Improved Genetic Evaluation of Health Traits using Metabolic Biomarkers in Nordic Dairy Cattle

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Abstract

In 2008, a joint Nordic genetic evaluation for health traits was developed for Denmark, Finland and Sweden. The sire model used up until 2017 for routine evaluation utilized records on veterinary treatments to provide breeding values for Reproductive Disorders, Metabolic Disorders, and Feet&Leg Problems. Today, with the accessibility of metabolic biomarkers (β-hydroxybutyrate (BHB) and Acetone) and with genomic prediction models prepared to include cows in the reference population, the addition of valuable indicator traits and the use of an animal model is a more optimal solution for the General Health (GH) evaluation.

In November 2017, the GH evaluation changed from having four sub-traits to five sub-traits. The four sub-traits were: Early and Late reproductive disorders, Feet and Leg problems and Metabolic disorders. In the new GH evaluation the later was split into Ketosis and Other Metabolic Disorders. This was motivated by the inclusion of BHB and Acetone, with the purpose of exploiting the high genetic correlations between Ketosis and BHB (~ 0.68) and Ketosis and Acetone (~ 0.78). Heritability estimates were significantly higher for BHB ($h^2 = 0.15$) and Acetone ($h^2 = 0.06$) compared to Ketosis ($h^2 = 0.012$) and Other Metabolic Disorders ($h^2 = 0.006$) in first lactation records for Holstein. This new information helped improving the reliability of breeding values for Ketosis and Other Metabolic disorders, from 0.29 to 0.34 and 0.36 for Other Metabolic Disorders and Ketosis, respectively in Holstein cows.

The new overall GH index is composed of five sub-traits: Early and Late Reproductive Disorders, Ketosis, Other Metabolic Disorders, and Feet&Leg Problems. Each of them is weighted according to a set of economical values. The improvements introduced to the GH evaluation affected the breeding values of the GH index considerably. For progeny tested AI bulls born after 2009 and with a reliability for GH index > 0.35 the correlations between the old and the new GH index, were 0.89 for RDC and 0.92 for HOL.

Keywords: Genetic evaluation, Health, Metabolic biomarkers, Animal model, Nordic Dairy Cattle, breeding values.

Introduction

Animal health is an important part of the total Nordic breeding goal in dairy cattle. Since 2008, the breeding values for General Health (GH) traits on Holstein (HOL), Red Dairy Cattle (RDC) and Jersey (JER) have been jointly evaluated for Denmark (DNK), Finland (FIN) and Sweden (SWE) by the Nordic Cattle Genetic Evaluation (NCGE) (Johansson *et al.*, 2008)

Veterinary treatments on health traits have been collected in the Nordic countries since the 1980's. These records have been long used in breeding programs to improve general disease resistance of dairy breeds in Nordic countries. It is important to revise and update the genetic evaluation if, for instance, changes in disease treatment policies and/or data recording occur. Since 2013, Denmark has collected phenotypic information on β-hydroxybutyrate (BHB) and Acetone (ACE). These metabolic indicator traits have been shown to be favourably correlated with Ketosis (Ane Closter, SEGES, Personal Communication, Jamrozik *et al.*, 2016). Ketosis is a metabolic disorder in milking cows where ketotic cows show a

decreased milk production. Diagnosis of ketosis can be difficult, especially subclinical cases. Easily measurable predictors of metabolic disease are of growing interest and many countries see opportunities in including them in genetic evaluations for metabolic health (references).

In the Nordic countries BHB and ACE have been included in routine evaluation as indicator traits for metabolic disorders since November 2017. Other change included in the November revision of the GH evaluation was the upgrade from a sire to an animal model. With this revision, cows with estimated breeding values (EBVs) for GH traits can be used in the reference population for genomic predictions. The aim of this paper is to describe the addition of these new predictors of metabolic disorders in the GH evaluation and to show the benefit of including those traits in the routine genetic evaluation for GH traits in the Nordic countries.

Material and Methods

Data

Data on 6,736818 HOL, 3,936732 RDC and 567,194 JER cows were included in the GH evaluation to calculate official estimated breeding values (EBV) for Early Reproductive Disorders (ERP), Late Reproductive Disorders (LRP), Ketosis (KET), Other Metabolic Disorders (OMD), Feet and Leg problems (FLP). Table 1 shows the five disease groups that represent various disorders pooled together according to their pathology as it is describe in Table 1. Embody

Disease frequencies vary across countries, while in first lactation HOL cows Denmark has the highest disease frequency for ERP with a 12%, for Finland and Sweden is LRP with an 8% and 13%, respectively. A similar pattern of disease frequencies is also seen in the RDC breed, whereas JER has the highest disease frequencies for OMB between first and third lactation of 2-15% and for FL of 5-7%.

Table 1. Disease groups Johansson *et al*. (2008) in the genetic evaluation with the most common treatments per group.

Early Reproductive Disorders	**Late Reproductive Disorders**	**Ketosis**	**Other Metabolic Disorders**	**Feet and Leg Problems**
Retained placenta Hormonal reproductive disorders Infective reproductive disorders Other reproductive disorders	Hormonal reproductive disorders Infective reproductive disorders Other reproductive disorders	Ketosis	Milk fever Other metabolic diseases Other feed related disorders Other diseases	Feet and leg problems

Data recording is based on health treatments registered mainly by veterinarians and in few cases by farmers. Observations are defined in the evaluation as a binary trait. Cows born 1985 onwards with health traits records are included in the evaluation for the estimation of EBVs. Data from herds with incomplete recording are removed. Basic editing rules are applied to veterinary treatments to harmonize data across countries. Differences in recording of disease data between Denmark, Finland and Sweden are taken into account by using in the evaluation those diseases that, to a large extent, are common across country. Those veterinary treatments are then defined with a window calculated in days in milk (DIM) as shown in Table 2. Disease frequencies are adjusted by differences in breed country and calving year.
Measures of BHB and ACE are obtained from milk samples collected on a regular basis through the milk recording scheme. Mid-infrared spectrometry technology (MilkoScan FT+, Foss Electric A/S, Hillerød, Denmark) is used on the milk to predict BHB and ACE levels. Records on BHB and ACE from cows with DIM from 10 to 60 are included in the evaluation and about 50% of the cows have repeated observations. Data on metabolic biomarkers are available for Danish cows since 2013. It is expected that in the near future BHB and ACE measures will also be available for Finland and Sweden. Trait definitions and abbreviations for these traits and the indicator traits in the GH evaluation are shown in Table 2.

The inclusion of BHB and ACE, known to have high genetic correlations with ketosis (Jamrozik *et al*., 2016), was combined with a re-definition of the traits included in the GH index. The new GH index changed from including four sub-traits to include five sub-traits by splitting the group of Metabolic Disorders into two traits: Ketosis (KET) and Other Metabolic Disorders (OMB). In this way, the high genetic correlations between Ketosis with BHB and Acetone were optimally utilized.

Table 2. Abbreviations and definitions of traits included in the evaluation.

Abbreviation	Definition
ERP	Early reproductive disorders (1) or not (0), 0 to 40 DIM
LRP	Late reproductive disorders (1) or not (0), 41 to 305 DIM
OMB	Other metabolic diseases (1) or not (0), -15 to 305 DIM
KET	Ketosis (1) or not (0), -15 to 305 DIM
FL	Feet and legs problems (1) or not (0), -15 to 305 DIM
BHB	β-hydroxybutyrate mmol/L, 10 to 60 DIM
ACE	Acetone, mmol/L, 10 to 60 DIM
CM	Clinical mastitis (1) or not (0), -15 to 305 DIM

For the estimation of genetic parameters a subset of the whole dataset was used which included data on 4,942 HOL, 1,682 RDC and 1,099 JER cows. For HOL and JER we used DNK data and for RDC we used SWE data. All cows were required to have a first lactation record. Offspring from high reliability bulls were included (50 offspring in 50 herds for HOL, 25 offspring in 25 herds for RDC and JER). Cows were also required to be in "large" herds (≥ 25 cows with record per herd-year for HOL and JER, ≥ 10 cows with records per herd-year for RDC).

Statistical analysis

T A multi-trait multi-lactation animal model is used in the prediction of EBVs for GH traits. A total of 22 traits (7 traits x 3 lactations and 1st lactation CM) are analysed using DMU 5.3 (Madsen and Jensen, 2010). The general model is as follow:

$$\hat{Y}_{ijkl} = CHY_i + CCA_j + CYM_k + A_l + b_1 \cdot BR_{ijkl} + b_2 \cdot HET_{ijkl} + e_{ijkl} \quad (\mathbf{1a})$$

$$\hat{Y}_{ijklmn} = CHY_i + CCA_j + CYM_k + A_l + PE_m + b_1 \cdot BR_{ijklmn} + b_2 \cdot HET_{ijklmn} + b_3 \cdot LS1_{ijklmn} + b_4 \cdot LS2_{ijklmn} + e_{ijklmn} \quad (\mathbf{1b})$$

Where, $\hat{\boldsymbol{Y}}_{\boldsymbol{ijkl}}$ and $\hat{\boldsymbol{Y}}_{\boldsymbol{ijklm}}$ are the individual observation for veterinary treatments and metabolic biomarkers, respectively, $\boldsymbol{CHY_i}$ is the country*herd * year, $\boldsymbol{CCA_j}$ is the country*calving age, $\boldsymbol{CYM_k}$ is the country*year-month of calving, $\boldsymbol{A_l}$ is the animal genetic random effect. Only for metabolic biomarkers we included $\boldsymbol{PE_m}$ which is the cow permanent environmental effect and $b_3 \cdot LS1_{ijklm}$ and $b_4 \cdot LS2_{ijklm}$ are (fixed) regression for lactation stage modelled as a second order Legendre polynomial. For HOL, breed proportions ($\boldsymbol{b_1 \cdot BR_{ijkl}}$) and heterosis ($\boldsymbol{b_2 \cdot HET_{ijkl}}$) effects were included as (fixed) regression and $\boldsymbol{e_{ijkl}}$ is the residual random effect. For computational reasons, residual correlations between lactations were set to zero and residual correlations between the veterinary treatments and metabolic biomarkers are set to zero except for KET and OMB.

A two-trait multi-lactation sire model was used for variance component estimation using DMUAI software (Madsen and Jensen, 2010). Genetic parameters for BHB and ACE where estimated for HOL and used in all three breeds. For JER, and RDC there were too few records to estimate breed specific parameters. Only those traits affected in the inclusion of BHB and ACE (i.e. KET and OMB) were re-estimated using the same model as describe above changing the animal random effect for a sire random effect. Variance components, genetic and residual correlations between these four traits and all other traits in the evaluation were estimated using a series of bivariate analyses with sire models.

All veterinary treatments traits used in the analysis were pre-corrected for heterogeneous variance due to breed, year of calving and country.

Results and Discussion

Heritabilities on the observed scale for the health traits are low, around 1-2% and agree with other published studies (Koeck *et al.*, 2012; Jamrozik *et al.*, 2016). Heritabilities for BHB and ACE were higher compared to veterinary treatments, around 15% and 6%, respectively. BHB and ACE are objectively measured and as indicator traits for metabolic disorders provide diagnosis by veterinarians to identify potential cases for subclinical and clinical ketosis.

Table 3. Genetic correlations between veterinary treatments traits (from 1st lactation records) for Holstein, Red Dairy Cattle (RDC) and Jersey.

	Holstein				RDC				Jersey			
Trait	**LRP**	**KET**	**OMB**	**FL**	**LRP**	**KET**	**OMB**	**FL**	**LRP**	**KET**	**OMB**	**FL**
ERP	0.40	0.29	0.40	0.35	0.24	0.26	0.30	0.00	0.32	0.39	0.47	0.28
LRP		0.21	0.29	0.36		-0.08	0.09	-0.01		0.10	-0.05	0.04
KET			0.74	0.19			0.64	-0.06			0.55	0.34
OMB				0.38				0.39				0.22

Genetic correlations among veterinary treatments traits ranged from low to moderate (Table 3). Across breeds, genetic correlations were lowest between LRP and KET (-0.08 – 0.21) and highest between ERP and KET (0.26 – 0.39). For some traits, genetic correlations ranged widely between breeds. For instance, genetic correlations between LRP and FL ranged from -0.01 for RDC to 0.36 for HOL. There were some genetic correlations very close to zero, meaning that for some health traits there is little gain from correlated information.

The two new indicator traits for metabolic disorders, BHB and ACE, showed both highest correlations to KET. Moderate genetic correlations were found between the metabolic biomarkers and OMB. These favourable genetic correlations support the use of these metabolic biomarkers as predictors for metabolic disorders in the Nordic GH evaluation. These results also corroborate other studies suggesting the use of these traits as indicator traits for metabolic disorders (Pryce *et al.*, 2016).

Table 4. Genetic correlations between ketosis (KET) and other metabolic disorder (OMB) traits1 and metabolic biomarkers[1] (BHB and ACE) for Holstein, RDC and Jersey.

	Holstein		RDC		Jersey	
Trait	**BHB**	**ACE**	**BHB**	**ACE**	**BHB**	**ACE**
KET	0.65	0.76	0.63	0.74	0.33	0.40
OMB	0.48	0.65	0.46	0.62	0.60	0.72

[1]Genetic correlations are from 1st lactation records

Table 5. Approximate reliabilities for seven across-lactation indexes and the GH index, for cows with observations but without own progeny, separate for cows with or without BHB and ACE observations.

	Holstein		RDC		Jersey	
BHB observations	**Yes**	**No**	**Yes**	**No**	**Yes**	**No**
GH Index	0.32	0.30	0.30	0.28	0.29	0.28
ERP	0.30	0.29	0.28	0.27	0.28	0.27
LRP	0.28	0.28	0.27	0.27	0.25	0.25
KET	0.36	0.29	0.34	0.27	0.31	0.27
OMB	0.34	0.29	0.32	0.27	0.28	0.26
FL	0.28	0.28	0.26	0.26	0.27	0.27
BHB	0.44	0.25	0.43	0.23	0.35	0.24
ACE	0.41	0.27	0.41	0.25	0.33	0.25

The benefit of including BHB and ACE in the GH evaluation was evaluated by looking at the increase in cow's EBV reliability. As expected, the largest increase in reliability for the veterinary treatments was for KET in all three breeds followed by OMB. The relative increase in reliability for the GH index for HOL and RDC was 6% (Table 5).

Direct comparison of these results with other studies is difficult because disease treatment policies and recording systems might vary widely across countries, and only few countries have large databases with veterinary treatment records.

Conclusions

Metabolic biomarkers BHB and ACE were found to be favorable correlated with metabolic disorders. The inclusion of these traits as indicator traits for Ketosis and Other metabolic disorders showed to increase reliability the Nordic evaluation for health traits, especially for cows. Milk fever is the most important diagnosis in the other metabolic disorders. With an increased reliability of the breeding value for this trait, farmers in the Nordic countries have the opportunity to reduce the frequency of the disorder through breeding.

As a consequence of the introduction of BHB and ACE the GH index changed from four to five sub-traits: Early and Late reproductive disorders, Feet and Leg problems, Ketosis and Other metabolic disorders. This was done by splitting the group of metabolic disorders into: Ketosis and Other metabolic disorders. The new GH evaluation allows farmers, from November 2017, to select for Ketosis and Other metabolic disorders in addition to the already existing traits. Official breeding values are available for all five traits, but also BHB and ACE are publically available. Since February 2018, genotyped cows with EBV for health traits are included in the reference for genomic predictions for all breeds.

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