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Original Article

Investigating the Efficacy of a Low-Histamine Diet for Reducing Cognitive 'Brain Fog' in Post-COVID Syndrome

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ABSTRACT

Background: Persistent cognitive difficulty is a common feature of post-COVID syndrome, and histamine-related inflammatory pathways have been proposed as one possible contributor. Objective: To evaluate whether a structured low-histamine diet improves cognitive performance and peripheral inflammatory biomarkers in adults with persistent post-COVID brain fog. Methods: This single-site, parallel-group randomized controlled trial was conducted in Chitral District, Pakistan, from June 2025 to January 2026. Sixty-four adults were randomized equally to a six-week low-histamine diet or habitual-diet standard care. MoCA, CFQ, FSS, plasma histamine and serum hs-CRP were assessed. Complete-case analyses included 60 participants. Results: Post-intervention MoCA scores were higher in the intervention group than in controls (26.2±1.8 vs 22.8±2.0; mean difference 3.40, 95% CI 2.42–4.38; $p<0.001$). Plasma histamine was lower by 13.30 ng/mL (95% CI −16.08 to −10.52), and hs-CRP was lower by 1.90 mg/L (95% CI −2.32 to −1.48; both $p<0.001$). CFQ and FSS scores were also lower in the intervention group. Time × group interactions were reported for MoCA and plasma histamine. Conclusion: A six-week low-histamine dietary programme was associated with improved cognitive and patient-reported outcomes and lower peripheral inflammatory biomarkers. Larger intention-to-treat trials with standardized diets and longer follow-up are required. Keywords: Biomarkers; C-Reactive Protein; Cognitive Dysfunction; Diet; Histamine; Post-Acute COVID-19 Syndrome.

INTRODUCTION

Post-COVID syndrome, commonly termed long COVID, encompasses persistent or newly emerging symptoms that continue beyond the acute phase of SARS-CoV-2 infection and affect multiple organ systems (1–3). Cognitive difficulties are among its most disabling neurological manifestations and are frequently described by patients as “brain fog.” These difficulties may include impaired attention, slowed information processing, memory lapses and reduced executive functioning, with consequent effects on occupational performance, daily activities and quality of life (4). However, subjective cognitive complaints do not always correspond directly with performance-based cognitive impairment and may also be influenced by fatigue, sleep disturbance, anxiety, depression and other persistent post-infectious symptoms.

The biological mechanisms underlying post-COVID cognitive dysfunction remain incompletely understood and are likely multifactorial. Proposed mechanisms include persistent immune activation, endothelial dysfunction, blood–brain barrier disruption, neurovascular abnormalities and dysregulated

inflammatory signalling (5). Preliminary clinical observations have also suggested that symptoms in some patients may respond to antihistamine treatment, raising interest in the possible contribution of histamine-mediated pathways (6). Other proposed mechanisms include mast-cell activation, altered microglial activity and persistent neuroimmune signalling, although these pathways remain under investigation and should not be considered established explanations for all cases of post-COVID cognitive dysfunction (7–9).

Mast cells release histamine and several other inflammatory mediators as part of the innate immune response. Persistent or dysregulated mast-cell activation has been proposed as one possible contributor to post-acute COVID-19 symptoms, including fatigue, cognitive complaints and autonomic manifestations (8). Circulating inflammatory mediators may influence neurovascular and immune processes, but peripheral histamine concentrations do not directly measure central histaminergic activity or neuroinflammation. Plasma histamine and serum high-sensitivity C-reactive protein may nevertheless provide complementary information regarding systemic inflammatory activity when interpreted alongside clinical and cognitive outcomes.

The interaction between diet, intestinal function, immune regulation and neurological symptoms has also received increasing attention in post-viral conditions (10). Histamine intolerance has been associated with an imbalance between accumulated histamine and the body's capacity to metabolize it, particularly through intestinal diamine oxidase activity (11,12). Dietary histamine is found in varying concentrations in fermented foods, aged cheeses, cured or processed meats and other foods affected by storage, maturation and microbial activity. Some foods have also been proposed to promote endogenous histamine release, although classifications vary considerably between dietary protocols and are not uniformly supported by clinical evidence.

A low-histamine diet aims to reduce exposure to foods containing high or variable histamine concentrations. Such diets have been used primarily in patients with suspected histamine intolerance or mast-cell-related symptoms, but food lists, restriction thresholds and intervention durations differ across clinical recommendations (11–13). High dietary histamine exposure may affect intestinal barrier and systemic inflammatory pathways in susceptible individuals, providing a plausible rationale for dietary modification (14). However, restrictive dietary interventions may also alter overall dietary quality, energy intake, food processing exposure and other nutritional factors independently of histamine. Consequently, any observed benefit must be interpreted as the effect of the overall dietary programme rather than definitive evidence of a histamine-specific biological mechanism.

Previous research on post-COVID cognitive dysfunction has largely focused on symptom characterization, neuroimmune mechanisms and pharmacological management (5,6,15,16). Although clinical guidance is available for the dietary management of suspected histamine intolerance, controlled evidence concerning low-histamine diets in post-COVID cognitive dysfunction remains limited (17). In particular, few studies have combined a performance-based cognitive assessment with patient-reported cognitive symptoms, fatigue outcomes and peripheral inflammatory biomarkers. This evidence gap limits the development of standardized nutritional recommendations for individuals experiencing persistent cognitive symptoms following COVID-19.

This randomized controlled trial therefore evaluated whether a structured six-week low-histamine dietary intervention improved cognitive performance in adults with persistent post-COVID brain fog compared with habitual-diet standard care. Change in Montreal Cognitive Assessment score was treated as the principal cognitive outcome. Patient-reported cognitive failures and fatigue, together with plasma histamine and serum high-sensitivity C-reactive protein concentrations, were evaluated as additional clinical and peripheral biomarker outcomes. It was hypothesized that participants assigned to the low-histamine diet would demonstrate greater cognitive improvement and larger reductions in peripheral inflammatory biomarkers than participants receiving standard care.

MATERIALS AND METHODS

A single-site, parallel-group randomized controlled trial was conducted in Chitral District, Khyber Pakhtunkhwa, Pakistan, between June 2025 and January 2026. The overall eight-month study period included participant screening, enrolment, baseline assessment, delivery of the dietary intervention and post-intervention assessment. Each enrolled participant completed a six-week intervention or control period. The study compared a structured low-histamine dietary programme with habitual-diet standard care among adults experiencing persistent cognitive symptoms following COVID-19.

Adults aged 18–60 years were screened for eligibility. Participants were eligible if they had a confirmed previous history of SARS-CoV-2 infection and reported persistent cognitive difficulty or "brain fog" for at least three months following the infection. Cognitive symptoms included difficulties with attention, memory, information processing or executive functioning. Individuals were excluded if they had a pre-existing neurological disorder, a severe psychiatric condition, known mast-cell activation syndrome, a history of substance misuse or current use of antihistamines, oral corticosteroids or immunomodulatory medication. These criteria were applied to reduce the potential influence of major neurological, psychiatric, pharmacological and mast-cell-related factors on cognitive and inflammatory outcomes.

The required sample was determined as 64 participants using a power analysis informed by effect estimates reported in related dietary-intervention research examining cognitive and systemic inflammatory outcomes. Following eligibility screening and baseline assessment, 64 participants were enrolled and assigned in a 1:1 ratio to either the low-histamine dietary intervention group or the habitual-diet control group, with 32 participants initially allocated to each group.

The random allocation sequence was generated electronically. Allocation concealment was maintained using sequentially numbered, opaque, sealed envelopes managed by an independent research assistant. The envelopes were opened only after completion of baseline assessment and participant enrolment. Blinding of participants and the dietitian was not feasible because the intervention required active dietary modification and counselling. However, outcome assessors, laboratory personnel and data analysts remained unaware of treatment allocation during outcome assessment, biomarker measurement and statistical analysis.

Participants assigned to the intervention group followed a structured low-histamine diet for six weeks. The programme restricted foods commonly classified as having high or variable histamine content, including fermented products, aged cheeses and cured meats. Spinach, tomatoes and selected citrus fruits were also excluded under the dietary protocol used in the study. Dietary restriction was accompanied by guidance on suitable lower-histamine food alternatives. The intervention was intended to reduce the overall dietary histamine load while maintaining an achievable daily eating pattern. The selection of restricted foods was consistent with established approaches to dietary management in suspected histamine intolerance, while recognizing that histamine concentrations vary according to food processing, maturation, storage and preparation (17,18).

Participants in the intervention group received biweekly nutritional counselling from a registered dietitian. Counselling reinforced the permitted and restricted food categories, supported meal planning and addressed difficulties with dietary adherence. Participants completed a three-day food diary each week throughout the intervention. Weekly telephone contact was used to review adherence and reinforce the assigned dietary programme. Adherence of at least 80% to the prescribed dietary protocol was considered acceptable, whereas adherence below this threshold was recorded as suboptimal.

Participants allocated to the control group continued their habitual diet and received standard post-COVID wellness advice without a prescribed dietary restriction. They were asked not to initiate a low-histamine or other therapeutic elimination diet during the six-week study period. Weekly telephone

contact was maintained to document continued participation and identify changes in health status or usual dietary practice.

Outcomes were assessed at baseline and after completion of the six-week intervention period. The principal cognitive outcome was performance on the Montreal Cognitive Assessment, a standardized cognitive screening measure covering attention, executive function, memory, language, visuospatial ability, abstraction, calculation and orientation. Higher scores represented better cognitive performance. Subjective cognitive difficulty was evaluated using the Cognitive Failures Questionnaire, with higher scores indicating more frequent cognitive errors in everyday activities. Fatigue was assessed using the Fatigue Severity Scale, on which higher scores represented greater fatigue-related functional burden.

Peripheral biomarker outcomes included plasma histamine and serum high-sensitivity C-reactive protein. Blood specimens were collected at baseline and after the six-week study period. Plasma histamine and serum high-sensitivity C-reactive protein concentrations were determined using enzyme-linked immunosorbent assay procedures. These measures were interpreted as peripheral systemic biomarkers and not as direct measurements of central nervous system inflammation.

Data were analysed using IBM SPSS Statistics version 26.0. Continuous variables were summarized as mean ± standard deviation, while categorical variables were reported as frequencies and percentages. Distributional normality was evaluated using the Shapiro–Wilk test. Baseline continuous characteristics were compared using independent-samples t-tests, and categorical characteristics were compared using an appropriate test of proportions.

Within-group changes between baseline and post-intervention assessment were evaluated using paired-samples t-tests. Between-group comparisons at the post-intervention assessment were performed using independent-samples t-tests, with mean differences and 95% confidence intervals reported for principal outcomes. A repeated-measures analysis of variance was used to assess the effects of time, treatment group and the time × group interaction. The interaction term represented the principal test of whether cognitive and biomarker trajectories differed between the intervention and control groups over the six-week period.

Pearson correlation analysis was conducted among participants in the intervention group to examine the relationship between reductions in plasma histamine and improvements in Montreal Cognitive Assessment scores. Histamine reduction was expressed so that a larger positive value represented a greater decrease from baseline, while cognitive improvement was expressed as the post-intervention Montreal Cognitive Assessment score minus the baseline score. All statistical tests were two-sided, and $p<0.05$ was considered statistically significant.

Baseline characteristics were evaluated using the complete randomized sample of 64 participants. Four participants did not complete the post-intervention assessment, leaving 60 participants, comprising 30 participants in each group, with complete baseline and follow-up data. Outcome and longitudinal analyses were therefore conducted as complete-case analyses using these 60 participants. No participant-level values were reconstructed or imputed for individuals without post-intervention outcome data.

RESULTS

A total of 115 individuals were screened for eligibility, of whom 64 were enrolled and randomly assigned in a 1:1 ratio to the low-histamine dietary intervention or habitual-diet control group, with 32 participants in each group. During the six-week study period, two participants in the intervention group discontinued because they were unable to maintain the dietary restrictions, and two participants in the control group were lost to follow-up after relocating outside Chitral District. Consequently, 60 participants completed the post-intervention assessment, representing an overall retention rate of 93.8%. Complete outcome data were available for 30 participants in each group.

Baseline demographic, cognitive and peripheral biomarker characteristics were summarized for all 64 randomized participants. The groups were similar in age, sex distribution, Montreal Cognitive Assessment score, Cognitive Failures Questionnaire score, plasma histamine concentration and serum high-sensitivity C-reactive protein concentration. The absolute standardized mean differences ranged from 0.09 to 0.18, indicating limited baseline imbalance across the reported variables.

Table 1. Baseline Demographic and Clinical Characteristics of the Randomized Sample

Characteristic	Total sample (N=64)	Intervention group (n=32)	Control group (n=32)	p-value	Standardized mean difference
Age, years	41.2 ± 8.4	40.8 ± 8.1	41.6 ± 8.7	0.710	−0.10
Female sex, n (%)	36 (56.3)	19 (59.4)	17 (53.1)	0.618	0.13
MoCA score	22.4 ± 2.1	22.3 ± 2.0	22.5 ± 2.2	0.712	−0.10
CFQ score	46.8 ± 7.5	47.2 ± 7.1	46.4 ± 8.0	0.673	0.11
Plasma histamine, ng/mL	32.5 ± 6.8	32.8 ± 7.1	32.2 ± 6.5	0.731	0.09
Serum hs-CRP, mg/L	4.2 ± 1.1	4.3 ± 1.2	4.1 ± 1.0	0.484	0.18

Data are presented as mean ± standard deviation unless otherwise stated. Standardized mean differences were calculated as intervention minus control; values for continuous variables used the pooled standard deviation. CFQ, Cognitive Failures Questionnaire; hs-CRP, high-sensitivity C-reactive protein; MoCA, Montreal Cognitive Assessment.

At the post-intervention assessment, participants assigned to the low-histamine diet had a higher mean MoCA score than participants in the control group. The unadjusted between-group mean difference was 3.40 points (95% CI 2.42 to 4.38; p<0.001), corresponding to a Hedges' g of 1.76. Plasma histamine was lower in the intervention group by 13.30 ng/mL (95% CI −16.08 to −10.52; p<0.001), while serum hs-CRP was lower by 1.90 mg/L (95% CI −2.32 to −1.48; p<0.001). The corresponding standardized mean differences were −2.45 for plasma histamine and −2.33 for hs-CRP.

Table 2. Post-Intervention Comparison of the Principal Cognitive and Peripheral Biomarker Outcomes

Outcome	Intervention group (n=30)	Control group (n=30)	Mean difference (95% CI)	p-value	Hedges' g
MoCA score	26.2 ± 1.8	22.8 ± 2.0	3.40 (2.42 to 4.38)	<0.001	1.76
Plasma histamine, ng/mL	18.6 ± 4.5	31.9 ± 6.1	−13.30 (−16.08 to −10.52)	<0.001	−2.45
Serum hs-CRP, mg/L	2.1 ± 0.7	4.0 ± 0.9	−1.90 (−2.32 to −1.48)	<0.001	−2.33

Data are presented as mean ± standard deviation. Mean differences and Hedges' g were calculated as intervention minus control using the reported complete-case aggregate values. Positive values for MoCA indicate higher scores in the intervention group; negative values for histamine and hs-CRP indicate lower concentrations in the intervention group. CI, confidence interval; hs-CRP, high-sensitivity C-reactive protein; MoCA, Montreal Cognitive Assessment.

The reported repeated-measures analyses demonstrated time × group interactions for MoCA and plasma histamine. For MoCA, the interaction was (F(1,58)=14.23), p<0.001, with a derived partial eta-squared of 0.20. For plasma histamine, the interaction was (F(1,58)=18.56), p<0.001, with a derived partial eta-squared of 0.24. These interaction estimates indicated that the pattern of change over the six-week period differed between the intervention and control groups for the two reported outcomes.

Table 3. Reported Time × Group Interaction Analyses

Outcome	F statistic	Degrees of freedom	p-value	Partial η²
MoCA score	14.23	1, 58	<0.001	0.20
Plasma histamine	18.56	1, 58	<0.001	0.24

Partial eta-squared was derived from the reported F statistic and degrees of freedom. MoCA, Montreal Cognitive Assessment.

Patient-reported outcomes were also lower in the intervention group at the post-intervention assessment. The mean CFQ score was 32.4 ± 5.9 in the intervention group and 45.1 ± 7.2 in the control group, producing an unadjusted mean difference of −12.70 points (95% CI −16.10 to −9.30; p<0.001). The corresponding Hedges' g was −1.90. The mean Fatigue Severity Scale score was 24.8 ± 4.6 in the

intervention group and 36.5 ± 5.8 in the control group, with a mean difference of −11.70 points (95% CI −14.41 to −8.99; p<0.001) and a Hedges' g of −2.21.

Table 4. Post-Intervention Comparison of Patient-Reported Outcomes

Outcome	Intervention group (n=30)	Control group (n=30)	Mean difference (95% CI)	p-value	Hedges' g
CFQ score	32.4 ± 5.9	45.1 ± 7.2	−12.70 (−16.10 to −9.30)	<0.001	−1.90
FSS score	24.8 ± 4.6	36.5 ± 5.8	−11.70 (−14.41 to −8.99)	<0.001	−2.21

Data are presented as mean ± standard deviation. Mean differences and Hedges' g were calculated as intervention minus control using the reported complete-case aggregate values. Lower CFQ and FSS scores represent fewer perceived cognitive failures and lower fatigue severity, respectively. CFQ, Cognitive Failures Questionnaire; CI, confidence interval; FSS, Fatigue Severity Scale.

Within the intervention group, a greater reduction in plasma histamine was moderately associated with a greater increase in MoCA score. The correlation coefficient was 0.48 (95% CI 0.14 to 0.72; p=0.007). This analysis indicates an association between the two changes but does not establish that the reduction in plasma histamine mediated the improvement in cognitive performance.

Table 5. Association Between Plasma Histamine Reduction and MoCA Improvement in the Intervention Group

Variables	n	Pearson's r	95% CI	p-value
Plasma histamine reduction and MoCA score increase	30	0.48	0.14 to 0.72	0.007

The confidence interval was calculated using Fisher's z transformation. Positive change values represented a reduction in plasma histamine and an increase in MoCA score. CI, confidence interval; MoCA, Montreal Cognitive Assessment.

DISCUSSION

This randomized controlled trial found that participants assigned to a structured six-week low-histamine dietary programme had higher post-intervention cognitive performance and lower peripheral histamine and hs-CRP concentrations than participants who continued their habitual diets. Patient-reported cognitive failures and fatigue severity were also lower in the intervention group. The reported time × group interactions for MoCA and plasma histamine further indicated different trajectories between the two groups during the intervention period. However, these findings were based on complete-case analyses of 60 participants and should be interpreted as preliminary evidence of short-term benefit rather than definitive proof of long-term clinical effectiveness or a histamine-specific causal mechanism.

The cognitive findings are relevant to emerging evidence that persistent cognitive symptoms after COVID-19 may involve interacting neurological, vascular and immune processes (5,9,16). Previous observational work has described improvement in selected long-COVID symptoms following antihistamine treatment, providing indirect support for investigating histamine-related pathways (6). Mast-cell activation and persistent release of inflammatory mediators have also been proposed as contributors to post-acute COVID-19 symptoms (7,8,13). Nevertheless, these mechanisms remain incompletely established, and the present study did not directly assess mast-cell activity, blood–brain barrier integrity, microglial activation or central nervous system inflammation.

The lower plasma histamine concentration observed in the intervention group is consistent with the intended biological target of the dietary programme. Histamine intolerance has been associated with impaired intestinal histamine degradation and increased sensitivity to histamine-containing foods, although diagnostic definitions and dietary thresholds remain heterogeneous (11,12,15). Histamine content may vary considerably according to food type, fermentation, maturation, storage and microbial contamination, making dietary exposure difficult to standardize (14,18). Clinical recommendations for suspected histamine intolerance therefore generally support individualized restriction followed by controlled reintroduction rather than indefinite broad elimination (17).

The simultaneous improvements in MoCA, CFQ and FSS scores suggest that the intervention may have influenced several related dimensions of post-COVID symptom burden. Improved MoCA performance may reflect changes in attention, memory or executive functioning, whereas lower CFQ scores indicate fewer perceived cognitive errors in daily life. Reduced fatigue may also have contributed to improved test performance and subjective cognitive functioning. Because fatigue, sleep quality, psychological symptoms and cognitive performance may influence one another, the available results cannot determine whether cognitive improvement occurred independently of broader symptomatic recovery.

The moderate association between plasma histamine reduction and MoCA improvement provides a possible link between physiological and cognitive change. However, correlation within the intervention group does not establish mediation or causal direction. Both outcomes could have been influenced by other components of the dietary programme, including reduced consumption of processed foods, changes in overall dietary quality, altered energy intake, participant expectations or increased contact with a dietitian. Peripheral histamine also does not directly represent histamine activity within the central nervous system.

The reduction in hs-CRP is compatible with a decrease in systemic inflammatory activity, but hs-CRP is nonspecific and may be affected by infection, body composition, metabolic health, physical activity and other dietary factors. The findings therefore support an association between assignment to the low-histamine programme and lower peripheral inflammatory markers, rather than confirming that dietary histamine reduction directly suppressed neuroinflammation. Further work incorporating more specific immunological measures and direct assessments of neurovascular or central inflammatory processes would be required to evaluate the proposed mechanism (20).

The potential clinical value of a dietary intervention lies in its accessibility and compatibility with multidisciplinary post-COVID rehabilitation. Nutritional programmes may be scalable when they use clearly defined protocols, trained counselling staff and monitoring procedures adapted to local dietary practices (19). However, broad dietary restriction may increase treatment burden and could compromise nutritional adequacy if implemented without professional guidance. The findings therefore support further structured evaluation rather than routine unsupervised adoption of a restrictive low-histamine diet.

The study had several strengths. Random allocation reduced systematic treatment-selection bias, while blinding of outcome assessors, laboratory personnel and data analysts reduced the risk of measurement and analytical bias. The inclusion of a performance-based cognitive assessment, patient-reported measures and peripheral biomarkers provided complementary perspectives on clinical and physiological change. Equal attrition in the two groups also reduced concern that differential loss to follow-up alone explained the between-group findings.

Several limitations should be considered. The study was conducted at one site in Chitral District and included a relatively small complete-case sample, limiting generalizability to populations with different dietary patterns, healthcare access and post-COVID characteristics. Participants and the treating dietitian could not be blinded, and the control condition was not matched for the intensity of nutritional counselling. Attention, expectation and behavioural-support effects may therefore have contributed to the observed differences.

The analysis excluded four randomized participants without post-intervention data and consequently did not constitute a full intention-to-treat analysis. The post-intervention comparisons were also unadjusted for baseline values, although the reported baseline characteristics were broadly similar. The use of self-reported food diaries may have introduced adherence-measurement error, and the six-week follow-up did not determine whether the observed changes were sustained. Repeated administration of MoCA over a relatively short period may also have introduced a practice effect, although the between-group design provides some protection against a practice effect shared equally across groups.

Finally, the intervention consisted of a broader dietary programme rather than an isolated manipulation of histamine exposure. The findings cannot distinguish the effects of reduced histamine intake from other dietary changes, and the reported outcomes do not establish the long-term nutritional safety of continued restriction. Larger multicentre trials should use a standardized and nutritionally balanced dietary protocol, an attention-matched comparator, prospectively defined outcome hierarchy, baseline-adjusted longitudinal models and longer follow-up. Evaluation of sleep, psychological symptoms, acute COVID-19 severity, reinfection, medication use, dietary quality and nutritional status would also help clarify treatment response and potential mechanisms.

CONCLUSION

A structured six-week low-histamine dietary programme was associated with higher cognitive performance, fewer self-reported cognitive failures, lower fatigue severity and lower peripheral histamine and hs-CRP concentrations than habitual-diet standard care among adults with persistent post-COVID brain fog. The findings support further investigation of professionally supervised dietary modification as a potential component of post-COVID rehabilitation, but they do not establish a histamine-specific mechanism, central anti-inflammatory effect or sustained clinical benefit. Larger preregistered trials using standardized interventions, active comparison conditions, intention-to-treat analyses and longer follow-up are required before routine clinical implementation can be recommended.

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