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A total diet replacement weight management programme for difficult-to-treat asthma associated with obesity

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Abstract

Background: Obesity is often associated with uncontrolled, difficult-to-treat asthma and increased morbidity and mortality. Previous studies suggest that weight loss may improve asthma outcomes but with heterogenous asthma populations studied and unclear consensus on optimal method of weight management. The Counterweight-Plus weight management programme (CWP) is an evidence-based, dietitian-led, total diet replacement (TDR) programme.

Research question: Can use of the CWP compared to usual care (UC) improve asthma control and quality of life in patients with difficult-to-treat asthma and obesity?

Study design and methods: We conducted a 1:1 (CWP:UC) randomised, controlled single centre trial in adults with difficult-to-treat asthma and body mass index ≥30kg/m^2. CWP: 12-week TDR phase (800kcal/day low-energy formula); stepwise food reintroduction and weight loss maintenance up to 1 year. Primary outcome: change in asthma control questionnaire (ACQ6) score over 16 weeks. Secondary outcome: change in asthma quality of life questionnaire (AQLQ) score.

Results: 35 participants were randomised (36 screened) and 33 attended 16-week follow-up (17 CWP, 16 UC). Overall, mean (95%CI) ACQ6 at baseline was 2.8 (2.4, 3.1). Weight loss was greater in CWP than UC (mean difference -12.1kg; 95%CI -16.9, -7.4; p<0.001). ACQ6 improved more in CWP than UC (mean difference -0.69; 95%CI -1.37, -0.01; p=0.048). A larger proportion of participants achieved minimal clinically important difference in ACQ6 with CWP than UC (53% vs 19%; p=0.041; NNT 3 (95%CI 1.5, 26.9)). AQLQ improvement was greater in CWP than UC (mean difference 0.76; 95%CI 0.18, 1.34; p=0.013).

Interpretation: Utilising a structured weight management programme results in clinically important improvements in asthma control and quality of life over 16 weeks compared to usual care, in adults with difficult-to-treat asthma and obesity. This generalisable programme is easy to deliver for this challenging phenotype. Longer-term outcomes continue to be studied.

Abbreviations

ACQ6 (Asthma Control Questionnaire-6); AQLQ (Asthma Quality of Life Questionnaire); ATS (American Thoracic Society); BMI (body mass index); BTS (British Thoracic Society); CRF (Clinical Research Facility); CWP (Counterweight-Plus programme); ERS (European Respiratory Society); FeNO (fractional exhaled nitric oxide); FEV_1 (forced expiratory volume in one second); HAD (Hospital Anxiety and Depression score); MCID (minimal clinically important difference); MRC (Medical Research Council); PEFR (peak expiratory flow rate); SIGN (Scottish Intercollegiate Guidelines Network); TDR (total diet replacement); UC (usual care); WtH (waist-to-hip ratio); WtHt (waist-to-height ratio); 6MWT (six minute walk test).

Approximately 17% of people living with asthma have difficult-to-treat disease due to factors including poor inhaler technique, treatment non-adherence and co-morbidities, such as obesity [1, 2]. Asthma associated with obesity is less steroid-responsive, linked with poorer control and quality of life, increased morbidity and mortality and has limited treatment options [3, 4]. The pathophysiological effects of obesity on asthma are multifactorial. Weight excess has direct effects on thoracic wall mechanics [5], as well as increased airway closure [6, 7], airway hyperresponsiveness [8, 9], and airway inflammation [10-12]. A Cochrane review [13] of four studies (total n = 197) has suggested that weight loss may improve asthma control, but the quality of the evidence was poor and further well-constructed randomised controlled trials were recommended.

In the UK, the Counterweight-Plus weight management programme (CWP) is a commercially available dietitian-supported regime of total diet replacement (TDR), stepwise food re-introduction and weight loss maintenance. It has shown efficacy in obesity (mean weight loss 10kg; approximately a third achieving loss of ≥15kg) and type 2 diabetes mellitus (remission in 46% of cases) [14, 15]. Its effects in asthma have not been evaluated and we hypothesised that utilisation of CWP would result in improvements in asthma control and asthma-related quality of life. To test this hypothesis we performed a randomised, controlled proof-of-concept feasibility trial of CWP in patients with obesity and difficult-to-treat asthma. Here, we report the primary outcome results for the first 16 weeks of treatment, after completion of the first phase of the intervention programme.

Study design and methods

A randomised, controlled, open-label, parallel study of a TDR weight loss programme compared to usual care in individuals with difficult-to-treat asthma and obesity. Participants were randomised 1:1 using a password-protected, online, third-party randomisation service to CWP or usual care (UC) [16]. Study visits were scheduled at baseline and 16 weeks with further visits planned for 1- and 2-year follow-up. The trial was approved by the West of Scotland Regional Ethics Committee (18/WS/0216), sponsored and funded by an NHS Greater Glasgow and Clyde Endowment Fund, and registered at ClinicalTrials.gov (NCT03858608), where trial protocol is described [17]. The funder and contributors to the fund had no input in study design or the trial outcomes. Due to the coronavirus (COVID-19) pandemic, face-to-face follow-up study visits were substituted for telephone consultations where necessary to optimise data collection. Recruitment and randomisation was undertaken by the Clinical Research Fellow. Study visits and data collection were performed by the Clinical Research Fellow and Clinical Research Nursing team at the Glasgow Royal Infirmary Clinical Research Facility (CRF).

Participants

Eligible participants aged 18–75 years, with body mass index (BMI) ≥30.0 kg/m^2, a diagnosis of asthma as per Global Initiative for Asthma guidelines [18], and difficult-to-treat disease as per Scottish Intercollegiate Guidelines Network (SIGN)/British Thoracic Society (BTS) guidelines [19], were identified from secondary and tertiary asthma clinics and ward admissions across NHS Greater Glasgow and Clyde (see online supplement for further detail). Asthma clinicians and asthma specialist nurses referred patients to the Clinical Research Fellow for screening after a brief explanation of the programme. Asthma clinicians were aware of participation in the trial (consent forms were uploaded to electronic patient healthcare records), but not involved in recruitment, study visits or data analysis. Eligible participants were provided with written information and invited

to attend the CRF where written informed consent was obtained prior to randomisation and baseline data collection (Visit 1). Participants were enrolled and randomised by the Clinical Research Fellow.

Measurements

Baseline demographics, asthma and other medical history, and medications were obtained at Visit 1. At all visits, Asthma Control Questionnaire (ACQ6) and Asthma Quality of Life Questionnaire (AQLQ) scores were recorded. ACQ6 is a validated asthma control score comprising 6 questions [20], a score ≥1.5 reflecting poor disease control, and with a minimal clinically important difference (MCID) of 0.5. AQLQ is a validated score comprising 32 questions covering several domains (symptoms, activity limitation, emotional function and environmental stimuli) assessing quality of life in asthma [21]. A higher score reflects better quality of life and MCID is 0.5.

At all visits, other data collected included anthropomorphic measures; healthcare usage; MRC dyspnoea score; Hospital Anxiety Depression (HAD) scale; blood sampling; spirometry (Vitalograph ALPHA™ spirometer, Buckingham, UK) as per European Respiratory Society (ERS)/American Thoracic Society (ATS) standards [22]; peak expiratory flow rate (PEFR); fractional exhaled nitric oxide (FeNO; NIOX VERO®, Aerocrine AB, Solna, Sweden) as per ATS guidelines [23]; 6-minute walk test (6MWT) as per ERS/ATS standards [24]; and accelerometery (see online supplement for further detail).

Counterweight-Plus weight management programme (CWP)

CWP consisted of three phases: TDR (0-12 weeks), food reintroduction (13-18 weeks), and weight loss maintenance (19-52 weeks), and was delivered by experienced dietitians with CWP training (see online supplement for further details).

The TDR phase comprised of a low-energy liquid diet consisting of 825-853 kcal/day (approximately 59% carbohydrate, 13% fat, 26% protein, 2% fibre), administered via sachets of dried soups and shakes in a variety of flavours, made up with water by the participant. The dietitian team reviewed participants at one week and then fortnightly. To allow flexibility for participants, acknowledging other commitments or logistical limitations, this phase was extended to 20 weeks if participants did not lose >15kg by week 12. Conversely, if a participants BMI fell to <23.0 kg/m^2 then food reintroduction was introduced earlier.

The food reintroduction phase involved a reducing formula diet and stepwise reintroduction of calorie-controlled meals (with fortnightly dietitian review continuing). Flexible periods of 2-8 weeks were used for this phase based on participant confidence with weight loss management.

In the weight loss maintenance phase, dietitians provided individually tailored calorie prescription for weight stabilisation and to prevent weight regain, with monthly reviews. All programme phases were underpinned by recognised behaviour change strategies [25, 26].

Dietitian-led relapse treatments to correct weight regain were available [27].

Usual care

Standard asthma care was continued in all participants in all groups. This included continuation of previously initiated asthma medication, but also modification of asthma treatment based on clinical need; those with worsening asthma had treatment escalation, whilst those with improving disease or lack of treatment efficacy had medication removal. All participants continued to be reviewed at their original secondary asthma clinic as part of usual care. All participants had opportunity for weight management advice (I.e., healthy eating and promoting exercise if in usual care), inhaler technique and asthma education as needed at each study visit.

Primary outcome

The primary outcome was difference in change in ACQ6 from baseline (Visit 1) to 16 weeks (Visit 2), between CWP and UC.

Secondary outcomes

Secondary measures included difference in change in AQLQ from baseline to 16 weeks between CWP and UC groups, overall and in each AQLQ domain (symptoms, activity, emotional and environmental); and the difference in proportion of participants with ≥0.5 change (MCID in ACQ6 [20] and AQLQ [21]) between groups at 16 weeks. For other outcomes see online supplement.

Sample size

To demonstrate a difference of 0.5 between mean changes in ACQ6 in CWP and UC groups from baseline to 16 weeks, based on a SD of 0.5 from a similar population [28] a sample size of 30 (15 per group) was required, assuming an alpha of 0.05, beta 0.2 and power 0.8. A target of 40 was chosen to allow for a 25% dropout-rate.

Statistical analysis

Participants attending Visits 1 and 2 were included for intention-to-treat analysis. Continuous variables were described as mean (95%CI) or median (IQR) based on distribution and compared using independent t-tests or Mann-Whitney U tests respectively. Change in continuous variables over time was analysed using ANCOVA with the baseline variable as a covariate and comparing change in variable using t or Mann-Whitney U tests depending on distribution. Categorical variables were described as number (percentage) and compared using Pearson's chi-square or Fisher's exact test as appropriate. Analyses were performed using IBM SPSS Statistics for Mac, v28 (IBM Corp., Armonk, N.Y., USA); graphs were produced using GraphPad Prism for Mac, v9.3.1 (GraphPad Software, San Diego, CA, USA). A p-value of ≤0.05 was significant. All data analysis was performed by the Clinical Research Fellow using anonymised data.

Results

Participation and baseline characteristics (Figure 1; Table 1; Supplementary Table E1)

Participants were recruited from August 2019 until August 2021, with two-year follow-up scheduled to finish August 2023. 16-week follow-up visits continued until December 2021. Of 36 participants screened, one was ineligible (see online supplement) and 35 were randomised. Two patients were lost to follow-up and 33 attended Visit 2 to be included in intention-to-treat analysis (17 in CWP, 16 UC group). Recruitment was halted before the target of 40 due to a lower-than-expected dropout rate.

Overall, mean age was 53 years, 63% were female, with 54% ex-smokers and 43% never-smokers. Co-morbidity was common including atopy (71%), allergic (54%) and perennial (46%) rhinitis, gastro-oesophageal reflux disease (86%), mental health problems (51%) and osteopenia/osteoporosis (43%). There was significant treatment burden with, notably, 17% taking maintenance prednisolone, and just over a third receiving biologic treatment. The study population consisted of frequent exacerbators with uncontrolled disease as reflected by the median (IQR) for oral corticosteroid courses in the previous 12 months of 3 (2 to 5) and mean ACQ of 2.8 (2.4, 3.1). Mean overall AQLQ was 3.8 (3.4, 4.2). Median weight was 101.7 (91.4 to 118.7) kg, with a median BMI of 37.5 (35.0 to 42.3) kg/m^2, mean waist-to-hip (WtH) ratio of 0.99 and mean waist-to-height (WtHt) ratio of 0.74 all suggestive of a morbidly obese, high-risk population. Low median FeNO and eosinophil count (18 ppb and 0.11x10^9/L respectively) suggest predominance of a T2-low endotype within the population.

Individuals in CWP were slightly older, had lower baseline PEFR and forced expiratory volume in 1 second (FEV_1), and were more sedentary with accelerometery data demonstrating more inactive time and less time spent in light/moderate-vigorous physical activity compared to the UC group; there were no other between-group differences.

Primary outcome (Table 2; Supplementary Table E2; Figure 2)

Over 16 weeks, mean change in ACQ6 was –0.45 (-1.02, 0.13) for CWP and 0.23 (-0.17, 0.63) for UC with a mean difference of –0.69 (-1.37, -0.01; p=0.048) between groups.

Secondary outcomes (Tables 2 and 3; Supplementary Table E3; Figures 2 and 3)

Over 16 weeks, mean change in overall AQLQ was 0.81 (0.28, 1.35) for CWP and 0.08 (-0.32, 0.48) for UC with a mean difference of 0.76 (0.18, 1.34; p=0.013) between groups. Likewise, mean changes in AQLQ symptom, activity and environmental domains favoured CWP with mean between-group differences, respectively, of 0.72 (0.14, 1.31; p=0.018), 0.78 (0.08, 1.47; p=0.029) and 0.98 (0.01, 1.96; p=0.048). Change in AQLQ emotional domain was not significantly different between groups.

A greater proportion of participants achieved ACQ6 MCID with CWP compared to UC (53% vs 19% respectively, p=0.041; NNT=3 (95%CI 1.5, 26.9)), but no significant differences were seen for proportions achieving MCID for AQLQ overall or within the four AQLQ domains.

There were no changes in number of prednisolone courses, out-of-hours GP or emergency department attendances, hospital admission or intensive care admissions between the two groups.

Other outcomes (Table 3; Supplementary Table E4)

Mean weight loss was -13.5kg (-17.5, -9.6) for CWP and –1.4kg (-3.2, 0.4) for UC (mean difference -12.1kg, 95% CI -16.9, -7.4, p<0.001), with a mean total body weight loss of ~12% with CWP. BMI

change was -4.9kg/m^2 (-6.3, -3.5) for CWP and –0.3kg/m^2 (-1.1, 0.6) for UC (mean difference -4.6kg/m^2 (-6.3, -2.9); p<0.001).

Median change in MRC dyspnoea score was –1 (-1 to 0) for CWP and 0 (0 to 0) for UC (p=0.004). There were no significant between-group differences for spirometry, six-minute walk distance (6MWD), Borg breathlessness scale, HAD scores, peripheral eosinophils, FeNO or accelerometery.

Per-protocol analysis (Supplementary Tables E5, E6 and E7)

Of the 33 participants attending Visit 2, 2 did not tolerate CWP (see online supplement). 31 participants were included for per-protocol analysis. Mean weight loss was greater in CWP than UC (mean difference -13.3kg, 95% CI -17.2, -9.4, p<0.001), with a 13% loss of total body weight with CWP.

Over 16 weeks, mean change in ACQ6 was –0.60 (-1.20, 0.01) for CWP and 0.23 (-0.17, 0.63) for UC (mean difference –0.86 (-1.55, -0.18); p=0.015). Mean change in overall AQLQ was 0.97 (0.42, 1.53) for CWP and 0.08 (-0.32, 0.48) for UC (mean difference 0.95 (0.40, 1.50); p=0.001). Likewise, mean changes in AQLQ symptom, activity and environmental domains favoured CWP with mean between-group differences, respectively, of 0.89 (0.32, 1.46; p = 0.003), 0.97 (0.32, 1.62; p=0.005) and 1.18 (0.21, 2.14; p=0.018). Change in AQLQ emotional domain was not significantly different between groups.

A greater proportion of participants achieved MCID for ACQ6 and AQLQ with CWP compared to UC (ACQ: 60% vs 19%, p=0.018; AQLQ: 67% vs 31%, p=0.049). There were no significant between-group differences for separate AQLQ domains.

Weight loss extent and change in ACQ/AQLQ (Table 4)

Post-hoc analysis of changes in ACQ and AQLQ with CWP in groups based on extent of total body weight loss (<10%, 10-15% and ≥15%) showed trends towards greater benefit with greater weight loss. Within 10-15% and ≥15% weight loss groups, mean ACQ change was -0.7 (-1.6, 0.3) and –1.2 (-3.1, 0.7) respectively, and mean change in AQLQ was 0.6 (-0.1, 1.3) and 1.4 (-0.8, 3.6), respectively. Similar trends were seen for each of the four AQLQ domains.

Adverse events

There were no unexpected serious adverse events or intervention-related adverse events during the trial. Overall, 5 participants were hospitalised during the 16-week period: 3 UC participants (1 exacerbation of asthma ward level; 1 exacerbation of asthma requiring high dependency monitoring; 1 with COVID-19 pneumonitis) and 2 in CWP (1 COVID-19 gastroenteritis; 1 migraine).

Discussion

In this pragmatic open label, randomised, controlled trial we showed that delivery of a supported low-calorie total diet replacement programme (Counterweight-Plus) to patients with difficult-to-

treat asthma and obesity, was safe and led to significant improvements in asthma control and quality of life compared to usual care over 16 weeks. We demonstrated clinically significant improvements in favour of CWP for ACQ6 score, AQLQ score overall, and symptoms, activity and environmental AQLQ domains. Comparison by percentage total body weight loss showed that >10% loss is needed to gain clinically relevant benefits, though loss >15% likely imparts greater benefit. In addition, CWP had favourable impacts on exertional breathlessness and anthropometric measures, the latter likely to have important consequences for other aspects of general health. These findings suggest that conservative treatment targeting substantial weight loss in patients with difficult-to-treat asthma and obesity is safe and can favourably impact on patient-centred outcomes. Longer-term outcomes are awaited to determine whether benefits persist. This programme can be administered in a primary care setting.

A small number of trials have evaluated the impact of weight loss interventions in the obesity-associated asthma population, with varying methodology and outcome. Freitas et al [29] report improvements in ACQ and AQLQ in a randomised trial of cardiovascular exercise for 3 months compared to sham breathing/stretching in asthma (n=51). Weight loss was lower than our results (6kg), the population studied differed at baseline considerably (predominantly female (98%), lower weight (91kg), higher eosinophils (>0.3 x10^9/L) and lower ACQ score (2.0)), the definition/criteria for disease severity were not pre-specified and participants taking daily oral corticosteroids were excluded. Trial pragmatism and generalisability are unclear as from 645 participants screened only 55 were eligible (167 had no documented reason).

Conversely, a study of 330 participants (2022 screened) reported by Ma et al [30], showed no significant change in ACQ or quality of life with a lifestyle intervention protocol (calorie-reduction, moderate-intensity physical activity and behavioural self-management skills) compared to usual care. Baseline weight (104.2kg)/BMI (37.5 kg/m2) were comparable to our population, though baseline control was markedly better (mean ACQ 1.4). Participants requiring daily oral corticosteroids were excluded. However, their mean weight loss was much lower than our trial (5kg) at 6 months, probably insufficient to impact significantly on asthma-related outcomes. Sub-analysis suggested improved ACQ in those with weight loss >5%, and larger effects with weight loss >10%.

Scott et al [28] reported a randomised uncontrolled three-arm parallel trial of either dietary or exercise intervention or both over 10 weeks in participants with BMI 28-40kg/m^2 and asthma. Per protocol analysis showed mean (SD) weight loss was lower than our trial (8.5±4.2%, 1.8±2.6% and 8.3±4.9% with diet, exercise and combined interventions respectively), with improved mean ACQ in diet and combined groups (-0.6±0.5 and –0.5±0.7 respectively) and median AQLQ in all groups (0.9 [0.4 to 1.3], 0.49 [0.03 to 0.78] and 0.5 [0.1 to 1.0] with diet, exercise and combined respectively). However, as well as lacking a control group, the population was better controlled (ACQ range 1.00-1.36), had better quality of life (AQLQ range 5.8-6.8) and lower ICS doses (1000mcg BDP equivalent) at baseline compared to our difficult-to-treat population.

Özbey et al [31] performed a randomised controlled trial (n=55) of asthma and BMI ≥ 30.0kg/m^2, comparing usual care to a 10-week dietitian-led weight loss program. They report improved asthma control and quality of life scores, however studied an almost entirely female (96%) general asthma population with uncertainty around the diagnosis of asthma, active disease and disease severity. Furthermore, a mean Asthma Control Test (ACT) score of 21 suggests a well-controlled population. The authors correctly question the generalisability based on these limitations.

Grandi Silva et al [32] reported a trial of weight loss (nutritional support, psychology input and a varied exercise programme) in women with BMI 35-40kg/m^2 and moderate-to-severe asthma (n=51)

to assess the effect on dynamic hyperinflation. Post-hoc analysis showed improvements in ACQ and AQLQ in those that lost ≥5% weight, though no significant change in ACQ when compared to those that lost <5%. The lack of randomisation, control, as well as unclear details of the intervention and results are limitations.

There are several possible limitations in our trial. This proof-of-concept feasibility study was sufficient to detect significant effects, but a larger study is needed to generate definitive results. There were small differences between groups at baseline (age, PEFR, FEV_1 and accelerometery) though, due to randomisation, unlikely to impact on the primary and secondary outcomes we obtained. Baseline asthma control and quality of life measures (which are affected by factors such as lung function and activity levels) were similar in both groups suggesting that potential clinical gains would be similar in both groups. National lockdowns during the COVID-19 pandemic limited data collection (39% complete datasets) for variables requiring physical attendance (specifically blood tests, FeNO, spirometry, 6MWT and accelerometery), though data for primary and key secondary outcomes were complete (see online supplement). With a higher proportion of complete datasets, it would be possible to assess differences in other key outcomes (e.g., lung function and inflammation). As with all weight management studies, this was an open-label trial potentially subject to biases which may affect treatment effect estimates. This trial was conducted in a real-life clinical setting where asthma clinicians could be aware of the substantial effects on body weight from the intervention, and as such blinding would not be feasible. It is feasible that participants pleased with weight loss, in the intervention group, might be more included to minimise asthma symptoms and thus generate a more positive response the to the intervention than their physiology might reveal. However, this still constitutes a positive beneficial outcome from both patient and healthcare perspectives. Certain variables (e.g., number of exacerbations) were reliant on participant recollection, thus are subject to recall bias. Participants willing to take part in a weight loss trial are more likely to be motivated to lose weight leading to potential selection bias, though this would not detract from clinical value. Key strengths of the trial include the pragmatic and real-world applicability of the intervention. Randomisation led to broadly comparable CWP and UC groups, which adds confidence to reporting results. The population studied is one of difficult-to-treat asthma with frequent exacerbations, an at-risk group that have disease which is troublesome to manage.

Longer term follow-up is required to determine whether weight loss is maintained and whether asthma-related benefits persist. Additionally, a future trial with a greater sample size is justified to generate definitive results. Further research should explore the factors associated with successful treatment outcome, and efficacy in the overweight (BMI 25.0-29.9 kg/m^2) population with difficult-to-treat asthma.

Interpretation

Compared to usual care, use of the Counterweight-Plus weight management programme, with dietitian support, improves asthma control and quality of life as well as dyspnoea and anthropomorphic measures over 16 weeks, in individuals with difficult-to-treat asthma and obesity. Further research is needed to confirm the longer-term outcomes and identify predictors of treatment response.

Table 1: Baseline characteristics

Variable	Overall (n = 35)	CWP (n = 18)	UC (n = 17)
Age (years)	52.6 (48.3, 56.9)	56.7 (51.3, 62.1)	48.3 (41.5, 55.1)
Female sex	22 (62.9)	13 (72.2)	9 (52.9)
Smoking status: Current smoker Ex-smoker Lifelong non-smoker	 1 (2.9) 19 (54.3) 15 (42.9)	 0 (0.0) 12 (66.7) 6 (33.3)	 1 (5.9) 7 (41.2) 9 (52.9)
Smoking (pack years)	15.0 (6.0 to 30.0)	15.0 (5.0 to 22.5)	5.0 (0.0 to 20.0)
Age at asthma diagnosis (years)	30.9 (23.8, 38.1)	34.3 (24.1, 44.4)	27.4 (16.6, 38.2)
Duration of asthma (years)	21.7 (16.5, 27.0)	22.5 (13.7, 31.3)	20.9 (14.3, 27.5)
Atopy	25 (71.4)	12 (66.7)	13 (76.5)
Allergic rhinitis	19 (54.3)	9 (50.0)	10 (58.8)
Perennial rhinitis	16 (45.7)	7 (38.9)	9 (52.9)
Nasal polyps	4 (11.4)	3 (16.7)	1 (5.9)
Nasal surgery	4 (11.4)	3 (16.7)	1 (5.9)
Eczema	13 (37.1)	6 (33.3)	7 (41.2)
GORD	30 (85.7)	16 (88.9)	14 (82.4)
ILO/DFB	8 (22.9)	5 (27.8)	3 (17.6)
Psychological illness	18 (51.4)	8 (44.4)	10 (58.8)
Emphysema	5 (14.3)	3 (16.7)	2 (11.8)
Bronchiectasis	1 (2.9)	1 (5.6)	0 (0.0)
SAFS/ABPA	9 (25.7)	3 (16.7)	6 (35.3)
Diabetes mellitus	4 (11.4)	4 (22.2)	0 (0.0)
Hypertension	9 (25.7)	6 (33.3)	3 (17.6)
Cardiac disease	7 (20.0)	2 (11.1)	5 (29.4)
Osteopenia/osteoporosis	15 (42.9)	6 (33.3)	9 (52.9)
BDP equivalent dose (mcg)	1600 (1600 to 2000)	1600 (1600 to 1600)	2000 (1600 to 2400)
LAMA	33 (94.3)	18 (100.0)	15 (88.2)
Maintenance prednisolone	6 (17.1)	4 (22.2)	2 (11.8)
Prednisolone dose (mg)	4.5 (1.2, 7.8)	4.5 (-1.9, 10.9)	4.5 (-1.9, 10.9)
Montelukast	27 (77.1)	14 (77.8)	13 (76.5)
Theophylline	22 (62.9)	10 (55.6)	12 (70.6)
Azithromycin	7 (20.0)	6 (33.3)	1 (5.9)
Omalizumab	4 (11.4)	1 (5.6)	3 (17.6)
Mepolizumab	8 (22.9)	4 (22.2)	4 (23.5)
Antihistamine	24 (68.6)	11 (61.1)	13 (76.5)
Nasal steroid	24 (68.6)	12 (66.7)	12 (70.6)
PPI/H2A	30 (85.7)	17 (94.4)	13 (76.5)

Previous 12 months:			
Prednisolone courses	3 (2 to 5)	4 (2 to 5)	3 (2 to 5)
Out of hours GP attendance	0 (0 to 0)	0 (0 to 0)	0 (0 to 0)
ED attendance	0 (0 to 0)	0 (0 to 0)	0 (0 to 0)
Hospital admissions	0 (0 to 1)	0 (0 to 0)	0 (0 to 1)
ICU admissions	0 (0 to 0)	0 (0 to 0)	0 (0 to 0)
Weight (kg)	101.7 (91.4 to 118.7)	103.3 (96.9 to 118.3)	97.0 (86.5 to 122.0)
BMI (kg/m^2)	37.5 (35.0 to 42.3)	38.2 (35.6 to 45.3)	36.1 (32.7 to 42.5)
MRC dyspnoea scale	3 (3 to 4)	3 (3 to 4)	3 (3 to 4)
ACQ6	2.8 (2.4, 3.1)	2.8 (2.2, 3.3)	2.8 (2.2, 3.3)
AQLQ:			
Overall	3.8 (3.4, 4.2)	3.8 (3.3, 4.4)	3.8 (3.2, 4.4)
Symptom domain	3.8 (3.4, 4.2)	3.7 (3.2, 4.3)	3.8 (3.2, 4.5)
Activity domain	3.8 (3.4, 4.2)	3.9 (3.4, 4.4)	3.7 (3.0, 4.3)
Emotional domain	3.8 (3.2, 4.3)	3.6 (2.8, 4.5)	3.9 (3.1, 4.7)
Environmental domain	4.1 (3.6, 4.6)	4.0 (3.4, 4.6)	4.2 (3.4, 5.0)
HAD:			
Anxiety score	8 (6 to 11)	9 (7 to 11)	7 (5 to 11)
Depression score	8 (5 to 11)	8 (5 to 11)	9 (7 to 14)
Eosinophils (x10^9/L)	0.11 (0.08 to 0.42)	0.17 (0.08 to 0.42)	0.1 (0.04 to 0.51)
FeNO (ppb)	18 (11 to 33)	15 (10 to 35)	20 (13 to 51)
PEF (L/min)	375 (334, 415)	318 (275, 360)	435 (374, 496)
Spirometry:			
Pre-BD FEV_1 (%)	72.1 (66.0, 78.1)	65.8 (57.1, 74.6)	78.7 (70.7, 86.7)
Pre-BD FEV_1/FVC (%)	70.4 (67.2, 73.5)	67.9 (62.5, 73.2)	73.0 (69.7, 76.2)
Post-BD FEV_1 change (%)	3.4 (1.3, 5.4)	5.1 (1.5, 8.7)	1.5 (-0.5, 3.6)
6MWD (m)	326 (284, 367)	315 (250, 381)	337 (282, 393)

Continuous variables described as mean (95% confidence intervals) if parametric or median (first quartile to third quartile) if non-parametric.
Categorical variables described as no. (%).
Abbreviations: ABPA (Allergic Bronchopulmonary Aspergillosis); ACQ6 (Asthma Control Questionnaire-6); AQLQ (Asthma Quality of Life Questionnaire); BD (Bronchodilator); BDP (Beclomethasone dipropionate); BMI (Body Mass Index); CWP (Counterweight Plus); DFB (Dysfunctional breathing); ED (Emergency Department); FeNO (Fractional exhaled Nitric Oxide); FEV_1 (Forced Expiratory Volume in 1 second); FVC (Forced Vital Capacity); GORD (Gastro-oesophageal Reflux Disease); HAD (Hospital Anxiety and Depression scale); H2A (H2-receptor antagonists); ICU (Intensive Care Unit); ILO (Inducible Laryngeal Obstruction); LAMA (Long-acting anti-muscarinic); LPA (Low Physical Activity); MRC (Medical Research Council); MVPA (Moderate to Vigorous Physical Activity); OOH (Out-of-hours); PEF (Peak Expiratory Flow); ppb (parts per billion); PPI (Proton pump inhibitor); SAFS (Severe Asthma with Fungal Sensitisation); UC (Usual Care); 6MWD (6 minute Walk Distance).

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Table 2: Intention-to-treat comparison of asthma control and quality of life outcomes between CWP and UC over 16 weeks

Change in variable	CWP group (n = 17)	UC group (n = 16)	Mean difference between CWP and UC	p-value*
ACQ6	-0.45 (-1.02, 0.13)	0.23 (-0.17, 0.63)	-0.69 (-1.37, -0.01)	**0.048**
AQLQ	0.81 (0.28, 1.35)	0.08 (-0.32, 0.48)	0.76 (0.18, 1.34)	**0.013**
AQLQ Symptom	0.98 (0.44, 1.52)	0.25 (-0.13, 0.63)	0.72 (0.14, 1.31)	**0.018**
AQLQ Activity	0.53 (0.01, 1.05)	-0.13 (-0.73, 0.46)	0.78 (0.08, 1.47)	**0.029**
AQLQ Emotional	1.47 (0.59, 2.35)	0.66 (0.07, 1.25)	0.72 (-0.16, 1.59)	0.104
AQLQ Environmental	0.52 (-0.26, 1.30)	-0.52 (-1.30, 0.26)	0.98 (0.01, 1.96)	**0.048**

Variables described as mean (95% confidence intervals).
*Comparison of mean difference using ANCOVA with baseline variable as covariate.
Abbreviations: ACQ6 (Asthma Control Questionnaire); AQLQ (Asthma Quality of Life Questionnaire); CWP (Counterweight Plus); UC (Usual Care).

Table 3: Intention-to-treat comparison of other outcomes between CWP and UC

Change in variable	CWP group		UC group		Mean difference between CWP and UC	p-value*
	N	Difference	N	Difference		
Weight (kg)	13	-13.5 (-17.5, -9.6)	9	-1.4 (-3.2, 0.4)	-12.1 (-16.9, -7.4)	**<0.001**
Total body weight (%)	13	-12.3 (-15.7, -8.8)	9	-1.2 (-3.0, 0.7)	-11.1 (-15.4, -6.9)	**<0.001**
BMI (kg/m^2)	13	-4.9 (-6.3, -3.5)	9	-0.3 (-1.1, 0.6)	-4.6 (-6.3, -2.9)	**<0.001**
MRC dyspnoea scale	16	-1 (-1 to 0)	15	0 (0 to 0)	n/a	**0.004**
HAD:						
Anxiety	17	1 (-1, 3)	16	1 (-1, 2)	0 (-3, 3)	0.972
Depression	17	-1 (-3, 2)	16	1 (-1, 2)	-1 (-4, 2)	0.445
Eosinophils (x10^9/L)	8	0.05 (0.00 to 0.11)	6	0.00 (-0.23 to 0.12)	n/a	0.228
FeNO (ppb)	8	1 (-3 to 21)	6	-6 (-28 to 18)	n/a	0.573
PEF (L/min)	9	38 (-16, 91)	6	7 (-36, 49)	31 (-37, 99)	0.343
Spirometry:						
Pre-BD FEV_1 (%)	8	5.5 (-3.2, 14.2)	6	3.7 (-1.4, 8.8)	1.8 (-7.5, 11.1)	0.671
Pre-BD FEV_1/FVC	8	-1.96 (-4.23, 0.32)	6	1.09 (-4.25, 6.43)	-3.0 (-8.4, 2.3)	0.224
Post-BD FEV_1 (%)	8	3.4 (-2.8, 9.6)	6	4.2 (-7.3, 15.7)	-0.8 (-11.5, 9.9)	0.874
Annualised healthcare use:						
Prednisolone courses	17	-2 (-2 to 0)	16	-2 (-3 to 1)		0.790
OOH GP attendances	17	0 (0 to 3)	16	0 (0 to 3)		0.737
ED attendances	17	0 (0 to 0)	16	0 (0 to 0)	n/a	0.557
Hospital admissions	17	0 (0 to 0)	16	0 (-1 to 0)		0.510
ICU admissions	17	0 (0 to 0)	16	0 (0 to 0)		1.000
6MWD (m)	8	8 (-16, 31)	5	0 (-50, 50)	8 (-34, 49)	0.698

Variables described as mean (95% confidence intervals) for parametric or median (first quartile to third quartile) for non-parametric.
*Comparison using independent t test for parametric or Mann Whitney U test for non-parametric data.
Annualised healthcare use variables compare change from baseline data (number of events in prior 12 months) to 16-weeks ([number of events x 365]/number of days between visits).
Abbreviations: BD (Bronchodilator); BMI (Body Mass Index); CWP (Counterweight Plus); ED (Emergency Department); FeNO (Fractional exhaled Nitric Oxide); FEV_1 (Forced Expiratory Volume in 1 second); FVC (Forced Vital Capacity); HAD (Hospital Anxiety and Depression scale); ICU (Intensive Care Unit); MRC (Medical Research Council); OOH (Out-of-hours); PEF (Peak Expiratory Flow); ppb (parts per billion); UC (Usual Care); 6MWD (6 minute Walk Distance).

Table 4: Post-hoc comparison of asthma control and quality of life with CWP by percentage weight loss

Change in variable	<10% group (n = 3)	10-15% group (n = 6)	≥15% group (n = 4)	p value*
ACQ6	-0.1 (-2.0, 1.8)	-0.7 (-1.6, 0.3)	-1.2 (-3.1, 0.7)	0.390
AQLQ	0.2 (-2.1, 2.5)	0.6 (-0.1, 1.3)	1.4 (-0.8, 3.6)	0.309
AQLQ Symptom	0.5 (-1.1, 2.0)	0.9 (0.1, 1.8)	1.7 (-0.4, 3.9)	0.259
AQLQ Activity	-0.1 (-4.2, 4.0)	0.4 (-0.3, 1.0)	1.3 (-0.5, 3.1)	0.236
AQLQ Emotional	0.8 (-2.7, 4.3)	1.0 (-0.4, 2.4)	1.4 (-1.8, 4.6)	0.876
AQLQ Environmental	-0.4 (-3.8, 3.0)	0.3 (-1.7, 2.3)	0.9 (-1.2, 2.9)	0.625

Variables described as mean (95% confidence intervals).
*Comparison of mean difference using ANOVA.
Abbreviations: ACQ6 (Asthma Control Questionnaire); AQLQ (Asthma Quality of Life Questionnaire).

Figure captions

Figure 1: CONSORT flow chart.

Figure 2: Change in Asthma Control Questionnaire (ACQ6) score (top left), Asthma Quality of Life Questionnaire (AQLQ) score overall (top right), symptom domain (middle left), activity domain (middle right), emotional domain (bottom left) and environmental domain (bottom right), between Counterweight-Plus group (CWP) and usual care (UC) at baseline (V1) and 16-weeks (V2). P value compares change in variable between CWP and UC with independent t test.

Figure 3: Proportion of participants achieving minimal clinically important difference in Asthma Control Questionnaire (ACQ6) and Asthma Quality of Life Questionnaire (AQLQ) with Counterweight-Plus group (CWP) and usual care (UC) over 16-weeks. Compared using chi-square or Fisher's exact. * denotes significant result; ns = not significant.

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Take home point

Study question: Can use of the Counterweight-Plus weight management programme improve asthma control and quality of life in patients with difficult-to-treat asthma and obesity, compared to usual care? Results: Over 16 weeks, the Counterweight-Plus programme resulted in clinically relevant improvements in both asthma control and quality of life indices, with substantial weight loss, as compared to usual care. Interpretation: Initial results using this programme are encouraging, and adherence to the programme was better-than-expected, though longer-term outcomes are awaited to assess sustainability of the benefits seen.

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Figure 1 – CONSORT flow chart

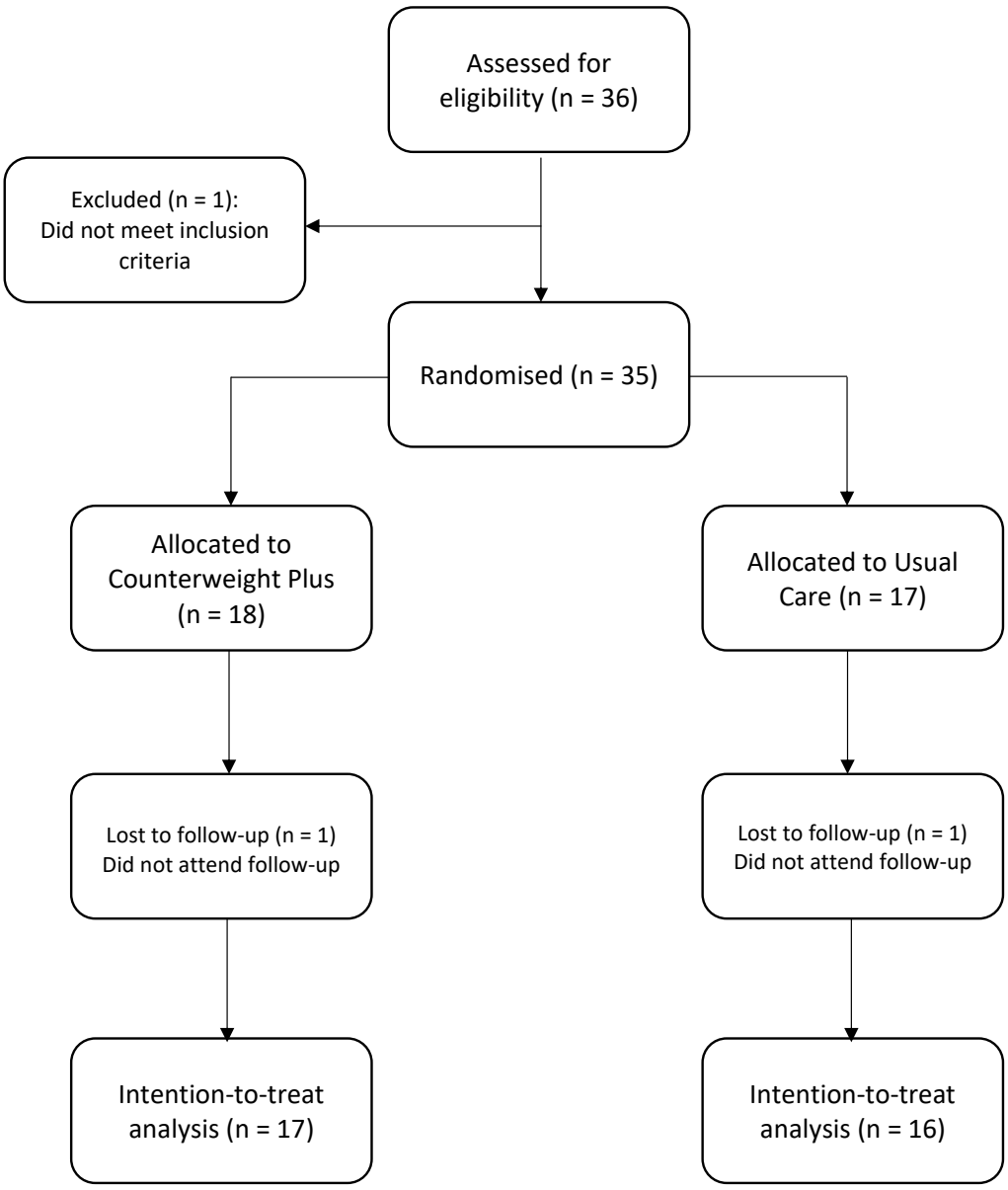

Figure 2

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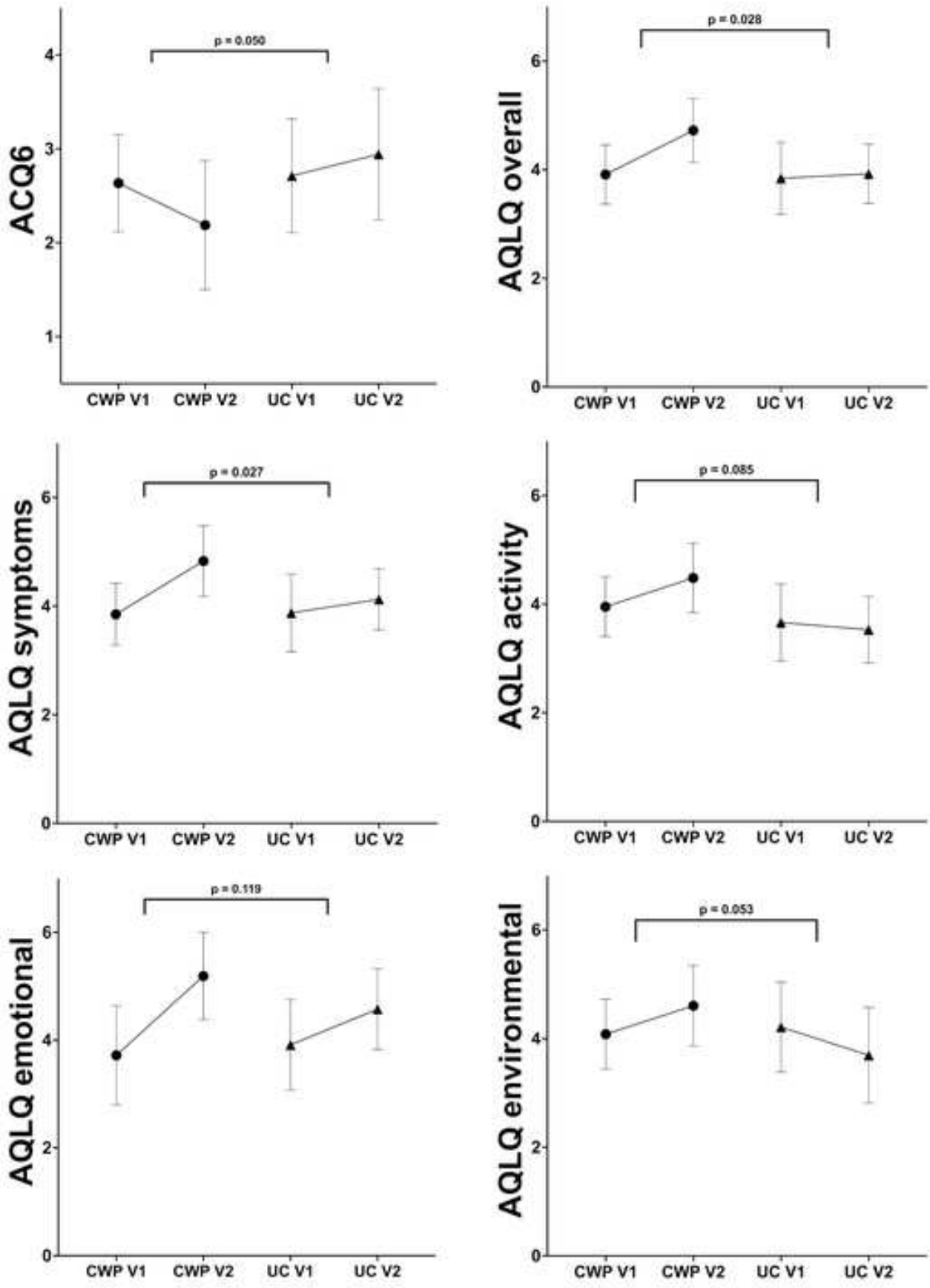

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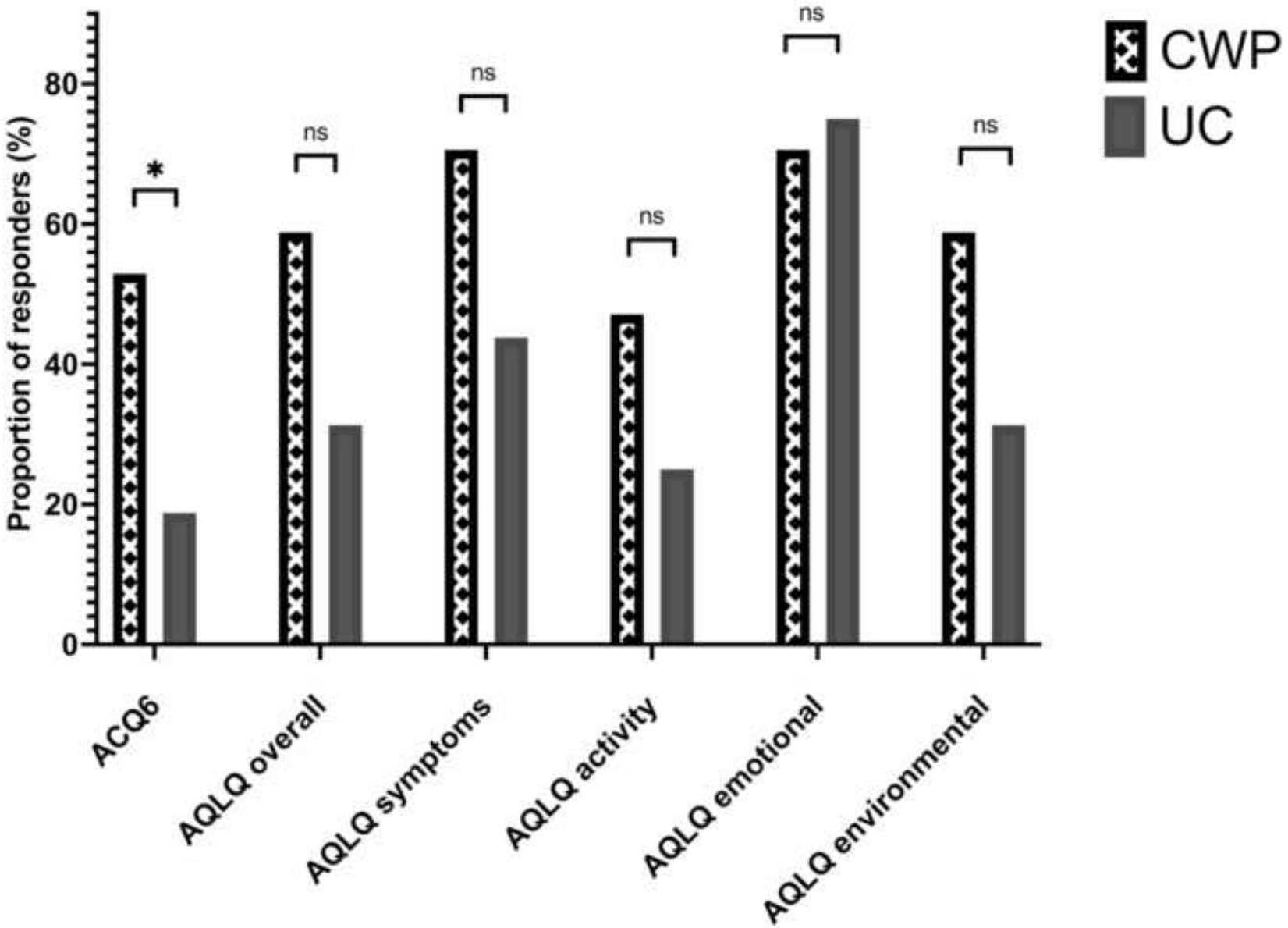
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