



## Pre-conceptional maternal metabolic status influences hepatic metabolome in male offspring

Sofiane Safi-Stibler, Delphine Rousseau-Ralliard, Mélanie Jouin, Luc Jouneau, Claudine Junien, Etienne Thevenot, Christine Baly, Anne Gabory

### ► To cite this version:

Sofiane Safi-Stibler, Delphine Rousseau-Ralliard, Mélanie Jouin, Luc Jouneau, Claudine Junien, et al.. Pre-conceptional maternal metabolic status influences hepatic metabolome in male offspring. World congress developmental origins of health and disease (DOHAD) 2019, Oct 2019, Melbourne, Australia. , 2019. hal-02408206

**HAL Id: hal-02408206**

**<https://hal.science/hal-02408206>**

Submitted on 5 Jun 2020

**HAL** is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

## State of the art

Since the 1980's we observe an obesity pandemic [1]. According to the Developmental Origin of Health and Disease (DOHaD) concept, the nutritional environment has an important impact during early development and may influence long term health [2]. This leads to the later onset of non communicable diseases [3]. Obesity causes fertility troubles and obstetrical complications as well as metabolic syndrome in the offspring [4]. Worldwide, 55% of women aged 18 years and over are overweight or obese [5], this is therefore a major public health issue. In order to reduce those effects, recommendation for overweight or obese women planning a pregnancy, is to lose weight before conception [6]. But, because of a lack of interventional studies, the effect on long term health of the offspring has yet to be determined [7].

The **TPMP project** (Trajectoires Pondérales Maternelles Préconceptionnelles; Preconceptional Maternal Weight Trajectories) aim to identify:

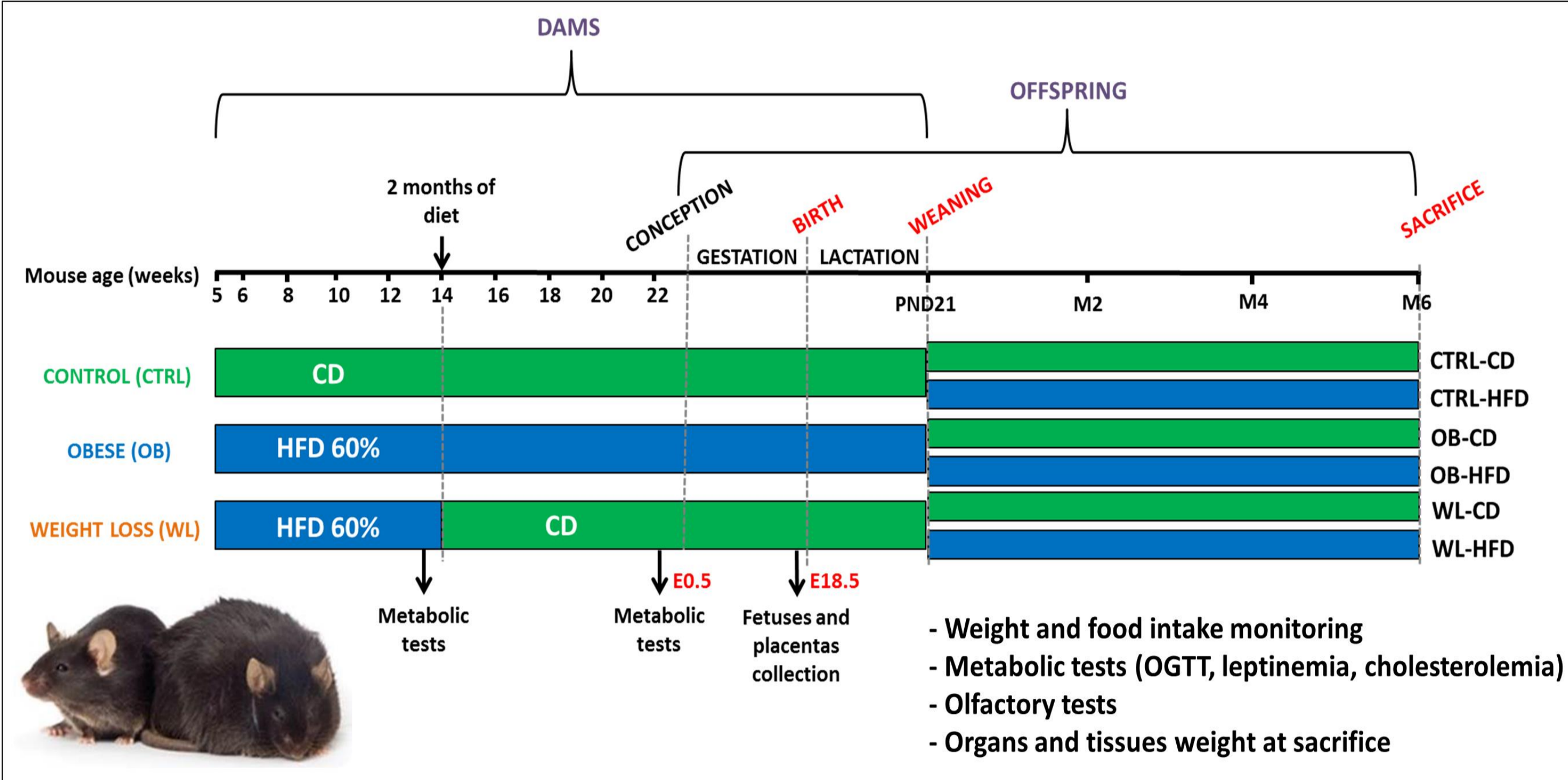
- how maternal obesity prior to conception can lead to metabolic syndrome at the adult age.
- weather maternal weight loss before conception can mitigate these affect and normalise the metabolic status.

A mouse model was developed to study foetus and offspring phenotype and molecular mechanisms.

**At the end of gestation, OB fetuses are lighter than CTRL, with an increase incidence of small for gestational age (SGA) phenotype (odd ratio = 3.2). The phenotype of WL fetuses is completely normalised.** Preconceptional weight loss appears beneficial for foetal and post-natal growth, but some effects of previous obesity were retained in offspring transcriptome [8].

**At the adult age, HFD offspring developed an obesity phenotype and OB male offspring showed a worsening of obesity when fed a HFD. The phenotype of WL offspring is similar to CTRL, excepted for olfactory sensitivity which is reduced [9].**

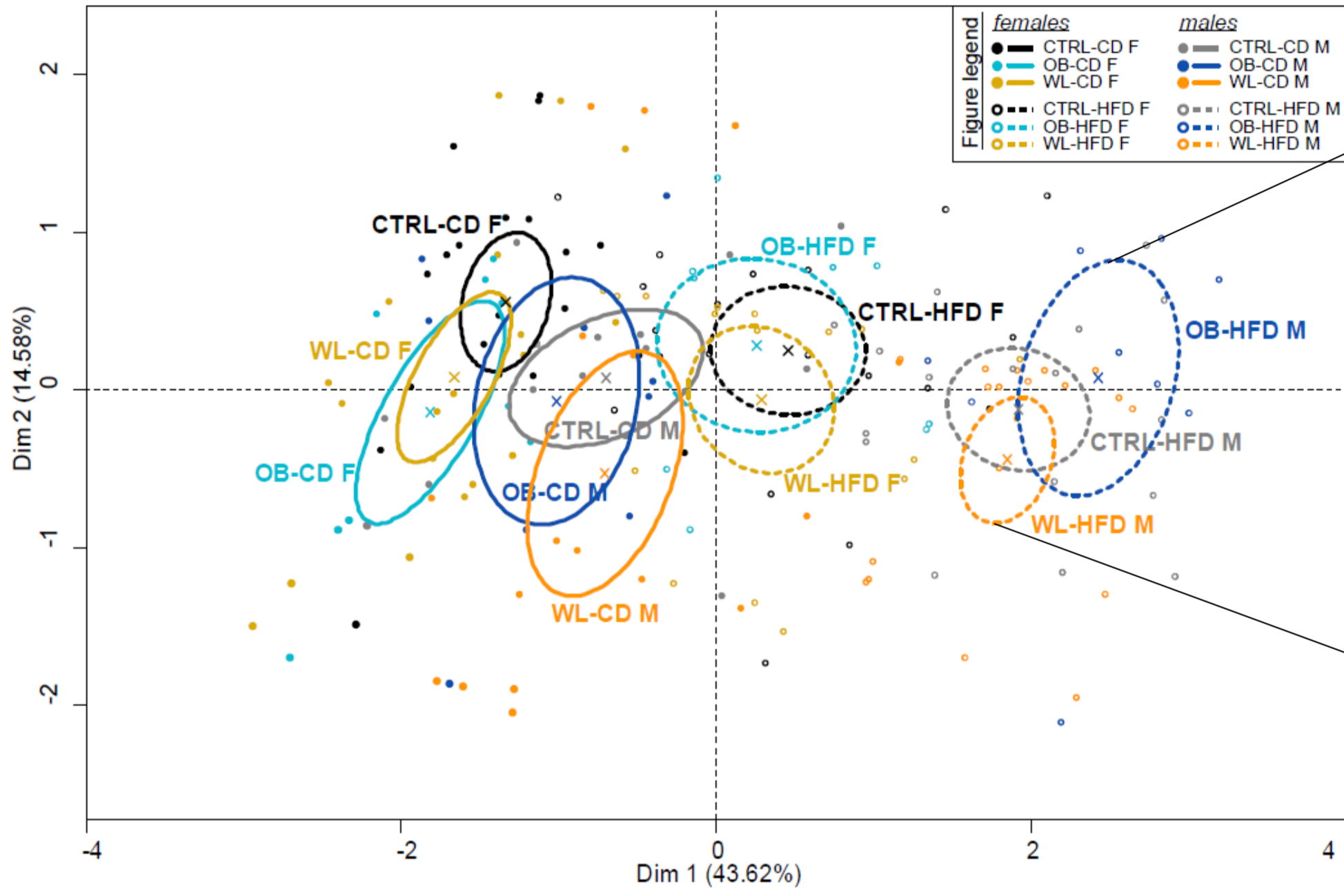
**To analyse deeper the offspring phenotype, we performed a metabolomics analysis** on male liver, olfactory bulb and hypothalamus, with Liquid Chromatography – High Resolution Mass Spectrometry (LC-HRMS).



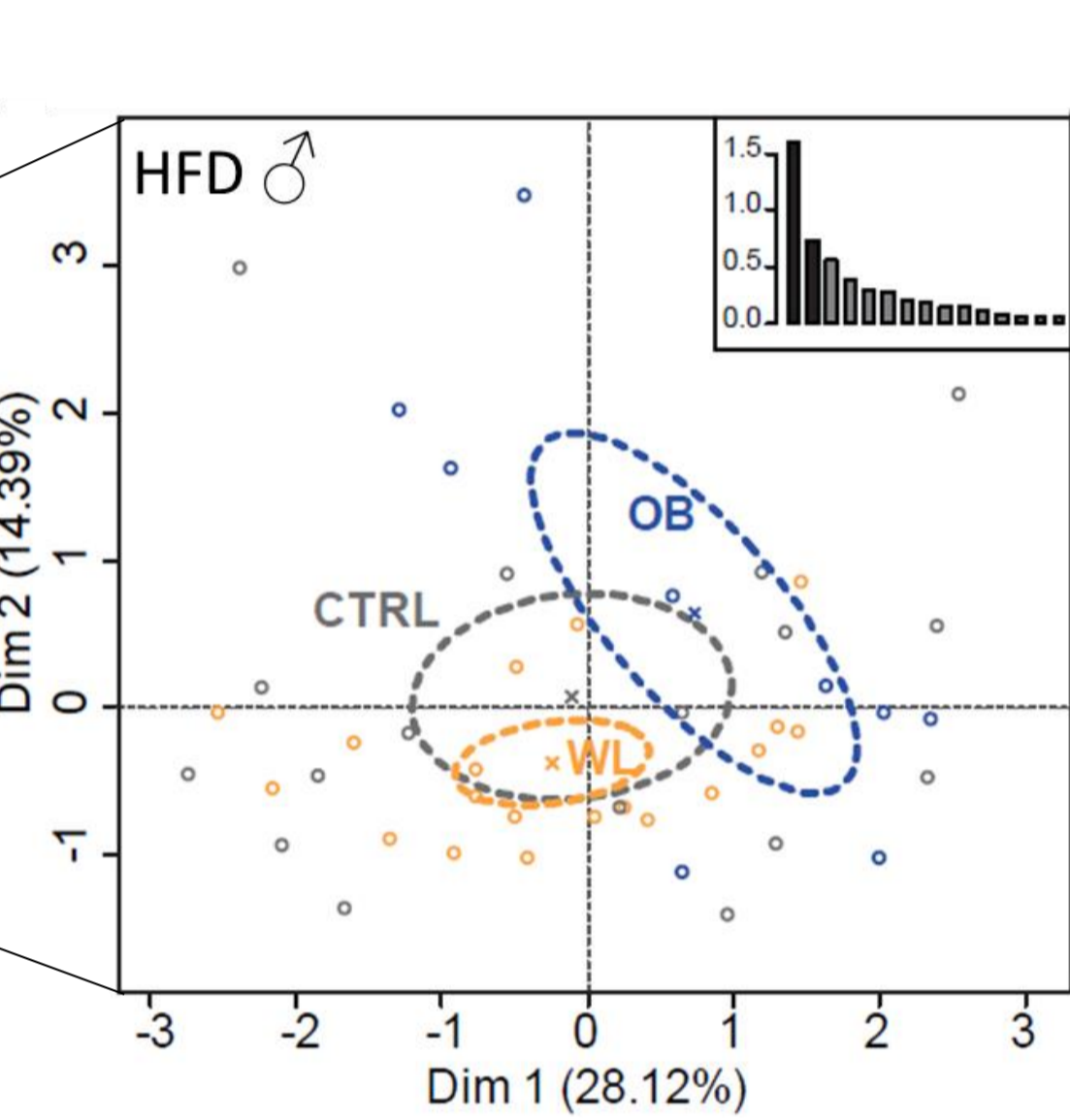
## Results

### Multiple Factorial Analysis (MFA): impact of maternal group in HFD males

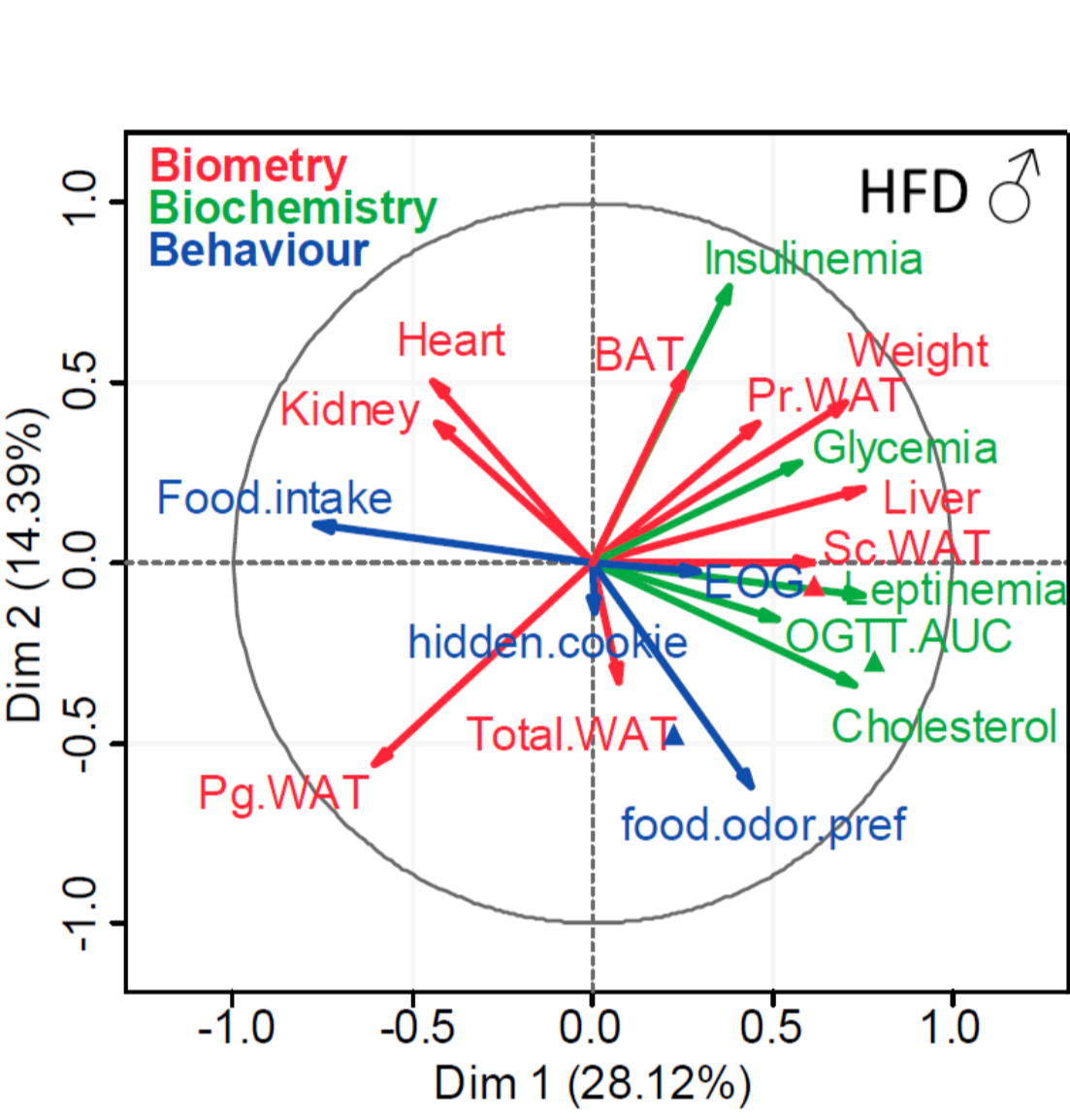
#### 1 – Impact of post-weaning diet and sex



#### 2 – Impact of maternal group

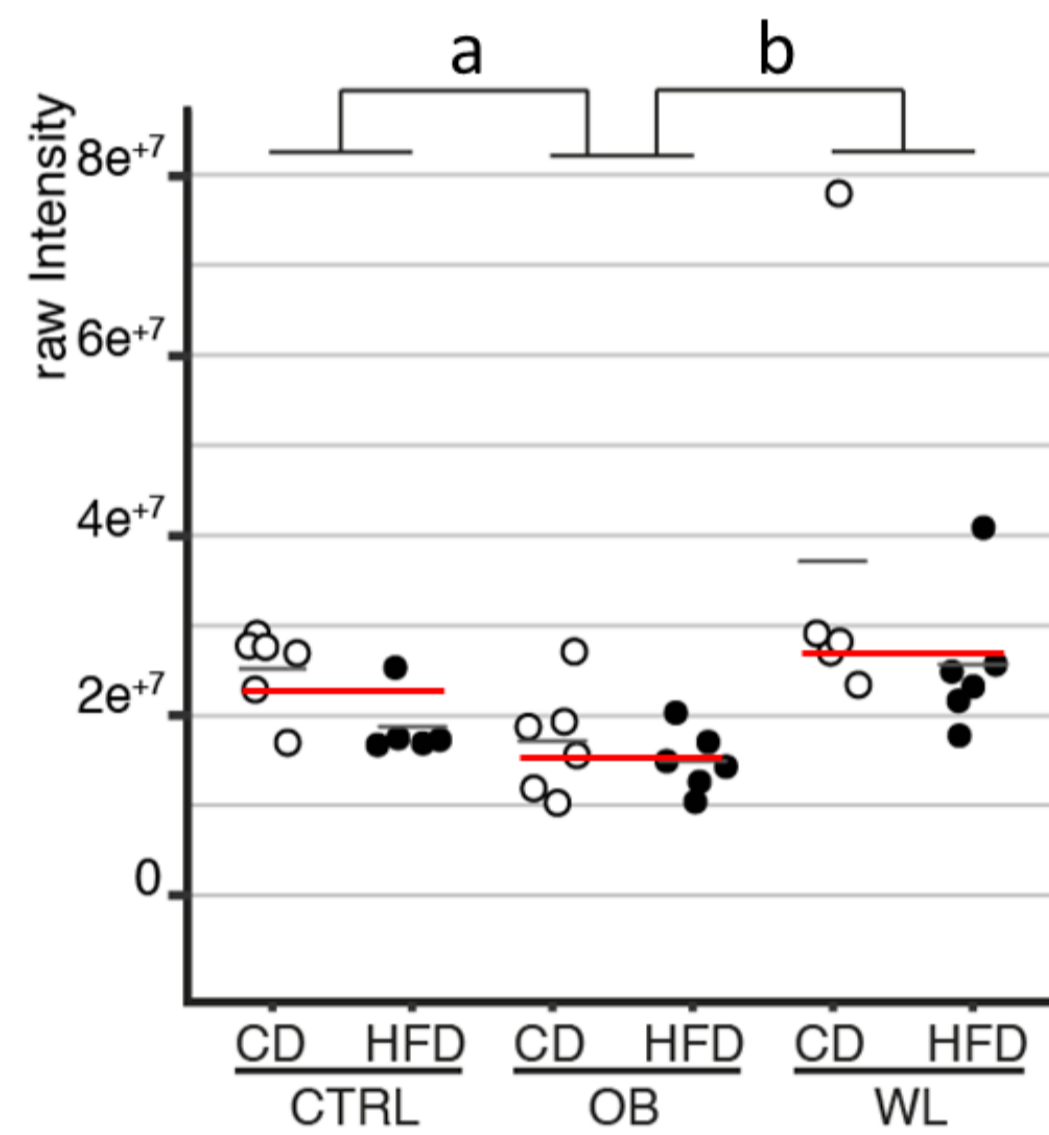


#### 3 – Phenotypic deregulation



### Maternal obesity programmed anserine abundance in the liver

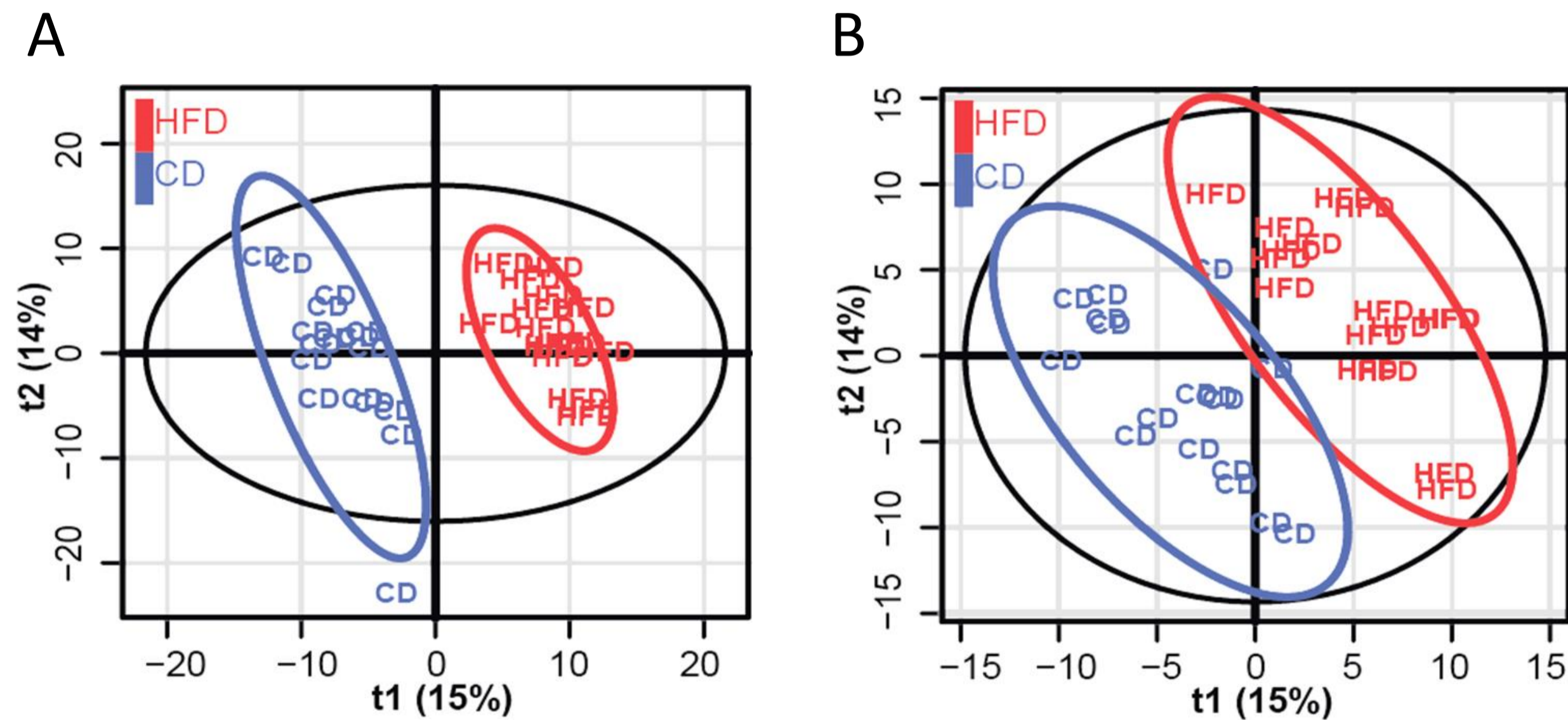
#### 4 – Impact of maternal group on anserine abundance



**4 – Abundance of anserine** is lowered in context of **maternal obesity (OB)** compared to CTRL, revealing a programming effect of maternal obesity on anserine abundance. In the context of **maternal weight loss (WL)** there is a normalization of anserine abundance. 2-ways ANOVA, FDR < 0,05 ; a: CTRL vs OB ; b: WL vs OB

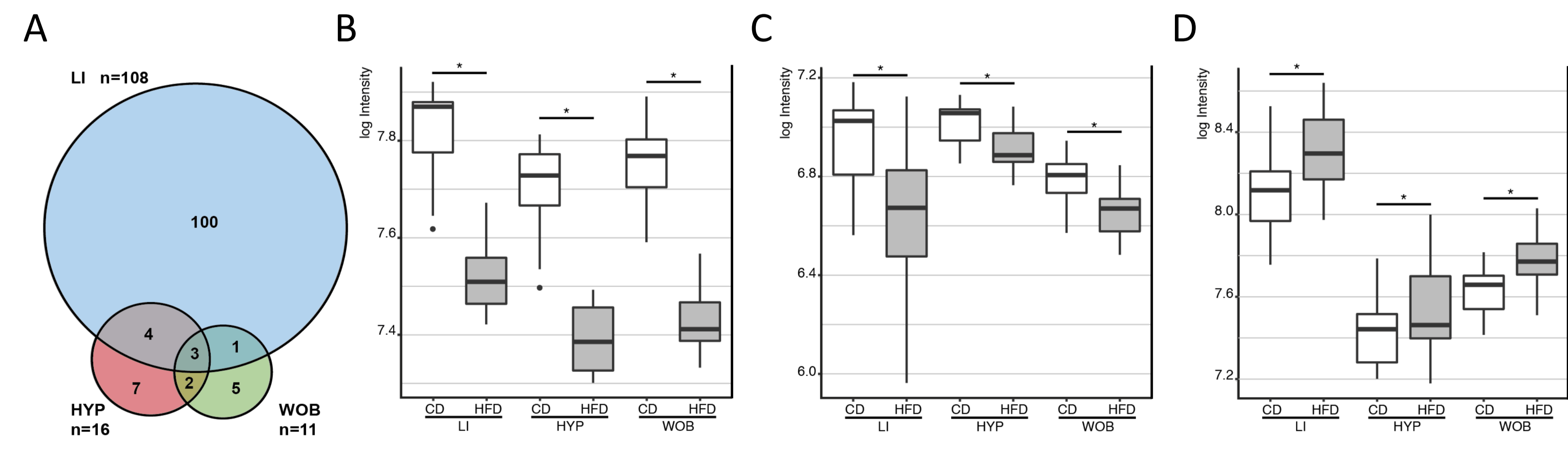
### Post-weaning diet is the main actor of metabolic differences

#### 5 – PLS-DA model : global impact of HFD on liver (A) and hypothalamus (B)



**5 – Post weaning diet** have a global impact on **liver and hypothalamus** metabolites abundance. **Maternal group** have no global impact on metabolites abundance. No model was built for olfactory bulb. p = 0.001

#### 6 – Significant HFD-impacted metabolites (A) and metabolites shared by all three tissues (B, C, D)



**6 – (A) Post-weaning diet** causes metabolites abundance differences (2-ways ANOVA, p-value fdr corrected <0,05). Interestingly, there are three metabolites whose abundance varies in the three tissues : **(B) 1,5-Anhydroglucitol** (HFD/CD=0,48), **(C) Saccharopine** (HFD/CD=0,7) and **(D) β-Hydroxybutyric acid** (HFD/CD=1,5 to 2). \*: CD vs HFD

## Discussion

In our model, we highlight the **dominant effect of post-weaning diet** upon maternal metabolism on phenotype. However, an effect of maternal group is significant and can participate to the offspring phenotype. The MFA study shows an impact of maternal group on HFD males only, with OB and WL males that separates from each other but not from CTRL. The actors of this difference are mainly biometry and physiology variables even if there is a participation of behavior variables on OB/WL differences. LC-HRMS study on HFD males liver, hypothalamus and olfactory bulb reveal a major effect of post-weaning diet on metabolites profiles and a small effect of maternal group.

In the liver, maternal obesity programmed a reduction of **anserine** abundance, while preconceptional weight loss normalize it. Anserine alimentary supplementation reduced NAFLD in a context of HFD [10]. Therefore, in our model, the programmed reduction of anserine can explain the conditioning effect of maternal obesity on HFD-fed males, leading to a worsening of obesity.

There is a **global impact of HFD on liver and hypothalamus metabolome**, as revealed by PLS-DA, while 2-ways ANOVA revealed an **impact of HFD in all three tissues**. This impact occurred mainly on amino-acids metabolism, revealing an implication of amino-acids metabolism in a fasting state in individuals under chronic HFD. Interestingly, three of the impacted metabolites were discriminant in the three tissues: **1,5-anhydroglucitol**, is a glycaemic marker in diabetes context [11], produced by the liver and transmitted to the rest of the organism via the blood stream [12]. This pictures the direct effect of HFD on metabolism, leading to metabolic disorders. **Saccharopine** is an intermediate of lysine catabolism [13], and may lead to the production of hydroxybutyrate in a context of moderate fasting in individuals under chronic HFD. **β-hydroxybutyric acid**, is a ketone body, allowing energy production in a context of fasting. Moreover, this metabolite is a signal of energy deficit [14] and have a negative action over glutamate and GABA production in the brain [15]. Those effects may lead to the establishment of a **vicious circle**, increasing food intake and participating in obesity development.

This study reveals the interest of maternal weight loss, reversing the maternal obesity programming effect on anserine abundance in the liver, which is linked to a reversion of the obesity worsening of HFD-fed males born to obese mother. We also reveal here that the post-weaning diet has a major effect upon maternal weight trajectories on phenotypic parameters and metabolome of the offspring. Thus, establishing an healthy dietary environment for the future generations should be one of the major goal to achieve.

#### References:

- [1] Ng et al., Lancet. 2014 Aug 30;384(9945):766-81
- [2] Barker et al., Lancet. 1989 Sep 9;2(8663):577-80.
- [3] Hanson and Gluckman, Physiol Rev. 2014 Oct;94(4):1027-76.
- [4] Hochner et al., Circulation. 2012 Mar 20;125(11):1381-9.
- [5] WHO report, 2016.
- [6] Haute Autorité de Santé. 2011.
- [7] Forsum et al., Food Nutr Res. 2013;57.
- [8] Panchenko et al., Clin Epigenetics. 2016 Feb 27;8:22.
- [9] Panchenko et al., Nutrients. 2019.
- [10] Chen et al., J. Agric. Food Chem. 2017
- [11] Kim and Park, Endocrine 2013
- [12] Yamanouchi et al., Diabetes 1986
- [13] Papes et al., Biochem. J. 1999
- [14] Rojas-Morales et al., J. Cell. Sig. 2016
- [15] Juge et al., Neuron. 2010