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Behavioral patterns as indicators of resilience after parturition in dairy cows

I. D. E. van Dixhoorn,[1]* R. M. de Mol,[1] S. K. Schnabel,[2] J. T. N. van der Werf,[1] S. van Mourik,[3] J. E. Bolhuis,[4] J. M. J. Rebel,[5] and C. G. van Reenen[1]
[1]Wageningen Livestock Research, 6708 WD Wageningen, the Netherlands
[2]Biometris, Wageningen, Plant Research, Wageningen University and Research, 6708 PB Wageningen, the Netherlands
[3]Wageningen Farm Technology Group, Wageningen University and Research, 6708 PB Wageningen, the Netherlands
[4]Wageningen Adaptation Physiology, Wageningen University and Research, 6708 WD Wageningen, the Netherlands
[5]Wageningen Bio-Veterinary Research, Wageningen University and Research, 8221 RA Lelystad, the Netherlands

ABSTRACT

During the transition phase, dairy cows are susceptible to develop postpartum diseases. Cows that stay healthy or recover rapidly can be considered to be more resilient in comparison to those that develop postpartum diseases. An indication of loss of resilience will allow for early intervention with preventive and supportive measures before the onset of disease. We investigated which quantitative behavioral characteristics during the dry period could be used as indicators of reduced resilience after calving, using noninvasive Smart Tag neck and Smart Tag leg sensors in dairy cows (Nedap N.V.). We followed 180 cows during 2 wk before until 6 wk after parturition at 4 farms in the Netherlands. Serving as proxy for loss of resilience, as defined by the duration and severity of disease, a clinical assessment was performed twice weekly and blood samples were taken in the first and fifth week after parturition. For each cow, clinical and serum value deviations were aggregated into a total deficit score (TDS total). We also calculated TDS values relating to inflammation, locomotion, or metabolic problems, which were further divided into macro-mineral and liver-related deviations. Smart Tag neck and leg sensors provided continuous behavioral activity signals of which we calculated the average, variance, and autocorrelation during the dry period. Diurnal patterns in the behavioral activity signals were derived by fast Fourier transformation and the calculation of the nonperiodicity. To select significant predictors of resilience, we first performed a univariate analysis with TDS as dependent variable and the behavioral characteristics that were measured during the dry period, as potential predictors with cow as experimental unit. We included parity group as fixed effect and farm as random effect. Next, we performed multivariable analysis with only significant predictors, followed by a variable selection procedure to obtain a final linear mixed model with an optimal subset of predictors with parity group as fixed effect and farm as random effect. The TDS total was best predicted by average inactive time, nonperiodicity ruminating, nonperiodicity of bouts standing up and fast Fourier transformation stand still. Average inactive time was negatively correlated with average eating time, and these 2 predictors could be exchanged with only little difference in model performance. Our best performing model predicted TDS total at a cutoff level of 60 points, with a sensitivity of 79.5% and a specificity of 73.2% with a positive predicted value of 0.69 and a negative predicted value of 0.83. The models to predict the other TDS categories showed a lower predictive performance as compared with the TDS total model, which could be related to the limited sample size and therefore, low occurrence of problems within a specific TDS category. Furthermore, more resilient dairy cows are characterized by high averages of eating time with high regularity in rumination and low averages of inactive time. They reveal high regularity in standing time and transitions from lying to standing, in the dry period. These behaviors can be used as indicators of resilience and allow for preventive intervention during the dry period in vulnerable dairy cattle. However, further examination is still required to find clues for adequate intervention strategies.

Key words: transition period, resilience, postpartum disease, sensor data

INTRODUCTION

Around the time of calving 30 to 50% of dairy cows are affected by some form of postpartum disorder (LeBlanc, 2010; Wisnieski et al., 2019). During this transition phase, dairy cows face metabolic and physiological changes in preparation for calving and milk production. Failure to adequately adapt and cope can lead to metabolic stress, which increases the risk for

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*Corresponding author: ingrid.vandixhoorn@wur.nl

postpartum disorders (LeBlanc et al., 2006; Belaid et al., 2021). As a consequence, postpartum disorders may occur, including ketosis, a fatty liver, digestive issues, macro-mineral imbalance and inflammatory complications, or more frequently, a combination of these (Sordillo and Mavangira, 2014; Sundrum, 2015; Wankhade et al., 2017).

Resilience is defined for animals as the capacity to remain healthy, or respond minimally and recover rapidly in response to challenges (Ge et al., 2016; Scheffer et al., 2018; Wright et al., 2019; Friggens et al., 2022). These challenges might be intrinsically driven, such as pregnancy, parturition, or milk production, or may be generated externally by factors such as pathogens or stress due to regrouping, overcrowding, inadequate housing, or farm management. During the transition phase of dairy cows, both internal and external challenges can occur simultaneously. Cows that do not develop postpartum disorders or recover rapidly can be considered as highly resilient animals. The variation in clinical manifestation of impaired health in terms of severity, duration and recovery of postpartum disease can therefore be used as a measure or deviation of resilience during the periparturient period in the life of a dairy cow (van Dixhoorn et al., 2018). An indication of a cow's lack of resilience before the lactation period even starts, may allow for early intervention with preventive or supportive measures.

At present, it remains debatable which indicators, or combinations thereof, reflect the capacity to adequately cope with the transition period. Metabolic stress biomarkers and other indicators associated with oxidative stress or inflammation have been described as predictors of postpartum disease, but may require invasive blood sampling (LeBlanc, 2010; Ospina et al., 2010; Huzzey et al., 2011; Wisnieski et al., 2019). In addition, the time of measurement might influence the outcome, and a multitude of sampling time points are required to assess dynamic patterns. When using noninvasive accelerometers in dairy cows, specific behavioral activity signals can be obtained recording their lying, walking, standing, eating, or even ruminating motions. Moreover, activity patterns that span multiple days, as well as deviations from these patterns, can be quantified. Variance and autocorrelation (**AC**) can be calculated from the longitudinal data and the data can also be converted into individual spectral components, which provide frequency information about the respective signals. Variance, autocorrelation, the skewness of deviations, the slope of a reaction norm and circadian rhythm patterns derived from behavioral measurements, have previously been proposed as potential dynamic indicators of resilience (**DIOR**) in individual animals (Scheffer et al., 2018; van Dixhoorn et al., 2018; Berghof et al., 2019; van der Zande et al., 2020; Poppe et al., 2022).

In this paper we aimed to investigate if behavioral characteristics during the dry period could be used as indicators of resilience using noninvasive Smart Tag Neck and Smart Tag Leg sensors (Nedap N.V.) in dairy cows. We tested the hypothesis that behavioral activity signals measured in the dry period can be used as predictors for disease severity after calving. We designed a statistical model and evaluated various potential sensor-based behavioral variables that were measured during the dry period as predictors for decreased resilience in terms of disease severity and duration after parturition. Subsequently, we tested the reliability of the detection method in terms of true and false positive rates.

MATERIALS AND METHODS

The established principles of laboratory animal use and Dutch laws related to animal experiments were adhered to in this study. The Wageningen University Animal Care and Use Committee (Lelystad Department) approved the experiment under protocol number AVD401002016749 with samples size of 170 cows based on a prediction of a total deficit score (**TDS**) value with sensor data.

Animals, Housing, and Diet

The present study was conducted between July 2017 and September 2018 at 4 commercial dairy farms located in the Netherlands. A total of 180 Holstein-Friesian dairy cows were monitored from 2 wk before expected parturition until 6 wk after parturition. Cows enrolled in the study once based on the expected day of parturition. Cows were used in the analysis when they showed no clinical signs of illness before parturition and when a complete data set until 6 wk after calving was available, resulting in 173 cows (37 primiparous, 43 parity 2, 38 parity 3, and 55 parity 4 and higher). At all 4 farms dry and lactating cows were housed in cubicles in the same building in which a straw bedded maternity pen also was present. Cows were moved to the maternity pen with the first signs of parturition and they stayed there until 1 to 3 d after calving. Thereafter they were introduced into pens with lactating cows. Thus, group size and composition changed due to (re)introduction but cows remained in the same group after calving until the next dry period. Postpartum cows were milked twice daily and water was provided ad libitum on all farms.

Farm 1 had 125 cows with an average production of 9,050 kg of milk per year (with 4.35% fat and 3.71%

protein). Cows were milked twice daily at 7:00 a.m. and 6:15 p.m. and fed TMR once per day at 9:30 a.m. and this was pushed to the feeding fence at 8:30 p.m. and 10:15 p.m. Feed residues were removed from the fed bunk before each new TMR delivery. Lights were on at 6:30 a.m. and off at 11:00 p.m.

Farm 2 had 100 cows with an average production of 9,430 kg of milk per year (with 4.35% fat and 3.55% protein). Cows were milked twice daily at 6:00 a.m. and 5:45 p.m. and fed TMR once per day at 8:30 a.m. and this was pushed to the feeding fence at 5:30 p.m. Feed residues were removed from the fed bunk before each new TMR delivery. Lights were on at 5:15 a.m. and off at 10:15 p.m.

Farm 3 had 75 cows with an average production of 8,900 kg of milk per year (with 4.53% fat and 3.52% protein). Cows were milked twice daily at 5:45 a.m. and 5:00 p.m. and fed TMR once per day at 1:30 p.m., and this was pushed to the feeding fence at 5:40 a.m., 4:55 p.m., 8:00 p.m., and 10:30 p.m. Feed residues were removed from the fed bunk before each new TMR delivery. Lights were on at 5:45 a.m., and nightlights were switched on at 10:30 p.m.

Farm 4 had 150 cows with an average production of 8,900 kg of milk per year (with 4.34% fat and 3.59% protein). Cows were milked twice daily at 5:30 a.m. and 4:30 p.m. and fed TMR once per day at 4:30 p.m., and this was pushed to the feeding fence at 8:30 a.m. and 10:30 p.m. Feed residues were removed from the fed bunk before each new TMR delivery. Nightlights were switched on based on a dusk sensor.

Clinical Examination and Blood Sampling

Cows were scored clinically by 4 veterinarians twice weekly until 6 wk after parturition. The veterinarians scored 19 different clinical signs (Table 1) of the cows and they estimated overall condition according to measurements and cutoff values as earlier described by Hajer et al. (2011) in which clinical examination according to a fixed format is described as well as normal and deviating clinical values per organ system. The following aspects were scored: heart rate (beats per minute), breathing rate (breaths per minute), rectal temperature (°C), rumination (chews per minute), BCS according to Edmonson et al. (1989), and locomotion score and lameness according to Hulsen (2012). Udder condition was scored per quarter in terms of skin temperature (too warm, too cold, or normal), color (red, abnormal, normal), painful during palpation (yes or no), swollen (yes or no), and teat condition was scored in terms of flexibility (yes or no), color (red, normal, abnormal), and painful during palpation (yes or no). Retained placenta was scored if it was protruding from the vulva after more than 24 h after calving. Uterus condition and excretion were scored by rectal palpation, the size was estimated and assigned as normal or abnormal according to the expected involution. The color and smell of vaginal discharge and the amount of mucus or pus was estimated. The consistency and digestion of the manure was scored according to Hulsen (2012). Other specific clinical diagnoses consisted of hypocalcemia, or a displaced abomasum, confirmed by auscultation. Interobserver variation between the trained veterinarians was verified every 4 mo. The veterinarians were blinded to scores of other veterinarians and the individual cow treatments. Blood samples were collected from the coccygeal vein into 10-mL sterile serum tubes (Vacutainer, Becton Dickinson) in the first (1.8 ± 1.2 d) and fifth week (29.8 ± 1.6 d) after calving. Samples were submitted to the routine veterinary laboratory of Royal GD (Deventer, the Netherlands). This laboratory performed all analyses and works according to a quality management system meeting NEN-EN-ISO 9001:2015 requirements and Clinical-chemical parameters were assessed using UniCel DxC 600 Synchron Clinical System (Beckman Coulter). Test procedures for all parameters (except for calcium, magnesium, IL6, and haptoglobin) were NEN-EN-ISO/IEC 17025:2017 accredited by the Dutch Accreditation Council (2023). Colorimetric methods were used to analyze serum calcium, phosphorus (ammonium-molybdate method), magnesium, total bilirubin, (dimethylsulphoxide method), haptoglobin, total protein (**TP**; Biuret method) and albumin concentrations (Bromocresol Green method). The globulins were calculated by subtraction: TP − albumins (g/L). Enzymatic methods were used to analyze serum urea (urease method), nonesterified fatty acids (**NEFA**) and β-hydroxybutyric acid (**BHBA**) concentrations. Aspartate aminotransferase (**AST**) and gamma-glutamyl transferase concentrations were analyzed using enzymatic methods according to the International Federation of Clinical Chemistry reference procedures for the measurement of catalytic activity concentrations of enzymes at 37°C. Interleukin-6 concentrations in serum were analyzed using an AlphaLISA Bovine IL-6 Detection Kit (PerkinElmer Inc.) following the kit's instructions. The interassay coefficient of variation was below 10% for all methods.

Postpartum TDS

As measure for disease severity was calculated as previously described by van Dixhoorn et al. (2018) and was referred to as TDS**.** Briefly, all aberrant clinical findings were used to calculate TDS. Table 1 lists which clinical values were assigned to metabolic stress, inflammation, and locomotion. This resulted in 4 different TDS scores:

Table 1. Overview of the clinical observations that were assessed twice per week by trained veterinarians on 4 selected farms (in total, 180 cows enrolled in the study from 2 wk before expected parturition day until 6 wk after parturition)[1]

Clinical observation	Points	TDS
Ears cold	1 if yes	Inflammation, Metabolic, Total
Secretion from nose visible	1 if yes	Inflammation, Total
Jugular pulse visible above mid neck region	1 if yes	Inflammation, Total
Rectal temperature	1 if >39.2 2 if >40	Inflammation, Total
Breathing abnormal (>30 breaths/min)	1 if yes	Inflammation, Total
BCS[2]	1 if difference between BCS in dry period >1	Metabolic, Total
Rumen visible when standing behind cow	1 if no	Metabolic, Total
Rumen fill weak	1 if yes	Metabolic, Total
Rumen score[2]	0 if score 3–5; 2 if score = 0; 1 if score = 1	Metabolic, Total
Udder edema palpable	1 if yes	Total
Udder score per quarter		
Firm LF, RF, LB, RB[3]	0.5 if yes per quarter	Inflammation, Total
Red LF, RF, LB, RB[3]	0.5 if yes per quarter	Inflammation, Total
Abnormal uterus fill, excreta	1 if yes	Inflammation, Total
Manure score[2]	2 if score = 1, 1 if score is 2 and 5, 0 if score is 3 to 4	Metabolic, Total
Abnormal digestion visible in manure	1 if yes	Metabolic, Total
Locomotion score[2]	0 if score 1 or 2; 1 if score = 3–5	Locomotion, Total
Lame LB, LF, RB, RF[3]	1 if yes per leg	Locomotion, Total
Cow is diagnosed with a disease	2 if yes	Assigned to specific TDS depending on disease
Treatment	2 if yes	Assigned to specific TDS depending on disease

[1]The values assigned to the total deficit score (TDS) categories per deviating clinical observation, are presented. The TDS categories consisted of total, inflammation, locomotion, and metabolic. Each suboptimal clinical value (according to the references values) was scored with 0.5, 1, or 2 points.

[2]References used for interpretation of observations and score systems for BCS, manure score, locomotion, and rumen score according to Royal GD, Deventer, the Netherlands (Gezondheidsdienst, Hajer et al., 2011).

[3]LF: left front, RF: right front, LB: left back, RB: right back. Diseases that could be diagnosed were mastitis, metritis, displaced abomasum, milk fever, lameness, respiratory disease, diarrhea.

TDS total, TDS inflammation, TDS locomotion, and TDS metabolic. In addition, serum values contributed to TDS when they were below or above specific thresholds (Table 2). Based on specific serum values, TDS metabolic was subdivided into scores related to liver function (TDS liver) and macro-mineral shortage (TDS macro-minerals). The points assigned to the different TDS categories are shown in Table 1 and 2. Suboptimal clinical findings were counted as one point of the TDS (dimensionless) per sampling moment during the 6-wk period after calving. When the veterinarian diagnosed a specific disease (retained placenta, metritis, mastitis, lameness, displaced abomasum, respiratory infection, milk fever, diarrhea), the specific diagnosis was reported and 2 points were assigned to the respective TDS. In addition, related treatments received 2 points. Each corresponding deviating serum value at the 2 sampling moments (wk 1 and 5 after parturition) received 6 TDS points. As a consequence, healthy cows showed low TDS values in contrast to cows with high TDS values, suffering more health-related issues during the 6-wk study period.

Cutoff values for serum value parameters were based on the upper and or lower limit of the reference intervals for the corresponding parameters as provided by veterinary laboratory of Royal GD (Deventer, the Netherlands), except for BHBA, NEFA, and calcium. The cutoff value for BHBA was chosen based on the threshold for subclinical ketosis (Duffield et al., 2009), whereas the for NEFA was chosen based on the threshold for an increased risk of early-lactation culling, and clinical diseases (Ospina et al., 2010; Roberts et al., 2012; Ospina et al., 2013). The cutoff value for calcium was chosen based on the thresholds for clinical hypocalcemia as described by Kimura et al. (2006) and Martinez et al. (2012).

Predictive Behavioral Variables

Behavioral activity data were obtained during the 2 wk before calving using the Smart Tag neck and leg sensors manufactured by Nedap N.V. The sensors were previously validated for accuracy by Borchers et al. (2021). The neck sensor provided 4 activity features per cow: eating, ruminating, inactive, or active [time spent (min/h), Table 3]. We aggregated the basic data into hourly data by aggregating the minutes per clock hour. In addition, the neck sensor provided an overall activity level per 15 min, which was registered as a dimensionless measure provided by the manufacturer.

Table 2. Overview of the serum parameters that were taken from 180 cows on 4 farms in wk 1 and 5 after calving; the cutoff values per serum parameter are specified for wk 1 and wk 5 separately, and the total deficit score (TDS) categories to which the points were assigned are given[1]

Parameter[2]	Unit	TDS	Wk 1	Wk 5
Total protein	g/L	Inf, Total	>85	>85
Total protein	g/L	Met, Total	<55	<55
Albumin	g/L	Met, Total	<31	<31
Urea	mmol/L	Met, Total	<3.3	<3.3
Urea	mmol/L	Met, Total	>6.6	>6.6
NEFA[3]	mmol/L	Met, Total	>0.8	>0.4
BHBA[4]	mmol/L	Met, Total	>1.2	>1.2
Calcium	mmol/L	Macro, Met, Total	<2.00 (d 0–1) <2.20 (d 2–7)	<2.20
Magnesium	mmol/L	Macro, Met, Total	<0.78	<0.78
Phosphorus	mmol/L	Macro, Met, Total	<0.9	<1.1
AST[5]	IU/L	Liver, Met, Total	>115	>115
GGT[6]	IU/L	Liver, Met, Total	>34	>34
Total bilirubin	µmol/L	Liver, Met, Total	>7	>7
Haptoglobin	g/L	Inf, Total	>0.6	>0.3
IL-6	ng/mL	Inf, Total	>10	—
Globulins (TP[7]-albumin)	g/L	Inf, Total	>49 and TP <85 and albumin >31	>49 and TP <85 and albumin >31

[1]The TDS categories consisted of TDS total, TDS inflammation (Inf), and TDS metabolic (Met), with TDS metabolic subdivided into TDS scores related to liver function (Liver) and macro-mineral shortage (Macro). Per sampling point (wk 1 and wk 5), a level exceeding the values as indicated in the last 2 columns counted as 6 points in the TDS.

[2]Cut-off values of serum metabolites parameters were based on the upper and or lower limit of the reference intervals for the corresponding parameters as provided by veterinary laboratory of Royal GD (Deventer, the Netherlands; Gezondheidsdienst voor Dieren, 2023), except for BHBA, NEFA, and calcium. The cutoff value for BHBA was chosen based on the threshold for subclinical ketosis (Duffield et al., 2009), whereas the cutoff value for NEFA was chosen based on the threshold for an increased risk of early-lactation culling and clinical diseases (Ospina et al., 2010, 2013; Roberts et al., 2012). The threshold for calcium was based on Kimura et al. (2006) and Martinez et al. (2012). The average DIM of blood sample collection were 1.8 ± 1.2 d and 29.8 ± 1.6 d for the sampling time points at the first and fifth weeks, respectively.

[3]NEFA = nonesterified fatty acids.

[4]BHBA = β-hydroxybutyric acid.

[5]AST = aspartate aminotransferase.

[6]GGT = gamma-glutamyl transferase.

[7]TP = total protein.

Overall activity level was aggregated in an activity level (dimensionless) per hour. The leg sensor recorded 3 behaviors per cow per 15 min (Table 3): lying, standing still, and walking. These behavioral durations were expressed in full minutes. During each 15-min time segment, the leg sensor provided a count of steps and a count of transitions from lying to standing or walking. We computed this basic data into hourly data by aggregating the 4 hourly time slots with starting times at each clock hour. The leg sensor revealed the partition or count per cow per hour as follows: time spent lying, standing still, walking, not lying (standing still + walking, min/h), counts of steps, and counts of transitions from lying to standing (bouts standing up).

Next, we calculated average, variance, autocorrelation (with lag $\tau = 1$ h), nonperiodicity and fast Fourier transformation (**FFT**) for each variable using the hourly data per cow for the dry period, starting 15 d before calving up to and including the day before calving. The variance describes the distribution of the data

Table 3. Predictive behavioral explanations of the measurements recorded by the Smart Tag neck and Smart Tag leg sensors (Nedap N.V.)

Sensor	Measurement	Explanation
Neck	Eating time	Time spent eating, min/h
	Ruminating time	Time spent ruminating, min/h
	Active time	Time spent active, min/h
	Inactive time	Time spent inactive, min/h
	Activity level	Overall activity level per 15 min
Leg	Count of steps	Count of steps per 15 min
	Count of bouts standing up	Count of transitions from lying to standing per 15 min
	Lying time	Time spent lying, min/h
	Walking time	Time spent walking, min/h
	Standing still time	Time spent standing still, min/h

around the average and the autocorrelation describes the correlation (at lag 1) between successive values of hourly data of the sensor variable, thus the similarity between successive values. Nonperiodicity was defined as the mean squared difference of a correlogram with a sinusoid with a 24-h cycle and an amplitude of 0.25, where the correlogram is a plot of the autocorrelation for a range of time lags as visualized by van Dixhoorn et al. (2018). The lags were based on hourly intervals with the exception of active time and the count of bouts standing up where a 6-h period was used instead as hourly data were often zero. Thus, the nonperiodicity was used as a measure for the regularity in daily pattern of the sensor data. The Fourier analysis was used as the conversion from the time domain to a representation in the frequency domain. This was done to identify prominent frequencies that may be present in the sensor data, because cows have a daily pattern in their eating and lying behavior. Patterns in the sensor data will then become visible as frequencies with high peaks. This conversion from the time to the frequency domain was done using the FFT algorithm (Chatfield and Xing, 2019). For our application, FFT was defined as the sum of the peak heights at 1, 2, 3, and 4 in the amplitude spectrum of the variable determined with a FFT. This was interpreted as a measure of the regularity of behavior occurring once, twice, 3 or 4 times per day. Hence, the outcome of FFT indicated the extent to which cows display circadian (i.e., once every 24 h) to ultradian rhythms (several cycles of behavior within a day).

Statistical Analysis

Descriptive statistics (range, average, median, and standard error of the mean) were calculated for the different TDS categories per farm and per parity group. Differences in the average of TDS level per TDS category between farms and parity groups were tested using a general linear model. Correlation coefficients (**r**) were calculated between the different TDS categories as well as between all behavioral variables. For statistical analysis R was used (RCoreTeam, 2020), with the packages lmerTest, emmeans, MuMin, ROCR, and car (Sing et al., 2005; Kuznetsova et al., 2017; Fox and Weisberg, 2019; Barton, 2020; Lenth, 2021). Due to the large number of behavioral predictors, we narrowed down the number of these variables first by a univariate analysis. Cow was the experimental unit and the different TDS categories (TDS total, TDS inflammation, TDS locomotion, TDS metabolic, TDS liver, TDS macro-minerals) were analyzed as dependent variables with parity group as fixed effect and farm as random effect. Three parity groups were chosen: group 1 with first parity only, group 2 with parity 2 and 3 and group 3 with parities 4 and higher. The TDS was transformed to ln (TDS + 0.5) for the analysis to comply with the model assumptions. If $P \leq 0.2$ in the univariate analysis, the predictive behavioral variables were selected for the multivariable approach. For the multivariable approach we used the selected predictors as described above and applied backward selection to obtain optimal subset of predictors for a linear mixed model with parity group as fixed effect and farm as random effect. All models were built according to the following formula in which the linear mixed model assumptions were met:

$$\text{Ln (TDS + 0.5)} \sim \text{Parity group} + \text{(activity descriptors)} + \text{random (Farm)}.$$

First, we investigated models with only Smart Tag leg or only Smart Tag neck variables. Subsequently, combinations of Smart Tag neck and leg variables were included in the selection of variables. We retrained 3 candidate models per TDS based on backward selection. Additionally, an all possible subset selection procedure was performed to test if additional candidate models were proposed among the best performing models based on Akaike information criterion (**AIC**). Of all candidate models resulting from the backward selection and all possible subset selection procedures, the marginal R^2 (variance explained by the fixed effects) and the conditional R^2 (including random farm effect, variance explained by the entire model) as described by Barton (2020) were calculated. A small difference between marginal and conditional R^2 indicates that the additional degree of variation in the TDS values by type of farm is small. Best performing models with the highest marginal and conditional R^2 as well as smallest difference between marginal and conditional R^2 were then selected and the predictive behavioral variables of these best performing models per TDS were calculated. In this paper we aimed to elucidate animal related indicators of resilience that were farm independent, and models were not further examined when differences between marginal and conditional R^2 were large.

Next, the best performing models were further evaluated to select the final model. The variables in the models were tested for significance and co-linearity was tested by calculating the variance inflation factor (**VIF**) as earlier described by Fox and Monette (1992). When the VIF was higher than 5, marginal and conditional R^2 were investigated for models where one of the correlating variables was left out. The final models per TDS included significant variables only, met all linear mixed model assumptions and were best in comparison with the other candidate models and in terms of having little difference between marginal and conditional R^2. Subsequently we investigated if interaction of the variables with parity group was significant ($P < 0.05$). Models with and without the significant interactions were compared and tested for robustness and predictive performance. Robustness was tested with a 10-fold cross validation. The root mean squared error (**RMSE**) was calculated and the estimated coefficients were monitored. We split the data randomly into 10 equally sized parts and used 90% of the data to train the model and continued to test it on the remaining 10% of the data.

We calculated the sum of squares to get insight in the contribution of each variable to the explained variation in the final model and created receiver operating characteristic (**ROC**) curves of the final models to estimate sensitivity and specificity for the optimal cutoff values per TDS. These optimal cutoff values were chosen based on highest area under curve (**AUC**) and positive and negative predictive values were assessed from the ROC curves per model.

RESULTS

Total Deficit Score Distribution and Descriptive Statistics

Our final data set included 173 cows, of which 136 were multiparous and 37 were primiparous. The average DIM of blood sample collection were 1.8 ± 1.2 d and 29.8 ± 1.6 d for the sampling time points in the first and fifth weeks, respectively. Summary statistics of the TDS values of all cows studied are shown in Table 4. The TDS values per farm are visualized with boxplots in Figure 1. The TDS total, inflammation, and locomotion scores were affected by farm ($P < 0.05$). The descriptive statistics and pairwise differences are added in Supplemental Table S1.1 (van Dixhoorn, 2023; https://doi.org/10.6084/m9.figshare.21696293.v1). Farm 3 had remarkably high TDS locomotion compared with the other 3 farms. The TDS metabolic, liver, and macro-minerals scores did not differ between farms.

The TDS values per parity group are visualized with boxplots in Figure 2. For all TDS categories, except for TDS macro-minerals, an effect of parity group was seen. Post hoc comparison showed that TDS total and TDS locomotion values were higher for cows in the parity 4 and higher group as compared with the younger parity groups ($P < 0.05$). The parity 4 and higher group had higher TDS metabolic and TDS liver values than parity 1 cows, with the group cows of parity 2 or 3 in between ($P < 0.05$). For TDS inflammation, values were higher for the parity 4 and higher group as compared with the parity 2 or 3 group, with the first parity group in between ($P < 0.05$, Figure 2). The descriptive statistics

Table 4. Descriptive statistics per total disease score (TDS) category of 173 cows at 4 farms; TDS was calculated by summing aberrant clinical findings and deviating serum values that were assessed during 6 wk after calving[1]

TDS	Range	Median	Average	SEM
TDS total	12–172	55	60	32
TDS inflammation	03–61	21	23	13
TDS locomotion	00–74	8	12	13
TDS metabolic	03–114	20	24	15
TDS liver	00–84	12	14	12
TDS macro-minerals	00–84	15	17	12

[1]The range, median, average, and SEM are given. The TDS total includes TDS inflammation, TDS locomotion, and TDS metabolic. TDS metabolic includes TDS macro-minerals and TDS liver.

and pairwise differences are included in Supplemental Table S1.2 (van Dixhoorn, 2023; https://doi.org/10.6084/m9.figshare.21696293.v1).

Individual TDS total calculations are shown in Figure 3. A gradual linear increased TDS value was observed until TDS total reached a level of 75 points (140 cows with TDS <75). Above 75 (36 cows), TDS total values increased exponentially from 75 with a maximum TDS of 179 (Figure 1). The TDS inflammation values ranged from 3 to 61 with an average of ± 13 (SD).

Significant correlation coefficients ($P < 0.05$) were found between all different TDS categories and TDS total (TDS total with TDS inflammation: 0.82, with TDS locomotion: 0.68, with TDS metabolic: 0.74, with TDS liver: 0.66, and with TDS macro-minerals: 0.66). Significant correlations were seen between TDS liver, TDS macro-minerals and TDS metabolic (all 3 with an r >0.80). Between TDS locomotion and the other TDS categories r was low (<0.20) and not significant except for the correlation with TDS inflammation (r = 0.47). A significant correlation was found between TDS inflammation and TDS metabolic (r = 0.40).

Correlations Between Behavioral Predictive Variables

Significant correlations coefficients ($P < 0.05$) above 0.6 were not found for the nonperiodicities of inactive time and count of standing up and FFT calculations of inactive, standing still and eating time. All calculations of walking time and count of steps were highly correlated. The AC of steps and walking were positively correlated with FFT count of steps and walking, and in addition, nonperiodicities for walking time and count of steps were negatively correlated with FFT of these variables. Nonperiodicity and FFT calculation of rumination were also correlated. A significant correlation was found between average time ruminating and eating with variance of eating time and a negative correlation

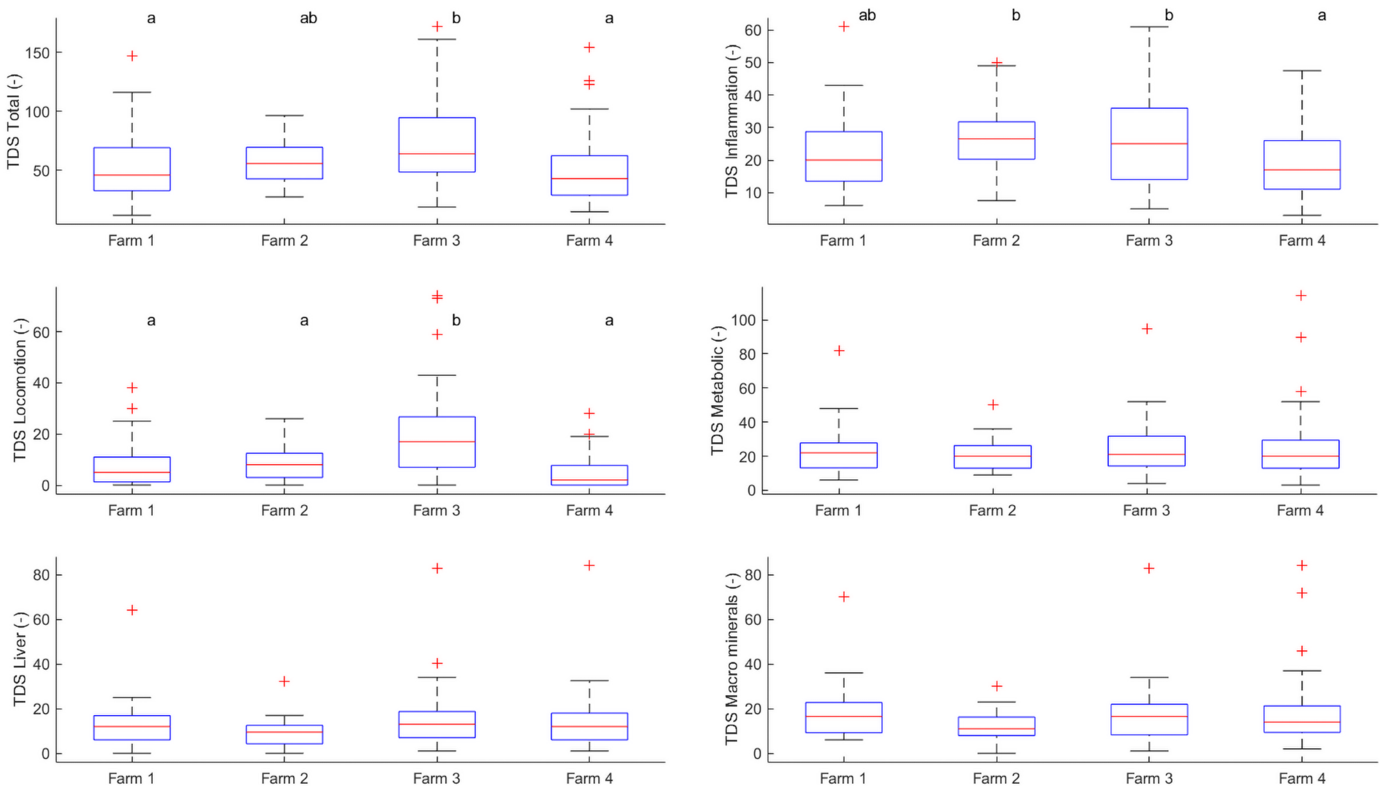

Figure 1. Boxplots of the observed total deficit score (TDS) values per farm. From top left to bottom right, the TDS total, TDS inflammation, TDS locomotion, TDS metabolic, TDS liver, and TDS macro-minerals are shown. The number of cows per farm were 19 for farm 1, 20 for farm 2, 75 for farm 3, and 59 for farm 4. The bottom and top of each box are the 25th and 75th percentiles, respectively. The distance between the bottom and top of each box is the interquartile range. The red line in the middle of each box is the median. The outliers are marked as red + sign and are the values that are more than 1.5 times the interquartile range away from the bottom or top of the box. The whiskers go from the end of the interquartile range to the furthest observation (minimum and maximum values). An overall farm effect was seen for TDS total, TDS inflammation, and TDS locomotion, but not for TDS metabolic, TDS liver and TDS macro-minerals. Letters a and b indicate significant difference ($P < 0.05$), with a being the lower value as compared with b.

was found between these 3 variables and average of inactive time.

Average of eating time was also positively correlated with average of count of steps and walking time, and in addition, AC eating time was correlated with AC walking time and count of steps, which was also the case for the nonperiodicities of walking time and count of steps and eating. Nonperiodicity of eating and walking were also correlated. The nonperiodicities of eating and walking for 2 cows are visualized in Figure 4. One cow with high nonperiodicities and one cow with low nonperiodicities for eating and walking are presented. Variance of lying time was correlated with variance of standing still time, and autocorrelation of lying time with autocorrelation standing still time.

Selected Behavioral Variables

The selection of single predictive behavioral variables per sensor recorded before calving are shown in Table 5. Predictors with $P \leq 0.2$ were included in the multivariable steps. The direction of the effect is indicated per variable as positive (higher value of the variable relates to a higher TDS) or negative (higher value of the variable relates to a lower TDS). Ten variables were selected for TDS total, 7 for TDS inflammation,13 for TDS metabolic, 11 for TDS locomotion, 24 for TDS liver, and 12 for TDS macro-minerals. For TDS inflammation, only variables measured with the Smart Tag neck sensor were selected. Averages for eating, active and inactive time, activity scores, count of steps, and lying, walking, and standing still time were all included in the multivariable approach. Averages of scores for ruminating and bouts standing up were excluded. Autocorrelations of all measurements except for active time were included. Variances of behaviors were all included except for inactive time and bouts standing up. Most FFT and nonperiodicity calculations were included except nonperiodicity of eating, lying and standing still. Autocorrelation calculations were

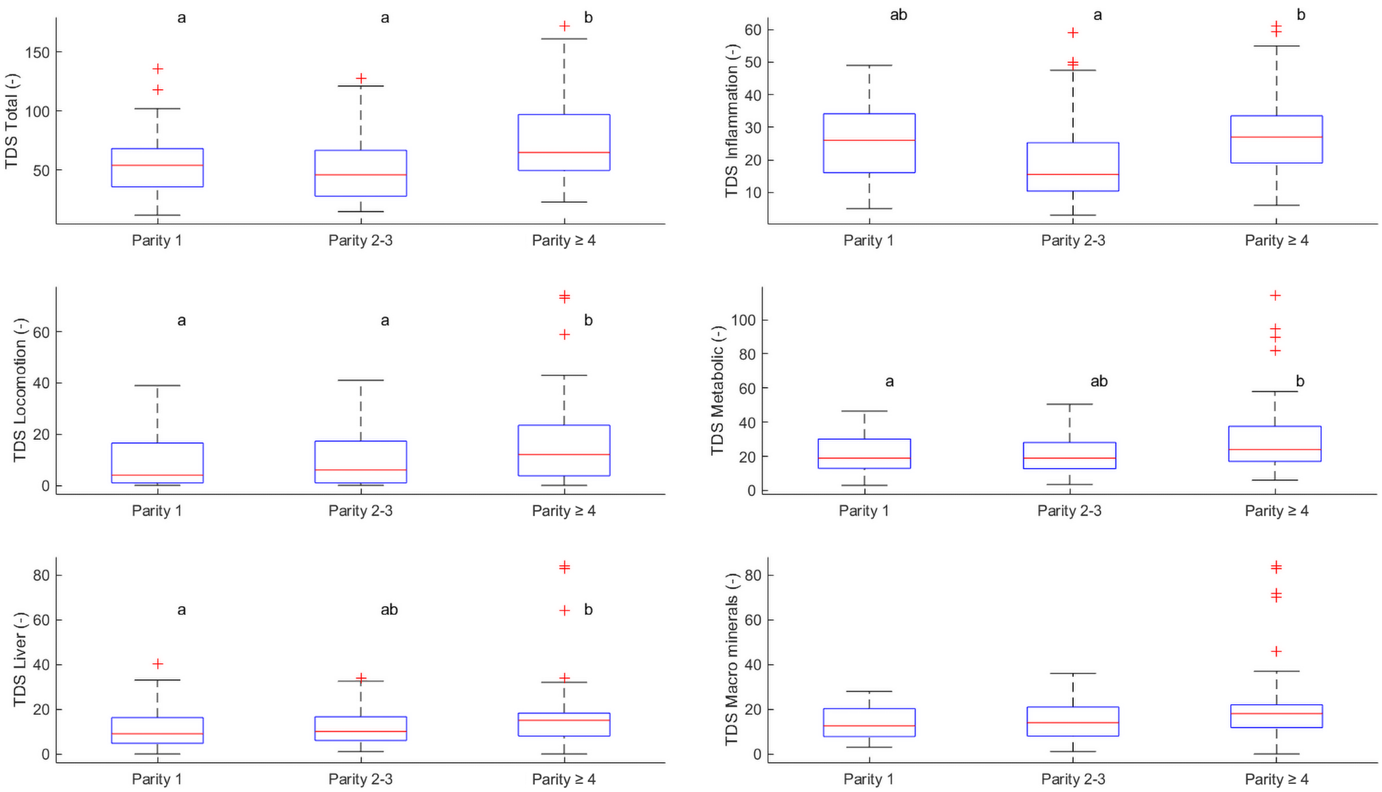

Figure 2. Boxplots of the observed total deficit score (TDS) values per parity group. From top left to bottom right, the TDS total, TDS inflammation, TDS locomotion, TDS metabolic, TDS liver, and TDS macro-minerals are shown. The number of cows per parity group: 37 with parity 1, 81 with parity 2 or 3, and 55 with parity 4 or higher. The bottom and top of each box are the 25th and 75th percentiles, respectively. The distance between the bottom and top of each box is the interquartile range. The red line in the middle of each box is the median. The outliers are marked as red + sign and are the values that are more than 1.5 times the interquartile range away from the bottom or top of the box. The whiskers go from the end of the interquartile range to the furthest observation (minimum and maximum value). An overall parity group effect was seen for TDS total, TDS inflammation, TDS locomotion, TDS metabolic, and TDS liver, but not for TDS macro-minerals. Letters a and b indicate significant difference ($P < 0.05$), with a being the lower value as compared with b.

always positively related to TDS scores except for AC ruminating. Nonperiodicity of bouts standing up had a positive effect on TDS liver but negative on TDS total and TDS locomotion.

Multivariable Regression Results per TDS

Total Deficit Score Total Model. The backward and all possible subset selection procedures identified 4 best candidate models based on best AIC, R^2 marginal, and R^2 conditional calculations. Assumptions for the mixed models were met and VIF of the models were low, so no effect of collinearity was expected. The predictive behavioral variables of the 4 candidate models with highest R^2 values are shown in Table 6. Two models included only Smart Tag neck variables (models 1 and 3, Table 6), one model included only Smart Tag leg variables (model 2, Table 6) and 2 models included both Smart Tag neck and leg variables (models 4 and 4a, Table 6). The following 4 behavioral predictors were present: average minutes inactive, nonperiodicity of frequency of standing up and FFT standing still. The positive effects of average minutes inactive per day indicate that the more inactive the cows, the higher the TDS value. The positive effects of the nonperiodicities of ruminating and frequency of standing up bouts on TDS total indicate that reduced regularity results in increased TDS total. The negative relation of TDS total with FFT of minutes standing indicates that high regularity is associated with low TDS total. High regularity in standing still behavior relates to a low TDS total.

Model 4 had lowest AIC, highest R^2, and smallest difference between R^2 marginal and R^2 conditional and was the final model. Model 4a was similar to model 4 but also included the parity-FFT standing still interaction. For models 4 and 4a the cross validation was performed and ROC curves were calculated. Variation in RMSE after 10-fold cross validation was limited, but somewhat larger in the model with the interaction as compared with model without the interaction.

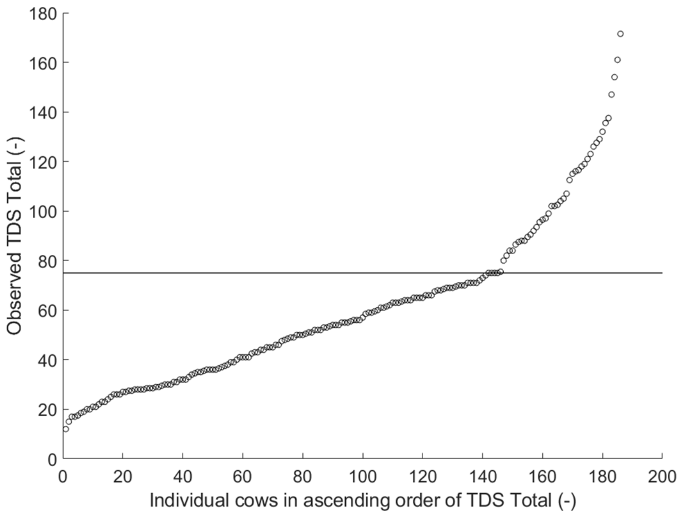

Figure 3. Observed total deficit score (TDS) values per cow in which all clinically detected deficits and deviating serum values are combined into one TDS total value, which is dimensionless, indicated as (−). On the x-axis, the cows are plotted in ascending TDS total order, and on the y-axis the TDS total value of each cow is given. The horizontal line indicates the TDS value of 75 at which TDS value changes from a gradual increase to an exponential increase of TDS value.

Variation calculated for the estimate coefficients in the model was limited for all estimates in both models, indicating good model stability independent of input. R^2 marginal and R^2 conditional improved to 0.37 and 0.37 in model 4a as compared with model 4 (R^2 marginal and R^2 conditional of 0.33 and 0.35, respectively).

We calculated the AUC of the ROC curves for both models 4 and 4a [Table 6, 0.78 and 0.80 respectively, with an optimal threshold of TDS of 60 (lnTDS of 4.1)]. For model 4 this corresponded to a sensitivity of 79.5% and a specificity of 63.9% with a positive predicted value of 0.62 and a negative predicted value 0.81. For model 4a this corresponded to a sensitivity of 79.5% and specificity of 73.2% with a positive predicted value of 0.69 and a negative predicted value 0.83. The parity × FFT standing still interaction improved the model, rendering model 4a best performing and its equation is added in the supplementary materials. The sum of squares of the effects, the model sum of squares as well as the variance components for the random effects for models 4 and 4a are included in Table 6. The transformed values from the model prediction for model 4a were back-transformed to a TDS value and plotted against the original TDS value in Figure 5.

Total Deficit Score Inflammation Model. The backward selection procedure and all possible subset procedures identified 2 candidate models with only Smart Tag neck variables as selected indicators after evaluation. For these 2 models the assumptions required for mixed models were met. The predictive behavioral variables of these 2 candidate models are shown in Table 7. The VIF of the model with 2 variables (model 2 in Table 7) was low, so no collinearity was expected. Only 2 behavioral predictors were present in the models: average minutes eating and nonperiodicity ruminating. The negative relation of average minutes eating indicates that eating more in the dry period results in lower TDS inflammation. The positive relation of nonperiodicity ruminating indicates that the more regular the behavior of ruminating (low nonperiodicity), the lower the TDS inflammation value will be. The variable nonperiodicity ruminating was not significant, hence model 1 was chosen as the final model (Table 7). The interaction of minutes eating and parity was not significant and was therefore not included in the model. The AUC was 0.78 with an optimal threshold of TDS inflammation of 22 (lnTDS of 3.11) which corresponded to a sensitivity of 79.7% and a specificity of 67.0% with a positive predicted value of 0.68 and a negative predicted value of 0.79. We calculated the sum of squares of the effects and these were 5.47 for parity and 3.67 for the average minutes eating (Table 7). The equation for the final model (model 1) is added in the supplemental materials (van Dixhoorn, 2023; https://doi.org/10.6084/m9.figshare.21696293.v1).

Total Deficit Score Metabolic Model. The backward and all possible subset selection procedures identified 3 candidate models based on best AIC, R^2 marginal, and R^2 conditional calculations. The predictive behavioral variables of the candidate models 1, 2, and 3 are shown in Table 8. These models included both Smart Tag neck and leg variables. The following behavioral predictors were present: nonperiodicity inactive time, nonperiodicity ruminating, nonperiodicity of count of steps, AC activity, AC count of steps, FFT inactive time, variance lying time, and variance stand still, all shown in Table 8. Nonperiodicities of inactive time, of ruminating, and of count of steps influenced TDS in a positive direction, indicating that the higher the nonperiodicity (the less regular in the respective behavior), the higher TDS metabolic values will be and the more regularity in lying behavior, the lower the TDS metabolic will be.

Assumptions for the mixed models for TDS metabolic were met except for collinearity in model 3. Variance of lying and variance of standing still were highly correlated, leading to a high VIF in model 3. Therefore, we left out one of the 2 correlated variables and tested the model performance. No difference was found in model performance where we left out "variance lying" or "variance stand still," indicating that these variables can be exchanged. We therefore only show the results of model that included "variance lying" only (model

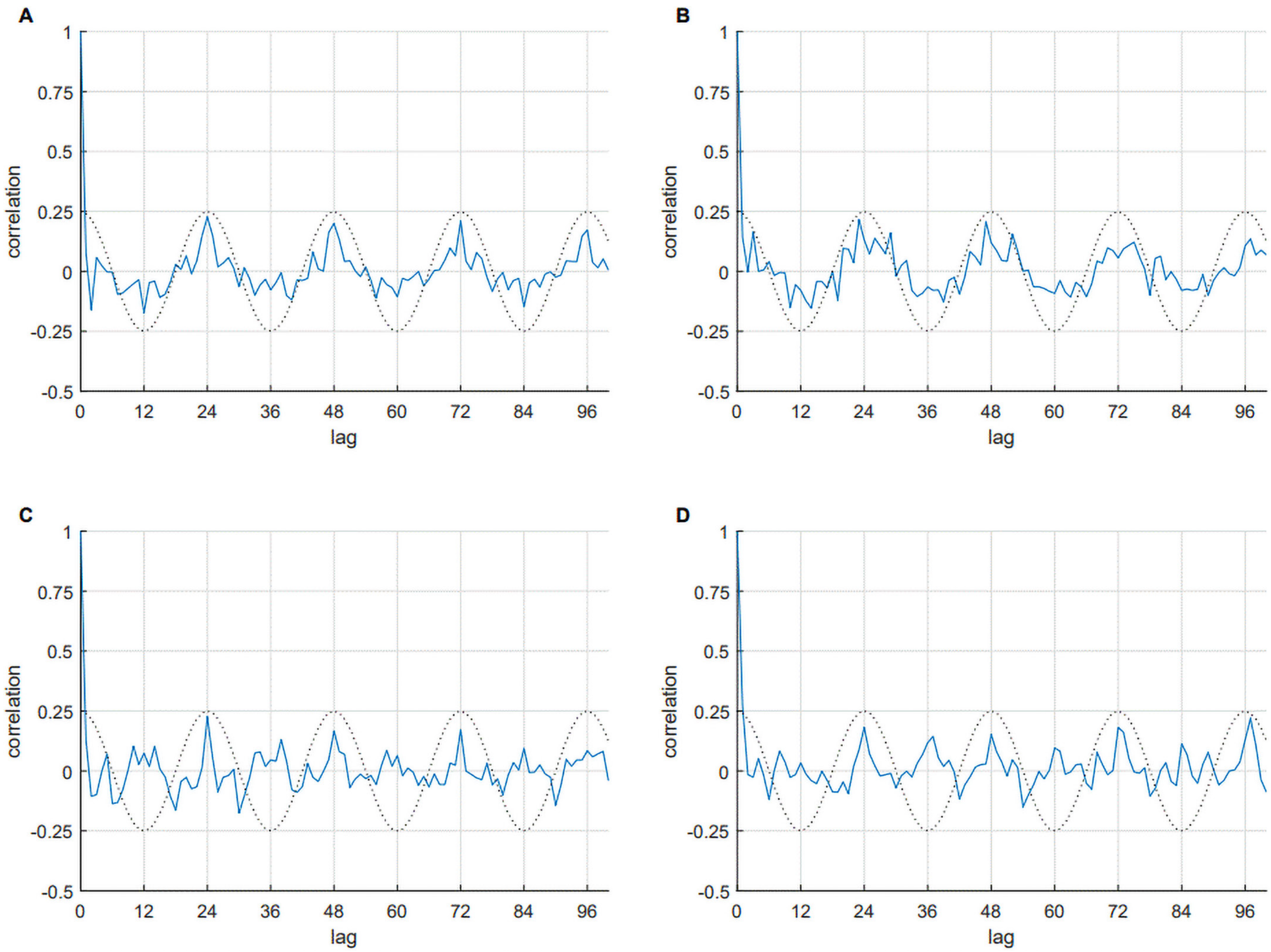

Figure 4. Visualization of the nonperiodicity of eating time and walking time as metric of the regularity in the daily pattern of 2 different cows. Correlograms are made of hourly data assessed during the dry period (from 14 d before parturition until parturition). Eating time and walking time correlograms of cow no. 506 (second parity) are depicted in panels A and B and of cow no. 23 (first parity) in panels C and D. The correlogram of eating time assessed with Smart Tag neck sensor (Nedap N.V.) is depicted on the left (A and C), and the correlogram of walking time assessed with the Smart Tag leg sensor (Nedap N.V.) is depicted on the right (B and D). Nonperiodicity is the calculation of the mean squared error (MSE) of the correlogram (blue line) with a sinusoid with a 24-h cycle and an amplitude of 0.25 (dotted line). Cow no. 506 showed more regularity (low nonperiodicity) with an MSE for eating time of 0.0173 (A) and walking time of 0.0158 (B) as compared with cow no. 23, with an MSE for eating time of 0.0361 (C) and walking time of 0.0412 (D).

4). Marginal and conditional R^2 both decreased to 0.12 in model 4 as compared with model 3 with marginal and conditional R^2 of 0.15. We tested the significance of the parity × variance lying interaction leading to model 4a which was similar to model 4 but with the significant parity × variance lying interaction and the marginal and conditional R^2 increased to 0.18 and 0.18, respectively (model 4a).

For models 3, 4, and 4a, the cross validation was performed and ROC curves were made. Variation in RMSE after 10-fold cross validation was limited in all tested models as was the variation calculated for all estimated coefficients, indicating good model stability independent of input. We calculated the AUC of the ROC curves with an optimal threshold of TDS metabolic of 25 (lnTDS metabolic of 3.24). The AUC, as well as the sensitivity and specificity, were higher in model 4 with an AUC of 0.67, a sensitivity of 80%, a specificity of 49% with a positive predicted value of 0.44 and a negative predicted value of 0.83, as compared with the model 3 with an AUC of 0.54, a sensitivity of 80%, a specificity of 24%, with a positive predicted value of 0.35 and a negative predicted value of 0.70. Including the parity × variance lying interaction in the model improved predicative performance with an AUC of 0.72, a sensitivity of 80%, a specificity of 57%, with a positive

Table 5. Overview of the selection of the single predictive behavioral activity variables; sensor data were recorded during the 14 d before calving using Smart Tag neck and leg sensors (Nedap N.V.) that were attached to 173 cows at 4 different farms[1]

Sensor	Measurement	Calculation	Direction	TDS
Neck	Eating	Average	Negative	Inflammation
		Autocorrelation	Positive	Locomotion, Metabolic, Total
		Variance	Negative	Inflammation
		FFT	Positive	Locomotion
	Ruminating	Autocorrelation	Negative	Inflammation
		Variance	Negative	Metabolic, Macro
		Nonperiodicity	Positive	Inflammation, Metabolic, Macro-minerals, Total
		FFT	Negative	Inflammation, Macro-minerals, Liver
	Active time	Average	Negative	Inflammation, Locomotion
		Variance	Negative	Locomotion, Total
		Nonperiodicity	Negative	Liver
		FFT	Positive	Liver
	Inactive time	Average	Positive	Inflammation
		Autocorrelation	Positive	Liver, Total
		Nonperiodicity	Negative	Metabolic, Macro-minerals, Liver
		FFT	Positive	Metabolic
	Activity score	Average	Negative	Locomotion
		Autocorrelation	Positive	Metabolic, Macro-minerals, Liver
		Variance	Negative	Locomotion, Total
		Nonperiodicity	Negative	Liver
		FFT	Positive	Liver
Leg	Count of steps	Average	Positive	Liver
		Autocorrelation	Positive	Metabolic, Macro-minerals, Liver, Total
		Variance	Positive	Liver
		Nonperiodicity	Negative	Locomotion, Metabolic, Macro-minerals
		FFT	Positive	Locomotion
	Bouts standing up	Autocorrelation	Positive	Liver
		Nonperiodicity	Negative	Locomotion, Total
		Nonperiodicity	Positive	Liver
		FFT	Positive	Liver
	Lying	Average	Negative	Metabolic, Macro-minerals, Liver
		Autocorrelation	Positive	Macro, Liver
		Variance	Positive	Metabolic, Liver
		FFT	Positive	Liver
	Walking	Average	Positive	Liver
		Autocorrelation	Positive	Metabolic, Macro-minerals, Liver, Total
		Variance	Positive	Liver
		Nonperiodicity	Negative	Locomotion
		FFT	Positive	Locomotion
	Standing still	Average	Positive	Metabolic, Macro-minerals, Liver
		Autocorrelation	Positive	Macro-minerals, Liver
		Variance	Positive	Metabolic, Liver, Total
		FFT	Negative	Total

[1]Average, variance, autocorrelation, nonperiodicity, and fast Fourier transformation (FFT) were calculated per activity measurement and related to total deficit score (TDS) categories (total, locomotion, and metabolic, with metabolic subdivided into TDS scores for liver and macro-minerals), and that were assessed during 6 wk after calving. Only predictors with $P \leq 0.20$ in the univariate step to predict a TDS category are shown. The direction (positive or negative) indicates how the predictive variable increases or decreases TDS, respectively.

predicted value of 0.48 and a negative predicted value of 0.85 in model 4a, rendering model 4a best performing and its equation is added in the supplementary materials. We calculated the sum of squares of the effects and these were added in Table 8.

Total Deficit Score Liver Model. All possible subset selection was not possible with too many available input variables when both Smart Tag neck and leg sensor variables were included. The predictive behavioral variables of the best performing candidate models are shown in Table 9. Variance of minutes eating was present in both models which included Smart Tag neck variables. Variance in minutes standing still and AC of minutes lying were present in both models, which included Smart Tag leg variables. Nonperiodicity of frequency of standing up was included in the model with only Smart Tag leg variables. The negative effects of variance of minutes eating and standing still per day indicate that the more variance the cows show in eating and standing still behavior, the lower the TDS liver. High nonperiodicity of bouts standing up reflects low regularity, which was related to higher TDS liver. This was also the case for high autocorrelation of lying time related to high TDS liver score. The VIF was low

Table 6. Predictors and model performance of the candidate models to predict total deficit score (TDS) total using a data set of 173 cows originating from 4 farms[1]

Sensor	Predictor	Model[2] 1	2	3	4	4 Ssq	4a	4a Ssq	Effect on TDS total
	Parity	Y	Y	Y	Y	3.44	Y	0.44	
Smart Tag neck	Average min inactive	Y	N	Y	Y	1.26	Y	1.78	Positive
Smart Tag neck	Nonperiodicity ruminating	N	N	Y	N		N		Positive
Smart Tag leg	Nonperiodicity of bouts standing up	N	Y	N	Y	1.19	Y	1.23	Positive
Smart Tag leg	FFT[3] stand still	N	Y	N	Y	1.31	Y	1.43	Negative
	Parity × FFT stand still	N	N	N	N		Y	0.63	
Model sum of squares						7.20		5.51	
Model performance									
R^2 marginal		0.26	0.29	0.26		0.33		0.37	
R^2 conditional		0.30	0.33	0.31		0.35		0.37	
Variance components residuals						0.18		0.18	
Variance component farm						0.006		0.002	
AUC[4]						0.78		0.80	
Sensitivity %						79.5		79.5	
Specificity %						63.9		73.2	

[1]The effect of the behavioral predictors on TDS is indicated as positive (a higher value of the predictor increases TDS) or negative (a higher value of the predictor reduces TDS). The behavioral predictors were calculated from data that were measured during the 14 d before calving using Smart Tag neck and leg sensors (Nedap N.V.).

[2]Included predictors per model are indicated as Y = yes, predictor is present in the model, or N = no, predictor is not present in the model. Ssq = sum of squares of the effects for models 4 and 4a.

[3]Fast Fourier transformation.

[4]Area under curve.

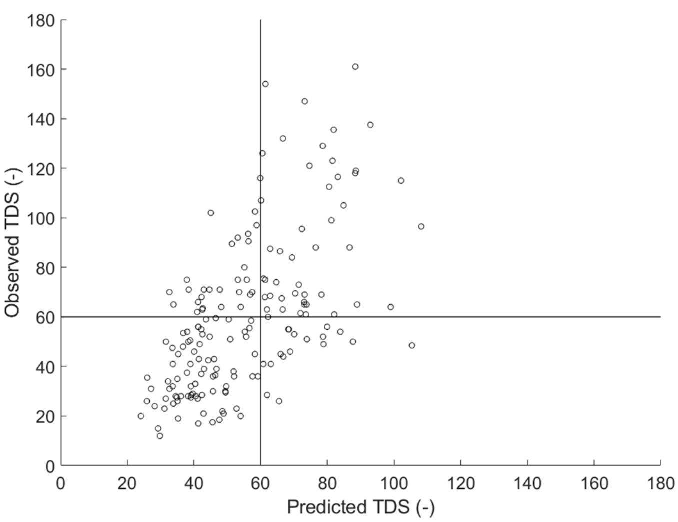

Figure 5. Scatter plot of the observed versus predicted values of total deficit score (TDS) of 173 cows, using the variables average minutes inactive, nonperiodicity ruminating, nonperiodicity of bouts standing up, FFT stand still, and the interaction parity × FFT stand still. The transformed values from the model prediction were back-transformed to a TDS value and plotted against the original TDS value. The model is based on the transformation of ln (TDS + 0.5). This figure visualizes what the model means in terms of actual TDS value at cutoff value of 60. FFT = fast Fourier transformation calculation.

for the models 1, 2, and 3, so no risk for collinearity existed. The other assumptions for the mixed models for TDS liver were also met.

Model 3 performed best yielding the lowest AIC, highest R^2, and smallest difference between R^2 marginal and R^2 conditional (Table 9). Model 3a was similar to model 3 but also included the parity × variance minutes eating interaction. For models 3 and 3a, the cross validation was performed and ROC curves were calculated. Variation in RMSE after 10-fold cross validation was limited, but somewhat larger in the model including the interaction as compared with the model without the interaction. Variation calculated for the estimate coefficients in the model was limited for all estimates in both models, indicating good model stability independent of input. The marginal and conditional R^2 both improved to 0.20 and 0.20, respectively in model 3a as compared with model 3 with a marginal and conditional R^2 of 0.16 and 0.16, respectively.

We calculated the AUC of the ROC curves for models 3 and 3a (Table 9) and these were 0.68 and 0.70, respectively with an optimal threshold of TDS of 11 (lnTDS of 2.44). For model 3 this corresponded to a sensitivity of 79.5% and a specificity of 41.5%, with a positive predicted value of 0.59 and a negative predicted value of 0.65. For model 3a this corresponded to a sensitivity of 79.5% and specificity of 47.6%, with

Table 7. Predictors and model performance of the candidate models to predict total deficit score (TDS) inflammation using a data set of 173 cows originating from 4 farms[1]

Sensor	Predictor	Model 1	Model 1 Ssq[2]	Model 2	Effect on TDS inflammation
	Parity	Y	5.47	Y	
Smart Tag neck	Average min eating	Y	3.67	Y	Negative
Smart Tag neck	Nonperiodicity ruminating	N		Y	Positive
Model sum of squares			9.14		
Model performance	R^2 marginal		0.20	0.19	
	R^2 conditional		0.23	0.23	
	AUC[3]		0.78		
	Sensitivity %		79.7		
	Specificity %		67.0		

[1]Included predictors per model are indicated as Y = yes, predictor is present in the model, or n = no, predictor is not present in the model. The effect of the behavioral predictors on TDS is indicated as positive (a higher value of the predictor increases TDS) or negative (a higher value of the predictor reduces TDS). The behavioral predictors were calculated from data that were measured during the 14 d before calving using Smart Tag neck and leg sensors (Nedap N.V.).

[2]Sum of squares of the effects for model 1.

[3]Area under curve.

a positive predicted value of 0.62 and a negative predicted value of 0.68. Including the parity × variance minutes eating interaction improved the model, making model 3a the best performing model. We calculated the sum of squares of the effects and these were added in Table 9. The equation for model 3a is provided in the supplementary materials.

Total Deficit Score Locomotion Model. For all candidate models, R^2 marginal with values between 0.16 and 0.18 and an R^2 conditional with values between 0.32 and 0.33 were found. The candidate models that included FFT walking and FFT count of steps showed a high VIF, indicating collinearity. Apart from the variables FFT walking and FFT count of steps,

Table 8. Predictors and model performance of the candidate models to predict total deficit score (TDS) metabolic using a data set of 173 cows originating from 4 farms[1]

Sensor	Predictor	Model 1	Model 2	Model 3	Model 4	Model 4a	Model 4a Ssq[2]	Effect on TDS metabolic
	Parity	Y	Y	Y	Y	Y	2.68	
Smart Tag neck	Nonperiodicity inactive	Y	Y	N	N	N		Positive
Smart Tag neck	Nonperiodicity ruminating	Y	Y	N	N	N		Positive
Smart Tag leg	Nonperiodicity n steps	Y	Y	N	N	N		Positive
Smart Tag leg	AC[3] activity	N	Y	Y	Y	Y	1.82	Negative
Smart Tag leg	AC count of steps	N	N	Y	Y	Y	1.08	Positive
Smart Tag neck	FFT[4] inactive	N	N	Y	Y	Y	1.26	Negative
Smart Tag leg	Variance lying	N	N	Y	Y	Y	1.18	Positive
Smart Tag leg	Variance stand still	N	N	Y	N	N		Negative
	Parity × variance lying	N	N	N	N	Y	3.30	
Model sum of squares							11.32	
Model performance								
	R^2 marginal	0.09	0.10	0.15	0.12		0.18	
	R^2 conditional	0.09	0.10	0.15	0.12		0.18	
	AUC[5]			0.54	0.67		0.72	
	Sensitivity %			80	80		80	
	Specificity %			24	49		57	

[1]Included predictors per model are indicated as Y = yes, predictor is present in the model, or n = no, predictor is not present in the model. The effect of the behavioral predictors on TDS is indicated as positive (a higher value of the predictor increases TDS) or negative (a higher value of the predictor reduces TDS). The behavioral predictors were calculated from data that were measured during the 14 d before calving using Smart Tag neck and leg sensors (Nedap N.V.).

[2]Sum of squares of the effects for model 4a.

[3]Autocorrelation.

[4]Fast Fourier transformation.

[5]Area under curve.

Table 9. Predictors and model performance of the candidate models to predict total deficit score (TDS) liver using a data set of 173 cows originating from 4 farms[1]

Sensor	Predictor	Model 1	Model 2	Model 3	Model 3a	3a Ssq[2]	Effect on TDS liver
	Parity	Y	Y	Y	Y	2.22	
Smart Tag neck	Variance min eating	Y	N	Y	Y	6.09	Negative
Smart Tag leg	Variance min stand still	N	Y	Y	Y	1.20	Negative
Smart Tag leg	AC[3] min lying	N	Y	Y	Y	2.40	Positive
Smart Tag leg	Nonperiodicity number of bouts standing up	N	Y	N	N		Positive
	Parity × variance min eating	N	N	N	Y	3.78	
Model sum of squares						15.69	
Model performance							
R^2 marginal		0.13	0.14	0.16		0.20	
R^2 conditional		0.13	0.14	0.16		0.20	
AUC[4]				0.68		0.70	
Sensitivity %				79.5		79.5	
Specificity %				41.5		47.6	

[1]Included predictors per model are indicated as Y = yes, predictor is present in the model, or n = no, predictor is not present in the model. The effect of the behavioral predictors on TDS is indicated as positive (a higher value of the predictor increases TDS) or negative (a higher value of the predictor reduces TDS). The behavioral predictors were calculated from data that were measured during the 14 d before calving using Smart Tag neck and leg sensors (Nedap N.V.).

[2]Sum of squares of the effects for model 3a.

[3]Autocorrelation.

[4]Area under curve.

the candidate models included different combinations of nonperiodicities of walking, count of steps, and count of standing up. Nonperiodicity of count of steps and walking were also highly correlated, resulting in a high VIF. All locomotion models showed a low R^2 marginal with values between 0.13 and 0.18 as compared with R^2 conditional with values between 0.32 and 0.38 indicating a large farm effect on TDS locomotion and were not further evaluated. The candidate models for the prediction of TDS locomotion and their performance are provided in the supplemental materials (Supplement 2, van Dixhoorn, 2023; https://doi.org/10.6084/m9.figshare.21696293.v1).

Total Deficit Score Macro-Minerals. Three candidate models for TDS macro-minerals included Smart Tag neck variables only and 4 models included Smart Tag leg variables only. Three models were identical to the TDS metabolic models but the explained variance for TDS macro-minerals was lower with an R^2 marginal and R^2 conditional of ≤0.10. Due to the low explained variance, no further analysis of these models was investigated. The candidate models for the prediction of TDS macro-minerals and their performance are provided in the supplementary materials.

DISCUSSION

With this study we investigated which behavioral characteristics during the dry period could be used as indicators of resilience using noninvasive Smart Tag neck and Smart Tag leg sensors in dairy cows. We tested if behavioral activity signals and patterns measured in the dry period could be used as predictors for a total disease severity score and for scores related to specific diseases after calving. The data showed that cows with reduced resilience have higher average of inactive time, and lower regularity in bouts standing up and in time standing still during the dry period. As the variables of inactive time, eating, and ruminating were highly correlated, more resilient cows are more active, eat and ruminate more, with a larger variation during the day. These resilient cows reveal distinct active periods and alternate this with resting periods in regular diurnal patterns in contrast to the more vulnerable cows. These behavioral variables may therefore serve as indicators of a cow's resilience and their daily activity patterns as DIOR, as earlier described by Scheffer et al. (2018) and van Dixhoorn et al. (2018). It can be noted that the combination of both Smart Tag leg and neck behavioral predictors increased model performance.

A remarkable aspect of this study was the gradual linear increase of TDS total points reaching a value of 75 points, followed by an exponential increase up to 172 points. This trajectory of points of TDS total values might reflect the "tipping point hypothesis" indicating that complex dynamic systems can absorb disturbances and continue to function up to a certain tipping point at which the ability to self-recover or absorb disturbances is lost (van Nes et al., 2016). Once this tipping point is surpassed, intrinsic processes inside the system form a positive feedback loop, leading to an alternative state (van Nes et al., 2016). The hypothesis that cows are characterized by a self-propelled accelerating change (positive feedback loop) when they cannot adequately adapt to all requirements during the transition phase, leading to postpartum disease (as tipping point) was previously proposed (van Dixhoorn et al., 2018). This phenomenon of a self-accelerating positive feedback loop in cows can be initiated when physiological mechanisms are no longer able to effectively re-organize and adjust to all requirements of the transition phase. This can be caused by the gap between nutrient intake and demand, resulting in metabolic disorders, inducing other health issues, such as infections (Trevisi et al., 2012; Esposito et al., 2014; Sundrum, 2015). A subsequent reduced nutrient intake reinforces hampered metabolism potentially affecting health status at other physiological sites (Mulligan and Doherty, 2008; Sundrum, 2015). This positive feedback loop can also be initiated by other disorders, such as lameness, difficult parturition or cesarean section, retained placenta, reduced feed intake (due to e.g., overcrowding), or when resources, such as nutrients or resting and feeding areas, simply are limited. These destructive feedback loops were similarly described as the result of intertwined components of metabolic stress of altered nutrient metabolism, dysfunctional inflammatory responses, and oxidative stress (Sordillo and Mavangira, 2014). This justifies the use of a TDS total in our study approach, in which all postpartum problems are included, signifying that postpartum related disorders should be approached as a complex disorder. Comorbidity after parturition in our study was confirmed by the high correlation coefficients between TDS metabolic and TDS inflammation. These 2 TDS categories were calculated by the sum of independent points derived from their respective clinical and serum values. However, the sample size and consequently low incidence of diseases in our study could have driven the correlation between TDS metabolic and TDS inflammation. The TDS locomotion correlated less with the other TDS categories with the exception of TDS inflammation. Locomotion problems are typically less related to the transition phase in contrast to metabolic and inflammation disorders (Daros et al., 2020). However, locomotion and cow comfort problems may cause discomfort and pain and give rise to reduced feed intake, intensifying postpartum diseases (LeBlanc et al., 2006; Daros et al., 2020).

In line with our study, Wisnieski et al. (2019) also showed that prediction performance of models for combinations of early lactation diseases was better in comparison to a single disease approach when using biomarkers. The biomarkers related to inflammation, oxidative and nutrient stress in their study were assessed at dry off, occurring approximately 48 d before parturition (Wisnieski et al., 2019). They identified candidate models for each metabolic stress component (nutrient metabolism, oxidative stress and inflammation) and for the combined model including all stress components. Prediction of specific postpartum diseases can thus be performed when variables are used relating directly to the particular disorder. The behavioral patterns that we used as predictors of resilience are not direct indicators of metabolic stress and inflammatory issues. However, specific behavior, reduced eating behavior for example, may lead to or reinforce metabolic stress, rendering cows vulnerable to other postpartum diseases as well. In addition, the variables were collected noninvasively and thus easier to implement on a commercial setting. Although they may not be as accurate as blood measurements, they are more practical.

Prepartum behavior has been used by others to detect cows at risk of postpartum diseases (Belaid et al., 2021). In that study behavior was described as time spent at the feed bunk (min/d), frequency of meals (n/d), step count (n/d), count of lying bouts per day and lying time. Decreased eating time, increased lying, and decreased active time measured prepartum (described in min/d) were previously associated with postpartum related disorders (Kaufman et al., 2016; Piñeiro et al., 2019a,b; Cattaneo et al., 2020; Menichetti et al., 2020; Hut et al., 2021; Hendriks et al., 2022), which is in line with our study. In addition, more lying bouts, fewer meals, and fewer steps taken were seen in cows with metritis or ketosis after calving (Belaid et al., 2021). Reduced rumination time was also previously found as a predictor for early detection of metritis, albeit not as adequate predictor for SCC (Cocco et al., 2021). Stangaferro et al. (2016a,b,c) used a combination of rumination and activity to timely detect postpartum diseases. All these studies focused on daily averages or total time spent on behaviors. Variance and autocorrelation of daily step count has also been calculated and tested as indicator trait for resilience by Poppe et al. (2022). They showed that mean and autocorrelation, as well as mean negative residuals, were candidates for resilience indicators based on heritability and genetic associations with health, fertility, and BCS. Heritability and genetic associations of the nonperiodicities and FFT calculations might as well serve as new traits for cow resilience.

The farm effect in the prediction of locomotion-related problems was larger as compared with that in the other TDS prediction models. This suggests that farm specific housing and management factors play a relatively large part in the development of locomotion-related problems. This makes it more difficult to predict locomotion-related problems in the dry period based on sensor data variables in the dry period alone. Sensor variables, however, have been proven to be of value to actually diagnose lameness (Rutten et al., 2013). In our study we focused on farm-independent prediction of loss of resilience. Risk factors at farm level are probably more indicative for the propensity to develop locomotion problems.

Even with the low explained variance, the final TDS total model had an acceptable predictive ability, when using a cutoff value of Total TDS of 60, which makes it possible to identify cows at risk for postpartum diseases with sensor data alone during the dry period. With regards to the contribution of the individual effects to the total explained variance, it appeared that the of sum of squares was more less comparable, which indicates equal importance in the final TDS total model. The variance component for the farm effect was smaller in the model without interaction, which suggests that some variation was captured in the interaction term. In the TDS inflammation and TDS metabolic model the sum of squares of the parity effect was larger as compared with the other effects. This indicates that the contribution of behavioral variables in these models was limited. In the TDS liver model the contribution of the variance of minutes eating was relatively high as compared with the other effects. To include standard deviation of eating time in monitoring models to detect cows with ketosis was previously suggested to be of value by González et al. (2008). However, the results of the specific TDS categories should be interpreted with caution due to the low incidence of problems within a specific TDS category.

The predictive capacity that we found for the TDS total is comparable to models using biomarkers as predictors for metabolic stress components (Wisnieski et al., 2019) and other predictions or early detection of diseases using sensor data only (Urton et al., 2005; Stangaferro et al., 2016a,b,c; Belaid et al., 2021). Indeed, combinations of metabolic components increase predictive ability (up to a sensitivity of 88.2% and specificity of 87%; Wisnieski et al., 2019), which is superior to the predictive performance of our models. In our study, the use of noninvasive sensors is beneficial, in contrast to models that require invasive blood sampling.

The approach used in this research however has several limitations. We were only able to reasonably predict TDS total, with rather low conditional and marginal R^2. These values were even lower in the other models for predicting specific TDS categories and therefore we were not able to differentiate between specific diseases. This means that with our research approach, we were only able to detect cows at risk for some kind of postpartum disease, without knowing the exact underlying primary cause. This will still require further individual examination to find clues for early intervention strategies that might prevent or reduce postpartum diseases.

The low predictive value of sensor data for specific TDS categories could be related to the low number of disease cases per category, likely resulting in insufficient statistical power. Belaid et al. (2021) were able to identify metritis, displaced abomasum, and ketosis, but not mastitis and retained placenta, using differences in feeding behavior, but included a larger number of cows in their study (489 multiparous cows). The low sample size in our study is an important limitation of our study. Therefore, more research with larger sample sizes and more cases per disease category are needed to draw conclusions on the predictive value of sensor data for TDS related to specific diseases. This would also allow for a better assessment of the merit of using a TDS total score.

In the study of Belaid et al. (2021), the diseases diagnosed, with the exception of ketosis, were based on clinical cases, and the cows that were not diagnosed as diseased could have included subclinical cases. The merit of using the additive scoring system to calculate the TDS values, including blood values, is that it includes subtle changes in health status. More subtle deficits, could relate to subclinical issues and when they are present for a longer period, this will lead to a higher TDS value. These subtle changes can be missed when diseases are assessed as absence or presence and not as a build-up score such as our TDS, inclusive of the severity and duration of the deviations in health status. A binary evaluation of a specific disease might miss subclinical issues. An option could be to lower the cutoff values in models with a binary outcome, which will increase the risk of false positives, reducing specificity of the models (Wisnieski et al., 2019). The lower specificity will identify a relatively large number of false positives, which may possibly lead to unessential interventions. whereas we included blood values and the cows diagnosed implications: on one hand,

Models predicting cows at risk with low specificity might be more of value to detect shifts in the predicted percentage of cows at risk within the herd. An increased percentage of cows at risk requires preventive measures at herd level, which will be beneficial for the health of all cows. However, over-treating cows, may have negative effects to the economics and production efficiency (Salar et al., 2017). Intervention aims to reduce the percentage of cows at risk instead of the prevention of diseases in individual cows. In addition, these models could be used to evaluate management measures that are intended to increase overall cow resilience within the herd. Effective interventions should result in a lower percentage of cows at risk within the herd.

By combining the sensor data using a general linear model, a prediction accuracy for TDS total of 73.2% was achieved with a cutoff value of 60 with 20.5% false positives and 26.8% of false negatives. Still, a large number of false positives and false negatives will be assigned. This cutoff is 15 points below the value of 75, which was indicated as a tipping point, as described above. The question is whether this margin of 15 points is sufficiently chosen to interfere and turn the tide at the individual cow level or if a lower cutoff value is necessary, increasing the number of false positives. Some additional care for cows at a predicted TDS level of 50 could be beneficial. The question remains if it is possible to increase predictive performance for loss of resilience in individual cows when using sensor data alone.

The uncertainty of unknown events influencing the outcome during the time-frame between measurement (sensor data acquisition) and the manifestation of diseases will limit predictive performance in general. To assess cows at risk before diseases occur often while the animal is still healthy, is more challenging as compared with diagnosing diseases at the moment of occurrence as disease specific symptoms or other disease specific values are not present before the onset of disease. When the disease is already present, it is too late for prevention, leaving treatment as the only solution left. Our predictive models of resilience in cows allow for timely implementation of interventions to prevent disease development after calving, although the exact nature of effective intervention strategies remains to be determined. The behavioral patterns that are observed in cows at risk may provide clues for management adjustments, which may include improvement of environmental and housing factors to improve cow comfort, nutrition, or dry cow treatments (LeBlanc et al., 2006).

CONCLUSIONS

The risk to develop some kind of postpartum disease can be predicted when using sensor data alone during the dry period when all clinical aberrations are integrated into one score. More resilient dairy cows eat more, are more active, and show high regularity in rumination, standing time, and transitions from lying to standing as compared with vulnerable cows. These behaviors can be used as indicators of resilience and may allow for preventive intervention during the dry period in dairy cattle. However, additional examination of the cows at risk is still required to find clues for adequate intervention strategies. With our research strategy, the scores for specific disease categories could not be predicted accurately using sensor data, which could be related to the low number of cases per category.

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