Genetic variability for key biomarkers involved in body reserves dynamics in sheep

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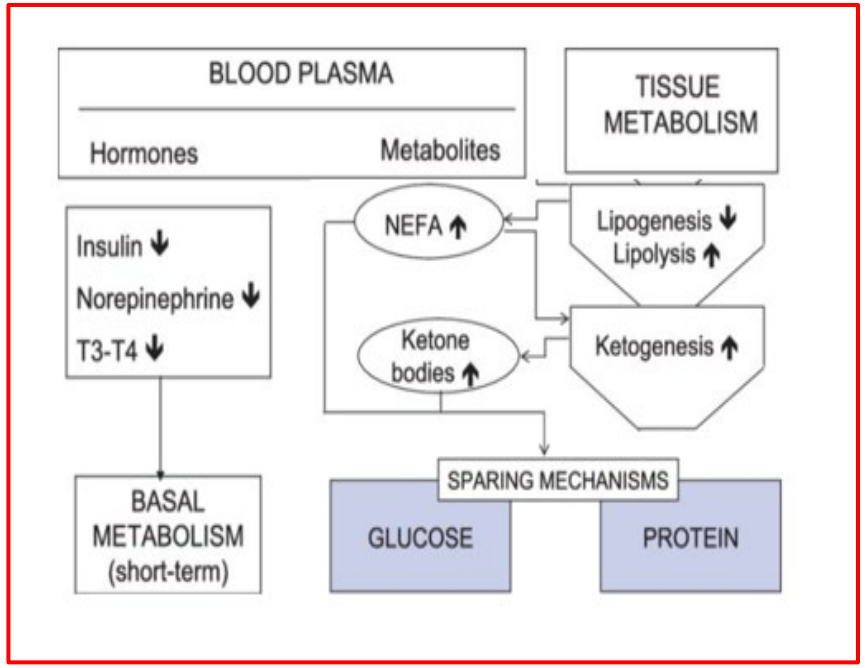
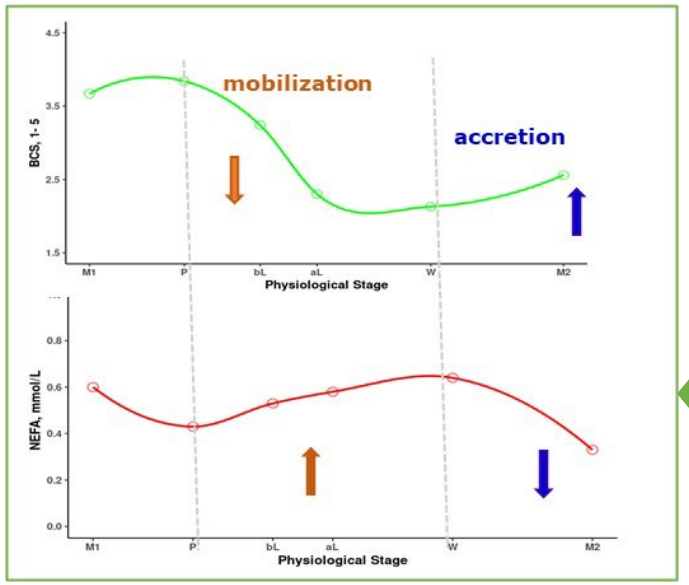
Background

- Ruminants mobilize body reserves (**BR**) as a biological mechanism to manage negative energy balance (**NEB**) periods*
- When facing NEB, **lipolysis** causes a shift in the levels of key plasma metabolites and hormones involved in lipid metabolism (Chilliard *et al*.,1998)

Metabolic and endocrine adaptations to undernutrition in the ruminant



Trajectories of metabolic and hormonal profiles for BR dynamics



- In our study (under review in JAS), trajectories and levels of body condition score (**BCS**) and plasma biomarkers (e.g. Non-Esterified Fatty Acids (**NEFA**) was in agreement with literature

*Li *et al*., 2020; Puppel *et al*., 2019

Adapted from our previous study (submitted for publication)

Background

- In this study, we investigated the **genetics of plasma biomarkers** as potential **proxies** for body reserve dynamics in ruminants
- In cows, the genetic determinism underlying these dynamics has been well-documented
- For example, moderate heritability (***h²***) estimates for plasma NEFA (**0.19** to **0.28**) and beta-hydroxybutyrate (**β-OHB**) (**0.1** to **0.37**) were reported in the literature*
- In small ruminants, information on zootechnical traits (e.g., BCS) have been used to characterize genetic component of body reserve dynamics (Macé *et al*., 2018 ; McLaren *et al*., 2023)
- Therefore, studying the dynamics of these plasma biomarkers and their genetic determinism can provide a **new lever** to improve **resilience** in ruminants

*Benedet *et al*. (2020), Belay *et al*. (2016)

Objectives

Main objective:

- To dig into the **genetic determinism** of key plasma **biomarkers** associated with body reserves

Specific objectives:

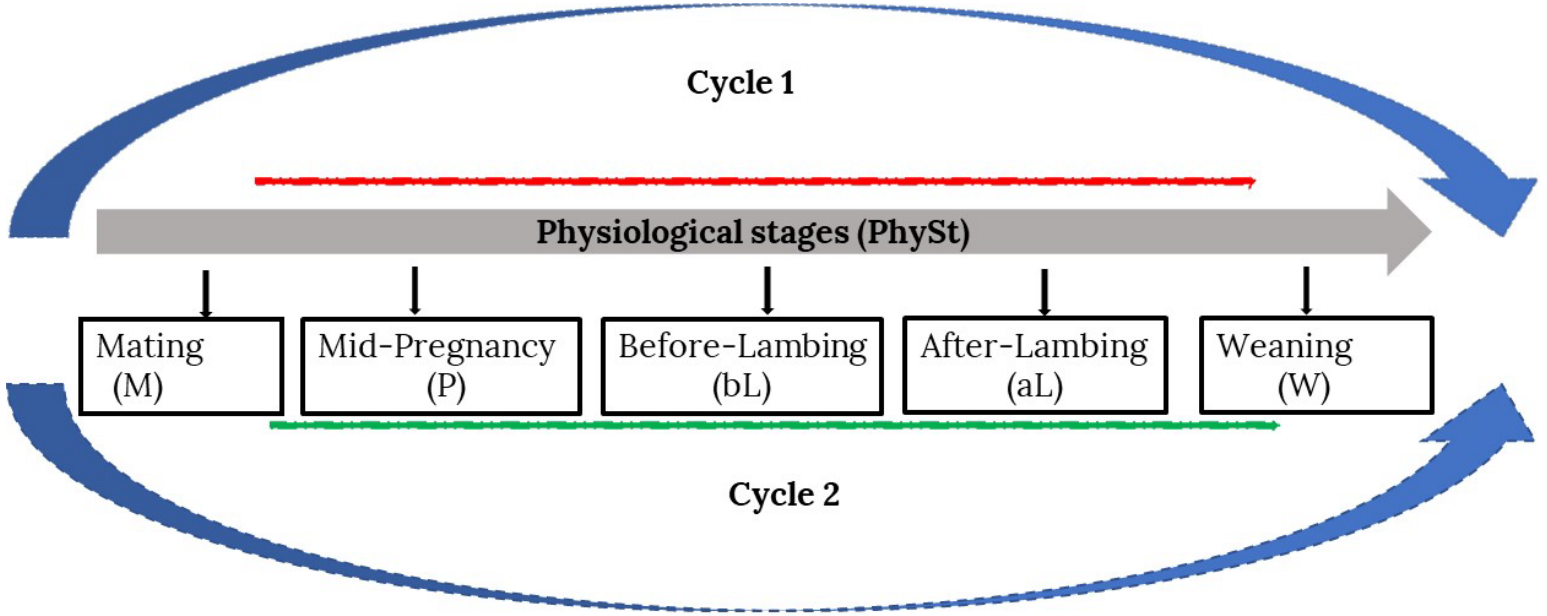
- To analyze the genetic variability of **biomarkers** plasma concentrations at key **physiological stages** and **changes** in plasma concentrations over time
- To analyze the genetic relationships between key physiological stages for each biomarker and between biomarkers

Hypothesis

- Concentrations and changes over time in **biomarkers are genetically controlled**

Experimental design

- We used a total of **659 ewes** monitored during two complete productive cycle
- The ewes were reared in two farming systems and are offspring of 30 sires
- All the animals were genotyped (15K or 50K)
- Blood samples were taken from primiparous and multiparous ewes at **key physiological stages** per production cycle



Phenotypes

Measurements at key physiological stages

1. Plasma concentration of **NEFA**, **β-OHB**, Insulin (**INS**), and Triiodothyronine (**T3**) biomarkers at each PhySt: blood sampling before first meal in the morning.

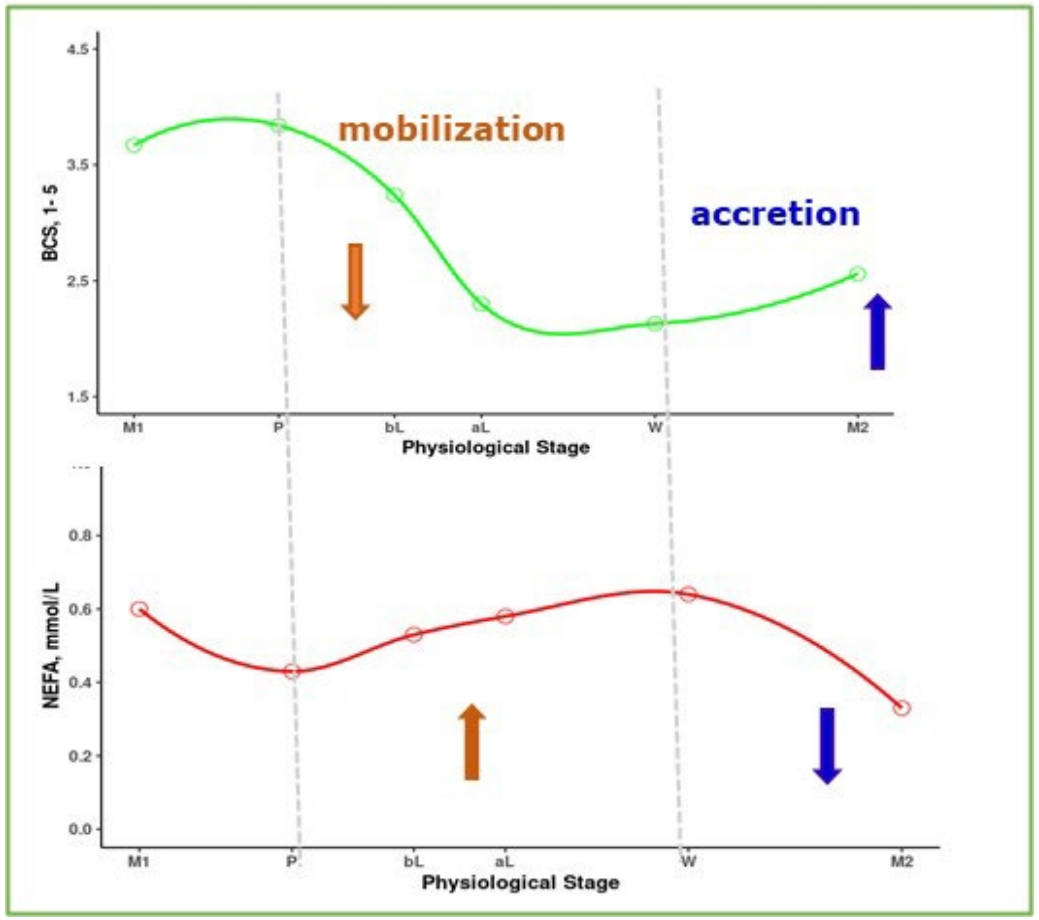
2. **Changes over time** = range of variation between two successive PhySt

   - for BR mobilization:

   $$\boldsymbol{biomarker_{aL} - biomarker_{bL}}$$

   - for BR accretion:

   $$\boldsymbol{biomarker_{W} - biomarker_{M}}$$



Statistical analysis

- **ANOVA** (R software): to evaluate the effect of fixed effects on phenotypes
- Estimation of genetic parameters was done in **BLUPF90+** family program (Misztal et al., 2024). We performed genetic analysis **with** and **without genotypes**
- Only **results without genotypes** will be discussed, as there were **no major differences** between the two
- Animal model included the permanent environment of the ewe to consider repeated measurements on the same ewe at a given parity
- The model was:

$$y = X\beta + Za + Wp + e$$

Phenotypes

Fixed effects

Random ewe additive genetic effect

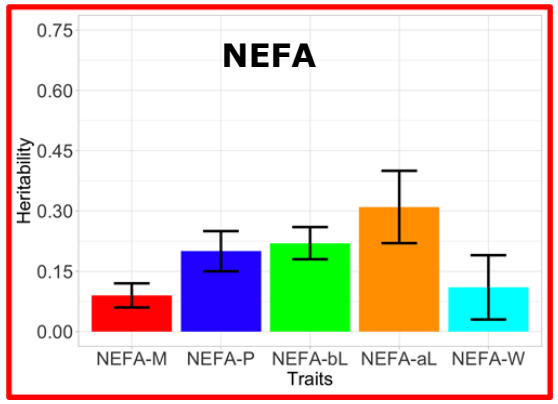
Permanent environment of the ewe

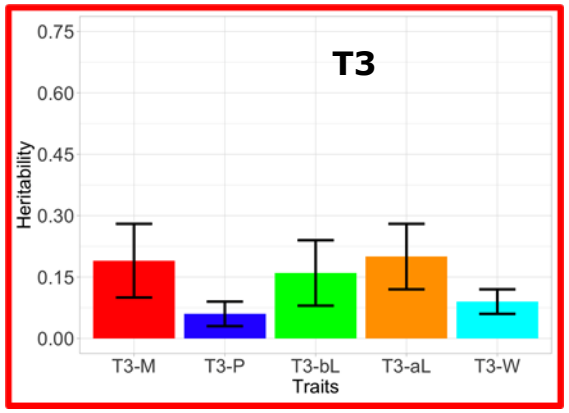
Random residual

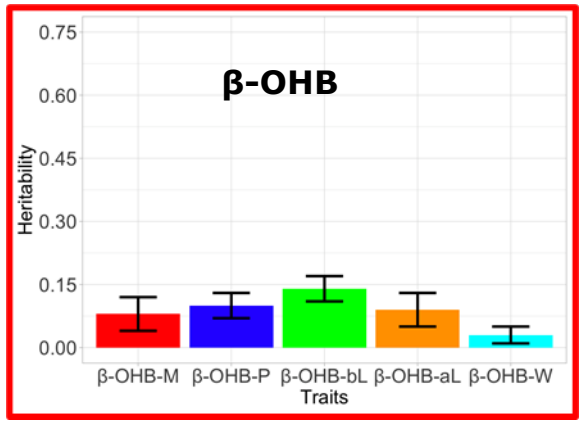
X, **Z**, and **W** are incidence matrices

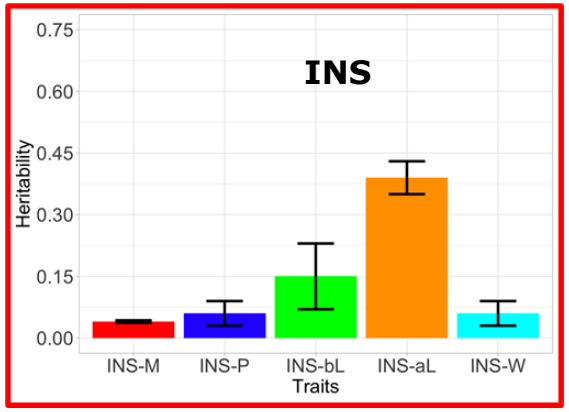
Results: Heritabilities for Biomarkers

Estimated h^2 for the **biomarkers at each PhySt**









- h^2 ranged from **0.06 to 0.39** across different PhySt
- h^2 **values were low** for all biomarkers throughout the PhySt, **except at before- and after-lambing**
- The genetic coefficient of variation (gCV (%) was generally moderate to high (**10** to **38.5%)** for all biomarkers, except for β-OHB-W and T3-P (**5.8%**)

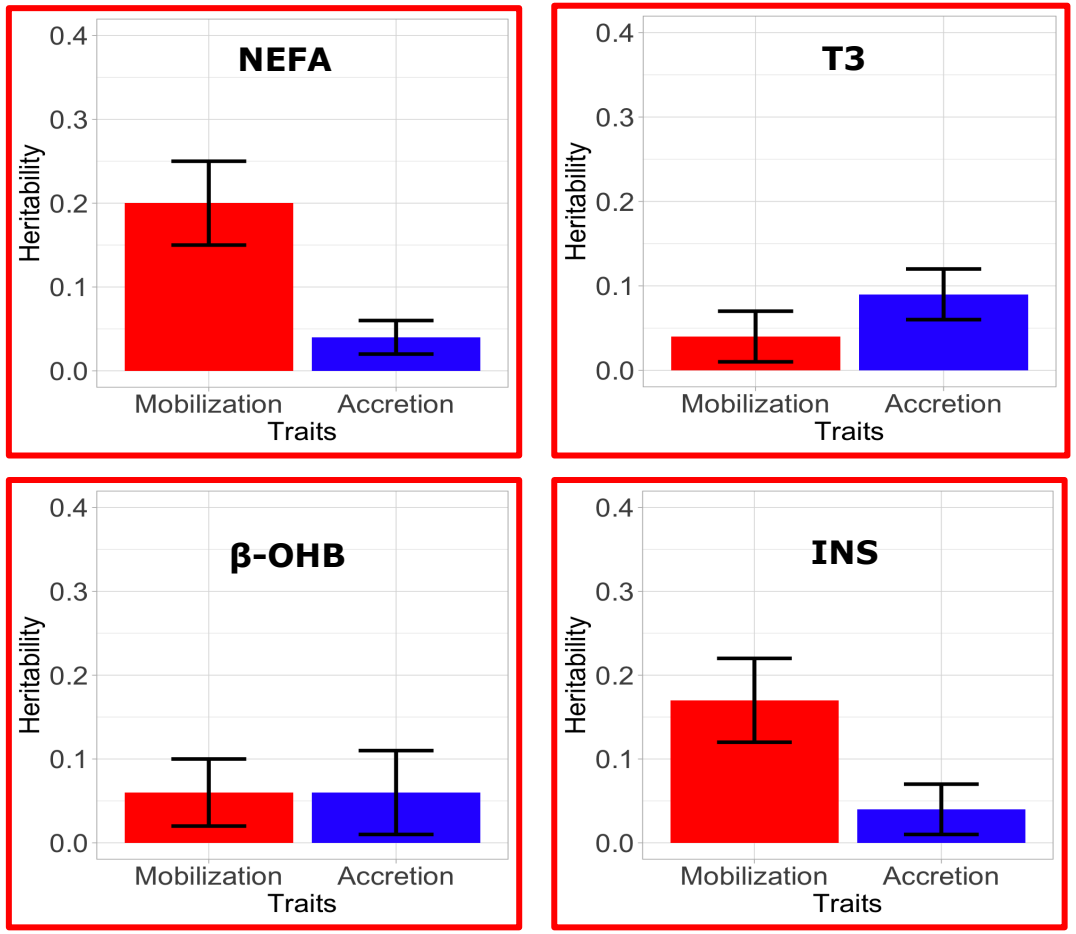
❖ Higher h^2 at before and after-lambing could be due to :

- Higher gCV observed at these stages (**0.14** to **0.39**)
- Significant physiological changes and increased gene expression during these periods, enhancing genetic influences on these traits (Wathes *et al*., 2009)

❖The moderate to high gCV indicates **substantial genetic variability** in these traits, suggesting they could respond well to selection

Results: Heritabilities for changes in Biomarkers

Estimated h^2 for the **changes in biomarkers** over time



- **Low h^2** was observed except for changes in NEFA **(0.20)** and INS **(0.17)** during the **mobilization period**

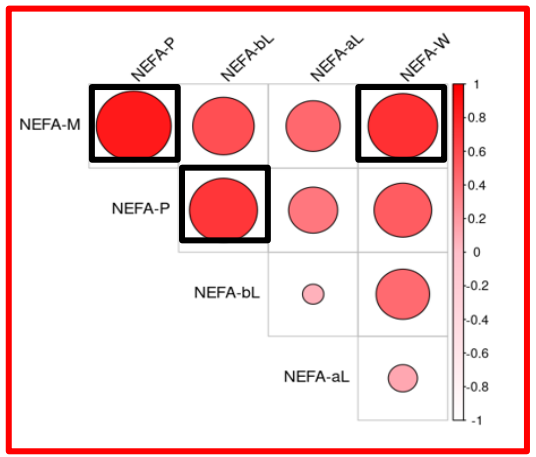
- Similarly low h^2 for changes in BCS (0.04 to 0.16)* and body weight (0.13 to 0.18)** were reported
- Indicating that these variations are under weaker genetic control than the overall plasma biomarker levels observed at key physiological stages

(*Pryce et al., 2001; Macé et al., 2018)
(**Rose et al., 2013; Macé et al., 2018)

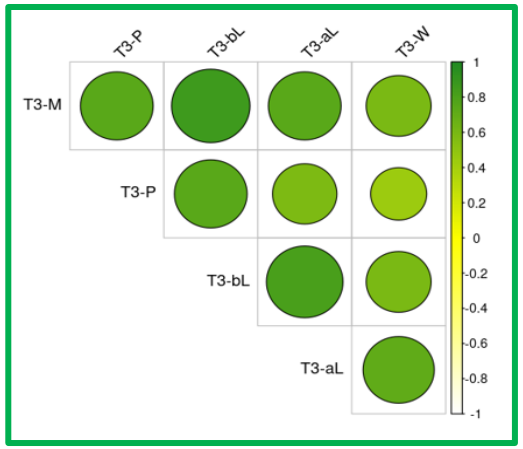
Results: Genetic correlations

Genetic correlations for each biomarker across **physiological stages**

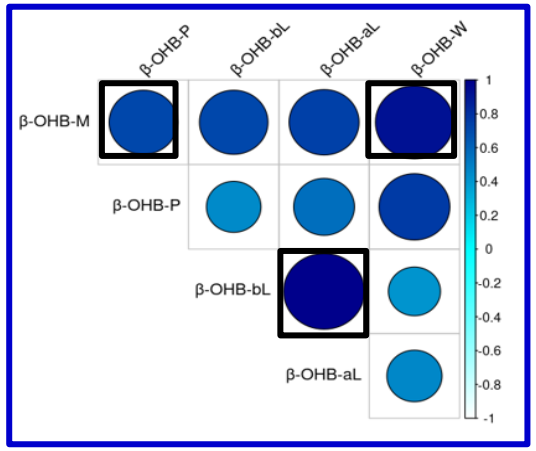
NEFA



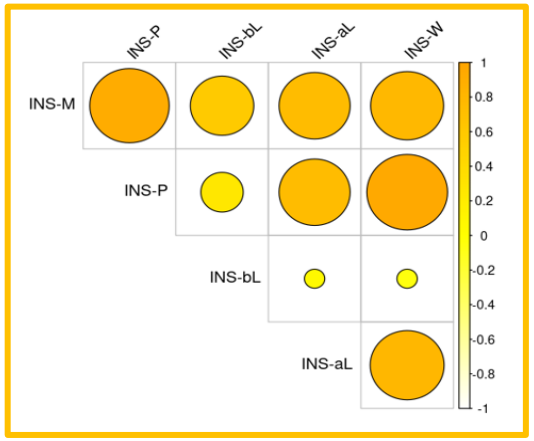
T3



β-OHB



INS



- For each biomarker : Several strong genetic correlations were observed
- Across all PhySt, T3 showed high correlations

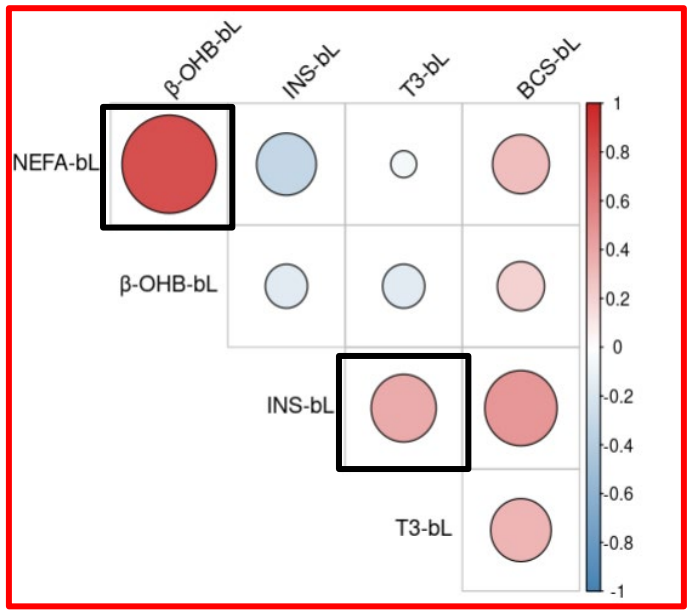
- This could be because the animal experiences similar physiological requirements at a given PhySt (e.g., at M and P)
- This finding is consistent with the high genetic correlations between PhySt for BCS reported by Macé et al. (2018)

Results: Genetic correlations

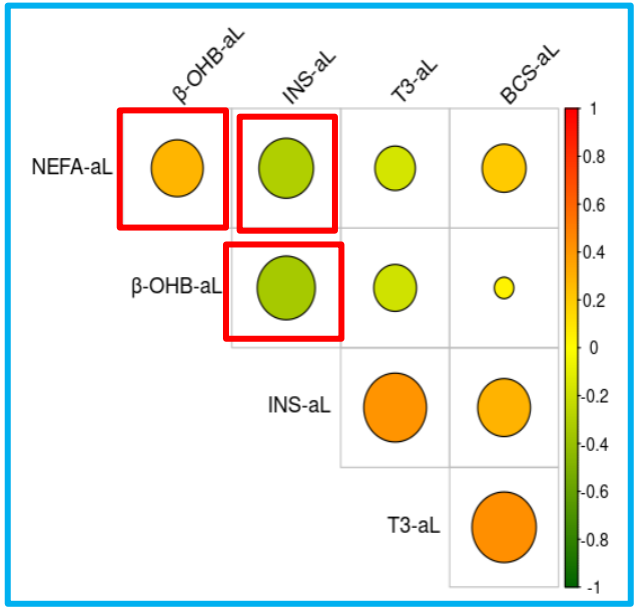
Genetic correlations among biomarkers and with BCS

At two physiological stages

Before-lambing



After-lambing



- A very **strong** positive **correlation** (**0.80**) was observed between **NEFA** and **β-OHB** at **before-lambing** (predictors of NEB)
- Additionally, a moderate positive correlation **(0.41)** was observed between INS and T3 at before-lambing

❖ This is consistent with:

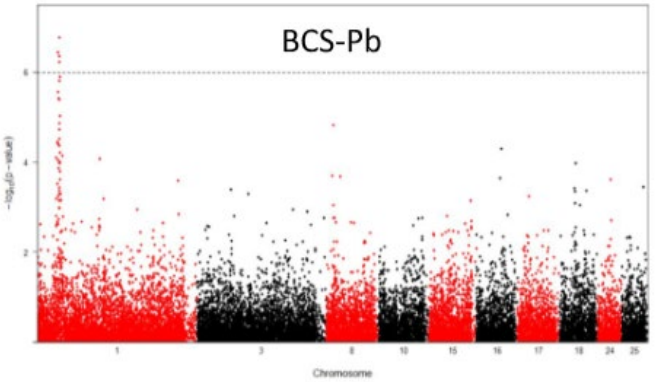
- higher **genetic variability** observed at this stage
- a **strong positive genetic** correlation (**0.65**) between changes over time (**mobilization**) for **NEFA** and **β-OHB**
- This suggests that changes in both traits occur together due to interconnected physiological processes and genetic factors

Conclusions

- Plasma biomarkers concentrations at key PhySt and their changes over time are **heritable** and genetically linked
- **Physiological stages around lambing appeared more promising to better understand individual differences in plasma biomarkers**
- These traits (biomarkers) can be targeted in **genetic programs** to improve **metabolic resilience** in small ruminants

Perspectives

- Perform Genome Wide Association Studies (GWAS) to identify candidate genes associated with body reserves
  - Mace et al. (2023): Leptin receptor gene associated with BCS levels in sheep
  - Nayeri et al. (2019): SCK1, SCK2, and DGAT1 genes associated with MIR-predicted milk **β-OHB** in Holsteins cattle
  - Potential use of genomic selection for resilience traits



Thank You for Listening

Photo credit Agnes Nyamiel, La Fage Romane flock