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► **To cite this version:**

Jean-Frédéric Brun, J. Myzia, E. Varlet-Marie, Jacques Mercier, E. Raynaud. The weight-lowering effect of low-intensity endurance training targeted at the level of maximal lipid oxidation (LIPOX max) lasts for more than 8 years, and is associated with improvements in body composition and blood pressure. *Science & Sports*, 2022, 37 (7), pp.603-609. 10.1016/j.scispo.2022.03.002 . hal-03825258

HAL Id: hal-03825258

<https://hal.science/hal-03825258>

Submitted on 23 Oct 2022

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The weight-lowering effect of low-intensity endurance training targeted at the level of maximal lipid oxidation (LIPOX max) lasts for more than 8 years, and is associated with improvements in body composition and blood pressure

L'effet amaigrissant de l'entraînement d'endurance à faible intensité ciblé sur le niveau d'oxydation lipidique maximale (LIPOX max) se prolonge sur plus de 8 ans, et s'accompagne d'améliorations de la composition corporelle et de la pression artérielle

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KEYWORDS

LIPOX max;
Exercise;
Endurance;
Weight loss;
Obesity

Summary

Introduction and purpose. – The major problem in the management of obesity is the weight gain that occurs after all treatments currently employed. Regular physical activity remains the most effective measure to stop this weight gain. Among the types of training offered, endurance at low to moderate intensities targeting the level of maximum lipid oxidation (LIPOX max) is one of the easiest to implement and seems to stand out for its unexpected long-term effectiveness on fuel metabolism, eating behavior, and body composition. Our objectives in this study were

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to investigate the effect of this type of exercise on body composition after prolonged follow-up over 8 years.

Methods. – We continued to follow the cohort presented in our previous works showing the effectiveness at 1 year, 2 years, 3 years and 6 years of this training. In this non-randomized longitudinal study, the subjects were trained with LIPOXmax (3 × 45 min/week at home with regular follow-up, after induction in a hospital environment) with exercise calorimetry and segmental bioelectrical impedance which were carried out at the beginning and at the 104th month. 8-year extended follow-up results are available for 10 subjects.

Results. – Over the 8 years of follow-up, subjects lost on the average a maximum of -13.73 ± 2.63 kg ($P < 0.0002$) of body weight (i.e. -14.50 ± 2.06 of the initial weight or $-69.81 \pm 9.53\%$ of the excess weight) and at 96 months their weight is maintained -9.08 ± 2.31 kg below the initial weight (i.e. $-9.53 \pm 1.86\%$ of the initial weight or $45.07 \pm 8.94\%$ of the excess weight). Body composition analysis performed at the end of the 8th year shows that this corresponds to -9.51 ± 2.74 kg ($P < 0.001$) of fat and -2.23 ± 0.67 kg ($P < 0.02$) of non-muscular lean mass while the muscle mass remains statistically unchanged. The waist circumference decreases (-5.54 ± 1.96 cm $P = 0.015$) but not the hip circumference. The maximum ability to oxidize lipids has increased ($P < 0.001$) and especially if expressed by units of muscle mass ($+96\%$ $P = 0.0005$). There is also a decrease in diastolic blood pressure (-14.44 ± 4.58 mmHg $P < 0.02$) and mean blood pressure ($P < 0.02$).

Conclusion. – The follow-up of this cohort is still in progress but it confirms the prolonged effectiveness of endurance training targeted at the LIPOXmax over a period of at least 8 years. At this time, we observe that this weight loss affects the different components of fat mass (truncal and appendicular) but also lean mass only in its non-muscular component. The beneficial effects noted at 2 years on blood pressure and on muscle's ability to oxidize lipids during exercise is still observed at 8 years.

MOTS CLÉS

LIPOX max ;
Exercice ;
Endurance ;
LIPOXmax ;
lipides ;
Oxydation ;
Perte de poids ;
Obésité

Résumé

Introduction et objectif. – Le grand problème de l'obésité est la reprise pondérale qui s'observe après toutes les thérapeutiques actuellement utilisées. L'activité physique régulière reste la mesure la plus efficace pour enrayer cette reprise de poids. Parmi les types d'entraînement proposés, l'endurance à des intensités faibles à modérées ciblée sur le niveau d'oxydation lipidique maximale (LIPOX max) est une des plus faciles à mettre en œuvre et semble se singulariser par une efficacité inattendue à long terme sur le métabolisme glucolipidique, le comportement alimentaire et la composition corporelle. Nos objectifs dans cette étude ont été d'étudier l'effet de ce type d'exercice sur la composition corporelle après un suivi prolongé sur 8 ans.

Méthodes. – Nous avons continué à suivre la cohorte présentée dans nos travaux précédents montrant l'efficacité à 1 an, 2 ans, 3 ans et 6 ans de ce réentraînement. Dans cette étude longitudinale non randomisée, les sujets ont été réentraînés au LIPOXmax (3 × 45 min/semaine à la maison avec suivi régulier, après l'induction en milieu hospitalier) avec calorimétrie d'exercice et impédance bioélectrique segmentaire ont été réalisées au début et au 96^e mois. Les résultats de suivi prolongé sur 8 ans sont disponibles pour 10 sujets.

Résultats. – À 8 ans, les sujets ont perdu au maximum en moyenne $-13,73 \pm 2,63$ kg ($p < 0,0002$) de poids corporel (soit $-14,50 \pm 2,06$ du poids initial ou $-69,81 \pm 9,53\%$ de l'excès de poids) et à 96 mois, ils sont en moyenne $-9,08 \pm 2,31$ kg au-dessous du poids de départ (soit $-9,53 \pm 1,86\%$ du poids initial ou $45,07 \pm 8,94\%$ de l'excès de poids). L'analyse de composition corporelle réalisée en fin de 8e année montre que ceci correspond à $-9,51 \pm 2,74$ kg $p < 0,001$ de masse grasse et $-2,23 \pm 0,67$ kg $p < 0,02$ de masse maigre non musculaire alors que la masse musculaire reste statistiquement inchangée. Le tour de taille diminue ($-5,54 \pm 1,96$ cm $p = 0,015$), mais non le tour de hanches. La capacité maximale à oxyder les lipides a augmenté ($p < 0,001$) et, notamment, si elle est ramenée à la masse musculaire ($+96\%$ $p = 0,0005$), et il y a une baisse de la pression artérielle diastolique ($-14,44 \pm 4,58$ mmHg $p < 0,02$) et de la pression moyenne ($p < 0,02$).

Conclusion. – Le suivi de cette cohorte se poursuit, mais confirme l'efficacité prolongée de l'entraînement en endurance ciblé au LIPOXmax sur une période d'au moins 8 ans. À 96 mois, on observe que cette perte de poids affecte les différentes composantes de la masse grasse (tronculaire et appendiculaire), mais aussi la masse maigre uniquement dans sa composante non musculaire. Les effets bénéfiques notés à 2 ans sur la pression artérielle et sur l'amélioration de la capacité du muscle à oxyder les lipides à l'exercice persistent à 8 ans.

1. Introduction

The major problem in the management of obesity is the weight gain that occurs after all treatments currently employed [1,2]. Regular physical activity remains the most effective measure to stop this weight gain [3,4]. Among the types of training that can be currently proposed, endurance at low to moderate intensities targeted at the level of maximum lipid oxidation (LIPOX max) is one of the easiest to implement and has been demonstrated to be unexpectedly efficient [5] and even more to have a prolonged beneficial effect on carbohydrate and lipid metabolism, eating behavior and body composition [6].

Which is the time course of the effects of this variety of training over many years is not well studied. We had the opportunity to follow over more than 8 years patients included in the exercise group of a previous trial over 3 years [7]. Therefore, this study presents the follow-up over 8 years of this cohort undergoing such a training protocol at the LIPOXmax, whose results on shorter periods has already been reported previously [6–9].

2. Materials and methods

2.1. Subjects

As said in the introduction, this study represents the extension over 8 years of a previously published nonrandomized controlled longitudinal study that was performed over 3 years [7]. At this time, data on 10 patients (2 men, 8 women, age = 30–78 years) that continued the protocol over 8 years are available (see Table 1).

Subjects were trained at LIPOXmax (3 × 45 min/week at home with regular follow-up, after induction in our hospital unit).

Exercise calorimetry and segmental bioelectrical impedance were performed between 90 and 96 months.

2.2. Bioelectrical impedance measurements

The body composition of the trained subjects was assessed with the bioimpedance device BIACORPUS RX 4000 Biacorpus RX4000 (Healthnesslink, 8 avenue Jean-Jaurès 92130 Issy-les-Moulineaux, France) with data analysis with the software BodyComp 8.4, which uses an alternative electric current of 50 kHz [10,11] and calculates fat mass and fat-free mass in each segment of the body according to manufacturer's database-derived disclosed equations. Total water with published equations using the classical cylindrical model and Hanai's mixture theory [12]. Muscle mass was assessed with Janssen's equation from hand-foot resistance at 50 kHz [13].

2.3. Exercise calorimetry

All subjects were asked to come and perform test in the morning after an overnight fast (12 hours). The test consisted of five six-minute steady-state workloads theoretically set at 20, 30, 40, 50 and 60% of Pmax. However, these intensity levels can be modified during the test according to the evolution of the respiratory exchange ratio (RER = VCO₂/VO₂) in order to obtain values of RER below and above 0.9 which is the level of the Crossover Point (COP) which is defined below. The subjects performed the test on an electromagnetically braked cycle ergometer (Ergoline Bosch 500). Heart rate and electrocardiographic parameters were monitored continuously throughout the test by standard 12-lead procedures. Metabolic and ventilatory responses were assessed using a digital computer-based breath to breath exercise analyzing system (COSMED Quark CPET). Thus, we could measure VO₂, VCO₂ mL/min and calculate the non-protein RER. Lipid oxidation (Lipox) and carbohydrate utilization (Glucox) rates were calculated by indirect calorimetry from gas exchange measurements according to the non-protein respiratory quotient technique as previously reported [14]. This technique provided carbohydrate and lipid oxidation rates at different exercise intensities. Additionally, after smoothing the curves, we calculated the two parameters quantifying the balance between carbohydrates and lipids induced by increasing exercise intensity: the maximal lipid oxidation point (LIPOXmax) and the Crossover Point (COP). The LIPOXmax is the exercise intensity at which lipid oxidation reaches its maximal level before decreasing while carbohydrate utilization further increases. It is calculated as previously reported as the derivative of the empirical equation describing the kinetics of lipid oxidation as a function of power.

2.4. Coaching and follow-up of patients

Each subject included in the exercise group was enrolled at the beginning of the study and had to perform eight exercise sessions of 45 min at the LIPOXmax determined with the above described exercise test in order to include in his/her everyday life at least 3 similar bouts of low intensity endurance exercise per week. Subjects were followed monthly in outpatient unit for the first year and then every 3 or 4 months [8].

2.5. Statistical analysis

Descriptive statistics were used. A one-way analysis of variance (ANOVA) was used to determine the effect of training as a function of time. A *P*-value less than 0.05 was used to assess statistical significance.

Table 1 Presentation of the 10 subjects followed over 8 years (mean ± SEM).

Gender (M/F)	Weight (kg)	Age (yr)	BMI (kg/m ²)	FFM (kg)	Fat mass (kg)	Waist circumference (cm)	Hip circumference (cm)
2 M/8 F	93.30 ± 8.77	52.00 ± 4.35	34.25 ± 1.95	51.70 ± 4.39	41.19 ± 4.65	103.11 ± 6.79	110.00 ± 2.98



Figure 1 Crude weight loss while continuing regular activity targeted on the LIPOXmax over 8 years. One-way ANOVA $P < 0.001$.

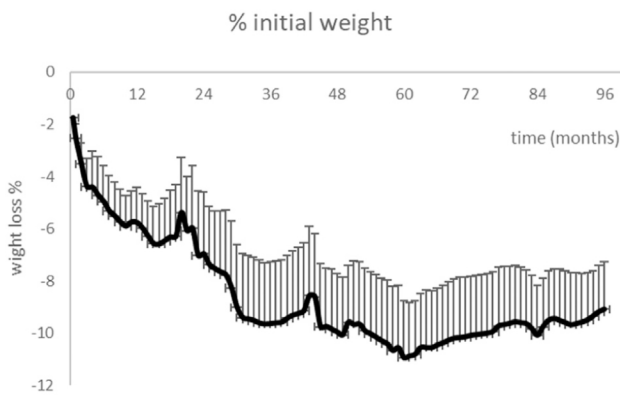


Figure 2 Weight loss expressed as percentage of the initial weight while continuing regular activity targeted on the LIPOXmax over 8 years. One-way ANOVA $P < 0.001$.

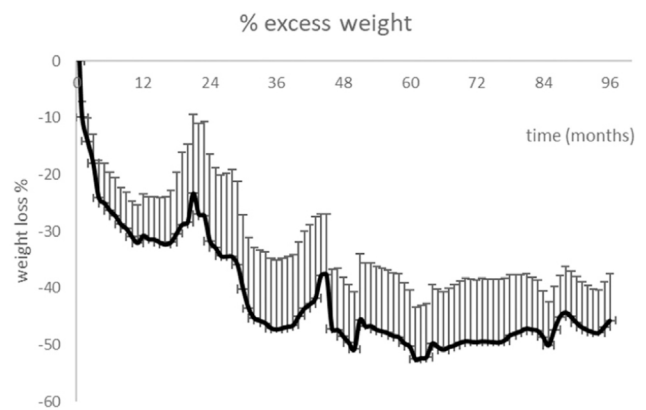


Figure 3 Weight loss expressed as percentage of the initial excess weight while continuing regular activity targeted on the LIPOXmax over 8 years. One-way ANOVA $P < 0.001$. This picture shows that the patients have lost during this period $-69.81 \pm 9.53\%$ of excess weight and that at 96 days they still maintain their excess body weight $-45.07 \pm 8.94\%$ below its initial value.

3. Results

As shown on Fig. 1, the previously demonstrated weight-reducing efficacy of endurance training at the LIPOX max is maintained over as long as 8 years. Fig. 2 shows the same results expressed in percentage of the initial weight and Fig. 3 shows the same results expressed in percentage of the initial excess weight. During the 8 years period subjects have lost up to -13.73 ± 2.63 kg so that at the 96 month they stand -9.08 ± 2.31 kg below the initial weight. This represents $-9.53 \pm 1.86\%$ of the initial weight i.e. $-45.07 \pm 8.94\%$ of excess weight. The average maximal weight loss in each subject was -14.50 ± 2.06 of the initial weight i.e. $-69.81 \pm 9.53\%$ of excess weight.

Fig. 4 shows the changes in body composition. In terms of body composition, there was a loss of fat mass -9.51 ± 2.74 kg $P < 0.001$ and a decrease in the non-muscular compound of fat-free mass (-2.23 ± 0.67 kg, $P < 0.02$) while muscular mass was not significantly changed (0.27 ± 0.73 kg NS).

Fig. 5 shows that lipid oxidation rates plotted against exercise intensity has increased. The maximal value of fat

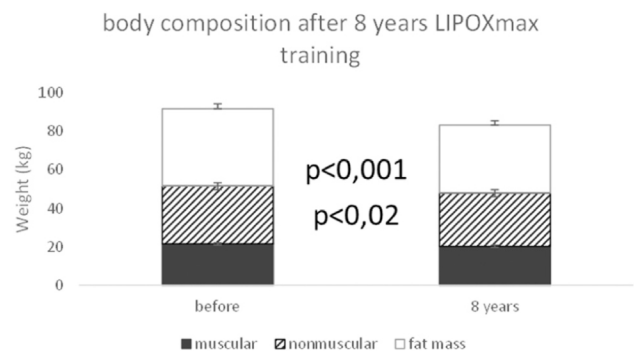


Figure 4 Changes in body composition. After 8 years, there is a decrease in fat mass -9.51 ± 2.74 kg $P < 0.001$ and a decrease in non-muscular fat-free mass (-2.23 ± 0.67 kg $P < 0.02$) while muscular mass was not significantly changed (0.27 ± 0.73 kg NS).

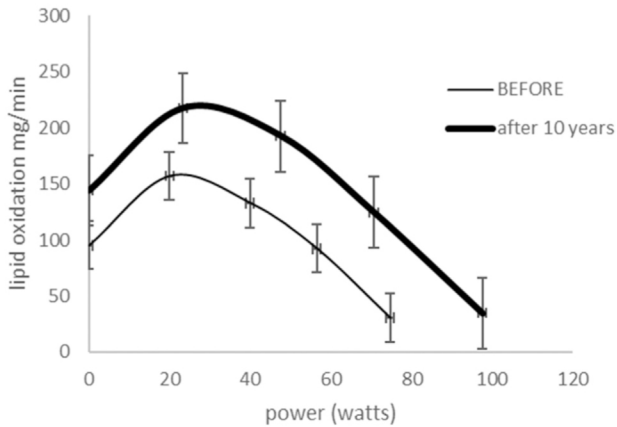


Figure 5 Lipid oxidation as a function of crude power intensity. There is an increase in the maximal fat oxidation flow rate (MFO) from 113.91 ± 24.44 to 189.13 ± 24.63 mg/min i.e. $83.28 \pm 12.01\%$ $P < 0.001$) while the intensity level at which this maximum occurs is not significantly improved. If LIPOX is expressed by kg of muscle mass, this improvement is even more important (5.99 ± 1.76 to 9.68 ± 1.41 , i.e. $+96.36\%$ $P < 0.001$).

oxidation flow rate (MFO) rises from 113.91 ± 24.44 up to 189.13 ± 24.63 mg/min i.e. an increase of $83.28 \pm 12.01\%$ ($P < 0.001$) which is even greater if LIPOX is expressed by kg of muscle mass (5.99 ± 1.76 to 9.68 ± 1.41 i.e. $+96.36\%$ $P < 0.001$). By contrast, the intensity level at which this maximum occurs is not significantly improved.

There is also an increase of VO_{2max} ACSM corrected by body weight (21.38 ± 2.53 to 29.90 ± 2.16 i.e. $+8.69 \pm 2.38$ mL/min/kg or $+40\%$ $P < 0.01$) while this tendency does not reach significance when VO_{2max} is expressed in crude units (2088.50 ± 321.58 to 2661.07 ± 357.96 $P < 0.05$).

Table 2 shows the improvement at 8 years of blood pressure, which is significant on this sample for diastolic and mean blood pressure.

4. Discussion

This study confirms that after 8 years, the weight-lowering effect of LIPOXmax training is maintained. There is a decrease in fat and in non-muscular fat-free mass while muscle mass remains statistically unchanged. There is also an improvement in aerobic working capacity and in the ability to oxidize lipids at exercise, and a decrease in blood pressure.

We think that the most important finding of the study is that individuals who continued over 8 years this training protocol have not regained their weight. It is well known that obesity has one of the highest refractory rates of all chronic diseases, in part because weight loss induced by calorie restriction, the first-line treatment for obesity, elicits biological adaptations that promote weight regain [15]. Research has shown that a variety of approaches are able to induce short-term weight loss but that more than 80% of successful individuals will then experience weight regain: after 1 year, 85%, after 2 years and over 95% after 3 years [16]. Actually, it becomes clearer that “dieting makes you fatter” because energy restriction induces adaptive fat overshooting via a physiological homeostatic mechanism [17].

Bariatric surgery which is the strongest strategy to lose weight at this time is also associated with a high percentage of weight regain [18]. Clearly, exercise is a strategy that minimizes this weight regain [19,20], but in, the case of high intensity high volume exercise, the RESOLVE study, despite its impressive results, shows that there is a trend to weight regain after 1 year [21].

Obviously, the average picture of weight loss over 8 years presented in this study does not mean that the evolution of weight was regular. In most persons, there has been one or more periods where weight started to increase but individuals were still in contact with our unit and came back for a closer follow-up to strengthen the adherence to the training protocol and weight decreased again. This was made possible by the fact that weight regain was much slower than what is found after diet. It can be logically assumed that diet induces mechanisms of active fat storage in response to caloric restriction [22], while a decrease in the volume of physical activity with more sedentary behavior leads to metabolic defects that increase fat storage, mostly in the trunk and the liver [23].

The unexpected efficacy of low intensity exercise strategies (and thus LIPOXmax training) is now demonstrated by several studies [24,25]. and meta-analyses [5]. Most of its effect is probably due to an effect on eating behavior [26,27] but also to epigenetic regulatory effects on factors regulating fuel metabolism [28]. More recently, myokines [29] and short term molecules generated by lipid breakdown called myometabokines [30] have been described and their action may explain why exercise training has beneficial effects beyond what could be expected from the traditional explanation that involves calorie deficit [31].

One of the main limitations of the study is that only patients that still remained in the training protocol are included in the final analysis at 8 years while we don't know

Table 2 Comparison of parameters of blood pressure before and after 8 years of targeted training at LIPOXmax (average values \pm SEM).

Systolic blood pressure (mmHg)	Diastolic blood pressure (mmHg)	Mean blood pressure (mmHg)	Pulse blood pressure (mmHg)
125.44 ± 3.19	81.89 ± 2.55	96.41 ± 1.56	43.56 ± 4.89
117.44 ± 3.91	67.44 ± 3.21	81.96 ± 4.08	50.00 ± 3.07
NS	$P < 0.02$	$P < 0.02$	NS

what has actually occurred with the other patients who have been lost of view. A quite wide range of percentages of attrition (from 10 to 80%) are reported in the literature [32]. An average rate of 50% was proposed by Fidelix [33]. Since the follow-up of our cohort is still in progress, we cannot exactly evaluate the rate of attrition but it is probably close of this value, and thus in agreement with what is generally reported in obesity studies.

Our findings at 8 years on body composition are similar to those previously reported by Hammoudi and coworkers after 2 years [9]. Consistent to what is observed after 2 years, there is a loss of both appendicular and truncal fat mass but also a decrease in fat-free mass. This loss of fat-free mass does not involve the muscular mass assessed by Janssen's equation but only the non-muscular component of fat free mass. As previously discussed in Hammoudi's paper [9], this finding should be interpreted under the light of the recent studies published by the team of I. Dionne [34] that pointed out a probable deleterious effect of higher values of fat-free mass on carbohydrate and fat metabolism. Therefore, a decrease in fat-free mass in this context should rather be interpreted as beneficial. The dramatic training-induced increase in the ability to oxidize fat expressed per unit of muscle mass is likely to mean that the metabolic properties of fat-free mass have been improved despite a slight volumetric reduction.

A moderate but significant effect on blood pressure is evidenced. Interestingly, this effect was not clearly evidenced in shorter studies [6–9] although it is very clearly found after a couple of months of interval training [35] and is thus not mentioned in the meta-analyses of Lipoxmax training [5,36]. It is clear that the effects of low intensity endurance and the effects of high intensity interval training are not similar and that interval training has strong blood pressure-reducing effects while those effects are not clearly found after short or middle-term training at low intensity [37,38]. It is thus interesting to notice that long term LIPOXmax training reduces blood pressure. Actually, the follow-up over 10 years of patients included in the STRIDE studies showed that the greatest 10-year reduction in blood pressure was found after moderate intensity exercise [39], further demonstrating that low intensity exercise is also able to improve blood pressure.

Some methodological aspects of the study need to be discussed. The protocol of exercise calorimetry used here is the one published in 2001 by Pérez–Martin's one [40]. This protocol uses 6 min steps, while other teams use 3 min steps. We have previously shown that such 3 min steps used by several investigators are actually too short to achieve a steady state in obese patients [41]. In addition, our protocol is based on the derivation of the equation of lipid oxidation, the point of maximal lipid oxidation being actually calculated as the point where the derivative of the equation plotting lipid oxidation against power intensity becomes equal to zero [14]. Therefore, this procedure called LIPOXmax is not fully equivalent to the FATmax procedure described by A. Jeukendrup and coworkers [42] and based on 3 min steps without such a calculation. On the whole, since the LIPOXmax is obviously a zone rather than a point, this technical difference is probably of minor importance for correct targeting of the exercise sessions. However, recent studies point out a poor reproducibility (and presumably reliability) of

peak fat oxidation in individuals with low cardiorespiratory fitness when assessed with steps of 4 minutes or less [43].

5. Conclusion

In conclusion, the follow-up of this cohort is continuing but our results confirm the prolonged effectiveness of endurance training targeted with LIPOXmax over a period of at least 8 years. At 96 months, we observe that this procedure results in a reduction of fat mass that is well maintained during this long period, together with an improvement in blood pressure. Despite a decrease in non-muscular fat free mass, muscle mass appears to be well maintained and there is a marked increase in muscle's capacity to oxidize lipids during exercise.

Further studies are needed to confirm this long-term effect and to see whether it is associated with alterations in other biological parameters and health issues.

Disclosure of interest

The authors declare that they have no competing interest.

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