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RESEARCH ARTICLE

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The UPHILL study: A nutrition and lifestyle intervention to improve quality of life for patients with pulmonary arterial hypertension

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Abstract

The aim of the UPHILL study (a nutrition and lifestyle intervention in patients with pulmonary arterial hypertension [PAH]: effect on quality of life [QoL]), was to determine the effect of innovative nutritional interventions on adjustments in nutritional intake and QoL. In this study a group of prevalent PAH patients at a single center in Amsterdam (the Netherlands) was informed about healthy nutrition using a newly designed video e-learning. They were subsequently instructed to follow a healthy diet during dietary intervention. Nutritional intake was assessed using a food frequency questionnaire (HELIUS) and QoL by the short-form (SF)-36 questionnaire. Nutritional parameters were determined in blood samples. Seventeen patients stable under treatment, who had been diagnosed with PAH 7.0 [3.0−14.0] years before, started and completed the intervention (2 males, 15 females; 45.35 ± 13.57 years). Since all patients in the intervention group made behavioral changes in nutritional intake, during study and follow-up, nutritional and lifestyle adaptations persisted. Despite the fact that patients had already high mean scores at baseline for both mental (74.10 [60.51−84.25]) and physical QoL (66.46 [50.21−73.84]), scores improved further during e-learning. Furthermore, patients who realized most nutritional adaptations, had the best improvement in QoL. This pilot study showed that e-learning modules on nutrition provide an unique opportunity to change nutritional intake in PAH patients and by that improve QoL.

KEYWORDS

diet, e-learning, lifestyle, nutrition, pulmonary hypertension

INTRODUCTION

Patients suffering from pulmonary arterial hypertension (PAH) have a reduced health related quality of life (QoL), even when optimally treated with PAH medication.[1] In patients with left heart failure nutritional education and interventions seem to improve QoL and energy, although RCT's are few and there is a low certainty of evidence.[2–5]

This questions whether a nutrition and lifestyle intervention can improve QoL in PAH patients stable on therapy. A recent study described the nutritional status in PAH, highlighted by a suboptimal nutritional intake and newly found deficiencies.[6] In a few review papers, the potential role for nutrition in PAH is discussed.[7–9] Furthermore, dietary reimbursement is not a worldwide privilege in this group of patients. Therefore, the aim of this pilot study is to assess the effect of innovative dietary approaches to improve nutritional intake and QoL in PAH patients using a newly designed video e-learning on nutrition, followed by a dietary intervention period with strict dietary guidelines.

METHODS

Population

Thirty-seven patients were included with the following inclusion criteria: idiopathic, hereditary, or drug related PAH, age <80 and >18 years, NYHA II or III and stable for at least 3 months, determined by a stable six-minute walk test (6MWT) with a difference of <10%, an estimated glomerular filtration rate of >60 mL/min and willing and able to sign the informed consent form. All participants provided written informed consent before any study-related procedures. Before start of the nutritional education, randomization was performed into a control group, group A (low-fat [LF] diet) and group B (high-fat [HF] diet). A complete description of the study design can be found in Figure 1. The UPHILL study was approved by the medical ethics committee with approval number 2018.538 and complies with the Declaration of Helsinki.

E-learning

For a period of 8 weeks, patients participated in a weekly video e-learning. Every video, with a duration of approximately 25 min (40–45 min including assignments), contained information and assignments regarding healthy nutrition in general and explicitly in PAH. This online educational video was especially designed for PAH patients, with patient empowerment as most important component. Through assignments and information, patients were made aware of their personal behavior. In addition, the content focussed on a positive approach on dietary intake, stressing beneficial

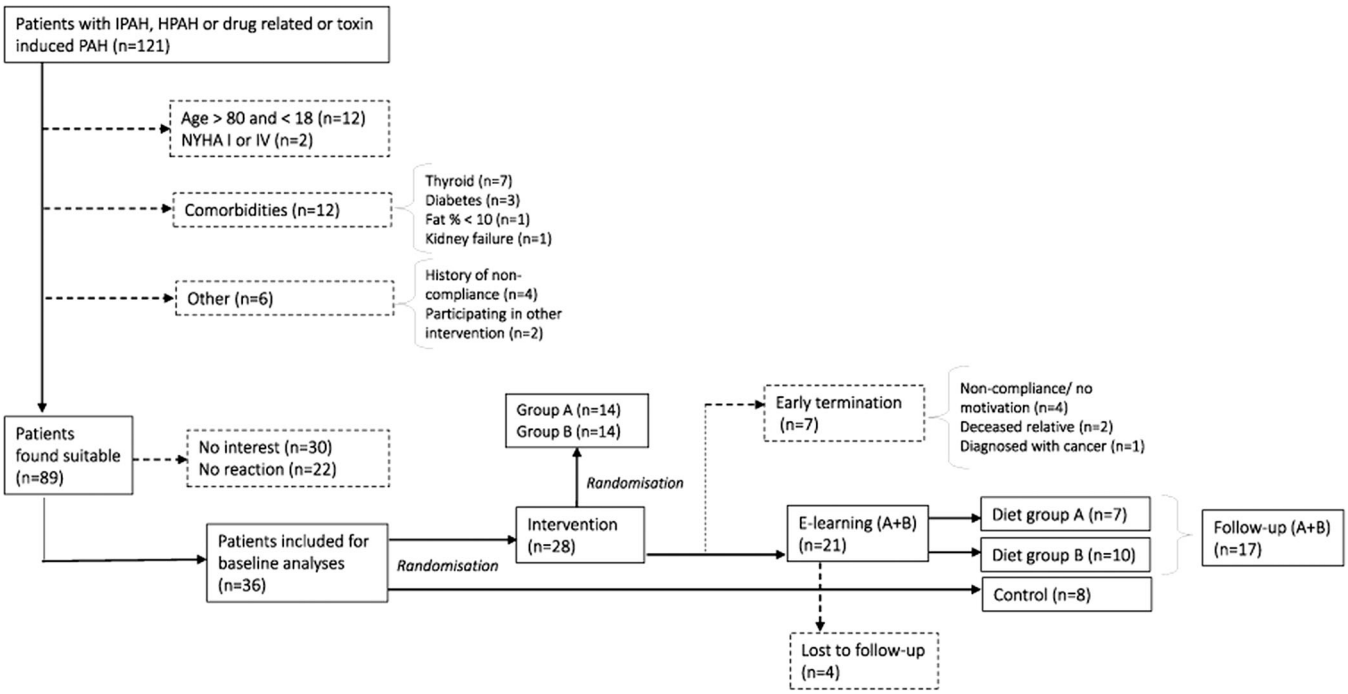

FIGURE 1 Study design. Flowchart of the study.

nutritional options rather than limitations. At the end of every session, patients were asked to specify at least one concrete goal regarding a nutritional change and with a maximum of three goals, to improve compliance. In addition, every week a mandatory video conference was organized by the investigator. In these sessions, with participation of maximally five patients, homework assignments, compliance toward nutritional adaptations, and additional recommendations were discussed. Questions got answered and patients were stimulated to actively participate in these sessions. A complete overview of the nutritional education is outlined in Figure 2. At the end of this period, nutritional intake and QoL were assessed and blood samples were collected. The introduction video of the e-learning is presented in Supporting Information: I (in Dutch).

Dietary intervention

In the dietary intervention, patients adhered to one out of two diets for a period of 3 months. Both diets are healthy diets with overlapping features from both the Mediterranean[3,4] and so-called DASH diet,[5] but also with significant differences. A HF and low-carb (HFLC) diet may also be beneficial in HF,[10,11] therefore patients received either a LF diet (group A) or a HFLC diet with a maximum of 125 g of carbs per day (group B), depending on randomization. A complete description of both diets is shown in Table 1. Six weeks after the start of the diet, patients received a phone call to discuss progress, compliance, and complementary recommendations, if desired. At the end of this period, nutritional intake and QoL were assessed and blood samples were collected.

Follow-up

After the e-learning and the dietary intervention, patients were followed for a period of 6 months to assess compliance with dietary adaptations. After 2 and 4 months, progress and questions were addressed in phone calls between patients and the investigator. At the end of this period nutritional intake and QoL were assessed and blood samples were collected.

Questionnaires

Nutrition

The Dutch version of the HELIUS (HEalthy LIfe in an Urban Setting) food frequency questionnaire (FFQ) was used to assess dietary intake. This FFQ was developed at

FIGURE 2 E-learning outline. Outline of the nutritional online education.

TABLE 1 Dietary intervention outline.

Overlapping features	
Limit sugar intake, preferably no sugar	
Eat many vegetables, perferably with every meal (500 g per day)	
Limit red meat intake, with a maximum of two times/week	
Increase fish intake, with a minimum of two times/week	
Increase vegetarian meals, with a minimum of 1 day/week	
Perferably no alcohol, with a maximum of 1 glass/day	
When you eat 80% of the time according to diet, you can loosen up 20% of the time	
(this means 6 days of the week strict diet and 1 "cheat-day")	
Group A (low-fat)	**Group B (high-fat, moderate low-carb)**
Exclusively low-fat products	Exclusively full-fat products
1.5–2.0 L fluid per day	Maximum of 1.5 L fluid per day
	Maximum of three meals per day
	No in betweens
	Maximum of one piece of fruit per day
	Maximum of one meal with starch per day,
	For example, one slice of bread
	(both fruit and starch only on daytime, in one meal)

Note: Outline of diet A (low-fat) and B (high-fat, moderate low-carb). Both diets are a combination of the Mediterranean diet and the DASH diet. In the Mediterranean diet, quality is most important within the selection of nutrition, preferably fresh and local products are used. It is characterized by the intake of fatty acids, such as olive oil and fish, a high amount of vegetables—raw or short heated, grains, nuts, and red wine. The Mediterranean diet is part of a lifestyle, in which stress reduction is of great importance. The DASH diet is characterized by a low salt, low red meat, low saturated fat, and a low sugar intake and is high in magnesium, potassium, calcium, amino-acids, fiber, fruit, vegetables, whole grain, and low-fat dairy products.

the Amsterdam UMC in collaboration with the National Institute for Public Health and the Environment (RIVM) and the Wageningen University.[12] The patients were given an online version of the FFQ. Average daily nutrient intake was calculated by multiplying the frequency of consumption by the consumed amounts and nutrient content per item using the NEVOtabel (Supporting Information: II, part 1). The following nutrients or nutrient groups were calculated (in grams per day) via the HELIUS FFQ: added fat, diary, eggs, fish, fluid, fruit, nuts, red meat, starch, sugar, vegetables, and vegetarian products.

QoL

The short-form (SF)-36 questionnaire was used for assessing QoL. The SF-36 is a set of generic, coherent, and easily administered QoL measures.[13]

Blood analysis

All blood samples were drawn and preanalytically processed according to routine laboratory protocols. All analyses were performed by an ISO15189:2012 accredited medical laboratory. The hematology parameters were analyzed with a NX1000 analyzer (Sysmex), the routine blood chemistry parameters were analyzed with a Cobas8000 analyzer (Roche). The trace metals were determined with Atomic Absorption Spectroscopy (Shimadzu) and all vitamins were analyzed chromatographically with HPLC (Shimadzu). All reported results did comply with the criteria of the external quality surveys.

6MWT

The 6MWT was used to asses exercise capacity, performed according to the ATS guidelines.[14]

Statistical analyses

Data are presented as mean ± (SD) for normally distributed data or as median [interquartile range] for non-normally distributed data. For non-normally distributed data, logarithmic transformation was performed before the analysis. Relationships between two continuous variables were assessed with a *T*-test. *P*-interaction is determined using two-way ANOVA with post hoc comparison. A p-value of < 0.05 was considered statistically significant. Statistical analyses and graphical illustrations were generated in R studio (version 3.5.2).

RESULTS

Patient characteristics

Twenty-five patients stable under treatment started and completed this study, 17 of whom in the intervention group and 8 in control group (Figure 1). The mean age in the intervention group was 45.3 ± 13.5 years, 12% of the subjects were males,

TABLE 2 Patient characteristics.

	Intervention group	Group A (low-fat)	Group B (high-fat)
n	17	7	10
Age—mean (SD)	45.35 (13.57)	48.86 (16.69)	42.90 (11.20)
Gender—*n*_male (%)	2 (12%)	1 (14%)	1 (10%)
6MWT—mean (SD)	543.70 (97.27)	506.50 (124.24)	506.00 (75.61)
NT-proBNP—median [IQR]	141.00 [84.80–216.00]	161.00 [71.55–382.50]	132.5 [93.85–188.25]
NYHA	II	II	II
BMI—mean (SD)	24.93 (3.34)	23.73 (3.61)	25.77 (3.03)
Diagnosis in years—median [IQR]	7.00 [3.00–14.00]	4.00 [2.50–9.25]	7.50 [3.50–8.75]
Hemodynamics			
mPAP—mean (SD)	44.50 (10.75)	41.57 (11.68)	48.11 (9.67)
PAWP—mean (SD)	12.06 (3.59)	13.43 (3.78)	11.00 (3.24)
Cardiac output (thermodolution)—mean (SD)	7.01 (3.07)	8.04 (3.93)	6.33 (2.15)
Cardiac index—mean (SD)	3.71 (1.75)	4.33 (1.98)	3.22 (1.48)
SvO_2—mean (SD)	68.94 (10.54)	68.29 (14.50)	69.44 (7.07)
PVR—mean (SD)	5.49 (3.15)	4.15 (2.79)	6.53 (3.17)
RVEF—mean (SD)	50.56 (9.29)	50.57 (12.03)	50.56 (7.28)
RV EDV BSA—mean (SD) male	95.25 (0.83)	95.83	94.66
RV EDV BSA—mean (SD) female	82.54 (17.53)	89.19 (23.24)	82.49 (10.61)
RV ESV BSA—mean (SD) male	53.23 (1.62)	52.08	54.37
RV ESV BSA—mean (SD) female	41.27 (16.16)	45.30 (22.46)	38.25 (10.03)
Therapy			
Mono—*n* (%)	1 (6%)	1 (14%)	0 (0%)
Double—*n* (%)	12 (71%)	4 (57%)	8 (80%)
Triple—*n* (%)	4 (23%)	2 (29%)	2 (20%)
Endothelin antagonists—*n* (%)	13 (76%)	6 (86%)	7 (70%)
Phosphodiesterase inhibitors—*n* (%)	16 (94%)	6 (86%)	10 (100%)
Postacyclin p.o.—*n* (%)	4 (23%)	2 (29%)	2 (20%)
Postacyclin i.v.—*n* (%)	3 (47%)	0 (0%)	3 (30%)
Calcium antagonists—*n* (%)	1 (6%)	1 (14%)	0 (0%)
Diuretics—*n* (%)	10 (59%)	5 (71%)	5 (50%)
Vitamin K antagonists—*n* (%)	8 (47%)	1 (14%)	7 (70%)

Abbreviations: BMI, body mass index; IQR, interquartile range; SD, standard deviation; 6MWT, six-minute walk test.

the median NT-proBNP was 147.00 [90.60–257.25], 71% received double combination therapy and the mean 6MWD was 543.70 ± 97.27 m. Detailed study population characteristics can be found in Table 2.

E-learning

As shown in Figure 3, there were adjustments in nutritional intake during the nutritional education. There was a signal of a decreased fluid intake

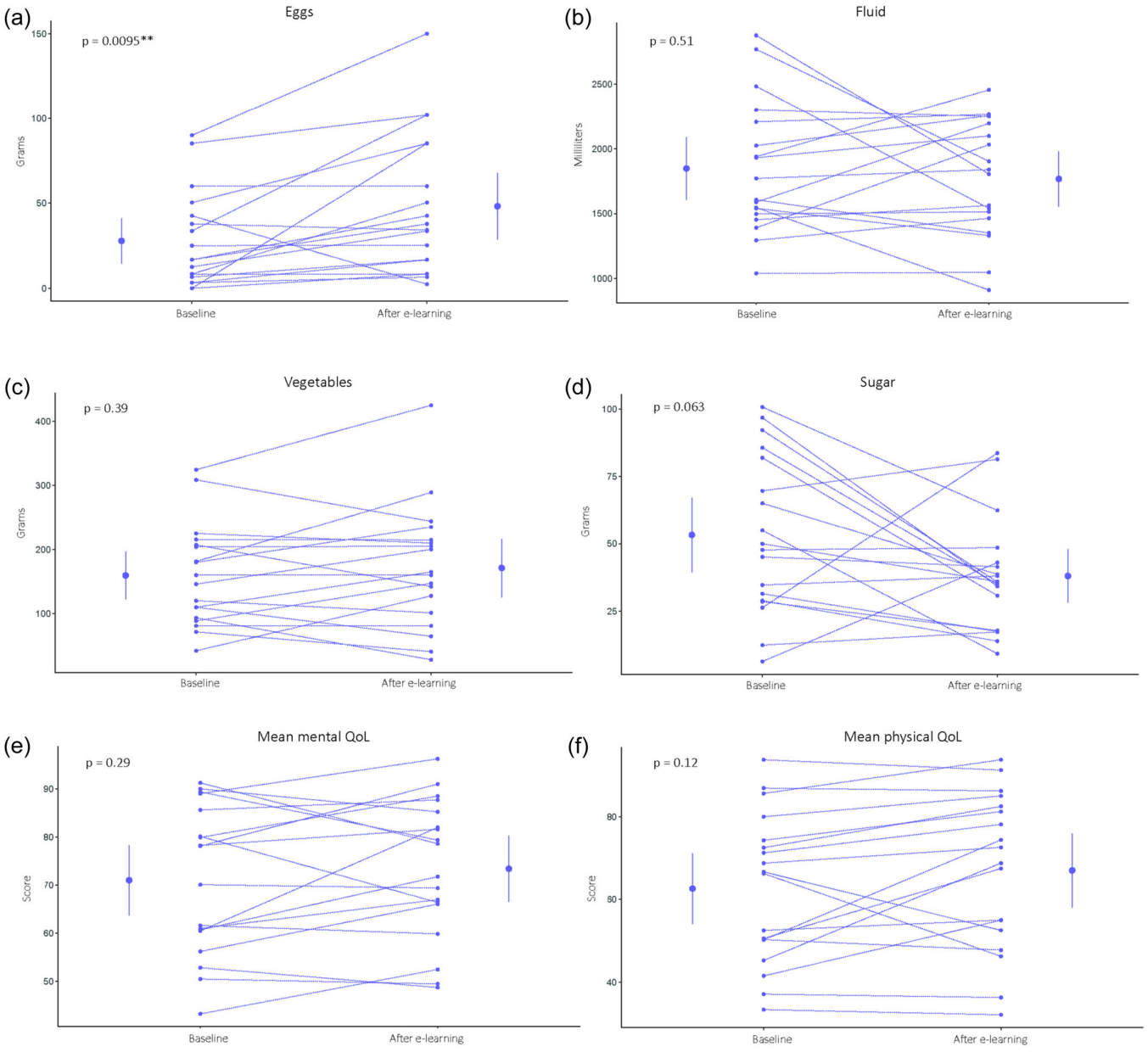

FIGURE 3 E-learning. Figure 3 shows a significant increased intake of eggs (a) with 42%, an increased intake of vegetables (d), a decreased fluid (b), and a decreased sugar intake (c) of 40%. There is improvement in mean mental QoL (e) and mean physical QoL (f). QoL, quality of life.

(Figure 3b) and a decrease in sugar intake (Figure 3c) of 40%. Figure 3a shows a significant ($p = 0.0095$) 42% increased intake of eggs and an increased intake of vegetables (Figure 3d). There were improvements in mean mental QoL and mean physical QoL (Figure 3e,f).

Dietary intervention

During the dietary intervention, no large changes in nutritional intake were observed, except for an increased intake of LF dairy in the LF group (group A) and full-fat dairy in the HFLC group (group B). Both groups A and B adopted a LF and, respectively, a HF diet in their daily intake. As shown in Figure 4d,f, group A decreased intake of fluids (11%) and intake of sugar (33%). Group B increased intake of fluids (1%) and sugar (20%). Figure 4e shows an increased of vegetables in both groups (group A 8.9%, group B 43.8%) Figure 4c shows a decreased intake of starch in group A (27%) and group B (21%). There were no changes in QoL in both groups (g, h).

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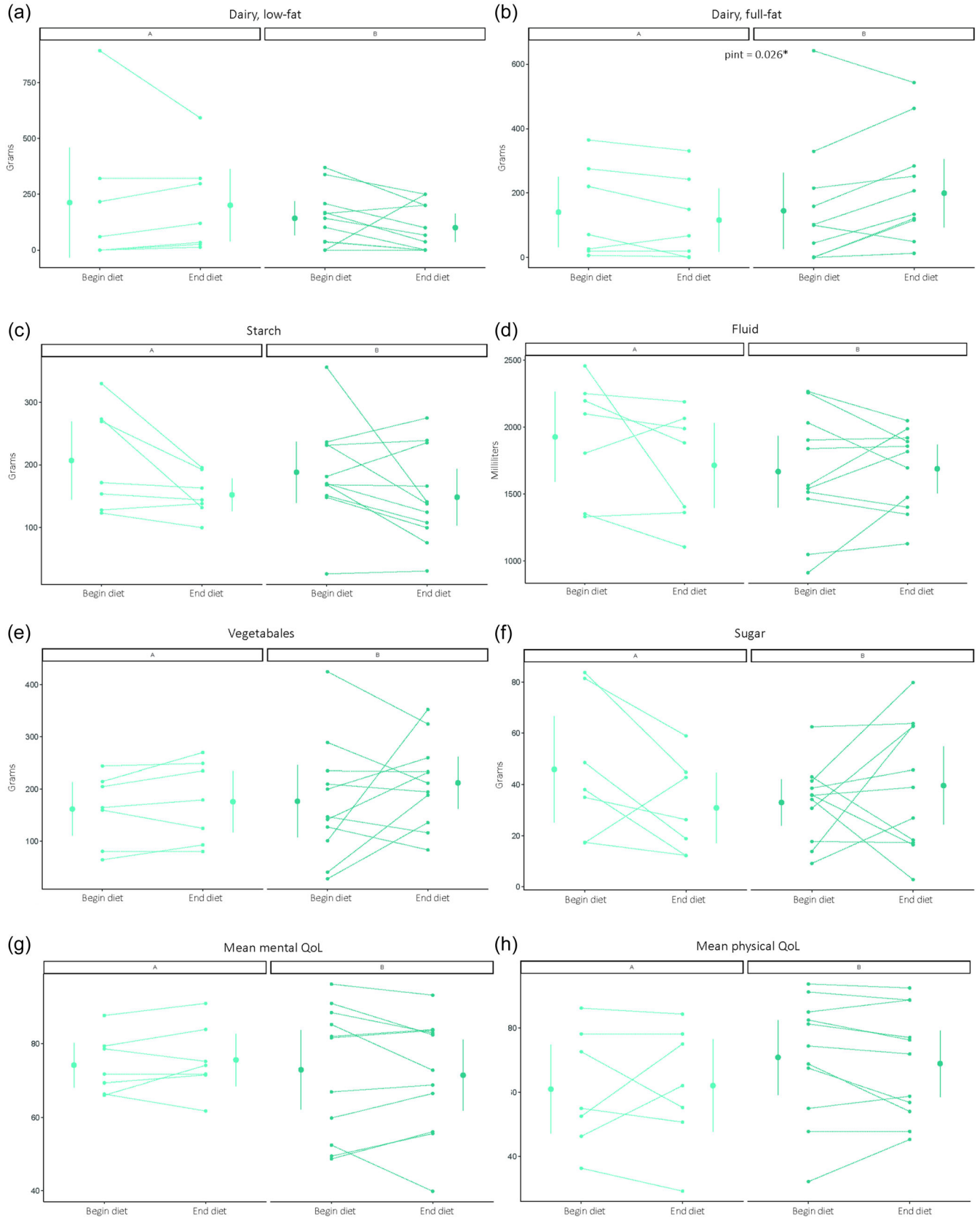

FIGURE 4 Dietary intervention. (a and b) show the biggest difference between diets in low-fat (LF) and full-fat dairy intake. Group A (LF) had decreased intake of fluid and intake of sugar and group B (high-fat, low-carb) had an increased intake of fluid and sugar (d, f). (c) shows a decreased intake of starch in group A (27%) and group B (21%). (e) shows an increased intake of vegetables in both groups (group A 8.9%, group B 43.8%) There were no changes in QoL in both groups (g, h).

Follow-up

Figure 5 shows a high adherence to the respective intervention during follow-up. There were no adjustments in vegetable, egg or fluid intake (Figure 5a–c), and relatively similar QoL scores (Figure 5g,h). The changes in LF and full-fat dairy that were accomplished during the dietary intervention, were sustained during follow-up (Figure 5e,f). As shown in Figure 5d, there was an decreased sugar intake during follow-up (24%). At the end of study, sugar and fluid intake were within reference values as published in the AHA guidelines.[15]

A complete overview of nutritional intake in grams per product per day and QoL scores throughout the study can be found in Supporting Information: II, part 2.

Vitamin and mineral status

There were minimal overall changes in vitamin- and mineral status or other blood values during the study and numbers compared well to those in the control group (Supporting Information: II, part 3). There was an increase in vitamin K1 and carotene levels in the overall study population, in addition there was a signal of triglyceride serum reduction. In group A there was an increase of magnesium levels. Group A, group B and controls showed a signal of elevated LDL cholesterol levels. Group B showed an increased cholesterol ratio, which remained within reference values.

All groups showed an elevation of vitamin D3 levels during summer.

DISCUSSION

To study the effects of nutritional interventions on dietary intake and QoL in PAH, patients participated in an e-learning followed by a diet highlighted by respectively a LF or a HFLC composition. With our design and a combination of questionnaires and blood analyses, we provide an overview of the effect of diverse innovative nutritional interventions in PAH, highlighted by nutritional adaptations of sugar, fluid, dairy, vegetables, starch, and eggs during e-learning. Furthermore, we show that during this study patients experienced an improvement in QoL.

E-learning

Nutritional education as e-learning is a new type of intervention in PAH. In other populations comparable interventions resulted in improvements in nutritional intake, exercise capacity, and QoL.[16–19] The component of active learning[20] appears to be the main factor of success leading to compliance with the educational intervention. The main focus in our intervention was on empowerment in goalsetting with respect to the adoption of healthy nutritional and lifestyle choices. Education was given on the relationship between nutrition, disease status, and QoL and focused on options instead of limitations in nutritional intake. The nutritional adaptations that patients made under these circumstances resulted in long-term adherence.

Besides the effects on intake and QoL, other advantages of video e-learning are worth mentioning. The burden of this intervention is low, patients can participate whenever they prefer and patients don't need to travel to the hospital for dietary advice or group sessions. Furthermore, this type of intervention is relatively inexpensive and accessible for patients throughout the world.

Dietary intervention

Although strict dietary guidelines were enforced, there still was room for cheat days during dietary intervention. Long-term compliance is a major issue in dietary interventions. Therefore, this approach focuses on intrinsic motivation and knowledge of nutrition and health obtained during the e-learning period to ensure long-term feasibility.

The adaptations in nutritional intake that occurred during the dietary period, were already apparent during the e-learning phase. Patients in the HFLC diet group (B) received dietary guidelines to reduce starch intake, patients in the LF diet group (A) showed a similar decrease in starch intake without these guidelines. This reduction may have been due to a higher intake of other products, such as vegetables and eggs, which provide fiber and protein, resulting in greater satiation.[21] Both groups received guidelines to limit sugar intake as much as possible. Remarkably, reduced sugar intake was observed in the LF group (A), whereas sugar intake in the HFLC group (B) slightly increased during dietary intervention.

The study included a LF and HFLC diet. The HFLC arm was advised to lower carb intake to improve dietary fat intake. Lowering carb intake and limiting meals per day, could improve patients' energy levels by stabilizing blood sugar levels and by that improving physical QoL. Patients lowered their carb intake in the HFLC group, however it did not result in a maximum of 125 g of carbs per day. A more strict diet may

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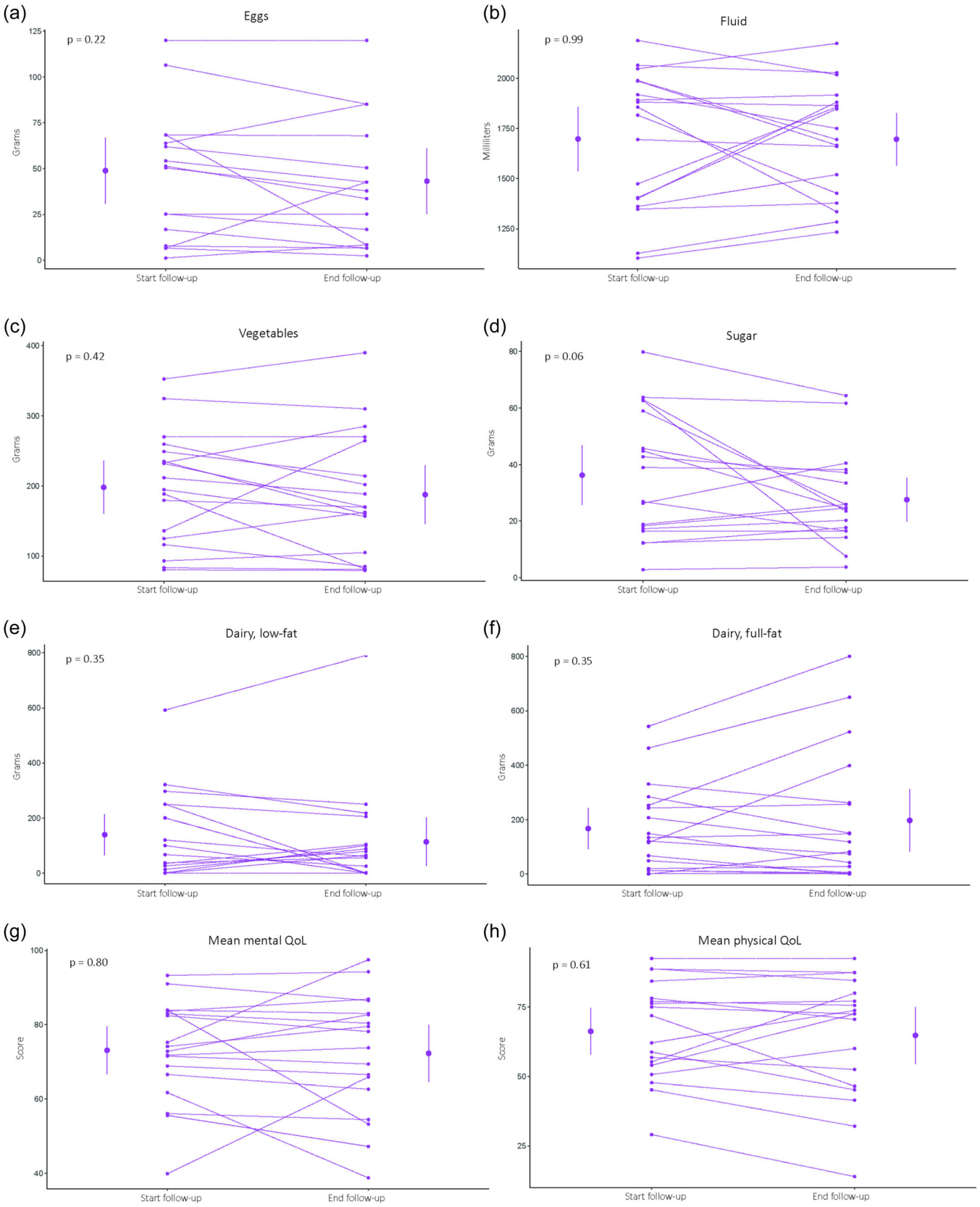

FIGURE 5 Follow-up. During follow-up were no adjustments in vegetable-, egg,- and fluid intake (a–c) and a relatively similar QoL (g, h). There was a decrease of sugar intake with 24% (d). Low-fat and full-fat dairy adaptation as advised during diet improved (e, f). QoL, quality of life.

led to a limited intake of carbohydrates, with no guarantee of similar long-term outcomes on nutritional adaptations.

During e-learning and dietary intervention there was a relation between fluid and sugar intake. This confirms a previously found correlation between these two nutrients in PAH patients.[6]

Follow-up

Overall, there was good compliance with the changes in nutritional intake during the intervention. This is a promising outcome in terms of long-term feasibility. Long-term studies of adherence to nutritional interventions in heart failure are limited, except for sodium intake.[22,23] Not all nutritional adaptations during the intervention were significant, still there was a clear signal of overall changes in intake. The combination of active learning and dietary advice in this study led to long-term compliance, whilst a dietary advice alone may be harder to implement in daily life. This suggests that education is needed to realize compliance toward dietary guidelines.

QoL

Patients in this study already experienced a high mean QoL at baseline, with a mean physical QoL score of 62.5 and a mean mental QoL score of 71. In the overall population, PAH patients have a mean physical QoL score of 37.2 and a mean mental QoL score of 46.4.[24] Regardless, improvements in QoL were observed during the e-learning and a signal was seen of improvement in QoL at end of study. Additionally, patients who demonstrated adaptations in nutritional intake showed improved QoL scores, strongly indicating that optimizing dietary intake may improve QoL. Larger studies are needed to asses the effect of nutritional education on QoL in PAH patients worldwide.

Vitamin and mineral status

No nutritional deficiencies were seen during e-learning or dietary intervention. There were some changes observed in blood markers in the intervention group. An increase in vitamin K1 plasma levels were observed, which could be a result of higher vegetable intake or an alternation of the microbiome due to nutritional changes, since vitamin K1 is also produced by gut bacteria.[25] After the e-learning and until end of study there was only in 12% of our population deficiencies in vitamin K1 plasma levels, which is remarkable since previous research showed a vitamin K1 deficiency in 60% of the PAH patients.[6]

The decrease in triglycerides plasma levels can be explained by a lower intake of ultra-processed foods.[26,27] Although there was a slight increase in cholesterol ratio in the fat enriched group, it was still widely within reference value.

Strengths and limitations

There are some limitations to our study. This is a small Dutch cohort in which 25 patients completed the study, compromising the statistical outcomes. In addition, our group of PAH patients was optimally treated, which is evident from the low median NT-proBNP values and a high mean 6MWD and QoL. PAH patients in a more severe condition may not have similar results or may lack the energy to participate in an 8-week online nutritional education or to follow a strict diet.

Since the study started during the Covid pandemic, it was challenging to include enough patients. On the other hand, an e-learning is a safe method to educate patients and lockdowns or other limitations during the pandemic did not affect this type of intervention. Unfortunately, 12 patients terminated study participation prematurely, from which 2 patients were lost to follow-up due to study related arguments. Ten patients terminated the study because of private circumstances (Figure 1). As a result, statistical power within this study was low. Nonetheless, clear signals of nutritional adaptations and improvements in QoL were observed during the intervention.

We used the HELIUS questionnaire, a very large questionnaire of more than 57 pages, to asses dietary habits over the previous 4 weeks. Patients may have been unaware of their actual nutritional intake or may have had problems with focussing on the load of questions. This may have led to under- or overreporting. However, prior research has indicated that the HELIUS questionnaire is very suitable for assessing nutritional intake in patients.[28,29] In our study, compliance with the HELIUS and the SF-36 questionnaires was low, and patients had to be reminded repeatedly to fill out their forms. More than 60% of controls refused to complete the forms for the second time, despite receiving repeated reminders by email and phone and being informed at the beginning of the study that they were required to complete the forms at baseline and after 6 months. The HELIUS questionnaire is a very large and intensive instrument, and it is possible that patients in control arm did not feel the need or were not sufficiently engagement to complete the form for the second time without intervention. This led to

exclusion of a control group for nutritional intake and QoL. For a larger cohort a simplified method on assessing nutritional intake and QoL must be considered, and different options such as an app should be explored.

CONCLUSION

This pilot study is the first to investigate the effects of nutritional interventions on adjustments in nutritional intake and QoL among patients with PAH. Patients in intervention group made behavioral changes in nutritional intake, during study and follow-up period, resulting in persistent nutritional and lifestyle adaptations. Remarkble changes in nutritional intake were observed during nutritional education via video e-learning. Patients had already high mean QoL scores at baseline and scores improved further during the nutritional e-learning. In conclusion, this novel digital approach of nutritional education provides an unique opportunity to change nutritional intake in PAH patients and by that improve QoL.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

ETHICS STATEMENT

Documented informed consent for publication has been obtained from each patient.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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