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Interaction between Atypical Antipsychotics and the Gut Microbiome in a Bipolar Disease Cohort

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Abstract: (250 words)

Objectives: The atypical antipsychotic (AAP) class is often associated with metabolic disease, but the mechanistic underpinnings of this risk are not understood. Due to reports linking gut bacteria function to metabolic disease, we hypothesize that AAP-treatment in adults results in gut dysbiosis potentiating metabolic criteria. This report describes recent findings linking AAP-treatment with differences in gut microbiota communities in a human cohort with bipolar disorder (BD).

Methods: In a cross- sectional design, we obtained 16S ribosomal sequences from 117 BD patients (49 AAP-treated, 68 non-AAP treated). Analysis of molecular variance (AMOVA) was used to detect significant clustering of microbial communities between groups and the inverse Simpson index was used to calculate alpha diversity. Detection of differentially abundant operational taxonomic units (OTUs) between groups was performed using linear discriminant analysis effect size.

Results: The AAP-treated cohort was significantly younger and had increased BMI compared to non-AAP treated patients. Groups did not differ in other psychotropic medication use with the exception of higher use of benzodiazepines in the AAP-cohort. We detected significant separation between microbiota communities of AAP-treated and non-treated subjects (AMOVA; p=0.04). AAP-treated females showed significant decreased species diversity when compared to non-AAP treated females (p=0.015). Males showed no significant diversity between treatment groups (p=0.8). Differentially abundant OTUs between treatment groups were OTU1, OTU25, and OTU32 that classified to *Lachnospiraceae*, *Akkermansia,* and *Sutterella* respectively.

Conclusions: These data suggest that AAP-treatment associates with specific representation of gut bacterial families in AAP-treated patients. Additionally, AAP-treatment is associated with decreased species richness in female AAP-treated patients.

Introduction:

Patients living with a serious mental illness show significant increases in cardiovascular disease (CVD) and metabolic disease compared with the general population. Up to 30 years of life are lost in this population, primarily due to cardiovascular disease[1]. For patients receiving an atypical antipsychotic (AAP), the risk of metabolic syndrome is more than twice that seen in the general population [2]. At least 40% of those taking an AAP meet metabolic syndrome criteria, which consist of a constellation of cardiovascular symptoms that together significantly increase CVD risk[3]. Additionally, a gender bias exists for AAP-associated CVD risks as seen by a comparison of Clinical Antipsychotic Trial of Intervention Effectiveness (CATIE) participants to matched healthy controls from NHANES III [4]. When investigators examined participants based on the 10-year coronary heart disease risk using the Framingham Heart Study formula, significant differences were seen for elevations in CVD risk (50% females v. 34% males) [5,6] and metabolic syndrome (137% more likely in females, 85% more likely in men) [7]. The mechanisms that lead to greater CVD risk in this population have not been defined.

There is a wealth of data pertaining to the role of the gut microbiota in CVD, diabetes, metabolism, and systemic inflammation[8, 9]. Without prospective studies, it is difficult to determine whether the gut microbiome predisposes subjects to these illnesses or if these illnesses modulate the microbiome. Gastric bypass surgery studies show that aside from sustained weight loss, this procedure also precipitates decreased type II diabetes *prior* to any weight decrease [10, 11]. Furthermore, gastric bypass directly affects glucose regulation, while other studies have cited a shift in microbiota composition, suggesting that the microbiome may improve metabolic function [13].

In a recent study of 18 human adolescent males (9-15 years old), chronic use of the AAP risperidone (> one year), was associated with a microbiome composition exhibiting robust differences from that of non-medicated controls [13]. Chronic risperidone- treated patients showed increased relative representation of the Firmicutes phylum, especially in those with increased body mass index (BMI). In addition, a longitudinal investigation in five males revealed

a gradual change in gut microbiota composition and a simultaneous increase in BMI during the months following the onset of risperidone treatment [13]. In rat models, studies of olanzapine treatment had significant effects on a number of physiologic, inflammatory, and microbial parameters that were more pronounced in females rats compared to males [14-16]. Specific microbiome alterations in olanzapine-treated female rats included overall decreased biodiversity and increased macrophage infiltration in adipose tissue [14]. In a follow-up study, co-administration of antibiotics attenuated the physiologic and inflammatory effects of olanzapine use [16].

The purpose of this study was to determine if treatment-specific differences in gut microbe communities were detectable in a well-characterized cohort of subjects with a serious mental illness. We hypothesized that AAP-treatment will associate with a significant separation in fecal microbiota communities from BD patients treated with AAPs compared to those patients with BD not treated with AAPs.

Methods

Participants

The Prechter Longitudinal Study of Bipolar Disorder is an ongoing observational study of BD at the University of Michigan (HUM00000606)[17]. Medication group for each patient was defined by the use of an AAP at the time of fecal sample collection. Atypical antipsychotics included in our cohort were clozapine, olanzapine, risperidone, quetiapine, asenipine, ziprasodone, lurasidone, aripiprazole, paliperidone, and iloperidone. Neither group differed in treatment with mood stabilizers or antidepressants (**Table 1**). The AAP-treatment group proportionally used more benzodiazepines. In addition to medication, we also noted age, BMI, and gender for these subjects.

Fecal collection and processing

One fecal sample from each subject was collected using the OMNIgene-Gut kit OMR-200 (DNA Genotek, Ontario, Canada). Total DNA was isolated from 250µL of the fecal sample using the PowerMag soil DNA isolation kit (MoBio, Carlsbad, CA), optimized for Eppendorf's epMotion liquid handling robot (Hauppauge, NY).

Sequencing

The DNA libraries were prepared by the Microbiome Core at the University of Michigan as described previously[18]. The bacterial V4 16S rRNA region was amplified with a bar-coded primer set using the Schloss protocol[18]. Approximately 5µl of a 4µM dual index primer stock, 0.15 µl of Accuprime High-Fidelity Taq, 2 µl of 10× Accuprime PCR II buffer (Life Technologies, Carlsbad, CA), 11.85 µl of PCR-grade water, and 1 µl of template were used in the PCR reaction, which was also spiked with 10 % PhiX for diversity. The cycling conditions for PCR were as follows: 95 ℃ for 2 minutes, 30 cycles of 95 ℃ for 20 s, 55 ℃ for 15 s, and 72 ℃ for 5 minutes, followed by 10 minutes at 72 ℃. Amplified DNA was sequenced using Illumina MiSeq V2 chemistry (Illumina Inc., San Diego, CA).

Data Processing and analysis

Sequence files were processed with mothur v.1.36.0 using the described operating procedure [18]. Assembled contigs were filtered for chimeric sequences using UCHIME [19], and aligned to a mothur-adapted RDB database. A 97% cutoff was used to bin sequences into operational taxonomic units (OTUs). A complete list of commands for data processing, statistical analysis and data presentation are available at: https://github.com/StephanieAFlowers/Evans_Microbiome

Statistics

Microbiome 16S sequencing data were analyzed using a combination of the software programs mothur and R v3.2.5. Demographic and microbial differences between treatment groups were determined through the use of standard t-tests, chi-squared tests, Wilcoxon tests, and Spearman Correlations. Differences in BMI between treatment groups (AAP-treated vs. non-AAP treated) were adjusted for known BMI-predictors such as age and gender. We used analysis of molecular variance (AMOVA) to compare microbial communities between medication groups. Deferentially abundant OTUs between treatment groups were identified using linear discriminant analysis (LDA) effect size (LEfSe) analysis. For significant OTUs defined by LEfSe analysis, we performed a regression to adjust for age, BMI, and gender. Alpha diversity for each subject was measured using an inverse Simpson's Diversity estimate. The second linear regression was adjusted for age, BMI, and benzodiazepine use but compared diversity estimates to medication and gender cohorts.

Results

Participant Demographics

Our BD cohort comprised 117 adults with bipolar disorder (BD) from the Prechter Longitudinal Study of Bipolar Disorder. Among the 117, 49 were treated with an AAP and 68 were not (**Table 1**). Significant demographic differences at baseline between medication groups included an older population who did not receive AAP treatment (p= 0.02) and higher BMI values in AAP users that remained significant after correcting for age and gender (p=0.04). There were no significant differences in treatment with lithium or mood stabilizers between the medication cohorts. The AAP-treated population had a greater use of benzodiazepines.

To investigate differences between the fecal communities of AAP-treated and non-AAP treated participants, we calculated the beta diversity using the Yue and Clayton distance (θ_{YC})[20]. Principal coordinates analysis (PCoA) from the θ_{YC} calculated distances revealed significant separation between the two medication groups using AMOVA (**Figure 1**; p=0.04) [21]. A biplot illustrating OTUs associating towards PCoA axes 1 and 2 showed three OTUs responsible for differing directions of the two medication cohorts: OTU1 (classified as *Lachnospiraceae*), OTU11 (classified as *Alistipes*), and OTU25 (classified as *Akkermansia*).

Differentially abundant OTUs were identified using linear discriminant analysis (LDA) effect size (LEfSe)[22]. LEfSe revealed three differentially represented OTUs between our medication groups that were in the top 50 abundant taxonomic units (**Figure 2**). Operational taxonomic unit 1 classified to *Lachnospiraceae* while OTU25 and OTU32 classified to *Akkermansia* and *Sutterella* respectively. *Lachnospiraceae*, or OTU1, was the only differentially abundant OTU identified as preferentially increased in subjects treated with AAPs. Operational taxonomic units 25 and 32 were preferentially abundant in the group that was not treated with AAPs. As our medication cohorts differed in both age and BMI, we performed linear regressions for the relative abundance of OTUs 1, 25 and 32 between medication groups adjusting for age, BMI, and gender. Only OTUs 1 and 25 remained significant (p=0.001 and p=0.03) after these adjustments.

Due to established associations between of OTU1 (classified to *Lachnospiraceae)* and OTU25 (classified to *Akkermansia*) to metabolic criteria, we further explored the interaction between BMI and AAP-treatments in regards in observed relative abundance (**Figure 3**) [23, 24]. When considering the obese (BMI ≥ 30) and non-obese populations independently, we observed no

appreciable differences in relative abundance of OTU1 between AAP and non-AAP treated populations. When independently comparing obese and non-obese populations for differences in relative abundance of OTU25, we observed no difference between medication groups in the obese population. However, when examining the relative abundance of OTU25 in the non-obese, we observed a significant decrease in OTU25 in those treated with AAPs.

A significant decrease in microbiome community diversity for AAP-treated patients was revealed when calculating the inverse Simpson Diversity index between the medication treatment cohorts (**Figure 4a**; p=0.045). When stratified by gender, we detected a greater decrease in diversity for AAP-treated females compared to non-AAP-treated females (**Figure 4b**; p=0.015). No significant difference in diversity was found in male subjects (**Figure 4c**; p=0.8). Differences in microbiota diversity between the female medication cohorts remained significant after adjusting for age, BMI, and benzodiazepine treatment (p=0.02, β=-4.6, R2=0.12).

Discussion

Although the pathogenesis of AAP-associated metabolic disease is undoubtedly multifactorial, the contribution of the gut to this phenotype is an avenue worth investigating. Our current study revealed a significant separation between fecal microbiota communities and differentially abundant OTUs between the two medication cohorts. Of particular interest, OTU25, *Akkermansia,* was significantly decreased in non-obese patients treated with AAPs. *Akkermansia* is a monotypic genus in the branched phylum *Verrucomicrobia*, with *A. muciniphila* as its only species. *Akkermansia muciniphila* is a mucin degrader in the intestinal tract, and has a notable inverse association with inflammation, insulin resistance, altered adipose metabolism, and atherosclerosis [24-26]. Data suggest that in response to AAPs without increases in BMI, both human and animal models incur metabolic phenotypes, such as glucose dysregulation. [27], This makes the decreased relative abundance of *A. muciniphilia* in non-obese patients notable.

We also observed significant decrease in species diversity for the AAP-treated cohort, a correlation that was stronger in AAP-treated females. Gut species diversity is often cited as a marker of gut health as it is decreased in a number of populations with metabolic syndrome risk factors such as obesity or diabetes[28]. Relevant to our findings, rat models of antipsychotic-induced weight gain and microbiome analysis also show a gender bias in which female rats experience greater weight gain and microbiota community differences than do males[14, 29,30]. Although our cohort was underpowered for male subjects to properly investigate gender

differences in medication response, a previous publication looking at microbiome changes in males observed an increase in gut microbiota diversity in those treated with AAPs[13].

This report contains some clear limitations. Atypical antipsychotic-induced metabolic disease has a greater association with specific agents within this class[7]; however, there was not enough power to examine the effects of specific agents on microbial communities. Generally, the addition of an AAP in BD may indicate increased seriousness of disease, which could also affect the gut microbiota community. In future work, it may be prudent to investigate the effects of this class of medications in different disease cohorts. This report included no information regarding diet, which is an important environmental factor that drives the composition of gut microbiota. In humans, AAPs are thought to induce weight gain through increased appetite[31,32] but this was not borne out in our previous work comparing diets in AAP-treated subjects with schizophrenia and normal controls using the NHANES database[33]. Although the schizophrenia cohort showed an increase in smoking, we found the patients with schizophrenia consumed fewer total calories, carbohydrates, and fats, as well as more fiber ($p < 0.03$) when compared to NHANES controls. Therefore, simply relating the metabolic complications seen from AAP to diet intake fails to truly understand this relationship.

Finally, stool is often sampled to examine gut microbiota due to the ease of collection. However, it is not clear to what degree the composition of fecal microbiota relates to the function of microbiota in the gut and microbiota in the intestinal mucosa. Short-chain fatty acids are metabolic products of microbiome fermentation and the presence of these microbial-derived metabolites has been correlated with many health benefits [34]. Although we did observe medication-specific microbiota differences in our cohort, it is not known how these translate into functional differences from the microbiome communities. In the future, obtaining this information will give us critical insight into how AAP-specific changes in microbiome composition affect microbiome output and ultimately, host phenotype.

In conclusion, these data support our hypothesis that AAP treatment results in measurable differences in gut microbiota composition in a well-characterized group of patients with BD.

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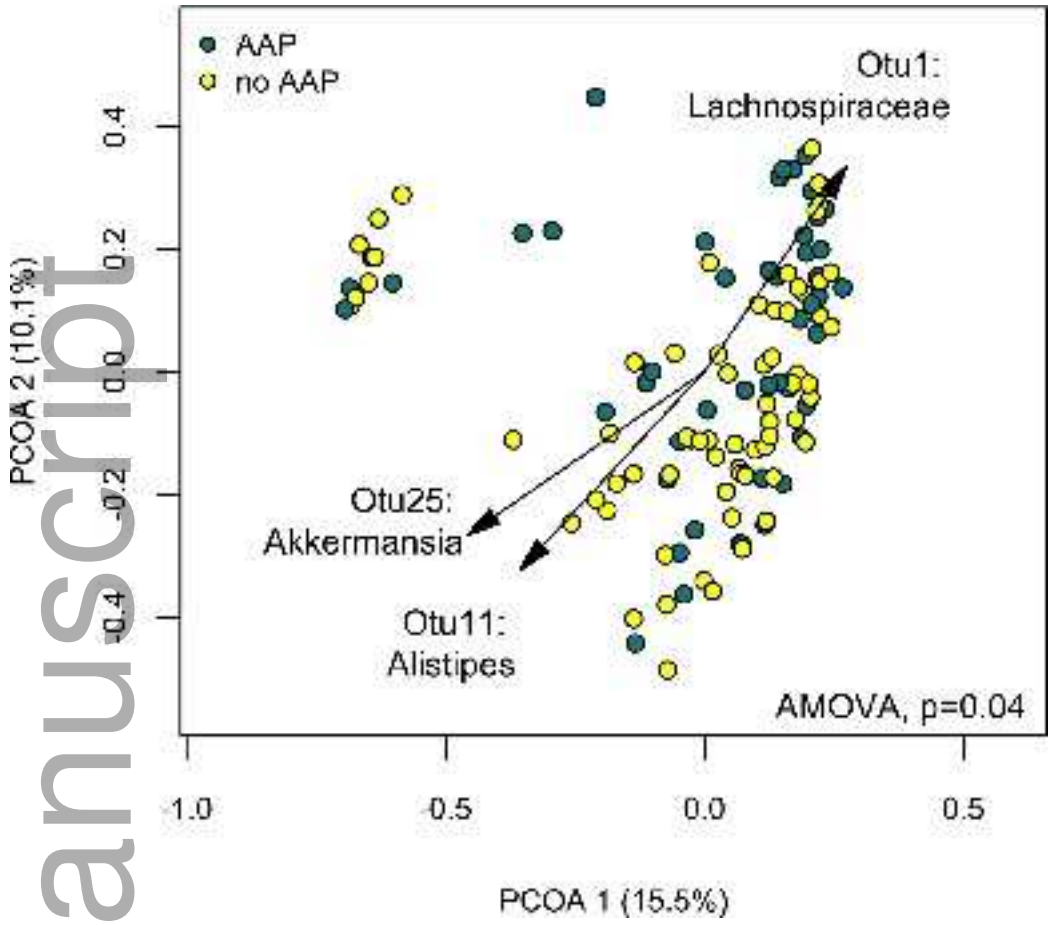
Table 1. Demographic characteristics at Baseline?

	No-AAP[a] N (%) or Mean (SD)	AAP[a] N (%) or Mean (SD)	p value
Gender			
Female	48	34	0.82
Male	21	12	
Age in years (SD)	51.7 (13.5)	46 (12)	0.02
Body Mass Index (SD)	27.5 (6)	31 (7)	0.006
Body Mass Index corrected by age and gender			0.04
Medications			
Antidepressant[b] (%)	26 (38)	26 (53)	0.16
Mood Stabilizer[c] (%)	32 (47)	28 (57)	0.37
Lithium (%)	20 (29)	11 (22)	0.53
Benzodiazepine[d] (%)	13 (19)	19 (39)	0.03

[a]AAP-atypical antipsychotic=clozapine, olanzapine, risperidone, quetiapine, asenipine, ziprasodone, lurasidone, aripiprazole, paliperidone and iloperidone; [b]Antidepressant = bupropion ,venlafaxine, sertraline, duloxetine, fluoxetine, citalopram, escitalopram; [c]Mood Stabilizer = topiramate, phenobarbitol, lamotrigine, gabapentin, divalproex sodium, carbamazepine; [d]Benzodiazepine = lorazepam, alprazolam, temazepam, clonazepam, diazepam.



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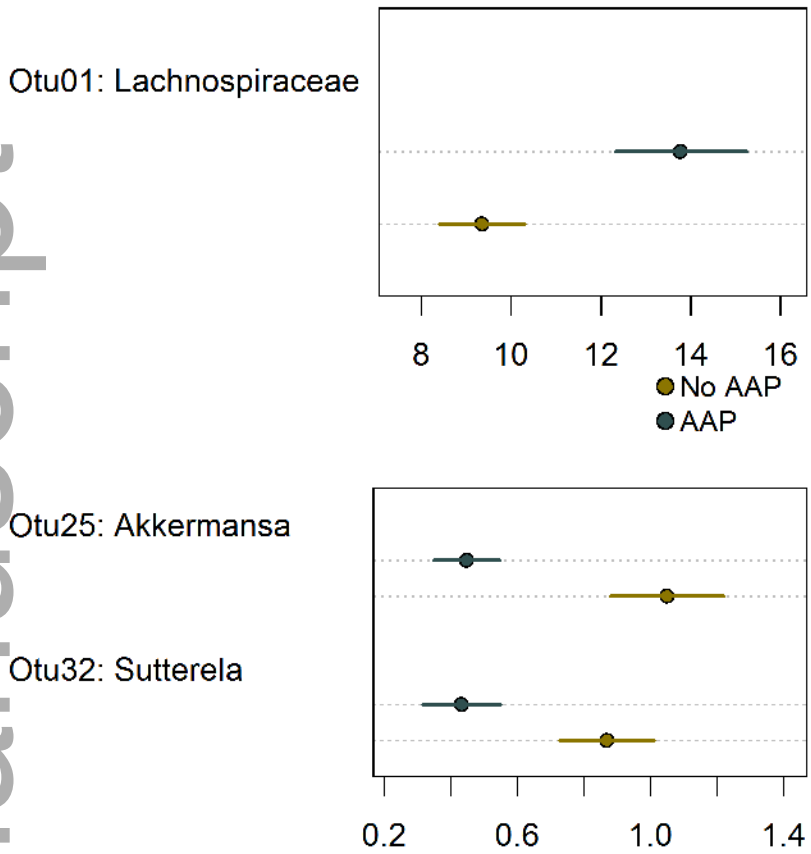

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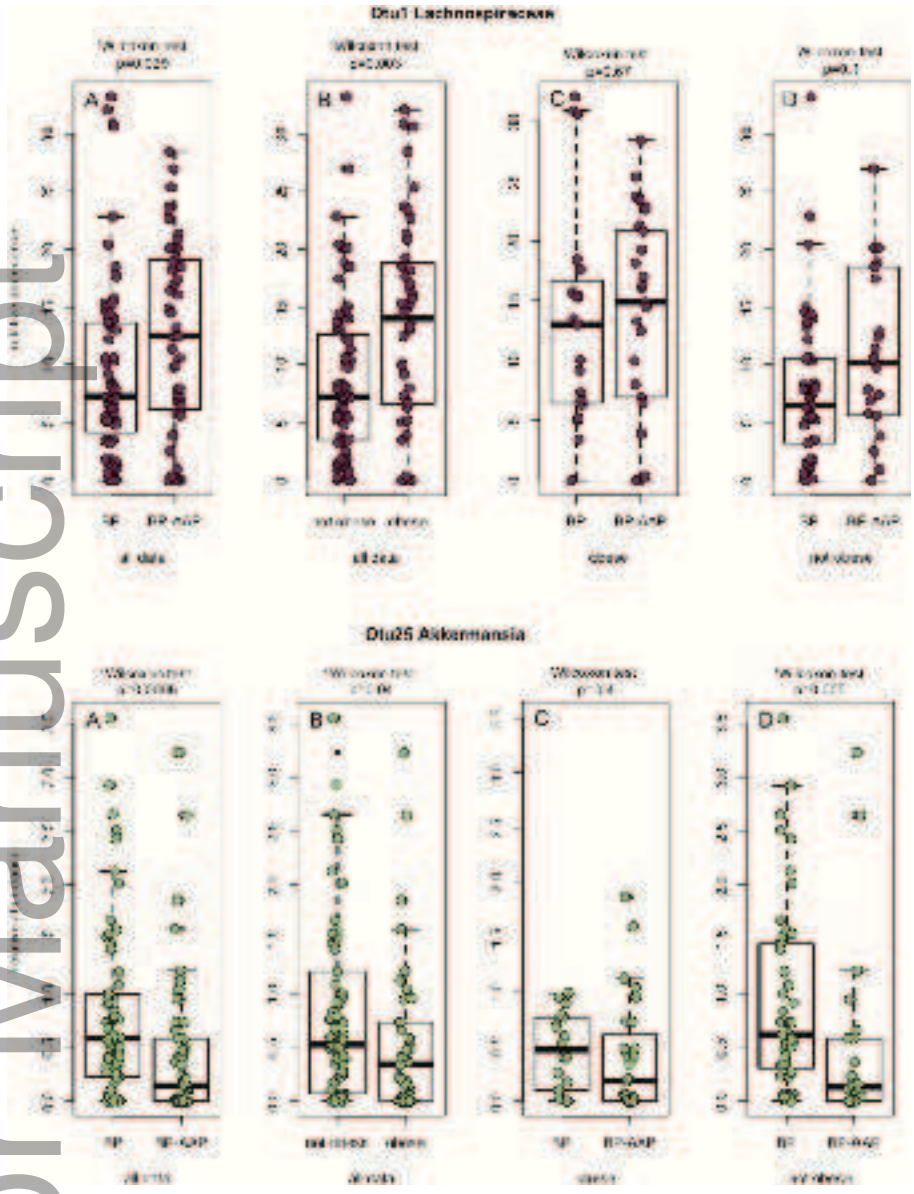

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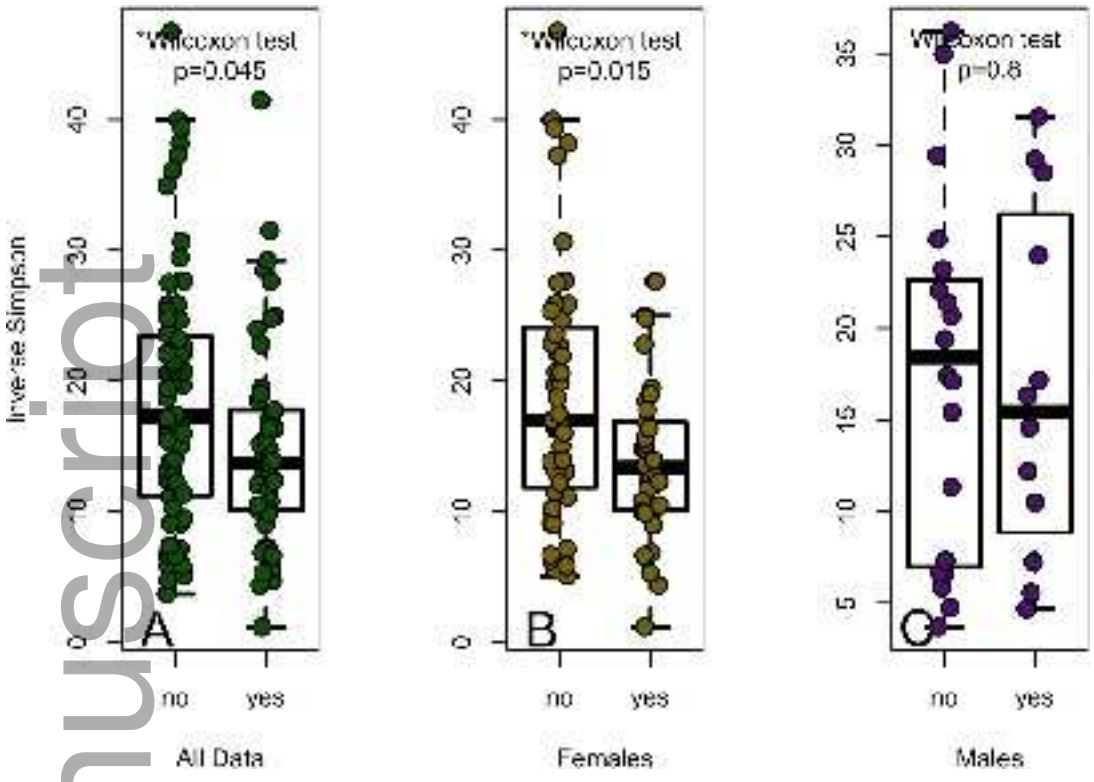

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