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Prospects for predictive modeling of transition cow diseases

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Review

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Abstract

Transition cow diseases can negatively impact animal welfare and reduce dairy herd profitability. Transition cow disease incidence has remained relatively stable over time despite monitoring and management efforts aimed to reduce the risk of developing diseases. Dairy cattle disease risk is monitored by assessing multiple factors, including certain biomarker test results, health records, feed intake, body condition score, and milk production. However, these factors, which are used to make herd management decisions, are often reviewed separately without considering the correlation between them. In addition, the biomarkers that are currently used for monitoring may not be representative of the complex physiological changes that occur during the transition period. Predictive modeling, which uses data to predict future or current outcomes, is a method that can be used to combine the most predictive variables and their interactions efficiently. The use of an effective predictive model with relevant predictors for transition cow diseases will result in better targeted interventions, and therefore lower disease incidence. This review will discuss predictive modeling methods and candidate variables in the context of transition cow diseases. The next step is to investigate novel biomarkers and statistical methods that are best suited for the prediction of transition cow diseases.

Introduction

Transition cow diseases are a set of disease conditions (e.g. mastitis, metritis, ketosis, displaced abomasum, and retained placenta) that occur during the transition period. The transition period for dairy cows is generally defined as approximately 3 weeks before to 3 weeks after calving (Drackley, 1999). During this time, disease susceptibility is greatest due to physiological changes that occur as the cow prepares for calving and transitions into milk production (Sordillo and Raphael, 2013). The enhanced energy demands during this time are accompanied by a diminished dry matter intake (DMI), resulting in a negative energy balance (NEB) (Hutjens and Aalseth, 2005). NEB results in the mobilization of energy stores from adipose tissue (Ingvartsen, 2006). These are normal physiological processes for cows during the transition period; however, failure to adequately maintain homeostasis may result in metabolic stress. Physiological processes that contribute to metabolic stress include abnormal nutrient utilization, oxidative stress, and unregulated inflammation (Sordillo and Mavangira, 2014). Biomarkers representing altered nutrient metabolism typically measure lipid mobilization, which is defined as the imbalance between lipogenesis and lipolysis within the adipose tissue (Contreras and Sordillo, 2011). Oxidative stress is defined as an imbalance caused by increased production of reactive oxygen species (ROS) and the biological system's inability to detoxify the intermediates, or repair damage caused by them (Betteridge, 2000). Lastly, inflammation typically occurs as a result of injury or tissue destruction. However, all dairy cows experience some degree of inflammation, especially postpartum, during the transition period (Bradford *et al.*, 2015). Inflammation manifests as a series of responses including the production of inflammatory mediators (Sordillo and Mavangira, 2014). Although described separately, these three physiological processes (i.e. nutrient utilization, oxidative stress, and inflammation) are interrelated, often difficult to differentiate, and have the potential to form destructive feedback loops. When homeostasis is interrupted, metabolic stress occurs and is associated with poor uterine health and risk of transition cow diseases (Esposito *et al.*, 2014; Sordillo and Mavangira, 2014).

Metabolic stress results in greater economic costs to the producer due to increased culling rates, treatment costs, impaired reproduction, and reduced milk yield (Melendez *et al.*, 2003; Petrovski *et al.*, 2006; LeBlanc, 2008). Despite advances in research on transition cow disease etiology, prevention, and treatment, transition cow disease incidence overall has remained

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stable with few exceptions (LeBlanc *et al.*, 2006). For instance, the percent of cows reporting clinical mastitis has steadily increased from 13.4% in 1995 to 24.8% in 2013 (NAHMS, 1996, 2018).

Biomarkers that indicate the energy state of the animal are frequently used for health monitoring. These biomarkers include non-esterified fatty acids (NEFA), beta-hydroxybutyrate (BHB), calcium, and body condition score (BCS). Threshold values for NEFA, BHB, and calcium have been established at the individual cow level to indicate high disease risk. To make whole herd decisions, usually a proportion of the herd is sampled. Then, if there is a percentage of the herd above a certain threshold of NEFA or BHB, dietary and environmental interventions are implemented. At the individual cow level, the sensitivity and specificity for serum BHB $\geq$1.4 mmol l^{-1} measured in the first and second weeks after calving for detecting subclinical ketosis ranges from 87 to 93% and 93 to 100%, respectively (LeBlanc, 2010). However, BHB has only been demonstrated as a valuable biomarker post parturition, when it is too late for proactive interventions to reduce disease incidence in that particular calving cohort. On the other hand, NEFA thresholds have been utilized for both pre-partum and post-partum cows, with threshold levels ranging from approximately 0.30 to 0.40 mmol l^{-1} (Oetzel, 2004; Ospina *et al.*, 2013). However, Ospina *et al.* (2010) reported lower sensitivity and specificity of NEFA measured pre-partum (threshold of $\geq$0.39 mmol l^{-1}) compared with post-partum (threshold of $\geq$0.57 mmol l^{-1}) for detection of any of the following diseases: displaced abomasum, clinical ketosis, metritis, or retained placenta (Ospina *et al.*, 2010). Pre-partum sensitivity and specificity were 48% (95% CI: 42–54) and 69% (95% CI: 67–72), while post-partum sensitivity and specificity were 75% (95% CI: 66–82) and 61% (95% CI: 58–64) (Ospina *et al.*, 2010). Calcium concentrations can be used to identify hypocalcemia, which occurs when calcium levels are below the normal reference range of 8.5–10 mg dl^{-1} (Goff, 2008*a*). Calcium serum levels below 9.4 mg dl^{-1} measured 1-week pre-partum had very low sensitivity at 35% for displaced abomasum, while specificity was 71% (Chapinal *et al.*, 2011). Herd-level sensitivity is negatively affected by low sensitivity at the individual level, so it is imperative to have high test sensitivity, especially pre-partum when there is still time to intervene (Ospina *et al.*, 2013).

A potential method to increase sensitivity in detecting cattle at risk of transition diseases is to use multiple biomarkers that can capture the physiological complexity of metabolic stress. For instance, metabolic syndrome in humans, an analogous condition to metabolic stress in cows, is diagnosed by measuring a cluster of cardiometabolic biomarkers (IDF, 2006; Sordillo and Mavangira, 2014). The biomarkers used for metabolic syndrome measure different processes involved, including insulin resistance, visceral adiposity, dyslipidemia, glucose intolerance, hypertension, proinflammatory state, and a prothrombotic state (Huang, 2009). A patient does not need to present with all criteria to be diagnosed with metabolic syndrome (IDF, 2006). Metabolic stress in dairy cattle is very similar to metabolic syndrome in dairy cattle, in that both conditions involve interconnected physiological processes, where some or all processes are dysregulated. For metabolic stress in dairy cattle, the three major physiological processes involved are altered nutrient metabolism, oxidative stress, and inflammation. Biomarkers covering these three pillars of metabolic stress need to be implemented in monitoring so that dairy cattle undergoing metabolic stress may be better identified.

Even when multiple biomarkers and other monitoring tools (e.g. milk production, feed intake) are assessed together in multivariable analyses, the models are typically explanatory and do not aim for prediction and application in the field. It is important to understand the differences between predictive and explanatory methods before beginning analysis, because variable selection, model evaluation procedures, and model validation vary greatly between the two methods. Explanatory modeling is used to test causal explanations between the predictors and the outcome, while predictive modeling is used if the goal is to predict future or current events (Sainani, 2014). Since the aim is to identify cattle that will later develop disease as a result of metabolic stress, the focus should be on predictive modeling. Often, methods between explanatory and predictive modeling are conflated, and researchers assume strong explanatory models have high predictive power, which is not always the case (Shmueli, 2010).

This paper will review predictive modeling methods in the context of transition cow diseases. Herein, we will discuss what predictive modeling is, suggestions for variable selection, study design considerations, and statistical analysis tools.

Predictive versus explanatory modeling

Explanatory modeling

Many studies assessing risk factors for transition diseases use explanatory methods, which are used to investigate or hypothesize a possible causal pathway between the variables (LeBlanc *et al.*, 2005; Huzzey *et al.*, 2007; Dubuc *et al.*, 2010; Seifi *et al.*, 2011; Sainani, 2014; Vanholder *et al.*, 2015). For example, Potter *et al.* (2010) explored potential risk factors for clinical endometritis. The study reported the relative risk (RR) and population attributable risk fraction (which assumes causality) between significant risk factors (e.g. gender of calf, assisted calving, and parity) and development of endometritis (Potter *et al.*, 2010). The methods were explanatory in that the aim was to explore a mechanism behind the development of disease. In explanatory modeling, potential variables are chosen based on their hypothesized role in the causal pathway. It is important to consider the primary predictors of interest, as well as *a priori* confounders, and variables that are noted to be confounders in the dataset (Dohoo *et al.*, 2003). Automated selection procedures, such as stepwise and best subset selection, are criticized for their use in explanatory models because they optimize model fit with no regard to the role of each variable (Sainani, 2014). Selection of variables is generally driven by *P*-values and the size of the coefficients (Sainani, 2014). Explanatory models are evaluated based on explanatory power and the strength of the relationship between explanatory variables and the outcome indicated by the model, and then validated based on model fit and internal validity (Shmueli, 2010).

Predictive modeling

To the best of our knowledge, only a few studies used predictive modeling methods to model disease risk in transition dairy cattle (Vergara *et al.*, 2014; Wisnieski *et al.*, 2019*a*, 2019*b*, 2019*c*). As opposed to explanatory modeling, predictive modeling is focused on predicting future or current events, rather than causal explanations. In predictive modeling, variables are chosen based on association, data quality, and availability of the predictors before the event of interest (Shmueli, 2010). The main goal of variable selection is to include the predictors that most improve the predictive value of the model (Sainani, 2014). Automated variable selection procedures are allowed, but it is suggested that Akaike's

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information criteria (AIC) or Bayesian information criteria (BIC) are used instead of the statistical significance and size of the coefficients of the variables (Shtatland *et al.*, 2001; Shmueli, 2010; Sainani, 2014). This is because AIC and BIC focus on the strength of evidence for a model rather than hypothesis testing (Mazerolle, 2006) and balance model performance against model complexity (Burnham and Anderson, 2004). Predictive models are evaluated based on information criteria, discrimination (e.g. receiver operator characteristic [ROC] curve analysis), calibration, and goodness-of-fit (Sainani, 2014), and validated based on internal and external validity (Shmueli, 2010; Sainani, 2014).

In the end, explanatory and predictive models can produce greatly different results. In addition to their different goals and variable selection strategies, explanatory and predictive models also differ regarding the bias-variance trade-off. Explanatory models aim to minimize bias through obtaining the most accurate representation of the underlying theory, while predictive modeling aims to minimize bias and estimation variance, sometimes sacrificing accuracy for precision (Shmueli, 2010). It is likely that the variables, explanatory power, and predictive ability differ between explanatory and predictive models (Shmueli, 2010). In an example from human medicine, Singal *et al.* (2013) compared two models for prediction of hepatocellular carcinoma. One model was a conventional regression model built with explanatory modeling methods and the other was a predictive forest plot built using machine learning techniques. The authors found that both the variables and the predictive ability differed between the two methods, with the forest plot having the higher predictive ability (Singal *et al.*, 2013). There is a need in transition cow research to consider predictive modeling techniques to determine which variables are most predictive, rather than explanatory.

Candidate variables

Candidate variables that have either demonstrated the ability to predict or are associated with transition cow diseases in prior studies should be considered during study design. Practical considerations, including ease of measurement and analysis, reliability, and affordability, should be incorporated in variable choice. Although not comprehensive, this section will review why some select variables merit attention for modeling transition cow diseases.

Biomarkers

There are generally three major classes of biomarkers: biomarkers of exposure, effect, and susceptibility. Biomarkers of exposure are generally used to assess environmental exposure to a substance, biomarkers of effect measure the success of a treatment, and biomarkers of susceptibility are used to identify who is at risk of a certain disease (Grandjean, 1995). For predictive disease modeling, biomarkers of susceptibility are of most utility as they can identify cows that have an elevated risk of disease. Specifically, biomarkers that are indicators of the underlying physiological processes that cause transition cow disease. As mentioned earlier, metabolic stress brought on by the physiological transition from dry-off to early lactation is a key contributor to disease development. Effective and predictive biomarkers for metabolic stress are needed to identify cattle that are not transitioning smoothly. There are three components of metabolic stress that should be considered when choosing potential biomarkers: nutrient utilization, oxidative stress, and inflammation (Sordillo and Mavangira, 2014). As mentioned earlier, typically lipid mobilization markers are used to identify aberrant nutrient mobilization. Although the lipid mobilization biomarkers, including NEFA, BHB, and calcium, have immense value in the identification of cattle undergoing metabolic stress, these biomarkers only capture some of the physiological changes that occur. In an analogous condition in human beings, metabolic syndrome, people typically only need to have three or more cardiometabolic criteria to be diagnosed with metabolic syndrome. Although the underlying physiological processes are interconnected, people with metabolic syndrome may not present with the same risk factors (IDF, 2006). Other groups have recognized that this is also true of metabolic stress in dairy cattle in that multiple biomarkers are needed to capture the variability in how metabolic stress presents (Ingvartsen *et al.*, 2003; Celi, 2010; Abuelo *et al.*, 2013; Sordillo and Mavangira, 2014; Wisnieski *et al.*, 2019*a*). There is a need to develop biomarkers that represent other physiological processes involved in metabolic stress, oxidative stress and inflammation, to better identify cows at risk. Although not exhaustive, specific oxidative stress and inflammation biomarkers that deserve consideration will be discussed in the following sections.

Oxidative stress biomarkers

The measurement of both pro- and anti-oxidants is essential in estimating an animal's oxidative status. Abuelo *et al.* (2013) showed that the use of an oxidative stress index that measured both pro- and anti-oxidants was superior compared with using pro- and anti-oxidants separately. Pro-oxidants, such as ROS, are inherently unstable molecules due to unpaired electrons (Betteridge, 2000). Although produced in response to normal metabolic activities, they can cause substantial damage in tissues when produced in excess (Sordillo and Aitken, 2009). The action of ROS can be counteracted by antioxidants, which are electron donors. There are a variety of pro- and anti-oxidant biomarkers as described in Celi (2010). This allows for flexibility depending on the researcher's resources and capabilities. For example, the measurement of Trolox equivalent antioxidant capacity is an extremely fast and simple measurement using spectrometry (Celi, 2010). However, this method has varying results with sample dilution and varying specificity (Celi, 2010).

Many vitamins also have anti-oxidant capabilities and can serve as biomarkers for transition diseases. Specifically, vitamins E and A, and their derivatives, are excellent candidates. Vitamins E and A are important cellular antioxidants and reduce the risk of clinical mastitis when supplemented in feed (LeBlanc *et al.*, 2004; Spears and Weiss, 2008; Sordillo and Aitken, 2009; Yang and Li, 2015). Not only do vitamins E and A have antioxidant roles, but also decrease inflammatory markers and support the immune system when supplemented in feed (Baldi, 2005; McDowell *et al.*, 2007), hence they can also be considered inflammatory biomarkers. Vitamins E and A have been studied in dairy cattle for more than 20 years, which speaks on the strength of evidence for their involvement in dairy cattle health (Weiss, 1998; Baldi, 2005).

Inflammatory biomarkers

Acute phase proteins (APPs) and white blood cells are key players in systemic inflammation. Tissue injury or infections stimulate inflammatory responses that increase APPs, including haptoglobin, serum amyloid A (SAA), and albumin (Yang *et al.*, 2006; Ceciliani *et al.*, 2012; Pepys, 2012). White blood cells travel to the area of infection or injury and remove foreign cells, dead

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cells, or microorganisms. They dissipate once the stimulus disappears (Malarkey and McMorrow, 2011). The use of assays for APP in dairy cattle has grown in popularity for investigating infectious and inflammatory diseases, thereby resulting in increased availability of assays that measure APP concentrations (Ceciliani *et al.*, 2012). In addition, epidemiological evidence has demonstrated relationships between APP and disease in dairy cattle. For example, a group in Canada found that haptoglobin and SAA were associated with multiple disease outcomes in transition dairy cattle, including retained placenta, mastitis, and lameness (Dervishi *et al.*, 2015, 2016; Zhang *et al.*, 2015). Another group found that high albumin levels pre-calving significantly increased the risk of a disease event (Saun, 2004). Wisnieski *et al.* (2019*c*) demonstrated that the average concentration of albumin in a cohort at dry-off was a good predictor of cohort-level early lactation disease incidence.

APPs can recruit white blood cells to the area of infection. For instance, SAA recruits monocytes to inflamed tissues (Badolato *et al.*, 1994). In many studies, leukocytes, including neutrophils, lymphocytes, and macrophages, are associated with uterine diseases (Kulberg *et al.*, 2002; Hammon *et al.*, 2006; Goff, 2008*b*; Galvão *et al.*, 2010). Milk somatic cell counts, which are comprised mostly of leukocytes, are used to diagnose subclinical mastitis in dairy cattle (Barkema *et al.*, 1998). The strong support for APP and leukocytes in relation to transition cow disease outcomes lends support for using these biomarkers in disease prediction.

Vitamin D is an optimal candidate biomarker for transition diseases due to the strong connection of vitamin D with inflammatory conditions in human beings, including obesity and metabolic syndrome (Autier *et al.*, 2014). Vitamin D is involved in both acute and chronic inflammation, and has potent immunomodulatory properties (Gombart, 2012). Vitamin D regulates the production of cytokines and inhibits the production of proinflammatory cells (Yin and Agrawal, 2014). In addition to its role in disease prevention, vitamin D is involved in calcium homeostasis, which is an important lipid mobilization biomarker involved in metabolic stress (Horst *et al.*, 1994). In transition dairy cattle, a vitamin D deficiency may lead to hypocalcemia, or milk fever (DeGaris and Lean, 2008).

Health record

Farm health records include information such as lactation number, DMI, disease history, milk yield, and milk quality. Most of these data are already routinely collected from farms, which makes them ideal candidate variables to consider for predictive modeling. Increasing lactation number, or parity, is associated with greater incidence of disease, including milk fever and mastitis (DeGaris and Lean, 2008; Abebe *et al.*, 2016). There are also many behavioral differences between heifers (cattle on their first lactation) and cows (cattle on their second or greater lactation), such as time spent feeding and frequency of visits to the feed bunk, which may affect DMI (Neave *et al.*, 2017). Lower prepartum DMI is associated with increased risk of metritis and milk fever (Goff and Horst, 1997; Huzzey *et al.*, 2007). Disease history can offer insight into the capability of a cow's immune system. For instance, cows infected with bovine leukemia virus have dramatic shifts in lymphocyte function, which could cause a higher risk for subclinical and clinical mastitis (Sordillo and Erskine, 2010). Milk yield, both from the current lactation and previous lactations, is also associated with disease risk. Cows with higher milk yield in the previous lactation have increased risk of retained placenta, mastitis, milk fever, and metritis (Grohn *et al.*, 1995; Fleischer *et al.*, 2001), whereas higher milk yield in the current lactation is associated with a greater risk of milk fever (Fleischer *et al.*, 2001).

Housing and nutritional management

Similar to information from the health record, information about housing and nutritional management is readily available. A comfortable environment is critical for cow health. Comfortable stalls and walkways, soft mats, or deep bedding lower the risk of lameness (Cook and Nordlund, 2009; de Vries *et al.*, 2015). Proper shade and cooling systems prevent heat stress, thereby improving DMI (Collier *et al.*, 2006). In addition, cow health improves with longer stall length and greater freedom to move (e.g. free stalls instead of tie stalls) (Cook, 2003; de Vries *et al.*, 2004; Zurbrigg *et al.*, 2005; Simensen *et al.*, 2010). Pen changes and stocking density should also be considered during variable selection. Each pen change results in the establishment of a rank order. Housing multiparous cows separately from heifers, avoiding overstocking, and careful management of maternity and sick pens can reduce social turmoil and disease incidence (Nordlund *et al.*, 2006). The nutritional composition of feed can also be incorporated in disease prediction. Proper nutritional management can quell the severity and length of NEB and heat stress during early lactation (Santos *et al.*, 2012; Das *et al.*, 2016). Supplements in feed (e.g. zinc, copper, vitamin E, selenium, and beta-carotene) can reduce the incidence of many transition cow diseases, including clinical mastitis, metritis, and retained placenta (Spears and Weiss, 2008; Heinrichs *et al.*, 2009). Information from health records and on housing and nutritional management are convenient variables that have consistent associations with disease. It is considered good practice to include a large pool of candidate variables when building predictive modeling, so that any information that can be incorporated from health records, housing, and nutritional management should be incorporated in model selection.

Study design considerations

When designing a study, it is important to consider the goal of the analysis and the characteristics of the target population. Noteworthy considerations for dairy cattle include: (1) the decision to estimate individual versus group-level predictions, (2) the clustering of the cows within farms, (3) the differences between primiparous and multiparous cows, and (4) the presence of critical time-points in the lactation cycle.

Individual versus group-level predictions

Dairy herd managers are often concerned about health at the herd level. Health at the herd/cohort level can be assessed using incidence rates, which are defined as the number of new cases of a disease that occur during a specified time of interest in the population of interest (Dohoo *et al.*, 2003). The cohort level, which is defined as cows at the same stage of lactation (e.g. dry-off, close-up, and calving), may be more useful in targeting immediate interventions. This is because it offers information on the most current group of cows undergoing the transition from pregnancy to lactation.

The choice of individual versus group-level prediction will guide which predictors are collected. If the goal is individual-level

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prediction, using only cohort-level data (e.g. group feed intake) may not capture the heterogeneity of cows within a cohort. This can result in assigning group-level characteristics to individuals that do not possess those characteristics, which is known as the "ecologic fallacy" (Gordis, 2014). However, cohort-level predictors are often already collected and can reflect important management factors that exert contextual effects on individual cows. There are other sources of cohort-level variation in outcomes though, such as uneven composition of cohorts with respect to individual-level predictors (Duncan, Jones, and Moon, 1998). Therefore, it is recommended to use both individual-level and cohort-level predictors, to avoid both the ecologic and atomistic fallacies, and to study both contextual and compositional effects (Duncan *et al.*, 1998).

Individual-level data can also be aggregated to the group level. In Wisnieski *et al.* (2019*b*), we demonstrated the utility in aggregating individual-level biomarkers and covariate data to predict disease incidence at the cohort level (Wisnieski *et al.*, 2019*a*, 2019*b*, 2019*c*). In another previous study, we demonstrated that individual-level disease predictions calculated from individual-level models can be aggregated to predict cohort-level disease incidence (Wisnieski *et al.*, 2019*a*, 2019*b*).

Hierarchical or 'clustered' data

A cluster refers to a group of observations that share some common features. For instance, clusters may be formed from individuals that share a common environment or from repeated measures collected from the same individual (Dohoo *et al.*, 2003). For dairy cattle, potential cluster variables may include factors such as farm or pen. Careful calculation of sample size is important when using clustered data. For instance, when using farm as a cluster variable, the estimated number of farms and number of animals needed will depend on the variation in the covariates between farms compared with within a farm. This estimate can be calculated using the intraclass correlation coefficient (ICC) and an adjustment to the sample size calculation can be made if needed. Clustered samples typically require a higher sample size than simple random sampling. The ICC ranges from 0 to 1: a high ICC (closer to 1) is indicative that the variation within a group is small relative to between groups, and a low ICC (closer to 0) means that most of the variation is within the groups (Dohoo *et al.*, 2003). As ICC increases, the optimal number of clusters increases and the sample size per cluster decreases (van Breukelen and Candel, 2012). For example, if the ICC estimating the variance between farms compared with the variance within farms was high, a greater number of farms would need to be enrolled. This would correspond to a smaller number of cows per farm needed.

Analyses must also be adjusted to account for the hierarchical structure of data. If clustering is not considered when it is present, the standard errors of the estimates may be underestimated. This increases the risk of falsely rejecting null hypotheses (making type-I errors by concluding there is a difference when there is not really one). Different methods to account for clustering include stratifying the model by cluster, adjusting the standard errors, including the cluster as a fixed effect, or including the cluster as a random effect (Dohoo *et al.*, 2003). However, predictive models for transition diseases should aim to be generalizable to different populations (e.g. farms). To build predictive models that are generalizable to different farms, farm must be used as a clustering variable and represented as a random effect (Galbraith *et al.*, 2010). That is only viable when a sufficient number of farms are available in the sample. There may also be more than one clustering variable in a given study. For instance, cows may be nested in cohorts, which are defined as groups of cows expected to calve around the same time. In this case, three-level models can be used to adjust for both cohort and farm; however, sample size must be sufficient at both levels (Nezlek, 2008).

Primiparous and multiparous models

There are many physiological differences between primiparous and multiparous cattle. For example, primiparous and multiparous cattle have differing concentrations of many biomarkers that are associated with disease risk (e.g. BHB, leptin, and NEFA) throughout the lactation cycle (Wathes *et al.*, 2007). In addition, as mentioned previously, multiparous cattle have a greater disease risk than primiparous. Including parity as a predictor in models may not be sufficient to adjust for the large physiological differences between primiparous and multiparous cows. It may be advantageous to either build separate predictive models for primiparous and multiparous cattle or allow for interactions between parity and other variables in the same model. For example, Huzzey *et al.* (2011) reported separate models for primiparous and multiparous cattle for the associations between cortisol and transition disease outcomes. The authors found that higher cortisol levels were protective for disease in primiparous cows but increased the risk for disease in multiparous cows (Huzzey *et al.*, 2011). This indicates differences in the physiological control of lipid mobilization in heifers and cows (Wathes *et al.*, 2007). Therefore, the relationships between lipid mobilization biomarkers and disease outcomes may also be different in heifers and cows.

Multiparous cows that have had previous lactations have additional information available in their health record that may improve disease prediction, including prior milk yield, peak milk, and days in milk (Grohn *et al.*, 1995; Fleischer *et al.*, 2001). If primiparous and multiparous cattle were combined in the same model, primiparous cows would have empty values for these variables and would be excluded from the analysis. To use all information available for prediction, separate models may be best. However, it is important to note that separate models have implications for sample size. Researchers must ensure ahead of sampling that they will have an adequate number of primiparous and multiparous cows for meaningful statistical power in both models. If sample size permits, researchers should explore separate models for primiparous and multiparous cows, given their many differences.

Critical time-points

There are critical time points during the lactation cycle that are indicative of huge physiological shifts and important management decisions. For instance, dry-off is the time point in the lactation cycle where the farm staff stop milking the cows in preparation for the next calving. At this time, cows receive vaccinations and dry cow treatment regimens that are associated with later risk of diseases (Green *et al.*, 2007). In addition, Putman *et al.* (2018) found that many metabolic biomarkers associated with metabolic stress in early lactation fluctuated in the immediate days following dry-off. Nutritional management of dry cows is also critical to aid calcium metabolism and to control the release of NEFA from adipose tissue (Overton and Waldron, 2004). In the period from late

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pregnancy to early lactation, all dairy cattle undergo physiological stresses, including insulin resistance, reduced immune function, and bacterial contamination of the uterus that increases risk of disease (LeBlanc, 2010). Dairy cattle researchers should aim to design studies that capture these critical time-points through a longitudinal study design. Thus, changes between the time-points can be monitored and optimal times for intervention strategies during the lactation cycle may be elucidated.

Statistical analysis

There are several types and variations of statistical analyses that can be used to create predictive disease models. However, it is the researchers' responsibility to choose a type of analysis that will work best for their research question and dataset. A few topics to consider when choosing a statistical model for transition disease prediction are as follows: (1) purpose of the analysis (e.g. farm or individual cow level predictions), (2) sample size availability, (3) scale of independent and dependent variables (e.g. continuous, categorical, and ordinal), and (4) if the data can satisfy the assumptions of the analysis (McCrum-Gardner, 2008). The following section reviews statistical analysis options to consider before model building.

Predictive models

Logistic regression

Logistic regression models are well-suited for testing the association between a binary outcome and continuous and/or categorical predictors (Peng *et al.*, 2002). In the case of modeling transition diseases, our binary response variables would be coded as 0 (i.e. no disease) or 1 (i.e. disease) (Long and Freese, 2006). The coefficients in the logistic regression may be converted to odds ratios (ORs) so that researchers can evaluate how each covariate contributes to prediction (Hosmer *et al.*, 2013). The coefficients can also be converted into RRs for prospective data within the generalized linear regression framework. RR estimates are more easily interpreted than ORs (Schmidt and Kohlmann, 2008). Logistic regression requires that the probabilities are a logistic function of the independent variables, that the model includes all relevant variables, that the observations are independent and measured without error, and that the variables are not linear combinations of each other (Harrell, 2015). In the literature, there are innumerable examples of studies that used logistic regression to model transition disease outcomes. For example, LeBlanc *et al.* (2004) investigated the associations of vitamin E, retinol, and beta-carotene with retained placenta and clinical mastitis in two separate models. The authors found that pre-partum alpha tocopherol was negatively associated with risk of retained placenta, and retinol levels were negatively associated with risk of clinical mastitis (LeBlanc *et al.*, 2004). In another study, Huzzey *et al.* (2007) used logistic regression analysis to test the associations of pre-partum feeding time and DMI with metritis. The authors found that increased feeding time and DMI were associated with a lower risk of metritis (Huzzey *et al.*, 2007). Wisnieski *et al.* (2019*a*) used logistic regression analyses to build individual cow-level models aim to predict an aggregate disease outcome (e.g. mastitis, metritis, retained placenta, and other transition diseases). The best model, which included multiple biomarkers of metabolic stress, had high sensitivity and specificity (both >85%) (Wisnieski *et al.*, 2019*a*).

The use of logistic regression is widespread, probably due to its ease of interpretation and its relationship to analyses of contingency tables (Lemeshow and Hosmer, 1982). Logistic regression models can accommodate categorical predictors, which are essential in transition disease prediction where many potential predictors are categorical (e.g. parity, prior disease, and co-morbidities). Another strength of logistic regression analysis for predictive modeling is that interaction terms can be used. Interaction occurs when the effect of two variables together is different than the sum of their individual effects (Dohoo *et al.*, 2003). Including interaction terms can improve predictive performance (Kerr and Pepe, 2011). Logistic regression models are excellent candidates for transition disease models and should be considered if the researcher has access to statistical packages. However, in the case of small sample sizes, perfect prediction or empty cells of certain covariate patterns are more likely to occur. This leads to unstable coefficients and standard errors, and may lead to the exclusion of important covariates (Zorn, 2005). Exact logistic regression, a variation of logistic regression, can be used to remedy this issue. Exact logistic regression handles small sample sizes and empty cells by constructing a statistical distribution that can be completely enumerated (Hosmer *et al.*, 2013).

Discriminant function analysis

Discriminant function analysis is used to determine which continuous variables discriminate between two or more groups (McLachlan, 2004). For instance, a researcher may investigate which variables discriminate between cows that develop mastitis and those that do not. Discriminant analysis is a two-step process: testing significance of a set of discriminant functions, which is computationally identical to multivariate analysis of variance (MANOVA), followed by classification. During classification, discriminant analysis automatically determines which set of variables best discriminates between the groups (McLachlan, 2004).

Discriminant analysis answers the same basic questions as logistic regression, but has additional assumptions. Discriminant analysis has the same assumptions as MANOVA, including equal sample sizes between groups, a normal distribution of the data, homogeneity of variances/covariances, absence of outliers, and independent means and variances. In addition, discriminant analysis requires that the variables used to discriminate between groups are not highly correlated, which can be determined by calculating tolerance values (Klecka, 1980).

To the best of our knowledge, discriminant factor analysis has not yet been used to model transition cow diseases but has been used to investigate multifactorial conditions in human beings, including metabolic syndrome (Leite *et al.*, 2007; Corica *et al.*, 2008). A benefit of using discriminant analysis is that it can handle smaller sample sizes than logistic regression. However, as mentioned earlier, another option for small sample sizes is exact logistic regression. Exact logistic regression may be a better option than discriminant analysis in transition dairy cattle disease studies, because discriminant analysis assumptions are often difficult to meet. Discriminant analysis requires that the groups (disease versus no disease) are approximately equal in size. It is unlikely that close to half of all cows will present with clinical disease. For instance, clinical mastitis, which is the most common transition disease, only has a median incidence risk of 14.2% (Van Saun and Sniffen, 2014). This issue can be addressed through retrospective studies (e.g. case-control) that can select equal numbers of diseased and non-diseased cows. In prospective studies (e.g. cohort), this can be addressed by collecting data on a

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much larger sample, then random subsampling from the healthy group to get balanced sample sizes. However, this option may not be cost-effective. Another consideration for discriminant analysis is that it does not handle categorical variables as well as logistic regression (Press and Wilson, 1978), so researchers may have to exclude important predictors, such as parity.

Factor analysis and structural equation modeling

The intent of factor analysis is to determine the number or nature of factors that account for variation and covariation among a set of variables or indicators (Brown, 2015). In other words, the goal is dimension reduction: combining many indicator variables into a smaller number of latent factors that are each broader constructs than the individual indicators. Factor analysis is a measurement model, in that latent factors are 'measured' by multiple observed variables. The latent factor is considered the cause of the observed variables that explains why they are correlated (Brown, 2015). In general, there are two types of factor analyses: exploratory factor analysis (EFA) and confirmatory factor analysis (CFA). EFA is used to explore the underlying factor structure of a set of variables, whereas CFA is based on prior knowledge or a conceptual foundation (Suhr, 2006). Typically, factor analysis is used in the social sciences for survey development to account for correlations between questions related to the same topic (Brown, 2015). This method is useful because it accounts for correlation between two topics. For example, in a mental health survey, all answers to the questions related to depression will be correlated and factor analysis can be used to derive a measure of depression as a latent construct that explains those correlations (Brown, 2015). This simplifies studying the relationship of depression to other constructs.

To the best of our knowledge factor analysis has not been used to model transition diseases. However, in theory, factor analysis could apply to grouping transition cow metabolic stress biomarkers, because they relate to the same physiological processes and most likely are correlated. In fact, multiple studies have used CFA to model biomarkers for human metabolic syndrome (Pladevall *et al.*, 2006; Li and Ford, 2007; Boronat *et al.*, 2009; Gurka *et al.*, 2014).

Factor analysis has many advantages, including its high-power data reduction capabilities and the ability to handle measurement errors efficiently (Brown, 2015). The output of factor analysis is a factor score, which is a composite variable that relays information about an individual's placement on the factor (DiStefano *et al.*, 2009). For the example of transition cow metabolic stress biomarkers, the factor score would correspond to the degree of metabolic stress an individual cow is undergoing. The factor scores can then be used in further analyses to predict disease risk, as in structural equation modeling. However, factor analysis has some disadvantages. The final factor scores may be difficult to interpret and there's often not a single solution. The lack of a single solution arises from the fact that the parameters are not uniquely defined, and the researcher has choices in how the model is specified (DiStefano *et al.*, 2009). This indeterminacy results in a variable number of solutions that can produce varying factor scores (Grice, 2001).

There are different variations of factor analysis that also allow for binary, count, and censored variables (Van der Ark *et al.*, 2012; Brown, 2015). However, the assumptions of factor analysis in its basic form are a normal distribution for each observed variable, normal bivariate distributions for each pair of observed variables, and a normal multivariate distribution (Suhr, 2006). Although transforming variables often solves the problem of non-normality for continuous variables, adjusting for non-linearity of the associations between biomarkers for metabolic stress and disease outcomes may be more difficult. In some situations, very low or very high levels of a biomarker are harmful, whereas intermediate levels are protective. For example, both low and high BCS at calving is associated with increased incidence of ketosis, metritis, retained placenta, and mastitis (Kim and Suh, 2003; Bewley and Schutz, 2008; Roche *et al.*, 2009). This suggests a quadratic relationship between BCS and disease, rather than a linear relationship.

Classification and regression trees

Classification and regression trees (CART) are obtained by partitioning the data in multiple steps to form a simple prediction model. The steps are portrayed as a decision tree (Loh, 2011). Classification trees are used when the dependent variable is categorical (i.e. high disease risk or low disease risk), whereas regression trees are used when the dependent variable is continuous (e.g. level of disease risk). The independent variables can be either categorical or continuous (Ma, 2018).

Steensels *et al.* (2016) developed a CART model to detect post-calving lameness and metritis, and reported acceptable sensitivity and specificity at 69 and 87%, respectively. CARTs have also been used to predict difficult calvings (Zaborski *et al.*, 2016; Fenlon *et al.*, 2017). CART models have many advantages, including ease of use, clear rules that are easy to interpret, and the absence of assumptions that statistical models require. This could be of great benefit for practical use in dairy farms. A potential limitation of CART models is that they can only handle one variable at a time, so there is no way to account for interactions between the variables (Loh, 2011). In addition, CART diagrams are unstable, as slight changes in the data can result in a vastly different tree (Li and Belford, 2002). Fenlon *et al.* (2017) reported that multinomial regression, which is similar to logistic regression, outperformed the CART diagram for prediction of difficult calvings. CART diagrams are a valid option for predictive modeling and should be considered if more advanced statistical models are unavailable or unfeasible.

Count models (Poisson and negative binomial)

Poisson models are particularly useful for modeling disease incidence, because the Poisson distribution provides more accurate estimates of count data compared with the normal distribution (Long and Freese, 2006). To calculate herd/cohort level incidence, an exposure offset can be included in a Poisson model that adjusts for the number of cows in the herd (Dohoo *et al.*, 2003).

Poisson models hold a strict assumption that the variance is equal to the mean. However, most distributions do not meet this assumption and have a higher degree of skewness. This higher degree of skewness, which is called over-dispersion, causes a greater difference between the observed and predicted values than expected (Hilbe, 2014). Models that incorporate a linear dispersion correction (e.g. negative binomial) may be used in place of Poisson regression to account for this discrepancy (Hilbe, 2014). Zero-inflated and zero-truncated models are versions of Poisson/negative binomial models, which can be used in situations when there are many zeros and few zeros, respectively (Long and Freese, 2006). Poisson and negative binomial models have been used to model transition diseases in numerous studies. For example, Richert *et al.* (2013) developed a Poisson model to investigate risk factors for mastitis, ketosis, and pneumonia. In Wisnieski *et al.* (2019*b*) and Wisnieski *et al.* (2019*c*), Poisson models were used to model transition disease incidence at the

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cohort level. If a researcher is interested in herd level prediction, Poisson or negative binomial is the viable option.

Generalized linear models

The general linear model (GLM) is comprised of both multiple regression and analysis of variance, which allow researchers to investigate the association between one or more independent variables and a continuous dependent variable. The generalized linear model (GLiM) is a flexible rendition of the GLM that can handle binary, count, and ordered and unordered categorical outcomes (Hardin and Hilbe, 2007). Due to this flexibility, the GLiM can adapt to both logistic and Poisson regression, which as mentioned earlier, can be used to predict disease risk. Model building requires specifying the model in two parts: equations linking the response and explanatory variables (e.g. identity, logit, log, and reciprocal), and the probability distribution of the response variable (e.g. normal, binomial, Poisson, and gamma) (Hardin and Hilbe, 2007). There are many advantages of GLiMs, including the ability to handle situations where the variance of the dependent variable is dependent on the mean (Turner, 2008). In addition, the GLiM has greater statistical power for non-normal response data compared with a standard linear model (Ngo, 2016).

The assumptions of the GLiM are homoscedasticity of the error terms, uncorrelated errors for individual cases, and the conditional expected value of the errors must be equal to zero. However, errors do not need to be normally distributed (Hardin and Hilbe, 2007). Logistic and Poisson regression are both special cases of GLiMs. They can be used in the GLiM framework as a more flexible approach to consider if researchers have difficulty in meeting certain model assumptions. Many researchers have utilized GLiMs to model transition cow diseases, both using Poisson regression (Lima *et al.*, 2012; McArt *et al.*, 2012, 2013) and logistic regression (LeBlanc *et al.*, 2002, 2004, 2005; Benzaquen *et al.*, 2007; Seifi *et al.*, 2011).

The assumption of uncorrelated errors for GLiMs requires that the observations are independent. This may not be the case if cows are clustered within cohorts or farms. As mentioned earlier, cows within farm or cohort may be more alike compared with cows in different farms or cohorts. Data can also be correlated if multiple measurements were taken from the same cow (e.g. multiple time points). Measurements from the same cow are more likely to be alike than measurements from different cows. Researchers can further relax the assumption of uncorrelated errors by moving to generalized linear mixed models (GLMMs). The GLMM can account for this correlation through the addition of a random effect term for each level of clustering (e.g. farm, cohort, and cow) (Rabe-Hesketh and Skrondal, 2008).

Summary

In summary, there are a variety of statistical models to consider, each with their own strengths, weaknesses, and assumptions. It is up to researchers to determine which predictive model is best for their analysis, but there are multiple factors to consider. For instance, if the sample size is limited, exact logistic regression, CART diagrams or discriminant factor analysis are best. For data not conforming to certain assumptions (e.g. normality of response variable), a more flexible analysis using GLiM may be warranted. Factor analysis may be a valid option for researchers having issues with multicollinearity of independent variables but should be wary of non-linear relationships between predictors and the outcome. If health at the cohort or herd level is the purpose of the analysis, count models may be a preferred choice, while many of the other models mentioned are useful for prediction at the individual cow level (e.g. logistic regression). These are not an exhaustive list of considerations, but as mentioned before, there are many factors to consider. Researchers should plan the statistical analysis while designing the study, so that the study design can support the type of statistical analysis that will work best with the resources available.

Additional techniques for predictive models

There are additional techniques specific for predictive models that have seldomly been used to model transition cow diseases. Some examples that deserve attention include model averaging and shrinkage.

Model averaging

Often modeling procedures, such as variable selection and CART, are sensitive to slight changes in the data (Shtatland *et al.*, 2004). Model averaging is a technique that reduces model uncertainty by combining or averaging multiple potential models (Ghosh and Yuan, 2009). There are many ways to implement model averaging, but most methods start with performing best subsets selection to identify a set of potential models. Then, regression coefficients or predictions can be averaged over multiple potential models (Shtatland *et al.*, 2004). A more advanced technique is Bayesian model averaging, which involves direct model selection, combined estimation, and combined prediction using Bayesian inference (Fragoso *et al.*, 2018). Bayesian methods incorporate the use of probability for quantifying and adjusting for uncertainty in inference (Gelman *et al.*, 2014).

Shrinkage

Typically, predictive models will not predict as well in future samples as they did in the samples used to build them (Ivanescu *et al.*, 2016). Shrinkage is a model validation tool that can account for this discrepancy (Ivanescu *et al.*, 2016). Shrinkage pulls the regression coefficients toward zero and moves the prediction toward the average risk and improves predictive value (Steyerberg *et al.*, 2001*a*). This also helps protect against overfitting, which occurs when there are few events compared with predictors. Overfitting causes the model to underestimate the risk in low-risk individuals and overestimate the risk in high-risk individuals (Pavlou *et al.*, 2015). There are a variety of shrinkage techniques to consider, including shrinking the coefficients by a common factor (e.g. 20%) or by penalized regression (e.g. lasso regression) (Pavlou *et al.*, 2015). Although not all researchers have the ability to incorporate model averaging or shrinkage, they should be considered as potential options to improve predictive ability.

Model evaluation and validation

As mentioned earlier, predictive models should be evaluated for their discriminant ability, calibration, and goodness-of-fit (Sainani, 2014). Discriminant power is the ability of the model to systematically assign higher predicted probabilities to those that have the outcome (disease) compared with those that do not (no disease) (Sainani, 2014). A common test that measures discriminant power is ROC curve analysis. From the ROC curve, the area under the curve (AUC) can be calculated which gives the probability that a randomly tested disease individual has a greater test value compared with a randomly selected individual with no disease (Dohoo *et al.*, 2003). Model calibration is a

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measure of the accuracy of predictions, which is usually assessed through calibration plots or can be tested through the Hosmer–Lemeshow deciles of risk test (Hosmer *et al.*, 2013; Sainani, 2014). Calibration plots and the Hosmer–Lemeshow deciles of risk test can group the observations based on deciles of predicted probabilities (e.g. 0.10, 0.20, 0.30, and so on) and compare the observed versus expected number of individuals in each decile group (Hosmer *et al.*, 2013). Goodness-of-fit tests depend on the statistical model used. For example, the Hosmer–Lemeshow deciles of risk test also serves as a goodness-of-fit test for logistic regression (Hosmer *et al.*, 2013), and the deviance and Pearson goodness-of-fit tests can be used for Poisson models (Long and Freese, 2006). It is the responsibility of the researcher to choose appropriate goodness-of-fit tests for the analysis.

Predictive models should also be validated. External validation involves testing the model in an entirely new data set. However, sometimes this is not feasible due to cost or time (Sainani, 2014). Internal validation is a method that aims to improve the performance of the model in new subjects by partitioning the current dataset and testing how the model performs in this hypothetical set of new subjects (Steyerberg *et al.*, 2001*b*; Pavlou *et al.*, 2015). Internal validation can be done using a split sample approach, where a proportion of the data is used to build the model and the rest of the data are used to test the model. Cross-validation is another option that is an extension of split sample, where a randomly selected proportion of the data are used to build the model, and the other proportion is used to test the data, and vise-versa. This procedure is performed multiple times and the results are then averaged (Steyerberg *et al.*, 2001*b*). The internal validation method that is most efficient and resistant to bias and variability is called bootstrapping (Steyerberg *et al.*, 2001*b*). The bootstrap procedure involves the random selection of a sample with replacement from the original dataset. The bootstrap procedure selects multiple samples (usually 200 or more), each the same size of the original dataset, and averages the predictive performance over all the random samples (Steyerberg *et al.*, 2001*b*; Pavlou *et al.*, 2015). If there is no opportunity for external validation in new datasets, researchers should explore internal validation options.

Conclusion

Transition cow disease incidence has remained steady over time, despite improved monitoring and management efforts. Currently, cows are monitored for risk using a multitude of factors, including nutrient mobilization biomarker levels, health records, and milk production. These factors are often assessed separately and not systematically. The biomarkers typically measured for monitoring, NEFA and BHB, are not validated for use in the early dry period and fall short in sensitivity and specificity. A potential solution to improving sensitivity and specificity is to incorporate additional biomarkers that can capture the biological complexity of metabolic stress, including biomarkers for oxidative stress and inflammation. In addition, most researchers use explanatory modeling methods, rather than predictive modeling methods. There is a need for transition cow epidemiologists to explore and evaluate modeling aimed toward prediction, rather than explanation.

References

Abebe R, Hatiya H, Abera M, Megersa B and Asmare K (2016) Bovine mastitis: prevalence, risk factors and isolation of *Staphylococcus aureus* in dairy herds at Hawassa milk shed, South Ethiopia. *BioMed Central Veterinary Research* **12**, 270.

Abuelo A, Hernandez J, Benedito JL and Castillo C (2013) Oxidative stress index (OSi) as a new tool to assess redox status in dairy cattle during the transition period. *Animal: An International Journal of Animal Bioscience* **7**, 1374–1378.

Autier P, Boniol M, Pizot C and Mullie P (2014) Vitamin D status and ill health: a systematic review. *Lancet Diabetes Endocrinology* **2**, 76–89.

Badolato R, Wang JM, Murphy WJ, Lloyd AR, Michiel DF, Bausserman LL, Kelvin DJ and Oppenheim JJ (1994) Serum amyloid A is a chemoattractant: induction of migration, adhesion, and tissue infiltration of monocytes and polymorphonuclear leukocytes. *The Journal of Experimental Medicine* **180**, 203–209.

Baldi A (2005) Vitamin E in dairy cows. *Livestock Production Science* **98**, 117–122.

Barkema HW, Schukken YH, Lam TJGM, Beiboer ML, Benedictus G and Brand A (1998) Management practices associated with low, medium, and high somatic cell counts in bulk milk. *Journal of Dairy Science* **81**, 1917–1927.

Benzaquen ME, Risco CA, Archbald LF, Melendez P, Thatcher MJ and Thatcher WW (2007) Rectal temperature, calving-related factors, and the incidence of puerperal metritis in postpartum dairy cows. *Journal of Dairy Science* **90**, 2804–2814.

Betteridge DJ (2000) What is oxidative stress? *Metabolism* **49**, 3–8.

Bewley JM and Schutz MM (2008) Review: an interdisciplinary review of body condition scoring for dairy cattle. *The Professional Animal Scientist* **24**, 507–529.

Boronat M, Saavedra P, Varillas VF and Novoa FJ (2009) Use of confirmatory factor analysis for the identification of new components of the metabolic syndrome: the role of plasminogen activator inhibitor-1 and haemoglobin A1c. *Nutrition, Metabolism & Cardiovascular Diseases* **19**, 271–276.

Bradford BJ, Yuan K, Farney JK, Mamedova LK and Carpenter AJ (2015) Invited review: inflammation during the transition to lactation: new adventures with an old flame. *Journal of Dairy Science* **98**, 6631–6650.

Brown TA (2015) *Confirmatory Factor Analysis for Applied Research*, 2nd Edn. New York, NY: The Guilford Press.

Burnham KP and Anderson DR (2004) Multimodel inference: understanding AIC and BIC in model selection. *Sociological Methods & Methods* **33**, 261–304.

Ceciliani F, Ceron JJ, Eckersall PD and Sauerwein H (2012) Acute phase proteins in ruminants. *Journal of Proteomics* **75**, 4207–4231.

Celi P (2010). Biomarkers of oxidative stress in ruminant medicine. *Immunopharmacology and Immunotoxicology* **33**, 233–240.

Chapinal N, Carson M, Duffield TF, Capel M, Godden S, Overton M and Santos JEP (2011) The association of serum metabolites with clinical disease during the transition period. *Journal of Dairy Science* **94**, 4897–4903.

Collier RJ, Dahl GE and VanBaale MJ (2006) Major advances associated with environmental effects on dairy cattle. *Journal of Dairy Science* **89**: 1244–1253.

Contreras GA and Sordillo LM (2011) Lipid mobilization and inflammatory responses during the transition period of dairy cows. *Comparative Immunology, Microbiology and Infectious Diseases* **34**, 281–289.

Cook NB (2003) Prevalence of lameness among dairy cattle in Wisconsin as a function of housing type and stall surface. *Journal of the American Veterinary Medical Association* **9**, 1324–1328.

Cook NB and Nordlund KV (2009) The influence of the environment on dairy cow behavior, claw health and herd lameness dynamics. *The Veterinary Journal* **179**, 360–369.

Corica F, Corsonella A, Apolone G, Mannuncci E, Lucchetti M, Bonfiglio C, Melchoinda N, Marchesini G and the QUOVADIS Study Group (2008) Metabolic syndrome, psychological status and quality of life in obesity: the QUOVADIS study. *International Journal of Obesity* **32**, 185–191.

Das R, Sailo L, Verma N, Bharti P, Saikia J, Kumar I and Kumar R (2016) Impact of heat stress on health and performance of dairy animals: a review. *Veterinary World* **9**, 260–268.

DeGaris PJ and Lean IJ (2008) Milk fever in dairy cows: a review of pathophysiology and control principles. *The Veterinary Journal* **58**, 69.

Dervishi E, Zhang G, Hailemariam D, Dunn SM and Ametaj BN (2015) Innate immunity and carbohydrate metabolism alterations precede

https://doi.org/10.1017/S1466252319000112 Published online by Cambridge University Press

occurrence of subclinical mastitis in transition dairy cows. *Journal of Animal Science and Technology* **57**, 46.

Dervishi E, Zhang G, Hailemariam D, Dunn SM and Ametaj BN (2016) Occurrence of retained placenta is preceded by an inflammatory state and alterations of energy metabolism in transition dairy cows. *Journal of Animal Science and Biotechnology* **7**, 8.

DeVries TJ, von Keyserlingk MAG and Weary DM (2004) Effect of Feeding Space on the Inter-Cow Disease, Aggression, and Feeding Behavior of Free-Stall Housed Lactation Dairy Cows. *Journal of Dairy Science* **87**, 1432–1438.

de Vries M, Bookers EAM, van Reenen CG, Engel B, van Schaik G, Dijkstra T and de Boer IJM (2015) Housing and management factors associated with indicators of dairy cattle welfare. *Preventive Veterinary Medicine* **118**, 80–92.

DiStefano C, Zhu M and Mindrila D (2009) Understanding and using factor scores: considerations for the applied researcher. *Practical Assessment, Research & Evaluation* **14**, 1–11.

Dohoo I, Martin W and Stryhn H (2003) *Veterinary Epidemiologic Research*. Charlottetown, Prince Edward Island, Canada: AVC Inc.

Drackley JK (1999) Biology of dairy cows during the transition period: the final frontier? *Journal of Dairy Science* **82**, 2259–2273.

Dubuc J, Duffield TF, Leslie KE, Walton JS and LeBlanc SJ (2010) Risk factors for postpartum uterine disease in dairy cows. *Journal of Dairy Science* **93**, 5764–5771.

Duncan C, Jones K and Moon G (1998) Context, composition, and heterogeneity: using multilevel models in health research. *Social Science & Medicine* **46**, 97–117.

Esposito G, Irons PC, Webb EC and Chapwanya A (2014) Interactions between negative energy balance, metabolic diseases, uterine health and immune response in transition dairy cows. *Animal Reproduction Science* **144**, 60–71.

Fenlon A, O'Grady L, Mee JF, Butler ST, Doherty ML and Dunnion L (2017) A comparison of 4 predictive models of calving assistance and difficulty in dairy heifers and cows. *Journal of Dairy Science* **100**, 1–13.

Fleischer P, Metzner M, Beyerbach M, Hoedemaker M and Klee W (2001) The relationship between milk yield and the incidence of some diseases in dairy cows. *Journal of Dairy Science* **84**, 2025–2035.

Fragoso TM, Bertoli W and Louzada F (2018) Bayesian model averaging: a systematic review and conceptual classification. *International Statistical Review* **86**, 1–28.

Galbraith S, Daniel JA and Vissel B (2010) A study of clustered data and approaches. *The Journal of Neuroscience* **30**, 10601–10608.

Galvão KN, Flaminio MJBF, Brittin SB, Sper R, Fraga M, Caixeta L, Ricci A, Guard CL, Butler WR and Gilbert RO (2010) Association between uterine disease and indicators of neutrophil and systemic energy status in lactation Holstein cows. *Journal of Dairy Science* **93**, 2926–2937.

Gelman A, Carlin JB, Stern HS, Dunson DB, Vehtari A and Rubin DB (2014) *Bayesian Data Analysis*, 3rd Edn. Boca Raton, FL: Taylor & Francis Group, LLC.

Ghosh D and Yuan Z (2009) An improved model averaging scheme for logistic regression. *Journal of Multivariate Analysis* **100**, 1670–1681.

Goff JP (2008a) The monitoring, prevention, and treatment of milk fever and subclinical hypocalcemia in dairy cows. *Veterinary Journal* **176**, 50–57.

Goff JP (2008b). Transition cow immune function and interaction with metabolic diseases. *Tri-State Dairy Nutrition Conference, April 22 and 23, 2008*. pp. 45–57.

Goff JP and Horst RL (1997) Physiological changes at parturition and their relationship to metabolic disorders. *Physiology and Management* **80**, 1260–1268.

Gombart G (2012) *Vitamin D: Oxidative Stress, Immunity, and Aging*. Boca Raton, FL: CRC Press.

Gordis L (2014). *Epidemiology*. Philadelphia, PA: Elsevier Saunders, pp. 209–210.

Grandjean P (1995) Biomarkers in epidemiology. *Clinical Chemistry* **41**, 1800–1803.

Green MJ, Bradley AJ, Medley GF and Brown WJ (2007) Cow, farm, and management factors during the dry period determine the rate of clinical mastitis after calving. *Journal of Dairy Science* **90**, 3764–3776.

Grice JW (2001) Computing and evaluating factor scores. *Psychological Methods* **6**, 430–450.

Grohn YT, Eicker SW and Hertl JA (1995) The association between previous 305-day milk yield and disease in New York state dairy cows. *Journal of Dairy Science* **78**, 1693–1702.

Gurka MJ, Lilly CL, Oliver MN and DeBoer MD (2014) An examination of sex and racial/ethnic differences in the metabolic syndrome among adults: a confirmatory factor analysis and a resulting continuous severity score. *Metabolism* **63**, 218–225.

Hammon DS, Evjen IM, Dhiman TR, Goff JP and Walters JL (2006) Neutrophil function and energy status in Holstein cows with uterine health disorders. *Veterinary Immunology and Immunopathology* **113**, 21–29.

Hardin JW and Hilbe JM (2007) *Generalized Linear Models and Extensions*, 2nd Edn. College Station, Texas: Stata Press.

Harrell FE (2015) *Regression Modeling Strategies: With Applications to Linear Models, Logistic and Ordinal Regression, and Survival Analysis*, 2nd Edn. New York: Springer.

Heinrichs AJ, Costello SS and Jones CM (2009) Control of heifer mastitis by nutrition. *Veterinary Microbiology* **134**, 172–176.

Hilbe JM (2014) *Modeling Count Data*. New York, NY: Cambridge University Press.

Horst R, Goff JP and Reinhardt TA (1994) Symposium: calcium metabolism and utilization. *Journal of Dairy Science* **77**: 1936–1951.

Hosmer DW, Lemeshow S and Sturdivant RX (2013) *Applied Logistic Regression*, 3rd Edn. Hoboken, New Jersey: John Wily & Sons, Inc.

Huang PL (2009) A comprehensive definition for metabolic syndrome. *Disease Models and Mechanisms* **2**, 231–237.

Hutjens MF and Aalseth EP (2005) *Caring for Transition Cows*. Fort Atkinson, Wisconsin: W.D. Hoards & Sons.

Huzzey JM, Veira DM, Weary DM and von Keyserlingk MAG (2007) Prepartum behavior and dry matter intake identify dairy cows at risk for metritis. *Journal of Dairy Science* **90**, 3220–3233.

Huzzey JM, Nydam DV, Grant RJ and Overton TR (2011) Associations of prepartum plasma cortisol, haptoglobin, fecal cortisol metabolites, and nonesterified fatty acids with postpartum health status in Holstein dairy cows. *Journal of Dairy Science* **94**, 5878–5889.

Ingvartsen KL (2006) Feeding- and management-related diseases in the transition cow: physiological adaptations around calving and strategies to reduce feeding-related diseases. *Animal Feed Science and Technology* **126**, 175–213.

Ingvartsen KL, Dewhurst RJ and Friggens NC (2003) On the relationship between lactational performance and health: is it yield or metabolic imbalance that cause production diseases in dairy cattle? A position paper. *Livestock Production Science* **83**, 277–308.

International Diabetes Federation (IDF) (2006) *The IDF Consensus Worldwide Definition of the Metabolic Syndrome*. Brussels, Belgium: IDF.

Ivanescu AE, Li P, George B, Brown AW, Keith SW, Raju D and Allison DB (2016) The importance of prediction model validation and assessment in obesity and nutrition research. *International Journal of Obesity* **40**, 887–894.

Kerr KF and Pepe MS (2011) Joint modeling, covariate adjustment, and interaction contrasting notions in risk prediction models and risk prediction performance. *Epidemiology* **22**, 805–812.

Kim IH and Suh GH (2003) Effect of the amount of body condition loss from the dry of near calving periods on the subsequent body condition change, occurrence of postpartum diseases, metabolic parameters and reproductive performance in Holstein dairy cows. *Theriogenology* **60**, 1445–1456.

Klecka WR (1980) *Discriminant Analysis. Series: Quantitative Applications in the Social Science*. Newbery Park, London, New Delhi: Sage Publications, Inc.

Kulberg S, Storset AK, Heringstad B and Larsen HJS (2002) Reduced levels of total leukocytes and neutrophils in Norwegian cattle selected for decreased mastitis incidence. *Journal of Dairy Science* **85**, 3470–3475.

LeBlanc SJ (2008) Postpartum uterine disease and dairy herd reproductive performance: a review. *Veterinary Journal* **176**, 102–114.

LeBlanc SJ (2010) Monitoring metabolic health of dairy cattle in the transition period. *Journal of Reproductive Development* **56** (Suppl), S29–S35.

LeBlanc SJ, Duffield TF, Leslie KE, Batement KG, TenHag J, Walton JS and Johnson WH (2002) The effect of prepartum injection of vitamin E on health in transition dairy cows. *Journal of Dairy Science* **85**, 1416–1426.

LeBlanc SJ, Herdt TH, Seymour WM, Duffield TF and Leslie KE (2004) Peripartum serum vitamin E, retinol, and beta-carotene in dairy cattle and their associations with disease. *Journal of Dairy Science* **87**, 609–619.

https://doi.org/10.1017/S1466252319000112 Published online by Cambridge University Press

LeBlanc SJ, Leslie KE and Duffield TF (2005) Metabolic predictors of displaced abomasum in dairy cattle. *Journal of Dairy Science* **88**, 159–170.

LeBlanc SJ, Lissemore KD, Kelton DF, Duffield TF and Leslie KE (2006) Major advances in disease prevention in dairy cattle. *Journal of Dairy Science* **89**, 1267–1279.

Leite MLC, Nicolosi A, Firmo JOA and Lima-Costa MF (2007) Features of metabolic syndrome in non-diabetic Italians and Brazilians: a discriminant analysis. *International Journal of Clinical Practice* **61**, 32–38.

Lemeshow S and Hosmer DW (1982) A review of goodness of fit statistics for use in the development of logistic regression models. *American Journal of Epidemiology* **115**, 92–106.

Li RH and Belford GG (2002) Instability of decision tree classification algorithms. *Proceedings of the 8th ACM SIGKDD International Conference on Knowledge Discovery and Data mining, Edmonton*. pp. 570–575.

Li C and Ford ES (2007) Is there a single underlying factor for the metabolic syndrome in adolescents? *Diabetes Care* **30**, 1556–1561.

Lima FS, Filho MF, Greco LF and Santos JEF (2012) Effects of feeding rumen-protected choline on incidence of diseases and reproduction of dairy cows. *The Veterinary Journal* **193**, 140–145.

Loh WY (2011) Classification and regression trees. *WIREs Data Mining and Knowledge Discovery* **1**, 14–23.

Long SJ and Freese J (2006) *Regression Models for Categorical Dependent Variables Using Stata*, 2nd Edn. College Station, Texas: Stata Press.

Ma X (2018) *Using Classification and Regression Trees: A Practical Primer*. Charlotte, NC: Information Age Publishing Inc.

Malarkey LM and McMorrow ME (2011) *Saunders Nursing Guide to Laboratory and Diagnostic Tests*, 2nd Edn. New York: Elsevier.

Mazerolle MJ (2006) Improving data analysis in herpetology: using Akaike's Information Criterion (AIC) to assess the strength of biological hypotheses. *Amphibia-Reptilia* **27**, 169–180.

McArt JAA, Nydam DV and Oetzel GR (2012) Epidemiology of subclinical ketosis in early lactation dairy cattle. *Journal of Dairy Science* **95**, 5056–5066.

McArt JAA, Nydam DV and Oetzel GR (2013) Dry period and parturient predictors of early lactation hyperketonemia in dairy cattle. *Journal of Dairy Science* **96**, 198–209.

McCrum-Gardner E (2008) Which is the correct statistical test to use? *British Journal of Oral and Maxillofacial Surgery* **46**, 38–41.

McDowell LR, Wilkinson N, Madison R and Felix T (2007) Vitamins and minerals functioning as antioxidants with supplementation considerations. *Florida Ruminant Nutrition Symposium, Gainesville, Florida*.

McLachlan G (2004) *Discriminant Analysis and Statistical Pattern Recognition*. Hoboken, New Jersey: John Wiley & Sons, Inc.

Melendez P, Barolome J, Archbald LF and Donovan A (2003) The association between lameness, ovarian cysts, and fertility in lactation dairy cows. *Theriogenology* **59**, 927–937.

National Animal Health Monitoring System (NAHMS) (1996) Part 1: Reference of 1996 Dairy Management Practices. Fort Collins, Colorado: United States Department of Agriculture Animal and Plant Health Inspection Service: Veterinary Sciences: Centers for Epidemiology and Animal Health (USDA: APHIS: VS: CEAH).

National Animal Health Monitoring System (NAHMS) (2018) Health and Management Practices on U.S. Dairy Operations, 2014. Fort Collins, Colorado: United States Department of Agriculture-Animal and Plant Health Inspection Service: Veterinary Sciences: Centers for Epidemiology and Animal Health (USDA: APHIS: VS: CEAH).

Neave HW, Lomb J, von Keyserlingk MAG, Behnam-Shabahang A and Weary DM (2017) Parity differences in the behavior of transition dairy cows. *Journal of Dairy Science* **100**, 548–561.

Nezlek JB (2008) An introduction to multilevel modeling for social and personality psychology. *Social and Personality Psychology Compass* **2**, 842–860.

Ngo THD (2016) Generalized linear models for non-normal data. *Proceedings from SAS Global Forum 2016, Las Vegas, NV, April 18–21, 2016*.

Nordlund K, Cook N and Oetzel G (2006). Commingling dairy cows: pen moves, stocking density, and health. *39th Proceedings American Association Bovine Practitioners, St. Paul, MN, September 20–24, 2006*. pp. 36–42.

Oetzel GR (2004) Monitoring and testing dairy herds for metabolic disease. *Veterinary Clinics Food Animal Practice* **20**, 651–674.

Ospina PA, Nydam DV, Stokol T and Overton TR (2010) Associations of elevated nonesterified fatty acids and beta-hydroxybutyrate concentrations with early lactation reproductive performance and milk production in transition dairy cattle in the northeastern United States. *Journal of Dairy Science* **93**, 1596–1603.

Ospina PA, McArt JA, Overton TR, Stokol T and Nydam DV (2013) Using nonesterified fatty acids and beta-hydroxybutyrate concentrations during the transition period for herd level monitoring of increased risk of disease and decreased reproductive and milking performance. *Veterinary Clinics of North America – Food Animal Practice* **29**, 387–412.

Overton TR and Waldron MR (2004) Nutritional management of transition dairy cows: strategies to optimize metabolic health. *Journal of Dairy Science* **87**(E. Suppl.), E105–E119.

Pavlou M, Ambler G, Seaman SR, Guttmann O, Elliot P, King M and Omar RZ (2015) How to develop a more accurate risk prediction model when there are few events. *British Medical Journal* **351**, h3868.

Peng CJ, Lee KL and Ingersoll GM (2002) An introduction to logistic regression analysis and reporting. *The Journal of Educational Research* **96**, 3–14.

Pepys MB (2012) *Acute Phase Proteins in the Acute Phase Response*. London: Spring-Verlag London Limited.

Petrovski KR, Trajcev M and Buneski G (2006) A review of the factors affecting the costs of bovine mastitis. *Journal of the South African Veterinary Association* **77**, 52–60.

Pladevall M, Singal B, Williams LK, Brotons C, Guyer H, Sadurni J, Falces C, Serrano Rios M, Gabriel R, Shaw JE, Zimmet PZ and Haffner SH (2006) A single factor underlies the metabolic syndrome. *Diabetes Care* **29**, 113–122.

Potter TJ, Guitian J, Fishwish J, Gordon PJ and Sheldon IM (2010) Risk factors for clinical endometritis in postpartum dairy cattle. *Theriogenology* **74**, 127–134.

Press SJ and Wilson S (1978) Choosing between logistic regression and discriminant analysis. *Journal of the American Statistical Association* **73**, 699–705.

Putman AK, Brown JL, Gandy JC, Wisnieski L and Sordillo LM (2018) Changes in biomarkers of nutrient metabolism, inflammation, and oxidative stress in dairy cows during the transition into the early dry period. *Journal of Dairy Science* **101**, 9350–9359.

Rabe-Hesketh S and Skrondal A (2008) *Multilevel and Longitudinal Model Using Stata*, 2nd Edn. College Station, Texas: Stata Press.

Richert RM, Cicconi KM, Gamrock MJ, Schukken YN, Stiglbauer KE and Ruegg PL (2013) Risk factors for clinical mastitis, ketosis, and pneumonia in dairy cattle on organic and small conventional farms in the United States. *Journal of Dairy Science* **96**, 1–17.

Roche JR, Friggens NC, Kay JK, Fisher MW, Stafford KJ and Berry DP (2009) Invited review: body condition score and its association with dairy cow productivity, health, and welfare. *Journal of Dairy Science* **92**, 5769–5801.

Sainani KL (2014) Explanatory versus predictive modeling. *Physical Medicine and Rehabilitation* **6**, 841–844.

Santos JEP, Bisinotto RS, Ribeiro ES, Lima FS and Thatcher WW (2012) Impacts of metabolism and nutrition during the transition period on fertility of dairy cows. *2012 High Plains Dairy Conference, Amarillo, Texas*. pp. 97–112.

Saun V (2004) Metabolic profiling and health risk in transition cows. *Proceedings 37th Annual American Association of Bovine Practitioners Convention, Ft. Worth, Texas, September 23–25, 2004*. pp. 212–213.

Schmidt CO and Kohlmann T (2008) When to use the odds ratio or the relative risk? *International Journal of Public Health* **53**, 165–167.

Seifi HA, LeBlanc SJ, Leslie KE and Duffield TF (2011) Metabolic predictors of post-partum disease and culling risk in dairy cattle. *The Veterinary Journal* **188**, 216–220.

Shmueli G (2010) To explain or to predict? *Statistical Science* **25**, 289–310.

Shtatland ES, Cain E and Barton MB (2001) The perils of stepwise logistic regression and how to escape them using information criteria and the output delivery system. *Proceedings from the 26th Annual SAS Users Group International Conference*. pp. 222–226.

Shtatland ES, Kleinman K and Cain EM (2004) A new strategy of model building in PROC LOGISTIC with automatic variable selection, validation, shrinkage, and model averaging. *Proceedings from SUGI'29, Cary, NC*. pp. 121–129.

https://doi.org/10.1017/S1466252319000112 Published online by Cambridge University Press

Simensen E, Ostera O, Boe KE, Kielland C, Rudd LE and Naess G (2010) Housing system and herd size interactions in Norwegian dairy herds; association with performance and disease incidence. *Acta Veterinaria Scandinavica* **52**, 14.

Singal AG, Mukherjee A, Elmunzer BJ, Higgins PDR, Lok AS, Zhu J, Marrero JA and Walijee AK (2013) Machine learning algorithms outperform conventional regression models in predicting development of hepatocellular carcinoma. *American Journal of Gastroenterology* **108**, 1723–1730.

Sordillo LM and Aitken SL (2009) Impact of oxidative stress on the health and immune function of dairy cattle. *Veterinary Immunology and Immunopathology* **128**, 104–109.

Sordillo L and Erskine R (2010) Bovine leukosis virus update II: impact on immunity and disease resistance. *Michigan Dairy Review* **15**, 4–5.

Sordillo LM and Mavangira V (2014) The nexus between nutrient metabolism, oxidative stress and inflammation in transition cows. *Animal Production Sciences* **54**, 1204–1214.

Sordillo LM and Raphael W (2013) Significance of metabolic stress, lipid mobilization, and inflammation on transition cow disorders. *Veterinary Clinics of North America: Food Animal Practice* **29**, 267–278.

Spears JW and Weiss WP (2008) Role of antioxidants and trace elements in health and immunity of transition dairy cows. *Veterinary Journal* **176**, 70–76.

Steensels M, Antler A, Bahr C, Berckmans D, Maltz E and Halachmi I (2016) A decision tree model to detect post-calving disease based on rumination, activity, milk yield, BW, and voluntary visits to the milking robots. *Animal: An International Journal of Animal Bioscience* **10**, 1493–1500.

Steyerberg EW, Eijkemans MJC and Habbema JDF (2001*a*) Application of shrinkage techniques in logistic regression analysis: a case study. *Statistica Neerlandica* **55**, 76–88.

Steyerberg EW, Harrell Jr FE, Borsboom GJJM, Eijkemans MJCR, Vergouwe Y and Habbema DF (2001b) Internal validation of predictive models: efficiency of some procedures for logistic regression analysis. *Journal of Clinical Epidemiology* **54**, 774–781.

Suhr DD (2006) Exploratory or confirmatory factor analysis. *SAS Users Group International Conference*. Cary: SAS Institute, Inc., pp. 1–17.

Turner H (2008) Introduction to generalized linear models. ESRC National Centre for Research Methods, UK and Department of Statistics, University of Warwick. Available at http://statmath.wu.ac.at/courses/heather_turner/glmCourse_001.pdf (Accessed 23 June 2018).

van Breukelen GJP and Candel MJJM (2012) Calculating sample sizes for cluster randomized trials: we can keep it simple and efficient! *Journal of Clinical Epidemiology* **65**, 1212–1218.

Van der Ark LA, Croon MA and Sijtsma K (eds.) (2012) *New Developments in Categorical Data Analysis for the Social and Behavioral Sciences*. New York, NY and Hove, East Sussex: Psychology Press.

Vanholder T, Papen J, Bemers R, Vertenten G and Berge ACB (2015) Risk factors for subclinical and clinical ketosis and association with production parameters in dairy cows in the Netherlands. *Journal of Dairy Science* **98**, 880–888.

Van Saun RJ and Sniffen CJ (2014) Transition cow nutrition and feeding management for disease prevention. *Veterinary Clinics of North America: Food Animal Practice* **30**, 689–719.

Vergara CF, Dopfer D, Cook NB, Nordlund KV, McArt A, Nydram DV and Oetzel GR (2014) Risk factors for postpartum problems in dairy cows: explanatory and predictive modeling. *Journal of Dairy Science* **97**, 4127–4140.

Wathes DC, Cheng Z, Bourne N, Taylor VJ, Coffey MP and Brotherstone S (2007) Differences between primiparous and multiparous dairy cows in the inter-relationships between metabolic traits, milk yield and body condition score in the periparturient period. *Domestic Animal Endocrinology* **33**, 203–225.

Weiss WP (1998) Requirements of fat-soluble vitamins for dairy cows: a review. *Journal of Dairy Science* **81**, 2493–2501.

Wisnieski L, Norby B, Pierce SJ, Becker T, Gandy JC and Sordillo S (2019a) Predictive models for early lactation diseases in transition dairy cattle at dry-off. *Preventive Veterinary Medicine* **163**, 68–78.

Wisnieski L, Norby B, Pierce SJ, Becker T, Gandy JC and Sordillo S (2019b) Cohort-level disease prediction by extrapolation of individual-level predictions in transition dairy cattle. *Preventive Veterinary Medicine* **169**, 104692.

Wisnieski L, Norby B, Pierce SJ, Becker T, Gandy JC and Sordillo S (2019c) Cohort-level disease prediction using aggregate biomarker data measured at dry-off in transition dairy cattle: a proof-of-concept study. *Preventive Veterinary Medicine* **169**, 104692.

Yang FL and Li XS (2015) Role of antioxidant vitamins and trace elements in mastitis in dairy cows. *Journal of Advanced Veterinary and Animal Research* **2**, 1–9.

Yang RZ, Lee MJ, Hu H, Pollin TI, Ryan AS, Nicklas BJ, Snitker S, Horenstein RB, Hull K, Goldberg NH, Goldberg AP, Shuldiner AR, Fried SK and Gong DW (2006) Acute-phase serum amloid A: an inflammatory adipokine and potential link between obesity and its metabolic complications. *PLoS Medicine* **3**, e287.

Yin K and Agrawal DK (2014) Vitamin D and inflammatory diseases. *Journal of Inflammation Research* **7**, 69–87.

Zaborski D, Grzesiak W and Pilarczyk R (2016) Detection of difficult calvings in the polish Holstein black-and-white heifers. *Journal of Applied Animal Research* **44**, 42–53.

Zhang G, Hailemariam D, Dervishi E, Deng Q, Goldansaz SA, Dunn SM and Ametaj BN (2015) Alterations of innate immunity reactants in transition dairy cows before clinical signs of lameness. *Animals* **5**, 717–747.

Zorn C (2005) A solution to separation in binary response models. *Political Analysis* **13**, 157–170.

Zurbrigg K, Kelton D, Anderson N and Millman S (2005) Tie-stall design and its relationship to lameness, injury, and cleanliness on 317 Ontario Dairy Farms. *Journal of Dairy Science* **88**, 3201–3210.

https://doi.org/10.1017/S1466252319000112 Published online by Cambridge University Press