



Milk yield residuals and their link with the metabolic status of dairy cows in the transition period

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ABSTRACT

The transition period is one of the most challenging periods in the lactation cycle of high-yielding dairy cows. It is commonly known to be associated with diminished animal welfare and economic performance of dairy farms. The development of data-driven health monitoring tools based on on-farm available milk yield development has shown potential in identifying health-perturbing events. As proof of principle, we explored the association of these milk yield residuals with the metabolic status of cows during the transition period. Over 2 yr, 117 transition periods from 99 multiparous Holstein-Friesian cows were monitored intensively. Pre- and postpartum dry matter intake was measured and blood samples were taken at regular intervals to determine β -hydroxybutyrate, nonesterified fatty acids (NEFA), insulin, glucose, fructosamine, and IGF1 concentrations. The expected milk yield in the current transition period was predicted with 2 previously developed models (nextMILK and SLMYP) using low-frequency test-day (TD) data and high-frequency milk meter (MM) data from the animal's previous lactation, respectively. The expected milk yield was subtracted from the actual production to calculate the milk yield residuals in the transition period (MRT) for both TD and MM data, yielding MRT_{TD} and MRT_{MM} . When the MRT is negative, the realized milk yield is lower than the predicted milk yield, in contrast, when positive, the realized milk yield exceeded the predicted milk yield. First, blood plasma analytes, dry matter intake, and

MRT were compared between clinically diseased and nonclinically diseased transitions. MRT_{TD} and MRT_{MM} , postpartum dry matter intake and IGF1 were significantly lower for clinically diseased versus nonclinically diseased transitions, whereas β -hydroxybutyrate and NEFA concentrations were significantly higher. Next, linear models were used to link the MRT_{TD} and MRT_{MM} of the nonclinically diseased cows with the dry matter intake measurements and blood plasma analytes. After variable selection, a final model was constructed for MRT_{TD} and MRT_{MM} , resulting in an adjusted R^2 of 0.47 and 0.73, respectively. While both final models were not identical the retained variables were similar and yielded comparable importance and direction. In summary, the most informative variables in these linear models were the dry matter intake postpartum and the lactation number. Moreover, in both models, lower and thus also more negative MRT were linked with lower dry matter intake and increasing lactation number. In the case of an increasing dry matter intake, MRT_{TD} was positively associated with NEFA concentrations. Furthermore, IGF1, glucose, and insulin explained a significant part of the MRT. Results of the present study suggest that milk yield residuals at the start of a new lactation are indicative of the health and metabolic status of transitioning dairy cows in support of the development of a health monitoring tool. Future field studies including a higher number of cows from multiple herds are needed to validate these findings.

Key words: milk yield, transition period, dairy cattle, modelling

INTRODUCTION

Monitoring dairy cow health with data-driven tools has been intensively studied in recent years (da Rosa

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Righi et al., 2020; Adriaens et al., 2021; Ho et al., 2021). In many cases, these tools are based on the cow's milk yield as a reflection of her general health and welfare status. Dysregulation of the animal's metabolism is oftentimes reflected in her production performance before clinical symptoms arise (Codrea et al., 2011). In essence, most of the data-driven tools start with predicting the expected milk production assuming a healthy cow status. Several data-based models have been developed to predict the unperturbed lactation profile using high-frequency milk meter data or low-frequency test-day (TD) data (Ehrlich, 2011; Poppe et al., 2020; Abdelkrim et al., 2021; Adriaens et al., 2021; Liseune et al., 2021). In these approaches, the unperturbed lactation is calculated as the expected daily milk yield under the assumption that the cow is healthy and not facing abnormal challenges such as infections or severe metabolic imbalance. This expected daily milk yield can then be subtracted from the actual yield to obtain milk yield residuals. Severe and consistent negative residuals often referred to as milk yield perturbations can indicate or be linked to health-disturbing events (Poppe et al., 2020; Adriaens et al., 2021).

The transition period, defined by Grummer (1995) as the period of 6 wk around calving, is a critical period for a dairy cow (Horst et al., 2021). Smooth transitioning is associated with good production performance, fewer health problems later in lactation and good fertility. Generally, the cow's energy demand in this transition from gestation to lactation exceeds the energy intake, resulting in a negative energy balance (NEB). In reaction to this NEB, different adaptations in the cow's metabolism of lipids, carbohydrates, and minerals occur. It has been estimated that 30% to 50% of the transitioning cows develop metabolic or infectious diseases, having long-lasting effects on milk yield (Mulligan and Doherty, 2008; Leblanc, 2010; Hostens et al., 2012). Also, the metabolic profile of transitioning animals has been studied extensively, often with the aim of identifying (un)favorable status (McArt et al., 2013a; De Koster et al., 2019; Heirbaut et al., 2023). In this regard, the actual milk yield has been varyingly associated with unfavorable or favorable metabolic profiles (Horst et al., 2021). Nevertheless, the actual milk yield is not only reflecting the cow's current metabolic performance, but is also affected by her genetic merit and environment in the past (e.g., rearing, infections). Therefore, the cow's residual milk yield (i.e., the difference between the actual milk yield and the expected milk yield) is hypothesized to better agree with her actual metabolic status and be less influenced by genetic merit or past environmental effects. This relation between the metabolic profiles of transitioning cows and their residual milk yield has not been studied so

far as models to predict the expected milk yield are generally not accurate at the start of lactation. This is because approximately no data on the current lactation is available at this stage to feed these models (Adriaens et al., 2018). Recently, 2 models have been developed to overcome this limitation in multiparous animals by considering data from the previous lactation of the respective cow. One of these 2 approaches, the subsequent lactation milk yield predictor (**SLMPY**) used high-frequency daily milk yield data from the previous lactation obtained with milk meters (**MM**) to predict the expected daily milk yield at any time point in a new lactation (Liseune et al., 2021). The second method, further referred to as the nextMILK model, used low-frequency daily milk yield data at 8 TD spanning the previous lactation to estimate the expected daily milk yield at the first TD of the next lactation (Salamone et al., 2022). Both models are fitted on the complete previous lactation and are able to combine information from the whole previous lactation to calculate their prediction. Validation of these models has shown that they both are accurate in predicting the expected healthy milk yield at the start of a new lactation (Liseune et al., 2021; Salamone et al., 2022) and can thus be used to calculate the milk yield residuals in the transition period (**MRT**). The main objective of this observational study was to link these MRT, calculated with MM as well as TD records, to the health, metabolic status, and DMI of high-producing multiparous Holstein-Friesian dairy cows in the transition period. As such, this study could support the development of a novel method to monitor animals and ultimately detect cows at risk of metabolic dysregulations in the transition period based on routinely collected milk yield data.

MATERIALS AND METHODS

Animals and Management

Data were collected between October 2018 and October 2020 at the dairy research farm of the Flanders Research Institute for Agriculture and Fisheries (**ILVO**). This study was approved by the Ethics Committee of ILVO (file no. 2018/329) and it shares the experimental setup, and the analyte and DMI determination protocol with the study published by Heirbaut et al. (2023). Over a time span of 2 yr, a total of 120 lactations and corresponding transition periods of Holstein-Friesian dairy cows were monitored. The average daily milk yield of the herd in that period was 31.5 kg/d, with a mean fat and protein content of 4.3% and 3.6%, respectively (milk recording, CRV, Arnhem, the Netherlands).

Dry cows were housed in a freestall barn and moved to a calving pen upon showing signs of imminent calving

or, at the latest, 3 d before the expected calving date. After calving, the cows stayed for 3 d in the calving pen before being relocated to a slatted floored cubicle barn with their lactating herd mates. The ration during the 3 wk before calving consisted of the partially mixed ration of the lactating animals supplemented with a dry cow mineral premix and balanced concentrate (on average 1 kg/cow per d) based on the Belgian-Dutch energy and protein evaluation systems. Lactating cows received a partially mixed ration. This ration is supplemented with balanced concentrate to fulfill the energy and protein needs, the concentrate is increased from 21 DIM to 6 kg of balanced concentrate and 1 kg of Cova-Soy (FeedValid, Poederloijen, the Netherlands) and 0.3 kg of soy meal. Concentrate intake was measured in the herringbone milking parlor (DeLaval, Tumba, Sweden) and automatic concentrate dispensers (Greenfeed, C-Lock, Rapid City, SD; DeLaval). Individual roughage intake was recorded by roughage intake control feeding bins (Insentec, Hokofarm Group, Marknesse, the Netherlands) from the start of the dry period until 35 d postcalving. During the period the cow resided in the calving pen, no roughage intake data were collected. A more detailed description of the ration can be found in Heirbaut et al. (2023). During the experiment, fresh lactating cows were milked twice a day in the milking parlor.

Data Collection

Blood Samples. Blood samples were collected from the coccygeal or jugular vein in the morning (between 0900 and 1000 h) of DIM 3, 6, 9, and 21, as described in detail by Heirbaut et al. (2023). Two types of vacuum tubes (BD Vacutainer, Becton Dickinson, Plymouth, UK) were filled using an 18-gauge needle (BD Vacutainer, Precision Glide, Becton Dickinson). In one of the tubes, a clot activation factor (serum separation tube, SST II) was present. This sample was used for the analysis of BHB, nonesterified fatty acids (**NEFA**), insulin, fructosamine, and IGF1. The other tube contained NaF (2.5 mg/blood + 2 mg/mL potassium oxalate) and was used for glucose testing. After collection, the blood tubes were gently inverted 10 times. The tubes with SST were kept at room temperature for 30 min, while those with NaF were placed on ice for transportation. Approximately 1 h later, the SST and NaF tubes were centrifuged at room temperature at $1,500 \times g$ for 15 min and $1,000 \times g$ for 10 min, respectively. Serum and plasma were harvested and divided into aliquots of 2 mL each. All samples were stored at -20°C except those for IGF1 analysis, which were held at -80°C . The BHB, NEFA, and glucose concentrations were analyzed with a Gallery Discrete

Analyzer (Thermo Fisher Scientific, Waltham, MA) using Randox kits (Randox Laboratories Ltd., Ibach, Switzerland) at the laboratory facility of the Flemish Animal Health Service (DGZ, Torhout, Belgium). Fructosamine was determined with the Nitroblue Tetrazolium method (Johnson et al., 1983; Jensen et al., 1993; Megahed et al., 2018). Insulin was measured with a Mercodia Bovine insulin ELISA kit (Mercodia, Uppsala, Sweden), whereas IGF1 was determined by the Poznań University of Life Sciences (Poland) using the Bovine IGF1 kit (LifeSpan Biosciences, Seattle, WA).

Production Data. The following data sets were collected by the milking system, sensor system or the milk recording database at the research farm of ILVO and made available for this study: general cow information (cow identifiers, inseminations, and calving dates), the daily milk yield as measured by the on-farm MM, TD milk yields and milk composition, individual disease events and daily DMI at cow level. The TD records were registered with an interval of 5 wk as part of the DHI program of the Dutch breeding organization CRV (Arnhem, the Netherlands). Apart from the lactation in which the transition was monitored, production data (MM and TD) of the previous lactation were available to feed the SLMPY and nextMILK models. Disease events were registered after diagnosis by a licensed veterinarian or farm staff, in which diagnoses were based on clinical symptoms only. No outlier removal techniques were used on the received data sets. Strict control for erroneous data had been done at the creation of these data sets, which made further cleaning of the data unnecessary.

Data Processing: Calculation of the MRT Period

The MRT were calculated using the 2 previously mentioned models: the nextMILK model which is a random forest model developed by Salamone et al. (2022), and the deep learning framework SLMPY model developed by Liseune et al. (2021). In its original publication, 3 nextMILK variants were trained using different numbers of features. In the present study the production variant of the nextMILK model was used, not relying on herd production performance and fertility traits. Briefly, the nextMILK model uses a sequence of 8 TD in the previous lactation to predict the production on the first TD in the subsequent lactation. Our monitoring window ran from DIM 0 to DIM 21, and thus only the milk yield on TD falling within this window are relevant for this study. The test farm of ILVO has a 5-weekly milk recording scheme, only 61 of the 120 monitored transitions had a TD in this monitoring window. To avoid having to remove approximately half of the monitored transitions, we therefore chose to use

a TD milk yield derived from the daily (MM) rather than the TD data for all the transitions. To this end, we used a random number generator to sample a DIM between 7 and 21 DIM. Next, the average daily milk yield of the last 7 d before the selected DIM was taken as the “virtual” TD, following the standard procedure of the DHI program.

The SLMYP model uses the daily milk yields of the entire preceding lactation, as measured with MM, to predict the expected daily milk production at any time point in the subsequent lactation. In parts of the previous lactation, cows were milked with a conventional milking system twice a day while being milked by an automated milking system at variable milking intervals in other parts of the lactation. This resulted in an unequal variability in the 24-h daily summed milk yields in the original data set. To be able to apply the SLMYP on the available MM data, an additional pre-processing of the MM data were needed. To correct for the variable milking intervals in the automated milking system, the first milking after midnight was partitioned into a part produced on the previous day and a part on the current day and proportionally assigned to these days.

Additionally, a set of features needed to be calculated from the previous lactation to run the SLMYP and nextMILK models: lactation number, the cumulative milk yield at DIM 21, 75, 305, and end of the lactation, milk yield minimum and maximum, average and standard deviation, age at first calving, calving interval, total DIM, the season of calving, and days open. Herd and within-lactation averages were calculated for these features.

Of the initial 120 transition periods, 6 were excluded due to missing data points (such as historical data and DMI during transition) or the death of an animal during the observation period. Using the nextMILK and SLMYP models, predictions were made for the remaining 114 transition periods. This nextMILK variant was used to predict the expected kg of milk produced on the virtual TD (between 7 and 21 DIM) of the lactation under study. The milk yield residuals based on TD (MRT_{TD}) were obtained by subtracting the expected production from the actual production at that first TD. The milk yield residuals based on MM data (MRT_{MM}) were obtained by subtracting the daily prediction of the SLMYP from the measured milk production for the first 21 d of lactation and calculating the average for that period.

Statistical Analysis

Programming and Access to Code. All statistical analyses were performed using R (R Core Team, 2020)

version 4.1.2 and the following packages: car (3.1–1, Fox and Weisberg, 2019), skimr (2.1.5, Waring et al., 2022), heplots (Friendly, 2007), MASS (7.3–54, Venables and Ripley, 2002), sjPlot (2.8.12, Lüdtke, 2021), and tidyverse (1.3.2, Wickham et al., 2019). The code used for the statistical analyses can be accessed in the following repository: <https://doi.org/10.5281/zenodo.8108763>.

Diseased Versus Not Diseased Transitions. A distinction was made between monitored transitions during which the cow was clinically diseased (DIS) or not clinically diseased (NDIS), this distinction was solely based on the presence of clinical symptoms, no subclinical state was evaluated. Differences between both MRT were tested using a one-sided paired *t*-test grouped by clinical state. The differences in plasma analytes, DMI, and MRT were compared between the DIS and NDIS groups. Before this comparison, the 6 plasma analyte variables (BHB, NEFA, insulin, IGF1, glucose, and fructosamine) were averaged over the 4 sampling days (3, 6, 9, and 21 DIM). Due to the lack of normality of the measured variables, a Mood’s median test was performed between the DIS and NDIS transitions for each variable. The significance level was set at $P < 0.05$.

Associations Between MRT and Blood Plasma Analytes, Lactation Number, and DMI. Two linear models were developed to link the plasma analytes, lactation number and DMI to the MRT_{MM} and the MRT_{TD} , using data from only NDIS transition periods. The exclusion of DIS transitions was motivated by the fact that these transitions are known to have a different analyte pattern compared with NDIS transitions (Leblanc, 2010). To avoid confounding, they were excluded from this part of the analysis.

In both linear models, the dependent variable was the respective MRT. The independent variables were the 6 plasma analytes variables averaged over 4 sampling days, the average DMI over 21 d prepartum, the average DMI over 21 d postpartum and the lactation number grouped in 3 categories (2, 3, 4+). All the continuous independent variables were standardized by subtracting the values with their respective means and dividing them by the standard deviation (z-score normalization). Before the model building, collinearity between variables was checked by calculating the generalized variation inflation factor with a threshold of $10^{1/(2 \times df)}$.

Variable selection was performed using the stepAIC function from the “MASS” package. It conducts a stepwise selection procedure in both forward and backward directions to include or exclude the independent variables based on the Akaike information criterion. Pairwise interactions between all blood plasma analytes

Table 1. Overview of the general production and reproduction key performance indicators of the research farm

Item	Mean \pm SD	Range (minimum; maximum)
305-d milk yield in previous lactation (kg)	9,974 \pm 1,589	6,346; 13,455
Age at first calving (yr)	2.14 \pm 0.19	1.79; 2.81
Calving interval (d)	406 \pm 72	312; 655

and DMI variables were also evaluated during this step. The significance level of each remaining variable or interaction was assessed, and nonsignificant effects ($P > 0.1$) were excluded. Ultimately, the remaining variables were used to build the final multivariate model. The sign and effect size of these variables were studied to determine their association with the MRT.

The residuals of the final model were checked for normality using the Shapiro-Wilk normality test, while the Breusch-Pagan test was used to investigate the homogeneity of variances. The fitting performances of the models were defined as the adjusted R^2 . Additionally, the partial η^2 was calculated to estimate the variable importance within the model. The partial η^2 is a value between 0 and 1, with a higher value indicating more variability being explained by that variable after accounting for the variability already covered by the other model variables. To ensure data independence, correlation between model residuals was evaluated with specific emphasis on animals for which more than one transition was monitored during the study period. Specifically, the correlations of the residuals extracted from the final linear model were tested using Pearson's product-moment correlation coefficients. The significance level in this test was set at $P < 0.05$.

RESULTS

Descriptive Analysis

The historical production levels and reproduction key performance indicator of the experimental farm are presented in Table 1. Among the monitored transition periods there were 48, 37, and 29 cows in their second, third, and fourth or higher lactation numbers, respectively. For 23 lactations, the animal was diagnosed with at least one or multiple disease events in the first 21 d: hypocalcemia ($n = 9$, downer cow responsive to calcium treatment), ketosis ($n = 7$, blood hyperketonemia, anorexia and decreased in milk production), clinical mastitis ($n = 4$, fibrin clots in milk potentially accompanied by fever), left abomasum displacements ($n = 10$, clinical symptoms and laparotomy), uterine infection ($n = 5$, abnormal vaginal discharge and enlarged uterus), and other ($n = 6$, other health issues such as leg problems). On average, these disease events

occurred at 5.56 DIM. Accordingly, 23 transitions were categorized as DIS and 91 transitions as NDIS.

Furthermore, in Figure 1A and 1B, the distributions of both MRT are visualized and grouped for NDIS and DIS transitions. The average MRT_{TD} were -3.05 ± 4.59 kg and -8.57 ± 7.32 kg for NDIS and DIS transitions, respectively, while the average MRT_{MM} were 3.70 ± 5.67 kg and -1.37 ± 5.61 kg, respectively. The MRT_{MM} was higher than the MRT_{TD} , both in NDIS as well as DIS transitions ($P < 0.001$). Figure 1C shows the relation between the MRT_{TD} and MRT_{MM} , resulting in a Pearson correlation coefficient of 0.79. The prevalence of a diseased transition in the top 25% (from third quartile to maximum) of both MRT was 2 out of 28 transitions, corresponding to a prevalence of 7%. In the bottom 25% (from minimum to first quartile) of both MRT_{TD} and MRT_{MM} , 13 out of 28 transitions were affected by a clinical disease event, corresponding to a prevalence of 46%. In Table 2, the median and range of the analyte concentrations, MRT and DMI are presented separately for DIS and NDIS transitions. Mood's median tests revealed both MRT to be lower in DIS transitions ($MRT_{TD} = P < 0.001$, $MRT_{MM} = P < 0.001$), though the absolute ranges of milk residuals between the DIS and NDIS transitions were similar in both. When the MRT were grouped by lactation number, lower values were found for DIS transitions in lactation 2 for MRT_{TD} ($P = 0.02$) and MRT_{MM} ($P = 0.02$) and lactation 4+ for MRT_{TD} ($P = 0.02$). Moreover, the Mood's mean tests showed DIS transitions to be associated with a lower DMI intake postpartum ($P < 0.001$) and plasma IGF1 concentration ($P = 0.04$), while the plasma NEFA concentration was higher ($P < 0.001$). There was a tendency for a higher plasma BHB concentration in the DIS transitions ($P = 0.09$).

Models

MRT Period for TD Data. In the case of MRT_{TD} , after the variable selection step, 5 variables and 2 interactions were retained in the final model. None of the variables exceeded the threshold for collinearity. Table 3 shows the summary of the final multivariate model. The adjusted R^2 for this final model was 0.47 and the model's residual errors were found to be normally distributed ($P = 0.96$) and homoscedastic

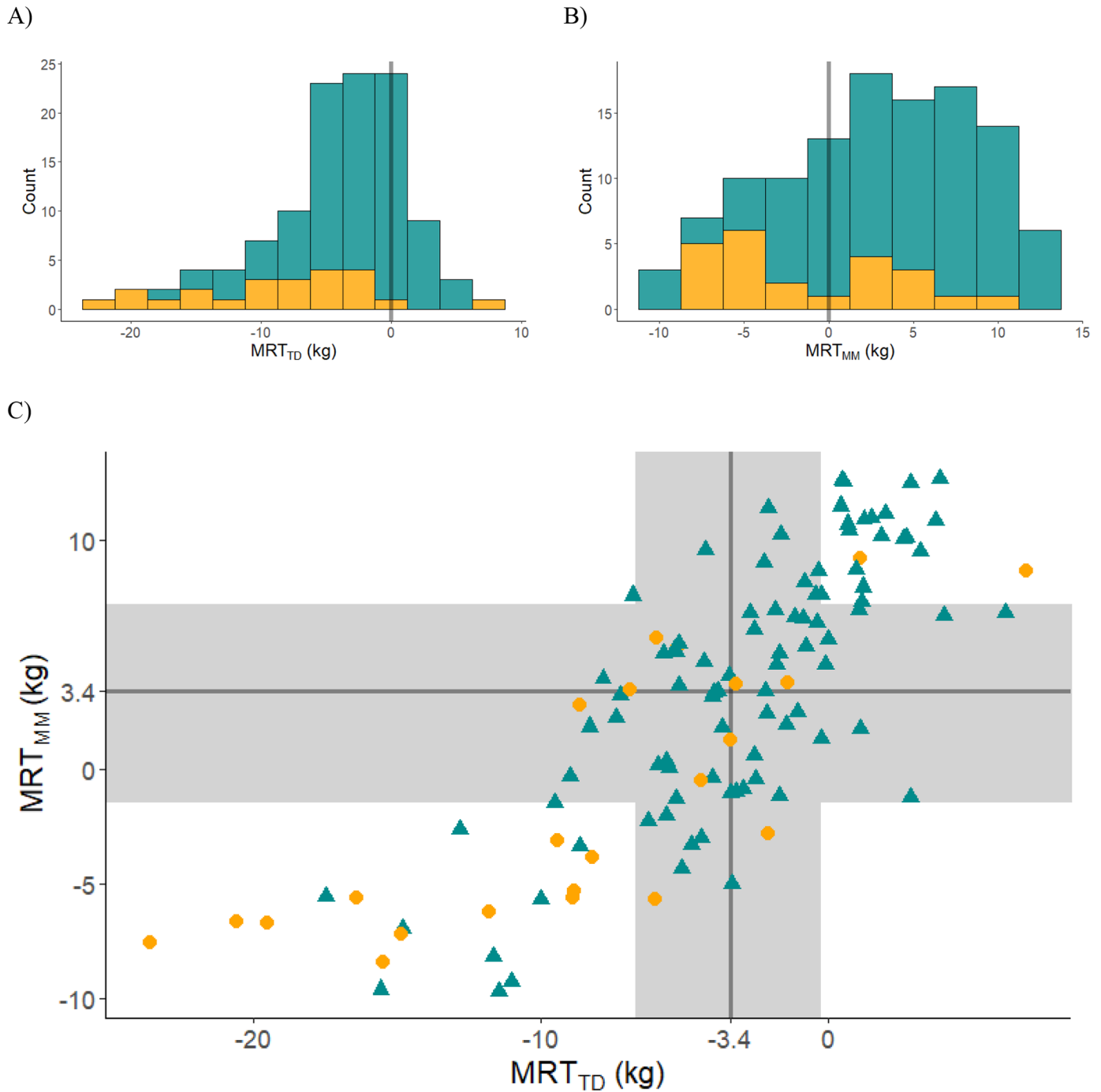


Figure 1. Panels A and B show the milk yield residuals in the transition period (MRT) for test-day (MRT_{TD}) and milk meter (MRT_{MM}) distribution. The colors distinguish between nonclinically diseased (green) and diseased (orange). Both colors are stacked on top of each other. The bin widths in panels A and B are 2.5. In panel C, the relation between the MRT_{TD} and MRT_{MM} is plotted. A distinction is made between the clinically diseased (●) and nonclinically diseased (▲). The axes are located on the median of each MRT. Distribution bands were also plotted to represent the interquartile ranges.

($P = 0.75$), thus respecting the general assumptions of linear regression. Based on the partial η^2 , the most important variable in this model was the interaction between the average DMI 21 d postpartum and the

NEFA concentration. This interaction is plotted in Figure 2A and suggests that the response of MRT_{TD} to NEFA is highly dependent on the DMI postpartum, a pivot point in the MRT response can be found around

Table 2. Comparison of transitions affected by a disease event (DIS) and not clinically diseased (NDIS) for all measured parameters and milk yield residuals in the transition period (MRT) for test-days (TD) and milk meter (MM)¹

Item		NDIS (n = 91)		DIS (n = 23)	
		Median	Range (minimum; maximum)	Median	Range (minimum; maximum)
MRT					
TD (kg)	*	-2.52	-17.5; 6.17	-8.21	-23.6; 6.91
MM (kg)	*	4.55	-9.74; 12.7	-3.13	-8.43; 9.19
MRT or lactation number					
TD (kg)					
2	*	-0.42 (n = 40)	-12.8; 3.91	-3.35 (n = 8)	-23.6; 1.12
3		-2.74 (n = 27)	-15.6; 6.17	-2.89 (n = 10)	-16.4; 6.91
4+	*	-4.59 (n = 24)	-17.5; -0.01	-8.82 (n = 5)	-20.6; -8.66
MM (kg)					
2	*	7.64 (n = 40)	-2.64; 12.7	2.39 (n = 8)	-7.59; 9.19
3		2.43 (n = 27)	-9.63; 10.9	-4.74 (n = 10)	-8.43; 8.64
4+		-0.65 (n = 24)	-9.74; 6.63	-5.29 (n = 5)	-6.69; 2.81
DMI					
Average 21 d prepartum (kg/d)		14.5	10.1; 19.3	13.6	10.5; 18.9
Average 21 d postpartum (kg/d)	*	21.4	13.8; 26.5	17.8	11.4; 23.0
Plasma analyte					
BHB (mmol/L)	°	0.88	0.46; 2.22	1.28	0.568; 3.66
NEFA (mmol/L)	*	0.56	0.17; 1.61	0.76	0.34; 1.58
IGF1 (ng/mL)	*	87.5	37.8; 250.0	58.8	36.2; 175.0
Fructosamine (μmol/L)		257	202; 391	252	198; 338
Insulin (ng/mL)		0.224	0.025; 0.697	0.158	0.062; 0.807
Glucose (mmol/L)		3.05	2.35; 3.98	3.10	2.35; 4.41

¹Results from the Mood's median test between NDIS and DIS are annotated with an asterisk, ° (degree) representing $\alpha < 0.05$ and $\alpha < 0.1$, respectively. NEFA = nonesterified fatty acids.

18.4 kg average daily DMI postpartum. Transitions where the DMI postpartum was lower (<18.4 kg/d) and blood plasma NEFA was high (0.87 mmol/L) were associated with the highest negative milk residuals, or

in other words, the lowest MRT_{TD}. In contrast, transitions for which DMI postpartum and NEFA were high (>18.4 kg/d and 0.87 mmol/L), the response of MRT_{TD} was inverted.

Table 3. Final multivariate linear model for the association of the dependent variable milk yield residuals in the transition period for test-days (MRT_{TD}) with the blood plasma analyte concentrations, DMI pre- and postpartum, and the lactation number as independent variables¹

Item	Estimate	SE	$P(> t)$	Partial η^2
Intercept	-0.69	0.56	2.21E-01	
Average DMI 21 d postpartum × NEFA	1.60	0.34	1.20E-05	0.21
Average DMI 21 d postpartum	1.21	0.40	3.63E-03	0.14
Lactation number ²				0.13
3	-1.46	0.89	1.04E-01	
4+	-3.14	0.90	7.49E-04	
Glucose	-1.10	0.42	1.01E-02	0.06
Glucose × insulin	-0.81	0.35	2.33E-02	0.06
NEFA	1.53	0.47	1.73E-03	0.04
Insulin	0.03	0.50	9.53E-01	0.02

¹Only the selected independent variables are presented, ordered by the partial η^2 . The partial η^2 represents each variable's relative contribution to the model's final performance. A × denotes interaction terms between 2 independent variables. NEFA = nonesterified fatty acids.

²Compared with the reference (lactation number 2).

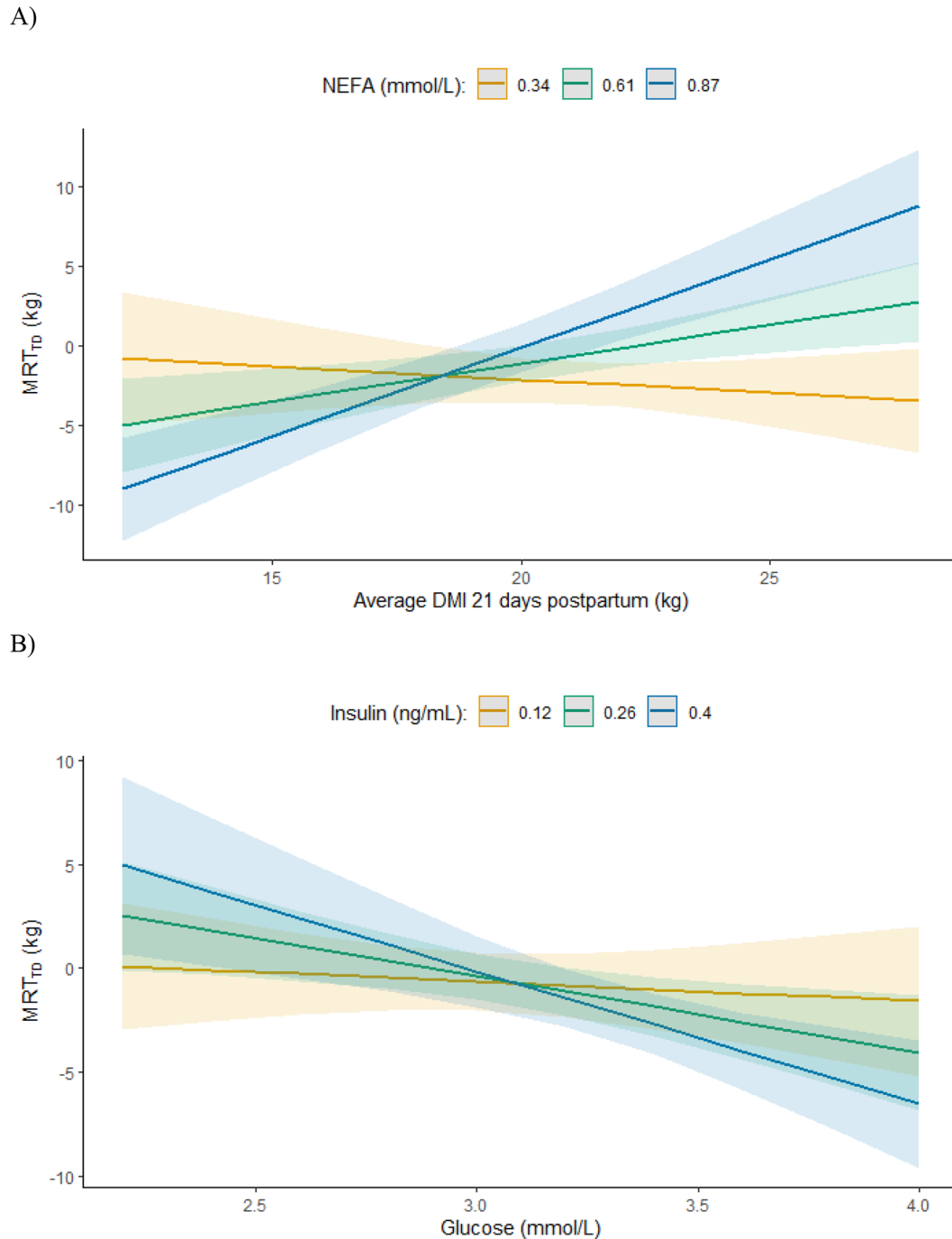


Figure 2. Interaction plots showing the 2 significant interactions in the linear regression model with the milk yield residuals in the transition period for test-days (MRT_{TD}) as the dependent variable. In panel A, the interaction between DMI during 21 d postpartum and plasma nonesterified fatty acid (NEFA) concentrations is shown, whereas panel B presents the interaction between plasma glucose and plasma insulin concentrations. The marginal effects of plasma NEFA (panel A) and plasma insulin concentrations (panel B) are plotted in 3 categories: average minus 1 SD (orange), average (green), and average plus 1 SD (blue). The bands are the 95% CI of these effects.

The lactation number was the third most important variable ranked by partial η^2 . The main effect of these categorical variables indicates that later lactations (3, 4+) were negatively associated with MRT_{TD} and had

more negative milk yield residuals in the transition period. Glucose, as the fourth important variable, was negatively associated with MRT_{TD} . The fifth in line is the significant interaction between insulin and glucose,

Table 4. Final multivariate linear model for the association of the dependent variable milk yield residuals in the transition period for milk meter data (MRT_{MM}) with the blood plasma analyte concentrations, DMI pre- and postpartum, and the lactation number as independent variables¹

Item	Estimate	SE	$P(> t)$	Partial η^2
Intercept	8.61	0.49	<2e-16	
Lactation number ²				0.65
3	-7.16	0.77	1.60E-14	
4+	-8.43	0.78	<2e-16	
Average DMI 21 d postpartum	1.91	0.36	1.09E-06	0.26
IGF1	2.01	0.35	1.89E-07	0.23
NEFA	1.80	0.42	4.09E-05	0.15
IGF1 \times NEFA	1.08	0.35	2.62E-03	0.11
Insulin	-1.23	0.40	2.90E-03	0.10
Glucose	-0.93	0.36	1.24E-02	0.08
NEFA \times glucose	0.74	0.36	4.63E-02	0.05

¹Only the selected independent variables are presented, ordered by the partial η^2 . The partial η^2 represents each variable's relative contribution to the model's final performance. A \times denotes interaction terms between 2 independent variables. NEFA = nonesterified fatty acids.

²Comparison to the reference (lactation number 2).

plotted in Figure 2B. In this interaction the response in MRT pivots at a concentration of glucose 3.1 mmol/L. Where a combination of higher glucose (>3.1 mmol/L) and high insulin (0.4 ng/mL) concentrations was found to be associated with a lower MRT_{TD} . In contrast, low glucose (<3.1 mmol/L) concentrations, in combination with high insulin (0.4 ng/mL) concentrations, resulted in higher values for MRT_{TD} . Ultimately, independency between repeated measures was affirmed by the Pearson's product-moment correlation ($P = 0.61$).

Milk Yield Residuals in the Transition Period for Milk Meter Data. In the final model for MRT_{MM} , 6 variables and 2 interactions were retained. The adjusted R^2 for the MRT_{MM} model was 0.73. The linear model assumptions were not violated (residual normality, $P = 0.20$ and homoscedasticity, $P = 0.20$).

The variables kept in the final model are reported in Table 4, ordered by partial η^2 . The most important variable in this model was the lactation number, for which, similar to the MRT_{TD} model, higher lactations had lower MRT_{MM} . The DMI postpartum was the second most important variable in this linear model. Between DMI postpartum and MRT_{MM} , a positive relation was found. The interaction between NEFA and IGF1 was found to have a significant association with MRT_{MM} . Its effect is visualized in Figure 3A. When the plasma IGF1 concentration was low (<50 ng/mL), the MRT_{MM} was also low, regardless of the plasma NEFA concentration. At higher concentrations of plasma IGF1, an increase in plasma NEFA resulted in an increase in MRT_{MM} . Furthermore, insulin concentrations were found to have a negative effect on the MRT_{MM} . An interaction was found between NEFA and glucose (Figure 3B). When NEFA concentrations were low (0.34 nmol/L), there was a negative association between glucose and MRT_{MM} . When NEFA concentrations were high (0.87

nmol), there was no effect of glucose on MRT_{MM} . Also, for this model the no significant correlation was found between the residuals of repeated measure ($P = 0.32$).

DISCUSSION

The objective of this study was to evaluate the association between the MRT and indicators of transition success. Even though there is no consensus on the definition of transition success, different authors have described favorable and unfavorable physiological processes or metabolic profiles (Leblanc, 2010; McArt et al., 2013a; De Koster et al., 2019; Pascottini et al., 2020; Horst et al., 2021). These definitions of success formed the general framework for the assessment of the MRT . This research evaluated the MRT in 2 steps. First, compared DIS and NDIS transitions and considered the development of clinical disease during the transition period as a sign of transition failure. Second, the explicit associations between MRT and the metabolic status of NDIS animals were explored. Definitions of transition success, such as being clinically not diseased and having high DMI postpartum, were associated with higher MRT in both approaches. Finally, the potential application of the MRT for early lactation monitoring is being discussed.

DIS Versus NDIS Transitions

The differences in MRT between NDIS and DIS transitions indicated that transitions affected by a disease event result in a lower milk yield during the transition period. This was confirmed by a difference in disease prevalence between the top 25% and bottom 25% of both MRT . Clinically diseased animals produce less than their healthy herd mates, which is in line with

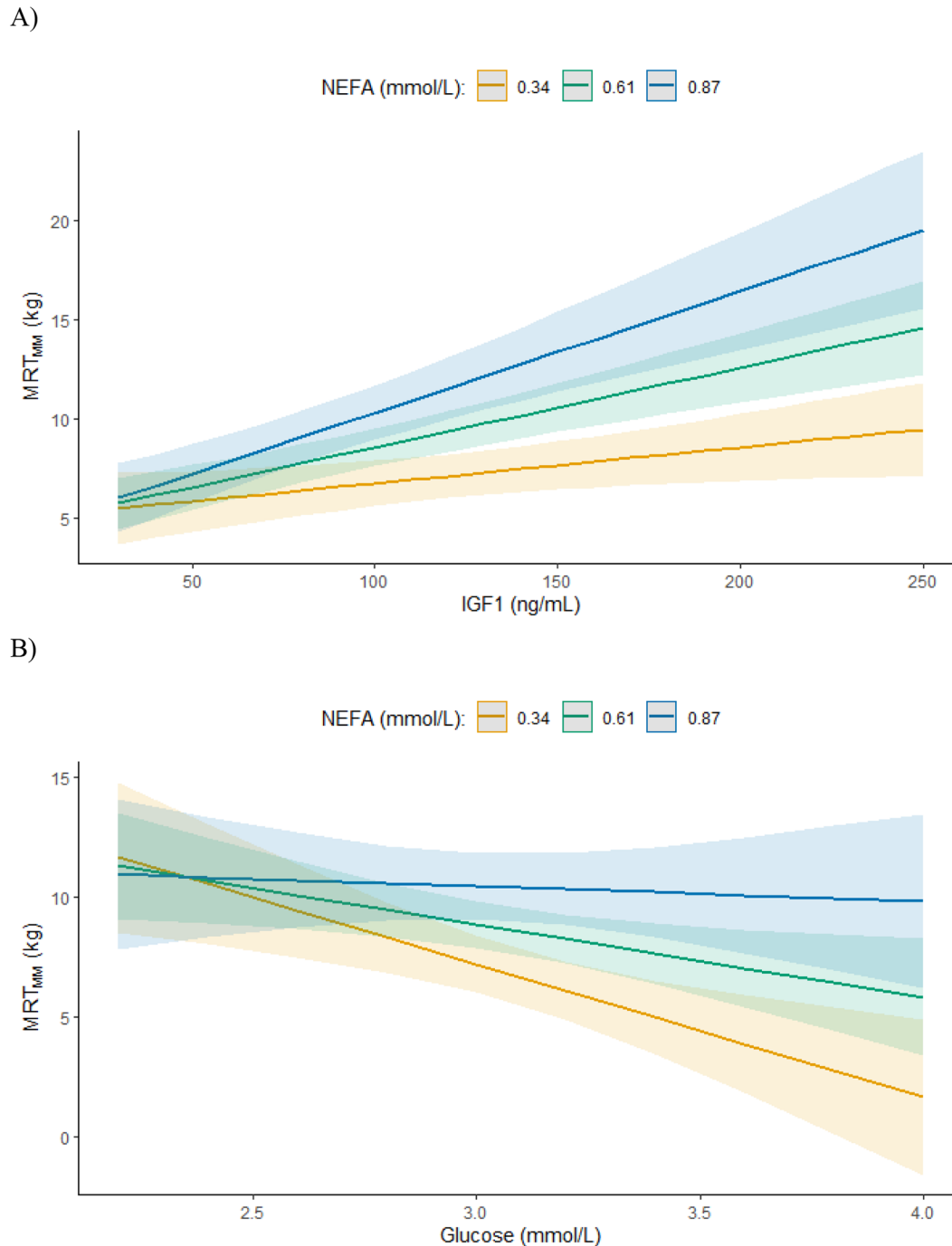


Figure 3. Interaction plots showing the 2 significant interactions in the linear regression model with the milk yield residuals in the transition period for milk meter data (MRT_{MM}) as the dependent variable. In panel A, the interaction between plasma IGF1 and plasma nonesterified fatty acid (NEFA) concentrations is shown, whereas panel B presents the interaction between plasma glucose and plasma NEFA concentrations. The marginal effects of plasma NEFA concentrations (panels A and B) are plotted in 3 categories: average minus 1 SD (orange), average (green), and average plus 1 SD (blue). The bands are the 95% CI of these effects.

previous studies (Deluyker et al., 1991; Leblanc, 2010; Adriaens et al., 2021). In this study, this difference was demonstrated using an individual-animal baseline derived from her previous lactation. Although diseases

in the past might have affected the daily milk yields in the previous transition of a cow (Erb and Grohn, 1988; Houben et al., 1993; Rasmussent et al., 1999; Saborío-Montero et al., 2017), the nextMILK and SLMYP were

not affected by that as they seem able to accurately predict the expected healthy production at the start of the next lactation, without any knowledge of disease incidence in the previous lactation.

Differences between the NDIS and DIS transitions with respect to NEFA, DMI postpartum, IGF1, and BHB (Table 2) were in line with previously published research. Pascottini et al. (2022) provided an updated overview of how the metabolism adapts during the transition period and described how it can evolve into a pathological state.

It is established that the energy demand for initiating a new lactation is 4 times higher than the maintenance level of a high-yielding dairy cow (VandeHaar et al., 2016). This increase in energy requirement often exceeds the energy intake, making the DMI one of the main determining factors of the cow's energy balance. The NEB resulting from the discrepancy between energy intake and energy demand initiates a cascade of adaptations, reduced insulin sensitivity, lipid mobilization, gluconeogenesis, ATP production through the β -oxidation of NEFA and production of ketone bodies (BHB, acetone, and acetoacetate). Increases of NEFA and BHB in blood plasma are traditionally seen as a key precursor to the development of clinical diseases such as displaced abomasum, mastitis, metritis and retained placenta (Overton et al., 2017; Horst et al., 2021). The differences found between DIS and NDIS transitions are also coherent with the physiological processes explained hereabove. Moreover, clinically diseased animals are known to have characteristically higher plasma BHB and NEFA, while having lower plasma IGF1 and DMI postpartum (Leblanc, 2010; Wathes et al., 2021). Nevertheless, the central role of BHB and NEFA as the key health and performance indicators during the transition period has been questioned in recent literature (Horst et al., 2021). This controversy is mainly based on the inconsistent effects of these markers over multiple studies and the reporting of numerous different thresholds. Their connection to metabolic imbalance is based on association studies more than controlled and intervening experimentation. In the case of the present study, no conclusion can be made on the intrinsic role of BHB and NEFA during the transition period. It is notable that based on the thresholds reported by McArt et al. (2013a), hyperketonemia and elevated NEFA occurred in DIS as well as NDIS transitions.

Using 3 different thresholds for BHB, hyperketonemia was seen in 14% (>1.4 mmol/L), 20% (>1.2 mmol/L), and 33% (>1.0 mmol/L) of the NDIS transition. When these thresholds are applied to the DIS transitions, 43%, 52%, and 56% of the transitions are identified as affected by hyperketonemia. Similarly, when a threshold of 0.7 mmol/L is used to define elevated NEFA,

61% of DIS transitions exceeded this threshold in contrast to 31% of the NDIS transitions. The percentage of animals that could be categorized as elevated in BHB or NEFA are in line with the numbers presented by McArt et al. (2013a).

Based on the results of our study, the fact that only 50% to 60% of DIS transitions present hyperketonemia or elevated NEFA indicates a lack of consistency of BHB and NEFA as a key analyte. Furthermore, as no information was available on subclinical diseases for this study, the presence of hyperketonemia and elevated NEFA in the NDIS transitions could also be linked to subclinically diseased animals.

The significantly lower plasma IGF1 for DIS transitions agreed with the literature. During transition, the circulating IGF1 has been described as an indicator of nutrient availability and is decreased in the case of aggravated nutrient and energy deficiencies or in the presence of an infection (Gross and Bruckmaier, 2019; Wathes et al., 2021).

Associations Between MRT, Blood Plasma Analytes, and DMI

The linear models revealed associations between the MRT of NDIS transitions and the blood plasma analytes, lactation number, and DMI.

The preponderant importance of the independent variable, "average DMI postpartum," based on the partial η^2 , indicated the close relationship between the milk residuals and the DMI. Although the relationship between milk yield and DMI has been described previously (Hristov et al., 2005), the associations between DMI and milk yield residuals have not yet been established. In both linear models (MRT_{MM} and MRT_{TD}), transitions with higher DMI intake resulted in a higher MRT. Furthermore, in the MRT_{TD} model, the interaction between DMI and NEFA concentration was found to be significant, Figure 2A. In this interaction, the elevated concentrations of NEFA were beneficial for the transition, yielding more positive MRT when combined with higher DMI. Similarly, in the MRT_{MM} model, positive associations were found between MRT_{MM} and NEFA in interaction with IGF1 concentration, Figure 3A. It is generally assumed that the mobilization of fat tissue is a physiological response to prioritize milk synthesis (Aschenbach et al., 2010; Sordillo and Raphael, 2013; Horst et al., 2021). Based on our results, it appears that the metabolization of NEFA toward milk synthesis is dependent upon the availability of sufficient nutrients, as indicated by DMI or IGF1 interactions. Furthermore, these associations are found at NEFA concentrations above what would be considered pathological (McArt et al., 2013a). This hypothesis could also explain the

high percentage of elevated NEFA concentration found in the NDIS transitions, these animals were seemingly able to convert their mobilized NEFA without detrimental consequences for their clinical status.

Furthermore, the associations of glucose and insulin in both MRT models seem to confirm the close relationship between the MRT and the physiological priority of milk production at the individual cow level. Glucose and insulin (for MRT_{TD}) were negatively associated with MRT, or in other words, when a higher concentration of glucose/insulin was found, the predicted yield exceeded the produced milk yield. The physiological relation between glucose and insulin can be summarized as follows: the decrease in plasma glucose is accompanied by a decrease in peripheral insulin. This decrease reduces the inhibitory effect of insulin on the lipase enzyme located in the adipose tissues, which causes the release of NEFA from these tissues (Sordillo and Raphael, 2013). In the case that glucose is high combined with high insulin or a low NEFA, the prioritization of milk production is less pronounced in those animals. Different studies have already described this inverse relationship between plasma glucose concentration and milk yield (Sorondo and Cirio, 2009; Ruoff et al., 2017). The genetic merit of an animal has been linked with plasma glucose concentrations postpartum. Animals with a high genetic merit for milk production generally have lower plasma glucose concentrations compared with animals with a lower genetic merit for production (Snijders et al., 2001). Another low-rank interaction was found between glucose and NEFA in the MRT_{MM} model. This interaction term indicates that a higher grade of fat mobilization seems to negate the negative association of glucose on the milk residuals. Further research is needed to unravel possible pathways for this interaction.

The difference in adjusted R^2 between both MRT is hypothesized to be associated with the difference in partial η^2 for the lactation number. For MRT_{MM} this variable seems to account for the majority of explained variance creating the difference with MRT_{TD} . The central role of lactation number in the MRT_{MM} linear model indicates that the SLMYP model is correcting insufficiently for lactation number. This was not reported in Liseune et al. (2021) and should be investigated further when applying this model in the future.

Both linear models found similar associations between MRT and the measured variables. Even though the MRT were extracted from 2 different prediction models based on 2 different modeling techniques (nextMILK model being a random forest model and the SLMYP being a deep learning model) running on 2 separate data types. The variables that were found to be associated with the MRT are intrinsically as-

sociated with the metabolic status of the cows in the transition period.

Limitations and Future Perspectives

The primary limitation of this study was the lack of a golden standard for the distinction between the healthy and subclinically diseased animals within the NDIS group. In our view, this does not undermine the general results of this research. Animals in this group are experiencing a varying level of metabolic challenge, which places them on a spectrum between healthy and subclinically diseased. Within the NDIS group, the linear models are still able to differentiate between cows, indicating a clear and logical relation with indicators for metabolic health and feed intake. The MRT can only be calculated for multiparous animals due to the requirement of historic data. This is a clear limitation of the MRT, but it does not diminish its significance, given that multiparous animals are the group that is most at risk of disease during the transition period (McArt et al., 2013b; Vanholder et al., 2015; Saborío-Montero et al., 2017; Horst et al., 2021).

The results from this research indicate that the metabolic profile of dairy animals during the transition period shows strong associations with the milk yield residuals as all associations seen within these results are in line with the current literature. While this research is not intended to validate the usage of MRT as a health monitoring tool, the results from the present study indicate the potential value of this indicator toward this goal. This should be further investigated with a longitudinal study including more animals and an experimental design in line with the research question. The effect of diseases in the previous lactation on the prediction of milk was not evaluated in this research. Although, the nextMILK and SLMYP model were trained with a variety of previous lactation curves (with and without diseases in the previous), the unavailability of a curated data set of the previous lactation regarding disease registration restricted the capabilities to incorporate this possible effect. It would be highly valuable to understand how health perturbations in the previous lactations affect the MRT and the established metabolic associations. It is important to note that averaging the metabolites over the different collection dates was linked with a loss of information. Yet, this was a necessary step given the high level of collinearity between the different variables if added separately. Further research could investigate the relations between MRT and metabolites on a daily basis during the transition period, using time series analysis methods. This would help us to better understand how MRT affects daily fluctuations in metabolism.

CONCLUSIONS

This study used 2 previously developed models (nextMILK and SLMYP) to predict the expected production of dairy cows during the transition period and subtracted these predictions from the actual milk production to obtain milk yield residuals (MRT). Furthermore, the link between these residuals and different blood plasma analytes, the DMI and the lactation number were studied. We demonstrated that the MRT derived from the SLMYP and nextMILK were higher for cows without clinical diseases and that there is a strong positive association between these MRT and the DMI postpartum. Moreover, animals producing less than predicted had lower DMI postpartum. Additionally, the MRT seems to be associated with the physiological prioritization of milk production through the effect of NEFA, insulin and glucose. We also found that a certain level of fat mobilization is not directly detrimental to the cows, as long as the DMI is high. Although this study establishes a solid foundation for using the milk yield residuals as a new and valuable metric for health and transition success monitoring, further research and validation is needed.

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