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RESEARCH: CLINICAL TRIALS

Physical activity, inactivity and sleep during the Diabetes Remission Clinical Trial (DiRECT)

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Abstract

Aims: As sustained weight loss is vital for achieving remission of type 2 diabetes, we explored whether randomisation to weight loss plus maintenance in the DiRECT trial was associated with physical activity, inactivity or sleep.

Methods: Participants were randomised to either a dietary weight management programme or best-practice care. The weight management group were encouraged to increase daily physical activity to their sustainable maximum. Objective measurement was achieved using a wrist-worn GENEActiv accelerometer for 7 days at baseline, 12 and 24 months in both groups.

Results: Despite average weight loss of 10 kg at 12 months in the intervention ($n = 66$) group, there were no differences in total physical activity or inactivity compared with the control ($n = 104$) at any time point. However, in our exploratory analysis, those who lost more than 10% of their baseline body weight performed on average 11 mins/day more light activity than the <10% group at 24 months ($p = 0.033$) and had significantly lower bouts of $\text{Inactivity}_{30\text{min}}$ (interaction, $p = 0.005$) across 12 and 24 months. At 24 months, the ≥10% group had higher daily acceleration (38.5 ± 12.1 vs. 33.2 ± 11.1 mg, $p = 0.020$), and higher

accelerations in the most active 5-hour period (59.4 ± 21.8 vs. 50.6 ± 18.3 mg, $p = 0.023$). Wakefulness after sleep onset decreased in the intervention group compared with the control group and also in the ≥10% weight loss group at 12 and 24 months.

Conclusions: Randomisation to a successful intensive weight loss intervention, including regular physical activity encouragement, was not associated with increased physical activity although sleep parameters improved. Physical activity was greater, and night-time waking reduced in those who maintained >10% weight loss at 12 and 24 months.

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KEYWORDS

diabetes remission, lifestyle intervention, physical activity, sleep, weight loss maintenance

1 | INTRODUCTION

The Diabetes Remission Clinical Trial (DiRECT) has demonstrated the feasibility of substantial weight loss in achieving remission of type 2 diabetes over 2 years and has shown the dependence of continued remission upon weight loss maintenance.[1,2]

Increasing physical activity is difficult for many with obesity and diabetes and not potent for inducing major weight loss.[3,4] However, sustained moderate activity is likely to be valuable for weight loss maintenance.[5] A review found that combined lifestyle interventions, targeting both dietary intake and physical activity, were effective for weight loss maintenance within 12 months of weight loss.[5] However, there is limited evidence beyond 24 months.

A pre-specified outcome of DiRECT was objective assessment of the effectiveness for weight loss maintenance, of physical activity advice at an intensity sustainable in routine primary care practice. Self reporting of physical activity indicated an increase in the weight loss group in DiRECT but as subjective reporting is prone to error, an objective measurement was performed using accelerometers worn during daily life. These objective tools allow us to also measure inactivity and sleep, which have strong interactions with diet and physical activity.[6] People living with type 2 diabetes are less likely to be physically active, more likely to be physically inactive, and have poorer quality sleep, than weight-, sex- and age-matched people without diabetes.[6] The present analysis tested whether physical activity, physical *in*activity and sleep were altered in intervention and control arm participants. An exploratory evaluation of whether these changes were associated with successful maintenance of weight loss was also carried out.

What is already known?

- Increased daily walking is useful to avoid weight regain.
- Previous exercise interventions have been resource-intensive.
- Subjective reports suggest that major weight loss may bring about increased activity.

What this study has found?

- A low-cost intervention, which included repeated advice to increase daily walking after substantial weight loss, produced no objectively measured effect by intention to treat.
- Wakefulness after sleep onset decreased in the intervention group.
- Weight loss ≥10% was associated with both increased physical activity and sleep quality.

What are the implications of the study?

- Additional resource is required to sustain increased physical activity after successful dietary weight loss in type 2 diabetes.

We postulated that simple but repeated delivery of advice to increase everyday physical activity would be successful in achieving behaviour change in an intention-to-treat analysis. Secondly, we postulated that those who achieved and maintained 10% or more weight loss would put into practice this advice more than those

who did not. Thirdly, we postulated that the intensity of advice able to be provided in routine NHS care without additional resources would have a positive impact on sleep patterns.

2 | METHODS

2.1 | Study design and participants

DiRECT was a 2-year, open-label, cluster-randomised controlled trial conducted at 49 primary care (general practitioner [GP]) practices across Scotland and the Tyneside region of England, UK. The detailed protocol has been published elsewhere,[7] and the primary study findings at 1[1] and 2 years.[2] Eligible participants were aged 20–65 years, had been diagnosed with type 2 diabetes within the previous 6 years, and had a BMI of 27–45 kg/m^2. Ethics approval for the trial was granted by West 3 Ethics Committee in January, 2014, with additional approvals by the National Health Service (NHS) health boards in Scotland and clinical commissioning groups in Tyneside. All participants provided written informed consent.

2.2 | DIRECT phases

GP practices were randomised (1:1) to either an evidence-based weight management programme (Counterweight-Plus; intervention) or best-practice care in accordance with guidelines (control). Randomisation was via a computer-generated list, and stratified by practice list size (>5700 or < 5700 people) and study region (Scotland or Tyneside). The intervention programme consisted of three phases: 1 – Total Diet Replacement (TDR, 825–853 kcal per day formula diet) for 3 months (with option to extend to 5 months depending on individual goals and circumstances), 2 – Stepped Food Reintroduction (FR, 6–8 weeks), and 3 – Structured support for Weight-Loss Maintenance (WLM, up to 24 months).[7] All these were delivered in a primary care setting by trained practitioners, which included NHS practice nurses and dietitians. After an initial 1-h appointment in TDR and FR, participants attended 30-min appointments fortnightly during these phases, and monthly in WLM.

2.3 | Physical activity intervention

One to one training on promotion of physical activity was provided for practitioners. This training included information on physical activity in the general population, and discussion of common barriers to and enablers of physical activity. Checklist-based fidelity assessments of the information and support provided at participant visits were carried out by the senior research dietitians, with immediate feedback to practitioners.

During TDR appointments, participants were advised not to change their usual physical activity patterns. During the FR and WLM appointments with a practitioner, participants were encouraged to increase their daily physical activity. During the first FR appointment, practitioners provided participants with a step counter and instructions on measuring current activity (steps) and gradually increasing it to reach and maintain their individual sustainable maximum, up to 15,000 steps/day.[7] During subsequent FR and WLM appointments, an individually tailored goal setting approach was used to increase activity. Recognised behavioural strategies[8] were used to support individuals to increase activity, including self monitoring, barrier identification, problem solving, and goal setting (Appendix A). Emphasis was given to goal setting and action planning as well as practical methods to achieve the goals. To measure changes in physical activity and sleep, participants were asked to wear a GENEActiv accelerometer for 7 continuous days at baseline, 12 and 24 months. The GENEActiv accelerometer is a fully waterproof wrist-worn tri-axial, raw data accelerometer for activity and sleep tracking in free living studies (http://www.geneactiv.org/actigraphy/geneactiv-original).[9]

2.4 | Accelerometer analysis

Raw accelerometer data were processed in R (www.cran.r-project.org) using R-package GGIR (Version 1.5–21) https://cran.r-project.org/web/packages/GGIR/GGIR.pdf.[10,11] Calibration error of the signals were inspected and corrected.[12] The first and last hour of the measurement were excluded as they are expected to be influenced by the monitor distribution and collection procedure. Only days with at least 16 h of valid data were retained for further analysis. The average magnitude of wrist acceleration per 5-s epoch was calculated with metric ENMO (1 mg = 0.001 × gravitational acceleration).[11] Monitor non-wear has been described previously[11] and was replaced by the average accelerometer data on similar time points on different days of the measurement.[13] The resulting time series were used to derive time spent in acceleration categories per day. Time spent in the following acceleration thresholds was calculated: inactivity (<40 mg cut-off), light physical activity (40–100 mg cut-off), and moderate-vigorous physical activity (MVPA) (≥100 mg cut-off).[14] Within each range, total activity time within waking hours was calculated. Additionally, time spent in >10 min bouts of MVPA ($MVPA_{10min}$) and time spent in >30 min periods of inactivity ($Inactivity_{30min}$) were

calculated. Acceleration for the least active 5 h (L5), most active 5 h (M5) and the difference between them (ΔM5L5) was also calculated.

Estimated total sleep duration, and wakefulness after sleep onset (WASO) were calculated. This is calculated as total night duration - total sleep duration, and a higher index indicates more time moving during the night, a proxy for the neurological state of wakefulness. Different intensity of night-wake movement was also calculated.

Only participants who had ≥3 days of wear time were included in the analysis. Reasons for missing data are shown in Appendix B. The clinical and metabolic characteristics of those with missing accelerometer data were compared with those with accelerometer data across all three time points. Missing cases were younger and had a higher body weight (Appendix C).

2.5 | Data analysis and statistics

Data were assessed for normality using histogram plots and the Kolmogorov–Smirnov test. Sleep duration <4 h per night were considered physiologically implausible and removed from sleep analysis. This meant for the sleep duration the following cases were excluded; baseline $n = 9$, 12 months $n = 16$, 24 months $n = 14$. A sensitivity analysis was performed with these excluded cases and can be seen in Appendix D. A z-score of >3 was used to identify any other outliers within other variables, of which there were none.

For the intention to treat analysis between control and intervention, a mixed-effects ANOVA with a random person-effect was undertaken to assess the within-subject effect of 'time' (baseline, 12-month, 24-month), the between-subject effect of 'group' (control vs. intervention),

TABLE 1 Clinical and accelerometer data at baseline, 12 and 24 months in the control and intervention arms ($n = 170$)

	Control ($n = 104$)			Intervention ($n = 66$)		
	Baseline	**12 months**	**24 months**	**Baseline**	**12 months**	**24 months**
Weight (kg)	98.7 ± 16.7	97.8 ± 17.2	96.5 ± 16.7	97.1 ± 15.6	86.3 ± 15.2	88.5 ± 15.2
BMI	34.1 ± 4.4	33.8 ± 4.6	33.4 ± 4.6	34.5 ± 4.3	30.7 ± 4.7	31.5 ± 4.7
HbA1C						
mmol/mol	59 ± 12	60 ± 13	58 ± 14	60 ± 14	49 ± 12	53 ± 15
%	7.5 ± 1.1	7.6 ± 1.2	7.4 ± 1.3	7.5 ± 1.3	6.6 ± 1.1	7.0 ± 1.4
Physical activity						
Light activity (mins/day)	201.9 ± 66.6	200.6 ± 68.1	192.2 ± 71.9	194.3 ± 69.3	197.6 ± 69.9	196.2 ± 62.7
MVPA (mins/day)	84.7 ± 40.6	83.3 ± 46.6	79.3 ± 45.7	76.9 ± 41.6	87.0 ± 47.8	77.8 ± 41.1
$MVPA_{10min}$ (mins/day)	8.6 ± 12.1	9.2 ± 16.9	8.6 ± 16.6	6.5 ± 11.9	11.3 ± 16.1	8.4 ± 13.5
Av accel (daily mg)	35.5 ± 9.9	35.4 ± 11.2	34.1 ± 11.7	33.6 ± 10.4	36.3 ± 12.7	34.1 ± 11.1
L5	4.4 ± 1.0	4.6 ± 1.6	4.4 ± 1.3	4.7 ± 1.7	4.7 ± 2.4	4.5 ± 1.4
M5	53.9 ± 15.8	53.6 ± 20.6	52.0 ± 19.5	50.5 ± 16.6	57.1 ± 22.7	52.2 ± 18.8
ΔM5L5	49.5 ± 15.6	49.0 ± 20.8	47.6 ± 19.4	45.9 ± 16.2	52.3 ± 22.1	47.7 ± 18.6
Inactivity (mins/day)	718 ± 108	720 ± 113	724 ± 126	717 ± 111	727 ± 118	715 ± 101
$Inactivity_{30min}$ (mins/day)	450 ± 171	460 ± 183	490 ± 194	471 ± 177	483 ± 186	474 ± 166
Sleep ($n = 93$ control, $n = 58$ intervention)						
Sleep duration (mins/day)	380.2 ± 67.5	374.4 ± 59.5	381.2 ± 64.1	389.3 ± 59.3	383.6 ± 65.3	402.8 ± 62.8
WASO	57.5 ± 24.3	59.8 ± 28.5	62.4 ± 28.5	64.9 ± 38.5	54.1 ± 25.6	59.6 ± 26.6
Very light night-wake (mins/night)	52.8 (22.8)	55.1 (27.0)	57.1 (26.5)	60.1 (35.8)	50.5 (24.4)	55.2 (24.9)
Light night-wake (mins/night)	3.4 (2.0)	3.5 (1.9)	4.0 (2.6)	3.7 (3.0)	2.8 (1.5)	3.4 (2.0)
Moderate night-wake (mins/night)	1.19 (0.93)	1.30 (1.14)	1.30 (1.15)	1.08 (0.86)	0.95 (0.72)	0.93 (0.67)
Vigorous night-wake (mins/night)	0.014 (0.038)	0.011 (0.031)	0.011 (0.027)	0.018 (0.482)	0.004 (0.011)	0.008 (0.016)

Note: Acceleration thresholds defined as: inactivity (<40 mg), light physical activity (40–100 mg), MVPA (≥100 mg).

Abbreviations: $Inactivity_{30min}$, time spent in >30 min periods of Inactivity; L5, least active 5 h; M5, most active 5 h; MVPA, moderate-vigorous physical activity; $MVPA_{10min}$ time spent in >10 min bouts of MVPA; WASO, wakefulness after sleep onset.

[a]HbA1c and WASO were log-transformed for regression modelling, and the model coefficients were back-transformed so that the estimates and CIs represent relative associations.

[b]Poor model fit. Non-parametric tests (Friedman and Wilcoxon), however, show similar patterns.

and any interaction effects. Between group estimates (β), 95% CI and *p*-values were recorded for each variable. Only participants who had accelerometer data across all three time points were included ($n = 170$).

For the second exploratory analysis, we defined those who had lost <10% or ≥ 10% of their body weight from baseline at 24 months. We used the 10% cutoff because there is a sharp cut-off in percentage of people achiving remission above and below this point.[15,16] Mixed-effects ANOVAs with a random person-effect were undertaken to assess the within-subject effect of 'time' (baseline, 12 month, 24 month), the between-subject effect of weight loss (<10% or ≥ 10%), and any interaction effects. Between weight loss group estimates (β), 95% CI and *p*-values were recorded for each variable. Any variables with non-normally distributed model residuals were log-transformed and model coefficients were back transformed so that estimates and CI's represent relative associations. For variables in which transformation did not improve model residuals, non-parametric tests were applied to confirm results of the model. All analyses were performed using IBM SPSS Statistics software (version 26, NY, USA), and data are presented as means ± SD, and *p* values <0.05 were considered statistically significant.

3 | RESULTS

3.1 | Intervention versus control analysis

Accelerometer data at all three timepoints were available for 170 participants ($n = 104$ in control and $n = 66$ in intervention).

Between-group difference			Time × group interaction
Baseline estimate (95% CI), *p*-value	**12-month estimate (95% CI), *p*-value**	**24-month estimate (95% CI), *p*-value**	**Interaction *p*-value**
−1.7 (−6.7, 3.4), $p = 0.516$	−11.5 (−16.6, −6.4), $p < 0.001$	−8.0 (−13.0, −2.9), $p = 0.002$	<0.001
0.3 (−0.1, 1.7), $p = 0.654$	−3.1 (−4.6, −1.7), $p < 0.001$	−1.9 (−3.4, −0.5), $p = 0.010$	<0.001
1.0 (0.9, 1.1), $p = 0.945$	0.8 (0.8, 0.9), $p < 0.001$[a]	0.9 (0.8, 1.0), $p = 0.012$[a]	<0.001
1.0 (0.96, 1.05), $p = 0.937$	0.9 (0.8, 0.9), $p < 0.001$[a]	0.9 (0.9, 1.0), $p = 0.017$[a]	<0.001
−7.6 (−28.6, 13.4), $p = 0.477$	−3.1 (−24.4, 18.3), $p = 0.778$	3.96 (−17.3, 25.2), $p = 0.714$	0.401
−7.8 (−20.5, 4.9), $p = 0.228$	3.7 (−10.9, 18.4), $p = 0.614$	−1.5 (−15.2, 12.2), $p = 0.827$	0.145
2.2 (−5.9, 1.6), $p = 0.256$	2.1 (−3.1, 7.2), $p = 0.428$[b]	−0.2 (−5.0, 4.6), $p = 0.936$[b]	0.254
−1.95 (−5.1, 1.2), $p = 0.224$	1.0 (−2.7, 4.7), $p = 0.604$	0.05 (−3.5, 3.6), $p = 0.977$	0.345
0.3 (−0.1, 0.7), $p = 0.160$	0.1 (−0.52, 0.72), $p = 0.755$[b]	0.04 (−0.37, 0.44), $p = 0.852$[b]	0.662
−3.4 (−8.4, 1.7), $p = 0.192$	3.5 (−3.2, 10.2), $p = 0.306$	0.1 (−5.9, 6.1), $p = 0.964$	0.183
−3.6 (−8.6, 1.3), $p = 0.149$	3.4 (−3.3, 10.0), $p = 0.317$	0.1 (−5.9, 6.1), $p = 0.974$	0.162
−1.4 (−35.4, 32.6), $p = 0.935$	6.4 (−29.4, 42.2), $p = 0.725$	−9.3 (−45.6, 27.0), $p = 0.613$	0.589
20.6 (−33.2, 74.5), $p = 0.451$	22.7 (−34.5, 79.9), $p = 0.434$	−15.2 (−72.2, 41.8), $p = 0.599$	0.155
9.0 (−12.3, 30.4), $p = 0.403$	9.2 (−11.3, 29.6), $p = 0.376$	21.5 (−0.5, 42.6), $p = 0.045$	0.414
−1.06 (0.91, 1.24), $p = 0.457$	0.9 (0.8, 1.1), $p = 0.207$[a]	0.9 (0.8, 1.1), $p = 0.421$[a]	0.060
7.3 (−2.1, 16.8), $p = 0.126$	−4.6 (−13.2, 4.0), $p = 0.289$	−1.8 (−10.4, 6.8), $p = 0.678$	0.015
0.25 (−0.55, 1.05), $p = 0.542$	−0.73 (−1.30, 1.63), $p = 0.012$	−0.66 (−1.44, 0.13), $p = 0.102$	0.018
−0.11 (−0.41, 0.19), $p = 0.485$	−0.35 (−0.69, 0.02), $p = 0.037$	−0.37 (−0.70, 0.05), $p = 0.026$	0.121
0.004 (−0.01, 0.02), $p = 0.589$	−0.006 (−0.014, 0.002), $p = 0.161$	−0.003 (−0.011, 0.004), $p = 0.406$	0.261

The intervention group was significantly lighter at 12 months (97.8 ± 17.2 vs. 86.3 ± 15.2 kg, $p < 0.001$) and 24 months (96.5 ± 16.7 vs. 88.5 ± 15.2 kg, $p = 0.002$) compared to the control group, and had a lower HbA1c at 12 months (60 ± 13 vs. 49 ± 12 mmol/mol (7.6 ± 1.2 vs 6.6 ± 1.1%), $p < 0.001$) and 24 months (58 ± 14 vs. 53 ± 15 mmol/mol (7.4 ± 1.3 vs. 7.0 ± 1.4%), $p = 0.017$) (Table 1). There were no differences in any of the physical activity variables at 12 and 24 months between the intervention and control groups. There was a trend towards improved sleep in the intervention group. Sleep duration was higher in the intervention group at 24 months (402.8 ± 62.8 vs. 381.2 ± 64.1 mins/night, $p = 0.045$), and there were significant group-by-time interactions observed for very light night-wake ($p = 0.015$) and light night-wake ($p = 0.018$) minutes (Table 1). Similar patterns were seen when all sleep cases were included in sensitivity analysis (Appendix D, Table 1).

3.2 | Exploratory analysis

A significant group-by-time interaction was observed for weight ($p < 0.001$), BMI ($p < 0.001$), and HbA1c ($p < 0.001$). At 24 months those who had lost more than 10% of their body weight had improved glycaemic control compared to the <10% group (HbA1c; 45 ± 12 vs. 58 ± 14 mmol/mmol) (6.3 ± 1.1 vs. 7.5 ± 1.3%) ($p < 0.001$; Table 2). There was a significant group-by-time interaction for light activity

TABLE 2 Difference in clinical and accelerometer variables between the <10% and ≥10% groups at baseline 12 months and 24 months

	<10%			≥10%		
	Baseline ($n = 141$)	**12 months ($n = 141$)**	**24 months ($n = 141$)**	**Baseline ($n = 29$)**	**12 months ($n = 29$)**	**24 months ($n = 29$)**
Weight (kg)	98.4 ± 16.3	95.6 ± 16.8	95.9 ± 16.1	96.5 ± 16.4	82.0 ± 15.7	81.1 ± 13.2
BMI	34.4 ± 4.4	33.4 ± 4.6	33.5 ± 4.5	33.9 ± 4.2	28.8 ± 4.6	28.4 ± 3.3
HbA1c						
mmol/mol	59 ± 13	57 ± 13	58 ± 14	59 ± 11	45 ± 10	45 ± 12
%	7.5 ± 1.2	7.4 ± 1.2	7.5 ± 1.3	7.5 ± 1.0	6.3 ± 0.9	6.3 ± 1.1
Physical activity						
Light activity (mins/day)	200.6 ± 65.7	197.5 ± 66.5	188.2 ± 67.5	191.2 ± 76.7	208.6 ± 78.6	220.9 ± 66.6
MVPA (mins/day)	80.7 ± 37.6	82.6 ± 44.0	75.8 ± 42.9	86.4 ± 55.4	95.4 ± 59.1	92.6 ± 47.5
$MVPA_{10min}$ (mins/day)	7.4 ± 11.5	8.9 ± 15.7	8.1 ± 15.5	9.5 ± 14.6	15.6 ± 19.8	10.9 ± 15.4
Average acceleration (daily mg)	34.8 ± 9.4	35.4 ± 11.6	33.2 ± 11.1	34.6 ± 13.2	37.1 ± 13.2	38.5 ± 12.1
L5 (mg)	4.4 ± 1.1	4.6 ± 1.7	4.5 ± 1.3	5.0 ± 2.1	4.9 ± 2.9	4.5 ± 1.5
M5 (mg)	52.5 ± 14.8	54.6 ± 21.0	50.6 ± 18.3	52.9 ± 21.8	56.5 ± 23.7	59.4 ± 21.8
ΔM5L5	48.1 ± 14.7	50.0 ± 21.0	46.1 ± 18.2	47.9 ± 21.0	51.6 ± 23.1	54.9 ± 21.5
Inactivity (mins/day)	719 ± 106	726 ± 111	728 ± 118	710 ± 126	706 ± 134	685 ± 102
$Inactivity_{30min}$ (mins/day)	453 ± 169	470 ± 183	495 ± 188	481 ± 194	463 ± 190	429 ± 147
Sleep ($n = 125$ control, $n = 26$ intervention)						
Sleep duration (mins/day)	387.2 ± 64.3	379.4 ± 61.4	390.0 ± 61.8	366.9 ± 63.3	371.1 ± 64.2	387.1 ± 76.3
WASO (wakefulness after sleep onset in mins)	57.2 ± 27.1	57.3 ± 26.5	61.7 ± 28.4	75.5 ± 41.2	59.3 ± 32.2	59.5 ± 24.6
Very light night-wake (mins/night)	52.5 (25.0)	52.9 (24.9)	56.6 (26.5)	70.2 (39.4)	55.2 (31.5)	55.1 (23.0)
Light night-wake (mins/night)	3.5 (2.4)	3.3 (1.8)	3.9 (2.4)	4.0 (2.2)	3.2 (1.3)	3.4 (2.3)
Moderate night-wake (mins/night)	1.13 (0.86)	1.19 (1.02)	1.18 (1.00)	1.25 (1.11)	1.04 (1.00)	1.03 (1.03)
Vigorous night-wake (mins/night)	0.016 (0.045)	0.009 (0.028)	0.010 (0.024)	0.013 (0.024)	0.003 (0.006)	0.010 (0.019)

Note: Acceleration thresholds defined as: inactivity (<40 mg), light physical activity (40–100 mg), MVPA (≥100 mg).

Abbreviations: $Inactivity_{30min}$, time spent in >30 min periods of Inactivity; L5, least active 5 h; M5, most active 5 h; MVPA, moderate-vigorous physical activity; $MVPA_{10min}$ time spent in >10 min bouts of MVPA; WASO, wakefulness after sleep onset.

[a]Poor model fit. Non-parametric tests (Friedman and Wilcoxon) however show similar patterns.

[b]HbA1c and WASO were log transformed for regression modelling, and the model coefficients were back-transformed so that the estimates and CIs represent relative associations.

($p = 0.001$) with those in the ≥10% group performing on average 11 mins/day more than the <10% group at 24 months ($p = 0.033$). There was a general trend of increased physical activity in the ≥10% group at 24 months with higher daily acceleration (38.5 ± 12.1 vs. 33.2 ± 11.1 mg, $p = 0.020$), and higher accelerations in the most active 5 hour period (59.4 ± 21.8 vs. 50.6 ± 18.3 mg, $p = 0.023$) (Table 2 and Figure 1). There was a significant group-by-time interaction for $Inactivity_{30min}$ ($p = 0.005$), at 24 months the ≥10% group had 65.8 mins/day ($p = 0.078$) lower $Inactivity_{30min}$ than the <10% group. A significant group-by-time interaction was observed for WASO ($p = 0.007$), driven by differences in very light night-wake (interaction $p = 0.001$). Those who managed to lose at least 10% of their body weight within 24 months had greater WASO at baseline (75.5 ± 41.2 vs. 57.2 ± 27.1 mins/day, $p = 0.014$), but similar levels at follow-up. Levels of light, moderate, and vigorous night-wake showed no evidence of differences between weight loss groups at any time point. When all sleep cases were included (main analysis plus those with <4 hours of sleep data), there was a similar decrease in WASO (Appendix D, Table 2). Total sleep duration did not differ between groups.

4 | DISCUSSION

Randomisation to the weight loss intervention, rather than conventional management, achieved the primary

Between group difference			Time × group interaction
Baseline Estimate (95% CI), *p*-value	12 months Estimate (95% CI), *p*-value	24 months Estimate (95% CI), *p*-value	Interaction *p*-value
−1.9 (−8.4, 4.7), $p = 0.570$	−13.6 (−20.3, −6.9), $p < 0.001$	−14.9 (−21.1, −8.6), $p < 0.001$	<0.001
−0.5 (−2.2, 1.2), $p = 0.573$	−4.6 (−6.4, −2.7), $p < 0.001$	−5.1 (−6.8, −3.3), $p < 0.001$	<0.001
1.0 (0.9, 1.1), $p = 0.975$	0.8 (0.7, 0.9), $p < 0.001$[a]	0.8 (0.7, 0.9), $p < 0.001$[b]	<0.001
1.0 (0.6, 1.1), $p = 0.992$	0.9 (0.8, 0.9), $p < 0.001$[a]	0.9 (0.8, 0.9), $p < 0.001$[b]	<0.001
−9.4 (−36.6, 17.9), $p = 0.498$	11.1 (−16.6, 38.7), $p = 0.433$	32.8 (5.7, 59.9), $p = 0.033$	0.001
5.7 (−10.8, 22.2), $p = 0.497$	12.8 (−6.0, 31.7), $p = 0.181$	16.8 (−0.8, 34.4), $p = 0.061$	0.336
2.0 (−2.8, 6.9), $p = 0.414$	6.7 (0.1, 13.3), $p = 0.047$[a]	2.8 (−3.4, 9.1), $p = 0.371$[a]	0.318
−0.2 (−4.3, 3.9), $p = 0.929$	1.7 (−3.1, 6.5), $p = 0.487$	5.4 (0.8, 9.9), $p = 0.020$	0.118
0.6 (0.1, 1.1), $p = 0.024$	0.3 (−0.5, 1.1), $p = 0.420$[a]	0.04 (−0.5, 0.6), $p = 0.884$[a]	0.399
0.4 (−6.1, 6.9), $p = 0.900$	1.9 (−6.8, 10.5), $p = 0.666$	8.9 (1.2, 16.5), $p = 0.023$	0.169
−0.2 (−6.6, 6.2), $p = 0.954$	1.6 (−7.0, 10.2), $p = 0.720$	8.8 (1.3, 16.4), $p = 0.023$	0.134
−9.2 (−53.2, 34.8), $p = 0.681$	−19.8 (−66.0, 26.5), $p = 0.400$	−43.1 (−89.7, 3.5), $p = 0.069$	0.219
27.6 (−42.2, 97.4), $p = 0.436$	−7.4 (−81.6, 66.9), $p = 0.845$	−65.8 (−139.0, 7.4), $p = 0.078$	0.005
−20.3 (−47.6, 7.0), $p = 0.144$	−8.3 (−34.6, 18.1), $p = 0.536$	−2.9 (−30.3, 24.6), $p = 0.838$	0.439
1.3 (1.1, 1.6), $p = 0.014$	1.0 (0.8, 1.3), $p = 0.783$[b]	0.99 (0.81, 1.20), $p = 0.887$[b]	0.007
17.6 (5.7, 29.5), $p = 0.004$	2.3 (−8.9, 13.4), $p = 0.688$	−1.6 (−12.6, 9.5), $p = 0.778$	0.001
0.5 (−0.5, 1.6), $p = 0.308$	−0.1 (−0.83, 0.67), $p = 0.827$	−0.4 (−1.46, 0.58), $p = 0.393$	0.139
0.12 (−0.3, 0.5), $p = 0.528$	−0.16 (−0.59, 0.28), $p = 0.475$	−0.15 (−0.58, 0.28), $p = 0.502$	0.211
−0.003 (−0.021, 0.015), $p = 0.740$)	−0.007 (−0.018, 0.004), $p = 0.230$	−0.001 (−0.011, 0.010), $p = 0.920$	0.702

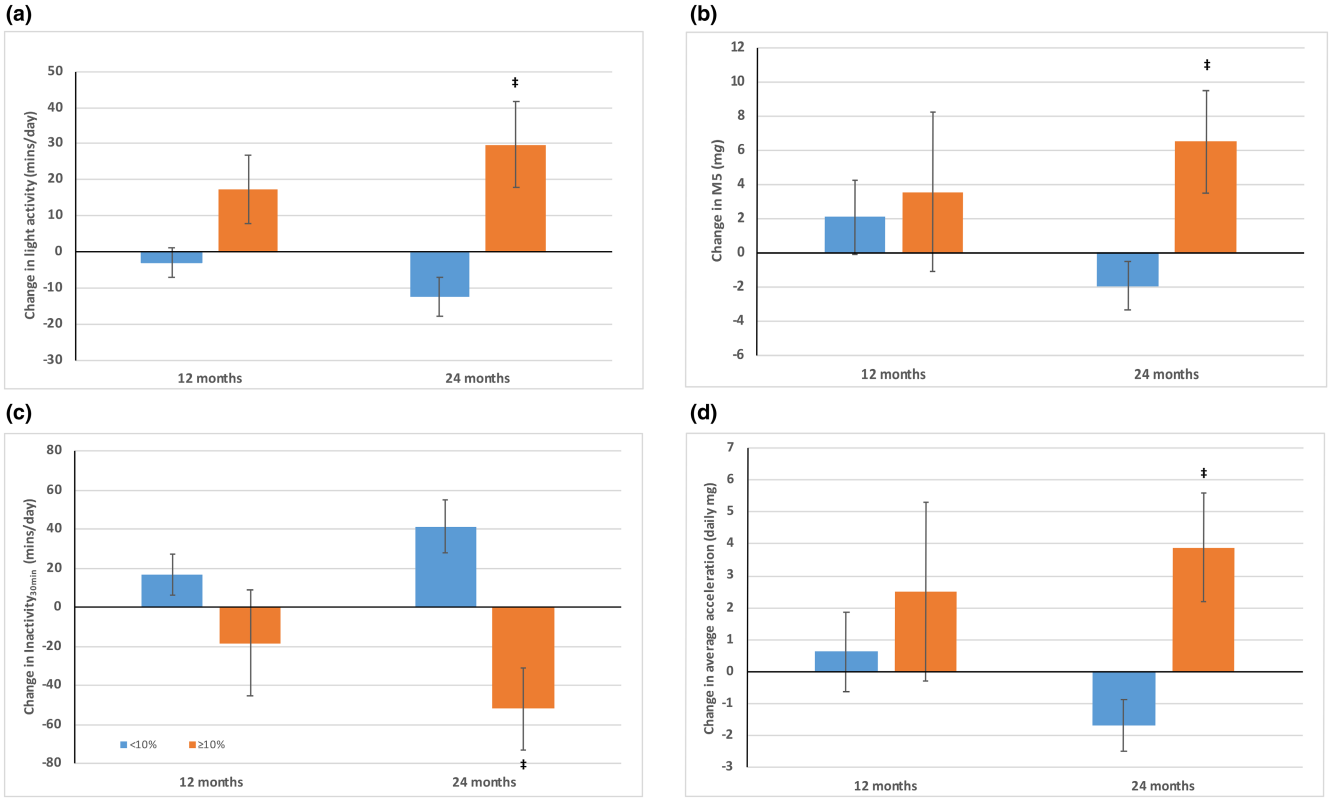

FIGURE 1 Change in A-light activity, B-M5, C- Inactivity$_{30min}$ and D-average acceleration in <10% group (blue bars) and ≥10% group (orange bars) at 12 and 24 months from baseline. ‡Change between baseline and 24 months is significantly different between <10% and ≥10% groups, $p < 0.05$. Error bars show standard error.

goals of decreasing body weight and diabetes remissions but with no increase in overall physical activity or decreased periods of inactivity. This contrasts with the subjective reports. Exploratory analysis of those who lost 10% or more of their baseline weight had higher rates of light physical activity and less sedentary time at 24 months. Randomisation to the weight loss intervention did improve sleep quality, and a similar pattern was seen in those who lost 10% or more of their baseline weight.

There is good evidence that long-term weight maintenance is optimised by sustainable daily physical activity combined with moderate restraint of food intake.[5,17] Indeed, the National Weight Control Registry demonstrated that 89% of those who maintained 13.6 kg of weight loss at 5.7 years reported using a combination of diet and physical acitivity as a strategy for weight loss.[18] Critically, the physical activity component of DiRECT was designed to be at a level able to be sustained in primary care without additional resources, and this intervention was delivered by NHS nurses or dietitians. The intended effect of regular reminders to build in more habitual physical acitivity was anticipated to be magnified by the reported much greater ease in moving around and undertaking physical tasks with successful weight loss.[19,20] However, the data clearly demonstrate that the feasible intensity of physical activity advice, delivered by non-specialist heathcare staff (Appendix A), did not bring about an objectively measurable change in physical activity.

Although there were no differences between intervention and control groups, the ≥10% group had successfully shifted sedentary time to light physical activity and to a lesser extent moderate and vigorous physical activity. Whether this reflects a beneficial effect of increased activity on avoidance of weight regain, or greater all round compliance in the >10% group cannot be distinguished. Light physical activity brings about reduction of cardiometabolic risk, possibly most important in metabolically impaired individuals.[21] Although most health promotion programmes and public health guidelines emphasise moderate and vigorous physical activity, light physical activity is more feasible to accommodate within daily living especially for people with type 2 diabetes. Improving the physical environment to promote activities of daily living at home, work and during transportation would help.[21] That being said, promoting more intense physical activity may be beneficial. In the National Weight Control Registry cohort, 1 h of moderate daily physical activity was important for weight loss maintenance,[17,18] and previous randomised controlled trial data in people

with[22,23] and without[24] type 2 diabetes who undergo more intensive physical activity counselling, have indicated improved weight loss maintenance. Overall, these data support the positive role of physical activity in weight loss maintenance following a low-energy diet and should be appropriately supported in future implementations.

Intensive use of qualified physical activity coaches, as in the DIADEM-I, IDES_2 and Look Ahead studies, can produce sustained enhancement in physical activity at 1,[23] 3[24] and 4 years[25] respectively, but their cost makes this unfeasible within routine NHS care at present. Further work is required on whether more intensive physical activity input can improve on the results of DiRECT, in a way that is affordable to health services. A systems-based approach with policies aimed at improving the social, cultural, economic and environmental factors that support physical activity alongside individually focused approaches are likely most effective.[21] Implementation of an effective longer term, community based physical activity intervention is central to further work in this area. In DiRECT, the advice regularly provided to intervention group participants encouraged any form of physical activity, and particularly specified walking. Given that the form of activity encouraged appears to be optimal from considerations of sustainability, further work on how to improve the effectiveness of such advice is needed in future studies.

Sleep quality and quantity are important determinants of well-being.[26] Too little or too much sleep have both been reported to be associated with type 2 diabetes and other chronic disease incidences.[27] Despite sleep restriction or sleep prolongation having a direct effect on both insulin sensitivity and appetite,[28] little is known about the effects of sleep on weight loss maintenance. Retrospective analyses show that people who report better quality sleep, or who were short sleepers and increased their sleep duration, were 33% more likely to achieve weight loss success.[29] A very low-energy diet improves sleep quality in people living with obesity who have obstructive sleep apnoea.[30] In the present study, an intention to treat analysis showed no impact of the dietary intervention on sleep duration but small reductions in WASO, indicating better sleep quality. The small improvements in sleep quality could be driven by changes in weight or by the increased physical activity in those who had successful weight loss.

Limitations of the present study must be considered. More partipants were lost to follow-up in the intervention group, which may have introduced bias. However, it is likely that the keenest participants were retained and the strikingly negative results are unlikely to have underreported any true difference. Secondly, accelerometer data for all three time points was not available for all of the intervention group, and those with missing data were slightly younger with higher body weight. Again, given the definitive demonstration of no change in physical activity as a result of the intervention, it is unlikely that a genuine effect would be missed. Thirdly, the exploratory analysis involves risk of type 1 statistical error. Fourthly, it is not possble to distinguish between the possibilities that the increase in physical activity in the ≥10% group was secondary to the weight loss itself, or reflected greater ability of some people to adhere to the range of advice given. Finally, the DiRECT population was largely of white European ethnicity and study of other ethnic groups is required.

Overall, these data demonstrate that repeated low-intensity advice to increase physical activity in the DiRECT intervention group did not produce change. However, those people who had long-term weight loss success with the low-energy diet had positive changes in physical activity and inactivity. As this successful weight loss programme at 2 years produced major health benefits with remission of type 2 diabetes in 36%,[2] and decreases in blood pressure with fewer drugs,[31] it is now important to optimise long-term weight loss maintenance by developing interventions encompassing restrained food intake together with effective but affordable physical activity/inactivity strategies.

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CONFLICT OF INTEREST

AB reports honoraria from Novo Nordisk and Eli Lilly and programme content creator for Discover Momenta Diabetes Remission Programme outside the submitted work. NB was previously employed by Counterweight Ltd and reports personal fees for freelance work and shareholdings from Counterweight Ltd during the conduct of the study and funding of PhD fees and conference attendance from Cambridge Weight Plan outside the submitted work. GT reports funding for PhD fees, conference attendance and departmental research support from Cambridge Weight Plan outside the submitted work. LM reports employment by Counterweight during the conduct of study and reports consultancy fees from Cambridge Weight Plan and Counterweight Ltd outside the submitted work.

WSL reports support for conference attendance from Cambridge Weight Plan, outside the submitted work. MEJL reports support for meeting attendance and departmental research support from Cambridge Weight Plan outside the submitted work, lecturing fees from Nestle and Oviva, and has provided unpaid consultancy to Counterweight Ltd. RT reports grants from Diabetes UK to conduct DiRECT, lecture fees from Novartis, Janssen, Nestle Healthcare and Lilly, authorship of book 'Life without Diabetes' and consultancy fees from Wilmington Healthcare outside the submitted work. All other authors declare no competing interests.

DATA AVAILABILITY STATEMENT

I confirm that my Data Availability Statement (pasted below) complies with the Expects Data Policy. The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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APPENDIX A

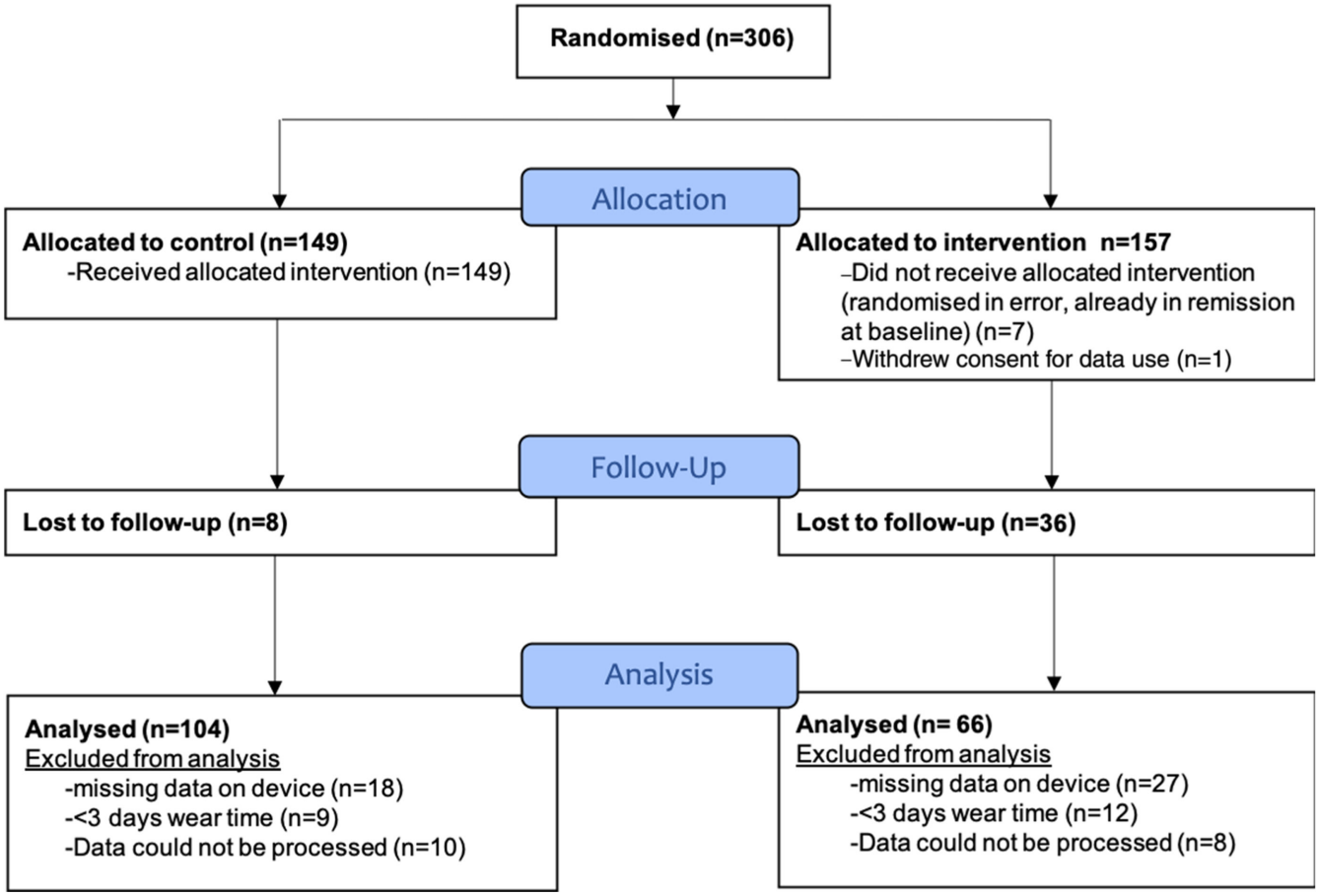
Behaviour change strategies used by healthcare practitioners to promote physical activity

The main behavioural strategies used by healthcare practitioners during the FR and WLM phases of DIRECT to promote physical activity are outlined below.

1. Provide information on consequences of behaviour. The 'Getting Active' section of the participant booklet included information on the benefits of being more active.
2. Goal setting and action planning. Participants were encouraged to increase daily walking with the goal of achieving up to 15,000 steps daily. Detailed planning of how these goals would be achieved was included.
3. Barrier identification/problem solving. This was particularly utilised in the first FR appointment. Participants were prompted to think about potential barriers and identify the ways of overcoming them.
4. Prompt review of behavioural goals. During subsequent appointments, a review of the extent to which previously set goals were achieved would take place, as well as a revision of goals and means to attain them if necessary.
5. Prompt self monitoring of behavioural outcomes. Participants were asked to keep a record of their behaviour using an activity log in the 'Daily Living Diary' and monitor their step count using their pedometer.
6. Provide information on where and when to perform the behaviour. Practitioners would give practical tips and recommendations to participants about when and where they may be able to undertake physical activity.
7. Teach to use prompts and cues. In the 'Getting Active' section of the FR booklet, there was information about identifying prompts to remind participants to be more active.

APPENDIX B

Reasons for missing data



APPENDIX C

The clinical and metabolic characteristics of those providing accelerometer data versus the complete DiRECT cohort at baseline. Independent-sample *t*-test was performed to compare the Intervention and control groups in the accelerometer versus complete DiRECT cohort (chi-square was performed for sex).

	Accelerometer cohort		Missing cohort	
	Control ($n = 104$)	Intervention ($n = 66$)	Control ($n = 41$)	Intervention ($n = 82$)
Age	57.0 ± 6.3	55.8 ± 6.6	53.2 ± 8.6*	50.8 ± 7.3**
Sex (male)	65 (63%)	36 (55%)	25 (61%)	47 (57%)
Weight (kg)	98.7 ± 16.7	97.1 ± 15.6	98.8 ± 14.4	104.1 ± 17.1*
BMI	34.1 ± 4.4	34.5 ± 4.3	34.2 ± 3.9	35.5 ± 4.7
SBP	137.4 ± 15.6	134.0 ± 18.2	138.2 ± 16.7	131.7 ± 17.0
DBP	85.3 ± 8.5	83.7 ± 9.8	86.1 ± 9.8	85.4 ± 10.4
HbA1c				
mmol/mol	58.6 ± 12.2	60.0 ± 14.0	57.8 ± 10.2	61.2 ± 13.2
%	7.51 ± 1.12	7.54 ± 1.28	7.4 ± 0.9	7.8 ± 1.2

Abbreviations: DBP, diastolic blood pressure; SBP, systolic blood pressure.

*$p < 0.05$ for independent *t*-test between the accelerometer versus missing cohort.

**$p < 0.001$ for independent *t*-test between the accelerometer versus missing cohort.

APPENDIX D

TABLE D1. Sensitivity analysis of sleep data at baseline, 12 and 24 months in the control and intervention arms in all individuals (including those <4 h of sleep)

	Control ($n = 104$)			Intervention ($n = 66$)			Between-group difference			Time × group interaction
	Baseline	12 months	24 months	Baseline	12 months	24 months	Baseline estimate (95% CI), *p*-value	12-month estimate (95% CI), *p*-value	24-month estimate (95% CI), *p*-value	Interaction *p*-value
Sleep duration (mins/day)	375.0 ± 75.0	358.2 ± 80.2	367.9 ± 81.7	374.9 ± 71.2	368.2 ± 77.3	383.7 ± 81.3	−0.1 (−23.0, 22.7), $p = 0.993$	10.0 (−14.6, 34.6), $p = 0.423$	15.8 (−9.6, 41.1), $p = 0.221$	0.417
WASO	60.2 ± 32.8	69.0 ± 56.4	70.1 ± 72.3	65.8 ± 40.6	57.0 ± 37.3	62.6 ± 33.1	5.6 (−5.6, 16.8), $p = 0.325$	−12.0 (−27.5, 3.5), $p = 0.129$	−7.5 (−26.2, 11.2), $p = 0.430$	**0.047**
Very light night-wake (mins/night)	55.5 (31.9)	64.2 (55.9)	64.9 (71.0)	64.2 (55.9)	58.3 (31.8)	58.3 (31.8)	5.5 (−5.2, 16.2), $p = 0.310$	−10.9 (−26.2, 4.4), $p = 0.160$	−6.6 (−25.0, 11.7), $p = 0.475$	0.060
Light night-wake (mins/night)	3.47 (1.94)	3.6 (1.97)	3.95 (2.57)	3.7 (2.89)	2.89 (1.69)	3.41 (1.98)	0.2(−0.5, 0.96), $p = 0.532$	−0.71 (−1.29, 0.13), $p = 0.017$	−0.55 (−1.28, 0.19)	**0.024**
Moderate night-wake (mins/night)	1.2 (0.93)	1.27 (1.10)	1.27 (1.10)	1.07 (0.86)	1.27 (1.10)	0.90 (0.66)	−0.14 (−0.42, 0.15), $p = 0.345$	−0.33 (−0.63, 0.03), $p = 0.032$	−0.37 (−0.67, 0.07), $p = 0.015$	0.164
Vigorous night-wake (mins/night)	0.01 (0.04)	0.01 (0.03)	0.01 (0.03)	0.02 (0.05)	0.01 (0.02)	0.01 (0.02)	0.003 (−0.01, 0.02), $p = 0.643$	−0.004 (−0.013, 0.004), $p = 0.319$	−0.003 (−0.010, 0.004), $p = 0.349$	0.390

[a]Change between baseline and timepoint is significantly different between control and intervention, $p < 0.05$.

TABLE D2. Sensitivity analysis of sleep data between the <10% and ≥10% groups at baseline, 12 and 24 months in all individuals (including those <4 h of sleep)

	<10% ($n = 141$)			≥10% ($n = 29$)				Difference between ≥10% and <10% weight loss groups		Time × group interaction
	Baseline	12 months	24 months	Baseline	12 months	24 months	Baseline estimate (95% CI), p-value	12-month estimate (95% CI), *p*-value	24-month estimate (95% CI), *p*-value	Interaction *p*-value
Sleep duration (mins/day)	378.2 ± 74.8	362.6 ± 79.7	373.6 ± 81.8	359.2 ± 64.8	359.6 ± 76.4	375.9 ± 82.5	−18.9 (−48.4, 10.5), $p = 0.206$	−2.96 (−34.8, 28.9), $p = 0.855$	2.2 (−30.7, 35.2), $p = 0.893$	0.374
Wakefulness after sleep onset (WASO)	59.5 ± 34.3	64.1 ± 50.6	67.6 ± 64.0	76.1 ± 41.4	65.3 ± 48.4	65.4 ± 36.7[a]	16.6 (2.2, 30.9), $p = \mathbf{0.024}$	1.2 (−19.0, 21.4), $p = 0.906$	−2.2 (−26.4, 22.1), $p = 0.861$	0.115
Very light night-wake (mins/night)	54.9 (32.6)	59.6 (49.8)	62.6 (62.7)	70.9 (39.6)	61.4 (47.9)	61.1 (35.9)	16.0 (0.2, 29.7), $p = \mathbf{0.021}$	1.8 (−18.2, 21.7), $p = 0.862$	−1.5 (−25.3, 22.3), $p = 0.903$	0.135
Light night-wake (mins/night)	3.5 (2.4)	3.4 (2.0)	3.8 (2.4)	3.9 (2.2)	3.1 (1.3)	3.3 (2.2)	0.46 (−0.5, 1.4), $p = 0.338$	−0.28 (−1.0, 0.48), $p = 0.471$	−0.50 (−1.45, 0.45), $p = 0.300$	0.109
Moderate night-wake (mins/night)	1.14 (0.87)	1.18 (0.98)	1.15 (0.97)	1.19 (1.07)	0.98 (0.97)	0.97 (0.99)	0.05 (−0.3, 0.4), $p = 0.790$	−0.200 (0.594, 0.194), $p = 0.317$	−0.180 (−0.571, 0.212), $p = 0.366$	0.250
Vigorous night-wake (mins/night)	0.02 (0.05)	0.01 (0.03)	0.01 (0.02)	0.01 (0.02)	0.00 (0.01)	0.01 (0.02)	−0.002 (−0.02, 0.02), $p = 0.847$	−0.009 (−0.20, 0.003), $p = 0.133$	−0.001 (−0.010, 0.008), $p = 0.906$	0.523

[a]Poor model fit. Non-parametric tests (Friedman and Wilcoxon) however show similar patterns.