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ORIGINAL RESEARCH—CLINICAL

Low Dietary Flavonoid Consumption Is Associated to Severe Inflammatory Bowel Disease

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BACKGROUND AND AIMS: Associations between diet habits and inflammatory bowel disease (IBD) have been widely described. Flavonoids are taken with vegetables, fruits, and green tea. Because of barrier-protective and anti-inflammatory effects, flavonoid consumption (FC) may influence the severity of IBD. The aim of this study was to reveal the role of FC in the course and severity of IBD. **METHODS:** A prospective cohort study including 204 IBD patients (Crohn's disease n = 126, ulcerative colitis n = 78) was conducted between 2016 and 2021. FC was calculated using questionnaires. In addition to standard activity scores and different treatments, a "severity index" was related to individual FC. Differences between groups and odds ratios were analyzed. **RESULTS:** Inverse correlation ($r = -0.0549$; $P = .01$) between FC and severity of IBD was found. Patients were assigned to 3 different severity index ranges: mild, moderate, and severe disease. FC of patients with severe disease (331 ± 330 mg/week) was less than FC of patients with mild (1404 ± 1086 mg/ week) disease ($P < .001$). The risk of IBD patients with low FC (1000 mg/week) experiencing overall severe disease was 17 times increased ($P < .001$) compared to patients with high FC (>1000 mg/week). Patients with UC and low FC had a 9.6-times higher risk for disease progression ($P < .001$). **CONCLUSION:** Consumption of dietary flavonoids and the overall severity of IBD are inversely correlated. Patients with mild diseases consume higher amounts of flavonoids than patients with severe diseases. Low dietary flavonoids were related to a considerable risk of severe IBD.

Keywords: Inflammatory Bowel Disease; Dietary Flavonoid Consumption; Overall Disease Severity; Activity of IBD

Inflammatory bowel disease (IBD) is an immune-mediated disease characterized by inflammation of the gastrointestinal (GI) tract. IBD encompasses both Crohn's disease (CD) and ulcerative colitis (UC).[1,2] These diseases share many common features but have distinctly different clinical characteristics.[3] The course of IBD is defined by alternating periods of remission and exacerbation,[4] while the burden depends on severity and manifestations.

The exact pathogenesis of the disease is not yet completely understood.[1,3] It is well accepted that the intersection between genetic, immune, and environmental factors plays a decisive role.[1] There is a consensus that IBD occurs in genetically predisposed subjects who exhibit a dysfunctional intestinal epithelium barrier with increased tight junction permeability. Patients develop an exaggerated immune response in the intestine toward intestinal microbiota, which is not controlled and leads to chronic intestinal inflammation.[5,6]

Diet is an environmental factor that has changed dramatically over the last century, and diet modifications were associated with an increase in the incidence of IBD around the world. The influence of diet and some of its components may be generated through several mechanisms: Altered pattern and function of intestinal microbiota may exert downstream effects on immune activity and also on permeability of the intestinal barrier.[7]

Flavonoid compounds are a large family of hydroxylated polyphenolic molecules. Flavonoids are found in many vegetables (broccoli, celery, root parsley, and tomatoes), fruits (apples, red grapes, oranges, strawberries, blueberries, and black chokberries), green tea, and olive oil. In contrast, the typical Western diet is characterized by high sugar, animal protein, and fat intake, especially n-6 polyunsaturated fatty acids, but reduced consumption of vegetables.

In the last 2 decades, much attention has been given to flavonoids and their proposed anticarcinogenic properties, especially regarding GI cancers.[8] Flavonoids have been suggested as a potential factor for the prevention and treatment of IBDs due to their anti-inflammatory effect.[6]

During the passage through the GI tract, digestion takes place, and flavonoids are metabolically broken down into smaller molecules. Flavonoids present in the intestine lumen bind to the toll-like receptor of the plasma membrane and are transported into the cytosol. Here, as ligands, they are attached to the Aryl hydrocarbon receptor (Ahr) and

Abbreviations used in this paper: **Ahr, Aryl hydrocarbon receptor; CD, Crohn's disease; FC, flavonoid consumption; GI-tract, gastrointestinal tract; HBI, Harvey-Bradshaw-Index; IBD, Inflammatory bowel disease; n.s., not significant; SI, severity index/severity indices; UC, Ulcerative colitis.**

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trigger translocation into the cell nucleus. The Ahr activates the target genes, which are transcribed into cytochrome P-450[9] and other protective enzymes. Additionally, regulatory T-cells and IL-22 are expressed and upregulated. The Ahr is localized mainly in lymphocytes and dendritic cells of the intestinal mucosa. Interleukin-22 is responsible for the intestinal integrity and the production of mucus and upregulation of beta-defensin-2.[9] The FN ligand is the major immune modulator and induces a beneficial pattern of cytokines and immune cells that counteract the inflammatory alterations of the intestinal mucosa.

Flavonoids may regulate the immune response by inhibiting reactive oxygen and nitrogen species generation, leukocyte migration, nuclear factor kappa B (NF-κB) activity, and reducing proinflammatory mediator production.[10] The imbalance between pro-oxidant and antioxidant mechanisms in IBD may be controlled in antioxidant treatment.[3,11]

In fact, flavonoids have shown efficacy in experimental models, and their mechanisms of action are similar to those described for drugs currently used in human therapy. However, translation of experimental data to its realization in humans and proof of efficacy in patients must yet be awaited.[10]

The aim of the present study is to add clinical knowledge to promising experimental data and to find out whether there is a correlation between the intake of flavonoids and the course and severity of the disease with IBD. If an association between the intake of flavonoids and the behavior of IBD is confirmed, this would stimulate interventional studies in patients.

Patients and Methods

Study Design

This is a prospective noninterventional cohort study. A questionnaire was given to a total of 204 consecutive patients with established IBD (125 with CD and 79 with UC) admitted to the 'Evangelisches Krankenhaus Kalk, Cologne, department of gastroenterology, a referral center for IBD, between January 2016 and March 2017. To complete the data, the medical history was followed until December 2020 using electronic records.

Patients

Patients with a change in their diet habits within 12 weeks prior to the study and indeterminate colitis or an unclear diagnosis were excluded from the study. Patients had to understand the diet questionnaire as checked by the attending doctor and answer it completely. Written informed consent was mandatory.

Questionnaire on Clinical Characteristics and Dietary Habits

A standardized questionnaire consisting of 7 pages was to be filled out by the patients. Clinical characteristics and details of the participating IBD patients were documented. In particular, questions for the kind of diet habits were included. Patients were asked about the frequency of dishes and drinks of flavonoid containing food and beverages during the past month.

In detail, the calculation of flavonoid consumption (FC) based on the United States Department of Agriculture database.[12] The database was created as a useful tool for flavonoid intake and health outcome studies for any population globally. It contains summarized data for 29 individual flavonoid compounds in 6 subclasses of flavonoids for every food in a subset of 2926 food items. We extracted from this file a list of 44 food items with the most relevant flavonoid content and developed a questionnaire (Table 1). The list included questions for 12 different fruits (apples, plums, peaches, strawberries, pomegranates, lemons, oranges, green kiwis, cherries, red grapes, bananas, and melons) and 17 different vegetables were listed, asking for the consumption of peas, carrots, beans, kohlrabi, cucumber, onions, garlic, tomatoes, salad, spinach, broccoli, plant egg, zucchini, mushrooms, sauerkraut, artichoke, and ginger. In addition, 12 different beverages were listed: green tea, black tea, fruit tea, orange/apple/grapefruit/cranberry juice, coffee, red wine, white wine, beer, and cocoa. A category called "other foods" included the consumption of chocolate (milk chocolate, chocolate with 50% cocoa content), nuts (macadamia, almonds, hazelnuts, and walnuts), and tofu.

The questionnaire (Table 1) asked for 6 different quantities of the intake of each of the 44 listed food items. Finally, the average FC was calculated in mg/100g and further expressed as the total flavonoid intake of each patient in mg/week.

Activity of Crohn's Disease and Ulcerative Colitis

Validated indices were applied by the attending physician to measure disease activity. Disease activity of patients with Crohn's disease was assessed by the Harvey-Bradshaw Index (HBI). This is a numerical index consisting of 5 clinical variables.[13]

The Simple Clinical Colitis Activity Index, consisting of scores for 5 clinical criteria, was used to determine disease activity in patients with UC.[14] Scores under 4 points were defined as clinical remission.

Severity of Crohn's Disease and Ulcerative Colitis

While disease activity reflects a cross-sectional assessment of biological inflammatory activity at a moment in time, disease severity gives a more complete picture of the overall burden of IBD. We assessed disease severity by means of recently developed severity indices (SIs) for CD and UC.[15] Both indices ask for multiple variables (CD = 11; UC = 8) including course of the disease and treatments, intestinal damage and complications, symptoms, biomarkers, and impact on daily life. According to a ranking, SI were created with scores ranging between 1 (mild severity) and 100 (most severe disease).

Table 1. Design of a Questionnaire on Flavonoid Consumption With Examples of Fruits as Consumed During the Last Month (Displaying Only Fruits as Examples)

Fruit	Never	Less than 1 dish/month	Min. 1–3 dishes/month	Min. 1 dish/week	Min. 2–4 dishes/week	Daily
Plumes						
Apples						
Oranges						
Strawberries						
Pomegranate						
Cherries						
Red grapes						
Bananas						

Ethics

The study was conducted in accordance with the Declaration of Helsinki and the International conference on Harmonisation guidelines of 'good clinical practice'. The protocol of the study and this work (processing number EK 11207200) was approved by the ethical committee of the Faculty of Medicine, Department of Clinical Pharmacology of the University of Dresden, Germany. The participants of this study were randomly recruited from outpatients of the GI-department of the Evangelic Hospital Köln Kalk, University of Cologne. The patients of this study gave their written formal consent to use the questionnaire for determination of the flavonoid uptake.

Statistical Analysis

All statistical analyses were performed using IBM SPSS Version 23 software (IBM Corp., Armonk, NY, USA). Descriptive analyses include absolute and relative frequencies for categorical variables and cross-tabulations with percentages. Metric variables were represented as mean value $\pm$ standard deviation. Normal distribution of flavonoid levels was tested using the Kolmogorov-Smirnov test. Between-group differences were assessed for continuous variables by Mann-Whitney-U-Test in two-group differences and Kruskal-Wallis-H-test in more than two-group differences. According to Pearson, a correlation was calculated between disease severity and flavonoid ingestion. Possible influences of variables on disease severity or flavonoid levels were examined with univariable linear regression. Two-sided significance level α is set to 5%.

All authors had access to the study data and reviewed and approved the final manuscript.

Results

A total of 204 patients with IBD, 125 with CD, and 79 with UC were included in the study. The age of the patients was in the range of 18–88 years. Additional details of patients are displayed in Table 2.

Dietary Intake of Flavonoids

A total mean content of 1008 mg of flavonoids per week was assessed in the diet of patients (n = 204). There was a considerably wide range between individuals from 17 mg/week up to 4864 mg/week. The weekly intake corresponds to 144 mg/day, meaning that an average of 4.3 g of flavonoids are consumed per month.

Females reported a significantly ($P = .02$) higher flavonoid intake of 1111 mg/week on average compared to men at 882 mg/week. The maximum flavonoid intake of 4660 mg/week (4.7 g/month) was observed in a female patient. The lowest flavonoid intake of just 17 mg/week is documented in a male Crohn`s patient. Table 3 displays current clinical characteristics and previous clinical events in relation to the weekly flavonoid intake. None of the variables listed is significantly related to either decreased or increased FC. In particular, the respective current disease activity did not show any relationship to altered flavonoid intake.

Dietary Intake of Flavonoids and Severity of IBD

The overall severity of the disease in individual patients was correlated to the severity score (16). Figure 1 displays a

Table 2. Biographic Data and Clinical Characteristics of Patients in the Study

	Total number of patients	Crohn's disease	Ulcerative colitis
Variable	n (%)	n (%[a])	n (%[a])
Patients	204	126 (62)	78 (38)
Male	91 (45)	48 (24)	43 (21)
Female	113 (55)	77 (38)	36 (18)
Bowel resection	42 (21)	37 (88)	5 (12)
Steroid-intake during last 4 wk	67 (33)	43 (64)	24 (36)
Immunosup-pression	124 (61)	83 (67)	41 (33)
Active disease	142 (70)	91 (64)	51 (36)
Clinical remission	62 (30)	34 (55)	28 (45)

[a]Percentage are calculated on the basis of total numbers of patients with the respective variable (100%).

Table 3. Dietary Intake of Flavonoids (Mean Flavonoid in mg/wk) in Patients With IBD

Variable	Flavonoid intake mean ± SD (mg/wk)	Flavonoid intake mean ± SD (mg/wk)	Difference *P*
Bowel resection	Variable existing 849 ± 1083	Variable not existing 1050 ± 996	.141
Steroid intake during last 4 wk	Variable existing 891 ± 932	Variable not existing 1190 ± 1113	.730
Immunosuppression	Variable existing 891 ± 932	Variable not existing 1190 ± 1113	.129
Clinical remission	Variable existing 1159 ± 1052	Variable not existing 957 ± 1000	.118

significant ($r = -0.055$; $P = .01$) inverse, nonlinear correlation. While weekly FC higher than 1000 mg/week is associated with mild disease, a strong correlation exists between FC below 1000 mg and an increase in the overall severity of IBD.

In order to further analyze the relationship between the severity of the disease and FC, patients with different SI of the disease were classified into 3 groups on the basis of an assigned point score: mild disease (scoring 1–19), moderate disease (scoring 20–39), severe disease (scoring $\geq$ 40) (Table 4). Again, the results confirm a clear relationship between disease overall severity and FC, while numbers indicate low flavonoid ingestion is associated with a more severe course of the disease.

In addition, 2 clinically relevant patient groups were compared: one group (SI 1–19) with mild severity, reflecting a course of the disease without major complications and long periods of clinical remission, and a second group (SI $\geq$ 20), reflecting a course of the disease with frequent flares, chronic activity, and major complications (Figure 2). Dietary flavonoid intake of patients with moderate to severe disease (SI $\geq$ 20) was almost a quarter of the flavonoid intake of patients with mild (SI $<$ 20) disease ($P < .001$).

Dietary Flavonoid Intake and Risk (Prognosis) for Severe IBD

The association between different amounts of dietary flavonoids and severity of the disease raises the question of whether there may be a relationship between flavonoid intake and disease prognosis. According to the correlation in Figure 1, we arbitrarily chose a threshold of 1000 mg/week intake. Low flavonoid intake was defined as consumption below this cutoff. As the patient groups with moderate (SI 20–39) and severe severity (SI $\geq$ 40) often comprised less flavonoid consumers, we compared weekly FC between patients with a SI $<$ 20 and a SI $\geq$ 20. The difference was highly significant ($P < .001$) in all groups (Figure 2). In addition, we calculated the risk ratios of a low-flavonoid diet for a combination of moderate and severe courses of the disease. The risk of IBD patients with a weekly flavonoid intake of $<$1000 mg experiencing a moderate to severe course of the disease was 17 times increased in comparison to patients with a high flavonoid diet of $>$1000 mg/week (odds ratio 17.2 [6.4; 45.4] $P < .001$).

Discussion

Our study demonstrates in individual patients an association between the type of diet and the overall severity of IBD. The weekly intake of flavonoids, a major ingredient of the so-called Mediterranean diet, was higher in patients with a milder form of IBD compared to the low consumption of flavonoids in patients with more severe disease.

Unselected IBD patients as studied here reported a mean amount of total flavonoids in their common diet of 1008 ± 1015 mg/week, corresponding to an average of 144 mg/day. There was no significant difference between CD and UC. To the best of our knowledge, no other detailed data has been published so far. Wide ranges of total flavonoid uptake have been observed in large population-based studies. Data from the Health Professional Follow-up Study and the Nurses' Health Study describe a medium total flavonoid intake between 223 mg and 247 mg per day.[16] The Danish Diet Cancer and Health Cohort shows flavonoid ingestion between 173 mg/day and 1201 mg/day depending on the subcohort investigated.[17] Apparently, certain characteristics of the population under different conditions influence the

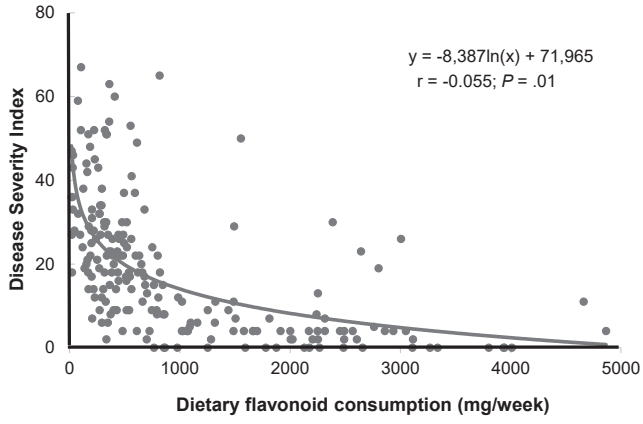


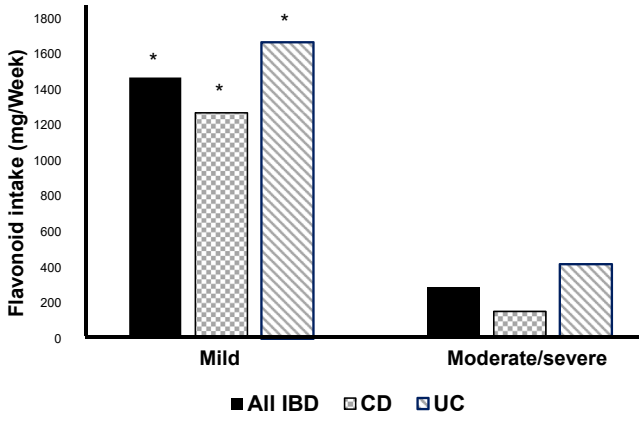
Figure 1. Correlation between severity of IBD and dietary flavonoid consumption.

Table 4. Mean Dietary Flavonoid Intake [mg/wk] in Relation to 3 Different Classes of Severity of IBD

	Mild disease	Moderate disease	Severe disease	
Variable	Mean ± SD (mg/wk)	Mean ± SD (mg/wk)	Mean ± SD (mg/wk)	Difference *P*
All IBD	1404 ± 1086 (n = 120)	474 ± 566 (n = 60)	331 ± 330 (n = 24)	<.001
Crohn's disease	1270 ± 971 (n = 79)	333 ± 194 (n = 39)	153 ± 124 (n = 8)	<.001
Ulcerative colitis	1667 ± 1255 (n = 41)	734 ± 874 (n = 21)	420 ± 367 (n = 16)	<.001

number of flavonoid uptakes. This perception is underlined when comparing different countries. The European Prospective Investigation into Cancer and Nutrition Cohort included 476,108 men and women from 10 European countries. The highest estimated median of total flavonoid intake in both sexes (females/males) occurred in Denmark (514/397 mg/day), while the lowest intake in women was observed in Norway (184 mg/day), respectively.[18]

Another reason for wide-ranging results may be caused by heterogeneous methods. The generalization of studies using dietary questionnaires is limited due to heterogeneity and nonvalidation. To make the best out of it, very detailed questionnaires were presented here and analyzed referring to an established database. Patients answered the questionnaires completely under the committed supervision of a doctor. We did not calculate the patient's overall food consumption, but significant changes prevented inclusion in the study. In fact, provided that patients consume meals with a similar percentage of dietary flavonoids then reduced food consumption would result in lower absolute amounts of flavonoid intake. But still, our study was designed to describe the association between the overall IBD severity and the absolute FC, irrespective of other dietary factors. Diet of female IBD patients contained a significantly higher amount of flavonoids, while age showed no relationship. Gender differences have been described in population-based studies.[19] History of IBD and previous bowel resections seem not to influence diet habits. Current therapy, steroid use, or immunosuppressants including biologics also showed no relationship to flavonoid uptake. It is noteworthy that current disease activity proved not to be related to any differences in diets as far as flavonoids are concerned.



*P < .001 for differences between mild and moderate/severe disease

Figure 2. Mean flavonoid intake in IBD patients. Mild disease (severity index 1–19); combined moderate and severe disease (severity index 20–39 and >40).

In a review of key studies addressing pathogenesis of IBD, Colombel and Mehandru highlighted the regulation of small and large intestinal barrier function by microbial, dietary, and immunological factors.[20] During the last decade, the beneficial properties of dietary polyphenols for intestinal function have been reported in several studies performed in cell culture models and experimental animals. A recent review describes in detail the current state of knowledge on the physiological relationship between polyphenols and barrier function.[21] Flavonoids may be of great utility in conditions of acute or chronic intestinal inflammation through different mechanisms including protection against oxidative stress, preservation of epithelial barrier function, and immunomodulatory properties in the gut. But the mainly experimental data need further studies in humans.[10]

Accordingly, given the physiological effects of flavonoids, it seems plausible that the beneficial impact of flavonoids from the daily diet, if any, may influence the long-term course of IBD. Established disease activity indices reflect a cross-sectional assessment of biological inflammatory activity at a moment in time. For this reason, we applied an alternative holistic approach consisting of a recently developed SI aimed to assess the long-term burden of CD and UC based on selected attributes that determine overall disease severity.[15] We found a significant inverse correlation between SI and patient`s flavonoid uptake. This finding is further underlined by the relationship between mild, moderate, and severe overall severity of both CD and UC and the amount of weekly-consumed flavonoids. Mild IBD had the highest flavonoid uptake, while consumption in moderate disease was low and lowest in patients with severe disease. Interestingly, low dietary flavonoids were related to a considerable risk of overall severe IBD, which may stimulate interventional trials in the future. In contrast to less accepted restrictive diets like low fermentable oligo-, di-, monosaccharides and polyols food, the advice to enrich meals with fruits, vegetables, and teas, even with chocolate and wine, may have good chances of being followed. This type of diet has demonstrated relevant bioavailability and relevant blood levels of polyphenols.[22] A plethora of studies have demonstrated beneficial effects of dietary flavonoids on diabetes mellitus, heart disease, and chronic

inflammation. A moderate habitual intake of flavonoids is inversely associated with all-cause, cardiovascular, and cancer-related mortality.[17]

As yet, a paucity of interventional studies on therapeutic effects of diets or nutritional supplements with flavonoids in IBD exists. Bioflavonoids such as a combination of apigenin and epigallocathechin-3-gallate have been available in clinical studies and serve as a beneficial source of flavonoids.[23,24] A three-armed, double-blinded, placebo-controlled pilot trial with 30 patients randomized found in active UC some therapeutic efficacy of epigallocathechin.[25] Therefore, it may be of interest to cast a glance at whether curcumins are as helpful as flavonoids when it comes to anti-inflammatory activity studies with curcumin. Curcumin is produced by plants of the Curcuma longa species. Chemically, curcumin is a diarylheptanoid, belonging to the group of curcuminoids, which are natural phenols but do not belong to the flavonoids.[26]

A significant limitation of the study is that it was conducted at a single tertiary center with a predominately Caucasian population; thus, the current findings may not be generalizable. Although 204 patients were included, larger numbers are necessary for confirmation. To exclude selection bias, multicentric cohorts would be advisable. Because this is an association study, the relationship may also go the other way. People who feel poorly may decrease their fruit and vegetable intake. So perhaps their disease was severe first, and then the patients decreased their flavonoid intake. However, the lack of association between the actual disease activity and FC argues against this possibility. Determination of the overall severity of the disease may not reflect actual severity of disease. In addition, to further analyze the effects of dietary polyphenols, more detailed dietary questionnaires asking for flavonoid subgroups might be of scientific interest. The disease SI as applied here is new and not yet widely established, but interestingly, a cutoff of $\geq$20 scoring points as applied here to separate mild from moderate to severe IBD agrees well with another validation study.[27]

Conclusion

Our *in vivo* study supports experimental data on beneficial effects of flavonoids. While current treatments are targeted at ongoing inflammatory reactions or prevention of flares, diets may influence the overall severity of IBD. Flavonoid-enriched diet favors a list of "do's" like vegetables and fruits, tea, and olive oil, but avoids strict "don'ts," which could facilitate satisfactory compliance. Nutritional supplements with stable flavonoid combinations can supply sufficient bioflavonoids and avoid flavonoid deficiencies.

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Authors' Contributions:
Beatrice Kölbel: study concept and design; acquisition of data; analysis and interpretation of data; drafting of the manuscripts; Stefanie Hamacher: statistical analysis; Martin Hellmich: statistical analysis; Wolfgang Kruis: study concept and design; acquisition of data; analysis and interpretation of data; drafting of the manuscripts; critical revision of the manuscript for important intellectual content; administrative and material support; study supervision.

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Data Transparency Statement:
All data underlying this article are available in the article.

Reporting Guidelines:
Helsinki Declaration.