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Weight loss and gut microbial changes associated with semaglutide among people living with schizophrenia receiving clozapine or olanzapine: An open-label 24-week semaglutide intervention and 76-week trial

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ABSTRACT

Objectives: In individuals with schizophrenia receiving either clozapine or olanzapine, this study examined changes in 1) body weight and other cardiometabolic measures and microbiota biodiversity and composition between commencement and completion of 24-week semaglutide intervention; 2) body weight between commencement and 76-week follow-up.

Methods: 24-week intervention (16-weeks full-dose (1.0 mg/week) after 8-weeks' titration) of open-label nurse-administered semaglutide in a public mental health setting, with one-year post-intervention follow-up (76-week trial-completion). Participants: people with schizophrenia without diabetes receiving clozapine or olanzapine with BMI > 27 kg/m^2. Primary endpoints: %body weight change at 24-weeks, and 76-weeks. Secondary endpoints: %change in waist circumference, HbA1c at 24-weeks and 76-weeks, body composition at 24-weeks. Gut microbiota changes were compared at baseline, 10-weeks and 24-weeks intervention completion.

Results: Mean age: 41.5 years (range 18–61), 65.4% female. Intervention completed by 65.4% (n = 17/26). 24-week intervention: intention-to-treat body weight reduction: −9.8% (95% CI: [−12.7%, −6.8%], $p < 0.001$) or − 10.1 kg (95% CI [−13.6, −6.6]); waist circumference reduction: −7.3% (95% CI: [−10.1%, −4.4%], p < 0.001); HbA1c non-significant reduction: −5.3% (95% CI [−10.4%, 0.1%], $p = 0.055$). Microbial alpha diversity decreased as time on semaglutide increased, with enrichment of *Parasutterella excrementihominis*. Trial completion: 88.2% (n = 15/17). Average body weight change baseline-76-weeks: −5.1% (95% CI: [−8.3%, −1.9%], $p = 0.001$) or − 5.3 kg (95% CI: [−8.9, −1.7]).

Discussion: Semaglutide was associated with significant weight loss in overweight/obese people with schizophrenia. These benefits attenuated following semaglutide discontinuation. Gut microbial compositional differences consistent with improvement in health outcomes may occur in semaglutide-treated people living with schizophrenia.

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1. Introduction

Shorter life expectancy is a deeply concerning reality for people living with schizophrenia which occurs largely due to multiple physical health comorbidities, highlighting the need to reduce premature cardiometabolic morbidity and mortality (Momen et al., 2022). Cardiometabolic disorders such as obesity and type 2 diabetes (T2DM) significantly contribute to reduced quality of life and life expectancy in people with schizophrenia (Firth et al., 2019; Lindekilde et al., 2022; Momen et al., 2020). Metabolic sequelae of antipsychotic medications such as obesity and T2DM are highly prevalent but use of antipsychotics significantly improves remission and recovery (Huhn et al., 2020; Lappin et al., 2018; Morell et al., 2019; Dazzan et al., 2020).

Glucagon-like peptide-1 receptor agonists (GLP-1RAs) are medications used in the treatment of obesity and T2DM, with typically body weight reductions of 6–11% (Shi et al., 2024). GLP-1RA have wide-ranging health benefits albeit with some risks including gastrointestinal disorders and hypotension (Xie et al., 2025). Semaglutide was the GLP-1RA most effective in reducing weight until recently (Shi et al., 2024), with weight loss of up to 15% over one year in general population, non-diabetic obese people (Wilding et al., 2021). The dual GLP-1/GIP receptor agonist agent tirzepatide, has since been associated with even greater weight loss in overweight/obese general population adults (Rodriguez et al., 2024), but its use is yet to be trialled in people with schizophrenia. Meta-analytic-level evidence demonstrates that the GLP-1RAs liraglutide and exenatide induce weight loss among individuals with schizophrenia (Larsen et al., 2017; Patoulias et al., 2023; Siskind et al., 2018) and recently a number of randomised placebo-controlled trials have demonstrated the safety and efficacy of semaglutide for weight loss and metabolic health in people with schizophrenia (Siskind et al., 2025; Sass et al., 2026; Ganeshalingam et al., 2025).

The microbiome has been implicated in the development of the life-shortening cardiometabolic conditions which occur frequently in people with schizophrenia (Gomes et al., 2018; Nguyen et al., 2018). Gut microbiota, located in the digestive system, comprise bacteria, archaea, fungi, viruses and other species (Long-Smith et al., 2020) which can both impact the metabolism of oral drugs and mediate drug response (Long-Smith et al., 2020). Our group previously demonstrated that gut microbial composition differed by 21 taxa between individuals with schizophrenia compared to controls and that participation in a 12-week lifestyle intervention was associated with significant increases in α-diversity (O'Donnell et al., 2022). Research is needed to better understand the impact on the microbiome of pharmacological and lifestyle interventions which target cardiometabolic conditions in this vulnerable population. Semaglutide's effects on the microbiome have never been examined in this population.

Clozapine and olanzapine are highly effective antipsychotic medications, often used in people with treatment-resistant illness, but which are associated with high risk for weight gain, prediabetes and metabolic disturbances (De Hert et al., 2011; Larsen et al., 2019), placing individuals at increased risk for later development of T2DM and cardiometabolic morbidity. The need to identify and treat obesity and prediabetes among the clozapine- and olanzapine-treated has led to their prioritisation in previous GLP-1RA trials: in the COaST RCT, individuals treated with semaglutide had a 13·5% larger body weight loss than controls (Siskind et al., 2025). Both liraglutide (Larsen et al., 2017) and exenatide (Siskind et al., 2018) induced weight loss, improved glucose tolerance (Larsen et al., 2017), and reduced glycated haemoglobin (HbA1c) (Siskind et al., 2018) with waist circumference reducing with liraglutide, though not exenatide (Larsen et al., 2017; Siskind et al., 2018). There were mixed findings regarding sustainment of weight loss following cessation of both liraglutide and exenatide (Siskind et al., 2018; Svensson et al., 2019). No study has yet examined the extent to which weight loss persists following semaglutide discontinuation in this population, though meta-analytic level evidence from general population samples indicates significant risk for weight re-gain and for reversal of any cardiometabolic benefits on discontinuation (West et al., 2026).

The current study examined the effects of nurse-administered semaglutide for 16-weeks (after 8-weeks' dose titration) on body weight, other cardiometabolic measures (waist circumference, glycated haemoglobin, total body fat) and microbiome biodiversity in individuals with schizophrenia receiving clozapine or olanzapine. The durability of weight change was examined at one-year post-intervention follow-up (76-week trial completion).

2. Methods and materials

2.1. Participants

Participants were recruited from the Eastern Suburbs Mental Health Service, Sydney, Australia. Inclusion criteria: 18–65 years; stable treatment with clozapine or olanzapine; schizophrenia spectrum diagnosis according to ICD-11 (World Health Organization, 2022); stable body weight (<5 kg change in 3 months prior to recruitment); body mass index (BMI) >27 kg/m^2. Exclusion criteria: T2DM (glycated haemoglobin >48 mmol/mol); treatment with glucose-lowering medications other than metformin; substance misuse/dependence (except nicotine); serious somatic illnesses.

The study was approved by the South Eastern Sydney Local Health District Human Research Ethics Committee (2021/ETH01135). All participants received oral and written information and provided written informed consent. Participants were compensated financially for their time upon completion of each outcome measurement: baseline; 8-weeks (dose-titration completion); 16-weeks; 24-weeks (intervention completion); 76-weeks (trial completion). The pre-written study protocol was prospectively registered in ANZCTR (ACTRN12621001434886). https://www.anzctr.org.au/Trial/Registration/TrialReview.aspx?ACTRN=ACTRN12621001434886

2.2. Intervention

Subcutaneously-injected semaglutide in prefilled pen injectors was administered weekly by the research nurse. Doses were escalated as follows: 0.25 mg/week Weeks 1–4; 0.5 mg/week Weeks 5–8; 1.0 mg/week Weeks 9–24 (Fig. 1). Routine care included access to the Keeping Body in Mind (KBIM) lifestyle and lifeskills intervention, which provides psychoeducation, expert dietary and exercise advice (Curtis et al., 2024).

2.3. Measures

Weight, waist circumference, and illness severity (Clinical Global Impression Scale severity score) (Busner and Targum, 2007), were recorded 4-weekly during the 24-week intervention and once at 76-weeks. HbA1c was recorded at baseline, 24-weeks and 76-weeks. Adverse effects scales (Table 3) were administered weekly during the 24-week intervention only. Participation in KBIM lifestyle intervention was recorded throughout the 24-week intervention and the 76-week trial. A brief, easy-to-use online questionnaire (*Healthy Eating Quiz*) was offered to gather information regarding diet.

In a subset of participants ($n = 8$), body composition was measured using total-body dual-energy X-ray absorptiometry (DXA) (Lunar iDXA GE HealthCare). To ensure DXA accuracy and consistency, daily quality assurance procedures were conducted, including scanning a lumbar spine phantom before each participant's DXA assessment.

2.3.1. Microbiome analysis: stool DNA extraction and sequencing

In a further subset of participants ($n = 10$) stool samples for microbiome analysis were collected prior to starting semaglutide and again at 8- and 24-weeks. In practice, it was not always feasible to collect the samples at the appointed time: there were $n = 9$ baseline samples collected at (mean ± s.d) 1.75 ± 1.70 weeks from first dose (baseline); n

= 10 s samples (S2) collected at 10.07 ± 3.30 weeks and n = 9 third samples (S3) collected at 23.13 ± 4.65 weeks. Stool samples were collected by participants using a ColOff® Specimen Collection Facilitator Device (ColOff® Industrial, Brazil). Collected stool was transferred into PSP® Stool Collection Tube containing DNA Stabilizer (STRATEC Molecular; Thermofisher, Invitek, Germany). Samples were stored at −80 °C within 72 h of collection. Total DNA was extracted using the PSP® Spin Stool DNA Plus Kit (STRATEC Molecular). Samples were shotgun-sequenced using NovaSeq X Plus generating paired end 150 bp reads.

2.3.2. Microbiome analysis: data processing

Sequencing data were quality checked with BBMap tool suite (v39.01) (Chen et al., 2018), using the repair.sh and clumpify.sh tools for deduplication (dedupe parameter); then reads were checked for quality, trimming and filtering with fastp (v0.23.4) (Chen et al., 2018). Next, decontamination of human host DNA was performed using minimap2 (v2.28-rl209) (Li, 2018) against the human reference genome GRCh38, and mapped reads were removed via filterbyname.sh (BBMap). The cleaned paired-end reads were concatenated and taxonomy profiled using MetaPhLAn4 (v4.1.0) (Blanco-Míguez et al., 2023) against the ChocoPhLAn (vOct22) reference database via the HUMAnN 3 (v3.8) workflow. The taxonomy output for each sample from MetaPhlAn were merged into a single feature table via the HUMAnN's utility python script, merge_metaphlan_tables.py. (Beghini et al., 2021). Species level features were then used in downstream microbial statistical analyses detailed in Section 2.5. Tool parameters were left at default settings.

2.4. Endpoints

Primary endpoints were change in body weight from i) baseline to 24-weeks (intervention completion) and ii) baseline to 76-weeks (trial completion). Secondary endpoints were changes in waist circumference and HbA1c between baseline and intervention-completion and trial-completion. In the subgroups, change in body composition between baseline and intervention-completion was a secondary endpoint among DXA participants. Microbiome richness, diversity and composition were compared at baseline, S2 and S3.

2.5. Statistical analyses

The primary outcome of body weight, and secondary outcomes of waist circumference and HbA1c (all log transformed) were modelled on the intention-to-treat (ITT) population with linear mixed models using the lme4 package (Bates et al., 2015) in R-4.4.0 (R Core Team, 2024), controlling for multiple testing with Dunnett's adjustment for the two endpoints. The models have a fixed effect for weeks from baseline (categorical) to model change over time, and a random intercept for participant, to account for repeated measures. Due to sample size, we did not include covariates for adjustment in the primary analysis. Models' assumptions were checked by visual inspection of plots of residuals. Estimates of relative and absolute changes were calculated using the emmeans package (R Core Team, 2024). Due to small sample size, there were influential points found upon inspection of residuals and leverage in all these analyses. Sensitivity analyses were conducted excluding these participants.

Microbial statistical analysis: examined conventional alpha-diversity, beta-diversity and differential abundance analysis using the species level features. Alpha-diversity, which summarises the biodiversity of a single sample, was measured using Shannon diversity index and fitted with linear mixed models over time using lmerTest package in R-4.2.2 to observe overall biodiversity changes. Beta-diversity, which compares overall community similarity between samples, was examined using Bray-Curtis dissimilarities and tested for differences using Permutational Multivariate Analysis of Variance (PERMANOVA) with restricted permutations for repeated measures via vegan (v2.6–4) (Oksanen et al., 2022) R package. All models accounted for covariates: sex, age, ethnicity and height. Significance was determined using α=0.05 threshold. Species-by-species differential abundance analysis was performed using MaAsLin2 (v1.16.0) (Mallick et al., 2021) to detect any potential markers showing considerable differential abundances between time points. The analysis included feature filtering handled internally within MaAsLin2, a minimum abundance of 0.01% in at least 10% of samples (min_abundance, min_prevalence) was specified; and using the default total sum squares (TSS) normalisation and LOG transform settings; subject_ID was set as the random_effect and covariates mentioned above was set as fixed_effects within MaAsLin2. By default, MaAsLin2 performs FDR adjustment for multiple comparisons and use a threshold of FDR $\leq$ 0.25 as significant; however, given the pilot nature of this study, for exploratory hypothesis generation, we included species with unadjusted $p < 0.01$. Two models were investigated in beta-diversity and differential abundance analysis: Model 1 did not control for time on treatment; Model 2 controlled for time due to the variability in S2 and S3 sample collection: adjusted time for baseline vs S2 (*weeks_from_start*), and baseline vs S3 (*weeks_from_start* + *weeks_from_stop*).

3. Results

3.1. Participant characteristics

The 76-week trial was conducted between June 2022 and December 2024. 343 people were assessed for eligibility. 177 did not meet inclusion criteria and were excluded (Fig. 2), most commonly for: BMI too low; T2DM; use of GLP-1RA. 140 declined to participate while 26 agreed and were included in efficacy analyses. Mean age was 41.5 years; two-thirds were female (Table 1). Altogether, 17 (65.4%) participants completed the 24-week intervention (Fig. 2). Of those who withdrew, reasons given were: 44.4% ($n = 4$) perceived lack of effectiveness; 22.2% ($n = 2$) adverse effects: 11.1% ($n = 1$) each nausea and headache); 22.2% (n = 2) change of mind while 11.1% (n = 1) was lost to follow-up. Overall adherence was high (95%): 25/26 had over 85% adherence. One participant received 2/6 doses before withdrawing. 9/17 engaged with lifestyle interventions during the intervention with a median attendance of one session (IQR = 4.0; range: 0–17). 6/15 engaged with lifestyle interventions during the 24–76-week follow-up with a median attendance of zero sessions (IQR = 2.0; range: 0–9).

3.2. Body weight and other metabolic endpoints at 24-week intervention completion

Mean body weight loss over 24-week intervention was −9.8% (95%

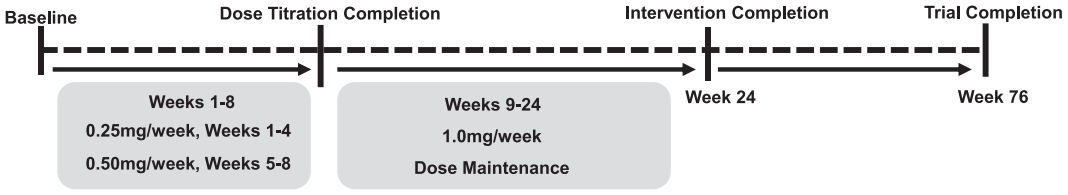

Fig. 1. Timeline of intervention phases.

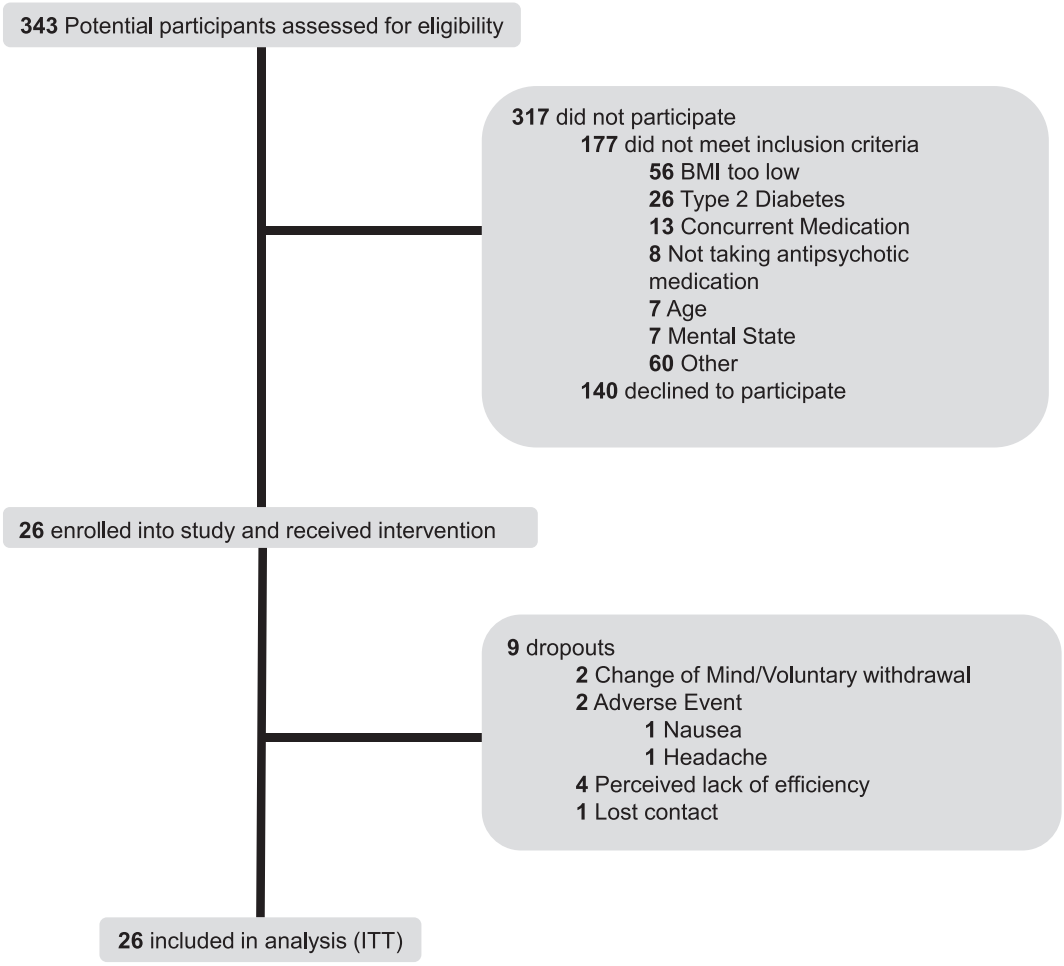

Fig. 2. Participant flow diagram.

CI: [−12.7%, −6.8%], $p < 0.001$), that is −10.1 kg (95% CI [−13.6, −6.6] Table 2, Fig. 3). Mean waist circumference reduced over 24-weeks: −7.3% (95% CI: [−10.1%, −4.4%], $p < 0.001$), that is −8.7 cm (95% CI: [−12.4, −5.1] Table 2, Fig. S1). HbA1c reduced non-significantly over 24-weeks: −5.3% (95% CI [−10.4%, 0.1%], $p = 0.055$), that is −1.9 mmol/mol in absolute terms (95% CI: [−3.9, 0.0] Table 2, Fig. S2). The sensitivity analyses showed qualitatively similar results for changes from baseline to 24-weeks for these three endpoints (see Supplementary). 14/17 (82.4%) participants achieved ≥5% weight loss, and 8/17 (47.1%) ≥10% weight loss. In the subgroup undertaking DXA, total body fat reduced: −2.6% (95% CI: [−3.6%, −1.6%], p < 0.001) while the proportion of lean body mass to total body mass increased (0.02; 95% CI: (0.01, 0.03), $p = 0.002$). There was no evidence for change in psychosis severity (CGI total symptom score mean change −0.1 (SD = 0.9, $p = 0.503$)). Four participants engaged in lifestyle interventions at least once during the 24-week intervention, and a further participant at least twice.

3.3. Adverse events and mental state

Gastrointestinal tract symptoms were common, particularly constipation and nausea (each reported by 84.6% participants), vomiting (69.2%), flatulence and abdominal pain (65.4% each) (Table 3; Supplementary). Other adverse events were fatigue (88.5%), dizziness (69.2%) and injection site pain/irritation (57.7%).

3.4. Microbiome

The overall gut microbial (alpha) biodiversity measured by Shannon diversity index was observed to decrease with time on treatment for the 10 subjects (estimated coefficient = −0.02 95% CI: [−0.03, −0.01]; $p = 0.02$) (Fig. 4A). Time was observed to have a significant association in the overall species community (beta-diversity) comparison. Without controlling for the varying weeks on treatment, there was significant difference between baseline and S2 ($n = 9$; 18 samples, $p = 0.05$). Although this significance was lost after adjusting for time ($p = 0.35$, Fig. 4B), the *weeks_from_start* covariate was significant (p = 0.05) contributing to 4.69% (R2) of the explained variance.

When comparing baseline vs S3 ($n = 8$; 16 samples), there was no statistically significant difference in overall species composition (Fig. 4C). With the variability in S3 collection times ranging between 0 and 5 weeks post last dose, there was a significant time effect ($p = 0.01$, R2 = 11.77% explained variance for *weeks_from_stop*). A similar trend was observed in the differential abundance analysis, with an increase from four to thirteen potential species markers detected after controlling for time (Fig. 4D and Supplementary S4). In particular, *Parasutterella excrementihominis* displayed considerable increase in relative abundance at both S2 and S3 compared to baseline.

3.5. 76-week trial completion

Data at 76-week trial completion (one-year post-intervention) were available for 15/17 (88.2%) participants. All remained on clozapine and/or olanzapine, except two (one switched to aripiprazole from

Table 1
Baseline characteristics

Sociodemographic and clincial characteristics	Treatment group			
	All (n = 26)	Completers (n = 17)	DXA sub study (n = 8)	Microbiome substudy (n = 10)
Sociodemographic				
Age, Mean (SD)	41.5 (13.1)	41.5 (12.7)	38.6 (16.1)	40.2 (13.8)
Female, n (%)	17 (65.4)	9 (52.9)	6 (75.0)	8 (80.0)
Country of Birth Australia, n (%)	19 (73.1)	13 (76.5)	7 (87.5)	7 (70.0)
Diagnosis, n (%)				
Schizophrenia	18 (69.2)	11 (64.7)	7 (87.5)	7 (70.0)
Schizoaffective Disorder	8 (30.8)	6 (35.3)	1 (12.5)	3 (30.0)
Treatment[a], n (%)				
Clozapine	24 (88.9)	15 (88.2)	8 (100.0)	10 (100.0)
Olanzapine	4 (14.81)	3 (17.65)	1 (12.5)	1 (10.0)
Metformin Treatment n (%) Yes	14 (53.85)	12 (70.59)	5 (62.5)	5 (50.0)
Clinical Characteristics, Median (IQR)				
Body Weight, kg	99.5 (21.9)	105.0 (24.4)	98.0 (24.3)	101.9 (24.7)
Waist Circumference, cm	115.0 (18.3)	118.0 (18.0)	114.0 (28.5)	115.5 (19.3)
Body Mass Index (BMI), kg/m^2	33.3 (10.9)	36.3 (11.4)	32.8 (12.1)	33.2 (10.9)
HbA1c (mmol/mol), Mean (SD)	36.9 (3.9)	36.5 (4.2)	36.9 (2.7)	37.5 (3.7)
Body Composition				
Visceral Fat (g), Mean (SD)			1493.4 (600.6)	
Android to gynoid fat ratio, Mean (SD)			0.649 (0.1)	
Total body fat (g), Mean (SD)			45,970 (16,971.6)	
Total body fat (%), Mean (SD)			47.1 (8.5)	
Lean body mass to total body mass ratio, Mean (SD)			0.6 (0.1)	
Smoker n (%)	10 (38.5)	7 (41.2)	3 (37.5)	3 (30.0)
Ethnicity, n (%)				
Anglo Australian	18 (69.2)			
First Nations	3 (11.5)			
Asian	2 (7.7)			
European	3 (11.5)			
Rating Scales				
CGI (mean)				
Positive Symptoms	2.5 (1.1)			
Negative Symptoms	2.6 (0.6)			
Depressive Symptoms	2.4 (0.9)			
Cognitive Symptoms	1.4 (1.3)			
Overall Severity	2.7 (0.9)			

[a] Some participants received both clozapine and olanzapine.

clozapine; one to brexpiprazole from olanzapine). At 76-weeks, two participants were on semaglutide, but no others were on any GLP-1RA. Average weight loss from baseline to 76-weeks was −5.1% (95% CI: [−8.3%, −1.9%], p = 0.001), that is −5.3 kg (95% CI: [−8.9, −1.7]). Results were similar when the two participants who received some semaglutide during follow-up were excluded: average weight loss from baseline to 76-weeks was −4.1% (95% CI: [−7.6%, − 0.6%], p = 0.021), that is −4.2 kg (95%CI: [−8.1, −0.4]. The sensitivity analysis found a smaller weight loss (see Supplementary). This implies an average weight increase from 24 to 76 weeks of 5.2% (95% CI: 1.9% - 8.6%), that is 4.8 kg (95% CI: 1.6–8.0). Results were largely unchanged when the two participants who received some semaglutide during follow-up were excluded: average weight increase from 24 to 76 weeks of 5.8% (95% CI: 2.2% - 9.4%, p = 0.001), that is 5.3 kg (95% CI: 1.9–8.8). The sensitivity analysis found a larger weight increase (see Supplementary). 8/15 (53.3%) participants had achieved ≥5% weight loss, and 3/15 (20.0%) ≥10% weight loss.

Average waist circumference reduction between baseline and 76-weeks was −4.1% (95% CI: [−7.1%, −1.1%], p = 0.006), that is −5.0 cm (95%CI: [−8.8, −1.1]). The sensitivity analysis found a smaller reduction (see Supplementary). Waist circumference increased, however, from 24 to 76 weeks by 3.4% (95% CI: 0.4% - 6.5%), that is 3.8 cm (95% CI: 0.3–7.2). The sensitivity analysis found a larger waist circumference gain (see Supplementary). There was no evidence for change in HbA1c from baseline at 76-weeks, with estimated relative change of −3.0% (95% CI: [−9.0%, 3.4%], p = 0.449), that is a reduction of −1.1 mmol/mol in absolute terms (95%CI: [−3.4, 1.2]). The sensitivity analysis found a larger change (see Supplementary).

4. Discussion

The current study provides important real-world support for recent RCT evidence (Siskind et al., 2025) that semaglutide is an effective weight loss intervention in people with schizophrenia treated with clozapine or olanzapine. Intention to treat analyses demonstrated highly clinically and statistically significant body weight loss of approximately 10%, with concurrent decreases in waist circumference and total body fat while glycated haemoglobin decreased non-significantly. Semaglutide administered weekly by a clinic nurse was feasible in overweight/obese people with schizophrenia, though approximately one-third withdrew early. This study adds to current knowledge by reporting the novel exploratory finding that microbial alpha diversity decreased as time on semaglutide increased. Differential abundance time-adjusted analysis indicated enrichment of several bacterial species after 8–10 weeks' semaglutide treatment compared to baseline, specifically *Clostridium sp AF12 28* and *Parasutterella excrementihominis*. *Parasutterella excrementihominis* enrichment was also detected at treatment endpoint compared to baseline. Finally, this study provides evidence for the first time in this population that at 12-month follow-up, weight loss compared to baseline was approximately 5%, half that lost at semaglutide intervention completion, indicating that approximately half of the lost weight had been regained.

In keeping with significant weight loss reductions observed in participants with schizophrenia exposed to semaglutide in recent RCTs (Siskind et al., 2025; Sass et al., 2026; Ganeshalingam et al., 2025), semaglutide was associated with highly effective weight loss. The high percentage of body weight loss also aligns with network meta-analysis evidence comparing GLP-1RAs in overweight/obese general population RCT studies which indicate semaglutide's effectiveness for weight loss, with −11.4% bodyweight change compared to lifestyle interventions (Xie et al., 2025). Waist circumference also decreased significantly with semaglutide treatment in the current study, aligning with RCT findings reported for semaglutide in clozapine- or olanzapine-treated people with schizophrenia (Sass et al., 2026). These positive health effects were maintained to a lesser extent at 12-month follow-up. Further, the DXA body composition findings demonstrate that the weight loss associated with use of semaglutide is predominantly through fat rather than through lean body mass. Finally, while during semaglutide treatment there was a trend for reduction in HbA1c, there was no evidence for any change between baseline and 76-week trial

Table 2
Change in cardiometabolic characteristics between baseline and intervention completion (24-weeks)

Characteristic	Participants		Estimated change from baseline	*p*
	Baseline (n = 26)	24-weeks (n = 17)		
Body Weight, kg (median, IQR)	99.5 (21.9)	95.7 (25.3)	−9.8% [−12.7%, −6.8%]	<0.001
Waist Circumference, cm (median, IQR)	115.0 (18.3)	112.0 (14.0)	−7.3% [−10.1%, −4.4%]	<0.001
HbA1c, mmol/mol (mean (SD))	36.9 (3.9)	34.8 (4.3)	−5.3% [−10.4%, 0.1%]	0.055
	Baseline (n = 8)	24-weeks (n = 8)		*p*
Body Composition, Mean (SD)				
Visceral Fat (g)	1493.4 (600.6)	1340.3 (633.8)	−153.1 [−442.6, −136.3]	0.240
Android to gynoid fat ratio	0.649 (0.1)	0.6 (0.1)	0.01 [−0.02, −0.04]	0.473
Total body fat (g)	45,970 (16,971.4)	39,634.5 (15,052.9)	−6335.5 [−9597.4, −3073.6]	0.003
Total body fat (%)	47.1 (8.5)	44.5 (8.2)	−2.6 [−3.6, −1.6]	<0.001
Lean body mass to total body mass ratio	0.5 (0.1)	0.5 (0.1)	0.02 [0.01, 0.03]	0.002

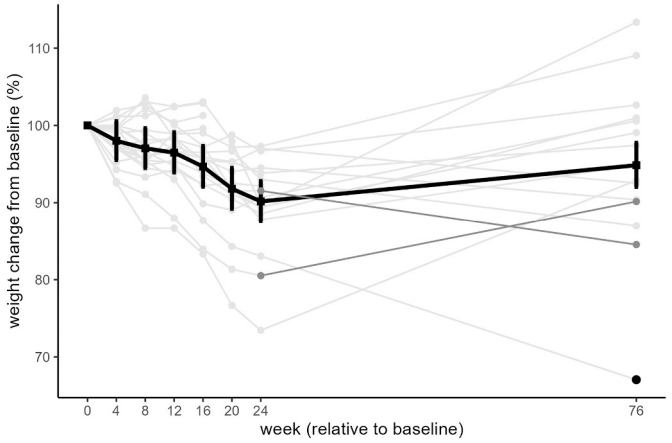

Fig. 3. Weight change from baseline (%) over 24-week semaglutide intervention and subsequent one-year follow-up (76-week trial completion).
Legend: Estimated relative weight change from baseline with 95% CI (black) with raw data (grey). In darker grey are the two participants that reported any semaglutide use after Week 24. The black point is an influential outlier.

completion. This is in contrast to findings of significantly reduced HbA1c at the end of 30-week (Ganeshalingam et al., 2025) and 26-week (Sass et al., 2026) semaglutide interventions in RCTs conducted in similar population groups, perhaps explained in the current study by small sample size.

Longitudinal follow-up demonstrated that body weight increased in the 12-months following trial completion despite access to treatment-as-usual lifestyle interventions, though there was still net, albeit less dramatic, weight loss from baseline. These findings align well with those reported in general population samples who experience reversal of both weight loss and cardiometabolic benefits following cessation of semaglutide and weight management medications considered more generally (West et al., 2026). This warrants serious consideration by prescribers as these findings raise the question whether there is risk for cardiometabolic harm on subsequent withdrawal of semaglutide. Support for this concern comes from the two other longitudinal follow-up studies of GLP-1RAs conducted in people living with schizophrenia: liraglutide-treated participants regained weight during 12-month follow-up, but the placebo-subtracted weight loss remained significantly reduced compared to baseline (Svensson et al., 2019). In contrast, individuals on exenatide had significantly greater weight gain compared to placebo (8.3 kg, SE 2.03 kg, $p < 0.001$) between endpoint and follow-up, having regained the weight lost (−4.2 kg) from baseline and a further mean 4.2 kg (Siskind et al., 2020). Participants remained on clozapine or olanzapine but there were important differences between studies including sample size and ongoing access to GLP1-RAs or metformin which prevent direct comparison.

The seminal STEP 1 study extension (Wilding et al., 2022) showed that participants regained two-thirds of prior weight lost in the 12-months following withdrawal of semaglutide after 68-week exposure. Further, in the STEP 4 study (Rubino et al., 2021), continuation on semaglutide was associated with 17.4% weight loss from baseline over 48-weeks following treatment, while switching to placebo led to weight regain of 6.9% from baseline. In both studies, concurrent lifestyle interventions were offered, while in the current real-world study engagement in treatment-as-usual lifestyle interventions was minimal, in line with evidence that lifestyle interventions, while effective, are challenging to implement in this population (Firth et al., 2019). Less than half the participants agreed to the offer of lifestyle interventions as part of routine care and among those, the average attendance was less than one session. West and co-authors' recent review of the relative benefits of weight management medications versus lifestyle interventions highlights that while weight management medications may offer a quick-fix for weight loss and cardiometabolic benefits, these gains are quickly lost following their cessation, while weight regain occurs less rapidly following cessation of lifestyle interventions (West et al., 2026). It is plausible that the notable rebound in body weight in individuals with schizophrenia may additionally be contributed to by the continued use of obesogenic antipsychotic treatments. Further, visceral fat and waist circumference increases are linked with the development of insulin resistance and diabetes (Neeland et al., 2012) and thus become targets for intervention among high-risk populations. Our group has shown in rat models that clozapine and olanzapine medications both increase glucagon levels and suppress GLP-1 (Smith et al., 2008; Smith et al., 2011; Smith et al., 2014). Importantly, antipsychotic treatment neither caused obesity directly nor potentiated diet-induced obesity; rather, it led to a preference for a high fat/high sugar diet. This was the first research to establish a mechanism for how drugs used to treat schizophrenia may promote diabetes. Of note, this is not classical insulin resistance but rather antipsychotics inducing a hyperglycaemic state associated with increased levels of glucagon and insulin and elevated hepatic glucose output. These effects reversed following GLP-1RA administration, reducing weight and normalizing both glucagon levels and glucose metabolism (Smith et al., 2009), demonstrating the important potential for their utility in obesity management in individuals receiving antipsychotics. It is unclear whether this may partly explain why the withdrawal of semaglutide in the current study, and exanatide in a similarly designed study (Siskind et al., 2020), led to rebound weight gain in participants with schizophrenia on clozapine and/or olanzapine while weight regain following semaglutide withdrawal in general population studies appeared less severe.

Microbial alpha diversity decreased as time on semaglutide increased. This finding was somewhat unexpected, as previous studies demonstrate an increase in bacterial abundance following weight loss in obese individuals (Remely et al., 2015). Differential abundance time-adjusted analysis indicated enrichment of several bacterial species after 8–10 weeks' treatment compared to baseline, specifically *Clostridium sp AF12 28* and *Parasutterella excrementihominis*. *Clostridium sp AF12 28* has not previously been genotyped and so there is much to learn

Table 3
Adverse events

Adverse Event (AE) or reaction	All participants (n = 26)		Participants on clozapine (*n* = 23)	
	No of participants, n (%)	No of total during active trial	No of participants, n (%)	No of total AE during active trial
Gastrointestinal Tract				
Constipation	22 (84.6)	150	20 (87.0)	147
Nausea	22 (84.6)	140	21 (91.3)	136
Vomiting	18 (69.2)	63	17 (73.9)	62
Diarrhoea	17 (65.4)	92	15 (65.2)	85
Flatulence	17 (65.4)	96	16 (69.6)	78
Abdominal Pain	17 (65.4)	61	17 (73.9)	47
Eructation	16 (61.5)	88	15 (65.2)	71
Dyspepsia	13 (50.0)	95	12 (52.2)	39
Abdominal Distension	9 (34.6)	18	8 (34.8)	15
Gastritis	7 (26.9)	9	6 (26.1)	8
Nervous System				
Fatigue	23 (88.5)	282	20 (87.0	258
Dizziness	18 (69.2)	138	17 (73.9)	131
Headache	3 (11.5)	4	3 (13.0)	4
Infection				
Respiratory Tract Infection	2 (7.7)	2	2 (8.7)	2
Injection site pain or irritation	15 (57.7)	53	14 (60.9)	51
Psychiatric Symptoms				
Low Mood	1 (3.85)	2	1 (4.3)	2
Paranoid Delusions	1 (3.85)	1	0	0
Grief	1 (3.85)	1	1 (4.3)	1
Other (Other physical symptoms unrelated to Semaglutide)	7 (26.92)	7	6 (26.10)	6

about the potential role of this bacterium in obesity. Studies examining the microbiome in obese subjects have found that different members of the *Clostridium* genus respond differently during weight loss, with some *Clostridia* clusters exhibiting increased and others decreased abundance (Remely et al., 2015). *Parasutterella excrementihominis* is a Gram-negative member of the Betaproteobacteria phyla (Ju et al., 2019). Relative abundance of *Parasutterella excrementihominis* is associated with improvement in multiple host health outcomes including obesity, diabetes, and inflammatory bowel disease (Shin et al., 2015). High-fat diet is associated with reduced *Parasutterella* sp. relative abundance in both human and animal studies (Kreutzer et al., 2017; Zhang et al., 2012). This exploratory finding shows exciting potential for future study and adds to a growing body of research showing gut microbiome alterations in people living with schizophrenia (Zhu et al., 2025a, 2025b). A caveat is that it is unknown to what extent the reported changes in gut microbiome were secondary to changes in use of semaglutide per se, and/or to associated changes in diet.

Nurse-administered semaglutide thus appears to be a feasible and effective treatment of obesity with absence of mental state destabilisation in this high-risk population, replicating the findings of safety and efficacy from the COaST study (Siskind et al., 2025). The feasibility of providing semaglutide to people with schizophrenia in the absence of clinical support for administration, however, is unclear. This is a difficult-to-engage population as demonstrated by the large number unwilling to participate and one third who withdrew early, somewhat more common than the approximate one-in-five withdrawals reported in general population groups (O'Neil et al., 2018). In the current study, reasons cited for withdrawal included perceived lack of effectiveness, change of mind and adverse effects. Adverse events associated with GLP-1RAs are most commonly gastrointestinal symptoms (nausea, vomiting, diarrhoea, constipation, abdominal pain) (Bessesen and Van Gaal, 2018), as found here. High dropout rates from research studies are common in people with schizophrenia (Martin et al., 2006; Villeneuve et al., 2010) while typical dropout rates in general population studies of GLP-1RAs are in the order of 10% (Astrup et al., 2009; Wilding et al., 2021; Wilding et al., 2022). Semaglutide, then, was not suitable for all in this real-world study. Among trial completers, however, adherence to semaglutide was very good with an average of 95%, aligning with the finding from an RCT of liraglutide among people with schizophrenia that once recruitment is achieved, adherence to medication is good (Whicher et al., 2021).

4.1. Limitations

Study limitations include small numbers, lack of placebo control or other comparison groups, and approximately one-third of participants' withdrawal before semaglutide intervention completion. Two further participants who completed the intervention did not participate in follow-up. Two participants had changes to their antipsychotic treatment during follow-up, so it is unclear to what extent this may have impacted subsequent weight gain, though in both cases clozapine ($n = 1$) and olanzapine (n = 1) were replaced by less-obesogenic drugs (aripiprazole and brexpiprazole). In future, larger, cohorts it would be valuable to examine subgroups by gender and medication profile and other variables such as engagement with lifestyle interventions. It would also be valuable to extend the study population to cohorts on antipsychotics other than clozapine. Collecting data on diet proved not feasible: an online diet questionnaire offered to all was completed by only one participant rendering these data unusable. Future studies should explore the potential to improve take-up of validated methods for collecting diet data in this challenging population, and to examine other markers of endocrine and metabolic effects of semaglutide.

DXA data and microbiome data were available only on a subset of participants, and so these findings must be considered preliminary until replicated in adequately-powered samples. Microbiome analyses were limited by not having clean baseline sample pre-exposure and by the range of sample collection times. Nonetheless, these pilot data show, for the first time, that compositional differences occur over time in gut microbiota of people with schizophrenia treated with semaglutide. Microbiota changes during semaglutide treatment have never previously been examined and these findings contribute to growing knowledge about the microbiome and obesity.

5. Conclusions

Consideration should be given to routine prescription of GLP-1RA such as semaglutide when treating people with schizophrenia receiving antipsychotics with high metabolic side effect profile. Weight loss attenuates, however, following drug discontinuation, suggesting the need to consider long-term treatment. Further study is required to examine the potential effectiveness of concurrent initiation of semaglutide and obesogenic antipsychotic treatments in preventing weight gain and how best to support optimal uptake of and maintenance on treatment. The impact on the microbiome of semaglutide and other drugs which optimize weight is an emerging area for research in this vulnerable population.

CRediT authorship contribution statement

Julia M. Lappin: Writing – review & editing, Writing – original draft, Supervision, Resources, Project administration, Methodology, Investigation, Funding acquisition, Conceptualization. **Patrick Bolton:** Writing – review & editing, Writing – original draft, Validation, Supervision, Resources, Project administration, Methodology, Investigation,

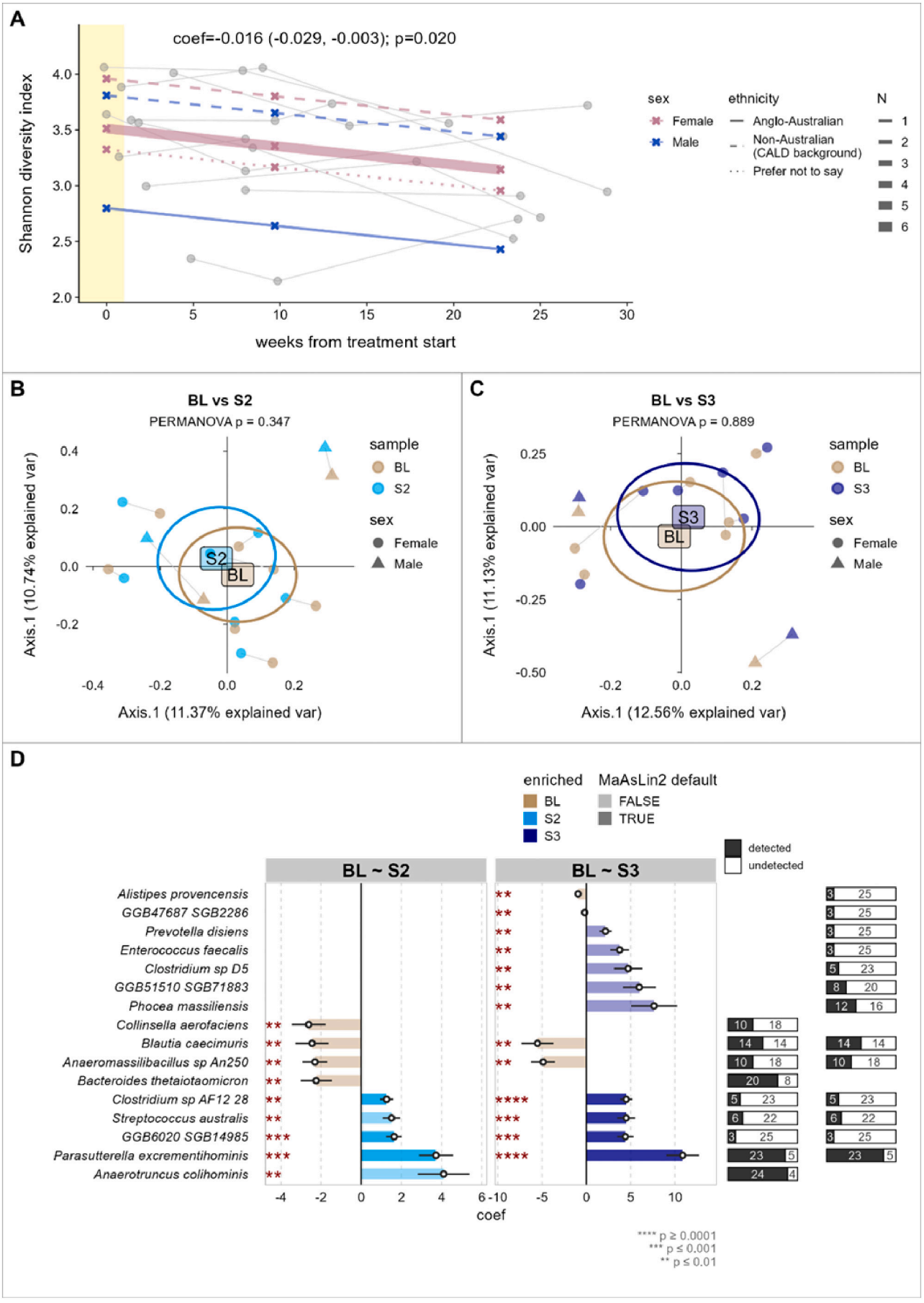

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Fig. 4. Microbiota diversity analysis
Legend: A) Change in alpha diversity with time on treatment.
B & C) PCoA comparing species composition between baseline vs S2 (8–18 weeks on treatment with mean ± SD = 10.07 ± 3.30 in B); and baseline vs S3 (0–5 weeks post treatment with mean ± SD = 2.84 ± 2.3 in C). Points represent samples where samples belonging to the same subjects joined by line. Labels show estimated centroids (BL-baseline, S2-second sample, and S3-third sample) with ellipses showing 95% confidence interval.
D) Differential abundance analysis using MaAsLin2 comparing baseline versus S2 (column 1) and baseline versus S3 (column 2). Bars ($x < 0$) denote that corresponding species are enriched in baseline compared to S2 or S3 and bars ($x > 0$) denote corresponding species are enriched in S2 or S3 compared to baseline. Dark shaded bars represent that the corresponding species meet default MaAsLin2 cutoff FDR = 0.25 after adjusting for multiple species comparisons. The black and white bar plot represents the species feature prevalence for the two pairwise comparisons. All models adjusted for covariates (age, sex, ethnicity and height); and pairwise comparisons between baseline vs S2 and baseline vs S3 were controlled for time since first and/or last dose.

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Declaration of competing interest

All authors declare no conflicts of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.schres.2026.06.021.

Data availability

The individual participant data generated or analysed during this study will not be publicity available due to ethical and privacy considerations. Data access is restricted in accordance with institutional and governance policies, and no individual participant data can be shared without ethics and governance approval.

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