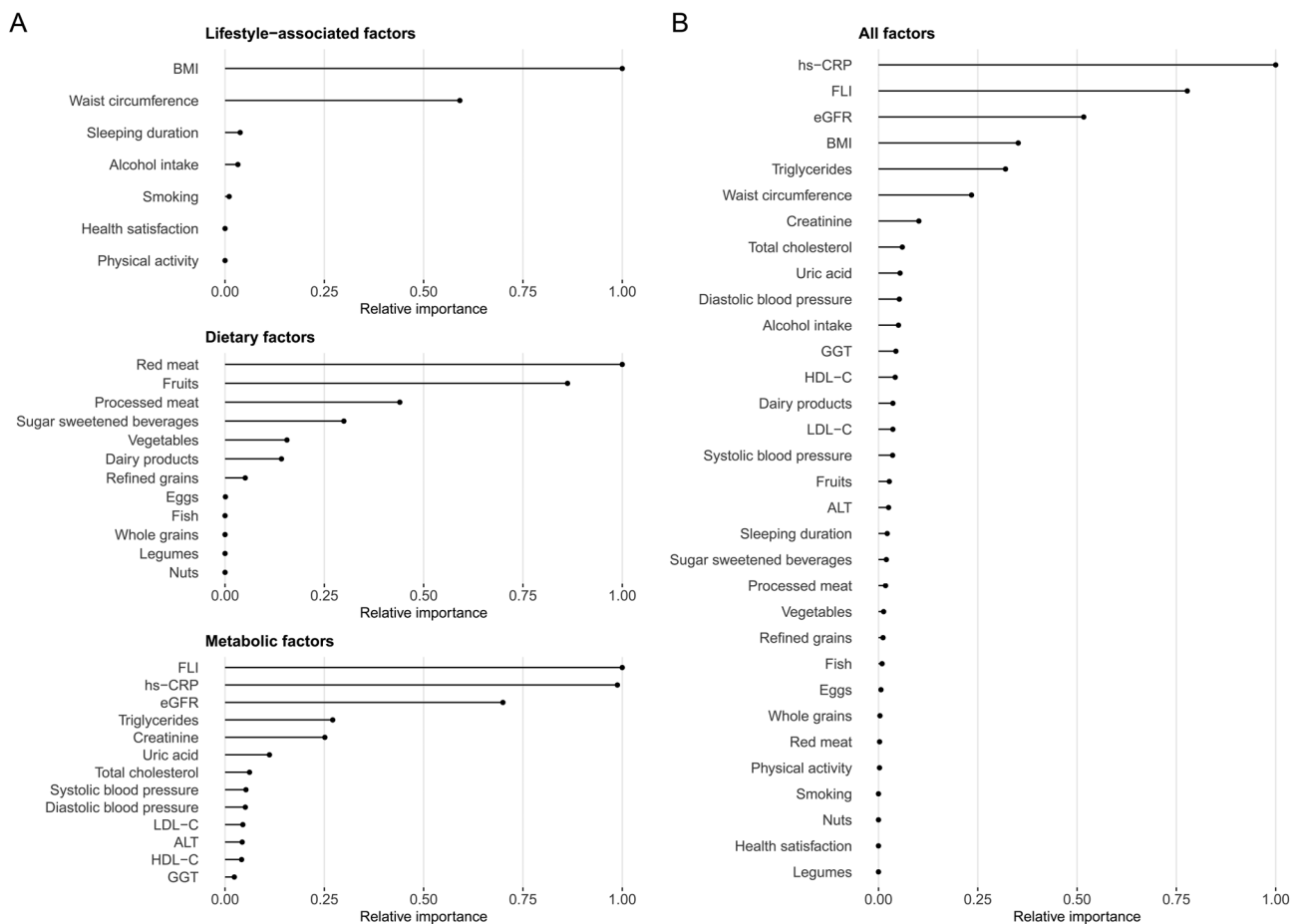


Figure 2 Relative variable importance from random forest regression for lifestyle-associated, dietary, and metabolic factors as predictors of chemerin concentrations (A) modeled separately per block and (B) modeled together. The potential predictors are plotted relative to the most important predictor of circulating chemerin by (A) block of lifestyle-associated, dietary, and metabolic factors and (B) all factors together. ALT, alanine aminotransferase; BP, blood pressure; eGFR, estimated glomerular filtration rate; FLI, fatty liver index; GGT, gamma-glutamyl transferase.

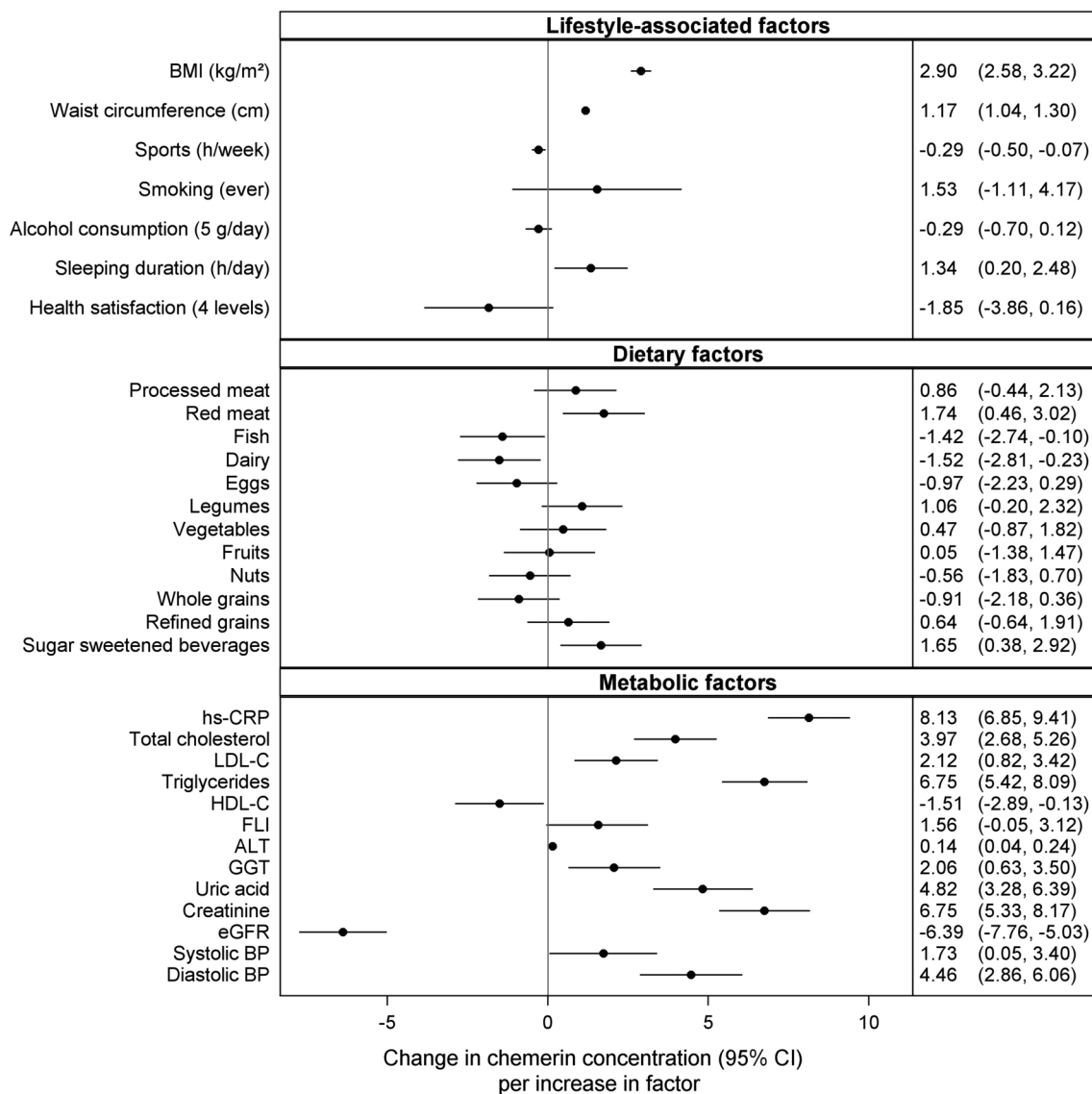


Figure 3

Multivariable linear regression showing change in chemerin concentration per increase in lifestyle-associated, dietary, and metabolic factors. Multivariable-adjusted model includes age, sex, BMI, residual waist circumference, physical activity, educational attainment, smoking status, prevalent hypertension, prevalent diabetes, prevalent cancer, prevalent cardiovascular disease, and antihypertensive medication. The lifestyle-associated factors were mutually adjusted for the remaining factors, that is, additionally adjusted for alcohol consumption, health satisfaction, and sleeping duration. Dietary factors and metabolic factors were not mutually adjusted for one another. Sleeping duration was additionally adjusted for sleeping disorders and consumption of caffeinated beverages (tea and coffee). Diet was z-score standardized and energy-adjusted; metabolic exposure variables were z-score standardized. ALT, alanine aminotransferase; BP, blood pressure; eGFR, estimated glomerular filtration rate; FLI, fatty liver index; GGT, gamma-glutamyl transferase.

causes contraction of arteries and increases reactive oxygen species (ROS) in endothelial cells (43). Overall, our data come in support of previous research that implicates chemerin as a biomarker of immunometabolism, linking obesity, inflammation, and metabolic disorders.

In addition to metabolic determinants, our results revealed a number of lifestyle-associated factors associated with elevated chemerin concentrations. Among these,

sleeping duration and alcohol consumption were rated among the most important predictors. Our results for an association between long sleep duration (sleep >8 h/day) and chemerin independent of potential confounders such as prevalent chronic diseases or age are in line with findings from a recent meta-analysis, where long sleeping hours were associated with higher levels of pro-inflammatory biomarkers, i.e., CRP and IL-6 (44). Recent evidence from

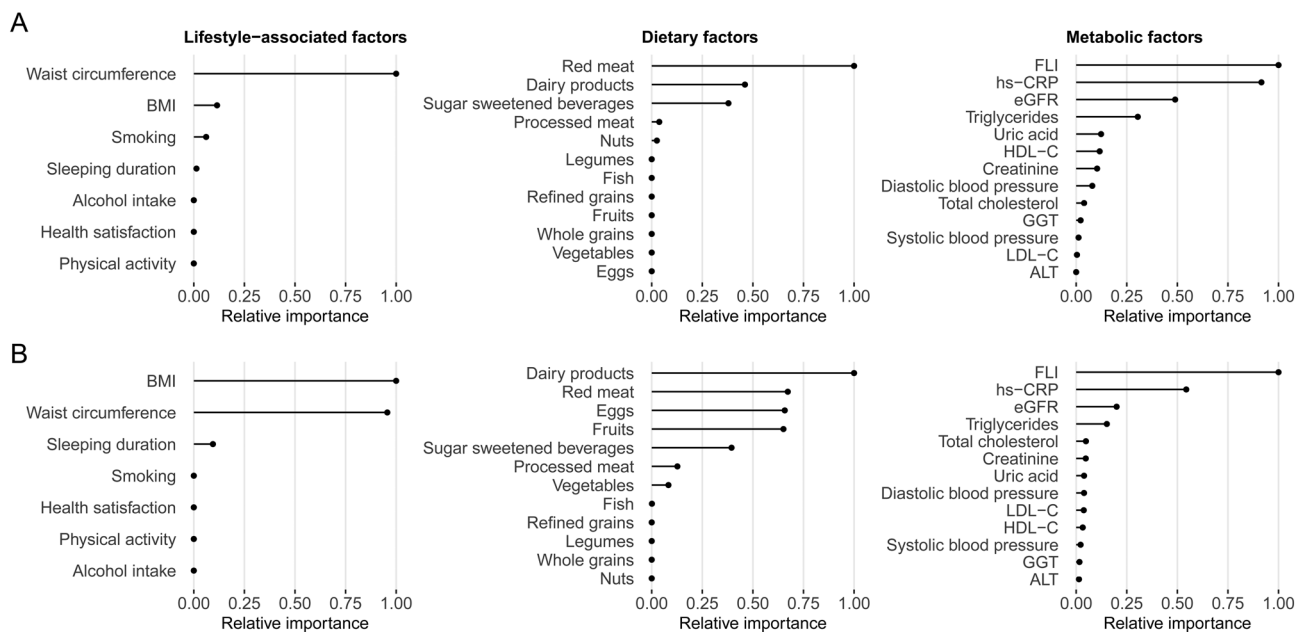


Figure 4

Relative variable importance from random forest regression for lifestyle-associated, dietary, and metabolic factors as predictors of chemerin concentrations in (A) men and (B) women. The potential predictors are plotted relative to the most important predictor of circulating chemerin per block (lifestyle-associated, dietary, and metabolic factors). ALT, alanine aminotransferase; BP, blood pressure; eGFR, estimated glomerular filtration rate; FLI, fatty liver index; GGT, gamma-glutamyl transferase.

prospective studies propose that the relationship between hours of sleep and risk of coronary events or mortality is U-shaped (45). Future prospective studies that account for additional potential confounders such as stress levels may be needed to better evaluate the association between sleep and chemerin levels. We also observed independent associations of chemerin with physical inactivity and health dissatisfaction. Not only is visceral fat accumulation a consequence of inactivity, but accumulating evidence suggests that exercise has anti-inflammatory effects independent of obesity status (46). One hypothesis is that exercise can downregulate the expression of TLR4 and reduce activation of NLRP3 inflammasome, reducing cytokine levels (46). The association with health dissatisfaction could be explained by the influence of prevalent disease status, mental health, and chronic stress, as inflammation is induced by these stressors (47). Overall, our data largely point to the importance of accounting for the complexity of chemerin determinants following a holistic approach that covers not just biological and physiological domains but also behavioral, emotional, and social well-being aspects.

Our data further revealed that higher alcohol consumption – and wine in particular – was associated with lower chemerin concentrations. This finding is in contrast to some previous studies which reported that alcohol was

positively associated with chemerin levels (13). However, those studies did not differentiate between type of alcoholic drink and did not adjust for other potential confounders such as dietary and metabolic factors. The hypothesis that moderate wine consumption may favorably influence inflammatory status is strengthened by experimental research showing beneficial properties of polyphenols abundant in wine in the regulation of chemerin expression (48, 49). Furthermore, wine consumption is typical for the Mediterranean-style diet as one of the most commonly reported dietary patterns in relation to lower inflammation levels (50). Further randomized control trials are warranted to evaluate the suggested link between wine consumption in modulating chemerin concentrations.

Among the dietary factors, our data suggested red and processed meat, fruits, SSB, vegetables, dairy products, and refined grains as potentially important determinants of elevated chemerin concentrations. Linear associations with high intakes of SSB and red meat and low intakes of dairy products with elevated circulating chemerin were observed. These findings come in support of the increasing evidence revealing the pro-inflammatory potential of consuming Western diets (51, 52, 53) vs the anti-inflammatory properties of food components of the Mediterranean diet (54). For example, dairy has been studied as part of high protein diet in previous work, and results

revealed decreasing effects on chemerin levels following dietary interventions (55, 56). The anti-inflammatory effects of dairy could be accounted for by various reasons, including benefits of specific fatty acids in dairy fat (such as branch-chain fatty acids, medium-chain saturated fats, specific trans fats), benefits of fermentation that may interact with microbiome, benefits of probiotics, or other unknown bioactivities (57). The importance of fruits comes in line with studies suggesting high intakes of fruits lead to a reduction in pro-inflammatory mediators and enhanced immune cell profile (58). The association, however, was not well captured in our linear regression model and seemed rather U-shaped, deserving attention in future research. The inverse associations found with fish and whole grains in women also fit to the hypothesis of protective effects of a Mediterranean-type diet; however, these variables were not selected as important predictors from RFR analyses.

Our findings suggested differences in variable importance by sex, that is, sleeping duration, smoking, and intake of eggs, fruits, vegetables, and nuts. Various physiological and psychosocial differences may have possibly accounted for these differences. For instance, women are more often exposed to stressors that may have inflammatory consequences (59). Having the reduced statistical power in these stratified analyses, further studies with larger samples are warranted to explore sex-specific associations with elevated chemerin concentrations.

We must acknowledge several limitations of our study: (1) the cross-sectional study design limits interpretation on temporal links between evaluated determinants and chemerin concentrations; (2) the measurement of dietary intakes is error prone and less precise than biomarker measurements. Assuming that measurement error was independent of chemerin concentrations or related factors, this would bias any potential association toward the null. Associations of chemerin concentrations with dietary factors could be underestimated; (3) chemerin concentrations may show day/night variations (59) which may influence observed associations with various traits. However, in our study, biosample collections were taken only over daytime, minimizing the potential influence of circadian variation; (4) residual confounding from subclinical disease could not be excluded in our adjusted models.

Conclusions

In this large population-based study, we explored potential determinants of elevated chemerin concentrations among a wide range of lifestyle-associated, dietary, and

metabolic factors. The findings come in support of the role of chemerin characterizing inflammatory and metabolic phenotypes in predominantly healthy adults. Modifiable dietary and lifestyle-associated determinants of elevated chemerin concentrations require further evaluation in a prospective study setting.

Supplementary materials

This is linked to the online version of the paper at <https://doi.org/10.1530/EC-21-0273>.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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