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The Effects of Time-Restricted Feeding on Handgrip Strength, Vigilance, and Perceived Anxiety and Depression in Older Adults: A Comparative Study Between Active and Sedentary Populations

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ABSTRACT

Background and Aims: Ramadan intermittent fasting (RIF), a form of time-restricted feeding, influences various physiological and psychological functions. However, its effects on older adults remain insufficiently understood. This study examined the impact of RIF on physical and mental health parameters, comparing active and sedentary older individuals. Specifically, we assessed handgrip strength (HGS), vigilance performance, anxiety, and depression levels to determine whether regular physical activity mitigates potential adverse effects of RIF.

Methods: Fifty-eight older adults (mean age 62.93 ± 3.99 years; 50% female) participated in this study. They were classified into an active group (n = 26) and sedentary group (n = 32) based on self-reported physical activity levels. Assessments were conducted before and during RIF and included HGS measurement using a handheld dynamometer, a digital psychomotor vigilance test, and validated questionnaires (General Anxiety Disorder-7, Geriatric Depression Scale, and Physical Activity Scale for the Elderly).

Results: During RIF, both groups showed significant improvements in vigilance, anxiety, and depression scores, with more pronounced benefits in the active group. However, sedentary participants experienced a decline in HGS, whereas active individuals maintained stable muscle strength.

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Conclusion: Regular physical activity during RIF appears to enhance vigilance and mental health while preventing muscle strength decline in older adults. These findings highlight the importance of maintaining an active lifestyle during RIF to support both physical and mental health in aging populations.

1 | Introduction

Aging is a multifaceted process characterized by progressive biological, physiological, and mental changes, ultimately increasing vulnerability to health complications [1–3]. One of the most prevalent consequences of aging is the decline in muscle strength and physical function, which significantly impacts mobility, independence, and quality of life [4]. Simultaneously, aging is often accompanied by a deterioration in mental health, as reflected in elevated levels of stress, anxiety, and depression—core components of mental health [5, 6]. Poor mental health has been found to contribute to accelerated physical decline, leading to a higher risk of frailty, falls, and disability [7].

Given the strong interrelation between mental and physical health, increasing attention has been directed toward identifying physical biomarkers that can serve as indicators of mental health in aging populations [8].

Handgrip strength has been recognized as a valuable biomarker for assessing overall health status, including mental health [8]. Lower HGS values have been associated with higher levels of depression and anxiety, whereas stronger grip strength has been linked to greater emotional resilience and mental stability [9]. This association has been attributed to the role of neuromuscular efficiency and systemic inflammation, both of which are directly connected to numerous mental health outcomes [7]. Furthermore, HGS has been widely recognized as a significant predictor of long-term health outcomes, including functional decline, frailty, and mortality risk in older individuals [10]. Given its ease of measurement and its ability to discern both physical and mental health, HGS has emerged as a critical tool for identifying individuals at an elevated risk of adverse health outcomes.

In addition to HGS, vigilance—defined as the capacity to sustain attention and to remain alert to stimuli over extended periods [11, 12] has been recognized as a cognitive function closely associated with mental health [13]. It is particularly sensitive to psychological states such as stress, anxiety, and depression. Moreover, vigilance constitutes a core component of executive functioning and plays a critical role in maintaining autonomy, functional capacity, and safety in everyday life, especially among older adults [14]. Despite its relevance, the influence of lifestyle-related factors, such as physical activity (PA) and nutritional habits, on vigilance performance in aging populations warrants further investigation.

In an effort to mitigate the age-related decline in muscle strength, cognitive function and mental health, several lifestyle interventions have been explored. Among these, intermittent fasting (IF) has gained substantial attention due to its potential to induce both metabolic and neurophysiological benefits [15]. One specific form of IF, religious intermittent fasting (RIF), is widely practiced for spiritual and religious reasons [16]. During RIF, healthy individuals abstain from food, drink, smoking, and other activities from dawn to sunset over a lunar month [17].

While several studies have examined the effects of RIF on metabolic health, its influence on mental health and functional status in aging populations remains controversial. Some findings suggest that RIF may alleviate symptoms of anxiety and depression, possibly due to its effects on stress regulation, circadian rhythms, and hormonal balance [18, 19]. However, other studies have reported no significant improvements in mental well-being following RIF [20]. Similarly, research on vigilance during RIF has yielded inconsistent results, particularly in middle-aged healthy adults [21, 22]. However, no studies have specifically examined its effects on vigilance in elderly populations, underscoring the need for further research. Furthermore, the impact of RIF on HGS has yet to be fully elucidated. While some evidence suggests that RIF does not significantly affect muscle strength in older individuals [23], the extent to which fasting-induced changes in mental health may influence or mediate grip strength remains unclear. Given the strong link between mental health and muscular performance [24], further research is warranted to explore whether RIF may modulate HGS through changes in anxiety and depression levels.

Beyond fasting, PA has been widely recognized as a crucial factor for maintaining muscle strength and mental well-being in older adults [25]. Regular PA has been shown to preserve HGS values, enhance neuromuscular function, and reduce the risk of sarcopenia [25]. In addition to its well-documented effects on muscle health, PA has been found to promote mental wellbeing by reducing stress, anxiety, and depressive symptoms [26]. Furthermore, PA contributes to improved reaction time and psychomotor performance, highlighting its role in supporting both physical and cognitive function [25]. Despite these established benefits, limited research has explored the combined effects of RIF and PA on HGS as a biomarker of mental health in aging populations. Given that both fasting and exercise independently influence metabolic, hormonal, and neuromuscular processes, investigating their potential synergistic impact on HGS and psychological well-being is essential for developing effective interventions for older adults.

Although various studies have examined the effects of RIF and PA separately, insufficient evidence exists regarding their combined influence on HGS as a biomarker of psychological health in aging populations. Addressing this gap is essential for understanding whether a structured lifestyle intervention incorporating both fasting and exercise could provide therapeutic benefits for mental well-being and muscle strength in older individuals. The present study aimed to (i) investigate the effects of RIF on anxiety, depression, and vigilance performance for active and sedentary older adults from before to during RIF, (ii) to examine the influence of RIF on HGS measures for active and sedentary older adults from before to during RIF, and (iii) to evaluate the relationships between HGS measures and behavioral alertness during a psychomotor vigilance test in active and sedentary older adults.

We hypothesized that active older adults would have a greater HGS measure and vigilance performance, and lower anxiety and depression scores than their inactive counterparts, from before to during RIF. Moreover, we hypothesized positive associations between HGS measures and vigilance performance in both groups would exist.

2 | Materials and Methods

2.1 | Participants

Out of 75 contacted older adults, seventy-one older adults expressed their willingness to participate in the present study (Figure 1). Eight subjects were excluded: three with visual disorders and five with neurological diseases (e.g., Parkinson disease). We identified 63 eligible older adults meeting the inclusion criteria: ≥ 60 years old, Islamic religion (*Sunnah*), having the Tunisian nationality, able to understand and speak Arabic language and able to fast during Ramadan. Active older people were required to have engaged in regular PA for at least 6 months before RIF. Due to their failure to complete all assessments, five participants were disqualified; two subjects contracted coronavirus disease 2019 (Covid-19) and three subjects missed more than one training session. Therefore, 58 right-hand dominant older people aged ≥ 60 years (62.9 ± 4.0 years; 50% female) were

included and categorized into two groups: control group (n = 32) who did not follow any training program before and during Ramadan, and active group (n = 26), who were engaged in at least 6 months of training before Ramadan and continued their respective training program while observing Ramadan. The characteristics of the participants are shown in Table 1. Some individuals had cardiovascular and/or chronic diseases. However, they were allowed to participate in the training program and/or fast during Ramadan without posing any danger to their health, per their physician's approval. The training program's compliance rate was 93.59%. To be included in the study, each subject provided written consent in accordance with the Declaration of Helsinki. Subjects were aware that they could withdraw from the study at any time. This investigation was approved by the research ethics committee CPP SUD N°0322/2021.

2.2 | Experimental Design

The present study was conducted in Tunisia in spring 2022, during the Ramadan month, which lasted from 02 April to 02 May. Two assessment sessions were carried out in the laboratory: 2 weeks before Ramadan (Mean temperature = $15^{\circ}C \pm 2.1^{\circ}C$; Mean humidity= $76\% \pm 10.2\%$), and during the fourth week of Ramadan month (Mean temperature = $18^{\circ}C \pm 1.0^{\circ}C$; Mean humidity = $72\% \pm 8.3\%$). All sessions were conducted in the afternoon (4:00–6:00 p.m.). About 11-12 h before their testing session during Ramadan, the participants consumed their last meal (i.e., *Suhur*) between 03:30 and 04:30 a.m. Physically active participants (i.e., active group) continued their physical training program while fasting throughout Ramadan at the same time as



FIGURE 1 | Flowchart illustrating the selection criteria and decision-making process for elderly participants undergoing ongoing assessments.

 TABLE 1
 I
 Demographic characteristics of the participants.

	Active group (n = 26)	Control group (n = 32)
Age (years) (Median [IQR])	61 [60; 63.5]	62 [60; 63.75]
BMI (kg/m ²) (Median [I	QR])	
Before-R	26.13 [22.86; 27.06]	26.63 [20.07; 28.28]
During-R	25.99 [22.6; 26.57]	26.37 [19.38; 28.63]
Sex [N (%)]		
Female	13 (50%)	18 (56.2%)
Male	13 (50%)	14 (43.8%)
Education attainment [N	[(%)]	
University	11 (42.3%)	7 (21.9%)
High school	9 (34.6%)	8 (25%)
Mild school	5 (19.2%)	12 (37.5%)
Primary school	1 (3.9%)	5 (15.6%)
Health status $[N(\%)]$		
Healthy	14 (53.8%)	19 (59.4%)
Chronic disease	12 (46.2%)	13 (40.6%)
Type 2 diabetes	5 (19.2%)	6 (18.8%)
Dyslipidemia	1 (3.8%)	1 (3.1%)
Cardiovascular diseases	6 (23.1%)	6 (18.8%)
(mainly arterial hyperten	sion)	

Abbreviations: BMI, body mass index; Before-R, before Ramadan; During-R, during Ramadan; IQR, Interquartile range; RIF, Ramadan fasting.

before (i.e., 5:30 p.m.), whereas the control group did not engage in any physical training activities. The physical training schedule encompassed three sessions per week of 1 h, interspersed with a recovery day. Each session began with 15 min warm up and finished with 10 min of stretching. The first session was based on team sports (i.e., volleyball or basketball), the second session included aquatic activities, while training circuits were carried out in the third session. Neither group experienced any fastingrelated side effects (e.g., headaches, hypoglycemia, or dizziness), thus reflecting the interventions feasibility. A similar evaluation process was performed by both groups, including an assessment of vigilance performance, based on validated digital psychomotor vigilance test [27]. Moreover, anxiety, depression, and physical and daily living activity were assessed with validated Arabic versions of the General Anxiety Disorder-7 (GAD-7) [28], the Geriatric depression scale (GDS) [29] and the physical activity scale for elderly (PASE-A) [30, 31]. HGS measures were evaluated with a handheld dynamometer.

2.3 | Psychomotor Vigilance Test (PVT)

PVT is a continuous 2-min attention task used to assess vigilance, and response speed to visual stimuli. During the test, participants are required to click on a box as soon as red numbers appear at random intervals. False starts (i.e., response times < 100 msec) are excluded from the final analysis, and the average response time is considered as the target variable [27].

2.4 | Handgrip Strength (HGS)

Muscle strength is measured using an analog handgrip with a calibrated dynamometer (T.K.K. 5401; Takei, Tokyo, Japan). Participants perform the test three times with both their non-dominant and dominant hands, with a 30-second rest period between assessments. HGS is determined by their maximum effort. To account for body mass influence, maximal HGS is standardized to the participants' body mass index (BMI) using the formula: Absolute handgrip strength (kg)/BMI (kg/m²) [32].

2.5 | General Anxiety Disorder-7 (GAD-7)

The Arabic validated version of the GAD-7 is used to evaluate anxiety levels. This seven-item test assesses the severity of GAD symptoms over the last 2 weeks [33]. Scores range from 0 to 21, withcut-points for mild, moderate, and severe anxiety at 5, 10, and 15, respectively [33].

2.6 | Geriatric Depression Scale (Gds)

Depression levels are assessed using the Arabic validated GDS-15 short version [29]. This 15-item questionnaire prompts participants to respond yes or no to statements about how they felt over the previous week. Scores of 0–4 are considered normal, 5–8 indicate mild depression, 9–11 suggest moderate depression, and 12–15 indicate severe depression, depending on age, education, and complaints [34, 35].

2.7 | Physical Activity Scale for the Elderly -Arabic Version (PASE-A)

The PASE is a validated and reliable instrument used in epidemiological studies to assess PA in older individuals [31]. It records the number of days per week and hours per day spent on various types of leisure activities. PASE scores are derived from the weighted frequency of 12 activity categories [30].

2.7.1 | Statistical Analysis

All statistical tests were processed using the statistical software STATISTICA (StatSoft, version 12, Paris, France). Values were presented as Mean ± SD for normally distributed data or as Median [IQR] for non-normally distributed data. The following formula was used to determine the variation (Δ) recorded from before to during Ramadan session: Δ = During Ramadan – Before Ramadan. The normality of the data distribution was verified using the Shapiro–Wilk test. The baseline characteristics of the participants (presented in Table 1), including sex, educational attainment, and health status, were compared between the two

groups using Pearson's chi-squared test. The non-parametric Mann–Whitney U test was performed as age and body mass index (BMI) were not distributed normally.

Handgrip nondominant scores were normally distributed across all tested variables. Therefore, a two-way mixed analysis of variance (ANOVA) was used with two groups (Control vs. Active) and two Ramadan sessions (Before Ramadan vs. During Ramadan). Then, a pairwise comparison was conducted using a Bonferroni post hoc test if the ANOVA revealed a significant interaction. Non-parametric tests were applied for other parameters for which normality could not be verified: The Mann-Whitney test was used to compare the means of the two groups before, during, and at the Δ level to analyze Ramadan \times Group interaction, whereas the Wilcoxon test was used to compare each group's comparison from before to during Ramadan. The significance for all analyses was set at p < 0.05. Effect sizes (ES) defined as partial eta-squared np^2 for the AN-OVA Group x Ramadan interaction, were used to assess the magnitude of significant findings [36]. The corresponding ηp^2 values for small, moderate, and large ES were demarcated at 0.01, 0.06, and 0.14, respectively [36]. Moreover, non-parametric partial correlation coefficients (i.e., Spearman's ρ test) were computed to investigate possible relationships between HGS and nHGS nondominant and dominant, and vigilance performance. The following assessment was given to the partial correlation coefficient *r*: < 0.19: no correlation; \ge 0.20 to \le 0.39: low correlation; ≥ 0.40 to ≤ 0.59 : moderate correlation; ≥ 0.60 to \leq 0.79: moderately high correlation; \geq 0.8: high correlation [37].

3 | Results

Regarding the participants' initial characteristics (Table 1), there were no significant differences between active and inactive participants.

The main results recorded before and during Ramadan are presented in Table 2. The two-way ANOVA (Ramadan × group) for handgrip nondominant scores revealed no significant Ramadan × group interaction ($F_{(1,56)} = 0.102$; p = 0.750; $\eta p^2 = 0.001$). Independent samples *t*-test revealed no significant differences between groups at any time period. Paired samples *t*-test showed that handgrip nondominant scores decreased significantly from before to during Ramadan in the sedentary group (p = 0.001), with no change in the active group (p = 0.132).

For the handgrip dominant values, the Mann–Whitney *U* test showed a significant difference between the two groups at Δ level (z = -2.833; p = 0.005), with a more pronounced decrease in the sedentary group (Δ HGS = -1.05 [-0.42; -3.6]) compared to active participants (Δ HGS = -0.4 [0.35; -2.1]). The Wilcoxon test showed HGS dominant decreased significantly in the sedentary group (p < 0.001), while there was no change from before to during Ramadan for the active group (p = 0.101).

Concerning the nHGS nondominant and dominant scores, no changes were recorded from before to during Ramadan for the active group whereas a significant decrease (z = -3.029, p = 0.002; z = -3.328, p = 0.001, respectively) were shown in sedentary group.

For vigilance performance, significant differences were observed in responses time between the two groups during Ramadan (z = -4.465, p < 0.001) and at Δ level (z = -2.056, p = 0.040), whilst no difference was observed before Ramadan. A significant increase of performance (i.e., lower responses time scores) from before to during Ramadan in reaction time was shown in the active (p < 0.001) and sedentary groups (p = 0.039), with a higher increase of performance in active compared to sedentary group (Δ response time = -94.5 [-63.5; -344] vs. -64 [20.75; -315], respectively).

A significant improvement was recorded from before to during Ramadan in the GAD-7 and GDS scores for active (p = 0.003; p = 0.010) and sedentary (p = 0.021; p = 0.010) older adults, with no significant difference between groups.

PASE-A scores differed significantly between the two groups before Ramadan (p < 0.001; r = 0.853), during Ramadan (p < 0.001; r = 0.827), and at Δ level (0.014; r = 0.321), with the lower values in the sedentary compared to the active group. Moreover, a significant decrease was shown between pre to during Ramadan in active (p < 0.001; r = 0.874) and sedentary (p < 0.001; r = 0.803) groups.

Spearman's ρ test revealed no significant correlation between HGS and nHGS nondominant and dominant, and vigilance performance for both groups (Supporting Information S1: Tables S1 and S2). Moreover, no other significant correlations were found between different studied variables.

4 | Discussion

This study represents a pioneering effort to assess the effects of RIF on anxiety, depression, vigilance performance, and HGS measures for active and sedentary older adults.

This study represents a pioneering effort to assess the effects of RIF on anxiety, depression, vigilance performance, and HGS measures for active and sedentary older adults. Before RIF, no significant differences were recorded in baseline scores for all parameters, except PASE-A scores, which could be explained by the physical training program started at least 6 months before the study in active group. During RIF, significant differences were shown in vigilance performance and PASE-A scores with greater values for physically active older adults. The two groups differed significantly at Δ level in PASE-A values, vigilance scores, HGS dominant, and nHGS nondominant and dominant, with greater performance in the active group. From before to during RIF, the sedentary group decreased significantly in HGS nondominant and dominant, and nHGS nondominant and dominant, whereas no change was shown in the active group for HGS and nHGS measures. Contrarywise, both groups revealed a significant increase in vigilance performance, whilst a significant improvement was recorded in GAD-7 and GDS scores, respectively, for active and inactive older adults. However, we found no significant correlations between vigilance response time scores, and HGS and nHGS measures.

Single studies revealed no effects of intermittent fasting on HGS measures in untrained adults [38, 39]. However, Bigard et al.

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		Me	dian [IQR]/Means :	±SD	Before-R		During	g-R	Φ	
					T test/		T test/Mann-		T test/Mann-	
Parameters	Groups	Before-R	During-R	Δ	Mann-Whitney	<i>p</i> -value	Whitney	<i>p</i> -value	Whitney	<i>p</i> -value
Total GDS	Active group	4.5 [7; 2]	3.5 [5; 2]a	-1 [0; -4]	z = -0.262	0.794	z = -0.613	0.540	z = -0.291	0.771
score (A.U)	Control group	5 [5.75; 2]	4 [5.75; 2]a	-1 [0; -3]						
Total GAD-7	Active group	6 [9; 3]	3 [5.75; 1]a	-3 [-2.25; -12]	z = -0.557	0.578	z = -1.377	0.168	z = -0.739	0.460
score (A.U)	Control group	8 [10.75; 1]	4.5 [7; 0]a	-3 [0; -10]						
HGS	Active group	24.87 ± 7.90	24.46 ± 7.10	-0.40 ± 1.32	t = 0.086	0.932	t = 0.589	0.559	t = 1.807	0.067
nondominant (kg)	Control group	24.71 ± 6.17	$23.52 \pm 5.04a$	-1.18 ± 1.85						
HGS dominant (kg)	Active group	27.3 [31.18; 12.3]	27.4 [30.63; 13.4]	-0.4 [0.35; -2.1]b	z = -0.039	0.969	z = -0.650	0.650	z = -2.833	0.005
	Control group	27.3 [30; 16.5]	25.55 [29.75; 16.9]a	-1.05 [-0.42; -3.6]						
- uon SDHn	Active group	0.93 [1.21; 0.47]	0.91 [1.18; 0.56]	0 [0.02; -0.12]b	z = -0.313	0.755	z = -0.797	0.425	z = -2.549	0.011
dominant (A.U)	Control group	0.95 [1.09; 0.39]	0.9 [1.03; 0.47]a	-0.04 [0; -0.21]						
nHGS	Active group	1.05 [1.2; 0.48]	1.06 [1.21; 0.56]	0 [0.02; -0.08]b	z = -0.188	0.851	z = -0.813	0.416	z = -2.924	0.003
dominant (A.U)	Control group	$0.97 \ [1.16; \ 0.56]$	0.94 [1.09; 0.57]a	-0.03 [0; -0.14]						
Vigilance response time (msec)	Active group	486 [514.75; 355]	340 [403.25; 277]ab	-94.5 [-63.5; -344]b	z = -0.524	0.600	z = -4.465	< 0.001	<i>z</i> = -2.056	0.040
	Control group	463 [611; 386]	450 [507.5; 358]a	-64 [20.75; -315]						
PASE-A scores (A.U)	Active group	150.31 [159.7; 143.8]b	123.02 [127.62; 100.89]ab	-36.85 [-17.63; -62.15]b	z = -6.496	p < 0.001	z = -6.301	p < 0.001	z = 2.447	0.014
	Control group	97.98 [121.78; 64.5]	79.72 [99.43; 63.12]a	-22.08 [-14.72; -28.63]						
Abbreviations: A.U, arbitra nondominant = handgrip : dominant, normalized han a. significantly different fro b. significantly different co	rry unit; Before-R, be strength nondomina. dgrip strength domi m before Ramadan mpared to control gi	fore Ramadan; During nt; HGS dominant, has nant; PASE-A, physica at $p < 0.05$. roup at $p < 0.05$.	g-R, during Ramadan; Δ ndgrip strength domina. I activity scale for elder ¹	, difference between dur nt, IQR, Interquartile rar ly in Arabic version.	ing and before Ramadan 1ge; kg, Kilogram; msec,	ı; GAD-7, Gener millisecond; nH	al Anxiety Disorder ⁻ GS, nondominant nc	7; GDS, Geriatric ormalized handg	Depression Scale; H ip strength nondomi	GS nant; nHGS

 TABLE 2
 Main findings before and during Ramadan for active and sedentary groups.

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[40] showed a decrease in muscular force in senior pilots during RIF, similar to present findings, in sedentary older adults. These findings may be attributed to reduced muscle protein synthesis, primarily caused by inadequate dietary protein intake, leading to potential alterations in the excitation-contraction coupling mechanism and the type II muscle fiber architecture crucial for anaerobic metabolism [41]. Regarding the active older participants, no changes were recorded from pre to during RIF in any HGS measures. These results are in line with the findings of Bouhlel et al. [42], also indicating a lack of significant alterations in HGS among trained men during RIF. The present findings highlight the potential effects of a continuous combined physical program that may have counteracted some harmful effects related to the inadequate dietary protein intake, maintaining muscular strength in physically active participants by positively influencing the type I and type II muscle fiber size [43]. Nonetheless, to avoid making decisions based on the often erroneously applied democratic principle of the majority, future studies on individual hormonal changes that depend on circadian rhythms and nutritional habits are warranted to bring more enlightenment in the understanding of these phenomena. Furthermore, our findings revealed a significant improvement in vigilance performance and mood status (i.e., less depression and anxiety) for both groups from before to during RIF. These results support the previous hypothesis that almost any form of fasting could be accompanied by greater alertness and subjective sensations of well-being, mood improvement, and, sometimes, feelings of euphoria [44, 45]. The enhancement in PVT scores in the two groups may be explained by a greater excitation of their respective dominant cerebral hemispheres [46]. In the case of right-handed individuals, the left hemisphere is usually the dominant side, responsible for overseeing language, speech, and fine motor skills. Consequently, during cognitive tasks like the PVT, the dominant hemisphere may play a significant role, leading to better performance [46]. This suggests that RIF positively influences the dominant areas of activation, predominantly the inferior parietal lobule and posterior parietal cortices that are dominant in the control of vigilant attention, more particularly, in a positive emotional situation devoid of sadness and anxiety-depressive disorders [46]. Furthermore, physically active individuals showed greater improvements in sustained vigilant attention than sedentary individuals, suggesting a positive effect of PA program adherence on vigilance performance [47] via the enhancement of brain-derived neurotrophic factor expression in the frontal cortex [48], with higher concentration in the dominant hemisphere compared to the nondominant [49]. This may explain the greater percent of increase in performance (i.e., lower response time scores) recorded in the active group, compared to the sedentary group, due to the combined effects of RIF and PA on the dominant hemisphere [50].

Furthermore, our study revealed RIF can have a beneficial impact on psychological factors, including stress and anxiety, for both groups, with greater scores in the active group, from before to during RIF. This suggests Ramadan may be associated with several lifestyle changes, besides fasting, such as having a spiritual dimension (i.e., Quran reading groups, and *Attarawih* prayers) and a social component (i.e., shopping, and social meetings), which may be absent from other types of fasting and may be beneficial for preventing depression and anxiety [51].

Whether the findings are moderated by cultural mindsets, for example, religions, has to be shown in more differentiated and interdisciplinary studies of individuals from various religions and/or nonreligious backgrounds. Because regular fasting is a crucial constituent of many cultures in their origins, the common and primary intention for people's health is at hand.

Tobacco abstinence, for instance, has been linked to reduced depressed symptoms during RIF [52]. Moreover, waking up for the predawn meal (i.e., Suhur) and dawn prayer in Ramadan period might shorten the sleep period for Muslim fasters. According to some studies, reduction in depressive symptoms is also linked to acute reduced sleep duration [53, 54]. However, a recent meta-analysis by [55], employing a methodologically rigorous approach, did not find conclusive evidence supporting the association between sleep deprivation and depressive outcomes. Therefore, investigating both main and side effects of extended sleep reduction, with a focus on recording daytime sleeping behavior is warranted. In this context, sleeping behavior during the day should be documented in future studies as well (actigraph and vigilance). These results are in line with previous studies revealing the potential effects of RIF on neuropsychological parameters, including anxiety and depressive symptoms [18, 56, 57]. Independent of cultural habits, regular PA in older individuals can help to reduce levels of anxiety and depression [26], suggesting older adults who engage in PA report higher levels of self-esteem, which helps with psychosocial growth and emotional balance [58].

Although vigilance was preserved, and even improved, due to the effect of RIF on the dominant hemisphere in both groups, HGS recorded a slight decrease in the active group and was significantly altered in the control group, suggesting that this decrease may not be related to the cognitive function decline but instead linked to an impairment of daily living activity score manifested by the decrease in PASE scores accentuated in sedentary subjects. This could explain the lack of associations between HGS measures and cognitive function (i.e., alertness) in both groups. Our results are in accordance with those of other studies revealing no association between HGS and nHGS nondominant and dominant, and executive function performance, including vigilance and sustained attention [32, 59].

4.1 | Limitations, Strengths, and Future Studies

Despite the novelty of our study, some limitations should be acknowledged and addressed in future studies. Coaches of the elderly individuals focused on maintaining the same duration and intensity in training sessions throughout the Ramadan month, as before RIF. Nevertheless, the reduction in PASE-A scores in both groups could not be attributed to the decline in PA level, particularly for the active group. This decrease in energy expenditure may be due to a change in daily habits (e.g., gardening, home organization). As such, it is advised to increase/maintain these everyday activities to regular frequencies. We advocate that future research should therefore evaluate and control these confounding factors. Despite the existence of numerous studies in the senior population confirming the strong association between hydration status, nutrition, and cognitive performance [60, 61], as well as between dietary intake and muscular strength [62], we did not investigate hydration status, and nutritional intake before and during RIF, as well as in predawn meal, and breakfast. Further investigations of these variables before and during RIF are needed. Furthermore, the absence of precise measurement of individual medication dosages among patients with chronic diseases in both active and sedentary groups represent another limitation in our study. However, despite the lack of detailed dosage information, it is important to note there was no observed difference in medication consumption profiles between the two groups. Strengths of this study include its pioneering approach to evaluating the effects of RIF on both physical and psychological parameters in older adults, as well as its inclusion of both active and sedentary participants. This design provides valuable insights into the potential benefits of PA in mitigating some of the adverse effects associated with fasting. Additionally, the study ensured that the number of participants with chronic diseases and their medication usage profiles were comparable between the two groups. This balance minimizes the risk of these factors disproportionately influencing the results, thereby enhancing the reliability of the findings.

For future studies, we recommend that researchers from countries practicing RIF explore the psychological impact of fasting across diverse cultural contexts. Such investigations could yield valuable insights, providing a broader perspective and enhancing the generalizability of findings. Additionally, future research should focus on the role of hydration, nutrition, and sleep patterns during RIF, as well as the long-term effects of fasting on physical and cognitive health in older adults. Investigating the impacts of several other cultural traditions using neurophysiological measurements is also warranted to identify possible underlying mechanisms. These areas of inquiry are critical for developing a more comprehensive understanding of the multifaceted impacts of RIF on health and well-being.

5 | Conclusion

Our findings indicate that RIF improves vigilance and reduces anxiety and depression in older adults, with greater benefits observed in those who are physically active. While HGS declined in sedentary individuals during RIF, it remained stable in the active group. These results suggest that regular, habitual PA during RIF helps preserve muscle strength and enhances mental health.

Author Contributions

Mohamed Ali Boujelbane: conceptualization, methodology, formal analysis, writing – original draft, writing – review and editing, investigation, data curation. **Khaled Trabelsi:** methodology, supervision, writing – review and editing, project administration, conceptualization. **Haitham Jahrami:** methodology, writing – review and editing, conceptualization. **Achraf Ammar:** methodology, writing – review and editing, formal analysis. **Mohamed Kerkeni:** data curation, writing – review and editing, formal analysis. **Amir Charfi:** writing – review and editing, data curation, visualization. **Omar Boukhris:** writing – review and editing, formal analysis, validation. **Cain C. T. Clark:** writing – review and editing, visualization. **Nicola Luigi Bragazzi:** methodology, writing – review and editing. **Wolfgang I. Schöllhorn:** writing – review and editing. **Jordan M Glenn:** resources, software, writing – review

and editing. **Hamdi Chtourou:** project administration; supervision, methodology, conceptualization, writing – review and editing.

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Ethics Statement

All participants provided written consent in compliance with the Declaration of Helsinki guidelines. Subjects were informed of their right to withdraw from the study at any time. This study was conducted under the approval of the research ethics committee CPP SUD N°0322/2021.

Conflicts of Interest

According to the authors, the study was carried out without any financial or commercial ties that might be viewed as a potential competing interest.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Transparency Statement

The lead author Achraf Ammar affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

References

1. D. Bartrés-Faz and N. L. Marchant, "Mental Health and Psychological Processes Associated With Cognitive Aging and Dementia," *Current Opinion in Neurology* 38, no. 2 (2025): 151–156.

2. B. S. Diniz, J. Seitz-Holland, R. Sehgal, J. Kasamoto, A. T. Higgins-Chen, and E. Lenze, "Geroscience-Centric Perspective for Geriatric Psychiatry: Integrating Aging Biology With Geriatric Mental Health Research," *American Journal of Geriatric Psychiatry* 32, no. 1 (2024): 1–16.

3. M. Mitina, S. Young, and A. Zhavoronkov, "Psychological Aging, Depression, and Well-Being," *Aging* 12, no. 18 (2020): 18765–18777.

4. N. E. Fritz, C. J. McCarthy, and D. E. Adamo, "Handgrip Strength as a Means of Monitoring Progression of Cognitive Decline—A Scoping Review," *Ageing Research Reviews* 35 (2017): 112–123.

5. J. M. Chonody, "Anxiety About Aging." Encyclopedia of Gerontology and Population Aging (Springer, 2022), 501–505.

6. I. Skoog, "Psychiatric Disorders in the Elderly," *Canadian Journal of Psychiatry* 56, no. 7 (2011): 387–397.

7. R. McGrath, N. Johnson, L. Klawitter, et al., "What Are the Association Patterns Between Handgrip Strength and Adverse Health Conditions? A Topical Review," *SAGE Open Medicine* 8 (2020): 2050312120910358.

8. R. G. Carson, "Get a Grip: Individual Variations in Grip Strength Are a Marker of Brain Health," *Neurobiology of Aging* 71 (2018): 189–222.

9. J. Firth, B. Stubbs, D. Vancampfort, et al., "Grip Strength Is Associated With Cognitive Performance in Schizophrenia and the General Population: A UK Biobank Study of 476559 Participants," *Schizophrenia Bulletin* 44, no. 4 (2018): 728–736.

10. A. A. Puiu, A. Botezatu, and E. Zbranca, "Handgrip Strength as a Biomarker of Aging: A Systematic Review," *Aging Research Reviews* 68 (2021): 101346.

11. J. S. Warm, "An Introduction to Vigilance," in *Sustained Attention in Human Performance*, eds. J. S. Warm (Wiley, 1984), 1–14.

12. J. S. Warm, "Vigilance and Target Detection," in *Workload Transition: Implications for Individual and Team Performance*, eds. C. D. Wickens and B. M. Huey (National Research Council, 1993), 139–170.

13. R. Langner and S. B. Eickhoff, "Sustaining Attention to Simple Tasks: A Meta-Analytic Review of the Neural Mechanisms of Vigilant Attention," *Psychological Bulletin* 139, no. 4 (2013): 870–900.

14. K. Brache, C. Scialfa, and C. Hudson, "Aging and Vigilance: Who Has the Inhibition Deficit?," *Experimental Aging Research* 36, no. 2 (2010): 140–152.

15. K. Gabel, C. M. Kroeger, J. F. Trepanowski, et al., "Differential Effects of Alternate-Day Fasting Versus Daily Calorie Restriction on Insulin Resistance," *Obesity* 26, no. 2 (2018): 547–554.

16. N. Shalihin and M. Sholihin, "Ramadan: The Month of Fasting for Muslim and Social Cohesion—Mapping the Unexplored Effect," *Heliyon* 8, no. 10 (2022): e10977.

17. N. Lessan and T. Ali, "Energy Metabolism and Intermittent Fasting: The Ramadan Perspective," *Nutrients* 11, no. 5 (2019): 1192.

18. H. A. Ghazi, A. M. Boughdady, and E. B. M. Elsayed, "Effect of Ramadan Fasting on Physical and Mental Health of Elderly People," *World Journal of Nursing Sciences* 4, no. 3 (2018): 56–65.

19. Y. Wang and R. Wu, "The Effect of Fasting on Human Metabolism and Psychological Health," *Disease Markers* 2022 (2022): 5653739.

20. T. Mirzaei, A. Ravari, F. Hoseini, et al, "The Effect of Ramadan Fasting on Elderly Muslims' Quality of Life," *Journal of Nutrition, Fasting and Health* 10, no. 1 (2022): 11–17.

21. S. Laraqui, N. Manar, O. Laraqui, A. Caubet, C. Verger, and C. H. Laraqui, "Influence Du Ramadan Vécu Sur La Vigilance Au Travail Chez Les Professionnels De Santé Au Maroc," *Archives des Maladies Professionnelles et de l'Environnement* 73, no. 5 (2012): 743–749.

22. S. Lotfi, I. Zerdani, A. Aggour, A. Fethidine, A. Tazi, and M. Talbi, "Effect of Ramadan Fasting and Triangular Exercise Progressive on the Vigilance, Mood and Blood Glucose in Trained Athletes," *Journal of Fasting and Health* 3, no. 3 (2015): 103–110.

23. S. Akın, F. F. Özer, G. G. Şahin, and N. T. Özer, "Effects of Ramadan Fasting on Lean Body Mass in the Older People," *European Geriatric Medicine* 11, no. 1 (2020): 163–168.

24. D. Bellón, M. Rodriguez-Ayllon, P. Solis-Urra, et al., "Associations Between Muscular Strength and Mental Health in Cognitively Normal Older Adults: A Cross-Sectional Study From the AGUEDA Trial," *International Journal of Clinical and Health Psychology* 24, no. 2 (2024): 100450.

25. A. Patti, D. Zangla, F. N. Sahin, et al., "Physical Exercise and Prevention of Falls. Effects of a Pilates Training Method Compared With a General Physical Activity Program: A Randomized Controlled Trial," *Medicine* 100, no. 13 (2021): e25289.

26. L. S. S. C. B. de Oliveira, E. C. Souza, R. A. S. Rodrigues, C. A. Fett, and A. B. Piva, "The Effects of Physical Activity on Anxiety, Depression, and Quality of Life in Elderly People Living in the Community," *Trends in Psychiatry and Psychotherapy* 41, no. 1 (2019): 36–42.

27. S. Loh, N. Lamond, J. Dorrian, G. Roach, and D. Dawson, "The Validity of Psychomotor Vigilance Tasks of Less Than 10-minute Duration," *Behavior Research Methods, Instruments, & Computers* 36, no. 2 (2004): 339–346.

28. H. Sawaya, M. Atoui, A. Hamadeh, P. Zeinoun, and Z. Nahas, "Adaptation and Initial Validation of the Patient Health Questionnaire-9 (PHQ-9) and the Generalized Anxiety Disorder-7 Questionnaire (GAD-7) in an Arabic Speaking Lebanese Psychiatric Outpatient Sample," *Psychiatry Research* 239 (2016): 245–252.

29. M. Chaaya, A. M. Sibai, Z. E. Roueiheb, et al., "Validation of the Arabic Version of the Short Geriatric Depression Scale (GDS-15)," *International Psychogeriatrics* 20, no. 3 (2008): 571–581.

30. A. Alqarni, V. Vennu, S. A. Alshammari, and S. M. Bindawas, "Cross-Cultural Adaptation and Validation of the Arabic Version of the Physical Activity Scale for the Elderly Among Community-Dwelling Older Adults in Saudi Arabia," *Clinical interventions in aging* 13 (2018): 419–427.

31. A. J. Schuit, E. G. Schouten, K. R. Westerterp, and W. H. M. Saris, "Validity of the Physical Activity Scale for the Elderly (PASE): According to Energy Expenditure Assessed by the Doubly Labeled Water Method," *Journal of Clinical Epidemiology* 50, no. 5 (1997): 541–546.

32. F. Herold, B. K. Labott, B. Grässler, et al., "A Link Between Handgrip Strength and Executive Functioning: A Cross-Sectional Study in Older Adults With Mild Cognitive Impairment and Healthy Controls," *Healthcare* 10, no. 2 (2022): 230.

33. B. Löwe, O. Decker, S. Müller, et al., "Validation and Standardization of the Generalized Anxiety Disorder Screener (GAD-7) in the General Population," *Medical Care* 46, no. 3 (2008): 266–274.

34. E. L. Lesher and J. S. Berryhill, "Validation of the Geriatric Depression Scale-Short Form Among Inpatients," *Journal of Clinical Psychology* 50, no. 2 (1994): 256–260.

35. J. A. Yesavage, T. L. Brink, T. L. Rose, et al., "Development and Validation of a Geriatric Depression Screening Scale: A Preliminary Report," *Journal of Psychiatric Research* 17, no. 1 (1982): 37–49.

36. D. Lakens, "Calculating and Reporting Effect Sizes to Facilitate Cumulative Science: A Practical Primer for *T*-Tests and ANOVAs," *Frontiers in Psychology* 4 (2013): 863.

37. W. Zhu, "Sadly, the Earth Is Still Round (p < 0.05)," *Journal of Sport* and *Health Science* 1 (2012): 9–11.

38. Á. Gutiérrez, M. González-Gross, M. Delgado, and M. J. Castillo, "Three Days Fast in Sportsmen Decreases Physical Work Capacity but Not Strength or Perception-Reaction Time," *International Journal of Sport Nutrition and Exercise Metabolism* 11, no. 4 (2001): 420–429.

39. A. S. Roy and A. Bandyopadhyay, "Effect of Ramadan Intermittent Fasting on Selective Fitness Profile Parameters in Young Untrained Muslim Men," *BMJ Open Sport & Exercise Medicine* 1, no. 1 (2015): e000020.

40. A. X. Bigard, M. Boussif, H. Chalabi, and C. Y. Guezennec, "Alterations in Muscular Performance and Orthostatic Tolerance During Ramadan," *Aviation, Space, and Environmental Medicine* 69, no. 4 (1998): 341–346.

41. D. K. Houston, B. J. Nicklas, J. Ding, et al., "Dietary Protein Intake Is Associated With Lean Mass Change in Older, Community-Dwelling Adults: The Health, Aging, and Body Composition (Health ABC) Study," *American Journal of Clinical Nutrition* 87, no. 1 (2008): 150–155.

42. H. Bouhlel, R. J. Shephard, N. Gmada, et al., "Effect of Ramadan Observance on Maximal Muscular Performance of Trained Men," *Clinical Journal of Sport Medicine* 23, no. 3 (2013): 222–227.

43. T. R. Lundberg, J. F. Feuerbacher, M. Sünkeler, and M. Schumann, "The Effects of Concurrent Aerobic and Strength Training on Muscle Fiber Hypertrophy: A Systematic Review and Meta-Analysis," *Sports Medicine* 52, no. 10 (2022): 2391–2403.

44. M. A. Boujelbane, K. Trabelsi, H. A. Jahrami, et al., "Time-Restricted Feeding and Cognitive Function in Sedentary and Physically Active Elderly Individuals: Ramadan Diurnal Intermittent Fasting as a Model," *Frontiers in Nutrition* 9 (2022): 1041216.

45. H. Chtourou, O. Hammouda, H. Souissi, K. Chamari, A. Chaouachi, and N. Souissi, "The Effect of Ramadan Fasting on Physical Performances, Mood State and Perceived Exertion in Young Footballers," *Asian Journal of Sports Medicine* 2, no. 3 (2011): 177–185.

46. N. P. Utama, M. Molavi, and J. Bin Yunus, "The Effect of Ramadan Fasting on Spatial Attention Through Emotional Stimuli," *Psychology Research and Behavior Management* 9 (2016): 105–114.

47. M. S. Hajar, H. Rizal, and G. Kuan, "Effects of Physical Activity on Sustained Attention: A Systematic Review," *Scientia Medica* 29, no. 2 (2019): 32864.

48. K. Seidler and M. Barrow, "Intermittent Fasting and Cognitive Performance—Targeting BDNF as Potential Strategy to Optimise Brain Health," *Frontiers in Neuroendocrinology* 65 (2022): 100971.

49. O. Schulteherbruggen, S. Chourbaji, H. Muller, et al., "Differential Regulation of Nerve Growth Factor and Brain-Derived Neurotrophic Factor in a Mouse Model of Learned Helplessness," *Experimental Neurology* 202, no. 2 (2006): 404–409.

50. W. S. Helton, J. S. Warm, L. D. Tripp, G. Matthews, R. Parasuraman, and P. A. Hancock, "Cerebral Lateralization of Vigilance: A Function of Task Difficulty," *Neuropsychologia* 48, no. 6 (2010): 1683–1688.

51. E. Berthelot, D. Etchecopar-Etchart, D. Thellier, C. Lancon, L. Boyer, and G. Fond, "Fasting Interventions for Stress, Anxiety and Depressive Symptoms: A Systematic Review and Meta-Analysis," *Nutrients* 13, no. 11 (2021): 3947.

52. R. Secades-Villa, A. González-Roz, Á. García-Pérez, and E. Becoña, "Psychological, Pharmacological, and Combined Smoking Cessation Interventions for Smokers With Current Depression: A Systematic Review and Meta-Analysis," *PLoS One* 12, no. 12 (2017): e0188849.

53. E. M. Boland, H. Rao, and D. F. Dinges, et al., "Meta-Analysis of the Antidepressant Effects of Acute Sleep Deprivation," *Journal of Clinical Psychiatry* 78, no. 8 (2017): e1020–e1034.

54. M. Ioannou, C. Wartenberg, J. T. V. Greenbrook, et al., "Sleep Deprivation as Treatment for Depression: Systematic Review and Meta-Analysis," *Acta Psychiatrica Scandinavica* 143, no. 1 (2021): 22–35.

55. P. Mitter, J. Wirth, H. Stassen, and A. Delini-Stula, "Sleep Deprivation as a Treatment for Major Depressive Episodes: A Systematic Review and Meta-Analysis," *Sleep Medicine Reviews* 64 (2022): 101647.

56. S. K. Sulaiman, F. I. Tsiga-Ahmed, T. Arora, et al., "Changes in the Mental Wellbeing Among Nigerians Due to Ramadan Intermittent Fasting: A Nationwide Cross-sectional Study." preprint, Research Square, March 29, 2022, https://doi.org/10.21203/rs.3.rs.1486892/v1.

57. S. Yousuf, A. Syed, and M. Y. Ahmedani, "To Explore the Association of Ramadan Fasting With Symptoms of Depression, Anxiety, and Stress in People With Diabetes," *Diabetes Research and Clinical Practice* 172 (2021): 108545.

58. A. M. R. Souza, G. G. Fillenbaum, and S. L. Blay, "Prevalence and Correlates of Physical Inactivity Among Older Adults in Rio Grande Do Sul, Brazil," *PLoS One* 10, no. 2 (2015): e0117060.

59. K. E. Kobayashi-Cuya, R. Sakurai, N. Sakuma, et al., "Hand Dexterity, Not Handgrip Strength, Is Associated With Executive Function in Japanese Community-Dwelling Older Adults: A Cross-Sectional Study," *BMC Geriatrics* 18, no. 1 (2018): 192.

60. K. L. Tucker, "Nutrient Intake, Nutritional Status, and Cognitive Function With Aging," *Annals of the New York Academy of Sciences* 1367, no. 1 (2016): 38–49.

61. M. T. Wittbrodt and M. Millard-Stafford, "Dehydration Impairs Cognitive Performance: A Meta-Analysis," *Medicine & Science in Sports & Exercise* 50, no. 11 (2018): 2360–2368.

62. A. Mithal, J. P. Bonjour, S. Boonen, et al., "Impact of Nutrition on Muscle Mass, Strength, and Performance in Older Adults," *Osteoporosis International* 24, no. 5 (2013): 1555–1566.

Supporting Information

Additional supporting information can be found online in the Supporting Information section.