Clinical Research

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EFFECTIVENESS OF TWO PHYSICAL ACTIVITY PROGRAMS ON NON-ALCOHOLIC FATTY LIVER DISEASE. A RANDOMIZED CONTROLLED CLINICAL TRIAL.

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ABSTRACT:

Background & Aims: Several studies have shown that lifestyle modification (reduced energy intake and/or increased physical activity) reduces Non-Alcoholic Fatty Liver Disease (NAFLD). We hypothesized that Aerobic exercise is more efficient to reduce NAFLD score in a primary care setting. Primary aim of this study was to estimate the effectiveness of two physical activity programs on NAFLD

Methods: Participants come from a survey conducted in the Apulian region of Italy. Subject with moderate or severe NAFLD were invited to participate. After informed consent, they completed a questionnaire, underwent ultrasonography and anthropometric measurements. Thus, they were randomized: Aerobic or Combined

Exercise programs and followed-up for six months. Adherence to the intervention was measured. A mixed linear model was applied to the data.

Results: Adherence to Aerobic Exercise was homogeneous and increased with time. Combined Program adherence was equal to 100% in every month for all subjects. There was no significant difference in NAFLD mean score by treatment at baseline (p=0.22) and after six months (p=0.65). However, there was a significant reduction in NAFLD mean score for treatments after six months (p< 0.01). The NAFLD measured score was reduced, on average, 22% in the Aerobic treatment group.

Conclusions: Combined program after 6 months was less or not as effective as Aerobic Exercise in reducing NAFLD score. This finding is relevant as Aerobic exercise programs are simple to implement and the cost-effectiveness is higher. Moreover, Aerobic exercise program is a realistic intervention which could be part of primary prevention of several chronic diseases.

INTRODUCTION

Non-alcoholic fatty liver disease (NAFLD) is the most common chronic liver disease in the Western World[1,2] is considered the hepatic manifestation of metabolic syndrome and is commonly associated with obesity and diabetes.[3,4] Moreover, NAFLD is an independent risk factor for cardio metabolic disease.[5,6] Worldwide prevalence varies between 20% and 33%. In northern Italy, prevalence of NAFLD was found to be approximately 25% in the general population, and is associated with most features of metabolic syndrome.[7]

Since there are a few pharmacological agents available to reduce ectopic fat, lifestyle interventions have become a focus of research. Therefore, weight loss is the recommended management strategy.

Weight loss via diet and physical activity reduce liver fat.[8,9] Nevertheless, a reduction of more than 3% of body weight is needed for hepatic benefit, with greater weight loss leading to superior benefits.[10]

Furthermore, several studies have shown that lifestyle modification based on reduced energy intake and/or increased physical activity induces improvement in biochemical and metabolic parameters, improves intrahepatic triacylglycerol concentrations and reduces steatosis and necro-inflammation detected in paired histologic analyses.[11-16]

Both aerobic and resistant training-based exercise programs improve liver fat contents [17] Several studies have shown that aerobic exercise programs of different intensity and duration with or without weight loss improve liver fat content.[12,18] On the other hand, also resistant training lead to a reduction of liver fat[19,20] and it has recently been reported either approach to be equally effective.[21] However, most studies have been hospital-based with highly selected patients.

To estimate the prevalence of some liver diseases in this Mediterranean area of Southern Italy a cohort was assembled[22] and a NAFLD prevalence of 24.6% was found. Furthermore, a sex-age specific NAFLD prevalence was found.

As most NAFLD patients are seen at the primary care setting the objective of this Randomized Clinical Trial (RCT) was to estimate the effectiveness of two different Physical Activity Programs on the NAFLD score as measured by Liver Ultrasonography (LUS) in this free-living population belonging to the Mediterranean Area.

PATIENTS AND METHODS

Study design

This study is registered at www.clinicaltrials.gov NCTO1798719. NutriEpatt was a parallel-group randomized controlled clinical trial. The sampled population was taken from the NutriEp survey, conducted at the National Institute of Gastroenterology, "Saverio de Bellis" Research Hospital (Castellana Grotte, Italy), from July 2005 to January 2007 and its details have been published elsewhere.[22,23] In brief, in collaboration with 12 General Practitioners (GP) working in Putignano (Puglia, Italy) and, after testing the hypothesis that the sex-age group specific mean was the same among the general population and subjects of the GP clinics, a random sample was drawn from the GP patients' list: 2550 subjects were invited to participate in the survey. Among these subjects, 2301 (90.2%) provided their written consent.

Participant Selection

Subjects with NAFLD were identified during the NutriEp enrolment process. Eligible participants were those individuals identified as having moderate or severe NAFLD (n=203). The exclusion criteria included: 1) overt cardiovascular disease and revascularization procedures; 2) stroke; 3) clinical peripheral artery disease; 4) Type 2 Diabetes Mellitus (T2DM) (current treatment with insulin or oral hypoglycaemic drugs, fasting glucose >126 mg /dl, or casual glucose >200 mg/dl); 5) good physical condition and normal exercise tolerance test; 6) other serious medical condition; 7) no pregnancy for women.

Subjects were invited to participate in the trial, and after a new assessment of the severity of NAFLD using LUS, those who agreed to participate provided their written informed consent.

The trial was designed and conducted by the authors at the Laboratory of Epidemiology and Biostatistics of the National Institute of Gastroenterology, "Saverio de Bellis", Research Hospital, Castellana Grotte (Italy), from March to December 2013 and data were analysed in 2016. All experimental subjects participated on voluntary basis, and the protocol was approved initially by the Technical-Scientific Review Board and then by the Ethical Institutional of National Institute of Gastroenterology, "Saverio de Bellis" Research Hospital (DDG n° 207, 07/04/2010). All participants provided written consent according to the Helsinki Declaration.

Randomization and Masking

Participants were randomly assigned, according to a computerized random numbers sequence, to one of two treatment groups and a one-to-one ratio was used to allocate them. Randomized group assignment was issued on completion of baseline assessments. Participants and exercise supervision personnel could not be practicably blinded to group assignment; however, the main study outcome was measured by blinded radiologists.

Each physical activity group was followed by one exercise supervisor who was initially assigned on random basis.

Sample Size

Sample size was estimated taking into account the repeated measurement of the outcome. From a previous study, [24] the mean (SD) score of NAFLD was estimated to be 4.5 (1) and 4.0 (0.5) for the treatment and control group respectively. Probabilistic errors type I and II were fixed at 5% and 10% respectively. Then the power of the study reached 90%. The correlation between baseline/follow-up (FU) measurements of the outcome was set to 0.4. A minimum sample size of n1=n2=40 was estimated, to obtain a 1-point reduction in NAFLD score after six months.

Intervention

Aerobic Exercise

Four non-consecutive day sessions lasting 45 minutes of moderate intensity aerobic activity (measured heart rate to ensure 65-75% VO2). Aerobic exercise intensity was monitored every 5 minutes using an automated heart rate monitor. Total weekly exercise duration: 180 minutes. The intervention occurred outdoor or indoor. The outdoor structure was a communal circuit of 3 km length located at Putignano where is possible to do physical activity.

Combined Exercise

Three non-consecutive day sessions including: a) 30 minutes of

moderate intensity aerobic activity (measured heart rate to ensure 65-75% VO2). Aerobic exercise intensity was monitored every 5 minutes using an automated heart rate monitor; b) two set of 11 exercises, each to volitional fatigue: leg press, adductor/abductor, glutei, biceps curl, triceps extension, three different abdominal exercises, let machine, low row, shoulder flexion. Approximate duration of each session about 40 minutes. The weight lifting was increased when 10 repetitions were completed with good form. Total weekly exercise duration: 210 minutes. The intervention occurred at 4 gyms located at Putignano: Nadir, Inda Club, New Sporting House and GymEnjoy.

Exposure Measurements

On the first visit, subjects were interviewed to complete a pre-coded questionnaire regarding socio-demographic issues, medical history and potential risk factors pertaining to some liver diseases. Alcohol consumption[25] and dietary habits (European Prospective Investigation on Cancer and Nutrition, EPIC) were also probed. Subjects were invited to complete a four day (including a one week-end day) dietary to estimate the actual dietary behaviour and the energy intake. Participants also completed the International Physical Activity questionnaire-IPAQ.[26] On the second visit, a fasting venous blood sample was collected. Liver function tests and others biochemical serum markers were assessed using standard laboratory test techniques. At this point in time, the staff also reviewed (and completed if necessary) the EPIC questionnaire, taking the opportunity to highlight the advantages of following the physical activity programs.

Body weight, height, and blood pressure were measured in standard conditions. During this second visit, participants were randomly assigned to one of two Physical Activity Interventions. The purpose of the study was explained in detail in a face-to-face interview. Personal advice was also provided in both groups, at the baseline visit and monthly thereafter. At the second visit, participants were instructed by a nutritionist to maintain the calorie intake determined at baseline. The monthly FU visit also included a face-to-face interview with the exercise supervisor to assess the compliance with the Physical Activity Program assigned and to give, if needed, personal recommendations to achieve the "group assigned" goal. During the baseline period, participants were instructed by nutritionist to continue a diet in order to maintain caloric intake and record the daily consumption of selected foods.

All exposure, anthropometric, biochemical and outcome measures were repeated at the third and sixth month of follow.

All intervention providers had high expertise and were trained during two months before the trial. Exercise Supervisors were specifically trained to reach the research goals as programmed. Nutritionists held meeting in order to advice to not change their dietary habits.

Fitness Evaluation

To evaluate the initial physical condition, the right training program and to compare the initial with FU assessment of physical condition, three field tests were carried out: the cardio respiratory, the strength and the flexibility fitness. Cardio-respiratory fitness was assessed by means of the 2-km Walking test as it is suitable for adults[27] whereas strength and the flexibility fitness were evaluated by means of the push-up test (also called press up test) [28] and the Sit and Reach test respectively.[29] All tests were repeated at third and sixth month FU.

Outcome Measurement

All subjects underwent LUS (Hitachi HI Vision E) testing. To obtain a semi-quantitative evaluation of fat in the liver, a scoring system was adopted. [30] NAFLD was then categorized as: absent (0), mild (1-2), moderate (3-4) and severe (5-6). A sub-sample of 30 subjects (ten subjects at enrolment, first and second FU respectively randomly chosen) underwent LUS by the two radiologists separately. An overall weighted Kappa of 0.9 was obtained. Only one of two radiologists performed outcome measurements each day and this order was also randomly assigned. In the outcome measurements relating to the third and sixth months, radiologists were unaware of the previous measurement.

Statistical Analysis

The primary analysis was intention-to-treat. In this paper only socio-demographic, biochemical, BMI and Fitness Index (at baseline) data were considered. For descriptive purposes, age at enrolment (<40, 40-59 and ≥60 years old), BMI (Normal, Overweight and Obesity), Glutamic pyruvic and Glutamic oxaloacetic transaminases (altered ≥40 U/l), Triglycerides (altered ≥165 mg/dl), Cholesterol (altered ≥200 mg/dl for men and ≥220 mg/dl for women), -glutamyl transpeptidase (altered >25 UI/l for men and >14 UI/l for women), Insulin (altered >29 >UI/ml), Glucose (altered ≥ 127 mg/dl), physical activity (Low <3 METs, Moderate 3-6 METs and High >6 METs), Systolic Blood Pressure (high >130mmHG) and Diastolic Blood Pressure (high >90mmHg) were categorized. A composite indicator of Socio-Economic Position (SEP) was built.[31]

Cross-tabulations between interventions and socio-demographic, life-style and biological variables were performed and proportion differences test was applied.

For the adherence to the physical activity programs (APAP), the four central months were assessed. The first, second, third, and fourth week of the second, third, fourth, and fifth month respectively were chosen to evaluate adherence. APAP was estimated as the proportion of effective gym or field sessions frequency/ time/ intensity in relation to the expected weekly frequency, time per session and intensity for the Aerobic Exercise group plus expected load for the Combined Exercise group. APAP was estimated by age-group, gender, and month and expressed as percentage.

A Mixed Linear Model was performed for the NAFLD score (outcome). Gender (categorical), BMI, Fitness Index, Cholesterol, Triglycerides, HOMA-Test Insulin, Glucose, and Age (continuous) were included as covariates as well as an interaction between Treatment and Time. The results are expressed as estimated coefficient 95% Confidence Interval (95% CI).

Statistical analysis was performed in Stata, version 141.

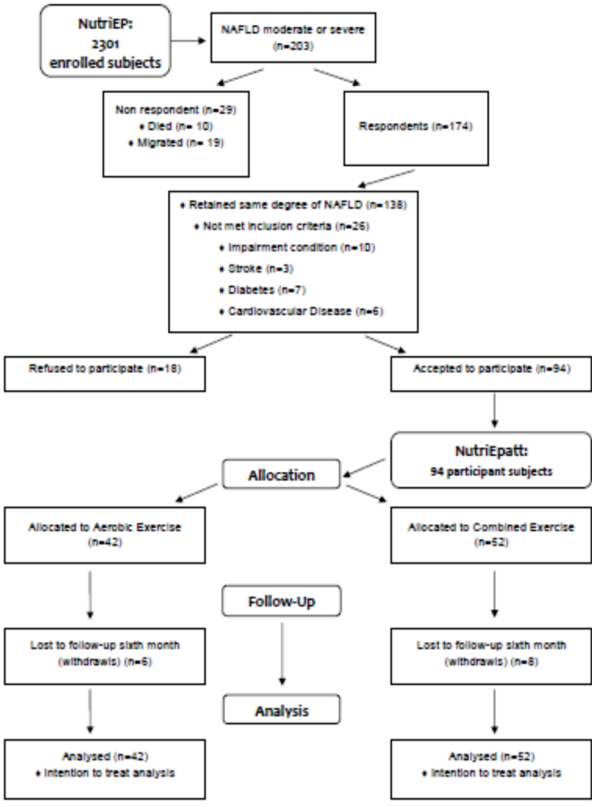
Patient involvement

After the assessment of NAFLD persistence at the first visit, subjects were invited to participate in small groups (6 subjects). In these groups were informed by the exercise supervisor and nutritionist about the research question and outcomes measures. All included subjects had the opportunity to choose where to do their aerobic program (indoor/outdoor), how to do it (walking, cycling, treadmill walking) and the week-days. Moreover, they chose the gym closer to their homes. Participant subjects had the opportunity to monitor their performance at each time. At the end of the trial, a workshop (subjects and operators) was organized and the results were disseminated.

RESULTS

NutriEp study had identified 203 participants as having moderate or severe NAFLD; 174 of these individuals responded to our letter to take part in the trial. Of these 174, 138 had preserved the grade of severity of NAFLD (Figure 1).

Ninety-four individuals agreed to participate and were randomly assigned to the Aerobic Exercise (n=42, six lost FU) or Combined Exercise (n=52, 8 lost FU) group.



NAFLD: Non-Alcoholic Fatty Liver Disease

Table 1 shows socio-demographic and some phenotypic characteristics of subjects by treatment groups.

	Treatment			
	Aerobic		Combined	
	No.	%	No.	%
Gender*				
Male	36	46.2	42	53.8
Female	6	37.5	10	62.5
Age(years)*				
<50	10	45.5	12	54.5
50-64	26	48.1	28	51.9
65 or >	6	33.3	12	66.7
Education*				
Illiterate	2	100.0	0	0.0
Elementary School	4	18.2	18	81.8
Middle School	12	46.2	14	53.8
High School	20	52.6	18	47.4
College	4	66.7	2	33.3
Job*				
Farmer	2	33.3	4	66.7
Worker	4	33.3	8	66.7
Employee	10	41.7	14	58.3
Trader	4	50.0	4	50.0
Freelance	6	75.0	2	25.0
Pensioneer	8	66.7	4	33.3
Housewife	4	40.0	6	60.0
Craftsman	4	28.6	10	71.4
Table 1 – part 1 Status*				
Single	2	100.0	0	0.0
Married	38	42.2	52	57.8
Widowed	2	100.0	0	0.0
SEP*				
Low	4	20.0	16	80.0
Medium	24	60.0	16	40.0
High	10	50.0	10	50.0
Body Mass Index*				
Overweight	14	58.3	10	41.7
Obesity I	18	37.5	30	62.5
Obesity II	10	45.5	12	54.5
NAFLD*				
Moderate	18	42.9	24	57.1
Severe	24	46.2	28	53.8
Fitness Score*				
Clearly below average	34	44.7	42	55.3
Slightly bellow average	4	33.3	8	66.7
On average	4	66.7	2	33.3
Total	42	44.7	52	55.3

*Proportion differences were not significat (α=0.05)

Table 1 – part 2
Biological and socio-demographic characteristics, NAFLD and Fitness scores (at baseline) of subjects by treatment groups. NutriEpatt project, Putignano (BA), Italy, 2013.

There were more men than women and most subjects had between 50 to 64 years old. An elevated percentage of people had finished high school education. Almost every participant was married, presented obesity and had a fitness score clearly below average. Men were mainly employee, freelance or pensioner whereas women were mainly employee and craftsman. Most participants belonged to medium or low SEP. Approximately half of subjects had a severe NAFLD score.

Aerobic Exercise NAFLD mean score was 4.9, SE 0.17 at the baseline and 2.8, SE 0.4 after six-months. Combined Exercise NAFLD mean score was 4.6, SE 0.12 at the baseline and 3.13, SE 0.4 after intervention. There was no significant difference in NAFLD mean score by treatment at baseline (p=0.22) and after six months (p=0.65). However, there was a significant reduction in NAFLD mean score for treatments after six months (p< 0.01).

About half of participants showed altered HOMA-Test, SGPT, -glutamyl transpeptidase, Total Cholesterol and Systolic Blood Pressure (Table 2).

*Proportion differences were not significat (α=0.05)

Table 2
Biochemical characteristics (at baseline) of subjects by treatment groups. *NutriEpatt* project, Putignano (BA), Italy, 2013.

	Treatment			
	Aerobic Exercise		**Mix Exercise**	
	No.	%	No.	%
HOMA Test (Baseline)*				
Normal	22	42.3	30	57.7
Altered	20	47.6	22	52.4
SGOT				
Normal	42	44.7	52	55.3
SGPT*				
Normal	34	43.6	44	56.4
Altered	8	50.0	8	50.0
Gamma-GT*				
Normal	36	46.2	42	53.8
Altered	6	37.5	10	62.5
Cholesterol*				
Normal	22	44.0	28	56.0
Altered	20	45.5	24	54.5
HDL-Cholesterol*				
Normal	38	47.5	42	52.5
Altered	4	28.6	10	71.4
Triglycerides*				

Normal	30	53.6	26	46.4
Altered	12	31.6	26	68.4
Systolic Blood Pressure (Baseline)*				
Normal	30	40.5	44	59.5
High	12	60.0	8	40.0
Diastolic Blood Pressure (Baseline)*				
Normal	42	44.7	52	55.3
Total	42	44.7	52	55.3

*Proportion differences were not significant (α=0.05)

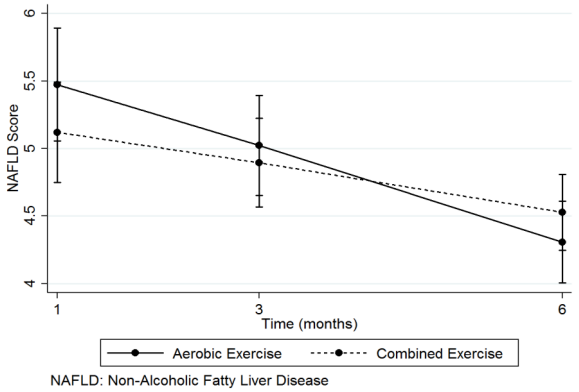
For male, adherence to Aerobic Exercise was homogeneous for weekly frequency, expected time per session (increasing with time) and expected intensity. On the contrary, women presented lower adherence mainly for the second item. Regarding to the Combined Program, adherence was equal to 100% in every month for all subjects (Table 3).

Table 3

Adherence to the physical activity program in the Aerobic Exercise group: percentage of the expected weekly frequency, time per session and intensity by sex and age. *NutriEpatt* project, Putignano (BA), Italy, 2013.

		Frequency (%)		Expected Time (%)		Expected Intensity (%)	
		Male	Female	Male	Female	Male	Female
Age (yrs)	**Month**						
<55	2nd	100		76.7		99.4	
	3rd	91.7		77.5		97.4	
	4th	100		92.1		94.4	
	5th	100		96.1		97.9	
55-64	2nd	100	100	71.4	65.0	97.8	100
	3rd	100	100	88.7	90.0	96.8	98.6
	4th	100	66.7	77.8	66.7	85.4	64.5
	5th	100	83.3	90.0	83.3	90.2	81.7
65>	2nd	100		60.0		100	
	3rd	100		80.0		100	
	4th	90.2		78.2		88.8	
	5th	100		87.3		96.5	

A complete factorial structure for treatments and time (main and interaction effects) was included in the model, adjusting by gender, age, BMI and biochemical covariates. Aerobic Exercise program was chosen as baseline. Even though the joint effect between treatment and time was significant, it is noteworthy the strong main effect of the latter. After 6 months of physical activity, the NAFLD score measured in subjects was reduced, on average, 22%. Combined program after 6 months was less or not as effective as Aerobic Exercise in reducing the NAFLD score (interaction term estimate was positive and equal to 0.5749, p=0.033). These results are displayed in Figure 2.



NAFLD: Non-Alcoholic Fatty Liver Disease

Mixed model presented an improvement of estimation process as regard of linear regression model (p<0.001 for likelihood ratio test, table 4).

Table 4 presents the results of mixed linear regression model.

Table 4

Results from mixed linear regression model of NAFLD score (outcome): estimates of physical activity programs and time effects. *NutriEpatt* project, Putignano (BA), Italy, 2013.

	Coefficients*	Standard Error	p value	95%CI**
Combined Program (Aerobic)	-0.353	0.281	0.211	-0.905, 0.199
Time				
3 months	-0.450	0.185	0.015	-0.813, -0.086
6 months	-1.166	0.216	0.001	-1.591, -0.741
Treatment*Time				
Combined-3 months	0.224	0.238	0.347	-0.243, 0.692
Combined-6 months	0.574	0.270	0.033	0.045, 1.104
Gender				
Female (Male)	-0.781	0.228	0.001	-1.229, -0.332
Age (continuous)	0.012	0.009	0.177	-0.005, 0.030
BMI (continuous)	0.168	0.021	0.001	0.126, 0.209
Random effects Parameters	Estimate	Standard Error		95%CI
Subject cluster				
Var(Time)	0.017	0.007		0.008, 0.040
LR test vs. linear model: chi2 (3) = 69.24; Prob > chi2 = 0.0000; *Adjusted for HOMA Test, Gamma GT, Tryglicerides and Cholesterol; ** 95%CI: 95% Confidence Interval.				

A high proportion of the outcome variability was captured by this model (conditional intra-class coefficient)

DISCUSSION

In this RCT, the Aerobic Exercise program was associated with a more intense reduction of the NAFLD score than the Combined Exercise program, measured by LUS. It indicates that 45 min four times a week of moderate-intensity walking (75% VO2 max obtained from HRM) results in a significant decrease (22%) of the NAFLD mean score.

Regular physical activity is now an established therapy preventing the onset and progression of several chronic diseases including NAFLD. [32] As the efficacy of exercise is now acknowledged, research has been focused in the optimal type, duration, frequency and intensity of physical activity training and most studies have conformed to doses recommended by the American College of Sport Medicine. [18]

Exercise influences hepatic metabolism and the adoption of either aerobic or strength exercise regimes result in reduction of hepatic fat accumulation, increased insulin sensitivity and fat oxidation, even in absence of weight loss. [33,34]

Aerobic exercise seems to increase the intracellular synthesis of triglycerides at muscle level, decrease fatty acids metabolites accumulation and suppress the inflammatory state associated with insulin resistance. [35,36] Although the risk to develop NAFLD or more advanced grades of liver diseases seems to be exercise dose-related, [37,38] recently it has been shown no significant differences in different intensity aerobic exercise regimens: all of them reduced liver's fat. [21]

Resistance exercise seems to induce a beneficial effect on NAFLD by enhancing circulating fatty acids and glucose uptake. Thus, it reduces the impact of hepatic insulin-stimulated de novo lipogenesis. [33,34] The efficacy of resistance training alone is not as clear as aerobic exercise but it has been shown a significant reduction of liver fat. [38,39]

Recently, it has been published that, at the community level, a combined exercise program is effective in reducing liver fat in NAFLD patients with an effect that is proportional to the degree of

weight loss but also without it[14] Moreover, several effect modifiers such as age, sex and ethnicity have been suggested as high-risk groups in the general population.[39]

This work aimed to estimate the effectiveness of two different programs of physical activity in this Mediterranean area and at population level. Aerobic Exercise program was more effective in reducing liver fat as measured by LUS. It is noteworthy that both programs may be associated with considerable health benefit as not only they reduce liver fat content but also contribute to improve many domains of life related to health.[40]

This study has several strengths namely: the characteristics of the study subjects, who are drawn from a survey of a population sample; the statistically adequate sample size and the controlled nature of the physical activity intervention.

A few subjects were lost in the FU stages. An intention-to-treat analysis was applied, thus there is no reason to assume that deviation from the protocol is related to prognosis.[41] To control for residual confounding several covariates were included in the linear mixed model in order to obtain more precise and reliable estimates. Diagnosis of NAFLD was performed by LUS which has generally considerable sensitivity and specificity [42,43] but may fail to detect hepatic fat content <25-30% thus underestimating the actual liver fat. The effect of this non-differential misclassification could, however, only produce a bias toward the null. [44] Moreover, other diagnostic methods such as liver biopsy, proton magnetic resonance spectroscopy or computed tomography are impossible in this setting due to ethical or economic reasons. The NutriEpatt study compares the effectiveness of an Aerobic Exercise with a Combined Exercise program and illustrates that the Aerobic Exercise program is more effective in reducing NAFLD scores in subjects who do not seek medical attention. This finding is relevant as Aerobic exercise programs are simple to implement and the cost-effectiveness is higher. In addition, Aerobic exercise program is a realistic intervention which could be part of primary prevention of metabolic and cardiovascular diseases.

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