Re-evaluating transition cow dogmas, are they Really Immune Suppressed?

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Nutritionists are Often Incorrectly Blamed for:

- High NEFA
- Hyperketonemia
  - Clinical and subclinical ketosis
- Subclinical hypocalcemia

- These are due to 1 of 2 things:
  - High productivity in healthy cows (profitable dairy producer)
    - The nutritionist deserves a raise
  - Metabolic reflection of immune activation
    - Likely stemming from metritis, mastitis, pneumonia or GIT inflammation
      - These are mostly management issues and not caused by nutrition

Everything in today's talk is thoroughly covered in our recent review

Horst et al., 2021, JDS 14:8380-8410

J. Dairy Sci. 104:8380–8410
https://doi.org/10.3168/jds.2021-20330

Invited review: The influence of immune activation on transition cow health and performance—A critical evaluation of traditional dogmas

E. A. Horst, S. K. Kvidera, and L. H. Baumgard*
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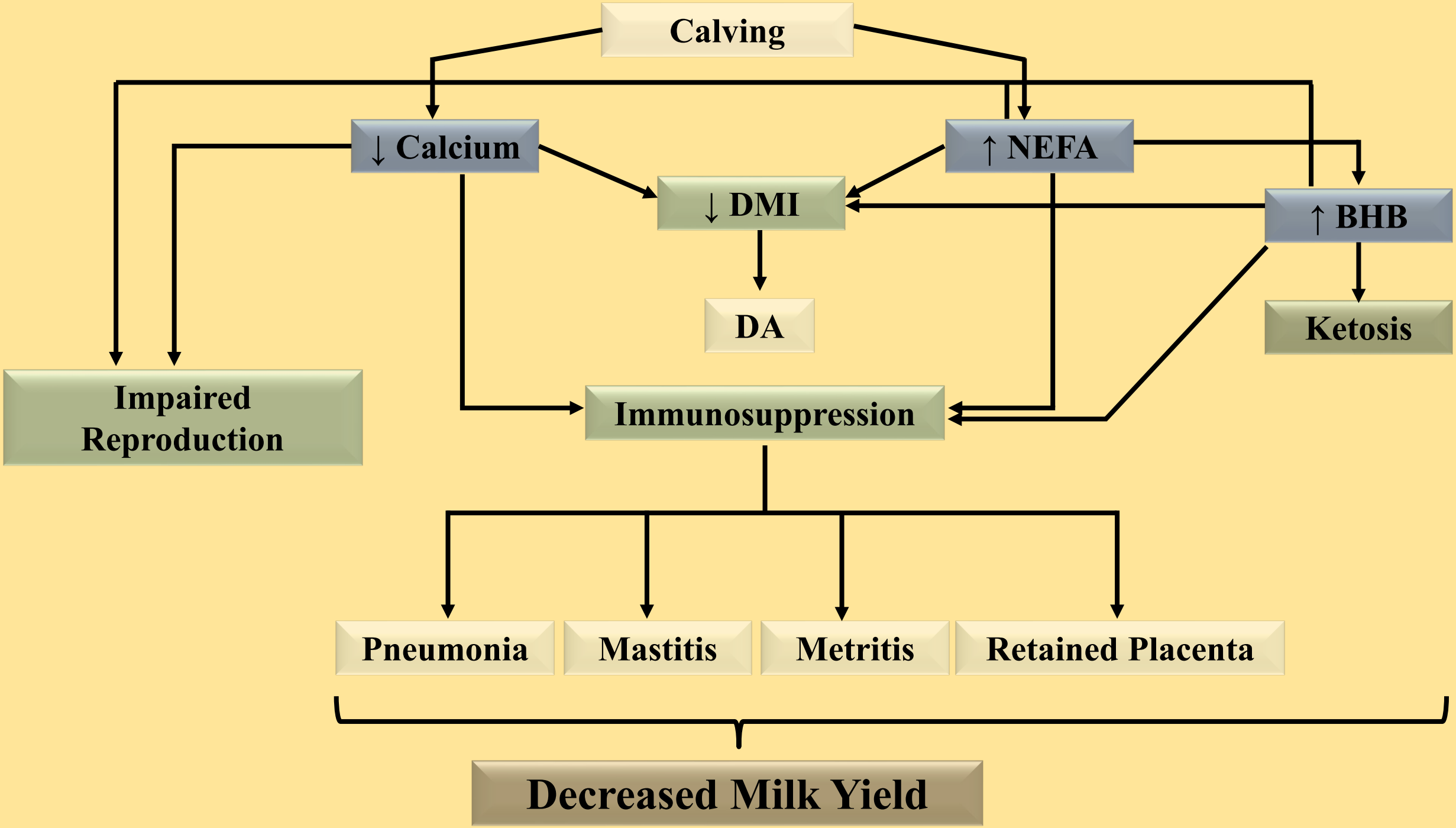
ABSTRACT

The progression from gestation into lactation represents the transition period, and it is accompanied by marked physiological, metabolic, and inflammatory adjustments. The entire lactation and a cow's opportunity to have an additional lactation are heavily dependent on how successfully she adapts during the periparturient period. Additionally, a disproportionate amount of health care and culling occurs early following parturition. Thus, lactation maladaptation has been a heavily researched area of dairy science for more than 50 yr. It

feed intake and causes hypocalcemia. Our tenet is that immune system utilization of glucose and its induction of hypophagia are responsible for the extensive increase in NEFA and ketones, and this explains why they (and the severity of hypocalcemia) are correlated with poor health, production, and reproduction outcomes. In this review, we argue that changes in circulating NEFA, ketones, and calcium are simply reflective of either (1) normal homeorhetic adjustments that healthy, high-producing cows use to prioritize milk synthesis or (2) the consequence of immune activation and its sequelae.
Key words: inflammation, hypocalcemia, ketosis,

Traditional Belief

Increased NEFA, Hyperketonemia, and Hypocalcemia…..**CAUSE** production and health problems


Calving
↓ Calcium
↑ NEFA
↓ DMI
↑ BHB
DA
Ketosis
Impaired Reproduction
Immunosuppression
Pneumonia
Mastitis
Metritis
Retained Placenta
Decreased Milk Yield

Retrospective and Observational Studies

- Hundreds of studies *associate* and correlate NEFA, BHBA and Ca with:
  - Increased risk of ketosis, decreased milk yield, LDA, metritis, retained placenta, laminitis, or poor reproduction
    - Chapinal et al., 2011; Huzzey et al., 2011; Ospina et al., 2010a, 2010c; Duffield et al., 2009; LeBlanc et al., 2005
- Many papers do not agree…..inconsistent effects in the literature
- Plasma NEFA are markedly increased (>700 mEq/L) following calving in almost all cows
  - ~15-20% get clinical ketosis
  - What makes these cows more susceptible to ketosis?
    - Predisposition to developing fatty liver?
- Reductionist approach (one metabolite = one disease)

Cause and Effect??

- The incidence of health problems is highest in the first month of lactation
- The largest swings in energetic metabolites, hormones and minerals occurs in the first month of lactation
- Thus…a lot of moving parts and events occurring simultaneously
  - Consequently they will all be correlated
- Causality and correlation are incorrectly interchanged when an observational relationship between 2 events is claimed to be inevitable rather than coincidental.

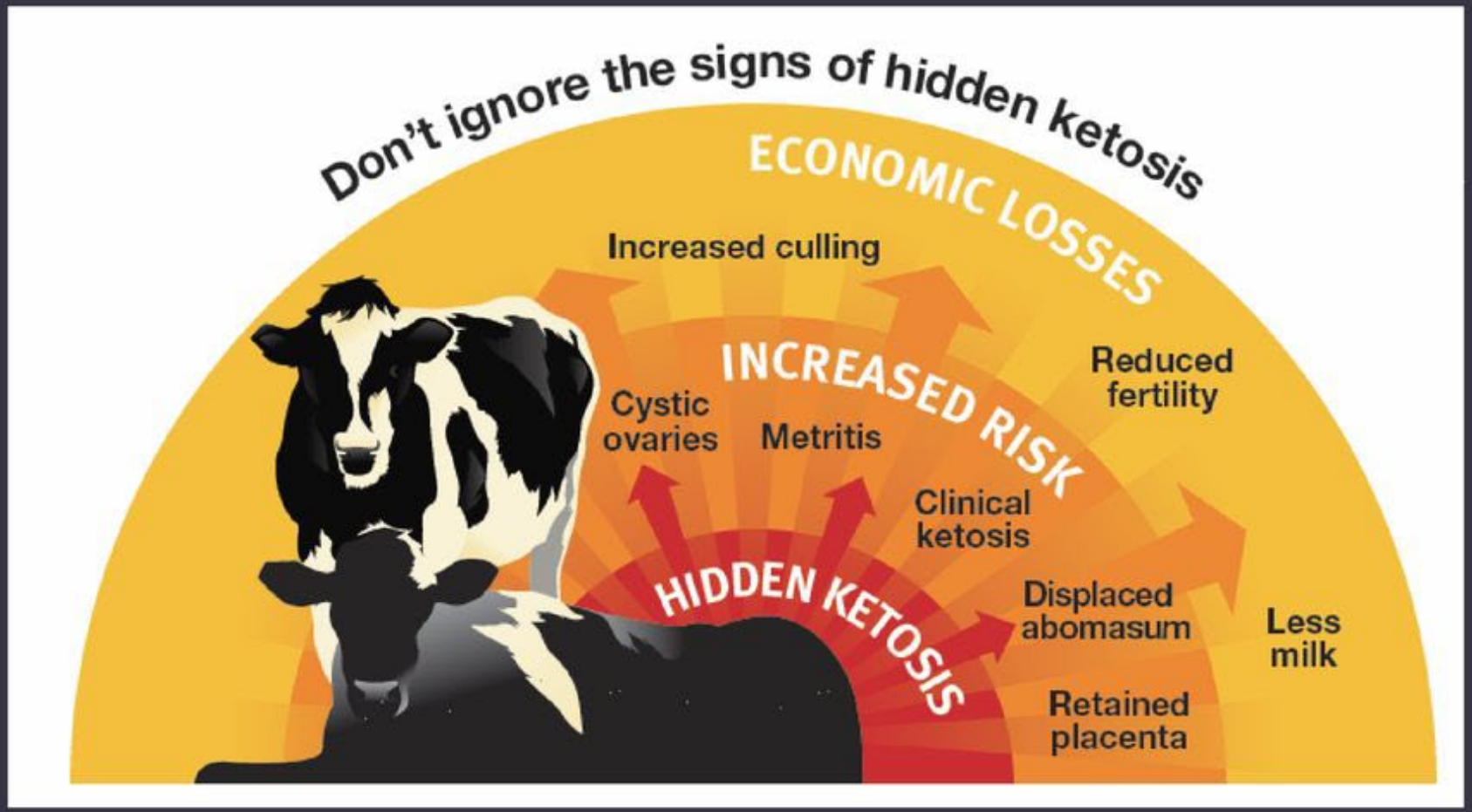
This correlation interpretation then causes suspect decision making and unnecessary farm expenses

Traditional Belief

Assuming Correlation Equals Causation

Increased NEFA, Hyperketonemia, and Hypocalcemia…..**CAUSE** production and health problems

Dogma: Ketones cause problems



https://slideplayer.com/slide/13774593/

holstein.PNG
(Taylor Leach)

By **MAUREEN HANSON** August 7, 2024

Dairy Herd Management

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1. **Subclinical ketosis -- $18 billion**
2. **Clinical mastitis – $13 billion**
3. **Subclinical mastitis – $9 billion**
4. **Lameness – $6 billion**
5. **Metritis – $5 billion**
6. **Ovarian cysts – $4 billion**
7. **Paratuberculosis/Johne's disease – $4 billion**
8. **Retained placenta -- $3 billion**
9. **Displaced abomasum – $0.6 billion**
10. **Dystocia – $0.6 billion**
11. **Milk fever/hypocalcemia – $0.6 billion**
12. **Clinical ketosis – $0.2 billion**

In total, the economic losses due to dairy disease totaled about $65 billion per year.

[2]Section of Ep
[3]Global Burde
[4]Faculty of Ve
[5]School of Ma
[6]Agri-food and
[7]Department of Livestock and One Health, Institute of Infection, Veterinary & Ecological Sciences, University of Liverpool, Liverpool, UK
[8]Infection Medicine, Biomedical Sciences, Edinburgh Medical School, University of Edinburgh, Edinburgh, UK

If hyperketonemia, high NEFA and subclinical hypocalcemia are pathological….it stands to reason that therapeutically treating these disorders would improve cow health

Culling Trends Over Time

Culling Reason	NAHMS (1996)	NAHMS (2002)	NAHMS (2014)
Voluntary Reasons	21.3	19.3	21.1
Re			
Injury	4.1	6.0	5.2
Death	3.8	4.8	4.2
Disposition			
Lameness	14.2	16.3	16.8
Other	3.9	4.1	

Despite emphasis, time and money spent on preventing high NEFA, hyperketonemia and subclinical hypocalcemia herd health is not improving

Maybe we're "medicating" the wrong things??

National Animal Health Monitoring Systems

How (and why) do NEFA, Hyperketonemia and Hypocalcemia cause problems

- Biological plausibility?
  - Why would evolution favor a scenario where the mother endangers herself and compromises her ability to nourish her young?

- There remains little mechanistic evidence for how NEFA, ketones and Ca can directly have such a large influence on a variety of seemingly unconnected systems and diseases

- Best line of evidence is extrapolated from their purported role in immunosuppression.

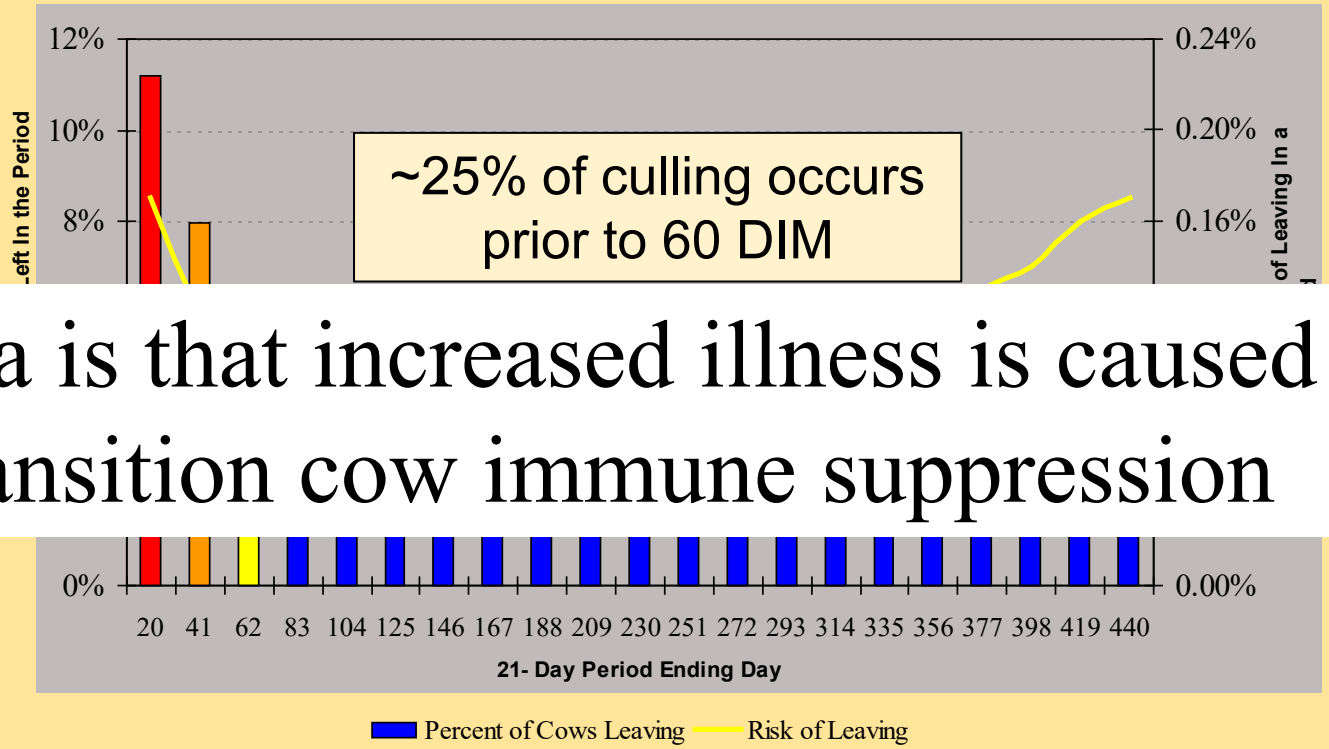
Transition Period Morbidity

Disorders affects 50%:

- Dystocia
- Milk fever
- Retained placenta
- Metritis
- Ketosis
- DA
- Fatty liver
- Lameness
- Death

Drackley, 1999

When cows leave the herd



Dogma is that increased illness is caused by transition cow immune suppression

Source: 2002, Steve Stewart, DVM, Dipl.-ABVP, Univ. of Minnesota, College of Vet. Med.

Evaluating Risk

- The risk of dying in a plane crash is 1 out of 7.7 million flights
  - But, the risk of dying in a plane crash if you do not fly is zero
    - Is this akin to transition cow morbidity (metritis, mastitis, DA)?
      - She's very unlikely to get metritis or a DA at 100 Days in Milk.
  - Using modern classification systems, I don't think 50% of transition cows have an adverse health event. Are academics "alarmists"?

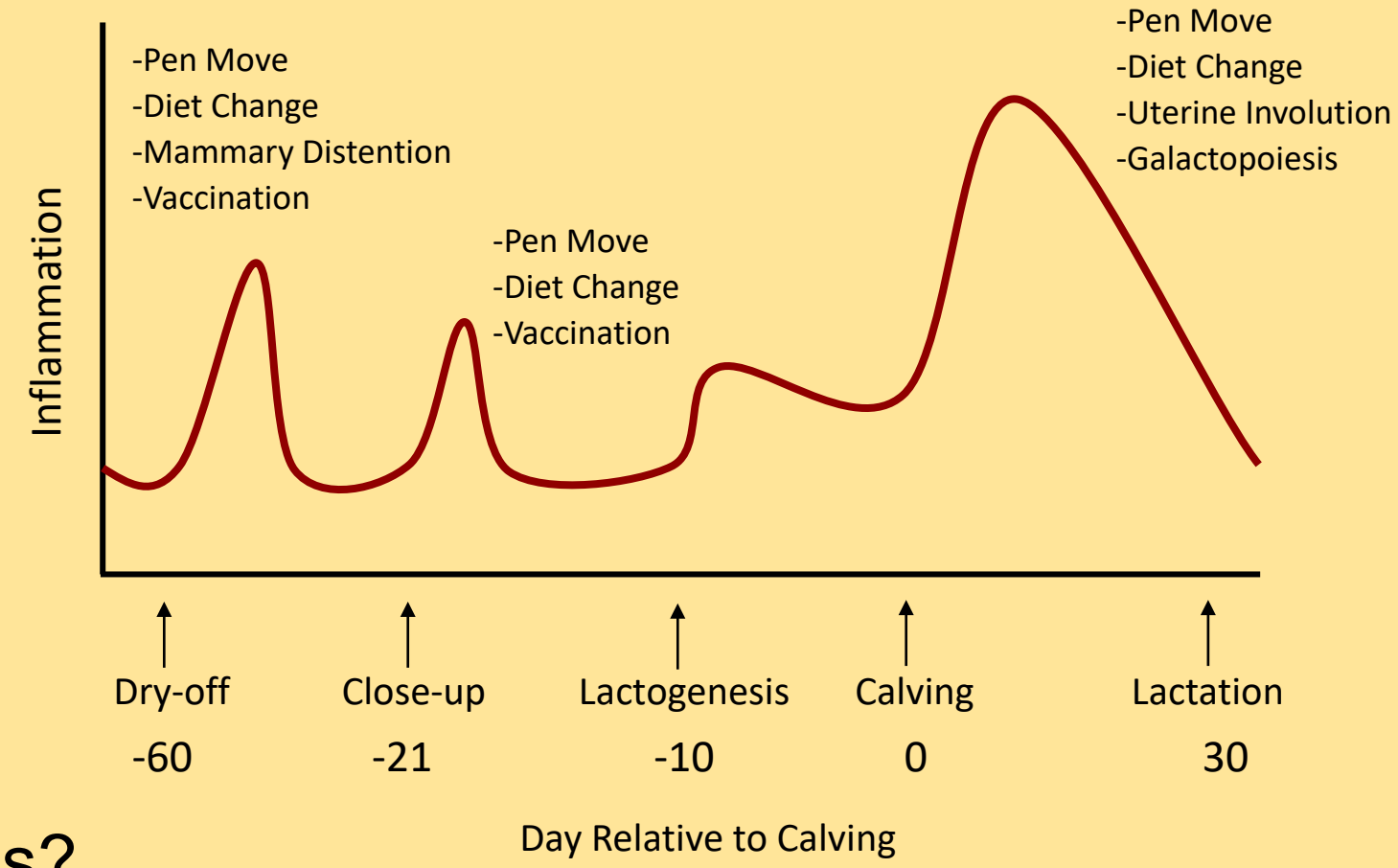
Inflammation in Transition Cows

- Observed in all cows

(Bertoni et al., 2008; Trevisi and Minuti, 2018)

- What is the source?
  - Mammary Gland
  - Uterus
  - Gastrointestinal tract

- What are the consequences?

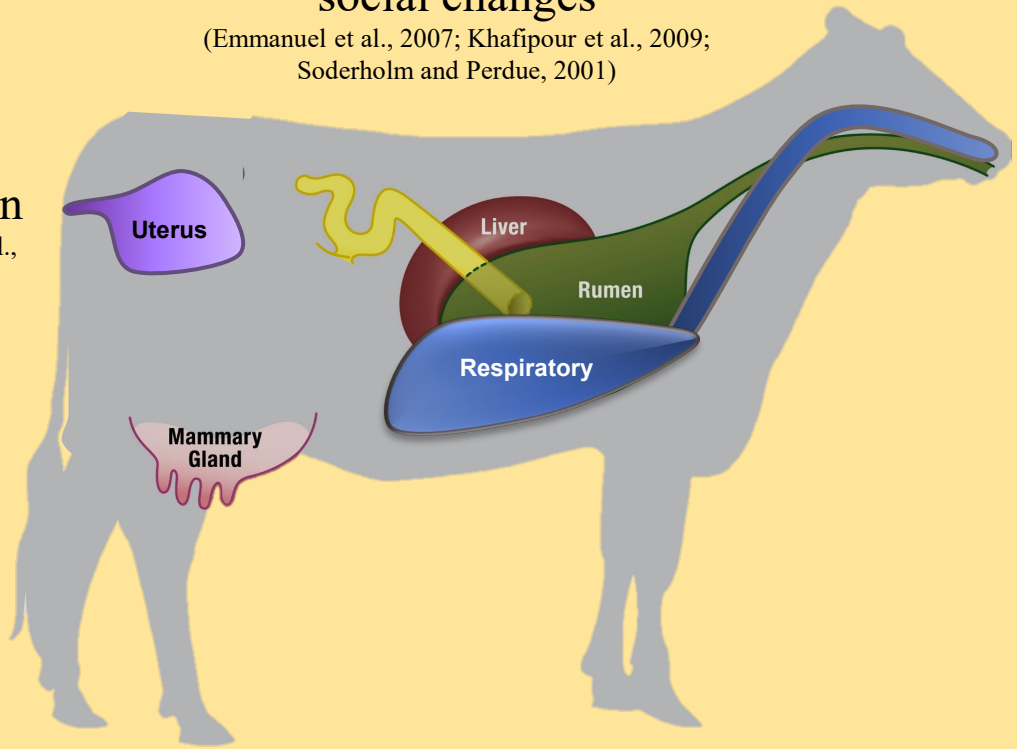


Dr. B. Goetz

Heightened risk of antigen insult in early lactation

Increased gut permeability via diet and social changes
(Emmanuel et al., 2007; Khafipour et al., 2009; Soderholm and Perdue, 2001)

Uterine bacterial contamination post-parturition
(Paisley et al., 1986; Földi et al., 2006; Norman et al., 2007; Sheldon et al., 2008)

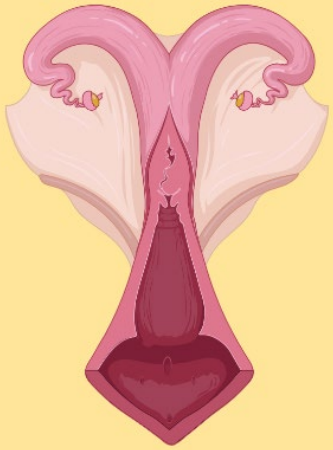


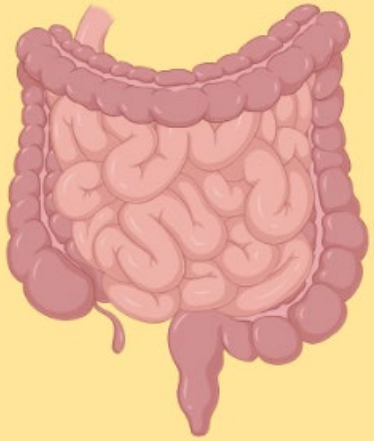
Lactogenesis and galactopoeisis
(Akers and Nickerson, 2011)

<u>Sterile Inflammation</u>
Parturition
Placenta Expulsion
Uterine Involution

Inflammation sources:

LPS

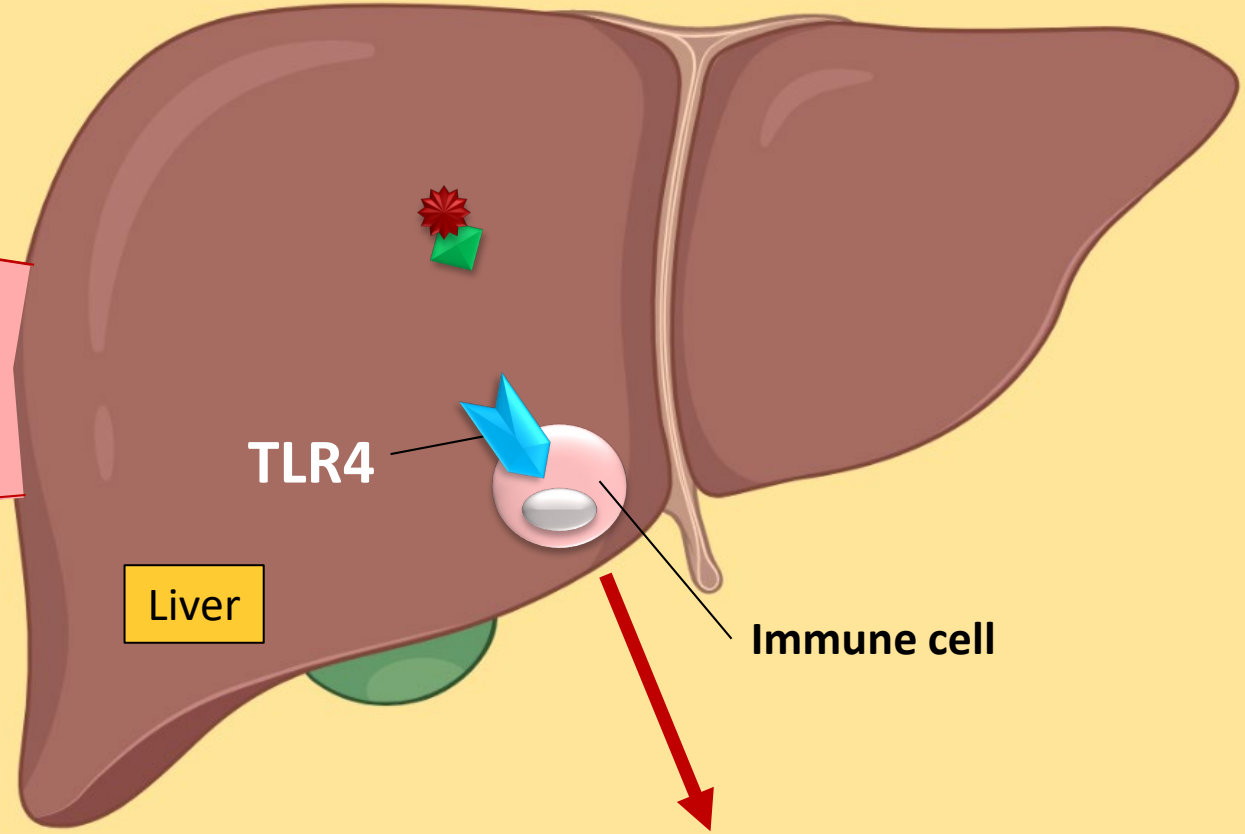




Complex LPS/LBP

LBP

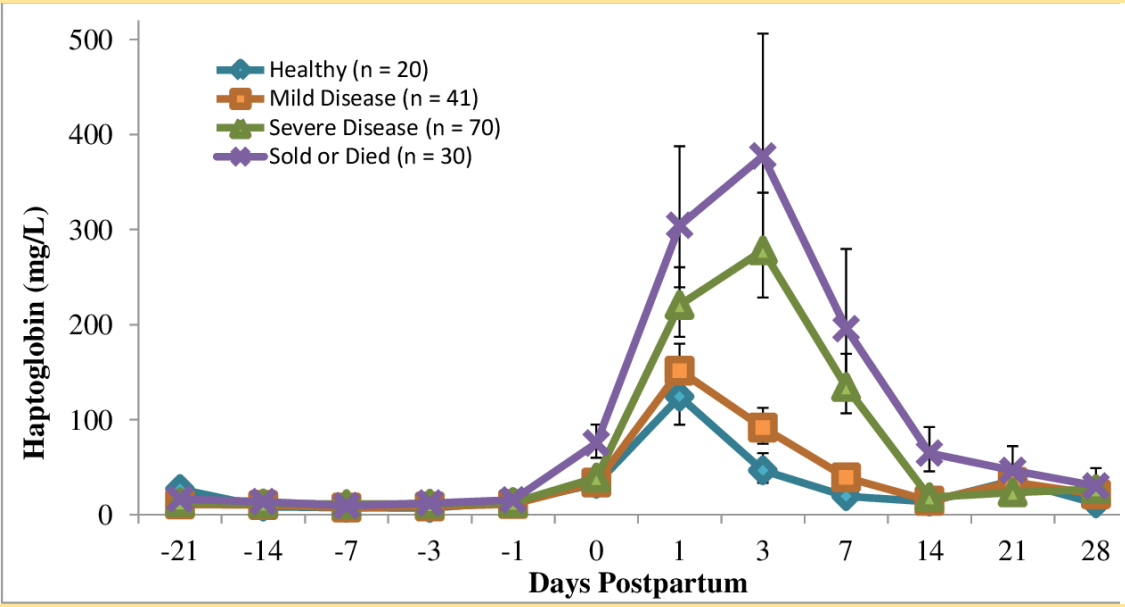
Circulation



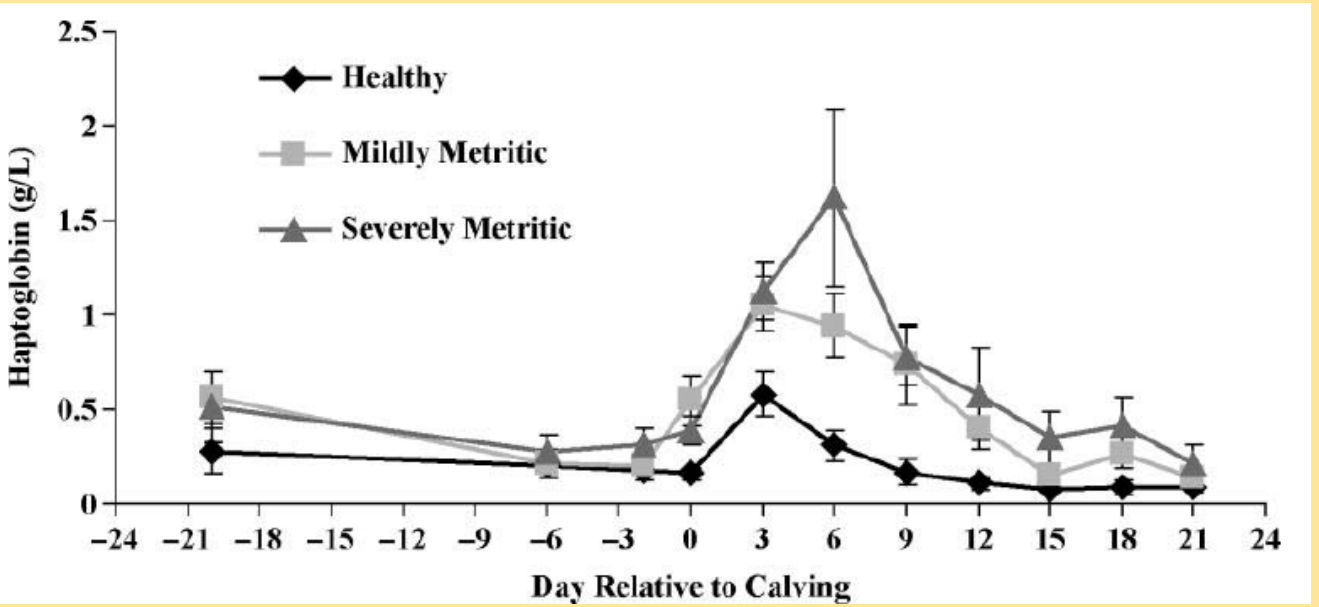
↑ Inflammatory response
↑ Cytokines
↑ APPs:
- SAA
- Hp
- LBP

Sara Kvidera

Immune Activation (Haptoglobin) Precedes Clinical Disease

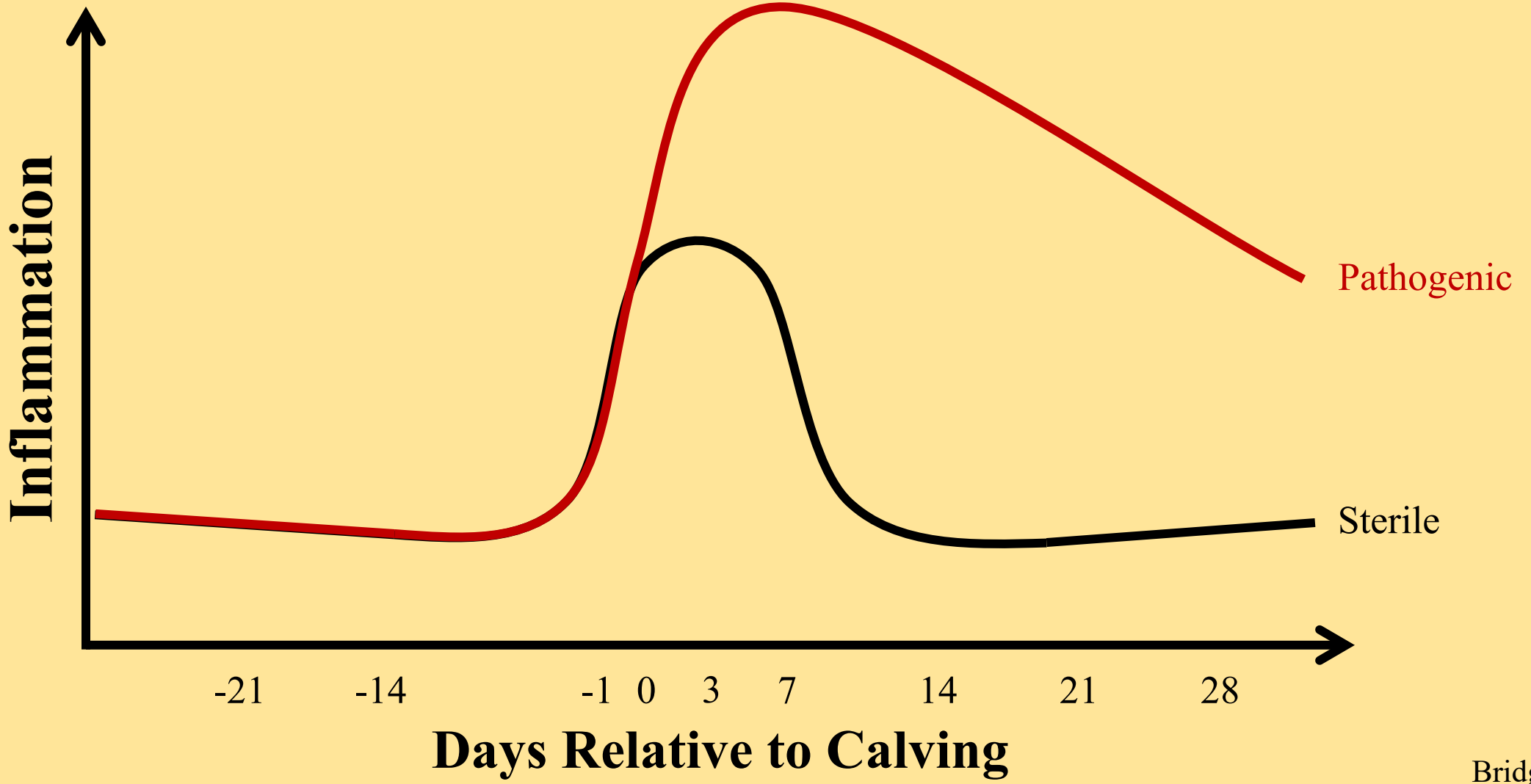


Sebedra 2012



Huzzey et al., 2012

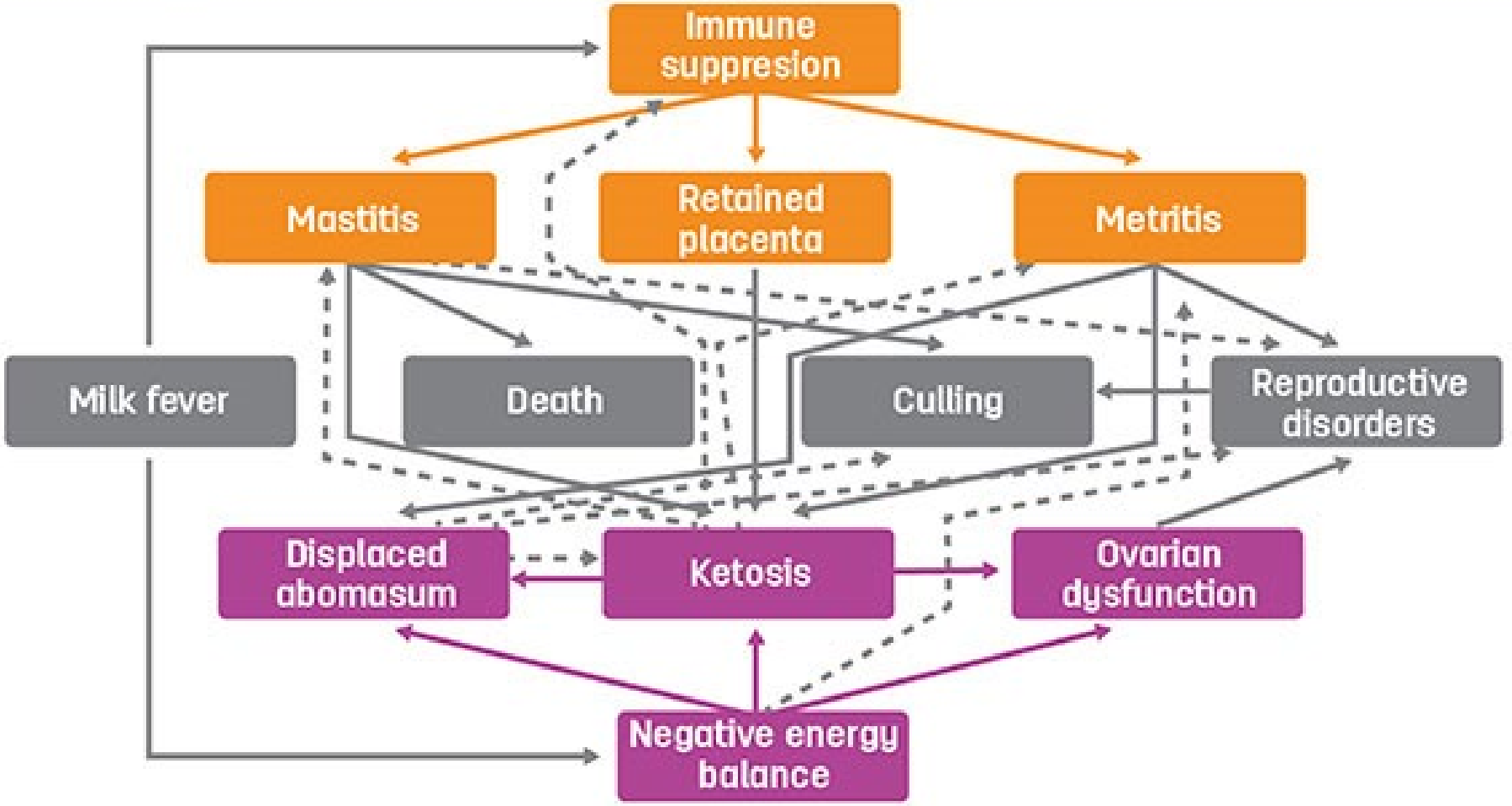
Transition Cow Inflammation



Bridget Buol

Dogma: Example model of how immune suppression and negative energy balance CAUSE problems

FIGURE 1 The impact and consequences of negative energy balance and immune suppression



https://www.progressivedairy.com/topics/herd-health/four-ways-to-reduce-the-risk-of-transition-cow-problems

Research in Veterinary Science 1979, **26**, 97–101

The pathogenesis of experimental *Escherichia coli* mastitis in newly calved dairy cows

A. W. Hill, A. L. Shears and K. G. Hibbitt

Agricultural Research Council, Institute for Research on Animal Diseases, Compton, Newbury, Berkshire

Slow diapedesis of neutrophils appears to be associated with the most severe cases of *E coli* mastitis. The animals appear to suffer from an impaired chemotaxis of cells which is associated with parturition or the stress of early lactation. This

Veterinary Immunology and Immunopathology, 4 (1983) 153–176
Elsevier Science Publishers B.V., Amsterdam — Printed in The Netherlands

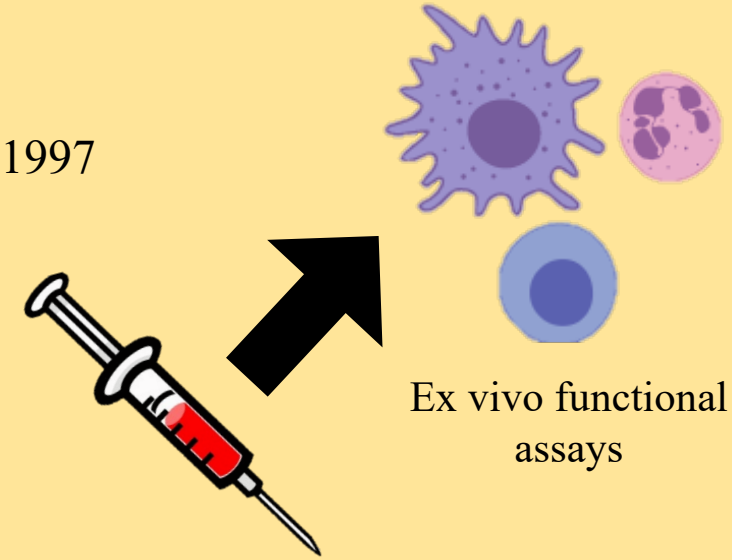
EFFECT OF PREGNANCY AND LACTATION UPON INFECTION

S. LLOYD
Department of Clinical Veterinary Medicine, University of Cambridge, Madingley Rd., Cambridge CB3 0ES, England

More information is required as to the economic importance of infections arising as a result of periparturient immunosuppression in livestock. Also, information is required on the role periparturient immunosuppression may play in the epidemiology of a variety of infectious diseases of domesticated animals and man.

Periparturient cows are more susceptible to disease

- Reduced leukocyte effector functions
  - e.g., oxidative burst, cytotoxicity
  - Kehrli et al., 1989; Cai et al., 1994; Detilleux et al., 1995; Shafer-Weaver et al., 1997



Ex vivo functional assays

- Delayed leukocyte recruitment
  - e.g., adhesion, migration
  - Hill et al., 1979; Frost and Brooker, 1986; Lee and Kehrli, 1998

- **Immunosuppression:** *"immunological unresponsiveness manifest as an increased susceptibility to infection and/or a recrudescence of infection during pregnancy and lactation"* (Lloyd, 1983)

Periparturient Immune Suppression

- < -14 DIM: highly functional
  - Kehrli e
- 1-21 D
  - Guidry
    1998; M
    93; Lee et al.,
- +21 DIM: return to highly functional
  - Gilbert et al., 1993; Meglia et al., 2001; Jahan et al., 2015

But are these fair comparisons?

Is it apples to apples?

Neutrophils continue to mature while in circulation and this affects their ex vivo functionality properties

Trends in Immunology

CellPress

Series: Neutrophils in Action

Review

Aging: A Temporal Dimension for Neutrophils

José M. Adrover,[1] José A. Nicolás-Ávila,[1] and Andrés Hidalgo[1,*]

Neutrophils are first-responders, providing early protection against invading pathogens. Recent findings have revealed a temporal dimension to neutrophil function, associated with the clearance cycles for aging neutrophils, and also with a program that endows circulating neutrophils with distinct phenotypic and functional properties at different times of the day, before they are cleared from blood. We review here the process of neutrophil aging and its impact on homeostasis and inflammation. We outline the features of aged neutrophils, examine proposed mechanisms that drive aging, and discuss how these processes may contribute to tissue homeostasis and pathology. In this context we propose that neutrophil aging may optimize host defense by allowing neutrophils to anticipate infections while avoiding permanent activation and subsequent damage.

Trends

Acute inflammatory syndromes, as well as other types of disease, show circadian patterns of manifestation that parallel changes in the number of circulating leukocytes.

Neutrophils are the most abundant myeloid cells in blood, and their numbers follow circadian patterns of release and clearance.

Neutrophils undergo phenotypic changes from the time they are released into blood (fresh neutrophils) to the time they disappear from the circulation (aged neutrophils). This phenotypic drift, which occurs within a single day, is referred to

Introduction

frontiers in Physiology

REVIE
published: 20 February 20
doi: 10.3389/fphys.2018.001

Neutrophil: A Cell with Many Roles in Inflammation or Several Cell Types?

*Carlos Rosales**

Departamento de Inmunología, Instituto de Investigaciones Biomédicas, Universidad Nacional Autónoma de México, Ciuda de México, Mexico

Neutrophils are the most abundant leukocytes in the circulation, and have been regarde as first line of defense in the innate arm of the immune system. They capture an destroy invading microorganisms, through phagocytosis and intracellular degradatio release of granules, and formation of neutrophil extracellular traps after detectin pathogens. Neutrophils also participate as mediators of inflammation. The classic view for these leukocytes is that neutrophils constitute a homogenous population terminally differentiated cells with a unique function. However, evidence accumulate in recent years, has revealed that neutrophils present a large phenotypic heterogeneit and functional versatility, which place neutrophils as important modulators of bot inflammation and immune responses. Indeed, the roles played by neutrophils homeostatic conditions as well as in pathological inflammation and immune processe are the focus of a renovated interest in neutrophil biology. In this review, I present th concept of neutrophil phenotypic and functional heterogeneity and describe sever neutrophil subpopulations reported to date. I also discuss the role these subpopulation seem to play in homeostasis and disease.

OPEN ACCESS

Edited by:
Giovanni Li Volti,
Università degli Studi di Catania, Italy

Inflammation causes the bone marrow to release immature and incompetent neutrophils

Leliefeld *et al. Critical Care* (2016) 20:73
DOI 10.1186/s13054-016-1250-4

Critical Care

REVIEW Open Access

The role of neutrophils in immune dysfunction during severe inflammation

Pieter H. C. Leliefeld[1,3*], Catharina M. Wessels[1], Luke P. H. Leenen[1], Leo Koenderman[2,3] and Janesh Pillay[3,4]

Abstract

Critically ill post-surgical, post-trauma and/or septic patients are characterised by severe inf response consists of both a pro- and an anti-inflammatory component. The pro-inflam contributes to (multiple) organ failure whereas occurrence of immune paralysis predisp Strikingly, infectious complications arise in these patients despite the presence of a cle propose that dysfunction of neutrophils potentially increases the susceptibility to infectior inability to clear existing infections. Under homeostatic conditions these effector cells of t system circulate in a quiescent state and serve as the first line of defence against invading inflammation, however, neutrophils are rapidly activated, which affects their functional capaci phagocytosis, intra-cellular killing, NETosis, and their capacity to modulate adaptive immunity. overview of the current understanding of neutrophil dysfunction in severe inflammation. We mechanisms of downregulation of anti-microbial function, suppression of adaptive immunity contribution of neutrophil subsets to immune paralysis.

Zonneveld *et al. Critical Care* (2016) 20:235
DOI 10.1186/s13054-016-1391-5

Critical Care

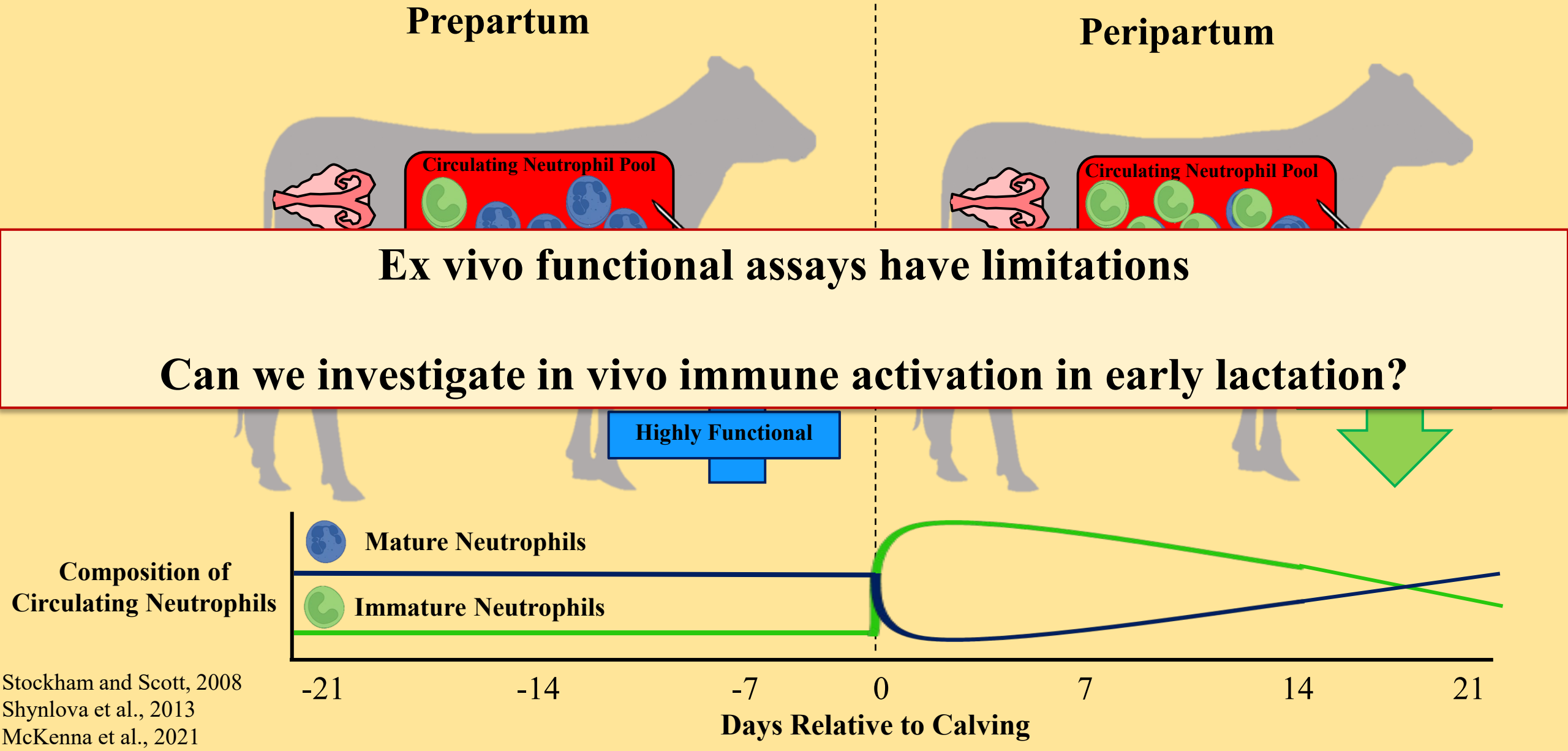
LETTER Open Access

Measurement of functional and morphodynamic neutrophil phenotypes in systemic inflammation and sepsis

Rens Zonneveld[1,2,3*], G. Molema[2] and Frans B. Plötz[3]

See related research by Leliefeld et al., http://ccforum.biomedcentral.com/articles/10.1186/s13054-016-1250-4.

Altered leukocyte dynamics



Ex vivo functional assays have limitations

Can we investigate in vivo immune activation in early lactation?

Stockham and Scott, 2008
Shynlova et al., 2013
McKenna et al., 2021

Modeling immune activation in transition cows

- Reasons to use mid-lactation cows:
  - Consistent milk yield and feed intake
  - Broader cow selection pool
  - Less variability in physiologic, metabolic, and inflammatory responses

- Obvious limitations exist:
  - The early lactation metabolic milieu is difficult to replicate
  - The periparturient immune status starkly contrasts with mid-lactation cows
  - The mammary gland's evolutionary drive to synthesize milk wanes over time

Modeling immune activation in transition cows

J. Dairy Sci. 97:330–339
http://dx.doi.org/10.3168/jds.2013-7222

Induced hyperketonemia affects the mammary immune response during lipopolysaccharide challenge in dairy cows

Connecting Metabolism to Mastitis: Hyperketonemia Impaired Mammary Gland Defenses During a *Streptococcus uberis* Challenge in

Immune activation models often attempt to characterize periparturient cow physiology… utilizing **mid-lactation cows**

Evaluating acute inflammation's effects on hepatic triglyceride content in experimentally induced hyperlipidemic dairy cows in late lactation

E. A. Horst,[1] L. M. van den Brink,[1] E. J. Mayorga,[1] M. Al-Qaisi,[1] S. Rodriguez-Jimenez,[1] B. M. Goetz,[1] M. A. Abeyta,[1] S. K. Kvidera,[1] L. S. Caixeta,[2] R. P. Rhoads,[3] and L. H. Baumgard[1]*
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[3]Department of Animal and Poultry Sciences, Virginia Tech University, Blacksburg 24061

J. Dairy Sci. 95
http://dx.doi.or

Local and systemic response to intramammary lipopolysaccharide challenge during long-term manipulated plasma glucose and insulin concentrations in dairy cows

M. C. M. B. Vernay, O. Wellnitz, L. Kreipe, H. A. van Dorland, and R. M. Bruckmaier[1]
Veterinary Physiology, Vetsuisse Faculty University of Bern, Bremgartenstrasse 109a, CH-3001 Bern, Switzerland

Effect of Lipopolysaccharide on Indices of Peripheral and Hepatic Metabolism in Lactating Cows[1]

M. R. Waldron,* T. Nishida,* B. J. Nonnecke,† and T. R. Overton*
*Department of Animal Science, Cornell University, Ithaca 14853 and
†National Animal Disease Center, USDA, ARS, Ames, IA 50010

J. Dairy Sci. 103
https://doi.org/10.3168/jds.2020-18268

Effects of maintaining eucalcemia following immunoactivation in lactating Holstein dairy cows

E. A. Horst, E. J. Mayorga, M. Al-Qaisi, M. A. Abeyta, S. L. Portner, C. S. McCarthy, B. M. Goetz, S. K. Kvidera, and L. H. Baumgard*
Department of Animal Science, Iowa State University, Ames 50011

J. Dairy Sci. 107:6225–6239
https://doi.org/10.3168/jds.2023-24350

Intravenous lipopolysaccharide challenge in early- versus mid-lactation dairy cattle. I: The immune and inflammatory responses

J. Opgenorth,[1] E. J. Mayorga,[1] M. A. Abeyta,[1] B. M. Goetz,[1] S. Rodriguez-Jimenez,[1] A. D. Freestone,[1] J. L. McGill,[2] and L. H. Baumgard[1]*
[1]Department of Animal Science, Iowa State University, Ames, IA 50011
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Objecti

id-lactation dairy cows

J. Dairy Sci. 107:6240–6251
https://doi.org/10.3168/jds.2023-24351

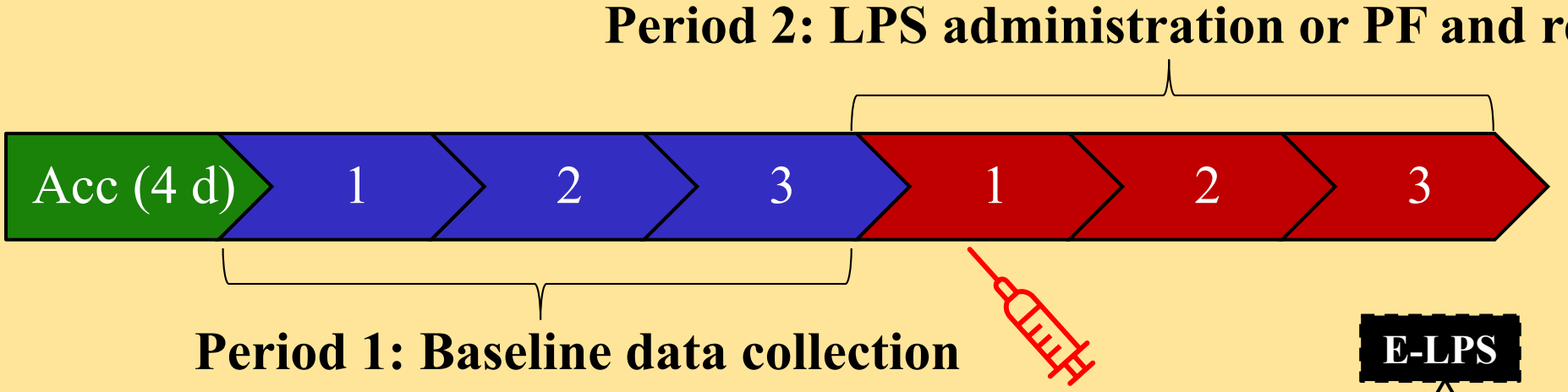
Intravenous lipopolysaccharide challenge in early- versus mid-lactation dairy cattle. II: The production and metabolic responses

J. Opgenorth, E. J. Mayorga, M. A. Abeyta, S. Rodriguez-Jimenez, B. M. Goetz, A. D. Freestone, and L. H. Baumgard*
Department of Animal Science, Iowa State University, Ames, IA 50011

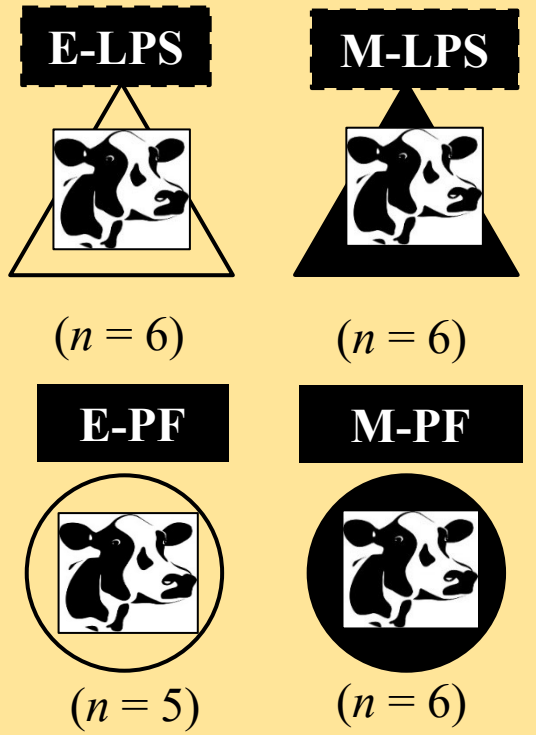
Hypoth

mmune and inflammatory response towards LPS

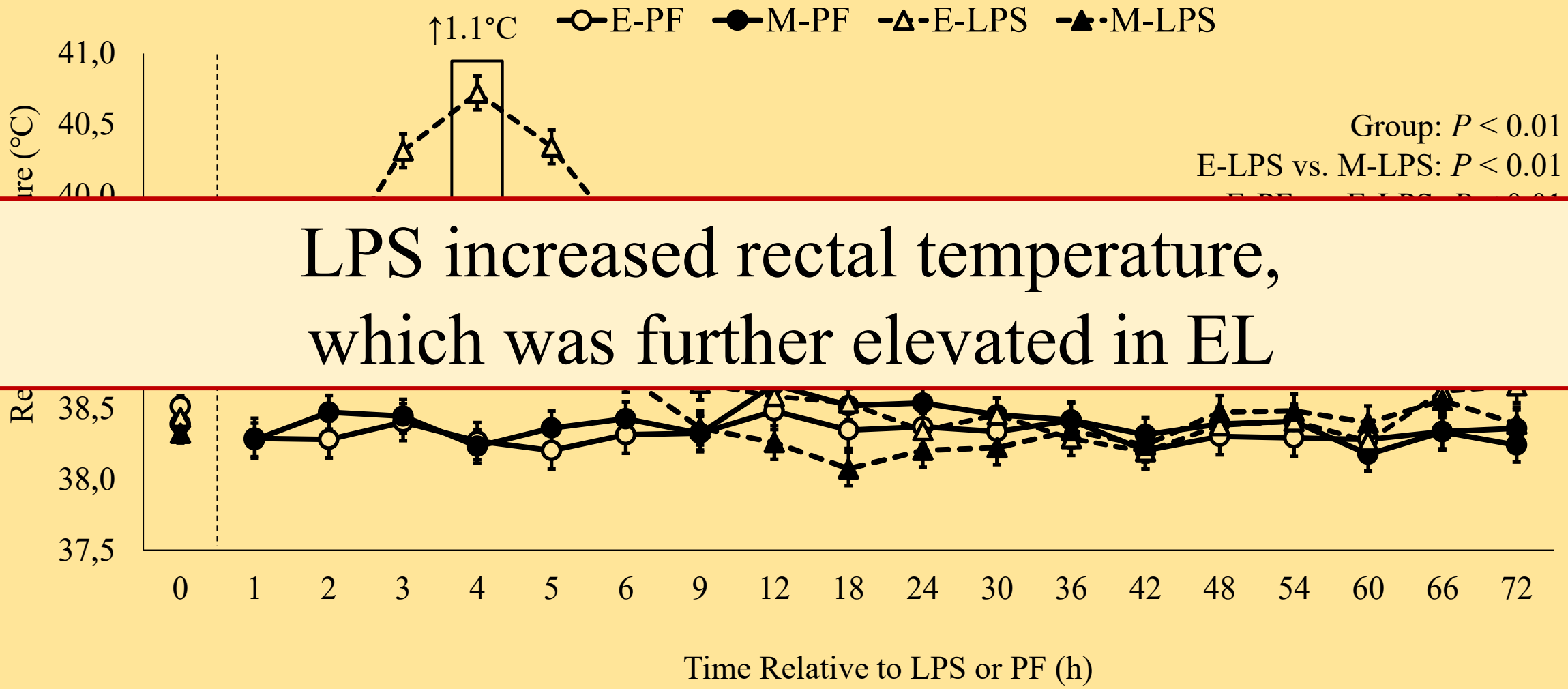
Experimental schematic



- 23 multiparous Holstein cows in 2 replicates
  - EL: 20 ± 2 DIM (n = 11)
  - ML: 131 ± 31 DIM (n = 12)
- Treatments administered at beginning of P2
  - LPS: lipopolysaccharide *Escherichia coli* O55:B5 (0.09 µg/kg BW)
  - PF: sterile saline and pair-fed relative to LPS counterparts
- 2 × 2 factorial
  - Group: LPS or PF
  - LS: EL or ML

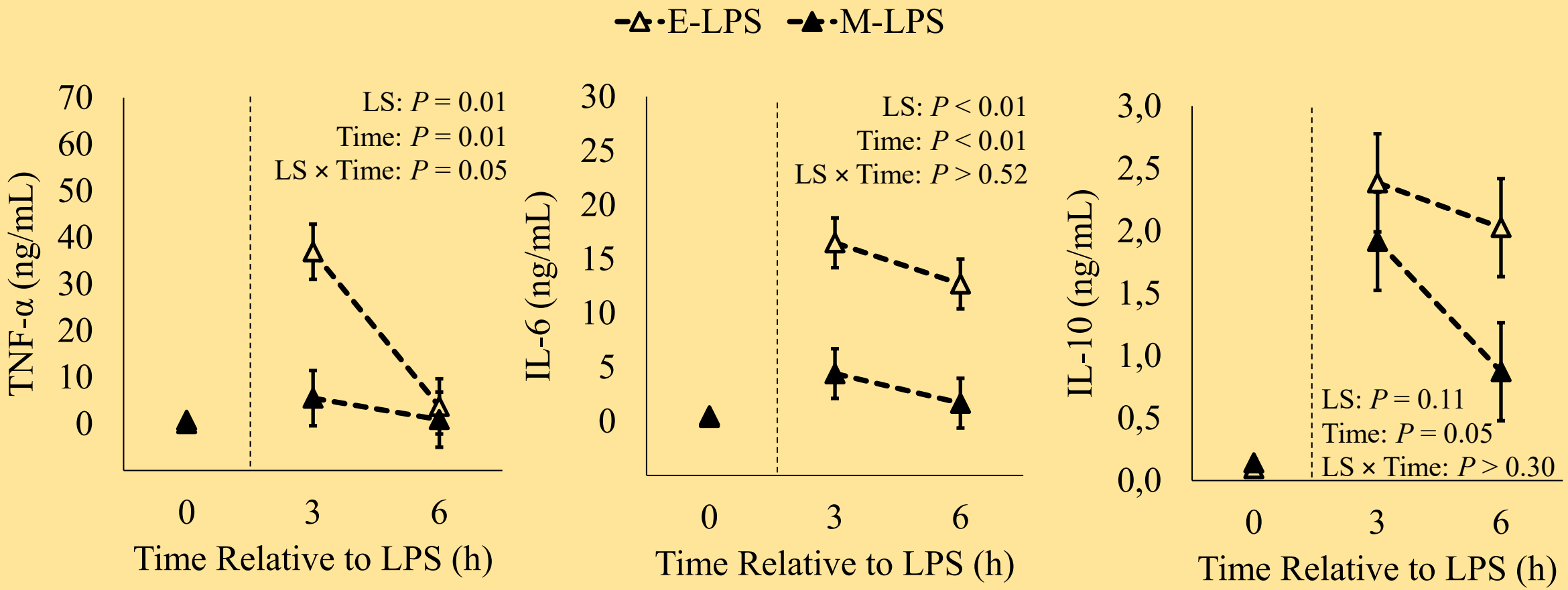


Febrile response

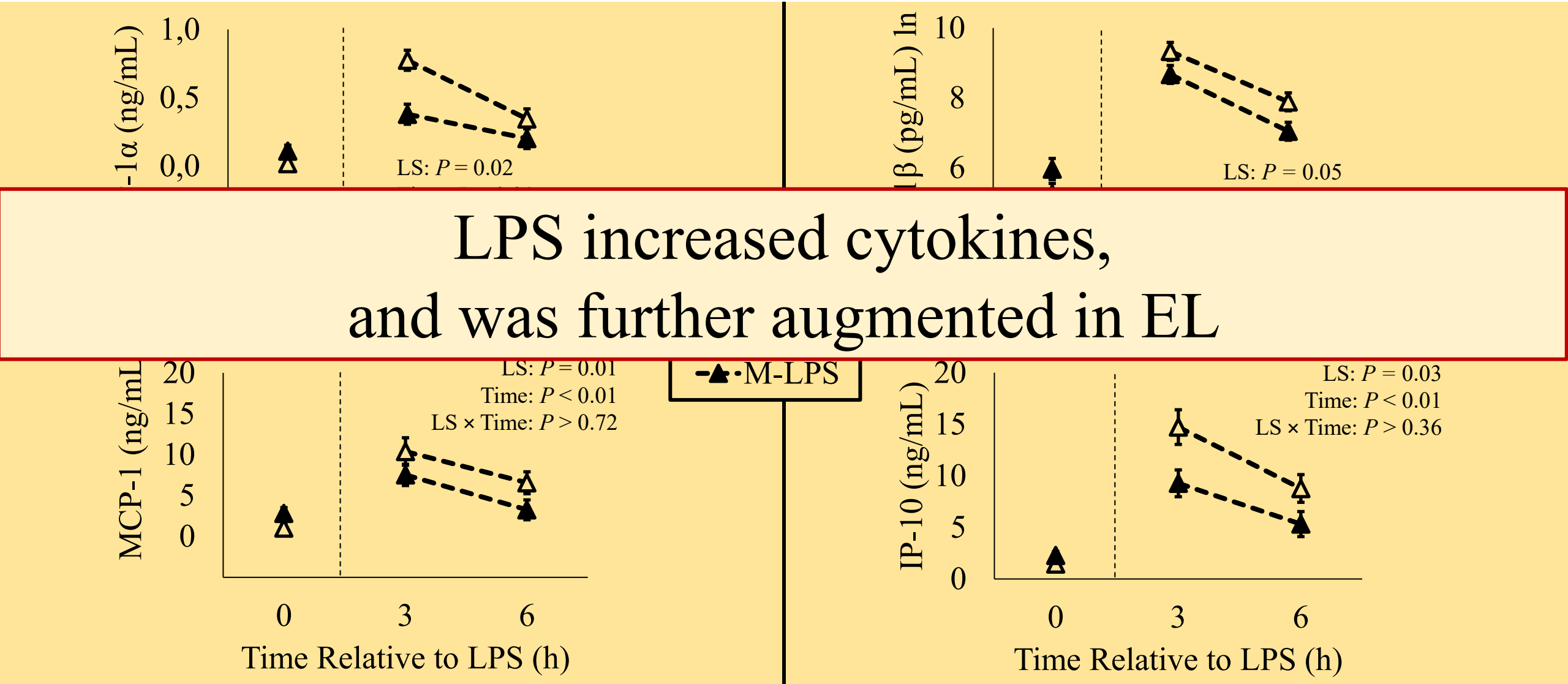


LPS increased rectal temperature,
which was further elevated in EL

Cytokines

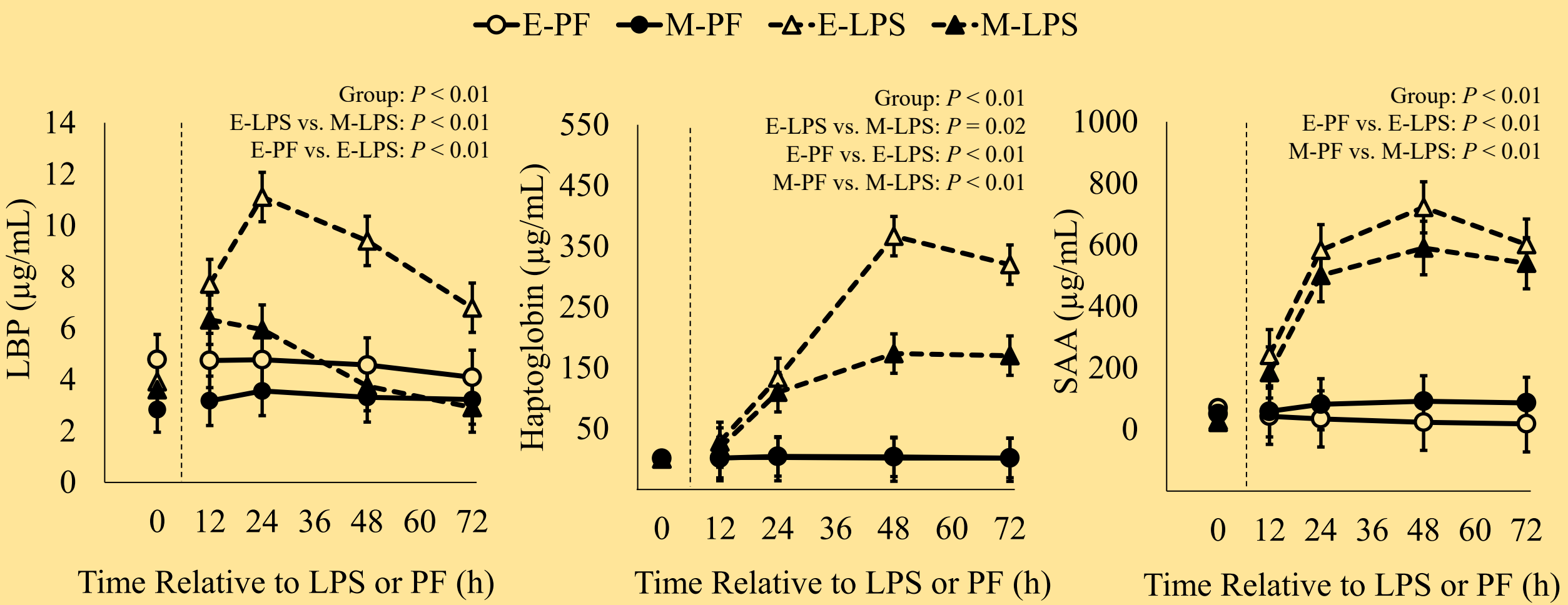

E-LPS
M-LPS
TNF-α (ng/mL)
70
60
50
40
30
20
10
0
LS: P = 0.01
Time: P = 0.01
LS × Time: P = 0.05
0
3
6
Time Relative to LPS (h)
IL-6 (ng/mL)
30
25
20
15
10
5
0
LS: P < 0.01
Time: P < 0.01
LS × Time: P > 0.52
0
3
6
Time Relative to LPS (h)
IL-10 (ng/mL)
3,0
2,5
2,0
1,5
1,0
0,5
0,0
LS: P = 0.11
Time: P = 0.05
LS × Time: P > 0.30
0
3
6
Time Relative to LPS (h)

Chemotactic cytokines

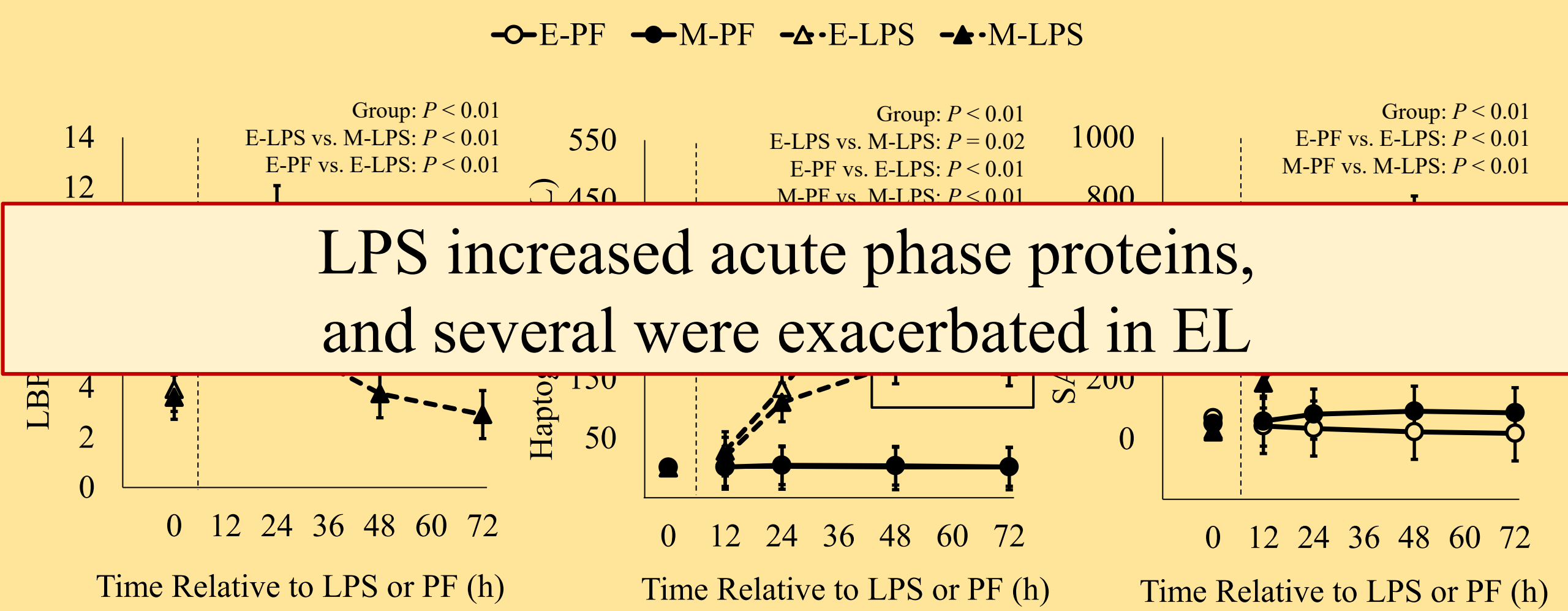


LPS increased cytokines,
and was further augmented in EL

Acute phase proteins

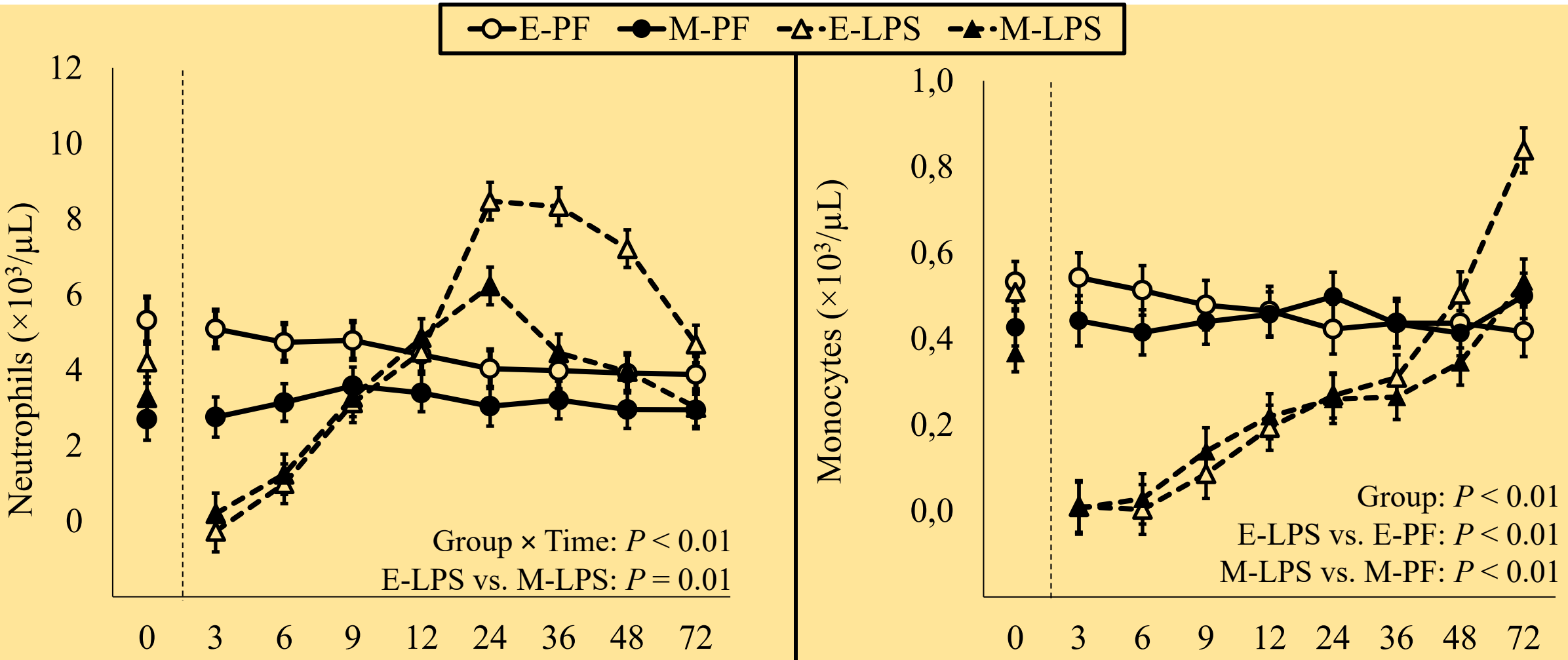


Acute phase proteins

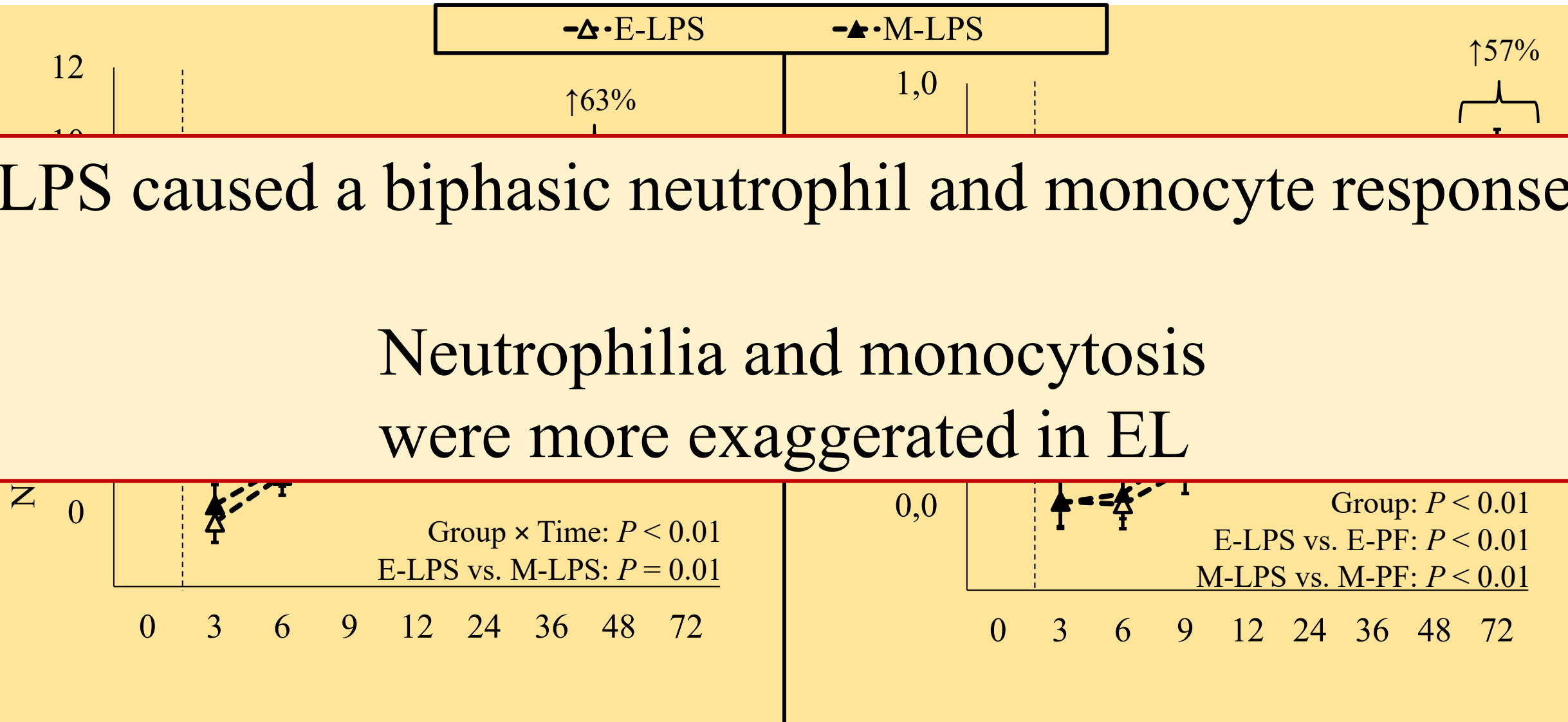


LPS increased acute phase proteins,
and several were exacerbated in EL

Complete cell blood count



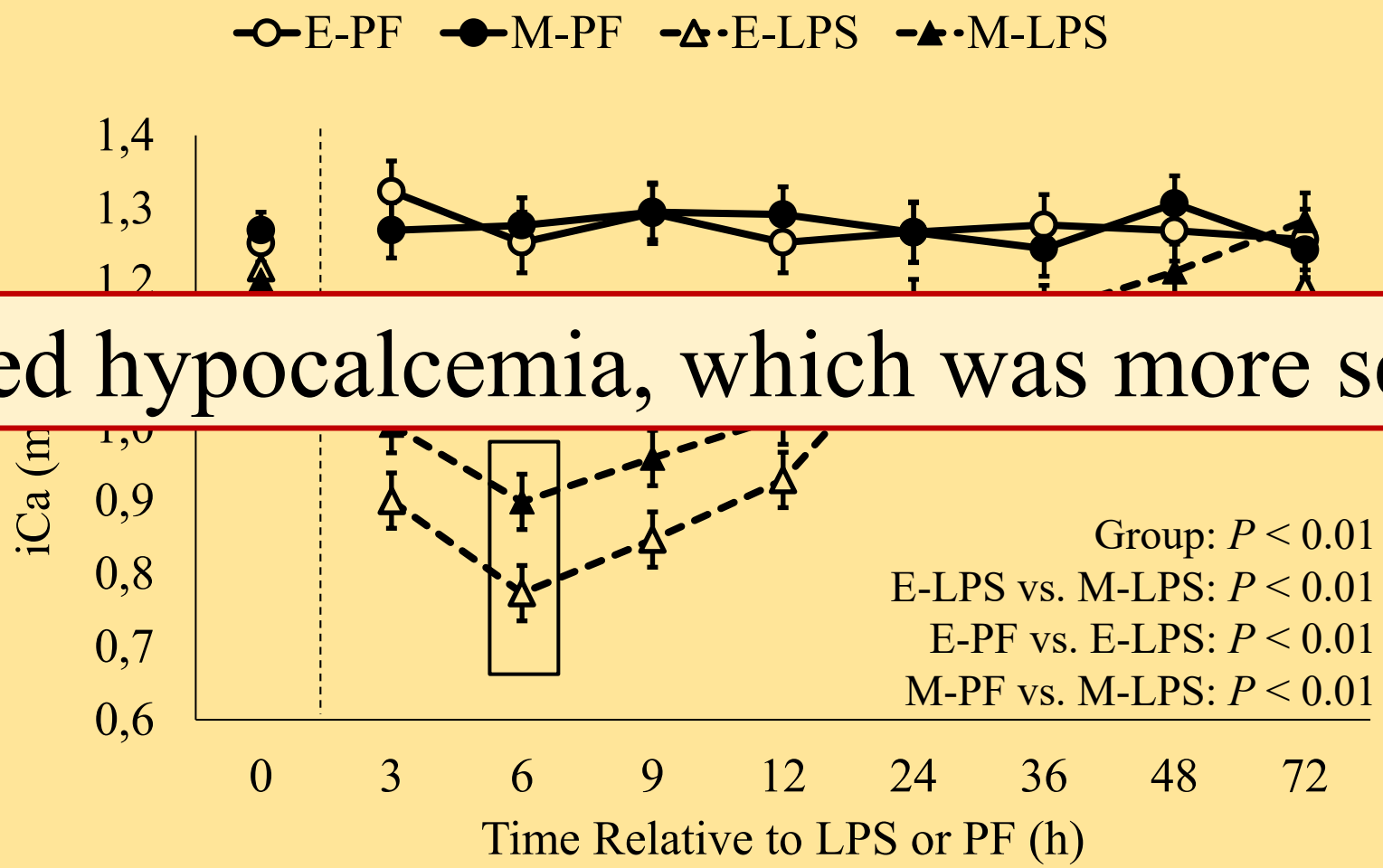
Complete cell blood count



LPS caused a biphasic neutrophil and monocyte response

Neutrophilia and monocytosis were more exaggerated in EL

Ionized calcium



LPS caused hypocalcemia, which was more severe in EL

Immune Activation/Inflammation Summary

- LPS:
  - Increased fever, cytokines, and acute phase proteins
  - Caused neutrophilia and monocytosis
  - Decreased ionized Ca
- …which were further augmented in EL

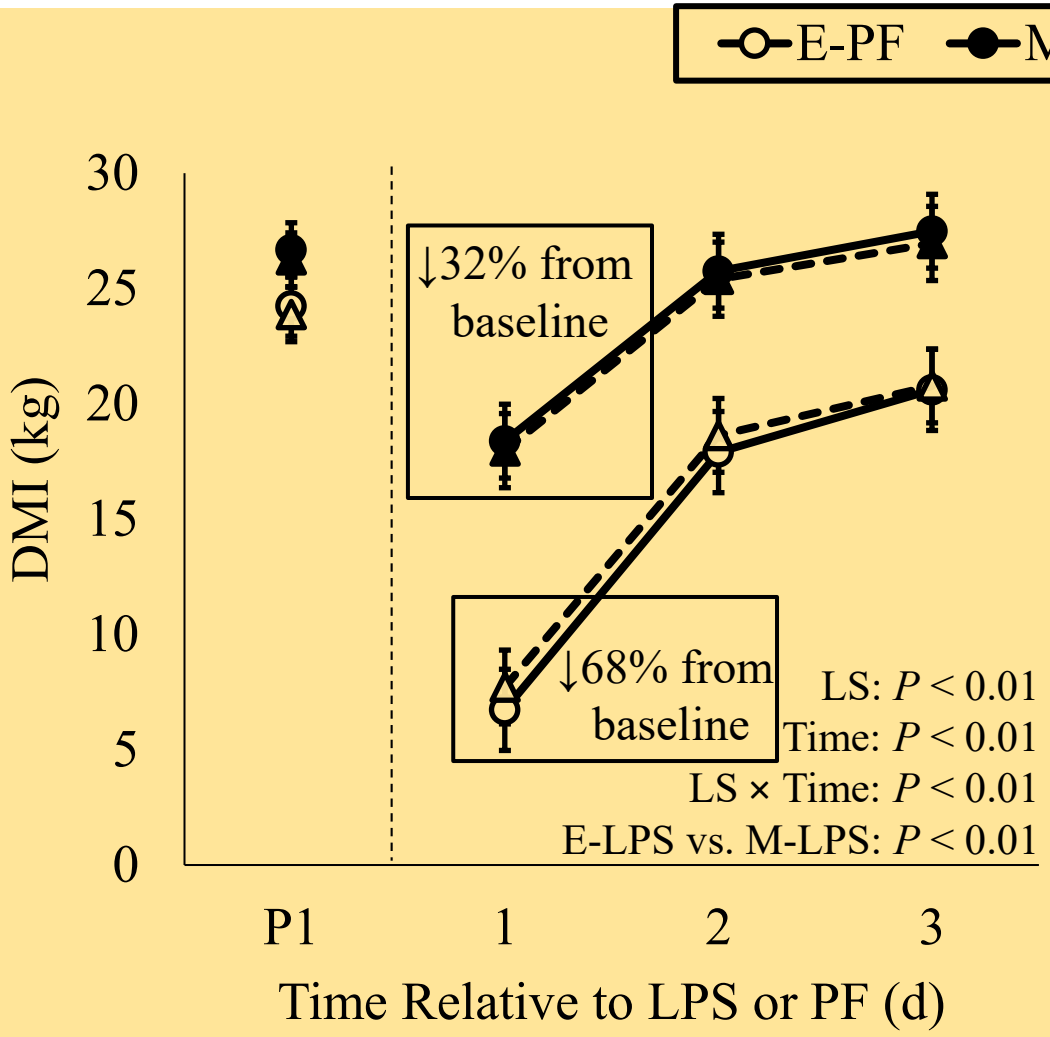
Our hypothesis could not have been more wrong

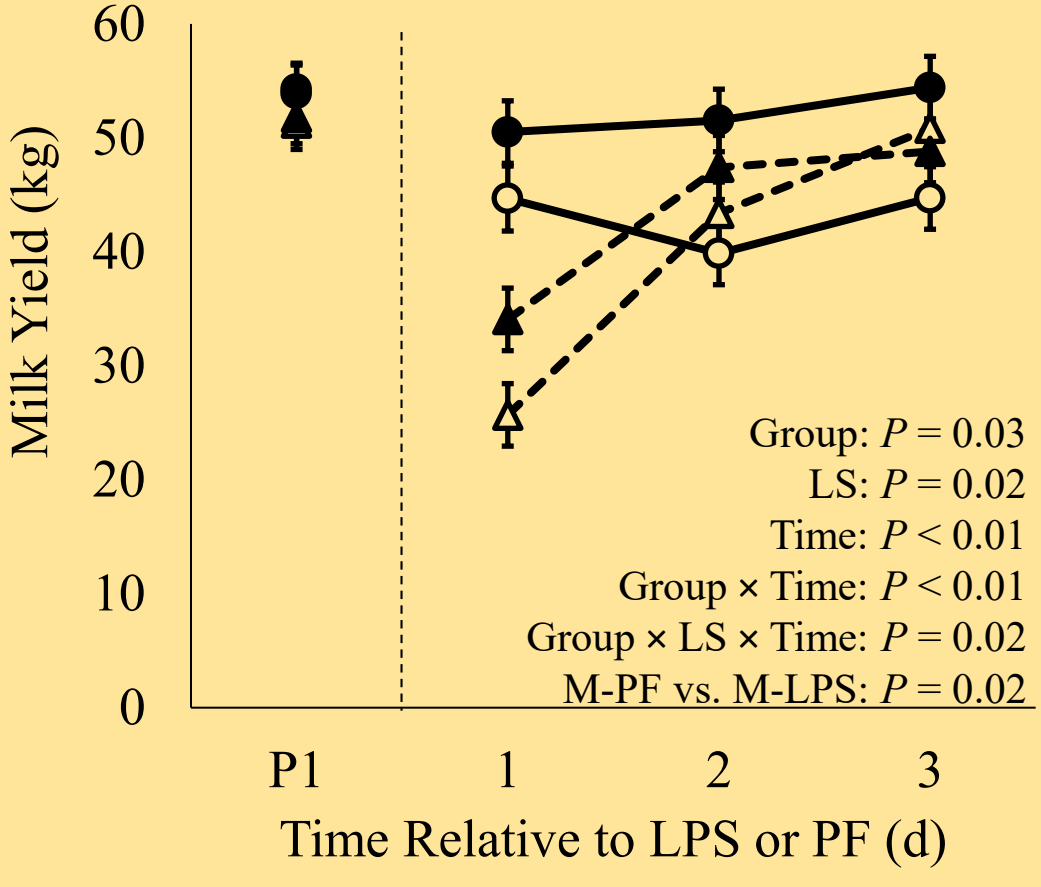
EL cows were *not* more LPS tolerant…

Some aspects of EL immunity are incredibly robust

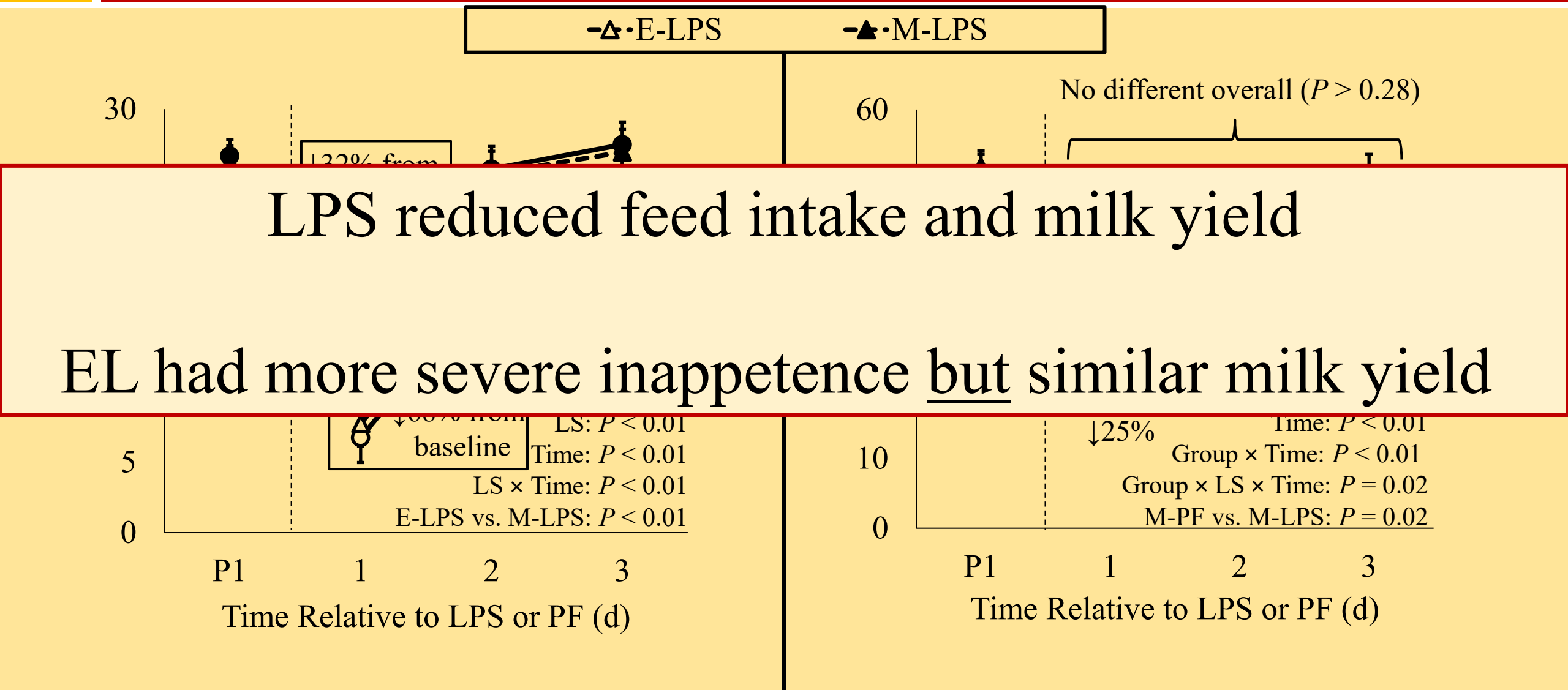
Early vs. Late Lactation Production and Metabolism Responses to Immune Activation

Feed intake and production





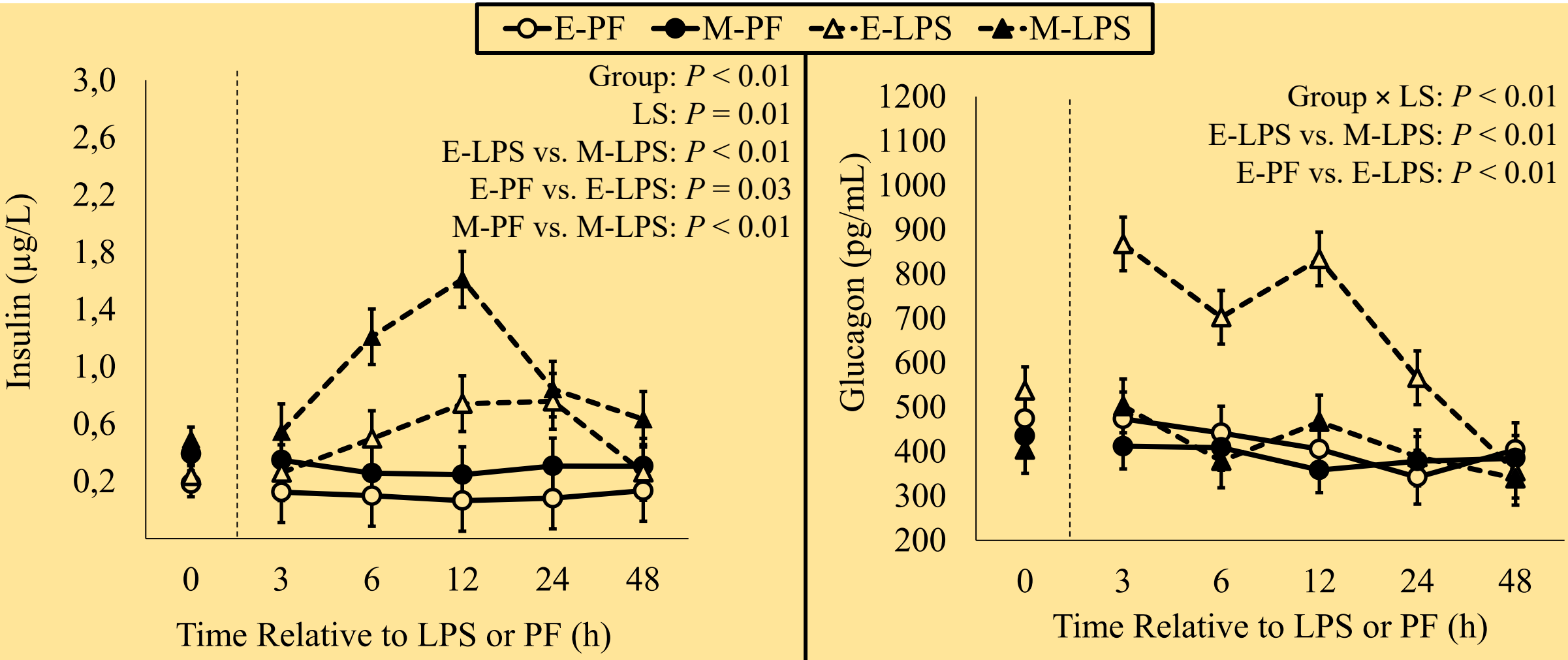
Feed intake and production



LPS reduced feed intake and milk yield

EL had more severe inappetence but similar milk yield

Metabolic hormones

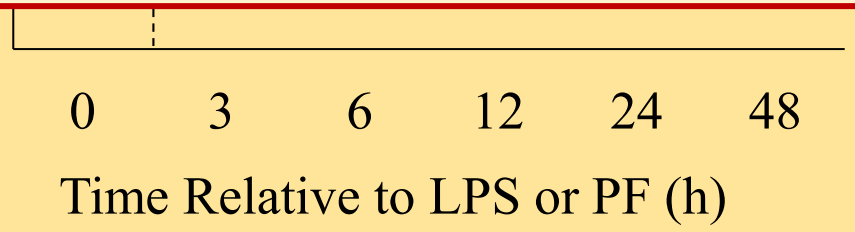


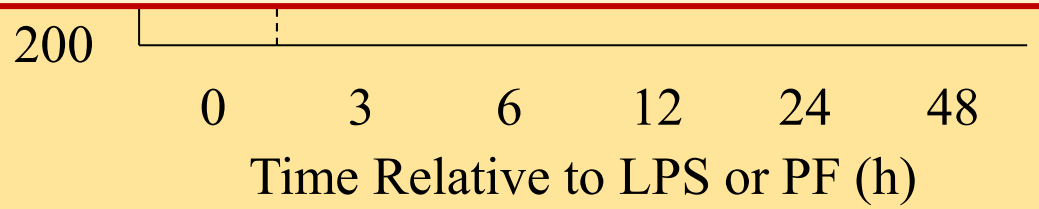
Metabolic hormones

LPS increased insulin (blunted in EL)

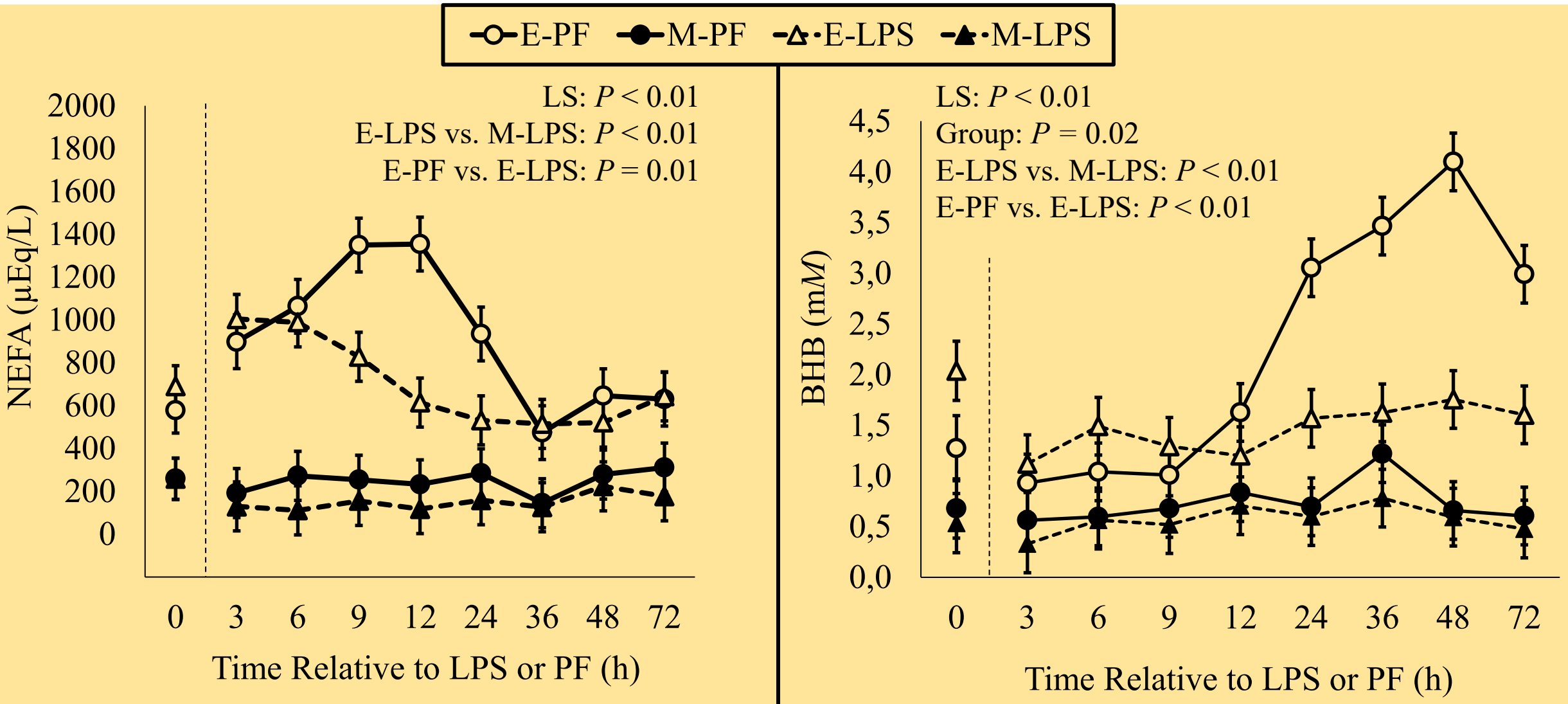
LPS increased glucagon in EL

EL had enhanced glucose sparing mechanisms in response to LPS

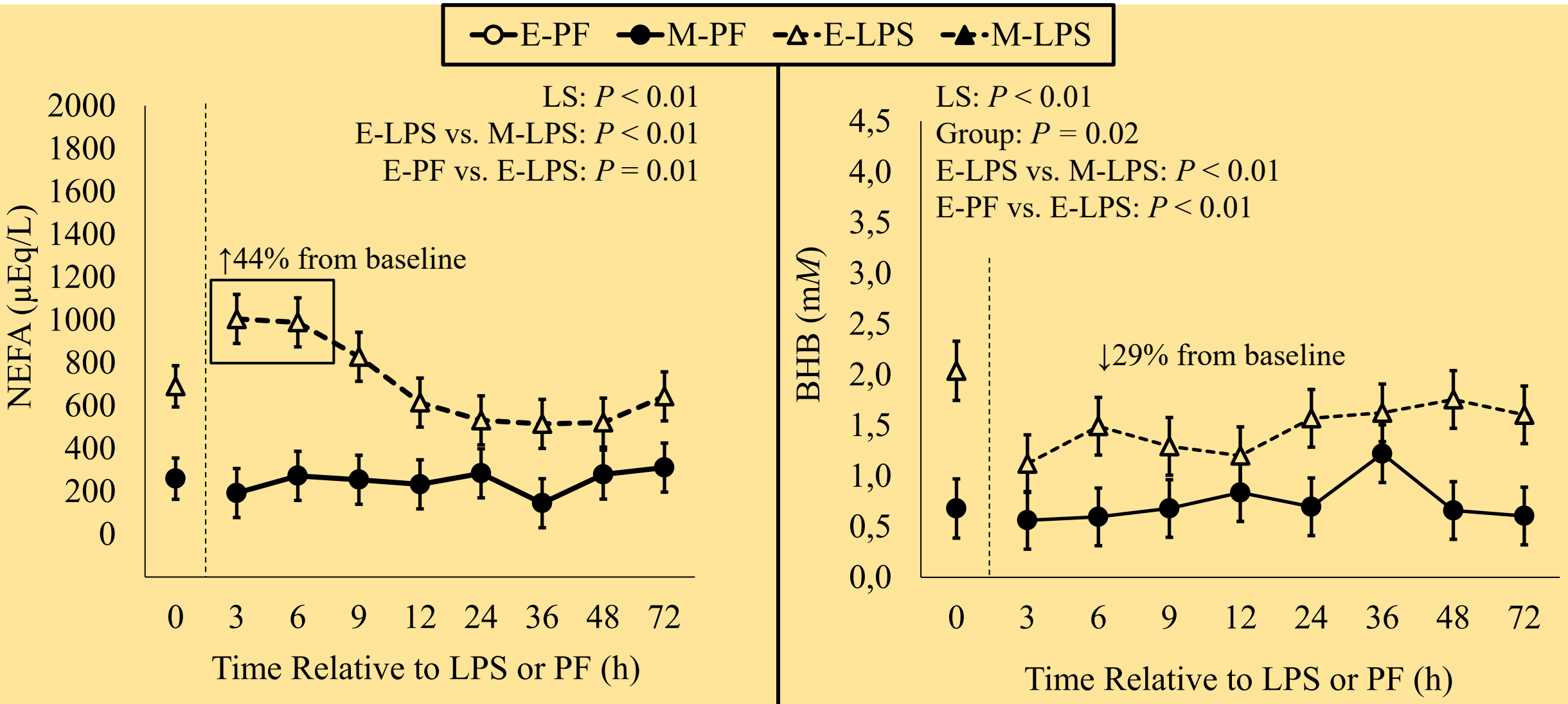




Auxiliary fuels



Auxiliary fuels



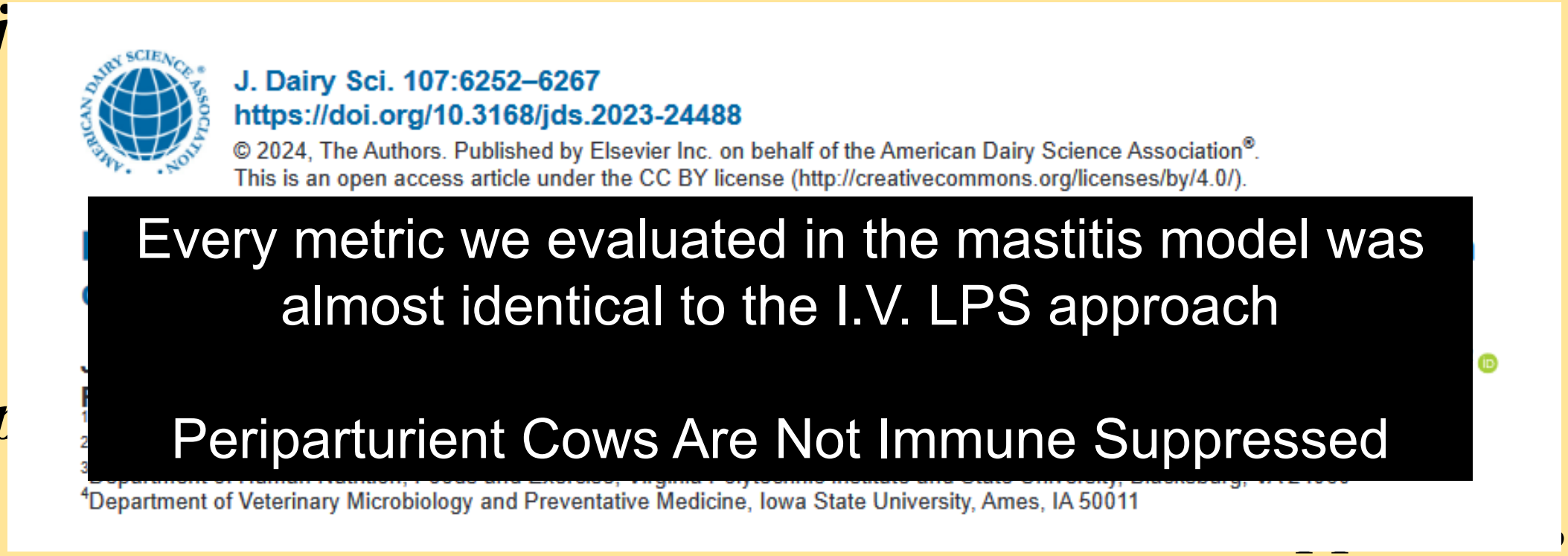
Metabolism Summary

- LPS:
  - Decreased feed intake and milk yield

Despite more severe hypophagia in EL, milk yield response did not differ from ML cows... Reflected by metabolic alterations favoring glucose sparing and catabolism

Does a mammary LPS challenge recapitulate the i.v. LPS challenge?

Obj



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Every metric we evaluated in the mastitis model was almost identical to the I.V. LPS approach

Peripartal Cows Are Not Immune Suppressed

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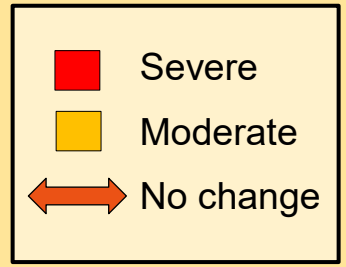
Hyp

, but have similar milk yield; reflected by enhanced metabolic flexibility

Immune Activation: Early vs. Mid Lactation Cow

Parameter	Early-Lactation Cow	Mid-lactation Cow
Febrile Response	↑↑↑	↑
Inflammatory/Chemotactic Cytokines	↑↑↑	↑
Leukocytosis	↑↑↑	↑
Acute Phase Proteins	↑↑↑	↑
Ionized Calcium	↓↓↓	↓
Insulin	↑	↑↑↑
Glucagon	↑↑↑	↑
NEFA	↑↑↑	↓
BHB	↔	↓
BUN (muscle mobilization)	↑↑↑	↑
Dry Matter Intake	↓↓↓	↓
Milk Yield	↓	↓



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Mucosal immune responses in peri-parturient dairy cattle

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[d] Zoetis, Inc. Parsippany, NJ, USA

"Contrary to previous reports of systemic immune-suppression, bovine mucosal responses appear to be intact during the peripartum period"

"The increases in local IFN-beta in the pre-partum period, and the IgA in the post-partum, despite published evidence of decreased systemic immune responsiveness during the same time frame (Heiser et al., 2015), provides support for further research to confirm whether there is an upregulation of mucosal immunity during the peripartum period."

Transition Cow “Immune Suppression”

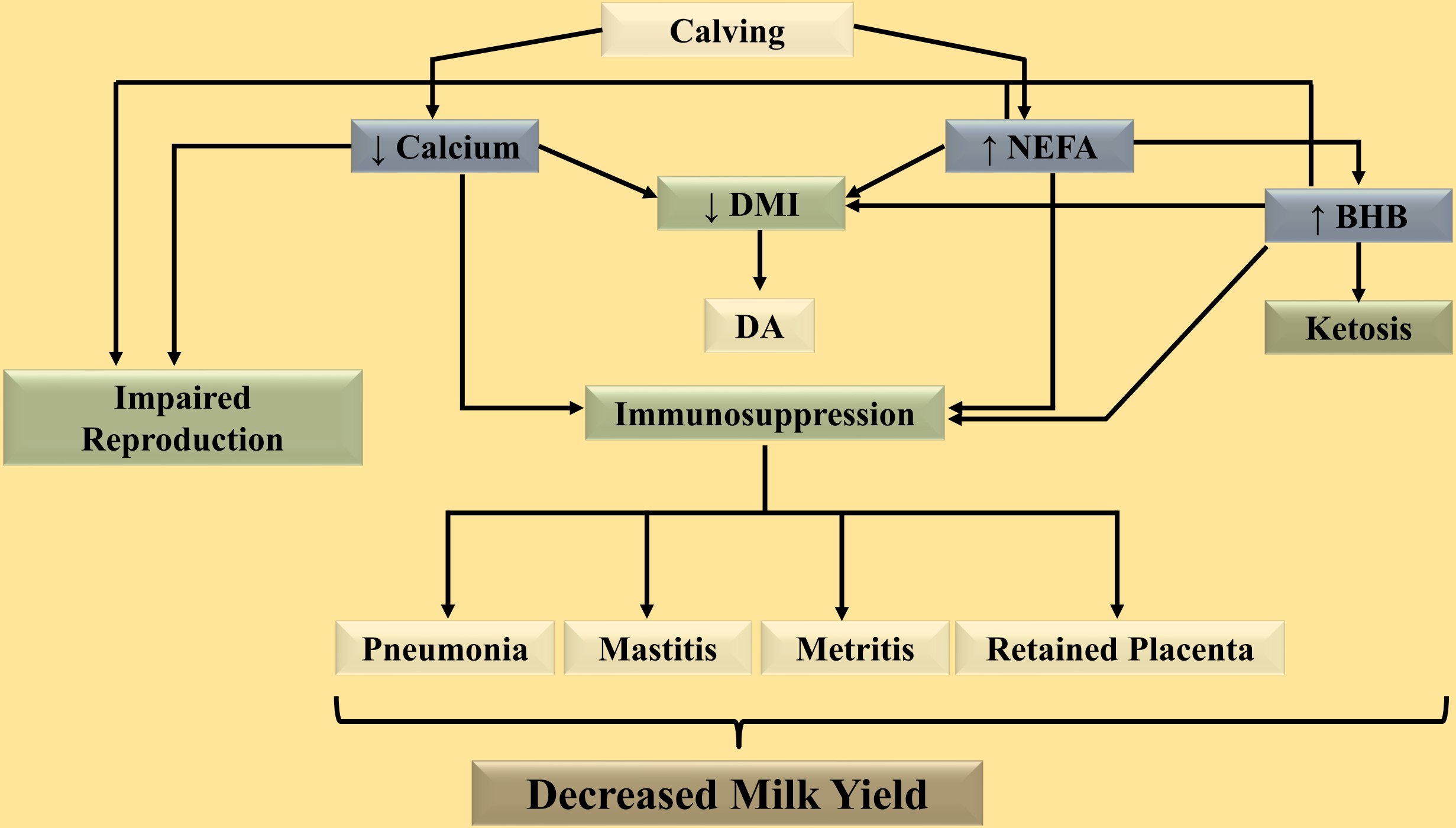
- Almost every immune system variable we measured was more robust in early lactation compared to late lactation cows.
- Despite exaggerated immune response, early lactation cows prioritized milk synthesis
  - Energetic collision of priorities (immune system AND milk synthesis)
    - Hypoglycemia, high NEFA and Hyperketonemia
  - Late lactation cows just give up trying to make milk
- Maybe if it weren’t for a super strong immune response morbidity would be even worse!
- If correct, what are the implications to dairy nutrition and management?
- I am not suggesting that inflammation is innocuous
  - Efforts should be to limit the peak and hasten the resolution

Practical on-farm Examples Supportive Our Tenet

- Imrestor™ (bovine granulocyte stimulating factor)
  - Increases circulating neutrophils
- Transition cows do not develop high pathogenic avian bird flu
  - https://www.canr.msu.edu/news/hpai-dairy-herd-infection-case-report
  - https://www.cidrap.umn.edu/avian-influenza-bird-flu/avian-flu-detections-dairy-cows-raise-more-key-questions
  - https://wwwnc.cdc.gov/eid/article/30/7/24-0508_article
- Transition cows are less sensitive to heat stress (an immune activating event)
  - (Maust et al., 1972; Perera et al., 1986)
- Effects of anti-inflammatory (NSAIDs) administration to transition cows are highly inconsistent
  - (Horst et al., 2021)

Traditional Belief

Increased NEFA, Hyperketonemia, and Hypocalcemia…..**CAUSE** production and health problems


Calving
↓ Calcium
↑ NEFA
↓ DMI
↑ BHB
DA
Ketosis
Impaired Reproduction
Immunosuppression
Pneumonia
Mastitis
Metritis
Retained Placenta
Decreased Milk Yield

Paradigm Shifting Concept

Increased NEFA and Hyperketonemia are ca d

Low Feed Intake, high NEFA, Hyperketonemia and hypocalcemia are merely SYMPTOMS….a reflection of prior immune stimulation

Hypocalcemia is a consequence of

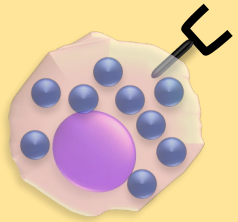
immune activation

Mycotoxins

Mastitis

Leaky Gut

Metritis



LPS/Inflammation

Impaired Reproduction

Fatty Liver

↓ DMI

Hypocalcemia

↑ NEFA

DA

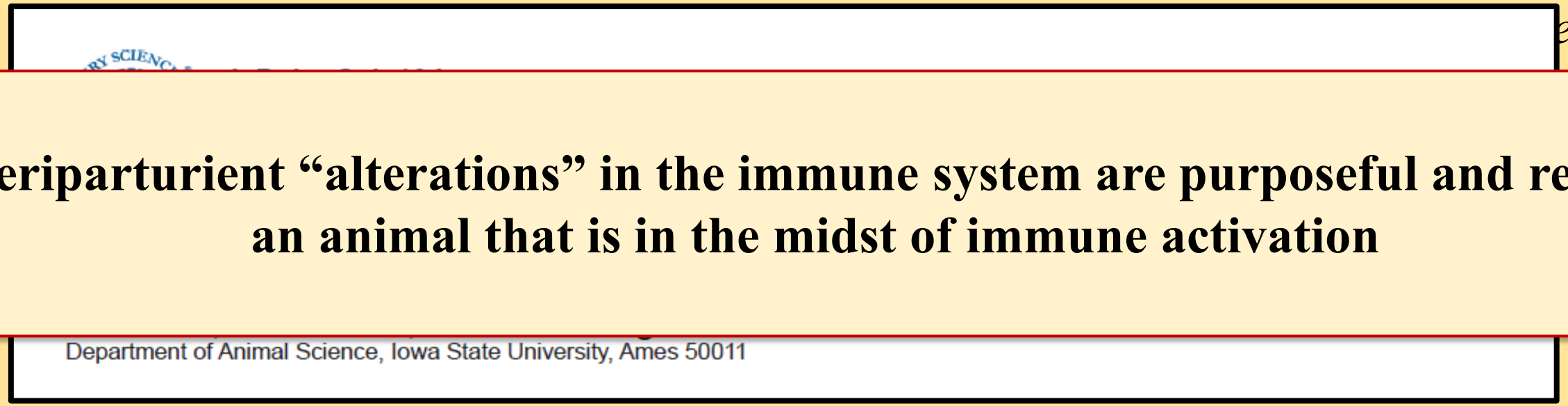
↓ Milk Yield

↑ BHB

Ketosis

Paradigm shift

- Immunosuppression does not seem evolutionarily advantageous



Periparturient "alterations" in the immune system are purposeful and reflect an animal that is in the midst of immune activation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Causation vs. Correlation: transition cow perspective