

*Note: for non-commercial purposes only*

Neonatal overfeeding in mice predisposes to glucose intolerance to offspring (F1) and grand-offspring (F2) of over nourished individuals (F0) through the paternal lineage: potential role of epigenetics



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International conference

The Power of Programming- Developmental Origins of Health and Disease

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# Introduction

- ✓ Excessive growth rate during childhood (first year of life) is associated with type 2 diabetes risk in young people (by age 20 years). [Leunissen RW *et al.* *JAMA* 2009]

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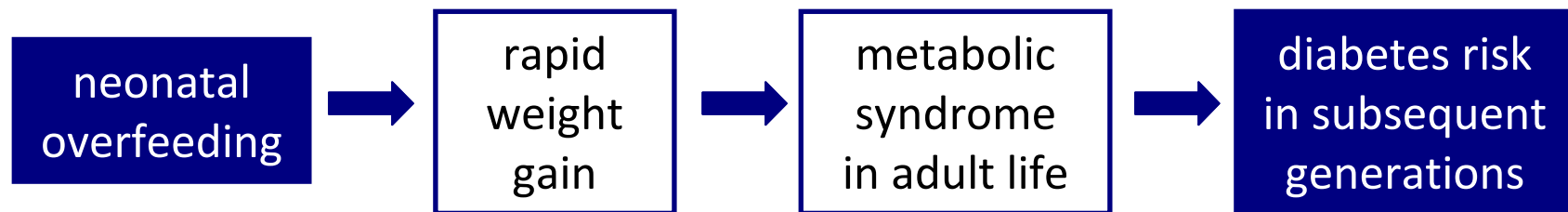
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- ✓ Increased growth rate during infancy is associated with increased visceral adiposity in 2 year old children. [Durmus B *et al.* *Clin Endocrinol.* 2009]

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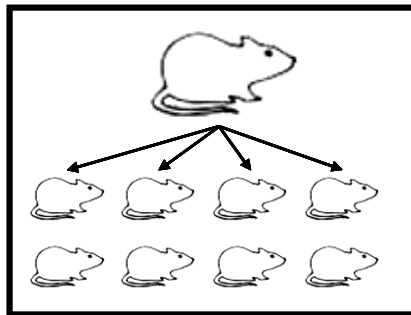
# Objective

- ✓ To develop a mouse model of neonatal overfeeding and accelerated neonatal growth rate that reproduces human physiology.
- ✓ To determine whether neonatal programming of adult disease might have transgenerational effects.

# Experimental Design

**C**

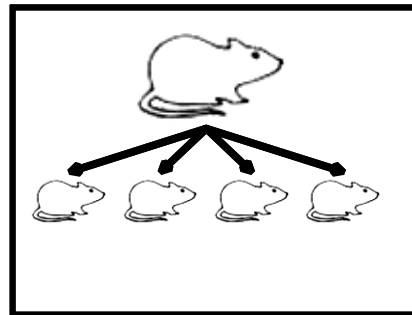
**Control Group**



8 pups/dam

**ON**

**Overnutrition Group**



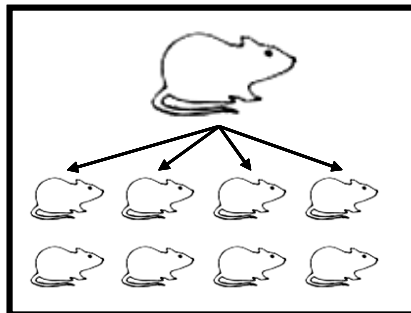
4 pups/dam

Neonatal overfeeding  
Accelerated postnatal growth

# Experimental Design

C

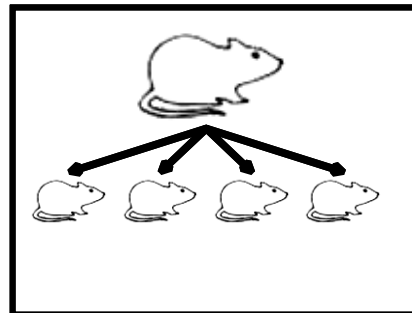
Control Group



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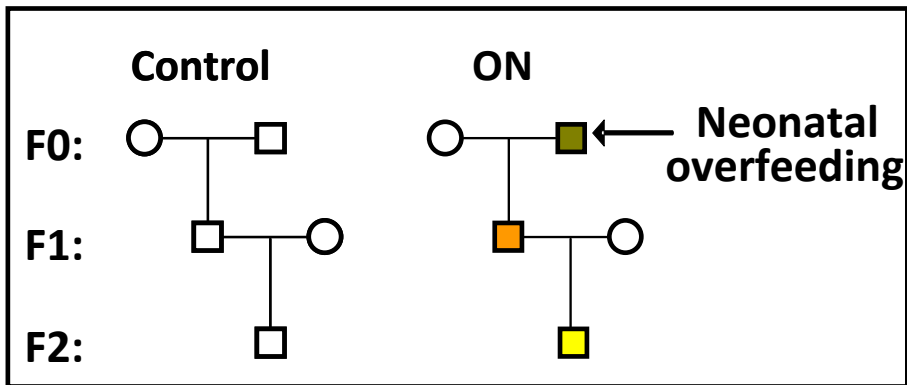
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Overnutrition Group



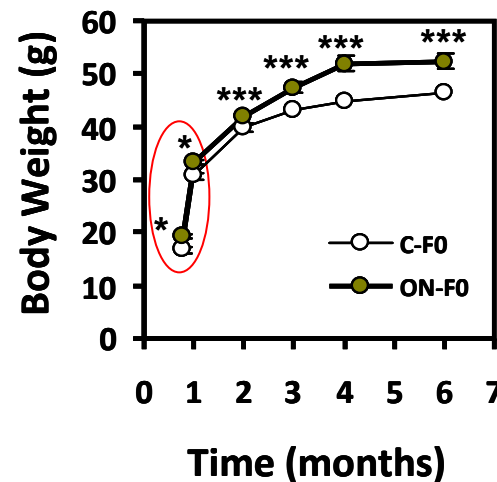
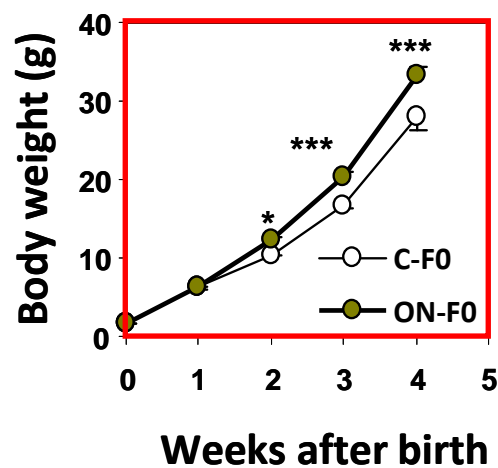
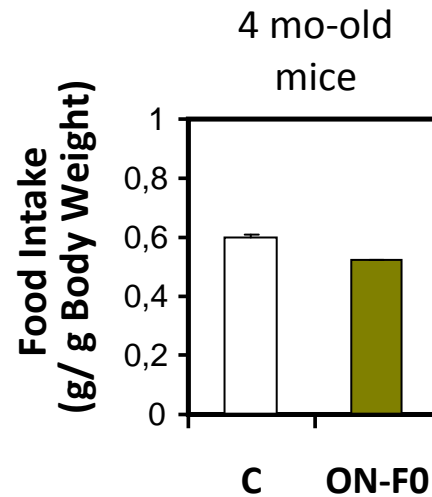
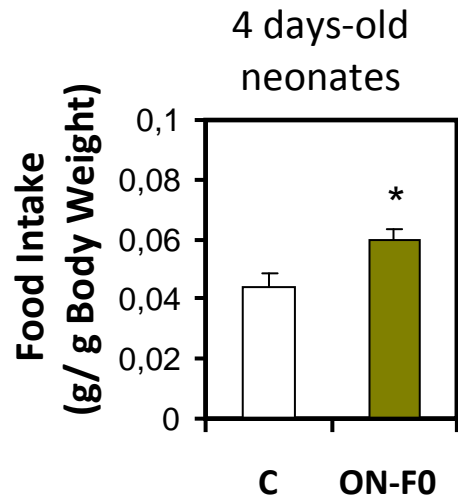
4 pups/dam

Neonatal overfeeding  
Accelerated postnatal growth



- ✓ Pups were nursed freely and weaned at 3 weeks onto standard chow, provided *ad libitum*.
- ✓ Metabolic analysis only in males.

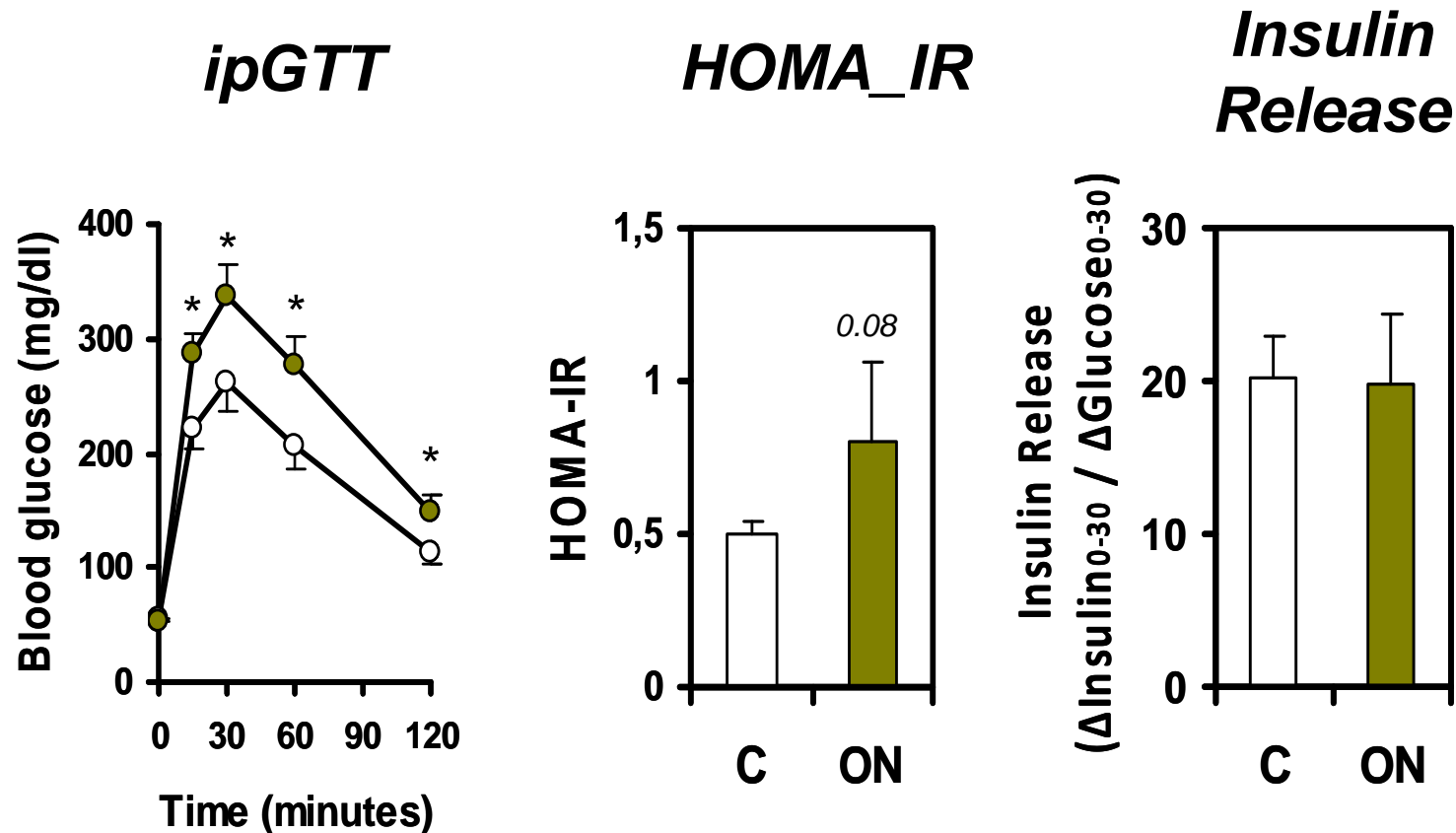
# Neonatal overfeeding in ON-F0 led to accelerated post-natal growth



Differences in body weight persisted until adulthood, despite normalization of food intake.

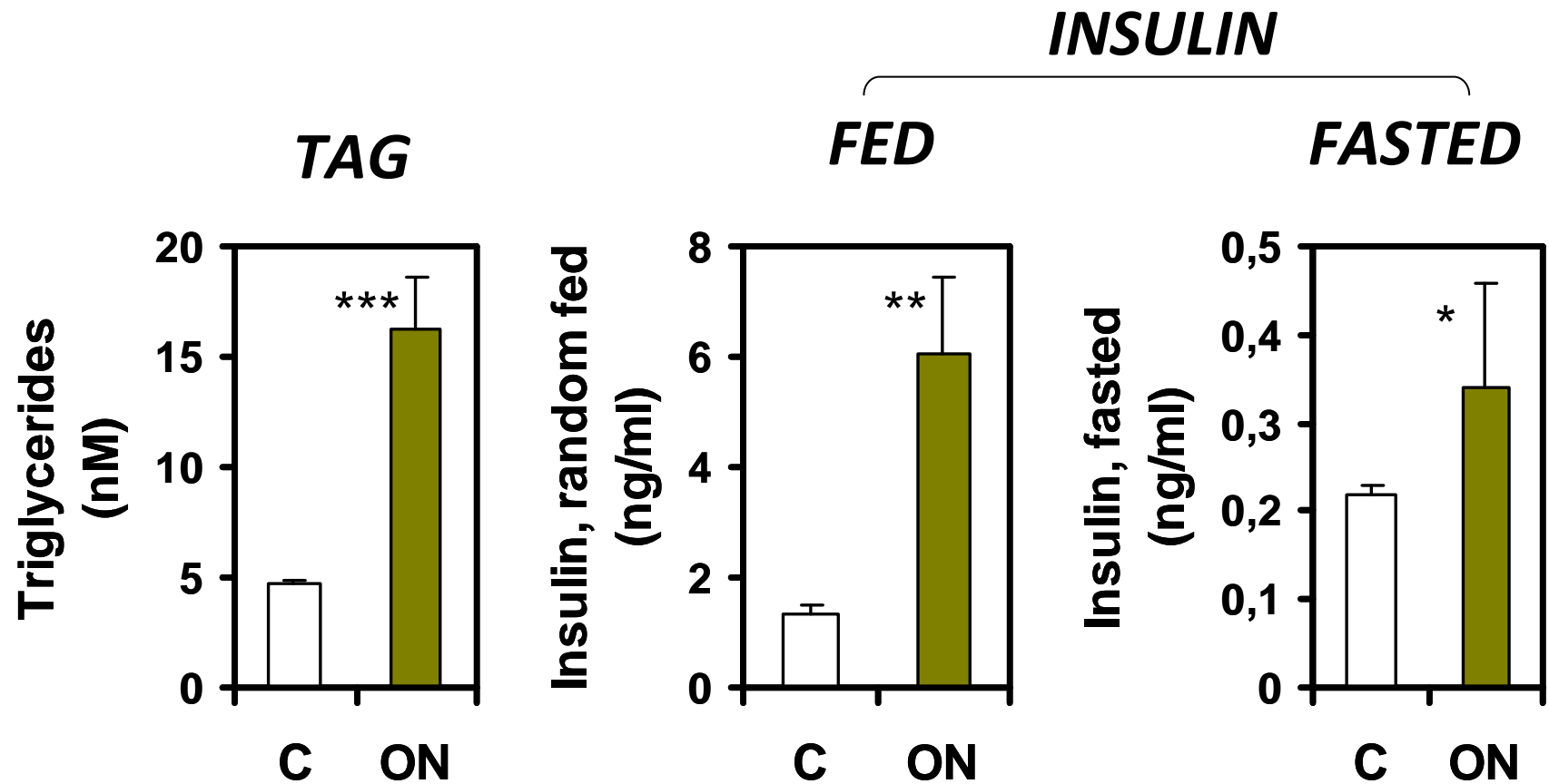
[\* $p \leq 0.05$ , \*\*  $p \leq 0.01$ , \*\*\*  $p \leq 0.005$ ]

# Insulin resistance in 4 month-old ON-F0 mice results in impaired glucose tolerance



[\*p<0.05, \*\* p<0.01, \*\*\* p<0.005]

# 4Months-old ON-F0 mice show many features of the metabolic syndrome

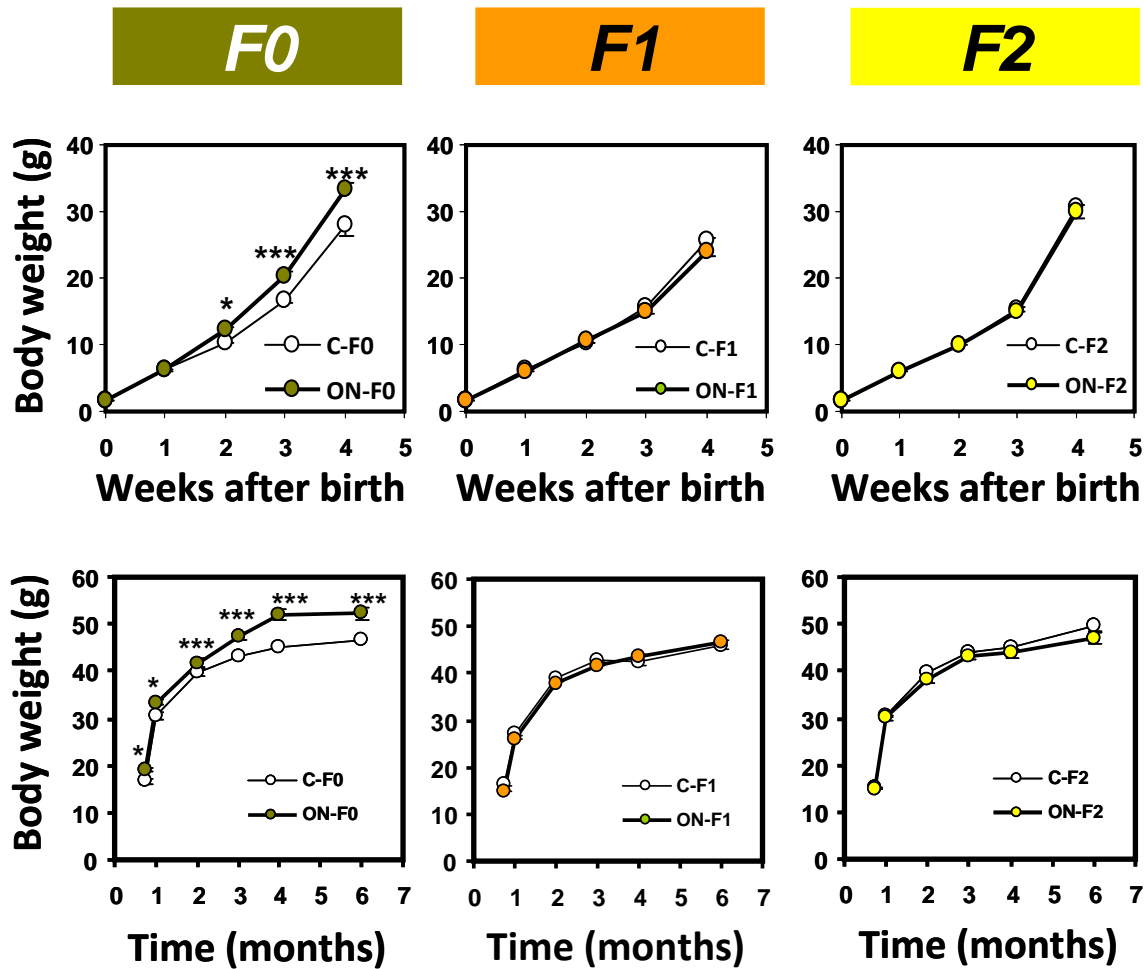


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## SUMMARY 1

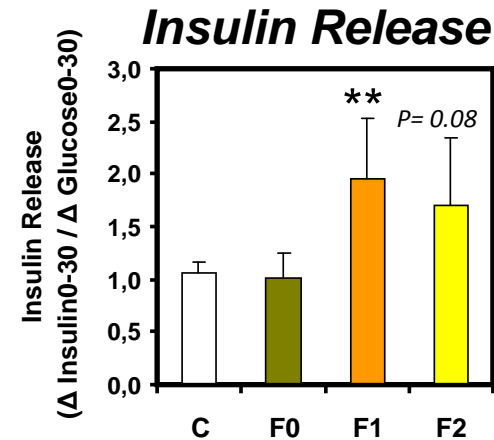
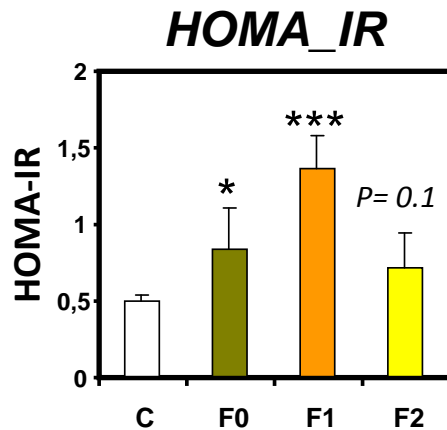
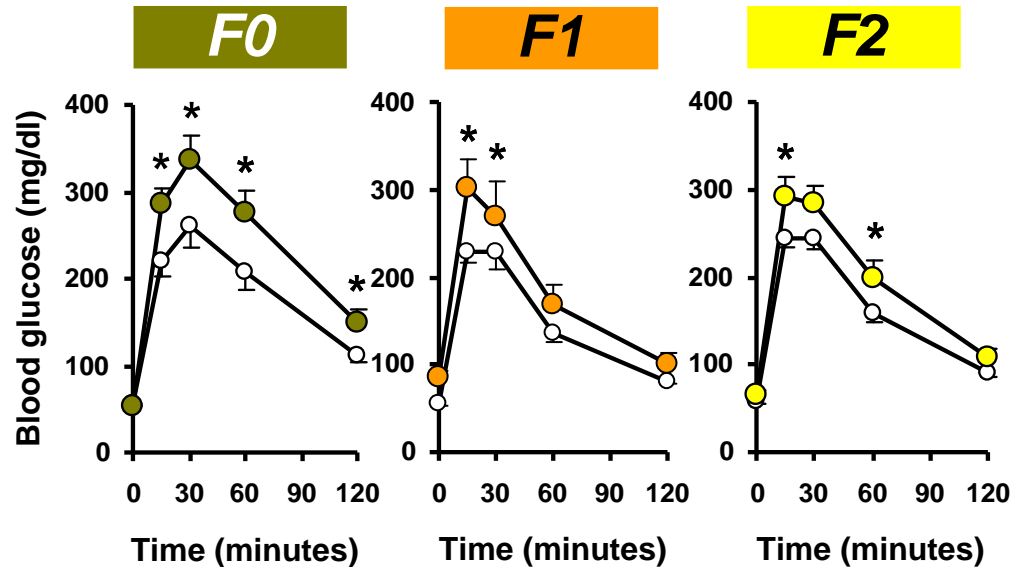
- ✓ Neonatal overfeeding promotes rapid weight gain and in adulthood they develop:
  - hypertriglyceridemia
  - hyperinsulinemia
  - insulin resistance
  - glucose intolerance
- ✓ Impaired glucose tolerance and diabetes in ON-F0 might be primarily attributed to peripheral insulin resistance rather than beta-cell dysfunction.

# Body weight on ON-F1 and ON-F2 mice was similar to controls



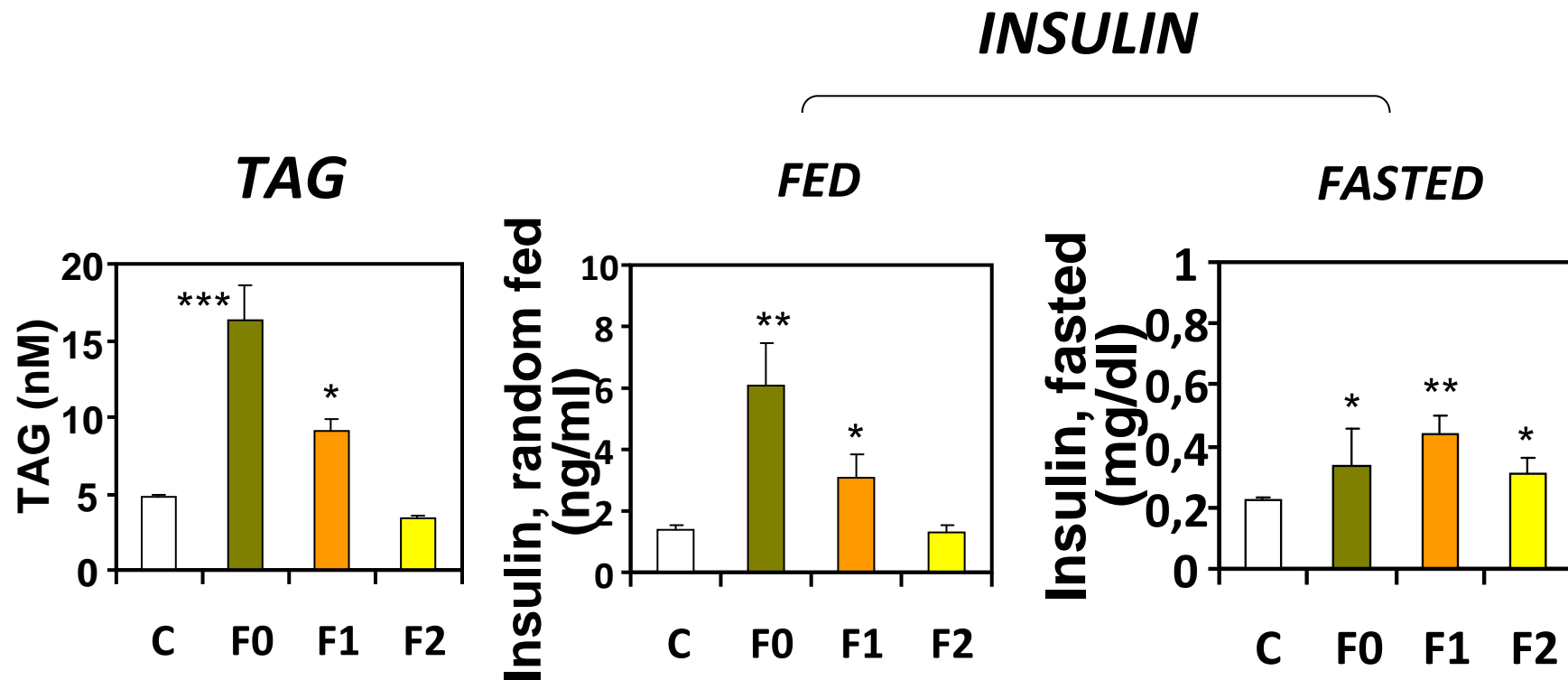
[\*p≤0.05, \*\* p≤0.01, \*\*\* p≤0.005]

# Some metabolic disturbances occurring in ON-F0 mice are inherited by ON-F1 and ON-F2



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## SUMMARY 2

✓ Some features of metabolic syndrome are inherited to subsequent generation, although it does not equally involve all components.

ON-F1: hypertriglyceridemia, hyperinsulinemia,  
insulin resistance, glucose intolerance

ON-F2: hyperinsulinemia, glucose intolerance

# Conclusions

- ✓ Neonatal overgrowth increases risk for glucose intolerance to exposed individuals (F0), their offspring (F1) and grand-offspring (F2).
- ✓ Neonatally associated transgenerational effects are transmitted through the paternal lineage. This suggests that inheritance of phenotypes might be mediated through epigenetic modifications.

# Acknowledgements



Josep C Jiménez-Chillarón

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