Center for
Nutrition and
Pregnancy

75th EAAP Annual Meeting
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NDSU
Animal Sciences

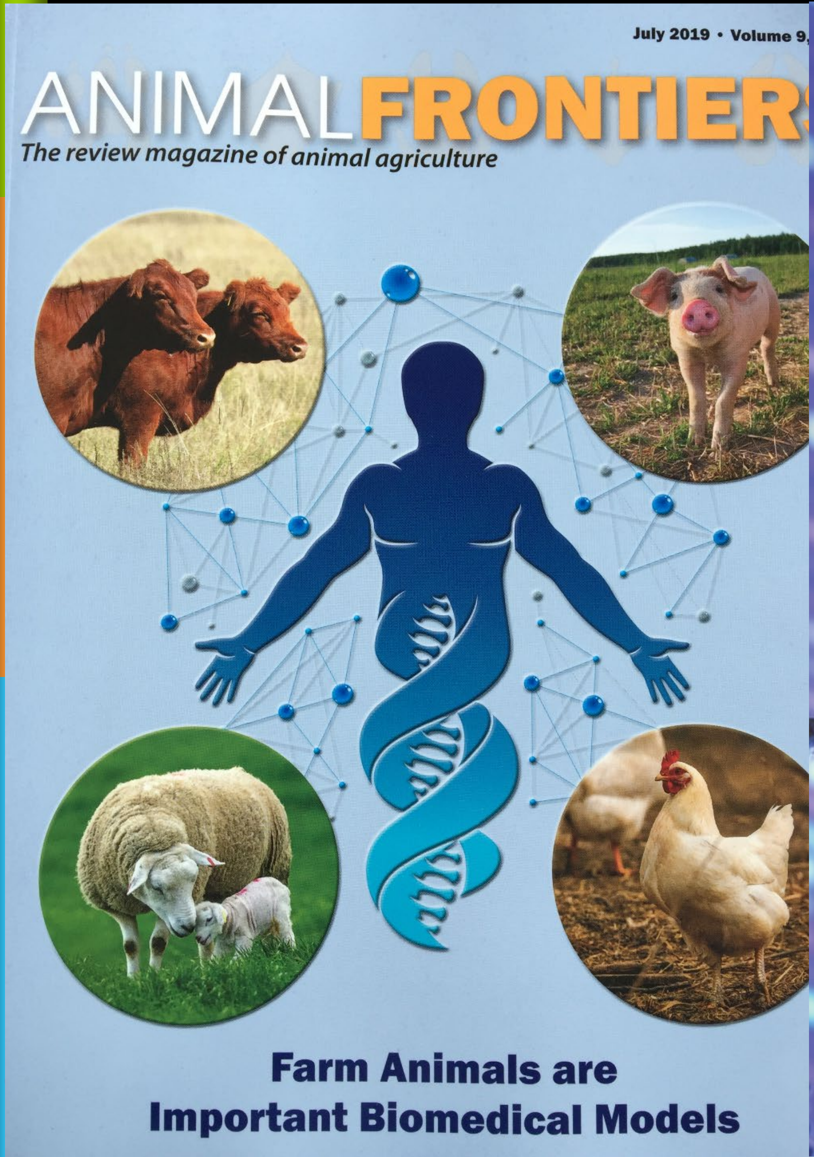
Micronutrient Supply, Developmental Programming, and Strategic Supplementation

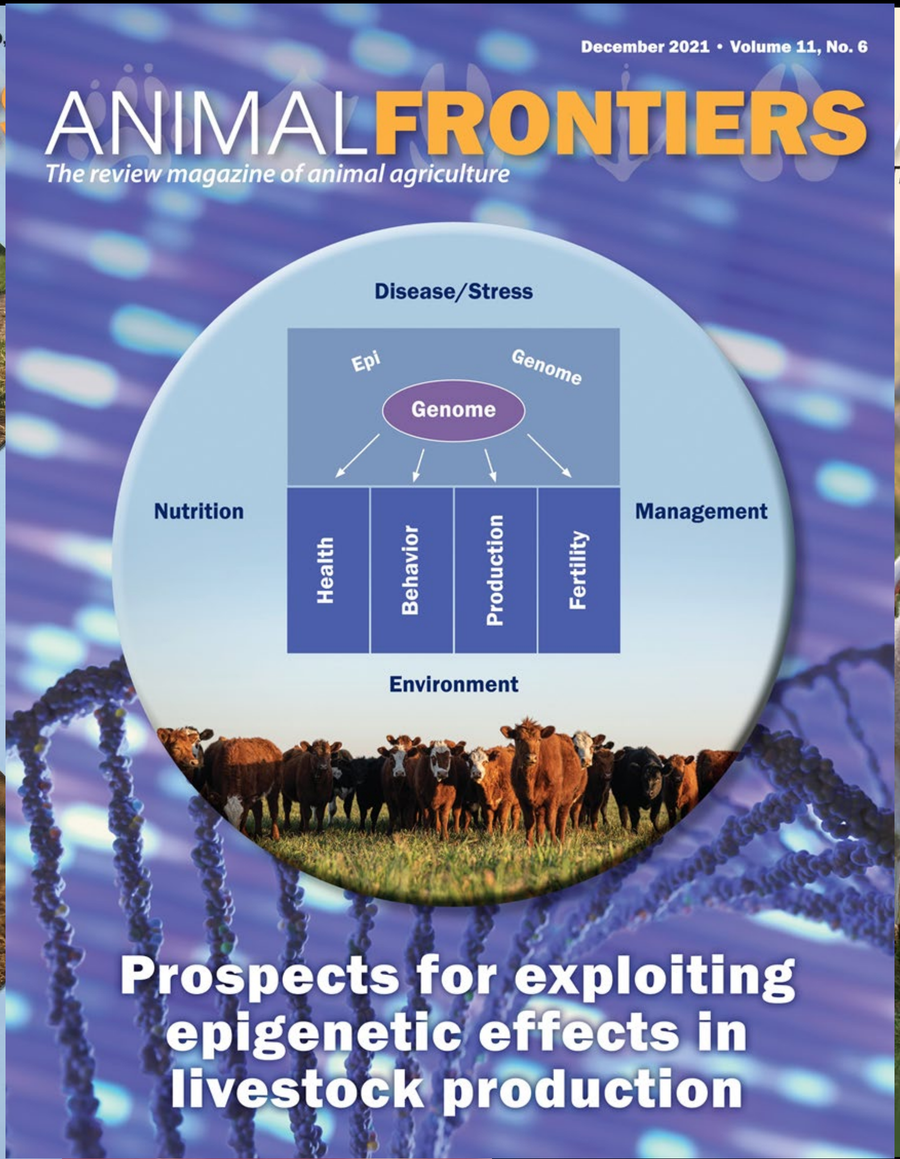
J. S. Caton
North Dakota State University, Fargo, ND,
Past-President, ASAS

Micronutrient Supply:
Defining and Delivering the Nutrient Requirements:
The Essence of Precision Nutrition

- Long history of discovery and application
- More in front of us than behind us
- Requirements for nutrients range from percentage of the diet to mg or mcg/kg DMI
  - Most expressed as proportion of diet
  - What about per unit of BW or Metabolic BW
- Requirements are fickle and depend upon many things
- Where the best of science and the art of management merge

Developmental Programming: Concepts, Realities, Mechanisms



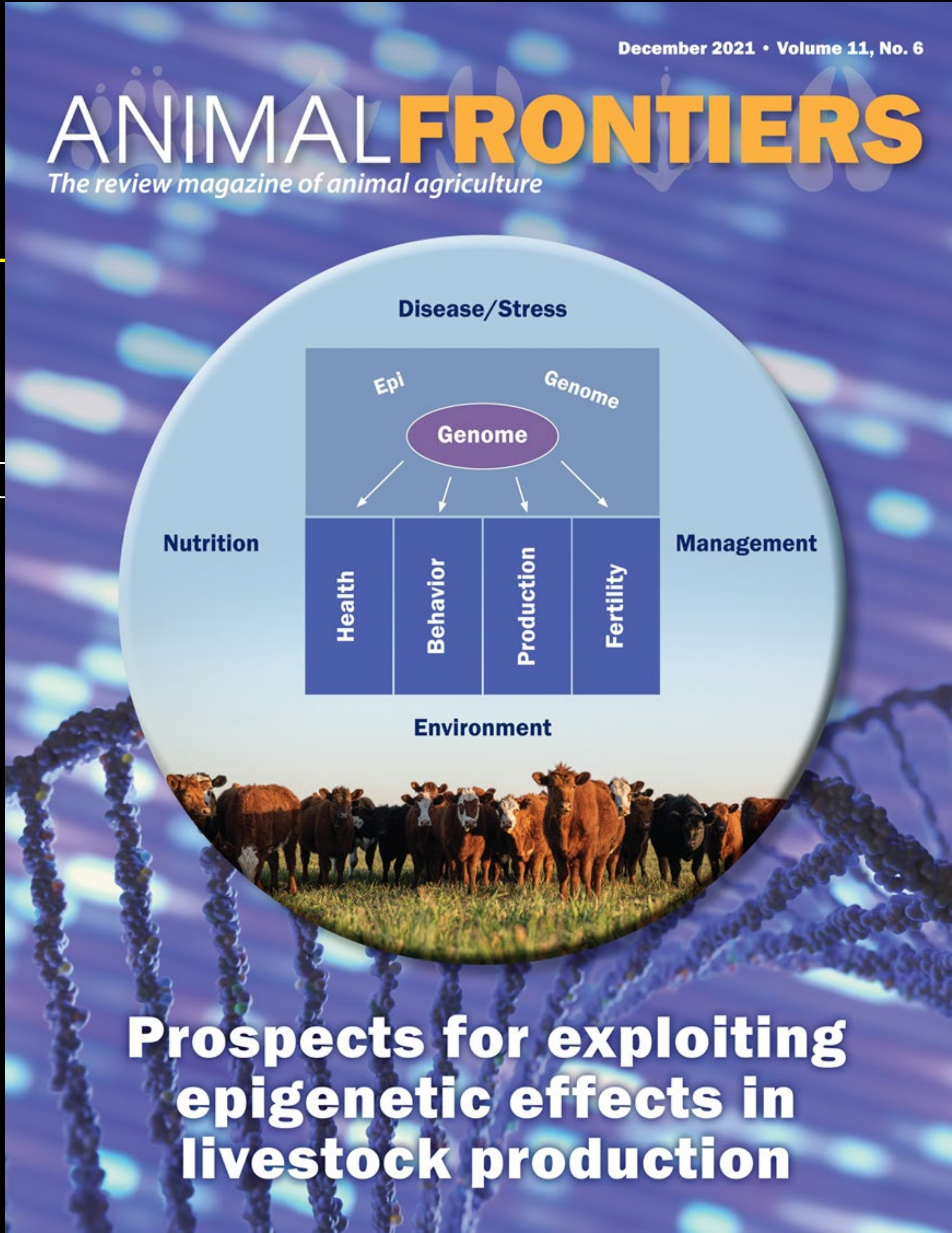


Epigenetics

- Mechanism
  - Changes to the epigenome
  - Change gene expression without altering the D
- Genetic marks
  - DNA methylation
  - Histone modifications
  - Chromatin remodeling
  - Non-coding RNAs

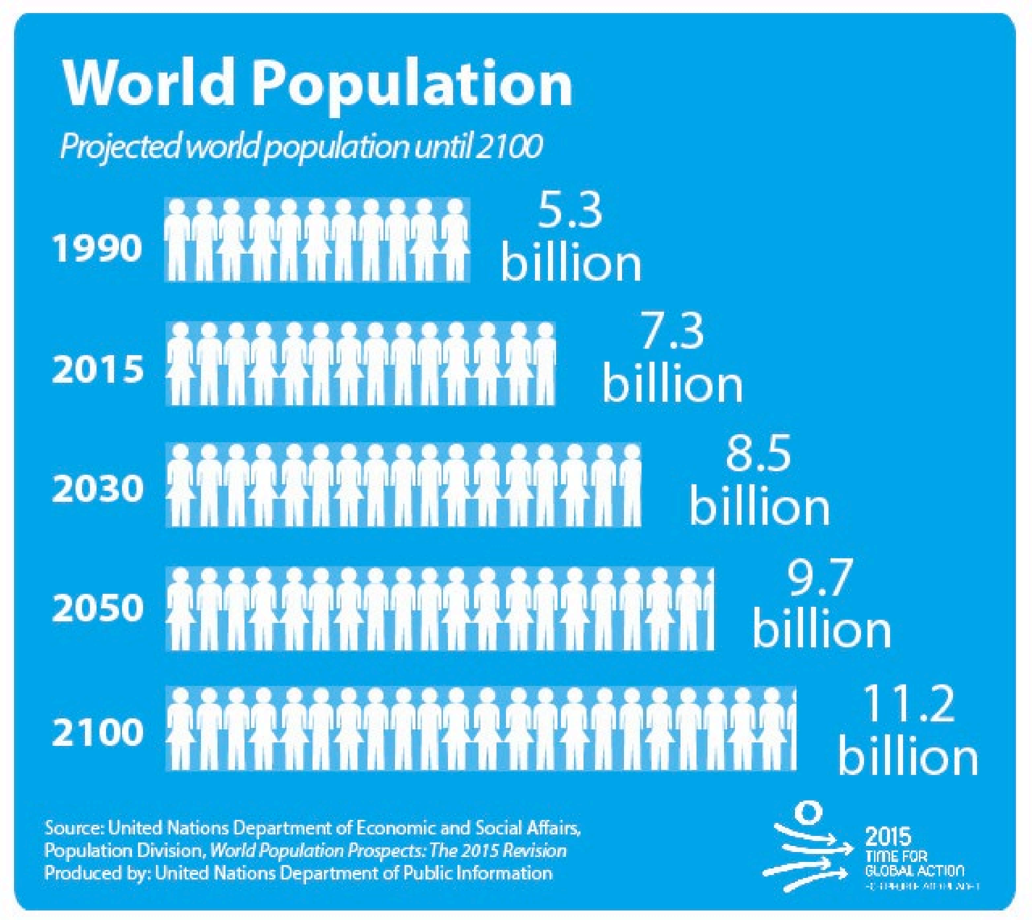
Meyer et al., 2012;
Reynolds et al., 2017
Crouse et al., 2022
Diniz et al., 2022
Diniz et al., 2024

Influenced by Micronutrients



Importance to Society: Broader Impacts

- Human Health and Wellbeing; Obesity, Metabolic Disease, Cancer
- Feeding the world population
- Sustainability
  - Lithosphere
  - Hydrosphere
  - Biosphere
  - Atmosphere



Developmental Programming: Animal Models

Most research focuses on maternal nutrition during mid to late gestation

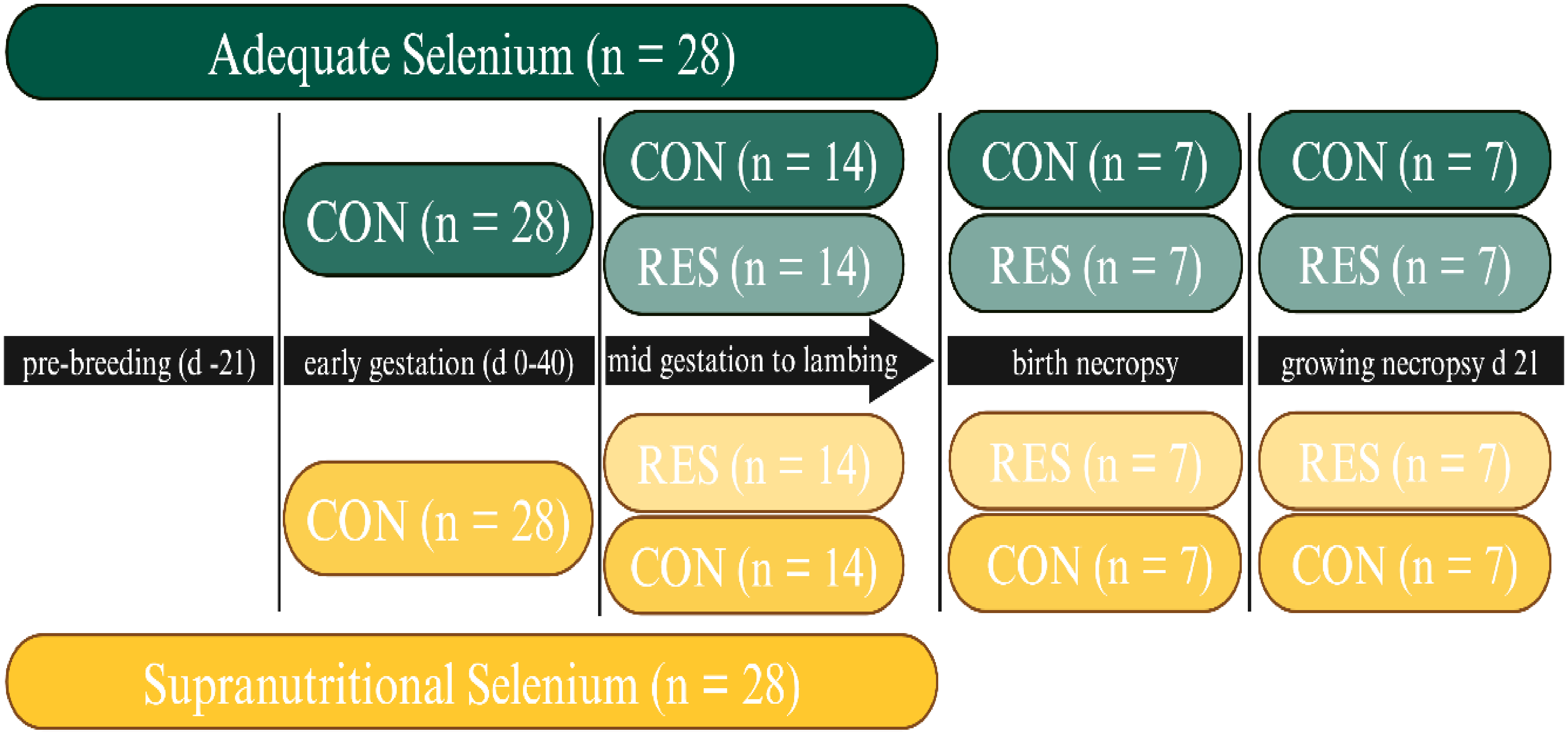
What about preconception

What about paternal

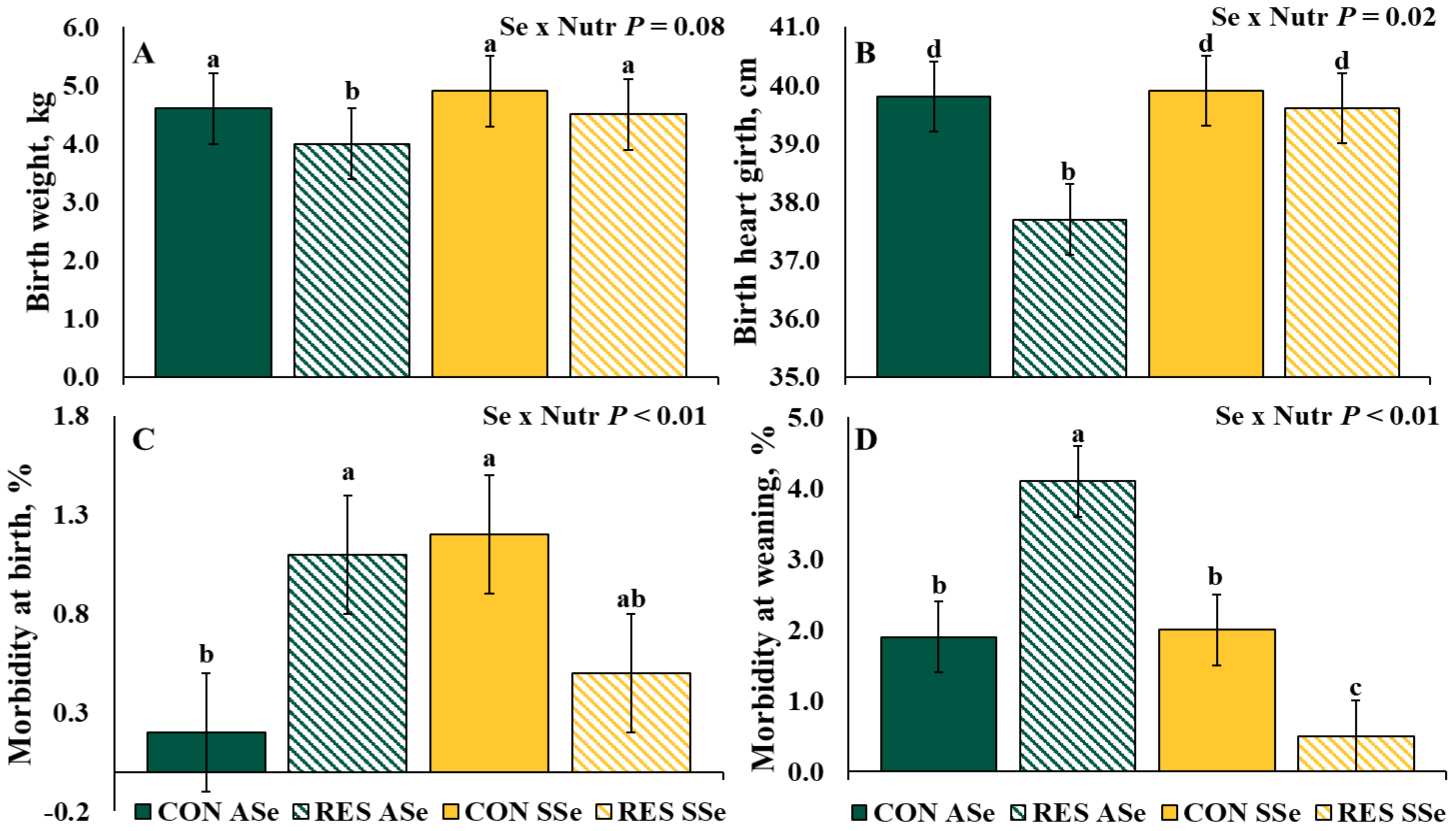
What about early pregnancy?

Nutritional Models of Developmental Programming: Specific Nutrients

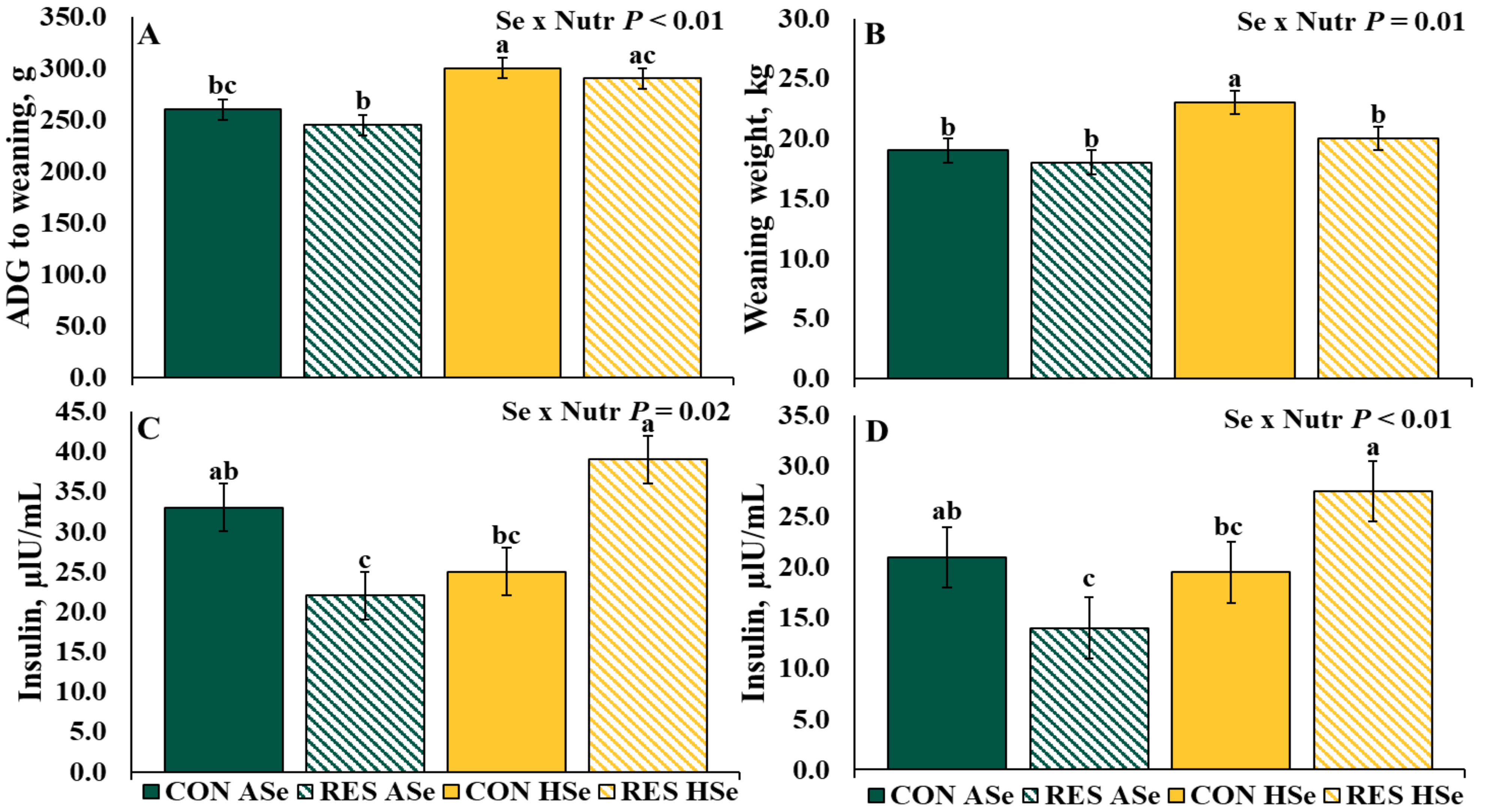
- Macro Nutrients:
  - Protein
  - Fats
  - Carbohydrates
- Micro Nutrients
  - Amino Acids: Methionine, Arginine
  - Vitamins: Folate, B12, Choline, B6
  - Minerals: Cobalt, Iodine, Selenium, Sulfur



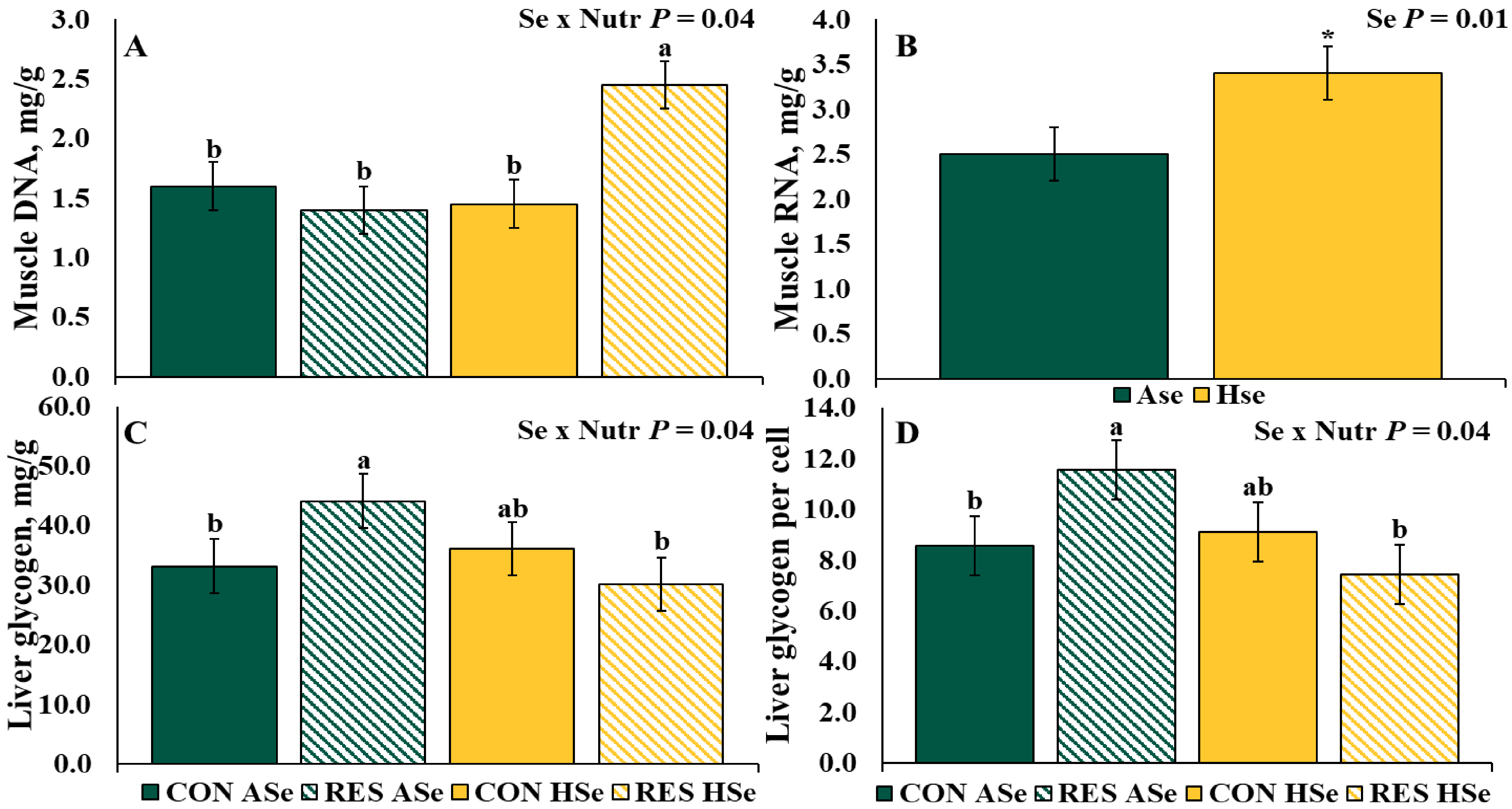
Experiment 1 timeline for ewes subjected to adequate nutrition vs undernutrition and adequate selenium vs supranutritional selenium in a 2 × 2 factorial. Ewes underwent selenium treatments 21 days pre-breeding through parturition. Nutrition treatments began in mid-gestation (day 40) through parturition. CON = adequate nutrition, RES = undernutrition; adequate selenium (9.5 μg/kg BW) or supranutritional selenium (81.8 μg/kg BW) in pelleted supplements.



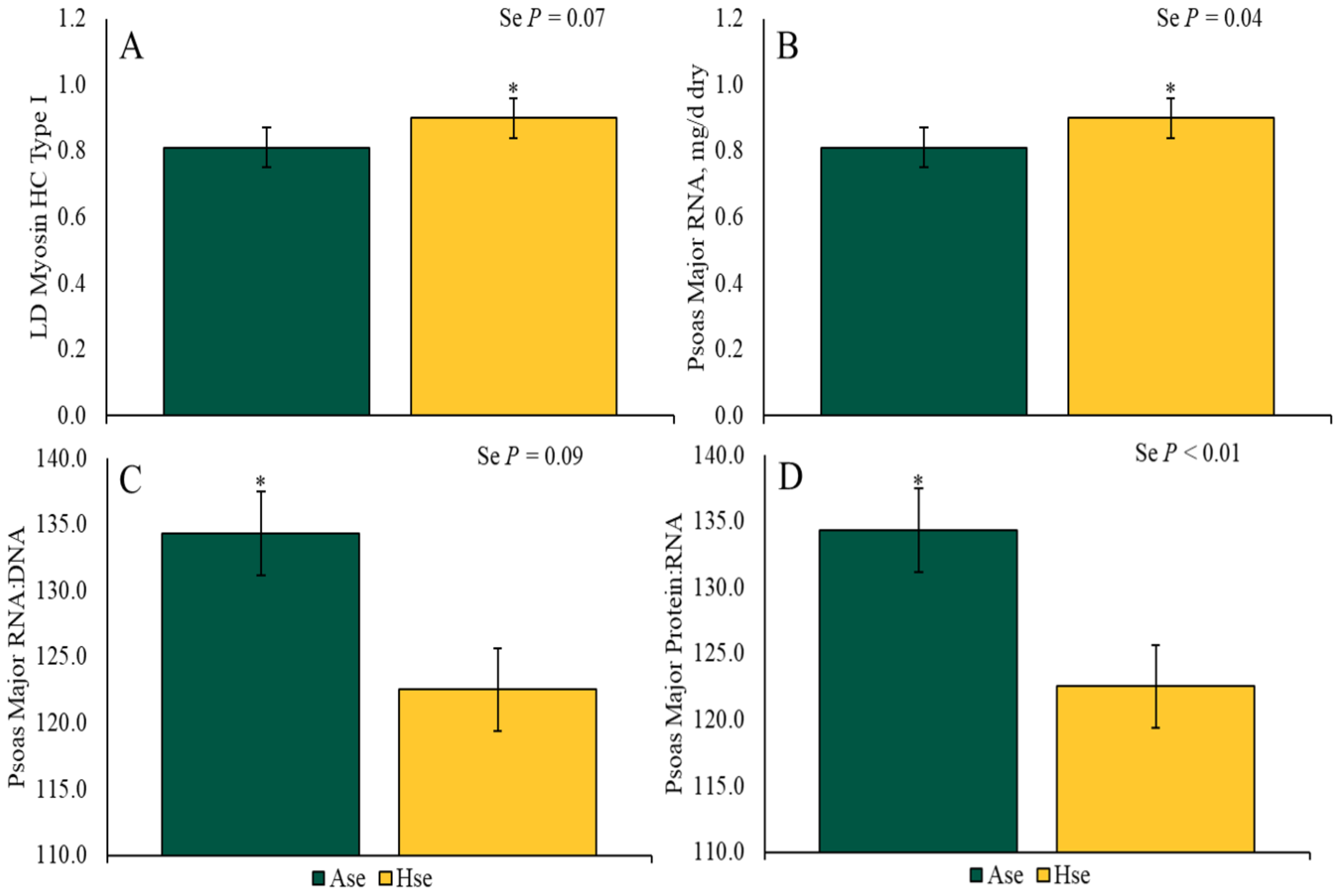
The effect of supranutritional selenium during undernourished pregnancies on offspring performance and health. **A)** Birth weights, **B)** birth heart girth, **C)** morbidity at birth, and **D)** morbidity at growing. CON ASe = adequate nutrition and selenium; RES ASe = undernutrition and adequate selenium, CON SSe = adequate nutrition and supranutritional selenium; RES SSe = undernutrition and supranutritional selenium, [a,b,c,d]differing superscripts indicates differences at $P \leq 0.05$ (Meyer et al., 2010; Hammer et al., 2011).



The effect of supranutritional selenium during undernourished pregnancies on offspring performance and metabolism. **A)** ADG to weaning, **B)** weaning weights, **C)** *in vivo* glucose stimulated insulin secretion on d 107 of age, and **D)** on d 148 of age. ADG = average daily gain; CON ASe = adequate nutrition and selenium; RES ASe = undernutrition and adequate selenium, CON SSe = adequate nutrition and supranutritional selenium; RES SSe = undernutrition and supranutritional selenium, [a,b,c,d]differing superscripts indicates differences at $P \leq 0.05$ (Meyer et al., 2010; Vonnahme et al., 2010).



The effect of supranutritional selenium during undernourished pregnancies on offspring skeletal muscle and liver function. **A)** muscle DNA content, **B)** muscle RNA content, **C)** liver glycogen content, and **D)** liver glycogen content per cell. CON ASe = adequate nutrition and selenium; RES ASe = undernutrition and adequate selenium, CON SSe = adequate nutrition and supranutritional selenium; RES SSe = undernutrition and supranutritional selenium, *[a,b,c,d]differing superscripts indicates differences at P ≤ 0.05 (Reed et al., 2007; Lekatz et al., 2010).



Maternal supranutritional selenium during gestation increased **A.** offspring skeletal muscle myosin heavy chain type I, **B.** and RNA but decreased **C.** RNA:DNA ratio, and **D.** protein:RNA ratio at slaughtered in finished lambs.

Offspring Responses

- Offspring from ewes fed HSe:
  - Intestinal mass
  - Visceral adiposity
  - Decreased intestinal DNA
  - Increased capillary area density in intestine
  - Altered angiogenic factor expression
  - Altered digestion coefficients
  - Lower heart mass
  - Altered insulin sensitivity

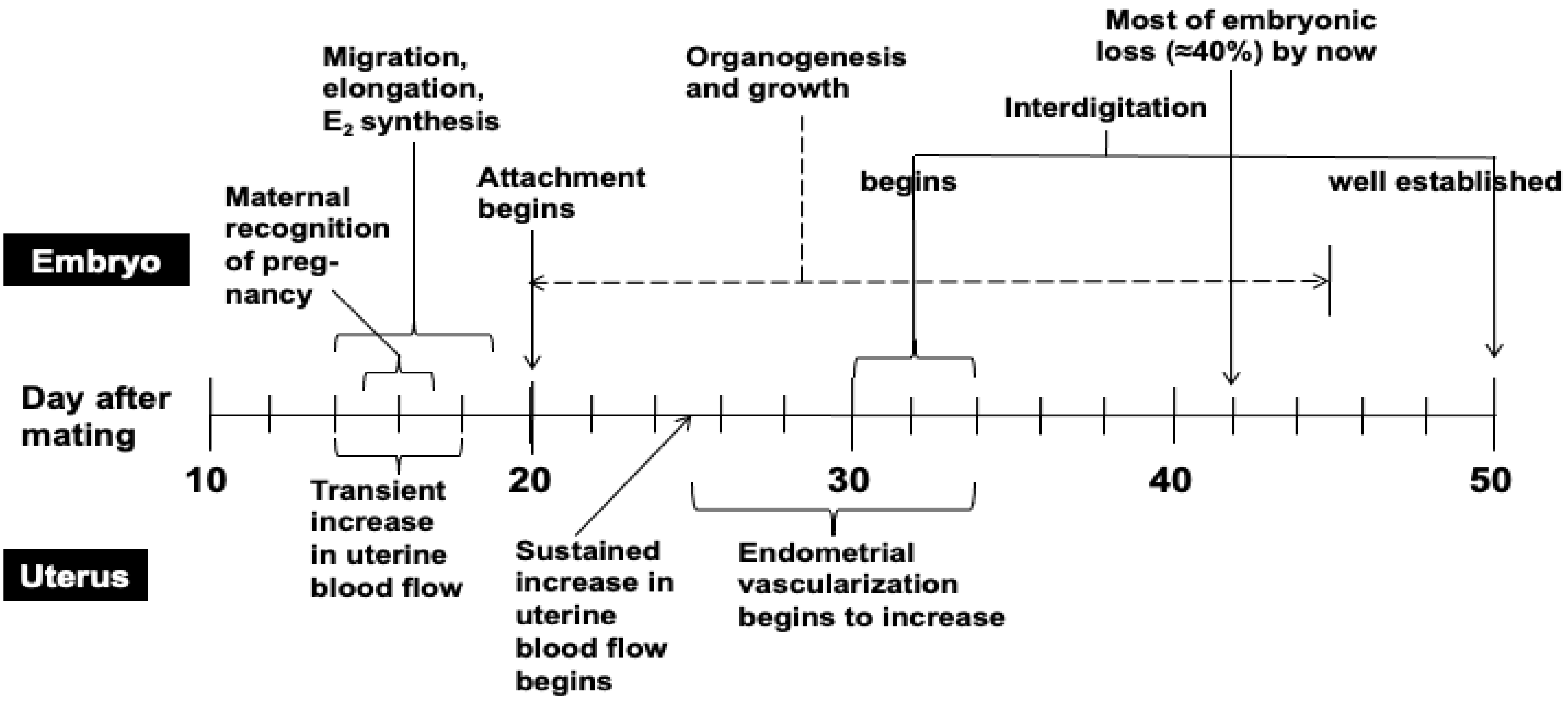
Key Vitamins and Minerals for Development and Function of Fetal Organs

Tissue/organ	Minerals	Vitamins
Muscle	Cu, Zn, Se, Mn	A
Nervous system	Fe, Cu, Zn, Se, I	E, B_6, B_{12}
Blood cells	Cu, Fe, Zn, Se	A, B_1
Liver	Fe, Se, Cu, Zn, Cd	A, B_{12}, B_9, choline
Kidneys	Fe, Cd, Zn, Pb	A
Lungs	Cu, Cd, Zn	A
Thyroid	Fe, Se, I	–
Proliferating cells	Fe, Zn,	A, B_{12}, B_9
Bones	Ca, Mg	C, D, E
Heart	Fe, Cu, Zn	A, D, E

Based on McArdle and Ashworth (1999), Ashworth and Antipatis (2001), Christian and Stewart (2010)

Diniz et al., 2024

Early Pregnancy: Beef Cattle



Caton et al., 2020

Functional categories for differentially expressed genes involved in tissue metabolism, accretion, and function; presented as upregulation (Upreg.) or downregulation (Downreg.) in fetuses from restricted (RES) compared with control heifers (CON).[1,2]

Category	Total genes[3]	Upreg.	Downreg.	*P*-value
Liver				
Metabolic pathways	43	32	11	0.017
Protein kinase	47	40	7	0.020
Nucleosome core	22	21	1	0.005
mRNA splicing	7	6	4	0.041
Complement/Coagulation	6	6	0	0.041
Fetal muscle				
Skeletal muscle	74	45	29	<0.001
Embryogenesis	14	12	2	<0.001
Signaling cascades	18	7	11	0.003
Cerebrum				
Hippocampus and neurogenesis	32	31	1	<0.001
Metal-binding	23	22	1	0.006
Cytoskeleton	5	5	0	0.003

[1]Table modified from Caton et al., 2020.

[2]CON average daily gain = 0.51 kg/d (NASEM, 2016), and RES received 60% of CON and had an average daily gain = -0.08 kg/d.

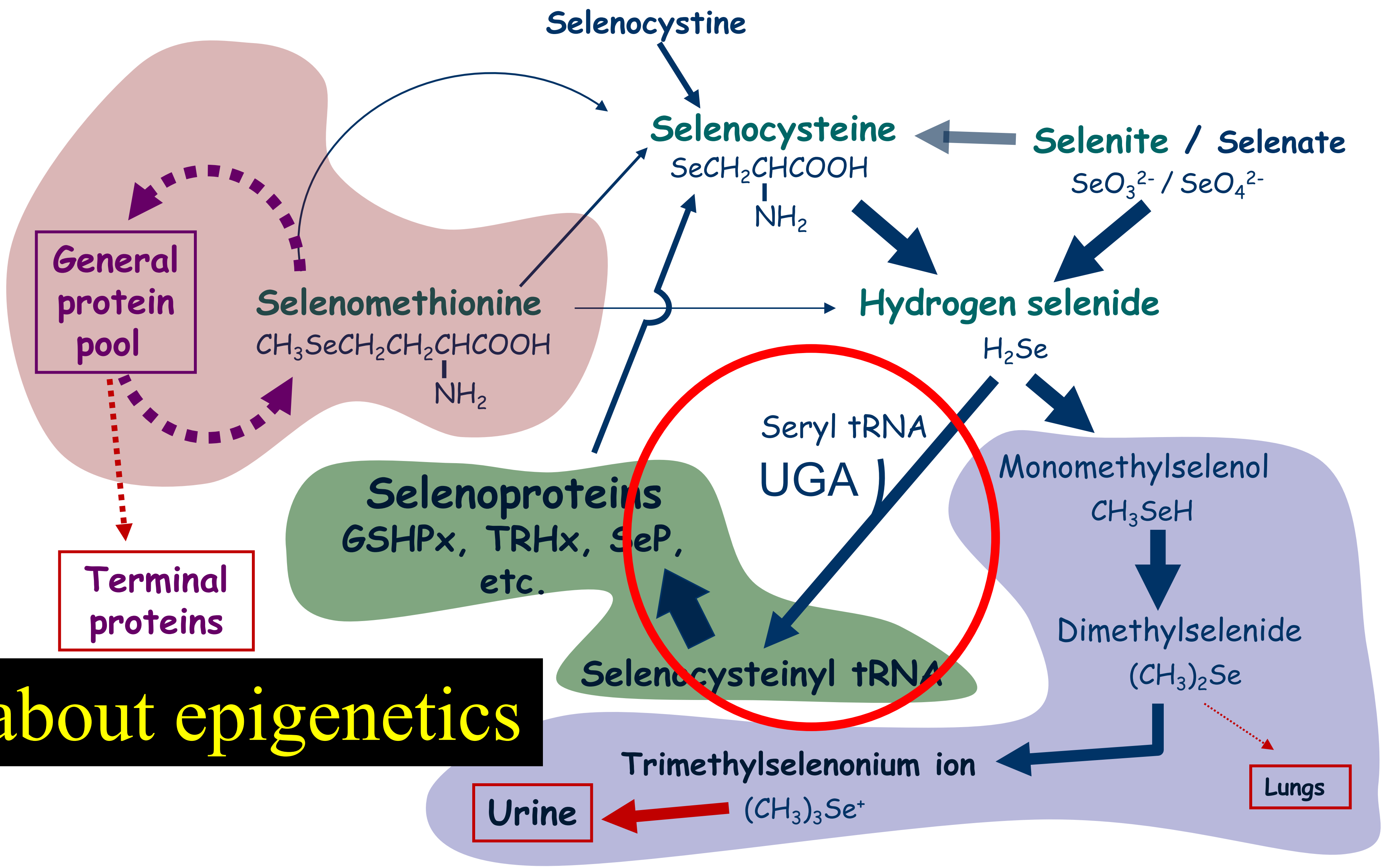
[3]Total number of differentially expressed genes associated with a category.

Se-Related Genes in Bovine Fetal Liver

Gene	Name	Functions	RES	CON
GSTA2	Glutathione S-transferase A2	detoxification of electrophilic compounds; antioxidant activity; glutathione metabolism		+
GSR	Glutathione S-Reductase	Glutathione metabolism		+
ETHE1	Sulfur Dioxygenase	Sulfur and glutathione metabolism	+	
GGT5	Gamma-Glutamyltransferase 5	Glutathione and arachidonic acid metabolism	+	
LTC4S	Leukotriene C4 Synthase	Glutathione metabolism; leukotriene production	+	
TRNAU1AP	TRNA Selenocysteine Associated Protein 1	Se-metabolism selenoprotein syn; RNA binding; Selenocysteine incorporation; translation; found in complex with tRNA(Sec)	+	

Crouse et al., 2017

Selenium Metabolism (abbreviated)



What about epigenetics

Article

Supranutritional Maternal Organic Selenium Supplementation during Different Trimesters of Pregnancy Affects the Muscle Gene Transcriptome of Newborn Beef Calves in a Time-Dependent Manner

Wellison J. S. Diniz [1,*], Gerd Bobe [2,3], Joseph J. Klopfenstein [4], Yunus Gultekin [2], T. Zane Davis [5], Alison K. Ward [6] and Jean A. Hall [7,*]

Genes **2021**, *12*, 1884. https://doi.org/10.3390/genes12121884

“Supranutritional maternal Se supplementation plays a pivotal role in programming muscle gene expression. Additionally, Se differentially modulates offsprings’ muscle gene expression according to the trimester of pregnancy. The results suggest a beneficial effect of Se supplementation during the last third of gestation as the myogenic factors were upregulated.”

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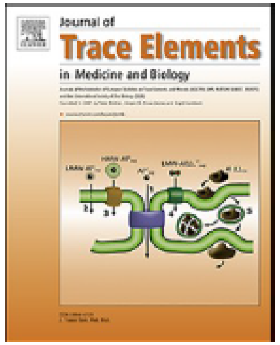
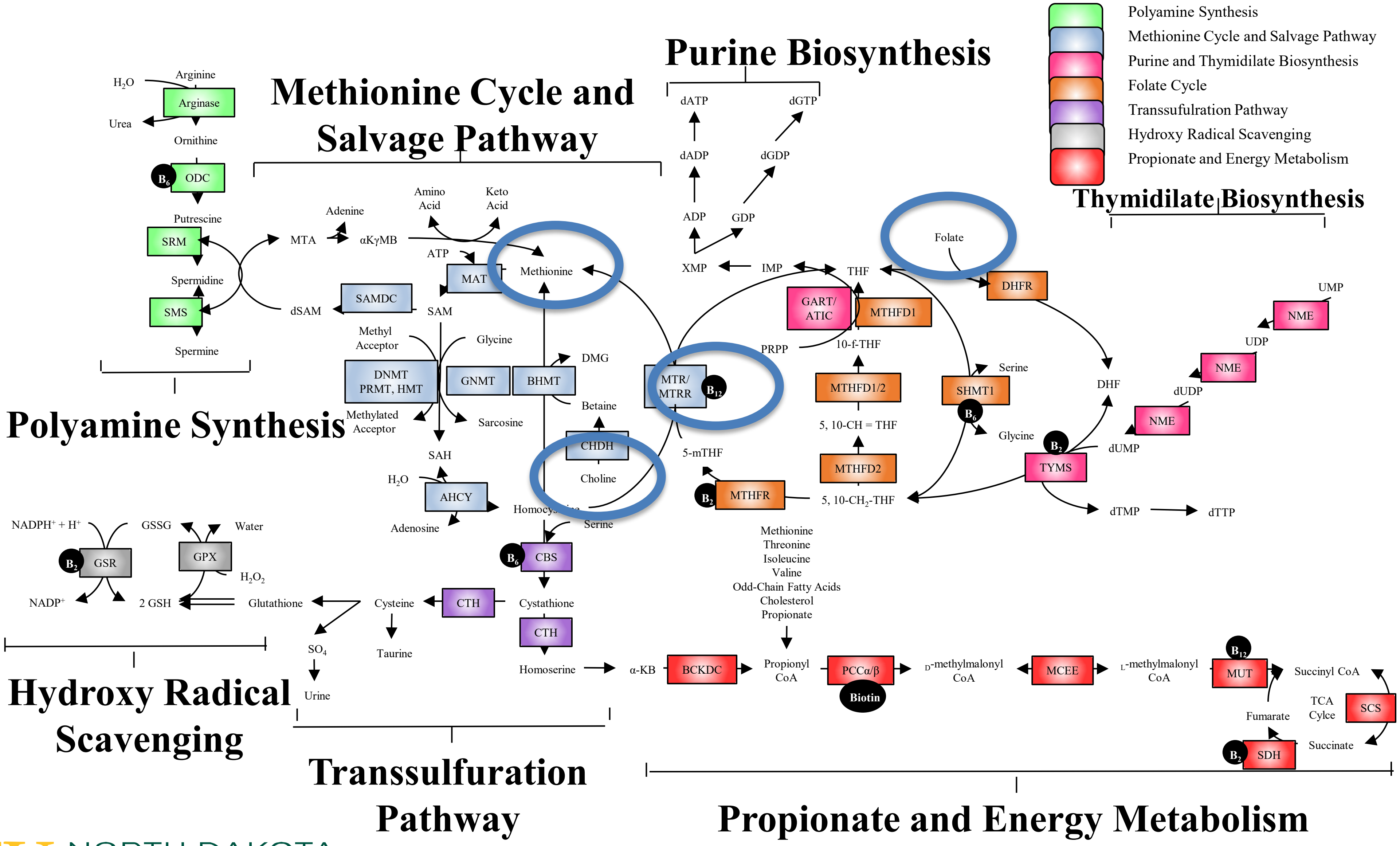
journal homepage: www.elsevier.com/locate/jtemb



The influence of serum selenium in differential epigenetic and transcriptional regulation of CPT1B gene in women with obesity

Lígia Moriguchi Watanabe [a,*], Vanessa Aparecida Batista Pereira [a], Natalia Yumi Noronha [b], Marcela Augusta de Souza Pinhel [b,c], Leticia Santana Wolf [b], Cristiana Cortes de Oliveira [b], Jessica Rodrigues Plaça [d], Isabella Harumi Yonehara Noma [e], Guilherme da Silva Rodrigues [b], Vanessa Cristina Oliveira de Souza [f], Fernando Barbosa Júnior [f], Carla Barbosa Nonino [a,b]

Interconnection of One-Carbon Metabolism, Energy, Metabolism, Nucleotide Synthesis, and Hydroxy Radical Scavenging.



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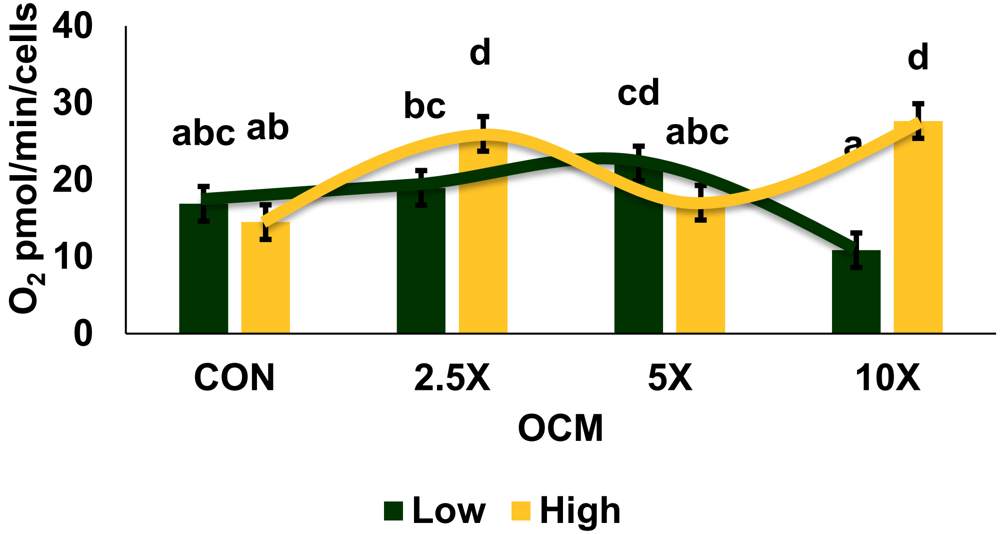
Crouse et al., 2019 Unpublished

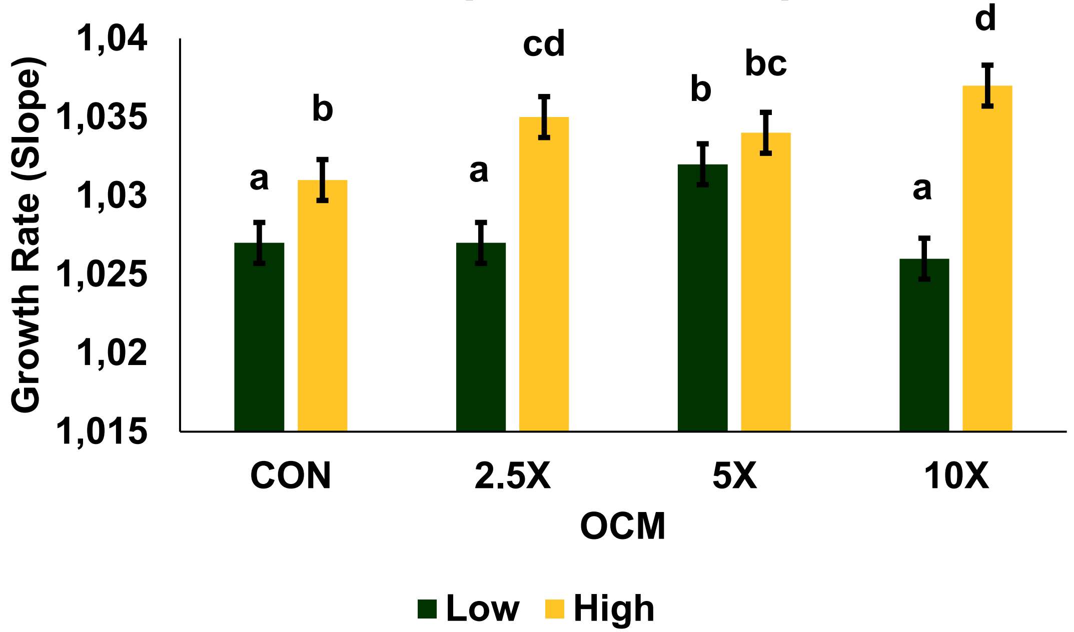
Cell Culture Study: Cells and Treatments

- Bovine Embryonic Tracheal Fibroblasts (EBTr)
- 2 × 4 Factorial Arrangement
- Glucose
  - 1 g/L **(Low)**
  - 4.5 g/L **(High)**
- One-Carbon Metabolite **(OCM)**
  - **CON**
    - Folate (1.0 mg/L), Choline (1.0 mg/L), Vitamin B_{12} (4 μg/L), Methionine (15 mg/L)
  - **2.5X, 5X, and 10X**
  - Methionine limited to 2X across all treatments

Reserve Mitochondrial Capacity



Total (h 1 to 72)



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Crouse et al., 2019c

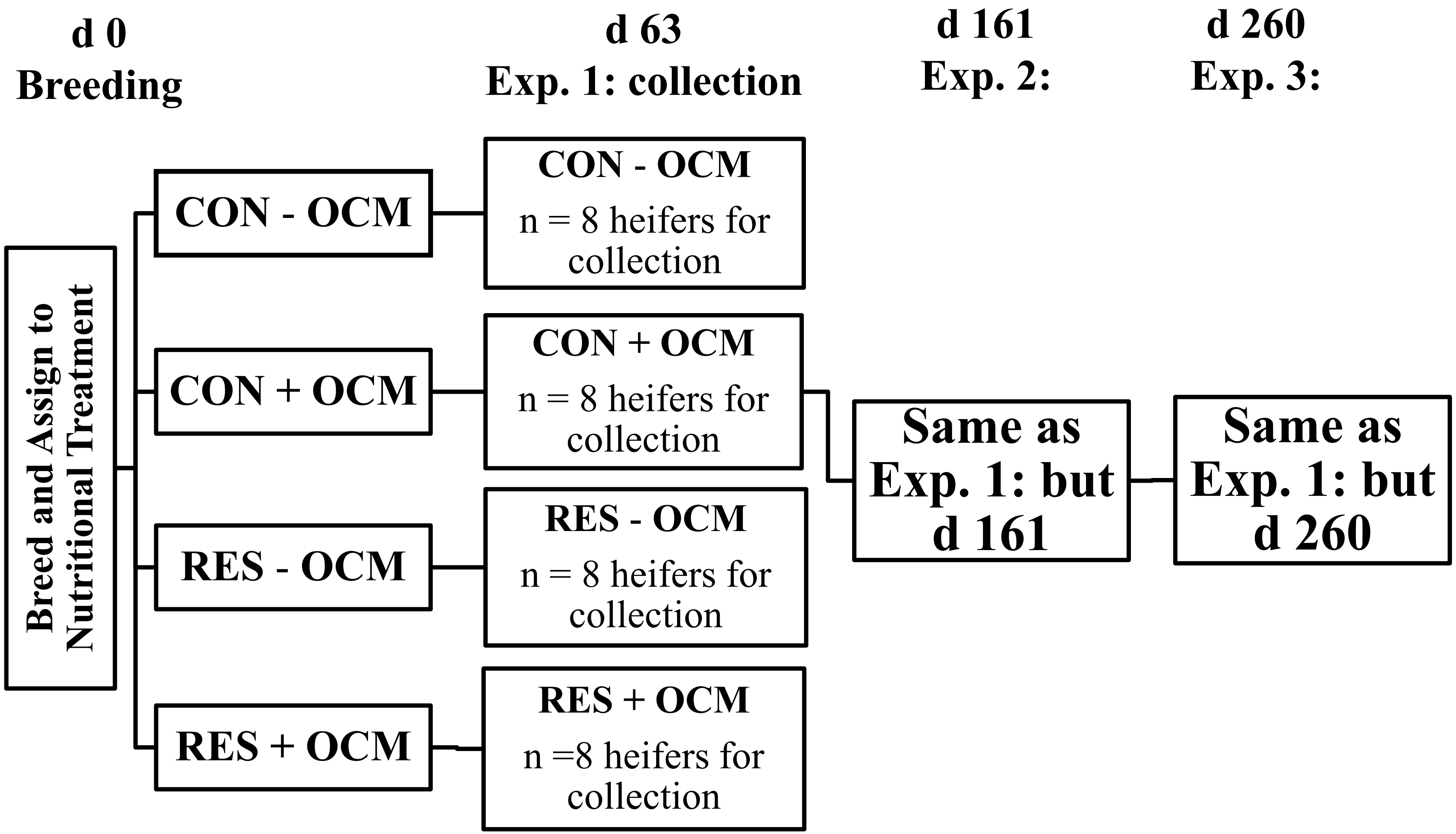
frontiers in Genetics

ORIGINAL RESEARCH
published: 24 February 2022
doi: 10.3389/fgene.2022.812764

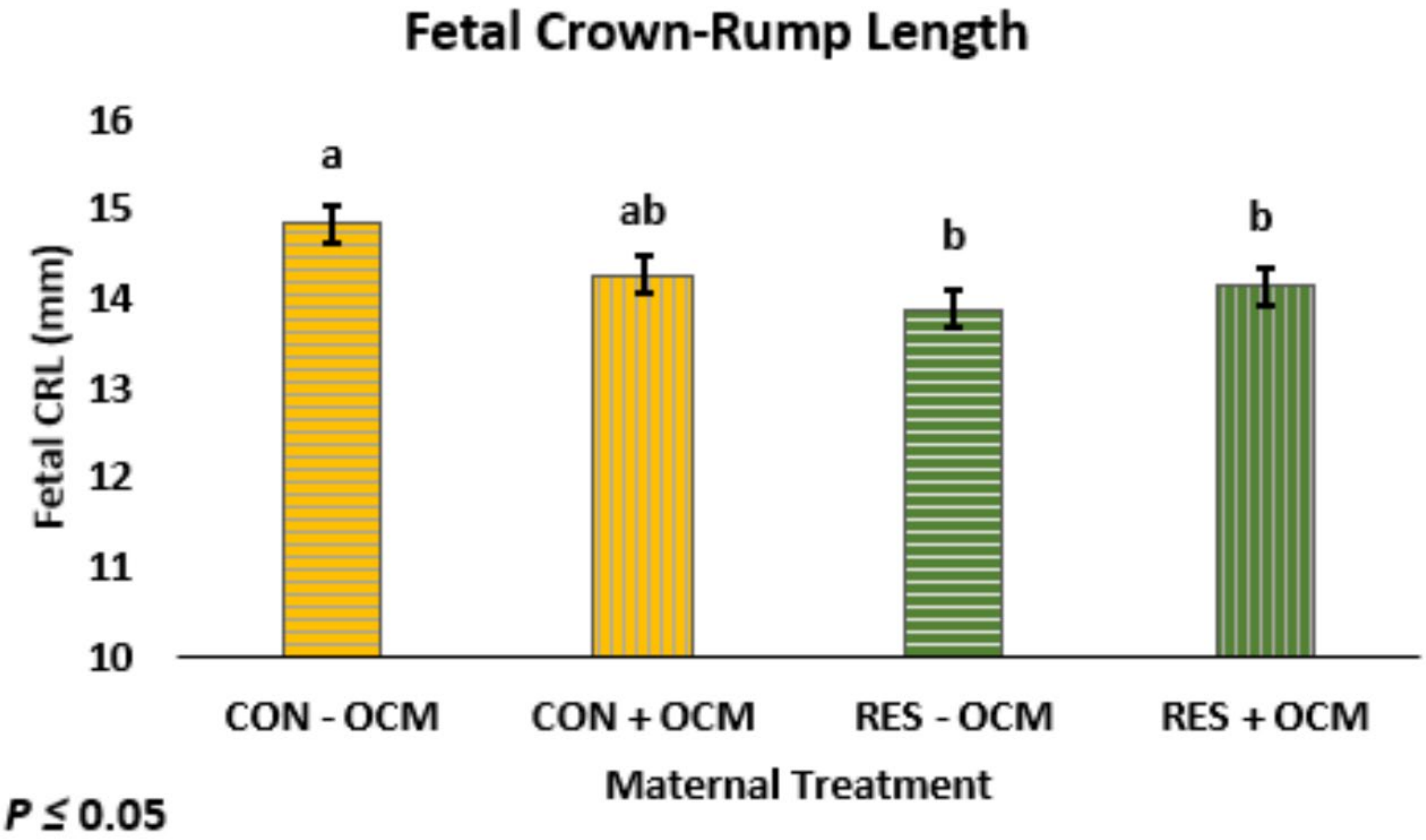
In Vivo Studies Should be Designed to Target Strategic Supplementation

Epigenetic Modifier Supplementation Improves Mitochondrial Respiration and Growth Rates and Alters DNA Methylation of Bovine Embryonic Fibroblast Cells Cultured in Divergent Energy Supply

Matthew S. Crouse[1], Joel S. Caton[2], Kate J. Claycombe-Larson[3], Wellison J. S. Diniz[4], Amanda K. Lindholm-Perry[1], Lawrence P. Reynolds[2], Carl R. Dahlen[2], Pawel P. Borowicz[2] and Alison K. Ward[2]*

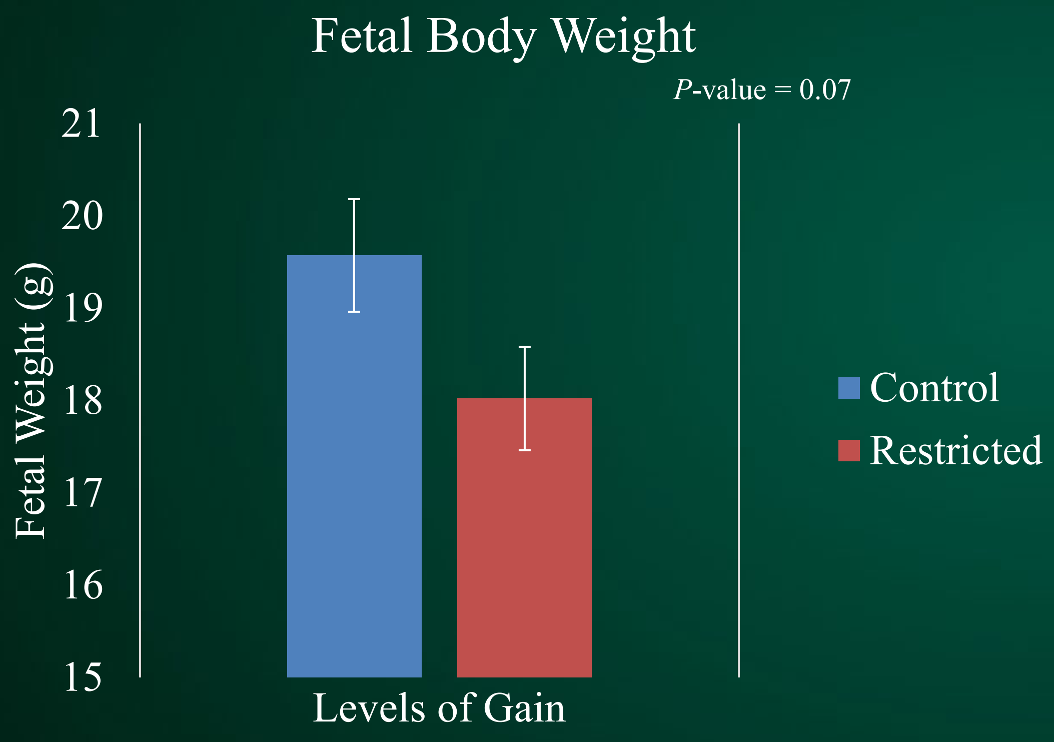


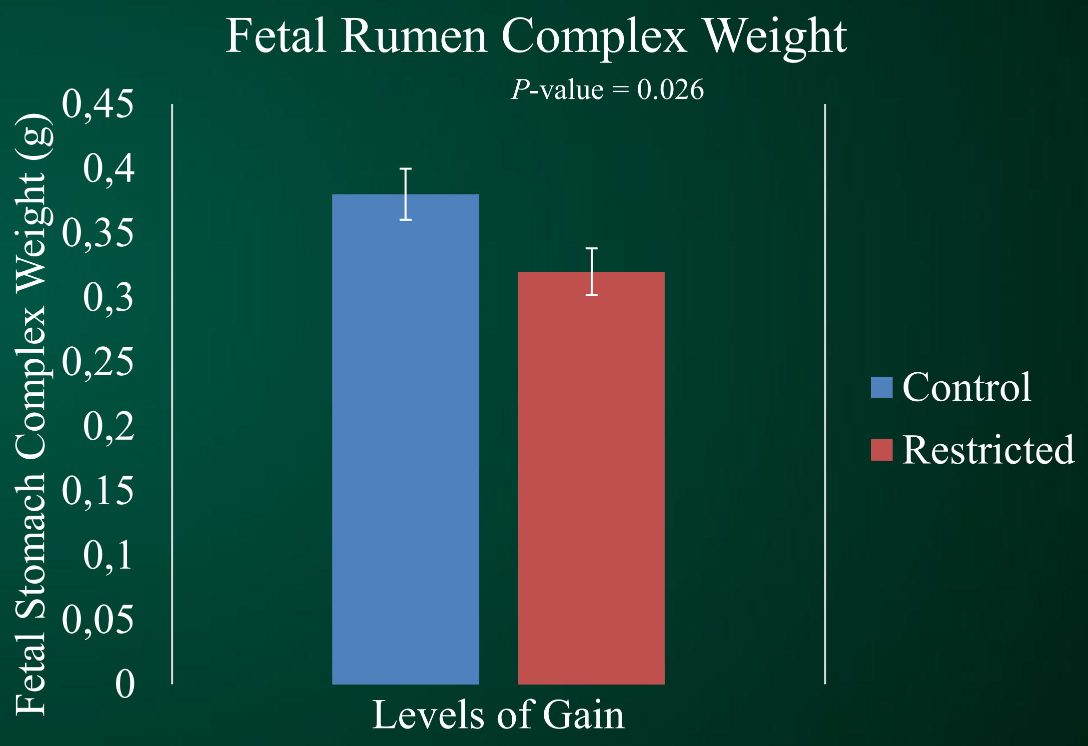
Experimental design schematic for Exp 1, 2, and 3; 2 × 2 factorial (2 rates of gain × 2 levels of OCM); collection days 63, 161, and 260 of gestation n = 32 individually fed pregnant heifers per experiment. **CON**: ADG 0.45 kg/d. **RES**: ADG -0.23 kg/d



Faust et al., 2024

Day 63 Fetal Main Effects





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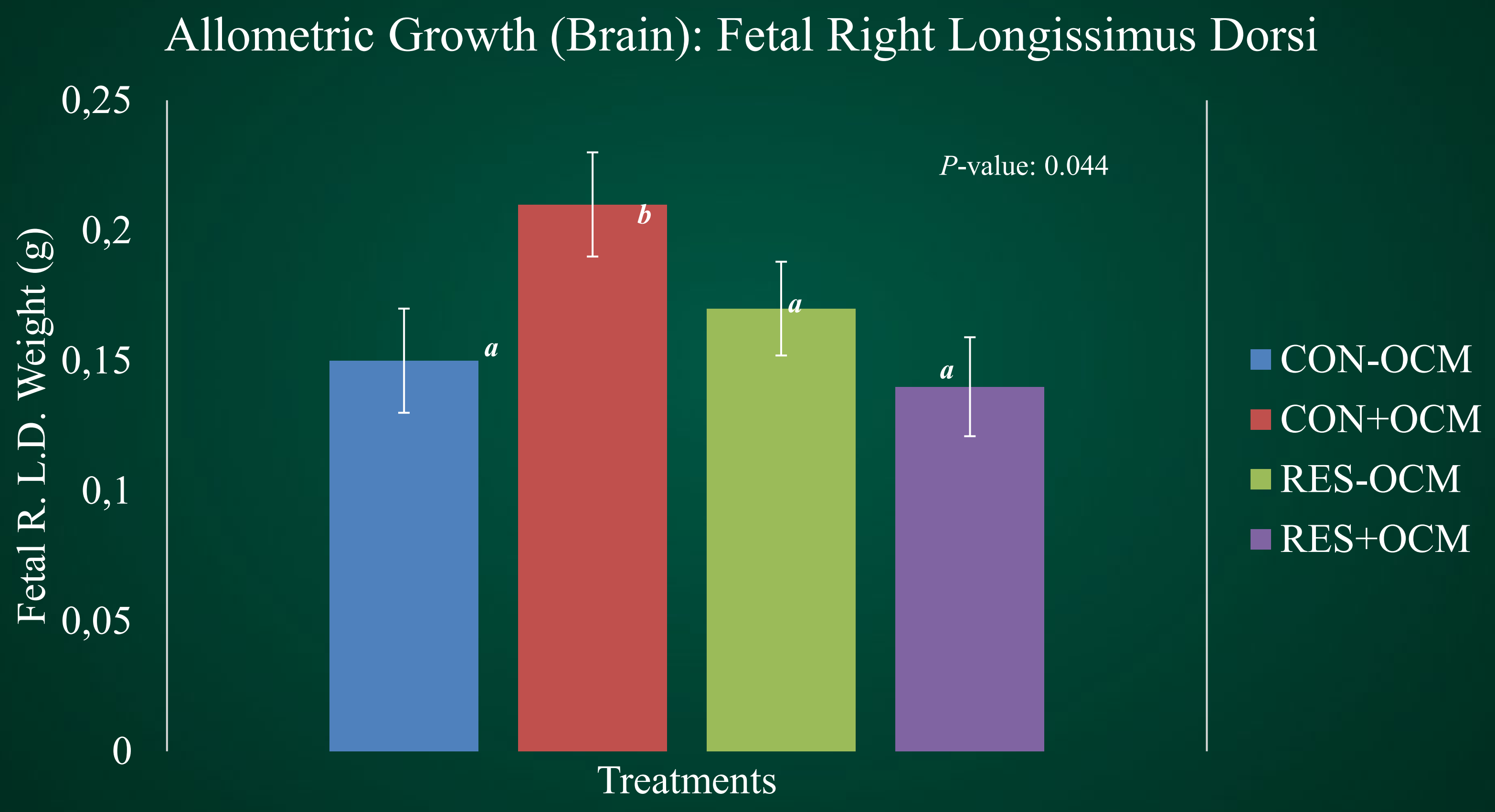
King, 2024

Day 63 Muscle



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King, 2024

Pathways derived from metabolomic analysis with significant enrichment scores for within maternal and fetal liver ($P \leq 0.05$)					
Tissues	Super-pathway	Total number of sub-pathways	Number of enriched sub-pathways		
			Gain	OCM	Gain × OCM
Maternal	Amino acid	15	13	12	6
	Cofactors and vitamins	12	9	3	3
	Carbohydrate	9	8	2	2
	Energy	2	1	1	0
Fetal	Amino acid	15	12	9	7
	Cofactors and vitamins	12	5	3	3
	Carbohydrate	9	4	1	4
	Energy	2	1	0	0

Nutrient restriction and one-carbon metabolite supplementation significantly influence metabolic pathways in maternal and fetal liver tissues at day 63 of gestation (Safain et al., 2024; JAS submitted).

Oxygen consumption rates and respiratory control ratios in isolated mitochondria from fetal day 161 liver samples using coupling assay.

	Restricted		Control		SEM	*P* value		
	-OCM	+OCM	-OCM	+OCM		Gain	OCM	Gain x OCM
State 3 respiration	586^{ab}	482^{a}	437^{a}	646^{b}	52.2	0.88	0.30	**0.004**
State 4o respiration	78.1^{b}	57.2^{a}	64.6^{ab}	72.9^{ab}	7.07	0.87	0.35	**0.04**
***RCR**	7.88	8.74	6.85	9.41	0.99	0.85	**0.08**	0.37

*Values with different superscript letters in the column are significantly different (p <0.05)
*RCR: respiratory control ratio (State 3: State 4o); State 3 and State 4o respiration data are presented as picomoles of O_2 consumed per microgram of mitochondrial protein per minute

Safain et al., 2023

Strategic Supplementation and Rate of Heifer Gain: Objective and Design

- The objective of this study was to evaluate the effects of feeding heifers a vitamin and mineral supplement and targeting divergent rates of weight gain during early gestation on the fetal liver amino acid, carbohydrate, and energy profile at d 83 of gestation.
- Seventy-two crossbred Angus heifers were randomly assigned in a 2 x 2 factorial arrangement to one of four treatments comprising the main effects of vitamin and mineral supplementation (VTM or NOVTM) and feeding to achieve different rates of weight gain (low gain [LG] 0.28 kg/day vs. moderate gain [MG] 0.79 kg/day).

Results

- Findings support greater metabolic activity in fetuses from heifers on an increased rate of weight gain and supplemented with vitamin/mineral.
- Fetal amino acid, carbohydrate, and energy metabolism can be altered by maternal nutrition during the first trimester of gestation, and suggest, along with other data, that these changes manifest in altered fetal size and calf birthweights.

metabolites

MDPI

Article

Vitamin and Mineral Supplementation and Rate of Weight Gain during the First Trimester of Gestation in Beef Heifers Alters the Fetal Liver Amino Acid, Carbohydrate, and Energy Profile at Day 83 of Gestation

Matthew S. Crouse [1,*], Kacie L. McCarthy [2], Ana Clara B. Menezes [3], Cierrah J. Kassetas [3], Friederike Baumgaertner [3], James D. Kirsch [3], Sheri Dorsam [3], Tammi L. Neville [3], Alison K. Ward [3], Pawel P. Borowicz [3], Lawrence P. Reynolds [3], Kevin K. Sedivec [4], J. Chris Forcherio [5], Ronald Scott [5], Joel S. Caton [3] and Carl R. Dahlen [3]

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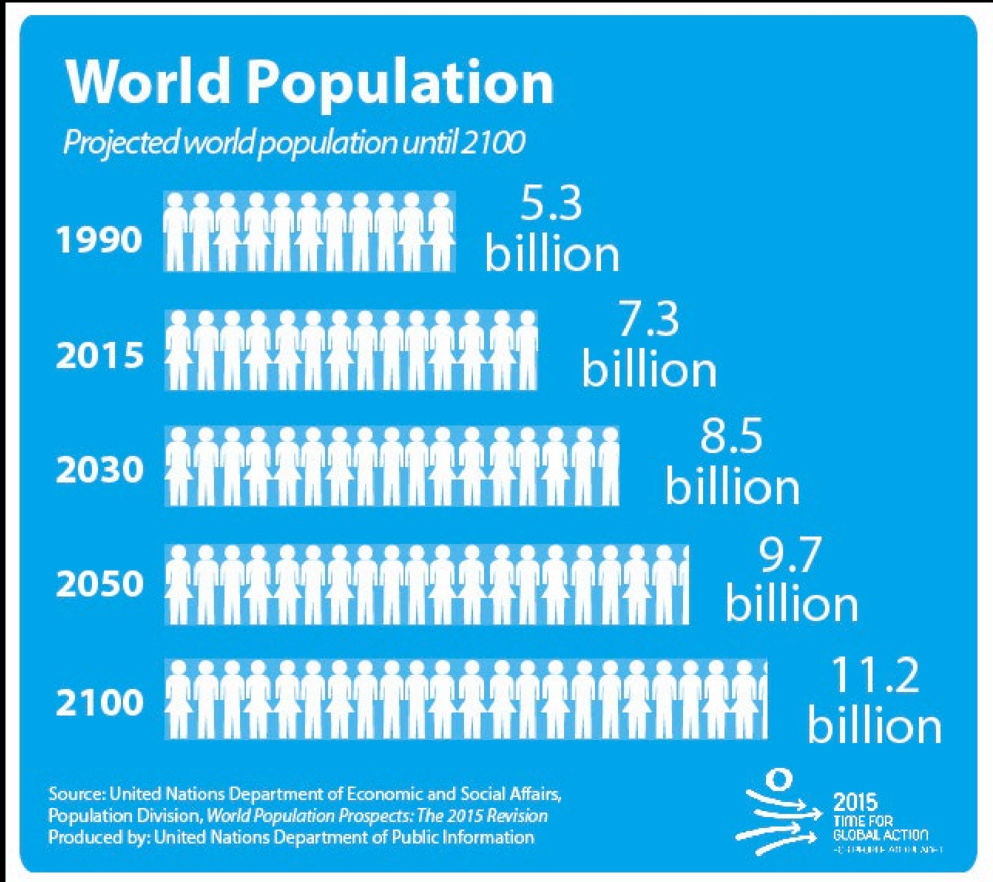
Metabolites **2022**, 12, 696.
https://doi.org/10.3390/metabo12080696

Current, Emerging, and Future Efforts.

- Strategic supplementation of micronutrients?
- Developmental Programming;
  - Mitigating negatives
  - Fostering postitives
- Transgenerational programming outcomes?
- Microbiome and developmental programming?
- Epigenetic regulation and modulation?
- Preconception programming effects?
- What about the bull?

Micronutrient Supply, Developmental Programming, and Strategic Supplementation: Practical Relevance

- Optimal animal growth and production
- Long-term environmental sustainability
- Sustained economic viability
- Increased food security
- Broad societal impacts



Micronutrient Supply, Developmental Programming, and Strategic Supplementation: Practical Relevance

Optimal animal growth and production

Long-term environmental sustainability

Sustained economic viability

Increased food security

Broad societal impacts

Known

Acknowledgements

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National Institutes of Health

Thank you

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North Dakota State University, Fargo!...Where?