EPIGENETICS:

how environment and life style affect genes

Prof. Dr. Geert Opsomer
Faculty of Veterinary Medicine
Ghent University

Aim of this presentation

- Explain what epigenetics is

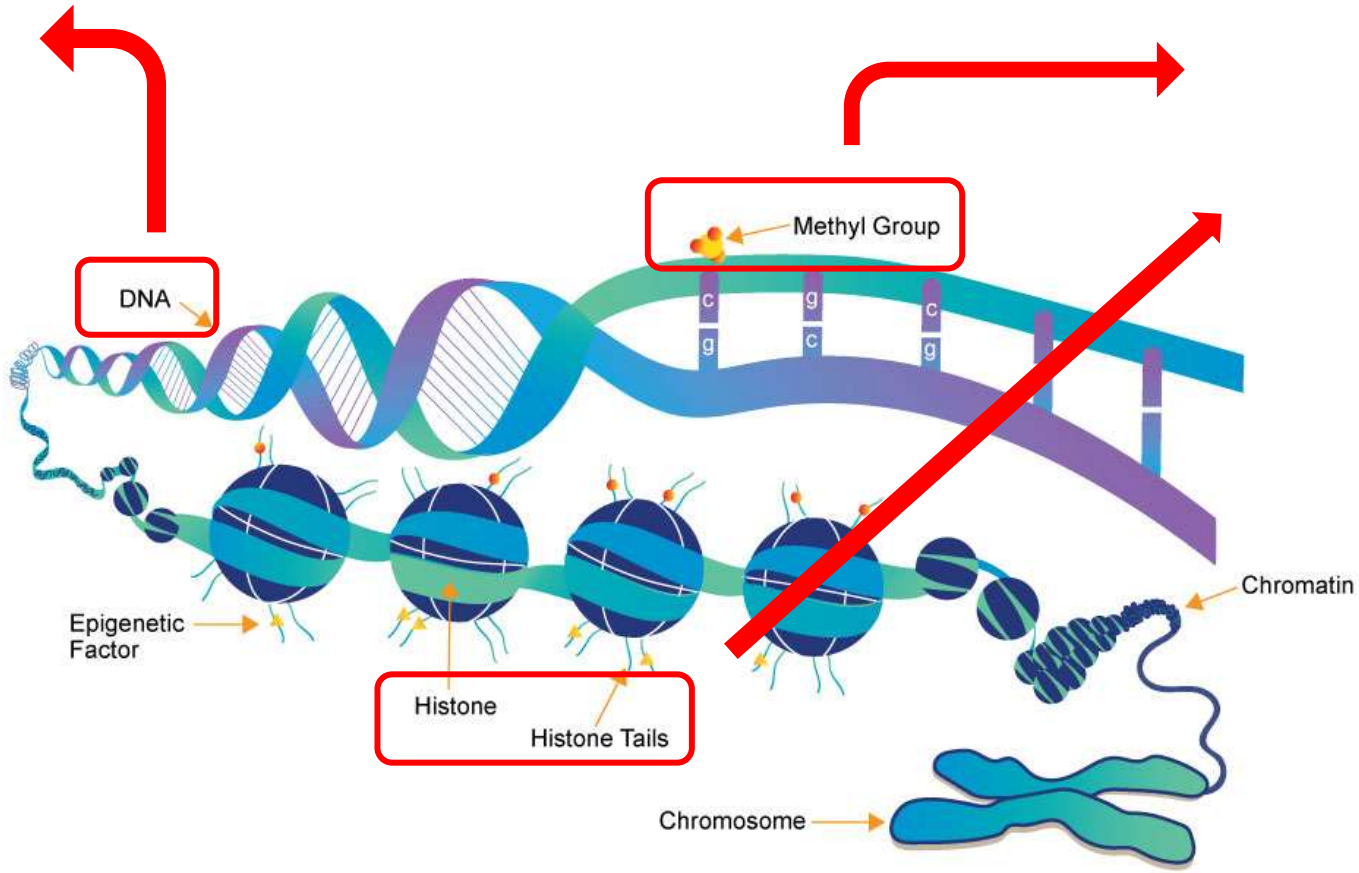
- Show a few examples of what is already known about epigenetics in cattle (especially dairy cattle…) based on our own research and what is known from the literature

  - **aim:** to encourage you to think about how using the principles of epigenetics may help you to further improve your herd

GENETICS ↔ EPIGENETICS

DNA sequence

Mutation
='*typo*'
in DNA



'In addition to'
DNA sequence

'reading the
available genes'

Epigenetics: consequences

- Genetic predisposit*ion (‘genotype’)* remains unchanged
- But the <u>expression</u> of that predisposition can change

→ Affects TRAITS/PERFORMANCE (‘*phenotype’)*

Immunity & health
Growth & muscle development
Fertility
Longevity
…

→ These traits will be <u>passed on to the next generations</u>

Effects of epigenetics on pregnant dairy cows:

Physical activity and health

Environment
- Ambient temperature
- Exposure to light

Signal tranducers

Epigenoom

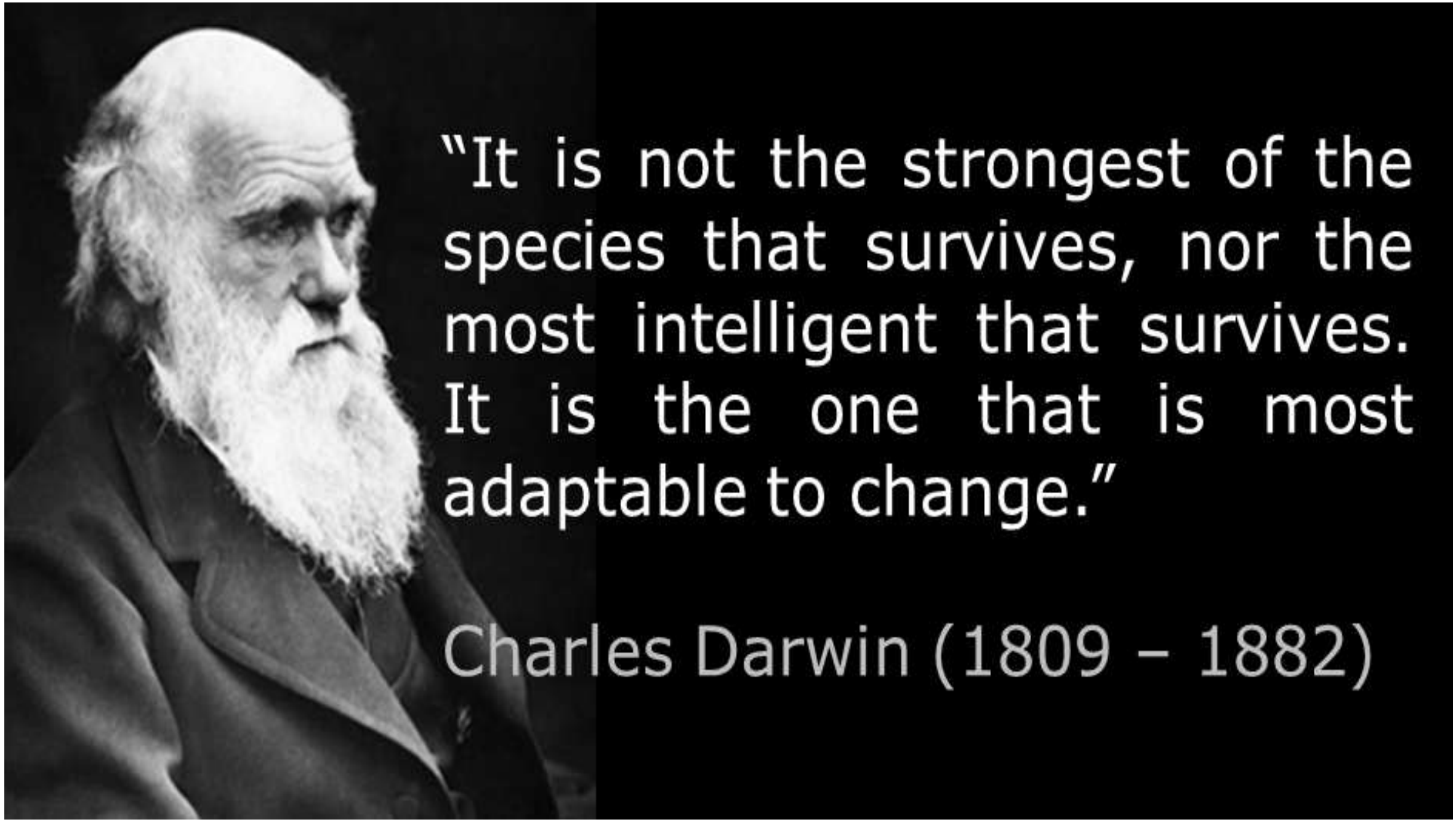
Substances regulating gene expression

DNA with all genes: **genome.**

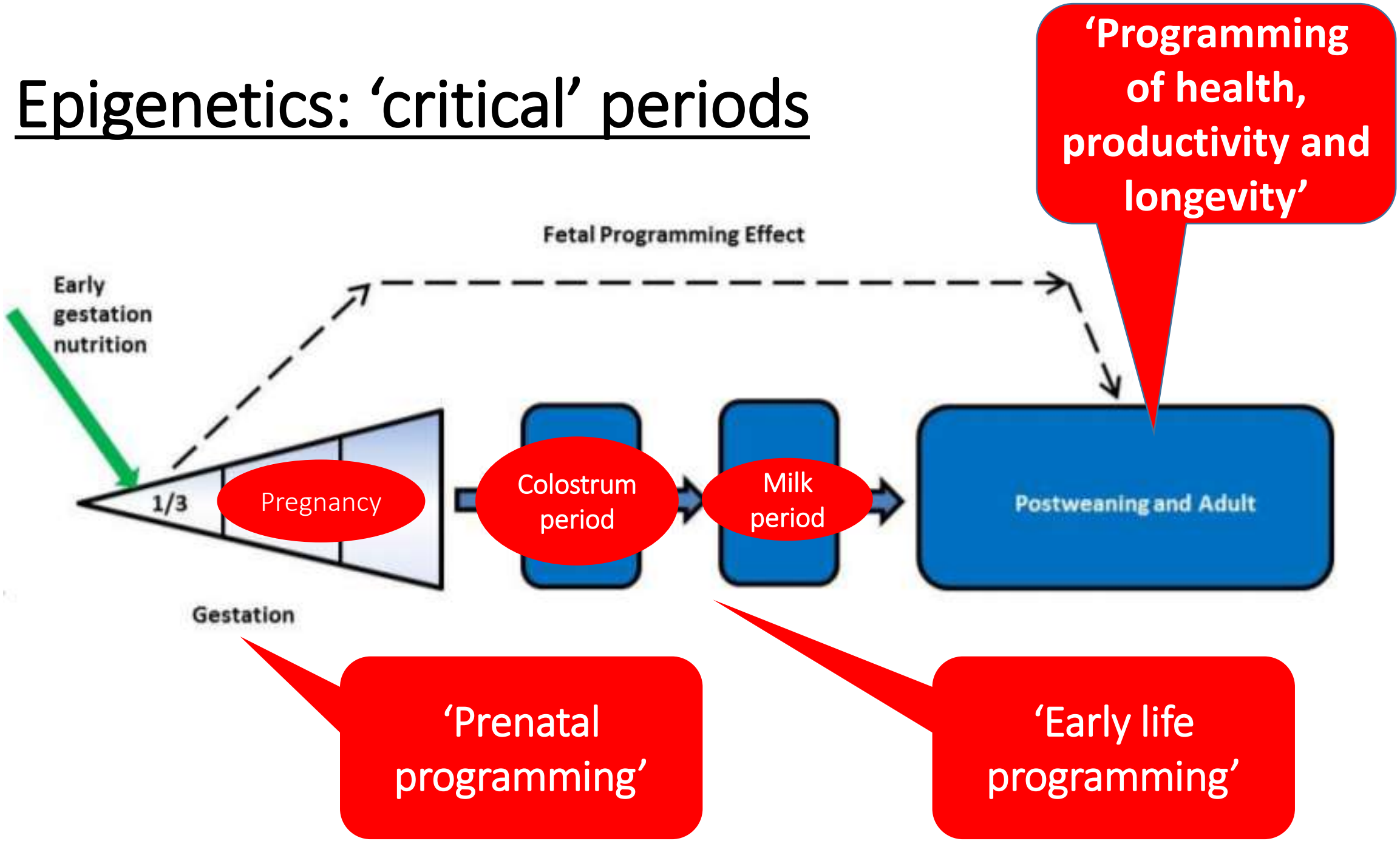
Genes are expressed or silenced

Diet (feed)
- Energy, protein
- Specific ingredients like methyl-donors

Management
- Stress management
- Improved welfare


"It is not the strongest of the species that survives, nor the most intelligent that survives. It is the one that is most adaptable to change."
Charles Darwin (1809 – 1882)

Epigenetics: 'critical' periods



Early life programming

Influences during ‘critical’ developmental periods

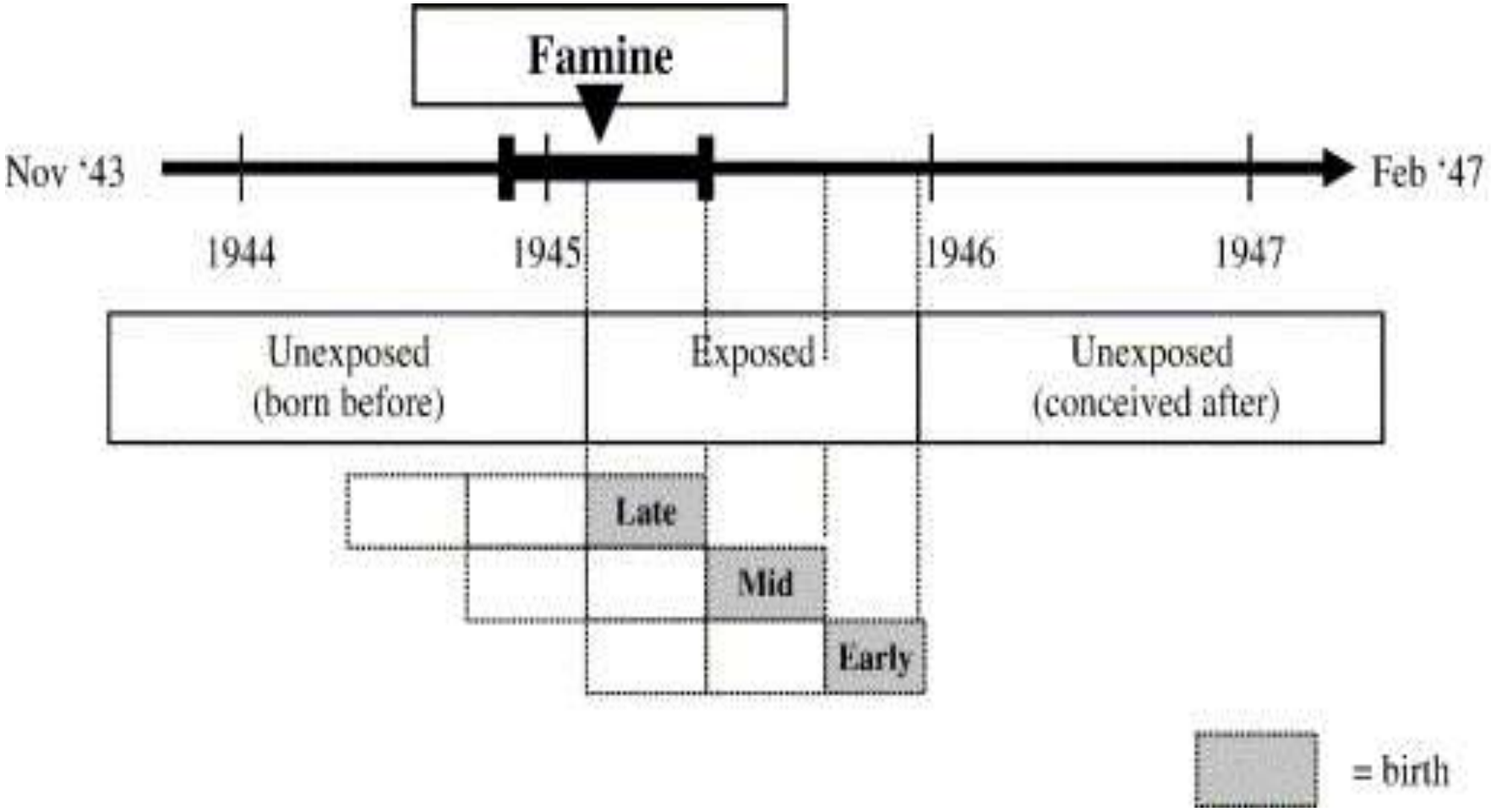
Permanent adjustment of an individual’s traits

Consequences in the short and long term for health, productivity and lifespan

Before birth (prenatal)

Early life programming: before birth

- Hunger Winter in the Netherlands (WW II)



Painter et al., 2005

Hunger Winter in the Netherlands (6 months – 1944–1945)

- Data on babies born during and after the Hunger Winter
  - birth weight: some babies exposed to famine during mid and early pregnancy had **lower** birth weights
- Data of these people 50 years later
- Health parameters at an age of ± 58 years
  - blood pressure
  - cancer incidence
  - glucose intolerance
  - IQ test

At an age of 50 and 58

- People exposed during <u>early pregnancy</u>:
  - ↑ cardiovascular disease
  - ↑ blood pressure in stressful situations
  - ↑ breast cancer (x5)
  - ↑ diabetes
    - ↓ glucose sensitivity and ↑ insulin secretion

      ⇒ insulin secretion defect
  - ↓ cognitive abilities

      ⇒ accelerated ageing of cognitive abilities?

Human/dairy cow comparison

HUMAN

undernourishment

during pregnancy

energy restriction for the embryo/foetus

birth weight
long-term health
consequences
longevity

DAIRY COW

high milk yield

and NEB

energy restriction for the embryo/foetus

birth weight
long-term health
lifetime milk production

Research Article

Season of Birth and Exceptional Longevity: Comparative Study of American Centenarians, Their Siblings, and Spouses

Leonid A. Gavrilov and Natalia S. Gavrilova

Center on Economics and Demography of Aging, NORC at the University of Chicago, 1155 East 60th Street, Chicago, IL 60637, USA

This study explores the effects of month of birth (a proxy for early-life environmental influences) on the chances of survival to age 100. Months of birth for 1,574 validated centenarians born in the United States in 1880–1895 were compared to the same information obtained for centenarians' 10,885 shorter-lived siblings and 1,083 spouses. Comparison was conducted using a within-family analysis by the method of conditional logistic regression, which allows researchers to control for unobserved shared childhood or adulthood environment and common genetic background. It was found that months of birth have significant long-lasting effect on survival to age 100: siblings born in September–November have higher odds to become centenarians compared to siblings born in March. A similar month-of-birth pattern was found for centenarian spouses. These results support the idea of early-life programming of human aging and longevity.

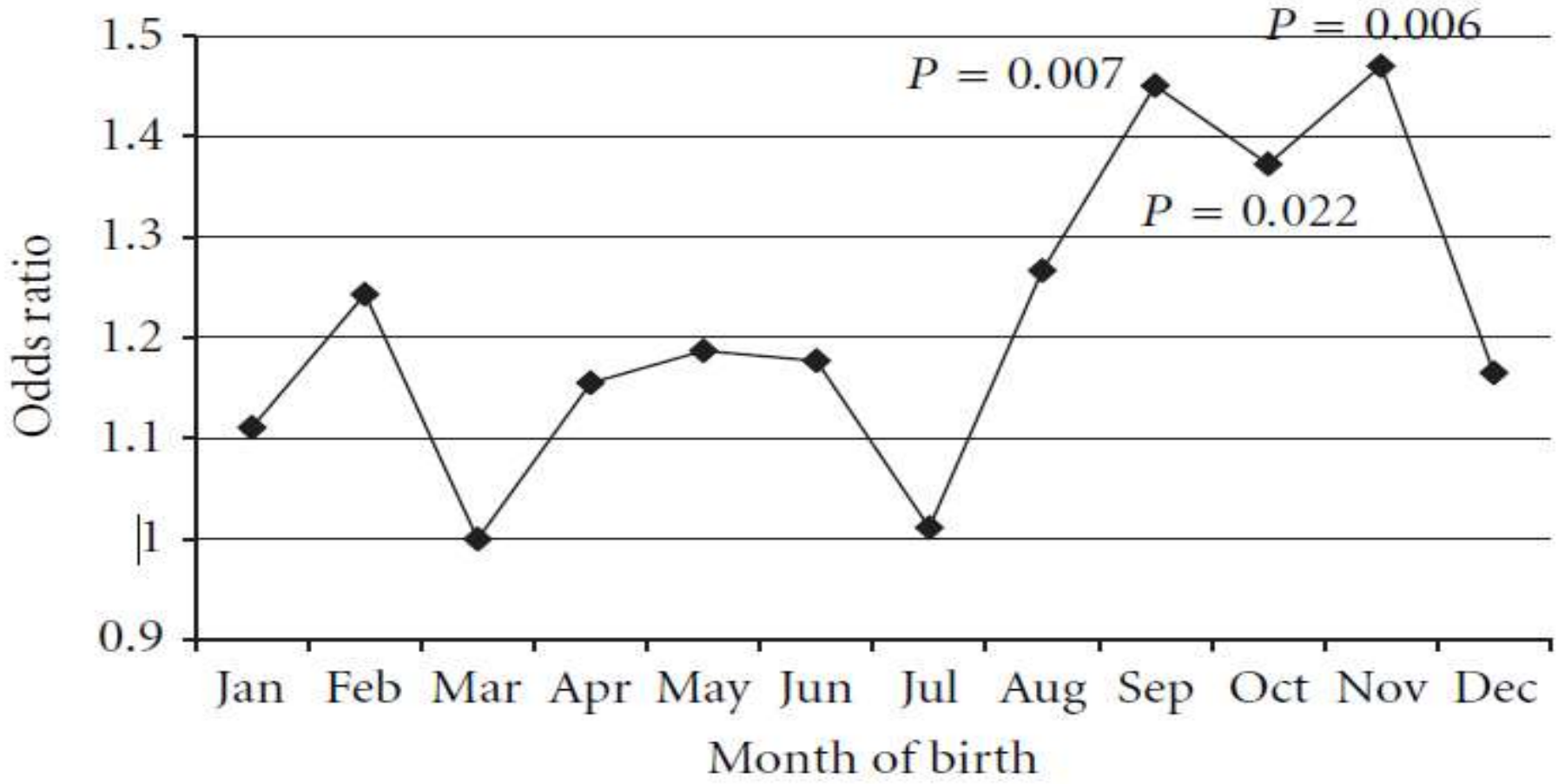


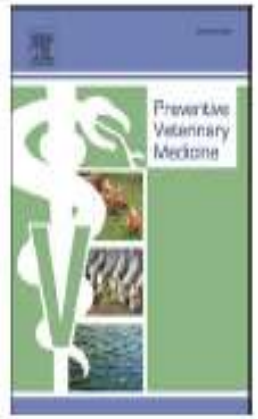
FIGURE 2: Month of birth and odds ratios for becoming a centenarian. A within-family-study of centenarians and their siblings survived to age 50 (9,724 studied persons). Being born in March is used as a reference level. Unadjusted *P* values are shown.

Preventive Veterinary Medicine 193 (2021) 105392

Contents lists available at ScienceDirect

Preventive Veterinary Medicine

journal homepage: www.elsevier.com/locate/prevetmed



Researching 100 t cows: An innovative approach to identify intrinsic cows factors associated with a high lifetime milk production

M. Van Eetvelde [a,*], K. Verdru [a], G. de Jong [b], M.L. van Pelt [b], M. Meesters [a], G. Opsomer [a]

[a] Department of Reproduction, Obstetrics and Herd Health, Faculty of Veterinary Medicine, Ghent University, Salisburylaan 133, 9820, Merelbeke, Belgium
[b] Cooperative CRV ua, Animal Evaluation Unit, PO Box 454, 6800 AL, Arnhem, The Netherlands

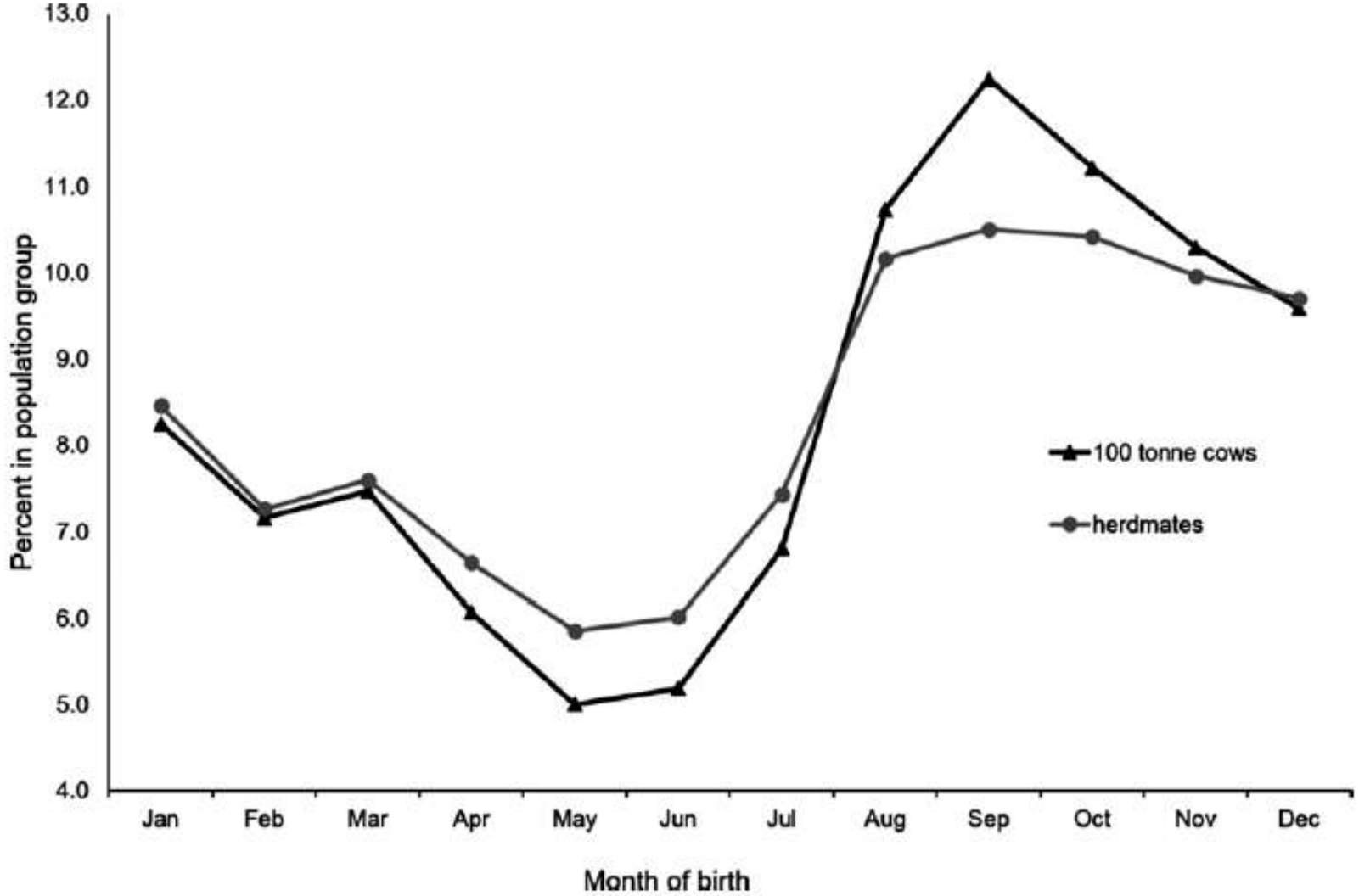


Fig. 2. Distribution of cows by month of birth. Values on the y-axis are percentages, adding up to 100 % within each population group (100 t cows and their herd mates).

Before birth

- Environment during pregnancy:
  - Immediate environment = dam:
    - age: mature milk producing cows vs. growing heifers
    - nutrition (grazing/pasture access)
    - health: infectious diseases – metabolic diseases
    - the level of milk yield during pregancy
    - …
  - Broader environment:
    - ambient temperature (heat stress)
    - day length
    - UV radiation
    - pollutants: endocrine disrupting agents (eg Bisfenol A: chemical present in polycarbonate plastics and epoxy resins acting as a xeno-estrogen disrupting fertility)
    - …

Birth weight

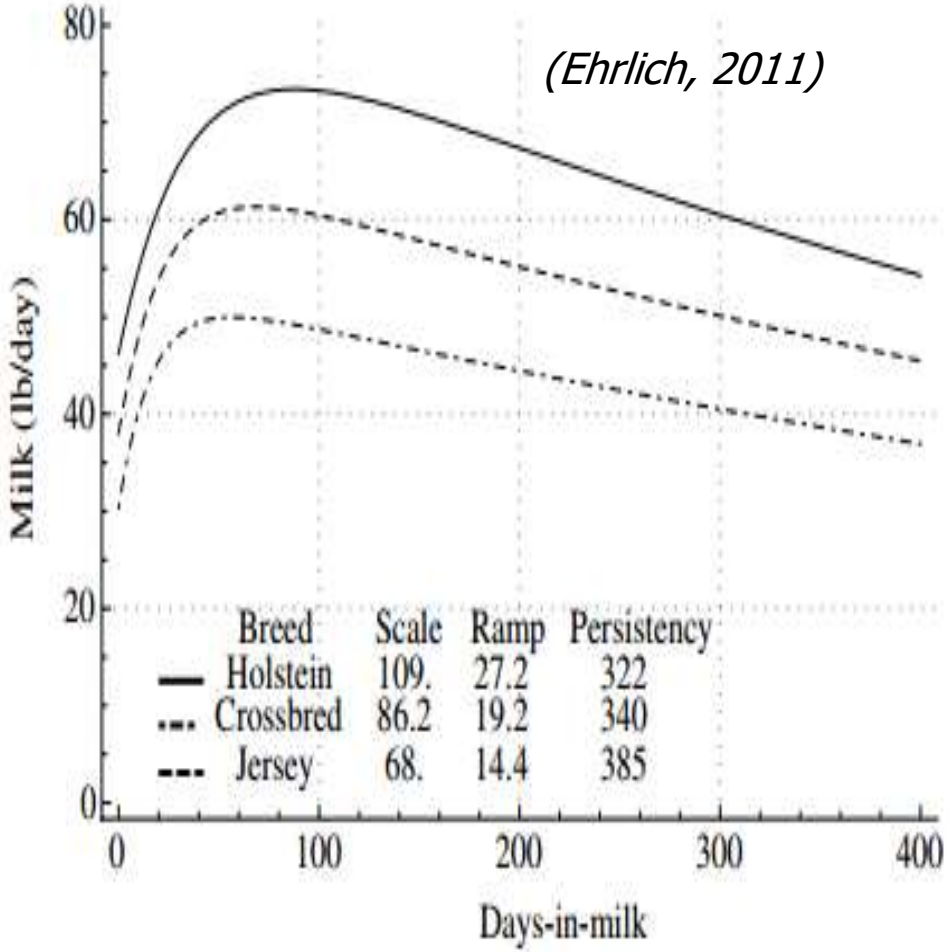
- Aim: assess effect of maternal body growth/ milk yield on fetal development

- Birth weight of 1,594 HF calves
  - 540 primiparous dams
  - 1,054 multiparous dams

Kamal et al., 2014

Birth weight

- Maternal factors:
  - parity / age
  - body measurements / body condition
  - lactation features (Milkbot)
    - during gestation
      - 6,193 kg milk
      - 446 kg glucose
      - 217 kg proteins



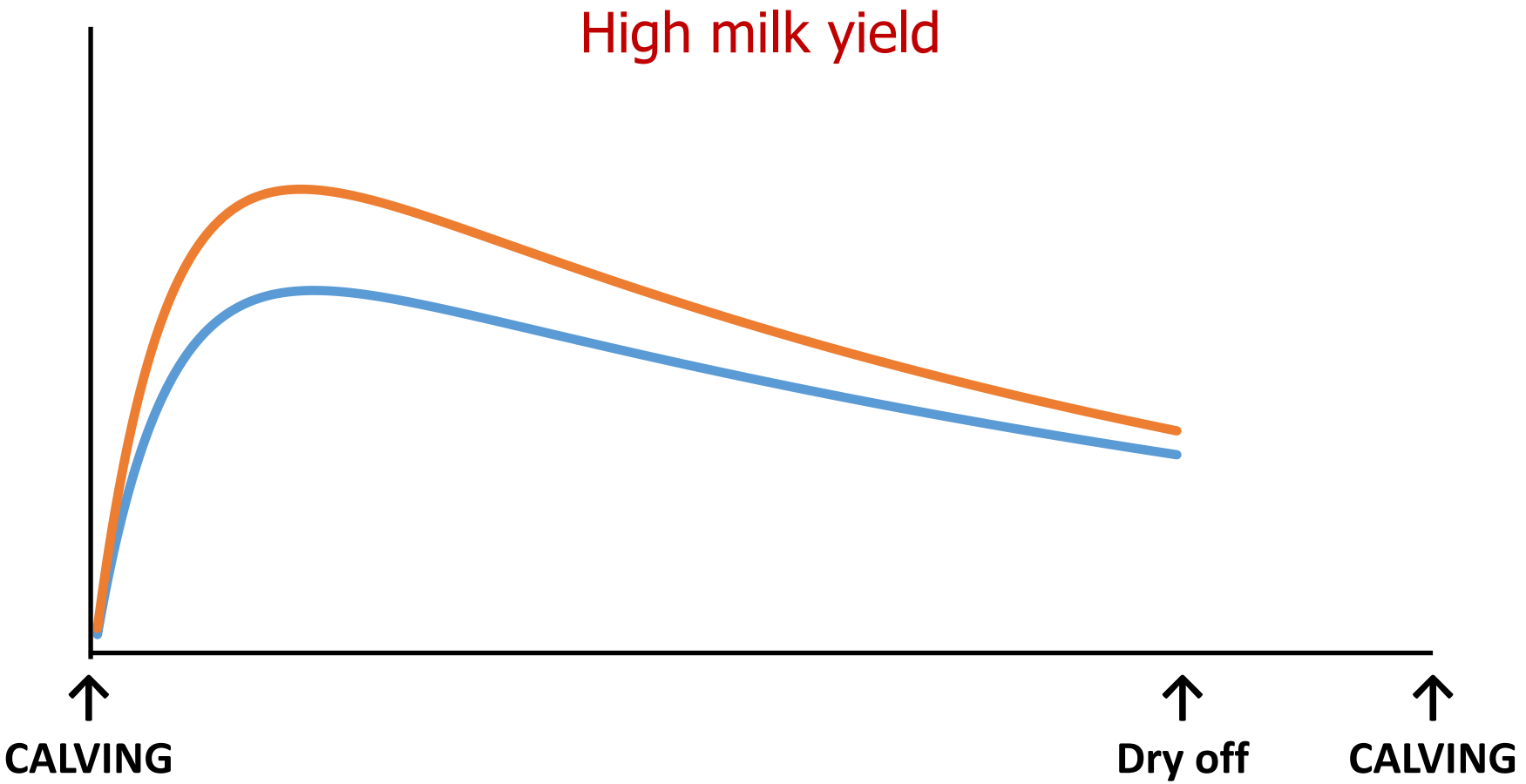
Kamal et al., 2014

Birth weight

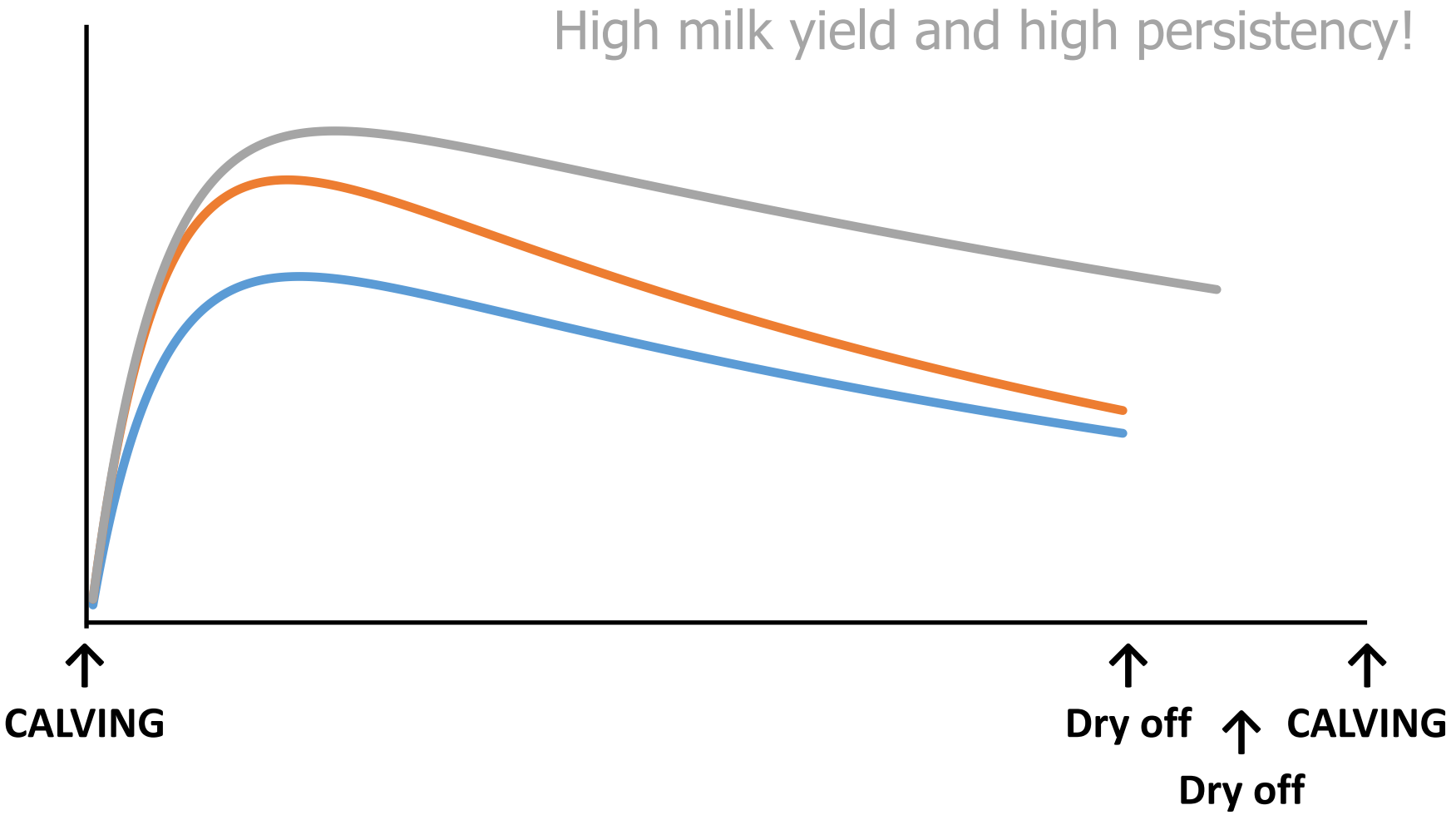
- Birth weight ↓:
  - female calves
  - primiparous dams
    - younger age at calving
  - multiparous dams
    - higher milk yield of dam during gestation
    - shorter dry period

Kamal et al., 2014

Birth weight

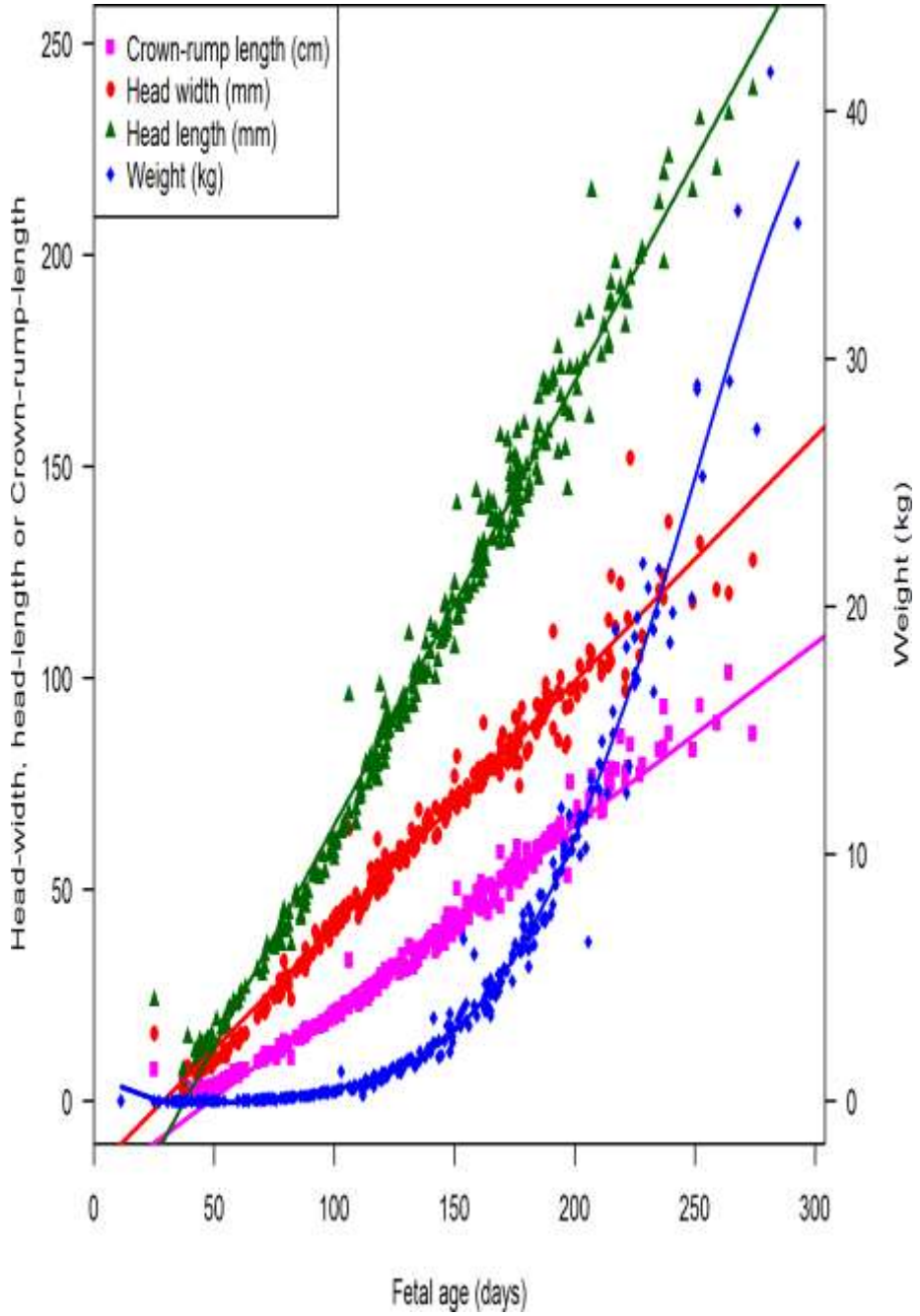


Birth weight



Before birth

- Exponential growth
  - Nutrition during the last months of pregnancy:
    → mainly affects size/weight
    farmers usually pay attention to this
  - BUT early pregnancy is crucial for organ development!
    → effect on later growth and muscle development
    → effect on later fertility
    → effect on later health



Calf metabolism

- Aim: assess effect of maternal body growth/ milk yield on metabolism of the neonatal calf

- 481 HF calves
  - basal glucose/insulin levels
    - proxy for insulin sensitivity
  - glucose stimulation (150 mg/ kg BW)
    - proxy for pancreatic development

Kamal et al., 2015

Calf metabolism

- ↑ basal insulin levels (more insulin resistant):
  - female calves
  - multiparous dams
    - *higher milk yield of dam during gestation*
    - *longer dry period*

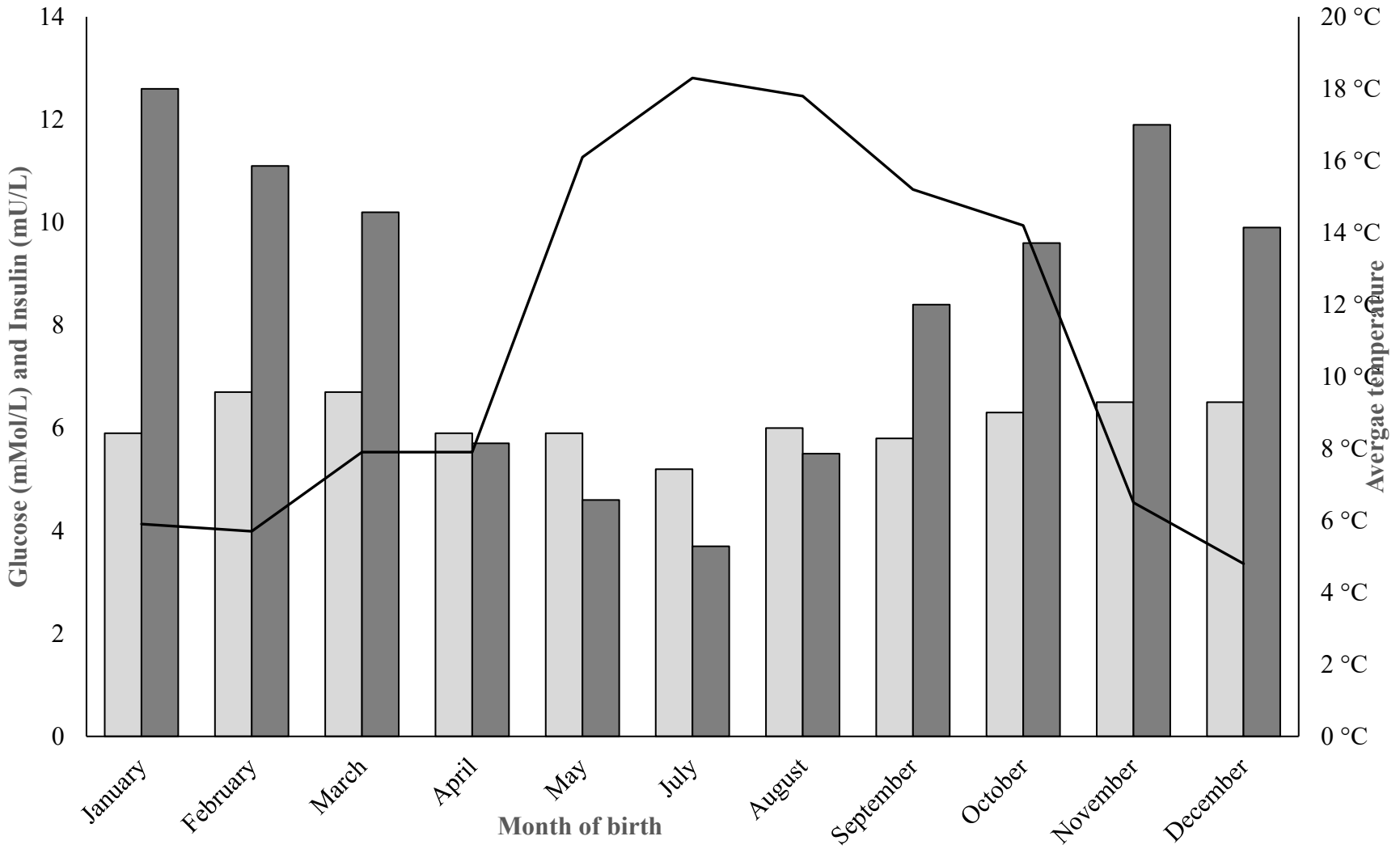
Kamal et al., 2014

Birth season

- Born during 'hotter' months
  - lower birth weights
  - higher insulin sensitivity in newborn calves

- High temperature at the end of pregnancy → sweating of the cows (peripheral vasodilatation) → less blood to the uterus → decreased nutrient supply to the fetus at the end of gestation?

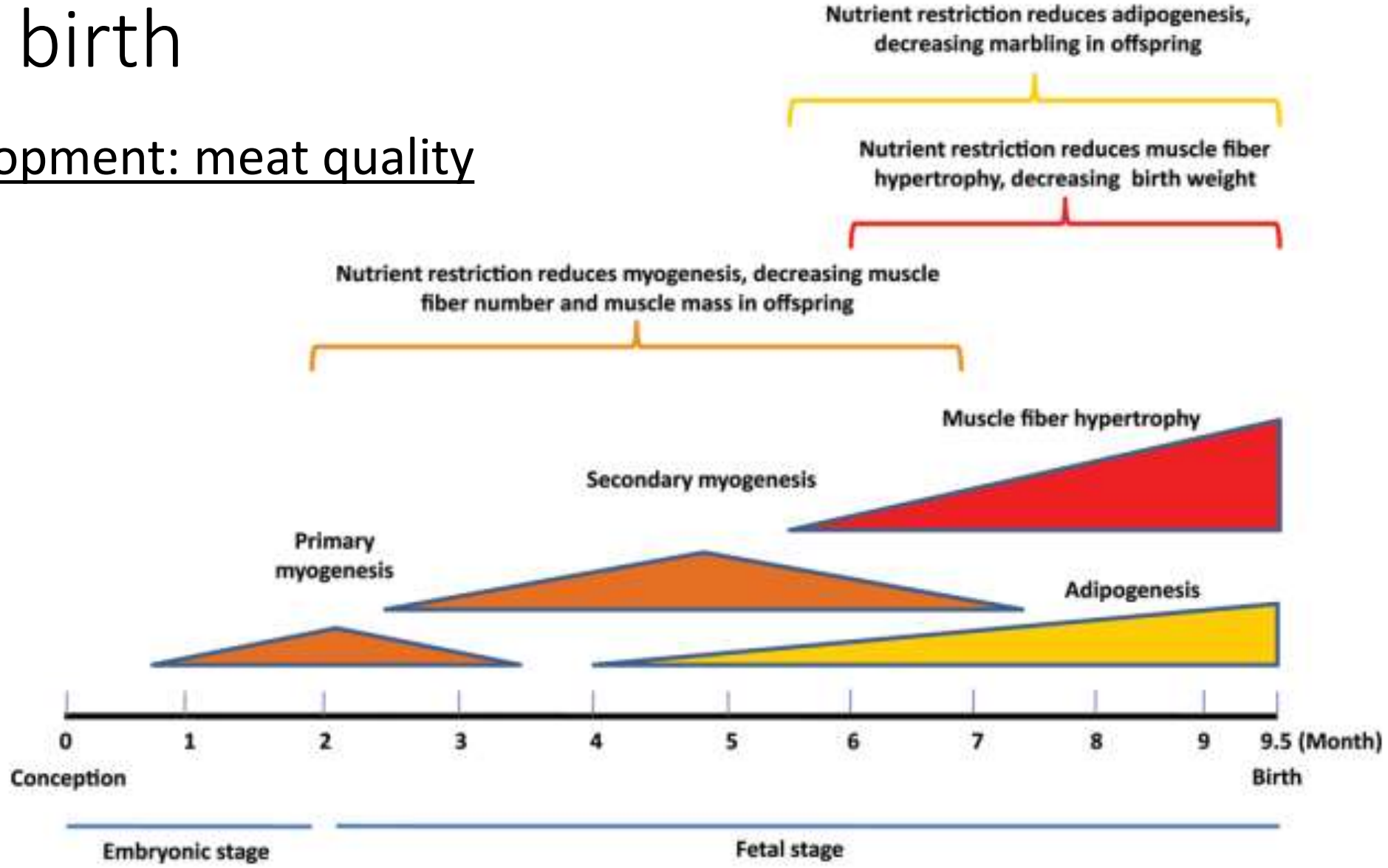
Kamal et al., 2014 and 2015; Van Eetvelde et al., 2016



Van Eetvelde et al., under review

Before birth

- Muscle development: meat quality



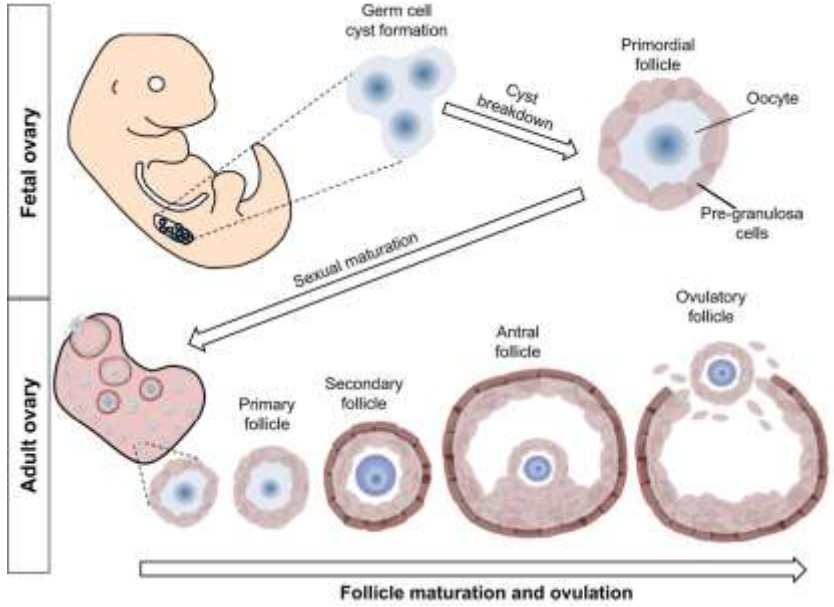
Before birth

- <u>Muscle development</u>
  - Number of muscle fibres is ~ formed by 8 months of gestation!
  - Undernutrition of dams in early–mid gestation:
    - Daily growth of offspring ≈
    - More fat – less muscle mass at slaughter
  - Extra protein supplementation early–mid gestation (0.5 kg 42% CP):
    - ↑ lean growth of offspring
    - ↑ marbling

Du et al., 2010; Long et al., 2015

Before birth

- <u>Ovary development</u>



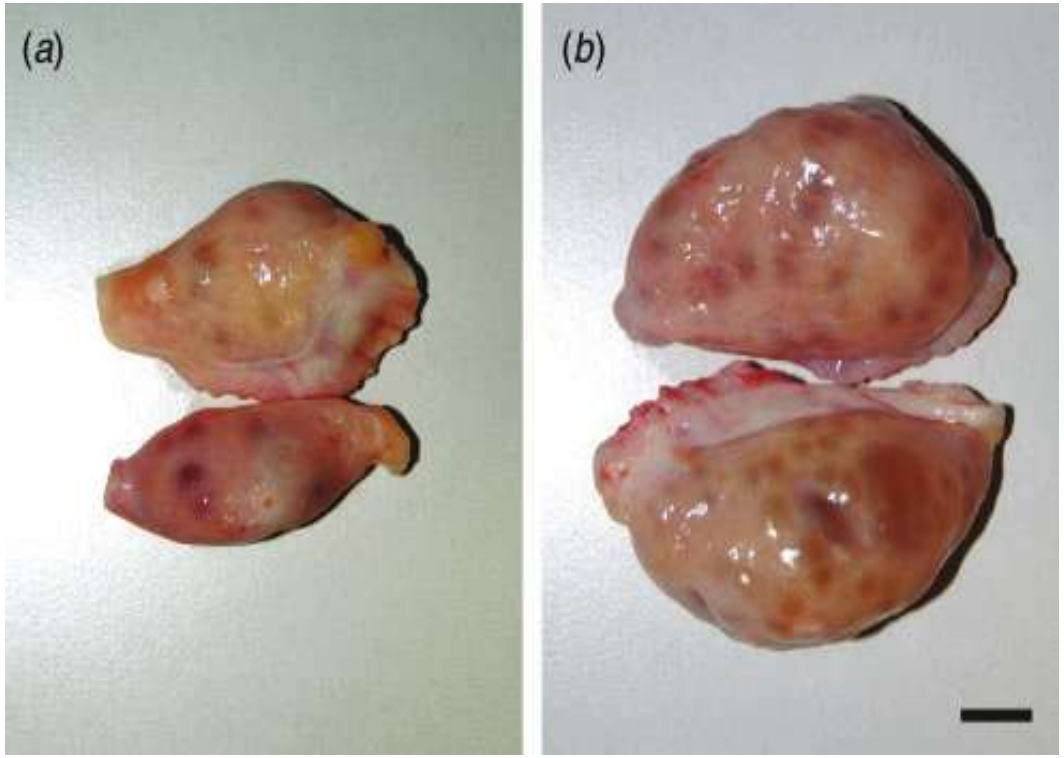
  - Oocyte development in the fetus starts between 90 and 140 days of gestation!

  - Undernutrition at the start of pregnancy:
    → no effect on newborn calf size
    → effect on offspring fertility (1.5–2 years later!)

Du et al., 2010; Long et al., 2015

Before birth

- <u>Ovary development</u>
  - ↓ energy supply to pregnant beef heifers
    - 60% of requirements day -11 to 110
    - 100% from day 110 to end of pregnancy

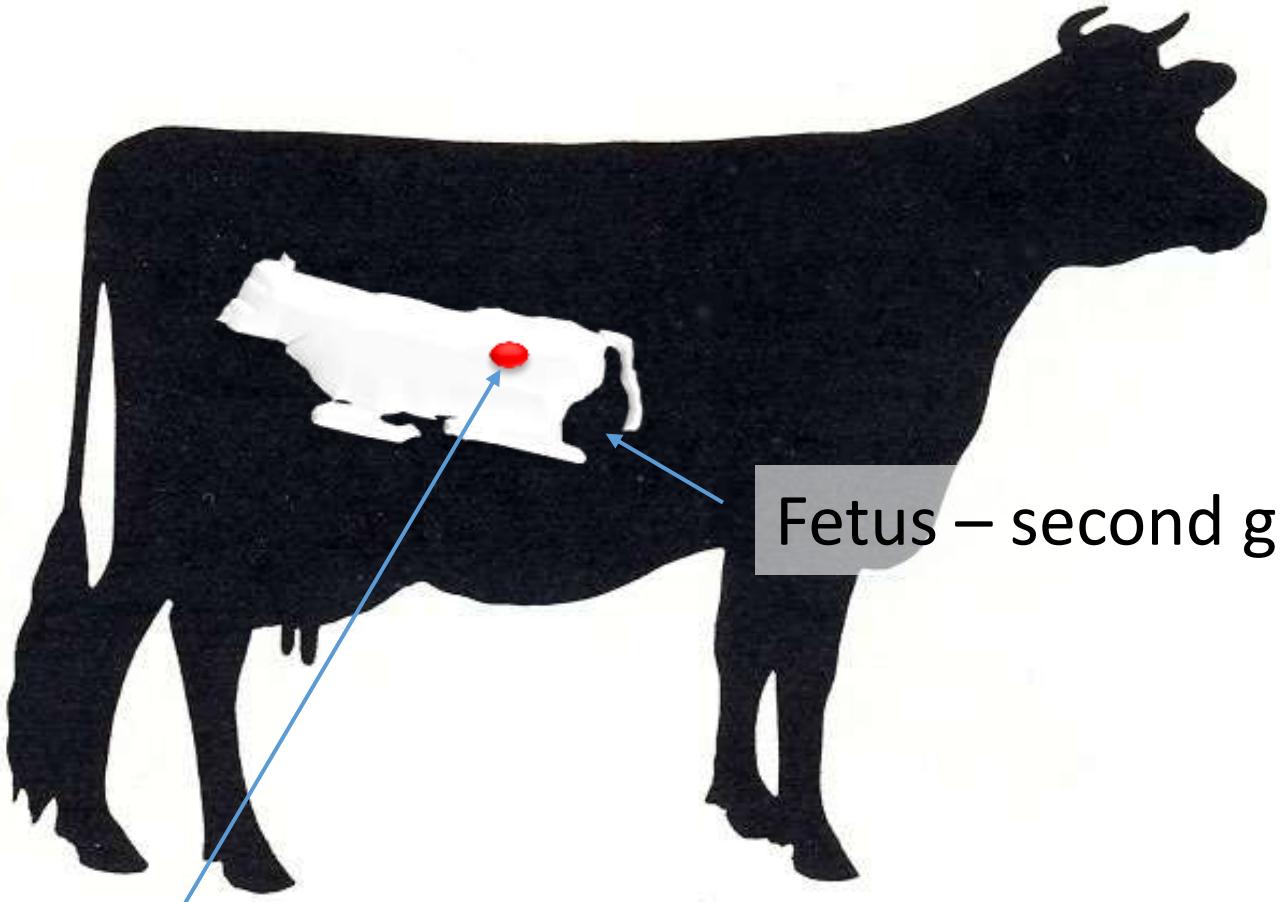


- Lower ‘reserve’ of follicles in female offspring → ↓ pregnancy % after first AI

→ ↑ animals not pregnant at end of season and longer calving intervals

Mossa et al., 2013

Mother – first generation



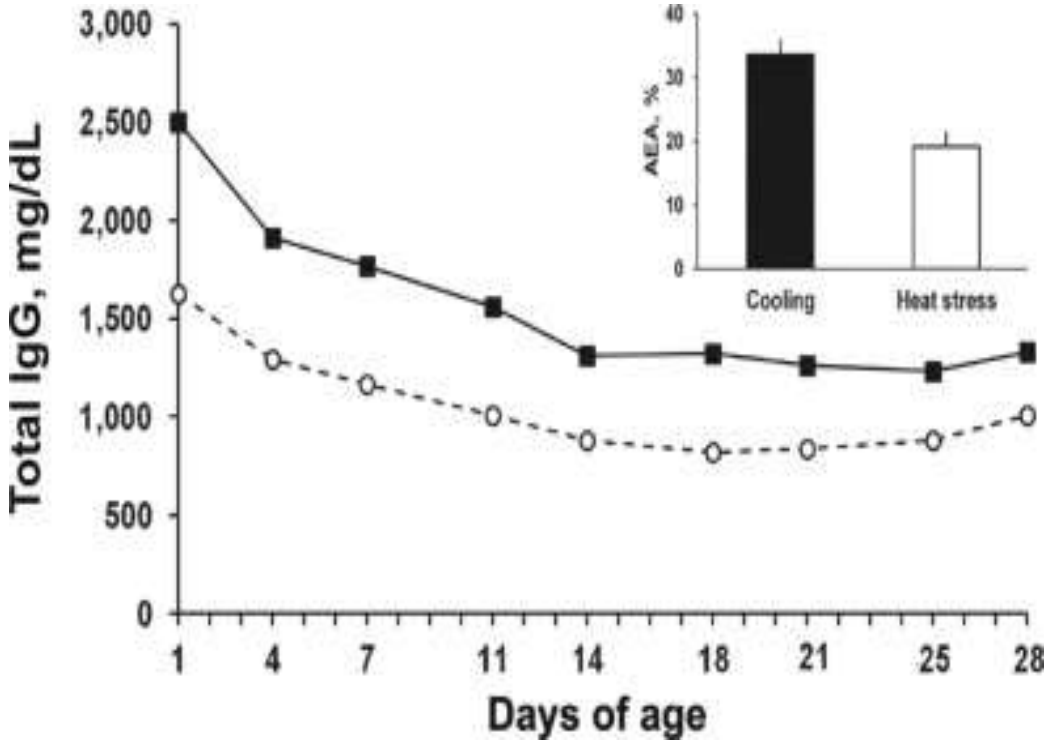
Fetus – second generation

Reproductive cells – third generation

Before birth

- High ambient temperatures during pregnancy

- ↓ immunity
  - ↓ colostrum antibody absorption efficiency
  - ↓ development of active immunity



Tao et al., 2012; Monteiro et al., 2014

Before birth

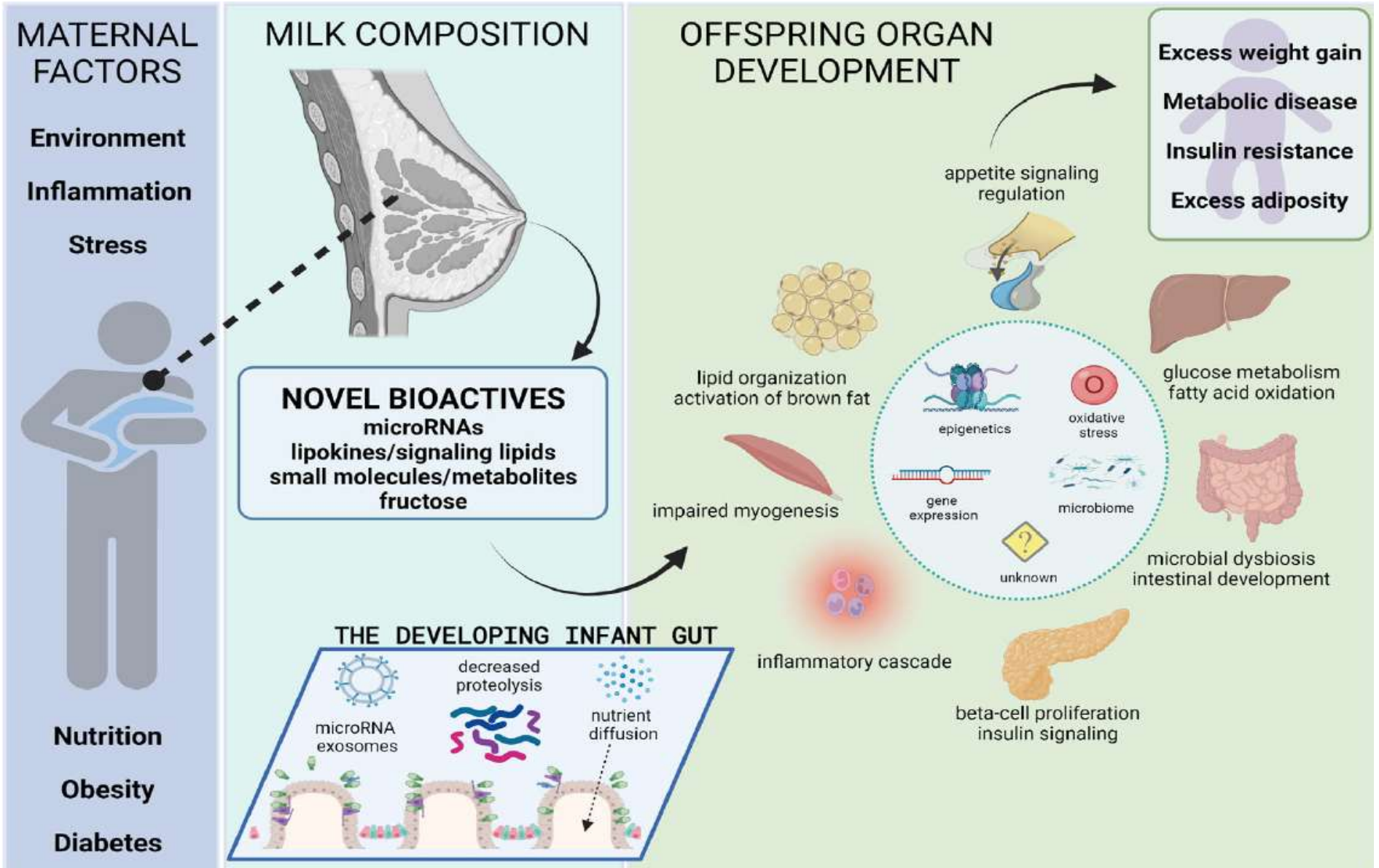
- High ambient temperatures during pregnancy:
  ↓ placental and fetal growth

- ↓ birth weight
- ↓ pre-weaning growth
- ↓ immunity

Tao et al., 2012; Monteiro et al., 2014

Colostrum period

Lactocrine programming



Bovine colostrum to supplement the first feeding of very preterm infants: The PreColos randomized controlled trial

June 2023 · Clinical Nutrition · 42(8)
DOI: 10.1016/j.clnu.2023.06.024

Bovine Colostrum for Preterm Infants in the First Days of Life: A Randomized Controlled Pilot Trial

Sandra Meinich Juhl [1], Xuqiang Ye [2], Ping Zhou [3 4], Yanqi Li [5], Elisabeth Omolabake Iyore [1], Lixia Zhang [2], Pingping Jiang [5], Johannes B van Goudoever [6 7], Gorm Greisen [1], Per Torp Sangild [5 8]

Affiliations + expand
PMID: 29019855 DOI: 10.1097/MPG.0000000000001774

Systemic immune markers and infection risk in preterm infants fed human milk fortified with bovine colostrum or conventional fortifier, a secondary analysis of the FortiColos trial

Ole Bæk [1 2], Tik Muk [1], Lise Aunsholt [2 3], Gitte Zachariasen [4 5 6], Per Torp Sangild [7 8 9 10], Duc Ninh Nguyen [11]

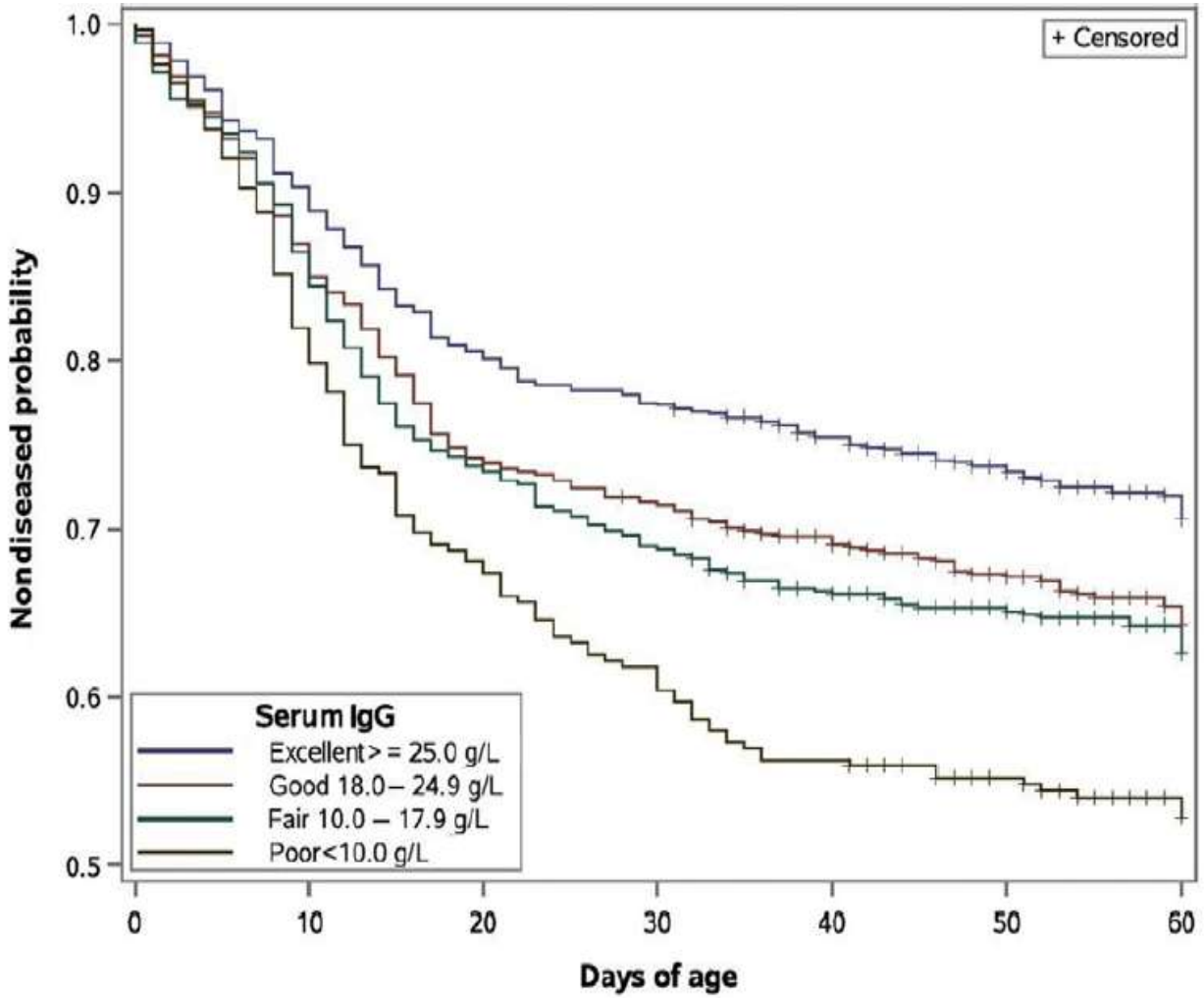
Randomized Control Trials

Bovine colostrum as a fortifier to human milk in very preterm infants – A randomized controlled trial (FortiColos) ☆

Agnethe May Ahnfeldt [a], Lise Aunsholt [a b], Bo Moelholm Hansen [c], Bente Hoest [d], Valdís Jóhannsdóttir [e], Susanne Soendergaard Kappel [a b], Anja Klamer [f], Sören Möller [g l], Bertha Kanijo Moeller [h], Per Torp Sangild [a b e l], Ann Lawaetz Skovgaard [i], Gerrit van Hall [j], Louise Dyrberg Vibede [k], Gitte Zachariassen [e g l] ✉

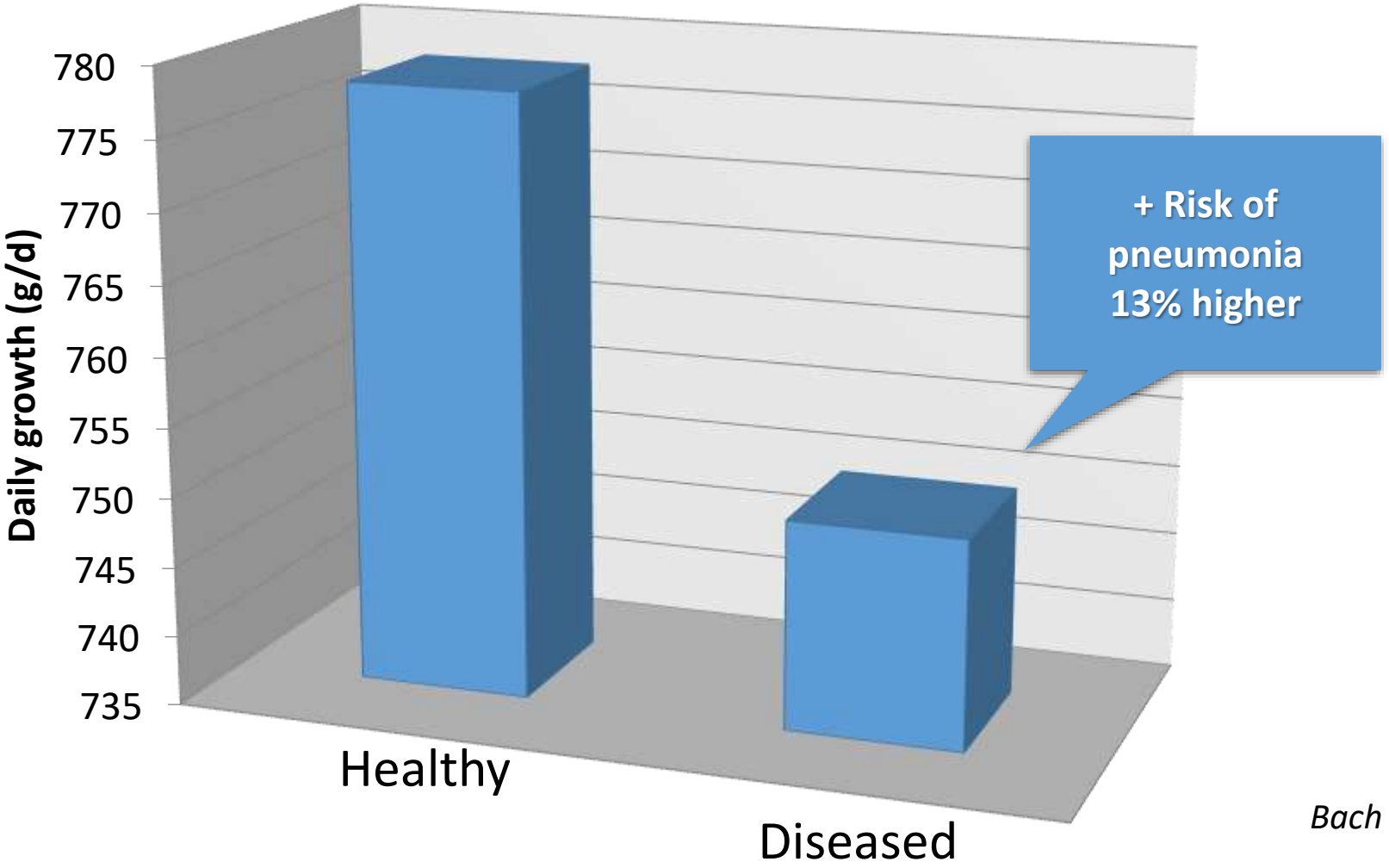
Colostrum period

- Affects % mortality and disease before weaning



Colostrum period

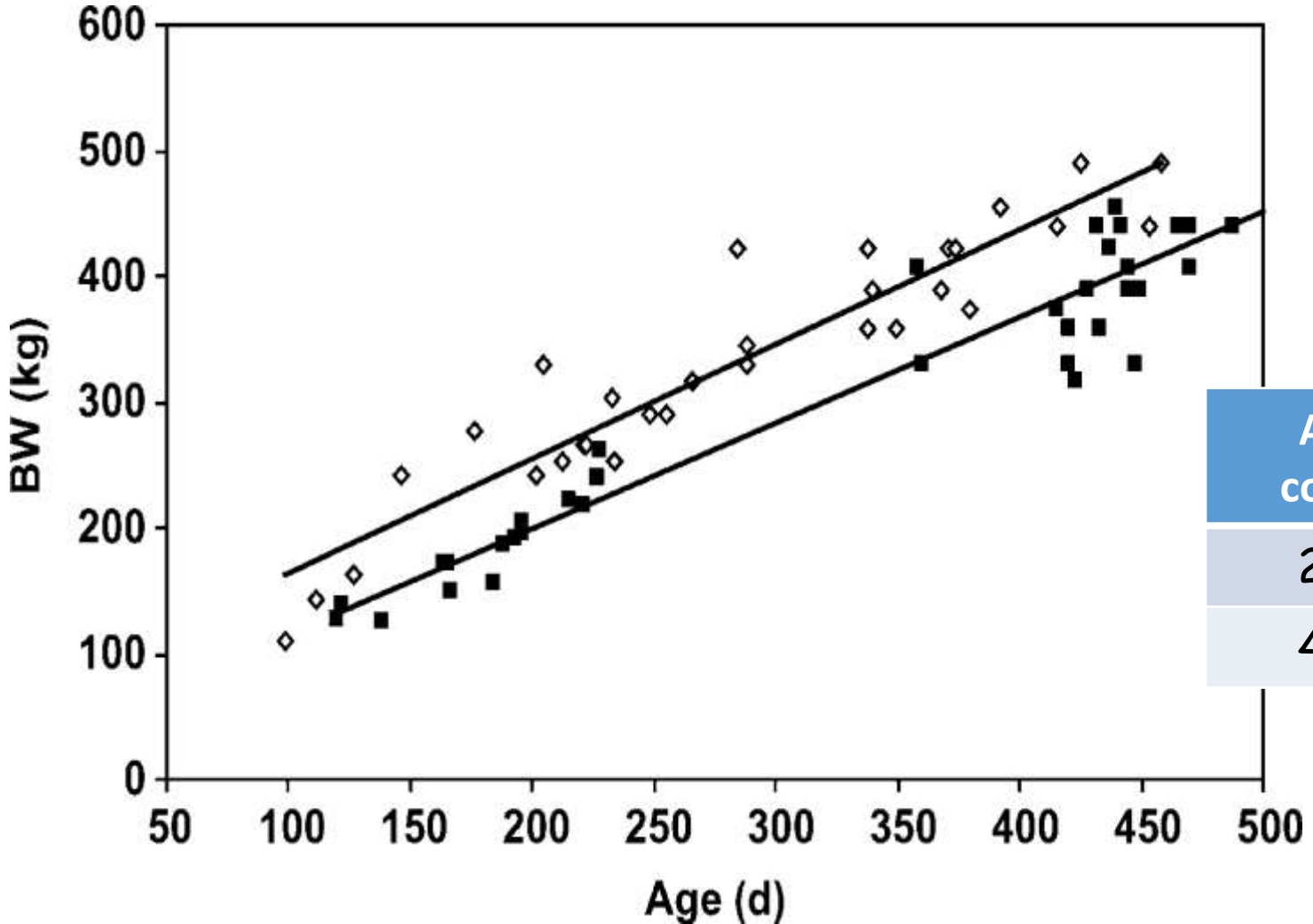
- Affects short-term growth (due to less disease)



Bach and Ahedo, 2008

Colostrum period

- Also affects longer-term growth!
  - reason: the calf must develop more immunity itself and that costs energy



Amount colostrum	Growth (g/day)
2 litres	800
4 litres	1030

Colostrum period

- Monitor immunity!
  - In colostrum: > 50 g Ig/L
    - Brix refractometer: > 22% Brix

Brix (%)	IgG (g/l)
< 15	< 28
15-21	28-49
22-30	50-80
> 30	> 80

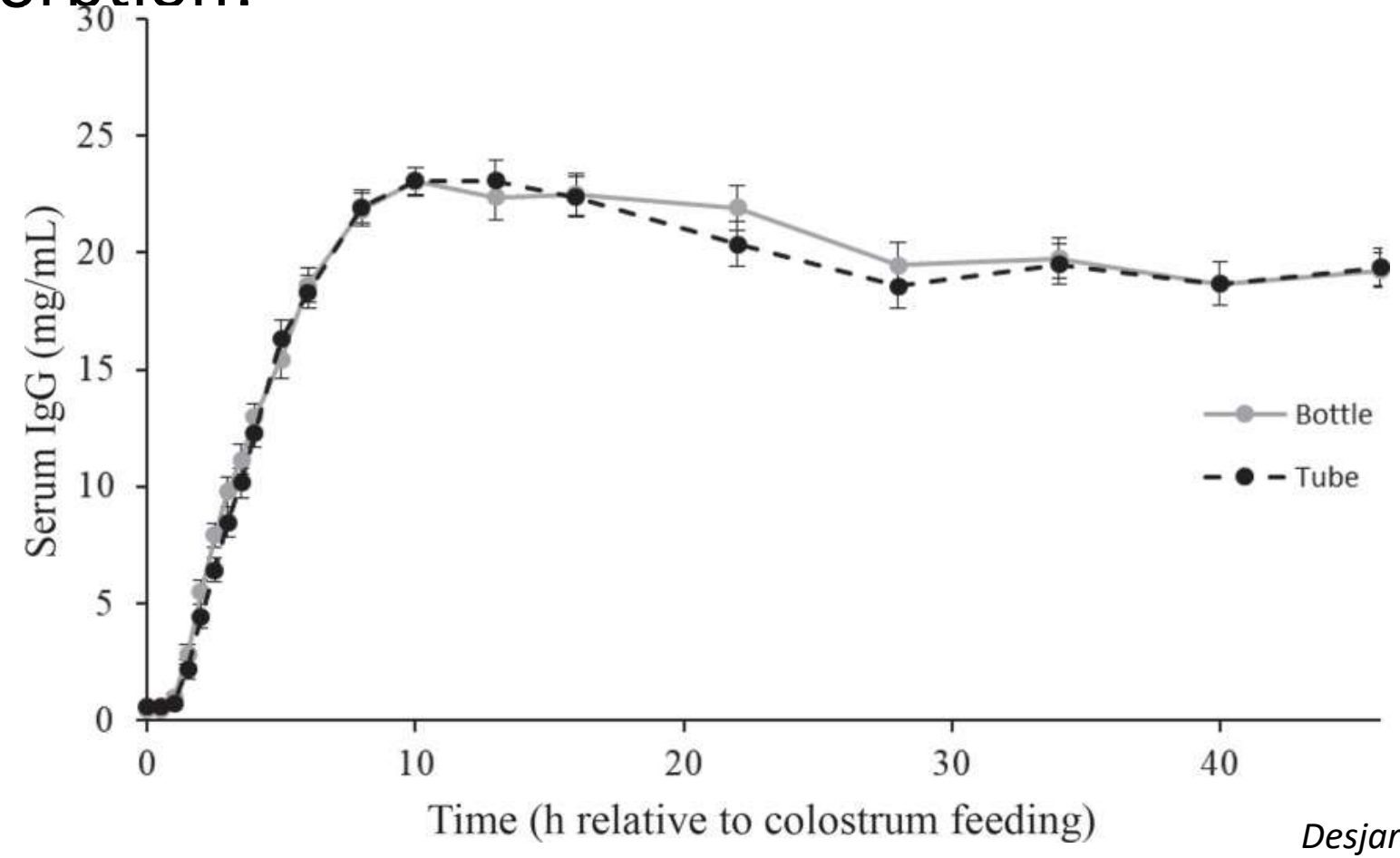
Colostrum period

- Monitor immunity!
  - In blood:
    - Gamma globulin: > 10 g/L
    - Total protein: > 55g/L

Identificatie Staalnr.	841 (001)	842 (002)	843 (003)	844 (004)	
	Resultaat	**Resultaat**	**Resultaat**	**Resultaat**	**Ref. DGZ**
A/G ratio (Electroforese)	0,56	0,34	0,36	0,46	0,84 - 0,94
Albumine (%)	35,9 %	25,3 %	26,7 %	31,7 %	> 38 %
Albumine (g/l)	19,0 g/l	18,0 g/l	21,1 g/l	20,6 g/l	27,3 - 36,5 g/l
Alpha Globuline (%)	26,9 %	25,8 %	16,6 %	21,0 %	12 - 16 %
Alpha Globuline (g/l)	14,3 g/l	18,3 g/l	13,1 g/l	13,7 g/l	7,5 - 15,7 g/l
Beta Globuline (%)	18,5 %	17,3 %	15,1 %	18,1 %	9 - 13 %
Beta Globuline (g/l)	9,8 g/l	12,3 g/l	11,9 g/l	11,8 g/l	5,5 - 9,4 g/l
Gamma Globuline (%)	18,7 %	31,6 %	41,6 %	29,2 %	31 - 36 %
Gamma Globuline (g/l)	9,9 g/l	22,4 g/l	32,9 g/l	19,0 g/l	
Totaal eiwit	53,00 g/l	71,00 g/l	79,00 g/l	65,00 g/l	65 - 75 g/l

Colostrum period

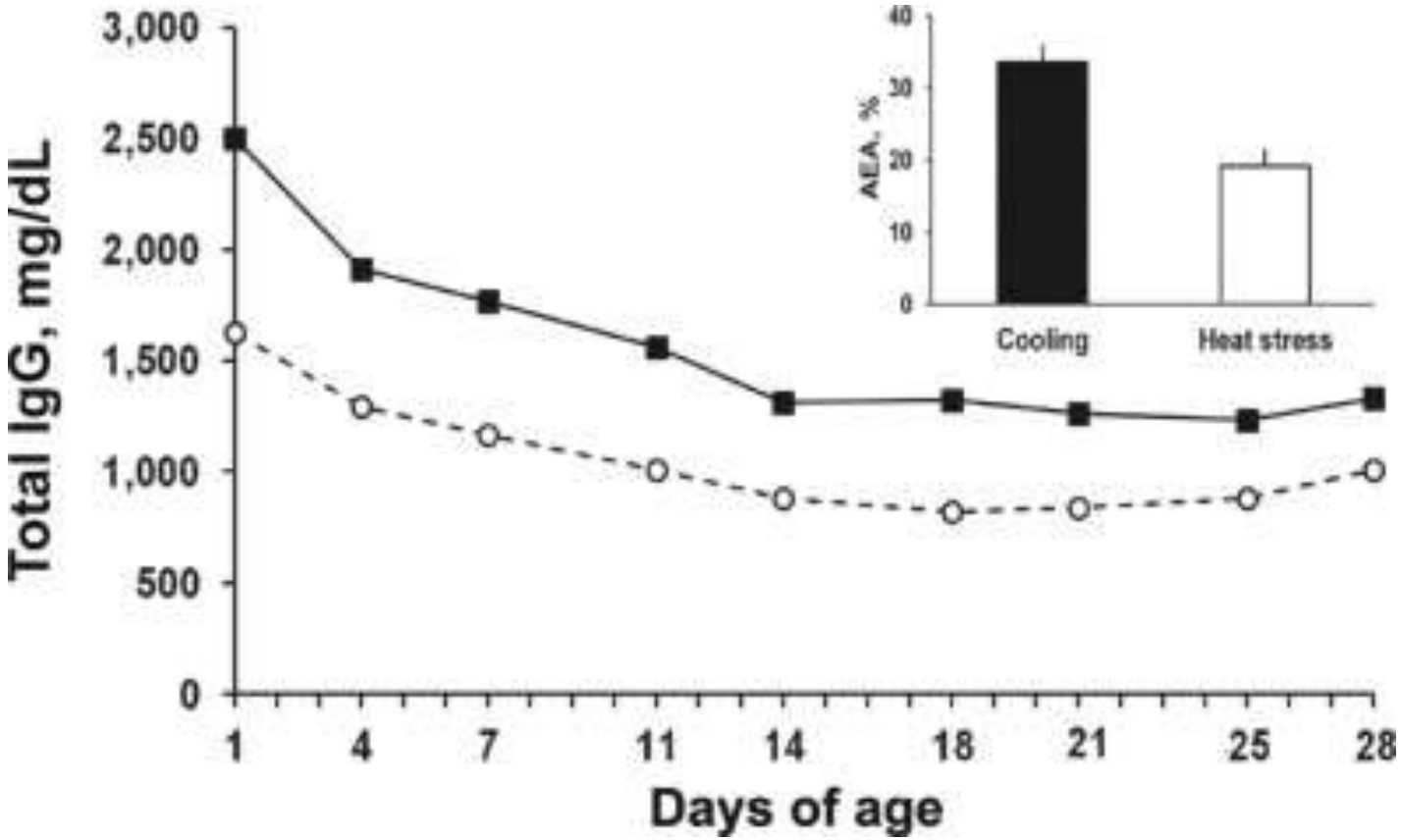
- Method of administration: no difference in antibody absorption!



Desjardins-Morrissette et al., 2018

Colostrum period

- <u>Absorption</u> efficiency: decreases with heat stress!
  - so in summer also be sure to provide enough colostrum!!



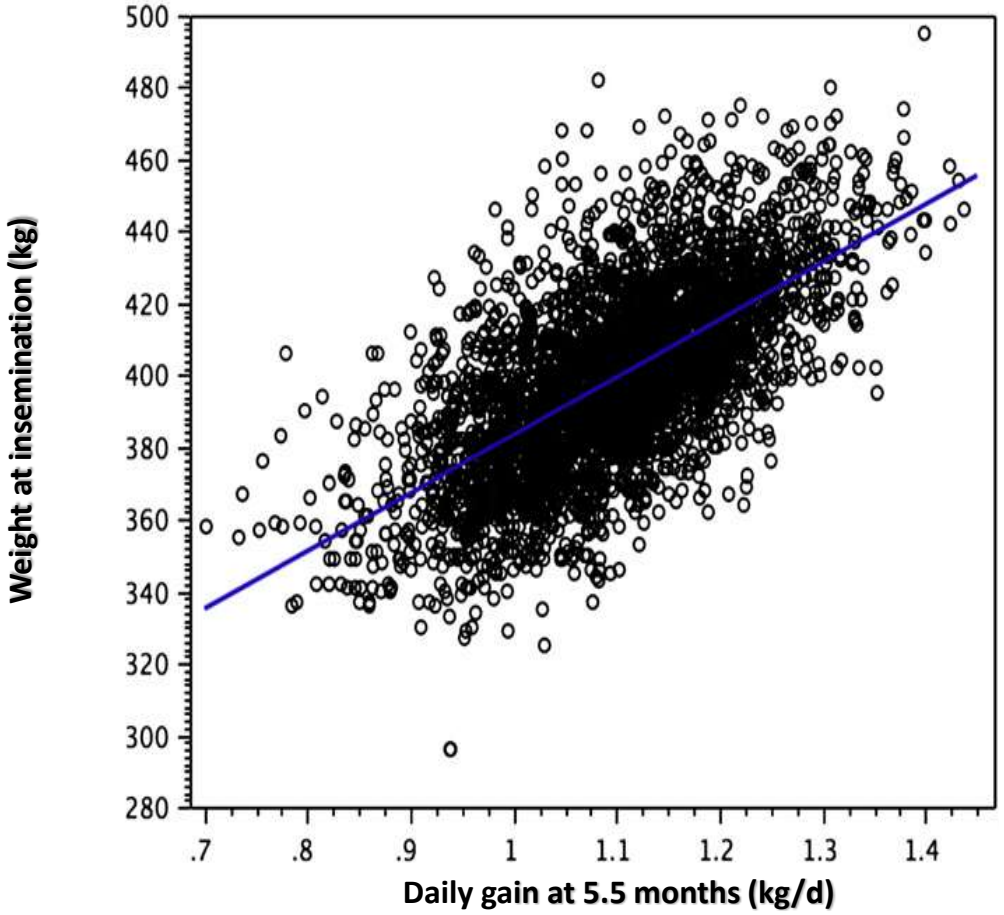
Tao et al., 2012

Milk period

Milk period

- In all cattle:

  growth during the first months affects weight at insemination



Bach & Ahedo, 2008

Milk period

- In all cattle:

  growth during the first months affects age at first breeding and at first calving

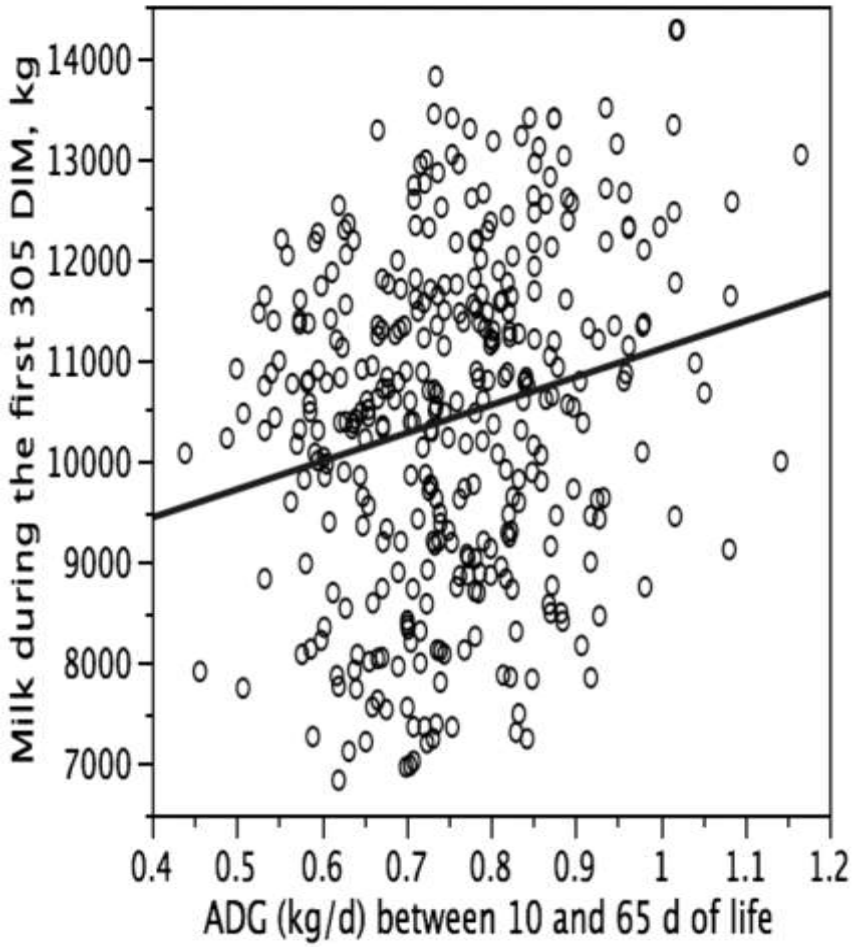
Growth period	Variable	AFB	AFC	S/C
30 to 180 d	BW (kg/d)	−124***	−94**	
	Girth (cm/d)	−370***	−346***	
	CRL (cm/d)	−253***	−253***	
	HT (cm/d)	−531***	−490***	

Brickell et al., 2009

Milk period

- In dairy cattle:

  pre-weaning growth affects milk yield during the 1st lactation



Bach & Ahedo, 2008

Milk period

- Effect of higher milk intake on organ development: 5 liters of milk (125 g/L) versus 10 liters of milk

Restricted: 0.6 kg/d MR

Enhanced: 1.3 kg/d MR

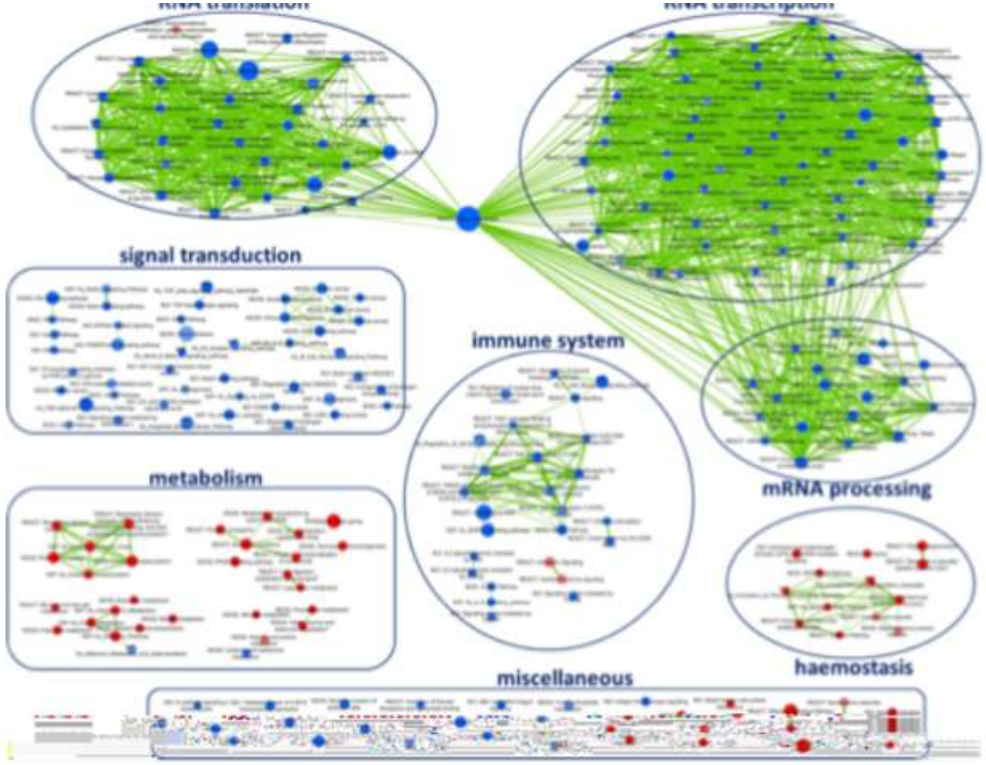
	Restricted (n=6)	Enhanced (n=6)	*P* value
Pancreas, g	32.90	29.47	0.61
Pancreas, % of BW	0.06	0.04	0.11
Liver, kg	1.35	2.35	< 0.01
Liver, % of BW	**2.23**	**2.84**	**< 0.01**
Kidney, g	183.60	319.72	0.02
Kidney, % of BW	**0.30**	**0.38**	**0.09**
Mammary gland, g	75.48	337.58	< 0.01
Parenchyma, g	1.10	6.48	< 0.01
Parenchyma, % of BW	**0.002**	**0.008**	**< 0.01**

Soberon & Van Aburgh, 2017

Milk period

- Effect of higher milk intake on gene expression → EPIgenetics (effect on next generation??)

	Changed (P<0.01)
Mammary	654
Fat	1045
Liver	176
Bone marrow	435
Muscle	651
Pancreas	103



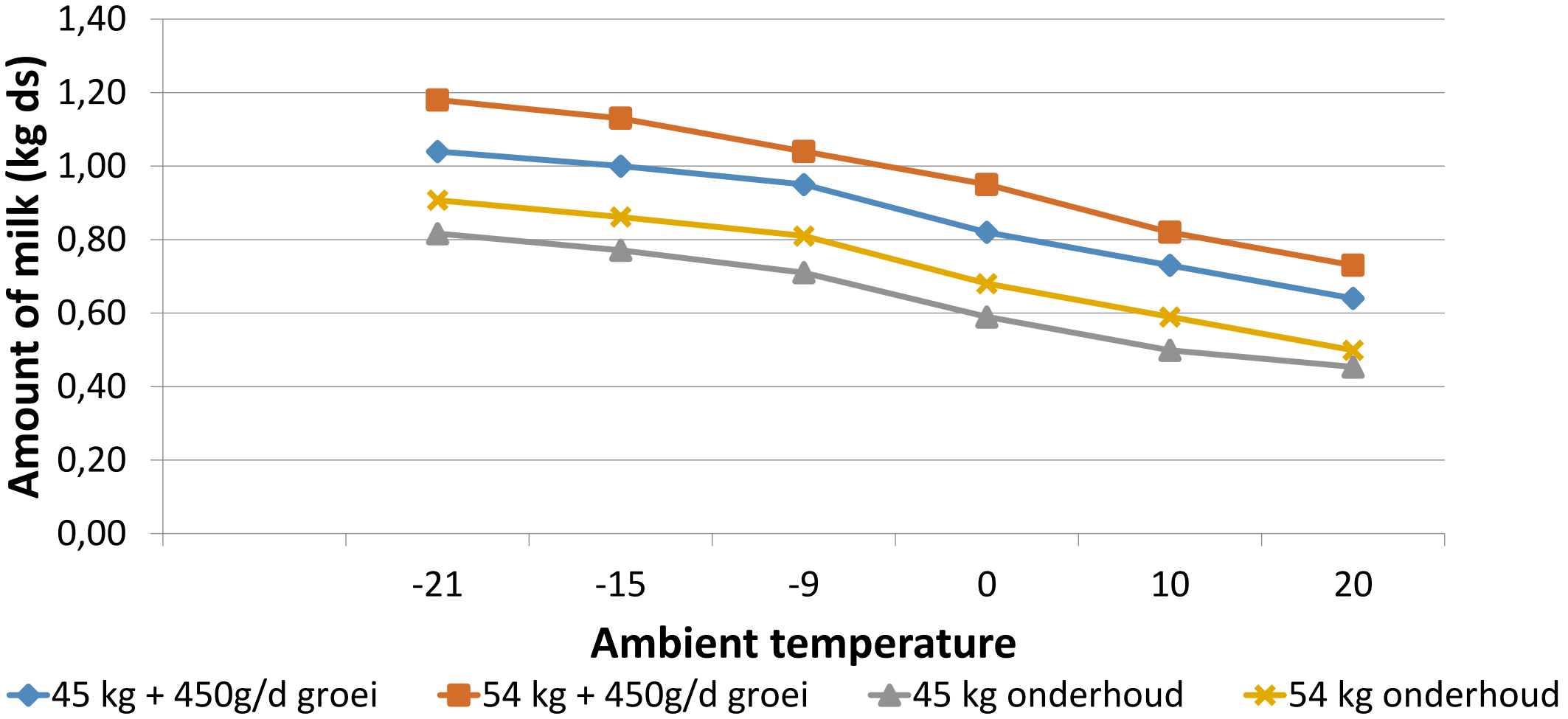
Leal et al., 2018; Hare et al., 2019

Milk period

- How to increase milk allowance?
  - Total DM intake is important!
  - Depends on requirements!
    - maintenance
    - growth

depending on ambient temperature!

Milk period


1,40
1,20
1,00
0,80
0,60
0,40
0,20
0,00
Amount of milk (kg ds)
-21
-15
-9
0
10
20
Ambient temperature
45 kg + 450g/d groei
54 kg + 450g/d groei
45 kg onderhoud
54 kg onderhoud

Milk period

- Voluntary intake of milk replacer (20% protein and 150 g fat/L)

	Day of Age								
Volume/d	3	4	5	6	7	8	9	10	11
>4	67	73	78	82	84	90	87	91	97
>5	62	61	63	61	70	74	79	81	91
>6	32	33	44	36	57	58	63	68	81
>7	23	23	35	29	39	39	47	57	64
>8	3	7	15	21	28	21	36	29	45
>9	3	2	5	11	16	11	19	19	28
>10	0	0	2	2	7	6	9	14	17
# Calves	39	84	101	107	106	106	104	106	104

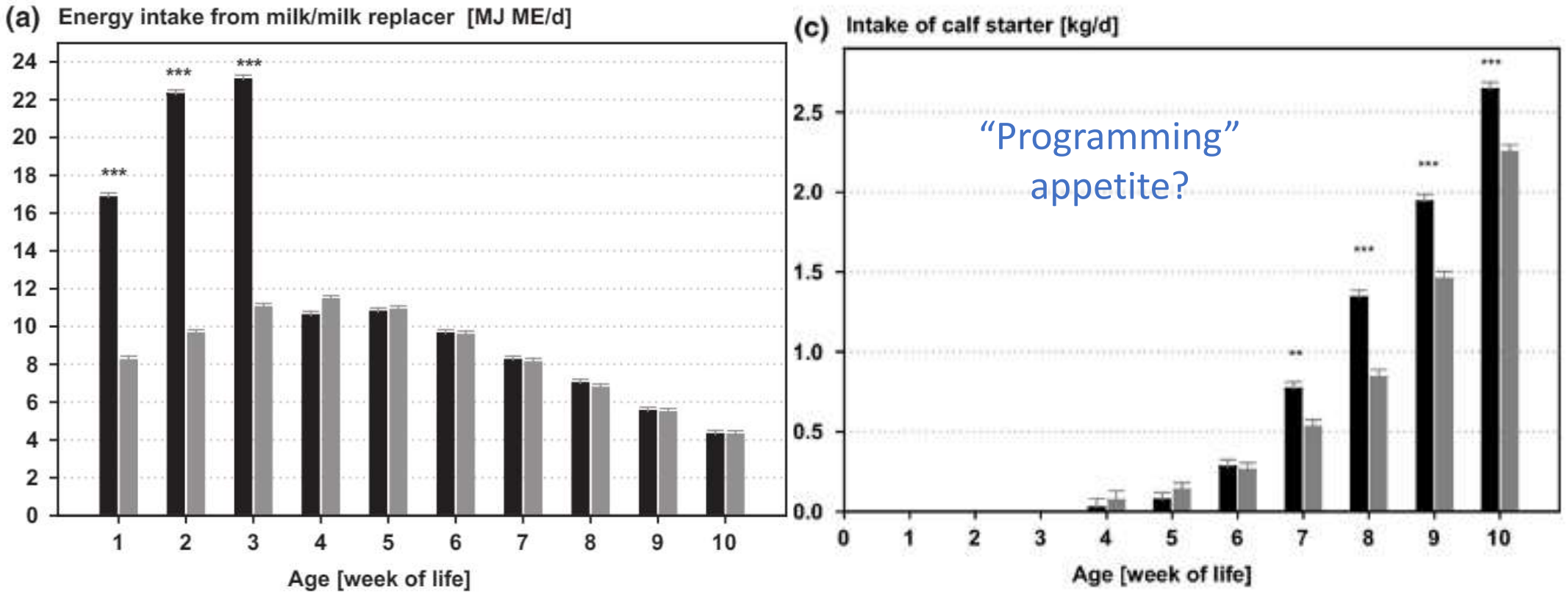
Anderson, 2010

At 7 days of age: >50% of calves drink >6 L/day

At 10 days of age: 70% of calves drink >6 L/day and 25% even >8 L/day

Milk period - **weaning**

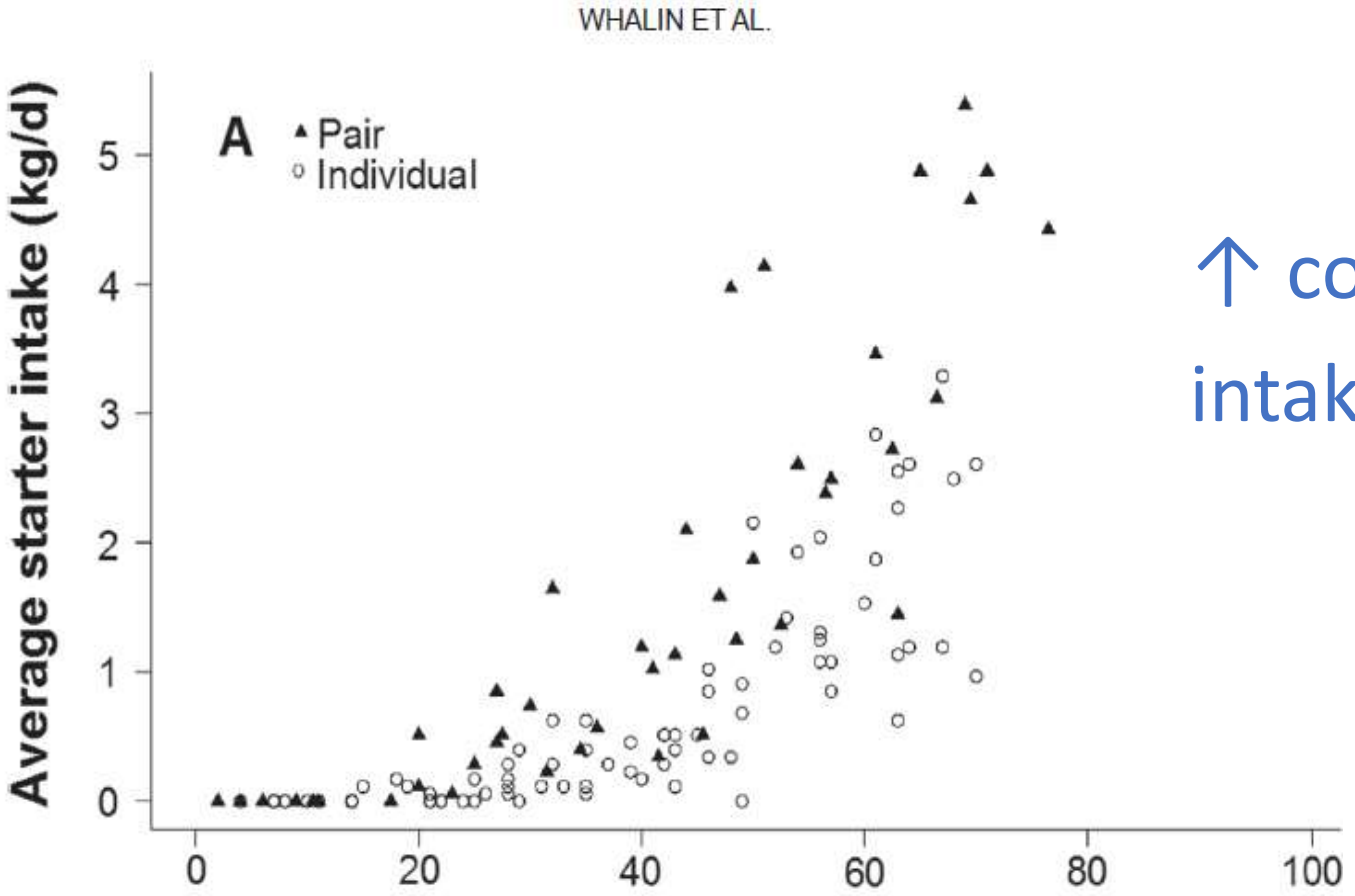
- Concentrate intake with higher milk allowance?



Maccari et al., 2015

Milk period - **grouping**

- *Grouping (>2) at 5 days old, total protein in blood >55 g/L!*
- *Individual hutches, shared outdoor run*

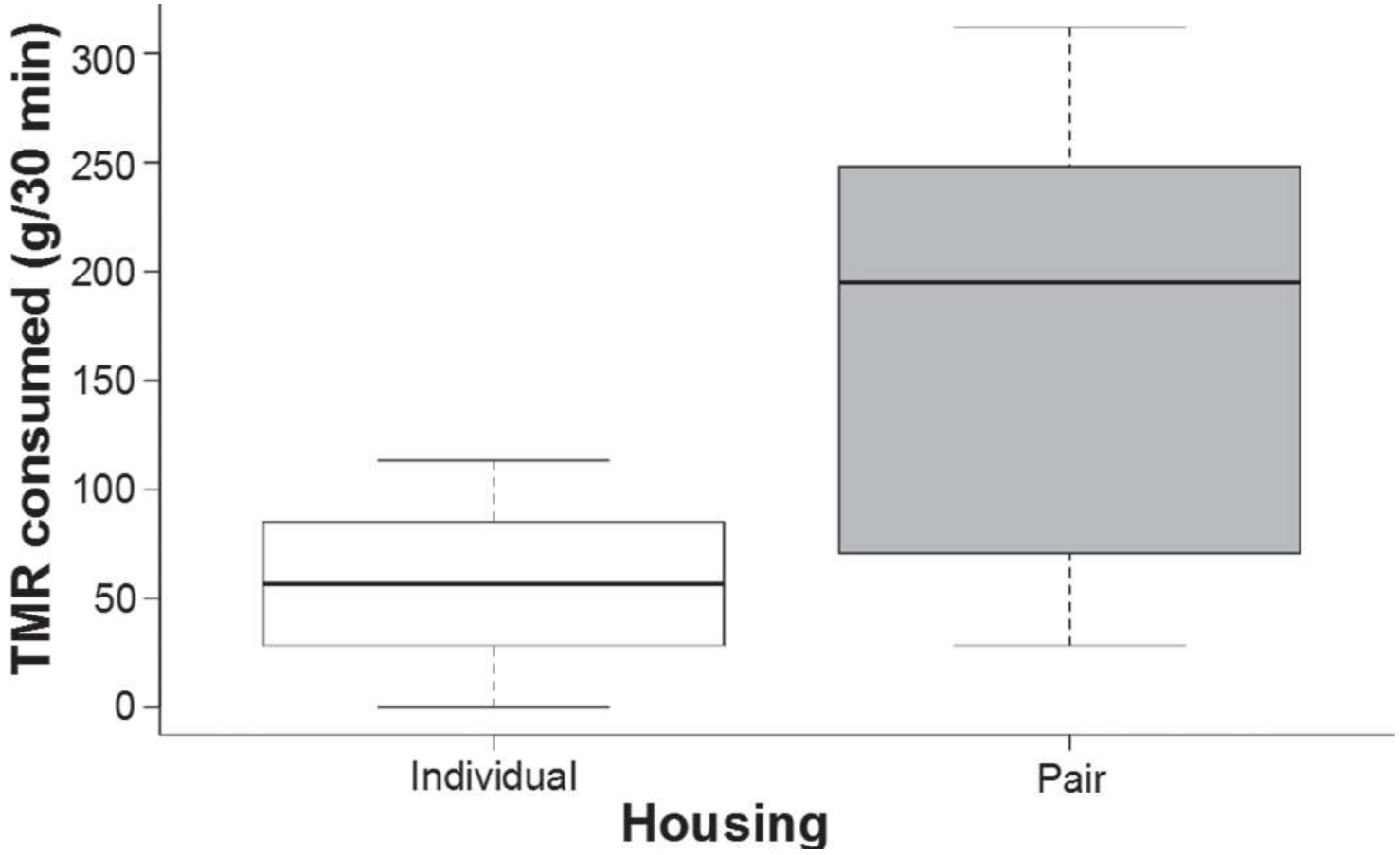


↑ concentrate intake

Whalin et al., 2018

Milk period - grouping

- *5 days old, TP >55 g/L – new feed offered around 60 days (again each in their own hutch so they cannot see each other eating)*

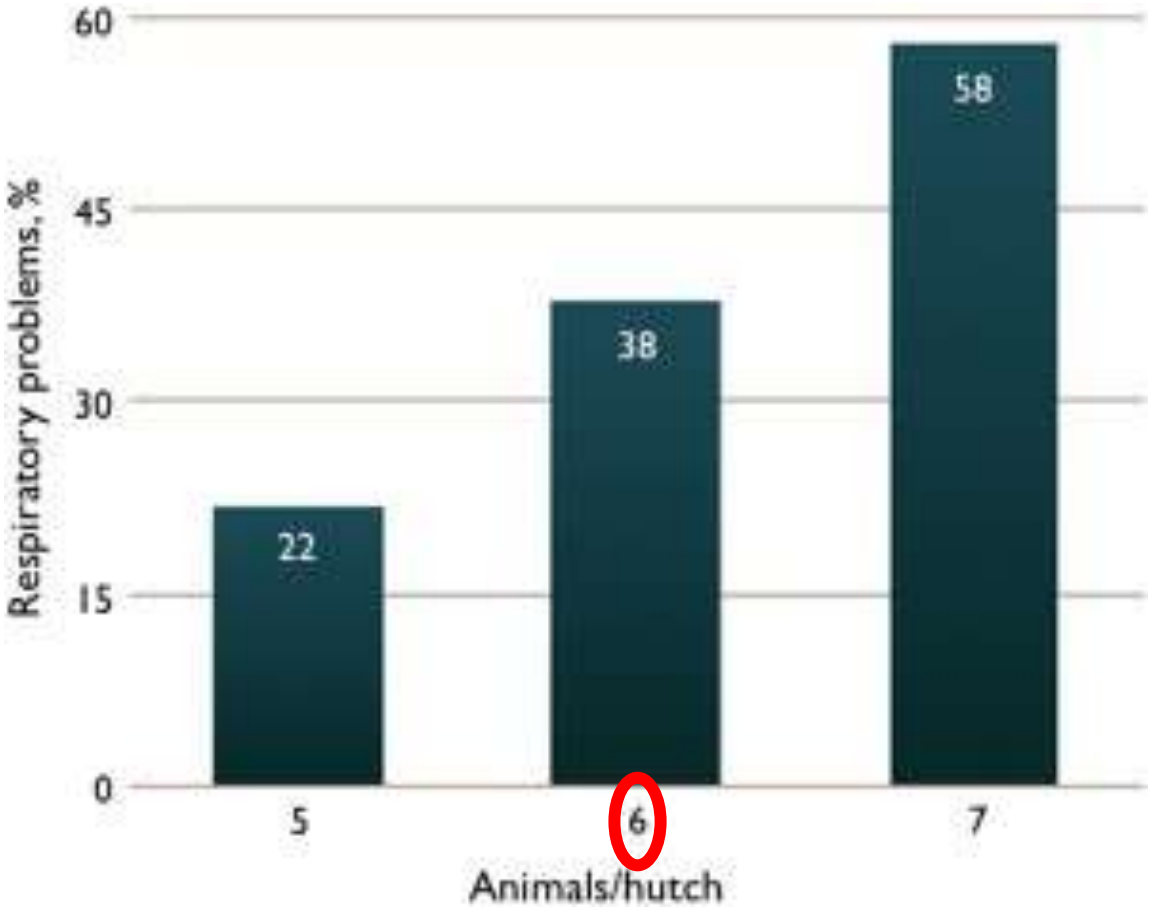


↑ intake of 'new' feed

Whalin et al., 2018

Milk period - grouping

- Number of animals?



Bach et al., 2010

Conclusions

- Pregnancy + first months of life are crucial for later performance!
- Extra attention to:
  - Nutrition of the pregnant dam – also early pregnancy!
  - Colostrum quality and immune monitoring
  - Milk allowance and early growth

Thank you!