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Early View

Original research article

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Working memory training efficacy in COPD: the randomized double-blind placebo-controlled Cogtrain trial

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Take-home message: Working memory training improved performance on the trained tasks but not overall cognitive performance, healthy lifestyle behaviours or cognitive stress susceptibility in patients with COPD.

Abstract

Background: Cognitive impairment (CI) is highly prevalent in chronic obstructive pulmonary disease (COPD) and is associated with a sedentary lifestyle, unhealthy diet and increased cognitive stress susceptibility. Enhancement of cognitive performance by working memory training (WMT) may reverse these effects. Therefore, this study aimed to investigate the efficacy of WMT in COPD on cognitive performance, healthy lifestyle behaviours and cognitive stress susceptibility.

Methods: The double-blind randomized, placebo-controlled Cogtrain trial consisted of a 12-week training phase comprising 30 active or sham WMT sessions, followed by a second 12-week maintenance phase with 12 sessions. Measurements took place at baseline and after the first and second phases. The primary outcome was cognitive performance. Secondary outcomes were the recall of prespecified healthy lifestyle goals, physical capacity and activity, dietary quality, and cognitive stress susceptibility. Motivation towards exercising and healthy eating and psychological wellbeing were exploratory outcomes.

Results: Sixty-four patients with moderate COPD (45% male, aged 66.2±7.2 years, median FEV_1 60.6% predicted) were randomized. WMT significantly increased patients' performance on the trained tasks in the first phase, which remained stable in the second phase. Of the 17 cognitive outcome measures only one measure of memory improved after the first phase and one measure of reaction time after the second phase. This intervention did not influence physical capacity and activity, recall of prespecified healthy lifestyle goals, psychological wellbeing, or cognitive stress susceptibility.

Conclusion: WMT improved performance on the trained tasks but not overall cognitive performance, healthy lifestyle behaviours or cognitive stress susceptibility in patients with COPD.

Introduction

Chronic obstructive pulmonary disease (COPD) is characterized by persistent airflow limitation and chronic respiratory symptoms [1]. Muscular [2] and metabolic abnormalities [3,4], anxiety, depression [5] and cognitive impairment (CI) are common comorbidities of COPD. A recent large review reported a 32% prevalence of any CI and a 25% prevalence of mild CI (MCI) in patients with COPD [7]. More recently, a 39.4% prevalence of CI was reported in clinically stable patients [8] and a 41.5 [9] and 56.7% [10] prevalence in patients referred to PR. In contrast, the prevalence of CI among non-COPD controls in the latter study was 13.3%. Disease-specific and lifestyle factors including hypoxia, a history of smoking, dietary insufficiencies and sedentary behaviour may contribute to this elevated prevalence [6].

It is important to consider CI in COPD management because it negatively impacts patients' health outcomes [11]. Lower working memory (WM) capacity, which refers to the ability to keep important information in mind, enabling this information to be mentally manipulated [12], is related to engagement in unhealthy lifestyle behaviours such as overeating [13] and smoking [14]. Furthermore, executive functioning (EF) is inversely related to cognitive stress reactivity [15] and perception [16]. EF encompasses inhibition, task switching and WM [17]. These functions are localized in the prefrontal cortex, a key area modulating the stress-activated hypothalamic-pituitary-adrenal gland (HPA) axis [18]. Because patients with COPD exhibit smaller hippocampal [19] and prefrontal cortex volumes [20] than healthy controls [21], COPD may negatively impact cognitive stress susceptibility.

Only one earlier study has investigated cognitive training in patients with COPD, which did not improve cognitive functioning [22]. However, this study had a relatively low training load and it specifically targeted attention, learning and logical-deductive thinking. In contrast, the above-mentioned literature indicates that WM training (WMT) could improve cognitive performance, adherence to healthy lifestyle behaviours and cognitive stress susceptibility.

It is still unclear whether WMT can improve cognitive performance in COPD. Its effects in healthy older adult populations are equivocal [23,24], and improved cognitive functioning on a trained task often generalizes only poorly into other domains [25].

Many patients with COPD lead a relatively unhealthy lifestyle, characterized by persistent smoking (in over one-third of patients) [26], physical inactivity (e.g., reported step counts of less than 3000 per day, whereas 5000 steps per day has been defined as the threshold of being considered sedentary) [27] and poor dietary quality (intake of macro- and micronutrients that is lower than the RDI and lower than in non-COPD controls) [28-30]. Dual-process theories of cognitive functioning [31] imply that WMT could improve lifestyle behaviours by strengthening top-down behavioural control [13,32]. These theories state that two distinct systems handle cognitive operations: an automated, unconscious system, which is responsible for executing relatively easy, well-known and / or highly automated cognitive processes, and a controlled, conscious system for more deliberate, controlled and conscious execution of harder cognitive tasks [33]. The interaction between these two determines the extent to which one's responses are automatic or controlled [13]. WMT is supposed to strengthen the

former system [34], thereby increasing conscious control over one's actions and enabling one to more carefully consider the degree to which actions, among others related to health behaviours (see e.g., [13] and [35]) are opportune [33,36]. To our knowledge, only one study has investigated the effects of WMT on dietary intake in otherwise healthy overweight individuals [37]; its effects on physical activity levels have not yet been investigated.

WMT could beneficially modulate cognitive stress susceptibility and perception: it attenuated the salivary cortisol stress response in patients with major depressive disorder [38] and improved functioning of the brain areas responsible for modulating cognitive stress. WMT increased prefrontal activity and connectivity [39], and cognitive training had beneficial effects on hippocampal activation [40].

The primary aim of the Cogtrain trial was to investigate whether a 12-week WMT program followed by a 12-week maintenance program could establish and maintain cognitive improvement in patients with COPD. Its secondary aims were to investigate the effects of the intervention on physical capacity and activity, dietary quality, cognitive stress susceptibility and perception and the recall of prespecified healthy lifestyle goals. In addition, depression and anxiety were investigated as exploratory outcomes and reported in the supplementary materials.

Methods

Study design

The double-blind randomized placebo-controlled Cogtrain trial consisted of a 12-week home-based intensive WMT (phase 1) followed by 12 weeks of active follow-up with weekly booster sessions (phase 2). The placebo group received sham training sessions in both phases (see Figure 1). Measurements took place at Maastricht University Medical Centre one week before baseline (T0), at baseline (T1), after phase 1 (T2) and after phase 2 (T3; see Table 1). All four of these visits lasted for 2.5-3 hours. The study was registered at ClinicalTrials.gov (NCT03073954) and the medical ethics committee at Maastricht University Medical Centre granted ethical approval (NL59883.068.17 / MEC 173010).

Patients

Patients were eligible to participate in the study if they were aged 18 or over, had a diagnosis of COPD based on the Global Initiative for Chronic Obstructive Lung Disease (GOLD) criteria [1]. Exclusion criteria were disease or disability limiting the ability to undergo neuropsychological testing and/or WMT (e.g., blindness, previous stroke, or lack of hand control), neurological disorders (e.g., Alzheimer's or Parkinson's disease), insufficient mastery of the Dutch language, participation in an inpatient pulmonary rehabilitation program, not having access to a suitable device to complete the WMT on (i.e., laptop or personal computer), or participation in another interventional study over the course of the study period. Baseline cognitive performance was not an inclusion criterium. Participants received 50 euros upon completion of the entire study.

Intervention

During phase 1, participants received 30 e-mails with a link to a 20- to 25-minute internet-based WMT session (*i.e.*, 2 to 3 sessions weekly). Each session had to be completed on patients' personal computer or laptop within 48 hours of receiving the respective e-mail or it would be marked as missed. Throughout the first phase, participants were invited to complete each session two days after completing the previous one. Participants were withdrawn from the study after missing six sessions. During phase 2 participants received 12 sessions (1 per week) without a minimum number of sessions to be completed.

The WMT protocol has been used before [35,41] and has been proven feasible and acceptable. It consisted of a visuospatial task, a backward digit span task and a letter span task, always presented in this order. See the supplementary file for a more detailed description of these tasks.

Participants in the intervention and placebo groups received the same tasks and the same number of trials. However, task difficulty was artificially held constant at three units throughout the intervention in the placebo group, whereas it was automatically adjusted on a trial-by-trial basis (adaptive WMT [37,41]) in the intervention group. The treatments in the intervention and placebo groups were therefore different in that learning effects were only expected in the intervention group.

Goal setting

During T1, participants were informed about their physical activity and dietary quality (based on the relevant results obtained during T0), and they discussed dietary and physical activity goals with the researcher administering the test day. Physical activity goals were expressed as changes in number of steps per day, or a consolidation of the current number if already adequate at baseline. See the supplementary file for a more detailed description of the goal setting procedure.

Baseline demographical and clinical characteristics

Gender, age, educational level, smoking status, and lung function were collected and assessed at baseline. Lung function was assessed using the SpiroPerfect system (Welch Allyn, Skaneateles Falls, New York, United States) before and 15 minutes after administering 400 µg salbutamol (Airomir Autohaler, Teva, Haarlem, The Netherlands). Additionally, Addenbrooke's Cognitive Examination-Revised (ACE-R) [42] was administered. This is a rapid (5-10 minute) cognitive screening tool which incorporates five sub-domain scores (orientation / attention, memory, verbal fluency, language and visuospatial abilities) and is scored on a scale of 0-100.

Outcomes

Manipulation check

Participants' maximum WM span for each home-based WMT session was averaged over the three tests. Increased WM span in the intervention group across phase 1 followed by a consolidation across phase 2 served as a validation of the intended effects of the intervention. Intervention compliance was assessed by the number of completed sessions.

Primary outcomes

Cognitive functioning

The Cambridge Neuropsychological Test Automated Battery (CANTAB) [43] is a validated computerized cognitive function assessment tool. The Motor Screening Task (MOT; measuring psychomotor speed), Paired Associates Learning Task (PAL; gauging visuospatial associative learning), Stop-Signal Task (SST; inhibition), Reaction Time Task (RTI; psychomotor speed, attention), Delayed Match-to-Sample (DMS; recognition memory), and Spatial Working Memory Task (SWM; working memory, executive functioning) were administered, in order to investigate a wide range of cognitive parameters (see Supplementary Table 1). The battery took 45-60 minutes to complete. Administration at T0 served to account for potential learning effects; data of T1 through T3 was used in the analyses.

Secondary outcomes

Healthy lifestyle goal recall

At T2 and T3 participants were asked to recall the assessment procedure for their physical activity and dietary intake during earlier visits ('procedure') and the specific healthy lifestyle goals that had been set at T1 ('content'). See the supplementary file for a more detailed description of the healthy lifestyle goal recall procedure.

Physical capacity and activity

Physical capacity was assessed using participants' obtained distance during the 6-minute walking test [44] and their score on the Short Physical Performance Battery (SPPB) [45].

Physical activity was assessed by 7-day accelerometry (activPAL, PAL Technology, Glasgow, United Kingdom). The accelerometer was affixed to patients' upper legs using special water resistant 3M Tegaderm tape. As such, the accelerometer was worn 24 hours per day for seven straight days, always consisting of five weekdays and two weekend days. No wear days were considered invalid because of insufficient wear time. Accelerometry data was subsequently processed using the activPAL software suite and quantified as number of steps per day and the amount of time spent sedentarily, standing up, walking, and in high-intensity physical activity. Additionally, the number of sedentary breaks and sedentary bouts ($\geq$ 30 minutes)

were assessed. The time participants spent in high-intensity physical activity, defined as > 110 steps per minute [46,47], was also calculated.

Dietary quality

Dietary intake was assessed using a 24-hour recall paradigm. The results were entered into the “Eetmeter” tool of the Dutch Voedingscentrum. If participants knew the weight of their intake, this information was entered into the application, but portion sizes could also be entered in terms of numbers of tablespoons, ladles, cups, glasses, etc., based on an assumed size of a standard serving. (e.g., a certain weight was assumed for a ladle of mashed potatoes, which could also be finetuned into a small, standard or large ladle). The "Eetmeter" application then calculated intake of a wide range of macro- and micronutrients. Dietary quality was quantified as the Alternative Healthy Eating Index (AHEI)-2010 score [48], based on intake of fruit, vegetables, wholewheat products, legumes / nuts, eicosapentaenoic and docosahexaenoic acid, the proportion of energy intake derived from polyunsaturated fatty acids, sodium, sweet drinks and juices, red and processed meat, and alcohol.

Cognitive stress susceptibility and perception

The socially evaluated cold pressor test (SECPT) [49] was administered as a measure of acute stress susceptibility; the cortisol awakening response (CAR) [50] served as a measure of chronic stress susceptibility. See the supplementary file for a more detailed description of the administration of these tests.

Exploratory outcomes

Healthy lifestyle motivation and psychological wellbeing served as exploratory outcomes. See the supplementary file for a more detailed description of these outcomes.

Sample size and power

The sample size calculation was performed using G*Power version 3.1.9.4 [51]. In a recent Canadian study examining the effects of cognitive training on cognitive decline, the authors reported an effect size of $f = 0.475$ [52]. Combined with a two-tailed paired-samples *t*-test, an α of 0.05 and a power of 95%, 60 individuals were required, or 30 per group. We anticipated 60 participants to complete, rather than to start, the trial so as to maintain adequate power throughout the study.

Statistical analyses

Data analysis was conducted according to the intention-to-treat principle using Stata 14 (StataCorp LP, College Station, TX). Data of participants that prematurely quit the study were used up to the point of their withdrawal. Missing data was considered as missing at random and was not imputed. Two-sided *p*-values smaller than 0.05 were considered statistically significant. Analyses were conducted semi-blinded (*i.e.*, participant allocation was revealed as ‘group 0’ or ‘group 1’, but not which of those was the intervention group), except for the

home-based WMT analyses, given the nature of the data. The WMT analyses were conducted after all other analyses had been run.

The normality of all outcome variables was checked. Descriptive statistics of normally distributed variables were expressed as mean ± standard deviation; those of non-normally distributed variables as median (inter-quartile range [IQR]).

Baseline between-group differences in WM capacity were tested using independent-samples *t*-tests. WM capacity development in the intervention group across phase 1 (*i.e.*, session 1 *versus* session 30) and phase 2 (*i.e.*, session 31 *versus* session 42) were tested using one-sample *t*-tests with the values at sessions 1 and 31 as test value and the values at sessions 30 and 42 as dependent variables, respectively.

Two-way repeated measures analyses of variance were conducted to compare differences over time and between the groups. Time point (T1-T3) and group (intervention *versus* placebo) were entered as independent variables. Phase 1 (*i.e.*, T1 *versus* T2) and phase 2 (*i.e.*, T2 *versus* T3) were analysed separately. Time, group, and the time × group interaction were entered as independent variables. Age, gender, and educational level were entered as covariates into the analyses with the cognitive parameters as dependent variables. Because these analyses are robust against a violation of the assumption of normality when the sample size exceeds 50 [53], non-normally distributed data was not transformed.

Results

Out of 301 patients assessed for eligibility, 68 were enrolled in the trial of whom 64 were randomized to the intervention (*n*=33) or placebo group (*n*=31) (see Figure 2).

Baseline demographical and clinical characteristics

At baseline, the study population (45% male, aged 66.2±7.2 years) was characterized by on average moderate airflow limitation (median FEV_1 60.6% predicted, IQR 45.6-77.0) and impaired exercise capacity (6MWD 457.7±84.7 meters) but a relatively high physical activity level for this population of chronically diseased patients (7525±3254 steps per day). Baseline cognitive functioning was relatively poor (median ACE-R score 88, IQR 83-94) compared to earlier reported normal values [42] (see Table 2). No parameters were different between the groups at baseline, except the BDI-II (*p*=0.002) and the REBS amotivation scale (*p*=0.027).

Manipulation check

During phase 1, 6 participants (18.2%) dropped out of the intervention group and 4 (12.9%) dropped out of the placebo group (see Figure 2). Participants in the intervention group completed on average 23.6±6.2 out of 30 WMT sessions during phase 1 and 7.7±3.6 out of 12 during phase 2, compared to 27.4±9.7 and 5.0±2.3, respectively, in the placebo group. The average WM span was not significantly different between the groups at baseline (*p*=0.888). The WM span of the intervention group increased significantly during phase 1 (*p*<0.001) and remained stable during phase 2 (*p*=0.399) (see Figure 3).

Primary outcomes

Table 3 reports the descriptive statistics of the primary outcome measures; Table 4 reports their effect sizes.

Across phase 1 and phase 2, the intervention had no effect on five of the six CANTAB tests. The only significant beneficial effect was found on the 'probability of an error given error' parameter of the DMS, which tended to decrease in the intervention group (p=0.077) and remained stable in the placebo group (p=0.223), leading to a significant interaction effect (p=0.038). Across phase 2, there was only a significant positive effect on the five-choice movement time of the RTI, which decreased in the intervention group (p=0.016) and remained stable in the placebo group (p=0.303), also leading to a significant interaction effect (p=0.017).

Secondary outcomes

Table 5 reports the descriptive statistics of the secondary outcome measures; Table 6 reports their effect sizes.

Healthy lifestyle goal recall

The intervention had no significant effects on the recollection of the goal setting procedure or the contents of the set goals at any time point.

Physical capacity and activity

The intervention did not influence participants' physical capacity and activity. The number of sedentary breaks per day increased significantly across both groups across phase 1 (p=0.004). However, this does not indicate an effect of the intervention, and the total amount of time spent sedentarily or the number of prolonged sedentary bouts were not significantly affected.

Dietary quality

The intervention did not affect participants' dietary quality, but the AHEI-2010 score improved significantly across phase 1 in both groups (p=0.029).

Cognitive stress susceptibility and perception

Across phase 1, the intervention did not significantly affect any stress susceptibility parameter. The SECPT-induced change in cortisol level decreased in both groups (p=0.019), indicating overall decreased stress reactivity. The magnitude of the SECPT-induced change in cortisol levels increased significantly in the intervention group across phase 2 (p=0.033), indicating increased stress reactivity, whereas it remained stable in the placebo group (p=0.462), leading to a significant interaction effect (p=0.047). This indicates an effect of the intervention.

Exploratory outcomes

See the supplementary file for the results of the motivational and psychological exploratory outcome measures.

Discussion

This clinical trial aimed to investigate whether WMT could improve cognitive performance, adherence to healthy lifestyle behaviours, recall of prespecified healthy lifestyle goals and cognitive stress susceptibility and perception in patients with COPD. The WMT was feasible as WM capacity on the trained tasks improved significantly in the intervention group across phase 1 and remained stable in phase 2. Nevertheless, this did not improve CANTAB task performance. The intervention significantly affected only 1 of 17 CANTAB parameters in both phases of the intervention, and these parameters were different in both phases. Overall, the intervention thus did not improve any of the six investigated cognitive domains. This is in line with earlier studies: cognitive training can improve performance on tests that are identical or similar to those that were trained [23,54], but these improvements generalize poorly into other cognitive tests or domains, and they are poorly maintained in the longer term [25]. The only earlier trial investigating cognitive training in patients with COPD did not significantly improve cognitive performance either [22].

Baseline cognitive performance was highly variable: the median ACE-R score of 88 indicates relatively poor performance, but the highest-performing quartile of participants, scoring 94 and above, showed normal cognitive performance. This, along with the fact that it is unknown whether WMT is more beneficial for those with poor baseline cognitive performance (because of their larger room for improvement) or for highly performing patients (because of their arguably higher cognitive and neural plasticity and therefore higher learning potential) may have contributed to the overall lack of effects of WMTs.

The effects of the intervention on healthy lifestyle outcomes, psychological wellbeing and healthy lifestyle motivation were also limited. This is not surprising, as cognitive improvement by WMT, which was hypothesized to enable a healthier lifestyle, was not attained in the first place. Regarding physical activity, the intervention improved only one of three indices of a sedentary lifestyle. Intrinsic motivation towards healthy eating improved, but not actual dietary quality (which interestingly improved in both groups across phase 1). WMT has improved healthy lifestyle behaviours such as caloric intake [13,55] or alcohol intake [35] in earlier trials, but these selectively included certain subgroups that stood to gain a lot from the interventions, such as overweight participants or substance abusers. These patients were therefore much more likely to improve than our patients with relatively high levels of physical activity and a relatively healthy diet.

Previous interventions aiming to improve dietary quality have combined WMT with education [e.g., 13], to make sure that WMT-induced increased abilities to override automatic responses would be aimed at the appropriate responses. This is relevant as 28.5% [56] and 30.2% [57] of patients with COPD have poor health literacy. In other words, patients might simply ‘not know

that they don't know' what is and is not healthy. Additionally, a motivational component such as motivational interviewing could have contributed to participants' willingness to change, thereby also increasing adherence to healthy lifestyle behaviours in the longer term [58,59]. The lack of educational or motivational components in the current trial might have contributed to its inability to significantly improve dietary quality.

Weaknesses also include the relatively low response rate (for instance because the high study load deterred potential participants or because they did not own a computer) and the fact that the foreseen sample size was not attained (53 instead of 60 patients completed the trial). However, given the pattern of the results, seven additional patients would probably not have made a larger difference. Moreover, the sample size was comparable to other recently published studies [60,61]. The study may also have suffered from selection bias towards relatively highly motivated patients with a healthier lifestyle and remarkably high levels of physical activity for a population of patients with chronic disease. This may have contributed to the lack of effects on physical activity. Furthermore, although the detrimental impact of smoking on cognitive performance has been well-documented [62,63], this or the effects of WMT on smoking cessation, as part of healthy lifestyle improvement, have not been further investigated in the current study. The equal division of current, former and never-smokers between the intervention and placebo groups was, however, verified at baseline.

Strengths of the trial are its rigorous double-blind, placebo-controlled design and its comprehensive neuropsychological assessment, which gives a much more comprehensive indication of cognitive performance than frequently used screening tools such as the Mini-Mental State Examination or the Montreal Cognitive Assessment [8,64]. The study had relatively few in- and exclusion criteria, aiming to include a representative population of community-dwelling COPD patients. Furthermore, the drop-out rate was equivalent to or lower than comparable studies [65,66].

In conclusion, WMT in its current form was not effective in improving cognitive performance, healthy lifestyle behaviours, cognitive stress susceptibility and perception, healthy lifestyle goal recall, healthy lifestyle motivation or psychological wellbeing in community-dwelling patients with COPD. Future research should consider incorporating additional interventional components, such as education, and investigate specific at-risk subgroups to examine the effectivity of WMT.

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Conflict of interest statement

None of the authors declares conflicts of interest.

Author contributions

Conception and design: HRG, KH, AMWJS

Data collection: MvB, SM, LS

Data analysis and interpretation: MvB, HRG, AMWJS

Writing manuscript – initial draft: MvB

Writing manuscript – review and editing: all authors

All authors critically revised the article and gave final approval of this version to be published. All authors had full access to all data, including statistical reports and tables, in the study and can take full responsibility for the integrity of the data and the accuracy of the data analysis.

Tables

Table 1

Outcome measures and time points at which they were taken

Instrument	T0	T1	T2	T3
Baseline demographical and clinical characteristics				
Age, gender, educational level, smoking status	X			
Spirometry	X			
Manipulation check				
WM span		X	X	
Number of completed sessions		X	X	
Primary outcome measures				
Cognitive functioning				
Cambridge Neuropsychological Test Automated Battery †	X	X	X	X
Addenbrooke's Cognitive Examination-Revised		X		
Secondary outcome measures				
Physical capacity and activity				
6-minute walking test		X	X	X
Short Physical Performance Battery		X	X	X
Accelerometry		X	X	X
Dietary intake				
Alternative Healthy Eating Index-2010	X		X	X
Cognitive stress susceptibility and perception				
Cortisol Awakening Response		X	X	
Perceived Stress Scale		X	X	X
Socially Evaluated Cold Pressor Test		X	X	X
Healthy lifestyle goal recall				
Healthy lifestyle goal recall ††			X	X
Exploratory outcome measures				
Healthy lifestyle motivation				
Behavioural Regulation of Exercise Questionnaire-2	X			X
Regulation of Eating Behaviours Scale	X			X
Psychological wellbeing				
Beck Depression Inventory-II		X	X	X
Generalized Anxiety Disorder-7		X	X	X

Note. T0: baseline minus 1 week; T1: baseline; T2: after the first phase (baseline + 12 weeks); T3: after the second phase (baseline + 24 weeks). † Administration at T0 took place to compensate for learning effects; †† Healthy lifestyle goals were set at T1.

Table 2

Baseline demographical and clinical characteristics

	Intervention		**Placebo**	
	n		***n***	
Age (years)	33	66.0±6.8	31	66.4±7.8
Gender (male / female)	33	13 / 20	31	16 / 15
Educational level	33		31	
Primary school (*n*, %)		2 (6.1%)		0 (0.0%)
Initial vocational education (*n*, %)		0 (0.0%)		3 (9.8%)
High school (*n*, %)		10 (30.3%)		10 (32.3%)
Intermediate vocational education (*n*, %)		6 (18.2%)		8 (25.8%)
Higher vocational education (*n*, %)		12 (36.4%)		10 (32.3%)
Academic (*n*, %)		3 (9.1%)		0 (0.0%)
Smoking status (never / current / former)	33	8 / 3 / 22	31	6 / 6 / 19
Lung function				
GOLD stage (I / II / III / IV)	31	8 / 11 / 11 / 1	30	5 / 15 / 7 / 3
FEV_1 (l)	31	1.75±0.76	30	1.69±0.69
FEV_1 (% predicted)	31	58.5 (44.7-82.5)	30	60.6 (44.9-71.8)
FVC (l)	31	3.55±1.03	30	3.49±0.98
FEV_1/FVC (%)	31	49.0±14.7	30	48.4±14.7
ACE-R (0-100)	33	88 (82-93)	31	88 (83-94)

Note. GOLD: Global Initiative for Obstructive Lung Disease; FEV_1: forced expiratory volume in the first second; FVC: forced vital capacity; ACE-R: Addenbrooke's Cognitive Examination-Revised. All data expressed as mean ± standard deviation or median (inter-quartile range) depending on the normality of the distribution of the data. No parameters were significantly different between the groups.

Table 3

Descriptive statistics of the primary (CANTAB) outcome measures

Test	Measure	T1		T2		T3	
		Intervention	**Placebo**	**Intervention**	**Placebo**	**Intervention**	**Placebo**
MOT	Mean latency (ms)	896 (696-1031)	894 (761-1056)	903 (755-980)	865 (736-961)	860 (771-940)	827 (745-976)
PAL	Total errors (*n*)	13.0 (11.0-20.0)	13.0 (8.0-17.0)	13.0 (10.0-16.0)	13.0 (11.0-17.0)	13.0 (9.0-18.0)	13.0 (9.0-21.0)
	Adjusted total errors (*n*)	20.0 (12.0-39.0)	19.0 (10.0-41.0)	14.0 (10.0-42.0)	16.0 (11.0-24.0)	17.0 (9.0-36.0)	14.5 (9.0-21.0)
	First attempt memory score	9.76±3.83	10.55±4.56	10.89±4.34	10.56±3.53	10.88±3.17	12.27±3.06
SST	Stop-signal reaction time (ms)	244 (220-272)	240 (213-275)	258 (240-276)	236 (215-262)	249 (224-267)	223 (208-253)
RTI	Median simple reaction time (ms)	328 (308-349)	340 (316-366)	331 (311-350)	349 (325-365)	341 (320-361)	361 (338-386)
	Mean simple movement time (ms)	253 (216-286)	243 (207-302)	250 (225-288)	264 (229-313)	272 (214-303)	272 (223-326)
	Median five-choice reaction time (ms)	399 (366-429)	392 (370-412)	399 (366-426)	392 (358-425)	425 (382-441)	419 (379-450)
	Mean five-choice movement time (ms)	290 (240-313)	283 (245-331)	282 (271-339)	309 (258-331)	272 (239-312)	307 (250-336)
DMS	Correct responses (%)	85.0 (80.0-90.0)	85.0 (75.0-90.0)	90.0 (85.0-95.0)	85.0 (75.0-95.0)	85.0 (80.0-95.0)	85.0 (77.5-92.5)
	Median correct latency (ms)	3027 (2494-3370)	3294 (2593-3488)	3003 (2478-4305)	3255 (2475-4342)	3295 (2411-4243)	3159 (2534-4490)
	Probability of error given error (%)	0.0 (0.0-20.0)	0.0 (0.0-16.7)	0.0 (0.0-0.0)	0.0 (0.0-20.0)	0.0 (0.0-25.0)	0.0 (0.0-21.0)
SWM	Between-errors (*n*)	16.0 (6.0-21.0)	15.0 (6.0-23.0)	15.0 (7.0-20.0)	17.0 (10.0-20.0)	16.0 (9.0-21.0)	12.0 (4.0-19.0)
	Between-errors 4 boxes (*n*)	0.0 (0.0-1.0)	0.0 (0.0-2.0)	0.0 (0.0-0.0)	0.0 (0.0-1.0)	0.0 (0.0-2.0)	0.0 (0.0-0.0)
	Between-errors 6 boxes (*n*)	3.0 (0.0-6.0)	4.0 (0.0-7.0)	4.0 (1.0-7.0)	4.0 (1.0-7.0)	2.0 (0.0-7.0)	2.0 (0.0-6.0)
	Between-errors 8 boxes (*n*)	11.0 (4.0-15.0)	10.0 (5.0-14.0)	10.0 (5.0-14.0)	11.0 (6.0-14.0)	12.0 (8.0-14.0)	10.0 (3.0-14.0)
	Strategy	8.0 (7.0-10.0)	8.0 (6.0-10.0)	9.0 (7.0-10.0)	9.0 (6.0-10.0)	8.0 (6.0-9.0)	9.0 (7.0-9.0)

Note. MOT: motor orientation task; PAL: paired associates learning; SST: stop-signal task; RTI: reaction time task; DMS: delayed match-to-sample; SWM: spatial working memory. All data expressed as mean ± standard deviation or median (inter-quartile range) depending on the normality of the distribution.

Table 4

Effect sizes of the primary (CANTAB) outcome measures

Test	**Measure**	**Phase 1**			**Phase 2**		
		***F* Time**	***F* Group**	***F* Int.**	***F* Time**	***F* Group**	***F* Int.**
MOT	Mean latency (ms)	0.21	0.35	0.84	0.44	0.09	0.36
PAL	Total errors (*n*)	1.23	0.31	3.79	4.63*	0.35	0.88
	Adjusted total errors (*n*)	3.79	1.09	0.30	0.68	0.67	0.01
	First attempt memory score	0.58	0.45	1.16	1.82	0.67	2.32
SST	Stop-signal reaction time (ms)	0.04	4.76*	0.39	2.88	4.41*	0.78
RTI	Median simple reaction time (ms)	1.96	1.30	0.00	7.53**	2.47	0.26
	Mean simple movement time (ms)	2.61	0.42	3.73	2.96	1.20	0.02
	Median five-choice reaction time (ms)	0.88	0.00	2.47	9.13**	0.77	0.27
	Mean five-choice movement time (ms)	1.10	0.05	0.01	1.00	0.17	6.20*
DMS	Correct responses (%)	1.25	1.12	0.00	1.91	0.99	0.04
	Median correct latency (ms)	2.11	0.63	0.11	0.23	0.22	1.31
	Probability of error given error (%)	0.13	0.51	4.63*	0.00	1.15	1.06
SWM	Between-errors (*n*)	0.04	0.10	1.91	0.55	1.25	3.54
	Between-errors 4 boxes (*n*)	0.14	0.52	0.01	0.16	0.14	2.54
	Between-errors 6 boxes (*n*)	0.10	0.41	0.14	1.28	1.83	1.87
	Between-errors 8 boxes (*n*)	0.02	0.09	1.92	0.19	0.78	2.65
	Strategy	0.40	0.25	1.12	0.10	0.46	2.05

Note. Int.: interaction; MOT: motor orientation task; PAL: paired associates learning; SST: stop-signal task; RTI: reaction time task; DMS: delayed match-to-sample; SWM: spatial working memory. All data expressed as *F*-values. * $p<0.05$ ** $p<0.01$ *** $p<0.001$.

Table 5

Descriptive statistics of the secondary outcomes of the intervention

	T1		**T2**		**T3**	
	Intervention	**Placebo**	**Intervention**	**Placebo**	**Intervention**	**Placebo**
Physical capacity and activity						
6MWD (m)	456.5±94.1	459.0±74.7	463.9±88.0	452.9±76.3	454.4±108.0	448.2±86.8
6MWD (% predicted)	73.6±13.9	72.5±10.9	74.9±13.8	71.9±12.5	73.2±16.7	71.3±15.2
SPPB total score (0-12)	10.0 (9.0-11.0)	11.0 (9.0-12.0)	10.0 (9.0-11.0)	10.0 (9.0-11.0)	11.0 (10.0-12.0)	10.0 (9.0-11.0)
Sedentary time (h/day)	18.1±1.9	18.4±1.7	18.3±1.8	18.5±1.8	18.3±1.6	18.2±1.7
Standing time (h/day)	4.2 (2.8-5.3)	3.8 (3.0-5.1)	4.0 (3.0-5.2)	3.7 (3.4-4.6)	3.7 (3.2-5.2)	4.0 (3.4-5.2)
Stepping time (h/day)	1.8 (1.1-2.2)	1.6 (1.0-1.8)	1.7 (1.1-2.1)	1.3 (0.9-1.9)	1.5 (1.2-2.2)	1.5 (1.1-1.9)
Sedentary breaks (#/day)	31.7 (26.1-40.9)	31.5 (25.4-39.6)	36.4 (27.6-40.1)	34.7 (30.1-38.3)	37.1 (29.0-39.7)	35.1 (27.9-38.6)
Sedentary bouts [>30 min] (#/day)	35±12	31±13	38±12	32±15	34±14	33±11
High-intensity PA	8.73 (4.09-20.21)	7.74 (4.08-17.86)	8.68 (2.29-26.58)	9.36 (4.29-16.07)	9.13 (3.42-15.64)	8.62 (2.75-15.31)
Dietary quality						
AHEI-2010	50.0±12.8	50.0±9.6	53.7±13.3	55.9±8.7	51.0±13.5	52.1±12.4
Cognitive stress susceptibility and perception						
AUC [CAR] (arbitrary units)	534 (270-609)	512 (341-690)	459 (264-759)	424 (342-630)	—	—
Delta [SECPT] (μmol/l)	0.00 (0.00-1.66)	0.00 (0.00-2.68)	0.00 (0.00-0.06)	0.00 (0.00-0.58)	0.00 (0.00-2.04)	0.00 (0.00-0.72)
Perceived Stress Scale	10.9±5.3	13.3±6.9	11.7±4.8	13.4±5.8	10.3±5.5	13.3±6.7
Healthy lifestyle goal recall						
Content recall (0-4)	—	—	0.3 (0.0-1.0)	0.3 (0.0-0.5)	0.0 (0.0-0.6)	0.0 (0.0-0.4)
Procedure recall (0-2)	—	—	1.0 (0.0-2.0)	0.0 (0.0-1.3)	0.0 (0.0-2.0)	0.0 (0.0-2.0)

Note. 6MWD: 6-minute walking distance; SPPB: Short Physical Performance Battery; PA: physical activity; AHEI: Alternative Healthy Eating Index; AUC: area under the curve; CAR: cortisol awakening response; SECPT: socially evaluated cold pressor test; --: not taken at this time point. All data expressed as mean ± standard deviation or median inter-quartile range) depending on the normality of the distribution of the data.

Table 6

Effect sizes of the secondary outcomes of the intervention

Measure	**Phase 1**			**Phase 2**		
	***F* Time**	***F* Group**	***F* Int.**	***F* Time**	***F* Group**	***F* Int.**
Physical capacity and activity						
6MWD (m)	0.10	0.05	0.61	1.00	0.11	0.20
6MWD (% predicted)	0.25	0.46	0.70	1.23	0.39	0.29
SPPB total score (0-12)	0.05	0.03	0.00	0.30	0.96	1.48
Sedentary time (h/day)	0.00	1.16	1.17	1.24	2.74	0.80
Standing time (h/day)	0.60	0.10	0.07	0.07	0.07	0.10
Stepping time (h/day)	0.35	1.04	0.03	0.19	1.14	2.01
Sedentary breaks (#/day)	9.14**	0.43	0.50	0.05	2.17	0.18
Sedentary bouts [>30 min] (#/day)	0.42	1.29	0.03	0.99	2.21	0.99
High-intensity PA	2.45	0.20	0.12	0.26	0.64	0.11
Dietary quality						
AHEI-2010	5.04*	0.11	0.26	1.87	0.31	0.00
Cognitive stress susceptibility and perception						
AUC [CAR] (arbitrary units)	0.02	0.14	0.74	—	—	—
Delta [SECPT] (μmol/l)	6.05*	0.08	0.14	0.93	1.46	4.19*
Perceived Stress Scale	0.52	2.41	0.10	2.55	2.27	1.05
Healthy lifestyle goal recall						
Procedure recall (0-4)	—	—	—	0.00	1.63	1.02
Content recall (0-2)	—	—	—	3.16	2.14	0.15

Note. 6MWD: 6-minute walking distance; SPPB: Short Physical Performance Battery; PA: physical activity; AHEI: Alternative Healthy Eating Index; AUC: area under the curve; CAR: cortisol awakening response; SECPT: socially evaluated cold pressor test; —: not taken. All data expressed as *F*-values. * $p<0.05$ ** $p<0.01$ *** $p<0.001$.

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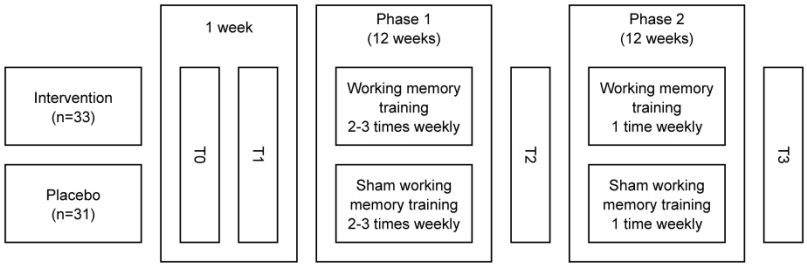

Figure 1 - Study design

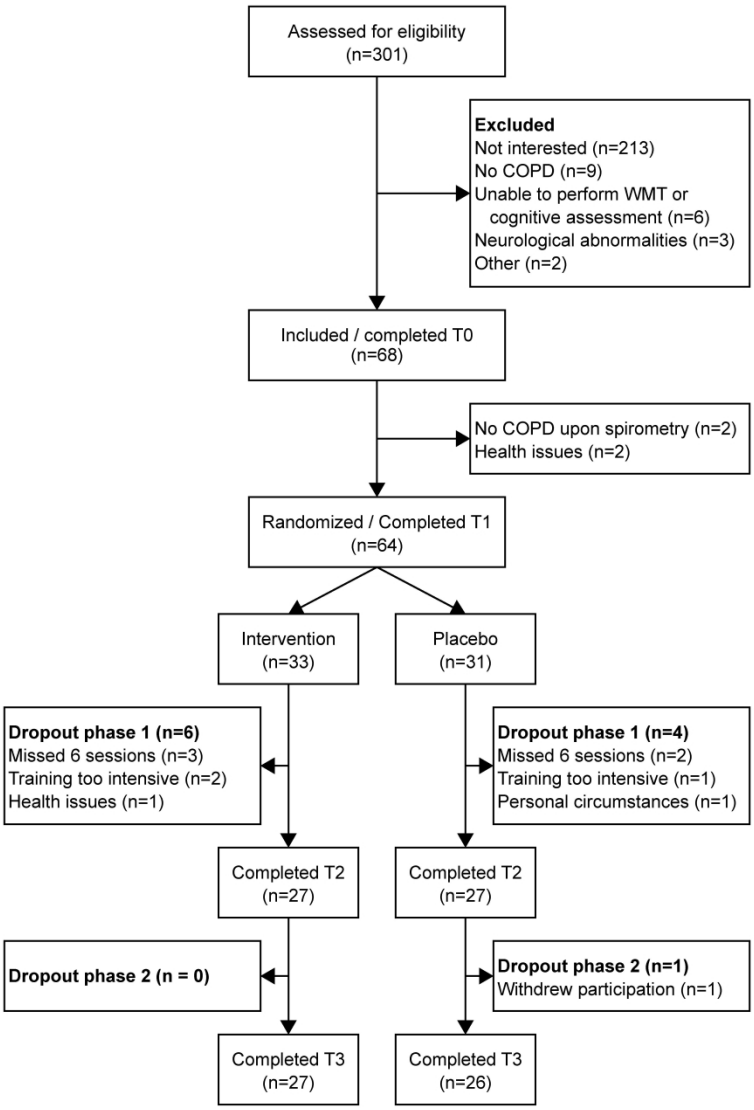

Figure 2 - Study flowchart

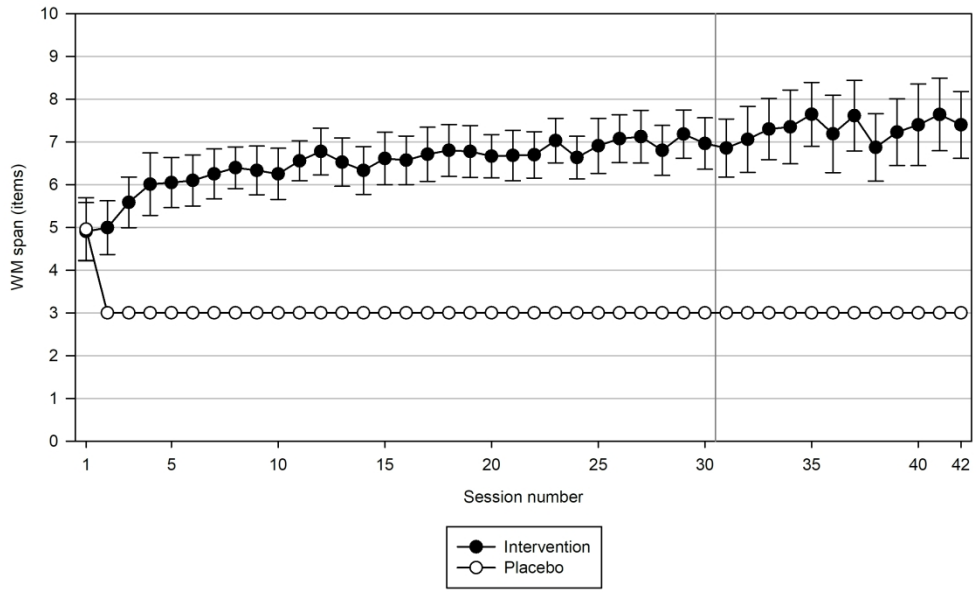

Figure 3 - Working memory span over the course of the first (session 1-30) and second phase (session 31-42) of the working memory training

Supplementary Material

Methods

Patients

Patients were recruited through patient databases from earlier studies within the department of respiratory medicine, physiotherapy practices, a pulmonary rehabilitation clinic, general practitioners, newspaper and magazine advertisements and through flyers at the Maastricht university hospital between October 2017 and August 2019.

Randomization

An independent researcher randomized participants to the intervention or control group before the start of the intervention using a randomization list generated through www.randomization.com. Participants were randomized in blocks of 10 (5× intervention, 5× control). After randomizing 40 participants, the same independent researcher verified whether the age and gender distribution between the groups was similar. All researchers involved in the study remained blinded until data collection was completed.

Intervention

In the visuospatial task, participants were shown a 4×4 grid of squares, some of which flashed in blue one after the other. Participants indicated which squares lit up and in which order, by clicking the squares. In the backward digit span task, single digits were presented one by one on a computer screen, and participants reproduced the sequence in reverse order. In the letter spans task, letters were presented one by one in the centre of the screen, and simultaneously with every letter an accompanying arm lit up. After all letters and their corresponding arms had been presented, one specific arm was indicated, and participants entered the letter belonging to that arm on the keyboard of their computer.

The first session assessed working memory (WM) performance in both groups, to rule out baseline differences in WM capacity. Each task started with a sequence of three items. One item was added after two consecutive responses. The task was aborted after two consecutive incorrect responses.

In the second session, every task started with a sequence of three items to which one item was added if participants responded correctly on two consecutive trials. After two consecutive incorrect answers, the difficulty was reduced by one item on the next trial. Each session after the second was similarly increased or decreased in difficulty but started at the same difficulty level at which the previous session had ended.

Personnel

Three people were involved in data collection. All those involved held master of science (MSc) degrees and the Basic Certificate on Regulations and Organization in Clinical Studies (BROK), which is required for those involved in running clinical trials in The Netherlands. Additionally, they were trained in the protocol of the study and the administration of the tasks before data collection began.

Goal setting

For easy interpretation and guided goal setting discussions, data was presented as a score and in graphical form. The individual Alternate Healthy Eating Index (AHEI)-2010 [1] formed the basis for the dietary component. All healthy lifestyle goals were always based on the individual participants' baseline data, so as to be feasible for every patient. It was also always discussed whether a participant perceived goals to be set as being feasible given his or her personal circumstances. The aim of this was to make reaching a goal maximally challenging but still attainable. For this reason, no uniform algorithm for determining the healthy lifestyle goals can be given. Diet-related goals could include dietary changes such as reducing red meat intake or increasing whole grain, fruit, or vegetable consumption. Physical activity was presented as daily step count and the amount of time spent in different physical activity categories (sitting / lying down, standing up and walking) in the form of graphs.

Healthy lifestyle goal recall

Participant responses were recorded in writing and scored using the procedure described by Hatchell *et al.* [2]. Field blank or no recall of the original message content was scored as 0 points, key points not directly related to the message themes as 1 point and key points directly related to the message themes as 2 points. As the correct answer to the 'procedure' question contained two elements (accelerometry and 24-hour dietary recall) the maximum score on this question was 4 points. For the 'content' question, participants could score 2 points per set goal. Their total number of points was subsequently divided by the total number of initially set goals, leading to a final maximum score of 2 for all participants, regardless of the number of initially set goals.

Cognitive stress susceptibility and perception

The socially evaluated cold pressor test was administered by an independent associate. Participants were asked to immerse their right hand up until the wrist in ice water (0-4°C) for as long as possible but for a maximum of 3 minutes. Participants' facial expression was simultaneously recorded as an additional stressor. Saliva samples to determine cortisol levels (Salivette, Sarstedt AG, Nürnbrecht, Germany) were taken immediately before and 20 minutes after the test. The latter time point was chosen as it is closest to the peak in SECPT-induced cortisol levels as reported earlier [3]. Samples were stored at -80°C until analysis. The pre-post immersion difference in cortisol levels served as outcome measure.

To determine participants' cortisol awakening response, participants were asked to take saliva samples (Salivette, Sarstedt AG, Nürnbrecht, Germany) on the morning of T2 and T3, upon waking and 30, 45 and 60 minutes after waking up. Samples were stored at -80°C until analysis. The area under the curve (AUC) [4] served as outcome measure.

Healthy lifestyle motivation

Participants' motivation towards healthy eating and exercising were measured using the Regulation of Eating Behaviours Scale (REBS) [5] and the Behavioural Regulation in Exercise Questionnaire (BREQ)-2 [6], respectively. These questionnaires investigate motivation from the perspective of self-determination theory [7]. The REBS results in six subscales (intrinsic, integrated, identified, introjected and external motivation and amotivation) with a range of 1-10; the BREQ-2 in five subscales (intrinsic, identified, introjected and external motivation and amotivation) with a range of 1-5.

Psychological wellbeing

Depressive symptomatology was assessed using the Beck Depression Inventory-II (BDI-II) [8]. Each of the questionnaire's 21 items corresponds to a symptom of depression and is answered on a scale of 0-3 as to reflect the way participants have felt for the past two weeks. Individual item scores are summed, leading to a maximum score of 63 points. A score below 13 indicates no depression, 14-19 indicates mild depression, 20-28 moderate depression, and 29 and higher severe depression [8].

Anxiety was measured using the Generalized Anxiety Disorder (GAD)-7 questionnaire [9]. It consists of seven questions answered on a scale of 0-3. Individual items are summed, leading to a maximum score of 21 points. Scores above 10 indicate the presence of a disorder [9].

Results

Healthy lifestyle motivation

The internal consistency of all subscales of the Regulation of Eating Behaviours Scale (REBS) ranged from acceptable to high except for introjected motivation at T0 and identified and introjected motivation at T3. The internal consistency of the intrinsic motivation and amotivation subscales of the Behavioural Regulation of Exercise Questionnaire (BREQ)-2 ranged from acceptable to high, but the consistency of the other scales was poorer (0.43-0.70) (see Supplementary Table 2).

Intrinsic motivation towards healthy eating showed a non-significant increase in the intervention group (p=0.113) and a non-significant decrease in the placebo group (p=0.086), leading to a significant interaction effect (p=0.021). Extrinsic motivation towards healthy eating and identified motivation towards exercising decreased significantly in both groups (p=0.020 and p=0.035, respectively) (see Supplementary Figures 1 and 2).

Psychological wellbeing

The internal consistency of the BDI and GAD-7 ranged from acceptable to high at all time points (see Supplementary Table 2).

The intervention did not affect participants' levels of depression or anxiety, but levels of depression were significantly higher in the placebo group than in the intervention group across phase 1 (p=0.006) (see Supplementary Figures 3 and 4).

Tables

Supplementary Table 1

CANTAB outcome measures

Task	Measure name	Description	Unit	Sense	Range (min-max)
MOT	Mean latency	The mean latency for a participant to correctly respond to the stimulus on screen during assessed trials	ms	—	0-6000
PAL	Total errors	The total number of times a participant selected an incorrect box when attempting to recall a pattern location, calculated across all assessed trials	#	—*	0-68
	Adjusted total errors	The number of times the participant chose the incorrect box for a stimulus on assessment problems (PALTE), plus an adjustment for the estimated number of errors they would have made on any problems, attempts, and recalls they did not reach. This measure allows comparison of performance on errors made across all participants regardless of those who terminated early versus those completing the final stage of the task.	#	—	0-70
	First-attempt memory score	The number of times a participant chose the correct box on their first attempt when recalling the pattern locations, calculated across all assessed trials	#	+	0-20
SST	Stop-signal reaction time	The estimate of time where an individual can successfully inhibit their responses 50% of the time. This covert measurement is sampled from the length of time between the go stimulus and the stop stimulus at which the participant is able to successfully inhibit their response on 50% of the trials. We can infer that this is the time before which all actions become ballistic and the participant is no longer able to cancel their action selection.	ms	—	0-500
RTI	Median simple reaction time	The median duration it took for a participant to release the response button after the presentation of a target stimulus. Calculated across correct, assessed trials in which the stimulus could appear in one location only.	ms	—	100-5100
	Mean simple movement time	The mean time taken for a participant to release the response button and select the target stimulus after it flashed yellow on screen. Calculated across correct, assessed trials in which the stimulus could appear in one location only.	ms	—	100-5100
	Median five-choice reaction time	The median duration it took for a participant to release the response button after the presentation of a target stimulus. Calculated across correct, assessed trials in which the stimulus could appear in any one of five locations.	ms	—	100-5100

Task	Measure name	Description	Unit	Sense	Range (min-max)
	Mean five-choice movement time	The median time taken for a participant to release the response button and select the target stimulus after it flashed yellow on screen. Calculated across correct, assessed trials in which the stimulus could appear in any one of five locations.	ms	—	100-5100
DMS	Correct responses	The percentage of assessment trials during which the participant chose the correct box on their first box choice. Calculated across all assessed trials (simultaneous presentation and all delays).	%	+	0-100
	Median correct latency	The median latency between the presentation of the response stimuli options and the participant selecting the correct box on their first attempt for trials containing a delay between target and response stimuli presentation. Calculated across all trials containing a delay.	ms	—	0-infinite
	Probability of error given error	The probability of an error occurring when the previous trial was responded to incorrectly. Calculated across all assessed trials (simultaneous presentation and all delays)	n/a	—	0-1
SWM	Between-errors	The number of times the participant incorrectly revisits a box in which a token has previously been found. Calculated across all assessed four, six and eight token trials.	#	—*	0-153
	Between-errors 4 boxes	The number of times a participant revisits a box in which a token has previously been found. Calculated across all trials with four tokens only.	#	—	0-35
	Between-errors 6 boxes	The number of times a participant revisits a box in which a token has previously been found. Calculated across all trials with six tokens only.	#	—	0-55
	Between-errors 8 boxes	The number of times a participant revisits a box in which a token has previously been found. Calculated across all trials with eight tokens only.	#	—	0-74
	Strategy	This measure is calculated based on the number of times a participant begins a new search pattern from the same box they started with previously. If they always begin a search from the same starting point, we infer that the participant is employing a planned strategy for finding the tokens. Therefore, a lower score indicates high strategy use (1 = they always begin the search from the same box), a high score indicates that they are beginning their searches from many different boxes.	n/a	—	1-12

Note. * Although a lower score is better, reaching a higher level (indicating better performance) is associated with increased likelihood of making mistakes. #: number; n/a: not applicable; MOT: motor orientation task; PAL: paired associates learning; SST: stop-signal task; RTI: reaction time task; DMS: delayed match-to-sample; SWM: spatial working memory.

Supplementary Table 2

Cronbach's α values for questionnaires at the different time points

Measure	T0/T1	T2	T3
REBS			
Intrinsic	0.876		0.886
Integrated	0.852		0.878
Identified	0.801		0.640
Introjected	0.513		0.461
External	0.764		0.786
Amotivation	0.720		0.800
BREQ-2			
Intrinsic	0.922		0.924
Identified	0.509		0.437
Introjected	0.586		0.682
External	0.734		0.914
Amotivation	0.583		0.695
Psychological wellbeing questionnaires			
BDI-II	0.826	0.834	0.895
GAD-7	0.868	0.771	0.790
PSS	0.802	0.738	0.823

Note. REBS: Regulation of Eating Behaviours Scale; BREQ-2: Behavioural Regulation of Exercise Questionnaire-2; BDI-II: Beck Depression Inventory-II; GAD-7: Generalized Anxiety Disorder-7; PSS: Perceived Stress Scale.

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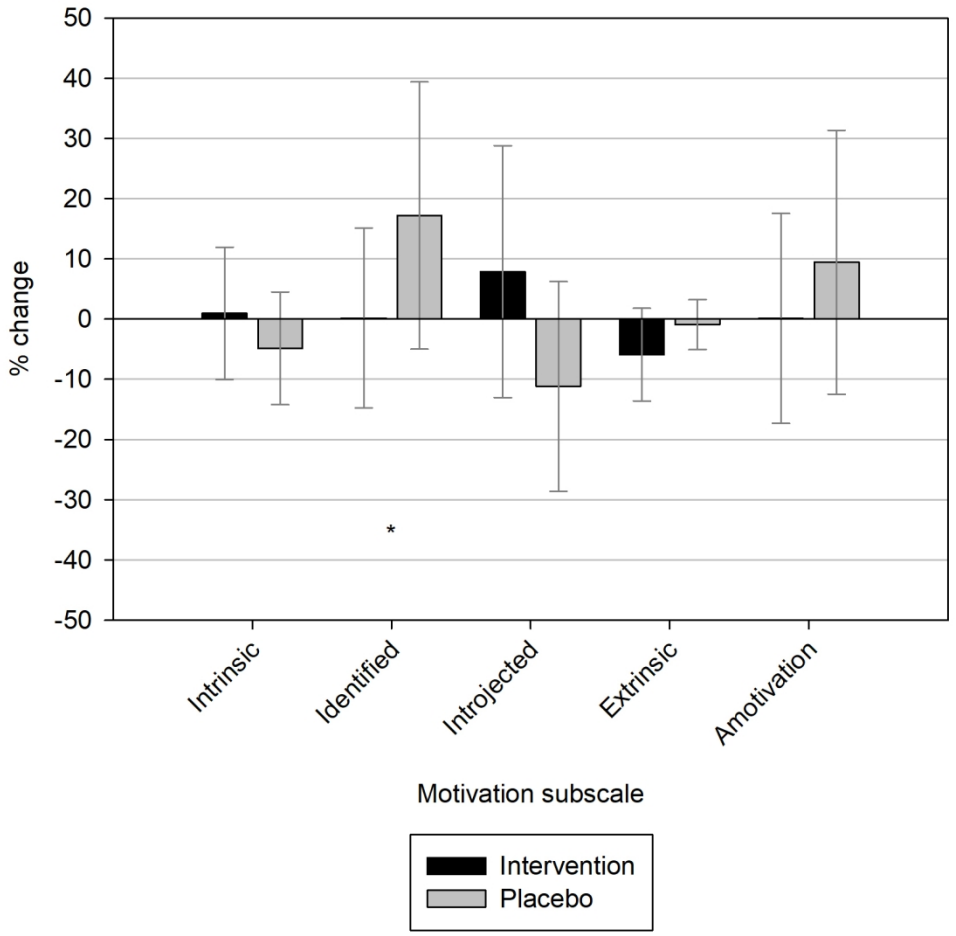
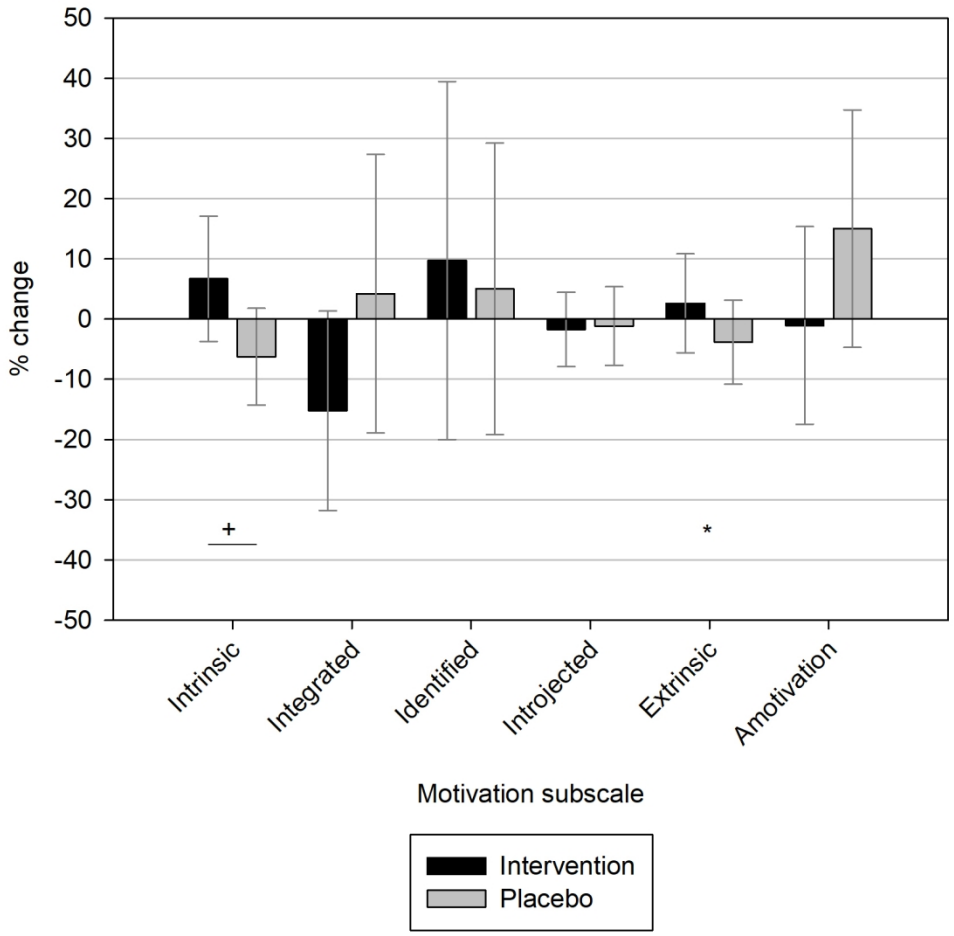
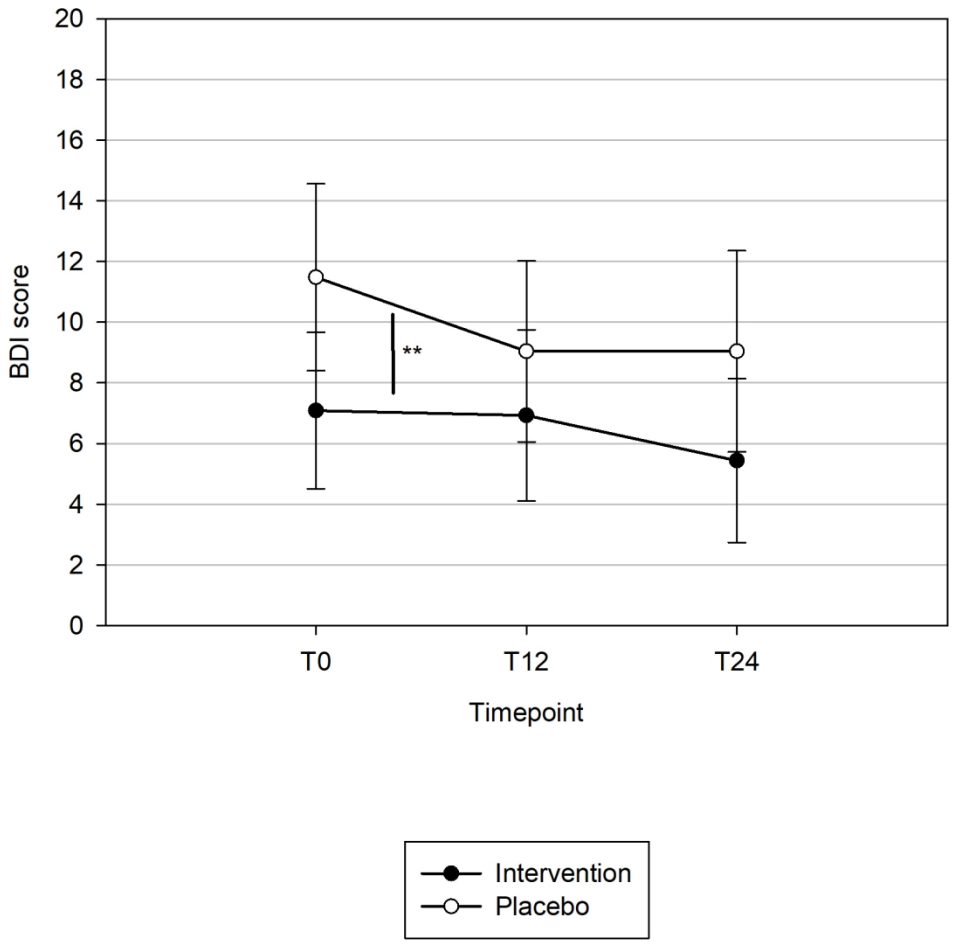


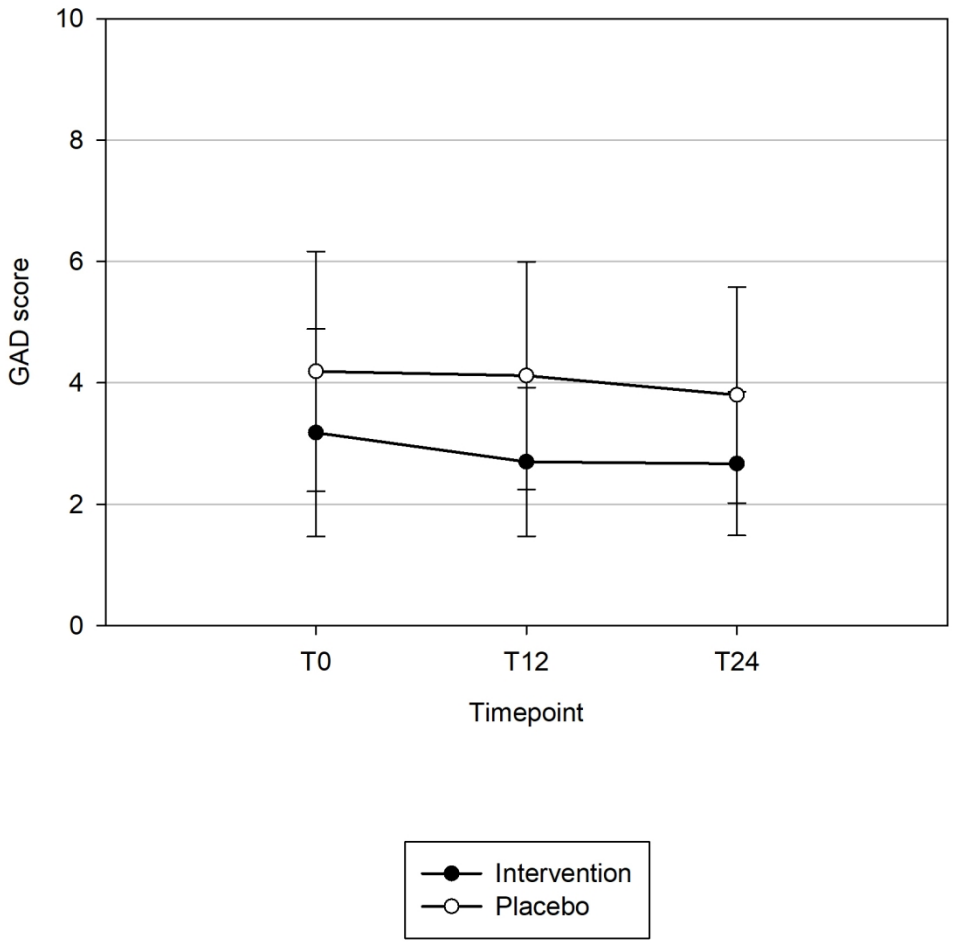
Supplementary Figure 1 - Development of motivation towards exercising over the course of the study



Supplementary Figure 2 - Development of motivation towards healthy eating over the course of the study



Supplementary Figure 3 - Development of depression scores over the course of the study



Supplementary Figure 4 - Development of anxiety scores over the course of the study