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Associations of parity with health disorders and blood metabolite concentrations in Holstein cows in different production systems

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ABSTRACT

Data were obtained from studies in Australia, Canada, and the United States using individual cow data from 28,230 Holstein cows to evaluate associations between parity and disease. Our goal was to develop understanding of disease risks for cows of differing parity. We hypothesized that there would be increased risks of disease and changes in metabolite concentrations with increased parity. Parity ≥5 represented 2,533 cows or 9.0%, parity 4 was 9.8% (2,778), parity 3 as 19.0% (5,355), parity 2 as 28.1% (7,925), and parity 1 was 34.1% (9,639) of the sample. Of these cows, 15.5% were in Australia, 14.7% in Canada, and 69.8% in the United States. Lactational incidence (LI) risk of clinical hypocalcemia increased with parity from 0.1% for parity 1 to 13% for parity ≥5 cows. The marked increase suggests profound differences in metabolism with increased parity. The LI of clinical mastitis was 17.4%. The odds of mastitis increased with parity to 2.5 times greater in parity ≥5 than in parity 1. The LI of lameness increased with parity; specifically, the odds of lameness was 5.6 times greater for parity ≥5 than parity 1. Dystocia incidence was 8.7% and greatest for parity 1 cows. The LI of retained placenta was 7.4% and increased with parity, with the odds for parity ≥5 2.3 times greater than for parity 1. The LI of metritis was 10% and of endometritis 14%, with the greatest odds in parity 1. The LI of clinical ketosis was 3.3% with a marked increase in odds with parity. The prevalence of subclinical ketosis was 26.8% with only cows in parity 1 having lower odds than other parities. Parity ≥5 cows had greater odds (odds ratio = 1.7) of respiratory disease than parity 1 cows, which were lesser than other parities. Metabolite concentrations were evaluated in 5,154 Holstein cows in the precalving, calving, and immediate postcalving data sets. Metabolic measures near peak lactation provided 1,906 observations. Concentrations of β-hydroxybutyrate (BHB) and nonesterified fatty acids increased with parity on d 1 to 3 of lactation and at peak lactation. On d 1 to 3 after calving differences in glucose, nonesterified fatty acids, and BHB indicated a greater reliance on mobilized lipid to export energy to peripheral tissues as BHB for greater parity cows. Differences in concentrations among parity groups were marked at times, for example >0.20 mM in Ca for parity 1 and 2 to parity ≥5 and >0.33 mM for all older parities compared with parity 1 for P on the day of calving. The marked increase suggests profound differences in metabolism with increased parity are probably influenced, in part, by increased production. We found marked differences in concentrations of metabolites with parity that are consistent with reduced reproduction, health, and body condition for higher parity cows. These unfavorable differences in metabolism in Ca, P, glucose, and cholesterol concentrations for higher parity cows also complement the often-substantial differences in disease risk with parity and suggest a need to carefully consider the parity structure in study design. Managers and advisors will need to consider methods to reduce risk of health disorders tailored to cows of different ages.

Key words: parity, disease, longevity, blood metabolites

INTRODUCTION

Many have noted a concern about the longevity of dairy cattle (De Vries and Marcondes, 2020; Dallago et al., 2021). Cows with parity ≥2 in a US-based study (Golder et al., 2019) and in large Australian studies were at 2 times greater risk for many diseases and had reduced odds and hazard of pregnancy than parity 1 cows (Golder et al., 2021). An evaluation of associations of parity with reproductive performance (Lean et al., 2022a), using studies conducted in Australia (**AU**), Canada (**CA**), and the United States (**USA**), found that only 9% of cows were in parity ≥5; additionally, parity 1 cows were 39%, parity 2

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were 27%, parity 3 were 17%, and parity 4 were 9% of the population. Consequently, 30% of cows entering parity 1 would not enter parity 2, 39.0% of parity 2 were lost before parity 3, and 46% of cows entering parity 3 would not enter parity 4 (Lean et al., 2022a). There was increased loss of older cows in early lactation. These findings indicate a need to further evaluate associations among parity, disease, and metabolite concentrations in blood.

Despite many studies that evaluate parity as part of an investigation of associations with disease (Rasmussent et al., 1999; Pötzsch et al., 2003), survival (Rajala-Schultz and Gröhn, 1999), or reproduction (Pryce et al., 1999; Rearte et al., 2018), relatively few studies have focused on associations of these outcomes with parity per se (Erb and Martin, 1980; Erb et al., 1985; Markusfeld, 1987; Bonneville-Hébert et al., 2011).

Although the associations among diseases and parity are important, there is a need to identify potential risk factors that may influence these associations. The pathogenesis of the increased risk of removal for reproductive failure (Lean et al., 2022a) and differences in odds or risk of disease with parity, as well as differences in blood metabolites with parity, may indicate aspects of metabolism that alter with parity.

We conducted a retrospective meta-analysis based on individual cow data to assess the associations of parity and pasture-based or intensively fed systems with health and metabolite concentrations. Our goal is to evaluate the risks for diseases associated with parity using data gathered in 3 countries from 1992 to 2020. We evaluated temporal effects in the statistical models evaluating the disease data. We hypothesize that the odds of the major disorders of dairy cattle and metabolite concentrations will differ with parity. Further, we hypothesized that differences in blood metabolites among parity groups exist before parturition, on the day of calving, 1 to 3 d postcalving, and at peak lactation. There is a need to better understand older dairy cows and the changes in metabolism associated with parity that underpin increases in health risks with increased parity.

MATERIALS AND METHODS

The studies used to produce the database for this study were approved by the relevant Animal Care and Use Committees at the time of conduct.

Study Selection Criteria

The present data were amalgamated from 18 data sets that were a convenience sample of data collected during previous studies. In general, commercial dairies were purposively selected for use in the original studies on the basis of good record keeping and a history of performance that suggested capability of maintaining attention to detail congruent with successful trial conduct. The study contributors had conducted large, prospective studies that allowed a rigorous evaluation of the original study hypotheses. Only Holstein or Holstein-Friesian cattle were analyzed (maximum n = 28,230 for health and 5,154 for metabolite data sets), as few cows of other breeds were in the disease or metabolite databases. Herds were considered to be in different production systems, predominantly pasture-fed or intensively fed. Herds that were predominantly pasture-fed were fed fresh pasture, and silage was the main forage source; additionally, the intensively fed cows were fed a TMR.

Tables 1 and 2 provide details on the prospective studies that were used to produce both a health database (n = 17 studies) and a metabolite database (n = 14 studies), respectively. Study inclusion criteria included being an observational or randomized controlled trial that provided details on parity, health, or blood metabolites. Veterinary diagnosis was used to determine disease for some studies, whereas others used diagnosis by farm staff using standard operating procedures. The studies were conducted between 1992 and 2020 in AU, CA, and USA (Tables 1 and 2).

When an intervention was applied in a herd, treatments within the herd were considered as separate "groups" for statistical analytical purposes. This provided control for treatment effects on study outcomes and was used to reduce the effect of potential differences in laboratory analytical methods used to determine concentrations by evaluating differences to a group mean, rather than the overall mean. Treated and control cows were approximately equal in number for those studies, with the exception of in Golder et al. (2021).

Animal Data

The first lactational incidence (**LI**) of a specific disease (or the point prevalence for ketonemia) is reported here. Consequently, times to relapse or recurrence of the same condition are not reported. Studies ended at variable times; in particular, some observed cows to ≥300 DIM, whereas others ended at 95 DIM (Table 1). The disorders that were recorded and their definitions differed between studies, hence denominators differ for the various reported disorders. The definition for dystocia was variably recorded across studies and, therefore, any recorded calving difficulty was defined as "dystocia," without controlling for the degree of difficulty or degree of intervention required. Lameness in most cases was only recorded if a treatment was administered and

Table 1. Summary of the 17 prospective studies used in the health database including year that the study commenced, country in which it was conducted, type of production system, number of cattle included in this database, intervention used (purpose of study), and the DIM that data were censored

Reference	Study year	Country[1]	Production system[2]	Cow (n)	Intervention	DIM censored[3]
Curtis and Lean (1998)	1992	AU	Pasture	238	Observational	No data
Duffield et al. (1999)	1995	CA	TMR	997	Monensin	95
T. Duffield, K. T. Leslie, J. Tenhag, and A. Peregrine. (Department of Population Medicine, Ontario Veterinary College, University of Guelph, Guelph, Ontario, Canada; unpublished)	1997	CA	TMR	1,139	Anthelmintic	63
LeBlanc et al. (2002)	1998	CA	TMR	977	Vitamin	120[4]
Duffield et al. (2002)	1998	CA	TMR	152	Monensin	120[4]
Moss (2001)	1999	AU	Pasture	705	Observational	No data
I. J. Lean (unpublished)	2003	AU	Pasture	338	Micronutrient	No data
DeGaris et al. (2010a)	2005	AU	Pasture	610	Observational	150
Chapinal et al. (2011)	2006	USA, CA	TMR	2,071	Observational	No data
Gohary et al. (2014)	2011	CA	TMR	592	Bovine somatotrophin[5]	No data
Pinedo et al. (2020)	2013	USA	TMR	11,489	Observational	60
Martinez et al. (2018a)	2014	USA	TMR	32	DCAD and vitamin D	30
H. M. Golder and I. J. Lean (unpublished)	2016	AU	Pasture	15	Enzyme	280
Golder et al. (2019)	2016–2017	USA	TMR	6,395	Enzyme	Not censored
Golder et al. (2021) Exp. 1	2016–2017	AU	Pasture	764	Calcidiol	300
Golder et al. (2021) Exp. 2	2017–2018	AU	Pasture	1,113	Calcidiol	300
H. M. Golder and I. J. Lean (unpublished)	2020	AU	TMR	603	AA	180

[1]AU = Australia; USA = United States of America; CA = Canada.

[2]Pasture = pasture-fed; TMR was intensively fed.

[3]No data = studies only reported that a disorder occurred and did not report the DIM of the occurrence.

[4]Clinical ketosis at 30 d.

[5]Only placebo group included.

included all categories of gait abnormality used in the original studies. Uterine infections diagnosed at <15 DIM were categorized as metritis and those diagnosed at ≥15 DIM as endometritis. Respiratory diseases included the diagnosis of respiratory disease or pneumonia. Both clinical and subclinical ketosis were defined according to the criteria used in the original studies, with the latter being defined based on concentrations of BHB in blood that were associated with increased risks of other disorders, with Pinedo et al. (2010) using BHB > 1.0 mmol/L and Moss (2001) > 0.7 mmol/L for subclinical ketosis.

The metabolite measures were categorized into 4 separate databases as follows: (1) precalving (−3 to −1 d relative to parturition), (2) day of calving, (3) immediate postcalving (1 and 3 d after calving), and (4) "peak lactation" (30 to 110 DIM). Metabolite concentrations were converted to SI units when these were not provided as SI units in the original data.

Sample Size Estimations

The unit of interest in this study was the cow. We targeted a difference in proportions of between 0.05 and 0.15 in parity 1 cows and 0.2 in cows of a greater parity, and with a power of 0.90, and $\alpha = 0.05$, which requires a minimum of 1,210 cows per parity, not accounting for clustering within group. The power calculations were made using Stata (version 17, StataCorp).

For the metabolite data, the power calculation was made post hoc. For a difference in mean metabolite value of 0.5 effect size difference between parities, with $\alpha = 0.05$, allowing for an intraclass correlation of 0.2, and with 10 cows per group for 30 groups, provided a power of 0.95 with 600 cows in total for each comparison. The power calculations were made using *rdpower* in Stata (version 17, StataCorp).

Statistical Analysis

All statistical analysis was conducted using Stata (version 17, Statacorp).

Health Data. The following mixed-effects multilevel model using the *melogit* function provided an evaluation of the odds of disease. The models included cow within group as a random effect.

The Stata 17 User's Guide (StataCorp LLC., 2021) states that the following model represents a series of

Table 2. Summary of the 14 prospective studies used in the metabolite databases including publication details, year that the study commenced, country in which it was conducted, type of calving system, intervention used (purpose of study), and whether data contributed to the precalving, d-0, postcalving, peak-lactation, or all databases[1]

Reference	Study year	Country[2]	Production system[3]	Intervention	Precalving	D 0	Postcalving	Peak
Curtis and Lean (1998)	1992	AU	Pasture	Observational			Y	
Duffield et al. (1998)	1995	CA	TMR	Monensin	Y		Y	Y
LeBlanc et al. (2004)	1998	CA	TMR	Vitamin	Y	Y	Y	
Duffield et al. (2003)	1998	CA	TMR	Monensin	Y	Y	Y	
Moss (2001)	1999	AU	Pasture	Observational				Y
I. J. Lean (unpublished)	2002	AU	Pasture	Protected fat				Y
DeGaris et al. (2010b)	2005	AU	Pasture	Observational	Y	Y	Y	
Chapinal et al. (2011, 2012)	2006	USA, CA	TMR	Observational	Y		Y	
Gohary et al. (2014)	2011	CA	TMR	Bovine somatotrophin[1]	Y		Y	
Pinedo et al. (2020)	2013	USA	TMR	Observational			Y	
Martinez et al. (2018b)	2014	USA	TMR	DCAD and vitamin D	Y	Y	Y	
H. M. Golder and I. J. Lean (unpublished)	2016	AU	Pasture	Calcidiol				Y
Golder et al. (2021), experiment 2	2017–2018	AU	Pasture	Calcidiol				Y
Connelly et al. (2019)	2019	USA	TMR	DCAD, Ca, and sugar	Y	Y	Y	

[1]Precalving = −3 to −1 DIM; d 0 = within 24 h of calving; postcalving = 1 to 3 DIM; peak lactation = (30 to 110 DIM; mean ± SD = 68.7 ± 27.3 DIM). Y = yes, included in the data set.
[2]AU = Australia; USA = United States of America; CA = Canada.
[3]Pasture = pasture-fed; TMR was intensively fed.

M independent clusters, and is conditional on a set of random effects (u_j):

$$\Pr(y_{ij} = 1|x_{ij},\ u_j) = H(x_{ij}\beta + z_{ij}u_j),$$

where $j = 1,\ldots M$ clusters, with cluster j consisting of $i = 1,\ldots n_j$ observations. The responses are the binary-valued y_{ij}, with the convention of treating $y_{ij} = 1$ if $depvar_{ij}$ (the dependent variable) $\neq 0$, and treating $y_{ij} = 0$ otherwise. Pr is the probability for $(y_{ij} = 1|x_{ij},\ u_j)$. The $1 \times p$ row vector (x_{ij}) are the covariates for the fixed effects, analogous to the covariates found in a standard logistic regression model, with regression coefficients (fixed effects) β. The logistic cumulative distribution function is H, and z_{ij} are the covariates corresponding to the random effects. As the logistic cumulative distribution function, H maps the linear predictor to the probability of a success; that is, when $y_{ij} = 1$. The fixed effects tested were parity (1 to ≥5), production system (pasture or TMR), and year of study (1992 to 2020), which was mean centered for ease of interpretation. Interactions of parity with system were evaluated, but sparse or lack of data for some parities and systems limited consistent assessment. Post hoc comparisons of marginal estimates of the odds were made using *pwcompare*.

For metritis, endometritis, ketosis, and subclinical ketosis, antecedent or concurrent clinical conditions were evaluated in the final logistic regression model for each variable that included dystocia, clinical hypocalcemia (**CH**), retained placenta, metritis, and endometritis. These variables did not act as confounders for parity estimates, except for CH on SCK. All logistic models were built using backward stepwise regression, with variables with $P < 0.05$ retained.

Collinearity among variables was subsequently explored for CH, mastitis, and respiratory disease models developed using the *collin* function, which provides the variance inflation factor and condition number. The mean variance inflation factor for the predictor variables parity, system, and year was 1.02, indicating little collinearity. Kendall's tau-b correlations (*ktaub*) were determined for retained placenta, metritis, and endometritis.

Metabolite Data. Initial data evaluation included tabulation of data by categorical outcomes, production of summary statistics, and visual appraisal of metabolite concentrations for normality of distribution. A Shapiro-Wilks test indicated that many of these were not normal; however, examination of centered variables versus residuals for normality of distribution and centered variable against BLUP of the random effects found no aberrant distributions. Consequently, metabo-

lite concentrations were not transformed for analysis. The metabolic variables were centered within group to control for the effects of treatment or study.

The following mixed-effects multilevel model, using the *mixed* function, provided an evaluation of the concentrations of metabolites in blood. The models included cow within group as a random effect. The fixed effects tested were parity (1 to ≥5), production system (pasture or intensively fed), and year of study (1992 to 2020), which was mean centered to provide ease of interpretation. The DIM for precalving, and metabolic measures obtained immediately after calving and at peak lactation, were tested as covariates. Interactions of parity with system were evaluated, but sparse or lack of data for some parity/systems limited consistent assessment. Post hoc comparisons were made using *pwcompare* to test parity differences, and included a statement to provide a Bonferoni adjustment, and *contrast* to evaluate the overall effect of parity.

The effects of group within system were examined for metabolites as random effects using the *gllamm* function to partition the variance components of the nested model (Rabe-Hesketh and Skrondal, 2005), but the random effect of system did not explain variation in responses beyond that explained by group alone for metabolic outcomes. The 2-level model that was used also did not have significant variance associated with group, perhaps due to the centering of the variables. All mixed models were built using backward stepwise regression with variables with $P < 0.05$ retained.

RESULTS AND DISCUSSION

We had a total of 28,230 Holstein cows in the health data set. We had 2,533 cows (9%) in parity ≥5, 10% (2,778) in parity 4, 19% (5,355) in parity 3, 28% (7,925) in parity 2, and 34.1% (9,639) in parity 1. Of these cows, 15.5% were in AU, 14.7% in CA, and 69.8% in the USA. There were 86.6% of cows fed intensively and 13.4% in pasture-dominant feeding systems. There were 17 studies in 163 herds, containing 255 separate analysis groups. The disorder that was most consistently recorded in the included studies was mastitis, with 27,857 Holstein cows evaluated. Table 1 provides details of the cow numbers available in each study.

For the metabolite data, we had a total of 5,154 Holstein cows, if the precalving, calving, and immediate postcalving metabolic data sets were combined; however, few, if any, cows contributed to all measures. Cows in parity 1 were 26.9% (1,385), parity 2 were 27.7% (1,431), parity 3 were 21.6% (1,115), parity 4 were 11.8% (608), and parity ≥5 were 615 cows or 11.9% of the sample population. Of these cows, 273 or 5.3% were in AU, 4,774 or 92.6% in CA, and 107 or 2.1% in the USA. Of these, only the 5.3% in AU were fed on pasture, and the rest were intensively fed. The metabolite measures precalving had 10 studies available for evaluation, of which the greatest number used for a single variable was 8; specifically, the greatest number of studies available to assess a single metabolite within 24 h of calving was 6 studies. For metabolite measures from d 1 to 3 after calving, the greatest number of studies available to assess a single metabolite measured on the day of calving was 9.

For peak lactation metabolite measures, 5 studies were available, containing 1,906 cows in 73 groups. The observations were between 30 and 110 DIM (mean 64.6, SD 15.2), with 90% of observations lying between 44 and 99 DIM. Cows in parity 1 were 27.7% (527), parity 2 were 25.5% (486), parity 3 were 21.1% (403), parity 4 were 11.8% (225), and parity ≥5 were 265 cows or 13.9% of the sample population. Of these cows, 1,016 (53.3%) were in pasture-dominant feeding systems in AU, and 890 or 46.9% were fed intensively in CA. The random effect of group contributed < 1% of the variance in models, probably reflecting the centering of the metabolic measures within group.

Limitations This study is an example of meta-analysis using raw data from original studies and provides the best form of evidence, despite limitations that include variable sensitivity and specificity of reporting of conditions; in fact, some studies based on veterinary diagnosis following farmer identification may have greater severity resulting in lower sensitivity of detection, but more likely to be highly specific, whereas other studies based on farmer diagnosis may be lacking in both sensitivity and specificity because farms often underreport disease and diagnosis might be less accurate. Interventions used in the original studies are noted in Tables 1 and 2 and were used to define groups within herds to allow for comparisons within group. Definitions of diseases also differed among studies, including retained placenta and dystocia. Further, potentially confounding factors such as month of calving were not considered due to the clustering of calving over relatively brief periods in many studies. These limitations may influence the estimates of LI or point prevalence, but are unlikely to differentially influence the estimates of associations with parity. Understanding the physiological mechanisms that underlie the risks of all the disorders studied, including CH and subclinical hypocalcemia with parity and how these change with parity, are influenced by a bias resulting from the loss of cows from the population. The role of selection bias is potentially significant in interpretation of our results and many of the studies cited in this paper. There is the potential for cows with unfavorable attributes to be removed from herds, possibly causing

"survivor bias." This means that the cows that remain in study or the herd long enough to meet the inclusion criteria have more or better health, milk yield, and reproductive performance than removed cows, resulting in biased apparent associations. Studies evaluating metabolism are seldom conducted with sufficient duration to evaluate characteristics of the original cohort of cows before initial calving, and then evaluate differences in metabolism and risk over multiple lactations. We also have differences in the observation period, resulting in differences in right censoring time for studies that will influence the estimated incidence of diseases that occur in later lactation. Lastly, for the metabolic data, different populations contribute to the different times at which measures are evaluated. This makes comparisons of parity responses at different times of sampling less robust than if the populations were identical and compared differences in concentrations among sampling times. Although the potential for bias highlights a need for cautious interpretation of findings, the marked differences in associations among parity for the health disorders investigated, and blood metabolite measures indicates (1) the need for prospective cohort studies to investigate these associations and their pathogenesis, (2) to elucidate further the role of milk and milk solids yields and parity effects, and (3) a need to carefully control for parity in study design and analysis.

CH

The overall LI was 2.7% with a mean time to diagnosis from calving of 1.76 d (SD 8.00), and the median time to diagnosis was the day of calving, with an interquartile range within the day of calving. The LI increased from 0.13% for parity 1 cows to 12.6% for parity ≥5. Reinhardt et al. (2011) estimated the incidences of CH in the USA in 2002 were 1% for parity 1, 4% for parity 2, 6% for parity 3, 10% parity 4, 8% parity 5, and 13% for parity 6, with an overall incidence of 5%. Similarly, Pacheco et al. (2018) reported an incidence of 0.07%, for first lactation, 0.30% for second lactation, and 11.2% for cows in parity ≥5 in 2 herds in Florida. The odds of CH increased with parity and was greater for TMR herds [odds ratio (**OR**) = 1.80; $P < 0.001$; Table 3]. The increases in odds of CH with parity were large, with parity 3 having 3.5 times, parity 4 having 8.6 times, and parity ≥5 having 20.2 times greater odds of CH than cows in parity 2. Odds of CH for older cows are compared with parity 2 cows, given the anticipated extremely low incidence in parity 1. The random effect of group explained 9% of the variance, a greater proportion than that of the other health outcomes in this study. This high percentage of variance may reflect that several of the studies evaluated interventions to reduce hypocalcemia. The decrease in odds of CH with study year may reflect interventions associated with control of CH in the studies used and greater adoption of methods to control CH (Lean et al., 2006; Wilkens et al., 2020). We are not aware of groups in this study that differed in diet for the nulliparous and parous cows.

The marked phenotypic increase in risk or odds with parity is of compelling importance. This increased risk of CH is associated with a decreased capacity to mobilize Ca from bone (Van Mosel et al., 1993b). Rodney et al. (2018b) found marked differences in vitamin D metabolites both pre- and postpartum between nulliparous and pluriparous cows, suggesting impaired vitamin D metabolism in greater parity cows. Serotonin, which can stimulate parathyroid hormone-releasing peptide in the mammary gland, was greater in serum of the nulliparous cows precalving. The nulliparous cows also had greater ionized and total Ca concentrations in serum after calving than that of the pluriparous cows. Importantly, plasma concentrations of crosslaps and osteocalcin (undercarboxylated and carboxylated) were markedly higher after calving in the primiparous cows (Rodney et al., 2018b), indicating a more active bone mobilization and metabolism than that of the older cows. Despite those differences in metabolic measures, the older cows produced 9 g of Ca/d more in colostrum, indicating the role of increased milk production in CH for greater parity cows. Reinhardt et al. (1988) proposed that there may be a reduced number of osteoclasts and a reduced resorptive bone surface in older cattle, a hypothesis consistent with some of the observations of Rodney et al. (2018b). However, the differences in vitamin D metabolites between parity groups also suggest that either feedback between bone hormones and vitamin D metabolites (Rodney et al., 2018c) or the differences in vitamin D metabolites observed for the different parities (Rodney et al., 2018b) may also increase the risk of hypocalcemia. Lastly, age may possibly impair uptake of Ca through mechanisms that reflect damaged absorption sites, such as the rumen or intestine caused by acidosis and other conditions.

Mastitis

Mastitis cases occurred at a median of 26 (interquartile range 6 to 62 d) and mean of 47.1 (SD 57.2) DIM. However, it is important to note that some studies did not evaluate the later lactation period, and 4 studies were conducted at <100 DIM.

We found a monotonic increase in the odds of mastitis with increased parity (Table 3). The overall LI was 17.4% and the effect of group accounted for 6% of the variance in mastitis. In contrast to CH, the odds of mastitis increased only moderately with parity (Table

Table 3. Associations of parity, year, and production system with health disorders from separate multilevel logistic regression models for each disorder[1]

		Parity[2] (*P*-value)						
Disorder	n	2	3	4	≥5	Study year	Production system[3]
Clinical hypocalcemia[4]	15,793	—	3.52 ± 0.74^{bde} (<0.001)	8.61 ± 1.78^{bc} (<0.001)	20.02 ± 3.94^{bcd} (<0.001)	0.95 ± 0.01 (<0.001)	1.80 ± 0.40 (0.008)
Mastitis	27,857	1.16 ± 0.05^{acde} (0.001)	1.69 ± 0.08^{abde} (<0.001)	1.91 ± 0.11^{abce} (<0.001)	2.46 ± 0.15^{abcd} (<0.001)	1.02 ± 0.01 (0.005)	NS
Lameness	26,464	1.55 ± 0.10^{acde} (<0.001)	3.09 ± 0.21^{abde} (<0.001)	4.32 ± 0.34^{abce} (<0.001)	5.63 ± 0.48^{abcd} (<0.001)	1.07 ± 0.02 (<0.001)	1.83 ± 0.40 (0.006)
Dystocia	26,653	0.55 ± 0.03^{ae} (<0.001)	0.49 ± 0.04^{ae} (<0.001)	0.50 ± 0.05^{ae} (<0.001)	0.70 ± 0.07^{abcd} (<0.001)	0.226 ± 0.3 (<0.001)	NS
Retained placenta	27,607	1.49 ± 0.10^{acde} (<0.001)	1.85 ± 0.13^{abe} (<0.001)	2.01 ± 0.17^{ab} (<0.001)	2.34 ± 0.20^{abc} (<0.001)	0.97 ± 0.01 (<0.001)	NS
Metritis	27,571	0.57 ± 0.02^{a} (<0.001)	0.55 ± 0.03^{a} (<0.001)	0.52 ± 0.03^{a} (<0.001)	0.59 ± 0.04^{a} (<0.001)	1.07 ± 0.02 (<0.001)	2.80 ± 0.67 (<0.001)
Endometritis	22,412	0.85 ± 0.04^{a} (0.001)	0.91 ± 0.06 (0.109)	0.81 ± 0.06^{a} (0.007)	0.97 ± 0.08 (0.738)	1.05 ± 0.023 (0.016)	NS
Displaced abomasum	25,721	1.50 ± 0.19^{acde} (0.002)	3.97 ± 0.46^{abe} (<0.001)	3.66 ± 0.51^{ab} (<0.001)	2.92 ± 0.45^{abc} (<0.001)	0.96 ± 0.01 (0.004)	3.06 ± 1.48 (0.021)
Clinical ketosis	12,593	1.47 ± 0.26^{acde} (0.029)	3.90 ± 0.65^{ab} (<0.001)	3.73 ± 0.73^{ab} (<0.001)	4.89 ± 0.96^{ab} (<0.001)	1.12 ± 0.03 (<0.001)	NS
Subclinical ketosis	11,964	1.06 ± 0.06^{cde} (0.343)	2.05 ± 0.13^{ab} (<0.001)	1.83 ± 0.15^{ab} (<0.001)	1.50 ± 0.14^{ab} (<0.001)	0.04 ± 0.02 (<0.001)	136.36 ± 93.31 (<0.001)
Pneumonia/respiratory	20,758	1.49 ± 0.18^{a} (0.001)	1.53 ± 0.21^{a} (0.002)	1.54 ± 0.26^{a} (0.009)	1.72 ± 0.32^{a} (0.004)	NS	NS

[a]Differs from parity 1 at $P < 0.05$.
[b]Differs from parity 2 at $P < 0.05$.
[c]Differs from parity 3 at $P < 0.05$.
[d]Differs from parity 4 at $P < 0.05$.
[e]Differs from parity 5 at $P < 0.05$.
[1]The odds ratio ± SE and *P*-values from each model including parity, study year, and production system are reported. Nonsignificant (NS) values were removed from the model.
[2]The referent is parity 1.
[3]The referent is pasture-fed.
[4]The referent is parity 2.

Continued

3). The increase in risk of mastitis with increased parity has been observed (Lucey and Rowlands, 1984; Barkema et al., 1998; Zadoks et al., 2001; Berry and Meaney, 2005); however, parity 1 cows may have increased risk of mastitis in early lactation compared with cows of higher parity (Barkema et al., 1998; Berry and Meaney, 2005). Estimates of the increase in the odds of mastitis with increased parity in this study (Table 3) are very similar to those of Lucey and Rowlands (1984). The physiological basis for the increase in odds of mastitis with parity may reflect physical changes for the mammary gland, with increases in size (Klaas et al., 2004) and changes in teat shape (Guarín and Ruegg, 2016) that may increase risk of trampling, milking machine failure, or leakage. Exposure to teat trauma during milking increases with parity. Although responses to combined treatments at dry off with intramammary antibiotics and teat sealant reduced the relative risk of clinical mastitis by 48% over untreated controls (Rabiee and Lean, 2013), a substantial proportion of the cow population remained susceptible to subsequent clinical mastitis. Metabolic changes associated with parity include a greater risk of clinical and subclinical hypocalcemia (Reinhardt et al., 2011) and increased risks of ketosis (Table 3; Dohoo et al., 1984; Gröhn et al., 1989). Hypocalcemia is associated with impaired immune function (Ducusin et al., 2003; Kimura et al., 2006), reduced muscle contractility including the teat sphincter (Goff, 2008), and increased risk of mastitis (Curtis et al., 1983). Ingvartsen and Moyes (2013) reviewed the potential for ketone bodies to inhibit chemotaxis, phagocytosis, the oxidative burst, reactive oxygen metabolite production, lymphocyte blastogenesis, and IgM secretion, indicating the potential for ketonemia to increase mastitis risk. However, the relationship between mastitis and ketosis may be bidirectional (Horst et al., 2021). Bradford et al. (2015) noted the pro-inflammatory actions of LPS released in mastitis, metritis, ruminal acidosis, and other conditions prevalent in the transition. Lean et al. (1994) found that cows with clinical ketosis had concurrent disease, whereas ketonemic cows with similar BHB and nonesterified fatty acid (**NEFA**) concentrations were able to sustain greater milk production and health similar to non-ketonemic cows. Similarly, increased concentrations of serum amyloid A, haptoglobin, and LPS were found in ketotic cows compared with their healthy counterparts before calving (Abuajamieh et al., 2016), findings consistent with other works (Bertoni et al., 2008). Lastly, some pathogens including *Staphylococcus aureus* have an extended duration of infection and are refractory to treatment. Consequently, the increased odds of mastitis may reflect the combined effects of increased exposure to milking, conformation

changes with age, and changes in metabolism resulting in reduced immune competence or immunosenescence.

Lameness

The mean days to lameness was 62.2 (SD 53.6) with a median of 45 d (Interquartile range 37 to 56 d). The LI of lameness was 9.1%; however, this should be interpreted with caution as only 1 study focused on lameness. Under-reporting of the condition is likely and depends on the definition of the condition used in each study and duration of a study; particularly, our recorded treated-based estimate of lameness is likely to be specific but under-estimated. Estimates of the prevalence of lameness ranged from 7 to 48% with a mean of 25% in a literature review (I. J. Lean and H. M. Golder, unpublished). Lactational incidence differs from prevalence as there can be a prolonged duration of lameness and recurrence of the condition. Whay (2002) estimated a 59-d duration of lameness in 1 herd, suggesting that the LI estimates in this study could be consistent with prevalence estimates from literature, depending on the duration of lameness.

The increase in odds of lameness was monotonic and marked, with parity ≥5 cows having 5.6 times greater odds of lameness than parity 1, similar to others (Pötzsch et al., 2003; Sogstad et al., 2005; Bicalho et al., 2009). There was an increase in the odds of lameness for TMR cows and an increase in the odds with calendar year (Table 3). Only 4% of the variance in odds of lameness was explained by the effect of group. Hoedemaker et al. (2009) found that the highest prevalence of sole ulcers was around peak lactation. Bicalho et al. (2009) speculated that in early lactation, lactating cows mobilized fat from the digital cushion and suggested that low BCS may be a risk factor for lameness. Bicalho et al. (2009) also found that prevalence of sole ulcers and white line disease was negatively associated with thickness of the digital cushion, and thickness of the digital cushion was positively associated with BCS. There is limited support for this hypothesis from Westin et al. (2016), who found an association between prevalence of lameness and low BCS; however, this association is bidirectional as lameness reduces BCS. We found that increased parity is associated with increased BW and lower BCS (Lean et al., 2022b), and this may influence the odds of lameness in greater parity cows.

Peri-parturient physiological and metabolic changes could further weaken or increase elasticity of the connective tissue component of the suspensory apparatus (Ossent, 1999; Tarlton et al., 2002) and increase the mobility of the distal phalanx. Movement of the distal phalanx could compress the corium beneath the distal phalanx and increase the risk of sole ulcer and white line disease (Lean et al., 2013). Increased energy density of the diet can increase the risk of lameness (Manson and Leaver, 1988a,b), and Bramley et al. (2013) demonstrated that herds with a higher prevalence of acidosis had a higher prevalence of lameness. Griffiths et al. (2018) found an association between the amount of concentrate fed and prevalence of lameness in herds. Higher parity cows have higher production than parity 1 cows and would have greater intake of diet in TMR systems; however, these cows may have been selectively fed more concentrates in the milk parlor in pasture-fed studies compared with those of parity 1. The higher allocation of concentrate to older cows may explain part of the increased risk in lameness; however, higher BW, lower BCS, and other changes in metabolism, including mineral metabolism, exposure to infrastructure including concrete for TMR systems and laneways for pasture-based groups, should not be discounted as potential factors influencing the difference in lameness with increased parity.

Dystocia

Dystocia was evaluated in 26,653 cows. The LI of 11.3% was greater in parity 1 than all other parities. Interestingly, TMR cattle had substantially lesser odds of dystocia (OR = 0.266), and, when accounted for, parity ≥5 cows had greater odds of dystocia than other parities, except parity 1 (Table 3). Further, the 22% of variance was attributable to group, indicating that environment and management play a strong role in dystocia risk. If compliance with reporting the condition differed with study, one might expect more intensively observed TMR-fed cows to have a higher apparent incidence. However, there may have been less well-grown heifers entering some pasture-fed study herds, which could increase the risk of dystocia. The greater odds of dystocia for cows in parity ≥5 may reflect the effects of hypocalcemia on uterine motility (Al-Eknah and Noakes, 1989). Cows with milk fever had 7.2 greater odds of dystocia (Curtis et al., 1985).

Retained Placenta

The LI assessed in 17,607 cows for retained placenta was 7.4%; however, for parity 1, it was 5.3% and for parity ≥5, it was 10.3%. Only 2.9% of the variance in retained placenta was explained by the group. Increased odds of retained placenta with age have been identified (Curtis et al., 1985; Mahnani et al., 2021). Mahnani et al. (2021) controlled for many risk factors for retained placenta in a large study of Holstein cows, and these found very similar increases in the odds of retained placenta with parity to those in the present

review. Risk factors for retained placenta include hypocalcemia, greater odds of retained placenta for parities >1, and increased odds for parity ≥4 cows (Table 3). Although control of hypocalcemia by use of acidogenic diets precalving has reduced incidence of retained placenta (Lean et al., 2019; Santos et al., 2019), hypocalcemia is not the only factor that may increase the risk of retained placenta with increased parity. Associations between lower BCS at calving and retained placenta have been identified (Curtis and Lean, 1998; Qu et al., 2014). Antioxidant status and treatments, particularly vitamin E and selenium, can reduce placental retention (Trinder et al., 1969; Eger et al., 1985; LeBlanc et al., 2002), and concentrations of plasma retinol and serum albumin that were associated with increased retained placenta decreased with increased parity (Curtis and Lean, 1998).

Metritis

The odds of metritis was greater in parity 1 cows than other parities, which did not differ from each other (Tables 3 and 4). Our analysis included 27,571 cows, of which 19.0% had metritis at mean 6.4 (SD 2.5) and median 6 DIM; additionally, group explained 7% of the variance. The TMR-fed cows had 2.8 times greater odds of metritis, in contrast with retained placenta for which system was not significant. Metritis was a key outcome in several of the studies (Curtis, 1997; LeBlanc et al., 2002; LeBlanc et al., 2004; Pinedo et al., 2020), which might have a greater sensitivity of detection, but the LI in our data is similar to that of others (Bartlett et al., 1986). Retained placenta is a major risk factor for metritis and endometritis; however, the direction of the odds of metritis differed from the odds of retained placenta. The increased risk of metritis for parity 1 cows may reflect a greater risk of dystocia, possible obstetrical interventions, and associated reproductive tract damage. However, it is remarkable that the incidence is so similar for parity 2 through ≥5, given the pattern of placental retention.

Endometritis

Parity 1 cows had the highest LI of endometritis (14.7%) in the 22,412 cows evaluated, with a mean of 36.4 (SD 37.6) and median of 25 DIM, but the odds of endometritis only differed from parity 2 and 4 cows (Table 3). Only 5% of the variance in endometritis was associated with group. We acknowledge that the case definitions of what we describe here as endometritis were heterogeneous and include purulent vaginal discharge ("clinical endometritis") and endometrial inflammation diagnosed by cytology, among others. Given the strong association between metritis and endometritis and the challenges with the definition of these conditions, the similarity in patterns of association with parity is unsurprising. Kendalls tau-b correlations for retained placenta, metritis, and endometritis were highly significant ($P < 0.001$), and cows with retained placenta had 4 times greater odds of endometritis ($P < 0.001$). However, the differences among parities in the odds of retained placenta, metritis, and endometritis raise questions about differences in risk factors for these highly correlated disorders. Parity 1 cows are slower to return to cyclicity than older cows (Rhodes et al., 2003), and this may influence the capacity to clear infection or allow infection to establish. The greater milk production of parity >1 cows does not appear to have impaired their capacity to clear or avoid metritis and endometritis.

Displaced Abomasum

Of the 25,721 observations, 2.6% of lactations resulted in displaced abomasum at a mean of 16.2 (SD 21.6) and median of 10 DIM. Parity 1 cows had the least odds of displaced abomasum and parity ≥4 cows had lesser odds than parity 3 cows, which had the greatest odds (Table 3). Parity 2 cows also had lesser odds of displaced abomasum compared with older cows. Only 2.7% of the variance in displaced abomasum was explained by group. The odds of displaced abomasum was greater for TMR cows (OR = 3.06; Table 3). Clinical hypocalcemia is a risk factor for displaced abomasum (Curtis et al., 1985), and hypocalcemia reduces smooth muscle contractility (Jørgensen et al., 1998) and feed intake (Goff and Horst, 1997), which could increase the risk of displaced abomasum LeBlanc et al. (2005); however, they did not identify hypocalcemia as a risk factor for displaced abomasum, rather concentrations of NEFA and BHB were greater before calving in cows that subsequently developed displaced abomasum, suggesting that inappetence or lipid mobilization disorders are also important in the pathogenesis of displaced abomasum. Stengärde et al. (2010) similarly identified NEFA, BHB, and reduced insulin sensitivity in cows with displaced abomasum, and found increased haptoglobin concentrations indicating an inflammatory response.

Clinical Ketosis

Clinical ketosis, which is variably defined in the studies that form this database, was evaluated in 12,593 cows that had a LI of 3.3%. The mean time to ketosis was 9.6 (SD 10.2) and the median time was 5 DIM. We noticed a marked increase in the odds of clinical ketosis

Table 4. Description of serum or plasma concentrations of metabolic markers from 14 studies described in Table 2, including the number of datapoints included, raw means ± SD by parity, and total mean across parities

		Parity					
Measure[1]	n	1	2	3	4	≥5	Total
Glucose (m*M*)							
−3 to −1 DIM	790	3.80 ± 0.71	3.45 ± 0.78	3.33 ± 0.72	3.41 ± 0.78	3.38 ± 0.67	3.50 ± 0.76
d 0	207	5.00 ± 1.21	4.40 ± 1.00	4.78 ± 1.80	4.54 ± 1.61	4.30 ± 0.87	4.65 ± 1.38
1 to 3 DIM	1,416	3.44 ± 0.76	3.14 ± 0.74	3.13 ± 0.76	3.12 ± 0.81	3.33 ± 0.97	3.24 ± 0.80
Peak milk	1,554	3.50 ± 0.50	3.25 ± 0.55	3.29 ± 0.49	3.32 ± 0.51	3.35 ± 0.47	3.36 ± 0.52
NEFA[2] (m*M*)							
−3 to −1 DIM	1,772	0.41 ± 0.29	0.32 ± 0.24	0.39 ± 0.35	0.42 ± 0.34	0.47 ± 0.41	0.39 ± 0.32
d 0	178	0.73 ± 0.39	0.71 ± 0.41	0.76 ± 0.47	0.10 ± 0.39	0.92 ± 0.47	0.79 ± 0.43
1 to 3 DIM	1,508	0.65 ± 0.39	0.65 ± 0.42	0.74 ± 0.43	0.82 ± 0.53	0.84 ± 0.45	0.71 ± 0.44
Peak milk	694	0.46 ± 0.20	0.44 ± 0.21	0.51 ± 0.24	0.52 ± 0.29	0.52 ± 0.27	0.48 ± 0.24
BHB (m*M*)							
−3 to −1 DIM	1,787	0.58 ± 0.31	0.54 ± 0.20	0.54 ± 0.27	0.58 ± 0.28	0.62 ± 0.35	0.56 ± 0.28
d 0	178	0.68 ± 0.28	0.67 ± 0.19	0.69 ± 0.37	0.80 ± 0.20	0.77 ± 0.30	0.70 ± 0.28
1 to 3 DIM	2,167	0.78 ± 0.47	0.87 ± 0.66	1.02 ± 0.79	1.17 ± 0.86	1.24 ± 1.23	0.96 ± 0.78
Peak milk	920	0.67 ± 0.25	0.76 ± 0.34	0.78 ± 0.47	0.86 ± 0.43	0.86 ± 0.71	0.77 ± 0.43
Cholesterol (m*M*)							
−3 to −1 DIM	509	2.12 ± 0.52	2.04 ± 0.40	2.06 ± 0.49	2.01 ± 0.40	2.12 ± 0.45	2.08 ± 0.46
1 to 3 DIM	511	1.97 ± 0.48	1.91 ± 0.37	1.89 ± 0.34	1.82 ± 0.30	1.74 ± 0.39	1.89 ± 0.40
Peak milk	693	5.46 ± 1.49	5.86 ± 1.72	5.65 ± 1.63	5.59 ± 1.64	5.03 ± 1.45	5.54 ± 1.60
Ca (m*M*)							
−3 to −1 DIM	1,780	2.39 ± 0.27	2.37 ± 0.29	2.32 ± 0.34	2.32 ± 0.30	2.32 ± 0.29	2.35 ± 0.29
d 0	210	2.29 ± 0.14	1.90 ± 0.51	1.81 ± 0.49	1.71 ± 0.68	1.92 ± 0.36	1.94 ± 0.50
1 to 3 DIM	2,124	2.20 ± 0.23	2.12 ± 0.30	2.08 ± 0.34	2.02 ± 0.38	1.94 ± 0.42	2.10 ± 0.33
Peak milk	1,871	2.25 ± 0.17	2.24 ± 0.19	2.21 ± 0.23	2.20 ± 0.18	2.16 ± 0.18	2.22 ± 0.19
P (m*M*)							
−3 to −1 DIM	323	2.02 ± 0.41	1.94 ± 0.46	1.96 ± 0.83	1.98 ± 0.34	1.87 ± 0.57	1.96 ± 0.54
d 0	130	1.89 ± 0.44	1.59 ± 0.50	1.41 ± 0.44	1.45 ± 0.54	1.33 ± 0.42	1.57 ± 0.50
1 to 3 DIM	900	2.01 ± 0.38	1.89 ± 0.44	1.86 ± 0.45	1.86 ± 0.53	1.79 ± 0.52	1.90 ± 0.45
Peak milk	1,871	2.05 ± 0.40	2.06 ± 0.39	1.88 ± 0.41	1.86 ± 0.40	1.84 ± 0.43	1.97 ± 0.42
Urea (m*M*)							
−3 to −1 DIM	494	4.39 ± 1.48	5.23 ± 1.72	5.20 ± 1.96	5.00 ± 1.46	4.37 ± 1.94	4.83 ± 1.74
d 0	143	4.81 ± 1.55	5.15 ± 1.67	5.04 ± 1.68	5.11 ± 1.83	5.19 ± 2.00	5.04 ± 1.70
1 to 3 DIM	900	4.46 ± 1.98	5.16 ± 1.88	5.08 ± 1.70	4.89 ± 1.57	4.79 ± 1.66	4.84 ± 1.82
Peak milk	1,554	5.90 ± 2.09	6.10 ± 2.21	6.27 ± 2.05	5.73 ± 2.14	5.42 ± 1.97	5.94 ± 2.12
Total protein (g/L)							
1 to 3 DIM	453	66.5 ± 6.77	66.1 ± 5.65	68.5 ± 6.20	70.0 ± 5.44	70.6 ± 5.03	67.7 ± 6.25
Peak milk	1,554	74.8 ± 6.34	75.9 ± 5.21	77.2 ± 6.55	78.3 ± 5.62	79.5 ± 7.12	76.6 ± 6.34

[1]Measures were taken at −3 to −1 DIM, d 0 (within 24 h of calving), 1 to 3 DIM, and at peak milk.

[2]NEFA = nonesterified fatty acids.

up to parity ≥3 (Table 3). A high proportion (37%) of variance was explained by group, perhaps reflecting true variability but also differences in definition of clinical ketosis, and the odds of clinical ketosis increased with year (Table 3). Most authors reported an increase in incidence of clinical ketosis with age (Shaw, 1956; Dohoo et al., 1984; Gröhn et al., 1989). Increased potential for milk production may be a risk factor for clinical ketosis; however, the primary determinant of clinical ketosis may be concurrent or pre-existing disease (Lean et al., 1994; Horst et al., 2021). In this study, dystocia (OR = 1.60; $P = 0.021$), CH (OR = 2.47: $P < 0.001$), displaced abomasum (OR = 8.13; $P < 0.001$), retained placenta (OR = 2.38; $P < 0.001$), and metritis (OR = 2.09: $P < 0.001$) were associated with increased odds of clinical ketosis. These conditions were likely antecedent or concurrent with clinical ketosis and did not substantially alter the association of parity with clinical ketosis. Diseases reported in these studies were either producer recorded, or diagnosed by a veterinarian following a request by a producer for an examination, in which concurrent disease may be detected. This reinforces the likelihood that a cow with a clinical ketosis diagnosis would have a high likelihood of a concurrent disease.

Subclinical Ketosis

The odds of subclinical ketosis was quite similar to clinical ketosis, with parity 1 and 2 being similar and having lesser odds than parities 3 to ≥5, which did not differ from each other (Table 3). The lactational prevalence was 26.8% in 11,382 cows. Estimates of the lactational prevalence will vary with cut-off points, methods used to define the condition, and the DIM

at assessment (Walsh et al., 2007; Dubuc et al., 2010; Ospina et al., 2010; McArt et al., 2011). Estimates of subclinical ketosis would be influenced by the use of monensin supplements (Duffield et al., 2008), which were present in many of the groups studied, and may influence the reported LI, system, and time effects. The odds of subclinical ketosis in the pasture-fed herds was much lower than for the intensive herds (OR = 0.042). Only displaced abomasum (OR = 4.03; $P < 0.001$), metritis (OR = 1.40; $P < 0.001$), and endometritis (OR = 1.33; $P < 0.001$) were associated with subclinical ketosis. These estimated odds were lower than for clinical ketosis, supporting studies suggesting that clinical ketosis is largely a manifestation of a concurrent disorder in ketonemic cows. Measurement of ketones is objective, whereas clinical ketosis identification is subjective, and the diagnosis relies on producers identifying clinical signs.

Respiratory Disease

The LI of conditions reported as respiratory disease, which included pneumonia, was 2.41% of 20,758 cows and occurred at a mean of 28.6 (SD 41.7) and median of 14 DIM. All older cows had greater odds of respiratory disease than cows in parity 1 (Table 3). Group only explained 2.1% of the variance, and neither year nor feeding system were significant (Table 3). Our hypothesis was that parity 1 cows would be at greater risk of respiratory disease based on being exposed to new respiratory pathogens as they entered the milking herd; however, this was not the case. Although there are many studies on calf and beef respiratory disease, there appears to be few such studies of adult dairy cows (Dohoo et al., 1984). Although the odds for the older cows ranged from 1.5 to 1.7 times greater than that of parity 1 cows, the low LI suggests that respiratory disease is not likely to markedly contribute to the loss of higher parity cows, a finding consistent with Dohoo and Martin (1984).

Glucose, NEFA, BHB, and Cholesterol

The concentrations of these metabolites indicate success in integrating metabolism during the transition period as BHB concentrations primarily reflect the net effect of generation of this energy source in the liver and uptake and metabolism of BHB in peripheral tissues. The precursors for BHB are NEFA mobilized from lipid and AA stores in response to energy demands that are not met from gluconeogenesis (Krebs, 1966; Lean et al., 1992). Table 4 provides the raw means for each metabolite by parity, whereas Table 5 presents the results for their marginal means centered by group.

Glucose. Blood glucose concentrations in the 3 d before calving were greatest in the parity 1 cows by at least 0.2 m*M*, and were lower and similar for all other parity cows (Tables 4 and 5). Mean glucose concentrations for all parities precalving were 3.50 ± 0.76 m*M* (SD) and were 4.64 ± 1.38 m*M* on the day of calving (Table 4). The difference in concentrations between parity 1 and 2 cows on the day of calving was >0.60 m*M*. Perhaps as a result of variation in the hyperglycemic response to calving and being measured in fewer cows (207) and groups (53) than the pre- and postcalving samples, the only significant difference in glucose on day of calving was between parity 1 and 2 (Table 5). For samples taken 1 to 3 d after calving, parities 2, 3, and 4 had ≥0.25 m*M* lower blood glucose than parity 1 (Table 4). Interestingly, parity ≥5 concentrations were not less than parity 1 (Tables 4 and 5). In peak lactation, however, parity 1 cows had at least 0.15 m*M* greater concentrations of glucose than other parities, which did not differ among themselves.

NEFA. Mean NEFA concentrations precalving were 0.39 ± 0.32 m*M*, were higher in parity ≥5 cows compared with parity 1, 2, and 3, and lower for parity 2 cows than all other parities (Tables 4 and 5). The concentrations were similar for all other parity comparisons. Concentrations of NEFA for all parities on the day of calving were numerically greater (0.79 ± 0.43 m*M*) than for 1 to 3 d before. For samples taken 1 to 3 d after calving, mean concentrations were 0.71 ± 0.44 m*M*, with a linear increase with parity ($P < 0.001$). Older parities had greater concentrations than parity 1, except for parity 2 and only parity 2 and 3, and 3, 4 and ≥5 did not differ (Table 5). Mean concentrations of NEFA in peak lactation were 0.48 ± 0.24 m*M* and increased with parity (Table 4); however, parity ≥5 concentrations only differed from parity 2 (Table 5). Overall, the NEFA results indicate a greater reliance on mobilized lipid stores in the older cattle, a result that is consistent with the increased risk of lipid mobilization disorders of ketosis and subclinical ketosis in older cows, noted in this study and by Markusfeld (1987), and with the blood glucose and parity changes in our study.

BHB. Mean concentrations of BHB before calving were 0.56 ± 0.28 m*M* (Table 4) and increased with parity ($P = 0.034$); however, we found no significant parity differences (Table 4). The mean BHB concentrations on the day of calving were 0.70 ± 0.28 m*M* (Table 4). We detected no significant effect of parity. Concentrations of BHB after calving were 0.96 ± 0.78 m*M* (Table 4), indicating substantial variance; in fact, we found a linear increase in BHB with parity ($P < 0.001$), and parities differed except for parity 2 and 1, parity 2 and 3, and parity 4 and ≥5 (Table 5). The

Table 5. Associations of parity and time relative to calving with blood concentrations of metabolic markers, including the number of datapoints, the marginal means ± SE centered by group, and *P*-values in parentheses when the main effect of parity was significant but, among parities, was not significant[1]

		Parity							
Measure[2]	n	1	2	3	4	≥5	Main effect	DIM precalving	DIM postcalving
Glucose									
−3 to −1 DIM	790	0.20 ± 0.04	−0.04 ± 0.04^{a}	−0.05 ± 0.04^{a}	−0.11 ± 0.06^{a}	−0.11 ± 0.06^{a}	<0.001	0.09 ± 0.02 (<0.001)	—
d 0	207	0.33 ± 0.16^{b}	−0.30 ± 0.15^{a}	0.09 ± 0.15^{ab}	−0.19 ± 0.22^{ab}	−0.05 ± 0.26^{ab}	0.075	—	—
1 to 3 DIM	1,416	0.18 ± 0.04^{c}	−0.10 ± 0.04^{a}	−0.09 ± 0.04^{ab}	−0.08 ± 0.05^{ab}	0.071 ± 0.05^{bc}	<0.001	—	−0.13 ± 0.02 (<0.001)
Peak milk	1,554	0.13 ± 0.02	−0.08 ± 0.02^{a}	−0.07 ± 0.03^{a}	−0.02 ± 0.03^{a}	−0.02 ± 0.03^{a}	<0.001	—	—
NEFA[3]									
−3 to −1 DIM	1,772	0.01 ± 0.01^{a}	−0.06 ± 0.01	0.01 ± 0.01^{a}	0.04 ± 0.02^{ab}	0.09 ± 0.02^{b}	<0.001	0.07 ± 0.01 (<0.001)	—
d 0	178	−0.03 ± 0.05^{a}	−0.09 ± 0.05^{a}	0.03 ± 0.05^{a}	0.07 ± 0.08^{a}	0.10 ± 0.07^{a}	0.163	—	—
1 to 3 DIM	1,508	−0.06 ± 0.02^{a}	−0.03 ± 0.02^{ab}	0.03 ± 0.02^{bc}	0.10 ± 0.03^{c}	0.10 ± 0.03^{c}	<0.001	—	NS
Peak milk	693	−0.01 ± 0.02^{ab}	−0.04 ± 0.02^{a}	0.01 ± 0.02^{bc}	0.03 ± 0.02^{bc}	0.05 ± 0.02^{c}	0.015	—	—
BHB									
−3 to −1 DIM	1,787	0.01 ± 0.01 (0.299)	−0.02 ± 0.01 (0.102)	−0.02 ± 0.01 (0.167)	0.02 ± 0.02 (0.290)	0.03 ± 0.02 (0.063)	0.034	0.04 ± 0.01 (<0.001)	—
d 0	178	−0.01 ± 0.03^{a}	−0.05 ± 0.03^{a}	0.03 ± 0.03^{a}	0.03 ± 0.05^{a}	0.03 ± 0.04^{a}	0.345	—	—
1 to 3 DIM	2,167	−0.11 ± 0.03^{a}	−0.07 ± 0.03^{ab}	0.03 ± 0.03^{b}	0.18 ± 0.04^{c}	0.18 ± 0.039^{c}	<0.001	—	0.09 ± 0.02 (<0.001)
Peak milk	920	−0.082 ± 0.025^{a}	0.000 ± 0.025^{ab}	0.020 ± 0.030^{ab}	0.071 ± 0.039^{b}	0.08 ± 0.04^{b}	<0.001	—	—
Cholesterol									
−3 to −1 DIM	509	0.05 ± 0.04^{a}	−0.02 ± 0.04^{a}	0.01 ± 0.05^{a}	−0.07 ± 0.05^{a}	0.001 ± 0.05^{a}	0.371	−0.06 ± 0.02 (0.017)	—
1 to 3 DIM	511	0.06 ± 0.03^{b}	0.04 ± 0.04^{b}	0.01 ± 0.04^{b}	−0.06 ± 0.05^{ab}	−0.15 ± 0.04^{a}	<0.001	—	0.06 ± 0.02 (0.002)
Peak milk	694	−0.24 ± 0.08^{a}	0.21 ± 0.09^{b}	0.24 ± 0.09^{b}	0.16 ± 0.13^{ab}	−0.33 ± 0.12^{a}	<0.001	0.02 ± 0.002 (<0.001)	—
Ca									
−3 to −1 DIM	1,780	0.02 ± 0.01^{c}	0.01 ± 0.01^{bc}	−0.01 ± 0.01^{ab}	−0.02 ± 0.02^{a}	−0.03 ± 0.02^{a}	<0.001		—
d 0	210	0.13 ± 0.03^{c}	0.03 ± 0.03^{bc}	−0.05 ± 0.03^{ab}	−0.10 ± 0.04^{ab}	−0.12 ± 0.05^{a}	<0.001	—	—
1 to 3 DIM	2,124	0.06 ± 0.01^{c}	0.03 ± 0.01^{bc}	−0.003 ± 0.01^{ab}	−0.06 ± 0.02^{a}	−0.13 ± 0.02	<0.001	—	0.08 ± 0.07 (<0.001)
Peak milk	1,871	0.03 ± 0.01^{c}	0.01 ± 0.017^{bc}	−0.01 ± 0.01^{b}	−0.02 ± 0.02^{ab}	−0.06 ± 0.01^{a}	<0.001	—	—
P									
−3 to −1 DIM	323	0.04 ± 0.05	−0.05 ± 0.05	0.07 ± 0.06	−0.01 ± 0.08	−0.08 ± 0.07	0.374	NS	—
0	130	0.22 ± 0.06^{c}	0.08 ± 0.07^{bc}	−0.17 ± 0.06^{a}	−0.11 ± 0.09^{ab}	−0.15 ± 0.07^{a}	<0.001	—	—
1 to 3 DIM	900	0.12 ± 0.02	−0.02 ± 0.03^{a}	−0.05 ± 0.03^{a}	−0.02 ± 0.04^{a}	−0.13 ± 0.03^{a}	<0.001	—	0.09 ± 0.02 (<0.001)
Peak milk	1,871	0.09 ± 0.09^{b}	0.06 ± 0.02^{b}	−0.08 ± 0.017^{a}	−0.10 ± 0.02^{a}	−0.11 ± 0.02^{a}	<0.001	—	—
Urea									
−3 to −1 DIM	494	−0.49 ± 0.10^{a}	0.29 ± 0.11^{b}	0.44 ± 0.13^{b}	−0.07 ± 0.15^{c}	−0.03 ± 0.14^{bc}	<0.001	NS	—
d 0	143	−0.24 ± 0.19^{a}	0.06 ± 0.19^{a}	0.14 ± 0.20^{a}	−0.16 ± 0.29^{a}	0.21 ± 0.25^{a}	0.539	—	—
1 to 3 DIM	900	−0.40 ± 0.09	0.27 ± 0.10^{a}	0.15 ± 0.11^{a}	0.11 ± 0.15^{a}	0.10 ± 0.12^{a}	<0.001	—	−0.60 ± 0.06 (<0.001)
Peak milk	1,554	−0.17 ± 0.07^{a}	0.29 ± 0.08^{c}	0.20 ± 0.08^{bc}	−0.13 ± 0.11^{ab}	−0.36 ± 0.10^{a}	<0.001	—	—
Total protein									
1 to 3 DIM	453	−1.45 ± 0.44^{a}	−1.67 ± 0.50^{a}	0.81 ± 0.57	2.76 ± 0.75^{b}	2.90 ± 0.65^{b}	<0.001	—	NS
Peak milk	1,554	−1.80 ± 0.27^{a}	−0.92 ± 0.29^{a}	0.53 + 0.32^{b}	1.75 ± 0.43^{bc}	3.07 ± 0.39^{c}	<0.001	—	—

$^{a-c}$Values within a row with different superscripts do not differ, $P < 0.05$.

[1]Measures were taken at −3 to −1 DIM, d 0 (within 24 h of calving), 1 to 3 DIM, and at peak milk (d 30 to 110). For the measures taken before calving, the day precalving (values are −3 to −1 DIM inclusive) was included as a covariable and the coefficients ± SE and *P*-values are reported. For the measures taken postcalving, the DIM postcalving (values are 1 to 3 DIM inclusive) was included as a covariable and the coefficients ± SE and *P*-values are reported. Nonsignificant (NS) values were removed from the model.

[2]We had insufficient data to evaluate cholesterol or urea at d 0.

[3]NEFA = nonesterified fatty acids.

Continued

latter oldest group had BHB concentrations that were 0.25 m*M* greater than those in parity 1 and 2 and could be considered to be subclinically ketotic on average (Dubuc et al., 2010; Roberts et al., 2012). Similarly, the NEFA concentrations on d 1 to 3 after calving (Table 4) could be considered elevated (Ospina et al., 2010). Concentrations of BHB were 0.77 ± 0.43 m*M* at peak lactation, and again increased with parity ($P < 0.001$); however, only parity 1 had greater concentrations than parities 4 and ≥5. Although the BCS was greater for parity 1 cows than for parity ≥5 cows (Lean et al., 2022b), we found evidence from reduced glucose and increased NEFA that the parity ≥5 cows were more reliant on body tissue mobilization than the parity 1 cows.

Cholesterol. Cholesterol concentrations before calving did not differ with parity ($P = 0.371$; Table 5). On the day of calving, cholesterol concentrations were 1.85 ± 0.51 m*M*, but we had too few observations for further evaluation. Mean concentrations of cholesterol 1 to 3 d after calving (1.89 ± 0.40 m*M*; Table 4) were significantly lower with parity ($P < 0.001$); specifically, parity ≥5 cows differed from parity 1, 2 and 3, but not parity 4 cows (Table 5). The mean cholesterol concentrations were 5.54 ± 1.60 m*M* at peak lactation (Table 4), and parity 1 and ≥5 cows had lesser concentrations than the other parities, but did not differ from each other (Table 5). No other differences among parities were significant. Greater blood cholesterol concentrations in lactation are an indicator of reproductive success (Westwood et al., 2002) and can reflect lipid (Grummer and Carroll, 1988) and overall diet intake, given that cholesterol is present in plants. The reduced concentrations in cows of parity 1 may reflect lower DMI for the parity 1 cows, but the biological basis for the lower blood cholesterol in older cows is not obvious and warrants further investigation.

Calcium

Concentrations of Ca before calving were 2.35 ± 0.29 m*M* and reduced with increased parity (Table 4; $P = 0.007$); however, the difference between parity 1 and parity ≥5 cows was only 0.07 m*M*, with only parity 1 and 5 differing. On the day of calving, mean Ca was 1.94 ± 0.50 m*M* and we found a marked reduction in concentrations with parity ($P < 0.001$). In this case, parity comparisons differed except between parities 3, 4, and ≥5 (Table 5), between 1 and 2, and for 2, 3 and 4. Calcium concentration was 0.37 m*M* lower in parity ≥5 than in parity 1 (Table 4). Similarly, Ca concentrations on d 1 to 3 after calving reduced with increased parity ($P < 0.001$), and the mean concentration was 2.10 ± 0.33 m*M*. At this time, parity ≥5 cows had lesser concentrations than other parities, and all parity comparisons differed except parity 1 with 2, 2 with 3, and 3 with 4 (Table 5). At peak lactation, Ca concentrations were 2.22 ± 0.19 m*M*, and again the reduction in concentrations with increased parity was significant ($P < 0.001$). The only pairwise comparisons that were not significant were parity 1 with 2, 2 with 3 and 4, and parity 4 with parity ≥5 (Table 5); however, the difference between parity ≥5 and parity 1 was only 0.08 m*M* (Table 4).

These observations provide further strong evidence for the CH findings that cows of higher parity struggle to maintain blood Ca concentrations and this effect extends from before calving to peak lactation. Although the metabolic demand for Ca in milk increases with greater milk output, it appears anomalous that the essential need for maintaining Ca homeostasis would not be similar in older cows to those of lesser parity. The use of centering and groups provide a rigorous evaluation of associations with parity within group and controls for the effect of interventions in the base studies. The marked vulnerability of cows with increased parity to CH was profound in this study and in others (Pacheco et al., 2018). The risks to longevity are indicated by associations between disease and subclinical hypocalcemia (Curtis et al., 1985; McArt and Neves, 2020).

Given the profound increase in risk of CH with parity and differences in blood Ca concentrations with parity, some consideration of the physiological basis is warranted. Declines in the ability to maintain Ca homeostasis with increased age have been noted in cattle (Reinhardt et al., 1988; Van Mosel et al., 1993a; Horst et al., 1994), chickens (Elaroussi et al., 1994), and humans (Fatayerji et al., 2000; Veldurthy et al., 2016). There is consistent evidence for reduced ability to maintain Ca homeostasis with age across species. There are numerous associations of this effect with other metabolic markers including intestinal absorption of Ca in humans (Veldurthy et al., 2016), reduced osteoclast numbers in rats (Reinhardt et al., 1988), reduced 1α-hydroxylase in chickens (Elaroussi et al., 1994), reduced concentrations of vitamin D metabolites and serotonin in cattle (Rodney et al., 2018b), reduced IGF-1 in human males (Fatayerji et al., 2000), and reduced osteocalcin concentrations in cattle (Taylor et al., 2008). Although use of acidogenic diets before calving has improved health and production of cattle (Lean et al., 2014; Lean et al., 2019; Santos et al., 2019), there may be further benefits in production, health, and reproduction from strategies to more effectively maintain Ca homeostasis.

Phosphorus

We had relatively few P samples, with 323 in 61 groups precalving that had a mean concentration 1.96 ± 0.54 m*M* (Table 4). The concentrations did not differ with parity ($P = 0.374$; Table 5). Concentrations on the day of calving were 1.57 ± 0.50 m*M* and reduced with increased parity ($P < 0.001$), with parity 1 having greater concentrations than parities ≥3 (Tables 4 and 5). Cows of parity 3 also had reduced concentrations to parity 2 cows. Mean concentrations of P were 1.90 ± 0.45 m*M* on d 1 to 3 after calving (Table 4) and again reduced with increased parity ($P < 0.001$; Table 5). Parity 1 cows had greater concentrations compared with other parities. Again, at peak lactation, parity 1 cows had the greatest concentrations of P and parity ≥5 the least, with P concentrations decreasing with increased parity ($P < 0.001$). Parity 1 had greater concentrations than parities ≥3, and parity ≥5 had lesser concentrations than parities <3. Parity 4 and 3 cows did not differ. The differences in concentrations among parities indicate that P homeostasis is also impaired in cows of higher parity (Table 4). Phosphorus is absorbed through active and passive pathways (Breves and Schröder, 1991), and the process is mediated, in part, through vitamin D metabolism (Braithwaite, 1978). Increases in blood P are a consistent response to 25 hydroxy-cholecalciferol supplementation (McGrath et al., 2012; Rodney et al., 2018a; Golder et al., 2021), supporting a role for vitamin D metabolism. The declines in P and Ca concentrations with parity reflect failures of homeostatic control that may in turn be associated with reduced production, health, and reproduction in older cows. The potential for reduced homeostatic control of Ca and P metabolism to influence health and reproduction in cows of greater parity requires further study.

Urea

When the effects of group were accounted for, urea concentrations were lesser for parity 1 cows than parities 2 and 3, and similar to 4 and 5 (Table 5). The mean blood urea concentrations precalving were 4.83 ± 1.74 m*M*. On the day of calving, concentrations were 5.04 ± 1.70 m*M* (Table 4) and did not differ among parities ($P = 0.539$; Table 5). At 1 to 3 d after calving, parities differed in urea concentrations ($P < 0.001$), with parity 1 cows having lesser blood urea than other parities. No other parity comparisons differed. Overall, the postcalving concentrations were similar to the precalving with a mean of 4.84 ± 1.82 m*M*. At peak lactation, the mean concentrations of urea were 5.94 ± 2.12 m*M* and were evaluated in 1,554 cows in 60 groups that were predominantly in pasture-fed herds. In this case, parity ≥5 cows had the least concentrations of urea and lesser concentrations than parity 2 and 3 cows, which had the greatest concentrations (Table 5). Urea concentrations will be influenced primarily by dietary protein intake, but also through catabolic processes such as AA oxidation (Westwood et al., 1998).

Plasma Protein

On d 1 to 3 after calving, plasma protein concentrations differed with parity ($P < 0.001$) with parities 3, 4, and ≥5 being greater than parity 1 and 2 (Table 5). At peak lactation, we detected monotonic and marked increase in plasma protein concentrations with increased parity (Table 5; $P < 0.001$). The mean concentrations of total protein at peak lactation were 76.6 ± 6.34 g/L (Table 4), similar to those reported by Bertoni and Trevisi (2013), whereas those on d 1 to 3 after calving were 67.7 ± 6.25 g/L and are lower than the range reported for dry cows by Bertoni and Trevisi (2013). We found a consistent association of increased parity with increased plasma protein in very early and peak lactation. Further investigation should identify the differential basis for the protein increase with parity, as an increase in all plasma proteins would suggest the potential for dehydration, whereas a differential increase in globulin content may indicate chronic responses to inflammation.

Overall Discussion

The pathogenesis of the interrelated conditions of the peri-parturient period (Curtis et al., 1985) remains elusive, notwithstanding the many studies conducted. Findings in this study are consistent with other findings in this investigation, as the hazard of death and reproductive failure increased with increased parity and cows became heavier, but were of lower BCS with parity (Lean et al., 2022a,b). There have been strong arguments and evidence presented to support a critical role of inflammation in the pathogenesis of peri-parturient health disorders (Bradford et al., 2015; Horst et al., 2021). The strong associations here of parity with CH and retained placenta contrast with those for metritis and endometritis, suggesting different pathogenesis associated with parity and lack of a unifying causal pathway. Changes in vitamin D and skeletal metabolism with parity, noted by Rodney et al. (2018b) and Rodney et al. (2018c), suggest that there need not be an antecedent inflammatory process to initiate CH or subclinical hypocalcemia and resultant health disorders. Further, evidence of the integration of energy and protein metabolism with skeletal and lactation

metabolism (Lean et al., 2014; Rodney et al., 2018c) suggests that this pathway is also critical in influencing milk production and risk of peri-parturient disease. It is likely that different metabolic challenges, as indicated by the differences in blood metabolite measures, will initiate increased risks for the interrelated diseases of the peri-parturient period. These diseases, which reflect disruptions to major metabolic pathways, have several initiating risk factors including metabolic changes with increased parity, inflammation from calving, infectious disease, adiposity, disrupted DMI, ruminal acidosis, and immune dysfunction.

The findings underline concerns that a greater consideration of parity may be required if cut-points in metabolite measures are used to predict subclinical disorders because risks of reproductive failure and death (Lean et al., 2022a). Health disorders concentrations of metabolites all differ with increased parity, consequently providing considerable risk of confounding, if parity is simply considered as nulliparous and pluriparous. There is a need to better understand the pathophysiology of older dairy cows and changes in metabolism associated with age that underpin the increases in health risks with increased parity.

CONCLUSIONS

We found greater than 4-fold increases with parity in the odds CH, lameness, and 2 to 4-fold greater odds with increased parity for retained placenta, displaced abomasum, mastitis, subclinical ketosis, and respiratory disease. The odds of metritis and endometritis were greatest for parity 1 cows, suggesting that despite strong associations among CH, retained placenta, metritis, and endometritis, the pathogenesis of the disorders differs. In toto, the results of the clinical and subclinical ketosis, glucose, NEFA, cholesterol ,and BHB indicate that there may be impairment of energy metabolism in older cattle. On d 1 to 3 after calving, differences in glucose, NEFA, and BHB indicated a greater reliance on mobilized lipid to export energy to peripheral tissues. Both Ca and P blood results indicated reduced concentrations of these minerals in blood, results consistent with the profound increase in risk of CH with parity. The differences in concentrations among parity groups were marked at times; for example >0.20 mM in Ca for parity 1 and 2 to parity ≥ 5, and >0.33 mM P for all older parities compared with parity 1 on the day of calving. Marked differences in odds of health disorders with increased parity, particularly for older parity cows, suggest a need to carefully consider the parity structure in study design and analysis. Managers and advisors need to consider the differing risks of health disorders in cows of different parity in planning preventive strategies.

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