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Perinatal and Direct Bisphenol A Exposure Shape Gut Microbiota and Behavior in a Sex-Specific Manner In mice

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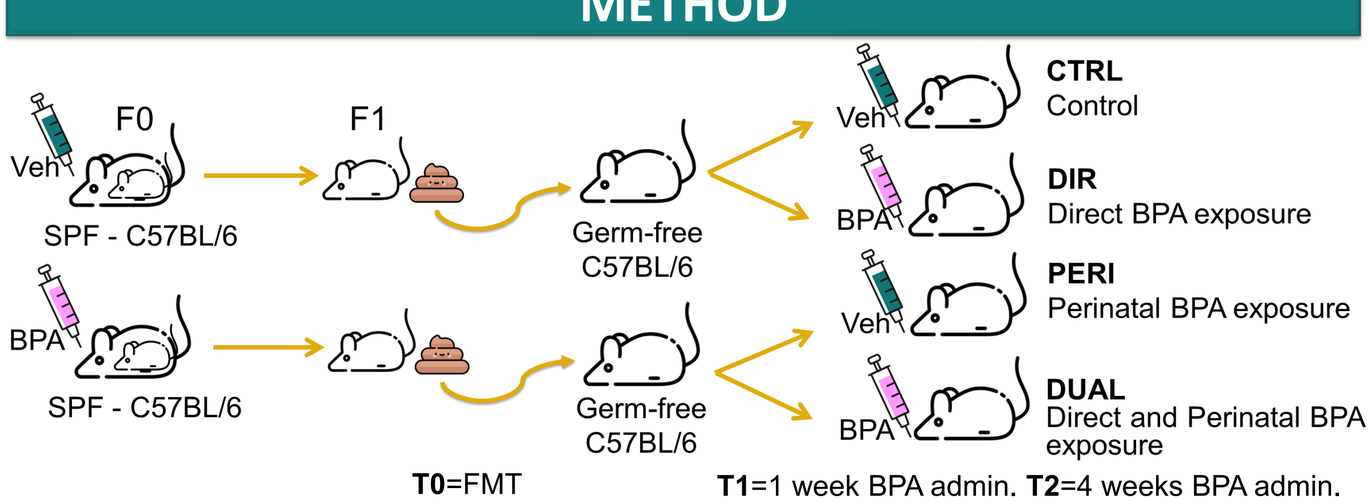
INTRODUCTION & AIM

The global rise in childhood obesity appears to parallel the increased environmental exposure to endocrine-disrupting chemicals. Among them, **bisphenol A** (BPA) has been increasingly linked to obesity and other chronic diseases. Early-life exposure to such contaminants is particularly concerning, being critical for gut microbiota development and long-term host health. We previously showed that perinatal BPA exposure combined with a high-fat diet increase body fat percentage in offspring. Here, we investigate whether **BPA-induced alterations in the microbiota are sufficient to drive obesogenic effects or whether direct BPA exposure is required**.

METHOD



RESULTS & DISCUSSION

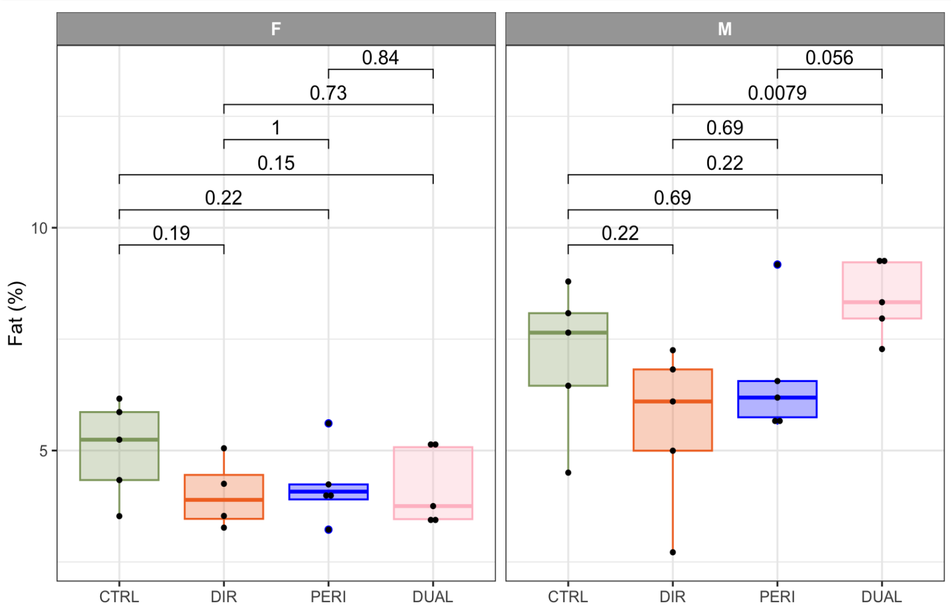


Figure 1. MRI assessment of mice body composition, showing the percentages of fat (%). Female (F) and Male (M).

Males from the DUAL group had a **higher fat percentage** compared to the DIR and PERI groups, although the difference was not significant when compared to the CTRL group.

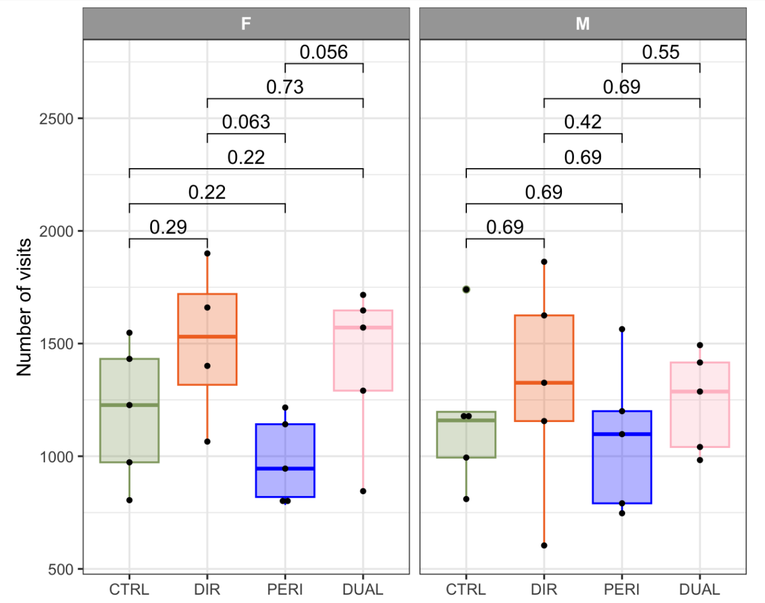


Figure 2. Behavioural activity monitored through Intellicage® system. Number of visits: N° of visits recorded during the 23-day experiment. Initial activity: N° of visits within the first half hour of the experiment.

Mice exposed to direct BPA (DIR and DUAL) exhibited **increased activity and anxiety-like behaviour**. However, during initial activity, females perinatally exposed (PERI and DUAL) displayed reduced exploratory behaviour.

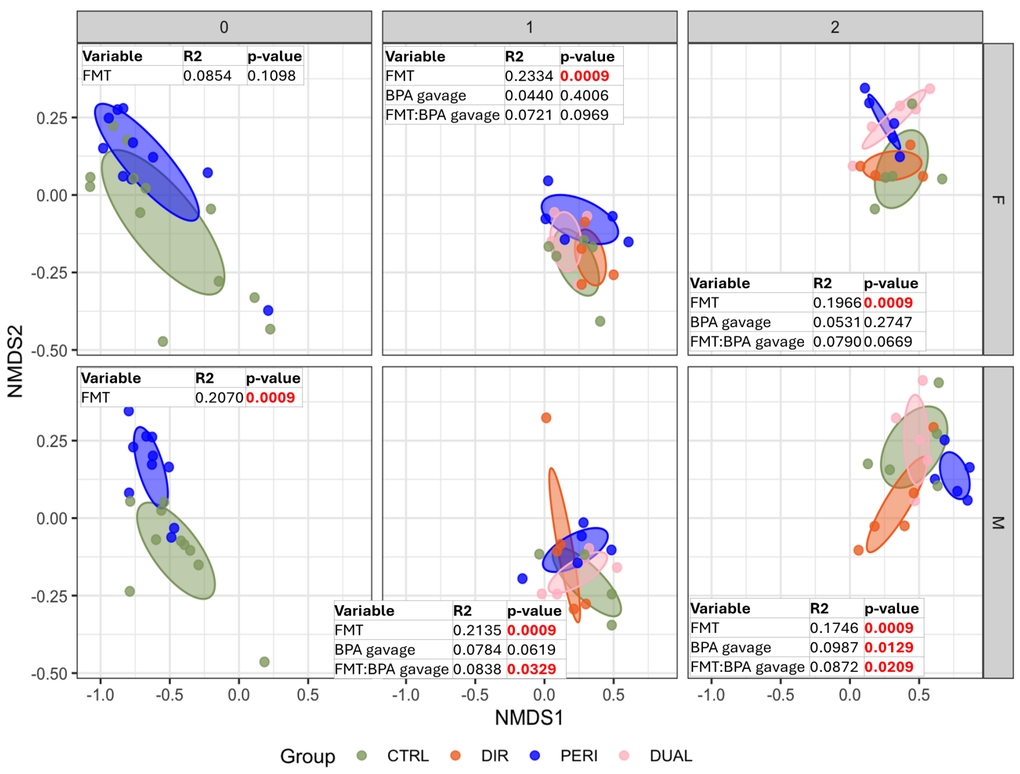


Figure 3. Nonmetric multidimensional scaling (NMDS) plot based on Bray-Curtis dissimilarity, showing samples by time point and sex. PERMANOVA results are shown in the plot.

Perinatal BPA exposure had an impact on microbiota composition, both after one week and four months of administration. In males, direct BPA exposure significantly altered microbiota composition after four months, and a synergistic effect between BPA perinatal and direct exposure was observed.

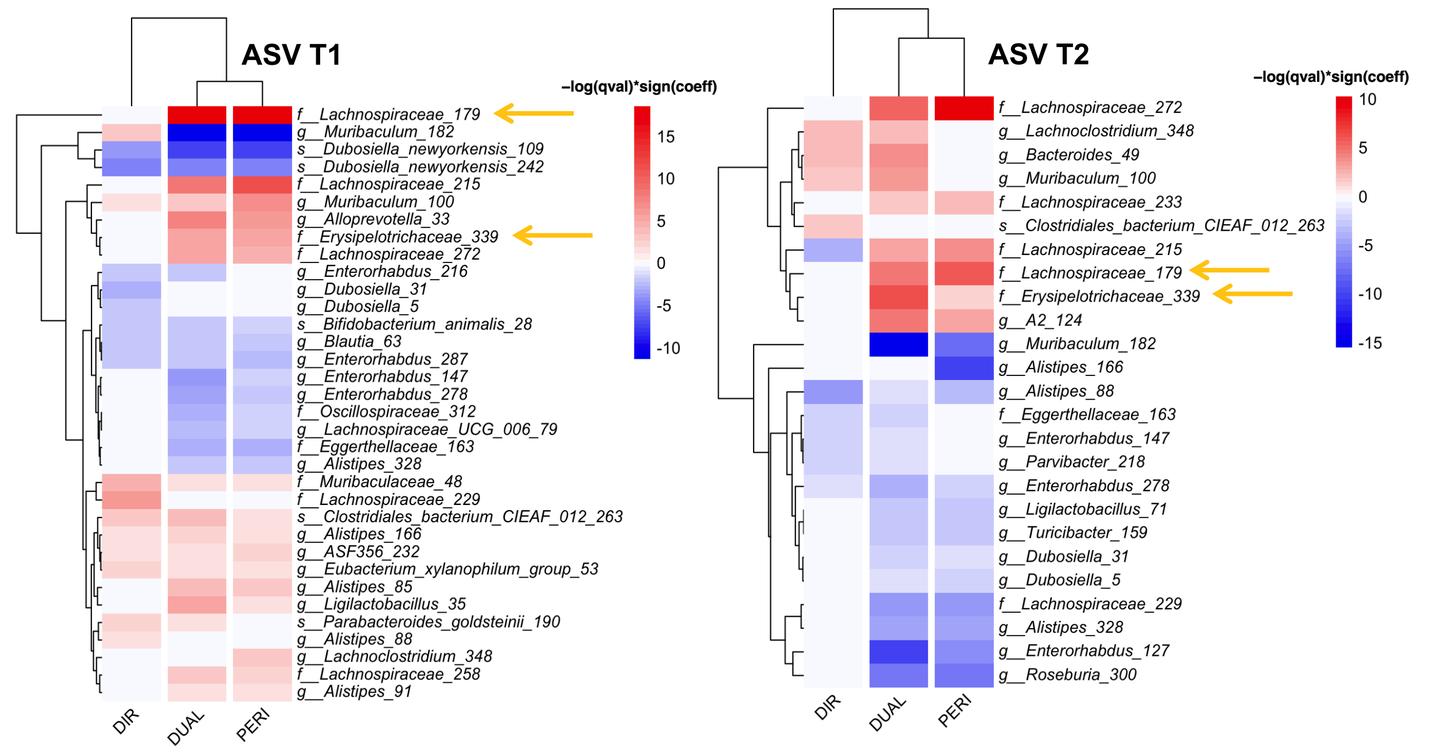


Figure 4. Heatmap showing ASVs with significant abundance changes between CTRL and other study groups at T1 and T2 through a Microbiome Multivariate Association with Linear Models (MaAsLin2). An increase in relative abundance is indicated in red, while a decrease is shown in blue.

Several ASVs were significantly increased or decreased in the experimental groups compared to the CTRL group. Interestingly, greater microbial variation was observed in the DUAL and PERI groups relative to CTRL. Notably, some ASVs emerged as potential microbial markers, such as ***Erysipelotrichaceae* (339) and *Lachnospiraceae* (179), which were consistently increased in the BPA perinatally exposed groups** (PERI and DUAL) at both time points.

CONCLUSION

This study provides evidence that **perinatal BPA exposure has a lasting and stronger effect on gut microbiota** composition than direct exposure, particularly in males. While altered microbiota alone did not trigger obesity, it may contribute to sex-specific physiological and behavioural changes.

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