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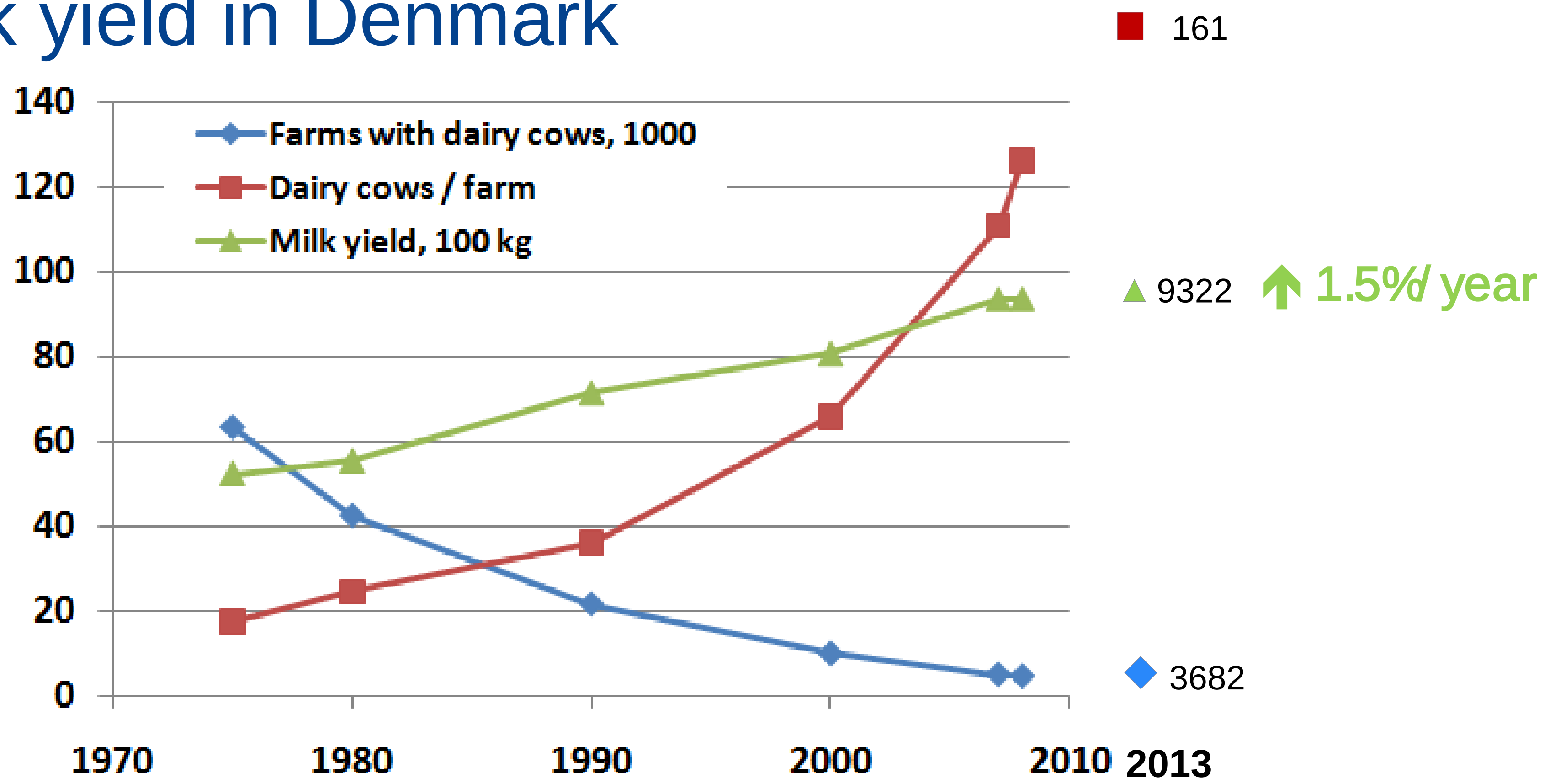
Physiological biomarkers for prevention of production diseases in dairy cows.

Klaus L. Ingvartsen,, K. Moyes*, T. Larsen, & L. Munksgaard

Dept. Anim. Science, Aarhus University

*Dept. Anim. and Avian Sciences, University of Maryland

Changes in the primary structure and average milk yield in Denmark



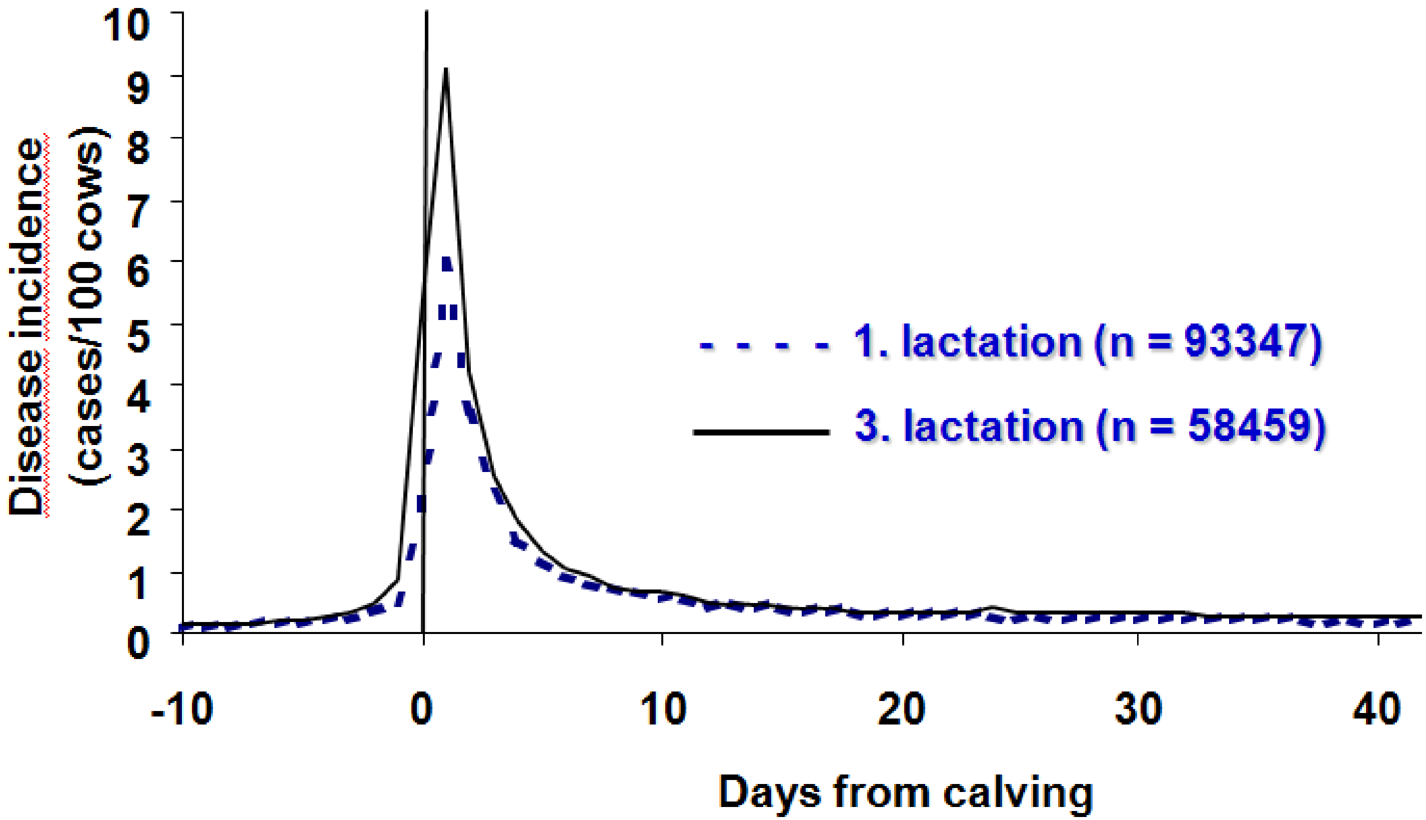
From 1984 and onwards these are farms with milk quota

Still high incidences of production diseases
Treatments / 100 cows / year in Danish Dairy cows

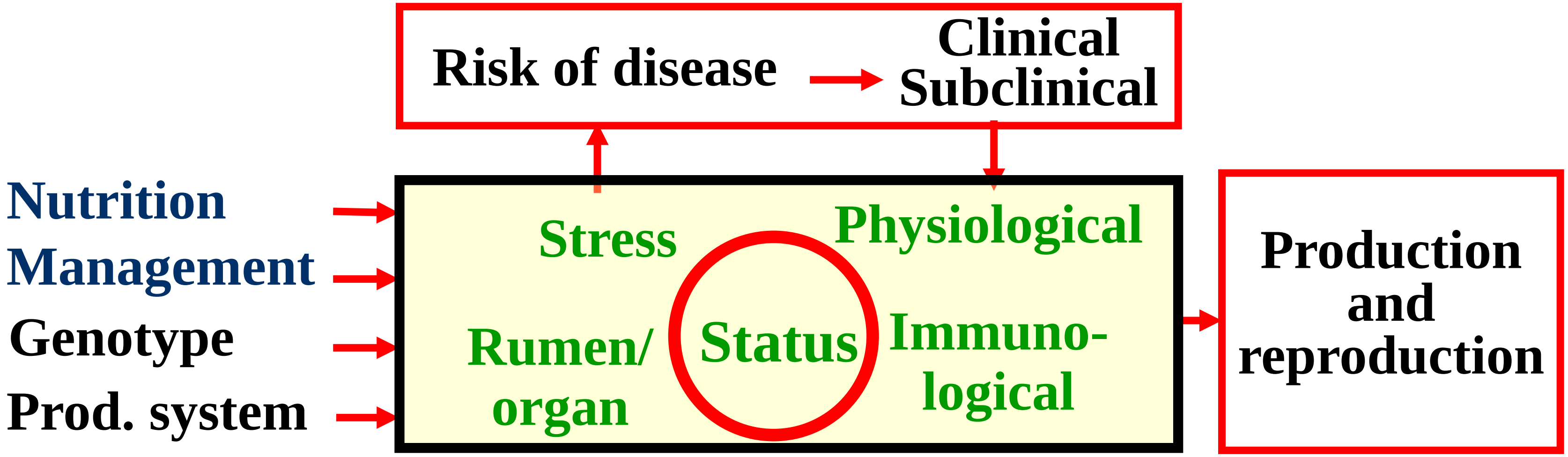
	1969-75 (A)	1990 (B)	2007 (C)
Calving assistance	7	7	0.8
Retained placenta	11	10	9.4
Reprod. Disorders/Metritis	10	10	7.1
Parturient paresis	12	5	3.8
Ketosis	3	4	3.2
Displaced abomasum			1.4
Other alim. disorders	12	12	3.1
Feet & leg disorders	17	8	12.1
Mastitis	55	56	43.9
Other diseases	10	14	18.2
TOTAL	145	132	103

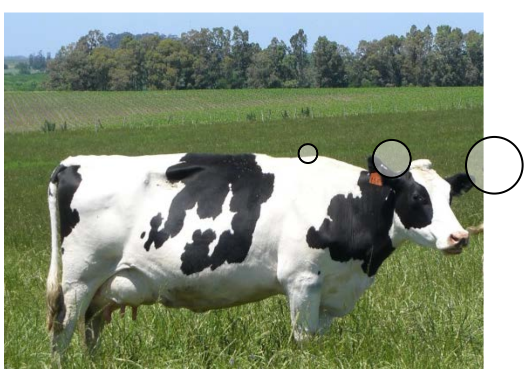
A: Jørgensen & Nielsen, 1977; B: Andersen, 1991; C: Krog & Trinderup, 2008

Disease incidence is high around calving and in early lactation (Ingvartsen et al., 2003)



Production diseases are multifactorial





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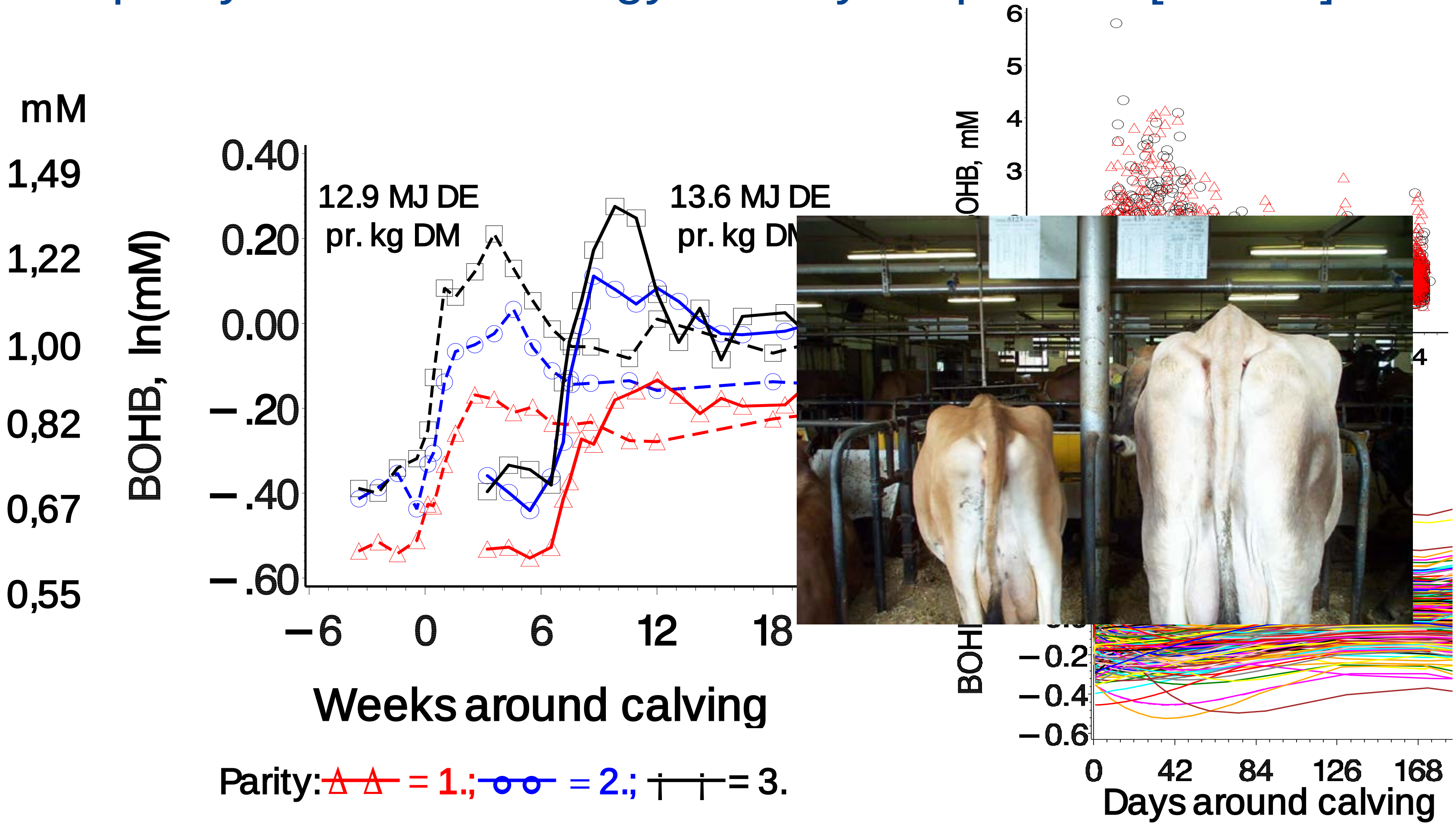
Individual vs group/herd

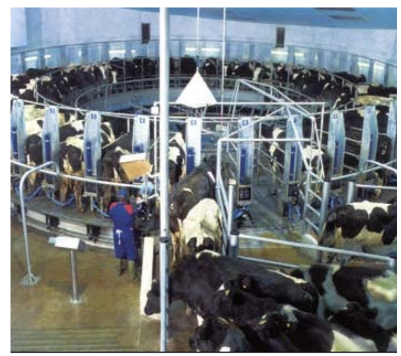
Effect parity and TMR energy density on plasma [BOHB]



Surveillance is essential for prevention

› Manual surveillance is important – but has its limitations
› Surveillance at feeding and milking has changed



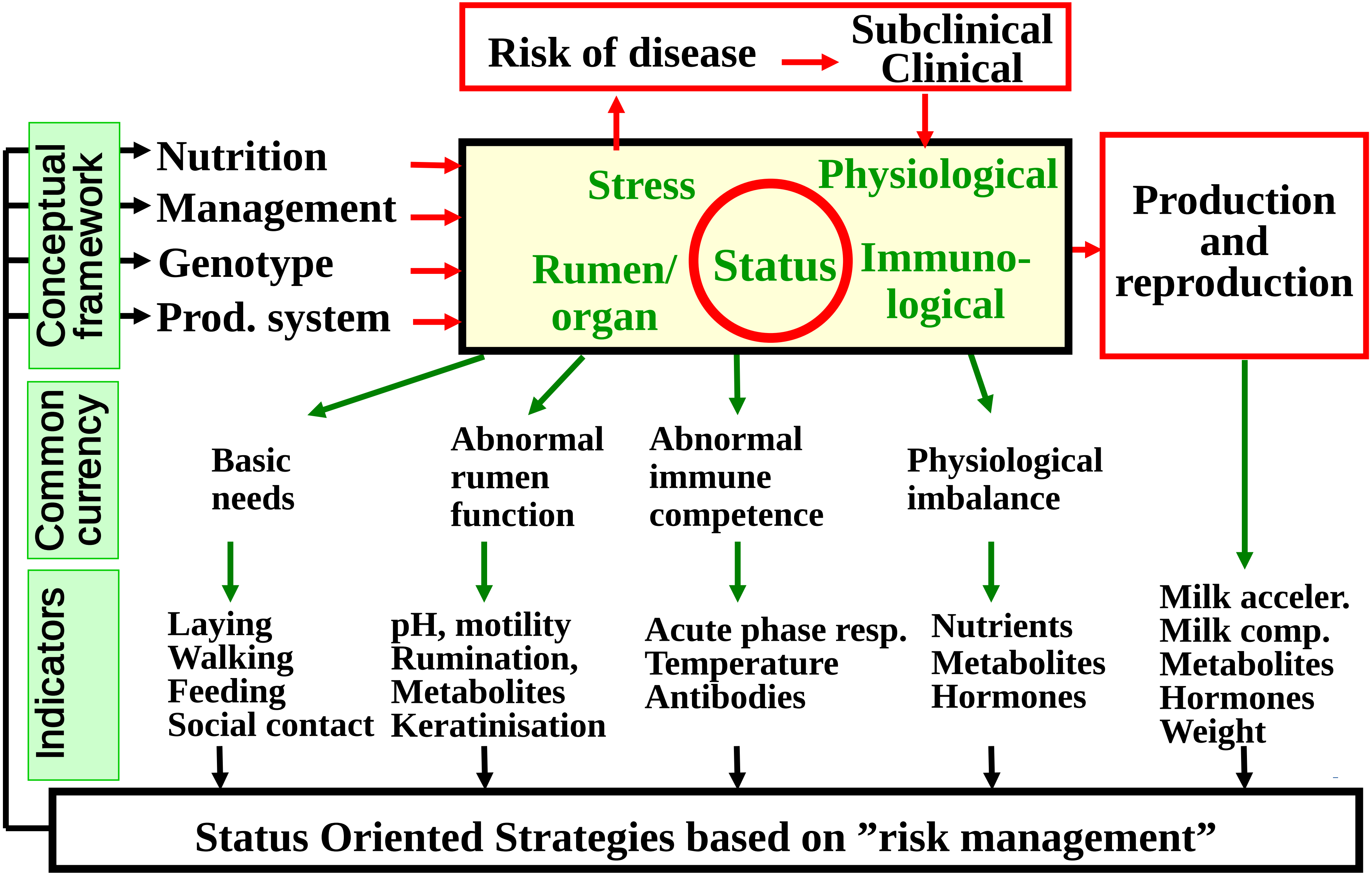



› Large herds
› Subclinical problems

Ketois: clinically low but subclinically ……

- Incidence
  - Clinical ketosis: 4 (1,6-10)% (Ingvartsen et al. 2003)
  - Subclinical ketosis: ?, 9-34% (Duffield, 2001)
- Ketosis is associated to other diseases, (e.g.: hepatic lipidosis, displaced abomasum, lameness)
- Affects the immune system negatively (mastitis, metritis)
- Reduces production and reproduction
- Reduces animal welfare
- Economic losses to the farmer

Prevention via risk management of individuals



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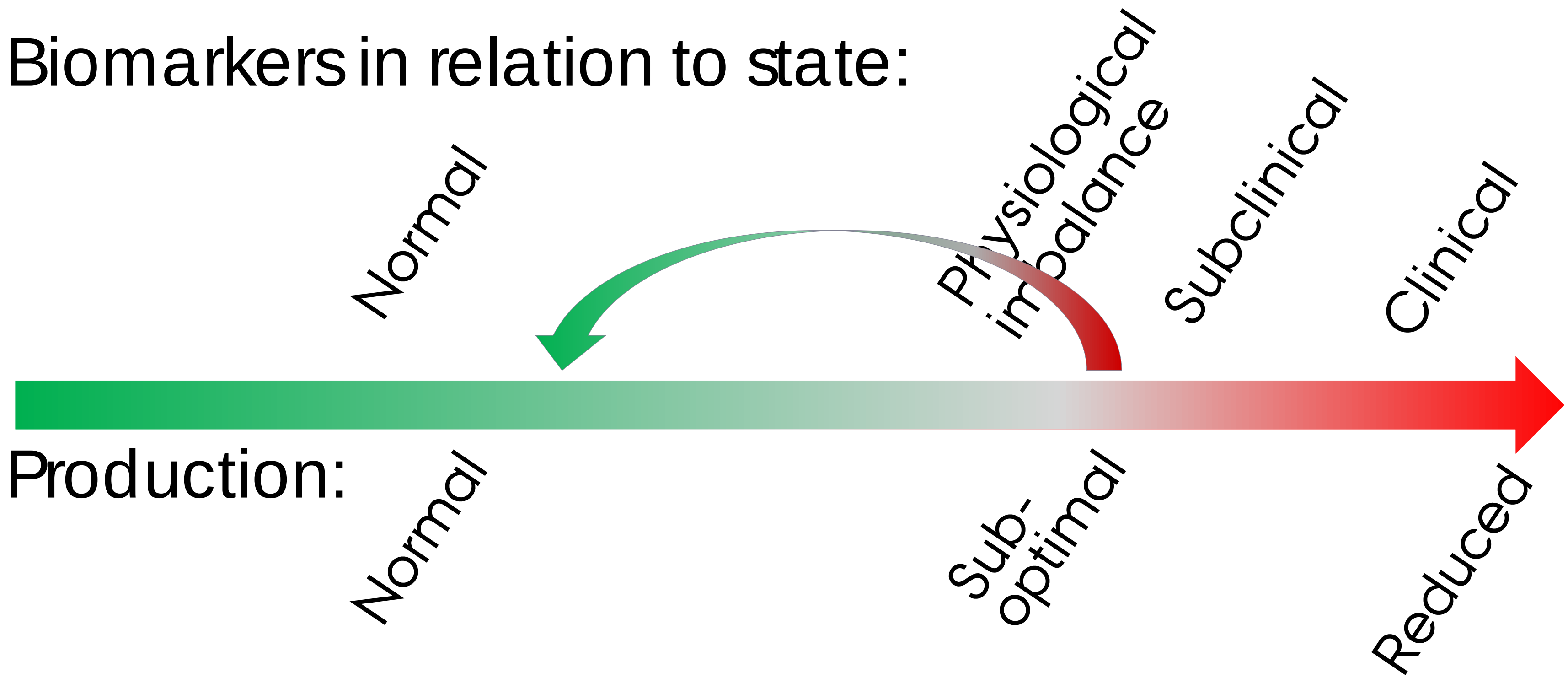
Early identification is key to reduced disease incidence and secure optimal production



What is needed for efficient disease prevention

- › Early identification of "risk cows"
- › Manage animal status & risk by
- › changing "input" to "risk cows"

Proactive management

Calls for **real-time on-farm solutions** based on:

- › Efficient biomarkers
- › Automated sampling
- › Automated analysis (sensors)
- › Biological and biometric models
- › Ability to describe animal status
- › Methods to describe risk for a disease
- › (autom.) change of "input" for prevention

	Condition Positive	Condition Negative
Test Outcome Positive	**True Positive**	**False Positive** (Type I error)
Test Outcome Negative	**False Negative** (Type II error)	**True Negative**

Cost effective

Milk yield data - what do we e.g. know?

› Milk yield data are easily available in modern milking systems

› Important production and economic factor

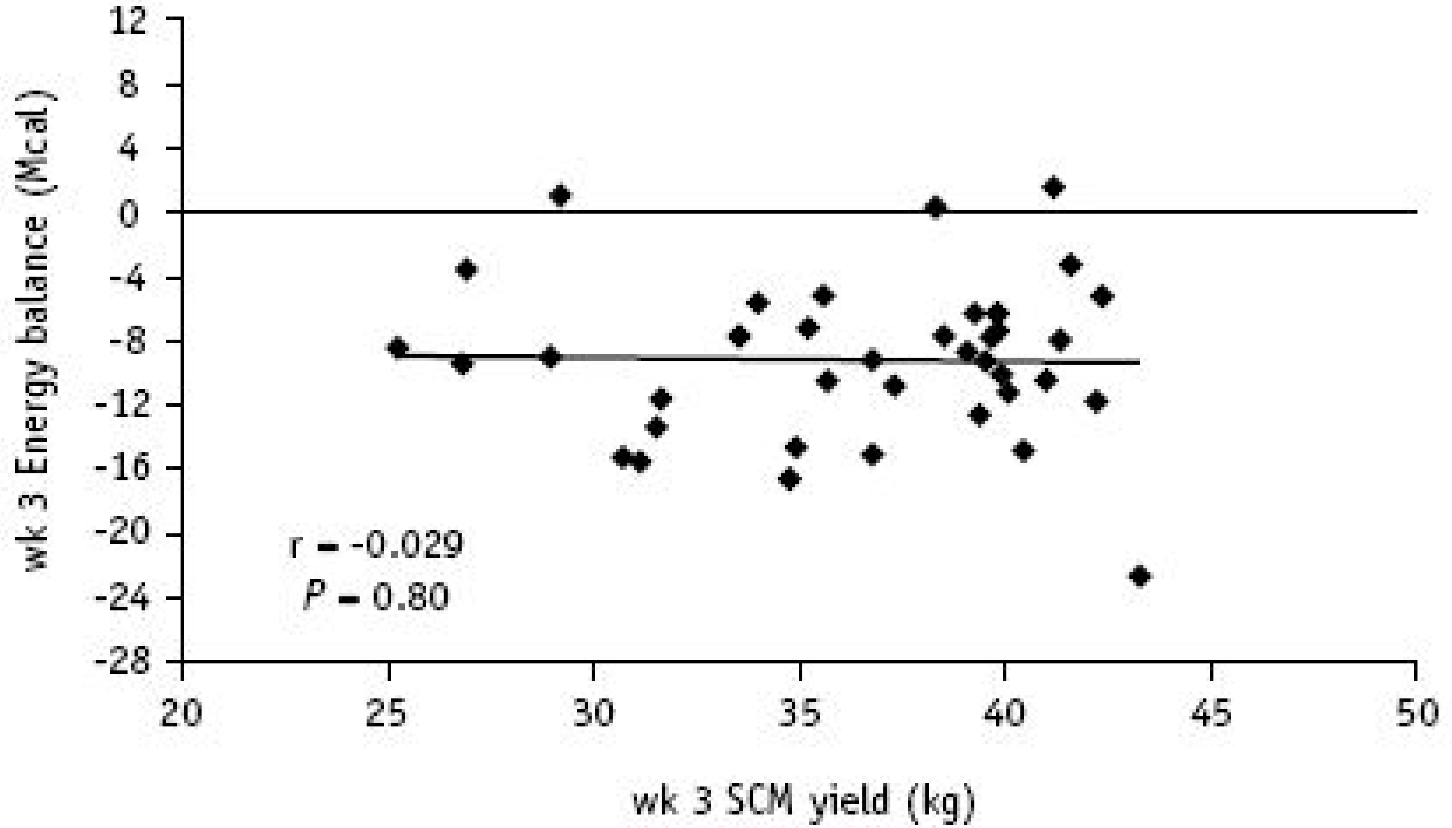
› No correlation between milk yield and EB in early lactation

› Disease changes milk yield and composition

› Milk yield per se is probably not a risk factor for prod. diseases

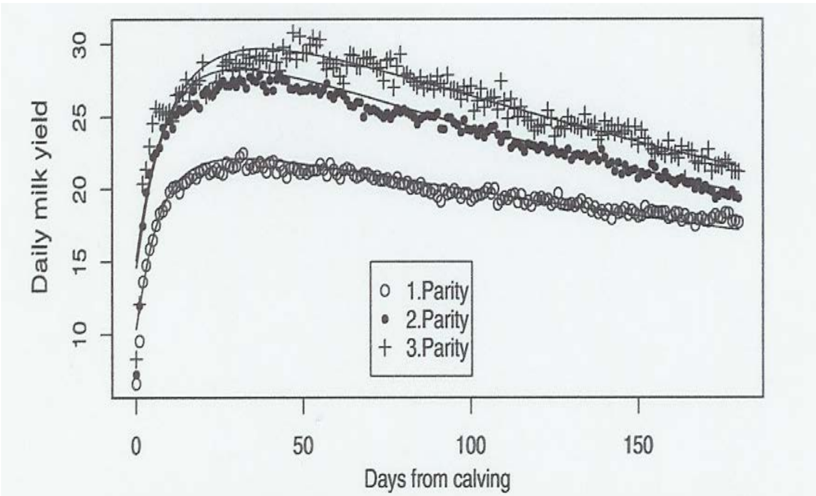
› Etc.

No correlation between milk yield and EB in early lactation (Drackley, 2006)

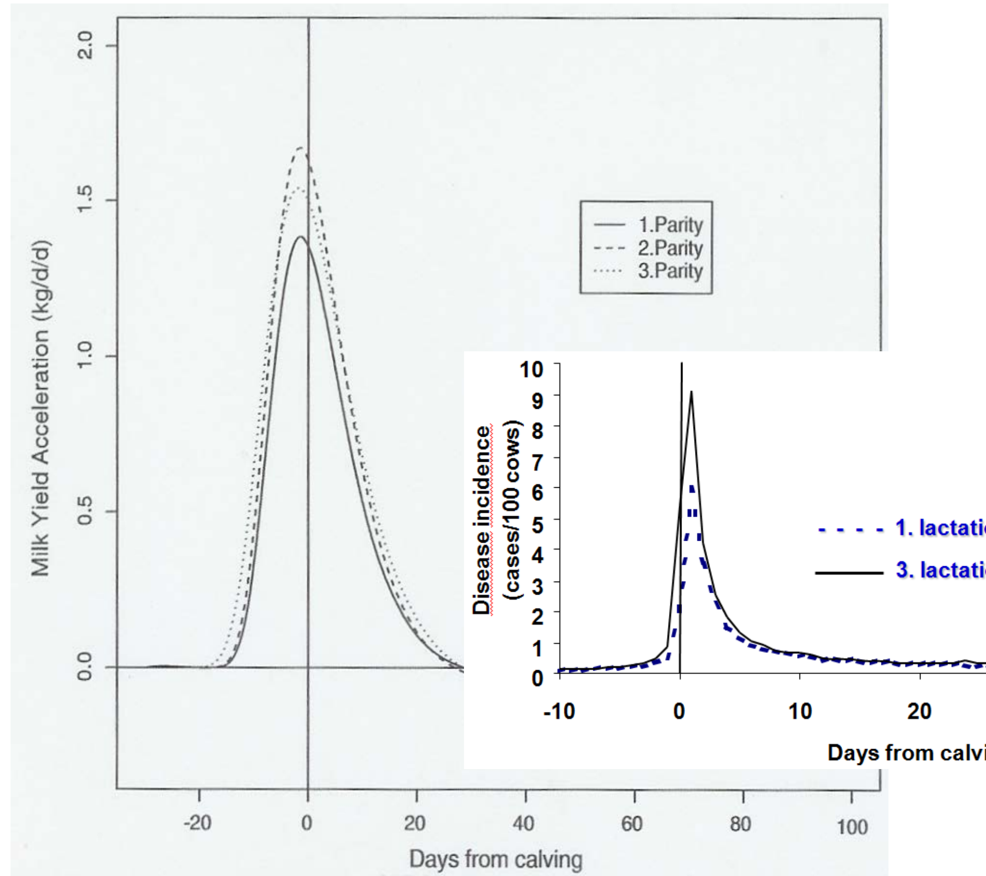


Acceleration in milk yield through lactation

(Ingvartsen et al., 2003, Hansen et al. 2006



- Cause of increased disease risk:
  - Probably not yield pre se
  - Rate of increase in daily milk yield (acceleration) ’ Adaptational problems. Physiological imbalance?



Hypothesis & definition regarding Physiological Imbalance (PI)

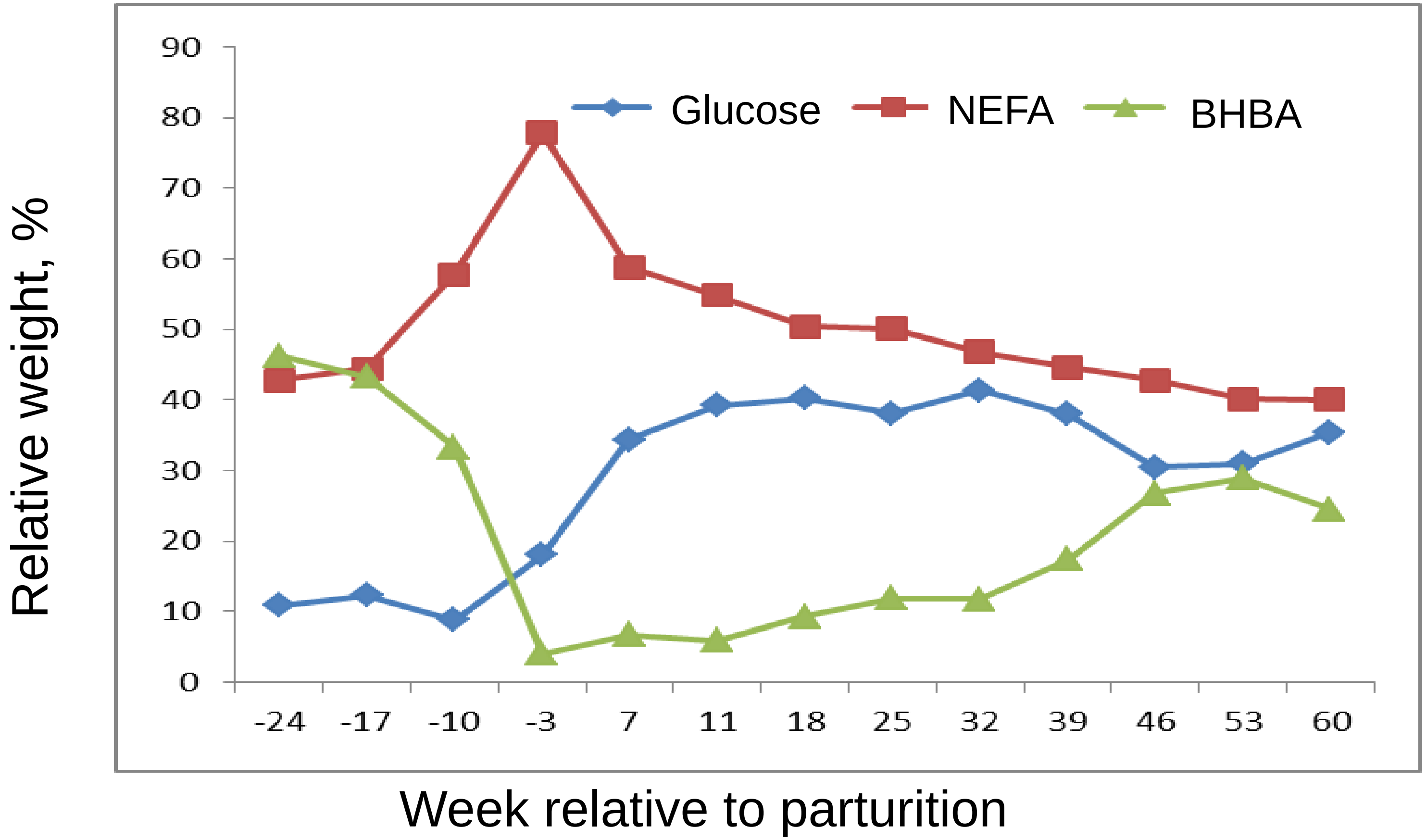
- Hypothesis: Immune function and health can be improved by reducing the PI in cows, and at the same time it will improve production and reproduction (Ingvartsen et al., 2003; Ingvartsen and Moyes, 2012)

- Definition of PI: cows whose parameters (e.g. glucose, BHBA, NEFA) deviate from the normal, and who consequently have an increased risk of developing diseases (clinical or subclinical) and reduced reproduction and/or production (Ingvartsen, 2006)

An index for Physiological Imbalance (PI)

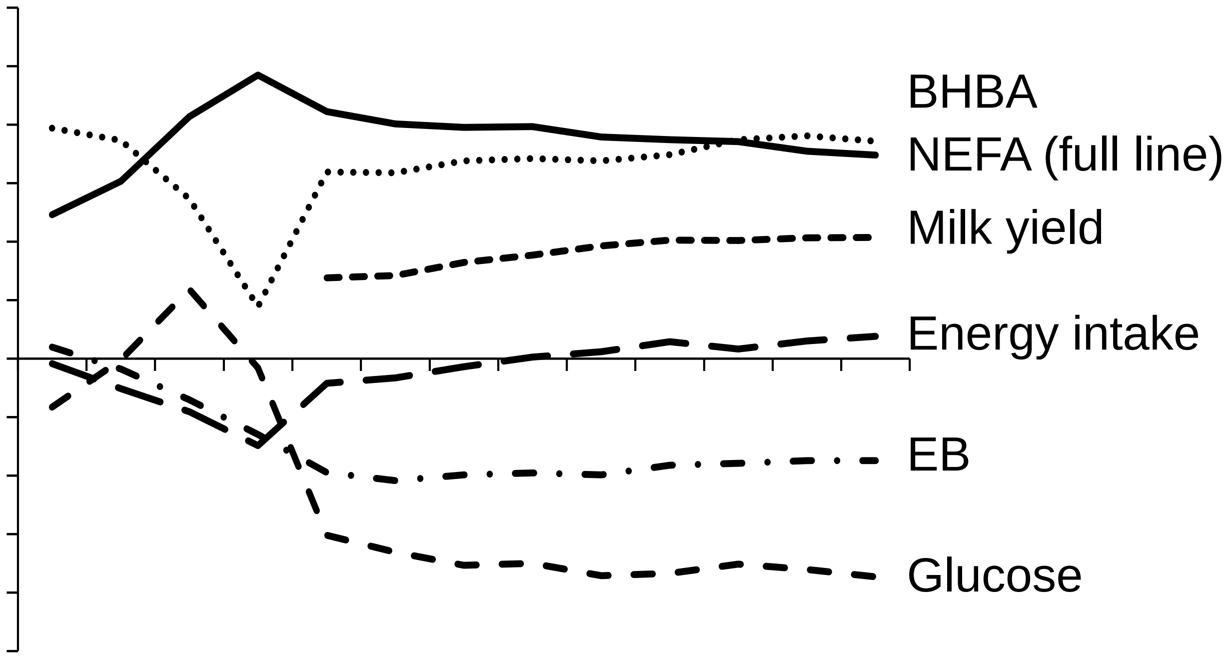
- Severe EB and e.g. NEFA and BHBA have been documented as risk factors for production diseases
- Why an index for PI?
  - We hypothesize that an index for PI, based on several metabolites in blood, will be a better predictor of risk of disease than e.g. the use of individual metabolites or standard methods used to calculate EBAL
- PI = $(x_1$

Relative weight of PI param. in explaining EB



Adapted from Moyes et al., 2013

Weekly correlations between degree of PI and EB, milk yield, energy intake, or plasma metabolites



(Moyes, Larsen and Ingvartsen, 2013)

PI and prediction of diseases (n=391 lactations

- For diseases that developed e2 wk after calving:
  - no variables were associated with risk of disease
- Prepartal PI and plasma NEFA and glucose were better predictors of disease at wk 1 than EBAL and plasma BHBA.

	Metritis				
Variable	Yes	No	SEM	*P*	SDiff
PI	18.3	-3.1	5.1	<0.001	4.2
EBAL	-7.6	-1.1	6.9	0.36	-0.94
NEFA	0.17	-0.02	0.05	<0.001	3.8
BHBA	0.03	-0.01	0.03	0.20	1.3
Glucose	-0.08	-0.01	0.03	0.03	-2.3

	Mastitis				
Variable	Y	N	SEM	*P*	SDif
PI	3.2	-3.1	2.0	<0.01	3.2
EBAL	1.7	-1.1	2.7	0.38	1.0
NEFA	0.06	-0.02	0.02	<0.001	4.0
BHBA	0.009	-	0.01	0.24	1.4
Glucose	0.04	-0.01	0.01	<0.001	5.0

(Moyes, Larsen and Ingvartsen, 2013)

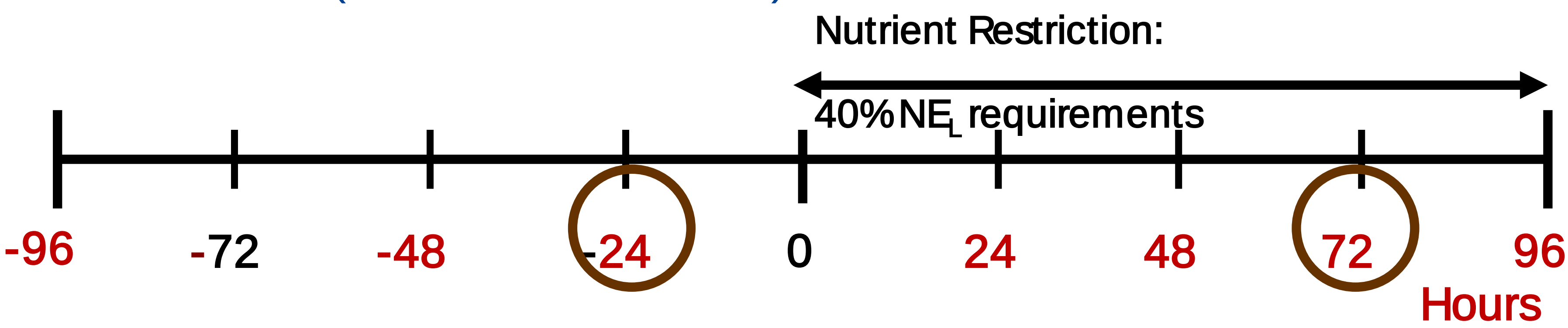
Problem and challenge

› EB, blod/urine variables and PI based on blood is not possible at commercial settings!

› Our objective was therefore:
Identify potential biomarkers in milk for degree of PI that allow automation (as e.g. in “Herd Navigator” system)

"Off feed" challenge – Cows, design, sampling

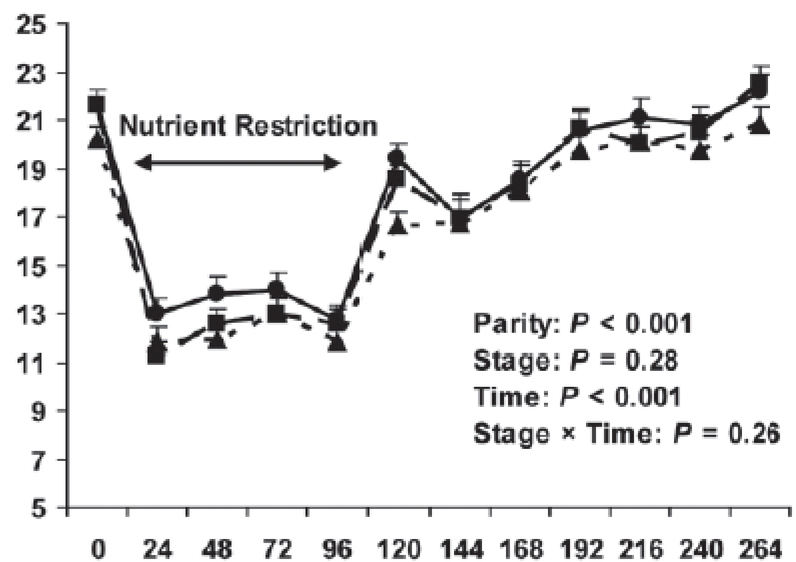
- 29 healthy Holstein cows:
  - early lactation (n = 14; 22-86 DIM)
  - mid-lactation (n = 15; 100-217 DIM)



- **Daily registrations: Feed intake, milk yield and components**
- **Blood collection for analysis of NEFA, BHBA, and glucose**
- **Milk for detailed analysis**
- **Liver samples collected for:**
  - **1. Chemical analysis**
  - **2. iTRAQ-based quantitative profiling using LC-MS/MS**

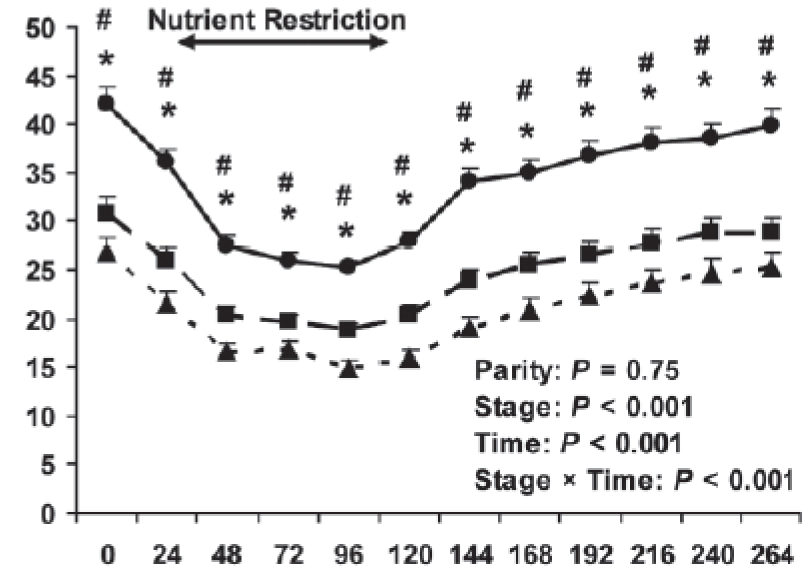
Change in energy density caused marked changes in DMI og milk yield

DMI, Kg/d



Time relative to restriction, h

Milk Yield, kg/d

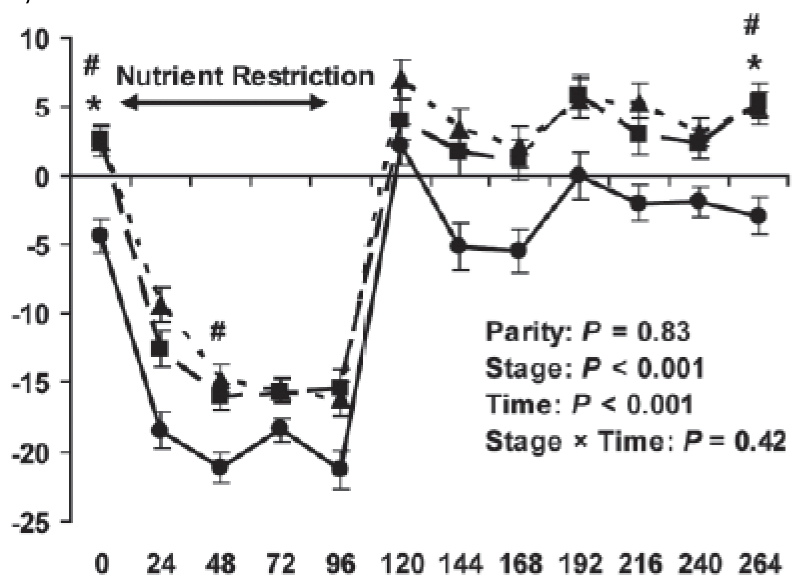


Time relative to restriction, h

Bjerre-Hapøth et al., 2012

EB was reduced by reduced energy density

EB, Mcal/d



Time relative to restriction, h

Bjerre-Hapøth et al., 2012

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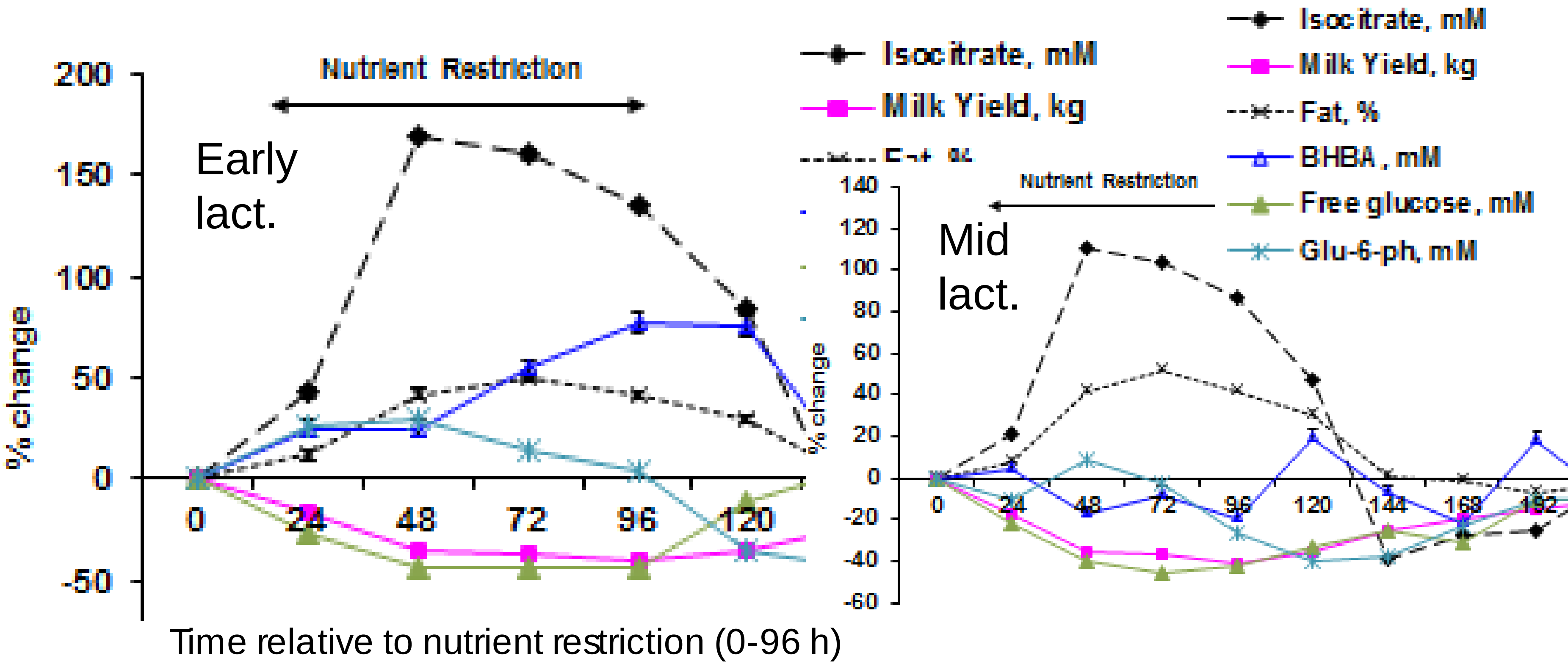
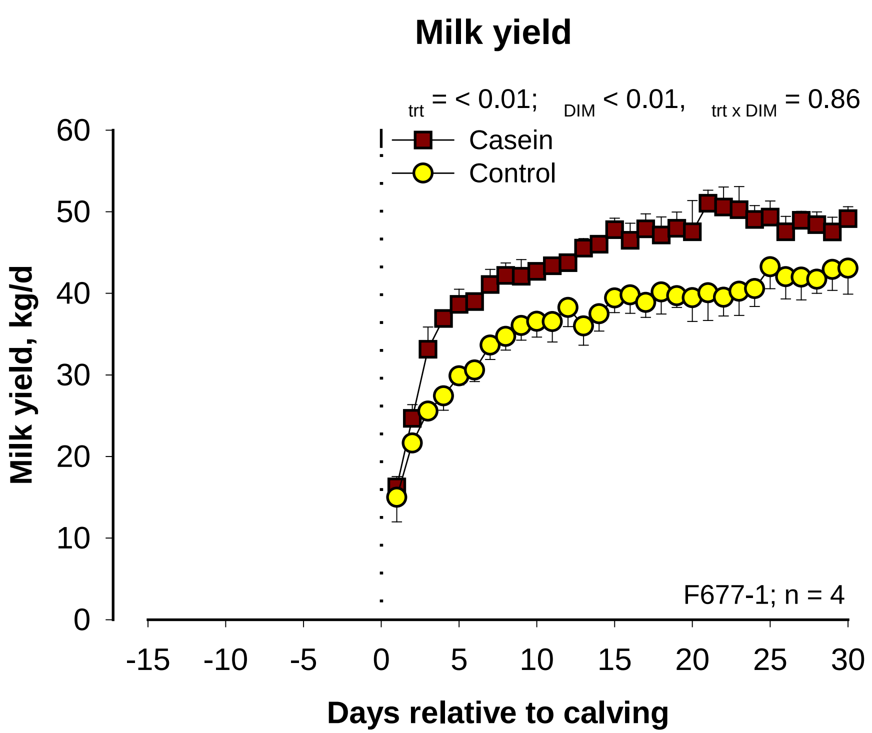
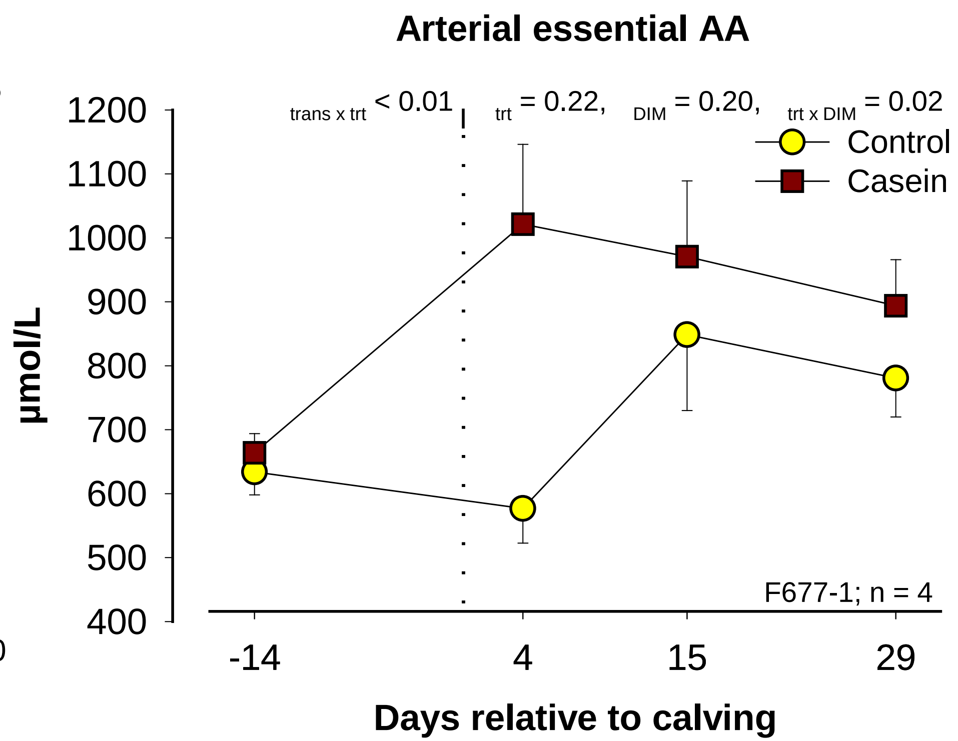
Changes in milk parameters during nutrient restriction – early and mid-lactation



Are control animals experiencing imbalance?





Mogens Larsen, pers. comm.

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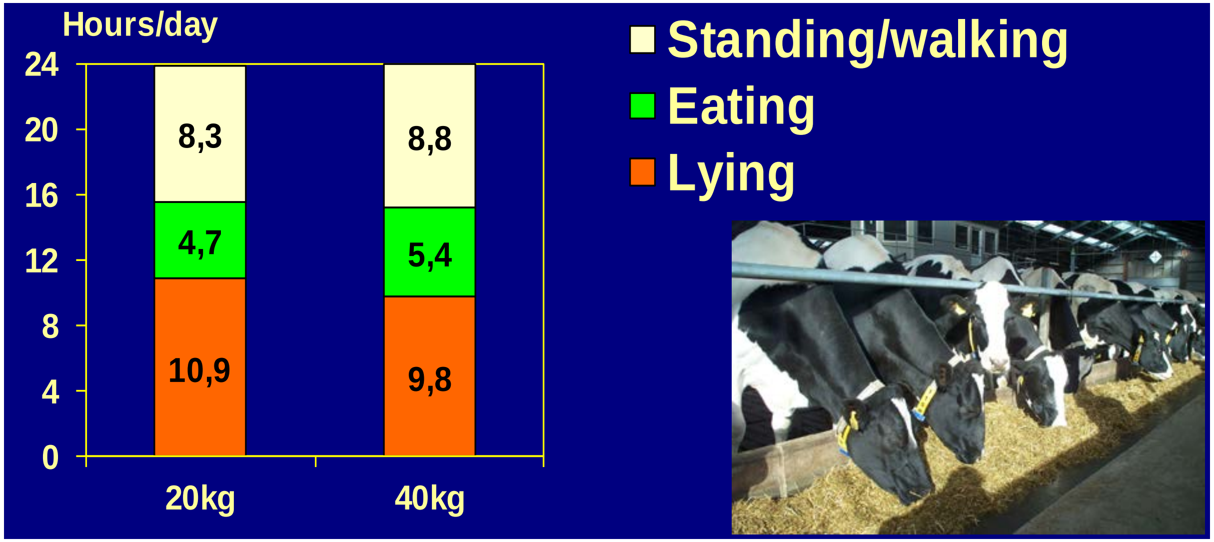
Animal behavior as indicators

- Diseases:
  - E.g. abnormal walking, reduced eating time, increased laying -> indicator of lameness.
- Basic needs:
  - Easy access to food and water, milking, resting.

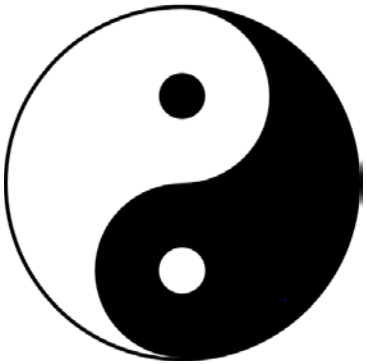
Effect of increasing milk yield



Need for automated precision management systems

There is a need for **cost efficient** automated precision management systems where equipment combines advanced technologies and biological knowledge to obtain:

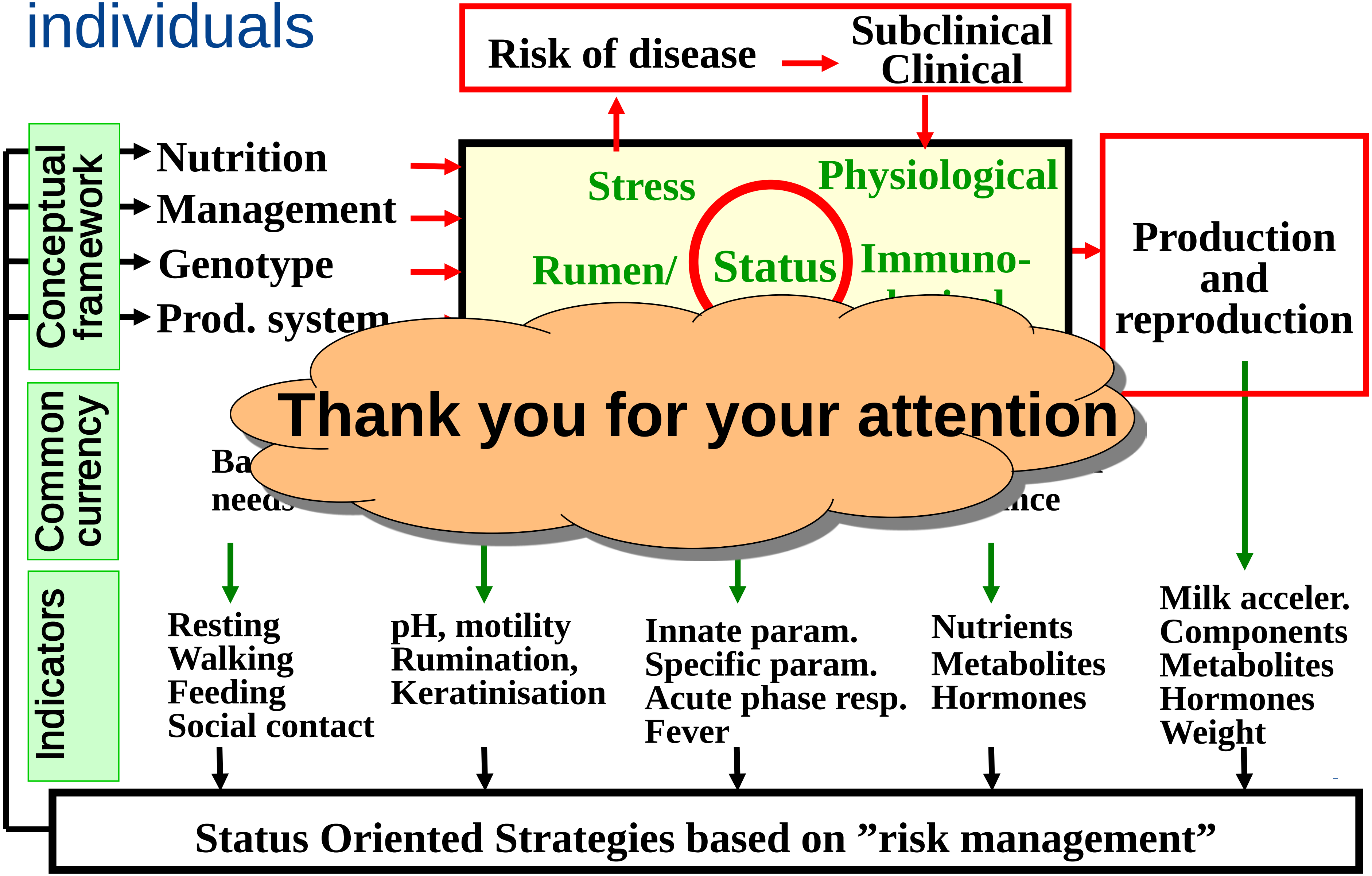
- low disease incidence and severity
- animal welfare
- low impact on the environment,
- requested product quality,
- optimal production and reproduction
- profitability for the producer.



Conclusion and future challenges

- To better understand the physiology and immunology of the dairy cow, particularly in the periparturient period, including basic needs, requirements (not only for production)
- Make better use of existing data (from data to information)
- To better understand the biological basis of individual differences, physiological imbalance and risk:
  - quantitative understanding
  - importance for e.g. immune function, risk of disease, reproduction etc.
  - proactive management - efficient surveillance and overcome the physiological imbalance by being able to predict individual animal responses to changes in e.g. nutrient supply or management
- We lack more biomarkers and sensors to take on the challenge of further develop future automatic and proactive management strategies

Prevention through risk management of individuals



Need and drivers of automation and precision management

- Structural development
  - Industrialization – most advanced in the broiler industry
- More animals / staff
- Labour
  - Lack of qualified staff
  - High cost
- Technological development
  - Sensors
  - Analytical equipment
  - IKT
  - Real-time management
- Optimisation of animal health, production and reproduction
- Economics
- Legislation & Animal welfare
- Industry demands
- Natural resource management
  - Nutrients (P, N)
  - Odour, grenhouse gas emissions
- Variety of products
  - Special composition (health)
- High product quality
  - Consistent products
  - Taste
- Assurance of food safety
  - Residues, trace elements
  - Microbial
- Traceability & product information
  - Production system, non-use, nutrition, ….)