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Impact of elevated body mass index (BMI) on cognitive functioning and inflammation in persons with post-COVID-19 condition: a secondary analysis

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Original Article

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Abstract

Background: Individuals who have recovered from the acute stage of SARS-CoV-2 infection may be at risk of developing post-COVID-19 condition (PCC), characterised by a spectrum of persisting, non-specific, and functionally impairing symptoms across multiple organ systems. Obesity has been implicated as a risk factor for PCC, mediated by chronic systemic inflammation. The foregoing has also been separately reported to mediate cognitive dysfunction in PCC. *Methods:* This is a post-hoc analysis of a randomised, double-blinded, placebo-controlled clinical trial evaluating vortioxetine treatment for cognitive impairments in persons with PCC who received vortioxetine or placebo for eight weeks. This analysis comprises baseline data, examining the impact of BMI on cognitive functioning measured by the Digit Symbol Substitution Test (DSST) and Trails Making Tests (TMT)-A/B, as well as inflammation, via serum c-reactive protein (CRP) and erythrocyte sedimentation rate (ESR). *Results:* Complete data from 70 participants were statistically analysed and adjusted for age and sex. BMI was negatively correlated with performance on the DSST ($\beta = -0.003$, $p = 0.047$), TMT-A ($\beta = -0.006$, $p = 0.025$), and TMT-B ($\beta = -0.006$, $p = 0.002$). BMI was positively correlated with serum CRP (unstandardized $\beta = 0.193$, standardized $\beta = 0.612$, $p < 0.001$) and ESR ($\beta = 0.039$, $p < 0.001$) levels. *Conclusion:* We observed a significant negative correlation between BMI and cognitive functioning, and a significant positive correlation between BMI and inflammation in persons with PCC, suggesting a bidirectional interplay between BMI, PCC, and cognitive function; individuals with an elevated BMI may be at a greater risk of developing PCC and/or presenting with greater cognitive deficits mediated by chronic systemic inflammation.

Significant outcomes

- BMI is negatively correlated with cognitive performance on the DSST, TMT-A, and TMT-B in persons with PCC.
- BMI is positively correlated with inflammation as measured by serum CRP levels in persons with PCC.
- Findings suggest a bidirectional interplay between PCC, BMI and cognitive functioning which may be mediated by chronic systemic inflammation.

Limitations

- BMI, inflammation biomarkers, and cognitive functioning were pre-specified as a primary or secondary outcome.
- The sample size in this post-hoc analysis is relatively modest and would need to be replicated in a much larger dataset.
- We delimited our assessment of cognitive functioning to only the DSST and TMT-A/B; therefore, it is possible that our findings may have been expanded if we utilised other cognitive assessments.

Introduction

Post-COVID-19 condition (long COVID)

Severe acute respiratory syndrome-associated coronavirus-2 (SARS-CoV-2) was first discovered in November 2019 in China. The coronavirus disease 2019 (COVID-19) rapidly became a global pandemic, resulting in over 750 million confirmed cases globally (WHO, 2023). Recently, it has been reported that individuals who recovered from acute COVID-19 may present with persisting, non-specific distressing, and functionally impairing symptoms (Vimercati *et al.*, 2021). Specifically, approximately 10–20% of individuals who have been infected with SARS-CoV-2 experience this phenomenon, defined as post-COVID-19 condition (PCC) (Quinn *et al.*, 2022; Soriano *et al.*, 2022). Commonly reported symptoms include fatigue, cognitive impairment – difficulties with memory, concentration, and executive function –, depression, and anxiety (Sudre *et al.*, 2021; Lechner-Scott *et al.*, 2021).

Amongst the symptoms reported in PCC, two of the most common features of this condition are cognitive impairment and fatigue (Ceban *et al.*, 2022). Research has reported that 78% of patients previously infected with SARS-CoV-2 exhibit decreased performance in one or more cognitive domains (Almeria *et al.*, 2020). Furthermore, it is reported that cognitive function may be affected by circulating pro-inflammatory markers during the index hospitalisation admittance for COVID-19 (Almeria *et al.*, 2020). In addition, mediational and correlational analyses indicated that cognitive deficits are a principal mediator of impaired quality of life and function in persons with PCC.

Recently, multiple sociodemographic, clinical, and biological factors have been implicated as risk factors for PCC (Bonsaksen *et al.*, 2022). For example, multiple lines of evidence indicated that elevated body mass index (BMI) is a risk factor for acute COVID-19, and PCC (Vgontzas *et al.*, 2006; Theoharides *et al.*, 2015). Persons with a BMI ≥ than 30 kg/m^2 (obese) have a 10% greater risk of reporting long COVID symptoms compared to those with a BMI within the range of 18.5–24.9 kg/m^2 (Subramanian *et al.*, 2022). A separate line of research indicates that high fat diets are associated with symptoms of cognitive impairment, such as memory, learning, and executive functioning (Elias *et al.*, 2005). Furthermore, extant literature has reported that there is an association between long-term consumption of high fat diets and chronic activation of the immune system (Port *et al.*, 2021).

The pathophysiological changes resulting from the interactions between elevated BMI and COVID-19 are currently unknown and require further investigation; however, neuroinflammation is implicated in patients with high BMI and those diagnosed with PCC (Miller and Spencer, 2014; Song *et al.*, 2021). With the aim of characterising the pathophysiology and pathology of PCC, studies have been investigating central nervous system changes and immune system disturbances associated with SARS-CoV-2 infections in humans. Despite the absence of viral neurotropism, there is emerging evidence of SARS-CoV-2-induced hypoxia and inflammation in adults (Klein *et al.*, 2021). Consistently, in humans and animal models of COVID-19, findings indicate that SARS-CoV-2 infection induces a 'systemic antiviral response' which results in a sustained, pathological inflammatory state that persisted 'well beyond clearance of the primary infection' (Frere *et al.*, 2022). In individuals with obesity, increased concentrations of serum free-fatty acids and pro-inflammatory cytokines (e.g., IL-6) have been associated with not only chronic systemic inflammation, but also morphological and functional brain changes which are associated with cognitive impairment (Popko *et al.*, 2010; Ellulu *et al.*, 2017; Samara *et al.*, 2019; Dalkner *et al.*, 2020).

The association between obesity and PCC, alongside multidisciplinary data documenting adverse effects of obesity on measures of general cognitive function in the general population and patients, provides the impetus to evaluate the effect of BMI on measures of cognitive functions in a well-characterized cohort of individuals with PCC. Herein, we sought to determine the effect of BMI on objective measures of cognitive functions in adults with PCC. As a secondary aim, we also preliminary evaluated the potential mediational role of peripheral inflammatory markers on objective cognitive function in individuals with PCC.

Methods

The present post-hoc analysis utilises data derived from a primary randomised-controlled trial (RCT) (McIntyre *et al.*, 2023). The overarching aim of the primary RCT was to compare vortioxetine to placebo on measures of cognitive function in individuals with PCC. The paper reporting the top-line results of the original study is currently under review.

Recruitment

Participants currently residing in Canada were recruited for this double-blind, case-control study. Recruitment began in November 2021 and ended in January 2023. Participants were recruited by media advertisements (e.g., Facebook, Instagram, Twitter, print) or referrals by medical practitioners. The study was conducted in accordance with the principles of Good Clinical Practice (ICH, 2016) and the Declaration of Helsinki (WMA, 2008). A local research ethics board approved the trial design, and all eligible patients provided written informed consent before participating.

Participants and randomization

A total of 200 eligible participants were recruited for the clinical trial. Participants aged at least 18-years old, a resident of Canada, who had a documented history of SARS-CoV-2 infection with acute-COVID-19 symptoms and provided documentation of a positive SARS-CoV-2 test (i.e., PCR, antigen, or serology) at some point during the course of the acute illness were included. In lieu of a prior positive test, confirmation of a presumptive prior acute-COVID-19 case from a healthcare provider, including the study physician, was acceptable. Participants provided written informed consent at the time of screening and baseline and met the WHO

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definition for PCC [4]. To ensure that the foregoing criterion was met, participants were only included in the study if they met all the requirements in the eligibility criteria for more than three months from the confirmed onset of acute-COVID-19 symptoms. Participants were excluded from the study, during pre-screening and/or screening, if they met any of the exclusion criteria (Supplementary Materials A). Eligible participants were randomised (1:1) to receive either vortioxetine (5–20 mg/d) or placebo for eight weeks of the double-blind treatment. Randomisation was completed internally by blinded staff members. Further information on the clinical trial's study methodology can be found in McIntyre *et al.* (2023).

Study visits

Study visits were conducted remotely (e.g., zoom, telephone) or in-person. All visits with the study physician primarily occurred via a secure online platform (i.e., Ontario Telemedicine Network) or telephone. If requested or required, in-person visits with the study physician were scheduled.

Participants were pre-screened via telephone to ensure that they met the inclusion and exclusion criteria. A visit with the study doctor was scheduled if there were concerns regarding the participants' eligibility during pre-screening. If eligible, the participants were emailed the informed consent form prior to their screening visit. Once participants provided a written, informed consent, they underwent a comprehensive assessment to determine their eligibility during the screening visit. Female participants were also asked to confirm that they were not pregnant by providing a urine/blood sample to their local laboratory for testing. Following the screening visit, participant visits occurred at baseline/screening (week 0), and at weeks 2, 4, and 8. Participants were emailed a secure, unique, and anonymous RedCap link to complete self-report questionnaires remotely within 24 hours of their scheduled visit (before or after).

Outcome measures

To ensure that treatment effects did not confound the results, this post-hoc only analysed participants' screening (week 0) and baseline (week 1) data. Anthropometrics (e.g., weight and height) were measured by trained personnel at the study site for participants that could attend in-person. Remote participants self-reported anthropometric data to the research coordinators.

For all remote and in-person visits, cognitive functioning was measured via the CogState Online Cognitive Battery, including International Digit Symbol Substitution Test – Symbols (IDSST-S), Detection Test, Identification Test, and One Card Learning Test (CogState, n.d.). As the CogState Online Cognitive Battery was added to the protocol after the trial was initiated, some participants did not complete the cognitive battery during their in-person visits. During in-person visits, participants completed additional pen and paper cognitive tests including, the Digit Symbol Substitution Test (DSST), Rey Auditory Verbal Learning Test, and Trail Making Tests A/B (TMT-A/B) (Peaker and Steward, 1989; Tombaugh, 2004; Jaeger, 2018). Herein, we delimited our analysis to the DSST and TMT-A/B as these are two of the most frequently utilised psychometric tools in studies evaluating obesity-cognition relationships.

To examine immune system disturbances, participants were provided with lab requisition forms to complete standard clinical blood assessments (i.e., blood tests) to examine levels of inflammatory markers and concentration of serum granulocytes. These include the count of white blood cells, neutrophils, lymphocytes, monocytes, eosinophils, basophils, immature granulocytes, c-reactive proteins (CRP), and erythrocyte sedimentation rate (ESR).

Statistical analysis

All statistical analysis was conducted using SPSS, version 28.0.1.1. BMI was calculated using participants' baseline anthropometrics. Descriptive analysis was conducted to examine the mean and percentage of the population for each BMI group, including underweight (BMI $<$ 18), normal weight (18 $\leq$ BMI $\leq$ 24.9), overweight (25 $\leq$ BMI $\leq$ 29.9), and obesity (BMI $\geq$ 30) (CDC, n.d.). Generalised linear model (GLM) analysis, with a Poisson probability distribution, was conducted to examine the relationship between BMI, cognitive functioning (DSST and TMT-A/B), and inflammation (CRP and ESR). A linear regression analysis was conducted when the data was not collected in the form of whole integers. Participants' age and sex will be treated as covariates. Significance was be determined at $p < 0.05$.

Results

Participant demographics

The total sample size at the end of the clinical trial was 152; however, data from 7 participants were excluded from analysis due to missing anthropometrics. Furthermore, data from 75 remote participants were excluded from statistical analyses as they did not complete the DSST and TMT-A/B cognitive tests in person.

In the sample ($N = 70$), the mean BMI was 30.5 kg/m^2 (SD = 8.96). Specifically, 2.85% of participants were underweight ($n = 2$), 30.0% were normal weight ($n = 21$), 28.5% were overweight ($n = 20$), and 38.5% were obese ($n = 27$). Detailed descriptive statistics on participant demographics are provided in Table 1.

Impacts of BMI on severity of cognitive impairments and inflammation

GLM analysis was performed to examine the impacts of BMI on cognitive impairments after controlling for the covariates. Results from the GLM analysis indicate that, after adjusting for the covariates, BMI ($\beta = -0.003$, $p = 0.047$) and age ($\beta = -0.004$, $p < 0.001$) are statistically significantly negatively correlated with performance on the DSST (Table 2). Consistently, BMI is also statistically significantly negatively correlated with TMT-A ($\beta = -0.006$, $p = 0.025$) and TMT-B scores ($\beta = -0.006$, $p = 0.002$) (Table 2). Results also indicate that sex is statistically significantly negatively correlated with performance on the TMT-A ($\beta = -0.147$, $p = 0.002$) (Table 2).

Further GLM and linear regression analysis was conducted to examine the impacts of BMI on inflammatory levels after adjusting for covariates. GLM results indicate that BMI is statistically significantly positively correlated with ESR levels ($\beta = 0.039$, $p < 0.001$) levels (Table 2). In addition to BMI, there is also a statistically significant negative correlation between ESR levels and sex ($\beta = -0.485$, $p < 0.001$) (Table 2). Results from the linear regression analysis indicate that there is a statistically significant association between sex, age, BMI, and serum CRP levels ($r^2 = 0.412$, adjusted $r^2 = 0.385$, $df = 3$, $F = 15.201$,

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Table 1. Baseline participant demographics

Shapiro-Wilk Descriptives	N	%	Mean	Std. deviation	W	*p*
BMI	70		30.5	8.96	0.92	<0.001
Underweight	2	2.85	17.1	0.27		
Normal weight	21	30.0	22.5	1.75		
Overweight	20	28.5	27.9	1.59		
Obese	27	38.5	39.6	7.20		
Age	70		44.3	13.7	0.96	0.030
Sex	70					
Female	46	65.7				
Male	24	34.3				
DSST	70		67.3	15.2	0.98	0.760
TMT-A	70		29.7	24.8	0.42	<0.001
TMT-B	70		55.4	46.9	0.41	<0.001
ESR	70		12.6	11.7	0.83	<0.001
CRP	69		2.44	2.80	0.75	<0.001

BMI, body mass index; DSST, digit symbol substitution test; TMT-A, trail making test-A; TMT-B, trail making test-B; CRP, c-reactive protein; ESR, erythrocyte sedimentation rate.
a. Empty cells represent inapplicable information.

Table 2. Generalised linear model of the relationship between BMI, executive functioning, and ESR in persons with post-COVID-19 condition

DV	Model	β	Standard error	95% Confidence interval		*P*-value
				Lower	Upper	
DSST						
	BMI*	−0.003	0.0017	−0.007	−4.124E-5	0.047
	Age*	−0.004	0.0011	−0.006	−0.002	<0.001
	Sex	0.003	0.0308	−0.057	0.064	0.910
TMT-A						
	BMI*	−0.006	0.0025	−0.011	−0.001	0.025
	Age*	0.001	0.0016	−0.002	0.004	0.581
	Sex	−0.147	0.0475	−0.240	−0.054	0.002
TMT-B						
	BMI*	−0.006	0.0019	−0.009	−0.002	0.002
	Age	0.001	0.0012	−0.002	0.003	0.637
	Sex	−0.051	0.0342	−0.118	0.016	0.133
ESR						
	BMI*	0.039	0.0032	0.033	0.046	<0.001
	Age	0.001	0.0027	−0.004	0.006	0.719
	Sex*	−0.485	0.0804	−0.642	−0.328	<0.001

DV, dependent variable; BMI, body mass index; DSST, digit symbol substitution test; TMT-A, trail making test-A; TMT-B, trail making test-B; ESR, erythrocyte sedimentation rate.
*$p < 0.05$.

$p < 0.001$); however, only BMI is statistically significantly positively associated with serum CRP levels (unstandardized $\beta = 0.193$, standardized $\beta = 0.612$, $p < 0.001$) (Table 3).

Discussion

Key findings

In this secondary analysis, the relationship between BMI and PCC was investigated by examining factors related to neuroinflammation, including cognitive impairments and haematology markers related to inflammation. Herein, we observed a significant association between BMI and cognitive functions in individuals with PCC. Evidently, our data replicates the finding that while PCC is associated with a decrease in cognitive ability, a higher BMI in PCC leads to an exacerbation of objective cognitive deficits (Popko *et al.*, 2010; Ellulu *et al.*, 2017; Samara *et al.*, 2019; Sudre *et al.*, 2021; Lechner-Scott *et al.*, 2021; Subramanian *et al.*, 2022). Our data extends knowledge further by identifying BMI as a covariate that is significantly associated with measures of objective cognitive function. We observed a statistically significant finding using a reliable and valid measure of executive function (i.e., DSST) and processing speed (i.e., TMT-A/B).

Our observation of BMI influences on cognitive function coheres with multiple lines of evidence that have documented an obesity-cognition association. For example, in the general population, an association between BMI and cognitive performance as well as neurocognitive disorders has been replicated (Kim *et al.*, 2016; Michaud *et al.*, 2018; de Wit *et al.*, 2022). Separately, persons living with and/or at risk for mood disorders, a population known to have significant cognitive impairment evince greater cognitive deficits as a function of increased BMI (McIntyre *et al.*, 2017; Bora *et al.*, 2019). Moreover, bariatric surgery, a highly effective treatment for obesity, has been associated with improvements in cognitive performance (Thiara *et al.*, 2017).

In people with obesity, dysregulation of the endocrine homeostasis and subclinical inflammation of adipose tissue may interact with the impaired central inflammatory response, leading to neurodegeneration and cognitive impairment (Misiak *et al.*, 2012). Furthermore, it is well established that obesity and SARS-CoV-2 infection are each associated with inflammation, as evidenced by elevations in acute-phase reactants, cytokines, chemokines, complement, cell-adhesion molecules, and CRP (Popko *et al.*, 2010; Ellulu *et al.*, 2017; Samara *et al.*, 2019; Song *et al.*, 2021; Klein *et al.*, 2021; Frere *et al.*, 2022). It is also observed that the hazards of obesity on aspects of cognition, including executive functioning, are mediated by inflammatory markers. For example, in a well-characterized cohort of persons with bipolar disorder (mean age = 52; mean BMI = 27.6), CRP concentrations were a significant predictor of performance on TMT-B (Dalkner *et al.*, 2020). Separately, it has also been reported in PCC that peripheral inflammatory markers may mediate cognitive performance (Damiano *et al.*, 2023; He *et al.*, 2023). For example, in a cohort of persons previously infected with SARS-CoV-2, performance on TMT-A/B was worse amongst persons with an elevated BMI compared to normal weight individuals ($p = 0.047$). Moreover, within the COVID-19 group, performance on the TMT-A/B was statistically significantly negatively correlated with abnormally elevated tumour necrosis factor α (TNF-α) ($r = -0.19$, $p = 0.040$), a major regulator of inflammatory responses (Jang *et al.*, 2021; He *et al.*, 2023; Bradley, 2008). Consistently, the results from our secondary analysis reveal that BMI is significantly positively correlated with serum levels of ESR and CRP. This is consistent with results from previous studies indicating that in patients hospitalised for COVID-19, obese patients had higher peak levels of CRP and ESR compared to non-obese patients ($p < 0.01$) (McNeill *et al.*, 2021; Foulkes *et al.*, 2022). These findings

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Table 3. Linear regression model of the relationship between BMI and serum CRP levels in persons with post-COVID-19 condition

Model	Unstandardised coefficients		Standardised coefficients Beta	95% Confidence interval		t	*P*-value
	β	Standard error		Lower	Upper		
Constant	−3.485	1.509		−6.499	−0.471	−2.309	0.024
BMI*	0.193	0.030	0.612	0.133	0.253	6.419	<0.001
Age	0.025	0.019	0.122	−0.014	0.064	1.278	0.206
Sex	−0.764	0.557	−0.131	−1.877	0.348	−1.372	0.175

BMI, body mass index; CRP, c-reactive protein.
*$p < 0.05$.

support the hypothesis that there is greater systemic inflammation in patients with PCC who have an elevated BMI compared to those that have a lower BMI. The combination of findings from the present secondary analysis and previous literature suggests that the relationship between obesity and increased systemic inflammation may modulate the severity of cognitive impairments in persons with PCC.

Potential mechanism underlying obesity and SARS-CoV-2 infection interactions

Based on the existing evidence, this paper hypothesises that people with an elevated BMI will experience more severe post-COVID-19 symptoms. Following a SARS-CoV-2 infection, toll-like receptor activation results in increased secretion of pro-inflammatory cytokines, including interleukin-1 (IL-1), IL-6, tumour necrosis factor-, and type 1 interferon (Khanmohammadi and Rezaei, 2021). Therefore, this study proposes that compared to healthy individuals with obesity, those with comorbid acute-COVID-19 and obesity will have a higher concentration of circulating pro-inflammatory cytokines because of the additive effects of SARS-CoV-2 and progressive adipocyte enlargement resulting from a caloric excess (Ellulu *et al.*, 2017; Longo *et al.*, 2019). Previous work has shown that in individuals with obesity, the excess circulating free-fatty acids and cytokines enter the brain at the hypothalamus and initiate local inflammation (Miller and Spencer, 2014). This may not only induce synaptic remodelling and neurodegeneration in the hypothalamus, but also alter the internal hypothalamic circuitry and outputs to neighbouring brain regions (Miller and Spencer, 2014; Samara *et al.*, 2019). As a result, the increased concentration of pro-inflammatory cytokines may further induce local inflammation in brain regions, impact white-matter integrity, and decrease the functional connectivity between these regions. While the specific underlying mechanisms and the brain regions impacted are unknown, people with obesity and acute-COVID-19 may experience greater neuroinflammation and impairments to reward systems and hypothalamic regulatory pathways.

Limitations and avenues for further research

There are several methodological limitations that affect inferences and interpretations of our data. Based on findings from this study and available literature, individuals with an elevated BMI are at a greater risk of experiencing more severe acute-COVID-19 outcomes and developing PCC as a result of a stronger and more extensive systemic inflammatory response. Despite this, the results of the present study invite the need for further experimental studies that seek to characterise how obesity contributes to the systemic inflammation resulting from SARS-CoV-2 infections. As aforementioned, studies on animals and humans have found increased serum levels of pro-inflammatory cytokines resulting from both SARS-CoV-2 infections and obesity, independently (Ellulu *et al.*, 2017; Foulkes *et al.*, 2022). Furthermore, recent evidence suggests that the development of the post-COVID-19 condition may result from lasting and unique perturbations after recovery from SARS-CoV-2 infections (Frere *et al.*, 2022). However, it remains unclear whether having an elevated BMI increases the severity of PCC symptoms or is restricted to only increasing the likelihood of developing PCC after recovering from acute-COVID-19.

Firstly, our study is a post-hoc analysis and associations between BMI, inflammatory markers, and cognitive function was not a pre-specified primary or secondary outcome. Secondly, our sample size is relatively modest and would need to be replicated in a much larger data set. Thirdly, the results of our study are influenced by the eligibility criteria which excluded participants from participation if they met criteria for a current mental disorder. We also interpret this as potentially a strength of the study as our data are not confounded by additional comorbidities. Fourthly, we delimited our cognitive assessment to TMT-A/B and DSST. It is possible that our findings would have been different/expanded with different cognitive assessments. With respect to collection of inflammatory markers, we did not standardise time-of-day collection which could have also influenced study outcome.

Notwithstanding the limitations of our analysis, our data augment evidence-based evidence indicating that BMI significantly influences cognitive performance in persons with PCC. In light of the common occurrence of cognitive impairment in PCC and its contribution to functional outcomes and quality of life, there are significant implications for better characterising the neurobiological substrates of cognitive impairment in PCC for both prevention and treatment purposes. For example, our data provides preliminary support for recommendations to persons with PCC and increased BMI who are significantly impaired should be considered for cognitive assessment. It would be a viable and testable hypothesis that persons with PCC and increased BMI, who successfully lose and sustain excess weight, would demonstrate improvement on cognitive functions. The foregoing observation, along with beneficial effects on patient reported outcomes, would justify cognitive functions as a primary therapeutic target in persons PCC and elevated BMI.

Conclusion

Evidence from the findings, overweight and obese individuals with PCC experience more severe systemic inflammation. Despite this, a statistically significant relationship between BMI and cognitive

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impairment was only observed in performance on the TMT-A but not TMT-B and DSST. In combination with evidence from existing literature, these findings suggest that individuals with an elevated BMI may be at a greater risk for developing PCC and experiencing cognitive impairments as a result of chronic systemic inflammation. Further research is required to determine the underlying biological interactions between obesity and PCC, and how this impacts symptom presentation and severity.

Supplementary material. The supplementary material for this article can be found at https://doi.org/10.1017/neu.2024.16.

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Ethical statement. The study was registered on https://clinicaltrials.gov (NCT05047952) and the trial design was approved by Advarra (IRB#00000971), a local research ethics board. The protocol complies with Health Canada regulations, 21 CFR parts 56 and 312.3 and 45 CFR 46. The study complied with the principles outlined by the Declaration of Helsinki (WMA, 2008) and Good Clinical Practice guidelines by the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH, 2016). All participants in this study gave written informed consent prior to participation.

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