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ORIGINAL ARTICLE

Associations of the Baltic Sea diet with obesity-related markers of inflammation

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***Introduction*. Inflammation is an important contributor to the development of chronic diseases. We examined whether a healthy Nordic diet, also called the Baltic Sea diet, associates with lower concentrations of inflammatory markers.**

***Methods*. We used two independent cross-sectional studies: the DILGOM study including Finnish participants aged 25–74 years ($n = 4579$), and the Helsinki Birth Cohort Study including individuals born at Helsinki University Central Hospital between 1934 and 1944 and who participated in a clinical examination in 2001–2004 ($n = 1911$). Both studies measured anthropometrics, drew blood, and assessed concentrations of leptin, high-molecular-weight adiponectin, tumor necrosis factor α, interleukin 6, and high-sensitivity C-reactive protein (hs-CRP). A food frequency questionnaire was used to measure dietary intake over the past year and calculate the Baltic Sea Diet Score (BSDS).**

***Results*. In both studies, linear regression adjusting for age, sex, energy intake, lifestyle factors, obesity, statin medication, and upstream inflammatory markers revealed an inverse association between the BSDS and hs-CRP concentrations ($P < 0.01$). Especially, high intake of Nordic fruits and cereals, low intake of red and processed meat, and moderate intake of alcohol contributed to the emerged association ($P < 0.05$). The BSDS did not associate with other inflammatory markers.**

***Conclusion*. The Baltic Sea diet is associated with lower hs-CRP concentrations.**

Key words: Baltic Sea Diet Score, cross-sectional, Finland, inflammation, Nordic diet, obesity

Key messages

- The Baltic Sea diet is associated with lower concentrations of high-sensitivity C-reactive protein independently of obesity, statin medication, and upstream markers of inflammation in two independent study populations.
- Chronic low-grade inflammation is an important risk factor for type 2 diabetes and cardiovascular disease; adopting the Baltic Sea diet may be beneficial in Nordic countries, where these diseases are the leading causes of premature death.

Introduction

Adipose tissue is not merely storage for extra fat, but is an active organ that is involved in many metabolic processes. In obese individuals, the expanded adipose tissue disturbs the metabolism of anti- and pro-inflammatory cytokines, potentially causing insulin resistance and atherosclerosis (1,2). Consequently chronic low-grade inflammation is an important risk factor for type 2 diabetes and cardiovascular diseases (CVD). Even though inflammation plays an important role in disease progression, interactions between inflammatory markers are poorly understood. Some evidence suggests that the inflammatory markers are strongly connected; regulation of cytokine production in adipose tissue depends on changes in the excretion of anti-inflammatory adiponectin and pro-inflammatory leptin. These adipokines induce macrophage production in adipose tissue and stimulate the production of tumor necrosis factor alpha (TNF-α) and interleukin 6 (IL-6). These two along with adipokines are the main moderators of acute-phase, inflammatory C-reactive protein (CRP) production (3–6). CRP activates pathways culminating mainly in nuclear transcription factor kappa B, by which CRP amplifies events related to lipid deposition and oxidation (4). Elevated CRP concentration is, thus, considered an independent atherosclerosis progression risk factor (1,2).

The role of diet in regulating inflammatory responses remains little studied (7). The traditional diet of the Mediterranean area is related to various health benefits, for example, lower inflammation

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grade (8). The health effects related to the Mediterranean diet have, however, been inconsistent in different non-Mediterranean countries, probably due to differences in food culture and in resources (9,10). When the Mediterranean diet has been culturally modified it is associated with lower CRP and higher adiponectin concentrations in Western populations (11,12).

Nordic nutritionists have proposed a diet comprising healthy Nordic foods, the Baltic Sea diet, as an alternative to the Mediterranean diet (13). Nordic trials that included hypercholesterolemic subjects (14) and individuals with the metabolic syndrome (15) have reported better lipid profiles and fewer signs of inflammation in their healthy Nordic diet groups compared to their control groups. Thus far, the association between inflammatory markers and the Baltic Sea diet has not yet been assessed in large epidemiological studies.

We hypothesized that high adherence to the Baltic Sea diet, as assessed by the Baltic Sea Diet Score (BSDS) (16), associates with inflammatory markers of lower concentrations. We tested our hypothesis in two Finnish cross-sectional study populations. The DIetary, Lifestyle, and Genetic determinants of Obesity and Metabolic syndrome (DILGOM) study is a population-based study encompassing a wide range of measurements which allow us to assess variation in inflammation versus variation in the BSDS. The Helsinki Birth Cohort Study (HBCS) is a birth cohort study of individuals examined at age 60 to 70. The HBCS lets us explore whether the association between inflammatory responses and the Baltic Sea Diet exists in an elderly Finnish population and allows replication of the findings from the DILGOM study.

Materials and methods

The DILGOM study was implemented in the framework of the National FINRISK 2007 Study (17). The National FINRISK 2007 Study conducted between January and March 2007 included men and women aged 25 to 74 years (18). A random sample of 10,000 subjects from the Finnish population register was drawn and stratified by sex, 10-year age groups, and by five geographical areas. The participants received an invitation to a health examination and a self-administered health questionnaire via mail. In total 6258 individuals participated in the health examination (participation rate: 63%). To gather more precise information on obesity all participants of the National FINRISK 2007 Study were invited to the DILGOM study between April and June 2007. This phase included a more detailed health examination and questionnaires on dietary habits, physical activity, and other health-related behavior (17). Of the invited, 5024 individuals participated (participation rate: 80%). After exclusions of participants with missing background information, a total or partly empty food frequency questionnaire (FFQ), extreme high or low energy intake (19), or with incomplete measurement of inflammatory markers, and women who were pregnant, the sample size for the present study was 4579 participants (2165 men and 2414 women).

The participants of HBCS were born at Helsinki University Central Hospital as singletons between 1934 and 1944 (20). Using random number tables, a sample of 2902 participants from this cohort was derived and invited to a clinical examination conducted in the years 2001–2004. Eventually, 2003 individuals participated. The clinical study has been described in detail elsewhere (20). After exclusions of participants with a total or partly empty FFQ, extreme high or low energy intake (19), or incomplete measurement of inflammatory markers, the sample size for the present study was 1911 participants (887 men and 1024 women).

The studies were conducted according to the guidelines laid down in the Declaration of Helsinki, and the Ethics Committee of the Hospital District of Helsinki and Uusimaa approved all procedures involving human subjects. Written informed consent was obtained from all participants.

In both studies, participants filled in a standardized and validated FFQ designed to measure the habitual diet over the previous 12 months (21–23). Participants reported the consumption of each 130 FFQ-item using nine frequency categories ranging from 'never or seldom' to 'six or more times a day'. The predefined portion sizes for the food items appeared as household and natural units (e.g. 'glass', 'slice'). After the participant had filled in the FFQ, a trained study nurse reviewed the questionnaire. A nutritionist entered the data into the study database. The average daily food, nutrient, and energy intakes were calculated, using the Finnish National Food Composition Database (Fineli®) and in-house software (24).

We have described the development of BSDS in detail elsewhere (16). In brief, the BSDS includes nine dietary features: high intake of Nordic fruits (apples, pears, and berries); Nordic vegetables (tomatoes, cucumber, leafy vegetables, roots, cabbages, peas); Nordic cereals (rye, oat, and barley); low-fat and fat-free milk; Nordic fish (salmon and freshwater fishes); ratio of PUFA to SFA and trans-fatty acids; low intake of red and processed meat; total fat (E%); and moderate or low intake of alcohol (ethanol). Study- and sex-specific quartiles of average daily intakes served as cut-offs when each component, except alcohol, was scored from 0 to 3 according to the predictable impact of the component for health. Participants received 1 point if alcohol intake was moderate (<20 g/d ethanol for men and <10 g/d ethanol for women) and 0 if above. The final BSDS ranged from 0 to 25. Higher score values indicate higher adherence to the Baltic Sea diet and vice versa.

In both studies, trained study nurses measured height, weight, and waist circumference according to international guidelines (25). They also drew blood for serum and plasma samples which were stored at $-70°C$ prior to analysis. Research laboratories analyzed high-sensitivity CRP (hs-CRP) with immunoturbidimetric methods, using Abbot Architect ci8200 analyzer (Abbott Laboratories, Abbott Park, IL, USA) in the DILGOM study, and Konelab T-serie High Sensitivity CRP analyzer (Thermo Fisher Scientific Oy, Vantaa, Finland) in the HBCS. High-molecular-weight adiponectin (HMW-adiponectin) was analyzed with an enzyme-linked immunosorbent assay (HMW adiponectin ELISA kit, Millipore, St Charles, MO, USA) in both studies. IL-6, TNF-α, and leptin were analyzed with multiplex sandwich immunoassays (HBCS: IL-6, TNFα, leptin, and DILGOM: leptin, with Milliplex Human Metabolic Hormone Panel, Millipore; and DILGOM: IL-6 and TNFα, with Milliplex High Sensitivity Human Cytokine kit, Millipore). In the DILGOM study, the highest between-run variations (CV%) were 20.1% for IL-6 and 21.9% for HMW-adiponectin. In the HBCS, the highest between-run variation was 13% for IL-6 and TNF-α. For all the other inflammatory markers, the between-run variations were under 10% in both studies. In the DILGOM study, the amount of samples with concentrations below or above the measurement range of the analysis method were $<1\%$ for HMW-adiponectin, leptin, TNF-α, and hs-CRP, and 18% for IL-6. The corresponding figures in the HBCS were 3% for HMW-adiponectin, 59% for leptin, 4% for TNF-α, 5% for hs-CRP, and 50% for IL-6.

Participants filled in self-administered questionnaires inquiring about socio-economic characteristics and lifestyle factors. Educational attainment was assessed in years. Smoking status was assessed using three categories: never smokers, former smokers, and current smokers. Leisure time physical activity (PA) assessed activities outside of work using three categories: inactive (mainly

light activities, e.g. reading, watching television), moderately active (e.g. walking, cycling, or gardening at least 4 h per week), active (physically demanding activities, e.g. running, cross-country skiing, or swimming at least 3 h per week). Medication use was derived from The Social Insurance Institute's register of reimbursements of pharmaceutical expenses, linking the data with personal social security code, a unique feature of the social security systems in Nordic countries.

Because the distributions of inflammatory markers were skewed, we logarithmically transformed them closer to approximate normal distribution. Inflammation marker concentrations below or above the measurement range of the analysis method were included to the analyses. In the DILGOM study, all the values below measurement range had been assigned the value of the lower limit of the measuring range, and vice versa. In the HBCS, the original concentrations had been reported even if they were below or above the measurement range. When we analyzed association between BSDS and hs-CRP we excluded participants with hs-CRP $>$ 10 mg/L (the DILGOM study: 121 values, HBCS: 138 values) since these concentrations are likely to indicate acute inflammation. All the analyses were also run without any exclusion, and the results did not change remarkably from those obtained after exclusions. In the Results section, we present the results that were run with the exclusions.

We used R statistical software version 2.15.1 (26) to analyze the data. We analyzed men and women together since strong evidence of interaction between the BSDS and sex did not emerge in either study ($P > 0.05$). We calculated the descriptive data by the BSDS quintiles as means ± standard errors (SE) or percentages (%). After that we calculated these estimates for inflammatory markers, and then assessed the trends across BSDS fifths with linear regression using the median values of BSDS fifths in continuous form. Confounding variables used in the models were determined with linear regression analysis (27). We adjusted Model 1 for age (years; continuous), sex (dichotomic), and energy intake (kJ; continuous); Model 2 we additionally adjusted for educational attainment (years; continuous), smoking (former smoker, ex-smoker, current smoker; categorical), leisure time physical and activity (low, moderate, high; categorical); and Model 3 we further adjusted for waist circumference (cm; continuous). HMW-adiponectin was adjusted also for anti-diabetic medication (oral drugs and insulin injections) and hs-CRP for statin medication (Model 4). Finally, if relevant, Model 5 was adjusted for other inflammatory markers. To explore whether specific score components drove the associations that emerged in the main analyses, we ran Model 3 for each BSDS component separately.

To take into account possible misreporting of energy intake, we calculated the ratio of reported energy intake (EI) to predicted basal metabolic rate (BMR) (28), and classified participants as either under-reporters (EI:BMR $\leq$ 1.14) or plausible reporters (EI:BMR $>$ 1.14) (29,30). Finally, we confirmed our results re-running analyses without under-reporters.

Results

DILGOM study

Participants with higher adherence to the Baltic Sea diet were older, more educated, less often smokers, and physically more active (Table I). Use of statins and anti-diabetic medications were similar between the BSDS quintiles.

In the regression analysis, HMW-adiponectin concentrations associated inversely with the BSDS (Model 1; $P = 0.044$) (Table II). Adjustments for length of education, leisure time PA, smoking, and waist circumference strengthened this association (Model 3; $P = 0.003$), which did not change after further adjustments for the use of anti-diabetic medication and other inflammatory markers (Models 4 and 5; $P = 0.005$–0.006). The result attenuated, but remained statistically significant after excluding under-reporters (Model 3; $P = 0.038$) (data not shown). Furthermore, hs-CRP concentrations associated inversely with the BSDS

Table I. Age- and sex-adjusted means (and SE) or percentages for participants' characteristics by the BSDS quintiles in the DILGOM study and the HBCS.

	DILGOM ($n = 4579$) BSDS quintiles							HBCS ($n = 1911$) BSDS quintiles						
Characteristics	1	SE	3	SE	5	SE	P[a]	1	SE	3	SE	5	SE	P[a]
BSDS[b,c]	7.4	0.04	13.5	0.04	19.0	0.04	<0.001	7	0.1	13	0.1	19	0.1	<0.001
Age, y[d]	46.9	0.4	53.1	0.4	58.4	0.5	<0.001	61.2	0.1	61.5	0.1	61.8	0.2	<0.01
Women participants, %[e]	51.6		52.1		48.7		0.49	49.6		42.5		54.4		0.47
Study years	12.4	0.1	12.6	0.1	13.0	0.1	<0.001	11.6	0.2	12.3	0.2	12.9	0.2	<0.001
Current smokers, %	25.8		14.5		8.8		<0.001	39.9		21.8		11.1		<0.001
Physically inactive participants, %	30.1		15.8		10.0		<0.001	18.1		10.2		5.3		<0.001
BMI, kg/m^2	27.1	0.2	26.8	0.2	26.7	0.2	0.19	27.7	0.2	27.3	0.2	27.4	0.3	0.71
Waist circumference, cm	92.6	0.4	91.2	0.4	90.1	0.5	0.10	96.5	0.6	94.9	0.6	94.0	0.7	<0.05
Beta-blockers, %	19.7		20.6		19.0		0.66	16.5		17.6		19.8		0.19
Calcium channel-blockers, %	8.7		8.5		8.0		0.79	8.7		11.4		8.0		0.92
ACE channel-blockers, %	9.0		9.7		8.1		0.27	10.7		10.1		10.5		0.98
Oral diabetes medication, %	5.0		4.0		6.0		0.32	5.0		3.9		9.0		<0.05
Insulin users, %	1.0		1.0		1.0		0.12	2.0		1.1		3.3		0.15

BSDS = Baltic Sea Diet Score; DILGOM = Dietary, Lifestyle, and Genetic Determinants of Obesity and Metabolic Syndrome; HBCS = Helsinki Birth Cohort Study; SE = standard error.

[a]*P*-value for trend was derived from linear regression (continuous variables) or logistic regression (categorical variables) using median values of BSDS quintiles in continuous form.

[b]Baltic Sea Diet Score components: fruits and berries (berries, apples, and pears), vegetables (tomatoes, cucumbers, cabbages, roots, legumes, and lettuce), cereals (rye, oats, and barley), low-fat milk (fat-free and $<$2% fat), meat products (beef, pork, processed meat, and sausage), fish, ratio of polyunsaturated fatty acids to saturated and trans-fatty acids, total fat content of the diet (as percentages of total energy intake), alcohol (as ethanol). Scoring by quartiles 0–3 points: positive scoring (the more consumed, the higher points) was used for other score components except meat products, which were scored negatively (the more consumed the lower points). Men consuming 20 g or less of alcohol and women consuming 10 g or less of alcohol were given 1 point; otherwise a score of 0 was given.

[c]Values are additionally adjusted for daily intake of energy.

[d]Values are adjusted only for sex.

[e]Values are only adjusted for age.

Table II. Participants' mean (SE) concentrations of markers of inflammation by the BSDS quintiles in the DILGOM study ($n = 4579$).

	BSDS quintiles										
Markers of inflammation	1	SE	2	SE	3	SE	4	SE	5	SE	P^a
Leptin, pg/mL											
Model 1[b]	9490	1.03	9600	1.03	8890	1.03	8740	1.03	8600	1.03	0.002
Model 2[c]	8930	1.03	9460	1.02	9040	1.03	8970	1.03	9076	1.03	0.82
Model 3[d]	8880	1.02	9240	1.02	8960	1.02	9210	1.02	9260	1.02	0.23
HMW-adiponectin, ng/mL											
Model 1	3710	1.02	3640	1.02	3630	1.02	3580	1.02	3460	1.03	0.044
Model 2	3750	1.02	3650	1.02	3630	1.02	3560	1.02	3420	1.03	0.011
Model 3	3760	1.02	3680	1.02	3630	1.02	3530	1.02	3400	1.03	0.003
Model 4[e]	3750	1.02	3680	1.02	3620	1.02	3530	1.02	3420	1.03	0.005
Model 5[f]	3740	1.02	3680	1.02	3620	1.02	3530	1.02	3420	1.03	0.006
TNF-α, pg/mL											
Model 1	5.87	1.02	5.59	1.02	5.71	1.02	5.58	1.02	5.56	1.02	0.08
Model 2	5.81	1.02	5.58	1.02	5.73	1.02	5.61	1.02	5.61	1.02	0.30
Model 3	5.81	1.02	5.57	1.02	5.72	1.02	5.62	1.02	5.62	1.02	0.37
IL-6, pg/mL											
Model 1	3.19	1.04	2.52	1.04	2.84	1.05	2.72	1.05	2.68	1.05	0.055
Model 2	3.07	1.04	2.5	1.04	2.87	1.05	2.77	1.05	2.77	1.05	0.44
Model 3	3.07	1.04	2.49	1.04	2.86	1.05	2.79	1.05	2.79	1.05	0.56
hs-CRP, mg/L											
Model 1	1.21	1.03	1.14	1.03	1.12	1.03	1.06	1.03	0.93	1.04	<0.001
Model 2	1.14	1.03	1.12	1.03	1.14	1.03	1.09	1.03	0.98	1.04	0.003
Model 3	1.14	1.03	1.11	1.03	1.13	1.03	1.11	1.03	1.00	1.03	0.010
Model 4	1.14	1.03	1.11	1.03	1.13	1.03	1.11	1.03	1.00	1.03	0.009
Model 5	1.13	1.03	1.12	1.03	1.12	1.03	1.11	1.03	0.99	1.03	0.006

BSDS = Baltic Sea Diet Score; DILGOM = Dietary, Lifestyle, and Genetic Determinants of Obesity and Metabolic Syndrome; HMW-adiponectin = high-molecular-weight adiponectin; hs-CRP = high-sensitivity C-reactive protein; IL-6 = interleukin 6; TNF-α = tumor necrosis factor-alpha.

[a]*P* for trend across quintile groups was assessed with linear regression using quintiles' median values as continuous form.

[b]Model 1 is adjusted for age, sex, and intake of energy.

[c]Model 2 is Model 1 adjusted for educational attainment, smoking status, and leisure time physical activity.

[d]Model 3 is Model 2 adjusted for waist circumference.

[e]Model 4 is Model 3 adjusted for oral diabetes medication and insulin injections (HMW-adiponectin) or for statin medication (hs-CRP).

[f]Model 5 is Model 4 adjusted with other markers of inflammation which were significantly associated with the BSDS in Model 1.

($P < 0.001$) in Model 1 and remained unchanged after adjustments for length of education, lifestyle factors, waist circumference, statin medication, and other inflammatory markers (Models 2–5). It remained significant also after excluding under-reporters (Model 3; $P = 0.023$) (data not shown). The BSDS did not associate with other inflammatory markers in Model 3.

We examined the individual associations of the single BSDS components with HMW-adiponectin and hs-CRP concentrations. In Model 3, participants with high intake of alcohol had higher HMW-adiponectin concentration than others ($P < 0.001$) (data not shown). Lower intake of fat (E%) tended to associate with higher adiponectin concentration ($P = 0.096$), but, on the contrary, participants with a high fat ratio tended to have lower adiponectin concentration ($P = 0.059$) (data not shown). Furthermore, we found that participants with high intake of fruits and berries ($P = 0.003$) and cereals ($P = 0.046$), low intake of red and processed meat ($P = 0.001$), and moderate intake of alcohol ($P = 0.019$) had lower hs-CRP concentration than the others (Table III). Other BSDS components did not show any statistically significant association with the inflammatory markers studied.

HBCS

Participants with higher adherence to the Baltic Sea diet were slightly older, more educated, less often smokers, physically more active, had smaller waist circumference, and were more likely to use oral diabetes medication (Table I). These results were univocal with the ones observed in the DILGOM study. Use of other medication was similar between the BSDS quintiles.

In the regression analysis, hs-CRP concentrations associated inversely with the BSDS ($P < 0.01$) in all three basic models (Table IV). Neither adjustment for statin medication ($P = 0.006$) nor the adjustment of upstream inflammatory markers removed the statistically significant association ($P = 0.004$). The result remained significant also after excluding under-reporters ($P = 0.011$) (data not shown). Other inflammatory markers did not associate with the BSDS in the HBCS.

We examined the individual associations of the single BSDS components with hs-CRP concentrations (Table III). In Model 3, participants with high intake of fruits and berries ($P = 0.023$) and cereals ($P = 0.021$), and low intake of red and processed meat ($P = 0.003$), and moderate intake of alcohol ($P = 0.045$) had lower hs-CRP concentration than others.

Discussion

Results from two independent studies showed that individuals adhering to the Baltic Sea diet had lower hs-CRP concentrations than the others. This association is independent of lifestyle factors, abdominal obesity, statin medication, and other markers of inflammation. In the DILGOM study, HMW-adiponectin concentrations were lower among participants adhering to the diet compared to the others. However, this finding was not replicated in the HBCS study. The Baltic Sea diet did not associate with any of the other inflammatory markers studied in neither of the studies.

We expected that the Baltic Sea diet would associate positively with adiponectin and inversely with other inflammatory markers.

Table III. Participants' mean (SE) hs-CRP concentrations (mg/L) by the BSDS component quartiles in the DILGOM study and HBCS.

	BSDS component quartiles[a,b]								
BSDS components	1	SE	2	SE	3	SE	4	SE	*P*[c]
DILGOM ($n = 4458$)									
Fruits and berries	1.18[c]	1.03[c]	1.09	1.03	1.10	1.03	1.03	1.03	0.003
Vegetables	1.11	1.03	1.11	1.03	1.06	1.03	1.12	1.03	0.89
Cereals	1.14	1.03	1.12	1.03	1.08	1.03	1.05	1.03	0.046
Low-fat milk[d]	1.10	1.03	1.10	1.03	1.09	1.02	1.09	1.03	0.84
Fish	1.16	1.03	1.11	1.03	1.05	1.03	1.08	1.03	0.12
Meat products	1.19	1.03	1.10	1.03	1.07	1.03	1.03	1.03	0.001
Fat ratio[e]	1.11	1.03	1.09	1.03	1.12	1.03	1.07	1.03	0.45
Total fat, E%	1.11	1.03	1.09	1.03	1.15	1.03	1.04	1.03	0.19
Alcohol[f]	1.05	1.03	1.09	1.03	1.12	1.03	1.15	1.03	0.019
HBCS ($n = 1773$)									
Fruits and berries	1.50	1.05	1.52	1.04	1.43	1.04	1.32	1.05	0.023
Vegetables	1.40	1.05	1.55	1.04	1.45	1.04	1.37	1.05	0.34
Cereals	1.52	1.05	1.51	1.04	1.44	1.04	1.31	1.05	0.021
Low-fat milk[d]	1.43	1.04	1.35	1.05	1.48	1.04	1.52	1.05	0.14
Fish	1.58	1.05	1.39	1.04	1.40	1.05	1.41	1.05	0.23
Meat products	1.58	1.05	1.50	1.04	1.44	1.04	1.26	1.05	0.003
Fat ratio[e]	1.45	1.04	1.42	1.04	1.55	1.04	1.35	1.05	0.39
Total fat, E%	1.51	1.04	1.44	1.04	1.46	1.04	1.36	1.04	0.11
Alcohol[f]	1.38	1.04	1.29	1.05	1.53	1.05	1.59	1.05	0.045

BSDS = Baltic Sea Diet Score; DILGOM = Dietary, Lifestyle and Genetic Determinants of Obesity and Metabolic Syndrome; HBCS = Helsinki Birth Cohort Study; hs-CRP = high-sensitivity C-reactive protein.

[a]Model is adjusted for sex, age, educational attainment, smoking status, leisure-time physical activity, and waist circumference.

[b]Study and sex specific cut-off quartiles were used. Participants in the higher quartiles of presumably beneficial effect were assigned higher points than participants in the lowest quartiles. In contrast, participants in the lower quartiles of presumably detrimental effects were assigned higher points than persons in the highest quartiles.

[c]*P* value for trend was obtained from linear regression using food intake quartiles' median values as continuous variable in the model.

[d]Fat-free milk and milk $<2\%$ of fat.

[e]Ratio of polyunsaturated fatty acids to saturated and trans-fatty acids.

[f]In component specific analyses, alcohol consumption was cut in quartiles from lowest intake (first quartile; median <1 g/d) to moderate intake (fourth quartile; median = 15 g/d). This was done in order to obtain wider range to alcohol intake.

Table IV. Participants' mean (SE) concentrations of markers of inflammation by the BSDS quintiles in the HBCS ($n = 1911$).

	BSDS quintiles										
Markers of inflammation	1	SE	2	SE	3	SE	4	SE	5	SE	*P*[a]
Leptin, pg/mL											
Model 1[b]	12000	1.05	12600	1.05	11500	1.05	12200	1.05	11600	1.06	0.72
Model 2[c]	11900	1.05	12500	1.05	11500	1.05	12200	1.05	11800	1.06	0.87
Model 3[d]	11600	1.05	12600	1.05	11700	1.05	11900	1.05	12300	1.06	0.69
HMW-adiponectin, ng/mL											
Model 1	4860	1.04	4420	1.04	5100	1.04	4640	1.04	4380	1.05	0.23
Model 2	4870	1.04	4420	1.04	5100	1.04	4620	1.04	4360	1.05	0.14
Model 3	4920	1.04	4410	1.04	5030	1.04	4690	1.04	4310	1.05	0.13
TNF-α, pg/mL											
Model 1	8.89	1.05	9.27	1.05	8.66	1.05	8.78	1.05	8.48	1.07	0.50
Model 2	8.86	1.05	9.27	1.05	8.68	1.05	8.68	1.05	8.52	1.07	0.51
Model 3	8.83	1.05	9.27	1.05	8.70	1.05	8.65	1.05	8.56	1.07	0.55
IL-6, pg/mL											
Model 1	20.6	1.12	21.6	1.12	22.6	1.12	16.8	1.12	17.8	1.15	0.20
Model 2	19.9	1.12	21.5	1.12	23.0	1.12	17.2	1.12	18.6	1.15	0.42
Model 3	19.9	1.12	21.5	1.12	23.0	1.12	17.1	1.12	18.6	1.15	0.43
hs-CRP, mg/L											
Model 1	1.67	1.05	1.57	1.05	1.45	1.05	1.29	1.05	1.20	1.06	<0.001
Model 2	1.58	1.05	1.54	1.05	1.45	1.05	1.34	1.05	1.23	1.06	0.002
Model 3	1.53	1.05	1.54	1.05	1.47	1.05	1.33	1.05	1.29	1.06	0.005
Model 4[e]	1.53	1.05	1.54	1.05	1.47	1.05	1.33	1.05	1.29	1.06	0.006
Model 5[f]	1.54	1.05	1.53	1.05	1.49	1.05	1.33	1.05	1.28	1.06	0.004

BSDS = Baltic Sea Diet Score; HBCS = Helsinki Birth Cohort Study; HMW-adiponectin = high-molecular-weight adiponectin; hs-CRP = high-sensitivity C-reactive protein; IL-6 = interleukin 6; TNF-α = tumor necrosis factor-alpha.

[a]*P* for trend across quintile groups was assessed with linear regression using quintile median values as continuous form.

[b]Model 1 is adjusted for age, sex, and intake of energy.

[c]Model 2 is Model 1 adjusted for educational attainment, smoking status, and leisure time physical activity.

[d]Model 3 is Model 2 adjusted for waist circumference.

[e]Model 4 is Model 3 adjusted for statin medication (hs-CRP).

[f]Model 5 is Model 4 adjusted with other markers of inflammation which were significantly associated with the BSDS in Model 1.

In our study, the Baltic Sea diet associated with lower hs-CRP concentrations. Only few epidemiological studies have reported associations between healthy diet scores and markers of inflammation. The Alternate Healthy Eating Index (AHEI) and the Mediterranean Diet Score have associated inversely with high CRP concentration (31,32). Mechanistic cell and animal studies indicates that regulation of CRP production depends on leptin, adiponectin, TNF-α, and IL-6 excretion. We expected that these upstream inflammatory markers would explain the association between the Baltic Sea diet and CRP concentrations (3–6). In theory, small changes in the upstream markers could cumulate to induce an increase in CRP production. After adjusting the analyses for these markers, the association between the Baltic Sea diet and CRP remained, however. In the study of Fargnoli et al. (31) the AHEI did not associate with CRP when other upstream inflammatory markers were adjusted.

In examining the single BSDS components, the foods associated significantly with lower CRP concentrations were higher intake of Nordic fruits and berries, and cereals. They contain several antioxidant components, such as polyphenols, vitamins, minerals, and dietary fiber, which reduce CRP concentration and improve endothelial function (33–35). The specific mechanisms are not clear. Furthermore, lower CRP concentrations were found in participants who had low intake of red and processed meat. This association has been reported in two recent epidemiological studies (36,37), but it has not been confirmed in a randomized trial (38). High intake of red and processed meat has also been consistently related to higher incidence of chronic diseases (39–41). The metabolic mechanisms explaining how red meat increases CRP production are not clear. Heme iron, for which the predominant source is red meat, has been associated with increased CRP concentrations (42). It is known that catabolism of heme iron produces reactive oxygen species increasing oxidative stress that could trigger the inflammatory response (43). Another component associating with lower CRP concentration was moderate alcohol intake. We found no other study that had explored this association before.

In contrast to our hypothesis, higher BSDS did not associate with higher adiponectin concentrations. In the DILGOM study we found inverse association, and in the HBCS no association emerged. Adherence to the AHEI and to the Mediterranean Diet Score associated with higher adiponectin concentrations, alcohol being the key component driving this association (12,31,44). Higher alcohol intake also increased adiponectin concentrations in some animal (45,46) and human trials (47). In the DILGOM study, our observations are in line with the current evidence: The only component significantly associated with adiponectin was alcohol. In the HBCS, the range of alcohol intake was maybe too narrow to detect any association. Furthermore, the number of participants having alcohol intake above moderate (20 g/d for men and 10 g/d for women) was somewhat equal between BSDS quintiles which might explain why no association emerged. Along with alcohol, adiponectin concentration may increase due to higher intake of unsaturated fat (12,31,44), especially omega-3 fatty acids (48). In the DILGOM study, we observed that a high fat ratio (more polyunsaturated fat) associated with lower adiponectin concentrations, but, on the other hand, lower total fat intake slightly increased adiponectin concentration. More research on the association of whole diet quality and adiponectin is needed.

In either study cohorts, the BSDS did not associate with leptin, TNF-α, or IL-6—a finding which is not in line with our hypothesis. Fairly equal anthropometric characteristic—BMI and waist circumference—distribution among the participants across the BSDS quintiles could in part explain why these associations did not occur. A growing body of evidence shows that a 5%–10% weight loss achieved with a healthier diet is needed to improve concentration of inflammatory markers (7). The association of the AHEI and the Mediterranean Diet Score with TNF-α or leptin has not been yet studied in an average healthy population. The association between the AHEI and IL-6 is unclear (11,31). The Mediterranean Diet Score has been associated with IL-6, but the studies did not adjust the analyses for upstream inflammatory markers (11,32).

The strength of the DILGOM study included random sampling and a population-based approach. Repeating the analyses in the HBCS, which represents an independent cohort, enhances the reliability of our results. The cross-sectional designs, however, limit the conclusions. Both studies used validated and standardized questionnaires and measurements. The same FFQ (21–23), food composition database, and nutrition calculation software were used in both studies (24). Along with these, careful testing and controlling of several confounding variables in the analyses are strengths of this study. Different laboratory analyzing methods between the studies, however, resulted in unequal concentration levels. This was especially seen in the IL-6 concentrations between the DILGOM study and the HBCS. Consequently, this makes the comparison of the absolute IL-6 concentrations impossible. This affects neither our results nor the conclusions since we were only interested in exploring the associations between the BSDS and the inflammatory markers.

In conclusion, adherence to a healthy Baltic Sea diet, illustrated by a higher BSDS, is associated with lower hs-CRP concentrations. Neither anthropometric, lifestyle, and other health-related variables nor the CRP production controlling adipokines and cytokines can fully explain this association. The BSDS did not associate with other markers of inflammation. Future studies should extend the CRP finding by investigating the association of BSDS with chronic diseases and whether the association is mediated through changes in CRP concentration.

Declaration of interest: The authors report no conflicts of interest.

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