ORIGINAL ARTICLE

THE IMPACT OF INTERMITTENT FASTING ON COGNITIVE FUNCTION AND INFLAMMATORY MARKERS IN MIDDLE-AGED AND OLDER ADULTS: A COMPREHENSIVE SYSTEMATIC REVIEW AND META-ANALYSIS

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ABSTRACT

Intermittent fasting (IF) has shown potential health benefits, including improved glucose homeostasis, stress resistance, and reduced inflammation, as well as slowing cognitive decline. However, studies focusing on older adults have been limited and often contradictory. This systematic review and meta-analysis aim to comprehensively examine the impact of IF on cognitive function and inflammatory markers in middle-aged and older adults. The meta-analysis showed that IF significantly enhances cognitive function, as measured by the Mini-Mental State Examination (MMSE) (MD = 0.48, 95% CI (0.21, 0.75), p = 0.0006). However, IF did not significantly reduce inflammatory markers: C-reactive protein (CRP) (MD = -0.24 mg/L, 95% CI (-1.06, 0.57), p = 0.56), high sensitivity CRP (hs-CRP) (MD = -0.00 mg/L, 95% CI (-0.09, 0.08), p = 0.91), interleukin 6 (IL-6) (MD = -0.16 pg/mL, 95% CI (-0.79, 0.48), p = 0.63), and tumor necrosis factor-a (TNF-a) (MD = 0.13, 95% CI (0.01, 0.26), p = 0.04). These results suggest that while IF can enhance cognitive function, it is ineffective in reducing inflammatory markers. Nevertheless, an association was found between IF, cognitive function, and inflammation. Recommendations for future work include larger randomized controlled trials to confirm the cognitive benefits of IF and mechanistic studies to clarify its effects on inflammatory markers.

Keywords: *Intermittent fasting (IF), Cognitive function, Inflammatory marker, middle-aged adults, older adults*

INTRODUCTION

Cognitive function, encompassing the brain's ability to learn, remember, and make decisions, often declines with age. This decline is linked to chronic age-related diseases that accelerate neuron dysfunction, neuron death, and cognitive impairments[1]. Additionally, aging is associated with higher levels of inflammatory markers, which negatively affect cognitive processes, including overall cognitive function[2].

Intermittent fasting (IF) is a dietary approach alternating between periods of energy restriction and normal food intake, inducing a metabolic switch from glycogen to ketone utilization[3,4]. This metabolic shift is associated with neuroprotective and anti-inflammatory effects[3,4]. Various IF regimens, such as time-restricted feeding (TRF), alternate-day fasting (ADF), periodic fasting (PF), and fasting-mimicking diets (FMD), are non-invasive strategies that may support brain health[3].

Emerging evidence suggests that IF positively influences both cognitive function and systemic inflammation. Preclinical and human studies indicate that IF enhances synaptic plasticity, promotes neurogenesis, and improves neuronal resistance to oxidative stress[3,5-9]. IF also modulates inflammatory pathways by reducing circulating levels of pro-inflammatory cytokines[3]. These effects are especially relevant given that chronic, low-grade inflammation or "inflammaging" accelerates age-related cognitive decline. Elevated levels of pro-inflammatory cytokines in midlife adults have been linked to impaired cognition and accelerated cognitive decline with age[10-11].

Demographic projections underscore the urgency of identifying effective, non-pharmacological strategies to preserve cognitive function; by 2050, individuals aged 60 years and older are expected to represent 22% of the world's population, as compared to 12% in 2015[12]. At the same time, pharmacological interventions for dementia show limited efficacy in preventing or reversing cognitive decline[13-14], highlighting the need for lifestyle-based approaches that target modifiable risk factors and support healthy brain aging.
Although previous studies have examined IF's effects on inflammatory biomarkers and, separately, on cognitive outcomes, none have synthesized both domains together. This leaves

the available findings limited and unclear. The scarcity and ambiguity of existing evidence highlight the need for a comprehensive systematic review and meta-analysis to clarify whether improvements in inflammatory status with IF translate into measurable cognitive benefits in middle-aged and older adults.

To address this gap, the present study reviews current human evidence documents as a reference for future, larger trials, positioning IF as a promising non-invasive intervention to reduce inflammatory marker levels and as an early preventive strategy to slow down cognitive decline and promote successful aging. In particular, we assess how IF affects middle-aged and older adults' inflammatory biomarkers and cognitive function, and we investigate any possible connections between inflammatory marker alterations and cognitive performance. This provides an integrated summary to guide future research and clinical strategies.

METHODS

This systematic review and meta-analysis were conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. The PRISMA checklist for this study is presented in Supplementary Table 1.

The research question was formulated using the PICO model as follows. 'P' indicates population, which refers to the subject of the study, middle-aged and older adults. 'I' indicates the intervention of this study, which is IF. 'C' indicates a comparison. The comparison group in this study was non-fasting participants. 'O' indicates the outcome of the study. This study focuses on IF's impact on enhancing cognitive function and reducing inflammatory markers.

The research questions formulated using this model are

1. Among middle-aged and older adults, what is the effect of IF compared to non-fasting in enhancing cognitive function?
2. Among middle-aged and older adults, what is the effect of IF compared to non-fasting in reducing inflammatory markers?
3. Among middle-aged and older adults, what are the associations between IF, cognitive function, and inflammation?

Database searches

A thorough search was conducted to identify relevant studies. We systematically searched online medical databases, including PubMed, Scopus, and Science Direct, up to March 2022. The relevant keywords were combined with Boolean operators as follows: (Group 1 AND Group 2); (Group 1 AND Group 3); (Group 1 AND Group 2 AND Group 3).

Group 1 ('Intermittent fasting" OR "Alternate day fasting" OR "Time-restricted feeding" OR "Time-restricted eating" OR "Fasting mimicking diet" OR "Periodic fasting" OR "Ramadan fasting"); Group 2 ("cognitive function" OR "cognitive performance" OR "cognitive status" OR "cognitive evaluation" OR "cognitive assessment'); Group 3 ("inflammation" OR "inflammatory" OR "pro-inflammatory" OR "interleukin" OR "cytokine" OR "C-reactive protein" OR "tumor necrosis factor").

As registration is not mandatory, this study was not registered with PROSPERO or any other database, given the uniqueness of the topic and minimal risk of duplication in the current literature. Data extraction was performed independently by two reviewers, and discrepancies were resolved through discussion with a third reviewer.

Inclusion and Exclusion criteria

This systematic review included studies with participants aged ≥40 years practicing IF, published between 2010 and 2021, that reported IF's impact on cognitive and inflammatory outcomes (mean ± standard deviation [SD]) and were available in full text. Studies were excluded if they involved animal models, participants aged <40 years, or were not published in English to ensure comprehensive data extraction.

Study selection

Studies were selected based on predefined inclusion and exclusion criteria. Two reviewers independently screened all titles and abstracts for eligibility, and discrepancies were resolved by consensus with a third reviewer. Full texts of potentially eligible studies were then retrieved and assessed for final inclusion. The number of studies screened, reasons for exclusion at each stage, and meta-analysis eligibility decisions are reported in the Results and illustrated in the PRISMA flow diagram (Figure 1).

Quality assessment

The selected studies were appraised using the Cochrane Risk of Bias assessment scoring system with the aid of Cochrane Review Manager 5 software[15]. This tool evaluates potential sources of bias, categorizing the risk as high, low, or unclear across six domains: selection, performance, detection, attrition, reporting, and other biases.

Statistical analysis

Meta-analysis was conducted using Review Manager 5 software. Data from selected studies were analyzed in terms of mean difference (MD) and standard deviation (SD) to assess the pooled effect size of the intervention with a 95% confidence interval. Forest plots were used to present the results, with a P-value of <0.05 considered statistically significant. Statistical heterogeneity among studies was quantified using the I^2 statistic, interpreted according to Cochrane

guidelines[16]. This meta-analysis includes results supporting I^2 values below 50%.

RESULTS

Study selection

Database searches identified 3,186 papers, of which 1,904 duplicates were removed. After screening titles and abstracts, 104 full-text papers were reviewed, and 12 studies met all criteria for the systematic review.

The review had two objectives: to examine the effects of IF on cognitive function and on inflammatory markers. One study, Ooi et al., reported outcomes for both objectives, contributing to both subgroups[7]. Thus, although the total number of studies remained 12, the PRISMA flow diagram (Figure 1) showed 5 studies for cognitive outcomes and 8 for inflammatory markers (13 counts total), reflecting this overlap.

The included studies varied in design (interventional, observational, and secondary analysis), population (middle-aged and older adults), and IF interventions (TRF, ADF, and PF). Cognitive outcomes included the Mini-Mental State Examination (MMSE), Montreal Cognitive Assessment (MoCA), Short Portable Mental Status Questionnaire (SPMSQ), Digit Span Test, Digit Symbol Test, and Rey Auditory Verbal Learning Test (RAVLT), while inflammatory outcomes included C-reactive protein (CRP), high-sensitivity CRP (hs-CRP), interleukin-6 (IL-6), and tumor necrosis factor-alpha (TNF-α). Detailed characteristics of the included studies are presented in Tables 1 and 2.

Risk of bias assessment

Five studies were analyzed to assess the impact of IF on cognitive function. Four studies showed a high risk of bias in one or more domains, while one study had low and unclear risk in some domains (see Figure 2 (a)). For studies investigating the effect of IF on inflammatory markers, four were found to have a high risk of bias in certain domains, while the remaining four had low to unclear risk (see Figure 2 (b)). Bias levels were determined based on systematic errors or limitations in study design or conduct.

Meta-analysis

For the meta-analysis, four of the five cognitive studies were included; Currenti et al. was excluded, as it was the only study assessing cognitive status with the SPSMQ[6]. Similarly, seven of the eight inflammatory studies were included, with Ooi et al. excluded because their results were reported in units not comparable with other studies[7]. In both cases, the studies could not be included in the meta-analysis because they were the only ones with those specific measures, and a meta-analysis requires a minimum of two individual studies providing comparable quantitative outcome data to be statistically pooled[17].

a) Effect of intermittent fasting on cognitive function

Four studies were included in the meta-analysis of cognitive outcomes. The pooled analysis demonstrated a significant difference in MMSE scores between the intervention and non-fasting groups, favoring IF (MD = 0.48; 95% CI [0.21, 0.75], p = 0.0006; I^2 = 0%, p = 0.38) (Figure 3a). However, no significant difference was observed in MoCA scores, with moderate heterogeneity (MD = 1.70; 95% CI [-0.51, 3.91], p = 0.13; I^2 = 42%, p = 0.19) (Figure 3b).

b) Effect of intermittent fasting on inflammatory markers

Seven studies were included in the meta-analysis of inflammatory biomarkers. IF did not significantly lower CRP (MD = -0.24 mg/L; 95% CI [-1.06, 0.57], p = 0.56; I^2 = 81%, p = 0.006) (Figure 4a) or hs-CRP (MD = -0.00 mg/L; 95% CI [-0.09, 0.08], p = 0.91; I^2 = 0%, p = 0.59) (Figure 4b). Similarly, IF was not associated with a significant reduction in IL-6 (MD = -0.16 pg/mL; 95% CI [-0.79, 0.48], p = 0.63; I^2 = 91%, p = 0.0009) (Figure 4c). For TNF-α, a statistically significant difference was observed between groups (MD = 0.13 pg/mL; 95% CI [0.01, 0.26], p = 0.04; I^2 = 81%, p = 0.02), with levels lower in the non-fasting group (Figure 4d). This suggests that IF may not consistently reduce TNF-α, highlighting the variability across studies.

DISCUSSION

This review and meta-analysis summarized the best available evidence on the effects of IF on cognitive function and inflammatory markers among middle-aged and older adults. Of the five studies, three reported that IF improved cognitive function as compared to non-fasting or baseline, while two studies found no significant differences. Importantly, none reported adverse effects.

A study by Ooi et al. demonstrated that 36 months of IF enhanced cognitive function among older adults, with 24.3% of participants aging successfully and 73% reverted to normal aging[7]. Similarly, Currenti et al. reported that TRF within an IF regimen was linked to a better cognitive status and brain health, with a lower likelihood of cognitive impairment[6]. Spanaki et al. observed significantly higher MMSE scores in middle-aged and older adults following the Christian Orthodox Church fasting diet as compared to non-fasters ($p < 0.001$), with a lower prevalence of MMSE scores <27 in the fasting group[8].

Conversely, Anton et al. and Domaszewski et al. found no significant differences in cognitive scores between IF and non-fasting groups[5,9]. Nevertheless, both groups exhibited good cognitive scores, suggesting no detrimental effects of IF. Domaszewski et al. recommended

the 16:8 TRF protocol as a favourable alternative to traditional diets[9]. Anton et al. noted a 5-8% improvement in mental health among fasting participants, though statistical significance was not achieved[5].

The two meta-analyses conducted showed diverging outcomes. MMSE assessments indicated enhanced cognitive function among IF participants. MoCA evaluations presented contrasting findings likely due to differences in cognitive assessment tools. Both MMSE and MoCA employed a 30-point scale to screen for neurological deficits. However, MoCA offers a more comprehensive evaluation, including more visuospatial items and fewer orientation items, potentially leading to lower scores in cognitively impaired individuals.

Differences in cutoff scores for these assessments further compounded the discrepancies. The studies by Spanaki et al. and Domaszewski et al. used MMSE and employed a common cutoff score of 24[8,9]. In contrast, MoCA assessments varied; Ooi et al. used a cutoff of 22/23[7,18], while Anton et al. adopted a cutoff of 26[5,19]. These differences likely influenced the individual study outcomes and the pooled analysis results, resulting in no significant findings.

A review by Gudden et al. offers insights into the impact of IF on cognitive function[20]. The review highlights that sustained IF triggers a metabolic switch to ketone production, which acts as a signalling molecule affecting transcription factors in brain neurons, thereby improving cognitive functioning[20]. These metabolic, cellular, and circadian mechanisms improve brain health and prevent the progression of brain-related diseases[20].

This notion is supported by Ooi et al., who revealed a link between IF and lipid metabolism, crucial for ketone body synthesis and degradation[7]. Their findings indicated a significant decrease in blood glucose levels and an increase in ketone body production among older adults practicing IF. Metabolomics analysis further indicates that elevated levels of key metabolites such as 3-hydroxybutyrate, 3-hydroxy-3-methylglutaryl-CoA, and acetoacetate are associated with ketogenesis among regular intermittent fasters[7]. This metabolic shift occurs after 10 to 14 hours of fasting, as liver glycogen reserves depleted.

According to this analysis, the effect of IF on cognitive function is heterogeneous and domain specific. This could be due to variances in the socio-demographic profiles of study subjects and discrepancies in the cognitive test employed. Despite these variations, evidence from individual studies, considering each study's limitations, suggested that IF might be beneficial in enhancing cognitive function, particularly as assessed by MMSE.

Next, inflammatory markers, such as CRP, IL-6, and TNF-α, are considered factors associated with aging[21-22]. It is found that IF may reduce inflammation by reducing the release of pro-inflammatory cells termed monocytes in the blood circulation[20]. Research demonstrated that these pro-inflammatory cells shift into "sleep mode" and are less inflammatory during fasting than the monocytes in those fed[23].

The analysis of CRP markers revealed significant differences among studies, preventing a meta-analysis. Overall, no significant reduction in CRP levels with IF. This contrasts with prior research, where some studies showed decreased CRP levels with IF, while others found no significant changes. Excluding Ooi et al., which reported lower CRP levels in the IF group, might have biased our findings due to differences in CRP measurement units (nmol/mg protein)[7]. Regarding hs-CRP analysis, studies included showed no significant heterogeneity suitable for meta-analysis. However, the results were not statistically significant, indicating that IF does not lower hs-CRP levels. All included studies reported similar hs-CRP levels between IF and the control group.

The analyses for IL-6 and TNF-α revealed substantial heterogeneity, limiting the reliability of the pooled estimates. Although TNF-α showed statistical significance ($p = 0.04$), the effect favored the non-fasting group, suggesting that IF may not consistently reduce pro-inflammatory cytokines. Trepanowski et al. and Gabel et al. similarly reported no reductions in IL-6 or TNF-α[24,25]. Trepanowski et al. observed an increase in IL-6 at week 12, contrary to other studies that showed decreased results, likely due to their premenopausal women cohort[24]. Gabel et al. found no impact on IL-6 and TNF-α, with baseline levels remaining normal throughout[25]. Collectively, these findings highlighted the heterogeneity across studies and indicated that the effects of IF on inflammatory pathways remain inconclusive.

Immune senescence reduced the production of anti-inflammatory proteins and increased inflammatory responses, leading to a pro-inflammatory brain profile[2]. Research indicated that levels of IL-6 and other pro-inflammatory markers increase with age[10,21,23,24]. Persistent neuroinflammation increases sensitivity and contributes to neurodegeneration. The cytokines and microglia-driven inflammation damage brain cells, especially in the hippocampus and basal ganglia, key regions for cognition[2,20,24].

Another objective of this study was to investigate the relationship between IF, cognitive function, and inflammation in middle-aged and older adults. A meta-analysis was not possible due to a

lack of studies; however, Ooi et al. provided relevant data[7]. They found that 24.3% of older adults with mild cognitive impairment who practiced IF showed no cognitive impairment after three years. IF also reduced CRP levels, an inflammation marker, while non-fasters had increased CRP levels[7].

The study also indicated that IF lowers insulin levels, reducing insulin resistance linked to cognitive decline[7]. Insulin resistance can disrupt brain function and lead to cognitive issues. IF might improve cognitive function by enhancing insulin sensitivity and reducing inflammation. Currenti et al. also found that TRF, a type of IF, supported brain health by improving synaptic plasticity, neuroprotection, neurogenesis, and mitochondrial activity[6]. As aging increases inflammation and oxidative stress, IF may counteract these effects. In conclusion, IF may improve cognitive function and reduce inflammation in middle-aged and older adults by addressing insulin resistance and its negative impact on brain health.

Limitations and future directions

This systematic review and meta-analysis had limitations. Firstly, most studies were evaluated qualitatively rather than quantitatively. Furthermore, due to the scarcity of studies, many analyses included only two studies, the minimum criteria for a meta-analysis. The diverse research methods, varying sample sizes, intervention durations, and differences in subject conditions further complicated the result interpretation.

Future research should prioritize rigorous human trials to investigate the impact of IF on cognitive function and inflammation. More randomized controlled trials and cohort studies are needed, especially focusing on older adults experiencing cognitive decline. Standardizing research methodologies and expanding the diversity and sample sizes of participants will be crucial in enhancing the quality of evidence regarding the benefits of IF.

CONCLUSIONS

The meta-analysis of MMSE assessments indicates that IF can enhance various cognitive domains, including orientation, attention, and recall. However, IF did not significantly reduce inflammatory markers. The limitations and biases present in the included studies may have affected these results. Despite these limitations, our findings suggested a potential connection between IF, cognitive function, and inflammation, with IF potentially reducing insulin resistance and protecting against age-related inflammation. Future research with larger sample sizes and standardized methods is essential to better understand the effects of IF on cognition and inflammation. This could lead to improved applications of IF for enhancing cognitive health and reducing inflammation in older adults.

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Conflict of Interest

The authors report no conflict of interest related to the work.

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No competing financial interests exist.

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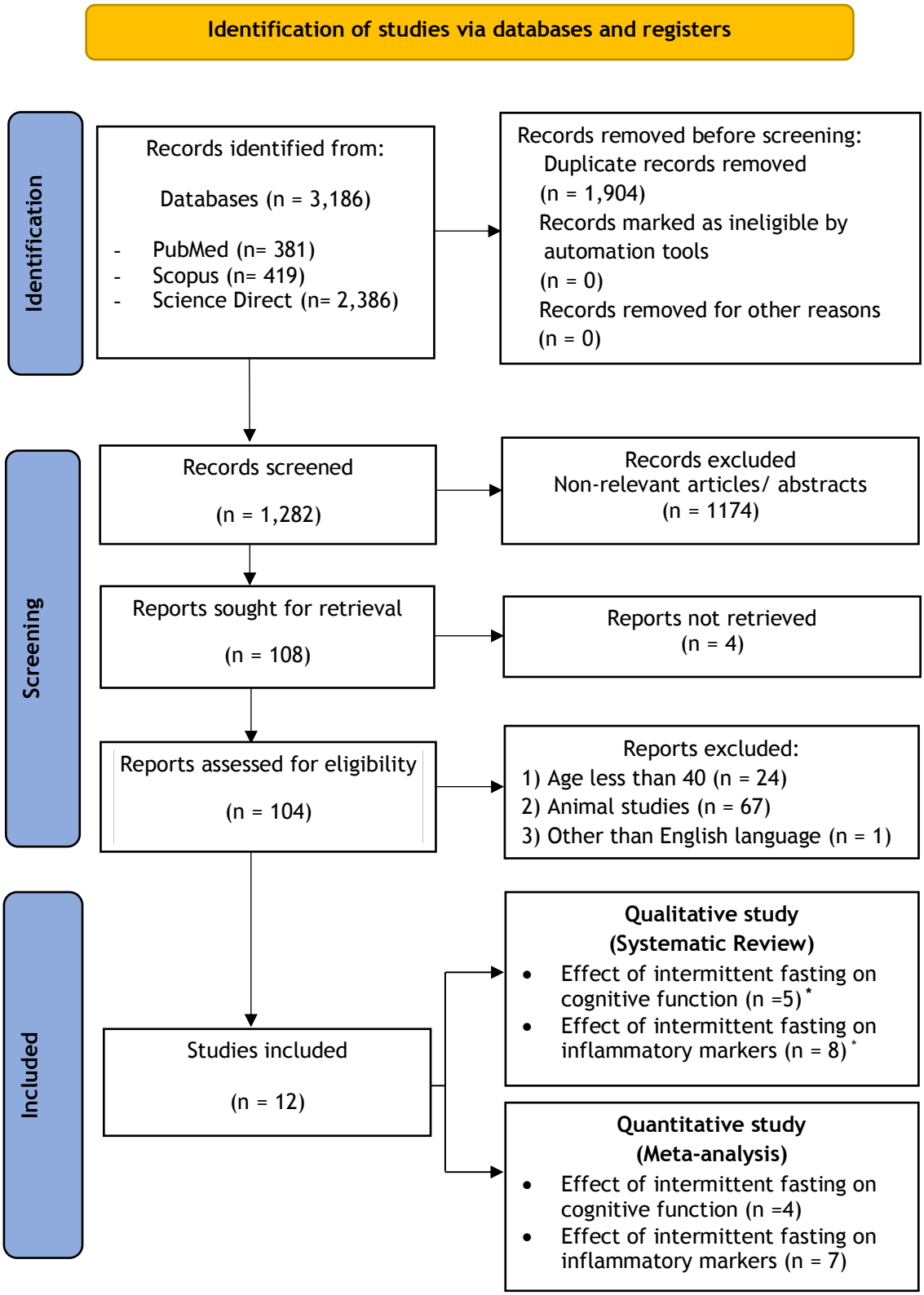


Figure 1: PRISMA flow diagram of the study. Screening was independently performed by two reviewers, and disagreements were resolved by consensus with a third reviewer. The number of excluded records and the reasons for exclusion at each stage are displayed within the diagram

*For the included studies, one study Ooi et al.[7], included in both review for effect of IF on cognitive function and effect of IF on inflammatory markers.

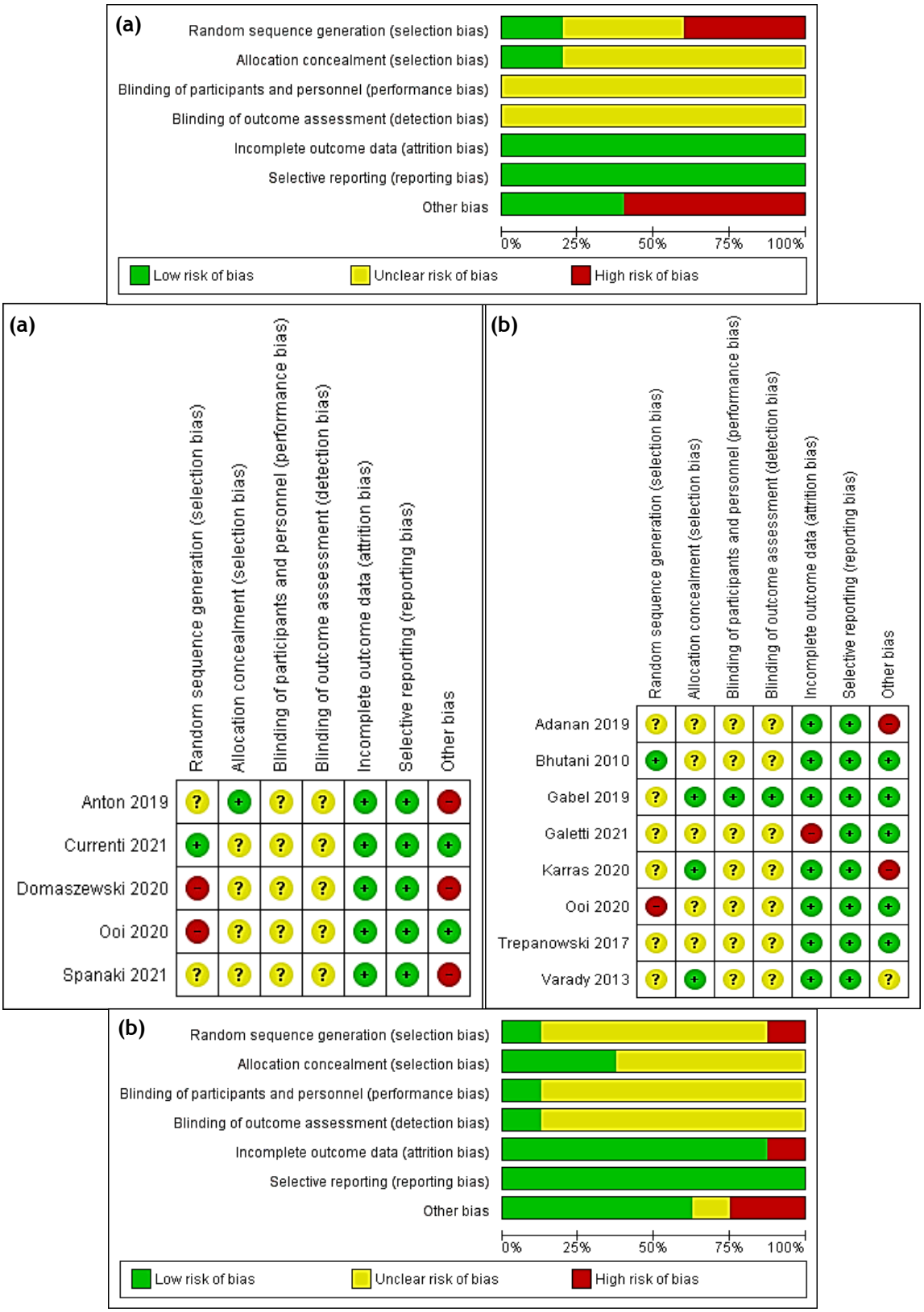
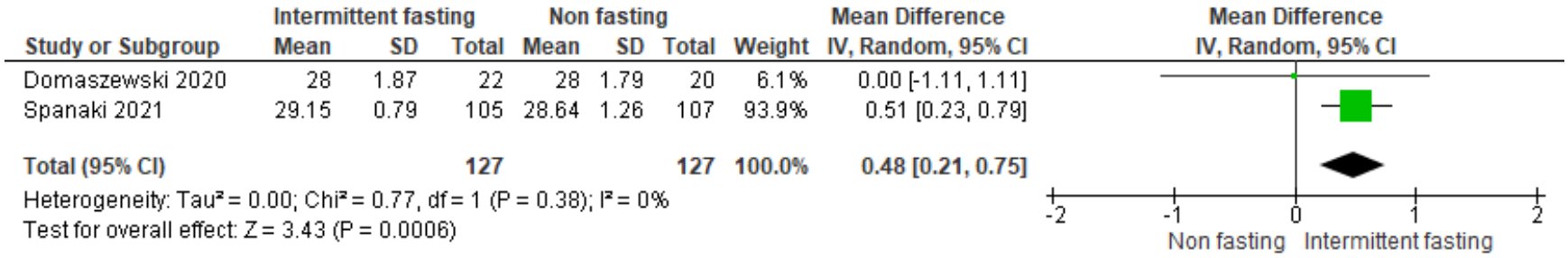


Figure 2: Risk of bias of included studies. **(a)** Risk of bias summary and graph for studies on the effect of IF on cognitive function. **(b)** Risk of bias summary and graph for the studies on the effect of IF on inflammatory markers.

(a)



(b)

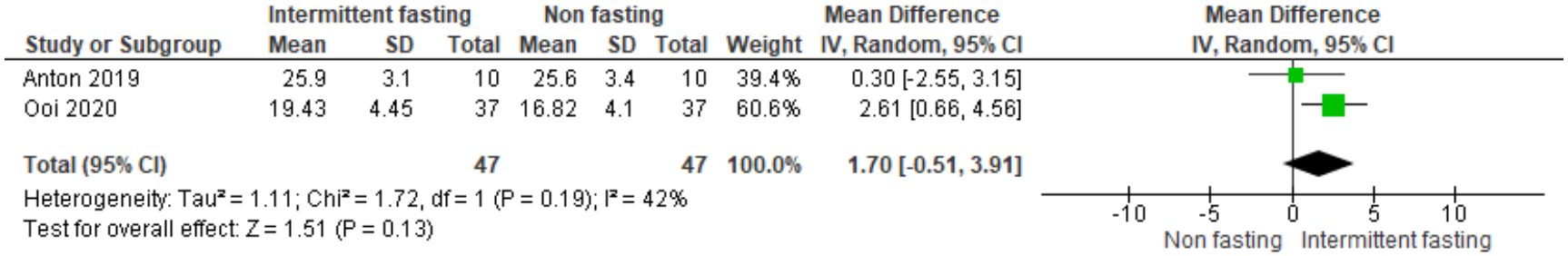


Figure 3: Forest plot of mean difference on the effect of IF on cognitive function between IF intervention and non-fasting group. **(a)** MMSE. **(b)** MoCA.

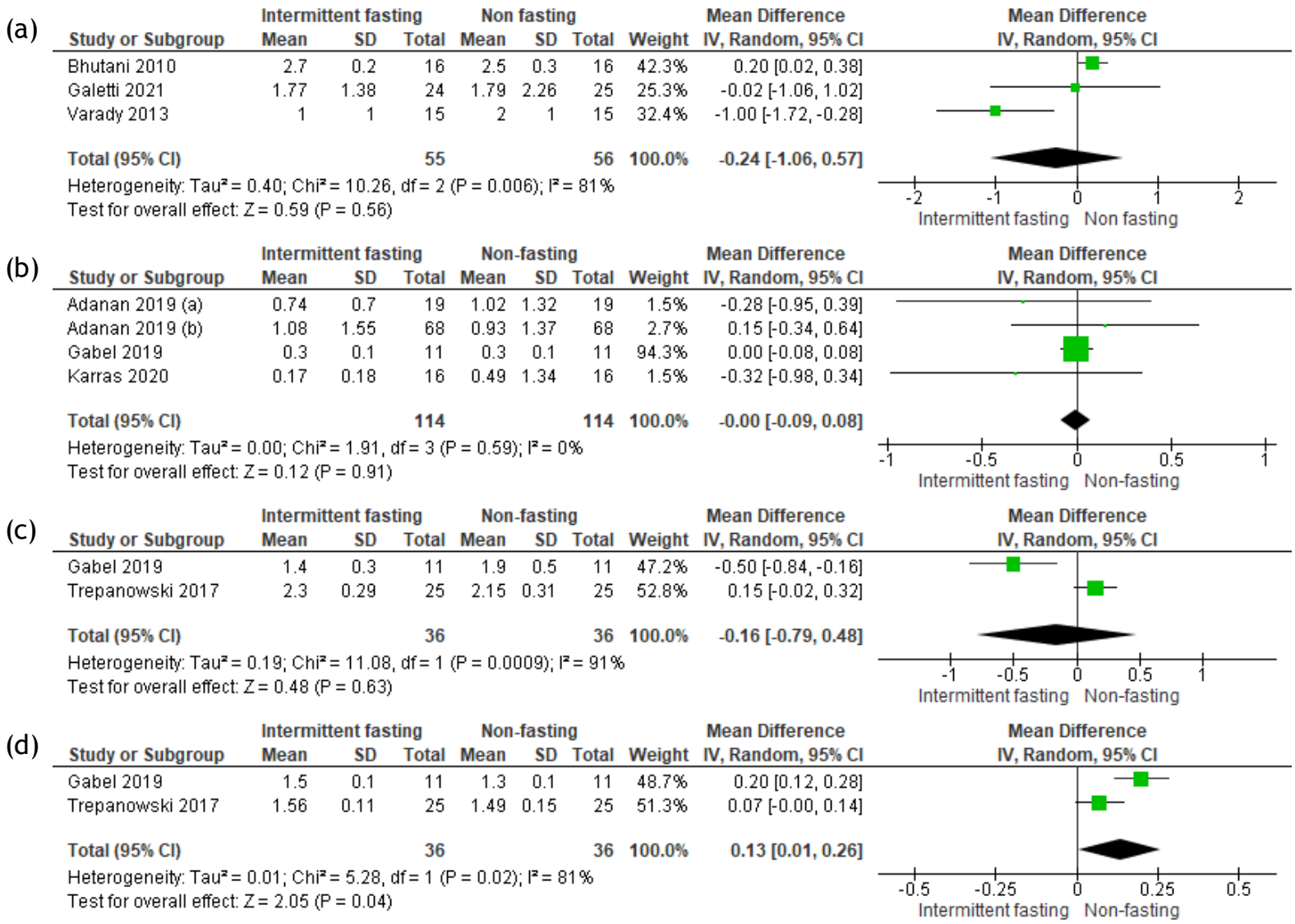


Figure 4: Forest plot of the effect of IF on inflammatory markers between IF intervention and non-fasting group. **(a)** CRP. **(b)** hs-CRP. **(c)** IL-6. **(d)** TNF-α.

Table 1. Characteristics of included studies on the effect of intermittent fasting intervention on cognitive function

Author, year	Study design	Population/ sample size	Mean age (SD) years	IF regimen	IF duration	Outcomes
Mini-Mental State Examination (MMSE)						
Domaszewski et al. (2020)[9]	Interventional	Non-smoking women NF = 20 IF = 22	NF = 66 (± 4.7) IF = 65 (± 4.0)	TRF	6 weeks	All subjects demonstrated an absence of signs of cognitive impairment and dementia. The average value of MMSE points was 28 in the IF group and 28 in the non-fasting group, both before and after the experiment. There was no significant difference between the IF group and the non-fasting group.
Ooi et al. (2020)[7]	Observational (Cohort study)	Muslim older adults NF = 37 IF = 37	68.7 (± 4.6)	ADF	36 months	IF significantly enhanced cognitive performance among older adults. MMSE score was higher after practicing IF, as compared to before practicing IF across time.
Spanaki et al. (2021)[8]	Observational (Cross-sectional)	Healthy adults NF = 107 IF = 105	NF = 58 (± 6.8) IF = 59 (± 6.6)	PF (Christian orthodox fasting)	Since childhood	Better cognitive functions were noticed in the IF group compared to non-fasting individuals. IF individuals had significantly higher MMSE scores as compared to non-fasters.
Montreal Cognitive Assessment (MoCA)						
Anton et al. (2019)[5]	Pilot interventional study	Overweight, sedentary older adults NF = 10 IF = 10	77.1	TRF	4 weeks	Both before and after IF, there were no changes in MoCA scores. There were no significant changes in cognitive function.
Ooi et al. (2020)[7]	Observational (Cohort study)	Muslim older adults NF = 37 IF = 37	68.7 (± 4.6)	ADF	36 months	The regularly practicing IF group had significantly higher scores as compared to the before fasting across time. There were significant changes in cognitive function before and after practicing IF.
Short Mental Status Questionnaire (SPMSQ)						

Author, year	Study design	Population/ sample size	Mean age (SD) years	IF regimen	IF duration	Outcomes
Currenti et al. (2021)[6]	Observational	Italian older adults NF = 785 IF = 98	NF = 65.1 (± 9.6) IF = 65.2 (± 9.4)	TRF	6 months	Individuals having TRF were less likely to have cognitive impairment compared to those with no eating time restrictions. There were significant changes in cognitive function in IF and non-fasting group.
Digit Span Test						
Ooi et al. (2020)[7]	Observational (Cohort study)	Muslim older adults NF = 37 IF = 37	68.7 (± 4.6)	ADF	36 months	Mean score of Digit span test were higher in regularly and irregularly practicing IF group older adults as compared to non-fasting group. There were significant differences among IF and non-fasting groups.
Digit Symbol Test						
Ooi et al. (2020)[7]	Observational (Cohort study)	Muslim older adults NF = 37 IF = 37	68.7 (± 4.6)	ADF	36 months	Mean score od Digit symbol test were higher in regularly and irregularly practicing IF group older adults as compared to non-fasting group. There were significant differences among IF and non-fasting groups.
Rey Auditory Verbal Learning Test (RAVLT)						
Ooi et al. (2020)[7]	Observational (Cohort study)	Muslim older adults NF = 37 IF = 37	68.7 (± 4.6)	ADF	36 months	T-score of RAVLT were higher in regularly and irregularly practicing IF group as compared to non-fasting group, and showed significant increase over time. There were significant differences among IF and non-fasting groups.

IF, intermittent fasting; NF, non-fasting; TRF, time-restricted feeding; ADF, alternate-day fasting; PF, periodic fasting

Table 2. Characteristics of the included studies on the effect of intermittent fasting intervention on inflammatory markers

Author, year	Study design	Population/ sample size	Mean age (SD) years	IF regimen	IF duration	Outcomes
C-reactive protein (CRP)						
Bhutani et. al. (2010)[26]	Interventional study	Obese adults NF =16 IF = 16	Women = 45 (± 3) Men = 46 (± 5)	ADF	10 weeks	There were no differences in CRP concentrations after 4 weeks of ADF or 8 weeks of ADF relative to baseline. There were no significant changes in CRP inflammatory markers.
Varady et. al (2013)[27]	Interventional (Randomized control trial)	Non-obese adults NF = 15 IF = 15	47 (± 3)	ADF	12 weeks	After a period of IF (12 weeks), CRP decreased in the ADF group relative to control group. There were significant changes in inflammatory markers in IF group compared to control group.
Ooi et. al. (2020)[7]	Observational (Cohort study)	Muslim older adults NF = 37 IF = 37	68.7 (± 4.6)	ADF	36 months	CRP level was lower in IF group as compared to non-fasting group. Higher level of inflammatory markers was found is subjects who did not practiced IF. There were significant differences in mean CRP levels among the control and IF groups across time.
Galetti et. al (2021)[28]	Observational	Healthy adults NF = 25 IF = 24	50.03 (± 9.48)	PF	60 days	There were no differences in CRP concentrations after 60 days of ADF relative to before fasting week. No significant changes in C-reactive level.
High-sensitivity C-reactive protein (hs-CRP)						
Gabel et al. (2019)[25]	Interventional (Randomized control trial)	Insulin-resistant adults NF = 11 IF =11	41 (±3)	ADF	12 months	hs-CRP values remained unchanged in both IF and control group. No significant effect of ADF on circulating levels of CRP.
Adanan et al. (2019) a[29]	Observational (Cohort study)	Adult Muslim patients undergoing haemodialysis NF = 19 IF = 19	54.3 (± 12.2)	TRF (Ramadan Fasting)	Less than 20 days	hs-CRP inflammatory marker remained unchanged both before and after IF. No significant changes in Hs-CRP level.

Author, year	Study design	Population/ sample size	Mean age (SD) years	IF regimen	IF duration	Outcomes
Adanan et al. (2019) b[29]	Observational (Cohort study)	Adult Muslim patients undergoing haemodialysis NF= 68 IF = 68	54.3 (± 12.2)	TRF (Ramadan Fasting)	More than 20 days	hs-CRP inflammatory marker, remained unchanged both before and after IF. No significant changes in Hs-CRP level.
Karras et al. (2020)[30]	Observational	Overweight healthy adults NF = 16 IF = 16	45.4 (± 9.2)	TRF	13 weeks	hs-CRP inflammatory marker, remained unchanged both before and after IF. No significant changes in Hs-CRP level.
Interleukin 6 (IL-6)						
Trepanowski et al. (2018)[24]	Secondary analysis	Overweight and obese adults NF = 25 Control =25	46 (± 2)	ADF	24 weeks	IL-6 level did not change in either intervention group relative to the control group. No significant changes in IL-6 level.
Gabel et al. (2019)[25]	Interventional (Randomized control trial)	Insulin-resistant adults NF = 11 IF = 11	43 (±3)	ADF	12 months	IL-6 values remained unchanged intervention and control groups. No effect of ADF on circulating levels of IL-6.
Tumour necrosis factor α (TNF-α)						
Trepanowski et al. (2018)[24]	Secondary analysis	Overweight and obese adults NF= 25 IF =25	46 (± 2)	ADF	24 weeks	TNF-α level did not change in either intervention group relative to the control group. No significant changes in TNF-α level.
Gabel et al. (2019)[25]	Interventional (Randomized control trial)	Insulin-resistant adults NF = 11 IF =11	43 (±3)	ADF	12 months	TNF-α values remained unchanged intervention and control groups. No effect of ADF on circulating levels of TNF-α.

IF, intermittent fasting; NF, non-fasting; TRF, time-restricted feeding; ADF, alternate-day fasting; PF, periodic fasting