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Received: 5 September 2023 | First decision: 25 September 2023 | Accepted: 4 October 2023

DOI: 10.1111/apt.17768

AP&T Alimentary Pharmacology & Therapeutics WILEY

Long-term follow-up of web-based and group-based behavioural intervention in NAFLD in a real world clinical setting

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Funding information
Fatty Liver—Inhibition to Progression, Grant/Award Number: HEALTH-F2-2009-241762

Summary

Background: The long-term results of web-based behavioural intervention in non-alcoholic fatty liver disease (NAFLD) have not been described in patients followed in specialised centres.

Aims: To analyse the long-term effectiveness of web education compared with the results achieved by a group-based behavioural intervention in the same years 2012–2014.

Methods: We followed 679 patients with NAFLD (web-based, $n = 290$; group-based, $n = 389$) for 5 years. Weight loss ≥10% was the primary outcome; secondary outcomes were attrition, changes in liver enzymes and in biomarkers of steatosis (Fatty liver Index) and fibrosis (Fibrosis-4 index).

Results: The cohorts differed in age, education, working status and presence of diabetes. Attrition was higher in the web-based cohort (hazard ratio: 1.53; 95% CI: 1.24–1.88), but not different after adjustment for confounders. Among patients in active follow-up, 50% lost ≥5% of initial body weight and 19% lost ≥10%, without difference between cohorts. Alanine aminotransferase levels fell to within the normal range in 51% and 45% of web- and group-based cohorts, respectively. Fatty Liver Index declined progressively and, by year 5, it ruled out steatosis in 4.8%, whereas 24.9% were in the indeterminate range. Fibrosis-4 index increased in both cohorts, driven by age, but the prevalence of cases ruling-in advanced fibrosis remained very low (around 1%). Improvements in the class of both surrogate biomarkers were associated with ≥5% weight loss.

Conclusions: Although burdened by attrition, web-based behavioural intervention is feasible and effective in NAFLD, expanding the cohort involved in behavioural programs and reducing the risk of progressive disease.

The Handling Editor for this article was Professor Vincent Wong, and it was accepted for publication after full peer-review.

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1 | INTRODUCTION

Non-alcoholic fatty liver disease (NAFLD) is one of the most common and rapidly growing conditions in the world, affecting approximately 25% of the total adult population.[1] Given its possible progression to advanced liver disease and hepatocellular cancer, with increasing direct and indirect costs,[2,3] NAFLD has become an important matter of concern for healthcare systems.[1–3] Despite intensive efforts by pharmaceutical companies, no drugs have so far been approved by regulatory agencies, and behaviour treatment aimed at healthy diet and habitual physical activity remains the sole effective NAFLD therapy.[4]

Unfortunately, adherence to behaviour programs remains low.[5] In the obesity and diabetes settings, where most of behaviour interventions have been developed, patients are trained to healthy diet and habitual physical activity via intensive face-to-face meetings or multiple group sessions that are very demanding for young individuals in their working life.[6] These approaches might result even less feasible in young NAFLD individuals, scarcely motivated to change lifestyle,[7] because they do not perceive a frequently asymptomatic liver disease as a threat for future life.[8,9]

To facilitate treatment adherence, online and offline web-based programs,[10] as well as apps and other telemedicine systems,[11] have been developed in the area of metabolic diseases.[12,13] They combine up to five technical key components: self-monitoring, counsellor feedback and communication, group support, structured programs or individually tailored programs.[14] The final aim is to increase awareness and motivation, by facilitating food planning and adequate calorie intake, and/or by recording time spent in physical activity and the intensity of exercise.[15]

Inside a European-funded program, in 2013 we expanded an original web-based behavioural program mimicking all the activities provided to patients attending our group-based obesity and diabetes classes.[16] The aim was to eliminate space and time constraints that limit attendance to hospital, to spare patients' and physicians' time, thus possibly expanding behavioural intervention to a much larger community. An initial 2-year report was published in 2018, supporting the use of the web-based intervention as possible alternative to hospital attendance.[17]

As part of the long-term surveillance of our NAFLD cohort, the aim of the present report is to provide a comprehensive and critical analysis of the 5-year real-world effectiveness and of the limits of intensive behavioural intervention in NAFLD, carried out either as group-based or web-based approach. We report a comparison in terms of adherence to follow-up, of successful body weight loss—the original primary outcome—and of changes in biochemistry and in surrogate biomarkers of both steatosis and fibrosis in the two cohorts.

2 | MATERIALS AND METHODS

2.1 | Patients

The study involved individuals with ultrasonography-diagnosed NAFLD attending the Unit of Metabolic Diseases and Clinical Dietetics, University of Bologna, from January 2012 to December 2014. During this period a web-based behavioural modification program was available, funded as part of the subproject FP7/2007–2013 FLIP (Fatty Liver—Inhibition to Progression), under grant agreement No. HEALTH-F2-2009-241762. They were part of the NAFLD cohort attending the outpatient service, a second-level centre for obesity and diabetes. According to our procedures, all NAFLD cases were routinely invited to enter a group-based behavioural modification program following initial assessment, diagnostic procedures and motivational interviewing.[18] Patients who agreed to treatment entered and completed the behavioural modification program (group-based intervention—GBBI); individuals who could not attend the program were provided with a user-id and a password to access a web-based intervention (WBBI), largely reproducing the protocol and the tools of GBBI. In addition, the study included a small group of patients ($n = 25$), enrolled into the web program following NAFLD diagnosis at the department of Gastroenterology, University of Turin.

The socio-demographic and clinical data of the present NAFLD cohort are described in Table 1. This long-term (5-year) follow-up analysis reports the effectiveness of interventions in 389 GBBI and 290 WBBI individuals until December 2019, when the SARS-COV-2 pandemic caused a disruption of hospital procedures. After enrolment in either program, all patients attended the clinic for follow-up visits every 6–12 months, according to disease severity, but no specific therapy for their liver disease. In the course of the years, patients with type 2 diabetes (30.7% of total) received drugs with possible hepatic effects: metformin, 73.1%; pioglitazone, 5.4%; glucagon-like peptide-1 receptor agonists, 3.8%; insulin, 6.8%; di-peptidyl-peptidase-4 inhibitors, 6.4%; sodium-glucose cotransporter-2 inhibitors, 2.9% (all drugs, no differences between WBBI and GBBI).

The study was initially approved by the ethical committee of Sant'Orsola-Malpighi Hospital, Bologna, as an interventional, non-pharmacologic study (No. 79/2009/U/Oss), and patients signed an informed consent before entering the program. Long-term comparison with the standard treatment (GBBI) is part of an internal audit to test the effectiveness of WBBI on specific outcomes.

2.2 | Weight loss programs

The protocols of both GBBI and WBBI are extensively reported in the original publication.[17] Both programs were not aimed at a severe calorie restriction, but at maintaining a control on long-term calorie intake aimed at progressive weight loss. The suggested calorie intake was between 1500 and 1800 calorie intake in males and between 1200 and 1500 in women, depending on BMI. No specific dietary plan was prescribed, but individualised advice was provided during follow-up visits to favour adherence. The web program required active participation to proceed and included a report on completeness of the five modules. Adherence to dietary counselling and habitual

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TABLE 1 Socio-demographic, clinical and biochemical values in NAFLD cases available for long-term follow-up.

	Total ($n=679$)	Web-treated ($n=290$)	Group-treated ($n=389$)	p value[a]
Sex (males, %)	52.9 (49.0–56.5)	63.1 (57.2–68.3)	45.2 (40.2–50.1)	<0.001
Age (years)	50.3 ± 11.6	46.5 ± 11.5	53.1 ± 10.9	<0.001
BMI (kg/m^2)	33.6 ± 6.0	33.9 ± 6.0	33.0 ± 6.0	0.339
BMI class				
Overweight (%)	29.2 (25.8–32.8)	31.7 (26.5–37.1)	27.2 (22.9–31.7)	0.146
Obesity (%)	70.8 (67.2–74.1)	68.3 (62.5–73.2)	72.8 (68.0–76.8)	
Waist circumference (cm)	106.7 ± 11.3	108.0 ± 13.6	105.7 ± 11.3	0.022
Hypertension (%)	42.8 (39.0–48.5)	33.6 (28.2–39.0)	49.6 (44.5–54.4)	<0.001
Diabetes (%)	30.7 (27.3–34.2)	16.3 (12.3–20.8)	41.4 (36.5–46.2)	<0.001
Prediabetes (IFG/IGT, %)	31.4 (27.9–35.0)	27.7 (22.5–33.1)	34.1 (29.4–39.0)	0.08
Education (%)				
Primary	1.6 (0.9–2.8)	0.7 (0.1–2.2)	2.3 (1.1–4.2)	<0.001
Secondary	12.5 (10.2–15.1)	7.6 (4.9–11.0)	16.2 (12.8−–20.0)	
Vocational	48.6 (44.8–52.3)	49.3 (43.4–54.9)	48.1 (43.0–52.9)	
Degree	37.3 (33.6–40.9)	42.4 (38.7–48.0)	33.4 (28.8–38.1)	
Employment status (%)				
Student	2.4 (1.4–3.7)	4.2 (2.3–6.9)	1.0 (0.3–2.4)	<0.001
Housewife	6.6 (4.9–8.7)	2.4 (1.1–4.7)	9.8 (7.1–13.0)	
Employed	62.4 (58.6–65.9)	65.7 (59.9–70.8)	59.9 (54.8–64.5)	
Self-employee	18.4 (15.6–21.5)	24.6 (19.8–29.7)	13.9 (10.7–17.5)	
Retired	10.2 (8.1–12.6)	3.1 (1.5–5.6)	15.4 (12.1–19.2)	
Fasting biochemistry				
Glucose (mg/dL)	111.2 ± 32.9	101.1 ± 25.2	118.5 ± 36.7	<0.001
Glycosylated haemoglobin (%)	6.64 ± 2.78	6.31 ± 3.22	6.81 ± 2.54	<0.001
AST (mU/mL)	34.2 ± 17.1	31.2 ± 17.1	36.5 ± 16.9	<0.001
ALT (mU/mL)	53.9 ± 30.8	47.2 ± 28.7	58.8 ± 31.1	<0.001
GGT (mU/mL)	55.1 ± 45.9	51.5 ± 53.9	57.7 ± 38.9	0.088
Total cholesterol (mg/dL)	212.1 ± 42.6	205.1 ± 42.4	217.3 ± 42.7	<0.001
HDL-cholesterol (mg/dL)	47.1 ± 13.4	45.8 ± 10.5	48.0 ± 15.2	0.036
Triglycerides (mg/dL)	179.7 ± 118.5	164.5 ± 139.8	190.9 ± 96.7	<0.001
LDL-cholesterol (mg/dL)	126.4 ± 45.9	124.6 ± 43.5	127.8 ± 47.6	0.366
Platelets (10^9/L)[b]	217.5 ± 45.6	228.0 ± 62.8	210.7 ± 27.5	<0.001
Surrogate markers				
Fatty liver index (score)	82.5 ± 17.2	81.6 ± 17.1	83.1 ± 17.2	0.247
FLI ≥ 60 (steatosis)	88.7 (86.0–90.8)	88.4 (83.9–91.5)	88.9 (85.3–91.6)	0.689
FLI (indeterminate)	10.3 (8.1–12.7)	10.9 (7.6–14.9)	9.8 (7.1–13.0)	
FLI < 30 (no steatosis)	1.0 (0.5–2.0)	0.7 (0.1–2.3)	1.3 (0.5–2.8)	
FIB-4 (score)[b]	1.19 ± 0.57	1.02 ± 0.50	1.21 ± 0.58	<0.001
FIB-4 < 1.30 (no severe fibrosis)	65.9 (61.4–69.9)	76.5 (69.6–81.7)	59.1 (53.2–64.4)	<0.001
FIB-4 (indeterminate)	32.0 (27.9–36.2)	22.5 (16.8–28.7)	38.1 (32.6–43.7)	
FIB-4 ≥ 2.67 (severe fibrosis)	2.1 (1.1–3.7)	1.1 (0.2–3.4)	2.7 (1.3–5.1)	

Note: Data are presented as means ± SD or as prevalence (95% CI).

[a]Student t test or χ^2 test.

[b]$N=478$ (Web = 187; Group = 291).

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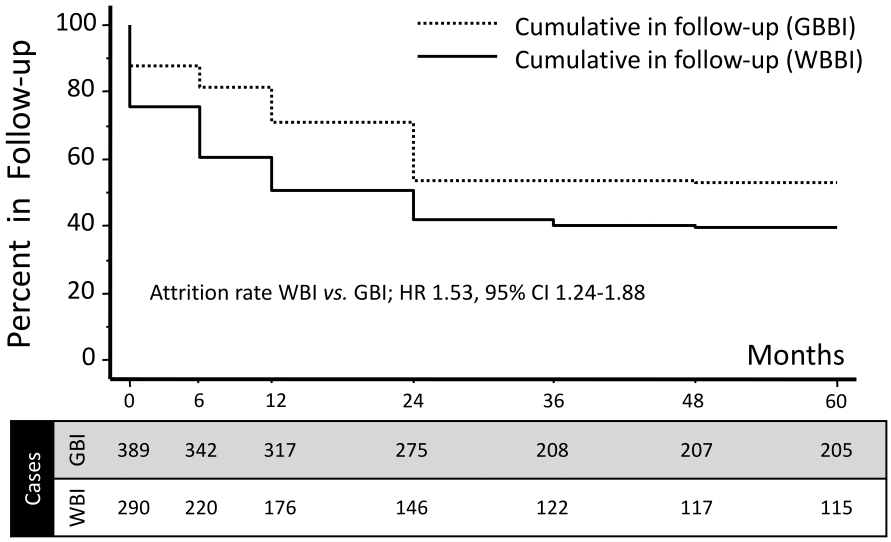

FIGURE 1 Attrition in the course of follow in subjects enrolled in the group-based (GBBI) and the web-based behavioural intervention (WBBI). Note that differences were no longer significant when adjusted for confounders.

TABLE 2 Paired comparison of non-invasive tests in subjects last seen at follow-up and in 5-year completers, compared with corresponding entry values.

Fatty liver index	**No steatosis**	**Indeterminate**	**Steatosis**	***p* value**
Class at entry *n* (%)	4 (0.8)	52 (10.6)	436 (88.6)	<0.001
Class at end of follow-up *n* (%)	23 (4.7)	117 (23.8)	352 (71.5)	
Class at entry in completers *n* (%)	2 (0.6)	30 (9.7)	277 (89.6)	<0.001
Class at 5-year in completers *n* (%)	15 (4.9)	77 (24.9)	217 (70.2)	
Fibrosis-4 Index	**No advanced fibrosis**	**Indeterminate**	**Advanced fibrosis**	***p* value**
Class at entry *n* (%)	265 (64.0)	140 (33.8)	9 (2.2)	<0.001
Class at end of follow-up *n* (%)	234 (56.5)	177 (42.8)	3 (0.7)	
Class at entry in completers *n* (%)	187 (61.9)	110 (36.4)	5 (1.7)	<0.001
Class at 5-year in completers *n* (%)	166 (54.9)	134 (44.4)	2 (0.7)	
Alanine aminotransferases[a]	**Above normal limits**	**Within normal limits**		***p* value**
Class at entry *n* (%)	479 (85.3)	83 (14.7)		<0.001
Class at end of follow-up *n* (%)	336 (59.8)	226 (40.2)		
Class at entry in completers *n* (%)	263 (83.2)	53 (16.8)		<0.001
Class at 5-year in completers *n* (%)	162 (51.3)	154 (48.7)		

[a]Note that for alanine aminotransferase levels also values at 6-month follow-up were available. ALT ≤ 31 in males and ≤19 in females were considered normal limits, according to Prati et al.[19]

physical activity was quantitatively measured at the end of the intensive program (4–6 months after enrolment).[17] Questionnaires were no longer used to quantitate food intake, as well as engagement in habitual physical activity after the first few months.

2.3 | Methods

The primary outcome for analysis was originally set at 10% weight loss. Many secondary outcomes were also tested: (a) attrition rates (continuers vs. cases lost to follow-up); (b) per cent changes in body mass index (BMI); (c) return of alanine aminotransferase (ALT) levels within normal values (defined according to the updated reference values of ≤31 mU/mL in males and ≤19 in females)[19]; (d) changes in surrogate biomarkers of steatosis (Fatty Liver Index—FLI)[20] and fibrosis (fibrosis-4 index—Fib-4)[21] and category of FLI and Fib-4 as derived from most recent guidelines.[22]

2.4 | Statistical analysis

Descriptive statistics was made by computing means ± standard deviation for the entire, the WBBI and the GBBI cohorts. For nominal data, the prevalence and the 95% confidence interval were calculated. Comparison between groups was carried out by Student *t* test for unpaired data and chi-square test, whenever appropriate.

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Attrition rates were tested for differences by Kaplan–Meier and Cox proportional hazard methods analysis. Longitudinal changes in clinical data were also compared by repeated-measures ANOVA, considering subjects in active follow-up. Factors associated with primary and secondary outcomes (dependent variable) were tested by logistic regression analysis, having type of intervention and confounders as independent variables. Given the large differences in baseline values between WBBI and GBBI groups, in a sensitivity analysis outcomes were also tested after adjustment for propensity score. The score was calculated by binary logistic analysis having socio-demographic and clinical data (age, sex, education, working status, BMI, ALT and presence of diabetes) as independent variables.

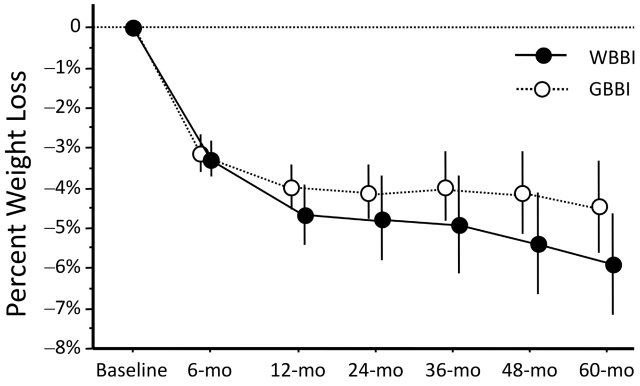
3 | RESULTS

3.1 | Baseline data

In general, the whole cohort (Table 1) was characterised by a larger prevalence of females in the WBBI group, as well as older age, lower education and different working status, and higher comorbidity rates, as also supported by different biochemistry, with similar obesity rates. The presence of steatosis was confirmed in nearly 90% of cases by FLI, with very few cases classified as indeterminate or no steatosis. FIB-4 was higher in the GBBI group, but very few cases ruled-in significant fibrosis.

3.2 | Attrition rates

A high attrition rate was observed soon after enrolment—more marked in the WBBI cohort—with nearly 20% of patients either not completing the behaviour program or missing the first 6-month control visit (only 562 patients available at follow-up). From that time on, attendance continued to decline sharply in both cohorts during the first 3 years (493 at year 1, 421 at year 2 and 338 at year 3) and stabilised thereafter (Figure 1). The population available to long-term follow-up (continuers) was older than the cohort lost to follow-up, had higher rates of hypertension, diabetes, a poorer educational status and was characterised by lower involvement in working activities (Table 2). Attrition rates were moderately higher in females, irrespective of treatment group (55.6% vs. 50.4% in male; $p=0.190$). At multivariable logistic regression analysis, attrition was significantly reduced by older age (OR: 0.76, 95% CI: 0.64–0.91 per decade), by the presence of pre-existing or newly developed diabetes (OR: 0.33; 95% CI: 0.22–0.49) and weight loss ≥5% (OR: 0.87, 95% CI: 0.75–0.99) and in retired people versus subjects actively working (OR: 0.45; 95% CI: 0.20–1.00), without any association with education or type of intervention. By the end of the observation period, 205 GBBI- and 115 WBBI-treated cases were available for analysis (52.7% and 39.7% of cases, respectively; $p<0.001$). Cox proportional hazard analysis confirmed a higher attrition rate in WBBI



Cases							
GBI	389	342	317	275	214	213	205
WBI	290	220	176	146	124	119	115

FIGURE 2 Per cent weight loss in NAFLD subjects enrolled in the group-based (GBBI) and the web-based behavioural intervention (WBBI). Data are plotted as mean ± 95% CI. The number of cases available at each time point is reported in the table.

versus GBBI (HR: 1.53; 95% CI: 1.24–1.88; $p<0.001$) (Figure 1), which, however, was not significantly different after adjustment for age, gender, prevalence of pre-existing and newly developed diabetes, education, job involvement and BMI at baseline (HR: 1.03; 95% CI: 0.78–1.35; $p=0.833$).

3.3 | Weight loss

The time course of weight loss in relation to treatment group is depicted in Figure 2. Weight loss reached a peak around 4%–5% in the whole population that remained in the programs in the period between year 2 and 5, without significant differences between groups (WBBI: −5.0 ± 6.6 vs. −4.0 ± 6.6 in GBBI; $p=0.075$). By year 5, 50% of cases in active follow-up had lost 5% or more of their initial body weight and 19% had lost 10% or more, whereas 8% had remained relatively stable (±2% of initial body weight). Only a few patients were able to reach a normal weight at last follow-up ($n=30$; 4.4%) but many more moved from obesity to the overweight class at ($n=84$, 17.5% of subjects with obesity at enrolment). The primary outcome (10% weight loss) in the 5-year observation period was totally unrelated to the type of intervention (WBBI: OR: 0.99, 95% CI: 0.62–1.57). Of note, only 8.8% of GBBI and only 2.6% of WBBI individuals had increased their body weight by 5% or more ($p=0.035$, Fisher's exact test).

3.4 | Biochemistry

At entry, alanine aminotransferases were within the normal range only in 48 GBBI- and 64 WBBI-enrolled patients (12.3% and 22.1%; $p<0.001$). In the course of follow-up ALT declined by approximately

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50% in both groups and normalised also in a large proportion of patients lost to follow-up (40%) (Table 2). By the end of the observation period, they were in the normal range in 51% and 45% of the two groups, respectively ($p=0.352$). Similar changes were observed in aspartate aminotransferase (AST) levels (Figure 3) and in γ-glutamyltranspeptidase (GGT) concentrations (not reported in details).

No differences in the time course of total cholesterol, HDL-cholesterol, triglyceride, LDL-cholesterol were observed during follow-up. Also fasting glucose and blood pressure were similar in GBBI- and WBBI-treated cases at the end of the observation period. HbA1c levels declined by 0.18 ± 1.19% in GBBI cases (p vs. baseline, 0.034) and increased by 0.08 ± 0.81% in WBBI group (p vs. baseline, 0.344), possibly driven by a moderately larger number of newly detected diabetes at follow-up ($n=31$ in GBBI vs. 17 in WBBI; HR: 1.62; 95% CI: 0.90–2.94; $p=0.108$). Finally, in continuers, GGT decreased on average by 14 U/L ($p<0.001$) and platelet count was minimally reduced (Baseline, $214 \pm 46 \times 10^9$/L; 60-month, 208 ± 29; $p=0.024$).

3.5 | Surrogate biomarkers

The scores of FLI and FIB-4 and their changes during the observation period are presented in Figure 4 and Table 2, together with percentage of cases ruling-in, ruling-out or being in the indeterminate range according to the cut-offs defined in the methods. FLI declined progressively and, by the end of follow-up, score values ruled out steatosis in 4.9% of cases, whereas 24.9% more were in the indeterminate range (no difference between treatment groups).

FIB-4 scores showed a progressive increase in both cohorts, largely driven by the increase in age and quantitatively larger (not significantly) in the WBBI cohort. Nonetheless, considering the lower average FIB-4 score at entry in WBBI, FIB-4 remained significantly lower in WBBI throughout the treatment period. The prevalence of cases ruling-in advanced fibrosis (FIB-4 ≥ 2.67) remained very low (around 1%), but the number in the intermediate range increased in the whole cohort from 31.4% at baseline to 44.4%. When split according to type of treatment, the distribution at 60-month follow-up was 46.0%, 53.5% and 0.5% (rule-out, indeterminate, rule-in) in GBBI versus 72.1%, 26.9% and 1.0% in WBBI, respectively ($p<0.001$).

By logistic regression analysis, improvement by one or more class in FLI was associated female sex (OR: 2.20; 95% CI: 1.12–4.28), with 5% weight loss (OR: 4.21; 95% CI: 2.99–5.94) and negatively with entry BMI (OR: 0.58; 95% CI: 0.52–0.66), not with age, education, working status, presence of diabetes and type of treatment (WBBI: OR: 1.40; 95% CI: 0.71–2.77).

Similarly, improvement in FIB-4 class was associated with age (OR: 1.05; 95% CI: 1.01–1.09) and with 5% weight loss (OR: 1.31; 95% CI: 1.06–1.61), not with gender, education, working status, BMI at entry or type of treatment (WBBI: OR: 0.62; 0.29–1.31). Deterioration in FIB-4 class was solely associated with age (OR: 1.04; 95% CI: 1.01–1.07), not with any other confounder. However, there was a remarkable trend in favour of a reduced risk of fibrosis progression in subjects treated by WBBI (OR: 0.53; 95% CI: 0.28–1.01; $p=0.053$).

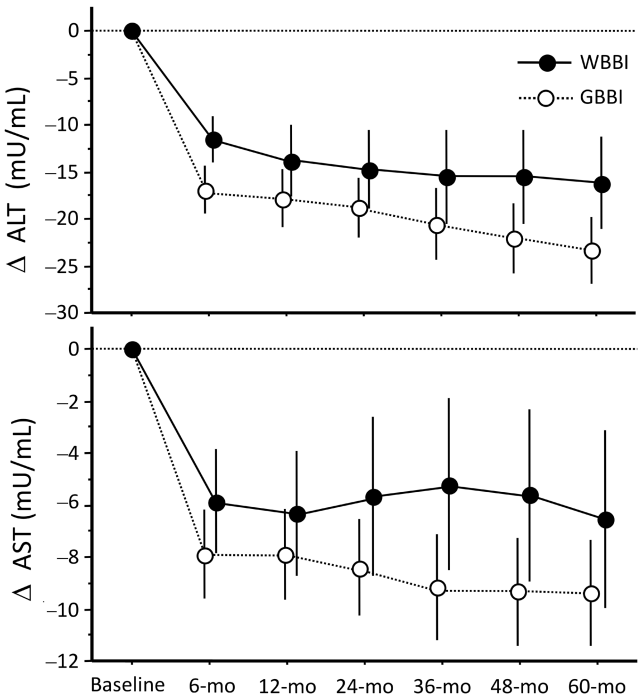

FIGURE 3 Changes in alanine (upper panel) and aspartate (lower panel) aminotransferase levels in the two groups of subjects enrolled in the group-based (GBBI) and the web-based behavioural intervention (WBBI). Data are plotted as mean ± 95% CI. No differences were observed between groups. For number of cases, see Figure 1. Note that liver enzyme levels were higher in the GBBI- versus the WBBI-treated cohort at entry.

3.6 | Sensitivity analysis by propensity score

In a sensitivity analysis, the risk of attrition and of changes in surrogate biomarkers was tested after adjustment for propensity score. The risk of attrition, although moderately increased in the WBBI cohort, was not significantly increased (OR: 1.27; 95% CI: 0.89–1.81). Improvements in FLI and FIB-4 by one class or more were also not different in the two cohorts (WBBI: OR: 1.29; 95% CI: 0.78–2.15 and OR: 0.70; 95% CI: 0.33–1.50, respectively). The analysis confirmed a trend towards a reduced risk of FIB-4 deterioration in the WBBI-treated cohort (OR: 0.57; 95% CI: 0.30–1.07; $p=0.082$) and no differences in ALT normalisation (OR: 1.15; 95% CI: 0.76–1.72).

4 | DISCUSSION

The main results of the present study are: (a) web-based education may be confidently used to promote healthy lifestyles, thus favouring weight loss, as a surrogate for intensive behavioural group treatment in patients with NAFLD who are reluctant to hospital-based intervention; (b) although attrition remains a crucial issue in

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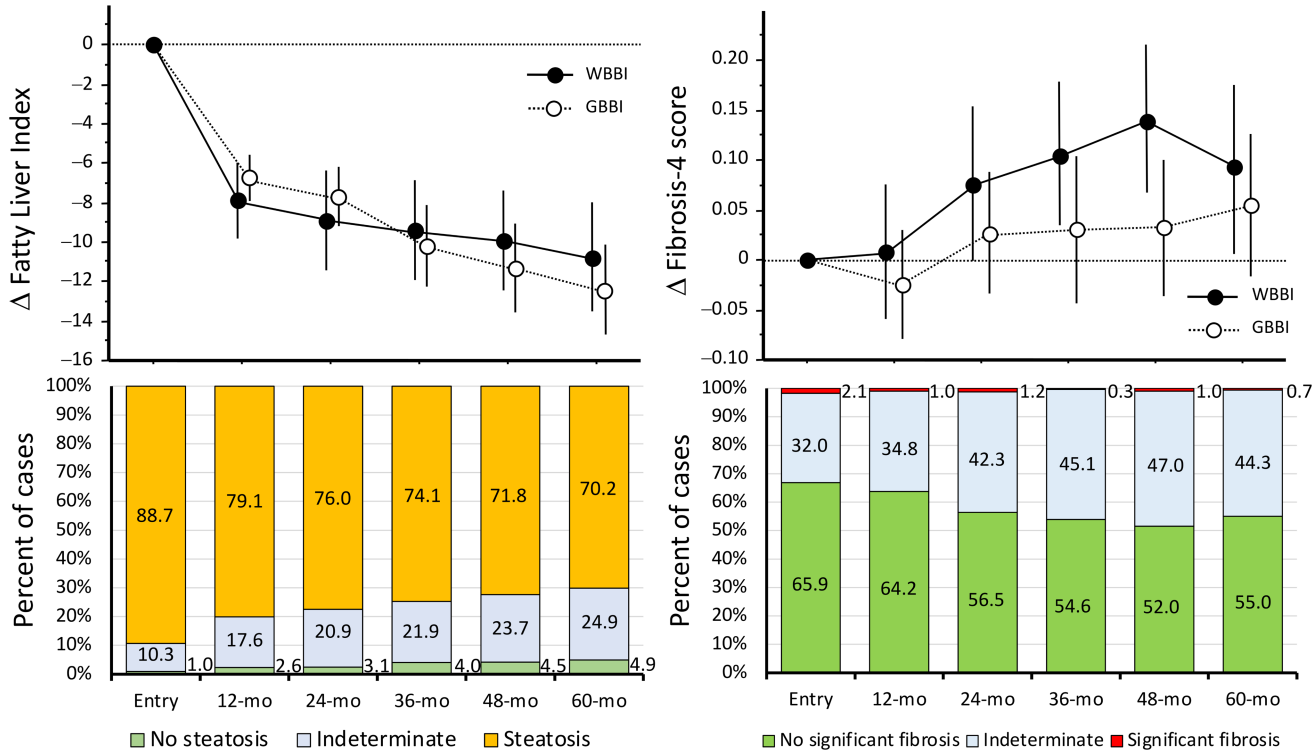

FIGURE 4 Changes in Fatty Liver Index and Fibrosis-4 score (upper panels) in subjects enrolled in the group-based (GBBI) and the web-based behavioural intervention (WBBI) and per cent of total cases classified as ruling-in, ruling-out or indeterminate for steatosis and advanced fibrosis (lower panels). Number of cases: for FLI, see Figure 1; for FIB-4 score the total numbers decreased from 478 at entry (WBBI, $n = 187$; GBBI, $n = 291$) to 302 after 60 months (WBBI, $n = 104$; GBBI, $n = 198$). Note the progressive shift towards lower steatosis score and the constantly low number of cases fitting the criteria for advanced fibrosis.

behaviour treatment—and even more in the web intervention—following treatment a remarkable proportion of patients attain and maintain a satisfactory weight loss, which is associated with stability or even improvement in surrogate biomarkers of steatosis and fibrosis after 5 years, consistent with low risk of progression. This conclusion is based on the ability of non-invasive tests to predict the natural history of NAFLD, and large studies recently confirmed that FIB-4 values predict both liver and non-liver-related events.[23,24] In addition, at least one study reported that retesting may also be useful to predict liver disease progression/regression,[25] and international guidelines recommend biomarkers for continuous management of low-risk NAFLD individuals.[22,26]

The use of internet to educate patients has long been tested in the area of chronic diseases, driven by the need for continuous lifestyle improvement requiring multiple interventions and the large number of patients at risk.[27] Following the reports of the seminal Diabetes Prevention Study[28] and Diabetes Prevention Program,[29] the methodology of behavioural modification to induce weight loss have been translated from the hospital setting into the web with different results. In a large meta-analysis, Joiner et al reviewed 22 studies and 26 interventions, including web-based and mobile phone applications, text messages, DVDs, telephone calls, telehealth video conferencing and video on-demand programing.[30] The majority of studies included post-baseline behavioural support provided by counsellors remotely or face-to-face, as we did at any control visit to our WBBI cohort. Weight loss averaged 4% after 15 months and was moderately higher in subjects given post-baseline support, particularly when provided in person (−4.65% of initial body weight). Later, three meta-analyses confirmed the positive results,[31–33] providing evidence that eHealth is feasible and effective in the short term. In short-term interventions, an individualised web-based intervention limited to training support was also considered in NAFLD setting.[34] When delivered to a cohort of 41 patients (93.2% of enrolled cases), the exercise program (8-week intervention) produced an increase in physical fitness (VO_2 peak) and decreased aminotransferase levels, markers of inflammation, surrogate scores of steatosis and fibrosis (including FLI and FIB-4) and transient elastography.[34] Body weight decreased as well during intensive intervention, but a remarkable weight regain was observed by the end of follow-up (12 weeks). In the present study, body weight continued to decline in subjects who remained in the programs, although only few reached the desired target. This underlines the importance of continuous care for the treatment of obesity.[35] Reinforcement by pharmacologic treatment might be a future suitable option.[36]

As for any weight loss intervention, attrition and weight regain during follow-up remain critical issues. Attrition was very large in the first 3 years and stabilised thereafter. Initial attrition might stem from unpreparedness to the demanding procedures associated with weight loss intervention (food choices and calorie counting, physical activity measures) and poor motivation, despite accurate selection

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by motivational interviewing in the baseline assessment,[18] also adapted for group setting in our department.[37] We described even higher attrition rates soon after enrolment in a multicentre Italian study involving treatment of patients with obesity, independent of NAFLD, and in the long-term attrition rates exceeded 80%;[35] the present data indicate that NAFLD is not sufficiently perceived as a robust additional factor stimulating adherence, in keeping with the scarce preparedness of both patients and healthcare institutions to manage NAFLD treatment.[38] A recent study showed that knowledge of liver fibrosis stage is a drive to adherence to behavioural strategies;[39] the low severity of disease, as measured by FIB-4 in our patients, might have contributed to diminish motivation and adherence. In general, we could not find any baseline difference between continuers and drop-outs at follow-up in terms of liver disease, not even raised liver enzymes, a mark of disease usually perceived as important by NAFLD patients. The only significant factors increasing attrition were socio-demographic parameters likely to influence time to dedicate to treatment—not completely resolved by WBBI–, together with diabetes, a disease perceived as significantly harming future life. A detailed analysis of diabetes in our NAFLD cohorts has already been published; the risk of newly detected diabetes was indeed reduced by intervention in comparison with rates expected from the literature.[40]

In the mid-term, attrition remained high. A post hoc analysis of attrition between one- and 3-year follow-up failed to demonstrate differences in per cent weight loss between continuers and individuals lost to follow-up; thus, also unsatisfied results do not seem to be a likely reason for attrition,[41] as suggested in other settings.[42] Finally, after 3 years, attrition was no longer a problem and NAFLD patients' loyalty was nearly complete.

As for weight regain, the importance of treatment failure during extended care is well-documented and also in the course of eHealth interventions, again with a better outcome when face-to-face meeting are added to technology-based interventions.[43] A very recent systematic review and meta-analysis confirmed that in-persons interventions were associated with a reduced weight regain compared with technology-based approaches.[44] We did not observe any relevant weight regain in the long-term in patients who remained in the program, but data might be biased by attrition, that continued throughout the observation period, although at lower rates. Any possibility to adjust data of subjects lost to follow-up in epidemiological studies of obesity is biased by unpredictable changes after program stop. We can only remark that a non-negligible proportion of our compliant patients achieved a significant weight loss, favoured by continuing reinforce at follow-up visits and weight loss translated into a significant reduction of biomarker-assessed fatty liver and stability or improvement of fibrosis, independent of treatment type.

Weight loss was the most significant factor associated with favourable changes in steatosis, as measured by FLI. Epidemiological and clinical studies have consistently associated reduced BMI and/or reduced waist circumference to lower steatosis rates, measured by ultrasounds,[45] proton-magnetic resonance spectroscopy[46] and also histology.[47] Thus, improved FLI should not be regarded as a mere mathematical result, considering that waist circumference is part of the algorithm. We observed a progressive shift in continuers from the stages ruling-in or indeterminate for steatosis to lower grades, in keeping with reduced fat in the liver. This condition was also associated with reduced liver enzymes, expression of a reduced liver cell suffering from fatty infiltration, as well as with a lower risk of newly detected diabetes,[40] possibly reducing the stimulus to disease progression. Diabetes per se is indeed a marker of progressive liver disease, also increasing the predictive ability of biomarkers.[48] All events (improved FLI stage, regression of liver enzyme and reduced risk of de novo diabetes) were independent of the type of intervention, after correction for confounders.

The severity of fibrosis, measured by FIB-4 score, remained stable or showed a moderate shift towards the indeterminate stage, driven by a minimal decrease of platelets and population ageing. The negative effects of age on FIB-4 classification were probably counterbalanced by the higher adherence of the elderly to lifestyle changes, and age indeed was positively associated with improved FIB-4 stage. The cross-sectional association of Fib-4 score with histologic data is well-documented; longitudinal analyses of FIB-4 values measured during a drug intervention trial and following bariatric surgery confirmed an association between reduced FIB-4 and histological improvement[49,50] and the beneficial effects of weight loss.[51] These results lend support to our data confirming the association between weight loss, irrespective of treatment type, and FIB-4 improvement. It would be important to strengthen these results with longitudinal measurements of liver stiffness, now the gold-standard for fibrosis or magnetic resonance elastography.[52] Unfortunately, stiffness by transient elastography was measured only in a minority of cases at time of enrolment, and data were insufficient for analysis, whereas magnetic resonance elastography is not available in our hospital.

The low grade of fibrosis in our setting indicates that the large NAFLD population observed in the setting of diabetes and obesity units is probably different from that observed in Liver Units, more prone to severity and progression, despite the well-documented importance of diabetes as liver disease modifier.[53,54] The number of cases at risk, free living and in the working age, was the primary reason for translating the educational program into the web. Weight loss, independently of treatment, also resulted in a decreased occurrence of newly detected diabetes, as well as better diabetes management and glucose control in individuals with NAFLD and diabetes, likely to improve prognosis further.[40]

In conclusion, the long-term analysis of the cohort enrolled into a weight loss program either via group-based or web-based behavioural techniques gives a complete picture of the limits and the results of real-world interventions. It confirms the positive effects of intensive efforts to promote behavioural changes; only a limited proportion of cases will achieve complete remission of the ongoing liver damage, but progression is probably smoothened. The healthcare personnel of metabolic units, long trained to educational activities aimed at weight loss, remains an important nod in the network responsible for NAFLD management, as suggested by Clinical Practice

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Guidelines,[22,38] in order to reduce the burden of disease and to accelerate the public health agenda for NAFLD response.[55,56]

AUTHOR CONTRIBUTIONS

Maria Letizia Petroni: Conceptualization (equal); project administration (equal); writing – original draft (equal); writing – review and editing (equal). **Santo Colosimo:** Conceptualization (equal); writing – original draft (equal); writing – review and editing (equal). **Lucia Brodosi:** Data curation (equal); writing – review and editing (equal). **Angelo Armandi:** Data curation (equal); writing – review and editing (equal). **Flavio Bertini:** Data curation (equal); writing – review and editing (equal). **Danilo Montesi:** Data curation (equal); writing – review and editing (equal). **Elisabetta Bugianesi:** Conceptualization (equal); methodology (equal); writing – original draft (equal); writing – review and editing (equal). **Giulio Marchesini:** Conceptualization (equal); formal analysis (equal); writing – original draft (equal); writing – review and editing (equal).

ACKNOWLEDGEMENTS

Declaration of personal interests: The authors are indebted to the head dietitian Silvia Di Domizio, to psychologist Chiara Nuccitelli and pedagogist Elena Centis for continuous support in group sessions and web program development. Open access funding provided by BIBLIOSAN.

FUNDING INFORMATION

The web program was originally funded as part of the subproject FP7/2007–2013 FLIP (Fatty Liver—Inhibition to Progression), under grant agreement No. HEALTH-F2-2009-241762.

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REFERENCES

1. Younossi ZM, Golabi P, Paik JM, Henry A, Van Dongen C, Henry L. The global epidemiology of nonalcoholic fatty liver disease (NAFLD) and nonalcoholic steatohepatitis (NASH): a systematic review. Hepatology. 2023;77(4):1335–47. https://doi.org/10.1097/HEP.0000000000000004
2. O'Hara J, Finnegan A, Dhillon H, Ruiz-Casas L, Pedra G, Franks B, et al. Cost of non-alcoholic steatohepatitis in Europe and the USA: the GAIN study. JHEP Rep. 2020;2(5):100142. https://doi.org/10.1016/j.jhepr.2020.100142
3. Petta S, Ting J, Saragoni S, Degli Esposti L, Petroni ML, Shreay S, et al. Healthcare resource utilization and costs of nonalcoholic steatohepatitis patients with advanced liver disease in Italy. Nutr Metab Cardiovasc Dis. 2020;30(6):1014–22. https://doi.org/10.1016/j.numecd.2020.02.016
4. Petroni ML, Brodosi L, Bugianesi E, Marchesini G. Management of non-alcoholic fatty liver disease. BMJ. 2021;372:m4747. https://doi.org/10.1136/bmj.m4747
5. Burgess E, Hassmen P, Pumpa KL. Determinants of adherence to lifestyle intervention in adults with obesity: a systematic review. Clin Obes. 2017;7(3):123–35. https://doi.org/10.1111/cob.12183
6. Dalle Grave R, Calugi S, Centis E, Marzocchi R, El Ghoch M, Marchesini G. Lifestyle modification in the management of the metabolic syndrome: achievements and challenges. Diabetes Metab Syndr Obes. 2010;3:373–85. https://doi.org/10.2147/DMSOTT.S13860
7. Centis E, Moscatiello S, Bugianesi E, Bellentani S, Fracanzani AL, Calugi S, et al. Stage of change and motivation to healthier lifestyle in non-alcoholic fatty liver disease. J Hepatol. 2013;58(4):771–7. https://doi.org/10.1016/j.jhep.2012.11.031
8. Singh A, Dhaliwal AS, Singh S, Kumar A, Lopez R, Gupta M, et al. Awareness of nonalcoholic fatty liver disease is increasing but remains very low in a representative US cohort. Dig Dis Sci. 2020;65(4):978–86. https://doi.org/10.1007/s10620-019-05700-9
9. Wieland AC, Mettler P, McDermott MT, Crane LA, Cicutto LC, Bambha KM. Low awareness of nonalcoholic fatty liver disease among patients at high metabolic risk. J Clin Gastroenterol. 2015;49(1):e6–e10. https://doi.org/10.1097/MCG.0000000000000075
10. Duan Y, Shang B, Liang W, Du G, Yang M, Rhodes RE. Effects of eHealth-based multiple health behavior change interventions on physical activity, healthy diet, and weight in people with noncommunicable diseases: systematic review and meta-analysis. J Med Internet Res. 2021;23(2):e23786. https://doi.org/10.2196/23786
11. Lunde P, Nilsson BB, Bergland A, Kvaerner KJ, Bye A. The effectiveness of smartphone apps for lifestyle improvement in noncommunicable diseases: systematic review and meta-analyses. J Med Internet Res. 2018;20(5):e162. https://doi.org/10.2196/jmir.9751
12. El Benny M, Kabakian-Khasholian T, El-Jardali F, Bardus M. Application of the eHealth literacy model in digital health interventions: scoping review. J Med Internet Res. 2021;23(6):e23473. https://doi.org/10.2196/23473
13. Hsu CH, Alavi A, Dong M. Editorial: mHealth for non-communicable diseases. Front Public Health. 2022;10:918982. https://doi.org/10.3389/fpubh.2022.918982
14. Raaijmakers LC, Pouwels S, Berghuis KA, Nienhuijs SW. Technology-based interventions in the treatment of overweight and obesity: a systematic review. Appetite. 2015;95:138–51. https://doi.org/10.1016/j.appet.2015.07.008
15. Kempf K, Altpeter B, Berger J, Reuss O, Fuchs M, Schneider M, et al. Efficacy of the telemedical lifestyle intervention program TeLiPro in advanced stages of type 2 diabetes: a randomized controlled trial. Diabetes Care. 2017;40(7):863–71. https://doi.org/10.2337/dc17-0303
16. Forlani G, Lorusso C, Moscatiello S, Ridolfi V, Melchionda N, Di Domizio S, et al. Are behavioural approaches feasible and effective in the treatment of type 2 diabetes? A propensity score analysis vs. prescriptive diet. Nutr Metab Cardiovasc Dis. 2009;19(5):313–20. https://doi.org/10.1016/j.numecd.2008.06.004

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17. Mazzotti A, Caletti MT, Brodosi L, Di Domizio S, Forchielli ML, Petta S, et al. An internet-based approach for lifestyle changes in patients with NAFLD: two-year effects on weight loss and surrogate markers. J Hepatol. 2018;69(5):1155–63. https://doi.org/10.1016/j.jhep.2018.07.013
18. Miller WR, Rollnick S. Motivational interviewing. 2nd ed. New York: The Guilford Press; 2002.
19. Prati D, Taioli E, Zanella A, Della Torre E, Butelli S, Del Vecchio E, et al. Updated definitions of healthy ranges for serum alanine aminotransferase levels. Ann Intern Med. 2002;137(1):1–10. https://doi.org/10.7326/0003-4819-137-1-200207020-00006
20. Bedogni G, Bellentani S, Miglioli L, Masutti F, Passalacqua M, Castiglione A, et al. The Fatty Liver Index: a simple and accurate predictor of hepatic steatosis in the general population. BMC Gastroenterol. 2006;6:33. https://doi.org/10.1186/1471-230X-6-33
21. Vallet-Pichard A, Mallet V, Nalpas B, Verkarre V, Nalpas A, Dhalluin-Venier V, et al. FIB-4: an inexpensive and accurate marker of fibrosis in HCV infection. Comparison with liver biopsy and fibrotest. Hepatology. 2007;46(1):32–6. https://doi.org/10.1002/hep.21669
22. European Association for the Study of the Liver, European Association for the Study of Diabetes, European Association for the Study of Obesity. EASL-EASD-EASO Clinical Practice Guidelines for the management of non-alcoholic fatty liver disease. J Hepatol. 2016;64(6):1388–402. https://doi.org/10.1016/j.jhep.2015.11.004
23. Mozes FE, Lee JA, Vali Y, Alzoubi O, Staufer K, Trauner M, et al. Performance of non-invasive tests and histology for the prediction of clinical outcomes in patients with non-alcoholic fatty liver disease: an individual participant data meta-analysis. Lancet Gastroenterol Hepatol. 2023;8(8):704–13. https://doi.org/10.1016/S2468-1253(23)00141-3
24. Vieira Barbosa J, Milligan S, Frick A, Broestl J, Younossi Z, Afdhal N, et al. Fibrosis-4 index can independently predict major adverse cardiovascular events in nonalcoholic fatty liver disease. Am J Gastroenterol. 2022;117(3):453–61. https://doi.org/10.14309/ajg.0000000000001606
25. Hagstrom H, Talback M, Andreasson A, Walldius G, Hammar N. Repeated FIB-4 measurements can help identify individuals at risk of severe liver disease. J Hepatol. 2020;73(5):1023–9. https://doi.org/10.1016/j.jhep.2020.06.007
26. Rinella ME, Neuschwander-Tetri BA, Siddiqui MS, Abdelmalek MF, Caldwell S, Barb D, et al. AASLD practice guidance on the clinical assessment and management of nonalcoholic fatty liver disease. Hepatology. 2023;77(5):1797–835. https://doi.org/10.1097/HEP.0000000000000323
27. Hanlon P, Daines L, Campbell C, McKinstry B, Weller D, Pinnock H. Telehealth interventions to support self-management of long-term conditions: a systematic metareview of diabetes, heart failure, asthma, chronic obstructive pulmonary disease, and cancer. J Med Internet Res. 2017;19(5):e172. https://doi.org/10.2196/jmir.6688
28. Tuomilehto J, Lindstrom J, Eriksson JG, Valle TT, Hamalainen H, Ilanne-Parikka P, et al. Prevention of type 2 diabetes mellitus by changes in lifestyle among subjects with impaired glucose tolerance. N Engl J Med. 2001;344(18):1343–50.
29. Knowler WC, Barrett-Connor E, Fowler SE, Hamman RF, Lachin JM, Walker EA, et al. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. N Engl J Med. 2002;346(6):393–403. https://doi.org/10.1056/NEJMoa012512
30. Joiner KL, Nam S, Whittemore R. Lifestyle interventions based on the diabetes prevention program delivered via eHealth: a systematic review and meta-analysis. Prev Med. 2017;100:194–207. https://doi.org/10.1016/j.ypmed.2017.04.033
31. Beleigoli AM, Andrade AQ, Cancado AG, Paulo MN, Diniz MFH, Ribeiro AL. Web-based digital health interventions for weight loss and lifestyle habit changes in overweight and obese adults: systematic review and meta-analysis. J Med Internet Res. 2019;21(1):e298. https://doi.org/10.2196/jmir.9609
32. Rumbo-Rodriguez L, Sanchez-SanSegundo M, Ruiz-Robledillo N, Albaladejo-Blazquez N, Ferrer-Cascales R, Zaragoza-Marti A. Use of technology-based interventions in the treatment of patients with overweight and obesity: a systematic review. Nutrients. 2020;12(12):3634. https://doi.org/10.3390/nu12123634
33. Ufholz K, Bhargava D. A review of telemedicine interventions for weight loss. Curr Cardiovasc Risk Rep. 2021;15(9):17. https://doi.org/10.1007/s12170-021-00680-w
34. Huber Y, Pfirrmann D, Gebhardt I, Labenz C, Gehrke N, Straub BK, et al. Improvement of non-invasive markers of NAFLD from an individualised, web-based exercise program. Aliment Pharmacol Ther. 2019;50(8):930–9. https://doi.org/10.1111/apt.15427
35. Dalle Grave R, Melchionda N, Calugi S, Centis E, Tufano A, Fatati G, et al. Continuous care in the treatment of obesity: an observational multicentre study. J Intern Med. 2005;258(3):265–73. https://doi.org/10.1111/j.1365-2796.2005.01524.x
36. Petroni ML, Montesi L, Colosimo S, Caletti MT, Mazzotti A, Marchesini G. Combination of GLP-1 receptor agonists and behavioural treatment in type 2 diabetes elicits synergistic effects on body weight: a retrospective cohort study. Endocrinol Diabetes Metab. 2019;2(4):e00082. https://doi.org/10.1002/edm2.82
37. Centis E, Petroni ML, Ghirelli V, Cioni M, Navacchia P, Guberti E, et al. Motivational interviewing adapted to group setting for the treatment of relapse in the behavioral therapy of obesity. A clinical audit. Nutrients. 2020;12(12):3881. https://doi.org/10.3390/nu12123881
38. Francque SM, Marchesini G, Kautz A, Walmsley M, Dorner R, Lazarus JV, et al. Non-alcoholic fatty liver disease: a patient guideline. JHEP Rep. 2021;3(5):100322. https://doi.org/10.1016/j.jhepr.2021.100322
39. Carrieri P, Mourad A, Marcellin F, Trylesinski A, Calleja JL, Protopopescu C, et al. Knowledge of liver fibrosis stage among adults with NAFLD/NASH improves adherence to lifestyle changes. Liver Int. 2022;42(5):984–94. https://doi.org/10.1111/liv.15209
40. Petroni ML, Brodosi L, Armandi A, Marchignoli F, Bugianesi E, Marchesini G. Lifestyle intervention in NAFLD: long-term diabetes incidence in subjects treated by web- and group-based programs. Nutrients. 2023;15(3):792–807. https://doi.org/10.3390/nu15030792
41. Foster GD, Wadden TA, Vogt RA, Brewer G. What is a reasonable weight loss? Patients' expectations and evaluations of obesity treatment outcomes. J Consult Clin Psychol. 1997;65(1):79–85.
42. Dalle Grave R, Calugi S, Compare A, El Ghoch M, Petroni ML, Tomasi F, et al. Weight loss expectations and attrition in treatment-seeking obese women. Obes Facts. 2015;8(5):311–8. https://doi.org/10.1159/000441366
43. Dombrowski SU, Knittle K, Avenell A, Araujo-Soares V, Sniehotta FF. Long term maintenance of weight loss with non-surgical interventions in obese adults: systematic review and meta-analyses of randomised controlled trials. BMJ. 2014;348:g2646. https://doi.org/10.1136/bmj.g2646
44. Mamalaki E, Poulimeneas D, Tsiampalis T, Kouvari M, Karipidou M, Bathrellou E, et al. The effectiveness of technology-based interventions for weight loss maintenance: a systematic review of randomized controlled trials with meta-analysis. Obes Rev. 2022;23(9):e13483. https://doi.org/10.1111/obr.13483
45. Engl J, Sturm W, Sandhofer A, Kaser S, Tschoner A, Tatarczyk T, et al. Effect of pronounced weight loss on visceral fat, liver steatosis and adiponectin isoforms. Eur J Clin Invest. 2008;38(4):238–44. https://doi.org/10.1111/j.1365-2362.2008.01929.x
46. Wong VW, Wong GL, Chan RS, Shu SS, Cheung BH, Li LS, et al. Beneficial effects of lifestyle intervention in non-obese patients with non-alcoholic fatty liver disease. J Hepatol. 2018;69(6):1349–56. https://doi.org/10.1016/j.jhep.2018.08.011

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47. Vilar-Gomez E, Martinez-Perez Y, Calzadilla-Bertot L, Torres-Gonzalez A, Gra-Oramas B, Gonzalez-Fabian L, et al. Weight loss through lifestyle modification significantly reduces features of nonalcoholic steatohepatitis. Gastroenterology. 2015;149(2):367–78.e5; quiz e14-5. https://doi.org/10.1053/j.gastro.2015.04.005
48. Hagstrom H, Yan J, Talback M, Andreasson A, Walldius G, Bottai M, et al. Improved prediction of 10-year risk of severe liver disease in the general population using commonly available biomarkers. Aliment Pharmacol Ther. 2023;57(4):418–25. https://doi.org/10.1111/apt.17374
49. Chalasani N, Abdelmalek MF, Loomba R, Kowdley KV, McCullough AJ, Dasarathy S, et al. Relationship between three commonly used non-invasive fibrosis biomarkers and improvement in fibrosis stage in patients with non-alcoholic steatohepatitis. Liver Int. 2019;39(5):924–32. https://doi.org/10.1111/liv.13974
50. Schwenger KJP, Alali M, Ghorbani Y, Fischer SE, Jackson TD, Okrainec A, et al. Reliability of non-invasive liver fibrosis assessment tools versus biopsy in pre- and post-bariatric surgery patients with non-alcoholic fatty liver disease. Obes Surg. 2023;33(1):247–55. https://doi.org/10.1007/s11695-022-06380-7
51. Tapper EB, Lai M. Weight loss results in significant improvements in quality of life for patients with nonalcoholic fatty liver disease: a prospective cohort study. Hepatology. 2016;63(4):1184–9. https://doi.org/10.1002/hep.28416
52. Loomba R, Adams LA. Advances in non-invasive assessment of hepatic fibrosis. Gut. 2020;69(7):1343–52. https://doi.org/10.1136/gutjnl-2018-317593
53. Loomba R, Abraham M, Unalp A, Wilson L, Lavine J, Doo E, et al. Association between diabetes, family history of diabetes, and risk of nonalcoholic steatohepatitis and fibrosis. Hepatology. 2012;56(3):943–51. https://doi.org/10.1002/hep.25772
54. Younossi ZM, Tampi RP, Racila A, Qiu Y, Burns L, Younossi I, et al. Economic and clinical burden of nonalcoholic steatohepatitis in patients with type 2 diabetes in the U.S. Diabetes Care. 2020;43(2):283–9. https://doi.org/10.2337/dc19-1113
55. Lazarus JV, Ekstedt M, Marchesini G, Mullen J, Novak K, Pericas JM, et al. A cross-sectional study of the public health response to non-alcoholic fatty liver disease in Europe. J Hepatol. 2020;72(1):14–24. https://doi.org/10.1016/j.jhep.2019.08.027
56. Lazarus JV, Mark HE, Anstee QM, Arab JP, Batterham RL, Castera L, et al. Advancing the global public health agenda for NAFLD: a consensus statement. Nat Rev Gastroenterol Hepatol. 2022;19(1):60–78. https://doi.org/10.1038/s41575-021-00523-4

How to cite this article: Petroni ML, Colosimo S, Brodosi L, Armandi A, Bertini F, Montesi D, et al. Long-term follow-up of web-based and group-based behavioural intervention in NAFLD in a real world clinical setting. Aliment Pharmacol Ther. 2023;00:1–11. https://doi.org/10.1111/apt.17768

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