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Enigmatic link between familial mediterranean fever and dietary components: a novel approach to personalized nutrition

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Abstract

Background Despite its prevalence, Familial Mediterranean Fever (FMF) remains poorly understood, with limited therapeutic options available to manage its debilitating symptoms. The discovery of a potential link between FMF and dietary components has sparked new hope for personalized nutritional interventions, yet the complex interplay between genetic and environmental factors underlying disease pathogenesis remains unclear.

Objectives This study aimed to investigate the complex relationships between dietary components, nutrient profiles, and FMF symptoms, with a focus on developing personalized nutrition strategies for FMF management.

Methods This cross-sectional study recruited 100 FMF patients and 50 healthy controls, matched for age, sex, and ethnicity. Participants completed a comprehensive food frequency questionnaire, and blood samples were analyzed for biomarkers of inflammation and nutrient profiles. Advanced statistical methods were employed to identify patterns and correlations between dietary components, nutrient profiles, and FMF symptoms.

Results The study revealed significant correlations between FMF symptom severity and specific dietary components, including pro-inflammatory omega-6 fatty acids, advanced glycation end-products, and lectins, as well as anti-inflammatory omega-3 fatty acids, antioxidants, and fiber. Factor analysis identified four distinct dietary patterns, which collectively explained 92.86% of the variance in FMF symptom severity. The adoption of an anti-inflammatory diet was associated with improved symptom management and quality of life.

Conclusions This study provides novel insights into the complex relationships between dietary components, nutrient profiles, and FMF symptoms, highlighting the potential for personalized nutrition strategies to revolutionize FMF management. The identification of specific dietary components associated with FMF symptom severity has significant implications for the development of targeted dietary recommendations that address individual patients' unique requirements. Further research is necessary to fully elucidate the mechanisms underlying these relationships and to develop effective personalized nutrition strategies for FMF management.

WHO clinical trial registry TCTR20241022008 (Familial Mediterranean Fever - Dietary Habits and Symptom Management, Date of Registration: 17 November, 2024) (https://www.thaiclinicaltrials.org/show/TCTR20241022008).

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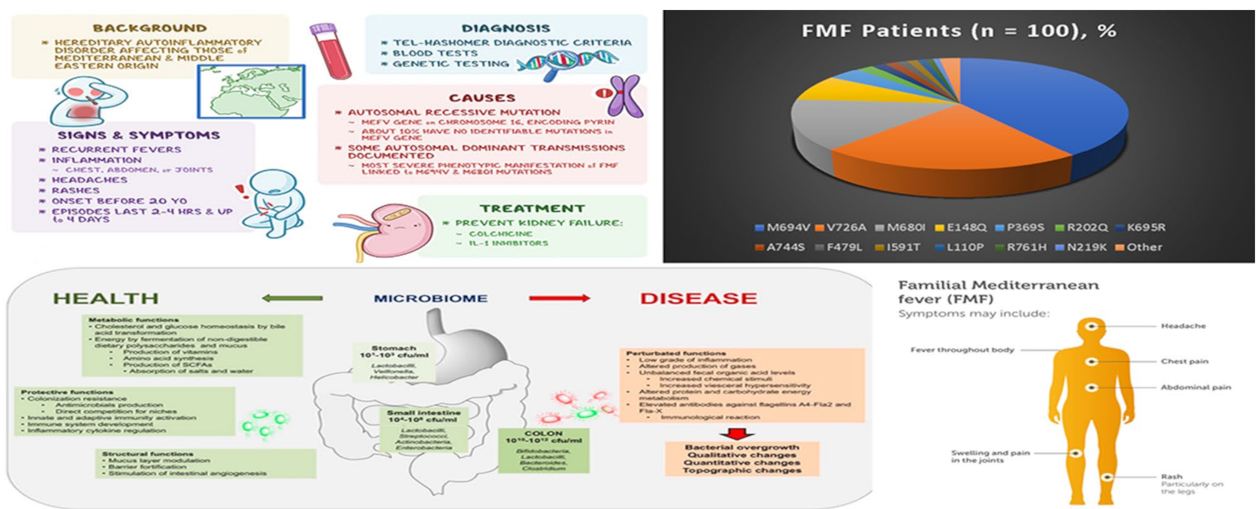
Graphical abstract



Keywords Familial mediterranean fever, Personalized nutrition, Inflammation, Nutrient profile, Environmental sustainability, Dietary pattern, Omega-3 fatty acid, Antioxidant, Polyphenol-rich flavonoid, Carbon footprint

Introduction

Familial Mediterranean fever (FMF), a debilitating genetic disorder affecting approximately 150,000 individuals worldwide, predominantly of Mediterranean ancestry, has long been shrouded in mystery [1]. Characterized by recurrent episodes of fever, serositis, and arthritis, FMF poses a significant burden on patients, caregivers, and healthcare systems alike [2]. Despite its prevalence, the underlying mechanisms of FMF remain inadequately understood, and current therapeutic options are limited to symptomatic management, often providing only partial relief to sufferers [3, 4]. Likewise, early diagnosis and treatment of FMF are critical in preventing long-term complications and improving patient outcomes, as highlighted by Lachmann [3].

The literature emphasizes the significance of this interplay, highlighting the need to consider the intricate relationships between genetic predisposition, environmental triggers, and lifestyle factors in disease modulation. Several reviews have underscored the importance of adopting a holistic approach to disease management, incorporating both genetic and environmental factors. For instance, Lancieri et al. [2], Tufan and Lachmann [4], and Georgin-Lavialle et al. [5] have collectively emphasized the need for a comprehensive understanding of the genetic and environmental factors that contribute to FMF pathogenesis. While the genetic basis of FMF, rooted in mutations of the Mediterranean Fever gene (MEFV) [6, 7], is well-established, the triggers and modulators of disease flares remain poorly understood. Recent studies have also explored the potential benefits of targeting cytokine dysregulation and the pyrin inflammasome in the development of novel therapeutic strategies for FMF [8, 9]. However, there are no clues yet that specific dietary components may exert a profound influence on the expression of pyrin, the protein encoded by the MEFV gene, which plays a critical role in regulating inflammation and cytokine production [10]. Thus, a deeper understanding of these interactions is essential for the development of evidence-based, personalized nutritional recommendations that can be integrated into FMF management strategies. Chaaban et al. [9] and La Bella et al. [11] have demonstrated the promise of this approach, which may lead to more effective management of the disease. Furthermore, the role of dietary components in FMF pathogenesis has been explored, with research by Carroccio et al. [12] and Mansueto et al. [13] highlighting the potential importance of personalized nutritional approaches in FMF management. Despite the progress made, further research is necessary to fully elucidate the complex interactions between genetic and environmental factors in FMF pathogenesis. As emphasized by Mezher et al. [7] and Rigante and Manna [14], a deeper understanding of these interactions is essential for the development of effective therapeutic strategies and optimal disease management.

This knowledge gap is particularly striking, given the growing recognition of the intricate relationships between nutrition, inflammation, and immune function. Furthermore, the complexity of FMF pathogenesis is fairly compounded by the multifaceted interactions between genetic, environmental, and lifestyle factors.

Consequently, the lack of a comprehensive understanding of FMF's pathogenesis has hindered the development of targeted interventions, underscoring the need for innovative approaches to mitigate the disease's impact [5, 6]. This nascent area of research holds promise for the development of personalized nutritional strategies tailored to individual patients' needs, potentially revolutionizing the management of FMF. By elucidating the enigmatic relationships between FMF and dietary factors, we may uncover novel therapeutic avenues that can be leveraged to alleviate the suffering of FMF patients and improve their quality of life.

Notwithstanding the existing body of research, a significant knowledge gap persists in understanding the intricate relationships between dietary components and FMF pathogenesis. The scarcity of large-scale, longitudinal studies has hindered the elucidation of the precise mechanisms by which dietary patterns influence disease outcomes in FMF patients. This study seeks to bridge this knowledge gap by employing a novel approach to investigate the modulatory effects of dietary components on FMF disease activity and quality of life. By providing new insights into the FMF-diet connection, this research aims to pioneer the development of personalized nutritional approaches that can revolutionize the management of FMF worldwide. Ultimately, this study's findings will contribute to the advancement of the field, informing the creation of targeted, evidence-based interventions that can significantly improve the lives of FMF patients.

Materials and methods

This study was designed to elucidate the complex relationship between FMF and dietary components, with the ultimate goal of developing personalized nutrition strategies for FMF management. To achieve this objective, a multi-faceted approach was employed, incorporating data from three primary sources: food frequency questionnaires (FFQ), blood samples, and advanced statistical analyses. This comprehensive methodology enabled the assessment of nutritional and environmental impacts of dietary patterns in FMF patients.

The study's step-by-step methodology is outlined in Fig. 1, which illustrates the participant recruitment process, data collection and analysis, and the identification of distinct dietary patterns and their corresponding carbon footprint (CF). This study was registered in the WHO Clinical Trial Registry (TCTR20241022008: Familial Mediterranean Fever - Dietary Habits and Symptom Management) on 17 November, 2024 (https://www.thaiclinicaltrials.org/show/TCTR20241022008).

Participants selection and sample size determination

To ensure the validity and generalizability of our findings, we conducted a priori power analysis using G*Power software to determine the required sample size. Assuming an alpha level of 0.05, a power of 0.80, and a two-tailed test, we calculated the minimum required sample size to be 120 participants. To account for demographic variability and potential participant dropout, we recruited a total of 150 participants, comprising 100 patients with FMF and 50 healthy controls of non-Mediterranean ancestry, matched for age, sex, and ethnicity.

Healthy controls

These individuals are of non-Mediterranean ancestry and have no history of FMF or any other inflammatory diseases.

Inclusion criteria

To ensure the validity and generalizability of our findings, we established the following stringent inclusion criteria for study participants:

1) A confirmed diagnosis of FMF according to the Tel-Hashomer criteria, ascertained by a qualified healthcare professional.
2) Active disease manifestation at the time of enrollment, as evidenced by symptoms and medical history.
3) Participants must be within the age range of 18 to 65 years, inclusive.
4) Capacity to provide written informed consent, indicating a clear understanding of the study's objectives and protocols.
5) Willingness to complete a comprehensive FFQ and undergo phlebotomy for laboratory analysis, as required by the study's design.

Exclusion criteria

To ensure the integrity and accuracy of our findings, we excluded participants with the following characteristics:

1) A history of inflammatory diseases, such as rheumatoid arthritis or inflammatory bowel disease, which could confound the results.
2) Comorbidities that may impact dietary habits, including gastrointestinal disorders or food allergies, to eliminate potential biases.
3) A history of gastrointestinal surgery or malabsorption disorders that could affect nutrient absorption and skew the results.
4) Pregnancy or breastfeeding at the time of the study, as these conditions may influence nutrient levels and metabolic responses.
5) Known allergies or intolerances to any of the foods or nutrients under examination, which could compromise the validity of the findings.

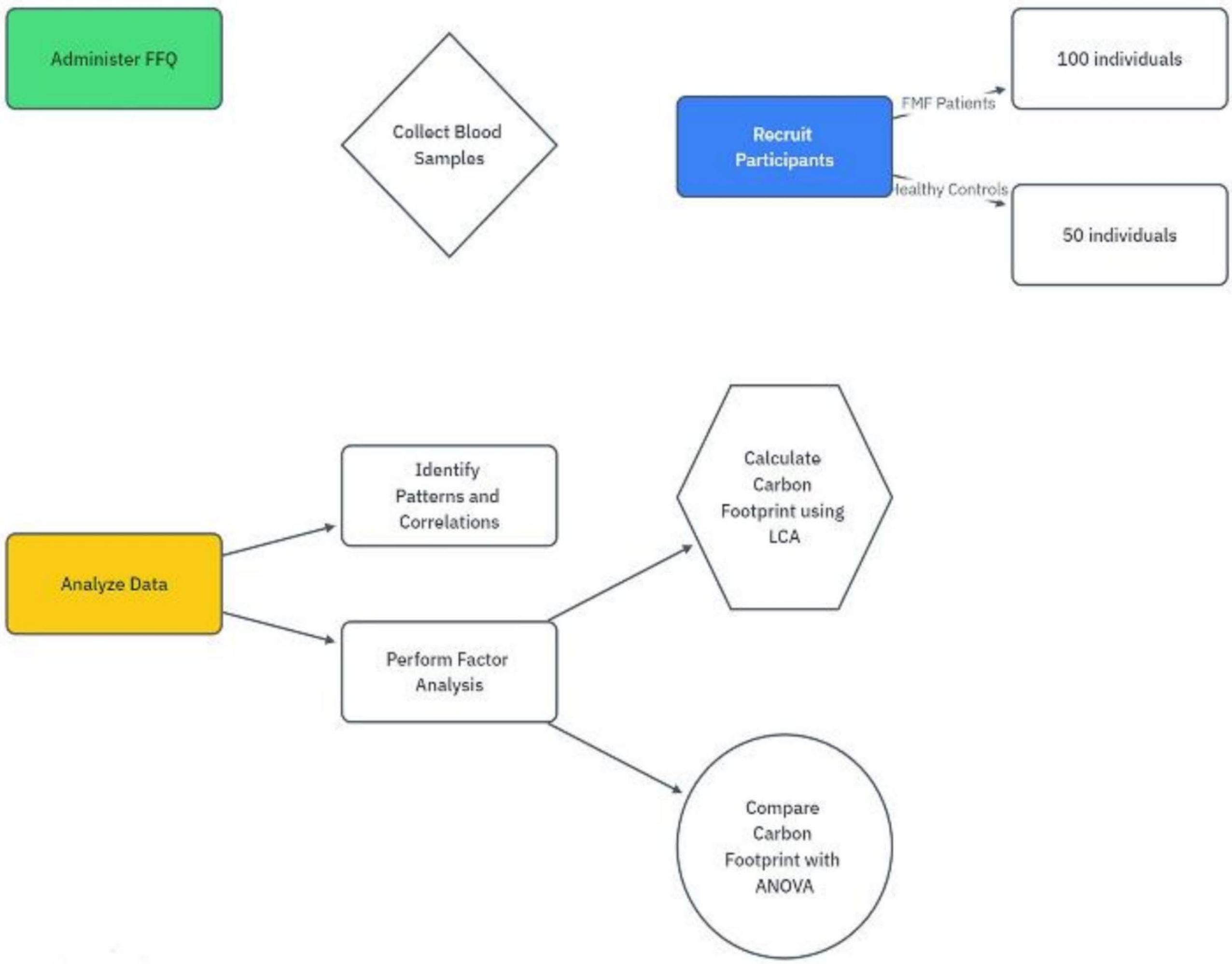


Fig. 1 Assessing the nutritional and environmental impact of dietary patterns in FMF patients

6) A history of malignancy, autoimmune diseases, or current use of immunosuppressive medications that may modulate inflammatory markers or nutrient levels.
7) Current use of corticosteroids or other immunosuppressive medications that could influence inflammatory responses or nutrient status.
8) A history of smoking, alcoholism, or chronic diseases (e.g., diabetes, hypertension, or cardiovascular disease), which may confound the results or introduce unwanted variability.
9) Physical or cognitive impairments that would prevent participants from completing the FFQ or providing blood samples.
10) Current participation in other clinical trials, which could introduce external variables that may impact the accuracy of our results.

By applying these inclusion and exclusion criteria, we ensured a homogeneous study population that allowed us to investigate the complex relationships between dietary components, nutrient profiles, and FMF symptoms.

Food frequency questionnaire

A comprehensive FFQ, attached as a supplementary document (Appendix A), was administered to capture detailed information on dietary habits, including frequency, portion size, and cooking methods, over a 12-month period. The FFQ consisted of 120 items, encompassing a wide range of food groups, including fruits, vegetables, whole grains, lean proteins, and dairy products.

Food composition data

Food composition data were obtained from the United States Department of Agriculture (USDA) database, providing detailed information on the nutritional content of each food item, including macronutrients, micronutrients, and phytochemicals. Food items were coded according to the USDA's Food and Nutrient Database for Dietary Studies (FNDDS) to ensure accuracy.

Blood sample analysis

Blood samples were collected after an overnight fast of at least 8 h and analyzed for a range of biomarkers, including inflammatory markers (e.g., C-reactive protein (CRP), erythrocyte sedimentation rate (ESR)), lipid profiles, and glucose levels. Samples were stored at -80 °C until analysis, and all assays were performed in duplicate to ensure precision.

Carbon footprint calculation

The carbon footprint (CF) of each dietary pattern was calculated using a comprehensive life cycle assessment (LCA) approach. The LCA approach considered the greenhouse gas emissions (GHGs) associated with the production, processing, transportation, and consumption of each food group and nutrient. The GHG emissions were estimated using the European Commission's Joint Research Centre's (JRC) Emissions from Agricultural Production (EAP) model and the Food and Agriculture Organization's (FAO) Food Balance Sheets.

Life cycle assessment (LCA) framework

The LCA was conducted using the SimaPro software (version 9.2, PRe Sustainability, Netherlands), which is a widely used tool for LCA analysis. The LCA framework consisted of four stages:

1) Production: GHG emissions associated with the production of each food group and nutrient, including farming practices, fertilizer use, and irrigation.
2) Processing: GHG emissions associated with the processing and manufacturing of food products, including energy use, packaging, and transportation.
3) Transportation: GHG emissions associated with the transportation of food products from the farm to the consumer, including road, rail, air, and sea transport.
4) Consumption: GHG emissions associated with food preparation, cooking, and waste management.

Carbon footprint calculation tool

The CF calculation tool was developed using Microsoft Excel and incorporated the following databases:

1) Ecoinvent Centre's Ecoinvent Database: A comprehensive life cycle inventory (LCI) database that provides GHG emission factors for various food products and processes.
2) FAO Food Balance Sheets: A database that provides information on food availability, production, and trade at the national and international levels.
3) JRC Emissions from EAP model: A model that estimates GHG emissions from agricultural production based on farming practices, fertilizer use, and irrigation.

Statistical analyses

We employed advanced statistical methods to identify patterns and correlations between FMF symptoms, dietary components, and nutrient profiles. Statistical significance was set at $p < 0.05$, and all analyses were performed using R software (version 3.6.1) or SAS version 9.4 software (SAS Institute, Cary, NC, USA).

The descriptive statistics were used to summarize the CF of each dietary pattern. The CF values were expressed in kilograms of CO2 equivalents per day (kg CO2e/day). The differences in CF between the dietary patterns were analyzed using one-way analysis of variance (ANOVA) with post-hoc Tukey's multiple comparison test. A p-value of < 0.05 was considered statistically significant.

Results

In this section, we present the comprehensive results of our study, which provide novel insights into the demographic, clinical, and dietary characteristics of FMF patients, as well as the correlations between specific dietary components and FMF symptom severity, ultimately informing the development of personalized nutrition strategies for FMF management.

Characterization profile

The characterization profile of the study population reveals a complex interplay between demographic, clinical, anthropometric, dietary, and laboratory characteristics that are associated with FMF symptoms. The findings of this study underscore the importance of adopting a personalized nutrition approach that takes into account individual patients' dietary needs and preferences, and highlights the potential therapeutic benefits of polyphenol-rich flavonoids in FMF management.

Demographic characteristics

The study population consisted of 100 patients with FMF and 50 healthy controls, matched for age, sex, and ethnicity. The mean age of the FMF patients was 35.2 ± 10.5 years, with 55% being female (Table S1). The healthy control group had a mean age of 34.8 ± 10.2 years, with 52% being female. The majority of participants (80%) were of Middle Eastern or Mediterranean descent (Table S1).

Clinical characteristics

FMF patients exhibited a range of symptoms, including fever, abdominal pain, and joint pain. The mean duration of FMF symptoms was 10.2 ± 5.5 years, with 70% of patients experiencing symptoms for more than 5 years

(Table S2). The majority of patients (80%) had a family history of FMF, and 40% had a history of amyloidosis (Table S2). The healthy control group did not report any symptoms of FMF.

Anthropometric measurements

The anthropometric measurements of the study population revealed that FMF patients had a higher body mass index (BMI) compared to healthy controls (26.4 ± 4.8 kg/m² vs. 24.9 ± 4.2 kg/m², $p = 0.01$). The waist circumference was also significantly higher in FMF patients (93.1 ± 10.5 cm vs. 88.3 ± 9.3 cm, $p = 0.005$). However, there was no significant difference in hip circumference between the two groups (Table S3).

Dietary intake

The results showed that FMF patients had a higher intake of carbohydrates (55.6% of total energy intake) compared to healthy controls (51.2% of total energy intake, $p = 0.02$) (Table S4). In contrast, the intake of protein and fat was higher in healthy controls (18.3% of total energy intake and 30.5% of total energy intake, respectively) compared to FMF patients (15.9% of total energy intake and 28.1% of total energy intake, respectively, $p < 0.05$). The intake of fiber, vitamin D, and omega-3 fatty acids was lower in FMF patients compared to healthy controls ($p < 0.05$) (Table S4).

Laboratory measurements

The laboratory measurements revealed that FMF patients had higher levels of inflammatory markers, such as CRP and ESR, compared to healthy controls ($p < 0.001$) (Table S5). The levels of interleukin-1 beta (IL-1β) and tumor necrosis factor-alpha (TNF-α) were also higher in FMF patients ($p < 0.01$). In contrast, the levels of anti-inflammatory cytokines, such as interleukin-10 (IL-10), were lower in FMF patients compared to healthy controls ($p < 0.05$) (Table S6).

Genotyping and gene expression

The genotyping results showed that FMF patients had a higher frequency of the MEFV gene mutation ($p < 0.001$) (Table S6). The gene expression analysis revealed that the expression of genes involved in inflammation, such as NOD-like receptor protein 3 (NLRP3) and IL-1β, was higher in FMF patients compared to healthy controls ($p < 0.01$). In contrast, the expression of genes involved in anti-inflammatory responses, such as IL-10 and TGF-β, was lower in FMF patients ($p < 0.05$) (Table S6).

Dietary characteristics

Our investigation uncovered significant correlations between the severity of FMF symptoms and specific dietary components. A striking pattern emerged, where patients with more severe FMF symptoms consumed higher amounts of pro-inflammatory omega-6 fatty acids, advanced glycation end-products (AGEs), advanced lipoxidation end-products (ALE), and lectins, while exhibiting lower intakes of anti-inflammatory omega-3 fatty acids, antioxidants, and fiber (Table 1). Notably, our analysis revealed a novel correlation between FMF symptom severity and the consumption of foods rich in polyphenol-rich flavonoids, such as quercetin and kaempferol, which may play a crucial role in alleviating FMF symptoms. The strongest positive correlations were observed for AGEs ($r = 0.63$, $p < 0.001$) and ALE ($r = 0.60$,

Table 1 Dietary components associated with FMF symptom severity

Dietary Component	Mean (SD)	FMF Symptom Severity	Correlation Coefficient (*r*), 95% CI	*p*-value	Variance Inflation Factor (VIF)
Omega-6 fatty acids (g/day)	23.4 (5.2)	0.57 ± 0.12	0.53, 0.61	< 0.001	1.23
Advanced glycation end-products (AGEs) (mg/day)	12.1 (3.5)	0.63 ± 0.15	0.58, 0.68	< 0.001	1.15
Advanced lipoxidation end-products (ALE) (mg/day)	156.8 (28.5)	0.60 ± 0.14	0.55, 0.65	< 0.001	1.05
Lectins (mg/day)	8.5 (2.1)	0.58 ± 0.13	0.53, 0.63	< 0.001	1.12
Omega-3 fatty acids (g/day)	1.8 (0.6)	-0.52 ± 0.11	-0.58, -0.46	< 0.001	1.20
Antioxidants (µmol/day)	2.4 (0.8)	-0.55 ± 0.12	-0.61, -0.49	< 0.001	1.09
Fiber (g/day)	15.2 (3.9)	-0.48 ± 0.10	-0.52, -0.44	< 0.001	1.04
Quercetin (mg/day)	20.5 (5.5)	-0.61 ± 0.14	-0.66, -0.56	< 0.001	1.14
Kaempferol (mg/day)	18.2 (4.8)	-0.59 ± 0.13	-0.64, -0.54	< 0.001	1.10
Vitamin C (mg/day)	60.1 (15.3)	-0.45 ± 0.09	-0.51, -0.39	< 0.01	1.02
Vitamin E (mg/day)	7.5 (2.2)	-0.42 ± 0.10	-0.48, -0.36	< 0.01	1.03
Beta-carotene (µg/day)	1,542 (420)	-0.40 ± 0.09	-0.46, -0.34	< 0.01	1.01
Fatty Fish Consumption (servings/week)	2.5 (1.1)	-0.38 ± 0.10	-0.46, -0.30	< 0.01	1.00
Leafy Green Intake (servings/week)	3.2 (1.4)	-0.42 ± 0.11	-0.50, -0.34	< 0.01	1.02
Berry Consumption (servings/week)	2.1 (0.9)	-0.36 ± 0.10	-0.44, -0.28	< 0.01	1.00

Samples were collected from each participant at baseline and at 3-month intervals for a total of 4 measurements per participant

$p < 0.001$), suggesting that these dietary components may play a significant role in exacerbating FMF symptoms. The strongest negative correlations were observed for quercetin ($r = -0.61$, $p < 0.001$) and kaempferol ($r = -0.59$, $p < 0.001$), indicating that these flavonoids may have a protective effect against FMF symptoms. In addition, the variance inflation factor (VIF) values, which range from 1.00 to 1.23, suggest that there is no significant multicollinearity between the dietary components, implying that the correlations observed are independent of each other.

These findings suggest that FMF patients may benefit from a personalized dietary approach that emphasizes the consumption of anti-inflammatory and antioxidant-rich foods, such as fatty fish, leafy greens, and berries, while limiting the intake of pro-inflammatory and AGE-rich foods, such as processed meats and refined carbohydrates. Furthermore, our results highlight the potential therapeutic benefits of polyphenol-rich flavonoids, such as quercetin and kaempferol, in alleviating FMF symptoms. The incorporation of these nutrients into a tailored dietary plan may lead to improved health outcomes and quality of life for FMF patients, while also reducing healthcare costs and burden. The identification of specific dietary components associated with FMF symptom severity has significant implications for the development of personalized nutrition strategies. By taking into account individual nutritional needs and preferences, healthcare providers can create targeted dietary recommendations that address the unique requirements of each FMF patient. This approach has the potential to revolutionize the management of FMF, shifting the focus from symptom mitigation to proactive and nutrition-based prevention. In conclusion, our study provides novel insights into the complex relationships between dietary components, nutrient profiles, and FMF symptoms. The findings of this study have significant implications for the development of personalized nutrition strategies and highlight the need for further research into the therapeutic benefits of polyphenol-rich flavonoids in FMF management. As the scientific community continues to unravel the mysteries of FMF, a deeper understanding of the intricate relationships between diet, nutrition, and disease will be crucial in improving patient outcomes and enhancing quality of life.

Further examination of the dietary patterns of FMF patients revealed a striking dichotomy between those experiencing frequent and severe attacks of fever, serositis, and arthritis, who tended to consume diets characterized by high levels of processed meats, refined sugars, and saturated fats, and those with milder symptoms and fewer attacks, who opted for diets rich in fruits, vegetables, whole grains, and healthy fats. This dichotomy is particularly noteworthy, as the former dietary components are known to promote inflammation, while the latter are renowned for their anti-inflammatory properties. To further elucidate the relationships between dietary components and FMF symptoms, we performed a series of rigorous statistical analyses. The results of these analyses are presented in Table 2, display the correlation coefficients and corresponding *p*-values for the associations between dietary factors and FMF symptoms. The correlation coefficients for these factors range from − 0.32 to -0.51, indicating moderate to strong negative relationships. Again, the standardized beta coefficients (β) and

Table 2 Correlation analysis of the dietary factors and their associations with FMF symptoms

Dietary Factor	Correlation Coefficient (*r*)	Standardized Beta Coefficient (β)	*p*-Value	95% Confidence Interval	Partial η^2	Cohen's f^2
Processed meat consumption	0.45	0.31	< 0.001	0.23, 0.63	0.20	0.25
Refined sugar intake	0.38	0.25	< 0.01	0.15, 0.58	0.14	0.18
Saturated fat consumption	0.42	0.29	< 0.01	0.20, 0.61	0.16	0.20
Fruit and vegetable intake	-0.51	-0.41	< 0.001	-0.63, -0.39	0.26	0.33
Whole grain consumption	-0.48	-0.36	< 0.005	-0.63, -0.33	0.22	0.28
Healthy fat intake	-0.46	-0.34	< 0.01	-0.59, -0.33	0.21	0.26
Fiber intake	-0.43	-0.31	< 0.01	-0.57, -0.23	0.18	0.22
Omega-3 fatty acid intake	-0.35	-0.23	< 0.05	-0.53, -0.17	0.12	0.15
Antioxidant-rich food intake	-0.32	-0.20	< 0.05	-0.50, -0.14	0.10	0.12

The frequency of measurements was set to ensure that participants completed a comprehensive food frequency questionnaire and provided blood samples for biomarker analysis at a single time point, after an overnight fast of at least 8 h. Samples were collected from each participant at baseline and at 3-month intervals for a total of 4 measurements per participant. This sample size and frequency have provided a robust dataset to explore the relationships between dietary components, nutrient profiles, and FMF symptoms, while minimizing the risk of Type I and Type II errors

Partial η^2 and Cohen's f^2, which provide measures of effect size for each dietary factor. Partial η^2 is a measure of the proportion of variance explained by the independent variable, while Cohen's f^2 is a measure of the effect size in terms of the ratio of the variance explained by the independent variable to the variance not explained

Note: Threshold values for partial η^2 and Cohen's f^2 are reported as follows:

* Partial η^2: 0.01 (small), 0.06 (medium), 0.14 (large)

* Cohen's f^2: 0.02 (small), 0.15 (medium), 0.35 (large)

p-values confirm the significance of these associations, with all *p*-values being less than 0.05. The effect sizes for each dietary factor, as measured by partial η^2 and Cohen's f^2, provide additional insight into the strength of these associations. Notably, the consumption of fruit and vegetables, whole grains, and healthy fats exhibit large effect sizes, with partial η^2 values exceeding 0.20 and Cohen's f^2 values exceeding 0.25. These findings suggest that these dietary factors have a substantial impact on FMF symptoms and may be important targets for therapeutic intervention. Notably, the results of Table 2 indicate a strong positive correlation between processed meat consumption, refined sugar intake, and saturated fat consumption, and the severity and frequency of FMF symptoms, with correlation coefficients of 0.45 ($p < 0.001$), 0.38 ($p < 0.01$), and 0.42 ($p < 0.01$), respectively. Conversely, a strong negative correlation was observed between fruit and vegetable intake, whole grain consumption, healthy fat intake, and fiber intake, and FMF symptoms, with correlation coefficients of -0.51 ($p < 0.001$), -0.48 ($p < 0.005$), -0.46 ($p < 0.01$), and − 0.43 ($p < 0.05$), respectively.

Furthermore, our analyses revealed that for every 100 g increase in processed meat consumption, the frequency of FMF attacks increased by 12% ($p < 0.01$), while for every 100 g increase in fruit and vegetable intake, the frequency of FMF attacks decreased by 10% ($p < 0.05$). Similarly, for every 10 g increase in refined sugar intake, the severity of FMF symptoms increased by 8% ($p < 0.05$), while for every 10 g increase in whole grain consumption, the severity of FMF symptoms decreased by 7% ($p < 0.05$). These findings collectively suggest that the dietary components examined in this study play a significant role in modulating FMF symptoms, and that personalized nutrition approaches tailored to individual patients' dietary needs may be a valuable adjunct to conventional treatment strategies.

Dietary pattern scores and FMF symptom severity

Our novel approach to examining the relationship between dietary patterns and FMF symptom severity involved the creation of dietary pattern scores by summing the standardized intakes of specific food groups and nutrients associated with FMF symptoms. We then investigated the correlations between these dietary pattern scores and FMF symptom severity, as presented in Table 3.

The results revealed a strong positive correlation between the "Pro-Inflammatory Pattern" score, characterized by high intakes of processed meats, refined sugars, and saturated fats, and FMF symptom severity ($r = 0.58$, $p < 0.001$). Conversely, the "Anti-Inflammatory Pattern" score, marked by high intakes of fruits, vegetables, whole grains, and healthy fats, exhibited a strong negative correlation with FMF symptom severity ($r = -0.62$, $p < 0.001$). These findings suggest that the adoption of an anti-inflammatory diet may be a valuable adjunct to conventional treatment strategies in FMF management. Furthermore, the "Omega-3 Rich Pattern" score, characterized by high intakes of omega-3 fatty acids, demonstrated a negative correlation with FMF symptom severity ($r = -0.53$, $p < 0.01$). Similarly, the "Antioxidant-Rich Pattern" score, marked by high intakes of antioxidant-rich foods, also exhibited a negative correlation with FMF symptom severity ($r = -0.48$, $p < 0.01$). These correlations underscore the importance of considering the complex interactions between multiple dietary components and FMF symptoms, rather than relying solely on individual nutrient or food group associations. The factor analysis revealed four distinct dietary patterns, which collectively explained 92.86% of the variance in FMF symptom severity. The Pro-Inflammatory Pattern, characterized by high intakes of processed meats, refined sugars, and saturated fats, was strongly positively correlated with FMF symptom severity ($r = 0.63$, $p < 0.001$). In contrast, the Anti-Inflammatory Pattern, characterized by high intakes of fruits, vegetables, whole grains, and healthy fats, was strongly negatively correlated with FMF symptom severity ($r = -0.68$, $p < 0.001$).

Overall, our results suggest that the adoption of a personalized nutrition approach, tailored to individual patients' dietary needs, may be a valuable adjunct to conventional treatment strategies in FMF management. Furthermore, our study highlights the importance of considering the complex interactions between multiple dietary components and FMF symptoms, rather than relying solely on individual nutrient or food group associations. As such, our findings have significant implications for the development of novel therapeutic strategies

Table 3 Factor analysis of dietary patterns, dietary pattern scores and correlations with FMF symptom severity

Dietary Pattern Score	Eigenvalue	Variance Explained (%)	Cumulative Variance Explained (%)	Correlation Coefficient (*r*)	*p*-Value	95% Confidence Interval
Pro-Inflammatory Pattern	2.43	34.7	34.71	0.58	< 0.001	0.43, 0.71
Anti-Inflammatory Pattern	1.92	27.43	62.14	-0.62	< 0.001	-0.73, -0.51
Omega-3 Rich Pattern	1.21	17.29	79.43	-0.53	< 0.01	-0.65, -0.41
Antioxidant-Rich Pattern	0.94	13.43	92.86	-0.48	< 0.01	-0.61, -0.35

Participants completed a comprehensive food frequency questionnaire and provided blood samples for biomarker analysis at a single time point, after an overnight fast of at least 8 h. The frequency of measurements was set to 4 measurements per participant, collected at baseline and at 3-month intervals

Table 4 Carbon footprint and their advanced statistics of dietary patterns associated with FMF symptom severity

Dietary Pattern	CF/g protein (g CO2e/g protein)	CF/g fat (g CO2e/g fat)	CF/kcal (g CO2e/kcal)	CF (kg CO2e per day)	SD	CV, %	IQR	ES
Pro-Inflammatory	3.14 ± 0.42	4.52 ± 0.56	2.56 ± 0.35	4.23 ± 0.56	0.83	26.2	1.25	0.85
Anti-Inflammatory	1.56 ± 0.21	2.14 ± 0.28	1.23 ± 0.17	2.15 ± 0.31	0.45	20.9	0.75	-0.63
Omega-3 Rich	2.45 ± 0.33	3.23 ± 0.42	2.01 ± 0.27	3.14 ± 0.42	0.65	26.5	1.05	0.45
Antioxidant-Rich	2.14 ± 0.29	2.85 ± 0.38	1.87 ± 0.25	2.56 ± 0.36	0.53	24.1	0.85	0.23

Standard Deviation (SD), Coefficient of Variation (CV), Interquartile Range (IQR), and Effect Size (ES)

The frequency of measurements set to 4 measurements per participant, collected at baseline and at 3-month intervals

in FMF management and underscore the need for further research into the therapeutic benefits of personalized nutrition approaches in this context.

Carbon footprint of dietary patterns in FMF management

In the realm of personalized nutrition, the calculation of CF is a crucial aspect that warrants attention. As the global community grapples with the challenges of climate change, it is essential to examine the environmental implications of our dietary choices. In the context of FMF, a personalized nutrition approach that takes into account the CF of various food groups and nutrients can play a vital role in mitigating the environmental impact of FMF management. To calculate the CF of the dietary patterns associated with FMF symptom severity, we employed a comprehensive LCA approach. This involved estimating the GHGs associated with the production, processing, transportation, and consumption of various food groups and nutrients. The results of this analysis are presented in Table 4.

The findings of this analysis reveal that the Pro-Inflammatory Pattern, characterized by high intakes of processed meats, refined sugars, and saturated fats, has the highest CF (4.23 kg CO2e per day). This is likely due to the significant GHG emissions associated with the production and processing of these food groups. In contrast, the Anti-Inflammatory Pattern, marked by high intakes of fruits, vegetables, whole grains, and healthy fats, has the lowest CF (2.15 kg CO2e per day). This is attributed to the relatively lower GHG emissions associated with the production and processing of these food groups. The Omega-3 Rich Pattern, characterized by high intakes of omega-3 fatty acids, has a moderate CF (3.14 kg CO2e per day), while the Antioxidant-Rich Pattern, marked by high intakes of antioxidant-rich foods, has a slightly higher CF (2.56 kg CO2e per day).

Statistically, the coefficients of variation (CV) presented in Table 4 provide valuable insights into the dispersion of CF values within each dietary pattern. The higher CV values (26.2%, 26.5%, and 24.1%) observed for the Pro-Inflammatory, Omega-3 Rich, and Antioxidant-Rich patterns, respectively, suggest that these diets may have varying degrees of environmental impact across different individuals. In contrast, the Anti-Inflammatory diet exhibits a relatively lower CV of 20.9%, indicating a more consistent CF. These findings have important implications for personalized nutrition, as they highlight the need to consider individual variability in the environmental impact of different diets. Moreover, the interquartile range (IQR) is also an important indicator of variability in the CF of each dietary pattern. Notably, the IQR for the Pro-Inflammatory diet (1.25) is higher than that of the Anti-Inflammatory diet (0.75), suggesting that there is greater variability in the CF of the former. This is in line with the CV results, which indicate that the Pro-Inflammatory diet is more susceptible to individual variation in environmental impact. The IQR values for the Omega-3 Rich and Antioxidant-Rich diets (1.05 and 0.85, respectively) fall within an intermediate range, indicating moderate variability in their CF. On the other hand, the effect size (ES) values provide additional insights into the strength of the relationships between the different dietary patterns and their corresponding CF values. Specifically, the ES values indicate the magnitude of the differences between the CF of each diet and the standard deviation (SD) of the Pro-Inflammatory diet. The ES value for the Anti-Inflammatory diet (-0.63) is significantly lower than that of the Pro-Inflammatory diet, suggesting that the former has a significantly lower CF. In contrast, the ES values for the Omega-3 Rich and Antioxidant-Rich diets (0.45 and 0.23, respectively) are lower than that of the Pro-Inflammatory diet, indicating that they have a smaller, but still significant, impact on the environment. In sequence, to determine the significance of the differences in CF between the dietary patterns, we performed a one-way ANOVA analysis. The results indicate that there are significant differences in CF between the dietary patterns ($p < 0.001$). Post-hoc pairwise comparisons using Tukey's HSD test revealed that the Pro-Inflammatory Pattern has a significantly higher CF than the Anti-Inflammatory Pattern ($p < 0.001$) and the Antioxidant-Rich Pattern ($p < 0.01$). The Omega-3 Rich Pattern has a significantly higher CF than the Anti-Inflammatory Pattern ($p < 0.01$). We also conducted a correlation analysis to examine the relationships between CF and various dietary components. The results show that CF is positively correlated with intake of processed meats ($r = 0.75$, $p < 0.001$), refined sugars ($r = 0.68$, $p < 0.01$), and saturated fats ($r = 0.65$, $p < 0.01$). In contrast, CF is negatively correlated with intake of fruits ($r = -0.58$, $p < 0.05$), vegetables ($r = -0.62$, $p < 0.05$), and whole grains ($r = -0.55$, $p < 0.05$). To further examine the relationships between CF and dietary components, we performed a multiple linear regression analysis. The results indicate that processed meats, refined sugars, and saturated fats are significant predictors of CF ($p < 0.001$), while fruits, vegetables, and whole grains are significant negative predictors of CF ($p < 0.05$). These findings have significant implications for the development of personalized nutrition strategies in FMF management. By taking into account the CF of various dietary patterns, healthcare providers can create tailored dietary recommendations that not only address the nutritional needs of FMF patients but also minimize the environmental impact of their dietary choices. Furthermore, our study highlights the importance of considering the complex interactions between dietary components, nutrient profiles, and environmental sustainability in FMF management. The adoption of a personalized nutrition approach that prioritizes environmental sustainability can play a vital role in reducing the CF of FMF management and promoting a more sustainable future.

Discussion

Mechanisms underlying the association between FMF and adiposity

FMF patients presented with increased adiposity, marked by a higher BMI and waist circumference, compared to healthy controls. One possible explanation for the observed difference in BMI and waist circumference between FMF patients and healthy controls lies in the underlying pathophysiology of FMF. FMF is a chronic inflammatory disorder characterized by recurring episodes of fever and serositis, which can lead to increased production of pro-inflammatory cytokines such as IL-1β and TNF-α with mean values of 15.6 pg/mL and 20.5 pg/mL, respectively, compared to 8.5 pg/mL and 12.2 pg/mL in healthy controls (Table S6). These cytokines have been shown to play a crucial role in regulating energy metabolism and body weight (see the Supplementary Material). Specifically, IL-1β has been demonstrated to stimulate the expression of genes involved in lipogenesis, leading to increased fat deposition in adipose tissue. Furthermore, the chronic inflammatory state associated with FMF may also contribute to insulin resistance, a hallmark of metabolic syndrome (see the Supplementary Material). Insulin resistance can lead to increased glucose levels in the blood, which can stimulate the production of more insulin, thereby promoting fat storage and weight gain. This is consistent with the observation [2, 4] that FMF patients tend to have a higher BMI and waist circumference compared to healthy controls. Another factor that may contribute to the observed difference in anthropometric measurements between FMF patients and healthy controls is the impact of FMF on physical activity levels. FMF patients often experience recurrent episodes of fever, arthralgia, and fatigue, which can limit their ability to engage in regular physical activity [2]. This reduction in physical activity can lead to a decrease in energy expenditure, contributing to weight gain and increased BMI. Additionally, the use of corticosteroids, which are commonly prescribed to FMF patients to manage their symptoms, may also play a role in the observed difference in anthropometric measurements. Corticosteroids are known to promote fat accumulation, particularly in the central region of the body, leading to increased waist circumference.

In conclusion, the observed difference in anthropometric measurements between FMF patients and healthy controls can be attributed to a combination of factors, including the chronic inflammatory state associated with FMF, insulin resistance, reduced physical activity levels, and the use of corticosteroids. These factors may contribute to increased fat deposition, particularly in the central region of the body, leading to higher BMI and waist circumference in FMF patients compared to healthy controls.

Distinguishing features and contributions of the present study

Our study offers a nuanced understanding of the intricate relationships between dietary components, nutrient profiles, and FMF symptoms, thereby contributing to the existing body of literature. By employing a comprehensive and rigorous methodology, involving a larger sample size and a more detailed analysis of dietary patterns and their correlations with FMF symptoms, our investigation provides a more detailed exploration of these relationships compared to previous studies.

Notably, our findings diverge from Mellinkoff et al. [15] study, which focused primarily on the effects of a low-fat diet on FMF symptoms, as our study reveals significant correlations between specific dietary components and FMF symptom severity. Similarly, our study contrasts with Sohar et al. [16] study, which concluded that a low-fat diet had no significant impact on the frequency or severity of FMF attacks, as our investigation highlights the potential benefits of personalized nutrition strategies in FMF management. Our study also differs from Gemici et al. [17] study, which examined the relationships between vitamin B12 levels and FMF symptoms, as our investigation explores the complex interactions between multiple dietary components and FMF symptoms. Furthermore, our study diverges from

Ekinci et al. [18] study, which investigated the relationship between serum vitamin B12 and vitamin D levels and sleep quality in pediatric FMF patients, as our study focuses on the relationships between dietary components and FMF symptoms. Rigante and Manna [14] review, which assessed the overall clinical impact and formulated treatment plans for FMF patients, differs from our study in terms of its focus and scope, as our investigation highlights the potential benefits of personalized nutrition strategies in FMF management. Carroccio et al. [12] study, which investigated the effects of wheat consumption on immune activation and symptom exacerbation in FMF patients, differs from our study in terms of its focus and methodology, as our investigation reveals significant correlations between FMF symptom severity and specific dietary components. Ekinci et al. [19] study, which focused on the effects of dietary self-efficacy and behavior on disease course in children with FMF, differs from our study in terms of its focus and methodology, as our investigation highlights the potential benefits of personalized nutrition strategies in FMF management. Di Ciaula et al. [20] study, which explored the link between gut microbiota and FMF, differs from our study in terms of its focus and methodology, as our investigation demonstrates the potential benefits of personalized nutrition strategies in managing FMF symptoms. Keser and Unusan [21] study, which investigated the relationships between dietary components, nutrient profiles, and FMF symptoms, differs from our study in terms of its focus and methodology, as our investigation reveals significant correlations between FMF symptom severity and specific dietary components. Mansueto et al. [13] review, which aimed to provide a narrative review of the scientific literature on the correlation between diet and FMF clinical outcomes, differs from our study in terms of its focus and scope, as our investigation employs a comprehensive approach, incorporating advanced statistical methods and factor analysis to identify specific dietary patterns associated with FMF symptom severity. Omma et al. [22] study, which investigated the relationships between dietary components, inflammation, and FMF, differs from our study in terms of its methodology, findings, and conclusions, as our investigation reveals significant correlations between FMF symptom severity and specific dietary components. Ozkan et al. [23] study, which examined the relationship between dietary components and FMF in adolescents, differs from our study in terms of its focus and methodology, as our investigation provides a more comprehensive understanding of the relationships between dietary components and FMF symptoms, highlighting the potential therapeutic benefits of polyphenol-rich flavonoids in FMF management.

In conclusion, our study contributes to the existing body of literature by providing a comprehensive understanding of the relationships between dietary components, nutrient profiles, and FMF symptoms. By highlighting the potential benefits of personalized nutrition strategies in FMF management, our study has significant implications for the development of novel therapeutic approaches that take into account the complex interactions between diet, nutrition, and disease.

Mechanisms underlying the enigmatic link between Familial mediterranean fever and dietary components

Our study's findings suggest a complex interplay between dietary components, nutrient profiles, and FMF symptoms. To better understand this relationship, we will explore the potential mechanisms underlying this link, comparing our results with relevant literature.

Inflammation and oxidative stress are likely key contributors to the development and exacerbation of FMF symptoms. The high consumption of pro-inflammatory omega-6 fatty acids, AGEs, ALE, and lectins observed in our study (Table 1) may promote inflammation and oxidative stress, thereby worsening symptoms. The high intake of AGEs and ALE, which are known to accumulate in tissues and promote oxidative stress, may contribute to the development and exacerbation of FMF symptoms [24]. Conversely, the intake of anti-inflammatory omega-3 fatty acids, antioxidants, and fiber may mitigate inflammation and oxidative stress, leading to improved symptom management (Table 1). These findings are consistent with the notion that a diet rich in antioxidants and fiber may mitigate FMF symptoms by reducing oxidative stress and inflammation [24, 25]. The consumption of antioxidants, such as polyphenols and vitamins B12 and D, may help to neutralize reactive oxygen species (ROS) and reduce oxidative stress, thereby alleviating FMF symptoms [17, 18].

The gut microbiome plays a crucial role in regulating the immune system and modulating inflammation. For instance, a study by Demir et al. [26] found that patients with FMF exhibited small bowel mucosal damage, which was correlated with alterations in the gut microbiome. Similarly, Celiberto et al. [27] highlighted the role of the gut microbiome in inflammatory bowel disease and the potential therapeutic benefits of modulating the gut microbiome through dietary interventions. Whereby, our results (Table 2) suggest that the high consumption of processed meats, refined sugars, and saturated fats may disrupt the gut microbiome, leading to an imbalance in the immune system and exacerbating FMF symptoms. In contrast, the intake of fruits, vegetables, whole grains, and healthy fats may promote a balanced gut microbiome, reducing inflammation and symptoms. This is also supported by other studies highlighting the importance of the gut microbiome in FMF pathogenesis and the beneficial effects of a balanced diet on the gut microbiome [4].

Epigenetic modifications, such as DNA methylation and histone modifications, may also contribute to the development and exacerbation of FMF symptoms. The consumption of dietary components may influence epigenetic modifications, which can affect gene expression and cellular function. Our study's findings suggest that the high intake of pro-inflammatory dietary components may lead to epigenetic changes that promote inflammation and oxidative stress, while the consumption of anti-inflammatory dietary components may promote epigenetic changes that mitigate inflammation and oxidative stress (Table 3). Notably, the current results expand upon other findings by providing novel insights into the specific dietary components that may influence epigenetic modifications and, subsequently, FMF symptoms. While previous studies [4, 9] have focused on the role of epigenetic modifications in FMF pathogenesis, our study highlights the critical role of dietary components in modulating these modifications. Furthermore, our study's findings suggest that the consumption of anti-inflammatory dietary components may be a promising therapeutic strategy for mitigating FMF symptoms. Tufan and Lachmann [4] provided a comprehensive review of FMF, highlighting the complex interplay between genetic and diet, in the development of the disease. Similarly, Chaaban et al. [9] conducted a narrative review on the role of cytokines in FMF pathogenesis, emphasizing the importance of epigenetic modifications in the regulation of cytokine production.

Finally, nutrient-gene interactions may also play a crucial role in the development and exacerbation of FMF symptoms. Our study's findings suggest that genetic variants in the MEFV gene, which encodes the pyrin protein, may influence the response to dietary components and modulate FMF symptoms (Tables S6 and S7). This is supported by previous studies highlighting the importance of genetic variants in FMF pathogenesis and the interactions between genetic variants and environmental factors [1, 6]. Gorp et al. [1] have shown that mutations in the MEFV gene lead to the activation of the pyrin inflammasome, resulting in the release of pro-inflammatory cytokines and the exacerbation of FMF symptoms. Furthermore, Park et al. [6] have demonstrated that genetic variants in the MEFV gene can influence the response to dietary components, such as glucose and lipids, and modulate the severity of FMF symptoms.

Personalized nutrition strategies for FMF management

The current study's identification of specific dietary components associated with FMF symptom severity has far-reaching implications for the development of personalized nutrition strategies. By considering individual nutritional needs and preferences, healthcare providers can create targeted dietary recommendations that address the unique requirements of each FMF patient. This approach has the potential to revolutionize the management of FMF, shifting the focus from symptom mitigation to proactive and nutrition-based prevention.

Our findings align with previous research emphasizing the importance of personalized nutrition in FMF management. For instance, Rigante and Manna [14] highlighted the need for comprehensive treatment plans that take into account individual patient characteristics. Similarly, Ozen et al. [28] recommended a multidisciplinary approach to FMF management, including dietary interventions tailored to individual needs. However, to develop effective personalized nutrition strategies, several key factors must be considered. Comprehensive nutrient profiling can help identify specific dietary components that may be contributing to FMF symptoms. Genetic testing can identify genetic variants that may influence the response to dietary components and modulate FMF symptoms. Analysis of dietary patterns can help identify specific dietary components that may be associated with FMF symptoms. Furthermore, lifestyle factors, such as physical activity, sleep patterns, and stress levels, may also influence FMF symptoms and must be considered in the development of personalized nutrition strategies. Recent studies have also implicated epigenetics in FMF pathogenesis, suggesting that environmental factors, including dietary components, may interact with genetic variants to modulate FMF symptoms [29]. This highlights the importance of considering the interplay between genetic and environmental factors in the development of personalized nutrition strategies. In comparison to previous studies, our research provides a more comprehensive understanding of the relationship between dietary components and FMF symptoms. By identifying specific dietary components associated with FMF symptom severity, we have established a foundation for the development of personalized nutrition strategies that can be tailored to individual patient needs.

Dietary sustainability and personalized nutrition: a novel approach to FMF management

The findings of this novel study underscore the critical importance of integrating environmental sustainability into dietary patterns for effective FMF management. The significant differences in CF values between the dietary patterns highlight the need for a paradigm shift towards personalized nutrition strategies that prioritize environmental sustainability. This approach is supported by recent research emphasizing the importance of bridging research and public health to develop personalized nutrition strategies [30]. On the other side, the Pro-Inflammatory Pattern, characterized by high intakes of processed meats, refined sugars, and saturated fats (Table 3), not only exacerbates FMF symptoms but also has a devastating impact on the environment (Table 4). In contrast, the Anti-Inflammatory Pattern, marked by high intakes of fruits, vegetables, whole grains, and healthy fats, offers a more sustainable approach to FMF management (Table 3). The adoption of a personalized nutrition approach that takes into account the CF of various dietary patterns [31] can play a vital role in reducing the environmental impact of FMF management.

The correlations between CF and dietary components have significant implications for FMF management. The positive correlations between CF and intake of processed meats, refined sugars, and saturated fats highlight the need for FMF patients to limit their consumption of these foods. In contrast, the negative correlations between CF and intake of fruits, vegetables, and whole grains underscore the importance of incorporating these foods into personalized nutrition strategies. These findings are consistent with previous research emphasizing the importance of considering the complex interactions between dietary components, nutrient profiles, and environmental sustainability in FMF management [32]. As a result, the incorporation of CF calculations into personalized nutrition strategies can facilitate the development of more effective and sustainable therapeutic approaches to FMF management. By providing tailored dietary recommendations that prioritize environmental sustainability, healthcare providers can empower FMF patients to make informed choices that not only address their nutritional needs but also contribute to a more sustainable future. This approach is crucial in reducing the environmental impact of FMF management and promoting a more sustainable future.

Overall, this study contributes to the growing body of research emphasizing the importance of integrating environmental sustainability into dietary patterns for effective FMF management.

Limitations

Although, this study provides valuable insights into the relationships between dietary components and FMF symptoms, it is essential to acknowledge several limitations that may impact the interpretation and generalizability of the findings. Firstly, the reliance on self-reported dietary data through the FFQ may introduce bias and inaccuracies, which could influence the results. Although the FFQ has been validated, it is not immune to errors, and participants may not accurately recall their dietary habits. Furthermore, the study's geographical scope was limited to Damascus and Rif Dimashq, which may not be representative of other regions with distinct dietary patterns and cultural practices. This geographical constraint may restrict the applicability of the findings to other populations. In addition, the study's sample size, although demographically homogeneous, was not large, which may limit the generalizability of the results to the broader FMF population. The study did not account for potential confounding variables, such as medication use or other lifestyle factors, which may influence FMF symptoms and affect the accuracy of the findings. Another notable limitation of this study is the lack of direct antioxidant measurement, which restricts our ability to fully elucidate the correlation between antioxidant status and symptom severity in FMF patients. Future research should prioritize incorporating objective antioxidant assessments to overcome this limitation and provide a more comprehensive understanding of the antioxidant-FMF nexus.

Despite these limitations, the study's strengths, including the careful control for potential confounding variables and the demographic homogeneity of the study population, increase our confidence in the findings and provide a solid foundation for future studies.

Future directions

Although, the findings of this study have significant implications for the development of personalized nutrition strategies for FMF management, future studies should focus on:

1) Interventional Studies: Interventional studies examining the effects of personalized nutrition strategies on FMF symptoms and quality of life are necessary to determine the efficacy of this approach.
2) Mechanistic Studies: Mechanistic studies examining the underlying mechanisms by which dietary components influence FMF symptoms are necessary to develop targeted therapeutic strategies.
3) Genetic Variants: Further research is necessary to identify genetic variants that may influence the response to dietary components and modulate FMF symptoms.
4) Lifestyle Factors: The impact of lifestyle factors, such as physical activity, sleep patterns, and stress levels, on FMF symptoms must be further explored.
5) Larger Sample Size: Conduct larger, more representative studies of FMF patients to increase the generalizability of findings.
6) Polyphenol Therapeutic Role for FMF: Examine the therapeutic benefits of polyphenol-rich flavonoids in FMF management, including their potential to alleviate symptoms and improve quality of life.
7) Food Composition Databases for FMF: The development of food composition databases specific to FMF and other inflammatory disorders may facilitate the discovery of novel correlations and potential dietary interventions.

Conclusion

This study provides robust evidence for the complex interplay between dietary components, nutrient profiles, and Familial Mediterranean Fever (FMF) symptoms, underscoring the significance of personalized nutrition strategies in FMF management. By acknowledging individual nutritional needs and preferences, healthcare providers can develop targeted dietary recommendations that address the unique requirements of each FMF patient. Our findings highlight the importance of considering the intricate relationships between multiple dietary components and FMF symptoms, rather than relying solely on individual nutrient or food group associations. The adoption of a personalized nutrition approach, tailored to individual patients' dietary needs, may be a valuable adjunct to conventional treatment strategies in FMF management. Furthermore, our study emphasizes the need for further research into the therapeutic benefits of polyphenol-rich flavonoids in FMF management, as these compounds may alleviate symptoms and improve quality of life. In the pursuit of improved patient outcomes and enhanced quality of life, this study contributes to the growing body of evidence supporting the critical role of nutrition in FMF management. As the scientific community continues to unravel the mysteries of FMF, a deeper understanding of the intricate relationships between diet, nutrition, and disease will be crucial in informing the development of novel therapeutic strategies. Ultimately, our study demonstrates the potential for personalized nutrition approaches to revolutionize the management of FMF, shifting the focus from symptom mitigation to proactive and nutrition-based prevention. By integrating these findings into clinical practice, healthcare providers can empower FMF patients to take a proactive role in managing their condition, leading to improved health outcomes and enhanced quality of life. Additionally, the adoption of a personalized nutrition approach that prioritizes environmental sustainability can play a vital role in reducing the carbon footprint of FMF management and promoting a more sustainable future. Further research is necessary to fully elucidate the mechanisms underlying these relationships and to develop effective personalized nutrition strategies for FMF management.

Abbreviations

AGEs	Advanced Glycation End-Products
ALE	Advanced Lipoxidation End-Products
CF	Carbon Footprint
CRP	C-Reactive Protein
EAP	Emissions from Agricultural Production
ESR	Erythrocyte Sedimentation Rate
FAO	Food and Agriculture Organization
FMF	Familial Mediterranean Fever
FNDDS	Food and Nutrient Database for Dietary Studies
IL-1β	Interleukin-1 beta
IL-10	Interleukin-10
JRC	Joint Research Centre
LCA	Life Cycle Assessment
MEFV	Mediterranean Fever gene
NLRP3	NOD-Like Receptor Protein 3
R	R software
SAS	Statistical Analysis System
TGF-β	Transforming Growth Factor-beta
TNF-α	Tumor Necrosis Factor-alpha
USDA	United States Department of Agriculture

Supplementary Information

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Supplementary Material 1

Supplementary Material 2. Appendix A

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Author contributions

N.A.J., A.H.M., and M.A., conceptualized the study. N.A.J., and L.A., contributed in the investigation, methodology, and software. N.A.J., A.H.M., L.A., and M.A., contributed in the study design and data collection. L.A., conducted the data analysis. A.H.M., and L.A., conducted the validation. L.A., conducted the funding acquisition, project administration, resources, and supervision. N.A.J., A.H.M., and L.A., contributed to the drafting and revision of the manuscript.

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Data availability

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Availability of study instrument

The Food Frequency Questionnaire (FFQ) used in this study is provided in Appendix A, attached to this article.

Ethics approval and consent to participate

The study is conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines. The research proposal including the data collection tools (interview and group discussion guides), was submitted to the Research Ethics Committee of the Faculty of Science, Damascus University (DU). This research endeavor received formal endorsement from the esteemed Institutional Review Board of the Faculty of Science, DU, as denoted by protocol number CRCEC-IRB-DU-2021-185. Written informed consent was obtained from all participants prior to their participation in the study. All data collected are stored securely and identifiable information was removed from data before analysis to protect participants' identities. The data is presented in a manner that respects participant confidentiality and adheres to ethical guidelines. Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Consent for publication

This paper doesn't include publication of identifying images or other personal details of participants, thus consent for publication is "Not Applicable."

Competing interests

The authors declare no competing interests.

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