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Effect of maternal obesity and preconceptional weight loss on foeto-placental growth and offspring health in mice: expression of epigenetic modifiers at the interface with metabolism

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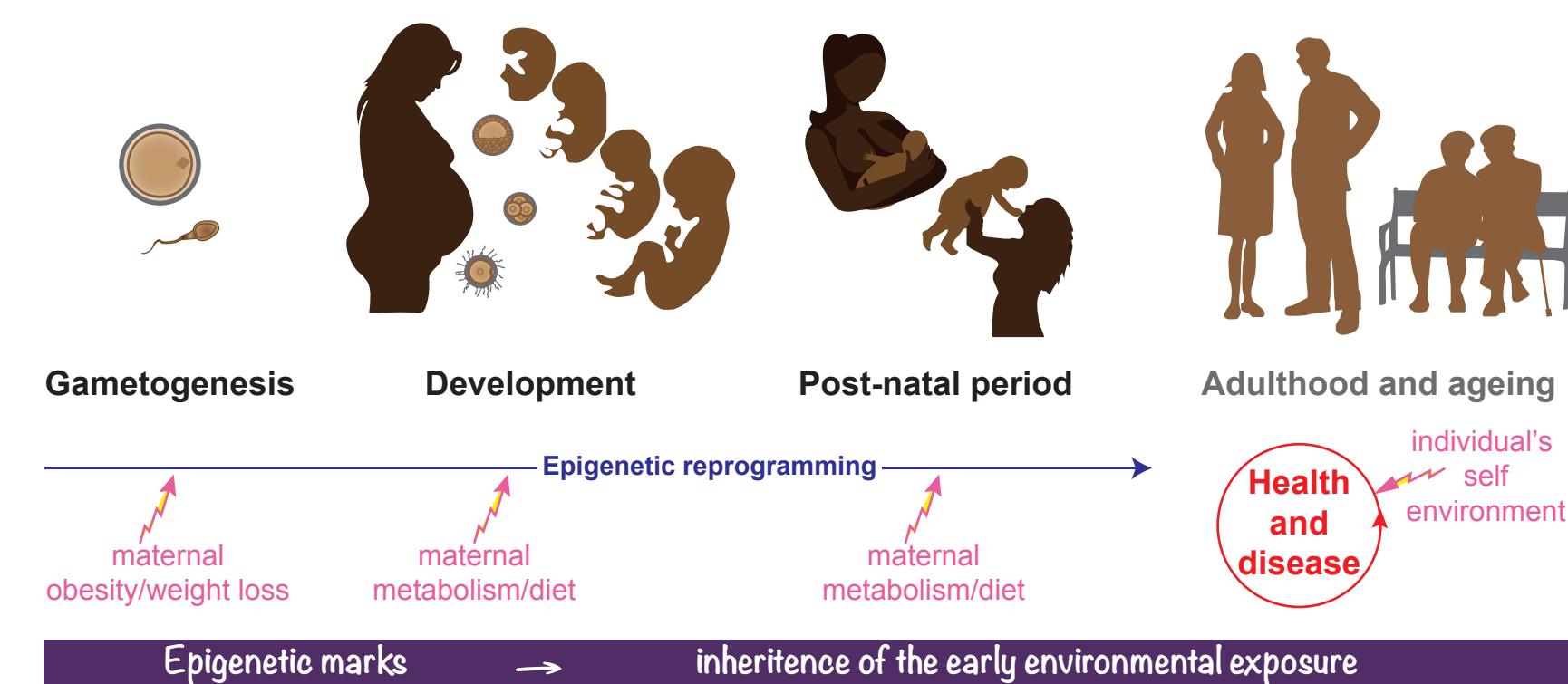
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Introduction: intergenerational transmission of obesity ... what about preconception weight loss?

Maternal obesity is associated to a wide range of fertility troubles, obstetrical and gestational metabolic complications [1]. The babies are also at risk for stillbirth, growth phenotype (small or large birthweight), congenital malformations [2-4]. Moreover, according to the 'developmental origins of health and disease' concept, maternal obesity predisposes the offspring to adult onset non-communicable diseases [5].

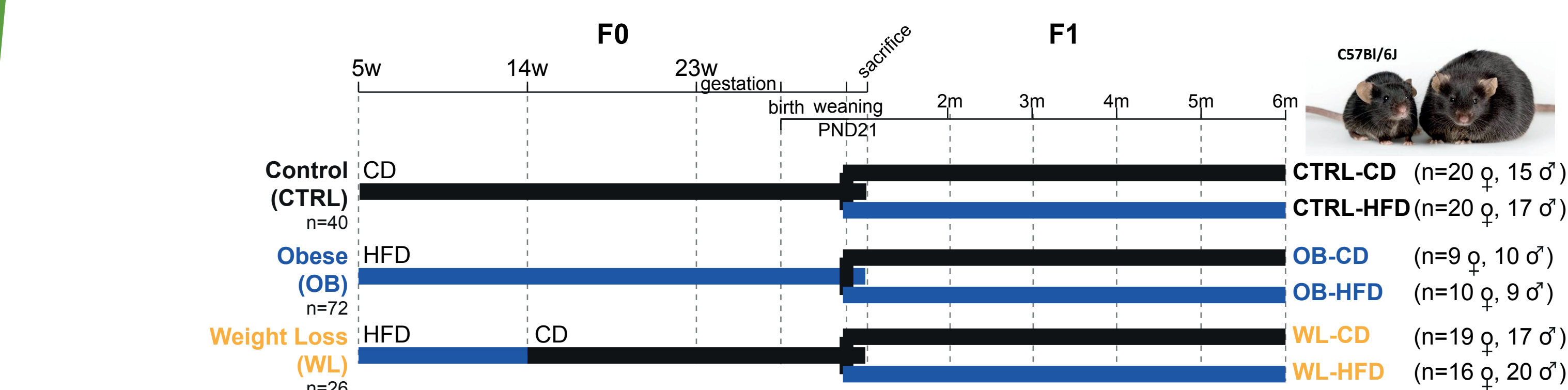
A preconceptional weight loss is widely recommended to obese women. However, its long-term outcomes on the offspring have been poorly assessed. In human cohorts, it may have positive or negative effects on fetal growth [6-11]. Interestingly, none of these studies followed up the metabolic development of these children and adolescents and additional studies are therefore needed to reveal the long-term health profiles of offspring born to obese mothers who lost weight prior to conception [12-13]. In animal, preconceptional weight loss has been assessed in rodents, sheep and non human primates (macaque). In two rat models, a nutritional intervention in obese dams was beneficial to the offspring, even if all parameters were not normalized [14-15]. In sheep, a strict nutritional intervention before mating had long-term benefits on offspring weight gain but deleterious effects on offspring stress response and glucose metabolism [16-17].

The epigenome is reprogrammed during gametogenesis and development, until final differentiation of tissue and continue to be modified with ageing. This plasticity makes the epigenome a good candidate to participate in DOHaD. Alteration of the epigenome early during ontogenesis, could be a mechanism of "memorization" of the *in utero* environment, contributing to particular gene expression patterns and thus to adult phenotype establishment.

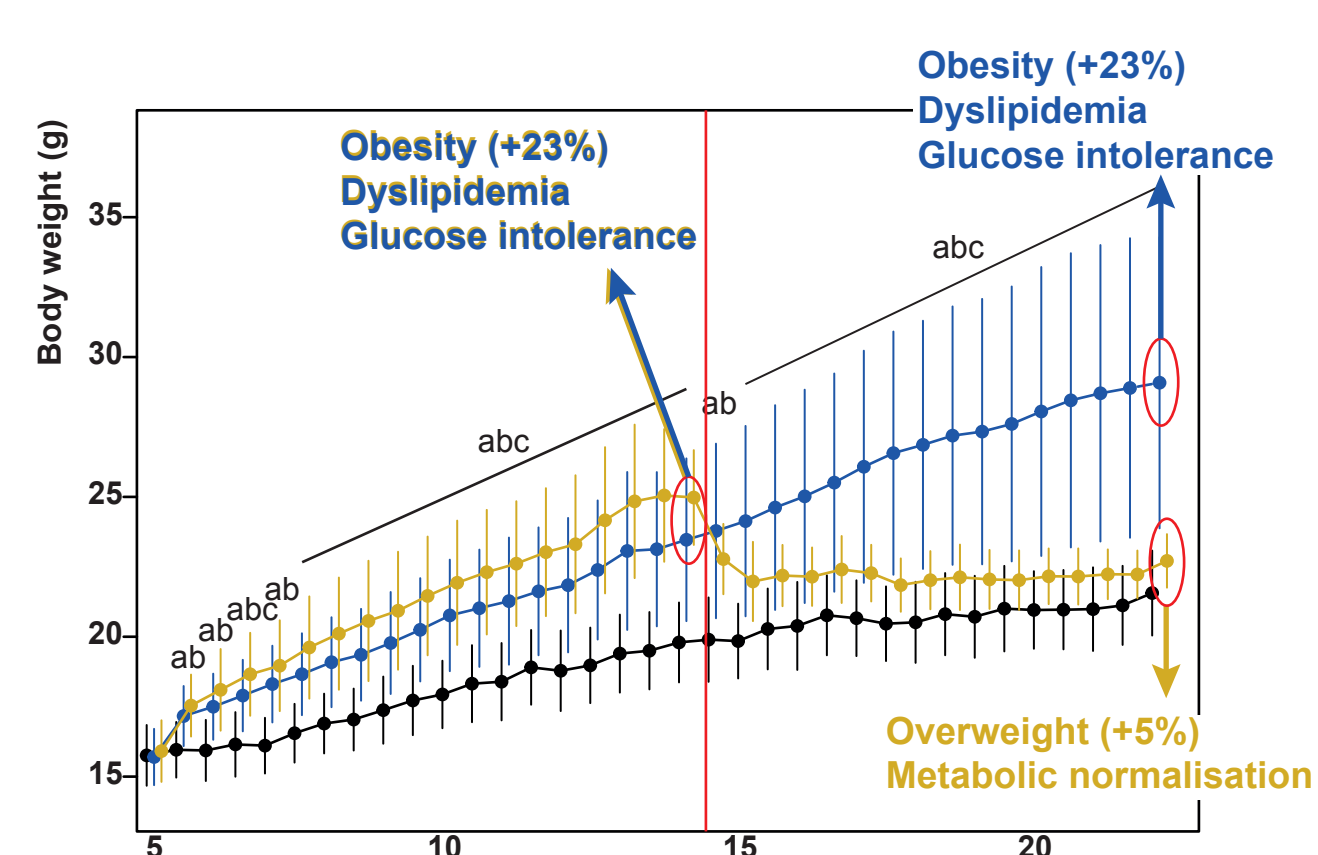


We recorded E18.5 mouse development and measured the mRNA expression of epigenetic modifiers and metabolic genes in foetal liver and placenta. Offspring born to 'control', 'obese' or 'weight-loss after diet-induced obesity' mothers were put on a control or high-fat diet, and we tracked their metabolic parameters and olfactory behaviour.

Results: Obesity induced foetal growth restriction, transcriptional changes and worsen diet-induced obesity in adulthood. Maternal weight loss is beneficial with some possible adverse outcomes.



1 Maternal phenotype



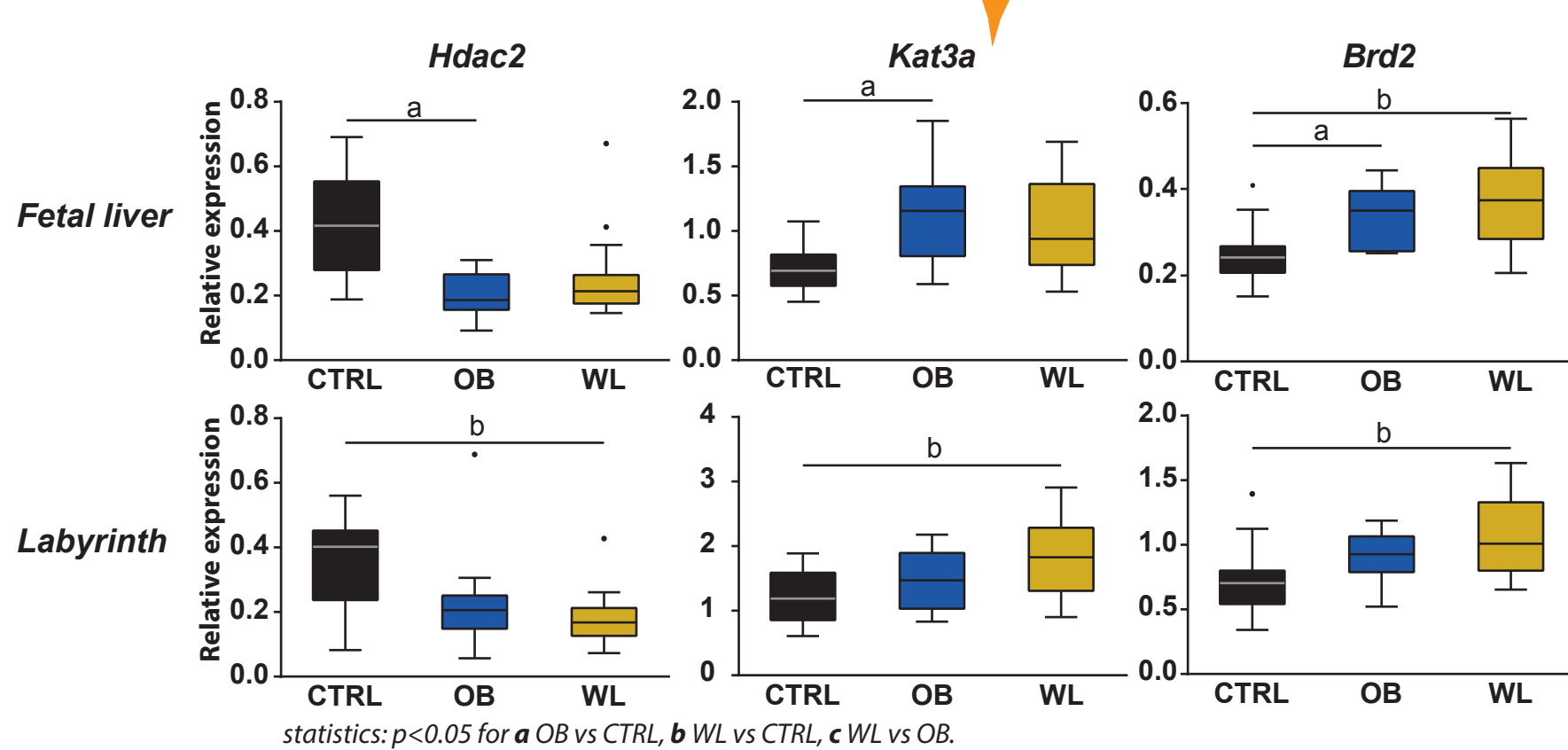
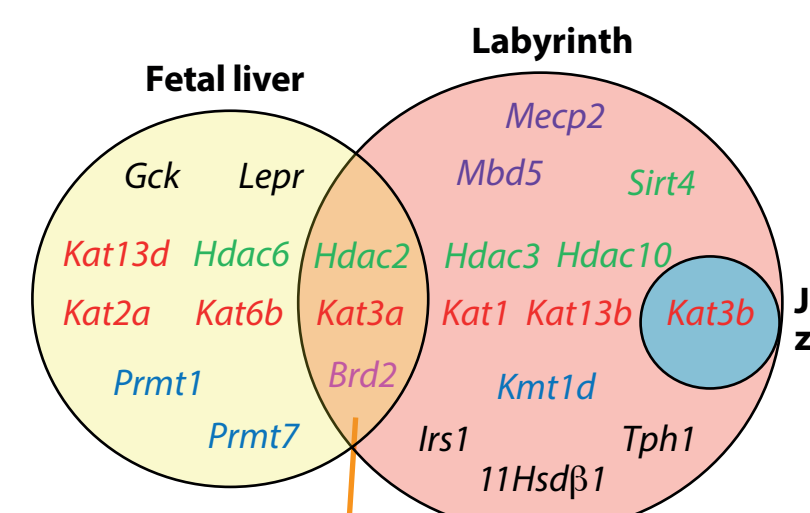
After 4 months of HFD, OB mothers presented the characteristics of the **metabolic syndrome**. Diet change induced **weight loss, normalisation of lipidic and glucidic metabolisms**, although WL mother kept a slight 5% overweight.

3 Foetal gene expression

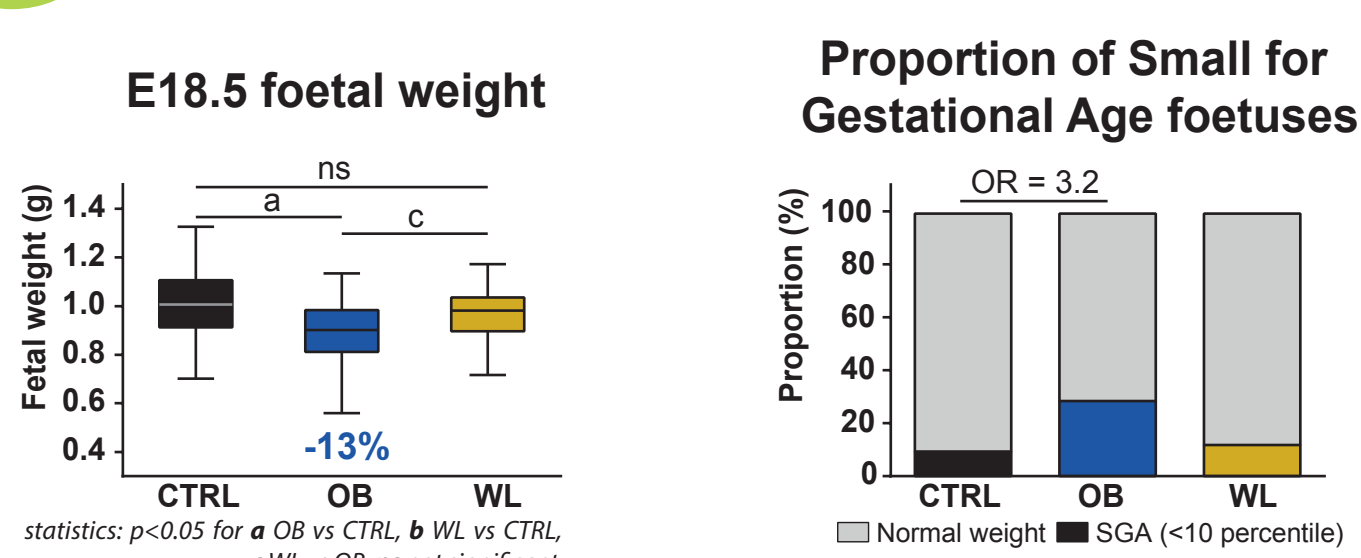
The expression of 60 epigenetic machinery genes and 32 metabolic genes was measured in the foetal liver, placental labyrinth, and junctional zone by RT-qPCR using TaqMan Low Density Assay.

- Epigenetic machinery (60 genes):**
 - DNA Methylation (13): DNMTs, Tet methylcytosine dioxygenases, methylated DNA binding proteins
 - Histone Methylation (18): Lysine demethylases KDMs, Lysine methyltransferases KMTs, Arginine methyltransferases PRMTs
 - Histone Acetylation (29): Histone deacetylases HDACs, Lysine acetyltransferases HAT, Bromodomain proteins Brd
- Candidate for metabolism/development (32 genes):**
 - Glucidic and lipidic metabolism: Ppara, Pparα, Pparδ, Ppck, Pgc-1α, C/Ebp-α, C/Ebp-β, Lpl, Gck, Rev-erba, Nocturnin, Oxt, Gcgr, Irs-1, Insr
 - Appetite regulation: Leptin, Lepr, Pomc, Npy, Bdnf
 - Glucocorticoids regulation and response: 11βHsd-1, 11βHsd-2, Gr
 - Serotonine pathway: Tph1, Slc6a4, Maoa, 5-HT-2a, 5-HT-1c
 - Feto-placental development: Gcm1, Gcgr, Igf2, Igf2r, Slc16a10, Irs-1, Insr

23 genes were affected by maternal weight trajectories in at least one of three tissues. The foetal liver and placental labyrinth were more responsive to maternal obesity than junctional zone. One third (18/60) of the epigenetic machinery genes were differentially expressed between at least two maternal groups. Genes involved in the **histone acetylation pathway** were particularly altered (13/18). In OB group, while most *Hdacs* were downregulated, *Kats* and *Brd2* were upregulated. In WL group, the expression of only a subset of these genes was normalized.



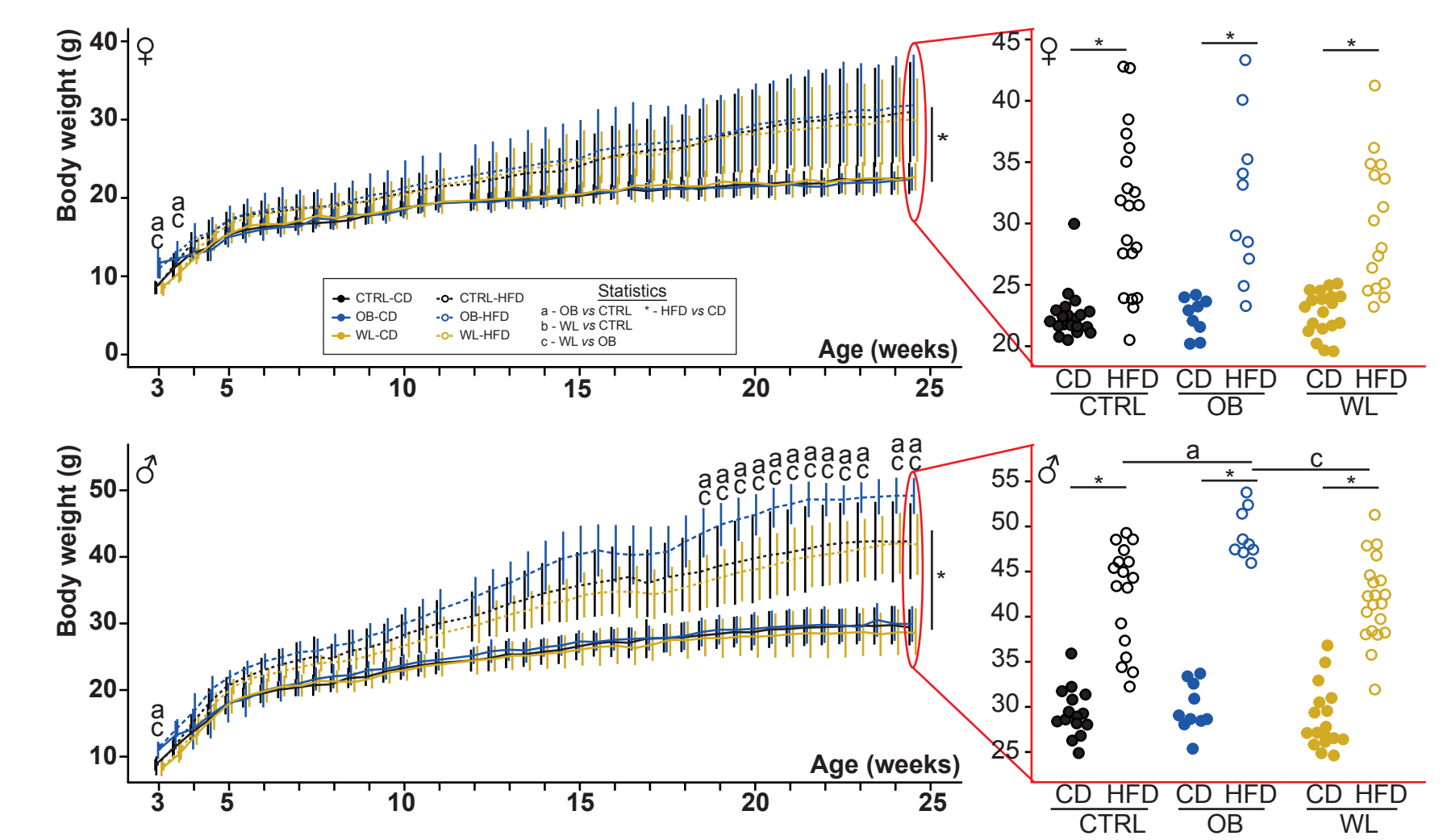
2 Offspring foetal phenotype



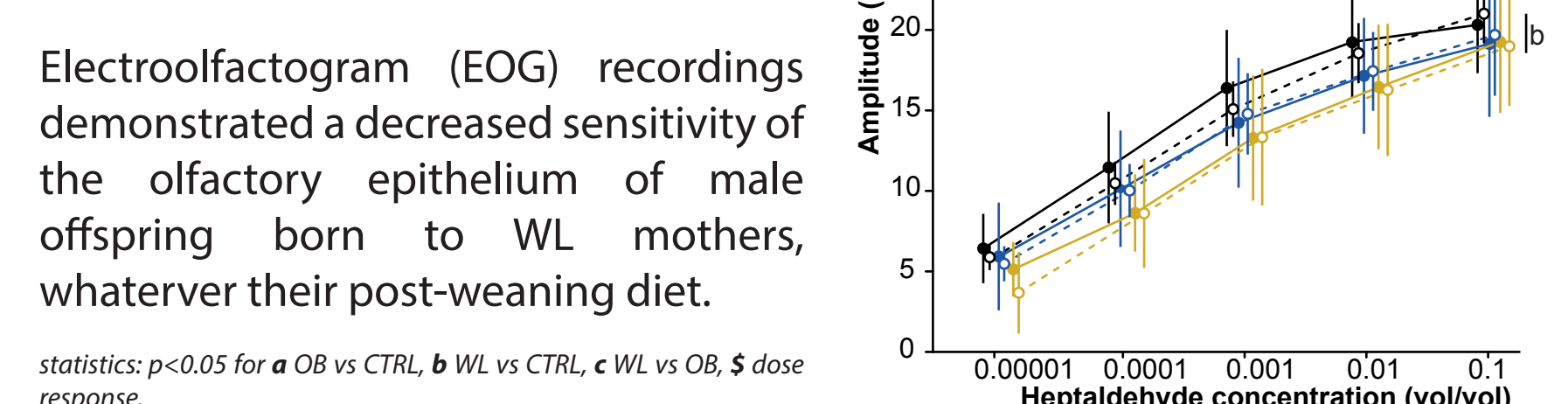
Maternal obesity is associated with **fetal growth restriction** (-13%) and increased proportion of **small for gestational age foetuses** (odds ratio = 3.2). Maternal preconceptional weight loss lead to a **complete normalisation** of the foetal growth phenotype.

4 Offspring long-term outcomes

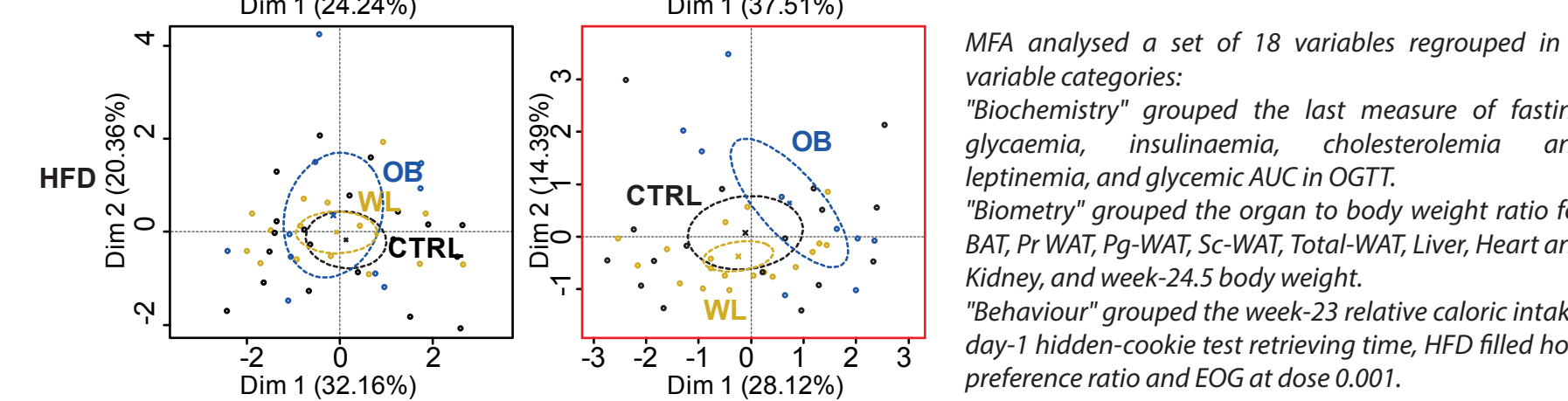
We tracked metabolic and olfactory behavioural trajectories of offspring born to CTRL, OB or WL mothers. After weaning, the offspring were either put on a CD or a HFD. The offspring's **own diet explained most of the variability** in metabolic and olfactory phenotypes. After only few weeks of HFD, the offspring developed obesity, metabolic alterations and olfactory impairments, independently of maternal context.



However, maternal obesity had a sex-specific conditioning effect: Male offspring born to obese mother gained even more weight under HFD than their counterparts born to lean mothers. **Preconceptional WL normalized the offspring metabolic phenotypes but had an unexpected programming effect on olfactory performance:** a reduction in olfactory sensitivity, along with a lack of fasting-induced, olfactory-based motivation.



Electroolfactogram (EOG) recordings demonstrated a decreased sensitivity of the olfactory epithelium of male offspring born to WL mothers, whatever their post-weaning diet.



Multiple factor analysis (MFA) confirmed that **post weaning diet** has a major effect on F1 phenotype and **HFD-fed males are additionally influenced by maternal group**.

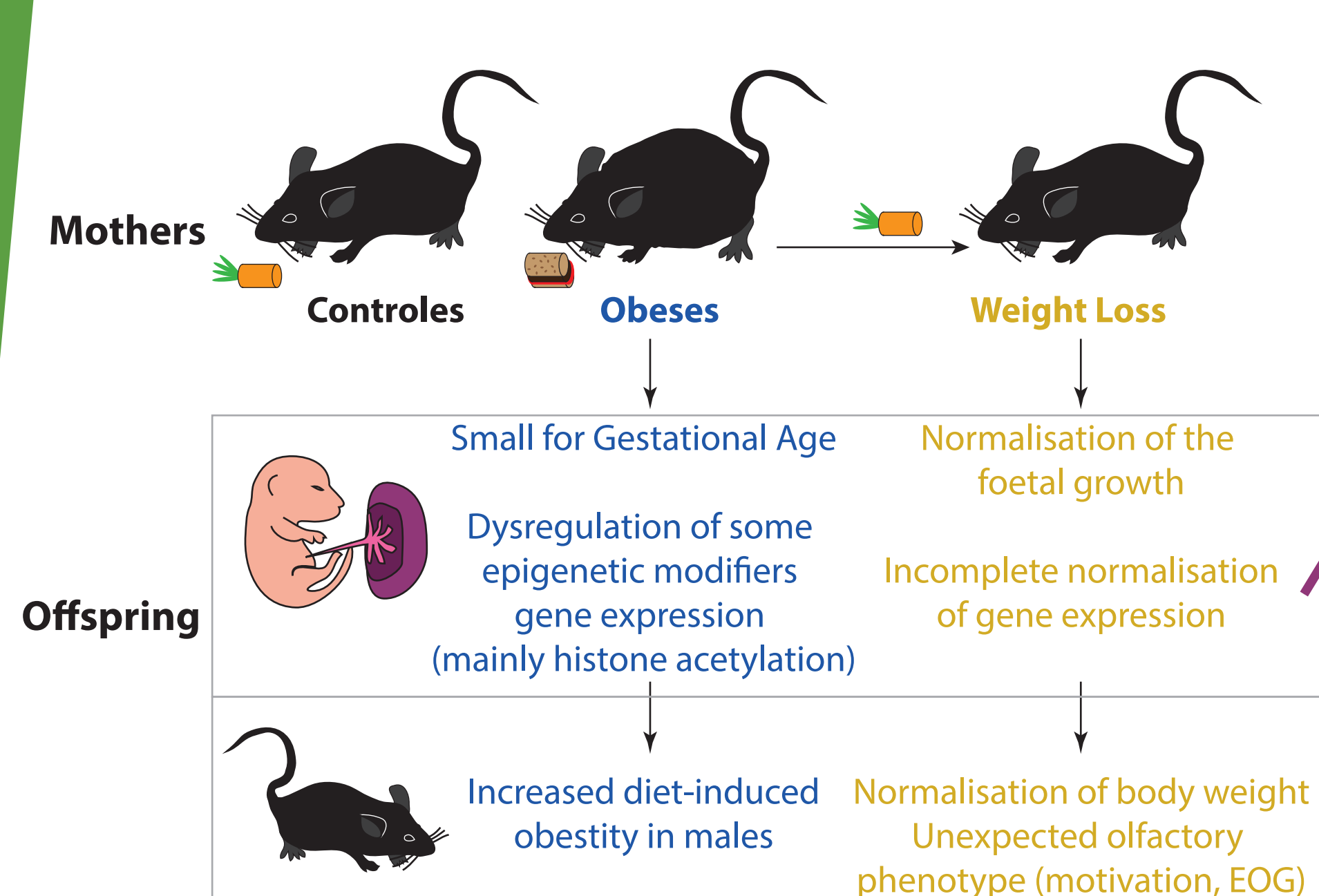
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Conclusions, discussion and future prospects:



Deciphering epigenetic mechanisms in DOHaD.

Most of the research projects studying the effect of maternal obesity focuses on DNA methylation. However our results, as well as other publications, point out that the **histone acetylation pathway** can be a key component [18-21]. This highlights the importance of investigating the mechanisms of regulation of **histone marks** in response to environmental insults. The link between histone modifiers, histone acetylation levels, and placental and hepatic function should be established.

Memory of weight loss or stress?

In our model, it is unclear whether the decrease in olfactory sensitivity in WL males and the resistance of WL-CD to fasting stem from:
- the preconceptional **caloric depletion** associated with the transition to CD in mothers
- to a **maternal stress linked to the transition** per se, as stress may lead to intergenerational phenotypes [22-23].

Further studies are needed to discriminate the effect of energy depletion from the effect of stress on the maternal effects reported herein.