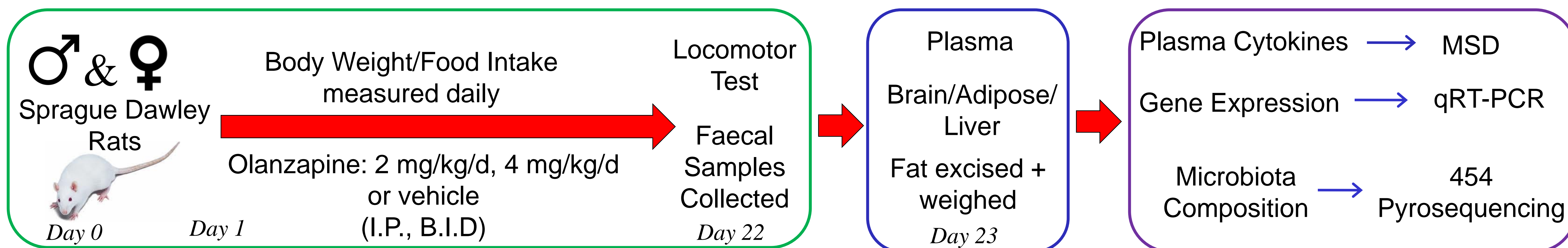


## Introduction

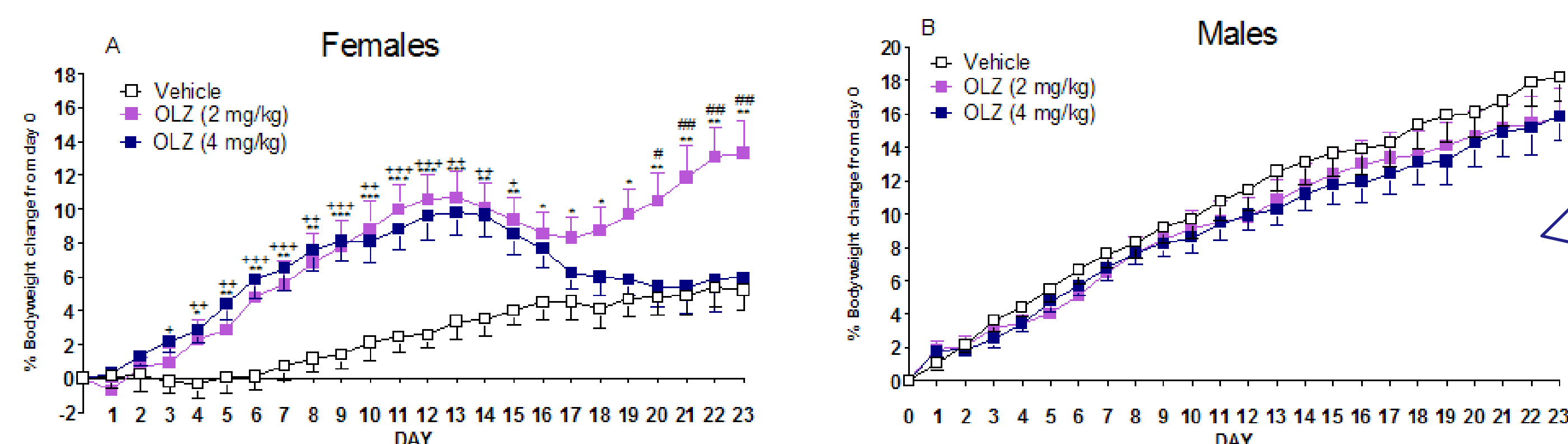
Olanzapine is an atypical antipsychotic used commonly in the treatment of schizophrenia and other psychiatric disorders. Olanzapine however is associated with a serious side-effect profile comprising weight gain, inflammation, metabolic dysfunction and ultimately an increased risk of type II Diabetes Mellitus and cardiovascular diseases (1). Moreover, increased susceptibility to these side-effects is often reported for females (2). The mechanisms underlying these side-effects and the possible gender differences in their occurrence are currently unclear, and evidence suggests both central and peripheral actions of the drug are involved. The gut microbiota has been realised in recent times as a major contributor to body weight regulation and metabolism (3). Therefore, we investigated possible gender differences in some of the side-effects of olanzapine including possible changes to the gut microbiota.

## Methods



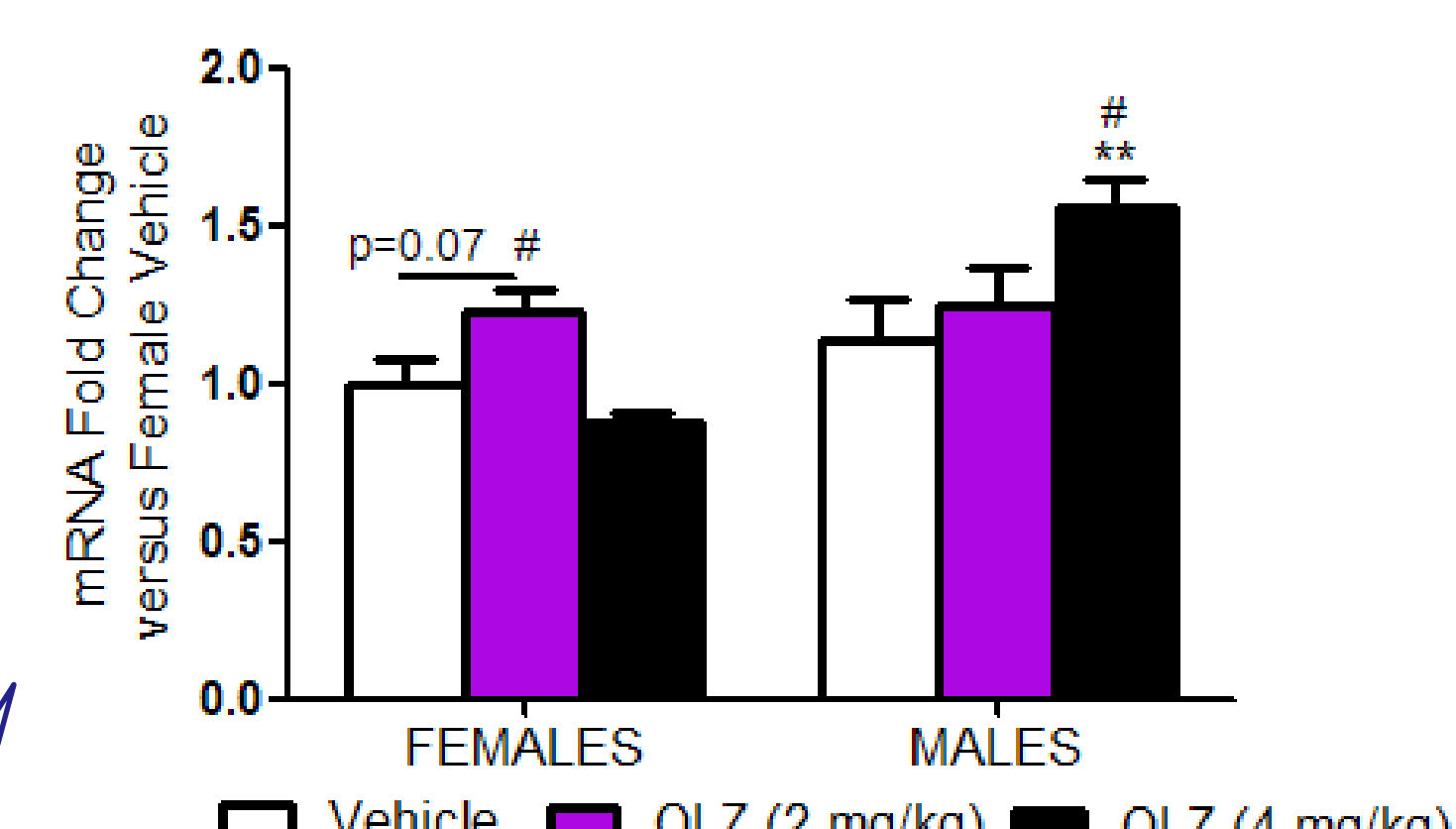
## Results

### 1. Body Weight Gain



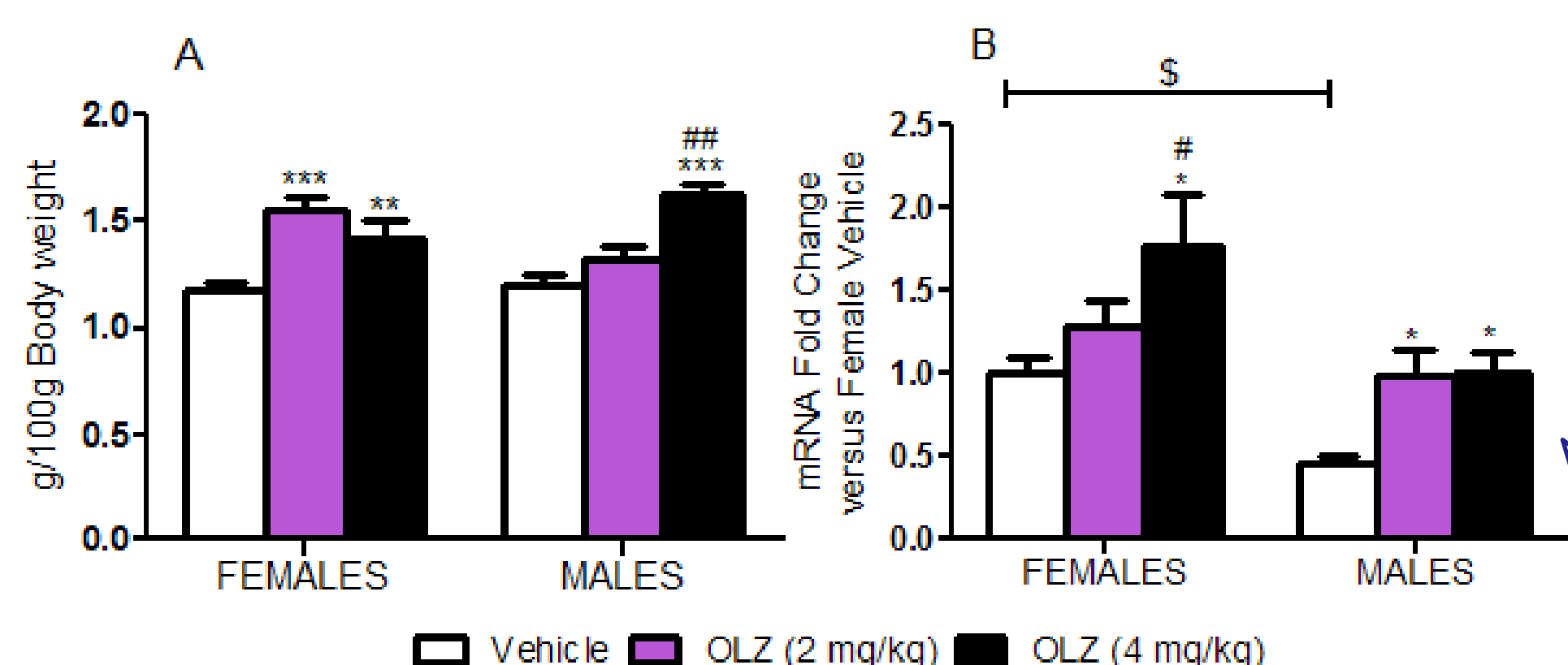
Olanzapine (OLZ) induced rapid weight gain in the female rats (A) though not in males (B). In the females weight gain subsided at the higher dose after day 13.

### 2. Hypothalamic Ghrelin Receptor 1a



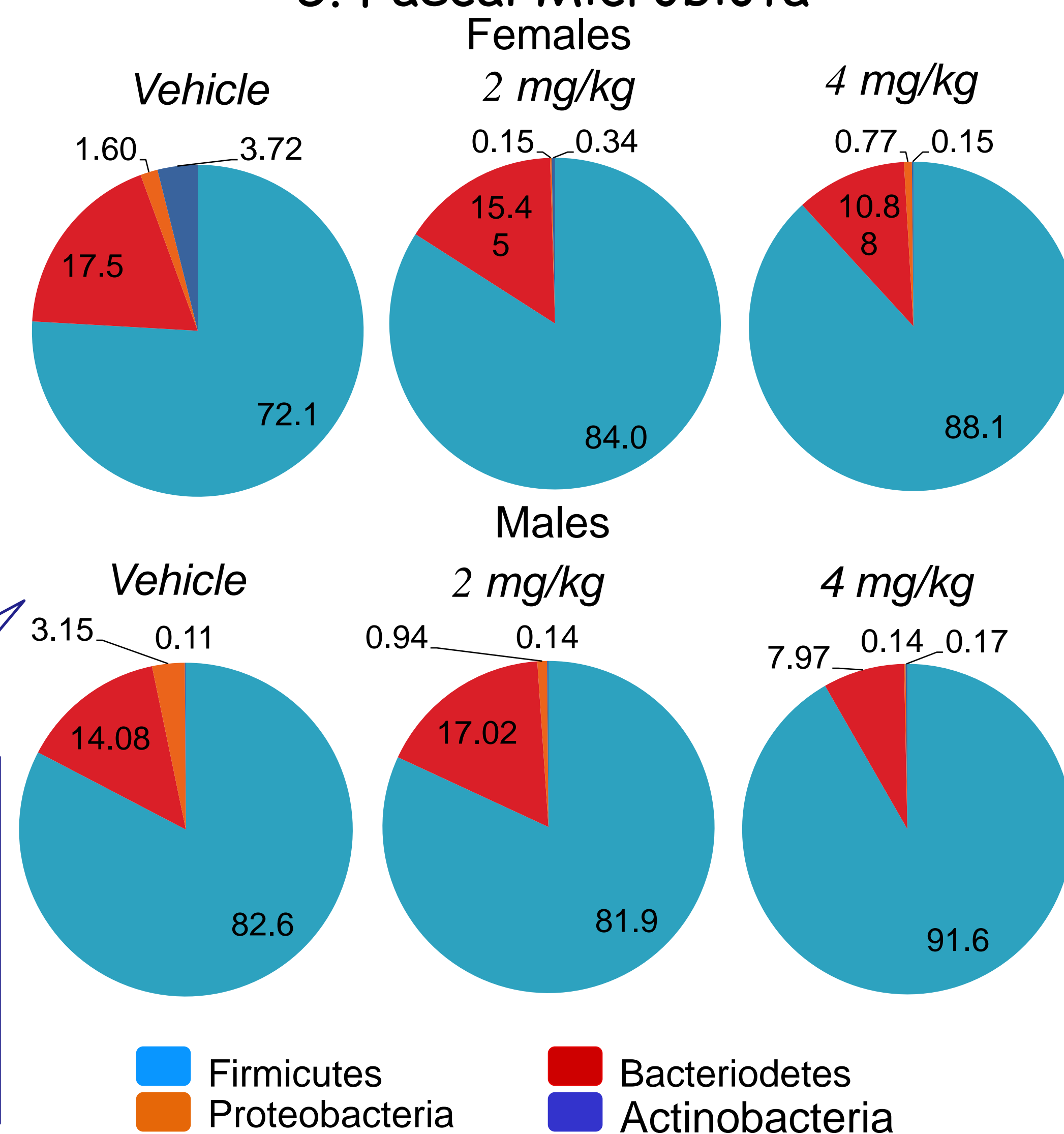
Olanzapine caused increased hypothalamic ghrelin receptor expression in the females at 2 mg/kg and the males at 4 mg/kg

### 3. Visceral Fat and CD68 Expression



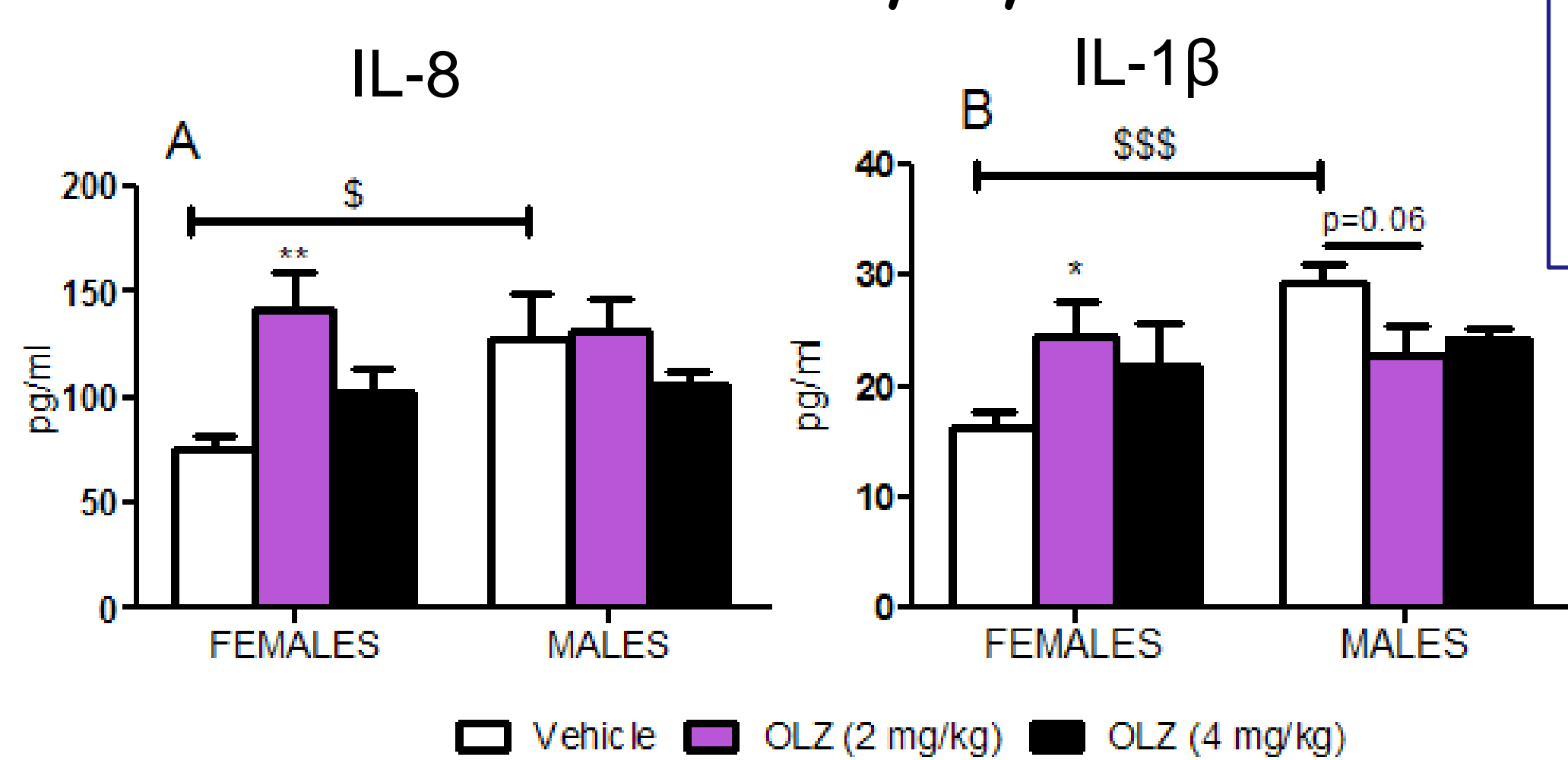
(A) Olanzapine caused increased visceral fat mass in the females at both doses and in the males at the higher dose. (B) Olanzapine treatment caused increase expression of CD68 indicating macrophage infiltration

### 5. Faecal Microbiota



Olanzapine treatment resulted in changes to the major phyla with increased levels of *firmicutes* and decreased *bacteroidetes*. This was seen in females at both doses, and in males at the higher dose

### 4. Proinflammatory Cytokines



Weight gain was associated with increased circulating levels of (A) Interleukin-8 and (B) Interleukin 1-beta

## Conclusions

- We have shown for the first time that the microbiota profile is altered following antipsychotic treatment. While preliminary, these data suggest that changes to the gut bacteria may be involved in, or exacerbate, the metabolic complications associated with olanzapine treatment
- Evidence of non-weight related effects emphasises the need to consider the double-threat posed by drugs such as olanzapine

- Central effects of ghrelin may also be important for not only the feeding alterations associated with olanzapine but also for peripheral effects such as increased visceral fat
- The gender differences in both baseline and olanzapine-induced changes lends support to the theory that gender should be an important consideration in antipsychotic use at the clinic, in particular in relation to patient monitoring

## Acknowledgements

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