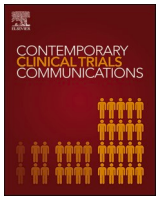
Contemporary Clinical Trials Communications 25 (2022) 100766

Contents lists available at ScienceDirect

Contemporary Clinical Trials Communications

journal homepage: www.elsevier.com/locate/conctc



Intermittent fasting & performance: The iFast clinical trial protocol

Abbass El-Outa [a], Lara Ghandour [a], Hani Hamade [b], Cecile Borgi [c], Elie-Jacques Fares [c], Tarek Gherbal [d], Afif Mufarrij [a,*]

[a] Department of Emergency Medicine, American University of Beirut Medical Center, Beirut, Lebanon
[b] Department of Internal Medicine, The MetroHealth System, Cleveland, USA
[c] Department of Nutrition and Food Sciences, Faculty of Agricultural and Food Sciences, American University of Beirut, Beirut, Lebanon
[d] University Sports, Office of Student Affairs, American University of Beirut, Beirut, Lebanon

ARTICLE INFO

Keywords:
Intermittent fasting
Nutrition
Sports medicine
Aerobic exercise
Exercise performance
Health biomarkers
Weight loss
Maximal oxygen consumption
FATMAX
VO_2max

ABSTRACT

There is increasing evidence from animal and human studies suggesting that fasting can play a role in disease prevention, weight control and longevity. However, few studies have compared exercise performances in individuals adhering to an intermittent fasting (IF) in comparison to individuals who are not. Given the rising popularity of IF we aim to investigate whether this type eating pattern will improve cardiovascular performance over a period of 12 weeks through VO_2 max measurements in participants from a Lebanese community. Additionally, we will study the variation of different health parameters, physical performance and biomarkers potentially affected by IF. Participants will be recruited from a large university community and randomized into 4 arms. Baseline information will be collected from all participants, which includes biological, physical, nutritional, medical and psychological data. Two arms will follow a time-restricted fasting diet with and without physical exercise, one arm will exercise without fasting, and one will act as a control group. Throughout the study, measurements will be repeated, and data analysis will follow to evaluate results.

1. Introduction

Intermittent Fasting (IF) is an umbrella term which covers many types of dietary timing patterns, all of which revolve around establishing periods of voluntary abstinence from caloric intake during the day or the week [1]. While fasting practices have been present for centuries, the IF practice is enjoying a noticeable rise in popularity in recent years [2]. There is an increasing amount of evidence from animal and human studies suggesting that IF may have beneficial effects on a multitude of health parameters. Studies found that fasting decreases the risk factors of cardiovascular diseases, reduces insulin resistance, helps in weight loss among other health benefits [3] (see Table 1)

While IF showed positive effects on metabolic health outcomes, its impact on physical performance, fat oxidation rate and muscle mass is still controversial. In the body of the current literature, performance is measured using VO_2max (aerobic capacity), which is considered an objective measure of cardiorespiratory fitness (CRF) and the gold standard for testing fitness performance. Athletes with high VO_2max produce more energy, achieve higher intensity and performance during their workout [4]. Moreover, low levels of VO_2max and CRF are considered as predictors for chronic diseases leading to an increase in cardiovascular diseases morbidity and all-cause mortality, therefore maintaining a considerably high CRF level is crucial for our health [4–6].

Studies found that vigorous to high intensity exercise are positively correlate with CRF [7], however, studies assessing the effect IF on physical performance have conflicting evidence. The lack of methodological homogeneity makes it difficult to draw definite conclusions using the existing literature [3]. In fact, some studies reported that IF accompanied with endurance, high-intensity or resistance exercises didn't show any performance benefit, yet in fact some results indicated a decline in performance [3,8–10]; however, other studies demonstrated that resistance training and IF improved body strength, performance and muscular endurance [11,12]. This is further supported by recent evidence [13].

In addition, enabling fat metabolism is crucial for exercise performance and health in general [14]. Studies showed that fasting for more than 6 h enhances fat oxidation [15]. The maximal fat oxidation rates

* Corresponding author. Department of Emergency Medicine, American University of Beirut Medical Center, P.O.Box - 11-0236 Riad El Solh, Beirut, 1107 2020, Lebanon.
E-mail address: am66@aub.edu.lb (A. Mufarrij).

https://doi.org/10.1016/j.conctc.2021.100766
Received 5 October 2020; Received in revised form 23 March 2021; Accepted 31 March 2021
Available online 15 April 2021

(FATMAX) is achieved during submaximal exercise (<65%VO_2max), it is when oxidation of free fatty acids is used as the main source to fuel the body. FATMAX is affected by gender, nutritional intake as well as exercise intensity and duration [16]. To our knowledge, few studies have evaluated the effects of undergoing IF combined with minimal workout on exercise performance. This study aims at investigating whether IF will improve CRF as measured by VO_2max in Lebanese individuals over a period of 12 weeks. Additionally, we will study the effect of IF on FATMAX, weight, metabolic measures, glycemic variation, blood lipids, cardiovascular health, appetite, sleep and anxiety.

2. Methods

2.1. Study settings and design

This study will be a randomized controlled, factorial, superiority, repeated-measures and open-label trial. It will be registered in WHO's Lebanese Clinical Trials Registry (LBCTR) and the United States Clinical Trials registry. It will be conducted in the period between May 2021 to August 2022 in a tertiary care medical center and in a nutrition laboratory. This study fully abides by the Declaration of Helsinki and is under the direct supervision of the Institutional Review Board of the American University of Beirut.

Participants will be assigned to four separate arms through block

Table 1
SPIRIT checklist of study events.

	STUDY PERIOD (12 weeks)							
	Enrolment	Allocation	Post-allocation					Close-out
TIMEPOINT	d_{-7}	d_0	d_{10}	d_{30}	d_{45}	d_{60}	d_{75}	d_{90}
ENROLLMENT:								
Eligibility screen*	X							
Informed consent	X							
Personal Information	X							
Allocation/ Randomization		X						
INTERVENTIONS:								
Fasting and Exercise Group			♦	—	—	—	—	♦
Fasting and Non-exercise Group			♦	—	—	—	—	♦
Non-fasting and Exercise Group			♦	—	—	—	—	♦
Non-fasting and Non-Exercise Group			♦	—	—	—	—	♦
ASSESSMENTS:								
Vital Signs and ECG		X				X		X
VO_2 Max and FATMAX		X				X		X
Body Composition		X		X		X		X
Resting Metabolic Rate		X				X		X
24-hour Food Recall			X	X	X	X	X	
*Blood Biomarkers***		X				X		X
Ketone Levels		X		X		X		X
Exercise and Fasting Log				X		X		X
Glucose Monitoring				♦	—	♦		
Appetite Rating Scale		X		X		X		X
Pittsburgh Sleep Quality Index		X		X		X		X
*Generalized Anxiety Disorder-7 Scale***		X		X		X		X

randomization. One arm will follow a time-restricted fasting (TRF) diet with physical exercise, one will follow a TRF diet without physical exercise, one arm will exercise without fasting, and one will act as a control group. All participants will be followed over a 3-month period. After a one-week period of diet standardization, the participants will present for the first visit, during which data collection, blood collection, body measurements, fat composition, RMR, FATMAX and VO_2max will be measured. A similar visit with similar tests will be repeated at the end of the 3-month period to observe for any changes. At the 1 month and 2-month limits, the participant will present for short visits during which body measurements will be made and the exercise log sheet is reviewed. Additionally, the patient will be required to fill the 24-hour food recall questionnaire on 5 separate occasions, either through a phone call or during the aforementioned visits. Study flow is shown in Fig. 1 (see Fig. 2).

After explaining all the instructions pertinent to each study group and recording baseline measurements, participants are dismissed. On day zero, each participant follows their corresponding instructions and their 3-month participation is initiated. After 10 days, a registered-dietitian in the team will contact the participants via phone call and administer the 24-hour food recall instrument and following the 5-step multiple-pass method. Factors that preserve the quality of the reported dietary data, such as respondent reactivity, non-directive probing, and portion size estimation will be taken into consideration [17,18], and any question or concern of participants will be address. The Nutritionist Pro software (N-squared Computing Nutritionist IV. Silverton, OR: N-squared Computing) will be used for the analysis of the participants' 24-hour recalls in order to calculate and assess the energy and macro-nutrients [19].

This recall will be obtained from participants 3 times throughout

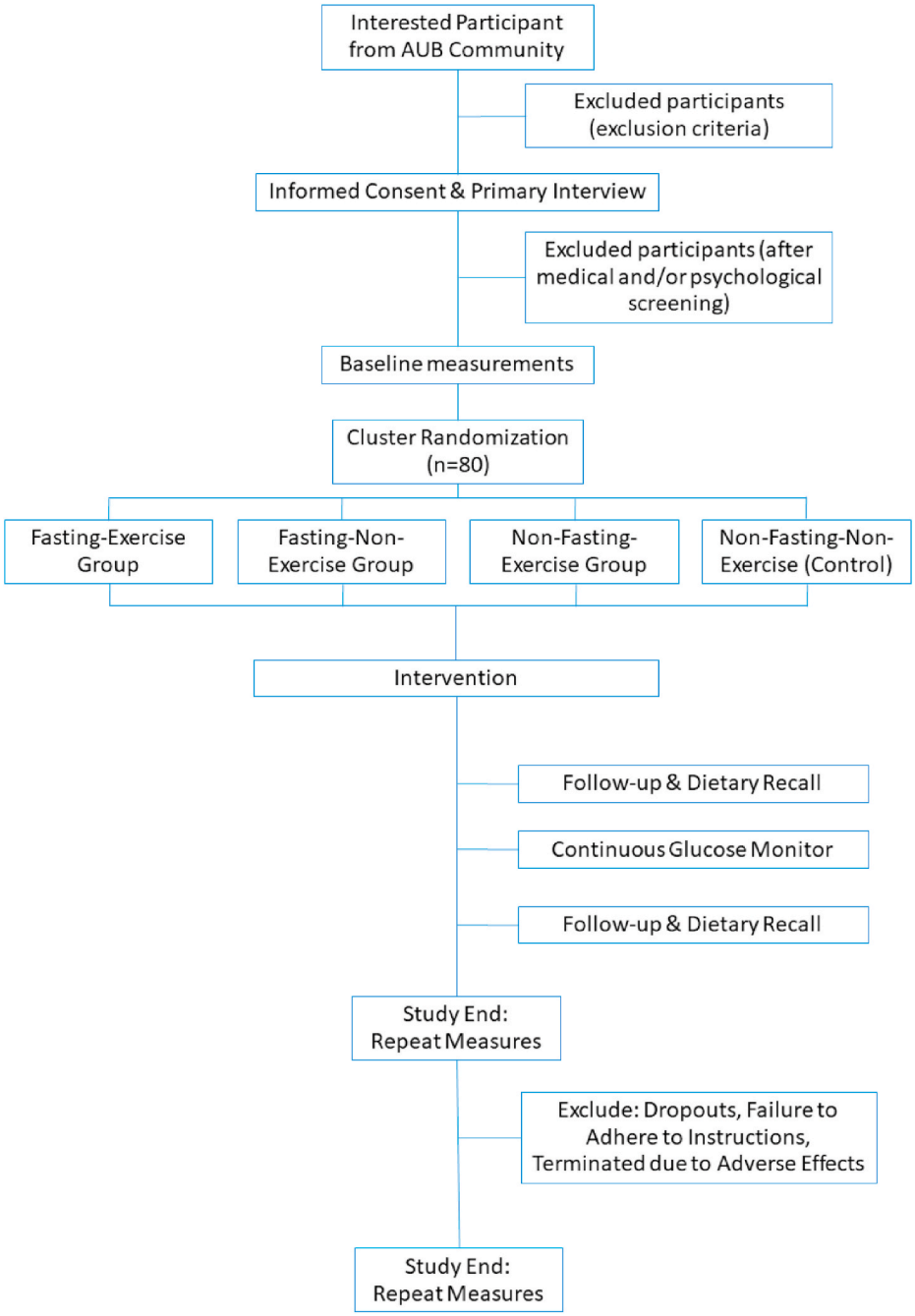


Fig. 1. Study design flowchart.

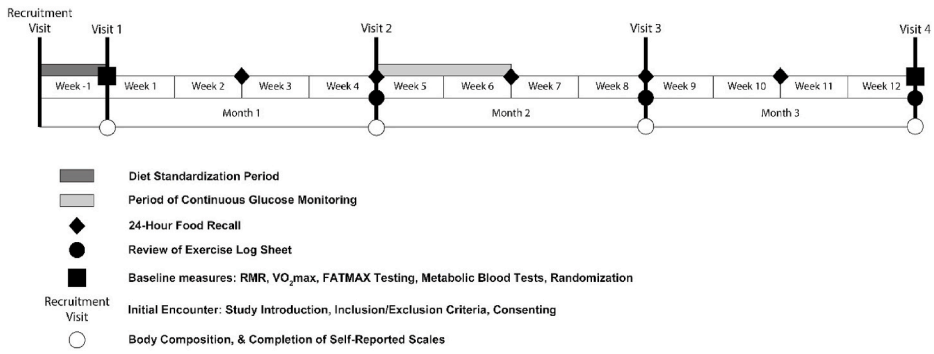


Fig. 2. Study timeline.

week days and 2 times during 2 weekends over the entire study duration (5 instances in total) in order to have a representative idea of what the participants are consuming (total calories, quantity and quality of food).

2.2. Sample size

Sample size was calculated according to two independent groups with the continuous outcome – the VO_2max being the primary outcome (VO2max fasting vs. VO2max non-fasting), with alpha = 0.05 and 90% power. Using the results obtained in a similar trial [20] as estimates for means and standard deviations, the calculated sample size was equal to 43 participants. Moreover, since that we have 4 study arms rather than 2, and given that we expect a participant dropout of around 15% (similar to other IF trials), a higher number of participants will be recruited. In fact, a sample size of 80 participants is the number set, divided equally into the 4 study arms, 20 subject each.

2.3. Participant identification and recruitment

Several tools will be used to promote participant identification and recruitment. An institutional email call-for-participation will be sent to a large email database. Additionally, contact information of candidates were collected from another study on intermittent fasting in which participants expressed their interest in participating in a clinical trial on IF.

Potential participants will be interviewed and screened to determine her/his eligibility in meeting the full inclusion criteria, and consent forms will be provided and signed.

2.3.1. Inclusion criteria

- Age: 18–64 years
- BMI: 20–35 Kg/m2
- Sedentary to lightly-active lifestyle (<7500 steps/day)
- Stable body weight for 2 months prior to the beginning of the study (<4 Kg weight loss or gain)

2.3.2. Exclusion criteria

- Pregnant, recently pregnant (<1 year), planning to become pregnant
- Breastfeeding
- Diabetes mellitus
- Dyslipidemia
- Metabolic disease
- History of cardiovascular disease (hypertension, arrhythmia, coronary artery disease, others …)
- Glaucoma/ocular hypertension
- Eating disorders
- Presently engaged in regular training
- Any systematic disease or condition that might reduce the adherence or tolerance to exercise or fasting
- Orthopedic or neurological conditions that might impair exercise training
- Taking weight loss, lipid or glucose lowering medication
- History of bariatric surgery or minor weight loss surgical procedures
- Smoking (any form of smoking including e-smoking)
- Suspicion of infectious disease

2.4. Fasting protocol

A registered dietitian will meet participants at day 0 in the intermittent fasting groups and will provide them with dietary instructions on IF, and she/he will answer their questions. Participants will abstain from eating and drinking caloric food and beverages for 16 h and consume *ad libitum* food and beverage intake for the remaining 8 h. During the fasting hours, participants should drink water and they can also drink non-caloric beverages such as sugar-free black coffee and tea.

2.5. Exercise routine and performance

The participant will be introduced to an intermediate-intensity calisthenics exercise routine of two exercises which will consist of push-ups (regression with knees on the ground is optional) and body-weight chair-seated squats (progression to air squats is optional) - participants will be asked to adhere to the form of exercise they start with. Participants will complete the maximum number of repetitions (to exhaustion or failure) of push-ups and sit-ups squats 3 times a week and will document the number of repetitions and the time taken to do them. Ideally, the exercise should be performed in the last 4 h before breaking the fast. However, to enhance compliance, the participant will be allowed to determine their preferred timing of exercises. They will be provided by brochure and notebook that explain the details of the exercise regimen, as well as a log sheet to record their exercise progress (following each exercise session, the participant will record the number of repetitions and the duration taken to perform the exercises).

2.6. VO_2max and FATMAX measurement

VO_2max is defined as "the oxygen intake during an exercise intensity at which actual oxygen intake reaches a maximum beyond which no increase in effort can raise it" [21] Therefore, the measurement VO_2max defines the limits of the cardiovascular and respiratory systems' ability to transport oxygen. It is the ultimate marker of performance [22].

Metabolic parameters (RMR, VO_2, FATMAX) are measured through indirect calorimetry (Cosmed Quark CPET, Cosmed srl, Rome, Italy) using a high-end Hans Rudolph® facemask. The participant will also be monitored during the resting and active stages using an electrocardiography (ECG) device and a blood pressure monitoring device. First, the participant's resting metabolic rate (RMR) will be determined. This will

be taken while the participant is resting inactively in the chair for a period for 40 min. This will be followed by the FATMAX and VO_2max tests, both tests will be performed successively on a cycle ergometer while breathing into the respirator, with 15-min break between both tests. During the FATMAX test the participant will cycle at 70 rev/minrev/min at an intensity of 30 W, which will be increased by 10 W every 3 min. The test will be terminated when the respiratory exchange ratio (RER) exceeded 1 for a continuous period of 30 s.

As for the VO_2max, a brief time-to-exhaustion increasing-intensity cycling and 5–15 min of exercise will be performed. VO2max will be determined as described by Broskey et al. [23]: briefly, the graded exercise cycling test will start with men participants pedaling at 60–65 rpm at 50 WW, with 25 WW increments every 2 min, and all women will start at 25 WW with increments of 25 WW. subjects should perform the test until volitional exhaustion. Visits 2 to 4 will be randomized.

Eventually, such setup will provide the respiratory quotient (RQ), RERmax, HRmax (maximum heart rate), FATMAX and VO_2max of each participant.

2.7. Continuous glucose monitoring

In a novel attempt, participants are asked toward the beginning of the 5th week to present for a live recall. In this recall, participants will receive an FDA-approved continuous glucose monitoring device (Abbott FreeStyle® Libre) to be worn for 14 days. This device consists of a sensor placed on the upper arm which is small, waterproof and non-invasively records their body glucose levels at constant intervals, and an external reader. At the end of the 2-week period, participants will return the readers and dispose the sensors.

2.8. Nutritional assessment and other measures

Nutritional assessment will include: body composition assessment and the 24-hour dietary recall (24-h recall). Body composition will be obtained using an InBody 770 multi-frequency bioelectric impedance analysis (BIA) unit (Inbody Co., Ltd., Seoul, Korea), which will determine the total body weight, fat and lean body mass, Moreover, during the study period the dietitian will contact the participants to collect the 24-h recall, this tool is used to accurately quantify and qualify the caloric intake of participants. In this study, the 24-h recall will be collected 5 times over the study period in order to insure consistency in dietary intake (3 times during week-days and 2 times during the weekend).

Other self-reported measures will include appetite, sleep and anxiety as measure by: appetite rating scale (using visual analogue scale to assess satiety [24]), Pittsburgh sleep quality index [25,26], and the generalized anxiety disorder (GAD)-7 scale [19], respectively.

2.9. Baseline measurements

Every participant will undergo baseline value recording. There will be health and nutritional baseline measurements for each individual before being randomly allocated to a study.

1 Medical Assessment

First, the participant will be invited to the study lab for physical measurement at day 0. Vital signs will be recorded, and proper hydration ensured. Pre-testing ECG will be done to screen for undetected cardiac diseases. A skilled and experienced emergency physician will read the ECG before moving to the exercise. On the occasion that an unanticipated disease was detected, the individual's participation in the study will be terminated, and the participant will be referred for proper work-up and management.

2 Nutritional Assessment

Body composition will be determined using multi-frequency bioelectric impedance analysis (BIA). Total body weight, fat and lean body mass will be obtained, as well as resting energy expenditure (REE).

3 Performance Measurement

After nutritional assessment, the participant will be seated on the performance measurement machine, and measurement will be done by an experienced physiotherapist and physical trainer with the presence of a physician.

These tests consist of bicycling on a cycle ergometer at a predetermined work rate, established to elicit a standard percentage of VO_2max. It is connected to an indirect calorimeter and ECG device. The RMR will be determined, followed by a brief FATMAX and time-to-exhaustion increasing-intensity cycling (VO_2max). This is estimated to take around 40 min of inactively sitting in the chair and 20–25 min of exercise.

VO_2max is defined as "the oxygen intake during an exercise intensity at which actual oxygen intake reaches a maximum beyond which no increase in effort can raise it" [21]. Therefore, the measurement VO_2max defines the limits of the cardiovascular and respiratory systems' ability to transport oxygen. It is the ultimate marker of performance [22].

4 Blood Withdrawal

Following cool-down, we will withdraw a 5-ml blood sample from the participant into a chemistry tube and another 5-ml into EDTA tube. These will be used for analysis to determine baseline values of biological parameters. Tubes will be labelled with study ID numbers and the dates of collection. The study ID numbers will be matched with the patient's name and contact information on an electronic document that will be kept on a password-protected computer. Eventually, tubes will be transported to the medical laboratory for subsequent analysis.

Biomarkers measured in blood: CBC-D, fasting blood glucose, blood ketones, cholesterol, HDL, LDL, triglycerides, CRP, and electrolytes (Na, K, Cl, CO_2, Ca, Mg, PO_4), BUN, creatinine.

Of special interest, quantitative blood ketone measurement will enable quantification of the ketosis state induced by intermittent fasting; this will also serve as an indicator of adherence to intermittent fasting in the respective group.

5 Self-reported and Psychological Measures Baseline

- Appetite rating scale: using visual analogue scale to assess satiety [24].
- Sleep quality: using Pittsburgh sleep quality index [25,26].
- Anxiety signs: using generalized anxiety disorder (GAD)-7 scale [19].

2.10. Participants randomization

To minimize procedural bias during baseline workup, participant randomization and allocation will only occur following establishing all the baseline measures. Therefore, after obtaining the mentioned baseline records for the participant, she/he will be digitally randomized into one of the four study arms using block randomization technique [27,28] using RStudio version 1.2.5042 (R version 4.0.0) with suitable packages.

2.11. Patient and public involvement

Neither patients nor their family members were involved in the study design. The results will be widely distributed in scientific reports as well as academic conferences to benefit leisure-time exercises, athletes, and clinicians.

2.12. Adverse effects

There are theoretical concerns that intermittent fasting could promote erratic eating patterns, binging, increase in eating-related thoughts, hunger, irritability, fatigue, difficulties concentrating, headaches, dizziness, weakness, muscle aches, overall decline in your mood, low blood sugar and might affect luteinizing hormone dynamics and menstrual cycle. No long-term adverse effects are known.

Secondary or adverse effects will be monitored closely by means of regular basic questioning and self-reported evaluation; additionally, throughout the sessions held in the research lab, an emergency physician will be always present with real-time ECG monitoring during performance testing. Participants will be instructed on contacting a researcher responsible for the monitoring in case any adverse or unfavourable event shall emerge. Eventually, a safety analysis will be maintained along the study period. Due to the detailed medical evaluation upon enrolment, we do not anticipate any major adverse effect.

By participating in performance testing, in rare and exceptional cases, adverse cardiovascular effects may occur, especially in patients with asymptomatic undetected heart diseases. However, through a comprehensive pre-interventional screening and work-up, this possibility would be minimized. Any serious adverse effect will be dealt with immediately the medical center; additionally, the facility is equipped with an immediately-accessible first aid equipment and an AED (automated external defibrillator). In the unlikely event that a non-serious adverse effect showed in which the participant felt they prefer to stop, the participant's enrolment will be terminated instantly and medical and psychological follow-up will follow for proper management. If an unlikely major adverse event occurred, the trial will be terminated and proper measures will be taken. All adverse effects will be reported to the institutional review board.

2.13. Participant compensation

Participants will be compensated at each follow-up visit as reimbursement for transportation. Moreover, upon completion of the study, they will receive a 6-month free membership in a premium fitness center and 6 free nutritional consultations.

2.14. End of study

The study is planned to last for 3 months. Starting from the 8th week, the study will conclude if the number of dropouts reaches 38 (so that sample size falls below 42, the minimum needed size). In case participants' compliance was ideal, we will conclude the study at week 12. We will repeat all the measurements done at the beginning of the study: health, physical and self-reported ones. Participants on fasting and/or exercising regimens may continue their routines if they desire to. They will be offered a copy of their blood and medical tests, nutritional tests and performance results. Data analysis will follow, and the results will be published.

2.15. Statistical analysis

Statistical analyses will be performed using SPSS version 24.0 (Armonk, NY: IBM Corp), in addition to RStudio version 1.2.5042 (R version 4.0.0) if needed for repeated measures and graphs. The distributions of the continuous and categorical variables will be presented as mean ± standard deviation and frequency/percentages respectively. Tests will be interpreted at a significance level alpha = 0.05. We will use the suitable parametric and/or non-parametric tests to analyse changes in values from baseline and detect significant intra- and inter-group changes. Regression models will be used as well to evaluate associations between fasting and VO_2max, FATMAX, biological parameters, and self-reported measures. Both intention-to-treat and per protocol analyses frameworks will be used.

2.16. Benefits and strength of the study

Intermittent fasting is a very trendy topic now-a-days, both in research field and people's interest. Only few trials studied the effects of IF on physical performance; furthermore, these studies evaluated short-term (7–14 days) different types of fasting. In addition, most of these trials comprised of very small sample sizes (6–21 participant). Therefore, a strong point in our study is the relatively larger sample size, long duration and the unique standardized performance measurement. Moreover, this will be the first fasting study to evaluate continuous measurement of glycaemic variation during fasting and exercise.

3. Discussion

Multiple animal and human studies have evaluated the effects of time restricted IF on a diversity of health parameter and performance. Rats placed on IF were shown to have decreased systolic blood pressure, body weight, total cholesterol, triglyceride, glucose, insulin and inflammatory cytokine levels among other biomarkers [29]. These results were replicated in some human studies. Stote et al. found reductions in glucose, LDL, HDL as well as a 4.1% decrease in weight in adults undergoing 8 weeks of TRF [30].

With regards to the fasting pattern, several patterns of intermittent fasting are described, with varying results with respect to health outcomes and weight loss, although all are reported to confer benefit. We have chosen the 16:8 fasting pattern since it is flexible, practical and easier to commit to and based on preliminary results of another study currently being conducted on preferences and trends of IF in a Lebanese sample (belonging to the same population that this study sample will be selected from) to ensure selecting more preferred IF pattern. In addition, Cho et al. (2019) conducted a similar trial but using alternate day fasting pattern. Therefore, using a different pattern allows the comparison of effect of the different IF patterns [31]. Furthermore, ketone testing will be performed at each visit for evaluation of adherence to intermittent fasting.

As for performance measurements, the gold standard technique is chosen to measure aerobic fitness known as VO_2Max. In addition to strict pre-participation medical screening, to ensure participants' safety and to minimize any health side effects, all participants are obliged to undergo a screening ECG to make sure adults with cardiovascular diseases are excluded.

Most studies assessing the impact of exercise with IF focused on resistance training or aerobic training, with a strict training program constituted of exercising at least 2 times a week for 30–60 min each session. These intensive workouts will improve muscle mass and endurance; however, they need high compliance. Although the exercise regimen developed for this study is basic, it is also easy to adapt, safe, not time consuming and doesn't require equipment or a specific setting (can be done at home, office or gym). These factors will help in compliance, unlike the heavy exercise regimen found in the body of literature which makes this study more significant and unique.

Moreover, other studies imposed a caloric deficit diet in their IF arm, which would lead to weight loss with or without IF and exercise. However, in the study of Del Corral et al. (2009), participants' adherence declined with the decrease in caloric intake [32]. Therefore, in this study, no dietary restriction beyond the course of IF will be imposed in the fasting arm, eventually allowing to evaluate relationship of IF and weight.

At the cellular level, energy restriction leads cells to develop a stress-resistant state by reducing insulin signalling and the total protein synthesis; this, on the long term, shows that the maintenance of an intermittent-fasting diet especially combined with regular exercise, leads to several adaptations that ultimately improve mental and physical performance and increase disease resistance [33].

In a recent systematic review and meta-analysis by Correia et al. (2020) which evaluated the effect of two modalities of intermittent

fasting (Ramadan intermittent fasting and time-restricted feeding), the review concluded that despite there were evidence suggesting that Ramadan intermittent fasting may negatively affect aerobic exercise performance, TRF may actually improve it [13].

One of the expected limitations in this study is participant compliance. We do anticipate a significant number of dropouts due to different reasons: inability to commit to the instructions, adverse effects, or personal reasons. To limit the effect of such a challenge, we have almost doubled the number of needed participants; additionally, during analysis phase, both intention-to-treat and per protocol analyses will be conducted.

Additionally, another limitation lies in the fact that several parameters are measured on the basis of self-reported tools. We have only included time-tested and cross-culturally adapted tools that have been used in our population.

Intermittent fasting is a very trendy topic now-a-days, both in research field and people's interest. With increasing number of studies evaluating the promising effect of IF on different health aspects from metabolic panel, weight loss, diabetes, and cardiovascular disease and others. This trial will be among the few currently available evidence that help better understand the effect of IF on aerobic physical performance, as well as on metabolism, glycemic control, and several health and self-reported parameters. This will set forth the ground for future research based on our results, ultimately serving both scientific and clinical fields.

Author contributions

AM conceptualized the study idea and serves as the principal investigator overseeing the study and is the medical personnel in charge of medical monitoring and follow-up. TG serves as the co-investigator designed the physical exercise elements of the study and responsible for supervising the exercise aspects. JJF serves as the co-investigator in charge of the nutritional design of the study and runs the nutrition lab where majority of phases of participation will take place. AEO, LG and HM constitute the research personnel who conducted extensive literature reviews, participated in study design, designed the analytical scheme of the study and drafted the original manuscript. AM, TG, and JJF provided critical review of the manuscript. All authors read and approved the final manuscript. CB participated in nutritional design of the study and in manuscript writing and serves as research personnel in the nutrition lab.

References

[1] R.E. Patterson, G.A. Laughlin, A.Z. LaCroix, S.J. Hartman, L. Natarajan, C. M. Senger, et al., Intermittent fasting and human metabolic health, J. Acad. Nutr. Diet. 115 (8) (2015) 1203–1212, https://doi.org/10.1016/j.jand.2015.02.018. Available from:.

[2] R.E. Patterson, D.D. Sears, Metabolic effects of intermittent fasting, Annu. Rev. Nutr. 37 (1) (2017 Aug 21) 371–393. Available from: http://www.ncbi.nlm.nih.gov/pubmed/28715993.

[3] E. Levy, T. Chu, Intermittent fasting and its effects on athletic performance, Curr. Sports Med. Rep. 18 (7) (2019 Jul) 266–269. Available from: http://journals.lww.com/00149619-201907000-00006.

[4] M.P. Harber, L.A. Kaminsky, R. Arena, S.N. Blair, B.A. Franklin, J. Myers, et al., Impact of cardiorespiratory fitness on all-cause and disease-specific mortality: advances since 2009, Prog. Cardiovasc. Dis. 60 (1) (2017 Jul) 11–20. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0033062017300439.

[5] J.A. Laukkanen, T.A. Lakka, R. Rauramaa, R. Kuhanen, J.M. Venäläinen, R. Salonen, et al., Cardiovascular fitness as a predictor of mortality in men, Arch. Intern. Med. 161 (6) (2001 Mar 26) 825. Available from: http://archinte.jamanetwork.com/article.aspx?doi=10.1001/archinte.161.6.825.

[6] K. Mandsager, S. Harb, P. Cremer, D. Phelan, S.E. Nissen, W. Jaber, Association of cardiorespiratory fitness with long-term mortality among adults undergoing exercise treadmill testing, JAMA Netw. Open 1 (6) (2018 Oct 19), e183605. Available from: http://jamanetworkopen.jamanetwork.com/article.aspx?doi=10.1001/jamanetworkopen.2018.3605.

[7] L.F. DeFina, W.L. Haskell, B.L. Willis, C.E. Barlow, C.E. Finley, B.D. Levine, et al., Physical activity versus cardiorespiratory fitness: two (partly) distinct components of cardiovascular health? Prog. Cardiovasc. Dis. 57 (4) (2015 Jan) 324–329. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0033062014001406.

[8] T.P. Aird, R.W. Davies, B.P. Carson, Effects of fasted vs fed-state exercise on performance and post-exercise metabolism: a systematic review and meta-analysis, Scand. J. Med. Sci. Sports 28 (5) (2018 May) 1476–1493. Available from:,, https://onlinelibrary.wiley.com/doi/10.1111/sms.13054.

[9] A.S. Roy, A. Bandyopadhyay, Effect of Ramadan intermittent fasting on selective fitness profile parameters in young untrained Muslim men, BMJ Open Sport Exer. Med. 1 (1) (2015 Sep 30), e000020. Available from: http://bmjopensem.bmj.com/lookup/doi/10.1136/bmjsem-2015-000020.

[10] MN Bin Naharudin, A. Yusof, The effect of 10 days of intermittent fasting on Wingate anaerobic power and prolonged high-intensity time-to-exhaustion cycling performance, Eur. J. Sport Sci. 18 (5) (2018) 667–676, https://doi.org/10.1080/17461391.2018.1438520. Available from:.

[11] T. Moro, G. Tinsley, A. Bianco, G. Marcolin, Q.F. Pacelli, G. Battaglia, et al., Effects of eight weeks of time-restricted feeding (16/8) on basal metabolism, maximal strength, body composition, inflammation, and cardiovascular risk factors in resistance-trained males, J. Transl. Med. 14 (1) (2016) 1–10.

[12] G.M. Tinsley, P.M. La Bounty, Effects of intermittent fasting on body composition and clinical health markers in humans, Nutr. Rev. 73 (10) (2015 Oct) 661–674. Available from: https://academic.oup.com/nutritionreviews/article-lookup/doi/10.1093/nutrit/nuv041.

[13] J.M. Correia, I. Santos, P. Pezarat-Correia, C. Minderico, G.V. Mendonca, Effects of intermittent fasting on specific exercise performance outcomes: a systematic review including meta-analysis, Nutrients 12 (5) (2020).

[14] A. Jeukendrup, Achten J. Fatmax , A new concept to optimize fat oxidation during exercise? Eur. J. Sport Sci. 1 (5) (2001 Dec) 1–5. Available from: http://www.tandfonline.com/doi/abs/10.1080/17461390100071507.

[15] J. Achten, A.E. Jeukendrup, Optimizing fat oxidation through exercise and diet, Nutrition 20 (7–8) (2004 Jul) 716–727. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0899900704000966.

[16] T. Purdom, L. Kravitz, K. Dokladny, C. Mermier, Understanding the factors that effect maximal fat oxidation, J. Int. Soc. Sports Nutr. 15 (1) (2018 Dec 12) 3. Available from: https://jissn.biomedcentral.com/articles/10.1186/s12970-018-0207-1.

[17] J.-S. Shim, K. Oh, H.C. Kim, Dietary Assessment Methods in Epidemiologic Studies, Epidemiol Health, 2014 Jul 22 e2014009. Available from: http://e-epih.org/journal/view.php?doi=10.4178/epih/e2014009.

[18] P. Moghames, N. Hammami, N. Hwalla, N. Yazbeck, H. Shoaib, L. Nasreddine, et al., Validity and reliability of a food frequency questionnaire to estimate dietary intake among Lebanese children, Nutr. J. 15 (1) (2015 Dec 12) 4. Available from: http://www.nutritionj.com/content/15/1/4.

[19] H. Sawaya, M. Atoui, A. Hamadeh, P. Zeinoun, 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, Psychiatr. Res. 239 (2016 May) 245–252. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0165178116304504.

[20] J.L. Bachman, R.W. Deitrick, A.R. Hillman, Exercising in the fasted state reduced 24-hour energy intake in active male adults, J. Nutr. Metabol. 2016 (2016) 1–7. Available from: https://www.hindawi.com/journals/jnme/2016/1984198/.

[21] A.V. Hill, C.N.H. Long, H. Lupton, Muscular exercise, lactic acid and the supply and utilisation of oxygen, Proc. R. Soc. B Biol. Sci. 97 (682) (1924 Dec 1) 155–176. Available from: http://rspb.royalsocietypublishing.org/cgi/doi/10.1098/rspb.1924.0048.

[22] P.G. Snell, J. Stray-Gundersen, B.D. Levine, M.N. Hawkins, P.B. Raven, Maximal oxygen uptake as a parametric measure of cardiorespiratory capacity, Med. Sci. Sports Exerc. 39 (1) (2007 Jan) 103–107. Available from: https://insights.ovid.com/crossref?an=00005768-200701000-00017.

[23] N.T. Broskey, A. Boss, E.-J. Fares, C. Greggio, G. Gremion, L. Schlüter, et al., Exercise efficiency relates with mitochondrial content and function in older adults, Phys. Rep. 3 (6) (2015 Jun), e12418. Available from:om: https://physoc.onlinelibrary.wiley.com/doi/full/10.14814/phy2.12418.

[24] C. Gibbons, M. Hopkins, K. Beaulieu, P. Oustric, J.E. Blundell, Issues in measuring and interpreting human appetite (Satiety/Satiation) and its contribution to obesity, Curr. Obes. Rep. 8 (2) (2019 Jun 29) 77–87. Available from: http://link.springer.com/10.1007/s13679-019-00340-6.

[25] D.J. Buysse, C.F. Reynolds, T.H. Monk, S.R. Berman, D.J. Kupfer, The Pittsburgh sleep quality index: a new instrument for psychiatric practice and research, Psychiatr. Res. 28 (2) (1989 May 15) 193–213. Available from: http://jcsm.aasm.org/ViewAbstract.aspx?pid=30744.

[26] T. Mollayeva, P. Thurairajah, K. Burton, S. Mollayeva, C.M. Shapiro, A. Colantonio, The Pittsburgh sleep quality index as a screening tool for sleep dysfunction in clinical and non-clinical samples: a systematic review and meta-analysis, Sleep Med. Rev. 25 (2016 Feb) 52–73. Available from: https://linkinghub.elsevier.com/retrieve/pii/S1087079215000210.

[27] M. Kang, B.G. Ragan, J.-H. Park, Issues in outcomes research: an overview of randomization techniques for clinical trials, J. Athl. Train. 43 (2) (2008 Mar) 215–221. Available from: http://natajournals.org/doi/abs/10.4085/1062-6050-43.2.215.

[28] K. Suresh, An overview of randomization techniques: an unbiased assessment of outcome in clinical research, J. Hum. Reprod. Sci. 4 (1) (2011) 8. Available from: http://www.jhrsonline.org/text.asp?2011/4/1/8/82352.

[29] L. Camelo, T. de S. Marinho, M.B. Águila, V. Souza-Mello, S. Barbosa-da-Silva, Intermittent fasting exerts beneficial metabolic effects on blood pressure and cardiac structure by modulating local renin-angiotensin system in the heart of mice

fed high-fat or high-fructose diets, Nutr. Res. 63 (2019 Mar) 51–62, https://doi.org/10.1016/j.nutres.2018.12.005. Available from:.

[30] K.S. Stote, D.J. Baer, K. Spears, D.R. Paul, G.K. Harris, W.V. Rumpler, et al., A controlled trial of reduced meal frequency without caloric restriction in healthy, normal-weight, middle-aged adults, Am. J. Clin. Nutr. 85 (4) (2007 Apr 1) 981–988. Available from: https://academic.oup.com/ajcn/article/85/4/981/4648934.

[31] A. Cho, J. Moon, S. Kim, K. An, M. Oh, J.Y. Jeon, et al., Effects of alternate day fasting and exercise on cholesterol metabolism in overweight or obese adults : a pilot randomized controlled trial, Metabolism 93 (2019) 52–60, https://doi.org/10.1016/j.metabol.2019.01.002. Available from:.

[32] P. Del Corral, P.C. Chandler-Laney, K. Casazza, B.A. Gower, G.R. Hunter, Effect of dietary adherence with or without exercise on weight loss: a mechanistic approach to a global problem, J. Clin. Endocrinol. Metab. 94 (5) (2009) 1602–1607.

[33] R. De Cabo, M.P. Mattson, Effects of intermittent fasting on health, aging, and disease, N. Engl. J. Med. 381 (26) (2019) 2541–2551.