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Toward Exercise Guidelines for Optimizing Fat Oxidation During Exercise in Obesity: A Systematic Review and Meta-Regression

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Abstract

Background

Exercise training performed at maximal fat oxidation (FAT_{max}) is an efficient non-pharmacological approach for the management of obesity and its related cardio-metabolic disorders.

Objectives

Therefore, this work aimed to provide exercise intensity guidelines and training volume **recommendations for maximizing fat oxidation in patients with obesity.**

Methods

A systematic review of original articles published in English, Spanish or French languages was carried out in EBSCOhost, PubMed and Scopus by strictly following the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) statement. Those studies that analyzed maximal fat oxidation (MFO) and FAT_{max} in patients with obesity (body fat > 25% for men; > 35% for women) by calculating substrate oxidation rates through indirect calorimetry during a graded exercise test with short-duration stages (< 10 min) were selected for quantitative analysis. The accuracy of relative oxygen uptake (% peak oxygen uptake [%VO_{2peak}]) and relative heart rate (%_{peak} heart rate [%HR_{peak}]) for establishing FAT_{max} reference values was investigated by analyzing their intra-individual and inter-study variation. Moreover, cluster analysis and meta-regression were used for determining the influence of biological factors and methodological procedures on MFO and FAT_{max}.

Results

Sixty-four manuscripts were selected from 146 records; 23 studies only recruited men (n = 465), 14 studies only evaluated women (n = 575), and 27 studies included individuals from both sexes (n = 6434). The majority of the evaluated subjects were middle-aged adults (aged 40–60 y; 84%) with a poor cardiorespiratory fitness ($\leq 43 \text{ mL}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$; 81%), and the reported MFO ranged from 0.27 to 0.33 $\text{g}\cdot\text{min}^{-1}$. The relative heart rate at FAT_{max} (coefficient of variation [CV]: 8.8%) showed a lower intra-individual variation compared with relative oxygen uptake (CV: 17.2%). Furthermore, blood lactate levels at FAT_{max} ranged from 1.3 to 2.7 $\text{mmol}\cdot\text{L}^{-1}$ while the speed and power output at FAT_{max} fluctuated from 4 to 5.1 $\text{km}\cdot\text{h}^{-1}$ and 42.8–60.2 watts, respectively. Age, body mass index, cardiorespiratory fitness, FAT_{max}, the type of ergometer and the stoichiometric equation used to calculate the MFO independently explained MFO values ($R^2 = 0.85$; $p < 0.01$). The MFO in adolescents was superior in comparison with MFO observed in young and middle-aged adults. On the other hand, the MFO was higher during treadmill walking in comparison with stationary cycling. Body fat and MFO alone determined 29% of the variation in FAT_{max} ($p < 0.01$), noting that individuals with body fat > 35% showed a heart rate of 61–66% HR_{peak} while individuals with < 35% body fat showed a heart rate between 57 and 64% HR_{peak}. Neither biological sex nor the analytical procedure for computing the fat oxidation kinetics were associated with MFO and FAT_{max}.

Conclusion

Relative heart rate rather than relative oxygen uptake should be used for establishing FAT_{max} reference values in patients with obesity. A heart rate of 61–66% HR_{peak} should be recommended to patients with > 35% body fat while a heart rate of 57–64% HR_{peak} should be recommended to

patients with body fat < 35%. Moreover, training volume must be higher in adults to achieve a similar fat oxidation compared with adolescents whereas exercising on a treadmill requires a lower training volume to achieve significant fat oxidation in comparison with stationary cycling.

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Key Points

The relative heart rate associated with exercise intensity that elicits maximal fat oxidation rate (FATmax) shows a lower intra-individual variation (coefficient of variation [CV]: 8.8%) compared with relative oxygen uptake (CV: 17.2%). The relative heart rate should be therefore recommended to establish FATmax reference values in patients with obesity.

Exercise intensity for optimizing fat oxidation in patients with obesity must be defined according to their body fat percentage. A sustained heart rate between 61 and 66% of peak heart rate should be used for enhancing fat oxidation in patients with a body fat percentage $\geq 35\%$ whereas a heart rate ranging from 57 to 64% of peak heart rate should be applied for patients with a body fat percentage $< 35\%$.

Age, body mass index, cardiorespiratory fitness and the type of exercise influence the maximal fat oxidation rate during exercise and must be considered when determining training volume at FATmax in patients with obesity. Specifically, adults would require a larger training volume than adolescents to achieve a similar fat oxidation, and individuals who train on a stationary bike would need a larger training volume to achieve significant fat oxidation in comparison with those who decide to walk on a motor-driven treadmill.

1 Introduction

Obesity is a major and growing public health challenge characterized by increased adiposity, chronic systemic inflammation, and metabolic inflexibility [1, 2]. This non-communicable disease is closely linked to the development of several cardio-metabolic disorders, including insulin resistance, oxidative stress, hypertensive status and an atherogenic profile [3]. Therefore, obesity is considered a risk factor for the development of type 2 diabetes (T2D) and cardiovascular diseases [4, 5].

Exercise is an effective non-pharmacological approach for the treatment and prevention of obesity and its related cardio-metabolic disorders [6]. The current exercise guidelines for patients with obesity provided by the American College of Sports Medicine and the World Health Organization are focused on increasing energy expenditure to achieve a negative energy balance and regulate body weight [7, 8]. Nevertheless, recent evidence suggests that prioritizing fat oxidation rates instead of energy expenditure during exercise might be more convenient for the prevention and management of obesity [9–12]. Indeed, over the past 20 years, several studies have demonstrated that exercise training performed at the intensity that elicits maximal fat oxidation (FATmax) improves body composition, cardiorespiratory fitness (CRF) endocrine function and metabolic flexibility in patients with obesity and type 2 diabetes [9, 13]. Previously, Maunder et al. [14] provided normative values for maximizing fat oxidation during aerobic exercise in men ($43 \pm 18\% \cdot \dot{V}O_{2max}$; N = 190) and women ($61 \pm 10\% \cdot \dot{V}O_{2max}$; N = 27) with obesity. However, such guidelines were based on a poor statistical power and were limited to young sedentary adults and stationary cycling [14]. Of note, the maximal fat oxidation (MFO) diminishes with aging in healthy individuals [15, 16], whereas fat oxidation rates are superior during running and rowing at FATmax in comparison with stationary cycling due to involvement of a larger muscle mass [17]. Thus, it seems that training recommendations for enhancing fat oxidation rate should be specific for age and exercise modality. Moreover, body fat and CRF are positively associated with MFO rates in patients with obesity [18–20], suggesting that exercise guidelines for optimizing fat oxidation in this population might depend on their physical fitness status.

With regard to methodological and analytical procedures, Peric et al. [21] reported that the stoichiometric equations used to calculate fat oxidation at FATmax create bias in the MFO values of around 7% in athletes. In addition, Amaro-Gahete et al. [22] demonstrated that analytical procedures used to model the fat oxidation kinetics during a graded exercise test (i.e., measured values vs polynomial regression) also influence the estimation of MFO and FATmax in lean subjects. To the best of our knowledge, the influence of stoichiometric equations or analytical procedures on the estimation of MFO and FATmax values in patients with obesity has not been yet investigated. Therefore, it is necessary to analyze whether the methodological approaches carried out to model fat oxidation kinetics should also be considered when prescribing exercise at FATmax in this population.

Several relatively accessible parameters are commonly used for exercise prescription in order to achieve a specific exercise intensity (i.e., heart rate, oxygen uptake, or workload) [6, 7]. However, the normative values provided by Maunder et al. [14] only reported the relative oxygen uptake at FATmax. According to previous studies, the absolute and relative heart rate associated with FATmax show a lower intra-individual variation [23–25], suggesting that FATmax heart rate may be more reliable to establish reference values for optimizing fat oxidation in patients with obesity. In addition, Bircher et al. [26] and San-Millán and Brooks [27] proposed that sustaining blood lactate (BLa) levels below ~ 2 mmol·L might be used for enhancing fat oxidation in patients with obesity and metabolic syndrome. However, such recommendation must be supported by further studies.

Considering the evidence discussed above, this review aimed to (i) evaluate the accuracy of different exercise intensity prescription methods for optimizing fat oxidation, and (ii) determine the influence of biological (i.e., age, body fat and sex), lifestyle (physical activity level [PAL]) and methodological (i.e., ergometer, stoichiometric equation, analytical procedures) factors on MFO and FATmax variation in patients with obesity.

2 Methods

2.1 Search Strategy

A systematic search was carried out in EBSCOhost, Pub-Med, and Scopus databases by introducing the following Boolean logic: (“maximal fat oxidation” OR “peak fat oxidation” OR “maximal lipidic power”) AND (FAT- max OR LIPOXmax) AND (obesity OR obese OR “type 2 diabetes”). Subsequently, the retrieved documents were filtered by language (English, French and Spanish) and publication date (from 1 January 2001 to 31 August 2022), since the first paper defining MFO and FATmax was published in 2001 [28]. The titles, abstracts, and full-text articles were independently screened by IACG and ARJ. A third author (FJAG) was consulted if there was uncertainty about article eligibility. In addition, the reference lists of relevant review manuscripts identified during the database search [9, 13, 29, 30] were screened to select potential studies based on the inclusion criteria (see Sect. 2.2). The Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) statement was strictly followed for the present report [31] (Fig. 1).

2.2 Inclusion Criteria

Studies with a cross-sectional or longitudinal design that analyzed MFO and FATmax by calculating fat oxidation rates through indirect calorimetry during a graded exercise test with short-duration stages (< 10 min) were selected for the present systematic review. The last criterion was based on the following arguments: (i) 10-minute stages are sufficient to reach a steady-state in gas exchange during low and moderate intensity exercise [32], and (ii) fat oxidation rates measured after 60 min of steady-

state exercise at FATmax are similar to MFO recorded during a single-graded exercise test (3-min stages) in men with obesity [18].

Obesity was defined according to body fat percentage (> 25 for men; > 35 for women) and fat mass index ($\geq 6.6 \text{ kg}\cdot\text{m}^{-2}$ for men; $\geq 9.5 \text{ kg}\cdot\text{m}^{-2}$ for women) cutoff points currently recommended for adults [33, 34]. In addition, children and adolescents were considered as obese if their body mass index (BMI) value was above the 95th percentile. Only the studies that evaluated MFO and FATmax in the morning were considered for quantitative analysis because both MFO and FATmax show a diurnal variation [35, 36].

2.3 Exclusion Criteria

Those studies that only reported the changes in MFO and FATmax induced by an exercise or nutritional intervention were excluded if the values at baseline could not be obtained from the corresponding author. Moreover, articles reporting duplicate data were also eliminated.

2.4 Data Collection Process

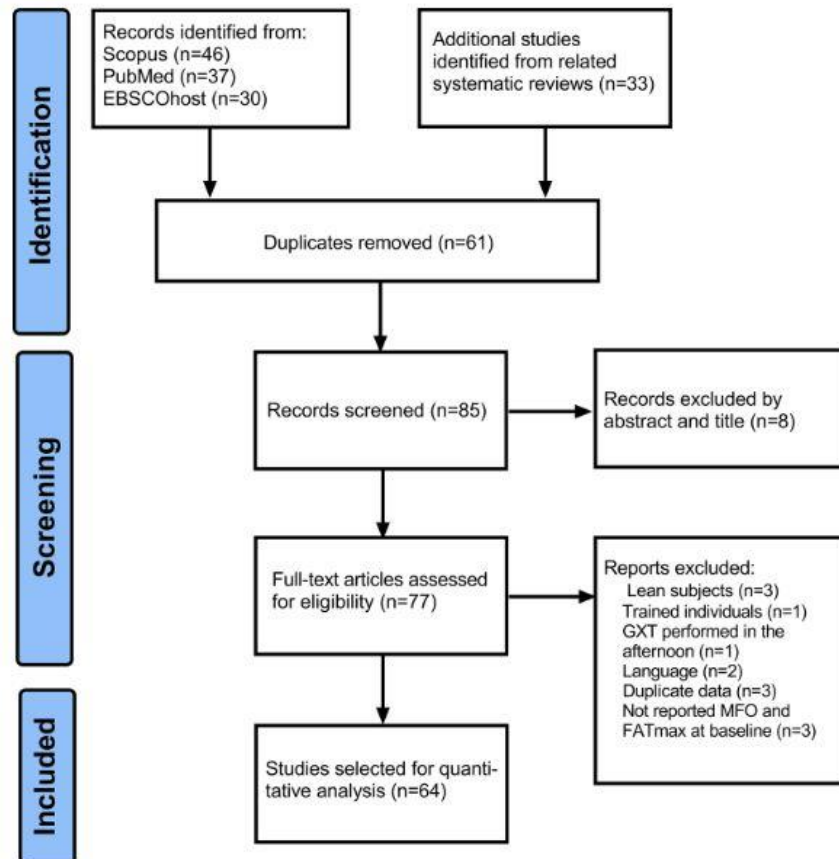
The following data were extracted from the included papers: author, publication date, sample size, study design, participants' characteristics (i.e., age, sex, ethnicity, BMI, body fat percentage, CRF), protocol of the graded exercise test (i.e., ergometer, initial workload, workload progression, stage duration), analytical procedure used for the assessment of MFO and FATmax (i.e., modeling of the fat oxidation curve, stoichiometric equations used to calculate macronutrient oxidation), MFO ($\text{g}\cdot\text{min}^{-1}$ or $\text{mg}\cdot\text{kg fat-free mass (FFM)}^{-1}\cdot\text{min}^{-1}$) and FATmax (i.e., % peak oxygen uptake [% $\text{VO}_{2\text{peak}}$], % peak heart rate (% HR_{peak}), oxygen uptake, heart rate, rate of perceived exertion, BLA levels, workload and energy expenditure). Additional data regarding the FATmax values were requested from the corresponding authors if the absolute or relative heart rate and workload data were not available in the manuscript. Furthermore, in those studies that did not report the MFO relative to FFM, this value was calculated from the mean absolute MFO and FFM reported in the manuscript using the following equation:

$$\text{MFO (mg}\cdot\text{kgFFM}^{-1}\cdot\text{min}^{-1}) = \frac{\text{MFO (g}\cdot\text{min}^{-1})(1000)}{\text{FFM (kg)}}$$

The guidelines provided by the American College of Sports Medicine were used to determine the CRF level according to age and sex in adults [37]. However, the CRF level in adolescents was interpreted based on the maximal oxygen uptake values reported for treadmill and cycle-ergometer exercise tests in this population [38]. Only the metabolic outcomes and physical fitness indicators measured at

baseline were considered from those studies that evaluated the chronic effect of any exercise or nutritional intervention over the MFO and FATmax. The data were independently recorded by ARJ, IACG and JFB using a template elaborated by IACG and FJAG in Microsoft Excel 2016 (IBM corporation, NY, USA) (Supplementary file 1, see electronic supplementary material [ESM]).

Fig. 1 Flowchart of the literature search and study selection process. *FATmax* exercise intensity eliciting MFO, *GXT* graded exercise test, *MFO* maximal fat oxidation



2.5 Statistical Approach

To determine the accuracy of the different intensity parameters used for exercise prescription, we computed their confidence intervals and intra-individual variation (coefficient of variation [CV]) using the mean and standard deviation reported in each study. However, to explore the influence of biological (i.e., age, body fat and sex), lifestyle (PAL) and methodological (i.e., ergometer, stoichiometric equation, analytical procedures) factors on the MFO and FATmax, we performed a cluster analysis (subgroup analysis) using the dendrogram, the sedimentation graph, the optimal number of clusters, and the K-means (Supplementary file 2, see ESM). Given that different metric units were used to represent the independent variables, the values were standardized by computing the Z-scores prior to performing the cluster analysis. Subsequently, a random effects meta-regression analysis was performed to validate the clustering and determine which of the associated variables independently predicted the variation of MFO and FATmax. For this analysis, the sample size of each study was used as the weight variable to correct for unequal variability in the observations retrieved from each study. Only the absolute MFO and relative oxygen uptake at FATmax were considered ($\text{g} \cdot \text{min}^{-1}$ and $\% \cdot \text{VO}_{2\text{peak}}$, respectively) for regression analysis since these outcomes showed the high-

est statistical power (see Table 1). All the obtained models met the assumptions of normality (Shapiro-Wilk), heteroscedasticity (Breusch-Pagan), non-collinearity (variance inflation factor [VIF]) and root mean square error (RMSE) (Supplementary file 3, see ESM). The analyses were performed in Jamovi version 2.3.13 and STATPGRAPHICS Centurion 16 version 16.1.03 (StatPoint Technologies Inc). In addition, the figures were elaborated in Prism version 8.1.

Table 1 Exercise intensity eliciting maximal fat oxidation in patients with obesity

Parameter	<i>n</i>	Mean (95% CI)	Intra-individual CV (95% CI)
% $\dot{V}O_{2peak}$	7188	44.8 (42.5–47.1)	17.2 (14.9–19.5)
$\dot{V}O_2$ (mL·kg ⁻¹ ·min ⁻¹)	683	14.4 (13.0–15.7)	19.7 (13.4–22.5)
%HR _{peak}	6351	61.7 (59.2–64.2)	8.8 (7.0–10.5)
Heart rate (beats·min ⁻¹)	6476	107 (101–113)	9.7 (8.0–11.5)
Power output (w)	5995	51.5 (42.8–60.2)	30.0 (23.5–36.3)
Speed (km·h ⁻¹)	196	4.6 (4.0–5.1)	17.1 (11.4–22.8)

%HR_{peak} percentage of peak heart rate, CI confidence interval, CV coefficient of variation, $\dot{V}O_2$ oxygen uptake, % $\dot{V}O_{2peak}$ percentage of peak oxygen uptake

3 Results

3.1 Literature Search and Selection

The search yielded a total of 146 records retrieved from databases and related systematic reviews. Then, 61 duplicate documents were removed leaving a total of 85 records for screening. After checking the document titles and abstracts, eight additional documents that were irrelevant to the topic of this review were eliminated. Full texts of the remaining 77 manuscripts were read and 13 were removed based on the inclusion and exclusion criteria, leaving 64 articles for quantitative analysis (Fig. 1) [18–20, 22–27, 36, 39–92].

3.2 Participant Characteristics

A total of 7474 individuals with obesity (2572 men and 4902 women) were evaluated in the analyzed studies (Supplementary File 1, see ESM), including 379 adolescents (< 18 years; 5%), 746 young adults (18–40 years; 10%), 6255 middle-aged adults (40–60 years; 84%) and

94 elderly adults (> 60 years; 1%). Eighty-one percent of the analyzed adults ($n = 5723$) had a very poor CRF according to their age and sex [37]. Furthermore, in 62% of the evaluated adolescents ($n = 234$), CRF was below normal values according to age and the ergometer used during the graded exercise test [38].

3.3 Methodological and Analytical Procedures for Determining MFO and FATmax

In 56 of the included studies (88%), the graded exercise test was performed after overnight fasting (10–12 h), whereas in four studies (6%), the graded exercise test was performed after 4 h of fasting. The exercise test was carried out in a postprandial state (2–4 h) in only four studies (6%). With regard to the type of exercise, 43 studies (67%) performed the graded exercise test on a stationary cycle-ergometer while 21 studies (33%) used a motor-driven treadmill for exercise testing. We identified four stoichiometric equations that were used to estimate fat oxidation rates during the graded exercise test: (i) the Frayn equation in 39 studies (61%), (ii) the Peronnet equation in 20 studies (31%), (iii) the Jeukendrup equation in three studies (5%), and (iv) the equation of Elia and Livesey in two studies (3%). Concerning the analytical procedure used for MFO and FATmax assessment, 33 studies (52%) used the measured values approach (i.e., visual inspection of the fat oxidation kinetics), 18 studies (28%) fitted a polynomial regression by plotting the fat oxidation rates against exercise intensity, nine studies (14%) used a mathematical equation that considered the lineal reduction in the respiratory exchange ratio with regard to the progressive increment of oxygen uptake and power output, and four studies (6%) conducted the sinusal mathematical modeling that considers the dilatation, symmetry and translation of the fat oxidation curve.

3.4 Maximal Fat Oxidation and FATmax

The absolute MFO rate ($0.30 \text{ g} \cdot \text{min}^{-1}$; 95% CI 0.27–0.33) was retrieved from 55 studies ($n = 7266$; 97%) while the MFO relative to FFM value ($4.4 \text{ mg} \cdot \text{kg FFM}^{-1} \cdot \text{min}^{-1}$; 95% CI 3.7–5.1) was available in 29 studies ($n = 6183$; 83%). The intra-individual variation of MFO ranged from 28 to 38% in the analyzed studies and was not influenced by age, BMI, CRF, ergometer or biological sex (not reported). In addition, the relative oxygen uptake was the most reported intensity parameter associated with FATmax, while the absolute and relative heart rates showed the lowest intra-individual variation (Table 1). Only five studies ($n = 185$; 2.5%) reported the BLa levels at FATmax ($2.0 \text{ mmol} \cdot \text{L}^{-1}$; 95% CI 1.3–2.7), whereas 10 studies ($n = 460$; 6.1%) reported energy expenditure corresponding to FATmax ($5.5 \text{ kcal} \cdot \text{min}^{-1}$; 95% CI 4.8–6.1).

3.5 Moderators of Maximal Fat Oxidation and FATmax

The MFO relative to FFM was not considered for statistical analyses due to low statistical power. Thus, the analysis of moderators was only possible for absolute MFO and FATmax. The cluster analysis revealed that two or three clusters were sufficient to adequately describe the participant characteristics and the associations between variables with 64–80% of the explained variance, respectively (Supplementary file 1, see ESM). Furthermore, the distribution of the second and third clusters through the standardized centroids of each variable was observed (Fig. S1, see ESM). The K-means analysis (Fig. 2A) revealed a solid arrangement of two clusters (> 1 SD of separation), where age was not a significant discriminating variable (< 0.5 SD). Individuals with higher BMI and body fat percentage also exhibited higher levels of MFO and FATmax. By adding a third cluster, the separation between the centroids (excepting age) generally decreased (Fig. 2B), especially the percentage

of body fat, BMI and FATmax (< 0.5 SD). When the stoichiometric equation used to calculate MFO was taken into account, separating the three clusters became more evident (Fig. 2C, D). Thus, we performed a multiple linear regression analysis to verify the clustering, considering both MFO and FATmax as the dependent variables. As can be seen in Fig. 3A, the regression analysis corroborated that age, BMI, CRF, FATmax, the type of ergometer and the stoichiometric equation used to calculate fat oxidation rates independently explained 85% of absolute MFO variation ($\text{g} \cdot \text{min}^{-1}$). Conversely, body fat and MFO alone determined 29% of the changes in FATmax (Fig. 3B). Neither biological sex, fasting lapse prior to the exercise test, nor the analytical procedure used to model the fat oxidation kinetics were associated with MFO and FATmax (not reported).

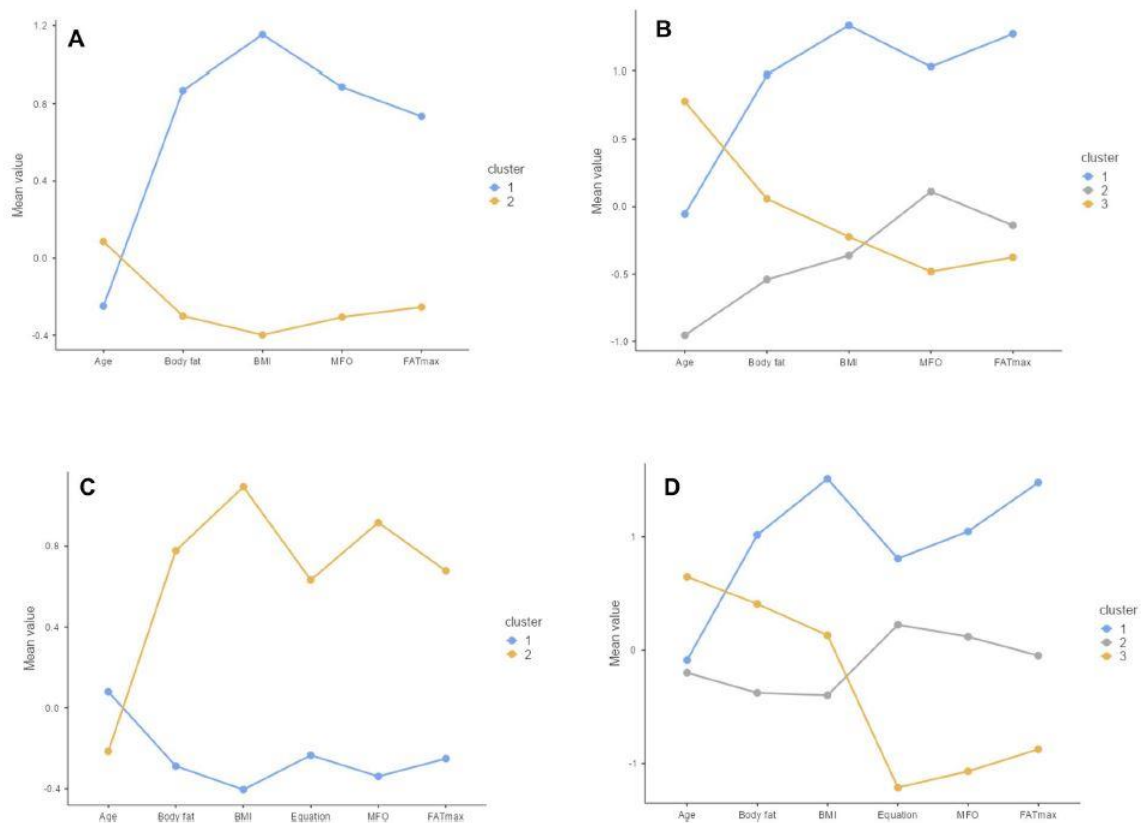


Fig. 2 Cluster analysis representing the biological and methodological factors influencing MFO and FATmax. Data are shown as standardized values of the K-means method. Two (A, B) and three (C, D)

cluster models. *BMI* body mass index, *FATmax* exercise intensity eliciting maximal fat oxidation, *MFO* maximal fat oxidation

4 Discussion

4.1 Exercise Intensity Guidelines for Optimizing Fat Oxidation in Patients with Obesity

The main purpose of this study was to provide exercise intensity guidelines that could be used by healthcare practitioners and exercise trainers to maximize fat oxidation in patients with obesity. In this regard, we found that relative oxygen uptake was the most reported intensity parameter corresponding to FATmax. However, the absolute (CV 9.7%) and relative (CV 8.8) heart rate at FATmax showed a lower intra-individual variation in comparison with oxygen uptake (CV 17.2), walking speed (CV 17.1), and cycling workload (CV 30%). This finding agrees with previous studies where the intra-individual variation of the relative heart rate

corresponding to different related metabolic thresholds (i.e., first lactate threshold, maximal lactate steadystate) was lower in comparison with relative oxygen uptake [93, 94], demonstrating that relative heart rate at FATmax is more convenient to establish reference values for exercise prescription. It should be mentioned that discrepancies between relative heart rate and relative oxygen uptake variation are mostly based on technological reasons rather than methodological ones, given that metabolic carts and their extrapolated value variables are well known to have a larger variation than heart rate recordings [95]. Of note, a complementary analysis revealed that the intra-individual variation of the heart rate at FATmax was not influenced by age, BMI, CRF, ergometer or biological sex (not reported). Hence, the absolute and relative heart rate seem to be the most convenient parameters for establishing FATmax exercise guidelines, independently of a participant's biological characteristics and the type of exercise used for that purpose. Recently, Chavez-Guevara et al. [13] reported that exercise training at FATmax improves cardiovascular function (i.e., ejection fraction and stroke volume) and CRF in patients with obesity over the long term. Therefore, it seems necessary to corroborate if the heart rate at FATmax remains stable across time or would require a repeated assessment to adjust the intensity corresponding to MFO. A previous study in young men with obesity reported that relative heart rate corresponding to FATmax remained stable after 15 days of FATmax training [65]; nevertheless, the effect of chronic exercise training performed at MFO over the heart rate corresponding to FATmax merits further analysis.

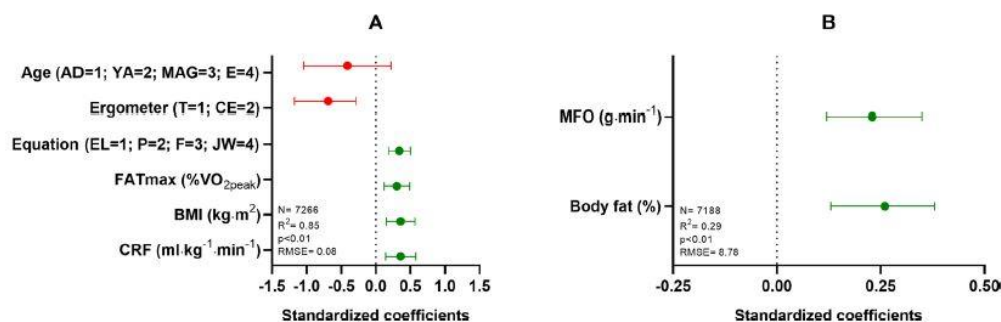


Fig. 3 Moderators of maximal fat oxidation rates (A) and FATmax (B) in patients with obesity. The plot presents the standardized coefficients (95% CI) determined by multiple linear regression. The R² denotes the variance of the dependent variable explained by the independent variables in combination. The green bars represent those moderators exerting a positive influence on the dependent variable while the moderators exerting a negative influence on the dependent variable are shown in red. Root mean square error, variance inflation

factor and the residual graphs were used as validation measures of the regression models. AD adolescents, BMI body mass index, CE cycle-ergometer, CRF cardiorespiratory fitness, E elders, EL Elia and Livesey, F Frayn, FATmax exercise intensity eliciting maximal fat oxidation, JW Jeukendrup and Wallis, MAG middle-aged adults, MFO maximal fat oxidation rate, P Peronnet, RMSE root mean square error, T treadmill, % VO_{2peak} percentage of peak oxygen uptake, YA young adults

On the other hand, Bircher et al. [26] and San-Millan and Brooks [27] reported that BLA levels at FATmax were close to $\sim 2 \text{ mmol} \cdot \text{L}^{-1}$, suggesting that this value should be used as a cutoff point for optimizing fat oxidation in patients with obesity. In this review, we only found five studies that determined the BLA values at FATmax in patients with obesity, estimating a confidence interval of 1.3–2.7 $\text{mmol} \cdot \text{L}^{-1}$ (Supplementary file 1, see ESM). Considering the upper limit of the aforementioned interval, the measurement error reported for different lactate analyzers (0.3–0.5 $\text{mmol} \cdot \text{L}^{-1}$) [96, 97] and the blood lactate level variation observed during steadystate exercise at FATmax [18], we recommend that sustaining BLA $< 3.0 \text{ mmol} \cdot \text{L}^{-1}$ would be a better criterion for optimizing fat oxidation in patients with obesity, given that some individuals would be working below their FATmax if sustaining BLA $\sim 2 \text{ mmol} \cdot \text{L}^{-1}$. Lactate accumulation within skeletal muscle fibers and into

the bloodstream down-regulates fat oxidation and adipose tissue lipolysis, respectively, through several mechanisms comprehensively described elsewhere [98, 99]. Recently, Chavez-Guevara et al. [94] reported that the first lactate threshold is located at BLa levels below $\sim 3.0 \text{ mmol} \cdot \text{L}^{-1}$ and is strongly associated with FATmax in young men with obesity ($R^2 = 0.77, p < 0.01$). Therefore, sustaining BLa levels below $\sim 3.0 \text{ mmol} \cdot \text{L}^{-1}$ might prevent the inhibition of the fat oxidation process in muscle fibers of patients with obesity, a hypothesis that merits further examination.

Although the walking speed and power output at FATmax show a larger intra-individual variation in comparison with absolute and relative heart rate, the narrow confidence interval observed for these parameters ($< 1 \text{ km} \cdot \text{h}^{-1}$; $< 20 \text{ watts}$) does not represent a relevant difference from the exercise prescription perspective. In fact, such ranges are lower than workload progression observed during a graded exercise test in this population ($+ 1 \text{ km/h}$ or 20 watts at each stage). Thus, walking at $4.0\text{--}5.1 \text{ km} \cdot \text{h}^{-1}$ or cycling at $43\text{--}60 \text{ watts}$ should also be recommended for maximizing fat oxidation in patients with obesity.

4.2 Moderators of Maximal Fat Oxidation

4.2.1 Biological Factors and Physical Fitness

The present review also aimed to determine the moderators of MFO and FATmax with the purpose of providing training volume recommendations according to biological characteristics, physical fitness and the type of exercise. In this regard, the meta-regression analysis revealed that age, BMI, CRF, FATmax, the type of exercise and the stoichiometric equations used to calculate fat oxidation rates explained 85% of absolute MFO variation in patients with obesity (Fig. 3A). Previous studies demonstrated that fat oxidation during exercise decreases in the transition from childhood to adolescence and the transition from adolescence to adulthood [15, 52, 100]. Such metabolic shifts are mainly observed in males and can be attributed to (i) a decrement in muscle mitochondrial oxidative capacity, (ii) a reduction in the proportion of type 1 muscle fibers and (iii) alterations in the endocrine response to exercise [101, 102]. The present analysis agrees with those observations by showing that age was inversely associated with absolute MFO in patients with obesity (Fig. 3A). The linear regression analysis revealed that adolescents exhibited a superior MFO in comparison with young adults ($0.32 \text{ g} \cdot \text{min}^{-1}$ [95% CI 0.23–0.41] vs $0.28 \text{ g} \cdot \text{min}^{-1}$ [95% CI 0.24–0.32]), although similar absolute MFO rates were observed among adolescents, middle-aged adults and elders (Supplementary file 4, see ESM). Of note, although the MFO relative to FFM was not considered in the cluster analysis due to low statistical power, a complementary regression analysis corroborated that MFO relative to FFM also decreases with aging (Supplementary file 4, see ESM). Therefore, adults would require a larger training volume in comparison with adolescents in order to achieve similar fat oxidation during exercise.

In agreement with previous studies, BMI and CRF were also positively associated with MFO [18–20]. Consequently, these factors should be considered when prescribing exercise at FATmax since patients with a higher BMI or CRF will achieve superior fat utilization during exercise. Interestingly, body fat percentage was not associated with MFO ($R^2 = 0.02$). Therefore, an elevated body weight might enhance energy expenditure during exercise, explaining the association between BMI and absolute MFO. Unfortunately, several studies included in the present systematic review did not report FFM values, limiting its inclusion in

the regression models. Thus, further studies are needed to corroborate the influence of body composition on MFO in people with obesity.

On the other hand, previous studies in young healthy individuals have consistently reported a sexual dimorphism in exercise fat oxidation [16, 103, 104]; nevertheless, our meta-regression analyses revealed that biological sex is not a critical determinant of MFO and FATmax in patients with obesity. Indeed, only four out of 64 studies included in this review directly compared the MFO values in men versus women with obesity [20, 43, 48, 84], and only Brun et al. [84] observed a modest difference in MFO between sexes (2.2 ± 0.7 vs 1.9 ± 0.1 mg \cdot kg FFM⁻¹ \cdot min⁻¹). To the best of our knowledge, the mechanisms that could explain the influence of nutritional status on the MFO sexual dimorphism have not been deeply investigated and require further examination.

4.2.2 Type of Exercise

The type of exercise was the major determinant of MFO with higher fat oxidation rates during treadmill walking in comparison with stationary cycling (0.37 [95% CI 0.33 – 0.42] vs 0.27 [95% CI 0.21 – 0.32] g \cdot min⁻¹). This finding supports the data reported in healthy lean individuals [17, 105, 106], and demonstrates that exercising on a treadmill would require a lower training volume to achieve significant fat oxidation in comparison with stationary cycling. Interestingly, a previous systematic review reported that walking is the preferred exercise modality of individuals with obesity [107]. Therefore, treadmill walking at FATmax might also favor a higher adherence to exercise training in this population.

The physiological mechanisms that could explain the discrepancies in fat oxidation between running and cycling are not fully understood. However, it has been proposed that treadmill running promotes a higher adrenergic response in comparison with cycling due to a larger recruitment of muscle mass [108]. An elevated adrenergic response may enhance adipose tissue lipolysis, increasing free fatty acids availability which is positively associated with MFO in healthy individuals [109]. However, further studies are needed to corroborate whether treadmill running stimulates a higher availability of circulating free fatty acids and a superior MFO in subjects with obesity. With regard to muscle mass activation, it has been proposed that a larger muscle mass recruitment will result in a higher energy expenditure, enhancing fat oxidation. Nevertheless, Filipovic et al. [17] reported that exercise performed on a rowing or elliptical ergometer does not result in superior fat oxidation in comparison with treadmill walking, even though a larger muscle mass is recruited during rowing and elliptical exercises. Therefore, it seems that muscle mass recruitment is not the major determinant of substrate oxidation. A possible explanation for the discrepancies in fat oxidation observed between cycling and walking on a treadmill might be the differences in muscle fiber recruiting patterns observed between exercise modalities. Interestingly, the increment in external mechanical power output during a sub-maximal exercise test was compensated for by augmenting the activity of the gastrocnemius, vastus lateralis and biceps femoris during cycling, whereas the increment in mechanical power output was compensated for by increasing the activity of the gastrocnemius during treadmill running [110]. According to Edgerton et al. [111], the gastrocnemius contains about ~ 50% of type I muscle fibers while the vastus lateralis contains only 32% of type I muscle fibers. Type I muscle fibers exhibit a superior oxidative capacity in comparison with type II muscle fibers and the former show a moderate correlation with MFO in healthy individuals [109]. Therefore, a larger activation of slow muscle fibers during running might favor a larger MFO in comparison with stationary cycling.

4.2.3 Analytical Procedures

With regard to the influence of stoichiometric equations used for calculating fat oxidation at FATmax, the equation proposed by Jeukendrup and Wallis predicted higher fat oxidation rates (0.44 [95% CI 0.34–0.55]) in comparison with the equations of Elia and Livesey (0.21 [95% CI 0.16–0.26]), Frayn (0.31 [95% CI 0.22–0.40]), and Peronnet (0.31 [95% CI 0.28–0.35]). This finding agrees with Peric et al. [37], who reported that stoichiometric equations used to calculate fat oxidation at FATmax bias the MFO values by around 7% in athletes. Interestingly, the majority of studies included in this review used the equations of Frayn and Peronnet to calculate fat oxidation during exercise whereas only three studies used the equation of Jeukendrup and Wallis. The equations of Frayn and Peronnet were validated for estimating substrate oxidation in resting conditions whilst the equation of Jeukendrup and Wallis is based on energy metabolism during exercise [112]. Therefore, a consensus is needed within the scientific community for a standardized analysis and report of MFO during exercise.

On the other hand, the analytical procedure used to model the fat oxidation kinetics did not influence the FATmax values in subjects with obesity, a finding that supports the observations of Amaro-Gahete et al. [22] and Cheneviere et al. [113] in lean sedentary individuals. This corroborates that FATmax could be determined by any procedure used to compute fat oxidation kinetics with the purpose of exercise prescription. However, it should be pointed out that mathematical modeling of the fat oxidation kinetics provides additional information (i.e., fat oxidation dilatation, symmetry and translation) that could be useful for evaluating the metabolic adaptations to exercise training.

4.3 Moderators of FATmax

Concerning FATmax, the meta-regression analysis showed that body fat percentage and MFO explained 29% of its variation (Fig. 3B), with body fat percentage as the major determinant of FATmax (Fig. 1A). Furthermore, this analysis revealed that the FATmax point is located between 61 and 66% HR_{peak} (44–47% VO_{2peak}) in individuals with a body fat percentage > 35%, a superior exercise intensity compared with that for individuals with a body fat percentage < 35% (57–64% HR_{peak}; 39–44% V O_{2peak}) (Supplementary file 4, see ESM). Therefore, body fat percentage must be taken into account to select an appropriate exercise intensity for maximizing fat oxidation. Specific exercise guidelines for optimizing fat oxidation in subjects with obesity are summarized in Fig. 4.

4.4 Study Strengths

The findings provided in the present review are based on the data reported by 64 studies that evaluated a total of 7474 individuals, representing a large statistical power. Such a significant amount of information retrieved for the statistical analyses was achieved by an exhaustive search of three different databases and an extensive search of the reference lists of review manuscripts related to MFO and FATmax. Moreover, the inclusion of manuscripts published in English, Spanish and French languages helped to overcome the language limitations. Finally, although the biological and methodological factors that influence MFO and FATmax have been exhaustively investigated in healthy individuals, this review was the first that analyzed their collective contribution to MFO and FATmax in patients with obesity.

4.5 Study Limitations

In this study, we were unable to consider the participants' ethnicity within the analysis of MFO and FATmax moderators because such information was only available in 18 of 64 studies (Supplementary file 1, see ESM). Recently, Demashkieh et al. [114] reported that MFO was superior in Chinese individuals in comparison with Indian and Malay men with obesity, therefore, the influence of ethnicity on MFO and FATmax in patients with obesity warrants further investigation. In addition, given that some exercise protocols were used by only one or two studies (Supplementary file 1, see ESM), we were unable to consider this methodological factor in the analysis of moderators. Previous studies have reported that stage duration of the graded exercise test [115, 116], and the time interval selected for calculating substrate oxidation can affect the estimated MFO values [22]. Hence further research addressing this topic is needed.

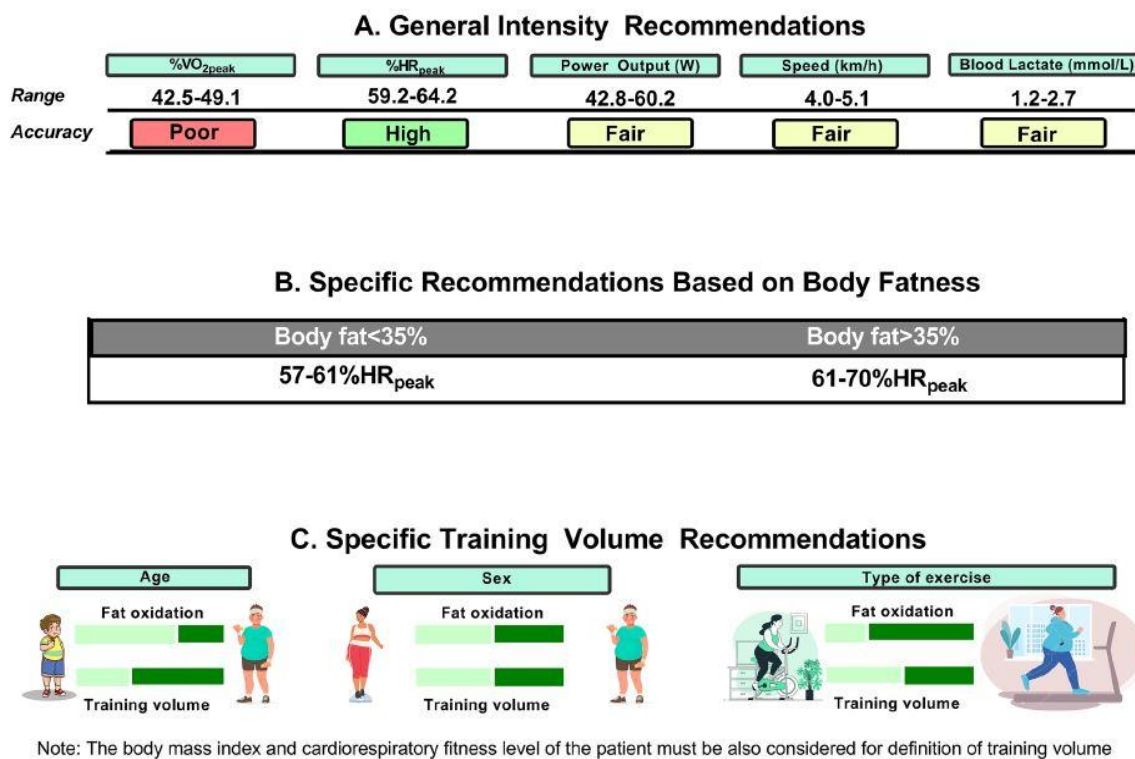


Fig. 4 Exercise guidelines for optimizing fat oxidation in subjects with obesity. HR_{peak} peak heart rate, VO_{2peak} peak oxygen uptake

The findings reported in this review are limited to exercise performed in the fasting state and should not be used for exercise prescription in the postprandial state. Previous studies have reported that the macronutrient content of the preceding meals affects substrate utilization during exercise in healthy individuals, with higher fat oxidation rates after consumption of high fat/low carbohydrate meals [59, 117]. Further studies are therefore needed to determine exercise guidelines for optimizing fat oxidation depending on the metabolic state (postabsorptive vs postprandial) and acute macronutrient consumption. In a similar way, we were unable to evaluate the influence of dietary phenotype on MFO and FATmax, given that the majority of studies did not assess the macronutrient intake of the diet. Fat and carbohydrate content of the diet are independent predictors of MFO in healthy individuals, explaining around 3% of the MFO variation [118, 119]. Moreover, recent studies conducted

in trained subjects reported that MFO increased ~ 2.0-fold after only 1–6 weeks of a low carbohydrate ketogenic diet [120, 121]. Thus, future studies are needed to establish exercise recommendations according to dietary phenotype.

Finally, the exercise intensity guidelines provided in this review can only be applied for exercise prescription in the morning (08:00–12:00 h), given that fat oxidation rates show a diurnal variation with a higher MFO in the evening versus morning [35, 36]. More research is needed to provide exercise guidelines specific to time of day and to elucidate the physiological mechanism associated with the circadian variation of fatty acid metabolism.

4.6 Future Directions

The present study provides practical exercise guidelines that can be easily used by exercise trainers and health care practitioners for exercise prescription in a basic clinical setting after performing routine analyses. However, it must be noted that both maximal oxygen uptake (CV: 2–4%) and maximum heart rate (CV: 1–3%) show considerable day-to-day variation [96], which may influence the reliability of the FATmax values reported herein. Indeed, previous studies in healthy individuals reported a large day-to-day variation in FATmax (Table 2; CV: 3–16%) [73, 122–127] that seemed to be influenced by methodological procedures rather than physical fitness [126]. Interestingly, Croci et al. [123] reported that relative heart rate at FATmax shows a higher reliability in comparison with relative oxygen uptake in healthy men. Nevertheless, to date, the reliability of FATmax in individuals with obesity has not yet been evaluated.

To overcome the limitations of exercise prescription based on maximum heart rate and oxygen uptake, several studies have investigated the accuracy of different metabolic and cardiopulmonary thresholds (i.e., first lactate thresholds, ventilatory thresholds, heart rate inflection point or heart rate variability thresholds) for an indirect and precise estimation of FATmax (Fig. 5) [94, 128, 129]. These studies are based on the metaboreflex paradigm that refers to a simultaneous transition in fat oxidation and cardiorespiratory function induced by muscle acidosis [94, 130]. However, as demonstrated by a recent systematic review, there is poor agreement between FATmax and lactate/ventilatory thresholds (limits of agreement: –25.6 to 13.7% VO₂max), which is highly dependent on the sex and physical activity of the subjects as well as the analytical procedures carried out for determining the lactate or ventilatory thresholds [131]. In a recent study, Chavez-Guevara et al. [94] demonstrated that both the heart rate inflection point and the first lactate threshold estimated by the log–log method proposed by Beaver et al. [132] could be used for determining FATmax in men with obesity with an estimation error of ~ 6 beats · min⁻¹, a variation that is commonly observed during steady-state exercise at FATmax [18]. Nevertheless, the reliability of such parameters and analytical procedures for an accurate estimation of FATmax in adolescents, middle-aged adults, elders and women with obesity warrants further investigation.

Establishing exercise guidelines for optimizing fat oxidation is of great relevance given that training at FATmax has proven to be more efficient than moderate continuous intensity training for body weight management and improvement of cardio-metabolic health [6, 9, 13, 133]. Indeed, only 2–3 d · wk⁻¹ of FATmax training (40–60 min · d) are sufficient to achieve significant body weight loss in subjects with obesity [13], whereas current guidelines provided by the American College of Sports Medicine state that 5–7 d · wk⁻¹ of moderate to vigorous exercise intensity (40–59% heart rate reserve) are necessary for achieving a weekly energy expenditure ≥ 2000 kcal that would favor a sustained weight loss in patients with

obesity [7]. According to the energy expenditure at FATmax reported by 10 of the analyzed studies in this review ($4.8\text{--}6.1 \text{ kcal} \cdot \text{min}^{-1}$), the weekly energy expenditure induced by 60 min of FATmax exercise performed 2–3 days per week would result in a weekly energy expenditure of 864–1098 kcal, which is lower than the recommendations of the American College of Sports Medicine. Therefore, targeting fat oxidation instead of energy expenditure during exercise seems to be more appropriate for the management of obesity. Indeed, recent studies have suggested that training in the lower limit of the FATmax zone (exercise intensity eliciting 90% of MFO) might be even more effective than training at FATmax for reducing body fat in patients with obesity by minimizing carbohydrate utilization during exercise and attenuating energy intake after exercise training [134, 135].

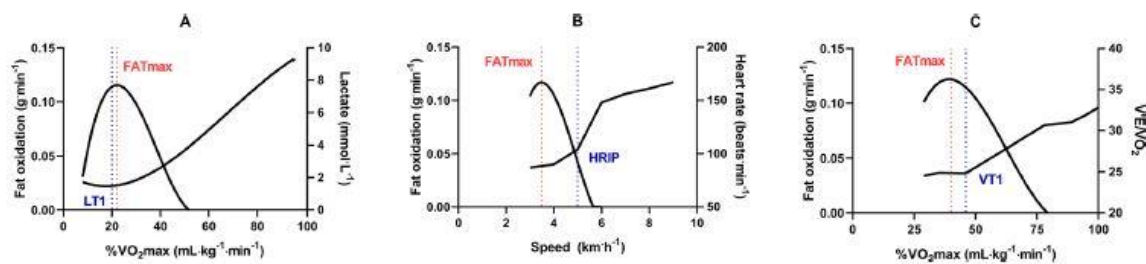


Fig. 5 Analysis of agreement between the exercise intensity that elicits maximal fat oxidation rate (FATmax) and the first lactate threshold (LT1) (A), the heart rate inflection point (HRIP) (B) and the first ventilatory threshold (VT1) (C). The kinetics of different physiologi-

cal parameters is based on the authors' own data collected during a graded exercise test in the fasting state. Fat oxidation and blood lactate kinetics were modeled by a polynomial regression analysis

It must be mentioned that exercise training at FATmax does not increase muscle mass in subjects with obesity [13]. Therefore, exercise training at FATmax should be combined with resistance training in order to improve the muscle strength and muscle mass of subjects with obesity.

In addition, a polarized training approach (i.e., intervals of high intensity and FATmax exercise) might provide superior benefits for cardiorespiratory and metabolic function, given that high intensity exercise promotes higher adaptations in CRF and MFO in comparison with moderate-intensity continuous training [136, 137]. Further research testing the aforementioned hypothesis is thus needed in order to optimize exercise prescription in people with obesity.

5 Conclusion

Relative heart rate rather than relative oxygen uptake should be used for the definition of FATmax reference values in patients with obesity. A heart rate between 61 and 66% HRpeak should be recommended to patients with body fat > 35%, while a heart rate between 57 and 64% HRpeak should be recommended to patients with body fat < 35%. Moreover, training volume must be higher in adults to achieve similar fat oxidation to adolescents, whereas exercising on a treadmill would require a lower training volume to achieve significant fat oxidation in comparison with stationary cycling.

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Conflict of interest

The authors declare that they have no conflicts of interests relevant to the content of this review. Availability of data and material The dataset supporting the findings reported in this review are available upon reasonable request from the lead author.

Author contributions

All authors contributed to the study conception and design. Data collection and analysis were performed by ARJ, IACG and JFB. The first draft of the manuscript was written by IACG and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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