



**Royal
Veterinary
College**

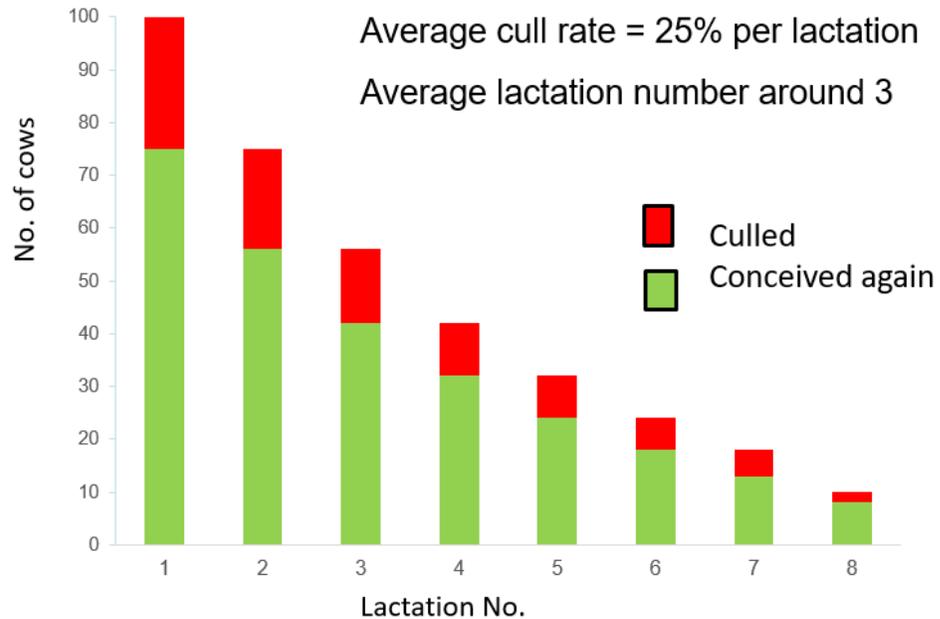
University of London

Fertility, metabolism and infection in
dairy cows – a journey through a
lifetime

Claire Wathes

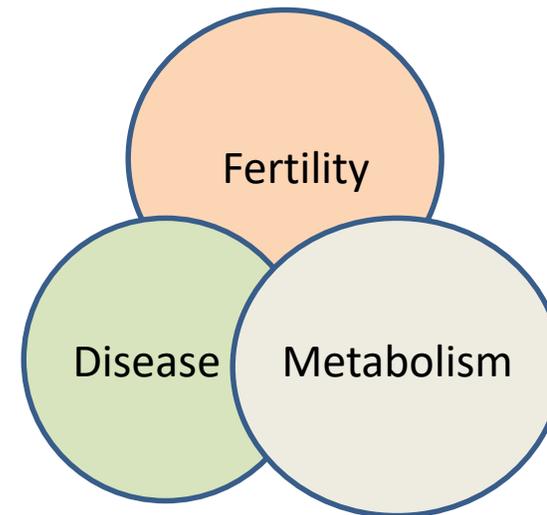
Lifetime losses

Cattle can potentially live for over 20 years.
Average UK lifespan in dairy cows is currently around 6 years.



Longer survival enables greater lifetime milk production, associated with higher profitability.

The main reasons for involuntary culling are infertility, mastitis and lameness.



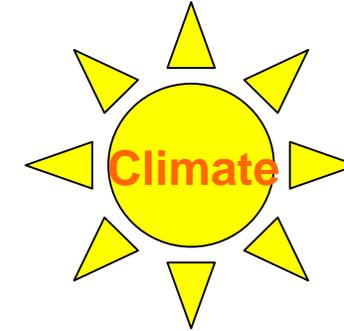
Consequences of poor fertility in dairy cows

- Loss of milk production through too many dry days.
- Disruption to the calving season and milk production pattern.
- Loss of mature animal milk yields through early culling.
- Additional AI costs.
- Extra veterinary costs.
- Reduced calf sales.
- More replacements needed.
- Loss of valuable genetics.

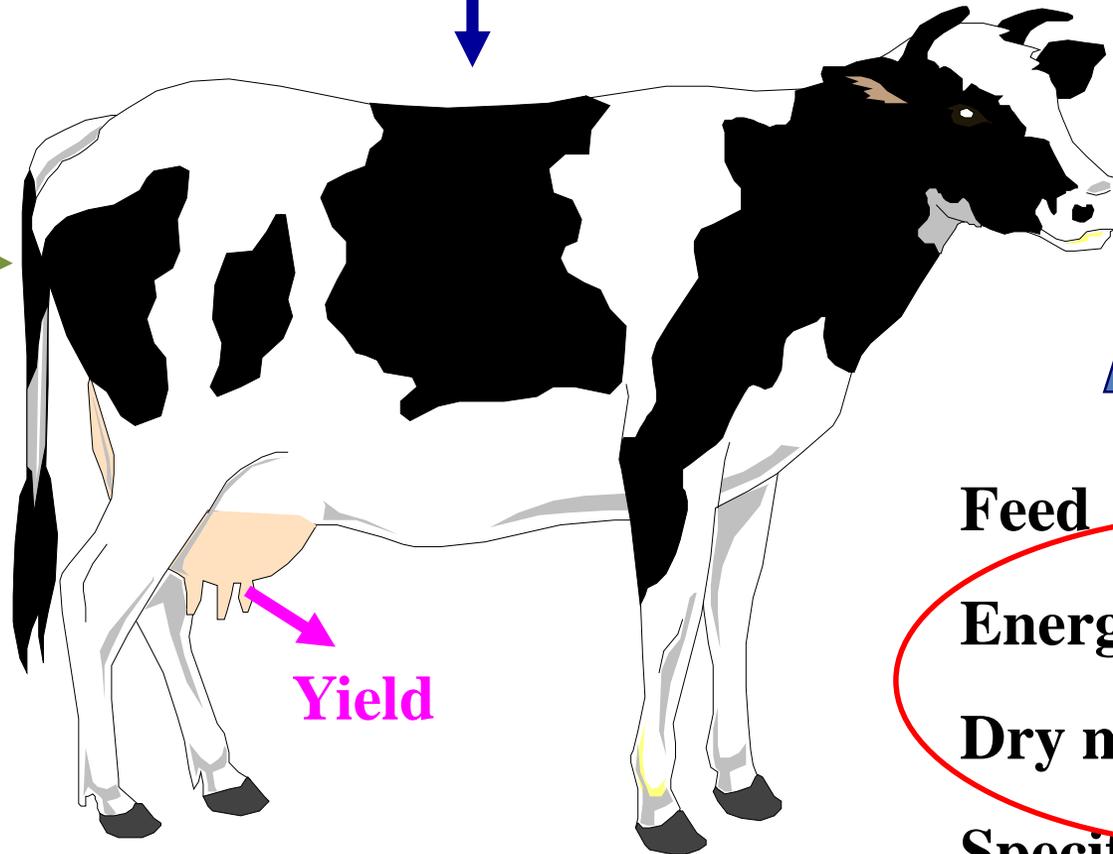
Factors Affecting Fertility in the Dairy Cow

Genotype

Age & Body condition



Metabolic and infectious diseases



Yield

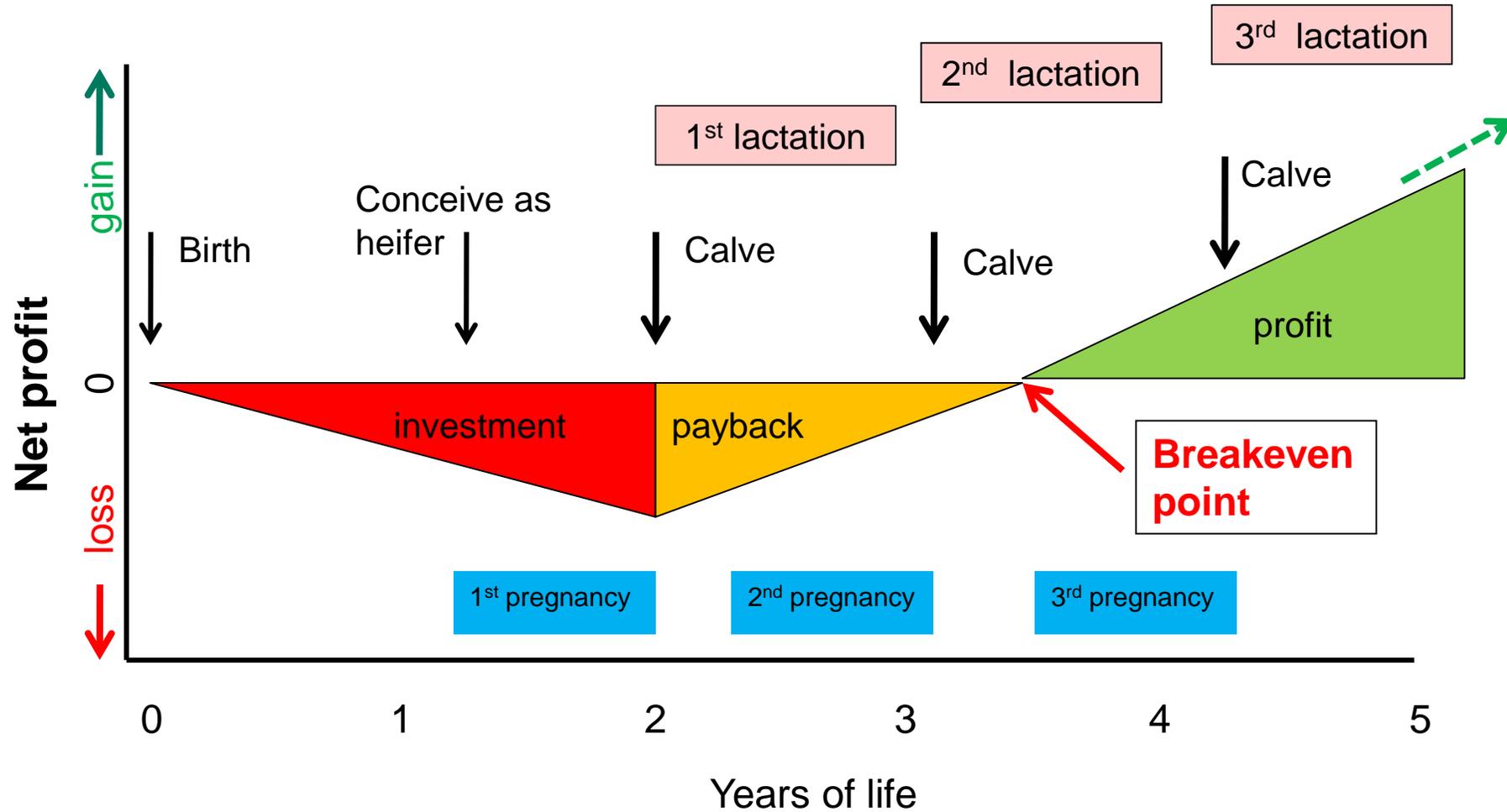
Feed

Energy/protein balance

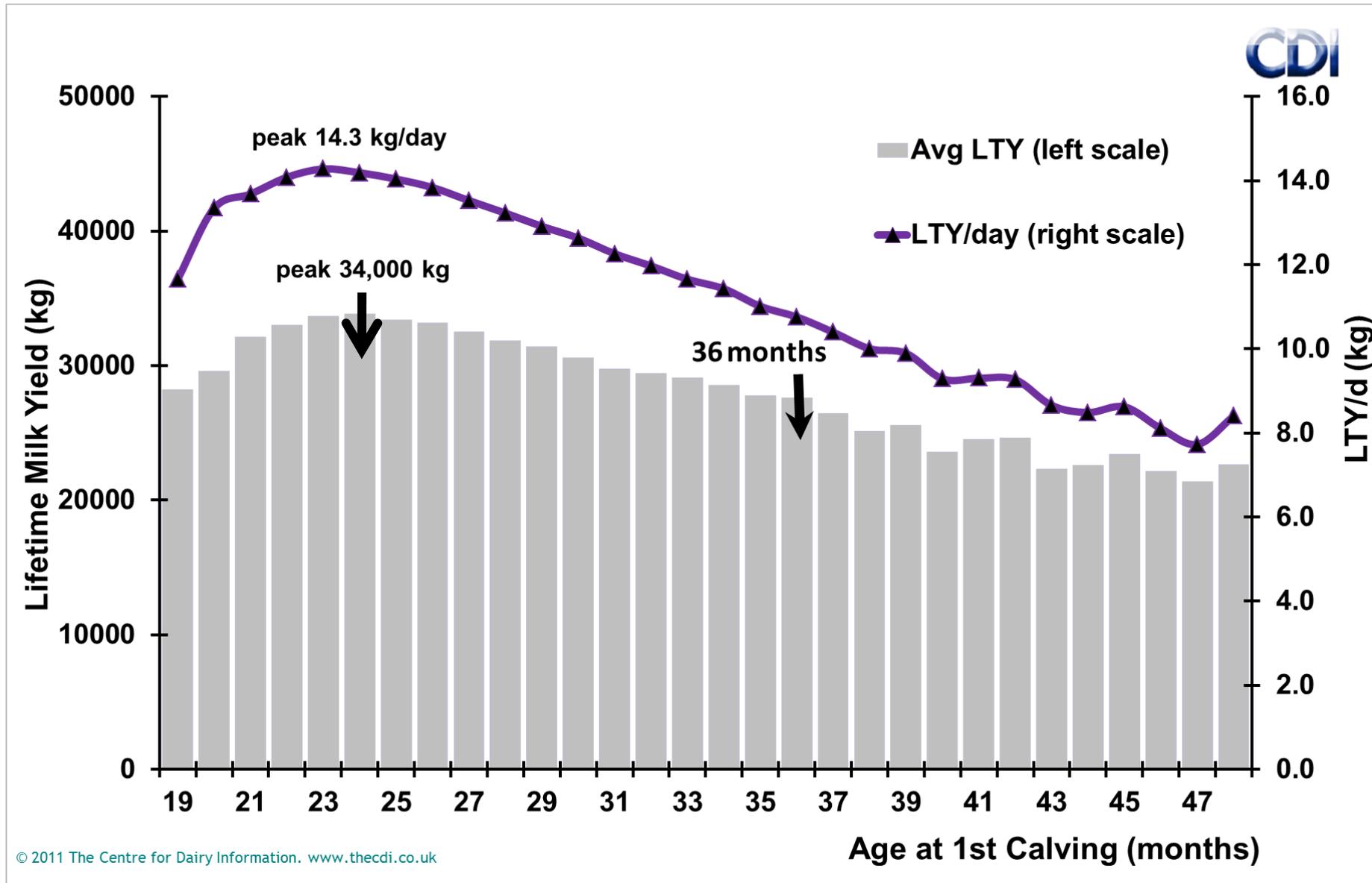
Dry matter intake

Specific constituents

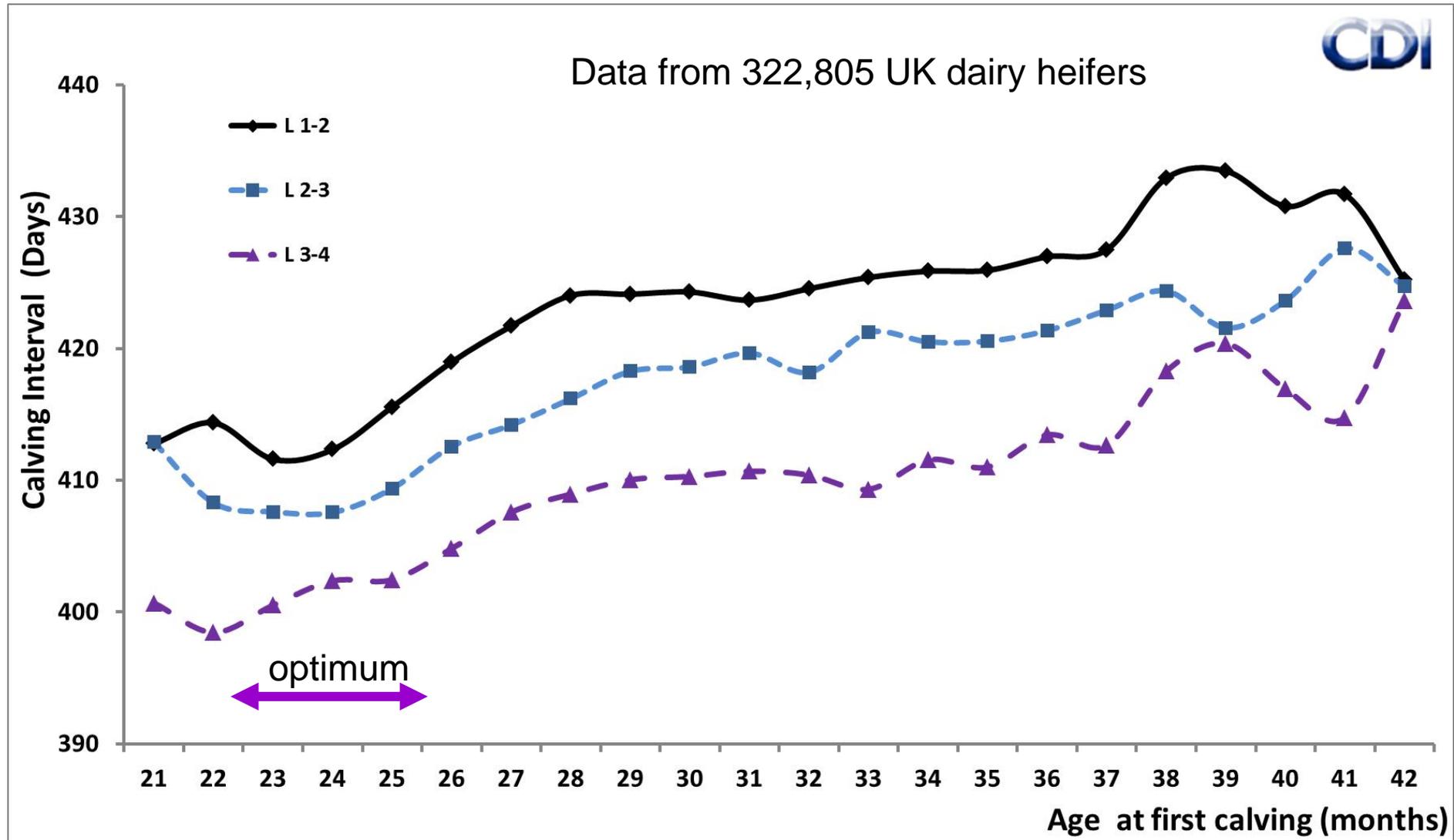
Lifetime Performance of a Dairy Cow



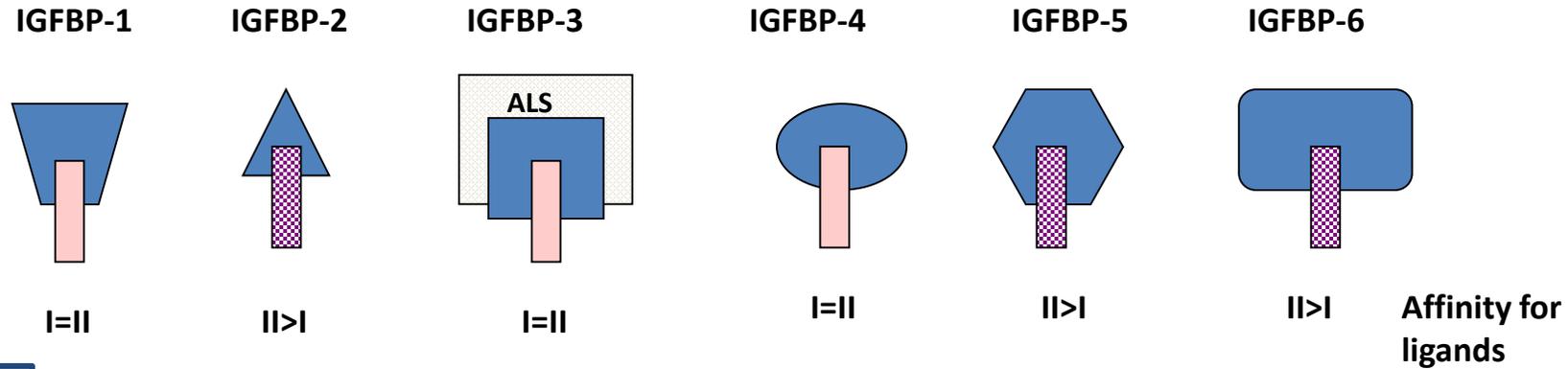
Relationship between AFC and subsequent milk production



Relationship between AFC and subsequent fertility

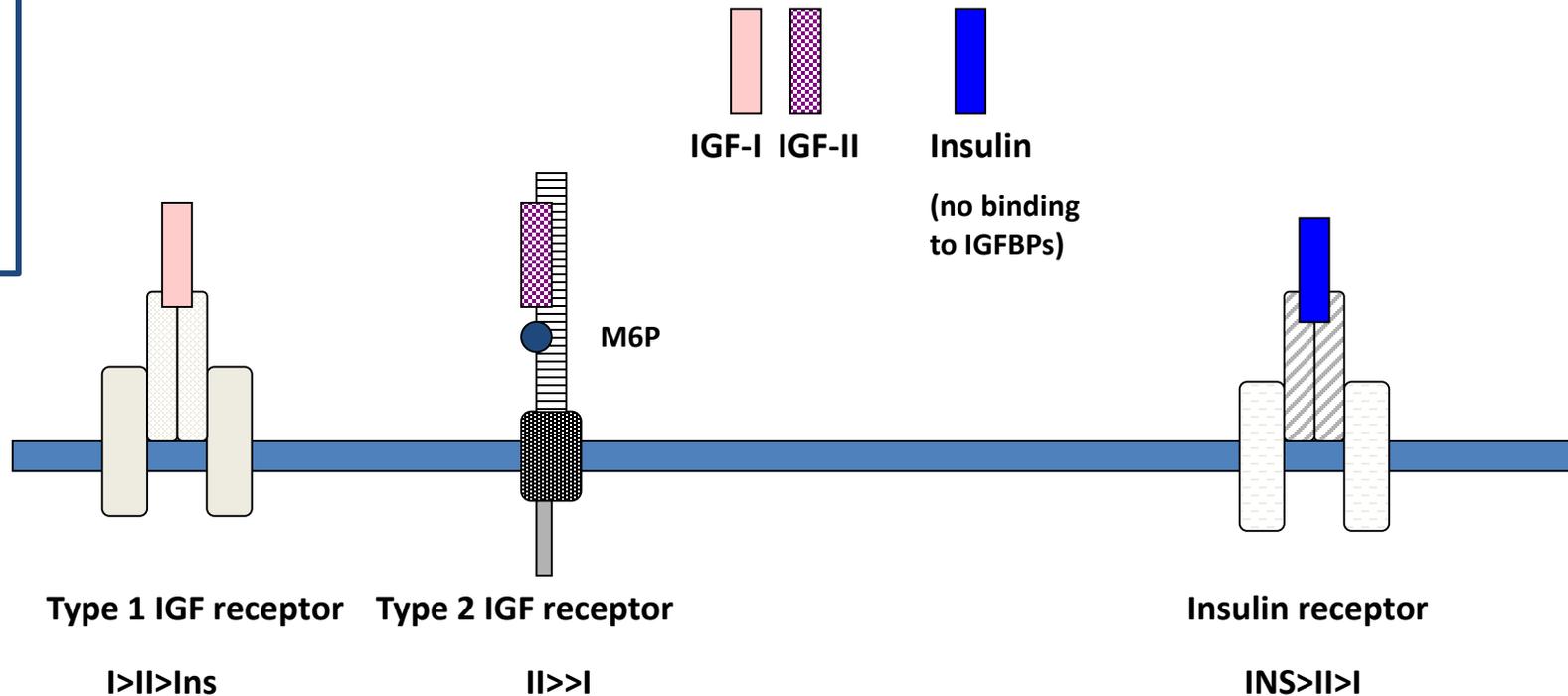


Summary diagram of the IGF system



Binding proteins influence:

- Half life of IGF1 in the circulation
- Receptor binding



Hepatic mRNA expression of IGF system members in early lactation is strongly influenced by negative energy balance

Gene	Mild NEB	Severe NEB	Difference (<i>P</i>)
IGF-I	36.8 ± 8.83	3.6 ± 0.47	<0.01
IGF-1R	0.8 ± 0.14	0.3 ± 0.03	<0.01
IGF-II	206.0 ± 49.51	100.3 ± 17.65	0.100
IGF-2R	2.3 ± 0.35	1.0 ± 0.12	<0.02
IGFBP-1	139.8 ± 71.81	85.6 ± 42.75	0.538
IGFBP-2	53.4 ± 7.71	109.5 ± 10.58	<0.01
IGFBP-3	20.2 ± 2.88	7.7 ± 1.04	<0.01
IGFBP-4	87.3 ± 23.69	33.9 ± 3.35	<0.05
IGFBP-5	0.6 ± 0.12	0.2 ± 0.02	<0.01
IGFBP-6	0.8 ± 0.06	0.4 ± 0.04	<0.01
IGFBP ALS	12.8 ± 3.63	0.9 ± 0.30	<0.02

- After calving there is a doubling in circulating IGFBP2 while IGFBP3 and ALS both decrease.
- This is mainly regulated through the hepatic GHR which also decreases in early lactation

Cost efficient heifer rearing will:

➤ Before 1st calving

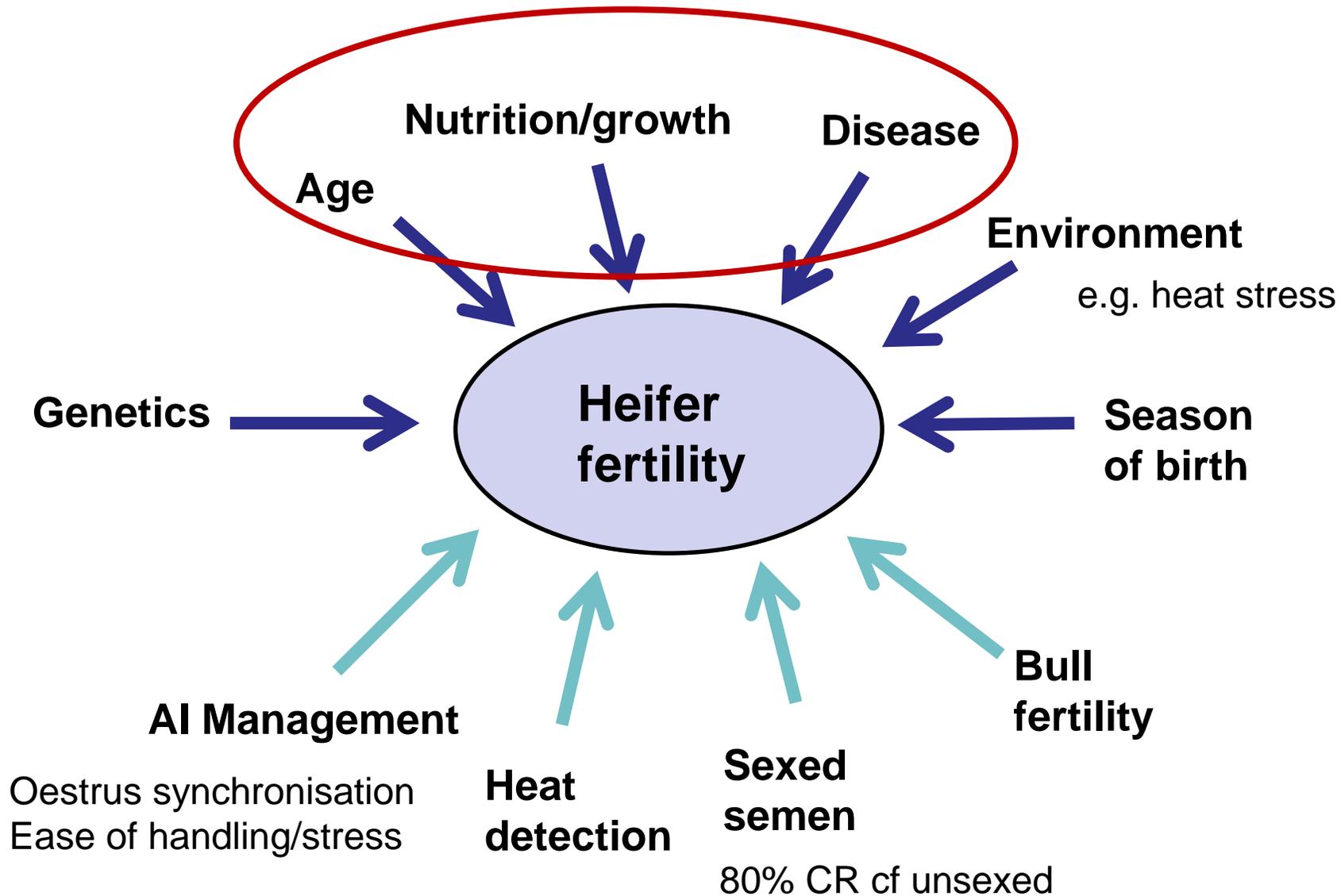
- Minimise mortality and health disorders and understand their true cost
- Optimize growth throughout the entire rearing period
- Achieve excellent fertility



➤ Aim to calve between 23-25 months

➤ After 1st calving

- Long-lived
- Capable of sustaining high milk yields
- Conceive at the desired time of breeding
- Remains healthy



Characterisation of Holstein Heifer fertility in the US

Heifer age(mo)	No. matings	Conception rate%
11-12	6,983	52.8 ± 1.0
15-16	20,7801	55.8± 0.8
19-20	51,264	52.7± 0.8
23-24	11,368	49.5 ± 0.9
26-27	1,754	42.4 ± 1.5

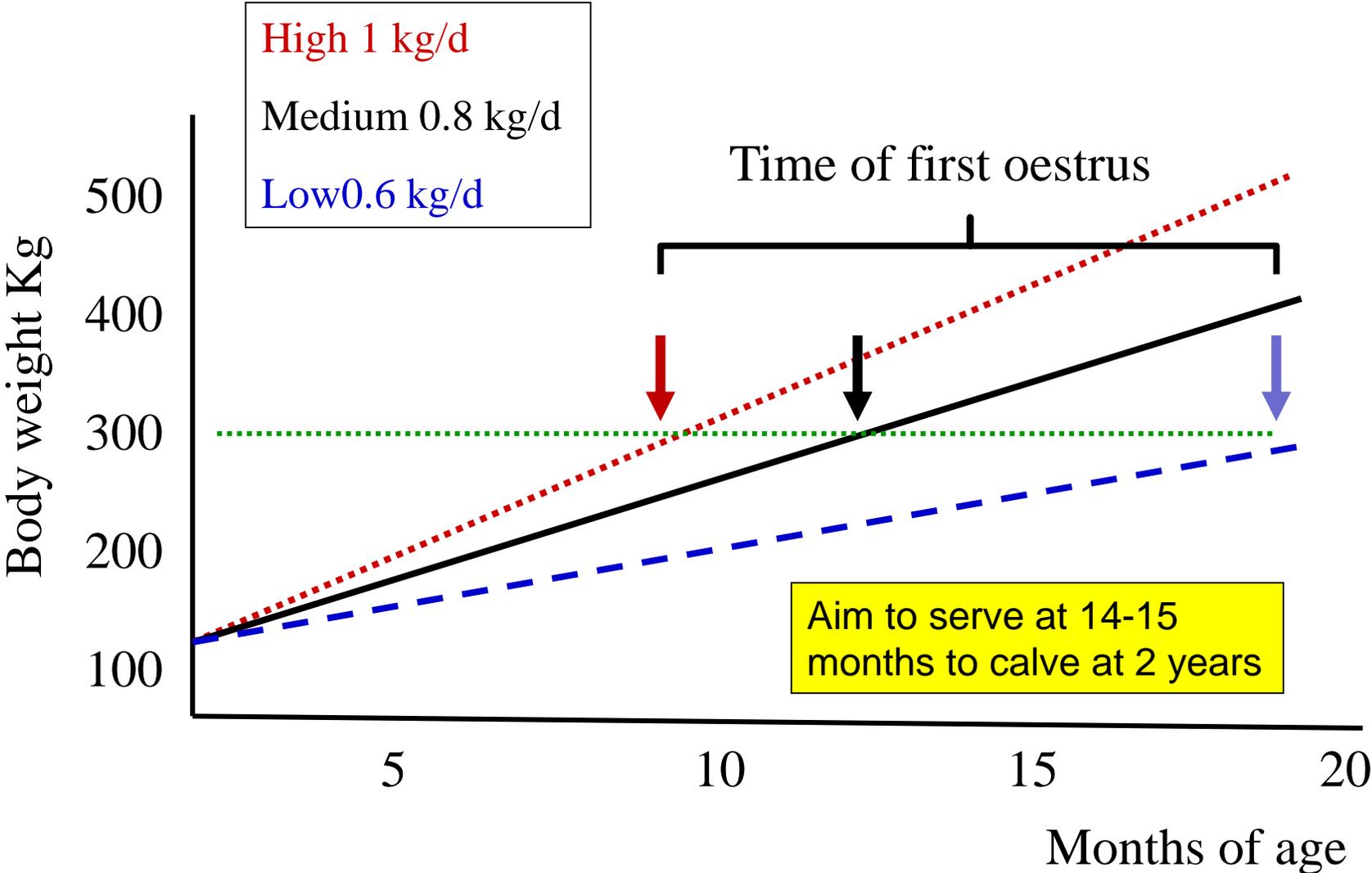
← Optimum

Kuhn et al. (2006) JDS 89:4907

Target weights (kg) for age

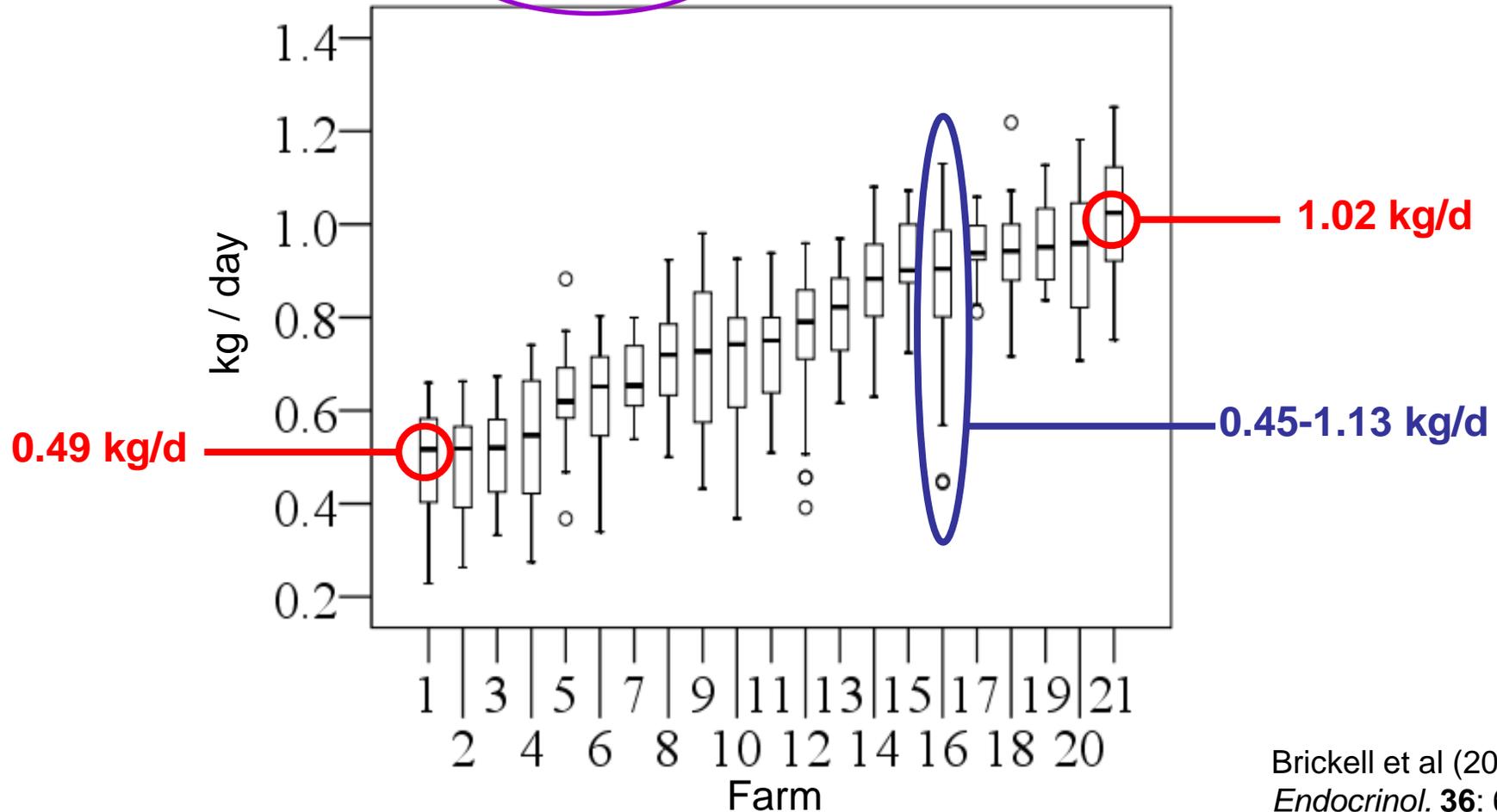
Holstein Friesian	% of mature weight	kg
Birth weight		40
Mature body weight		685
Puberty	40%	274
1 st breeding	60%	411
1 st calving	90%	616
Growth rate required to calve at 24 months		0.79 kg/d

Growth rates, weights and ages at first oestrus for Holstein heifers fed different planes of nutrition

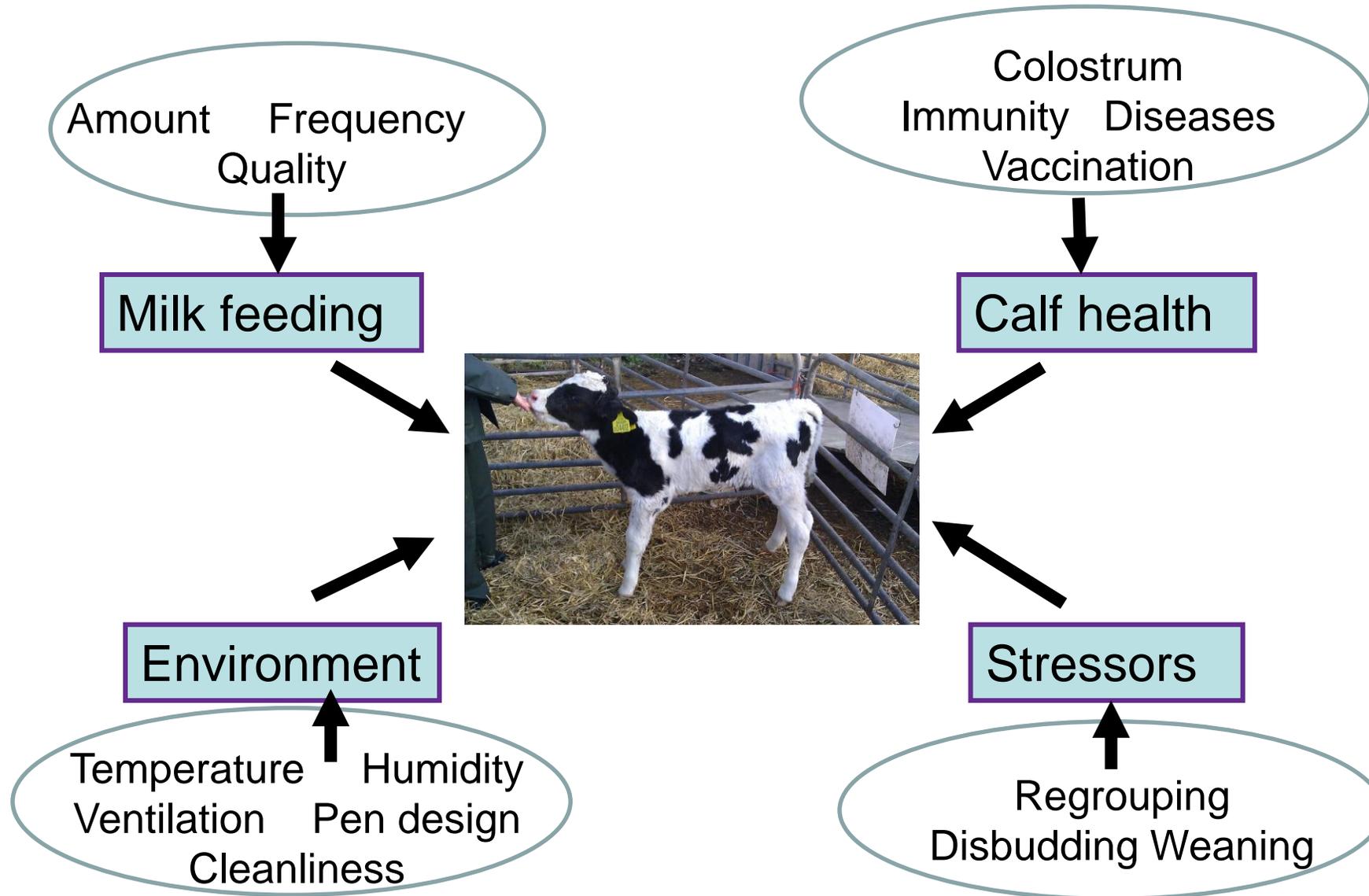


Body weight growth on dairy farms

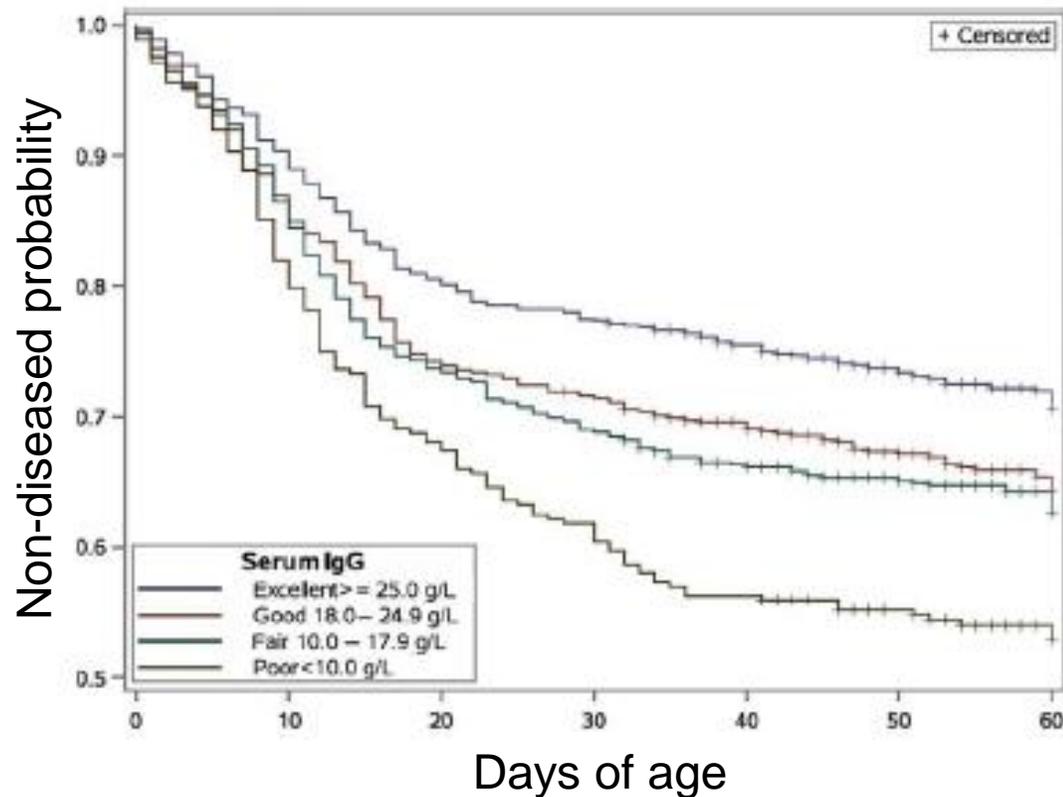
506 Holstein-Friesian heifers measured at 1 & 6 months of age
Mean growth rate was 0.77 kg /d



Factors affecting growth rates in pre-weaned dairy calves



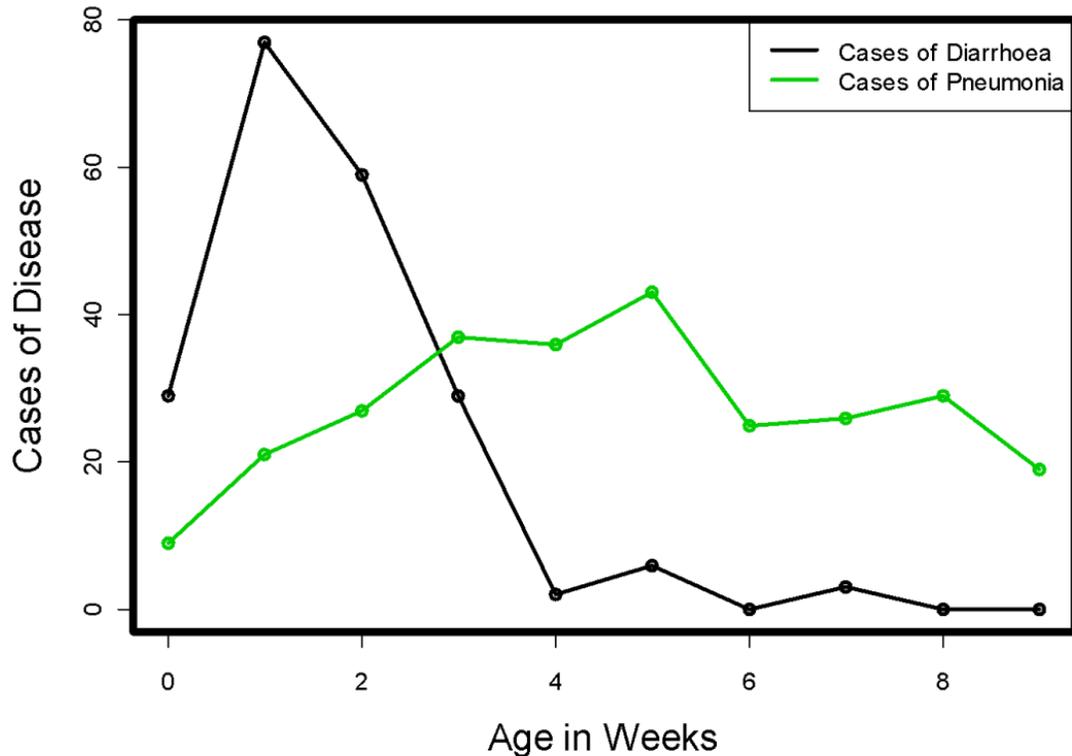
The probability of pre-weaned calves staying healthy is related to their passive transfer assessed by serum IgG



Category	Proposed IgG levels (mg/ml)	Equivalent serum total protein (mg/ml)	Proposed proportion of calves in each category (%)
Excellent	≥25	≥62	>40
Good	18.0-24.9	58-61	30
Fair	10.0-17.9	51-57	20
Poor	<10.0	<51	<10

From Godden et al. (2019) *Vet Clin Food Anim* 35: 535-556

Disease monitoring - UK herds



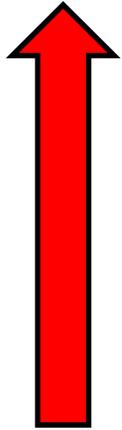
Based on weekly assessments using Wisconsin scoring system
11 farms, n=492 calves



Proportion affected pre-weaning:
48.2% of individuals had diarrhoea
46.5% of individuals had BRD

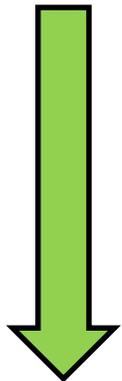
Variables influencing ADG in pre-weaned heifers from 1-63 days

Increased by: (10th to 90th percentile)



- increased feeding milk solids from 20.4 to 46.3 kg total
- serum IgG increased from 2.9-31.5 mg/ml
- IGF1 at 35 d increased from 16-108 ng/ml
- Calves that moved farm to a specialist rearing unit were predicted to be 4.8 kg larger at 63 days

Decreased by:



- increasing weight at recruitment from 28.7 to 48.4 kg
- diarrhoea for >2 weeks.
- ≥4 weeks of respiratory disease

Multivariable model included farm as a random factor, using a hierarchical model with calf nested within farm.

Risks for Respiratory disease

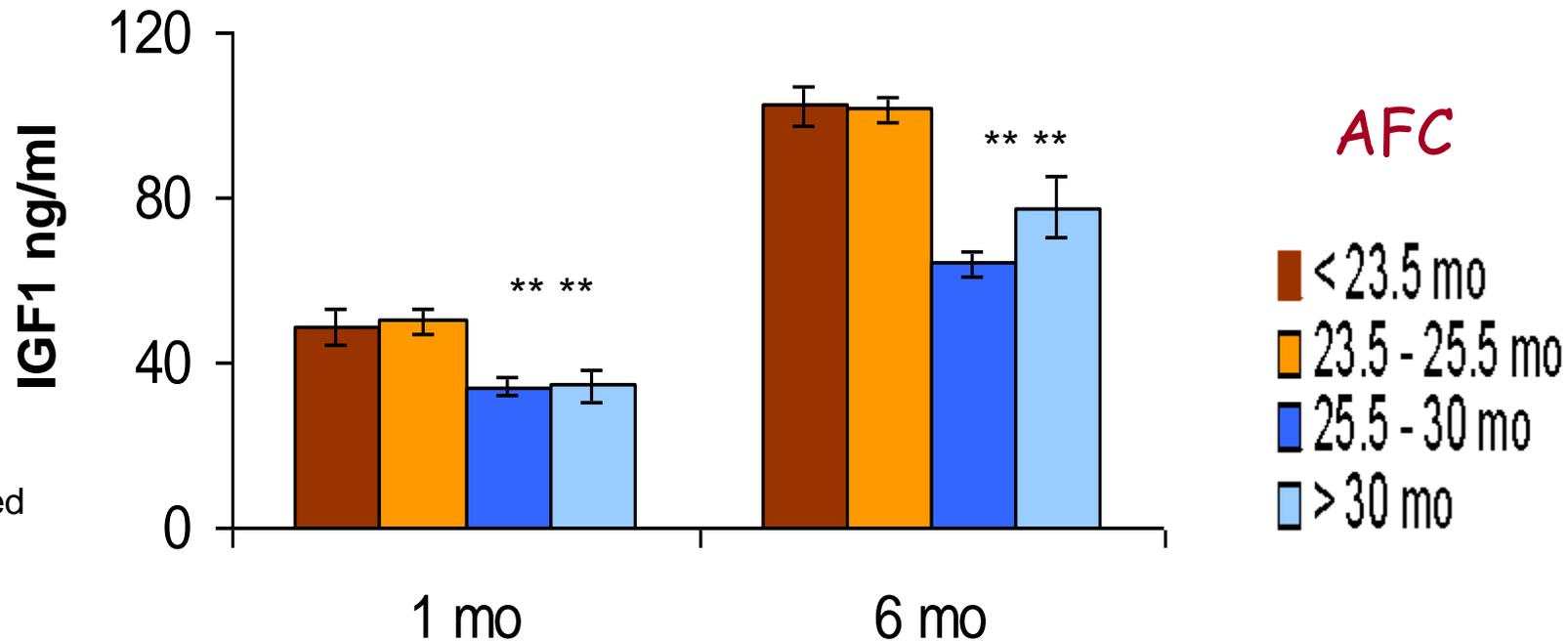
Variable	Estimate	95 % Confidence	p Value
(Intercept)	6.02	4.17 to 7.75	<0.001
Group Management (continuous flow)	(ref)		
Group Management (fixed groups)	-1.14	-2.07 to -0.21	<0.01
Mean Temperature in birth month (°C, log transformed)	-0.93	-1.56 to -0.22	<0.01
Total milk solids fed, day 1-63 (kg)	-0.031	-0.031 to -0.012	<0.01
IgG in first week (mg/ml)	-0.025	-0.056 to -0.014	<0.01
IGF-1 at recruitment (ng/ml, log transformed)	-0.39	-0.62 to -0.18	<0.001

Calves in a stable group, born in warm weather, fed more milk, and with good passive transfer of immunity are at less risk of respiratory disease

Effect of calf disease on AFC and later performance

- Correa et al. (1988) BRD in first 3 months delayed AFC by 3 months
- Heinrichs et al. (2005) more days of antibiotic treatment of calves increased AFC
- Bach (2011) 4 or more cases of BRD in young heifers increased their odds of not completing their first lactation by 1.87
- Svensson & Hultgren (2008) severe BRD in first 3 months increased calving intervals by 12% in mature cows

Replacement heifers with a delayed AFC are already distinguishable by 1 month of age!



n=506 heifers recruited from 19 farms

IGF1 is a key growth factor which serves as an indicator of metabolic health.

Heifer Fertility - take home messages:

Three key considerations which are critical cornerstones to having a good on-farm heifer breeding policy.

- This begins at birth – the pre-weaning period is absolutely critical to future success.
- Ensure that replacement heifers are sufficiently well grown and healthy to start breeding by 14 months of age.
- Have a robust system in place, whether using AI, natural service or a combination to ensure that all heifers conceive in a timely fashion.

Acknowledgements

Jessica Cooke (nee Brickell)
Alana Boulton
Kate Johnson

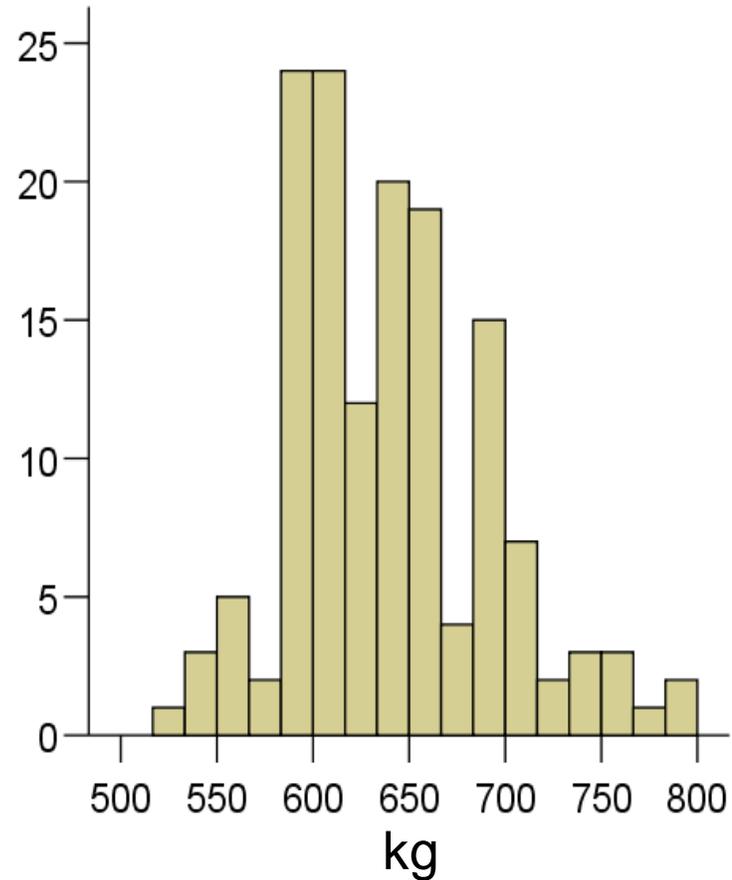
All the co-operating farms and vets



Body Weight at First Calving

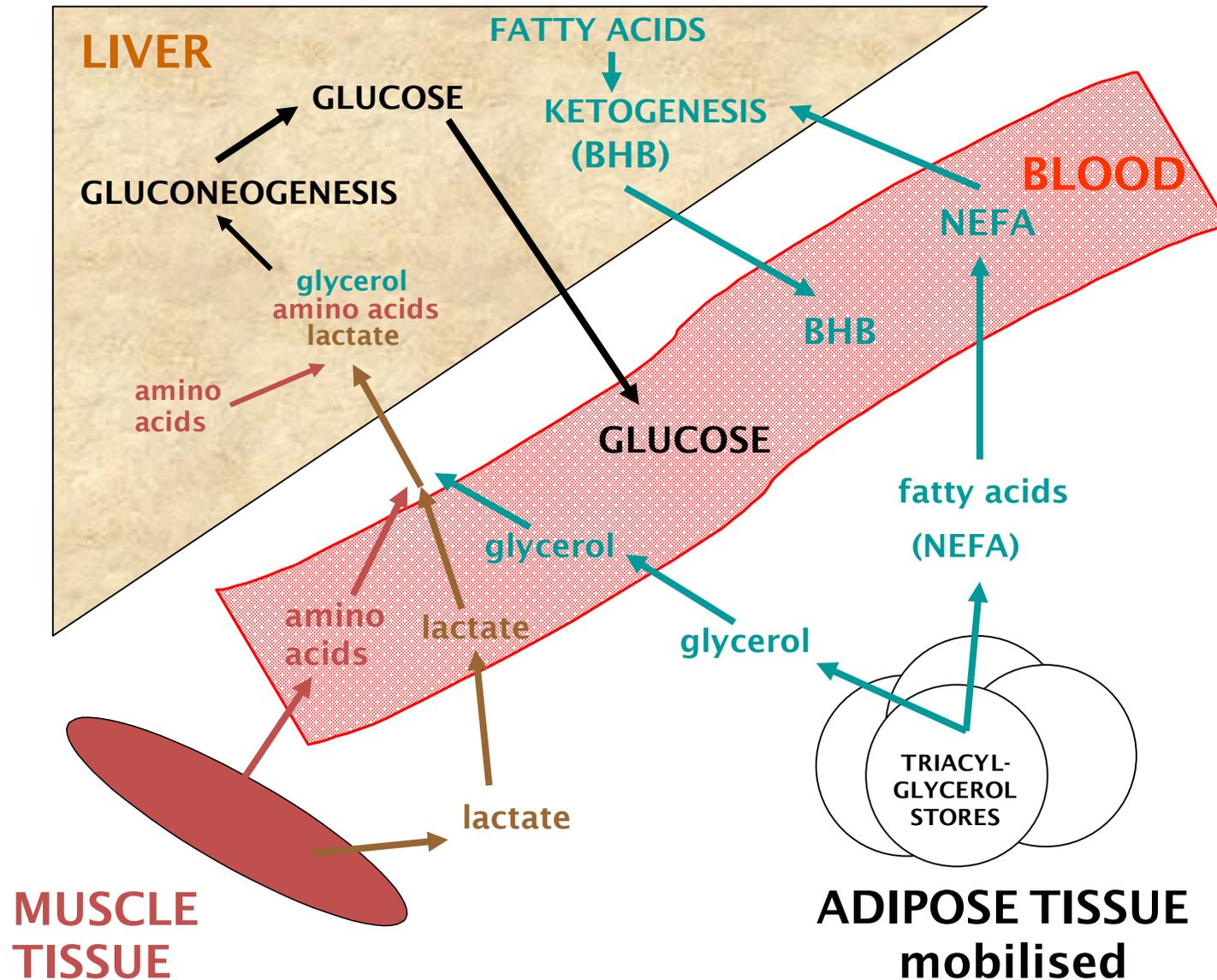
Data from all replacement heifers joining a single herd in one year.

n = 147, mean 639 kg,
range 518 – 786 kg



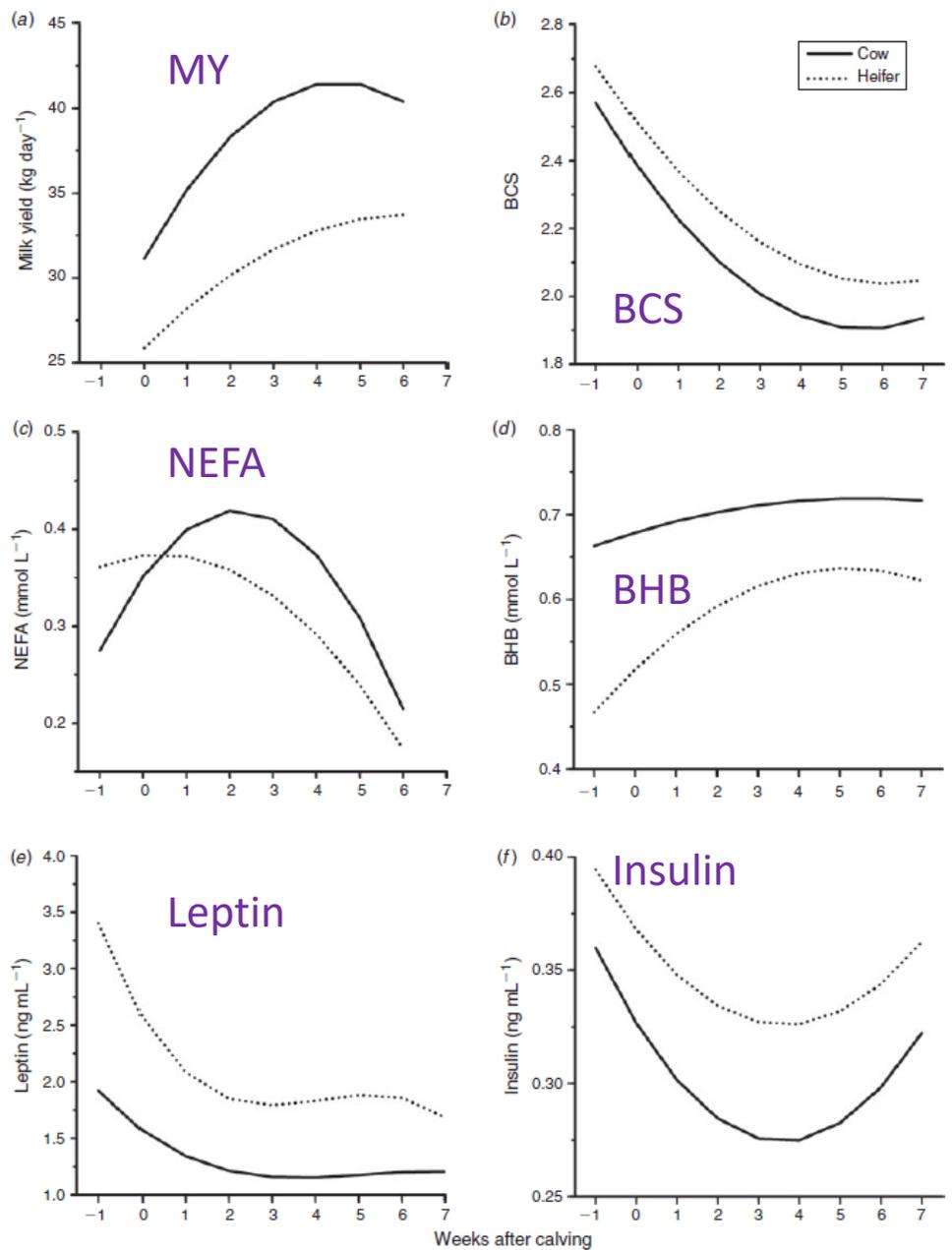
Need to achieve adequate frame size without excessive weight!
Optimum BCS 2.5-3.0

Metabolic responses during negative energy balance (NEB)



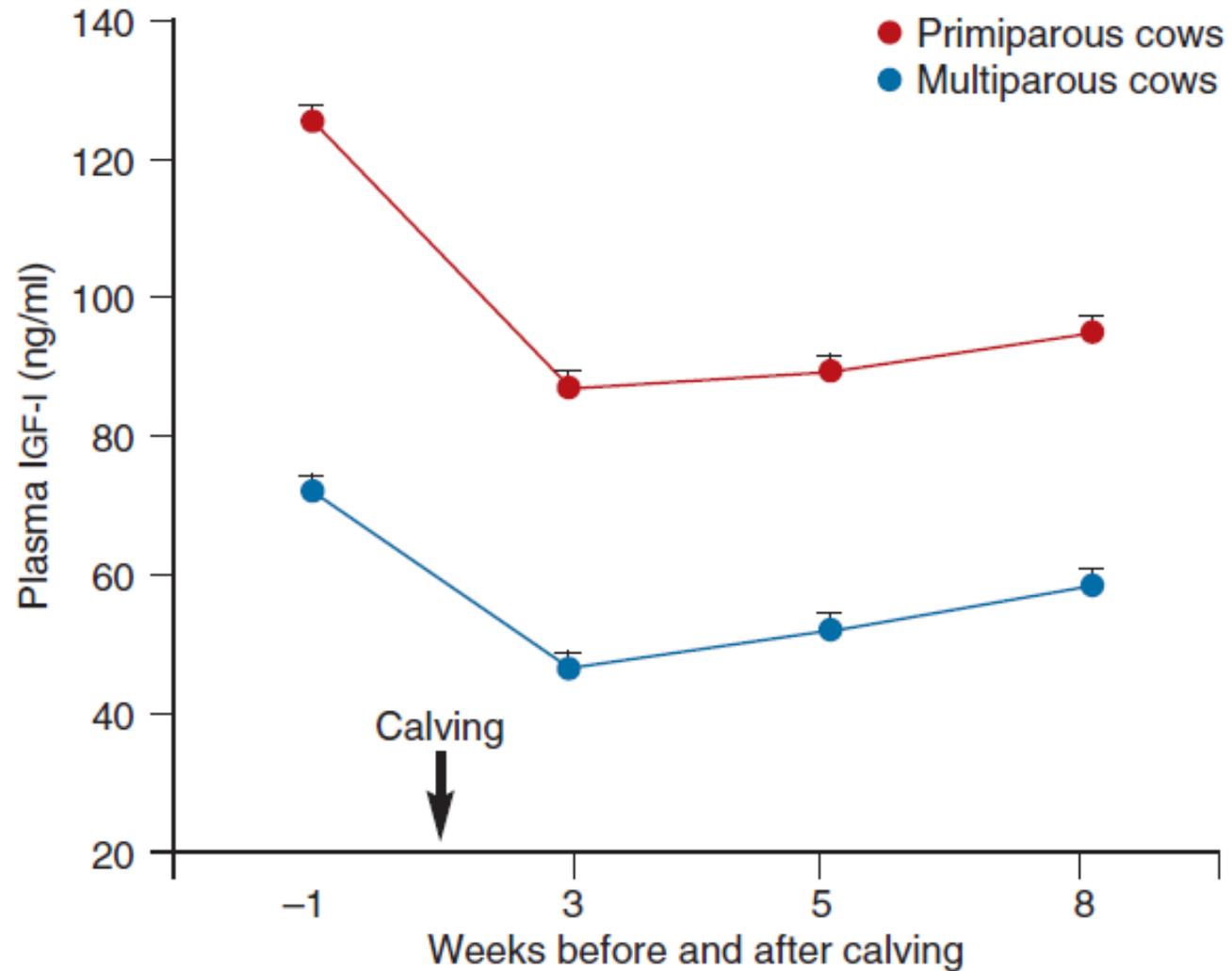
Metabolic changes around calving

Predicted LSM phenotypic values over time

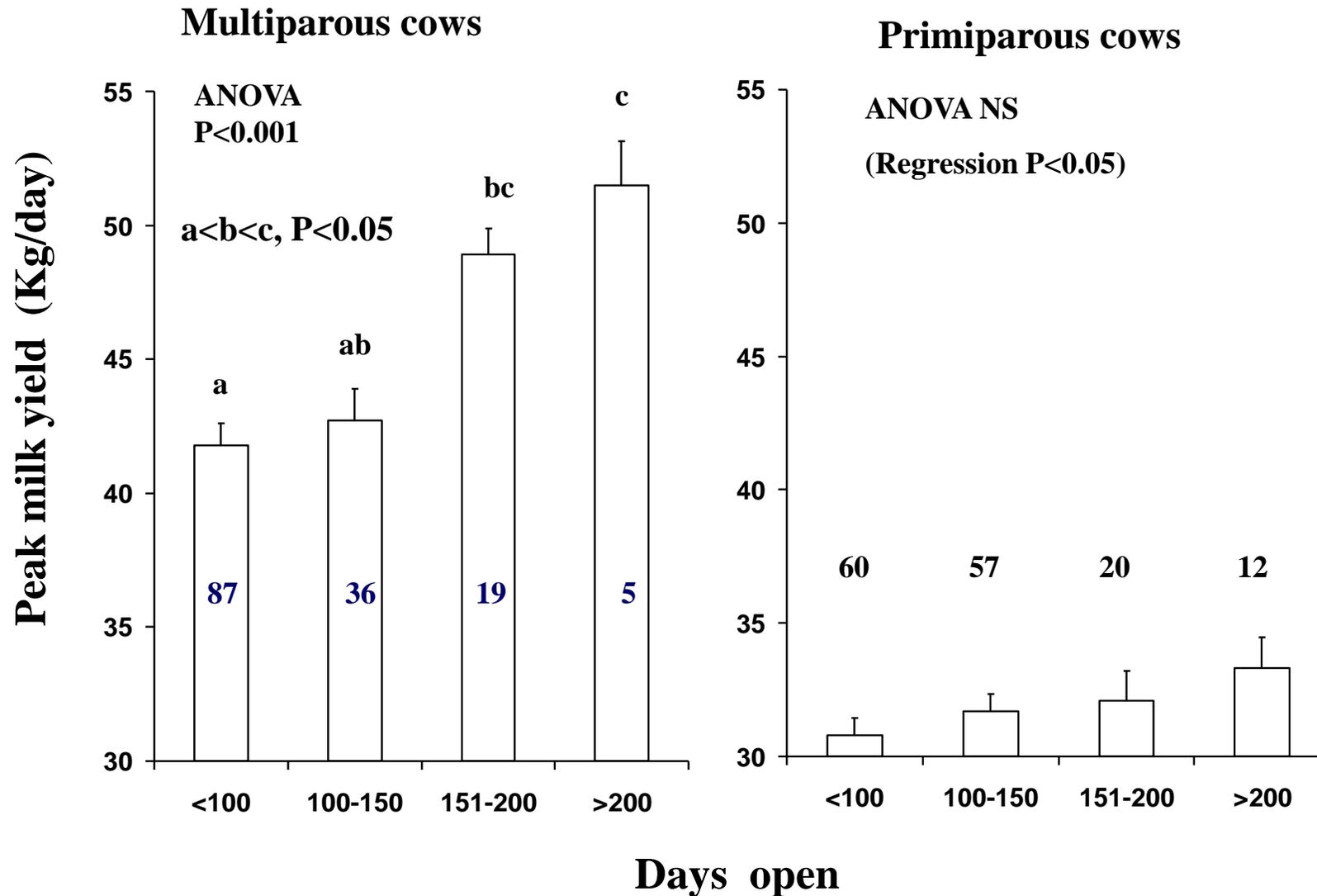


Wathes et al. (2007) DAE 33:203

IGF-1 Concentrations in the peripartum period



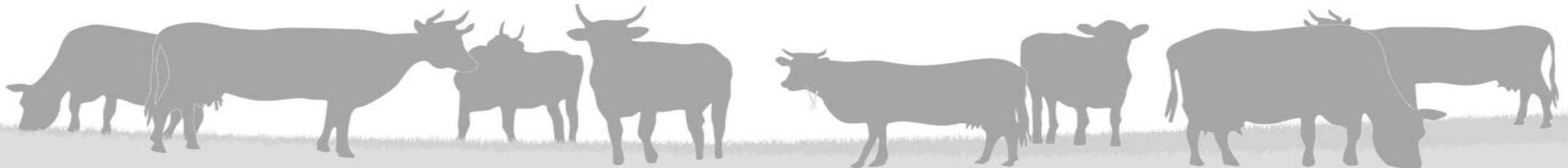
Relationship between peak milk yield and days open





*Genotype **plus** Environment*
Integration for a more sustainable dairy production system

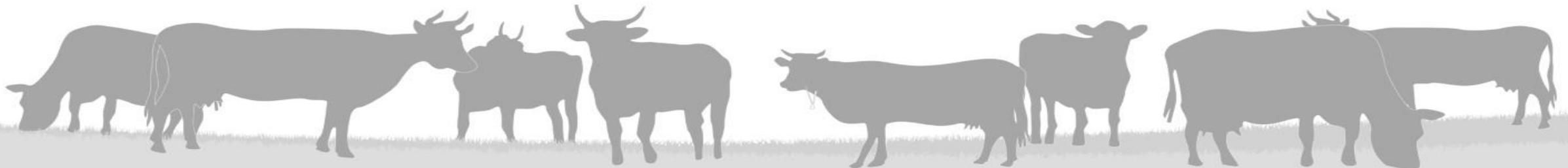
RNA-Seq analysis of whole blood from early lactation dairy cows used to investigate leukocyte gene expression



Materials and Methods: 1

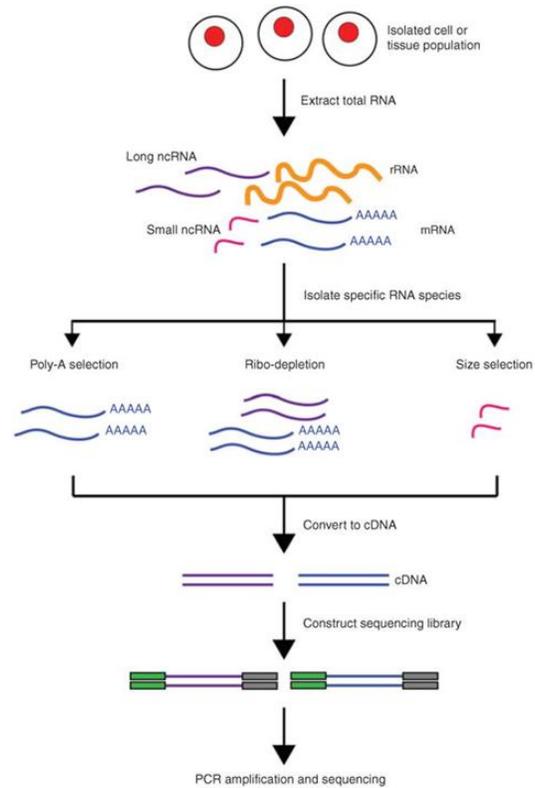
Cows and phenotypes

- Blood samples (229 cows, 6 herds) taken into Tempus tubes at 14±3 days in milk (DIM).
- White blood cells (leucocytes) processed for total RNA-Seq using Illumina NextSeq 500 platform.
- Phenotype data captured:
 - Body condition score (BCS) at calving, 14 and 35 DIM, change in BCS
 - Circulating metabolites and IGF1 at 14 and 35 DIM
 - Total milk yield and milk quality data 0-50 DIM
 - Fertility and health data recorded

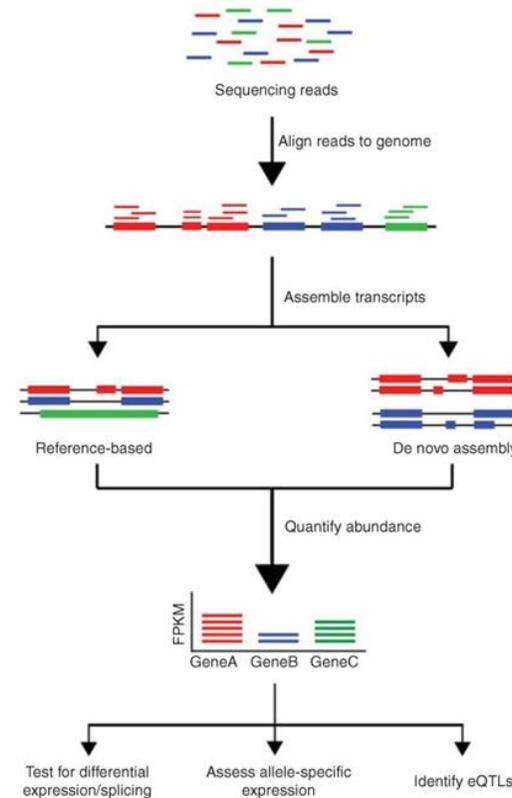


Materials and Methods: 2. RNASeq

1. Total RNA from leucocytes used for library preparation

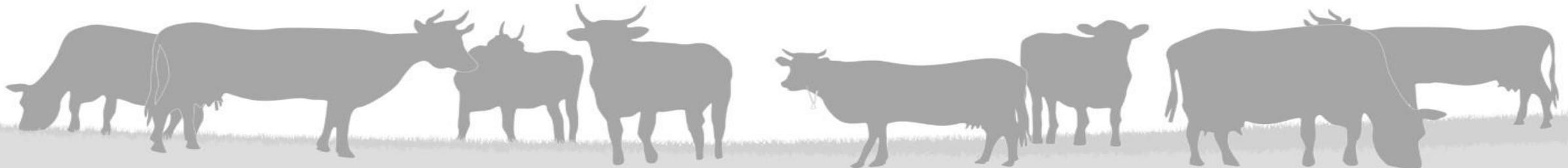


2. Libraries sequenced at 75 nt length single end reads to reach average 30 million reads/sample using Illumina NextSeq 500 platform.



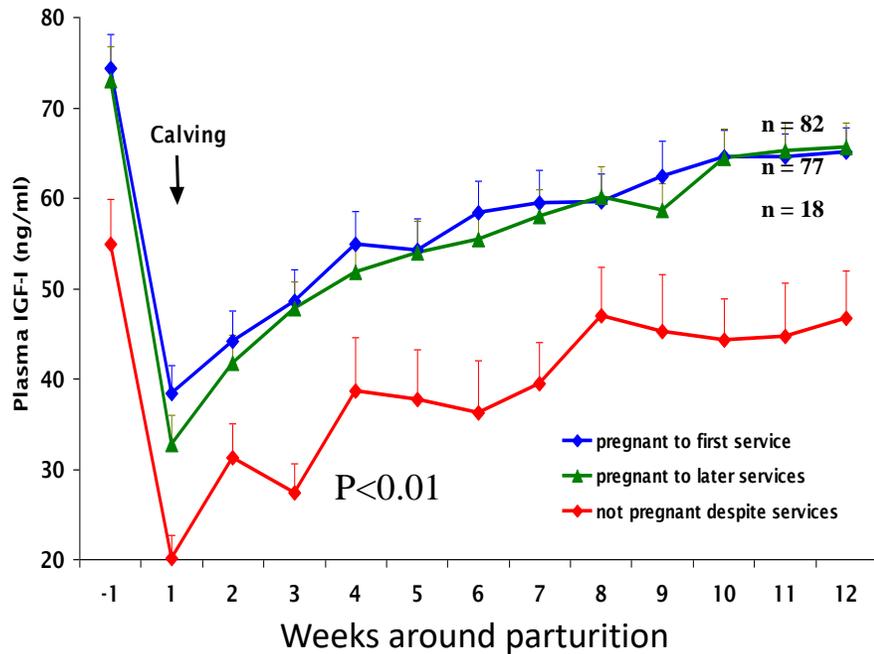
3. Fastq raw files were quality controlled and mapped onto *Bos taurus* ARS-UCD1.2 (new annotation gene tracks). StringTie used to count isoforms based in the new genome annotation

4. DEG between groups identified.



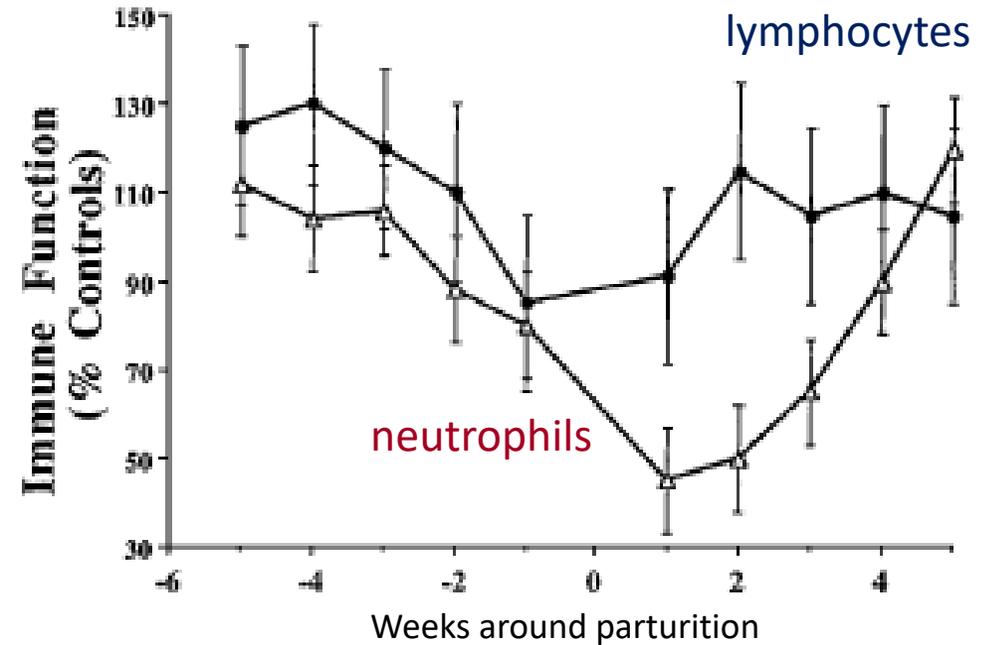
INTRODUCTION

Circulating IGF-I falls at calving and cows with a lower nadir are less likely to conceive

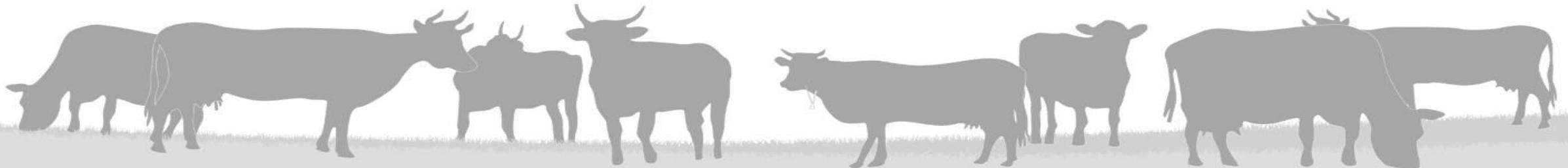


Taylor et al (2004) *Vet Rec.* 155, 583-588

Immune status is also suppressed around calving and circulating PMNs have reduced respiratory burst activity and cytotoxicity.



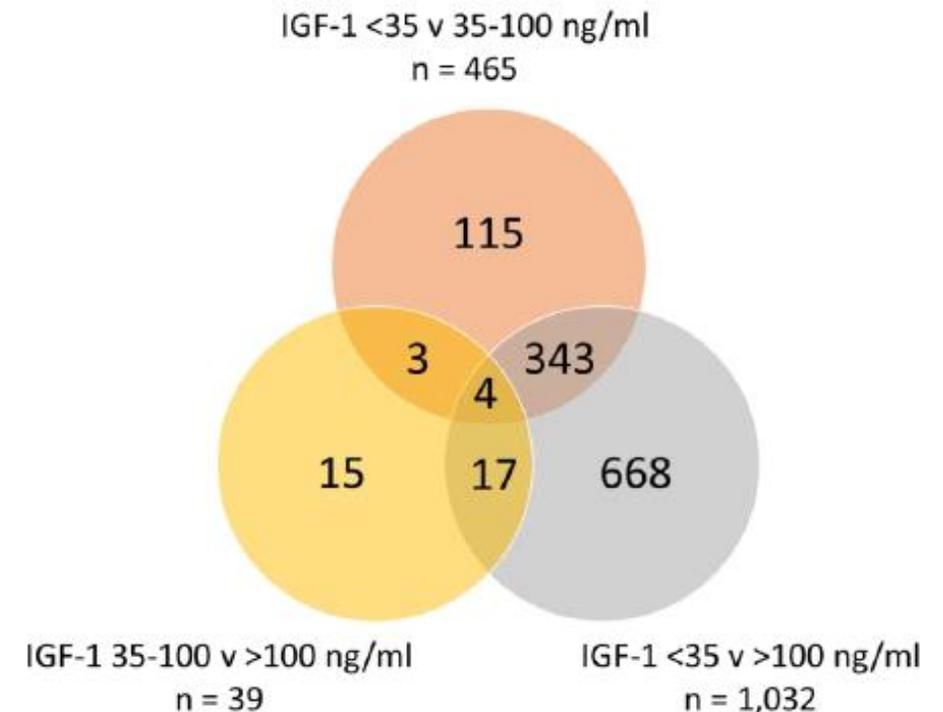
Goff & Horst (1997) *JDS* 80:1260



Analysis based on circulating IGF1 in early lactation

Methodology

- Multiparous cows subdivided into three groups defined as low IGF-1 (<35 ng/ml, n=35), moderate IGF-1 (35-100 ng/ml, n=92) or high IGF-1 (>100 ng/ml, n=43) at 14 DIM.
- Leucocyte gene expression from RNASeq analysed using CLC Genomics Workbench V21 (Qiagen Digital Insights, Redwood City, CA, USA).
- Compared between groups using negative binomial generalized linear modelling. IGF-1 groups were set as the test variable and herd as the controlling variable.
- DEG selected using criteria $P(\text{BH}) < 0.05$ and $\text{FC} > 1.2$



Lactation number, milk yield and milk quality data from weeks one and two of lactation according to the IGF-1 group at 14 days in milk.

	LOW <35 ng/ml	MOD 35-100 ng/ml	HIGH >100 P ng/ml	
Week 1				
n	32	84	38	
Lactation No.	3.9 ± 0.27 ^b	3.2 ± 0.11 ^a	2.6 ± 0.17 ^a	<0.001
Milk yield (kg/d)	29.2±1.32	31.0±0.76	31.7±0.67	0.21
Fat (F%)	4.9±0.20	4.8±0.12	4.5±0.10	0.40
Protein (P%)	3.5±0.08 ^a	3.5±0.04 ^a	3.9±0.05 ^b	<0.001
Week 2				
n	32	82	31	
Milk yield (kg/d)	30.2±1.24 ^b	33.3±0.79 ^{ab}	36.6±1.13 ^b	0.001
Fat (F%)	4.4±0.14	4.5±0.11	4.2±0.15	0.23
Protein (P%)	3.1±0.05 ^a	3.2±0.03 ^a	3.4±0.05 ^b	<0.001

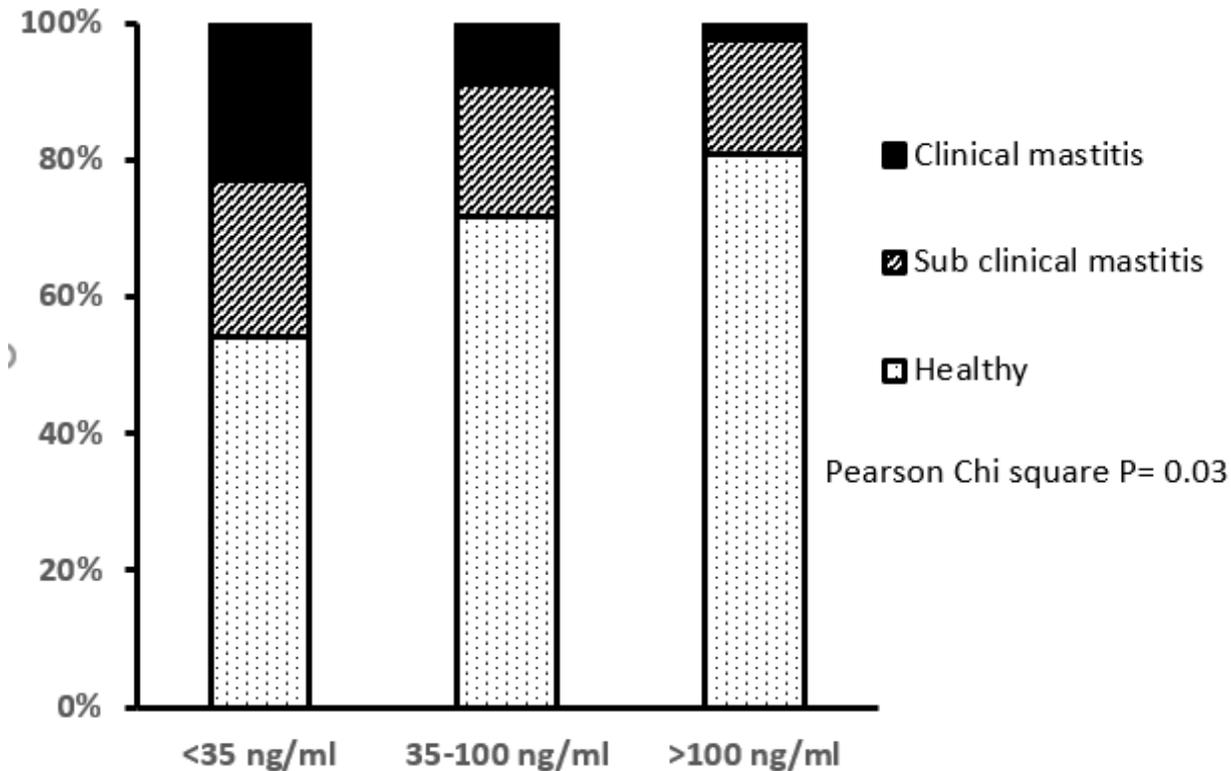
Blood metabolites, feed intakes and energy balance at 14 DIM according to the IGF-1 group at 14 days in milk.

Parameter	LOW	MOD	HIGH	P
	<35 ng/ml	35-100 ng/ml	>100 ng/ml	
n	34	88	41	
IGF-1 (ng/ml)	25±1.3 ^a	63±1.9 ^b	143±5.3 ^c	<0.001
Glucose (mM)	3.2±0.07 ^a	3.3±0.06 ^a	3.5±0.07 ^b	0.005
Fructosamine (µM)	246±3.0 ^a	247±2.0 ^a	258±2.7 ^b	0.003
BHB (µM)	0.79±0.082	0.75±0.077	0.52±0.044	0.082
NEFA (µekv/L)	884±82 ^b	740±47 ^{ab}	633±57 ^a	0.046
Urea (mM)	3.0±0.22 ^a	2.9±0.12 ^a	3.7±0.21 ^b	0.004
n	18	61	38	
Weight (kg, 7 day average)	671 ±18.9	670 ± 9.5	657 ± 10.4	0.288
DMI (kg/d, 7 day average)	16.4 ± 0.60 ^a	18.5 ± 0.38 ^b	19.8 ± 0.54 ^b	0.001
EB (MJoule/d 7d average)	-10.7±1.51 ^b	-7.5±0.70 ^{ab}	-5.0±1.09 ^a	0.005

Health data in the first 35 DIM according to the IGF-1 group at 14 DIM

	LOW <35 ng/ml	MOD 35-100 ng/ml	HIGH >100 ng/ml	P(χ^2)
n	35	92	43	
Assisted calving	6 (17.1%)	7 (7.6%)	7 (16.3%)	0.187
Twins	4 (11.4%)	6 (6.5%)	1 (2.3%)	0.267
Stillbirth	0 (0%)	2 (2.2%)	1 (2.3%)	0.672
Retained placenta	4 (11.4%)	5 (5.4%)	6 (13.9%)	0.221
Milk fever	2 (5.7%)	0 (0%)	0 (0%)	0.020
Displaced abomasum	4 (11.4%)	2 (2.2%)	0 (0%)	0.014
Lame	10 (28.6%)	27 (29.3%)	13 (30.2%)	0.987

Proportion of cows with mastitis in early lactation according to IGF-1 group at 14 DIM



Wathes et al., (2021) *Ruminants* 1, 147–177.

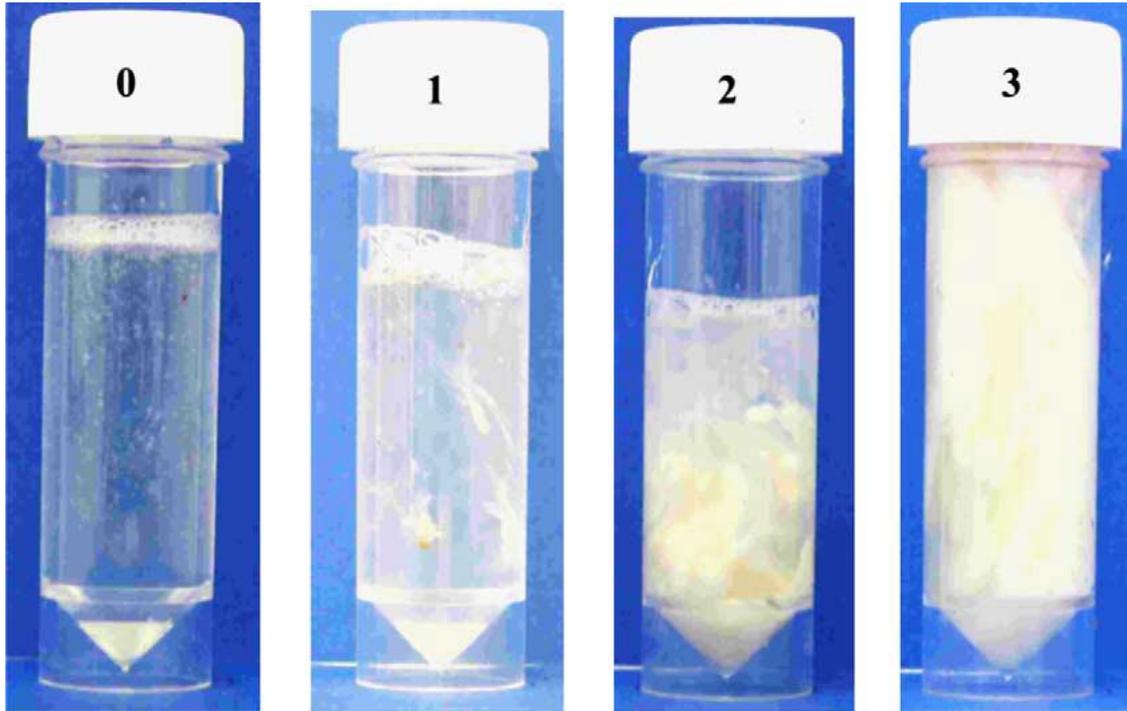
Dolecheck KA et al. (2019) Quantifying the effects of mastitis on the reproductive performance of dairy cows: A meta-analysis. *J Dairy Sci.* 102:8454-8477.

Compared with cows with no mastitis in the same time period:

- Mastitis pre-first insemination increased interval to first service by 13.3 d.
- Clinical mastitis pre-insemination increased open period by 22.3 d.
- Subclinical mastitis pre- or post-insemination increased open period by 20.0 d.

Scoring system for vaginal discharge

Williams, E.J. et al., Theriogenology **2005**, 63, 102–117.



Samples taken at 14 & 35 DIM

Appearance

0: clear or translucent mucus;

1: mucus containing flecks of white or off-white pus;

2: <50 mL exudate containing 50% white or off-white mucopurulent material;

3: >50 mL exudate containing 50% purulent material, usually white or yellow, but occasionally sanguineous.

Odour

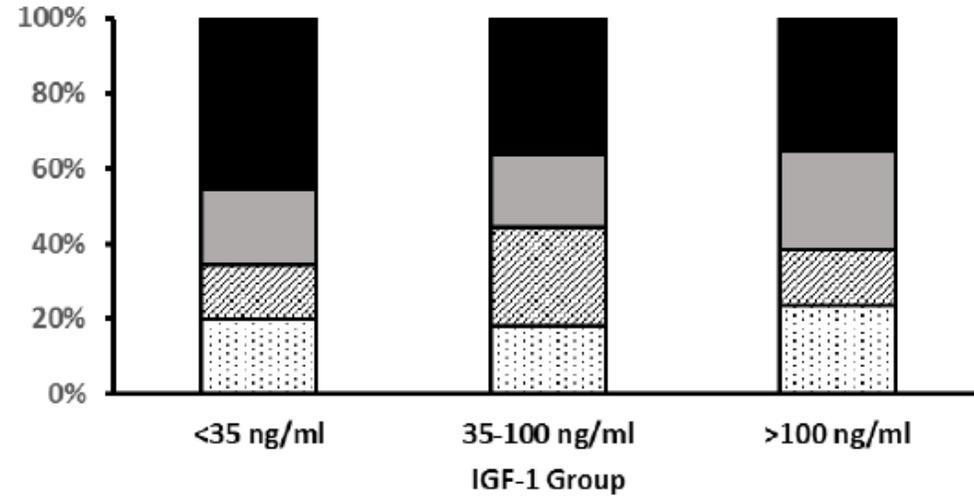
0: No smell

1: Fetid

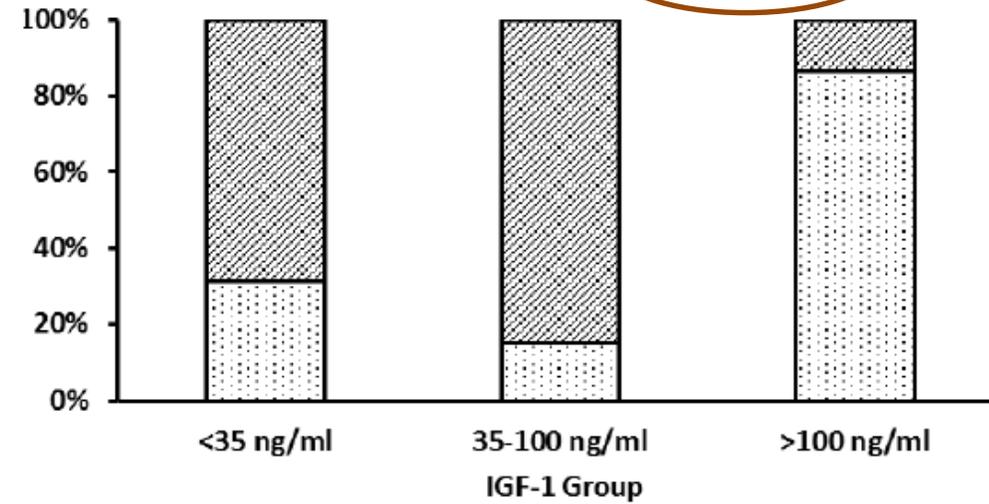
0 1 2 3

Uterine discharge scores according to the IGF-1 group at 14 DIM

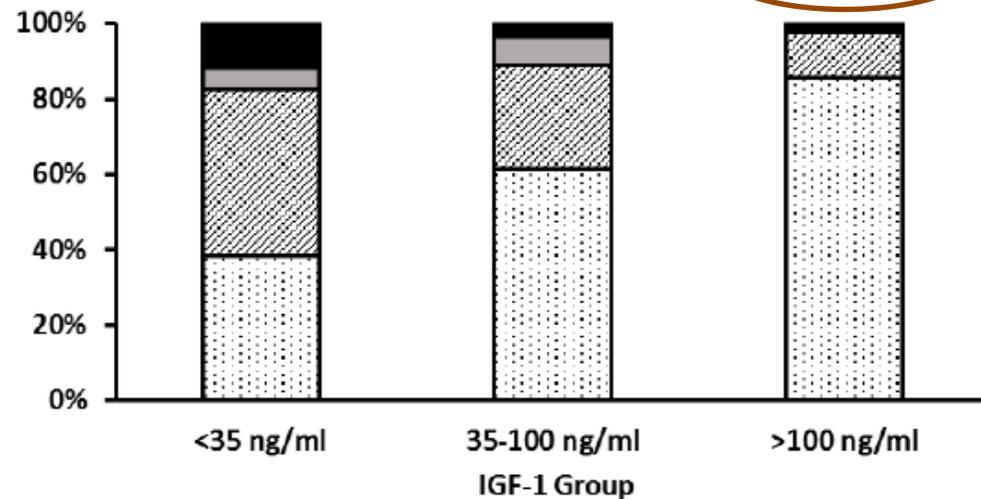
(A) D14 Uterine Discharge Appearance: P=0.259



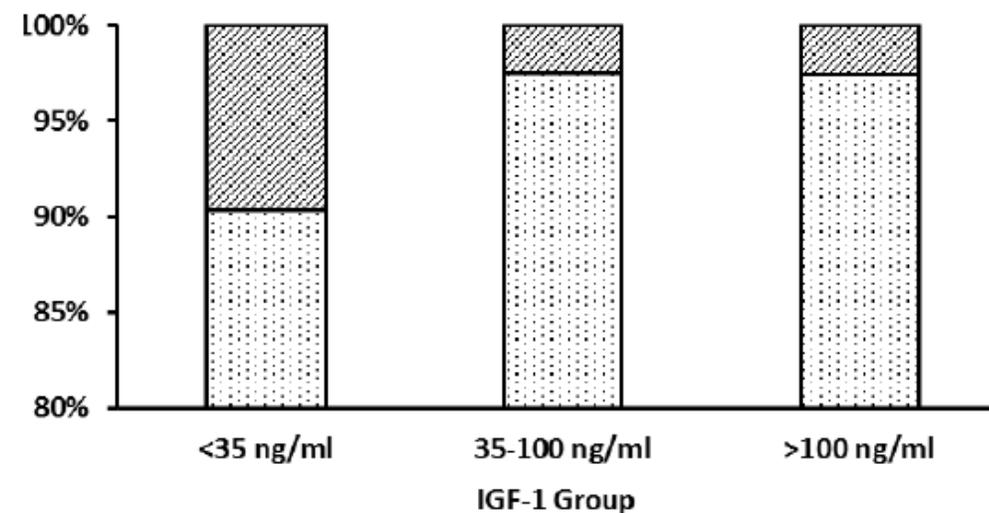
(B) D14 Uterine Discharge Odour: P<0.001



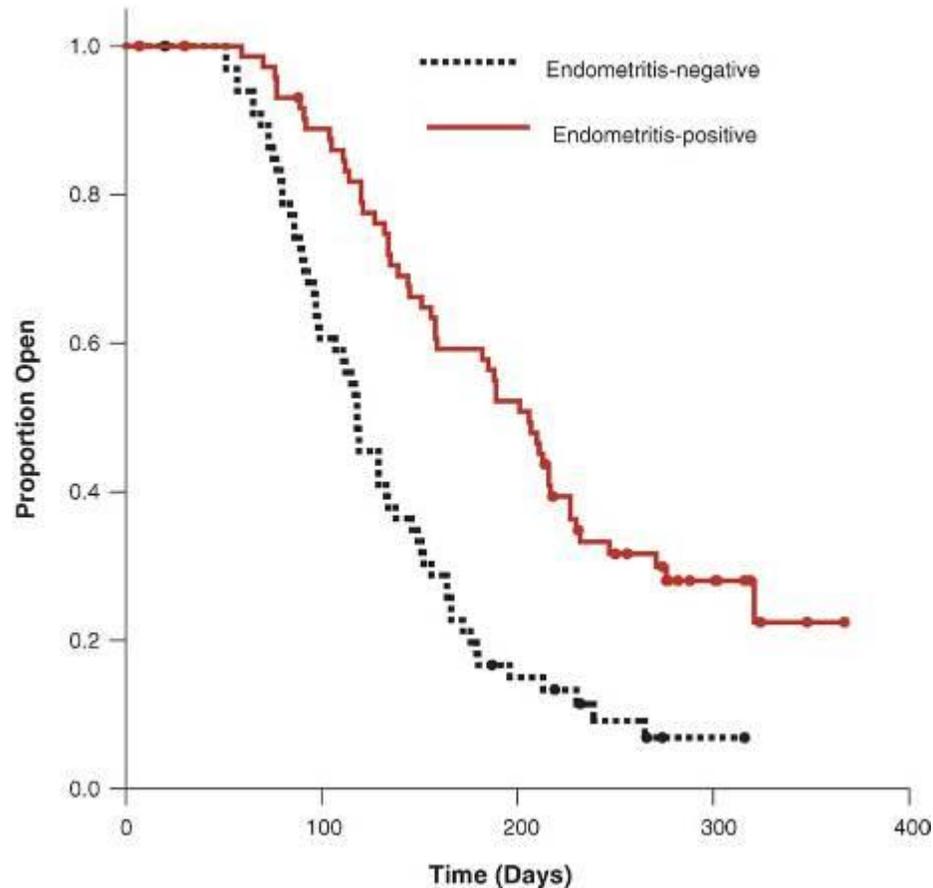
(C) D35 Uterine Discharge Appearance: P<0.001



(D) D35 Uterine Discharge Odour: P=0.189



Kaplan-Meier survival curves for days open for cows positive or negative for subclinical endometritis



- Pregnancy rate was lower for cows with endometritis ($P < 0.001$)
- Median days open was 206 for cows with endometritis and 118 for cows free of the condition;
- The proportion that never conceived were 31 and 10%, respectively ($P < 0.01$).

Top most significantly up-regulated genes in leucocytes of cows at 14 DIM according to the IGF-1 group

Gene Symbol	Gene name	Fold change [‡]	P(BH)
Up-regulated genes in LOW IGF-1 cows, ranked by FDR P-value[#]			
<i>PTX3</i>	Pentraxin 3	28.9	<0.001
<i>DMBT1</i>	Deleted in malignant brain tumors 1	16.2	<0.001
<i>ZCCHC14</i>	Zinc finger CCHC-type containing 14	1.48	<0.001
<i>ATP13A3</i>	ATPase 13A3	1.41	<0.001
<i>NRG1</i>	Neuregulin 1	2.03	<0.001
<i>DCSTAMP</i>	Dendrocyte expressed seven transmembrane protein	2.70	<0.001
<i>GATM</i>	Glycine amidinotransferase	1.83	<0.001
<i>PROK2</i>	Prokineticin 2	3.02	<0.001
<i>DGKH</i>	Diacylglycerol kinase eta	1.74	<0.001
<i>PDK4</i>	Pyruvate dehydrogenase kinase 4	2.10	<0.001
Up-regulated genes in LOW IGF-1 cows, ranked by RPKM values[#]			
<i>S100A12</i>	S100 calcium binding protein A12	1.57	<0.001
<i>S100A8</i>	S100 calcium binding protein A8	1.71	<0.001
<i>S100A9</i>	S100 calcium binding protein A9	1.93	<0.001
<i>HP</i>	Haptoglobin	2.16	<0.001
<i>RNASE6</i>	Ribonuclease A family member k6	1.23	0.028
<i>TSPO</i>	Translocator protein	1.21	0.022
<i>PKM</i>	Pyruvate kinase M1/2	1.26	<0.001
<i>CTSB</i>	Cathepsin B	1.23	0.008
<i>TALDO1</i>	Transaldolase 1	1.28	<0.001
<i>C10H15orf48</i>	Chromosome 10 open reading frame, human C15orf48	1.29	0.003

Wathes et al. (2021) *Ruminants* 1, 147–177.

KEGG pathway analysis based on all DEG in leukocytes collected from dairy cows with LOW (<35 ng/ml) v HIGH (>100 ng/ml) circulating IGF-1 concentrations, sampled at around 14 days in milk.

Term	Gene Count	Fold Enrich	P(BH)
bta04611:Platelet activation	24	3.61	3.23E-05
bta04640:Hematopoietic cell lineage	19	3.95	1.19E-04
bta04610:Complement and coagulation cascades	16	4.13	4.09E-04
bta04060:Cytokine-cytokine receptor interaction	26	2.28	0.010
bta04015:Rap1 signaling pathway	23	2.05	0.064
bta04978:Mineral absorption	9	3.91	0.064
bta04512:ECM-receptor interaction	13	2.86	0.064

Wathes et al., (2021) *Ruminants* 1, 147–177.

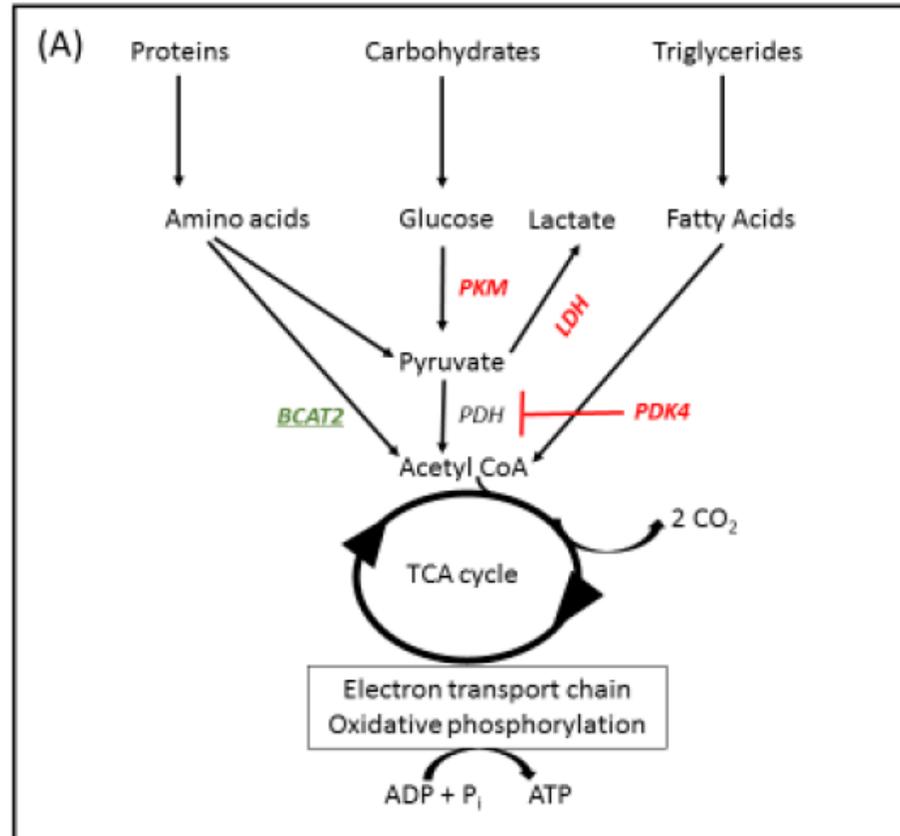
KEGG pathway analysis based on all DEG[#] in leukocytes collected from dairy cows with LOW (<35 ng/ml) v HIGH (>100 ng/ml) circulating IGF-1 concentrations, sampled at around 14 days in milk.

Term	Gene Count	Fold Enrich	P(BH)
bta01100:Metabolic pathways	44	2.72	1.78E-08
bta01230:Biosynthesis of amino acids	8	8.59	0.003
bta01200:Carbon metabolism	9	6.30	0.005
bta02010:ABC transporters	6	10.89	0.009
bta00410:beta-alanine metabolism	5	11.22	0.033
bta00620:Pyruvate metabolism	5	10.03	0.039
bta00770:Pantothenate and CoA biosynthesis	4	16.95	0.039

[#]Based on sub-list of 149 DEG with metabolic functions.

Wathes et al., (2021) *Ruminants* 1, 147–177.

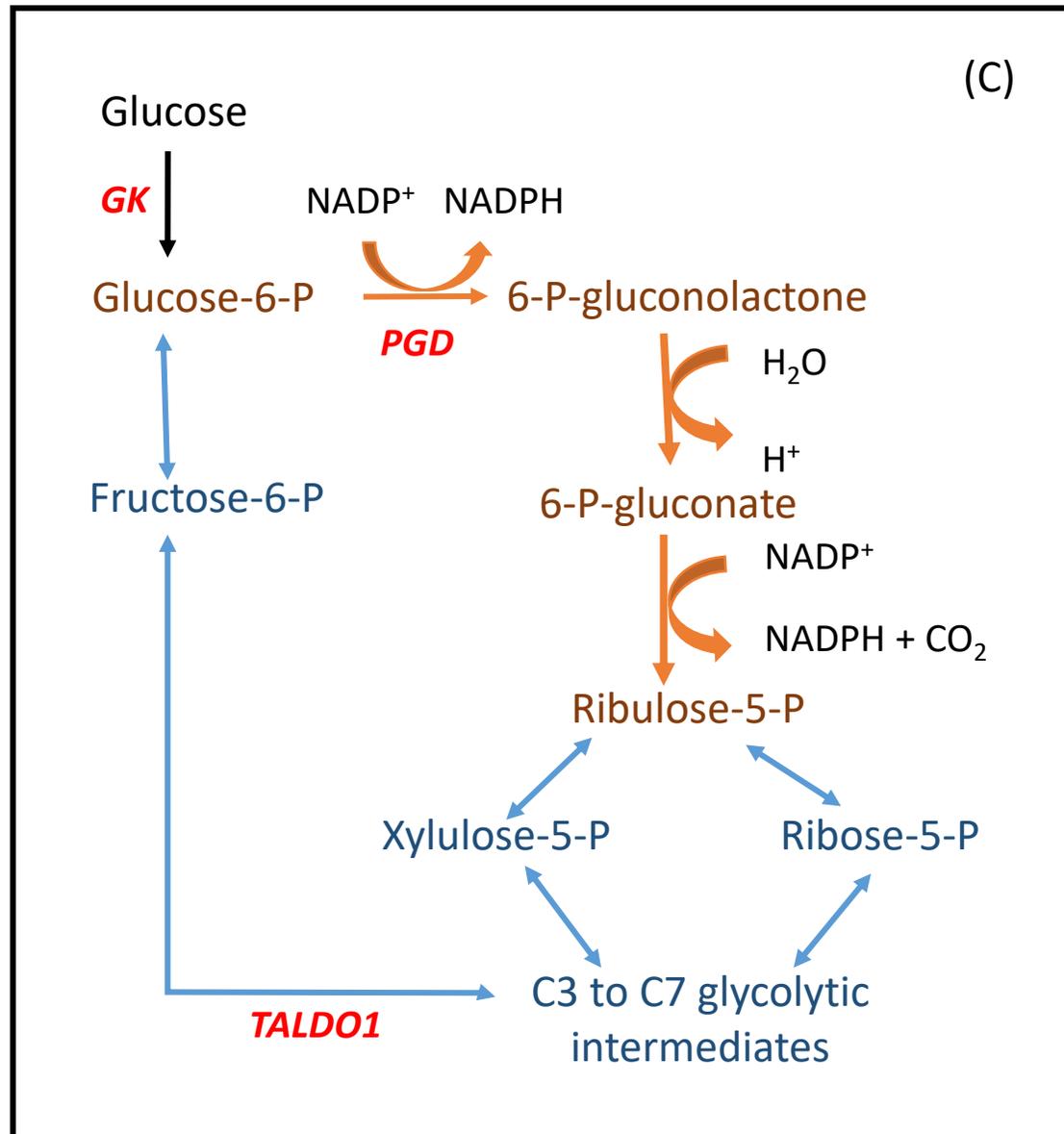
Metabolic pathways which were differentially influenced in leucocytes between cows with LOW (<35 ng/mL) vs HIGH (>100 ng/mL) IGF-1 in early lactation showing energy sources used for ATP and GTP synthesis via the TCA cycle



- In resting macrophages, most pyruvate is directed to the TCA cycle via acetyl-CoA to generate ATP via oxidative phosphorylation, although some is converted to lactate.
- In activated immune cells energy metabolism switches over to aerobic glycolysis, with the majority of the pyruvate converted into lactate.
- In this situation glycolytic intermediates and fatty acids provide the source of ATP.

Genes encoding enzymes which were **up-regulated** or down-regulated in LOW IGF-1 cows

Wathes et al., (2021) *Ruminants* 1, 147–177.



The pentose phosphate shunt

- This provides an alternative pathway for oxidation of glucose and has two phases:
- an oxidative phase, in which NADPH oxidase and ribulose-5-phosphate are generated.
- a non-oxidative phase, in which unused ribulose-5-phosphate is converted to other sugar intermediates and returned to the glycolytic pathway.

Genes encoding enzymes which were **up-regulated** in LOW IGF-1 cows

Wathes et al., (2021) *Ruminants* 1, 147–177.

Summary of the IGF-1 analysis

The metabolic status of individual cows is directly linked to the high incidence of health disorders during the critical peripartum period.

In this study 35/170 (20%) of all MP cows fell into the LOW IGF-1 category.

Most LOW IGF-1 cows are engaged in an energetically demanding battle against ongoing infection(s) involving the innate immune system.

- This reduces their appetite and milk yield.
- Previous evidence shows this will have an adverse effect on their subsequent fertility.

HIGH IGF-1 cows have higher nutrient availability and can use this to promote use of their adaptive immune system to better resist infection.

Immunosenescence

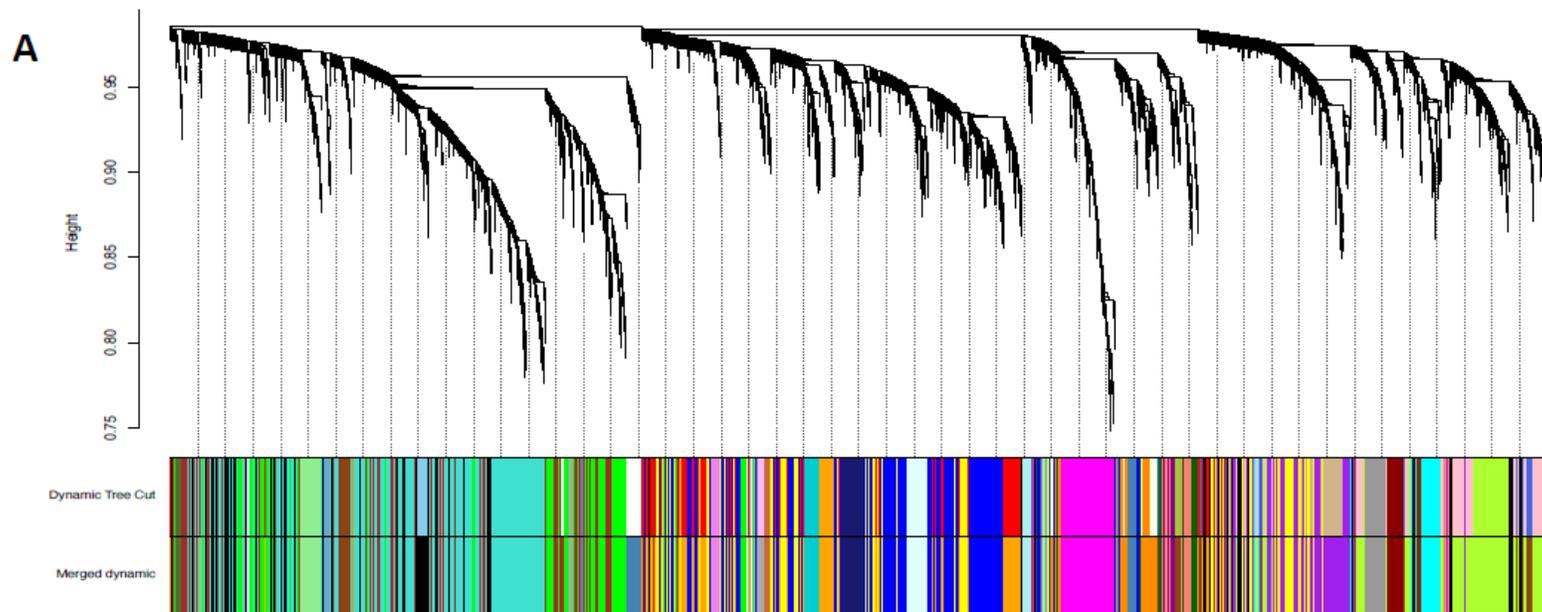
A series of age-related changes that affect the immune system and, with time, lead to increased vulnerability to infectious diseases

Inflammaging

Increased baseline inflammation in older individuals leading to age-associated frailty

WGCNA analysis based on lactation number of cows

- Samples divided into three lactation groups for analysis: i) primiparous (PP, n = 53), ii) multiparous in lactations 2-3 (MP 2-3, n = 121), and iii) MP in lactations 4-7 (MP>3, n = 55).
- Leukocyte expression compared between PP vs MP>3 cows with MP 2-3 as background using DESeq2 followed by weighted gene co-expression network analysis (WGCNA).



Cluster dendrogram of 13,769 genes clustered by their topological overlap dissimilarity scores.

Modules identified using the Dynamic Tree Cut algorithm, n=42.

Highly correlated smaller modules (agreement of 0.8) merged into 32 larger modules.

Hallmarks of cellular ageing

Previous studies in other species (humans and model organisms[‡]) of candidate genes whose expression is consistently associated with cellular ageing have been classified into six categories:

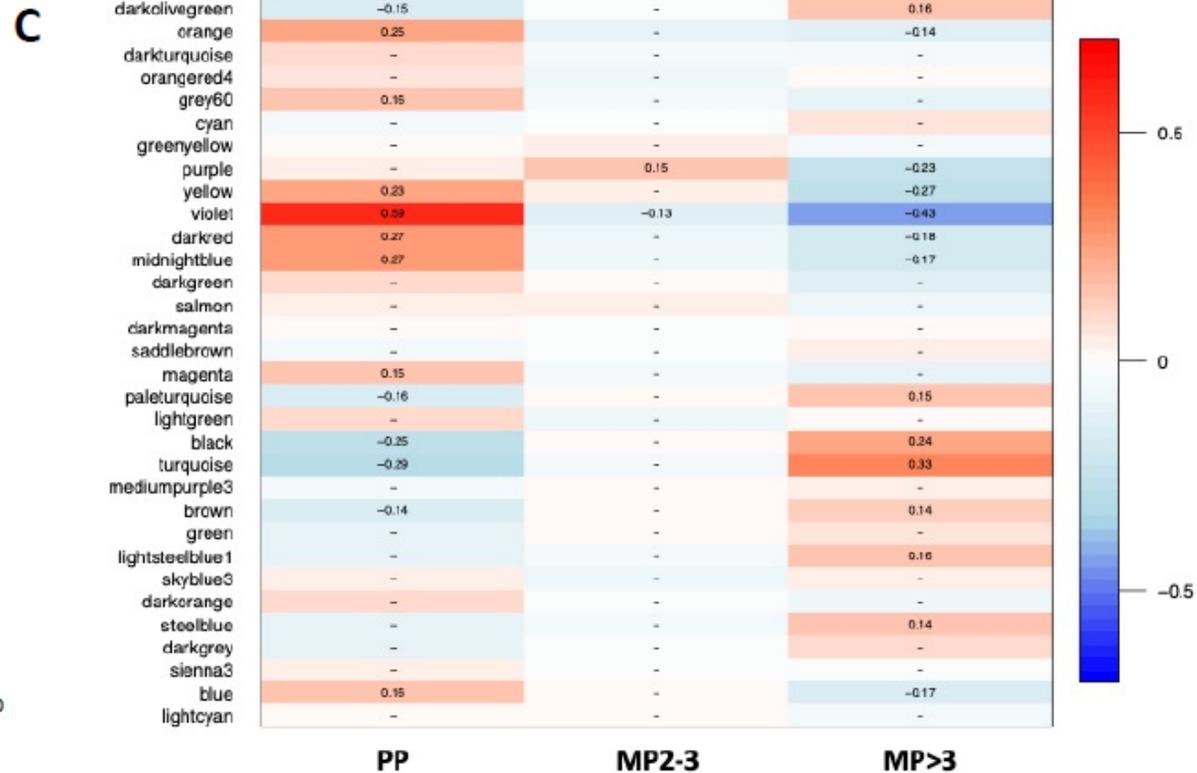
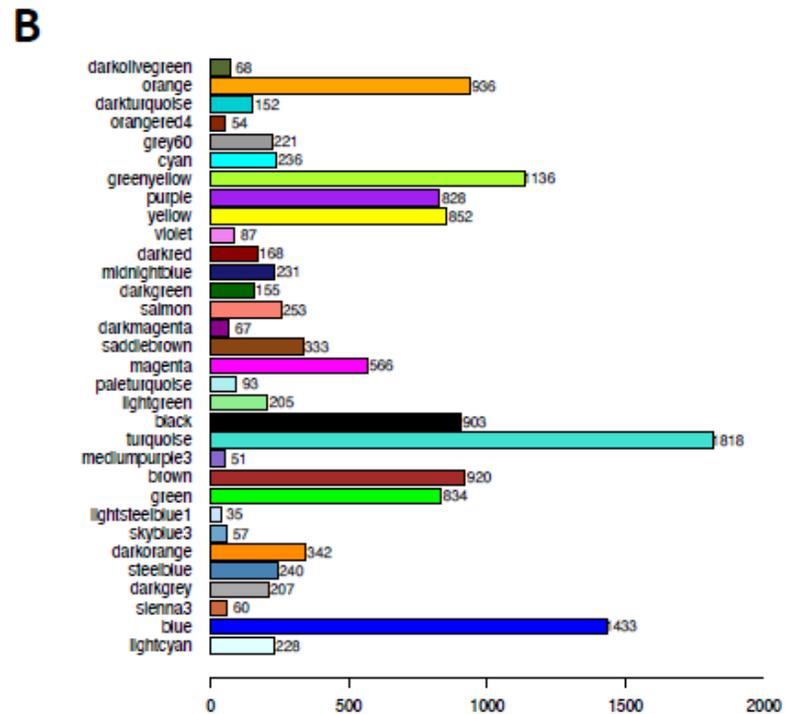
- downregulation of genes encoding mitochondrial proteins,
- downregulation of the protein synthesis machinery,
- dysregulation of immune system genes,
- reduction in growth factor signalling,
- constitutive responses to stress and DNA damage,
- dysregulation of gene expression and mRNA processing.

[‡]*C. elegans, Drosophila, mice*

Frenk S, Houseley J. Gene expression hallmarks of cellular ageing. Biogerontology. 2018;19:547–66.

WGCNA cont

- Seven of the 32 modules were significantly correlated ($r \geq 0.25$) to the trait lactation number.
- Genes from the modules which were more highly expressed in either the PP or MP>3 cows were pooled, and the gene lists subjected to David functional annotation cluster analysis.



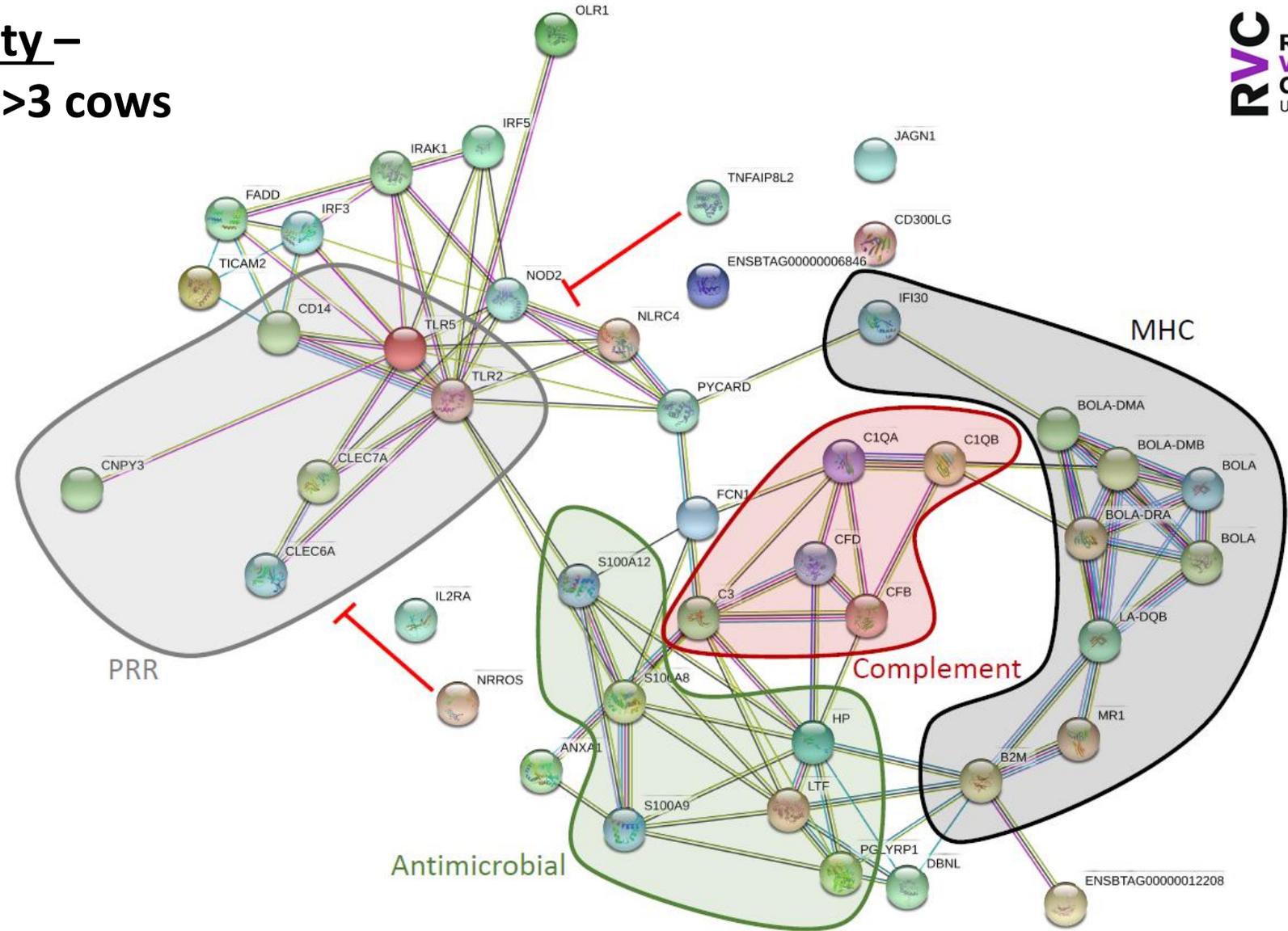
DAVID functional annotation cluster analysis of the DEG in the modules which were significantly positively or negatively correlated to lactation number

Cluster	Positive Modules Higher expression in PP cows	Negative Modules Higher expression in MP>3 cows	
1	ES 16.2, n=56 Krueppel-associated box Zinc finger C2H2-type/integrase DNA-binding domain	ES 29.7, n=471 Membrane component	
	2		ES 7.0, n=142 Zinc-finger Metal ion binding
			3
4	ES 5.0, n=61 Nucleotide binding	ES 7.3, n=254 Transmembrane region	
5	ES 2.0, n=31 BTB/POZ fold	ES 3.9, n=27 Glycolysis / Gluconeogenesis Biosynthesis of amino acids	
		ES 3.7, n=25 C-type lectin fold	
6	ES 1.9, n=50 Immunoglobulin-like domain	ES 3.3, n=45 Innate immunity	

ES: enrichment score



Cluster 6 Innate Immunity – higher expression in MP>3 cows



v.s. genes involved in adaptive immunity (mainly T-cell development and function) up-regulated in PP cows (e.g. *CCR7*, *CD27*, *IL7R*, *CAMK4*, *CD28*, *ITK*, *LCK*).

Comparison with ageing-associated genes from other species

Candidate genes were identified from previous studies of ageing in humans and model organisms.

- Of these 38/170 (22.3%) were present in our list of DEG
- Of these 16/38 DEG were previously identified as being age-related in the human blood transcriptome[‡]

Genes up-regulated in PP cows were mainly associated with:

T-cell development and function (*CCR7, CD27, IL7R, CAMK4, CD28*)

Protein synthesis within the mitochondria (*MRPS27, MRPS9, MRPS31*)

Premature ageing (*WRN*) – mutations in humans cause Werner's syndrome

DNA helicase
important for DNA
repair, replication,
transcription and
telomere maintenance

Genes up-regulated in MP>3 cows included genes involved in immune defence (*LYZ, CTSZ, SREBF1, GRN, ANXA5, ADARB1*).

[‡]Peters MJ, et al. *The transcriptional landscape of age in human peripheral blood. Nat Commun. 2015;6:1–14.*

Summary of key biological pathways in leukocytes which alter as cows age

- Changes in ribosome biogenesis, transcriptional regulation and DNA replication, elongation and repair: higher in PP cows.
- Differential expression of immune pathways: adaptive immunity higher in PP cows, innate immunity higher in MP>3 cows.
- Changes in pathways supplying leukocytes with energy: increased expression of genes encoding enzymes involved in beta-oxidation of fatty acids in PP cows whereas genes involved in glycolysis up-regulated in MP>3 COWS.
- Changes in mitochondrial function: differential expression of genes encoding mitochondrial ribosomal proteins between age groups.

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