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Optimisation of genetic evaluations for longevity in Holstein dairy cattle through special consideration of health traits, SNP marker data and genotype by environment interactions

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LIST OF ABBREVIATIONS

Abbreviation	Explanation
A matrix	Pedigree relationship matrix
ACID	Acidosis
AI	Artificial insemination
BTA	Bos taurus autosome
CLP	Corpus luteum persistens
CYST	Ovarial cysts
DD	Digital dermatitis
DIM	Days in milk
EBV	Estimated breeding value
ENDO	Endometritis
FDR	False discovery rate
FP	Fat percentage
G martix	Genomic relationship matrix
GBV	Genomic breeding values
GWAS	Genome wide association study
G×E	Genotype by environment interaction
H matrix	Combined relationship matrix
h^2	Heritability
h^2_{eff}	Effective heritability
h^2_{equ}	Equivalent heritability
HL	Herd life
HYP	Interdigital hyperplasia
KET	Ketosis
L1.1	First stage in first lactation
L1.2	Second stage in first lactation
L1.3	Third stage in first lactation
L2.1	First stage in second lactation
L2.2	Second stage in second lactation
L2.3	Third stage in second lactation
L3.1	First stage in third lactation
L3.2	Second stage in third lactation
L3.3	Third stage in third lactation
LPL	Length of productive life
LSM	Least-squares-means
M1S	Model with health status from different lactation stages in separate runs
M3S	Model with health status considering three stages from one lactation simultaneously, different runs for different lactations

Abbreviation	Explanation
M3Swd	Model without health status, different runs for different lactations
M9S	Model with health status considering nine stages from three lactations simultaneously
M9Swd	Model without health status, one run considering all lactations simultaneously
MSNP1	Model with one significant SNP, different runs for different SNP
MSNP2	Model considering six significant SNP simultaneously
MAF	Minor allele frequency
MAST	Clinical mastitis
MFEV	Milk fever
MOET	Multiple ovulation and embryo transfer
MY	Milk yield
NL	Number of lactations
OCD	Ovarial cycle disorders
QTL	Quantitative trait loci
r_g	Genetic correlation
RN	Reaction norm model
RP	Retained placenta
RR	Random regression model
SCC	Somatic cell count
SCS	Somatic cell score
SD	Standard deviation
SE	Standard error
SMAST	Subclinical mastitis
SNP	Single nucleotide polymorphism
STAY	Stayability
ST-A	Stayability according to age
ST-L	Stayability according to lactation
ST-LP	Stayability according to lactation period
SU	Sole ulcer
TMI	Total Merit Index
WLD	White line disease
ρ	Shape parameter of the Weibull distribution

SUMMARY

From an economic and welfare perspective, the increasing importance of longevity in the dairy cattle sector has resulted in the inclusion of longevity in many national animal breeding programs. Ideally, reliable estimates of longevity should be made early in life. However, phenotypic records of longevity are typically unavailable before the end of a cow's life. Thus, it is important to identify indicator traits that can be measured in the early stages of a cow's life in order to improve longevity. Furthermore, other traits used in breeding goals may have an impact on longevity, which could lead to a limited selection gain in longevity. Additionally, as a result of genotype by environment interactions (**G×E**), the same genotypes may respond differently in various environments, leading to a bias in estimated breeding values and restricted selection responses. Therefore, the estimation of G×E in different production systems (e.g., conventional and organic farms) is imperative for using in organic farms bulls proved in conventional production system. The main objectives of the present thesis were to (1) estimate genetic parameters for longevity traits based on a variety of definitions and study the genetic and phenotypic impact of health traits on longevity, (2) evaluate different statistical models on heritabilities of longevity and (3) demonstrate G×E interactions in organic and conventional dairy production systems with regard to longevity and health traits in German Holstein cattle.

The impact of diseases indifferent lactation periods on length of productive life (**LPL**) and stayability were investigated in **Chapter 2**. Length of productive life was defined as the number of days between calving and culling, and stayability was considered as survival of a cow in a specific lactation period in the first three lactations. The lactation periods were from calving to days in milk (**DIM**) 59, DIM 60 to DIM 299 and DIM 300 to the next calving date. The binary health status of 13 different diseases was successively defined for the aforementioned periods. Data from 90,215 German Holstein cows was used to estimate genetic parameters of LPL, and data from 129,386 German Holstein cows was used to evaluate stayability. In most cases, the occurrence of disease had a negative effect on LPL and stayability. The strongest detrimental impacts were observed for clinical mastitis and metabolic diseases. The genetic correlations ranged from -0.26 to -0.77 for mastitis and both longevity traits and from -0.06 to -0.98 for metabolic diseases and both longevity traits, which suggests the possibility of using these traits as early indicators of longevity. The heritability of LPL was 0.05, and the values for stayability in a specific lactation period ranged from 0.05 to 0.06. The genetic correlations between LPL and stayability were high (0.77–0.94), indicating

selecting for stayability in the early life of a cow may favor the genetic improvement of longevity.

Chapter 3 focuses on the evaluation of proportional Weibull hazard models to estimate the genetic parameters of the censored-uncensored LPL. In this regard, models with and without disease effects from different lactation stages of the first three lactations were compared. Additionally, this study examined the effects of including specific single nucleotide polymorphisms (**SNP**) in survival analyses. The detrimental effects of disease on culling risk increased with time and were stronger in later lactations and lactation stages. Furthermore, the inclusion of diseases in the proportional Weibull hazard models was associated with an increase in genetic variances and heritabilities for LPL compared to models that ignored the health status of cows. Heritabilities were smaller in hazard models that considered health status across lactations separately (0.01–0.17) compared to models that considered health status across all three lactations simultaneously (0.36–0.44). Finally, a genome-wide association study (**GWAS**) detected six significant SNP markers on chromosomes 1, 4, 10, 13 and 28 for LPL. However, the inclusion of these SNP markers in the proportional Weibull hazard models had no effect on genetic variance components, as heritabilities ranged from 0.05 to 0.12; this indicates weak effects of significant SNP on longevity.

In **Chapter 4**, G×E were studied for longevity, production and health traits in German Holstein cattle kept at 57 conventional farms and nine organic farms. The presence of G×E is suggested when the genetic correlation between a trait being expressed in the two production systems is lower than 0.8. Heritabilities of traits and genetic correlations between the same traits in the two systems were estimated using pedigree-based and SNP-based relationship matrices and the application of a single-step approach. Furthermore, GWAS were separately conducted for milk production traits (milk yield and fat percentage), health traits and LPL for genotyped cows from organic and conventional herds. Milk production traits were found to have high heritabilities, and genetic correlations for the same traits from organic and conventional production systems were larger than 0.80. Furthermore, with regard to the GWAS results, significant SNP markers for milk yield and fat percentage in conventional and organic herds essentially overlapped. However, small heritabilities and low genetic correlations were estimated for health traits and LPL; for example, genetic correlations in conventional and organic farms were 0.44 for mastitis and 0.33 for digital dermatitis using a single-step approach. Additionally, the significantly associated SNP markers differed in both production systems. These results indicate the existence of G×E for functional traits and suggest a separate selection index for cattle reared on organic farms.

In summary, the low heritabilities for longevity and the negligible contributions of significant SNP associated with longevity on culling risk ratios indicate the polygenetic nature of longevity. Furthermore, due to the favorable genetic correlations between longevity and health disorders, the inclusion of cattle health traits in breeding programs can accelerate the genetic improvement of longevity. However, more data from phenotyped and genotyped cattle at organic farms must be collected to improve the accuracy of genetic correlations between same traits from organic and conventional farms.

CHAPTER 1: GENERAL INTRODUCTION

1.1 Functional traits in dairy cattle breeding goals

Classical breeding schemes have focused on intensive selection for high production while neglecting functional traits (Essl, 1998; Oltenacu and Broom, 2010). However, over the past few decades, functional traits have become more important in overall dairy cattle breeding goals (Egger-Danner et al., 2015; Heringstad et al., 2018). Due to negative genetic correlations between production and functional traits, long-term selection for improved productivity was associated with impairments in health (Oltenacu and Broom, 2010; Pritchard et al., 2013a; Berry et al., 2014). According to Groen et al. (1997), functional traits refer to the ability of an animal to increase efficiency by reducing the costs of input. Basically, functional traits for dairy cattle has a broader range compared to production traits, which usually includes milk yield and milk composition traits. Groen et al. (1997) classified functional traits into health, reproduction, calving ease, feed efficiency and milkability. Furthermore, novel traits such as temperament, behavior and adaptability to extreme weather conditions have emerged due to growing emphasis on issues of animal welfare and climate change (Egger-Danner et al., 2015). Balanced productivity, combined with functional traits in breeding goals, may increase longevity, fitness and robustness in dairy cattle (Boichard and Brochard, 2012; Fuerst-Waltl et al., 2016). However, economic value estimates for functional traits are difficult, and some functional traits cannot be evaluated in terms of costs and revenues (Groen et al., 1997; Olesen et al., 2000). Nevertheless, favorable responses to selection for functional traits can be observed in simulated and real breeding schemes that integrate productivity and functionality (Pryce and Harris, 2006; Yin et al., 2015).

1.2 Longevity

A cow's survival after the third lactation has high economic importance due to the high efficiency of nutrient utilization after this period (van Vuuren and Chilibroste, 2013) and the achievement of highest annual milk yield (Horn et al., 2012; Fuerst-Waltl et al., 2016). Furthermore, the increase in longevity reduces replacement costs (Horn et al., 2012). However, a large percentage of cows do not achieve their maximum potential for milk production, because most milking cows are culled before the fourth lactation and cannot reach the optimal lifetime in Germany (Heise et al., 2016), Sweden (Ahlman et al., 2011), Denmark (Clasen et al., 2017), Belgium (Gengler et al., 2005), Poland (Oler et al., 2012), Portugal (Rocha et al., 2010),the United Kingdom (Bell et al., 2010) and the United States (Vries et al., 2010). Beyond the maximization of profitability, the improvement of longevity reduces involuntary cow culling due to health and reproductive problems (Cruickshank et al., 2002).

Subjective decisions made by dairy farmers are the main determinants of the actual length of a cow's life. Hence, a clear distinction between culling for productive reasons (voluntary culling) and culling for functional traits (involuntary culling) is necessary.

1.2.1 Trait definitions for longevity

In dairy cattle breeding, various definitions for longevity exist. For example, longevity can be measured on a continuous scale as (1) direct or indirect herd life (Nayeri et al., 2017), (2) the number of calvings (Steri et al., 2019) or lactations over a cow's lifespan (Stanojević et al., 2016) or (3) the length of productive life (i.e., the time period between first calving and culling; Pritchard et al., 2013b; van Pelt et al., 2018). Alternatively, longevity can be defined as binary stayability to a specific endpoint such as age (VanRaden et al., 2006) or number of parities (Berry et al., 2008), in other words, whether a cow is alive at a certain age or lactation (Figure 1.1). Some studies have used lifetime yield or lifetime effectivity to represent longevity (Eilers, 2014; Rohde, 2009). Furthermore, longevity can be adjusted for production levels in statistical models and labeled corrected or functional longevity (Dekkers, 1993).

Continuous traits:

- Length of productive life (**LPL**) = number of days or months from first calving to culling or the last test-day
- Herd life (**HL**) = number of days or months from birth to culling or to the last test-day
- Number of lactation (**NL**) = number of completed lactations

Binary traits:

- Stayability according to lactation (**ST-L**) = survival through one to three lactations
- Stayability according to lactation period (**ST-LP**) = survival to a certain period in one lactation (e.g., survival from first calving to 120 days in milk (**DIM**), from 120 to 240 DIM and from 240 DIM to second calving)
- Stayability according to age (**ST-A**) = survival to a certain age (e.g., 20–72 months of age or 12–48 months of productive life)

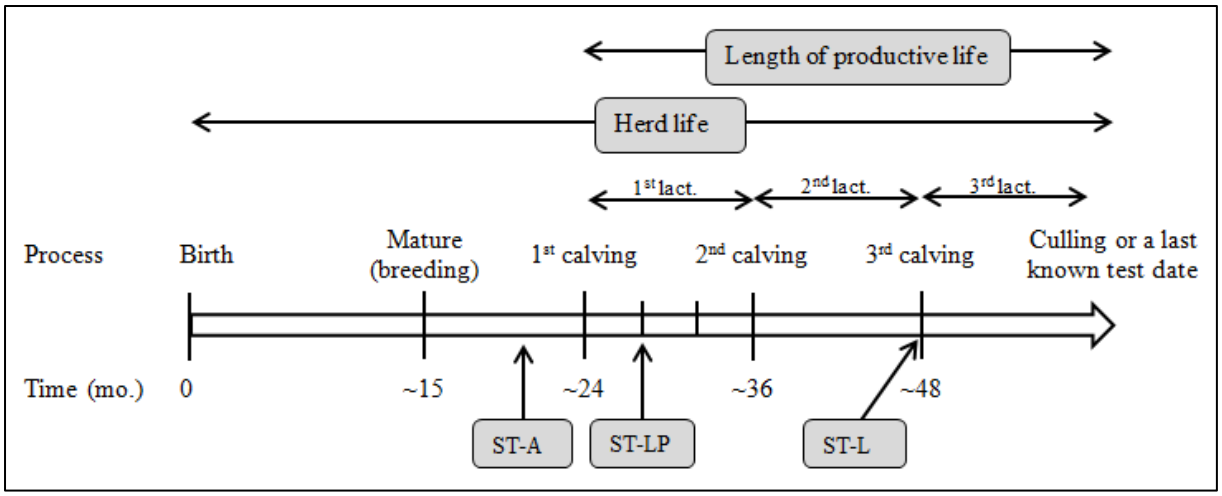

Figure 1.1: Definitions of longevity. (ST-A = stayability according to age, ST-L = stayability according to lactation, ST-LP = stayability according to lactation period)

A disadvantage of LPL is that it can be measured only after the death of the cow. Stayability as a binary trait can be measured at any point of a cow's life cycle, but it is inaccurate since the real lifetime after the given point remains unknown. Therefore, LPL is claimed to be the most frequently used and widely accepted definition of longevity in the literature.

1.2.2 Statistical models

Linear model

The linear mixed model, which includes varied fixed effects and random additive genetic effects (Henderson, 1975), can be used to estimate both continuous and binary longevity traits (Sewalem et al., 2007; Holtsmark et al., 2009). The model in matrix notation is as follows:

$$\mathbf{y} = \mathbf{Xb} + \mathbf{Zu} + \mathbf{e}$$

where **y** is a vector of longevity observations, **b** is a vector of fixed effects (e.g., herd-year-season, calving age and production level), **u** is a vector of additive genetic effects and **e** is a vector of random errors. **X** and **Z** are known design matrices that allocate the observations **y** to **b** and **u** vectors, respectively.

Moreover, a linear model with random regression coefficients for additive genetic and permanent environmental effects – the so-called "random regression model" (**RR**) – can also be used to analyze longevity data with repeated measurements (Veerkamp et al., 2001).

Threshold model

For binary survival traits (i.e., dead or alive at certain point in time) that do not follow any normal distribution, the threshold model is statistically more appropriate than the linear model (Boettcher et al., 1999a). Threshold analyses for categorical phenotypes simulate an

underlying normal distribution with truncation points that are also known as thresholds (Gianola, 1982). Thresholds determine the categories of the underlying liability or simulated continuous random variable. For a binary trait, a response takes the value of 1 if the liability is greater than the threshold. Otherwise, a value 0 is assigned to the response (Heringstad et al., 2003b). The threshold model can be classified as a generalized linear mixed model. Particular to binary traits with a logit or probit link function, the probabilities from binomial distribution can be explained through linear predictors. The logistic model can be written as follows:

$$logit(\pi_r) = \log\left(\frac{\pi_r}{1-\pi_r}\right) = \varphi + \gamma_r$$

where π_r is the probability of occurrence of a disease or survival for cow r, φ is the overall mean and γ_r is random additive genetic effects for cow r.

Proportional hazard model

The benefits of the proportional hazard model include the ability to use both censored and uncensored data and the addition of time-dependent variables (Ducrocq, 2002; Sewalem et al., 2005; Zavadilová et al., 2011). The use of specialized distributions (e.g., exponential and Weibull), which is more preferable for failure time data than a normal distribution, is another benefit of survival analysis (Ducrocq, 2005). Hence, the proportional hazard model provides the optimal analytical method to examine longevity data (Sasaki, 2013).

The hazard function is fundamental in survival analysis. The hazard of cows is defined as follows:

$$\lambda(t) = \lambda\rho(\lambda t)^{\rho-1}\, exp\,(S(t) + g)$$

where $\lambda_0(t)$ is the baseline Weibull hazard function, λ is the scale parameter and ρ is the shape parameter of the baseline hazard function, S(t) is the time-dependent fixed effect of calving season and g is additive genetic animal effects. The shape parameter (ρ) represents the flexibility of hazard rates. When $\rho = 1$, hazard rates remain constant over time, and $\rho < 1$ and $\rho > 1$ represent decreasing and increasing hazard rates over time, respectively.

The Survival Kit software package was developed (Ducrocq and Sölkner, 1998) and updated (Mészáros et al., 2013) for the calculation of risk ratios based on parameters in the proportional hazard model.

Model comparisons

The estimation of variance components and genetic parameters for continuous and binary longevity traits can be performed with a linear mixed model, a threshold model or a

proportional hazard model. From a breeding perspective, the linear mixed model is preferred, because linear analyses that involve even large amounts of data complete and converge within an acceptable computation time (Misztal et al., 2002; Madsen and Jensen, 2013) and estimated breeding values (**EBV**) are easy to interpret. Additionally, previous studies revealed that linear models demonstrated good fits for the genetic evaluation of binary longevity traits (Holtsmark et al., 2009; Heise, 2017; Täubert et al., 2017).

Survival analysis is more suitable for the evaluation of longevity traits with censored observations. Censored observations reflect partial information on longevity, because the cow is still alive at the time of measurement, but time to death remains unknown (Klein and Moeschberger, 2003). In this case, a Weibull or Cox proportional hazards model would be an appropriate estimation method for survival analysis. However, a disadvantage of the survival model is its considerably longer computation time compared to linear models (Heise, 2017).

1.2.3 The heritabilities of longevity in linear, threshold and proportional hazard models

The previously reported heritabilities of continuous longevity traits estimated with linear or threshold models are summarized in Table 1.1 and those of binary traits are reported in Table 1.2. The heritabilities of LPL have ranged from 0.02 to 0.18 and are comparable to values for herd life (0.03–0.15) and number of lactations (0.03–0.12). The binary traits (i.e., stayability according to age, stayability according to lactation and stayability according to lactation period) yielded heritability values between 0.01 and 0.15. There were no clear differences arising from the type of model or dairy cattle breed. However, higher heritabilities were reported for beef cattle; for example, the range was 0.20–0.22 for Nellore cattle (Silva et al., 2006; van Melis et al., 2010) and 0.18–0.30 for Angus cattle (Maiwashe et al., 2009). This is because longevity in beef cattle is understood as the cow's cumulative fertility (van Melis et al., 2010).

Previous studies have reported that heritability in Weibull proportional hazards models is generally higher than in linear models (Caraviello et al., 2004; Sewalem et al., 2005; Olechnowicz et al., 2016). However, estimated heritabilities from Weibull proportional hazards models ranged from 0.03 and 0.14 for h^2_{eff} and from 0.02 to 0.12 for h^2_{equ} (Table 3.1) and generally do not differ from values in linear or threshold models. Heritabilities obtained with different methodologies were similar.

These low to moderate heritabilities for different longevity traits demonstrate that the improvement of longevity in dairy cattle should be possible but are expected to take a long time.

Table 1.1: Literature overview of heritability estimates for continuous longevity traits in dairy cattle, sorted by year of publication

Reference	Gen. eff[1]	Model[2]	Breed[3]	Country[4]	Heritabilities	Trait[5]
Rogers et al., 1991	S	L	JER	USA	0.03	LPL
Boldman et al., 1992	S	L	HOL	USA	0.03, 0.03	HL, HLf
Short and Lawlor, 1992	S	L	HOL	USA	0.07, 0.06	HL, HLf
VanRaden and Klaaskate, 1993	S	L	HOL	USA	0.03–0.09	LPL
Vollema and Groen, 1996	S, A	L	HOL	NLD	0.03, 0.04	NL
					0.04	HL
					0.04	LPL
Brotherstone et al., 1997	S	L	HOL	GBR	0.06	NL
Vollema and Groen, 1997	S	L	HOL	NLD	0.09–0.11	NL
					0.06–0.08	NLf
					0.10–0.13	HL
					0.07–0.09	HLf
Lubbers et al., 2000	S	L	HOL	GBR	0.06	NL
Cruickshank et al., 2002	A	L	GUE	USA	0.12	HL, HLf
Pérez-Cabal and Alenda, 2003	A	L	HOL	ESP	0.08	HLf
Caraviello et al., 2004	A	L	JER	USA	0.07	LPL
Setati et al., 2004	A	L	HOL	ZAF	0.06	NL
Posadas et al., 2004	A	L	HOL	MEX	0.04	LPLr
Tsuruta et al., 2004	A	L-MT-RR	HOL	USA	0.09–0.18	LPLr
Hagiya et al., 2005	A	L	HOL	JPN	0.08	HL
					0.09	LPL
Tsuruta et al., 2005	S	L	HOL	USA	0.08–0.10	LPLr
Pérez-Cabal et al., 2006	A	L	HOL	ESP	0.10	LPL, LPLf
VanRaden et al., 2006	S	L	HOL	USA	0.07	LPL
					0.02–0.07	LPLr
Daliri et al., 2008	A	L-MT-RR	HOL	IRN	0.04, 0.03	LPL, LPLf
Krogmeier, 2009b	A	L	SIM, BSW	DEU, AUT	0.07–0.08	LPL
Zavadilová et al., 2009	A	L	SIM	CZE	0.05, 0.04	LPL, LPLf
Samoré et al., 2010	S	L-MT	BSW	ITA	0.06	LPLf
Ahlman et al., 2011	A	L-MT	HOL, RDC	SWE	0.09–0.18	LPL
Zavadilová and Štípková, 2012	A	L	HOL	CZE	0.03	LPLf
					0.05	NLf
Eaglen et al., 2013	S	L-MT	HOL	GBR	0.11	LPL
Pritchard et al., 2013b	S	L	HOL	GBR	0.06	LPL, HL
	A				0.06	LPL

Reference	Gen. eff[1]	Model[2]	Breed[3]	Country[4]	Heritabilities	Trait[5]
Raguž et al., 2014	S, A	L	SIM	HRV	0.04, 0.06	LPLf
van Pelt and Veerkamp, 2014	SMG	L-RR	HOL	NDL	0.15	LPL
Jenko et al., 2015	A	L-MT	BSW	SVN	0.09	LPL
Pfeiffer et al., 2015	A	L	SIM	AUT	0.15	LPLf
van Pelt et al., 2015	SMG	L-RR	HOL	NDL	0.11–0.15	LPL
Wasana et al., 2015	A	L	HOL	KOR	0.06–0.13	LPL
Weller and Ezra, 2015	A	L	HOL	ISR	0.14	HL
Eghbalsaied et al., 2016	A	L	HOL	IRN	0.11–0.12	LPL
					0.11–0.15	HL
Stanojević et al., 2016	A	L	HOL	SRB	0.07	LPL, NL
Clasen et al., 2017	A	L	HOL, JER	DNK	0.02–0.09	LPLr
Ghaderi-Zefrehei et al., 2017	A	L	HOL	IRN	0.11	HL
					0.09	LPL
Novotný et al., 2017	A	L	SIM	CZE	0.06, 0.05	NL, NLf
Saowaphak et al., 2017	A	L-MT	HOL	THA	0.10	LPL
Mirhabibi et al., 2018	A	L	HOL	IRN	0.03	LPL, LPLf
van Pelt et al., 2018	A	L-RR	HOL	NDL	0.12, 0.15	LPL, LPLf
Salem and Hammoud, 2019	A	L	HOL	EGY	0.12	NL
					0.14	LPL

[1]Additive genetic effect in the model: S = sire, A = animal, SMG = sire-maternal-grandsire;
[2]Model: L = linear mixed model, L-MT = linear multi-trait model, L-RR = linear random regression model, L-MT-RR = linear multi-trait random regression model;
[3]Breed ISO code: HOL = Holstein Friesian, SIM = Simmental, BSW = Brown Swiss, RDC = Red Dairy Cattle (Norwegian Red), JER = Jersey, GUE = Guernsey;
[4]Country ISO code: AUT = Austria, CZE = Czech Republic, DEU = Germany, DNK = Denmark, EGY = Egypt, ESP = Spain, GBR = the United Kingdom, HRV = Croatia, IRN = Iran, ISR = Israel, ITA = Italy, JPN = Japan, KOR = Korea, MEX = Mexico, NLD = the Netherlands, SRB = Serbia, SVN = Slovenia, SWE = Sweden, THA = Thailand, USA = the United States, ZAF = South Africa;
[5]LPL = length of productive life, LPLf = functional length of productive life, LPLr = restricted length of productive life, HL = herd life, HLf = functional herd life, NL = number of lactations, NLf = functional number of lactations.

Table 1.2: Literature overview of heritability estimates for binary longevity traits in dairy cattle, sorted by year of publication

Reference	Gen. eff[1]	Model[2]	Breed[3]	Country[4]	Heritabilities	Trait[5]
Rogers et al., 1991	S	L	JER	USA	0.08	ST-L
					0.04	ST-A
Short and Lawlor, 1992	S	L	HOL	USA	0.02	ST-L
					0.05, 0.04	ST-A
Vollema and Groen, 1996	S, A	L	HOL	NLD	0.01–0.03	ST-A
Brotherstone et al., 1997	S	L	HOL	GBR	0.03–0.08	ST-L
Vollema and Groen, 1997	S	L	HOL	NLD	0.01–0.03	ST-A
Boettcher et al., 1999a	S	L-MT	HOL	CAN	0.04–0.05	ST-L
		T			0.07	ST-L
Boettcher et al., 1999b	S	L-MT	HOL	CAN	0.04	ST-L
Veerkamp et al., 2001	A	L-RR	HOL	GBR	0.02–0.04	ST-L
Haile-Mariam et al., 2003	S	L-MT	HOL	AUS	0.02	ST-L
Posadas et al., 2004	A	L	HOL	MEX	0.03	ST-A
Gengler et al., 2005	A	L-MT-RR	HOL	BEL	0.03	ST-L
González-Recio and Alenda, 2007	A	TL	HOL	ESP	0.11	ST-L
Sewalem et al., 2007	A	L-MT	HOL	CAN	0.01–0.05	ST-LP
Holtsmark et al., 2008	S	TL	RDC	NOR	0.04	ST-L
Du Toit et al., 2009	S	L-MT	JER	ZAF	0.02–0.03	ST-L
	A				0.01–0.03	ST-L
Holtsmark et al., 2009	S	L-RP, L-CS	RDC	NOR	0.02	ST-L
		T-RP, T-CS			0.04	ST-L
		L-MT			0.02–0.03	ST-L
Ahlman et al., 2011	A	L-MT	HOL, RDC	SWE	0.01–0.30	ST-L
					0.03–0.06	ST-FU
Du Toit, 2011	S	L-MT	JER	ZAF	0.02–0.03	ST-L
	A				0.01–0.03	ST-L
Kern et al., 2014	A	T	HOL	BRA	0.09–0.15	ST-A
Wiebelitz et al., 2014	S	L-MT	HOL	DEU	0.03–0.06	ST-LP
van Pelt and Veerkamp, 2014	SMG	L-RR	HOL	NDL	0.00–0.01	ST-A
Sasaki et al., 2015	A	L-MT-RR	HOL	JPN	0.01–0.08	ST-LP
Tsuruta et al., 2015	A	TL-MT	HOL	USA	0.03–0.11	ST-L
van Pelt et al., 2015	SMG	T-RR	HOL	NDL	0.01–0.08	ST-A
Heise et al., 2016	S	L-MT	HOL	DEU	0.01–0.04	ST-LP
van Pelt et al., 2016	SMG	L	HOL	NDL	0.01, 0.02	ST-A
		T			0.05, 0.08	ST-A
Nayeri et al., 2017	G	L-MT	HOL	CAN	0.10	ST-A

Reference	Gen. eff[1]	Model[2]	Breed[3]	Country[4]	Heritabilities	Trait[5]
Sasaki et al., 2017	A	L-MT-RR	HOL	JPN	0.00–0.05	ST-LP
Täubert et al., 2017	A	L-MT	HOL	DEU	0.02–0.04	ST-LP
Tsuruta et al., 2017	A	TL-MT	HOL	USA	0.03–0.04	ST-L
Heise et al., 2018	S	L-MT	HOL	DEU	0.02–0.03	ST-L
Stefani et al., 2018	A	T	HOL	BRA	0.09	ST-A
Grayaa et al., 2019	A	L-MT-RR	HOL	TUN	0.03	ST-L

[1]Additive genetic effect in the model: S = sire, A = animal, SMG = sire-maternal-grandsire, G = genomic relationship matrix;
[2]Model: L = linear mixed model, L-MT = linear multi-trait model, L-RR = linear random regression model, L-MT-RR = linear multi-trait random regression model, L-RP = linear mixed repeatability model, L-CS = linear mixed cross-sectional model, T = threshold model, T-RR = threshold random regression model, T-RP = threshold repeatability model, T-CS = threshold cross-sectional model, TL = threshold-linear model, TL-MT = threshold-linear multi-trait model;
[3]Breed ISO code: HOL = Holstein Friesian, SIM = Simmental, RDC = Red Dairy Cattle (Norwegian Red), JER = Jersey;
[4]Country ISO code: AUS = Australia, BEL = Belgium, BRA = Brazil, CAN = Canada, DEU = Germany, ESP = Spain, GBR = the United Kingdom, JPN = Japan, MEX = Mexico, NOR = Norway, NLD = the Netherlands, SWE = Sweden, TUN = Tunisia, USA = the United States, ZAF = South Africa;
[5]ST-A = stayability to certain age, ST-L = stayability to certain lactation, ST-LP = stayability to certain lactation period, ST-FU = fertility or udder-health determined stayability.

1.2.4 Genetic evaluation of longevity

Despite the fact that longevity is cumulatively recorded and routinely evaluated in many countries, differences in the definition of longevity can be observed (Table 1.3).

Table 1.3: National genetic evaluation for longevity from the International Bull Evaluation Service (Interbull 2020)

Country[1]	Breed[2]	Trait[3]	Add. gen. eff.[4]	Model[5]
AUS	HOL, JER, GUE, RDC	ST	A	L
BEL	HOL, BBL	ST	A	L-MT-RR
CAN	HOL, RDC, BSW, GUE, JER	ST	A	L-MT
CHE	HOL, SIM	LPL	S-MGS	SA
CZE	HOL	LPL	S-MGS	SA
DEU, AUT	BSW	LPL	S-MGS	SA
DEU, LUX	HOL, RCD, JER	ST	A	L-MT
DNK, SWE, FIN	HOL, RDC	LPL	A	L-MT
ESP	HOL	LPL	S-MGS	SA
FRA	HOL, NMD, MON, SIM, BSW	LPL	S-MGS	SA
GBR	HOL, RDC, JER, GUE, BSW, SIM	NL	A	L-MT
HUN	HOL	LPL	S-MGS	SA
IRL	HOL, JER	ST	A	L-MT
ISR	HOL	LPL	A	L
ITA	HOL, BSW	LPL	S-MGS, S	SA
NDL	HOL, DFR	ST	A	L-RR
NOR	RDC	LPL	A	L-MT-RR
NZL	HOL, JER, GUE, BSW, RDC	ST	A	L-MT
POL	HOL	LPL	S	SA
SVN	HOL, SIM, BSW	LPL	S-MGS	SA
USA	HOL, SIM, BSW, GUE, RDC, JER	LPL	A	L
ZAF	HOL	ST	A	L-MT

[1]Country ISO code: AUS = Australia, AUT = Austria, BEL = Belgium, CAN = Canada, CHE = Switzerland, CZE = Czech Republic, DEU = Germany, DNK = Denmark, ESP = Spain, FIN = Finland, FRA = France, GBR = Great Britain, IRL = Ireland, ISR = Israel, ITA = Italy, LUX = Luxemburg; NDL = Netherlands, NOR = Norway, NZL = New Zealand, POL = Poland, SVN = Slovenia, SWE = Sweden, USA = United States, ZAF = Rep. of South Africa;
[2]Breed ISO code: HOL = Holstein Friesian, SIM = Simmental/Fleckvieh, BSW = Brown Swiss, RDC = Red Dairy Cattle (Ayrshire, Norwegian Red or Swedish Red), JER = Jersey, GUE = Guernsey, DFR = Dutch Frisian, BBL = Belgian Blue, MON = Montbéliard, NMD = Normandy;
[3]Trait: ST = Stayability to a certain lactation or lactation period, LPL = length of productive life, NL = number of completed lactations;
[4]Additive genetic effect: A = Animal, S = Sire, S-MGS = Sire-maternal-grandsire;
[5]Model: SA = survival analysis (proportional hazards model with a piecewise Weibull baseline hazard distribution), L = linear mixed model, L-MT = linear multi-trait model, L-RR = linear random regression model, L-MT-RR = linear multi-trait random regression model.

For example, longevity is defined as LPL in some countries but as stayability in others. In addition, models used to analyze longevity varied from a linear mixed model to a proportional hazard model with a piecewise Weibull baseline hazard distribution.

1.2.5 Economic importance of longevity

The importance of longevity is attributed to its contributions to decreasing the management of labor, environmental pollution and input costs. Improvements in cow longevity can lead to greater lifetime production, a reduction in the number of replacement heifers and a significantly lower environmental footprint for the dairy industry (Garnsworthy, 2004; Capper et al., 2009). Moreover, extended lactation can reduce methane emissions by 10% (Smith et al., 2007). Superiority in economic efficiency is also an important reason to breed for longevity. In high-yielding cattle herds, average longevity is usually less than three lactations, which implies that an increase in average longevity to four lactations would enhance nutrient efficiency by reducing the cost of rearing (van Vuuren and Chilibroste, 2013). Based on data from 9,755 US Holstein dairy herds, Vries (2017) reported that increasing the annual cow culling rate from 15% to 55% resulted in an increase in total annual cost from $USD 342 to $USD 420 per cow. Furthermore, cow longevity is considered to be an indicator of animal welfare in the political and societal agendas of many countries (Vries et al., 2011).

1.3 Production diseases in dairy cattle

Production diseases are diseases caused by production level, irrespective of nutrient intake, diet amount or environmental conditions (Mulligan and Doherty, 2008). Payne (1972) defined the term “production disease” as a number of metabolic disorders of increasing importance in agriculture. However, Joshi and Herdt (2006) suggested that production diseases should include metabolic and nutritional diseases as well as infectious diseases. From this point of view, we defined production diseases as the most common and important health issues (i.e., mastitis, claw and metabolic disorders and reproductive diseases).

1.3.1 Breeding strategies to improve disease resistance

In recent years, health traits have become increasingly important in breeding, because a cow’s health status has a crucial impact on the overall profitability of dairy cattle production. However, selection for improved health among dairy cows is hampered by low heritabilities, scarce health trait phenotypes and farmers’ interventions. Nevertheless, routine genetic evaluations for functional health traits have been conducted in many countries, and the

economic weight of health traits was even greater than that of production traits (Reents and Rensing, 2009). In the Scandinavian countries, health data has been included in selection indices since 1975 (Johansson et al., 2008 and Østerås et al., 2007), and positive responses to selection for mastitis resistance have been achieved (Philipsson and Lindhé, 2003). For German Holstein dairy cattle, longevity has been included in routine national genetic evaluations since April 2018, and direct health traits have been genetically evaluated since April 2019 (VIT, 2020). Moreover, for dual-purpose Austrian-German Fleckvieh, direct health traits have also been added to overall breeding goals (Fuerst et al., 2011). Selecting for improved health traits also improves longevity, because diseases are among the top reasons for involuntary cow culling. Additionally, udder and reproductive diseases have been phenotypically and genetically associated with culling in US Holstein cattle (Pinedo et al., 2010), Dutch and Chinese Holstein cattle (Zijlstra et al., 2016), Polish dairy cattle (Adamczyk et al., 2016) and German Holstein cattle (Hörning et al., 2005.; Wangler et al., 2009 and Heise et al., 2016). However, due to the difficulty of collecting direct health phenotypes, indicator traits rather than direct health traits are widely used in selection indices to improve the health status of dairy cattle. The availabilities of direct health traits and their indicator traits in different countries are listed in Table 1.4.

Table 1.4: National genetic evaluations of health indicator traits and direct health traits in different countries

Country[1]	Udder		Claw		Metabolic		Reproductive	
	Indic.[2]: SCS	Diagn.[3]	Indic.: conf.	Diagn.	Indic.: BHB	Diagn.	Indic.: FF	Diagn.
AUS	x	x	x				x	
CAN	x	x	x		x	x	x	
CHE	x	x	x				x	
DNK, SWE, FIN	x	x	x	x		x	x	x
DEU, LUX	x	x	x	x		x	x	x
DEU, AUT	x	x	x			x	x	x
ESP	x		x	x			x	
GBR	x	x	x				x	
NDL	x		x	x			x	
NOR	x	x	x	x		x	x	x
USA	x	x	x			x	x	x

[1]Country ISO code: AUS = Australia, AUT = Austria, CAN = Canada, CHE = Switzerland, DEU = Germany, DNK = Denmark, ESP = Spain, FIN = Finland, LUX = Luxemburg, NDL = Netherlands, NOR = Norway, SWE = Sweden, USA = United States;
[2]Indic. = indicator traits for health status. Somatic cell score (SCS) for udder health; conformation traits for claw disorders; betahydroxybutyrate in milk for metabolic diseases; and female fertility traits, (e.g., non-return rate, calving interval) for reproductive diseases;
[3]Diagn. = direct diagnosis.

1.3.2 Mastitis

Mastitis is the most common health problem among dairy cattle (Hogeveen et al., 2019). It is a complex disease defined by an inflammation of the mammary gland resulting from bacterial pathogen infections. *Staphylococcus aureus, Escherichia coli* and *Streptococcus agalactiae* are the major pathogens found in clinical mastitis. A cow with clinical mastitis presents with abnormal milk secretion from one or more quarters, with signs of inflammation of the udder tissues (e.g., heat and swelling; Kelton et al., 1998). Subclinical mastitis is the occurrence of infection without local inflammation (Thompson-Crispi et al., 2014) but a reduction in the quality and quantity of milk. According to Lund et al. (1999) and Negussie et al. (2010), clinical mastitis occurs mostly in early lactation and is rarely observed in later lactation (Svensson et al., 2006; Steeneveld et al., 2008). Mastitis is primarily caused by environmental factors such as poor hygiene and inadequate herd management (Kadarmideen et al., 2001). Despite great efforts to improve management and cow factors associated with mastitis, the incidence of mastitis has not decreased over time (Richert et al., 2013; Martin et al., 2018). As an alternative method, breeding can gradually improve mastitis resistance in a population at the genetic scale. Somatic cell count (**SCC**) and somatic cell score (**SCS**) are commonly used as indirect measurements instead of direct udder health traits to improve mastitis resistance

(Carlén et al., 2004; Miglior et al., 2005; Urioste et al., 2010). However, moderate genetic correlations and distinct genetic backgrounds between SCC and mastitis constrain the selection responses of mastitis. Thus, direct health records for clinical mastitis and SCS are included nowadays in national genetic evaluations for dairy cattle in several counties (Table 1.4)

1.3.3 Claw disorders

Lameness has serious implications for economics and the welfare of cows in the dairy industry (Rutherford et al., 2009) and is mostly caused by different claw disorders. The most prevalent claw disorders are digital dermatitis (also known as Mortellaro disease or strawberry foot rot), white line disease, interdigital hyperplasia and sole ulcer. According to the ICAR Claw Health Atlas (ICAR, 2015), digital dermatitis is defined as severe inflammation of the skin with erosion. The skin around the cow's heels and between its hooves is affected (Cramer et al., 2009b). Sole ulcer is erosion of the sole horn, resulting in exposed fresh or necrotic corium (Dirksen, 2006; ICAR, 2015). It is often located near the sole-heel (Booth et al., 2004). White line disease is characterized by breaks or fissures of the white line or the separation of the sole and wall horn (ICAR, 2015; Cramer et al., 2009b). The horn of the white line is softer than the sole and wall horn and thus most likely to become inflamed in damp conditions (Kofler, 2001; Nuss and Steiner, 2004). Interdigital hyperplasia is the growth of fibrous tissue between the inner and outer claw (ICAR, 2015; Gernand et al., 2012). This disease results from strong mechanical pressure and chronic irritation (Manske et al., 2002). Figure 1.2 depicts the claw zones with corresponding disease frequencies (Solano et al., 2016).

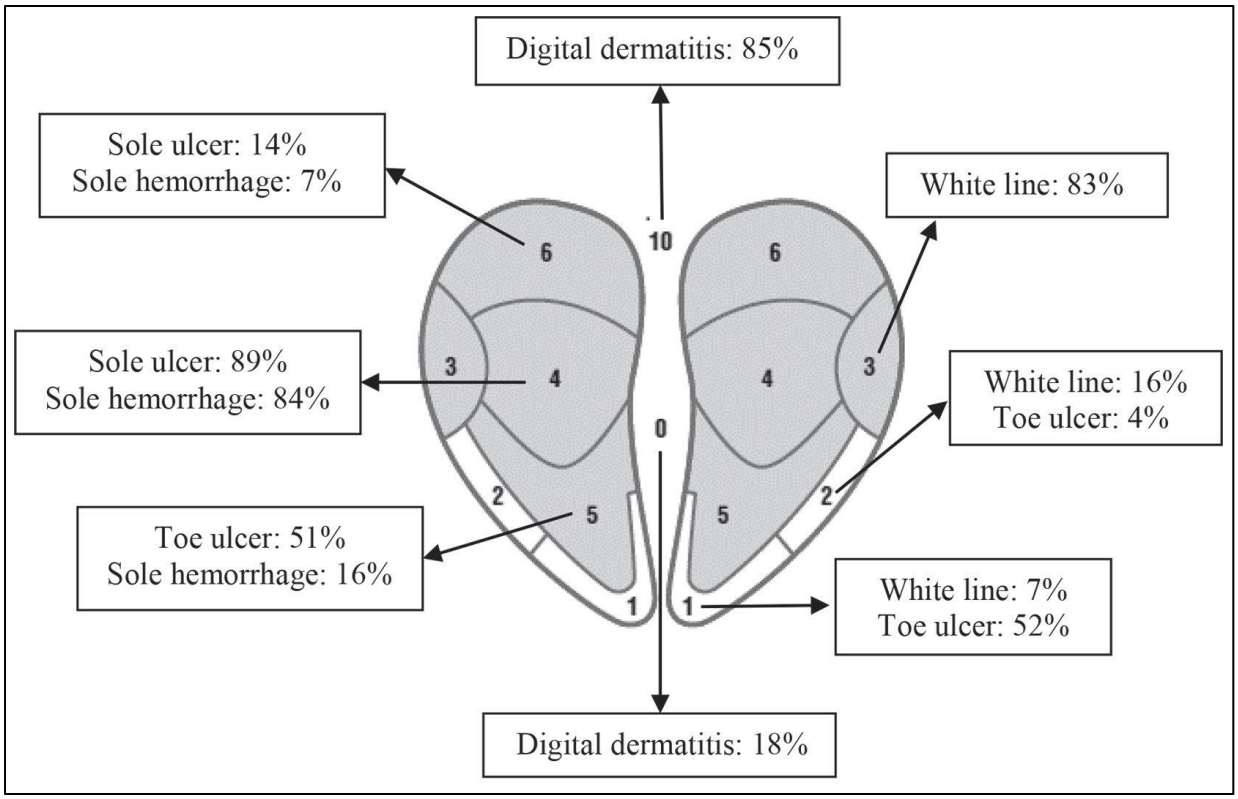

Figure 1.2: Most common foot lesions by claw zone among cattle (Solano et al., 2016)

Claw lesions can be divided into two groups: infectious (e.g., interdigital and digital dermatitis, heel erosion) and noninfectious (e.g., sole and toe ulcer, white line disease) (Dhakal et al., 2015; Charfeddine and Pérez-Cabal, 2017). Infectious lesions usually affect the skin of the foot and are associated with unhygienic floor conditions (Bell et al., 2009), frequency of alley scraping (Cramer et al., 2009a) and footbathing (Somers et al., 2005a; Somers et al., 2005b). Noninfectious lesions affect the claw horn and are caused by exposure to hard flooring (Manske et al., 2002; Somers et al., 2003) or metabolic changes associated with calving (Tarlton et al., 2002).

Conformation traits for the feet and legs are routinely recorded and selected to indirectly improve claw health (van der Waaij et al., 2005; van der Linde et al., 2010; Häggman and Juga, 2013). As shown in Table 1.4, claw disorders are included in routine genetic evaluations of dairy herds in Spain (Charfeddine et al., 2018), the Netherlands (Stoop et al., 2010), Denmark, Sweden and Finland (Sørensen et al., 2018) and Norway (Ødegård et al., 2013).

1.3.4 Metabolic disorders

Metabolic diseases result from imbalances in metabolic processes, especially for heifers and cows that are in the transition period, because of increased and altered nutrient demands

associated with calving (Ingvartsen, 2006). The transition period is defined as the interval from three weeks before to three weeks after calving (Sundrum, 2015). Energy demands increase due to the development of the fetus in late pregnancy and milk synthesis in early lactation (Bell, 1995). Therefore, negative energy balance in early lactation is inevitable (Collard et al., 2000). Fat-to-protein ratio is an indicator of energy balance (Buttchereit et al., 2011). A fat-to-protein ratio greater than 1.5 indicates ketosis (Heuer et al., 1999). Sweet smelling breath from a cow (exhalation of ketone bodies) is another indicator of ketosis (Pryce et al., 2016). Ketosis is characterized by the accumulation of large quantities of ketone bodies that are measurable in blood, urine and milk (Geishauser et al., 1998; Sutherland et al., 2013). In Canada, the genetic evaluation of subclinical ketosis uses the level of beta-hydroxybutyrate in milk samples as an indicator (Beavers and van Doormaal, 2016). Another important metabolic disease is milk fever or hypocalcaemia. Symptoms include a lower body temperature and partial to complete paralysis, which typically occurs close to calving (Pryce et al., 2016). The impossibility of maintaining normal blood calcium concentrations controlled by homeostatic mechanisms is the physiological reason behind milk fever (DeGaris and Lean, 2008; Chamberlin et al., 2013). In contrast to ketosis and milk fever, acidosis is independent from calving and triggered by an inappropriate feeding regime. A diet with large amounts of carbohydrates decreases ruminal pH, which in turn causes acidosis; however, this can be treated by increasing dietary fiber (Krause and Oetzel, 2006).

1.3.5 Reproductive diseases

Various reproductive diseases have been associated with significant reductions in reproductive performance in dairy cows. Routinely measured reproductive traits include calving interval, days open (interval from calving to conception) and non-return rate. Koeck et al. (2010a) divided reproductive disorders into (1) early reproductive disorders, which occur within 30 days after calving and are associated with calving damage (retained placenta) and (2) late reproductive disorders, which occur between 31 and 150 days after calving and are related to infection (metritis) or hormonal imbalance (cystic ovaries).

The main postpartum diseases are metritis and endometritis (i.e., inflammation of the endometrium caused by bacterial infections; Sheldon and Owens, 2017). The main symptom of metritis is an enlarged uterus with a purulent discharge, while endometritis is characterized by the presence of pus in the uterus (Sheldon et al., 2006). A retained placenta is a reproductive abnormality when a cow is unable to expel the placenta within 24 hours after

calving. The mechanism of placenta expulsion remains unclear; however, Kimura et al. (2002) have reported that impaired neutrophil function may contribute to placenta expulsion.

The group of diseases labeled "ovarial infertility" includes ovarian cycle disorders, ovarian cysts and corpus luteum persistens. Cystic ovaries are the presence of a large follicular structure (>17mm) that persists on the ovary for more than six days without a corpus luteum that is detectable through palpation or ultrasound (Silvia et al., 2002; Wiltbank et al., 2002; Peter, 2004). The follicle becomes cystic when it fails to ovulate and persists on the ovary (Vanholder et al., 2006). The exact pathogenesis remains unclear. A widely accepted hypothesis concerns imbalances in neuroendocrine functions directed by the hypothalamic-hypophyseal-gonadal axis (Peter, 2004). The reason for this hormonal disturbance maybe a negative energy balance due to high milk yield production (Hooijer et al., 2001; Nelson et al., 2010). Clinical signs of ovarian cysts are diverse and most frequently characterized by anestrus and irregular cycles (Hooijer et al., 2001; Vanholder et al., 2006). A diagnosis can be made from an ultrasound (Berry et al., 2014; Carthy et al., 2014). According to ICAR Central Health Key, corpus luteum persistens is described as the delayed regression of corpus luteum (ICAR, 2020). A corpus luteum is considered to be persistent if it remains in the ovary for at least 19 days (Garmo et al., 2009; Kafi et al., 2012). High yield production is associated with the occurrence of corpus luteum persistens (Taylor et al., 2003; Hommeida et al., 2005; Kafi et al., 2012).

In order to improve reproductive performance, breeding organizations in many countries have included fertility traits (e.g., calving interval, non-return rate or services per conception) rather than diagnoses of reproductive diseases into routine genetic evaluations (Interbull, 2020). However, EBV for direct reproductive diseases are also available for Scandinavian Red Dairy Cattle and Holstein (Østerås et al., 2007; Johansson et al., 2008), German Holstein (VIT, 2020), Austrian-German Fleckvieh (Fuerst et al., 2011) and US Holstein (Parker Gaddis et al., 2018) populations.

1.3.6 Disease heritabilities

The heritability of mastitis ranged from 0.01 to 0.11 in previous studies (Carlén et al., 2004; Hinrichs et al., 2011). Zwald et al. (2004a) and Heringstad et al. (2005) reported a small decrease in the heritability of mastitis with lactation number; however, an increase in heritability was found by Pritchard et al. (2013a). A negligible difference was found between heritabilities after calving (0–50 DIM) and over the entire lactation period (0–300 DIM)

(Hinrichs et al., 2005). However, Koeck et al. (2010b) stated that heritabilities after 50 DIM were much lower than those directly after calving.

The heritability of claw disorders was variable. For sole ulcers, heritability estimates from previous studies varied between 0.08 and 0.14 (König et al., 2008; Gernand et al., 2012; Häggman and Juga, 2013). However, lower heritabilities of approximately 0.01–0.02 (van der Waaij et al., 2005; Ødegård et al., 2013) and greater heritabilities of approximately 0.17–0.21 (Buch et al., 2011; Gernand and König, 2014) have also been reported. For digital dermatitis, heritabilities between 0.07 and 0.13 were found in some studies (König et al., 2008; Buch et al., 2011; Gernand et al., 2012). However, Onyiro et al. (2008) and Ødegård et al. (2013) reported a heritability of 0.03. Heritabilities for white line disease were between 0.09 and 0.14, as measured by König et al. (2008) and Gernand et al. (2012). The reported heritability values of interdigital hyperplasia were moderate, falling between 0.11 and 0.26 (König et al., 2008; Gernand et al., 2012; Gernand and König, 2014). These values indicated large additive genetic variances and rapid selection responses per generation.

Ederer et al. (2014) reported a heritability of 0.001 for acidosis. This low heritability could be due to low incidence of acidosis and large environmental influences. The heritability of ketosis decreased from 0.09–0.11 for first-parity cows to 0.04–0.06 for later-parity cows, as reported by Zwald et al. (2004a) and Parker Gaddis et al. (2014). By contrast, the heritabilities of milk fever increased from 0.09 to 0.13 with lactation number (Heringstad et al., 2005). Generally, for metabolic diseases, heritabilities estimated from linear models were lower than those estimated from threshold models (Koeck et al., 2013; Fuerst et al., 2011; Ederer et al., 2014).

Previous studies revealed that the heritability of endometritis ranged from 0.04 to 0.08 (Zwald et al., 2004a; Koeck et al., 2010a; Heringstad, 2010; Gernand et al., 2012). Heritabilities reported for ovarian cycle disorders and ovarian cysts were low, between 0.06 and 0.07 (Koeck et al., 2010a; Heringstad, 2010 and Gernand et al., 2012). The heritability of corpus luteum persistens was found to be 0.04 (Gernand et al., 2012), while heritabilities for a retained placenta were 0.06–0.07 (Koeck et al., 2010a; Heringstad, 2010; Neuenschwander et al., 2012).

1.3.7 Associations between longevity and health

Good health management can minimize losses due to health disorders and thus improve herd profitability and longevity. In several studies, the relationships between diseases and stayability or LPL was investigated. Heringstad et al. (2003a), Holtsmark et al. (2008) and

Pritchard et al. (2013a) found a negative correlation between mastitis and longevity, indicating that cows with a higher propensity to develop mastitis had a higher risk of being culled. In addition, Zwald et al. (2004b) and Parker Gaddis et al. (2014) reported negative correlations of LPL with ketosis, cystic ovaries, metritis and retained placenta, which indicated that increased genetic susceptibility to disease decreased longevity. For claw disorders, Charfeddine and Pérez-Cabal (2017) estimated decreased LPL in cases of digital dermatitis, sole ulcer or white line disease. On the other hand, Dhakal et al. (2015) reported a close-to-zero genetic correlation between claw lesions and LPL. Furthermore, Gonzalez-Peña et al. (2020) found negative correlations between mastitis, metritis, retained placenta, ketosis, milk fever and LPL using a pedigree relationship matrix augmented with genotypes (H matrix) among US Jersey cattle.

In several studies, hazard functions were employed to analyze associations between the occurrence of health disorders and culling risk. In a review, Beaudeau et al. (2000) reported that culling risk increased for cows with mastitis, ketosis, milk fever and locomotor disorders; however, reproductive diseases such as metritis, cystic ovaries or retained placenta had heterogeneous or nonsignificant effects. Cramer et al. (2009b) found a higher risk of culling when white line disease or sole ulcers occurred; however, no significant effect was found for digital dermatitis or interdigital hyperplasia. By contrast, using Cox's proportional hazards models, Booth et al. (2004) estimated higher hazard ratios for culling for cows with interdigital hyperplasia and lower hazard ratios for cows with digital dermatitis.

Most diseases demonstrated low to moderate heritabilities; however, they have a strong genetic correlation with LPL or stayability or a strong impact on culling risk. Therefore, health trait information can be useful for improving longevity.

1.3.8 Economic importance of production diseases

The published economic costs of mastitis are wide-ranging due to variations in calculation methods and input parameters. For example, Bar et al. (2008) reported an average cost of approximately $USD 179 per clinical mastitis case in US Holstein cattle. However, the cost increased to $USD 403 for cows with high expected future net returns. According to Fuerst-Waltl et al. (2016), the estimated costs of mastitis were around €341 per case for Fleckvieh and Brown Swiss cattle in Austria. In US dairy cattle, Rollin et al. (2015) reported costs of $USD 433 for primiparous cows and $USD 451 for multiparous cows per case of clinical mastitis that occurred in the first 30 DIM. Aghamohammadi et al. (2018) estimated annual costs of $CAD 662 per milking cow, including clinical and subclinical mastitis and preventive

measures. Cha et al. (2014) separately calculated costs for five mastitis pathogens; average costs per case ranged from $USD 477 for *Klebsiella* spp. to $USD 135 for *Staphylococcus* spp.

Several studies examined the average cost per case of specific claw disorders. For UK Holstein cattle, Willshire and Bell (2009) estimated overall costs of £76, £519 and £300 per case for digital dermatitis, sole ulcer and white line disease, respectively. Cha et al. (2010) reported that the average cost per case was $USD 133 for digital dermatitis and $USD 216 for sole ulcer. In Spanish Holstein cattle, Charfeddine and Pérez-Cabal (2017) reported costs for mild or severe lesions of dermatitis ($USD 53 or $USD 402), sole ulcer ($USD 232 or $USD 622) and white line disease ($USD 222 or $USD 590) per affected cow.

For subclinical ketosis, Raboisson et al. (2015) reported a cost of €257 per calving cow, and Gohary et al. (2016) estimated an economic loss of $USD 203 per case. Mostert et al. (2018) indicated that annual economic losses resulting from subclinical ketosis generally increased from €83 per case for first-parity cows to €175 per case for third-parity cows. Liang et al. (2017) estimated costs of $USD 77 per clinical ketosis case for primiparous cows and $USD 181 for multiparous cows. The total costs per case of milk fever have been reported to range from $USD 220 to $USD 246 (Kossaibati and Esslemont, 1997; Liang et al., 2017; Fuerst-Waltl et al., 2016).

The costs of a retained placenta were estimated to be $USD 386 (Gohary and LeBlanc, 2018) and $USD 150 or $USD 313 per case for primiparous cows or multiparous cows, respectively (Liang et al., 2017). For one case of metritis, farmers must spend an estimated $USD 146 to $USD 176 to cure inflected cows (Mahnani et al., 2015). Similarly, Liang et al. (2017) reported a cost of $USD 172 per metritis case for primiparous cows and $USD 263 for multiparous cows. Fuerst-Waltl et al. (2016) reported costs of €283 per case for early reproductive disorders. For ovarian cysts, estimated financial losses per case amounted to $USD 170 on Swedish dairy farms (Bartlett et al., 1986), €67 on Austrian dairy farms (Fuerst-Waltl et al., 2016) and approximately $USD 687 on Korean dairy farms (Kim et al., 2005). These differences in cost may be explained by the different models used to calculate economic losses.

1.4 Genome-wide association studies for longevity, health and milk production traits

Genome-wide association studies (**GWAS**) using single nucleotide polymorphism (**SNP**) markers provide a powerful approach to mapping quantitative trait loci (**QTL**) associated with important dairy traits in the genome.

Many GWAS have revealed genetic associations with milk production traits. A large number of significant SNP markers have been reported, and the strong functional candidate gene reported for milk yield and milk fat percentage in several dairy breeds is *DGAT1* (Grisart et al., 2004; Kühn et al., 2004; Raven et al., 2014). Another gene associated with an effect on milk yield and milk composition is *GHR* (Ashwell et al., 2004; Viitala et al., 2006). For fat percentage, the candidate genes *HEATR7A* (Jiang et al., 2014; Nayeri and Stothard, 2016), *VPS28* (Cole et al., 2011), *EPS8* (Jiang et al., 2019) and *CPSF1* (Weller et al., 2018) were identified. For protein percentage, the candidate gene *CAS1A* was reported (Nayeri and Stothard, 2016; Raven et al., 2014) and casein cluster on Bos taurus autosome (**BTA)** 6 with the genes *CSN1S1*, *CSN1S2*, *CSN2* and *CSN3* (Nayeri and Stothard, 2016; Raschia et al., 2018). However, some of these genes were found to be associated with milk in one study and with fat or protein yield in another. Using a GWAS of multiple dairy breeds, Raven et al. (2014) reported overlap between significant QTL and the same candidate genes for production traits in different cattle breeds. Thus, production traits are influenced by a few genes with a large effect that could be similar in different cattle breeds.

In dairy cattle, functional traits such health or longevity are complex and influenced by many genes with small effects rather than by a few genes with large effects. The identification of significant SNP markers for health and longevity is complicated by their low heritability and sensitivity to environmental variations. In previous studies, candidate genes for mastitis and its indicator trait SCS were proposed. The potential candidate genes (*LY6D, IFIH1, GC* and *NPFFR2*) are involved in regulating immune response (Tiezzi et al., 2015; Sahana et al., 2014; Cai et al., 2018). However, other researchers have reported associations with milk production traits (Jiang et al., 2014; Nayeri and Stothard, 2016). There are considerably fewer GWAS of reproductive diseases in dairy cattle than of fertility traits, such as number of services or calving interval. Naderi et al. (2018) identified the *FGF12* gene on BTA1 as having an effect on endometritis in German Holsteins, whereas Guarini et al. (2019) reported that the *CDKN3* gene on BTA10 and the *PFKFB2* gene on BTA16 were associated with the same disease in Canadian Holsteins. Additionally, previous studies have revealed diverse SNP associations and candidate genes for claw disorders. For example, Wu et al. (2016) identified QTL associated with feed and leg disorders in Danish Holsteins, Nordic Red Dairy Cattle and Danish Jerseys. However, they did not identify any QTL that were common to the three breeds. Additionally, van der Spek et al. (2015) and Kopke (2019) reported that there was no overlap between the SNP markers that were significantly associated with digital dermatitis in

Holstein cattle. Generally, previous studies have shown that candidate genes for disease resistance were inconsistent between different breeds and different populations of one breed.

A limited number of potential candidate genes significantly associated with longevity have been identified (Nayeri et al., 2017). Previous studies have also revealed SNP markers that have simultaneous effects on functional traits and longevity. For example, Cole et al. (2009) found marker associations on BTA18, with large effects on longevity, calving ease and conformation. Candidate genes for longevity identified by Steri et al. (2019) on BTA16 and 30 were related to fertility and reproductive disorders. For Australian Fleckvieh cattle, Mészáros et al. (2014) reported candidate genes for longevity on BTA5, 6, 8 and 14; these genes were also associated with fertility and nonspecific immunity in cattle (Dissen, 1995; Bashiardes et al., 2004 and Ndiaye et al., 2010). Cole et al. (2011) reported that many SNP associated with productive life were also associated with SCS or reproductive traits, indicating genetic relationships between longevity, health and fertility. The effect of the *DGAT1* gene on longevity is controversial. Tsuruta et al. (2017) reported an association between this gene and cow mortality, whereas Berry et al. (2010) identified no such association.

Using different methods to identify significant associations leads to greater agreement for milk production traits than for SCS and longevity (Daetwyler et al., 2008). Zhang et al. (2016) identified seven genomic regions in Holstein cattle and five regions in Red Dairy Cattle that were associated with longevity; however, subsequent meta-analyses revealed only two significant genomic regions on BTA6 and 18. Additionally, Raven et al. (2014) reported that significant associations for functional traits were inconsistent between breeds. Furthermore, a large variation in significant SNP for longevity was found between cows and bulls. In summary, detecting different associations within the same breed is expected to be more likely for functional traits than for production traits.

1.5 Genotype by environment interactions

1.5.1 The concept of genotype by environment interactions

The utilization of artificial insemination enables the convenient exchange of genetic materials worldwide. However, the performance of the cow's progeny can vary in different environments, implying the possible re-ranking of EBV or, in other words, the presence of genotype by environment interactions (**G×E**). Genotype by environment interactions can be divided into three categories: "no" interaction, noncrossover interaction and crossover interaction (Baye et al., 2011).

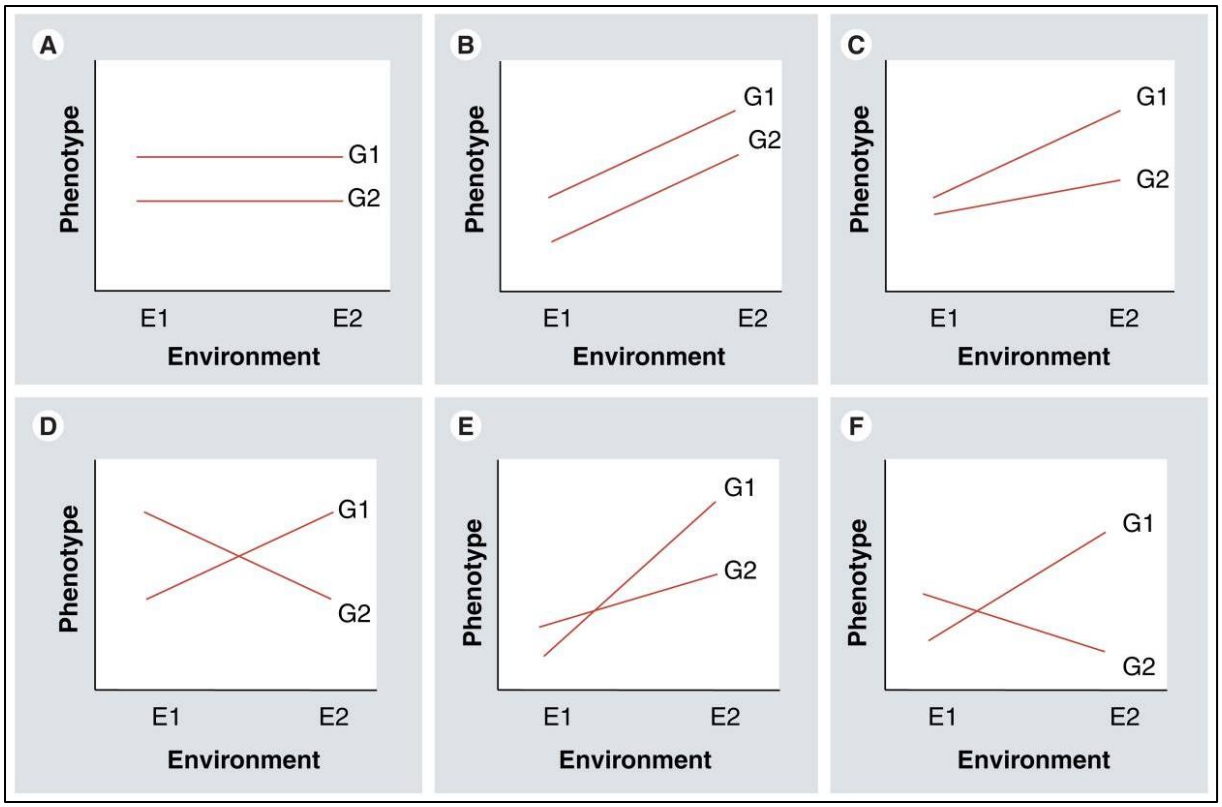

Figure 1.3: Graphic representations of "no" interaction (boxes A and B), noncrossover interaction (box C) and crossover interaction (boxes D to F) types of genotype by environment interactions (Baye et al., 2011)

G×E are not present when one genotype performs better than the other by the same amount, regardless of the environment. Hence, phenotypes of the two genotypes are parallel and stable (Figure 1.3, boxes A and B). A noncrossover G×E occurs when one genotype always performs better than the other in both environments. However, the differences between phenotypes of the two genotypes are not the same across environments (Figure 1.3, box C). The environment affects one genotype more than the other, but there is no re-ranking. A crossover G×E occurs when the ranks of the genotypes change from one environment to another and no genotype performs better in both environments (Figure 1.3, boxes D, E and F). Boxes D and F in Figure 1.3 demonstrate that the decrease in performance of one genotype and the increase in performance of the other genotype are of the same (box D) or different (box F) magnitude. In box E of Figure 1.3, the environment affects both genotypes in the same direction but by a different magnitude. For breeders, crossover interactions are more important, because the best genotype would be determined by the environment. Neglecting G×E in genetic evaluations based on data collected from multiple environments can lead to biased breeding values.

G×E can be estimated in two ways: (1) considering a trait expressed in different environments as different traits and estimating the genetic correlation between them or (2) applying reaction norm models by defining the phenotypic performance of an animal as a function of the environment. If the environment is divided into distinct classes, genetic correlations should be used to quantify G×E. Robertson (1959) determined that a genetic correlation lower than 0.8 indicated the presence of G×E. Discrete environmental classes can be, for example, countries (Weigel et al., 2001; Hammami et al., 2009; Montaldo et al., 2017) or within-country regions (Tsuruta et al., 2015; Ismael et al., 2016; Moreira et al., 2019). Moreover, herd characteristics such as low or high production (Castillo-Juarez et al., 2000), fertility level (Craig et al., 2018) and herd size (König et al., 2005) can be used as different classes. Other possible classes include management systems such as organic versus conventional (Nauta et al., 2006; Ahlman et al., 2014; Pfeiffer et al., 2017 and Liu et al., 2019) or feeding differences such as intensive grazing in organic systems versus concentrate feeding in conventional systems (Boettcher et al., 2003; Kearney et al., 2004b; Kearney et al., 2004a; van der Laak et al., 2016). In the presence of a continuous covariate that reflects changes in the environment, genetic parameters and EBV can be derived from reaction norm models through the environmental trajectory. Typical environmental covariates include the temperature-humidity index (Oseni et al., 2004; Fennewald et al., 2018), the production level in each herd-year cluster (Calus et al., 2004; Lillehammer et al., 2009; Streit et al., 2012), herd-level fertility such as age at first calving or number of inseminations (Fikse et al., 2003; Strandberg et al., 2009), herd-level somatic cell count (Streit et al., 2013) and feeding quality (Berry et al., 2003).

Several studies have reported high genetic correlations (>0.8) for production traits in different environments, which indicates the absence of G×E. However, for functional traits, genetic correlations vary according to traits and populations. For example, Boettcher et al. (2003), Sundberg et al. (2010) and Montaldo et al. (2017) reported G×E for different fertility traits but not for milk yield, fat or protein content. For longevity, Ahlman et al. (2011) and Pfeiffer et al. (2016) reported no or small G×E between animals from organic and conventional herds. Thus, the magnitude of G×E for longevity may be herd- or trait-specific.

1.5.2 Genotype by environment interactions between different production systems

Due to the globalization of artificial insemination, G×E have become an issue in dairy farming. Genetic material is distributed among multiple environments, and sire rank may change across environments. When re-ranking occurs, the genetic material tested in one environment may exhibit a different response in other environments. Thus, the presence of

G×E between selection and production environments reduces the efficiency of selection in breeding programs (Mulder and Bijma, 2005). G×E in organic and conventional production systems have been estimated in a few studies. Therefore, production systems must also be compared with other discrete environmental descriptors (e.g., small versus large herds, grazing versus confinement and low- versus high-production level farms).

Genotype by environment interactions for production traits

In general, researchers have previously reported the absence of G×E for production traits (Table 1.5) and shown that genetic correlations ranged from 0.78 to 1. One exception was a study conducted by Raffrenato et al. (2003), who reported a low correlation for production traits in Italian Holsteins between environments divided according to herd-year standard deviations for milk yield. The absence of G×E for grazing systems indicates similar diets on farms with and without grazing, because cows on the former graze for only part of the year and cows on the latter receive additional feeding. The definition of a production system according to mature-equivalent milk can be useful; however, values reported in previous studies indicated that no factors other than production level were responsible for G×E. A high genetic correlation between organic and conventional herds may suggest that production environments are similar due to strict animal welfare laws. König et al. (2005) showed that the choice of herd size was critical for G×E. Therefore, genetic correlations between the eastern and western states of Germany ranged from 0.90 to 0.95, but this value decreased to 0.79 when the eastern subset was narrowed only to large herds. By contrast, Calus (2006) noted that herd parameters such as nutrition and energy balance are the most important for G×E.

Table 1.5: Genetic correlations between different production systems for production traits

Reference	Environment difference[1]	Breed[2]	Milk yield (kg)	Fat		Protein	
				Yield (kg)	(%)	Yield (kg)	(%)
Sölkner et al., 2002	OC	SIM	0.97–1.00				
Raffrenato et al., 2003	HL-prod	HOL	0.63	0.66		0.48	
Boettcher et al., 2003	GRAZ		0.93	0.88	0.92	0.94	0.96
Kearney et al., 2004b	GRAZ	HOL	0.89	0.88		0.91	
König et al., 2005	HSIZE	HOL				0.79–0.99	
Nauta et al., 2006	OC	HOL	0.80	0.88	0.97	0.78	0.96
Fürst, 2006	OC	SIM	0.97		1.00		0.99
Gerber et al., 2006	OC	SIM	0.94	0.95		0.88	
Simianer, 2007	OC	BSW	0.86–0.92	0.81–0.91		0.89–0.90	
		SIM	0.96	0.98		0.97	
Sundberg et al., 2010	OC	HOL	0.96–0.97	0.97-1.00		0.98	
		RDC	0.96–0.98	0.95–0.96		0.95–0.97	
van der Laak et al., 2016	GRAZ	HOL	0.99	0.98		0.97	
Pfeiffer et al., 2016	HLCO	SIM	0.97–0.98				

[1]Environment difference: GRAZ = grazing vs. confinement farms, OC = organic vs. conventional farms, HL-prod = low- vs. high-production level farms, HSIZE = herd size, HLCO = high or low production conventional vs. organic farms;
[2]Breed ISO code: HOL = Holstein Friesian, SIM = Simmental, BSW = Brown Swiss, RDC = Red Dairy Cattle (Swedish Red).

Genotype by environment interactions for longevity and functional traits

Previously, researchers have reported genetic correlations for functional traits that ranged from 0.52 to 1 (Table 1.6) and for longevity, which ranged from 0.74 to 0.97 (Table 1.7).

For SCS, Kearney et al. (2004a) found that the genetic correlations of two random subsets differed from unity; however, the authors attributed this to a sampling error. Similarly, Simianer (2007) reported low correlations between different environments; however, as correlations between EBV for SCS. For reproduction-related traits, various correlations have been found between different production systems. Sundberg et al. (2010) reported a lower correlation for reproductive traits in Swedish Holsteins in the second lactation, whereas Liu et al. (2019) found the opposite G×E pattern for heifers but not for multiparous Danish Holstein cows.

As a result, no clear conclusion can be drawn regarding the presence or absence of G×E. The high correlations between different production systems indicate the similarity between

organic standards and conditions for conventional production. For example, in Sweden, there are relatively small differences between organic and conventional production environments (Ahlman et al., 2014).

Table 1.6: Genetic correlations (r_g) between different production systems for functional traits

Reference	Environment difference[1]	Breed[2]	r_g	Trait[3]	Explanation
Boettcher et al., 2003	GRAZ	HOL	0.64	REP	Calving interval
			1.00	UDD	Mammary system
			0.97	FL	Feet and legs
Kearney et al., 2004a	GRAZ	HOL	0.79–0.97	UDD	Lactation average SCS
			0.74-1.00	REP	Days open, days to first service, number of services per conception
Simianer, 2007	OC	SIM BWS	0.52–0.75	UDD	EBV-SCS
			0.69–0.87	REP	Interval from calving to first insemination
Sundberg et al., 2010	OC	HOL	0.94-1.00	UDD	SCC
			0.54-1.00	REP	Calving interval, intervals from calving to first insemination, from calving to last insemination, from first to last insemination, number of inseminations
Pfeiffer et al., 2016	HLCO	SIM	0.94–0.96	UDD	SCS
			0.89–0.99	REP	Non-return rate within 56d and interval from first to last insemination
			0.95–1.00	Diag_UDD	Clinical mastitis
			0.97–1.00	Diag_MET	Milk fever
			1.00	Diag_REP	Early fertility disorders and cystic ovaries
van der Laak et al., 2016	GRAZ	HOL	1.00	UDD	SCS
Liu et al., 2019	OC	HOL	0.61–1.00	REP	Number of inseminations, non-return rate within 56d, intervals from calving to first insemination and from first to last insemination

[1]Environment difference: GRAZ = grazing vs. confinement farms, OC = organic vs. conventional farms, HLCO = high- or low-production conventional vs. organic farms;
[2]Breed ISO code: HOL = Holstein Friesian, SIM = Simmental, BSW = Brown Swiss;
[3]Trait: UDD = udder-related traits, REP = reproductive traits, FL = exterior of feet and legs, Diag_UDD = udder diseases, Diag_REP = reproductive diseases, Diag_MET = metabolic diseases.

Table 1.7: Genetic correlations (r_g) between different production systems for longevity

Reference	Farm difference[1]	Breed[2]	r_g	Trait[3]
Simianer, 2007	OC	SIM, BWS	0.74	EBV-Long
Ahlman et al., 2011	OC	HOL	0.88–1.00	LPL, ST-L
		RDC	0.80–1.00	LPL, ST-L
Pfeiffer et al., 2016	HLCO	SIM	0.93–0.97	LPLf

[1]Farm difference: OC = organic vs. conventional farms, HLCO = high- or low-production conventional vs. organic farms;
[2]Breed ISO code: HOL = Holstein Friesian, SIM = Simmental, BSW = Brown Swiss, RDC = Red Dairy Cattle (Swedish Red);
[3]Trait: EBV-Long = estimated breeding value (EBV) for longevity, ST-L = stayability to certain lactation, LPLf = functional length of productive life.

Both the presence and absence of G×E could be found for some functional traits due to different environmental conditions among studies. Large standard errors for estimates due to low heritabilities and the small sample size for organic production systems complicated the estimation of G×E.

1.6 Organic farming

1.6.1 Production diseases in organic farming

The major principle of organic agriculture is to enhance and sustain animal health (IFOAM, 2020). Consequently, consumers associate organic production systems with improved animal welfare compared to conventional cattle production systems (McEachern and Willock, 2004). However, Sutherland et al. (2013) identified animal health as the primary welfare risk in organic livestock systems. Strong limitations in the application of preventive antibiotics, a poor nutrient supply based on homegrown feed and severe restrictions on feeding concentrates are well-known problems in organic farming, resulting in increased incidences of disease compared to conventional farming. Nevertheless, no significant differences have been identified in terms of the incidence of mastitis (and its indicator, SCC) or several fertility traits between conventional and organic herds in Germany (Müller and Sauerwein, 2010; Hansmann et al., 2019), Switzerland (Roesch et al., 2006), Norway (Garmo et al., 2010) and Sweden (Sundberg et al., 2009). Furthermore, Blanco-Penedo et al. (2012) estimated a similar incidence of clinical ketosis in organic and conventional cows. Ahlman et al. (2011) reported udder health and low fertility as the main culling reasons in both conventional and organic production systems, and no differences were found between both systems. Furthermore, a similar incidence of disease in organic and conventional herds may result from a higher percentage of lower-yielding dairy cows in organic farms. Several studies have reported that

lower-yielding dairy cows have greater disease resistance than high-yielding cows (Gandini et al., 2007; Curone et al., 2018). With regard to organic breeding goals, health (fertility and udder) and longevity-related traits are more important to organic farms, since organic farmers tend to strongly focus on robust and healthy cows (Bapst et al., 2005; Simianer, 2007; Ahlman et al., 2014 and Just et al., 2018).

1.6.2 Organic breeding strategies

Despite the possible presence of G×E between conventional and organic production systems, organic farmers often use semen from the same breeding bulls that conventional farmers do for artificial insemination (Nauta, 2009). However, the reliability of the bulls in organic environments is still in question. Functional traits are more important in organic production than in conventional production for both economic and ethical reasons (Pryce et al., 2004). In Switzerland, Austria, Germany and Canada, some attempts have been made to develop total merit indices for organic dairy production (Haas and Bapst, 2004; Rozzi et al., 2007; Krogmeier, 2009a). These indices could enable farmers to identify the conventional sires best suited to organic production systems.

1.6.3 Organic cow training sets

At the beginning of dairy cattle genomic selection, only bulls with highly reliable EBV were genotyped. It was difficult to avoid biased breeding value estimates caused by intensive pre-selection. Plieschke et al. (2016) suggested that the genotyping of cows can improve genomic breeding values (**GBV**). In order to adequately represent the entire production population, genotyped cows have been included in training sets in several countries. For example, the German project Kuh-L focuses on the creation of a database with phenotypes and genotypes from 20,000 cows (Naderi et al., 2018).

Generally, the success of genomic selection relies on factors such as the density of the marker panel, the heritability of the trait and the number of genotyped animals in the reference population (Hayes et al., 2009). VanRaden et al. (2009) reported that increasing the number of genotyped animals is more important for improving predictive ability than using high-density marker panels. In organic populations, small population sizes and the great importance of novel functional traits with low heritabilities decrease the reliability of EBV. However, adding genotyped cows to a population with a small population size (e.g., organic populations) improves the accuracy of genomic predictions and genetic gains (Thomasen et al., 2020). Moreover, in a stochastic simulation study, GBV reliabilities for novel functional

traits with low heritabilities increased with the inclusion of cows in the reference population (Plieschke et al., 2018). Therefore, the implementation of cow training sets is more important in organic farming than in conventional farming.

Against this background, approximately 1,000 cows from organic farms were genotyped as part of the "LongLife Project", which aims to perform association analyses of genotypes with functional traits and longevity for cows from organic farming systems compared to those from conventional farming systems. To the best of our knowledge, no other database of genotyped cows from organic farms currently exists.

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CHAPTER 2

Influence of common health disorders on the length of productive life and stayability in German Holstein cows

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ABSTRACT

The aim of this study was to infer phenotypic and genetic effects of health disorders on longevity traits, considering Holstein dairy cow records from large-scale co-operator herds. In this regard, we focused on 13 different disease traits and on 2 longevity definitions: length of productive life (LPL) and stayability (STAY). The LPL was defined as the interval in days from first calving to culling. For LPL, we considered 90,215 cows with known culling dates. For binary STAY, we defined 3 survival stages in the first 3 lactations: from calving to DIM 59, from DIM 60 to DIM 299, and from DIM 300 to the next calving date. Due to the earlier trait recording possibilities, 129,386 cows were considered for the STAY analysis. Accordingly, the presence or absence of diseases in lactation stages were defined as binary traits. A further data set for the 90,215 cows with a culling date included the subjective culling reasons defined by farmers. Comparison of culling reasons, as defined by farmers, with diagnoses from the disease data set indicated some disagreements. For example, only 18.71% of the cows with the farmer culling reason "metabolic diseases" were diagnosed with a metabolic disorder. Better agreements were identified for mastitis (84.09%). Phenotypically, in most cases, occurrence of diseases at different lactation stages had negative influence on LPL and STAY. In this regard, we identified strong detrimental effects of clinical mastitis and of metabolic disorders from early lactation stages on longevity traits. For example, the presence of clinical mastitis in the first stage of first lactation was associated with LPL decrease of 95.35 d. Using generalized linear mixed models for binary health disorders, heritabilities ranged from <0.01 (±0.079 standard error) for ruminal acidosis early in first, second, and third lactation to 0.24 (±0.039) for interdigital hyperplasia from the last stage in third lactation. Heritabilities from single-trait and bivariate animal models ranged from 0.03 (±0.003) to 0.10 (±0.007) for LPL, and from 0.01 (±0.002) to 0.06 (±0.007) for STAY. Genetic correlations between longevity traits and health disorders were mostly negative (i.e., favorable in a breeding sense). For improvements to longevity genetic evaluations for young bulls with a limited number of daughter culling dates, we suggest consideration of health traits from a well-organized co-operator herd monitoring system as early longevity predictors, especially for censored data. Genetic correlations between mastitis from different lactation stages with LPL and STAY ranged from −0.28 (±0.07) to −0.69 (±0.05), and from −0.26 (±0.08) to −0.77 (±0.08), respectively. Interestingly, only diagnoses for digital dermatitis showed opposite results phenotypically and genetically. Strong genetic associations between ruminal acidosis and STAY were observed (genetic correlations: −0.48 ± 0.18 to −0.98 ± 0.31), supporting the inferred phenotypic associations. Genetic correlations between longevity

traits LPL and STAY were quite large, between 0.77 (±0.11) and 0.94 (±0.02) for the different lactation stages, suggesting utility of early STAY information when attempting genetic improvements for longevity.

Key words: longevity, subjective culling reason, health disorder, genetic parameter

INTRODUCTION

Longevity, as an economically important trait, is included in overall dairy cattle breeding goals in many countries (Interbull, 2016). In most genetic evaluations, longevity is defined as the length of productive life (**LPL**), reflecting the period from first calving to date of culling. However, in genetic evaluations for LPL, data sets with culling dates for a large number of daughters are only available for old bulls. Hence, most LPL daughter records reflect a censored data structure. In consequence, it is imperative to identify proper early indicator traits, to improve the accuracy of genetic longevity evaluations. Several studies have identified strong influences of linear type traits (Buenger et al., 2001) or of SCS (Pritchard et al., 2013b) on LPL. However, type traits and SCS are only indicators for cow health. In this regard, Egger-Danner et al. (2015) highlighted the possible improvements in genetic evaluations when directly considering diagnoses for cow health. In further consequence, we suggest consideration of direct health traits as indicators in genetic evaluations for longevity. Such an attempt requires health disorder data sets from routinely recording systems, at best on a population-wide level. Population-wide recording of health traits was initiated in Scandinavia in 1978 (Philipsson and Lindhé, 2003) and recently has been established in other countries (Stock et al., 2013). As an alternative, instead of implementing population-wide recording, some German breeding organizations focus on health trait recording in a smaller sample of so-called co-operator herds. In such large-scale herds, cows are genotyped and phenotyped for a broad pattern of novel functional traits, which is a unique data pool when setting up cow training sets for genomic selection (Klein et al., 2019).

A further trait definition reflecting longevity considers the probability of survival at specific lactation stages. This binary trait definition is known as stayability (**STAY**). In Germany, since April 2018, STAY has officially been introduced in national genetic evaluations, considering different periods from first to fourth calving (VIT, 2018). Compared with LPL, STAY provides longevity information at earlier age stages, such as, first, for cows surviving the early lactation period. Furthermore, the STAY definition allows consideration of cows without culling dates—that is, cows surviving the last defined lactation stage. However, genetic correlations lower than 0.8 between STAY from different lactation stages (Wiebelitz

et al., 2014; Heise et al., 2016) indicate alterations of the genetic background with aging. Accordingly, correlations between EBV for different STAY periods, or between EBV of SCS from the respective periods, were only in a moderate range (Heise et al., 2016). Hence, the changing genetic background for STAY as well as for a STAY indicator trait (e.g., SCS, mastitis) indicate variations of genetic covariances between the trait categories longevity and health.

Further information related to cow health and cow longevity are cow culling reasons. Culling reasons are entries in a population-wide database system (ADR, 2017), but they reflect subjective appraisals by the herd owner. A disadvantage of this recording scheme is that some cows might have several culling reasons, but only 1 specific reason is considered in the database. Nevertheless, Heise et al. (2018) genetically analyzed cow culling reason and indicated the potential to improve genetic evaluations, as for cow health. As an alternative, we suggest strong consideration of veterinarian disease diagnoses from German co-operator herds. A co-operator herd system implies close collaborations between breeding organizations and veterinarian institutions, as with regard to implementation of systematic health monitoring. König et al. (2008a) emphasized the high data quality from German co-operator herds, due to estimates for intraherd genetic parameters.

The aim of the present study was to use comprehensive health and longevity data sets from co-operator herd cows for (1) the evaluation of culling reason data quality, (2) association analyses between health disorders with longevity traits LPL and STAY phenotypically and genetically, and (3) genetic correlation estimations between STAY and LPL.

MATERIALS AND METHODS

Data

Trait recording was accomplished in 57 large-scale co-operator herds located in the German federal states of Mecklenburg-Vorpommern and Berlin-Brandenburg. In total, data sets for longevity, test-day production, and health traits were available from 129,386 Holstein cows. Previous to our analyses, we excluded 15,326 cows that were sold for export. First calving years of the cows spanned the period from 2004 to 2017. Ages at first calving ranged between 18 and 42 mo. All cows had at least one official test-day observation within the first 100 DIM of the first, second, or third lactation (**L1**, **L2**, and **L3**, respectively). The pedigree file considered 277,341 animals. Cows with records could be traced back at least 3 generations. The oldest founder animals were born in 1940.

Longevity. For longevity evaluations, we focused on the 2 trait definitions LPL and STAY. The LPL was defined as the productive period from the first calving date until the culling date. The average LPL for the 90,215 cows with a culling date was 977.10 (±626.77 SE) days. Following the method of Heise et al. (2016), we created 3 different stages within lactations: early lactation, from calving to DIM 59; middle lactation, DIM 60 to 299; and late lactation, including the dry period, from DIM 300 to the next calving date. Thus, the third stage had variable lengths. For all 3 lactations, the considered 3 lactation stages were named as **L1.1**, **L1.2**, and **L1.3** in the first lactation, **L2.1**, **L2.2**, and **L2.3** in the second, and **L3.1**, **L3.2**, and **L3.3** in the third. Regarding STAY, a cow was coded as 1 when she was alive at the end of a stage; otherwise, for a culling date within the stage, a code 0 was assigned. For example, if a cow was culled at DIM 61 in L1, the STAY code for the stage L1.1 was 1, but the cow would be coded 0 for the following lactation stages. Consequently, our STAY definition implied 9 binary traits for all cows. For STAY, the analyses additionally considered cows without a culling date after the last stage (129,386 cows for the STAY analyses).

Health Disorders. For the recording of health disorders, veterinarians and herd managers used the hierarchical diagnosis key developed by Feucker and Staufenbiel (2003). The same diagnosis key is also used in the official guidelines of the International Committee for Animal Recording (ICAR; Stock et al., 2013). Official health trait recording was initiated in January 2008. In the present study, the cows from the longevity data set had health records for the period from January 2008 until January 2017. We considered 13 specific diseases from the overall disease categories of udder, claw, metabolism, and female fertility. These diseases are veterinarian diagnoses from the selected co-operator herds, with continuous entries over the whole recording period. The 13 diseases were clinical mastitis (**MAST**) from the udder health category; sole ulceration (**SU**), digital dermatitis (**DD**), white line disease (**WLD**), and interdigital hyperplasia (**HYP**) from the claw disorder category; acidosis (**ACID**), ketosis (**KET**), and milk fever (**MFEV**) for metabolism; and ovarian cycle disorders (**OCD**), endometritis (**ENDO**), ovarian cysts (**CYST**), corpus luteum persistens (**CLP**), and retained placenta (**RP**) for female fertility disorders. For at least one entry in the lactation stage, the respective disease was scored 1 (diseased); otherwise a score of 0 (healthy) was assigned. Consideration of the same lactation stages as used for the STAY definition implied 9 binary traits for each disease. In addition to lactation stage disease incidences, we calculated lactation disease incidences. At least one disease entry during lactation implied a score of 1 for the

respective disease; otherwise, a score of 0 was assigned. Incidences for the 13 diseases for the different lactation stages and lactations are given in Table 2.1.

Culling Reasons. The official scheme for cow culling reasons considers disposals due to udder diseases, infertility, claw disorders, metabolic diseases, other diseases, low milk yield, poor milkability, age, selling for breeding, and other problems. The cow culling reason database reflecting the answers of farmers only considers 1 culling reason per cow. The culling reason frequencies considering all cows (apart from the cows sold for breeding in other regions) were 24.21% due to udder diseases, 21.72% due to infertility, 16.97% due to claw disorders, 12.84% due to metabolic diseases, 7.57% due to low milk yield, 4.82% due to poor milkability, 0.16% due to age, and 5.81% due to other problems. We compared the health-related culling reasons with the disease entries from the health database.

Statistical Models

Phenotypic Effects of Diseases on Longevity. Linear models were applied to test the effects of each disease from the different lactation stages on Gaussian-distributed LPL in consecutive runs. We used the *lm* function in R (R Development Core Team, 2017). Model [1] was as follows:

$$y_{ijklmnop} = \mu + \Delta M_i + DIM_j + H_k + J_l + S_m + FCA_n + HS_o + e_{ijklmnop}, \quad [1]$$

where $y_{ijklmnop}$ = LPL (in days); μ = overall mean; ΔM_i = linear regression for the difference between the first test-day milk yield and the herd average; DIM_j = linear regression for days in milk; H_k = fixed herd effect; J_l = fixed effect of calving year; S_m = fixed effect of calving season (Jan. through Apr., May through Sep., or Oct. through Dec.); FCA_n = fixed effect for age at first calving (classes 20 to 23, 24 to 26, 27 to 29, or >29 mo); HS_o = fixed effect for the health status of the respective health disorder (0 = healthy, 1 = diseased); and $e_{ijklmnop}$ = random residual error.

Binary STAY was analyzed via generalized linear models applying the *glm* function in R (R Development Core Team, 2017). For this, we used a logit link function. Statistical Model [2] was as follows:

$$logit(\pi_{ijklmno}) = \log\left(\frac{\pi_{ijklmno}}{1-\pi_{ijklmno}}\right) = \mu + \Delta M_i + DIM_j + H_k + J_l + S_m + FCA_n + HS_o, \quad [2]$$

where $\pi_{ijklmno}$ = probability of cows being alive at a certain lactation stage (1 = alive, 0 = culled). Other effects were the same as defined in Model [1].

Genetic Parameter Estimations. For LPL, a linear animal model was applied. In scalar notation, statistical Model [3] was as follows:

$$y_{ijklmnop} = \mu + \Delta M_i + DIM_j + H_k + J_l + S_m + FCA_n + AG_o + e_{ijklmnop}, \quad [3]$$

where AG_o = random additive genetic effect. Other effects were the same as specified for Model [1].

For binary health traits and binary STAY, the following logistic animal model (Model [4]) was applied:

$$logit(\pi_{ijklmno}) = \log\left(\frac{\pi_{ijklmno}}{1-\pi_{ijklmno}}\right) = \mu + \Delta M_i + DIM_j + H_k + J_l + S_m + FCA_n + AG_o, [4]$$

with π_{ijklmn} = probability for the occurrence of the health disorder (0 = healthy, 1 = diseased) or for being alive in the respective lactation stage (1 = alive, 0 = culled). Other effects were the same as defined in Model [1].

Genetic variance or covariance components were estimated via single-trait or bivariate animal models for all trait combinations. Heritabilities for binary traits were calculated using the variance of the logit link function, which implies a correction of the residual variance by factor $\pi^2/3$ (Southey et al., 2003). Genetic correlations between binary STAY and binary health disorders were estimated via bivariate threshold-threshold models. For the runs including 1 Gaussian trait (LPL) and 1 binary trait (STAY or health disorders), bivariate threshold-linear models were applied. For estimation of genetic correlations between health disorders and LPL, we considered the disease (1 or 0) from the respective lactation stage. For the estimation of genetic correlations between STAY and diseases, we focused on STAY and diseases from the same lactation stage. To estimate genetic correlations between STAY and LPL, we considered the 0 or 1 trait coding for STAY from the 9 lactation stages in different runs.

The genetic (co)variance structure for bivariate linear models was:

$$\text{var}\begin{bmatrix} a \\ e \end{bmatrix} = \begin{bmatrix} G \otimes A & 0 \\ 0 & R \otimes I_n \end{bmatrix}$$

where **G** was a 2 × 2 (co)variance matrix for the additive genetic effects of the 2 traits; **A** was the additive genetic relationship matrix based on pedigree; **R** was a 2 × 2 (co)variance matrix for residual effects; $\mathbf{I_n}$ was an identity matrix for n observations, and was the direct matrix product. For estimation of genetic parameters, we used the AI-REML algorithm as implemented in the DMU software package (Madsen and Jensen, 2013).

RESULTS AND DISCUSSION

Disease Incidences

For biological reasons and associated very low disease incidences, some diseases were excluded from some stage-specific analyses. For instance, metabolic disorders typically occur shortly before or directly after calving (Probo et al., 2018). Consequently, we did not study the influence of metabolic disorders on longevity traits in second and third stages. Due to the relevance of MFEV only in later lactations (Erb et al., 1985), we considered MFEV only from stages L2.1 and L3.1. Full recovery of the uterus after calving requires 3 to 4 weeks (Sheldon and Owens, 2017), implying an ENDO diagnosis within the first 46 DIM (Gernand et al., 2012). In our study, a large percentage of cows diagnosed for ENDO in second stages was recorded for the same disease during first stages. Accordingly, we considered ENDO from second stages as the same disease. We excluded OCD, CYST, and CLP from first and third stages because they are generally diagnosed in the middle of lactation (Fleischer et al., 2001; Gernand et al., 2012). Retained placenta is relevant only for the first stages, directly after calving (Gernand et al., 2012; Koeck et al., 2012).

Lactation disease incidences (Table 2.1) from the German Holstein co-operator herd cows reflect results from other German federal states (Gernand et al., 2012). Generally, and in agreement with Heringstad et al. (2005), incidences of MAST, KET, MFEV, and RP increased with increasing lactation number. Hinrichs et al. (2011) reported highest mastitis rates during the early lactation period and a substantial decline afterward. In our study, MAST incidences in L1.1 and L1.2 were very similar. For later lactations, MAST incidences from the second stages were even larger than for the first stages. However, for the definition of the second stage, we considered a longer period than did most of the previous studies. The incidences for SU and DD in the early-lactation stage and on a lactation level were very similar to disease incidences from the same region 15 years ago (König et al., 2005). However, in the meantime, the health status for WLD and HYP appeared improved, possibly due to breeding and selection efforts. We found that DD incidences decreased with increasing lactation number from 15.03% in first to 12.82% in third lactation. Similarly, König et al. (2005) and Gernand et al. (2012) reported a decrease of infectious lesions with parity, explaining the decrease as being due to acquired resistance against specific bacteria. In agreement with Fleischer et al. (2001), the highest incidences for all claw diseases were identified in our study in the second stages. Collard et al. (2000) argued that periods of negative energy balance in the early lactation stage contribute to locomotive problems in the ongoing lactation. We observed quite high disease incidences for female fertility disorders.

Lactation disease incidences for ENDO and OCD were higher than 20%, indicating the health status decline for ovarian disorders in the past 25 years (Beaudeau et al., 1995; Gernand et al., 2012; Koeck et al., 2012). As expected, RP had relevance only in the early lactation stages, but CYST occurred in the middle of lactation. Lactation incidences for CYST in the range of 8 to 9.6% (Zwald et al., 2004a; Koeck et al., 2010) reflect the disease incidences from our study.

Table 2.1: Disease incidences (%) in different lactation stages within lactations 1, 2 and 3 for cows from co-operator herds[1]

Disease[2]	Lactation 1				Lactation 2				Lactation 3			
	Stage 1	Stage 2	Stage 3	Lact.[3]	Stage 1	Stage 2	Stage 3	Lact.[3]	Stage 1	Stage 2	Stage 3	Lact.[3]
MAST	14.90	14.04	5.69	28.0	14.70	25.03	7.75	35.6	18.44	29.00	8.97	40.3
SU	1.64	7.19	2.39	9.13	1.94	7.91	3.72	10.4	3.15	11.71	5.55	14.8
DD	3.45	10.71	5.29	15.0	4.13	10.23	4.91	14.4	4.04	9.19	3.97	12.8
WLD	0.33	1.25	0.67	1.90	0.51	2.02	1.21	2.95	0.95	3.31	1.94	4.71
HYP	0.51	1.41	0.88	2.27	1.11	2.33	1.22	3.59	1.53	2.89	1.35	4.32
ACID	0.22				0.31				0.55			
KET	0.77				1.80				3.31			
MFEV					1.17				4.46			
ENDO	19.59	5.38		22.9	17.92	6.31		21.7	20.76	6.94		24.6
OCD		20.71				21.66				22.59		
CYST		6.24				8.20				8.79		
CLP		2.65				3.19				3.35		
RP	6.52				8.38				10.60			

[1]Empty cells = no relevance of the disease in the respective lactation stage as explained in the manuscript text.
[2]MAST = clinical mastitis; SU = sole ulcer; DD = digital dermatitis; WL = white line disease; HYP = interdigital hyperplasia; ACID = ruminal acidosis; KET = ketosis; MFEV = milk fever; ENDO = endometritis; OCD = ovarial cycle disorder; CYST = ovarial cysts; CLP = corpus luteum persistens; RP = retained placenta.
[3]Lact. = lactation disease incidence.

Health-Related Culling Reasons

Farmers' most frequent answers for cow culling reasons were udder diseases (24.21%) and infertility (21.72%), followed by claw disorders (16.97%) and metabolic diseases (12.84%). Thus, culling reasons for co-operator herd cows correspond with reports from the broader German Holstein population (Wangler et al., 2009) and with results from international studies (Egger-Danner et al., 2015). Figure 2.1illustrates the frequencies of culling reasons for the different lactation stages. Culling frequencies due to udder diseases and claw disorders showed obvious peaks in the second stages for all lactations. The percentage of cows culled due to infertility increased from 0.31% in L1.1 to 21.52% in L1.3. The same pattern of culling

reasons due to infertility was identified in later lactations. A small percentage of culled cows had the culling reason "metabolic disorders" in L1, but the frequency increased over ongoing lactations. Interestingly, the highest culling frequencies due to metabolic disorders were identified in the second stages of all 3 lactations, although the disease mostly occurred in the early lactation period (Table 2.1). Nevertheless, the distributions for culling reasons across stages and lactations are in agreement with reports by Pinedo et al. (2010) and Heise et al. (2016).

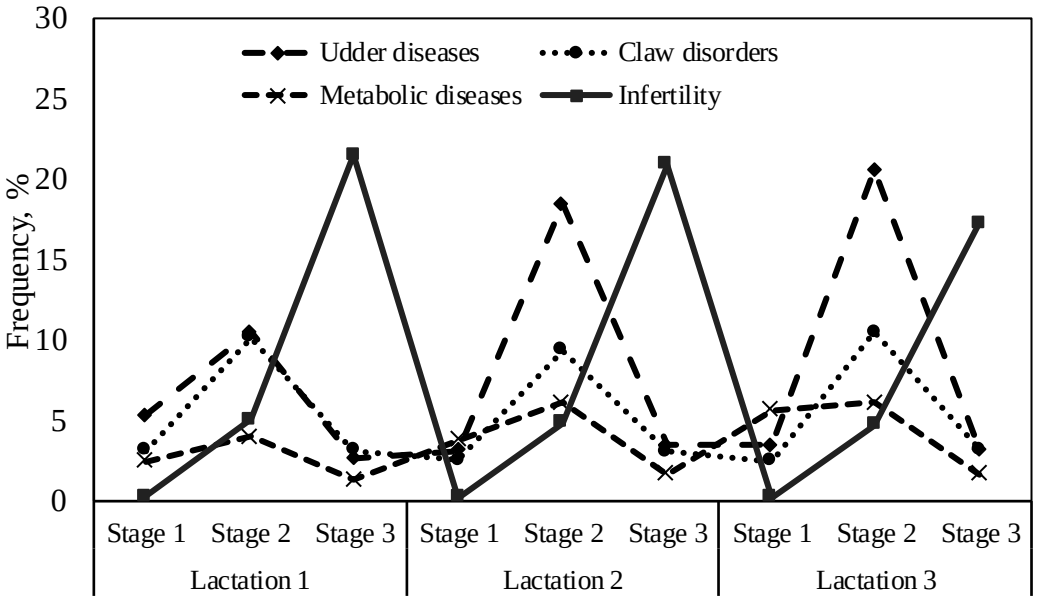

Figure 2.1: Distributions of culled cows (%) for the culling reasons udder diseases, claw disorders, metabolic diseases and infertility, as defined by farmers at different stages of the first 3 lactations.

Table 2.2 depicts the associations between culling reasons as defined by farmers and diagnoses from the health trait data set. The culling reason database includes entries for all culled cows, in most cases disease specifications, but also culling due to low milk yield or "other problems." The health trait data set considers the diagnoses for specific diseases as defined by veterinarians. In the co-operator herd systems, veterinarians collaborate closely with breeding organizations, implying high health trait data quality. Cows with no disease entry in the health trait database are considered to be healthy for the respective lactation stage. We identified high agreements between the culling reasons "udder" (84.09%) and "infertility" (76.03%) with the corresponding recorded diseases. Nelson et al. (2010) reported that 13.8% of Norwegian Red cattle slaughtered due to reproductive problems (farmer information) were never diagnosed for any ovarian disorder. Nevertheless, apart from ovarian disorders, some

other factors might cause infertility, such as poor cow nutrition or even the paternal components (semen quality of bulls). Our study detected some disagreements between culling reasons and diagnosed cow diseases for claw and metabolic disorders. For instance, only 45% of cows with the culling reason "claw disorders" had a corresponding claw disease diagnosis. Regarding the cows with metabolic diseases, the agreement with the culling reason "metabolism" was only 18.71%. Heise et al. (2018) discussed the opportunities when including farmer information for cow culling reasons in official genetic evaluations. Due to the partly poor agreements with the health diagnoses, we assume biased EBV for health traits when additionally considering cow disposal information. Nevertheless, we assume additional value when considering farmers' culling reasons in genetic evaluations, because some cullings might be due to subclinical diseases, which are not fully reflected in the official diagnosis key. Alternatively, a disorder might already be so severe that there is no diagnosis, implying that the cow may be culled without consulting a veterinarian. With regard to the cow culling reason database, farmers are able to enter only one answer. However, in most cases, diseases appear to occur in clusters (König et al., 2005). Thus, we assume better agreements between culling reasons and real diseases when considering several culling reasons per cow.

Table 2.2: Agreement between culling reasons as defined by farmers and veterinary disease diagnoses from the first 3 lactations[1]

Culling reason	No. of culled cows	No. of cows with respective diagnoses	Percentage of cows with respective diagnoses
Udder diseases	14,213	11,952	84.09
Infertility	15,218	11,570	76.03
Claw disorders	9,602	4,321	45.00
Metabolic diseases	6,573	1,230	18.71

[1]All culled cows have an entry for the culling reason in the database. Cows without diagnoses are considered to be healthy.

Phenotypic Influence of Diseases on Longevity

Differences in least squares means for LPL (results from Model [1]) and for STAY probabilities (results from Model [2]) addressing the comparison of diseased versus healthy cows are given in Table 2.3 and Table 2.4, respectively. For all lactation stages, cows with a MAST diagnosis had a significantly shorter LPL than did healthy animals. The increased culling risk for cows with MAST diagnoses is in agreement with several previous studies (Schneider et al., 2007; Hultgren and Svensson, 2009). A MAST diagnosis from the early or middle lactation stages contributed to shorter LPL, as described by Neerhof et al. (2000) and Pinedo et al. (2010). In agreement with Roxström and Strandberg (2002), the effect of MAST

from the late lactation stage on LPL was of minor importance. A MAST diagnosis strongly influenced STAY in the respective lactation stage but also contributed to time-lagged cow disposals in later lactation stages.

Table 2.3: Differences of LSM for the length of productive life (in days) for the comparison diseased minus healthy cows by lactations stages[1]

Disease[2]	Lactation 1			Lactation 2			Lactation 3		
	Stage 1	Stage 2	Stage 3	Stage 1	Stage 2	Stage 3	Stage 1	Stage 2	Stage 3
MAST	-91.35	-111.57	-97.13	-112.66	-105.73	-50.24	-88.88	-95.47	-37.78
SU	-63.12	-29.40	-60.98	-50.59	NS	-34.72	NS	26.85	NS
DD	NS	60.19	NS	NS	60.20	NS	NS	61.54	47.11
WLD	NS	NS	-58.09	-64.23	NS	NS	NS	32.51	NS
HYP	-79.17	NS	-53.15	NS	NS	-42.10	NS	NS	NS
ACID	-114.23			-94.24			-111.90		
KET	-49.77			-44.15			-39.04		
MFEV				-38.39			NS		
ENDO	NS	-69.00		NS	-48.78		12.81	NS	
OCD		NS			NS			35.03	
CYST		-34.63			-18.29			13.78	
CLP		NS			NS			32.84	
RP	-27.60			-13.61			NS		

[1]Empty cells = no relevance of the disease in the respective lactation stage as explained in the manuscript text. NS = difference not significant, $P > 0.05$.
[2]MAST = clinical mastitis; SU = sole ulcer; DD = digital dermatitis; WL = white line disease; HYP = interdigital hyperplasia; ACID = ruminal acidosis; KET = ketosis; MFEV = milk fever; ENDO = endometritis; OCD = ovarial cycle disorder; CYST = ovarial cysts; CLP = corpus luteum persistens; RP = retained placenta;

Effects of claw disorders on LPL differed among diseases and lactation stages. Diagnoses for SU, WLD, and HYP in all stages of L1 and L2 were associated with decrease in LPL. Charfeddine and Pérez-Cabal (2017) reported that occurrence of severe SU or WLD lesions contributed to LPL decline of 59 and 71 d, respectively. Heringstad et al. (2018) identified negative energy balances for cows with noninfectious hoof lesions, and negative energy balance also influenced LPL. However, for the claw disorder DD, we identified an opposite effect on LPL. The surprising positive effect of DD infection on longevity was also pointed out by Booth et al. (2004) for diagnoses from calving up to 240 DIM. One explanation might be the strong unfavourable correlation between DD and protein yield (Gernand and König, 2014) and the strong selection intensity for production traits (König et al., 2007). Generally, DD seems to be a specific trait, differing in response from other claw disorders. In heat stress studies, Gernand et al. (2019) found a DD reduction with increasing temperature–humidity

indices, the opposite of the remaining claw disorders. Among all claw disorders diagnosed early in lactation, only SU in L1.1 and L2.1was significantly associated with STAY. All claw disorders negatively influenced STAY in the late lactation stages. Hence, farmers treat and keep cows with claw problems throughout lactation, but these cows are not considered for later lactations (Booth et al., 2004).

Table 2.4: Differences of LSM for stayabilities (in %) for the comparison diseased minus healthy cows by lactations stages[1]

	Lactation 1			Lactation 2			Lactation 3		
Disease[2]	Stage 1	Stage 2	Stage 3	Stage 1	Stage 2	Stage 3	Stage 1	Stage 2	Stage 3
MAST	-1.66	-5.44	-6.88	-1.01	-7.59	-5.88	-0.88	-8.33	-6.16
SU	0.67	NS	-6.44	-1.09	1.97	-5.34	NS	3.51	-5.48
DD	NS	4.78	-3.94	NS	5.72	NS	NS	7.34	NS
WLD	NS	NS	-8.56	NS	4.14	-6.29	NS	4.04	NS
HYP	NS	2.30	-6.24	NS	3.33	-4.57	NS	2.96	NS
ACID	-2.50			-1.70			-2.88		
KET	-1.93			-2.14			-2.91		
MFEV				-1.27			NS		
ENDO	0.88	NS		0.75	NS		1.35	NS	
OCD		1.42			1.31			3.43	
CYST		1.57			1.63			2.58	
CLP		1.65			1.97			3.65	
RP	NS			0.27			0.55		

[1]Empty cells = no relevance of the disease in the respective lactation stage as explained in the manuscript text. NS = difference not significant, $P > 0.05$.

[2]MAST = clinical mastitis; SU = sole ulcer; DD = digital dermatitis; WL = white line disease; HYP = interdigital hyperplasia; ACID = ruminal acidosis; KET = ketosis; MFEV = milk fever; ENDO = endometritis; OCD = ovarial cycle disorder; CYST = ovarial cysts; CLP = corpus luteum persistens; RP = retained placenta

Metabolic diseases from the early lactation period had strong detrimental effects on LPL. Accordingly, Probo et al. (2018) stated that all metabolic diseases, especially MFEV, are associated with increased culling risk in the first 120 DIM. Beaudeau et al. (1995) addressed the differences among longevity responses to fertility disorders, depending on the lactation stage. In their study, ENDO diagnosed between 22 and 49 DIM was not associated with longevity, but ENDO diagnosed afterward had significant detrimental effect. We found similar influences on LPL for ENDO diagnosed in L1 or L2 but not for ENDO in L3. As identified by Oltenacu et al. (1990), CYST and RP diagnosed in L1 and L2 negatively influenced LPL. However, a diagnosis of CYST or RP increased STAY probabilities for the

same stages. Hence, there is a strong time-lagged effect of these female fertility disorders on longevity traits—that is, no significant negative influence on STAY but detrimental effect on time-lagged LPL.

Heritability Estimates

Health Disorders. We found that heritability estimates for the 13 diseases across stages and lactations from single-trait generalized linear mixed models ranged from <0.01 to 0.24 (Table 2.5). Standard errors (SE) ranged from 0.007 to 0.017 for udder diseases, from 0.009 to 0.059 for claw disorders, from 0.023 to 0.105 for metabolic disorders, and from 0.006 to 0.025 for reproductive disorders. Heritabilities for MAST from different periods were in a stable range (0.05 to 0.08), confirming estimates from Neuenschwander et al. (2012), Pritchard et al. (2013b), and Parker Gaddis et al. (2014). Claw disorders showed stronger heritability alterations in different lactation stages. Heritabilities of SU varied between 0.06 and 0.12, and from 0.09 to 0.13 for DD. In such context, König et al. (2005) discussed the possible effects of claw health pre-selection on disease incidences and genetic parameter alterations with increasing lactation number. In most lactation stages, heritabilities for WLD were low to moderate (0.11 to 0.19), and almost zero in L2.1. The largest claw disorder heritabilities were estimated for HYP (between 0.15 and 0.24). The potential for genetic HYP improvements, due to moderate heritabilities, was indicated in several previous studies (e.g., König et al., 2008b). For ACID, heritabilities were close to zero, in accord with the findings of Ederer et al. (2014), who reported low ACID heritabilities due to extremely low incidence and large environmental influence. Heritabilities for KET decreased from 0.13 in L1.1 to 0.08 in L3.1, similar to the KET heritability decrease with aging identified by Parker Gaddis et al. (2014). Also for KET, we assume strong selection against susceptible cows, explaining the decline of additive genetic variances and of heritabilities with increasing parity. By contrast, in agreement with Heringstad et al. (2005), heritabilities for MFEV increased from 0.08 in L2.1 to 0.13 in L3.1. Heritabilities for the liability of fertility diseases were quite small, in the range of 0.04 to 0.10.

Table 2.5: Heritabilities for diseases by lactation stages[1]

Disease[2]	Lactation 1			Lactation 2			Lactation 3		
	Stage 1	Stage 2	Stage 3	Stage 1	Stage 2	Stage 3	Stage 1	Stage 2	Stage 3
MAST	0.08	0.05	0.07	0.06	0.07	0.05	0.05	0.06	0.06
SU	0.12	0.11	0.12	0.08	0.10	0.12	0.06	0.07	0.08
DD	0.09	0.10	0.09	0.10	0.10	0.12	0.10	0.09	0.13
WLD	0.19	0.12[3]	0.18	0.15[3]	0.13[3]	0.11	0.11	0.09[3]	0.15
HYP	0.18	0.22	0.23	0.17	0.20	0.24	0.21	0.19	0.15
ACID	0.00			0.00			0.00		
KET	0.13			0.12			0.08		
MFEV				0.08			0.13		
ENDO	0.06	0.07		0.05	0.04		0.04	0.06	
OCD		0.06			0.05			0.04	
CYST		0.06			0.05			0.05	
CLP		0.07			0.07[3]			0.05	
RP	0.10			0.07			0.07		

[1]Empty cells = no relevance of the disease in the respective lactation stage as explained in the manuscript text. The SE ranged from 0.007 to 0.017 for udder diseases, from 0.009 to 0.059 for claw disorders, from 0.023 to 0.105 for metabolic disorders, from 0.006 to 0.025 for reproductive disorders.
[2]MAST = clinical mastitis; SU = sole ulcer; DD = digital dermatitis; WL = white line disease; HYP = interdigital hyperplasia; ACID = ruminal acidosis; KET = ketosis; MFEV = milk fever; ENDO = endometritis; OCD = ovarial cycle disorder; CYST = ovarial cysts; CLP = corpus luteum persistens; RP = retained placenta
[3]These runs did not fully converge with the default convergence criteria "norm of update vector room" = 1×10^{-7} and "norm of gradient vector" = 1×10^{-6}. In consequence, we slightly lowered the criteria to 1×10^{-6} and 1×10^{-5}, respectively.

Longevity. The LPL heritability from the single-trait model was 0.05, with a small SE of 0.006. Heritabilities from all bivariate runs, including LPL, ranged from 0.03 to 0.10, also associated with small SE (0.003 to 0.008). Considering data from 19 countries, Forabosco et al. (2009) estimated heritabilities for direct longevity, via linear model applications, in the range from 0.02 to 0.11. In Czech Holstein cows, Zavadilová and Štípková (2012) and Zavadilová and Zink (2013) estimated heritabilities for LPL of 0.03 and 0.09, respectively. In Spanish Holsteins, LPL heritabilities ranged from 0.08 to 0.10 (Pérez-Cabal and Alenda, 2003; Pérez-Cabal et al., 2006). In UK Holsteins, based on linear mixed model applications, heritabilities for both longevity definitions LPL and days of life were 0.06 (Pritchard et al., 2013b). In the Swedish Holstein population, LPL heritabilities were in the range of 0.09 to 0.13 (Ahlman et al., 2011). According to the genetic parameter estimates from different countries, heritabilities in European Holstein populations are very similar for LPL, irrespective of the statistical modelling approach (linear or threshold model applications).

Nevertheless, alternative LPL definitions were also addressed from a quantitative genetic perspective in past studies. VanRaden et al. (2006) defined LPL as the period from calving up to a particular month of age, but heritabilities in the range from 0.02 to 0.07 were almost identical compared with the "conventional" LPL definition. Tsuruta et al. (2005) developed longevity models considering restrictions for lactation length. Again, heritabilities were in the narrow range from 0.08 to 0.10. Van Pelt et al. (2015) considered the last official test date when defining the period for LPL, but heritabilities increased only marginally. At present, routine genetic evaluations of longevity mostly use survival analysis. Similar to our LPL heritabilities based on uncensored data, LPL heritabilities from the Weibull proportional hazards models were also in the range from 0.05 and 0.09 (Chirinos et al., 2007; Strapáková et al., 2013; Morek-Kopeć and Zarnecki, 2017), for both important European dairy and dual-purpose breeds Holstein and Fleckvieh. Thus there is only a small to moderate genetic background influencing longevity. Via survival analyses, Buenger et al. (2001) identified some other important environmental factors with larger effects on LPL, such as housing or bedding systems.

As a further longevity trait definition and statistical modeling alternative, we evaluated binary STAY and applied single-trait generalized linear mixed models with a logit link function for heritability estimations. The STAY heritabilities were quite stable for the different lactation stages, in the range from 0.05 to 0.06, with small SE between 0.008 and 0.033. In agreement with our results, heritability estimates for binary STAY via bivariate or multivariate threshold models ranged from 0.04 to 0.11 (González-Recio and Alenda, 2007; Holtsmark et al., 2008; Tsuruta et al., 2015). Studies addressing both linear and threshold modeling found high correlations with sire EBV (Boettcher et al., 1999; van Pelt et al., 2015). Against this background of nearly identical EBV and heritabilities from both approaches, linear models were suggested because of the computation time requirements (e.g., van Pelt et al., 2015). We observed a slight increase of STAY heritabilities in later lactations and in later lactation stages. Ahlman et al. (2011) estimated STAY heritabilities, via bivariate linear-linear models, of 0.05, 0.08 and 0.20 for the first, second, and third lactations, respectively. Among Canadian Holsteins, Sewalem et al. (2007) also found larger STAY heritabilities in later parities. Wiebelitz et al. (2014) created 2 stages within lactations. Comparable to our results, STAY heritabilities were slightly larger in the late lactation stages. The definition of smaller time windows (up to 6 periods) contributed to stronger heritability alterations, ranging from 0.04 to 0.11 (Heise et al., 2016). Heritabilities for categorical traits depend on the frequencies of cows in different classes—that is, the percentage of diseased cows (Heringstad et al.,

2000). Hence, the larger proportion of culled cows in later stages or lactations might be an explanation for the slight heritability increase.

Genetic Correlations Between Longevity Traits and Diseases

Genetic correlations between LPL and STAY with the studied diseases are listed in Table 2.6and Table 2.7, respectively.

Table 2.6: Genetic correlations between length of productive life and diseases recorded in different lactation stages. SE are presented below estimates[1]

Disease[2]	Lactation 1			Lactation 2			Lactation 3		
	Stage 1	Stage 2	Stage 3	Stage 1	Stage 2	Stage 3	Stage 1	Stage 2	Stage 3
MAST	-0.43	-0.56	-0.28	-0.69	-0.52	-0.29	-0.55	-0.47	-0.53
	0.05	0.06	0.07	0.05	0.05	0.09	0.08	0.08	0.10
SU	-0.32	-0.28	-0.32	-0.34	-0.28	-0.43	-0.46	-0.37	-0.62
	0.10	0.06	0.09	0.13	0.07	0.09	0.14	0.09	0.11
DD	-0.21	0.04	-0.01	0.04	0.13	-0.00	0.03	0.07	0.09
	0.08	0.06	0.08	0.09	0.07	0.09	0.12	0.09	0.11
WLD	-0.41	-0.15	-0.31	-0.48	-0.06	-0.02	0.07	-0.25	-0.19
	0.12	0.10	0.10	0.13	0.09	0.12	0.15	0.11	0.15
HYP	-0.26	-0.22	-0.27	-0.12	-0.21	-0.21	-0.26	-0.08	-0.33
	0.11	0.07	0.09	0.09	0.07	0.08	0.10	0.09	0.12
ACID	-0.51			-0.42			-0.40		
	0.13			0.23			0.26		
KET	-0.46			-0.38			-0.22		
	0.10			0.10			0.12		
MFEV				-0.66			-0.06		
				0.12			0.11		
ENDO	-0.29	-0.40		-0.21	-0.26		-0.19	-0.38	
	0.06	0.07		0.07	0.10		0.09	0.11	
OCD		-0.34			-0.35			-0.17	
		0.05			0.06			0.09	
CYST		-0.27			-0.11			-0.09	
		0.08			0.09			0.11	
CLP		-0.14			-0.04			-0.06	
		0.06			0.07			0.11	
RP	-0.32			-0.26			-0.23		
	0.07			0.08			0.11		

[1]Empty cells = no relevance of the disease in the respective lactation stage as explained in the manuscript text.

[2]MAST = clinical mastitis; SU = sole ulcer; DD = digital dermatitis; WL = white line disease; HYP = interdigital hyperplasia; ACID = ruminal acidosis; KET = ketosis; MFEV = milk fever; ENDO = endometritis; OCD = ovarial cycle disorder; CYST = ovarial cysts; CLP = corpus luteum persistens; RP = retained placenta.

Table 2.7: Genetic correlations between stayability and diseases from the same lactation stages. SE are presented below estimates[1]

	Lactation 1			Lactation 2			Lactation 3		
Disease[2]	Stage 1	Stage 2	Stage 3	Stage 1	Stage 2	Stage 3	Stage 1	Stage 2	Stage 3
MAST	-0.47	-0.56	-0.26	-0.62	-0.63	-0.36	-0.75	-0.69	-0.77
	0.11	0.07	0.08	0.13	0.06	0.09	0.12	0.06	0.08
SU	-0.21	-0.36	-0.32	-0.50	-0.24	-0.44	-0.55	-0.37	-0.60
	0.16	0.07	0.10	0.21	0.08	0.09	0.22	0.09	0.11
DD	-0.39	-0.08	-0.04	-0.33	0.10	-0.06	-0.38	0.26	0.09
	0.14	0.07	0.08	0.18	0.08	0.09	0.20	0.09	0.11
WLD	-0.08	-0.24	-0.26	0.14	-0.08	-0.16	0.09	-0.25	-0.32
	0.19	0.12	0.11	0.24	0.10	0.13	0.23	0.11	0.14
HYP	-0.13	-0.02	-0.17	0.00	-0.11	-0.20	-0.30	-0.20	-0.30
	0.18	0.09	0.10	0.19	0.08	0.08	0.18	0.09	0.12
ACID	-0.48			-0.98			-0.82		
	0.18			0.31			0.28		
KET	-0.47			-0.56			-0.76		
	0.15			0.17			0.17		
MFEV				-0.32			-0.18		
				0.26			0.17		
ENDO	-0.20	-0.38		-0.33	-0.51		0.08	-0.36	
	0.12	0.08		0.15	0.10		0.16	0.11	
OCD		-0.34			-0.48			-0.23	
		0.07			0.07			0.09	
CYST		-0.13			-0.05			-0.17	
		0.09			0.10			0.11	
CLP		-0.22			0.04			-0.09	
		0.08			0.08			0.11	
RP	-0.41			-0.40			-0.61		
	0.12			0.17			0.15		

[1]Empty cells = no relevance of the disease in the respective lactation stage as explained in the manuscript text.
[2]MAST = clinical mastitis; SU = sole ulcer; DD = digital dermatitis; WL = white line disease; HYP = interdigital hyperplasia; ACID = ruminal acidosis; KET = ketosis; MFEV = milk fever; ENDO = endometritis; OCD = ovarial cycle disorder; CYST = ovarial cysts; CLP = corpus luteum persistens; RP = retained placenta.

Favorable genetic correlations between LPL and MAST from different stages (−0.28 to −0.69), and between STAY and MAST (−0.26 to −0.77), suggest reason to perform selection on udder health at early stages of life, to improve longevity genetically. The negative correlations between MAST and LPL and between MAST and STAY reflect estimates from the United Kingdom (Pritchard et al., 2013a) and in Danish Holstein cows (Sander Nielsen et al., 1999). Different modeling approaches have been applied in the different studies. Nevertheless, with regard to bivariate modeling strategies, results are comparable, because

Vinson and Kluwer (1976) showed that genetic correlations from linear-linear and from linear-threshold models can be expected to be the same. Especially for the 3 stages of first lactation, MAST and STAY showed quite strong genetic relationships. The most obvious change in genetic correlations between diseases and STAY was observed for the transition from the second to the third lactation stage. Differences in genetic (co) variance components when comparing early and middle with late lactation stages have been identified for diseases (Zwald et al., 2006) and for STAY (Wiebelitz et al., 2014).

Genetic correlations between claw disorders with LPL and with STAY were also mostly negative, indicating that selection for improved claw health is associated with indirect favorable selection response in longevity traits. Favorable (i.e., negative) genetic correlations between claw disorders and longevity were reported by Sander Nielsen et al. (1999), considering survival from second lactations and the feet and leg diseases HYP and SU in Danish Holsteins, and by Pritchard et al. (2013a), who focused on a lifespan score and lameness for Holsteins in the United Kingdom. Again, as identified phenotypically, a DD diagnosis from some lactation stages was genetically unfavorably associated with LPL and with STAY. The different phenotypic and genetic mechanisms of DD, compared with the remaining claw disorders, suggest a need for ongoing studies in this regard. In Dutch Holstein cows, genetic correlations between DD and lifespan were close to zero but slightly negative (Onyiro et al., 2008). Dhakal et al. (2015) estimated a genetic correlation of −0.03 between DD and LPL for the US Holstein population. Genetic correlations between SU with STAY and with LPL decreased with increasing lactation number, suggesting reason to focus on indirect selection strategies on SU especially in parities 2 and 3 when aiming for longevity improvements. For WL and HYP, we observed different genetic correlation trends when comparing associations with either LPL or STAY. However, the quite large SE for genetic correlation estimates should be taken into consideration. The comparatively large SE could be due to the low disease incidences for WL and HYP in some lactation stages (van der Waaij et al., 2005).

Metabolic diseases, especially ACID and KET, had strong genetic effects on longevity, with genetic correlations up to −0.98. However, as for the metabolic disease with low incidences, these genetic correlations had quite large SE. Genetic correlations from −0.10 to −0.17 among metabolic diseases and longevity were estimated by Sander Nielsen et al. (1999) and Zwald et al. (2004b) for Danish and US Holstein populations, respectively. Diagnoses for ACID and KET in L1, as well as for MFEV in L2, had most obvious detrimental genetic effects on LPL. However, incidences for these diseases were higher in later lactations. Both longevity traits

LPL and STAY were negatively correlated with female fertility disorders, implying that selection on lower disease incidences will contribute to genetic longevity improvements. In this regard, the genetic correlations between ENDO, OCD, and RP with longevity traits were stronger than for CYST and CLP. Genetic associations between female fertility disorders and longevity in other Holstein populations followed the same pattern as that identified in our study—for instance, in Danish Holsteins with regard to RP, CYST, and ENDO (Sander Nielsen et al., 1999), and in US Holsteins for CYST and ENDO (Zwald et al., 2004b).

Genetic correlations between LPL and STAY across stages and lactations were quite large, in the range from 0.77 to 0.94 (Table 2.8). Hence, both longevity definitions LPL and STAY are genetically the same trait, as previously indicated (Short and Lawlor, 1992; Jairath et al., 1998; van Pelt et al., 2015). In this regard, we suggest selection on STAY in early lactations, to select young animals with high accuracy and simultaneously reduce generation intervals.

Table 2.8: Genetic correlations between the length of productive life and stayability from different lactation stages.

	Lactation 1			Lactation 2			Lactation 3		
Item	Stage 1	Stage 2	Stage 3	Stage 1	Stage 2	Stage 3	Stage 1	Stage 2	Stage 3
Correlation estimate	0.80	0.89	0.88	0.80	0.94	0.90	0.77	0.84	0.78
SE	0.07	0.03	0.02	0.10	0.02	0.02	0.11	0.04	0.04

CONCLUSIONS

We observed some disagreements between culling reasons, as subjectively defined by farmers, and veterinary diagnoses for cow diseases. Thus, despite the availability of large population-wide data sets for culling reasons, we suggest focusing on veterinarian diagnoses from cows in co-operator herds for genetic evaluations of health traits and when defining appropriate longevity indicators in survival analyses. Nevertheless, some cullings might be due to subclinical diseases, which are not fully reflected in the veterinarian diagnosis key, indicating additional information from the farmer culling answers in genetic evaluations. With regard to the monitored diseases, diagnoses for MAST and metabolic diseases had strong detrimental phenotypic effects on LPL and on STAY. Most of the disease traits had only small to moderate heritabilities, but MAST, SU, and metabolic disorders were strongly genetically correlated with LPL and STAY. Heritabilities for the different longevity definitions LPL and STAY across stages and lactations were quite stable in the range from

0.05 to 0.06. Genetic correlations between LPL and STAY from different periods were quite large (0.77 to 0.94), indicating similarities between the 2 trait definitions and suggesting the utility of early selection strategies based on STAY information.

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CHAPTER 3

Survival analyses in Holstein cows considering direct disease diagnoses and specific SNP marker effects

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ABSTRACT

The aim of the present study was to infer influences of health disorders and of specific SNP markers on longevity in Holstein cows via survival analyses. Longevity was defined as the length of productive life (**LPL**), reflecting the interval from first calving until the culling or censoring date. In this regard, we considered longevity records from 129,386 Holstein cows from 57 large-scale herds, with calving dates in first parity between January 2004 and December 2017 (30.27% censored records). We selected specific diseases from the overall categories claw disorders, udder diseases, metabolic disorders and female fertility disorders within three stages of parities 1, 2 and 3. Lactation stage 1 was the period from calving to DIM 59, lactation stage 2 from DIM 60 to DIM 299, and lactation stage 3 from DIM 300 to the next calving date. The effects of the diseases on culling risk ratios were estimated via Weibull proportional hazards models. In this regard, we used three different modelling strategies. In modelling strategy M1S, binary diseases from different parities and lactation stages for the same diagnosis were modelled as explanatory variables in separate runs. Modelling strategy M3S included diseases for the same diagnosis from stage 1, 2, and 3 in the same parity simultaneously. Modelling strategy M9S implied consideration of diseases for the same diagnosis from different lactation stages and from all three parities simultaneously. The impact of same diseases on culling risks from M1S and M3S were similar, with increasing detrimental impact of diseases recorded in later lactation stages and parities. The strongest disease impact on LPL was detected for clinical and subclinical mastitis recorded in the middle of the third lactation, with culling risks of 2.59 and 2.40, respectively, and for claw disorders from the last stage in third lactation (culling risks in the range from 1.85 to 2.29). The effective (ignoring the proportion of censoring; h^2_{eff}) and equivalent (considering proportion of censoring; h^2_{equ}) heritabilities for LPL when considering diseases from specific stages in parities 1 and 3 were quite low (h^2_{eff}: 0.02 – 0.17; h^2_{equ}: 0.01 – 0.12). Simultaneous consideration of same disease diagnoses across stages (M3S) and across lactations (M9S) contributed to a LPL heritability increase. Ignoring diseases as explanatory variables in survival analyses was generally associated with a decline of genetic LPL variances and LPL heritabilities. A genome-wide association study for LPL based on estimated de-regressed proofs from 17,362 genotyped cows. Six SNP located on Bos taurus autosomes 1, 4, 10, 13 and 28 were significantly associated with LPL (using a 5% false discovery rate). Gene annotations via Ensembl inferred the four potential candidate genes *ETV1*, *ONECUT1*, *MACROD2* and *SIRT1*, which directly (via disease resistance mechanisms) or indirectly (via milk productivity) influence dairy cow longevity. Genotypes of the six significantly

associated SNP were considered as fixed effects in Weibull hazard models, but their effects on culling risks were non-significant. Heritabilities for LPL from all SNP based survival models considering the single SNP separately or the six SNP simultaneously were 0.05 (h^2_{equ}) and 0.12 (h^2_{eff}). The small no. of significantly associated SNP in genome-wide associations and the minor impact of specific SNP on LPL in survival analyses underline the polygenetic nature of longevity.

Key words: Longevity, Weibull hazard model, health disorder, genetic parameter, SNP effect

INTRODUCTION

Longevity is a trait of superior importance in dairy cattle breeding programs, because increased longevity implies improvements of several functional trait categories, and positively influences farm economy (Sewalem et al., 2008; Knaus, 2009). For genetic evaluations, several longevity definitions have been introduced during the past decade, e.g., the no. of lactations (Stanojević et al., 2016), or stayability for specific periods (Heise et al., 2016). The most common definition is the length of productive life (**LPL**), reflecting the period from first calving to culling.

For genetic evaluations of LPL, mostly linear animal models have been applied (e.g., Jenko et al., 2015; Stanojević et al., 2016; Ghaderi-Zefrehei et al., 2017). However, the classical LPL definition implies full datasets, i.e., consideration of cow records with culling dates, addressing the challenge of a censored data structure. The exclusion of alive cows from genetic evaluations was associated with biased estimated breeding values (**EBV**) for longevity (López de Maturana et al., 2007). Hence, so-called survival analysis using a proportional hazard model (Cox, 1972; Kalbfleisch and Prentice, 1980) allowing consideration of censored records, was suggested for animal breeding applications (Smith, 1983; Smith and Quaas, 1984). Consequently, for survival analyses in an animal breeding context based on pedigree relationships, Ducrocq and Sölkner (1998b) developed the software package "Survival Kit". Specifically, from a methodological perspective, "Survival Kit" allows the definition of either Cox or Weibull proportional hazard models. For large datasets, Ducrocq and Sölkner (1998a) favoured the Weibull over the Cox model to study genetic and environmental influences on LPL. Caraviello et al. (2004) evaluated proportional hazard and linear models for LPL analyses. Also for a data structure with known culling dates, model evaluation criteria suggested proportional hazard model applications.

Survival analysis implies consideration of time-dependent variables when predicting genetic values for LPL (Gröhn et al., 1998). In this regard, considered early LPL predictors were

somatic cell count (Pritchard et al., 2013) or type traits (Buenger et al., 2001). Recently, based on historical data, Shabalina et al. (2019) identified strong impact of most of the cow diseases (e.g., mastitis, metabolic disorders) on longevity traits. Somatic cell count or type traits were only moderate or even weak indicators for cow health (König et al., 2005; Koeck et al., 2010), suggesting consideration of direct health diagnoses in genetic evaluations for LPL. The implementation of population-wide health recording systems based on a harmonized diagnoses key (Stock et al., 2013) offers new possibilities in this regard. Phenotypically, Charfeddine and Pérez-Cabal (2017) applied a Weibull hazard model, and they identified a detrimental effect of sole ulcer occurrence and of white line disease on LPL. Jensen et al. (1999) and Rajala-Schultz and Gröhn (1999) applied Weibull and Cox proportional hazards models, both reporting increased culling risk for cows with clinical mastitis.

According to Yazdi et al. (2002), heritabilities from proportional hazard Weibull modelling can be expressed as so-called effective heritabilities (h^2_{eff}, ignoring the proportion of censored cow records) and as equivalent heritabilities (h^2_{equ}, considering the proportion of uncensored cow records). For a large proportion of uncensored cows, both heritability estimates are the same. Heritability estimates for LPL in different cattle breeds estimated via Weibull hazard model applications ranged between 0.03 and 0.14 for h^2_{eff}, and between 0.02 and 0.12 for h^2_{equ} (Table 3.1). Roxström and Strandberg (2002) identified larger LPL heritabilities when considering fertility disorders or mastitis as explanatory variables in genetic-statistical modelling approaches. In contrast, Samore et al. (2003) used somatic cell score as an early LPL indicator, but the LPL heritability was smaller compared to a model neglecting any LPL indicator traits.

Table 3.1: Literature overview for estimates of effective (h^2_{eff}) and equivalent heritabilities (h^2_{equ}) for the length of productive life based on the application of Weibull proportional hazards models in dairy cattle

Reference	Breed[1]	Number of cows (sires)	Heritabilities[2]		Explanations
			h^2_{eff}	h^2_{equ}	
Imbayarwo-Chikosi et al., 2017	HOL	161,222 (2,051)	0.11	0.03-0.04	h^2_{equ} variations due to different datasets with different proportions of censored observations
Morek-Kopeć and Zarnecki, 2017	SIM	12,527 (294)	0.25	0.09	
Kern et al., 2016	HOL	132,922 (6,804)	0.08	0.04-0.07	h^2_{equ} variations due to different datasets with different proportions of censored observations
Strapáková et al., 2014	HOL	405,624 (4,563)		0.13	
Raguž et al., 2014	SIM	89,209 (713)		0.08	
Jenko et al., 2013	B	37,908 (886)	0.10		
Strapáková et al., 2013	SIM	214,634 (1,626)		0.05	
Jovanovac et al., 2013	SIM	49,659 (251)		0.06	
Mészáros et al., 2013	PIN	40,397 (334)		0.08	Sire model
				0.11	Animal model
Bonetti et al., 2009	BS	511,596 (20,896)	0.14	0.12	
Holtsmark et al., 2009	NR	808,750 (3,064)		0.02-0.04	h^2_{equ} variations due to different datasets with different proportions of censored observations
Terawaki and Ducrocq, 2009	HOL	95,718 (496)	0.05		Without effect of type trait indicators
		117,182 (568)	0.13		With effect of type trait indicators
Mészáros et al., 2008	PIN	21,985 (254)		0.05	
Chirinos et al., 2007	HOL	133,629 (1,606)			Range due to different regions
			0.03-0.04		With herd-year-season variance
			0.05-0.06		Without herd-year-season variance
Back and Lidauer, 2007	AYR	129,453 (2,138)		0.05	
Linde et al., 2006	HOL	1,403,747 (5,664)	0.04		
Ducrocq, 2005	HOL	8,682,630 (24,537)	0.11	0.02-0.04	h^2_{equ} variations due to different datasets with different proportions of censored observations

Reference	Breed[1]	Number of cows (sires)	Heritabilities[2]		Explanations
			h^2_{eff}	h^2_{equ}	
Pachova et al., 2005	HOL	230,028 (827)	0.04		
Sewalem et al., 2005	HOL	536,478 (2,090)	0.14		
	JER	92,627 (682)	0.10		
	AYR	43,794 (551)	0.09		
Samore et al., 2003	HOL	512,979	0.06		With SCS effect
		(4,511)	0.07		Without SCS effect
Roxström et al., 2003	SRB	733,492	0.14		With herd-year-season variance
		(2,766)	0.17		Without herd-year-season variance
Roxström and Strandberg, 2002	SRB	538,783 (1,334)	0.06		Dataset: All cows
		Not specified	0.10		Dataset: Cows culled due to infertility
		Not specified	0.18		Dataset: Cows culled due to mastitis

[1]HOL = Holstein Friesian, SIM = Simmental, PIN = Pinzgauer, B = Brown, BS = Brown Swiss, NR = Norwegian Red, AYR = Ayrshire, JER = Jersey, SRB = Swedish Red and White
[2]h^2_{eff} = effective heritability (= calculation without considering the proportion of censored cows); h^2_{equ} = equivalent heritability (= calculation considering the proportion of censored cows).

As an alternative to modelling early available phenotypic indicator traits, broad genotyping of cows from commercial dairy herds offers new LPL breeding prospects. In this regard, Brøndum et al. (2015) focused on genomic predictions for different productive and functional traits, and found that including single-nucleotide polymorphism (**SNP**) marker panels can increase the reliability for prediction. In genome wide association studies (**GWAS**), Steri et al. (2019) detected five SNP on BTA16 and 30 significantly influencing LPL in Italy Holstein cows. Annotated potential candidate genes were related to female fertility, reproductive disorders and heat stress. In the Austrian Fleckvieh population, Mészáros et al. (2014) inferred significant SNP associations with LPL on BTA 5, 6, 8 and 14. The annotated potential candidate genes influenced the follicular development and resistance mechanisms against pulmonary diseases. Identified significantly associated SNP and potential candidate genes differed between cattle breeds (Zhang et al., 2016), and were specific for specific longevity definitions (Nayeri et al., 2017). Apart from GWAS, it might be interesting to infer SNP marker effects on LPL via survival analyses and applying proportional Weibull hazard models.

Overall, we hypothesize that disease diagnoses and SNP marker are proper predictors for LPL, suggesting their consideration in LPL selection indices in addition to type or female

fertility traits. Against this background, the specific aims of the present study were i) to study the impact of disease diagnoses on LPL using the Weibull hazard function; ii) to estimate genetic parameters for LPL using the Weibull hazard function and considering disease diagnoses as explanatory variables, iii) to identify associated SNP via GWAS and to annotate potential candidate genes; and iv) to include detected significant SNP marker as LPL indicators in Weibull hazard functions.

MATERIALS AND METHODS

Cow traits

The data set consisted of calving date and culling date records, as well as test-day production traits, from 129,386 Holstein cows. The cows were kept in 57 large-scale contract herds, located in the German Federal states of Berlin-Brandenburg and Mecklenburg-West Pomerania. The calving years for first calving spanned the period from January 2004 to December 2017. Age at first calving ranged between 18 and 42 months. All cows had at least one official test-day record within the first 100 DIM in first, second and/or third lactation. Length of productive life (in days) was the period from first calving until the culling date or censoring date. Records for cows that were still alive in December 2017 were considered as right censored (30.27%). The average time to censoring was 865.42 d (±590.99 d), and average LPL for uncensored records was 977.11 d (±626.77 d). Descriptive statistics for LPL, considering the whole dataset and the sub-data for genotyped cows, are given in Table 3.2.

Table 3.2: Descriptive statistics for milk yield and the length of productive life (LPL; for uncensored records) and censoring time (for censored records) considering all cows and genotyped cows

	Uncensored records	Censored records
All cows		
No. of cows	90,215	39,171
Min. – Max. LPL or censoring time (days)	6 – 3,968	140 – 4,189
Average LPL or censoring time (days)	977.11 (±626.77)	865.42 (±590.99)
Mean of milk yield in lactation 1 (kg)	8,049.42 (±2,719.62)	8,463.31 (±2,068.71)
Mean of milk yield in lactation 2 (kg)	9,430.18 (±3,048.50)	9,143.25 (±3,339.20)
Mean of milk yield in lactation 3 (kg)	9,221.80 (±3,488.98)	9,479.79 (±3,405.35)
Genotyped cows		
No. of cows	7,501	9,861
Min. – Max. LPL or censoring time (days)	15 – 3,385	455 – 3,981
Average LPL or censoring time (days)	720.12 (±477.71)	1022.30 (±337.44)
Mean of milk yield in lactation 1 (kg)	8,314.96 (±2,269.64)	9,041.76 (±1,576.37)
Mean of milk yield in lactation 2 (kg)	8,362.85 (±3,626.90)	10,464.20 (±2,171.77)
Mean of milk yield in lactation 3 (kg)	7,478.58 (±4,104.48)	8,206.53 (±,3615.1)

The disease diagnosis dataset considered 13 health disorders (in analogy to Shabalina et al., 2019). The contract herd system implies close collaborations among breeding organisations, farmers and veterinarians, with detailed and specific agreements for disease trait recording. These diseases were veterinarian diagnoses or recorded based on the veterinarian diagnosis key (e.g., at claw trimming), with continuous entries from the calving until the culling date. Hence, all cow treatments were recorded, and not only observations made, e.g., at routine claw trimming. Diseases from three different lactation stages (stage 1: from calving to 59 DIM, stage 2: from 60 DIM to 299 DIM, stage 3: from 300 DIM to the next calving date) in parities one to three were considered as different traits. Disease recording from January 2008 to January 2017 based on the hierarchical diagnosis key as introduced by Stock et al. (2013). The 13 diseases included the udder diseases clinical mastitis (**MAST**) and subclinical mastitis (**SMAST**), the claw disorders sole ulcer (**SU**), digital dermatitis (**DD**), white line disease (**WLD**) and interdigital hyperplasia (**HYP**), the metabolic disorders acidosis (**ACID**), ketosis (**KET**) and milk fever (**MFEV**), and the female fertility disorders endometritis (**ENDO**), ovarian cycle disorders (**OCD**), ovarian cysts (**CYST**) and corpus luteum persistens (**CLP**). For each of the 13 diseases, at least one disease entry per lactation stage implied a score = 1, otherwise, a score = 0 for healthy cows was assigned. For several entries of the same disease within lactation stage, we considered the first diagnosis date. Disease incidences in lactation 1, 2, and 3 for both cow groups with uncensored and censored records are listed in Table 3.3.

The pedigree file included 277,341 animals. Cows with LPL records could be traced back for at least three generations.

Table 3.3: Disease incidences (%) in lactation 1, 2, and 3 for uncensored (with culling date) and censored records (without culling date)

Disease[1]	Uncensored records			Censored records		
	Lactation 1	Lactation 2	Lactation 3	Lactation 1	Lactation 2	Lactation 3
MAST	24.47	33.65	38.84	20.83	30.00	34.04
SMAST	1.34	2.18	2.47	1.12	1.97	2.21
SU	8.78	10.23	14.71	8.77	9.83	14.15
DD	14.08	13.81	12.26	14.19	13.07	11.59
WLD	1.85	2.92	4.67	1.78	2.76	4.37
HYP	2.15	3.46	4.16	2.11	3.10	3.71
ACID	0.29	0.46	0.72	0.20	0.26	0.35
KET	0.76	1.68	3.06	0.55	0.84	1.16
MFEV	0.17	1.41	4.36	0.12	0.69	1.48
ENDO	17.52	18.14	21.27	11.25	10.44	10.88
OCD	20.92	22.12	22.66	21.24	21.86	22.71
CYST	6.87	9.35	9.98	6.90	8.74	9.31
CLP	2.69	3.19	3.33	2.71	3.18	3.36
Healthy	31.45	28.87	26.01	33.90	30.05	27.22

[1]MAST = clinical mastitis; SMAST = subclinical mastitis; SU = sole ulcer; DD = digital dermatitis; WLD = white line disease; HYP = interdigital hyperplasia; ACID = ruminal acidosis; KET = ketosis; MFEV = milk fever; ENDO = endometritis; OCD = ovarian cycle disorder; CYST = ovarian cysts; CLP = corpus luteum persistens; Healthy = percentage of cows without any disease entry

Cow genotyping

Starting in 2013 in the framework of the German cow training set project (e.g., Klein et al., 2019), all first calving cows from the so-called contract herds were considered for genotyping. Hence, the genotyped 17,362 cows represent a random sample of the herd, especially for the birth years 2011 and later. However, genotyped older cows representing birth years 2004 to 2011 are from a subset of herds, and in most cases, these cows were pre-selected for genotyping, implying potential biases in genomic analyses.

The Holstein cows and sires were genotyped, using the Illumina BovineSNP50 BeadChip V2 (5,403 animals) and the Illumina Bovine Eurogenomics 10K low-density chip (15,913 animals). Animals with 10K genotypes were imputed to the 50K level as done for official national genetic evaluations (Segelke et al., 2012). Quality control was performed using PLINK v1.90b5.2 (Purcell et al., 2007). The filtering criteria for SNPs were: 1) call rate larger than 0.95; 2) minor allele frequency larger than 0.05; 3) non-significant deviation from

Hardy-Weinberg equilibrium (P-value >1×10-5); and 4) only consideration of SNP located on autosomes. Genotyped animals with a call rate lower smaller than 0.95 and a genomic relatedness larger than 0.95 were excluded. The final genotype dataset included 39,627 SNP from 19,698 genotyped Holstein cows and sires. 17,362 genotyped cows with LPL records (56.79 % right censored) were considered in survival analyses using Weibull proportional hazard models (see Table 3.2).

Statistical Models

Impact of health disorders on culling risks and genetic parameter estimation. A Weibull proportional hazard model as implemented in Survival Kit v6.12 (Mészáros et al., 2013b) was applied to evaluate the impact of the diseases from different lactation stages on LPL, and to estimate LPL heritabilities. The effects of 13 diseases diagnosis were studied one by one in consecutive runs. In this regard, we focused on the three different stages from the three lactations, considering same diseases from the different periods jointly or separately. For the evaluation of culling risks, the risk ratio for respective reference group (healthy cows) was set to 1. Values of risk ratios larger than 1 indicate a higher culling risk for the diseased cow group in relation to the reference group. A further evaluation criterion for the impact of health disorders on the culling risk was the shape parameter of the Weibull distribution (ρ). Estimates of the shape parameter of the Weibull distribution (ρ) larger than 1 indicate an increased culling risk with time. In the opposite direction, Weibull distributions with $\rho < 1$ indicate that the influence of the disease on cow culling decreases with time.

In model 1, diseases from different lactation stages and different lactations were considered separately (modelling strategy **M1S**). Model 1 was defined as follows:

$$\lambda(t) = \lambda_0(t)\, exp\{H_i + FCA_j + \Delta M_k + DIM_l + Y_m + S_n + HS_o(t') + g_p\} \qquad [1]$$

$\lambda(t)$ = hazard function of a cow t for the days from first calving to culling; $\lambda_0(t)$ = Weibull baseline hazard function; H_i= time-independent fixed effect of the herd; FCA_j = time-independent fixed effect of age at first calving (including five classes: 20-23, 24-26, 27-29, > 30 months); ΔM_k = time-independent covariate of milk yield from the first test-day relative to the herd average for first, second or third lactation; DIM_l = time-independent covariate for days in milk at the first test-day for first, second or third lactation; Y_m = time-independent fixed effect of calving year (15 classes, 2004-2017); S_n = time-independent fixed effect of calving season (January through April, May through September, October through December); $HS_o(t')$ = time-dependent fixed effect of health status within lactation stage (implying nine

different stages in consecutive runs); g_p = random additive genetic animal effect considering pedigree relationships from an animal model.

In Model 2, we considered disease diagnoses from three stages for the same disease within lactation simultaneously in the same run (modelling strategy **M3S**). Disease influences on LPL from the same disease in first, second and third lactations were analysed in separate runs. Model 2 was defined as follows:

$$\lambda(t) = \lambda_0(t)\, exp\{H_i + FCA_j + \Delta M_k + DIM_l + Y_m + S_n + HS_o(t'') + g_p\} \quad [2]$$

$HS_o(t'')$ = time-dependent fixed effect of the cow health status at stages 1, 2 and 3 within one lactation, with assumed change points at 0 d, 60 d and 300 d postpartum. Remaining effects were the same as defined in model 1.

In model 3, we considered disease diagnoses for the same disease from all nine stages simultaneously in the same run (modelling strategy **M9S**). Model 3 was defined as follows:

$$\lambda(t) = \lambda_0(t)\, exp\{H_i + FCA_j + \Delta M_k(t') + DIM_l(t') + Y_m(t') + S_n(t') + HS_o(t''') + g_p\} \quad [3]$$

$\Delta M_k(t')$ = time-dependent covariate of milk yield from the first test-day in relation to the herd average from the respective first, second and third lactation; $DIM_l(t')$ = time-dependent covariate of days in milk at the first test-day from the respective first, second or third lactation; $Y_m(t')$ = time-dependent fixed effect of calving year; $S_n(t')$ = time-dependent fixed effect of calving season with assumed changes at each calving date; $HS_o(t''')$ = time-dependent fixed effect of the health status at stages 1, 2 and 3 in lactations 1, 2 and 3 with assumed changes at 0 d, 60 d and 300 d postpartum of each lactation. Remaining effects were the same as defined in model 1. With regard to modelling approach M9S, some old cows with first calvings in 2004 and 2005 had disease entries during the third lactation, but not for previous parities. For such cases, diseases in parities one and two were considered as missing data.

Additionally, we focussed on the modelling strategies **M3Swd** and **M9Swd**, implying applications of the modelling strategies M3S and M9S, respectively, but ignoring the fixed effect of the respective disease.

Because of computational limitations of the Survival Kit software, cows were randomly allocated into ten groups with similar proportions of right censored data (29.74 - 30.76% of observations (cows)). The chosen approach implied ten runs per disease and modelling strategy. One group comprised 12,939 different cows, implying different relationship matrices per run. For all modelling strategies, presented results (impact of specific diseases on LPL, and LPL heritabilities) are the average from the ten groups. Nevertheless, the estimates from

the different runs were almost identical due to the large no. of cows per group with similar percentages of censored and uncensored records.

Heritability estimation for LPL. The effective (h^2_{eff}) and the equivalent heritability (h^2_{equ}) for LPL was calculated considering the additive-genetic variance from the respective run and survival modelling approach (output from model 1, 2 or 3). The calculations were performed according to Yazdi et al. (2002):

$$h^2_{eff} = \frac{\sigma_g^2}{\sigma_g^2 + 1}$$

$$h^2_{equ} = \frac{\sigma_g^2}{\sigma_g^2 + \frac{1}{p}}$$

with σ_g^2 = additive-genetic variance from the respective modelling approach and run for LPL; p = proportion of uncensored records from the respective modelling approach and run for LPL. As indicated above, presented heritabilities are the average from the ten runs (groups).

Calculation of de-regressed proofs. De-regressed proofs from genotyped cows were used as dependent traits in genomic analyses. In a first step, we estimated breeding values for LPL applying a linear mixed model, and using the AI-REML algorithm as implemented in the software package DMU v6 (Madsen and Jensen, 2013). The respective model 4 was defined as follows:

$$y_{ijklmno} = H_i + FCA_j + \Delta M_k + DIM_l + Y_m + S_n + g_o + e_{ijklmno} \quad [4]$$

$y_{ijklmno}$ = LPL; FCA_j = fixed effect of age at first calving (including five classes: 20-23, 24-26, 27-29, > 30 months); ΔM_k = linear regression for milk yield from the first test-day relative to the herd average for first, second or third lactation; DIM_l = linear regression for days in milk at the first test-day for first, second or third lactation; Y_m = fixed effect of calving year (15 classes, 2004-2017); S_n = fixed effect of calving season (January through April, May through September, October through December); g_o = random additive genetic animal effect considering pedigree relationships from an animal model; $e_{ijklmno}$ = random residual error.
Again, we corrected for DIM at the first test-day, comprising a very narrow interval from 8 d to 28 d after calving. The correction for the production level in milk yield at the first test-day was done in order to account for potential preferential treatment of farmers, i.e., defining the culling decision according to cow productivity. Following practical experiences and evaluations in the large-scale co-operator herds (Shabalina et al., 2019), the farmer's culling

decision or fixation of a slaughtering date according to first test-day milk yield also depends on the measuring date (i.e., extremely early in lactation or a bit later). In consequence, we made the correction for DIM at the first test-day in all models 1, 2, 3 and 4.

In a next step, estimated breeding values (**EBV**) of cows with genotypes were transformed into de-regressed proofs (according to Garrick et al., 2009):

$$y_i = \frac{EBV_i}{r_i^2}$$

y_i = de-regressed proof of cow i for LPL; EBV_i= estimated breeding value of cow i for LPL (h^2 for LPL = 0.13); r_i^2 = reliability of EBV_i.

Genome-wide association study. A single SNP linear mixed model as implemented in the software package GCTA v1.91.5beta (Yang et al., 2011) was used for GWAS, considering the genotyped cows with de-regressed proofs. The respective model 5 was defined as follows:

$$y_{ijk} = g_i + SNP_j + e_k \quad [5]$$

y_{ijk} = vector of de-regressed proofs for LPL; g_i = random additive genetic animal effect with g ~ N (0, $\mathbf{G}\sigma_g^2$), where **G** is the genomic relationship matrix (according to Yang et al., 2010) and σ_g^2 is the genomic variance; SNP_j = vector containing the respective marker genotype (0, 1 or 2); e_k = vector of random residual effects with e ~ N (0, $\mathbf{I}\sigma_e^2$), and $\sigma_e^2$is the residual variance.

The genome-wide significance level according to the Bonferroni corrected threshold (P_{Bonf} = 0.05/39,627 SNP markers) was 1.26×10^{-6}. In addition, a less conservative false discovery rate (**FDR**) (Benjamini and Hochberg, 1995) with a *P*-value ≤ 5% was used.

For potential candidate gene annotations, we focussed on a chromosomal segment 100 kb upstream or downstream from the significantly associated SNP. Potential candidate genes were queried and assigned to associated SNP markers using the current gene annotations from the ENSEMBL database (Zerbino et al., 2018).

Impact of significantly associated SNP on the culling risk ratio. We used the significantly associated SNP from model 5 as explanatory variables in survival analyses. The significantly associated SNP were analysed separately in consecutive runs (modelling strategy **MSNP1**) and simultaneously (**MSNP2**), applying a Weibull proportional hazard model. The respective models 6 (for MSNP1) and 7 (for MSNP2) were defined as follows:

$$\lambda(t) = \lambda_0(t)\, exp\{H_i + FCA_j + \Delta M_k(t') + DIM_l(t') + Y_m(t') + S_n(t') + SNP_o + g_p\} \quad [6]$$

$$\lambda(t) = \lambda_0(t)\, exp\{H_i + FCA_j + \Delta M_k(t') + DIM_l(t') + Y_m(t') + S_n(t') + SNP_{o1-6} + g_p\}$$ [7]

SNP_o= time-independent fixed effect of a single significantly associated SNP (levels: 0, 2 = homozygous and 1 = heterozygous) and SNP_{o1-6} = time-independent fixed effect of the six significantly associated SNP. Remaining effects were the same as defined in model 3.

RESULTS AND DISCUSSION

Shape parameter of the Weibull distribution

The estimates of the shape parameter of the Weibull distribution (ρ) were larger than 1, indicating an increasing culling risk due to diseases with time (Table 3.4). For the modelling strategy M1S, ρ ranged from 1.48 (first stage in lactation 1) up to 2.09 (third stage in lactation 3). For different runs with different diseases and for the 10 different subsets of the same disease, the shape parameter was very similar (SD across different diseases ranged from 0.001 to 0.025, and across different subsets for the same disease from 0.009 to 0.020). In analogy, Sasaki et al. (2015) reported an increase of the shape parameter with indicator trait information from later lactations and lactation stages. Linde et al. (2006) confirmed the shape parameter increase when considering cow records from later lactation stages. Only for our modelling strategy M3S, the shape parameters slightly decreased from 2.51 (disease diagnoses from first lactation) to 2.27 (disease diagnoses from third lactation). However, with regard to an across disease comparison for the shape parameter, the largest variation (SD = 0.061) was identified for first parity cow diagnoses (modelling approach M3S). Similar shape parameters across lactations were identified for modelling strategies M3Swd (range of ρ from 1.54 to 2.13) and M1S (range of ρ from 1.48 to 2.09).

Largest shape parameter were estimated based on modelling strategy M9S, in the range from 4.09 to 4.82 for different diseases. The extremely large shape parameter of the Weibull distribution from M9S might indicate a biased estimation (Friedrich et al., 2011), because some older cows in our dataset only have disease diagnoses in later parities. Hence, due to the inflated ρ from M9S, the health status from different lactations should be considered in separate runs (i.e., modelling strategies M1S or M3S). For modelling strategy M9Swd and ignoring diseases as explanatory variables, the ρ value of 1.48 was in line with LPL shape parameters from other Holstein dairy cattle populations, which ranged from 1.21 to 1.89 (Hultgren and Svensson, 2009; M'hamdi et al., 2010; Garcia-Ruiz et al., 2016). For the SNP based modelling strategies MSNP1 and MSNP2, ρ was identical (value 1.81).

Table 3.4: The shape parameter (ρ) of the Weibull distribution from different modelling strategies

Parameters[1]		Modelling strategy[2]								
		M1S			M3S	M3Swd	M9S	M9Swd	MSNP 1	MSNP 2
		Stage 1	Stage 2	Stage 3						
Lactation 1	ρ	1.48	1.48	1.49	2.51	1.54				
	SD_dis	0.001	0.002	0.002	0.061	-				
	SD_sub	0.010	0.011	0.008	0.058	0.005				
Lactation 2	ρ	1.66	1.70	1.85	2.38	2.10				
	SD_dis	0.006	0.013	0.003	0.021	-				
	SD_sub	0.010	0.009	0.011	0.017	0.006				
Lactation 3	ρ	2.09	2.08	2.06	2.27	2.13				
	SD_dis	0.013	0.025	0.008	0.029	-				
	SD_sub	0.017	0.020	0.016	0.014	0.011				
Lactations 1-3	ρ						4.55	1.48	1.81	1.81
	SD_dis						0.261	-	0.000	-
	SD_sub						0.053	0.013	0.000	0.000

[1]ρ = parameter of the Weibull distribution; SD_dis = standard deviation across different disease; SD_sub = standard deviation across different subsets for the same disease
[2]M1S = model with health status from different lactation stages in separate runs
M3S = model with health status considering three stages from one lactation simultaneously, different runs for different lactations
M3Swd = model without health status, different runs for different lactations
M9S = model with health status considering nine stages from three lactations simultaneously
M9Swd = model without health status, one run considering all lactations simultaneously
MSNP1 = model with one significant SNP, different runs for different SNP
MSNP2 = model considering six significant SNP simultaneously

Impact of specific diseases on the culling risk

The fixed effects of the herd, calving year, calving season and age at first calving had significant impact on culling risks, however, showing only slight differences for the different fixed effect class levels. A higher test-day milk production level in relation to the herd average was associated with a slight decline of culling risks.

Due to biological reasons and associated very low disease incidences, some diseases were excluded from some lactation stage-specific analyses (in analogy to Shabalina et al., 2019). For example, MFEV plays no role in first parity cows, and in stages 2 and 3 of later lactations. Detailed estimates for risk ratios from all modelling strategies are given in Supplementary Table S3.1 for udder diseases, in Supplementary Table S3.2 for claw disorders, in Supplementary Table S3.3 for metabolic disorders and in Supplementary Table S3.4 for female fertility disorders. Because of very similar estimates for the disease impact on LPL from modelling strategies M1S and M3S, and non-significant estimates from M9S, only

results from M1S are shown in Table 3.5. For all diseases, culling risk ratios increased with increasing lactation number. As expected, farmers prefer culling decisions for older cows with a disease diagnosis, compared to younger cows with the same disease.

The highest culling risks were observed for cows with MAST at the end and in the middle of lactation, as well as for cows with SMAST in the middle of lactation (Table 3.5). The estimated culling risks for udder diseases are in agreement with results by Pinedo et al. (2010), who identified highest culling risks for pregnant cows with a mastitis diagnosed in the period from 70 to 160 DIM. Accordingly, Roxström and Strandberg (2002) stated that the highest culling risk was due to mastitis, diagnosed in the middle of lactation. In contrast, Beaudeau et al. (1995) identified MAST during the dry period as predominant cow culling risk factor. Jensen et al. (1999) reported time-lagged culling decisions, implying that a large fraction of cows was diagnosed for MAST at the beginning or in the middle of lactation, but culled in the last lactation stage.

Table 3.5: Effects of disease diagnoses from different periods on culling risks (results from modelling strategy M1S, i.e., considering specific disease diagnoses from different lactation stages)[1]

Disease[2]	Lactation 1			Lactation 2			Lactation 3		
	Stage 1	Stage 2	Stage 3	Stage 1	Stage 2	Stage 3	Stage 1	Stage 2	Stage 3
MAST	1.29	1.49	1.88	1.74	2.14	2.15	1.95	2.59	2.50
SMAST	NS	NS	1.78	1.86	2.34	2.15	2.05	2.40	2.18
SU	NS	1.26	1.72	1.50	1.65	2.02	1.63	1.85	2.29
DD	NS	NS	1.59	1.27	1.40	1.74	1.44	1.53	1.89
WL	1.35	1.38	1.60	1.56	1.65	1.75	1.41	1.64	1.85
HYP	1.43	1.34	1.71	1.43	1.56	1.83	1.50	1.76	1.94
ACID	1.66			1.54			1.83		
KET	1.60			1.70			1.86		
MFEV				1.49			1.61		
ENDO	NS	1.36		1.32	1.71		1.52	1.72	
OCD		1.10			1.49			1.75	
CYST		1.28			1.55			1.76	
CLP		NS			1.58			1.72	

[1]Empty cells = no relevance of the disease in the respective lactation stage as explained in the manuscript text. NS = estimate not significant, *P*-value> 0.05.

[2]MAST = clinical mastitis; SMAST = subclinical mastitis; SU = sole ulcer; DD = digital dermatitis; WL = white line disease; HYP = interdigital hyperplasia; ACID = ruminal acidosis; KET = ketosis; MFEV = milk fever; ENDO = endometritis; OCD = ovarial cycle disorder; CYST = ovarial cysts; CLP = corpus luteum persistent

The risk ratios for culling due to claw disorders increased with increasing lactation stages (Table 3.5). The generally higher culling risk for lame cows compared to healthy cows was

reported by Rajala-Schultz and Gröhn (1999). In close agreement with our results, Cramer et al. (2009) estimated a culling risk of 1.72 for cows diagnosed for WLD, and of 1.26 for cows diagnosed for SU. Booth et al. (2004) identified differing culling risks for different claw disorders. For example, the culling risk of cows with a SU diagnosis increased with increasing lactation stage, but (and in contrast to our results) decreased for cows with a HYP diagnosis. Interestingly, with regard to DD, Booth et al. (2004) identified a lower culling risk ratio for diagnosed cows compared to healthy cows. Similarly, using historical population wide recorded culling and disease data, Shabalina et al. (2019) reported favorable estimates for longevity or survival definitions (e.g., stayability) for cows with a DD diagnosis.

However, in the present study, based on current data from selected large-scale contract herds, cows with a DD diagnosis always (i.e., for all lactations and all stages) had higher culling risks compared to healthy cows. The separate modelling strategy M1S, i.e., specifying the occurrence date for claw disorders via lactation stage definitions in separate runs, contributed to an increase of risk ratio significance levels for disease diagnoses in comparison to the modelling strategies M3S or M9S (see Supplementary Table S3.2).

Apart from ACID, culling risk ratios due to metabolic disorders were slightly larger for diagnoses recorded in later parities (Table 3.5). Our risk ratio estimates ranged from 1.49 to 1.61 for KET, and from 1.60 to 1.86 for MEFV, which reflect results from previous survival studies using Cox hazards model (Beaudeau et al., 1995; Gröhn et al., 1998). The metabolic disorder ACID in first parity cows was a major explanation for ongoing claw disorders (König et al., 2005), and significantly contributed to cow cullings in the present study. When modelling metabolic disorders from different lactations simultaneously (approach M9S), only diagnoses from the third lactation significantly influenced culling risks (see Supplementary Table S3.3), and diagnoses from earlier lactations were less important.

Inconsistent influence of ENDO on culling risks was reported in previous studies. For example, Gröhn et al. (1998) identified non-significant impact of ENDO diagnosed directly after calving, which reflects the results from our study. Based on modelling strategies M3S and M9S, culling risk ratios for cows with an ENDO diagnosis at the beginning in first lactation were even lower compared to the respective healthy cows (Supplementary Table S3.4). Relative hazard risk ratios of 1.5 and 1.4 for ENDO diagnosed cows after DIM 50 in first and second lactations (Beaudeau et al., 1995) confirm our estimates in later lactation stages when applying the separate modelling strategy M1S. The differences in culling risks for ENDO diagnosed early in lactation and in later stages might reflect the differences in disease pathogenicity. Endometritis early in lactation is mostly due to calving difficulties, but

ENDO diagnosed later has other reasons, e.g., bacterial infections (Sheldon and Owens, 2017). Oltenacu et al. (1990) and Gröhn et al. (1998) found increased culling risks for cows with a CYST diagnosis. In contrast, Rajala-Schultz and Gröhn (1999) reported quite low culling risks for CYST and OCD diagnosed in the period from calving to DIM 240 (0.4 - 0.8 for OCD, and 0.4 - 0.7 for CYST). Similar risk ratios smaller than 1 were estimated in the present study for OCD when considering diagnoses from all stages from three lactations simultaneously (modelling strategy M9S, Supplementary Table S3.4).

Genetic variances and heritability estimates for the length of productive life

According to Yazdi et al. (2002), heritabilities from Weibull hazard models can be estimated on a logarithmic scale, or as effective and equivalent heritability on the original scale. Heritabilities on a logarithmic scale are difficult to interpret, cannot be compared with heritability estimates from linear models, and were only weakly related with EBV reliabilities in genetic evaluations (Ducrocq, 1999). Hence, we focussed on the presentation and discussion of effective and equivalent heritabilities from the applied modelling approaches, which are given (plus the respective additive genetic variances) in Table 3.6.

The additive genetic variances for LPL from modelling strategy M1S were quite small for all runs with disease information from the first and second stages in parity 1 and all stages in parity 3 (range from 0.01 to 0.05). However, considering disease information separately in parity 2 substantially contributed to an increase of genetic LPL variances (up to 0.20). Moderate genetic variances for LPL also were estimated with disease indicators from parity 2 and modelling approaches M3S and M3Swd (0.21 and 0.23, respectively). Possible explanations for alterations of LPL genetic variances when considering indicator traits from different periods might be specific time related environmental or residual effects, contributing to an increase or a decrease of the genetic component (Mészáros et al., 2013a). For example, with regard to M1S, farmers have lactation stage specific strategies to treat diseased cows, potentially partly considered as genetic effect due to cow specific “preferential treatment”. The genetic LPL variance from M3S considering diseases from all stages within parity 1 simultaneously was larger (0.39) than from the modelling strategy M3Swd ignoring cow health (0.02). Accordingly, Roxström and Strandberg (2002) reported larger genetic variances when considering cause-specific longevity indicators, e.g., a genetic variance of 0.08 for mastitis-determined LPL, but of 0.03 for LPL when ignoring disease associated culling reasons.

Table 3.6: Estimated genetic parameters for the length of productive life

Parameters[1]		Modelling strategies[2]								
		M1S			M3S	M3S wd	M9S	M9S wd	MSNP1	MSNP2
		Stage 1	Stage 2	Stage 3						
Lactation 1	σ_g^2	0.02	0.03	0.20	0.39	0.02				
	SD_di	0.000	0.00	0.00	0.165	-				
	SD_su	0.005	0.00	0.00	0.034	0.00				
	h^2_{equ}	0.01	0.02	0.12	0.21	0.01				
	h^2_{eff}	0.02	0.03	0.17	0.28	0.02				
	ΔLPL	117.3	15.7	36.7	188.4	-				
Lactation 2	σ_g^2	0.20	0.20	0.19	0.21	0.23				
	SD_di	0.000	0.00	0.00	0.016	-				
	SD_su	0.000	0.00	0.01	0.013	0.00				
	h^2_{equ}	0.10	0.10	0.09	0.10	0.10				
	h^2_{eff}	0.17	0.17	0.16	0.17	0.19				
	ΔLPL	98.54	9.42	6.06	172.3	-				
Lactation 3	σ_g^2	0.03	0.02	0.01	0.04	0.06				
	SD_di	0.002	0.00	0.00	0.004	-				
	SD_su	0.009	0.00	0.00	0.003	0.00				
	h^2_{equ}	0.01	0.01	0.01	0.02	0.01				
	h^2_{eff}	0.03	0.02	0.01	0.04	0.06				
	ΔLPL	76.20	5.62	-	174.7	-				
Lactations 1-3	σ_g^2						0.79	0.02	0.13	0.13
	SD_di						0.048	-	-	-
	SD_su						0.025	0.002	0.000	0.000
	h^2_{equ}						0.36	0.01	0.05	0.05
	h^2_{eff}						0.44	0.02	0.12	0.12
	ΔLPL						440.51	-	-	-

[1] σ_g^2 = mean of genetic variance across different diseases; SD_dis = standard deviation of the genetic variance across different disease; SD_sub = standard deviation of the genetic across different subsets for the same disease; h^2_{equ} = equivalent heritability; h^2_{eff} = effective heritability

[2] M1S = model with health status from different lactation stages in separate runs

M3S = model with health status considering three stages from one lactation simultaneously, different runs for different lactations

M3Swd = model without health status, different runs for different lactations

M9S = model with health status considering nine stages from three lactations simultaneously

M9Swd = model without health status, one run considering all lactations simultaneously

MSNP1 = model with one significant SNP, different runs for different SNP

MSNP2 = model considering six significant SNP simultaneously

ΔLPL = mean difference in LPL between cows without diseases and in relation to cows with a disease

Interestingly, when using modelling strategy M1S, genetic variances for LPL partly altered when considering the cow health status for the same diagnosis from different lactations or lactation stages, but they were very similar when modelling different disease within stages or

lactations. Addressing M1S, with regard to all lactations and all stages, different types of diseases had similar effects on the genetic LPL variances. The SD of genetic LP variances from the different disease runs for same lactation stages were very small (range from 0 to 0.004 for the different stages). However, with regard to the remaining modelling strategies, different diseases had different influence on the genetic variances for LPL. For example for M3S, genetic LPL variances ranged from 0.28 (consideration of DD in first lactation) to 0.90 (consideration of ENDO in first lactation). Accordingly, the SD of genetic LPL variances from the different disease runs was quite large (0.165). In later lactations 2 and 3, genetic LPL variances were very similar for different disease indicator traits. The SD of genetic LPL variances from different disease runs was 0.016 in parity 2, and 0.004 in parity 3. Variation of genetic variances (SD = 0.048) was found when including different diseases in model M9S. The largest genetic LPL variance was estimated when including ENDO (0.90), but was close to 0.60 when modelling claw disorder diagnoses.

Heritabilities for LPL from M1S and considering diseases within stages 1 and 2 of first parity cows varied between 0.01 and 0.03 for h^2_{equ}, and between 0.01 and 0.05 for h^2_{eff} (Table 3.6). Comparable low heritabilities were estimated when ignoring disease information in modelling approaches M3Swd and M9Swd. Heritabilities for LPL were larger than 0.20 for M3S considering disease diagnoses from lactation 1, and larger than 0.30 for M9S. Alterations of genetic variances and heritabilities with progressing time (increasing lactations or DIM) are well known, especially for functional traits (e.g., Loker et al., 2011). As shown in Table 3.6, considered explanatory variables from different periods (here: disease indicators) contributed to alterations of genetic variances and heritabilities for the dependent trait (here: LPL). Hence, the disease status from different periods influenced genetic parameters unequally, probably due to different disease incidences in different lactations or lactation stages. Similarly, Santos et al. (2015) estimated different additive-genetic variances and heritabilities for milk flow when either including or ignoring milk yield as covariate in genetic statistical models. Furthermore, the interval (i.e., the measuring date of the response variable in relation to the explanatory variable) influenced estimates of genetic (co)variance components.

The question how to consider mutual effects between dependent traits is of increasing importance in dairy cattle breeding. For linear and threshold model applications, Gianola and Sorensen (2004) suggested structural equation modelling, to consider possible recursive relationships between explanatory and response variables. König et al. (2008) made a comprehensive evaluation, i.e., they compared genetic variances and heritabilities for claw disorders via linear and threshold models, either considering or ignoring mutual relationships

between claw disorders and milk yield from different test-days (very early and middle of lactation). Differences in genetic (co)variance components for claw disorders from different modelling approaches suggested deeper studies addressing model evaluation criteria, and model specifications according to biological systems as earliest proposed by Haldane and Priesly (1905).

However, in the present study, not only the genetic parameter estimates for LPL are of interest, but also the solutions for disease diagnoses from different recording periods on culling risks. Hence, from a practical perspective, it is imperative to modelling diseases as explanatory variable. In this regard, we suggest a modelling approach M9S, because diseases from different periods are considered simultaneously. However, the LPL heritabilities from M9S were significantly larger than from other modelling approaches, indicating a potential bias (as identified for the shape parameter in the present study). Nevertheless, the definition or consideration of a specific covariance structure for repeated disease diagnoses remains an open question. Furthermore, different cows with same diseases in different lactation stages contributed to differences in LPL (i.e., LPL of healthy minus LPL of diseased cows) (Table 3.6). In consequence, the LPL response variable altered across stages, with possible influence on genetic parameter estimates. Accordingly, Heise et al. (2016) clearly evidenced "that genetic background of survival varies between different periods of a cow's lifetime".

To our knowledge, this is a first study considering SNP markers as explanatory variables via Weibull proportional hazard modelling. The LPL heritabilities from MSNP1 and MSNP2 were on the same low level as estimated with approaches M3Swd and M9Swd. Comparability with estimates from modelling approaches ignoring disease information was expected, because the specific SNP effects only explained minor proportions of the genetic LPL variances (see the next chapter "genome-wide associations"). Nevertheless, recently, van der Heide et al. (2020) suggested a combination of genomic estimated breeding values with phenotypic indicator traits. Such modelling approach contributed to best predictions of cow survival and favoured modelling evaluation criteria.

Genome-wide associations and gene annotations

The Manhattan plot for LPL is shown in Figure 1. Not a single SNP surpassed the strict Bonferroni-corrected threshold. Six SNP surpassed the FDR corrected P-value ≤ 5 %. The SNP were located on BTA 1, 4, 10, 13 and 28.

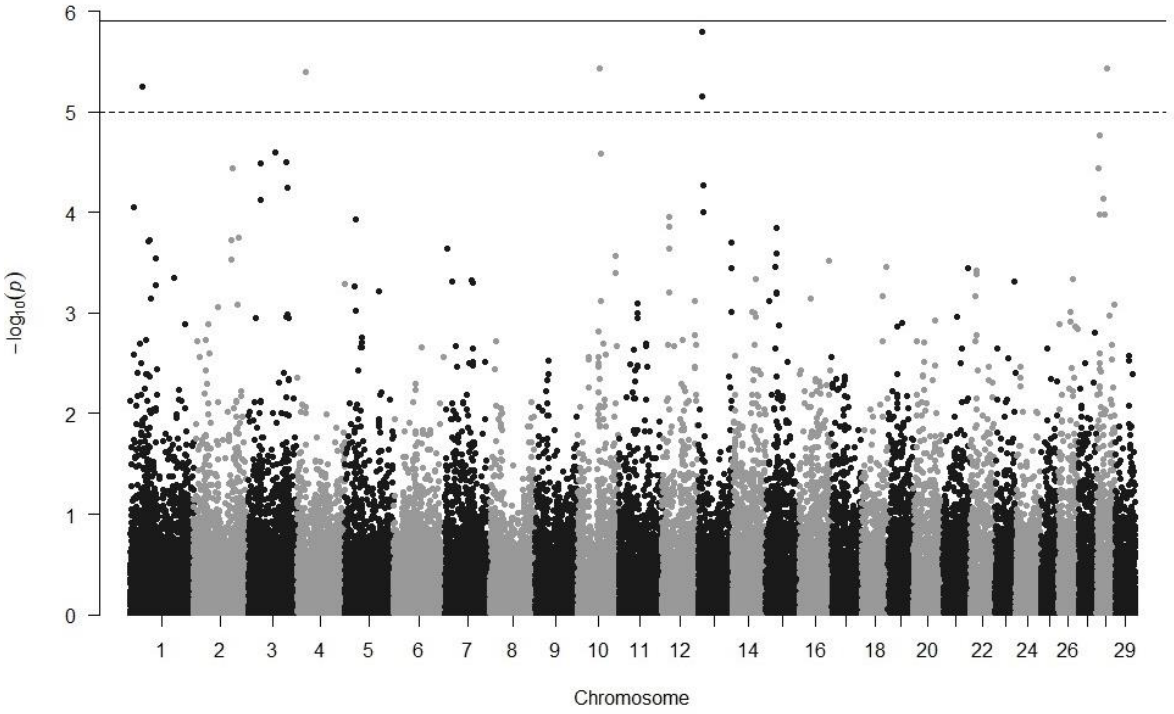

Figure 3.1: Manhattan plot from single-marker GWAS for the length of productive life. The solid line represents the Bonferroni-corrected threshold ($P_{Bonf} = 1.26 \times 10^{-6}$) and the points above the dashed line are significantly associated SNP according to a false discovery rate

We did not find any potential candidate gene in close distance to the significantly associated SNP at 31 Mb on BTA1. A genome scan conducted in Nellore cattle suggested one significant SNP for stayability on BTA1 at 64 Mb (Barreto Amaral Teixeira et al., 2017). The potential candidate gene *ETV1* in close chromosomal distance to the significant SNP ARS-BFGL-NGS-38914 on BTA4 influenced milk production (Raschia et al., 2018). Poor productivity is one reason for early cow disposals (Shabalina et al., 2019), but in the present study, we accounted for individual milk yield in relation to the herd average. The significantly associated SNP ARS-BFGL-NGS-19199 on BAT10 at 57 Mb is located in close chromosomal distance to the *ONECUT1* (one cut homeobox 1) gene, which influences immune responses to bovine streptococcal mastitis (Lewandowska-Sabat et al., 2018). In Holstein cattle, Zhang et al. (2016) identified one highly significant SNP on BTA10 located at 67 Mb, which was associated with ovulation rate. Associations between SNP within a window

of 59 to 63 Mb on BTA13 and longevity in Holstein and Fleckvieh populations were reported in previous studies (Daetwyler et al., 2008; Mészáros et al., 2014; Nayeri et al., 2017). The two significant SNP ARS-BFGL-NGS-25574 and ARS-BFGL-NGS-113280 on BTA13 from the present analysis are located within close chromosomal distance covering a segment of only 53 kb. The *MACROD2* gene is also located in this segment. *MACROD2* influences disease resistance against Bovine tuberculosis (González-Ruiz et al., 2019). The significant SNP (Hapmap39577-BTA-63767) on BTA28 at 24 Mb is located in close chromosomal distance to the *SIRT1* gene, which has impact on fat mass and body size in bovine (Li et al., 2013).

Some other studies (Cole et al., 2009; Cole et al., 2011; Raven et al., 2014) reported significant SNP associations with different definitions for longevity traits in Holstein and Jersey cows, but the detected signals substantially differed with the identified signals in the present study. Nevertheless, the minor allele frequencies of the six significant SNP as listed in Table 3.7were quite low, in the range from 0.05 to 0.08, with possible influence on the detection power in GWAS. Tabangin et al. (2009) studied the influence of minor allele frequencies on false positive associations, and neglected any concerns in this regard. Gorlov et al. (2008) highlighted the importance of rare SNP, because 60% of the variation in the human genome is explained by variants with a minor allele frequency smaller than 0.05.

Impact of significantly associated SNP on the culling risk

With regard to modelling strategies MSNP1 and MSNP2, the two homozygous SNP genotypes received the codes 0 and 2, and the heterozygous genotype received the code 1. In survival analyses, the effect of the heterozygous genotype was defined as a reference value for the culling risk. The estimates for SNP genotype dependent culling risk ratios from MSNP1 and MSNP 2 are given in Table 3.7. Generally, only minor impact of single SNP on culling risks was identified. The SNP with the strongest effect on LPL was Hapmap39577-BTA-63767 on BTA28, with a relative culling risk of 0.65 for the favourable AA genotype and a corresponding P-value of 0.08 in both modelling strategies. Also, the CC genotype of the SNP ARS-BFGL-NGS-113280 on BTA13 was the favorable. The favorable genotypes from both SNP Hapmap39577-BTA-63767 and ARS-BFGL-NGS-113280 had a very low frequency. The cows with the homozygous CC genotype for SNP ARS-BFGL-NGS-19199 had a 1.09 times higher culling risk than cows with the heterozygous genotype TC. The culling risks for cows with homozygous genotypes for SNP on BTA1 and on BTA4 only slightly differed from the culling risks of the heterozygous reference genotypes. Szyda et al. (2011) reported

influences of LEP-R25C gene polymorphisms from a model using a Weibull hazard function. In this regard, cows with genotyped CC had a 3.14 times higher culling risk compared to cows with the heterozygous genotype. Generally, the small no. of significantly associated SNP in genome-wide associations and their minor influence in survival analyses underline the strong polygenetic background of LPL.

Table 3.7:Culling risk ratios considering significant SNP markers from genome wide associations studies for the length of productive life

SNP marker	Genotype	No. of cows	Modelling strategy[2]			
			MSNP1		MSNP2	
			Risk ratio[1]	P-value	Risk ratio	P-value
BTA-18114-no-rs	TT	23	0.81	0.33	0.80	0.31
	TC	850	1.00		1.00	
	CC	6,628	1.01	0.79	1.01	0.82
ARS-BFGL-NGS-38914	AA	50	0.96	0.78	0.96	0.77
	AG	1,119	1.00		1.00	
	GG	6,332	1.02	0.64	1.02	0.66
ARS-BFGL-NGS-19199	TT	6,364	1.00	0.99	1.00	0.99
	TC	1,096	1.00		1.00	
	CC	41	1.09	0.62	1.10	0.57
ARS-BFGL-NGS-25574	AA	6,731	1.06	0.17	1.15	0.05
	AG	759	1.00		1.00	
	GG	11	0.68	0.22	0.74	0.39
ARS-BFGL-NGS-113280	TT	6,670	1.01	0.74	0.91	0.16
	TC	818	1.00		1.00	
	CC	13	0.73	0.28	0.87	0.68
Hapmap39577-BTA-63767	AA	18	0.65	0.08	0.65	0.08
	AC	761	1.00		1.00	
	CC	6,722	1.03	0.43	1.03	0.42

[1] The reference value is the estimate for the heterozygous genotype indicated with a risk ratio of 1.00 (no estimate of a *P*-value)
[2]MSNP1 = model with one significant SNP, different runs for different SNP; MSNP2 = model considering six significant SNP simultaneously

CONCLUSIONS

The influence of specific diseases on LPL was stronger for diagnoses from later lactations and lactation stages compared to diagnoses from first parity cows. Among all diseases, MAST and SMAST from the second and third lactation had strongest detrimental impact on LPL. Especially for claw and female fertility disorders, minor influence of first lactation diseases on LPL was observed. Consideration of the disease status in proportional Weibull hazard models contributed to an increase of genetic variances and heritabilities for LPL, especially

when considering all disease diagnoses simultaneously in approach M9S. Genome-wide associations detected six SNP significantly associated with LPL (according to the FDR threshold), which were located on the five different chromosomes BTA1, BTA4, BTA10, BTA 28 and BTA13 (two SNP). Survival modelling strategies with single SNP contributed to a slight LPL heritability increase (in comparison to modelling strategies ignoring health status or SNP information). However, the identified culling risk ratios for specific SNP were quite low, indicating the strong polygenetic background of LPL.

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Appendix

Supplementary table S3.1: Effect of clinical and subclinical mastitis on culling risk

Disease[1]	Period of disease diagnosis		Modelling strategy[2]		
			M1S	M3S	M9S
MAST	Lactation 1	Stage 1	1.29	1.11	1.13
		Stage 2	1.49	1.64	1.32
		Stage 3	1.88	1.95	1.30
	Lactation 2	Stage 1	1.74	1.44	1.28
		Stage 2	2.14	2.01	1.70
		Stage 3	2.15	1.82	1.37
	Lactation 3	Stage 1	1.95	1.77	1.56
		Stage 2	2.59	2.43	2.41
		Stage 3	2.50	1.81	1.74
SMAST	Lactation 1	Stage 1	NS	NS	NS
		Stage 2	NS	1.60	1.69
		Stage 3	1.78	1.90	NS
	Lactation 2	Stage 1	1.86	1.54	NS
		Stage 2	2.34	2.26	2.08
		Stage 3	2.15	2.25	1.79
	Lactation 3	Stage 1	2.05	2.03	2.07
		Stage 2	2.40	2.40	2.50
		Stage 3	2.18	1.94	NS

[1]MAST = clinical mastitis; SMAST = subclinical mastitis.
[2]M1S = model with health status from different lactation stages in separate runs
M3S = model with health status considering three stages from one lactation simultaneously, different runs for different lactations
M9S = model with health status considering nine stages from three lactations simultaneously
NS = estimate not significant, P-value > 0.05.

Supplementary table S3.2: Effect of claw disorders on culling risk

Disease[1]	Period of disease diagnosis		Modelling strategy[2]		
			M1S	M3S	M9S
SU	Lactation 1	Stage 1	NS	NS	NS
		Stage 2	1.26	1.15	NS
		Stage 3	1.72	1.42	NS
	Lactation 2	Stage 1	1.50	1.32	NS
		Stage 2	1.65	1.57	1.31
		Stage 3	2.02	1.65	1.32
	Lactation 3	Stage 1	1.63	1.44	1.41
		Stage 2	1.85	1.85	1.67
		Stage 3	2.29	1.68	1.53
DD	Lactation 1	Stage 1	NS	NS	NS
		Stage 2	NS	1.13	NS
		Stage 3	1.59	1.47	NS
	Lactation 2	Stage 1	1.27	NS	NS
		Stage 2	1.40	1.36	1.32
		Stage 3	1.74	1.49	1.27
	Lactation 3	Stage 1	1.44	1.38	1.41
		Stage 2	1.53	1.59	1.42
		Stage 3	1.89	1.50	1.42
WLD	Lactation 1	Stage 1	1.35	NS	NS
		Stage 2	1.38	1.33	NS
		Stage 3	1.60	1.97	NS
	Lactation 2	Stage 1	1.56	1.44	NS
		Stage 2	1.65	1.48	1.47
		Stage 3	1.75	1.68	NS
	Lactation 3	Stage 1	1.41	1.44	1.60
		Stage 2	1.64	1.67	1.51
		Stage 3	1.85	1.70	1.62
HYP	Lactation 1	Stage 1	1.43	NS	NS
		Stage 2	1.34	NS	NS
		Stage 3	1.71	2.05	NS
	Lactation 2	Stage 1	1.43	1.29	NS
		Stage 2	1.56	1.39	1.38
		Stage 3	1.83	1.71	NS
	Lactation 3	Stage 1	1.50	1.48	1.55
		Stage 2	1.76	1.71	1.62
		Stage 3	1.94	1.62	1.60

[1]SU = sole ulcer; DD = digital dermatitis; WLD = white line disease; HYP = interdigital hyperplasia.
[2]M1S = model with health status from different lactation stages in separate runs; M3S = model with health status considering three stages from one lactation simultaneously, different runs for different lactations; M9S = model with health status considering nine stages from three lactations simultaneously; NS = estimate not significant, P-value > 0.05.

Supplementary table S3.3: Effect of metabolic diseases on culling risk

Disease[1]	Period of disease diagnosis		Modelling strategy[2]		
			M1S	M3S	M9S
ACID	Lactation 1	Stage 1	1.66	1.85	NS
	Lactation 2	Stage 1	1.54	2.27	NS
	Lactation 3	Stage 1	1.83	2.57	2.05
KET	Lactation 1	Stage 1	1.60	1.16	NS
	Lactation 2	Stage 1	1.70	1.68	NS
	Lactation 3	Stage 1	1.86	2.14	1.75
MFEV	Lactation 2	Stage 1	1.49	1.45	NS
	Lactation 3	Stage 1	1.61	1.65	1.36

[1]ACID = ruminal acidosis; KET = ketosis; MFEV = milk fever.
[2]M1S = model with health status from different lactation stages in separate runs
M3S = model with health status considering three stages from one lactation simultaneously, different runs for different lactations
M9S = model with health status considering nine stages from three lactations simultaneously
NS = estimate not significant, P-value > 0.05.

Supplementary table S3.4: Effect of reproductive diseases on culling risk

Disease[1]	Period of disease diagnosis		Modelling strategy[2]		
			M1S	M3S	M9S
ENDO	Lactation 1	Stage 1	NS	0.90	0.80
		Stage 2	1.36	1.52	NS
	Lactation 2	Stage 1	1.32	1.26	1.13
		Stage 2	1.71	1.62	NS
	Lactation 3	Stage 1	1.52	1.75	1.46
		Stage 2	1.72	1.67	1.55
OCD	Lactation 1	Stage 2	1.10	1.17	0.87
	Lactation 2	Stage 2	1.49	1.59	1.16
	Lactation 3	Stage 2	1.75	1.97	1.65
CYST	Lactation 1	Stage 2	1.28	1.35	NS
	Lactation 2	Stage 2	1.55	1.58	1.18
	Lactation 3	Stage 2	1.76	1.81	1.67
CLP	Lactation 1	Stage 2	NS	1.32	NS
	Lactation 2	Stage 2	1.58	1.53	1.29
	Lactation 3	Stage 2	1.72	1.79	1.59

[1]ENDO = endometritis; OCD = ovarial cycle disorder; CYST = ovarial cysts; CLP = corpus luteum persistens.
[2]M1S = model with health status from different lactation stages in separate runs
M3S = model with health status considering three stages from one lactation simultaneously, different runs for different lactations
M9S = model with health status considering nine stages from three lactations simultaneously
NS = estimate not significant, P-value > 0.05.

CHAPTER 4

Proofs for genotype by environment interactions considering pedigree and genomic data from organic and conventional cow reference populations

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ABSTRACT

The aim of the present study was to prove genotype by environment interactions (**G×E**) for production, longevity and health traits considering conventional and organic German Holstein dairy cattle sub-populations. The full dataset included 141,778 Holstein cows from 57 conventional herds and 7,915 cows from 9 organic herds. The analysed traits were first-lactation milk yield (**MY**) and fat percentage (**FP**), the length of productive life (**LPL**) and the health traits mastitis (**MAST**), ovarian cycle disorders (**OCD**) and digital dermatitis (**DD**) in first lactation. A subset of phenotyped cows was genotyped and used for the implementation of separate cow reference populations. After SNP quality controls, the cow reference sets considered 40,830 SNP from 19,700 conventional cows and the same 40,830 SNP from 1,282 organic cows. The proof of possible G×E was made via multiple-trait model applications, considering same traits from the conventional and organic population as different traits. In this regard, pedigree (**A**), genomic (**G**) and combined relationship matrices (**H**) were constructed. For the production traits, heritabilities were very similar in both populations organic and conventional, i.e., close to 0.70 for FP and close to 0.40 for MY. For low heritability health traits and LPL, stronger heritability fluctuations were observed, especially for DD with 0.05 ± 0.01 (organic, **A** matrix) to 0.33 ± 0.04 (conventional, **G** matrix). Quite large genetic correlations between same traits from the two environments were estimated for production traits, especially for high heritability FP. For LPL, the genetic correlation was 0.67 (**A** matrix) and 0.66 (**H** matrix). The genetic correlation between LPL organic with LPL conventional was 0.94 when considering the **G** matrix, but only 213 genotyped cows were included. For health traits, genetic correlations were throughout lower than 0.80, indicating possible G×E. Genetic correlations from the different matrices **A**, **G** and **H** for health and production traits followed the same pattern, but the estimates from **G** for health traits were associated with quite large standard errors. In genome wide association studies, significantly associated SNP for production traits overlapped in the conventional and organic population. In contrast, for low heritability LPL and health traits, significantly associated SNP and annotated potential candidate genes differed in both populations. In this regard, significantly associated SNP for MAST from conventional cows were located on Bos taurus autosomes (**BTA**) 6 and 19, but on BTA 1, 10, and 22 in the organic population. For the remaining health traits and LPL, different potential candidate genes were annotated, but the different genes reflect similar physiological pathways. We found evidence of G×E for low heritability functional traits, suggesting different breeding approaches in organic and conventional

populations. Nevertheless, for a verification of results and implementation of alternative breeding strategies, it is imperative to increase the organic cow reference population.
Key words: Genotype by environment interactions, organic, conventional, genetic correlations, genome wide associations

INTRODUCTION

For more than 10 years, implemented national and international sire reference populations have been used for the estimation of genomic breeding values (**GBV**) for traits from official recording systems with moderate to large accuracy (Lund et al., 2010). Sire reference sets usually represent intensively pre-selected sires, implying possible biases in genomic predictions (Patry and Ducrocq, 2009). Consequently, current genomic selection schemes additionally consider cow reference populations, ideally representing cow records from a random sample of herds. Furthermore, cow reference sets are imperative when implementing genomic evaluations for novel functional traits (Swalve and König, 2007). Especially for health traits, moderate prediction accuracies were derived when considering a large number of genotyped cows from large-scale commercial herds (e.g., Naderi et al., 2018). Nevertheless, in the dataset of genotyped cows from large-scale German herds, Yin and König (2018) identified first signs for genotype by environment interactions (G×E) when stratifying the data according to phenotypic or genetic herd parameters.

Stronger impact of G×E is assumed when considering challenging environmental descriptors, such as heat stress indicators (Nguyen et al., 2016) or production system particularities (König et al., 2005). An obvious production system differentiation addresses the farming system organic or conventional. Such particularities, also for milk production, are defined in the basic principles for organic farming (IFOAM, 2020). Accordingly, longevity and health traits play an overriding role for organic dairy producers, but they have limited possibilities to prevent or to treat diseases, e.g., via antibiotic applications (Borell and Sørensen, 2004). An alternative and sustainable solution addresses the development of breeding strategies on improved cow health in organic populations. However, independent organic breeding programs are very rare or small in population size, and utilization of sires from conventional testing schemes raises the question of possible G×E.

Quantitative-genetic G×E studies considering cows from the two systems organic and conventional were carried out for production traits (Nauta et al., 2006), longevity (Ahlman et al., 2011; Pfeiffer et al., 2016), female fertility (Sundberg et al., 2010; Liu et al., 2019) and some health disorders (Pfeiffer et al., 2016). In all above-mentioned studies, classical

multiple-trait models have been applied, i.e., defining same traits in organic and conventional systems as different traits, and using pedigree relationships to estimate genetic correlations. Robertson (1959) suggested a genetic correlation lower than 0.80 as an indicator for considerable G×E. The existence of G×E might lead to re-rankings of genotypes in different environments, and consequently to limited genetic gain in organic populations. In simulations, Mulder et al. (2006) and Slagboom et al. (2019) identified strong sire re-rankings for genetic correlations lower than 0.65.

A more accurate estimation of genetic (co)variance components and breeding values may be possible when modeling the genomic relationship matrix (**G**) (Veerkamp et al., 2011). Potential obstacles in predictions, such as lacking pedigree information and insufficient genetic connectedness, can be avoided, because the **G** matrix is built on identity-by-state rather than identity-by-descent information (Yin et al., 2014). Nevertheless, it remains a challenge to establish specific organic reference populations for genomic predictions. In the framework of a European low input breeding approach, a quite small number of 930 genotyped Brown Swiss cows was considered to implement genomic selection for novel functional traits (Kramer et al., 2014).

Furthermore, large-scale genotyping of cows from organic herds allows the estimation of SNP effects in genome wide association studies (**GWAS**), and to inferring potential candidate genes, which might be specific for the organic production environment. With regard to cow reference populations from conventional herds, several studies identified significantly associated SNP and potential candidate genes for longevity, and a few GWAS focused on health disorders. Significant associations for SNP with longevity have been identified on BTA7 in U.S. Holsteins on BTA 9, 11, 17, 20 (Cole et al., 2011), on chromosome X in Australian Holstein and Jersey cattle (Raven et al., 2014), on BTA 5, 6, 8 and 14 in German-Austrian Fleckvieh (Mészáros et al., 2014) and on BTA 6 and 18 in a meta-analysis including Holstein, Nordic Red Dairy and Jersey cattle from Denmark, Sweden and Finland (Zhang et al., 2016). The most important diseases including mastitis, ovarian cycle disorders and digital dermatitis are complex traits with polygenic inheritance. Genes influencing diseases may be involved in the many biological processes. Therefore, it remains a challenge to infer significant SNP associations with diseases (Daetwyler et al., 2008), especially for small cow sample sizes (Hayes et al., 2009).

So far, to the best of our knowledge, there were no attempts to implement organic cow reference populations for GWAS and for the detection of G×E. Consequently, we focused on the implementation of a large cow reference population from large-scale commercial herds

plus on a smaller reference population only including cows from organic herds with a long organic breeding history. Both reference populations were used (i) to estimate heritabilities and variance components for production, longevity and health traits, (ii) to explore possible G×E for these traits using the genetic correlation approach, and (iii) to compare SNP associations and annotated potential candidate genes for the traits of interest in both systems.

MATERIALS AND METHODS

Cow traits

Production, longevity and health traits for Holstein cows considered data records from 9 organic and 57 conventional herds located in the federal states Mecklenburg-West Pomerania, Berlin-Brandenburg and Hesse, Germany. All herds participated in German health trait monitoring projects, implying close collaborations among herd managers, veterinarians and breeding organizations. For all trait categories, we considered the first calving years from 1998 to 2019 for cows from organic and from 2000 to 2016 for cows from conventional herds. With the aim of lactation analyses for production traits and diseases, we restricted the data to an almost complete 305-d lactation length. The respective requirement was a minimum of eight test-day records per cow and lactation. Lactation records with fewer test-day observations were excluded. Furthermore, data editing excluded cows with an age at first calving lower than 18 and larger than 42 months, as well as cows changing the herd.

Production traits included first lactation records for milk yield (**MY**) and fat percentage (**FP**). Longevity was defined as the length of productive life (**LPL**), i.e., the period from the first calving to the culling date. For LPL, we only considered cows with a known culling date, implying the exclusion of censored records for alive cows (22% of the cows) from the recent calving years. Such exclusion might bias genetic parameter estimations, but own previous survival analyses based on different sub-datasets and LPL definitions indicated quite stable results (Shabalina et al., 2020).

Considered health disorders were clinical mastitis (**MAST**), ovarian cycle disorders (**OCD**) including silent estrus, ovarian cysts and corpus luteum persistent, and the claw disorder digital dermatitis (**DD**). Diseases were recorded according to the definitions of the hierarchical diagnosis key as introduced by Stock et al. (2013). For at least one entry during first lactation for the respective disease, the cow received the score 1 (diseased); otherwise a score 0 was assigned for healthy cows. The data editing strategy with the requirements for the number of official test-days per lactation implied to ignore records from cows which were culled early in lactation. However, the number of cows with culling dates early in lactation

was quite small with less than 5%, and approximately 50% of the cows with an early culling date had a disease diagnosis. Disease trait selection for the present study considered the diseases with highest incidences as identified by Shabalina et al. (2019).

The number of records and descriptive statistics for production traits and LPL for cows kept in organic and conventional herds are given in Table 4.1. The incidences for the three diseases MAST, OCD and DD are indicated in Table 4.2.

Table 4.1: Descriptive statistics for milk yield (MY, kg), fat (FP, %) and length of productive life (LPL, days) from all and genotyped cows in organic and conventional production systems. Standard deviations in brackets

Trait	All cows		Genotyped cows	
	Organic	Conventional	Organic	Conventional
No. of records (cows) for production traits	7,915	141,778	1,159	16,660
MY, kg	7,070.28 (1,773.53)	8,810.25 (1,616.03)	7,742.60 (1,714.39)	8,959.39 (1,568.86)
FP, %	3.90 (0.48)	3.90 (0.47)	3.89 (0.45)	3.84 (0.45)
No. of records (cows) for LPL	6,084	100,945	236	6,498
LPL, days	1,342 (809)	1,179 (626)	1,565 (982)	777 (468)

Table 4.2: Incidences (%) for disease traits recorded in first-lactation German Holstein cows in organic and conventional herds

Disease[1]	All cows		Genotyped cows	
	Organic	Conventional	Organic	Conventional
No. of cows	3,689	100,114	758	15,837
MAST	9.58	23.15	14.10	23.86
OCD	28.81	28.19	33.93	27.54
DD	8.51	12.84	25.03	15.41

[1]MAST = Mastitis, OCD = ovarian cycle disorders, DD = digital dermatitis.

Genotypes

Holstein cows were genotyped with the Illumina *BovineSNP50 BeadChip V2* (5,403 cows from conventional and 997 cows from organic herds) and with the Illumina *Bovine Eurogenomics 10K low-density chip* (15,913 cows from conventional and 297 cows from organic farms). Animals with the low density 10K genotypes were imputed to the 50K level

as done for national official German genetic evaluations (Segelke et al., 2012). Genotyping quality control was performed using PLINK v1.90b5.2 (Purcell et al., 2007). The filtering criteria for SNP were: 1) call rate larger than 0.90; 2) minor allele frequency larger than 0.01; 3) non-significant deviation from Hardy-Weinberg equilibrium (*P*-value>1×10^{-3}); and 4) consideration of SNP located on autosomes. Genotyped animals with a call rate smaller than 0.90 and a genomic relatedness larger than 0.95 were excluded. The final genotype dataset included 40,830 SNP from 20,982 Holstein cows (19,700 cows from conventional and 1,282 cows from organic herds).

Statistical Models

Estimation of genetic parameters. In bivariate animal models, same traits recorded in organic and conventional production systems were considered as two different traits. In this regard, pedigree- (**A**), genomic (**G**) (according to VanRaden, 2008) and combined relationship matrices (**H**) (according to Legarra et al., 2009) were considered. The genetic-statistical model 1 was defined as follows:

$$\begin{bmatrix}\mathbf{y_1}\\ \mathbf{y_2}\end{bmatrix} = \begin{bmatrix}\mathbf{X_1} & \mathbf{0}\\ \mathbf{0} & \mathbf{X_2}\end{bmatrix}\begin{bmatrix}\boldsymbol{\beta_1}\\ \boldsymbol{\beta_2}\end{bmatrix} + \begin{bmatrix}\mathbf{Z_1} & \mathbf{0}\\ \mathbf{0} & \mathbf{Z_2}\end{bmatrix}\begin{bmatrix}\mathbf{a_1}\\ \mathbf{a_2}\end{bmatrix} + \begin{bmatrix}\mathbf{e_1}\\ \mathbf{e_2}\end{bmatrix} \quad [1]$$

where $\mathbf{y_i}$ was the observation vector for production traits, health traits, or LPL from the *i*th production system ($i = 1$ indicating the organic production system and $i = 2$ indicating the conventional production system); $\boldsymbol{\beta_i}$ was the vector of fixed effects including herd, calving year, calving season (including three classes: Jan. to Apr., May to Sep., and Oct. to Dec.), age at first calving (including four classes: 20-23, 24-26, 27-29, > 30 months) and lactation length as a covariate (linear regression) for MY, FP and health traits. For LPL, the covariate (linear regression) was the difference in milk yield from the first test-day in relation to the herd average (linear regression), in order to correct for a delayed farmer culling decision due to high milk yield of a cow in early lactation; $\mathbf{a_i}$ was the vector of random additive genetic effects; and $\mathbf{e_i}$ was the vector of random residual effects; $\mathbf{X_i}$, and $\mathbf{Z_i}$ were the incidence matrices for fixed and additive-genetic effects, respectively. Vector $\mathbf{a}\sim N(0; \mathbf{K}\otimes\mathbf{G_0})$, where **K** was a relationship matrix which equaled to **A**, **G** or **H**. The combined **H** matrix was computed by blending **A** and the weighted genomic relationship matrix ($\mathbf{G_w}$) (Legarra et al., 2009). $\mathbf{G_w}$ was calculated as follows: $\mathbf{G_w} = (0.95 \times \mathbf{G_1} + 0.05 \times \mathbf{A_{22}})$, where $\mathbf{A_{22}}$ is the submatrix of the pedigree-based relationship matrix for genotyped animals. $\mathbf{G_0}$ was a 2-by-2 matrix with (co)variances of traits measured in the two different production systems, and $\otimes$ denotes the

Kronecker product. Vector $\mathbf{e_i} \sim N(0; \mathbf{I}\sigma^2_{e_i})$, where **I** was an identity matrix and $\sigma^2_{e_i}$was the residual variance for the *i*th trait. Residual covariances did not exist, because cows represented either the organic or the conventional production system. The genetic-statistical analyses were performed using the AI-REML algorithm as implemented in the DMU software package (Madsen and Jensen, 2013).

Genome-wide association study. A single SNP linear mixed model as implemented in the software package GCTA v1.91.5beta (Yang et al., 2011) was used to conduct GWAS for production, health traits and LPL in both production systems separately. The respective model 2 was defined as follows:

$$y_{ijkl} = \beta_i + g_j + SNP_k + e_l \quad [3]$$

y_{ijkl} = phenotypes for production traits, health traits or LPL in both systems; β_i = vector of fixed effects and covariates as defined in model 1; g_j = vector of random additive genetic animal effects with g ~ N (0, $\mathbf{G_y}\sigma_g^2$), where $\mathbf{G_y}$ was the genomic relationship matrix (according to Yang et al., 2011) and σ_g^2 the genomic variance; SNP_k = vector containing the respective marker genotype (0, 1 or 2); e_l = vector of random residual effects with e ~ N (0, $\mathbf{I}\sigma_e^2$), and σ_e^2 was the residual variance.

The genome-wide significance level according to the Bonferroni-corrected threshold (P_{Bonf} = 0.05/40,830 SNP markers) was 1.22×10^{-6}. In addition, a less stringent candidate significance threshold was used, i.e., $P_{cand} = 1\times10^{-4}$ (Kurz et al., 2019). For the identification of potential candidate genes, we focussed on a chromosomal distance 100 kb upstream and downstream from the significantly associated SNP. Functional annotations of potential candidate genes were queried from the ENSEMBL database (Zerbino et al., 2018).

RESULTS AND DISCUSSION

Heritabilities in organic and conventional production systems

Table 4.3 includes the heritability estimates for production traits, LPL and health traits in organic and conventional production systems using the **A**, **G** and **H** matrices. The heritabilities for MY in the conventional and organic production systems only showed minor differences. Heritabilities for MY conventional were 0.43 and for MY organic 0.48 when using the **A** matrix, and 0.44 and 0.36, respectively, when using the **G** matrix. Heritabilities from the **H** matrix ranged in-between. In Austrian Fleckvieh cattle, Pfeiffer et al. (2017) estimated a heritability of 0.63 for milk yield in the organic farming system, of 0.59 when

considering low input conventional farms, and of 0.65 for cows kept in high input conventional herds. In Swedish Holstein, Sundberg et al. (2010) reported smaller heritabilities for milk yield in organic (0.27) than in conventional herds (0.35). In Dutch Holstein cows, Nauta et al. (2006) identified significantly different heritabilities for milk yield in organic (0.70) and in conventional (0.48) herds. In the present study, the heritabilities for FP using the **A**, **G** and **H** matrix were very similar in conventional (0.74, 0.70 and 0.73, respectively) and in organic (0.71, 0.75 and 0.74, respectively) farming systems, reflecting the estimates in Dutch Holstein (Nauta et al., 2006).

Table 4.3: Heritabilities for same traits recorded in conventional (h^2_{conv}) and organic (h^2_{org}) herds from bivariate models using pedigree- and SNP-based relationship as well as from the single step approach

Trait[1]	Pedigree-based		SNP-based		Single step approach	
	h^2_{org}	h^2_{conv}	h^2_{org}	h^2_{conv}	h^2_{org}	h^2_{conv}
Milk, kg	0.43 (0.02)	0.48 (0.01)	0.44 (0.05)	0.36 (0.01)	0.44 (0.02)	0.46 (0.01)
Fat, %	0.71 (0.02)	0.74 (0.01)	0.75 (0.03)	0.70 (0.01)	0.74 (0.02)	0.75 (0.01)
LPL[2], days	0.12 (0.02)	0.08 (0.01)	0.09 (0.04)	0.03 (0.01)	0.18 (0.02)	0.12 (0.01)
MAST	0.11 (0.03)	0.06 (0.01)	0.06 (0.06)	0.03 (0.01)	0.08 (0.02)	0.04 (0.01)
OCD	0.15 (0.03)	0.07 (0.01)	0.07 (0.07)	0.02 (0.01)	0.13 (0.03)	0.05 (0.01)
DD	0.33 (0.04)	0.08 (0.01)	0.10 (0.06)	0.05 (0.01)	0.18 (0.03)	0.05 (0.01)

[1]LPL = length of productive life, MAST = Mastitis, OCD = ovarian cycle disorders, DD = digital dermatitis.
[2]Due to the failed convergence for the SNP-based approach, the convergence criterion was relaxed to 1.0d-1 for the difference in variance estimates and to 1.0d-8 for the norm of the gradient vector (only for these specific LPL runs using **G** matrix)

The heritabilities for LPL when modelling the **A** matrix were 0.12 in organic and 0.08 in conventional herds. Estimates are comparable with results from Ahlman et al. (2011) in Swedish organic (0.09) and conventional Holstein cows (0.13). Heritabilities for LPL slightly differed when modelling the **G** or **H** matrix, but as identified for **A**, the LPL heritabilities were larger in the organic than in the conventional population.

Heritabilities for health traits were low to moderate in the range from 0.02 for OCD in conventional herds and modelling **G** to 0.33 for DD in organic herds and considering **A**. As indicated for production traits, heritabilities for health traits from the single step approach ranged in-between, but were closer to **A** than to **G** matrix estimates. Heritabilities for MAST are comparable with results from Parker Gaddis et al. (2014) in US dairy cattle, i.e., 0.06 from the pedigree relationships and 0.10 from the single step approach. Parker Gaddis et al. (2014) reported a heritability of 0.03 for cystic ovaries and of 0.04 for metritis in first lactation when

using the **A** matrix, and of 0.05 and 0.07, respectively, when using the **G** matrix. The heritability for DD as estimated in the conventional cow dataset reflect estimates from previous studies conducted in German Holstein cows (König et al., 2008; Gernand et al., 2012).

In the present study, in organic as well as in conventional herds, heritabilities for health traits were throughout larger when modelling pedigree relationships (Table 4.3). Substantial differences in this regard were observed for DD in organic herds. In Holstein cattle populations, Haile-Mariam et al. (2013) and Veerkamp et al. (2011) estimated smaller genetic variances and heritabilities when considering SNP instead of pedigree relationships.

The reason is the only medium sized marker density, implying imperfect linkage disequilibrium between the SNP markers and the quantitative trait loci (Haile-Mariam et al., 2013). For the modelling approaches with **A**, **G** or **H**, health trait heritabilities were larger in organic than in conventional herds. Nevertheless, also standard errors of heritabilities were larger in the organic population in the range from 0.02 for production traits to 0.07 for OCD, but 0.01 for all traits recorded in the conventional population. The reduced residual variances in the organic population is the major explanation for the increased heritabilities. The organic and conventional HF cow sub-populations reflect minor differences in birth years, with an older age structure for the organic cows. Furthermore, the conventional HF cows display a higher milk production level, due to the overriding importance of milk or protein yield in overall breeding goals during the past decades (Miglior et al., 2005). Selection itself influences genetic variability as clearly elaborated by Bulmer (1971). Regarding the time perspective and breeding program evaluations, Sitzenstock et al. (2012) emphasized the importance of the development of the average kinship within and between selection groups over time. Hence, both aspects, i.e., differences in selection strategies and in birth years in the two cow-subpopulations organic and conventional, might contribute to differences in genetic (co)variance components.

Genetic correlations in same traits between organic and conventional production systems

Genetic correlations are given in Table 4.4. Robertson (1959) suggested a genetic correlation lower than 0.80 as an indicator for considerable G×E. The genetic correlations between MY organic with MY conventional were 0.59 (**A** matrix), 0.82 (**G** matrix) and 0.75 (**H** matrix). Genetic correlations between milk yield from different housing systems ranged from 0.79 to 0.99 (Nauta et al., 2006), and the genetic correlation was 0.89 when considering grazing and

confinement herds (Kearney et al., 2004). The genetic correlations for MY close to 0.80 in the previous as well as in the present study indicate only a slight re-ranking of sires in the two production systems.

Genetic correlations between FP in organic and conventional herds were 0.85 when modelling the **A** matrix, 0.99 when modelling the **G** matrix, and in-between when modelling the **H** matrix (0.95). The large genetic correlations for the moderate to high heritability trait suggest that conventional and organic FP are the same trait. Accordingly, Nauta et al. (2006) estimated large genetic correlations for FP from different housing systems, and stated that same genes are involved in FP regulations across changing environments.

Table 4.4: Genetic correlations between same traits recorded in conventional and organic herds from bivariate models using pedigree- and SNP-based relationship matrices as well as from the single step approach

Trait[1]	Pedigree-based	SNP-based	Single step approach
Milk, kg	0.59 (0.06)	0.82 (0.06)	0.75 (0.04)
Fat, %	0.85 (0.03)	0.99 (0.02)	0.95 (0.01)
LPL[2], days	0.67 (0.13)	0.94 (0.19)	0.66 (0.05)
MAST	0.41 (0.21)	0.44 (0.45)	0.44 (0.17)
OCD	0.34 (0.18)	0.64 (0.52)	0.35 (0.14)
DD	0.30 (0.14)	0.51 (0.30)	0.33 (0.11)

[1]LPL = length of productive life, MAST = Mastitis, OCD = ovarian cycle disorders, DD = digital dermatitis.

[2]Due to the failed convergence for the SNP-based approach, the convergence criterion was relaxed to 1.0d-1 for the difference in variance estimates and to 1.0d-8 for the norm of the gradient vector (only for this specific LPL run using the **G**-matrix).

An increase of environmental sensitivity and a decrease of genetic correlation estimates with decreasing trait heritability was reported by Yin and König (2018). Genetic correlations for low heritability LPL differed when comparing the **A** matrix (0.67) or **H** matrix estimates with results from the G matrix (0.94). Genetic correlations from **A** and **H** were below the threshold of 0.80, indicating obvious G×E. For the interpretation of genetic correlation estimates based on **G** and **A**, the quite large standard error and especially the small number of genotyped cows as used for the construction of **G**, should be kept in mind. The single step approach contributed to a decrease of standard errors. In contrast to the estimates from the present study, Ahlman et al. (2011) reported quite large genetic correlations between longevity traits recorded either in organic or in conventional dairy herds. They only found G×E indications for fertility-determined survival in Swedish Red cattle. In Austrian Fleckvieh, genetic correlations between LPL organic and LPL conventional ranged from 0.89 to 0.97 (Pfeiffer et

al., 2016). Accordingly, in Australia, genetic correlations for survival traits from different regions and calving systems were throughout larger than 0.90 (Haile-Mariam et al., 2008).The authors expected the large genetic correlations, because the most important environmental and farm characteristics were similar across regions and calving systems. Hence, the differences in genetic correlations from different countries might be due to the country specific restrictions when converting from conventional to organic dairy cattle milk production. The countries with very strict organic feeding and husbandry regulations displayed moderate to low genetic correlations for longevity traits. Also in the present study, a detailed farm survey displayed pronounced feeding and husbandry differences in organic and in conventional herds, possibly explaining the low to moderate genetic correlation for low heritability LPL (Rolfes et al., 2020).

In the present study, for low heritability health traits, low to moderate genetic correlations were estimated. The genetic correlations ranged from 0.30 for DD to 0.41 for MAST when considering the **A** matrix, and from 0.44 for MAST to 0.64 for OCD when modelling the **G** matrix. Genetic correlations from the single step approach (**H** matrix) for the respective health trait ranked between the estimates from **G** and **A**, and were associated with smallest standard errors. Arguments for low genetic correlations are the comparatively small organic sample size (Haile-Mariam et al., 2008) and the genetic architecture of health traits displaying small heritabilities (Craig et al., 2018). Furthermore, increased standard errors of genetic correlations for health traits were identified, in the present study in the range from 0.14 to0.52. Largest standard errors of genetic correlations were observed when modelling the **G** matrix. The mentioned difficulties to prove G×E for low heritability health traits were summarized by Calus et al. (2004). However, also quite large genetic correlations for health traits in G×E studies were reported, e.g., genetic correlations larger than 0.95 between clinical mastitis organic with clinical mastitis conventional, and between cystic ovaries organic with cystic ovaries conventional (Pfeiffer et al., 2016). With regard to G×E for health indicator traits, Mulder et al. (2004) estimated genetic correlations between somatic cell score from automatic and milking parlor systems, which were slightly lower than 0.80.

Several studies addressed the breeding consequences in the case of low genetic correlations for functional traits from different production systems. Specific breeding strategies for organic and conventional populations were suggested in the case of genetic correlations lower than 0.65 (Slagboom et al., 2019; Mulder and Bijma, 2006; Mulder et al., 2006). From atheoretical perspective, ignorance of G×E implies a reduction in selection accuracy and in genetic gain (Liu et al., 2019). Specifically, Slagboom et al. (2019) identified a reduction in

genetic gain of 24% when implementing only one overall breeding program given distinct heterogeneous environments. However, it remains unclear if extra genetic gain compensates the extra costs when establishing different breeding programs and implementing specific organic breeding lines (Kargo et al., 2018).

Genome-wide associations

Genome-wide associations for the production traits MY (Figure 4.1) and FP (Figure 4.2) are displayed separately for the conventional and organic populations. For conventional MY, 27 SNP surpassed the stringent Bonferroni-corrected significance threshold and 8 of these SNP were significantly associated with organic MY. The significant SNP and annotated potential candidate genes for MY are given in Supplementary Table S4.1. According to the Bonferroni correction, 54 SNP were significantly associated with conventional FP and 38 SNP with organic FP, resulting in an overlap of 32 identical significant SNP for the same trait in both farming systems. The significant SNP and annotated potential candidate genes for FP are listed in Supplementary Table S4.2. The GWAS for MY and FP in both production systems organic and conventional identified the major gene *DGAT1* on BTA14 (Thaller et al., 2003).

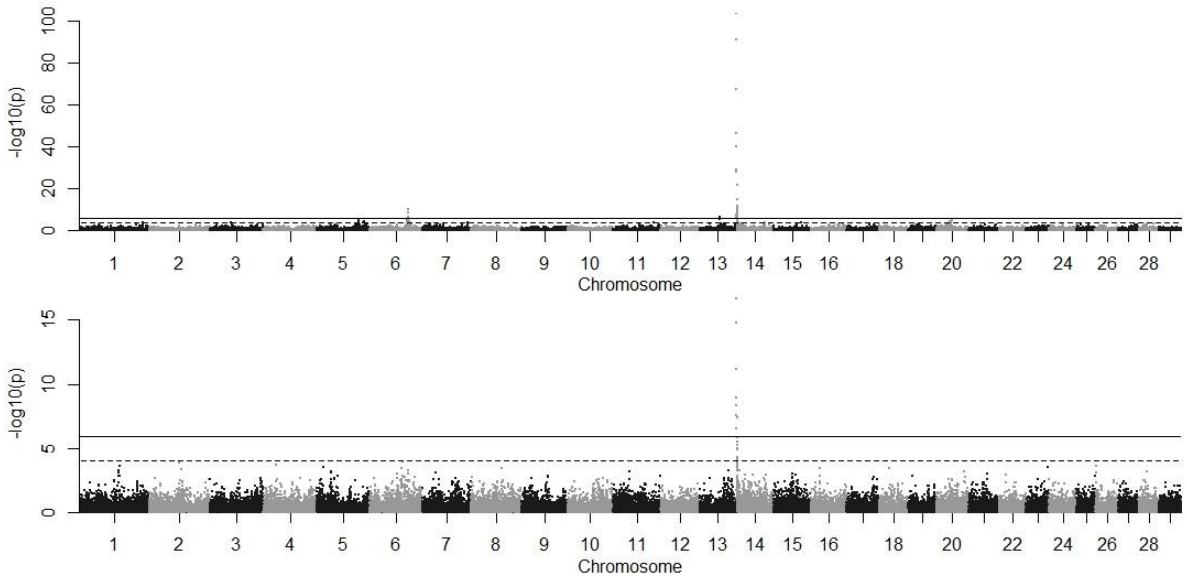

Figure 4.1: Manhattan plots from GWAS for milk yield in conventional (above) and in organic (below) production systems. The solid line represents the Bonferroni-corrected threshold ($P_{Bonf} = 1.22\times10^{-6}$), the dashed line represents the potential candidate threshold ($P_{cand} = 1\times10^{-4}$)

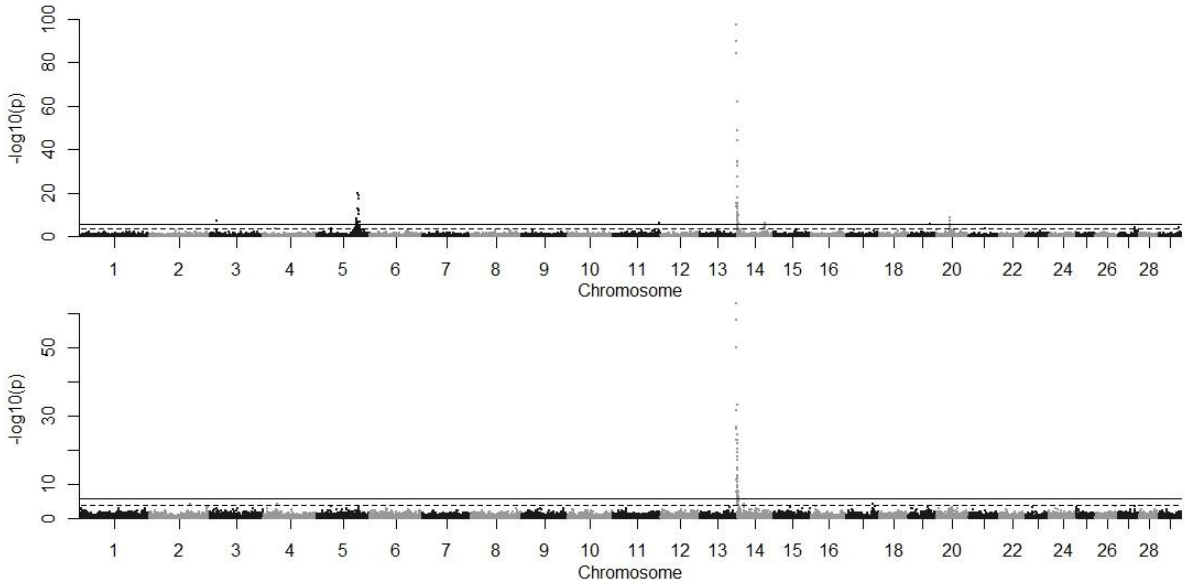

Figure 4.2: Manhattan plots from GWAS for fat percentage in conventional (above) and organic (below) production systems. The solid line represents the Bonferroni-corrected threshold ($P_{Bonf} = 1.22\times10^{-6}$), the dashed line represents the potential candidate threshold ($P_{cand} = 1\times10^{-4}$)

For LPL, only two SNP surpassed the stringent Bonferroni-corrected significance threshold ($P_{Bonf} = 1.22\times10^{-6}$). Consequently, the less conservative significance threshold for potential candidate SNP ($P_{cand} = 1\times10^{-4}$) was considered. Manhattan plots from the GWAS in the conventional and organic production systems are displayed in Figure 4.3.

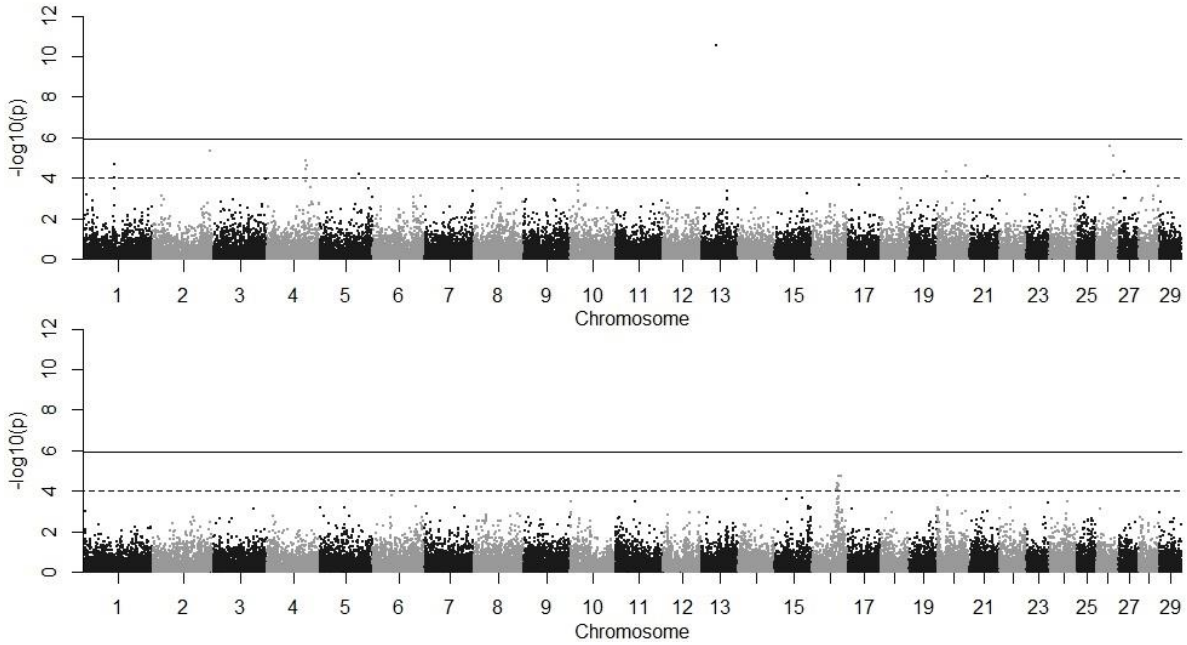

Figure 4.3: Manhattan plots from GWAS for length of productive life in conventional (above) and de-regressed proofs of length of productive life in organic (below) production systems. The solid line represents the Bonferroni-corrected threshold ($P_{Bonf} = 1.22 \times 10^{-6}$), the dashed line represents the potential candidate threshold ($P_{cand} = 1 \times 10^{-4}$)

The significantly associated SNP for LPL in the conventional production system were distributed across the whole genome (Table 4.5). Some of the detected potential candidate genes were reported in previous genomic longevity studies. For example, Szyda et al. (2011) identified a significant effect of a polymorphism in *LEP-R25C* on functional longevity. Further identified candidate genes in their study were associated with disease resistances, e.g., *SEMA5A* for mastitis resistance (Sugimoto et al., 2006), *DLG1* for immune response (Yoshida et al., 2008), *CACUL1* for age at first calving (Nascimento et al., 2018) and *NCMAP* and *RCAN3* for pre-weaning mortality (Garzon, 2019). Two potential candidate genes as identified in our study for conventional LPL are located in close distance to previously reported candidate genes for longevity, e.g. *MIER3* on BTA 20 (Raven et al., 2014) and *SYT1* on BTA 5 (Saowaphak et al., 2017).

Table 4.5: Significant SNP markers and annotated potential candidate genes influencing the length of productive life in conventional herds

SNP	BTA[1]	SNP position (bp)[2]	-log$_{10}$(*P-value*)	Gene name	Gene position (bp)[2]
Hapmap51434-BTA-34642	1	71,760,764	4.65	*DLG1*	71,513,093 - 71,780,855
ARS-BFGL-NGS-8433	2	128,377,966	5.35	*NCMAP* *RCAN3*	128,320,578 - 128,334,929 128,388,785 - 128,422,500
BTB-01323560	4	88,686,550	4.44		
Hapmap51964-BTA-100658	4	88,783,875	4.84		
ARS-BFGL-NGS-34894	4	92,474,426	4.61	*LEP* *RBM28*	92,436,922 - 92,453,653 92,499,373 - 92,531,680
Hapmap59389-rs29023212	5	88,560,515	4.22	*LDHB*	88,544,523 - 88,562,783
Hapmap59420-ss46527113	13	35,229,941	10.54	*MTPAP*	35,229,884 - 35,260,074
Hapmap49633-BTA-50009	20	19,983,821	4.31	*PDE4D*	20,014,955 - 20,315,593
BTB-00022582	20	63,746,476	4.60	*SEMA5A*	63,654,369 - 64,216,207
ARS-BFGL-NGS-116938	21	43,691,590	4.05		
BTB-00938770	26	32,533,877	5.55		
BTA-93527-no-rs	26	39,050,907	4.15	*CACUL1*	38,953,563 - 39,017,643
ARS-BFGL-NGS-84251	26	39,112,026	5.08		
BTB-00951635	27	12,235,101	4.32		

[1]BTA = *Bos taurus* autosome;
[2]bp = Position in base pairs, according to bovine reference genome *Bos taurus*ARS-UCD1.2

For organic LPL, the significantly associated SNP are only located on BTA 16 from 53.5 to 64.8 Mb (Table 4.6). The annotated potential candidate genes *KIAA0040*, *COP1*, *RASAL2* and *RALGPS2* play important but inconsistent roles in different types of cancer (Peng et al., 2008; Marine, 2012; Santos et al., 2016; Zhou et al., 2019). For the annotated gene *BRINP2*, Li et al. (2018) identified associations with fertility traits in buffalo. The low correlation between all SNP effects organic with all SNP effects conventional of 0.08 indicate inconsistent SNP associations with LPL in organic and in conventional herds.

Table 4.6: Significant SNP markers and annotated potential candidate genes influencing the length of productive life in organic herds

SNP	BTA[1]	SNP position (bp)[2]	-log$_{10}$(*P-value*)	Gene name	Gene position (bp)[2]
ARS-BFGL-NGS-53540	16	53,585,655	4.08		
BTA-39611-no-rs	16	56,426,595	4.20	*KIAA0040*	56,399,984 - 56,400,286
ARS-BFGL-NGS-108847	16	57,101,068	4.12		
ARS-BFGL-NGS-1152	16	57,144,029	4.39	*COP1*	57,201,765 - 57,426,155
ARS-BFGL-NGS-129	16	58,590,390	4.30	*BRINP2*	58,500,206 - 58,558,936
ARS-BFGL-NGS-21162	16	59,652,144	4.26	*RASAL2*	59,629,859 - 59,878,925
BTB-01492749	16	59,841,996	4.03		
BTB-00650214	16	60,355,931	4.71	*RALGPS2*	60,124,735 - 60,284,409
				FAM20B	60,375,301 - 60,417,812
ARS-BFGL-NGS-90008	16	64,795,470	4.73	*RGL1*	64,794,721 - 64,961,884

[1]BTA = *Bos taurus* autosome;
[2]bp = Position in base pairs, according to bovine reference genome *Bos taurus* ARS-UCD1.2

Manhattan-plots for SNP associated with MAST in conventional and organic production systems are shown in in Figure 4.4. The potential candidate genes for conventional MAST on BTA 6, i.e., *SLC4A4*, *GC* and *NPFFR2*, have been suggested in several studies as candidate genes for mastitis (Sahana et al., 2014; Wu et al., 2015; Cai et al., 2018; Weller et al., 2018). Significantly associated SNP on BTA 19 (54.7-57.4 Mb) were reported in previous GWAS for clinical mastitis and somatic cell count (Sahana et al., 2014; Wu et al., 2015). The candidate genes as identified in the organic dataset reflect general disease resistances. In this regard, *ALCAM* contributed to endoparasite resistance (May et al., 2019), and *GLDN*, *USP8*, *GABPB1* and *HDC* were associated with paratuberculosis infections in Holstein cattle (Pant et al., 2010; Mallikarjunappa et al., 2018). The correlation between SNP effects for conventional MAST with SNP effects for organic MAST considering all SNP was very close to zero (-0.004), indicating inconsistent genetic mechanisms for the same trait in two different environments. Comparing the associations for MAST in the two farming systems, we notice different mechanisms of the identified potential candidate genes. Genes inferred for organic MAST are involved in general resistances instead of mastitis-specific mechanisms. The explanation for the importance of general disease resistance in organic farms needs further

investigations, e.g., gene expression studies as conducted in heat stressed individuals (Cammack et al., 2009).

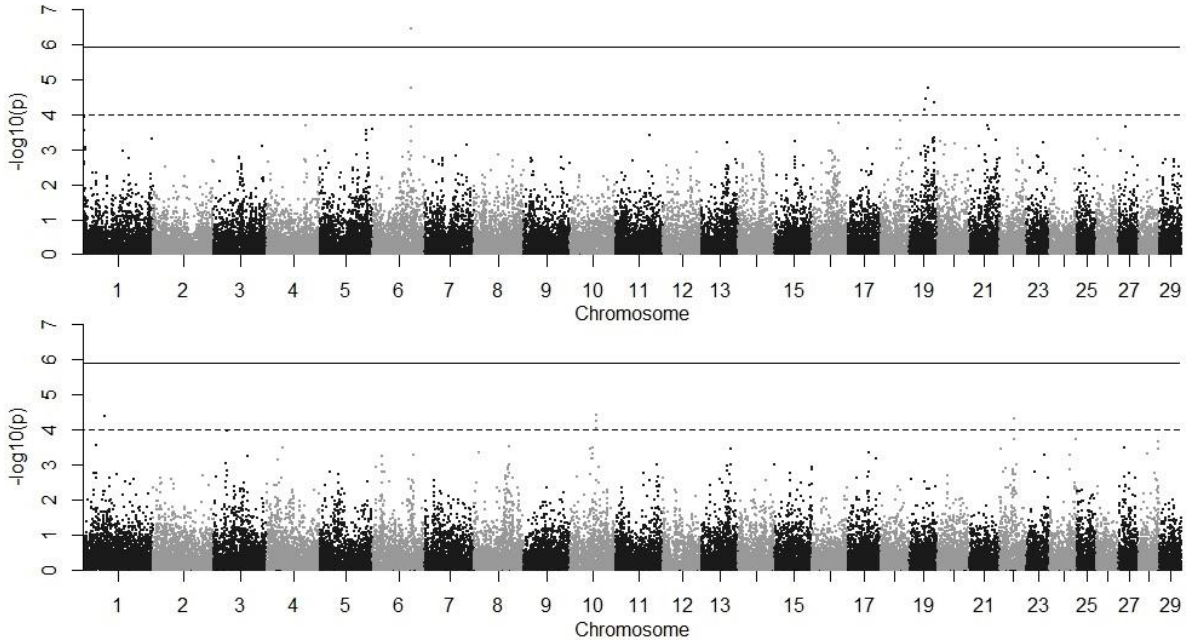

Figure 4.4: Manhattan plots from GWAS for mastitis in conventional (above) and organic (below) production systems. The solid line represents the Bonferroni-corrected threshold ($P_{Bonf} = 1.22 \times 10^{-6}$), the dashed line represents the potential candidate threshold ($P_{cand} = 1 \times 10^{-4}$)

Table 4.7: Significant SNP markers and annotated potential candidate genes influencing mastitis in conventional and organic herds

SNP	BTA[1]	SNP position (bp)[2]	-log$_{10}$(*P-value*)	Gene name	Gene position (bp)[2]
Conventional production system					
ARS-BFGL-NGS-118182	6	86,860,291	6.44	*SLC4A4* *GC*	86,381,836 - 86,809,131 86,953,984 - 87,007,062
BTB-01654826	6	87,156,735	4.76	*NPFFR2*	87,248,937 - 87,325,253
ARS-BFGL-NGS-105337	19	34,924,937	4.12	*FLCN*	34,915,672 - 34,932,182
BTB-01941088	19	38,115,441	4.44	*SKAP1*	38,060,253 - 38,364,401
ARS-BFGL-NGS-27742	19	43,345,214	4.74	*ARL4D* *DHX8*	43,342,402 - 43,344,318 43415313 - 43443775
Hapmap38228-BTA-46092	19	56,601,799	4.35	*TMEM104*	56,577,202 - 56,647,063
Organic production system					
BTB-01165120	1	50,064,432	4.36	*ALCAM*	49,930,775 50,160,291
ARS-BFGL-NGS-12407	10	59,026,013	4.26	*GLDN*	58,951,441 - 59,006,267
BTA-72298-no-rs	10	59,055,406	4.41	*CYP19A1*	59,102,240 – 59,156,607
Hapmap57627-rs29027143	10	59,785,440	4.04	*USP8*	59,758,633 - 59,849,849
Hapmap44561-BTA-72345	10	59,977,416	4.04	*GABPB1* *HDC*	59,890,308 - 59,967,550 59,982,866 – 60,004,776
ARS-BFGL-NGS-110665	22	33,306,246	4.31	*FAM19A1*	32,966,389 - 33,471,943
ARS-BFGL-BAC-4845	22	33,329,374	4.30		

[1]BTA = *Bos taurus* autosome;
[2]bp = Position in base pairs, according to bovine reference genome *Bos taurus* ARS-UCD1.2

Manhattan plots for SNP associated with OCD in conventional and organic production systems are plotted in Figure 4.5. The significant SNP and annotated potential candidate genes are listed in Table 4.8. In agreement with our results for the conventional dataset, Yang et al. (2016) confirmed the effect of the candidate gene *AKR1B1* on the degradation of the corpus luteum in ovary. The *ZNF23* gene induces cell death in human ovarian cancer cells (Huang et al., 2008) and plays a major role in ovarian dysfunctions. Regarding the organic cow population, the detected potential candidate gene *PLPPR4* influenced follicle

transformations, with ongoing effects on ovarian disorders (Yu et al., 2019). Effects of all SNP in the conventional population were independent from SNP effects in the organic population, because the correlation between SNP effects for organic OCD with SNP effects for conventional OCD was very close to zero (0.03). Different SNP and annotated potential candidate genes were associated with conventional and with organic OCD. Nevertheless, the identified potential candidate genes are involved in similar physiological pathways.

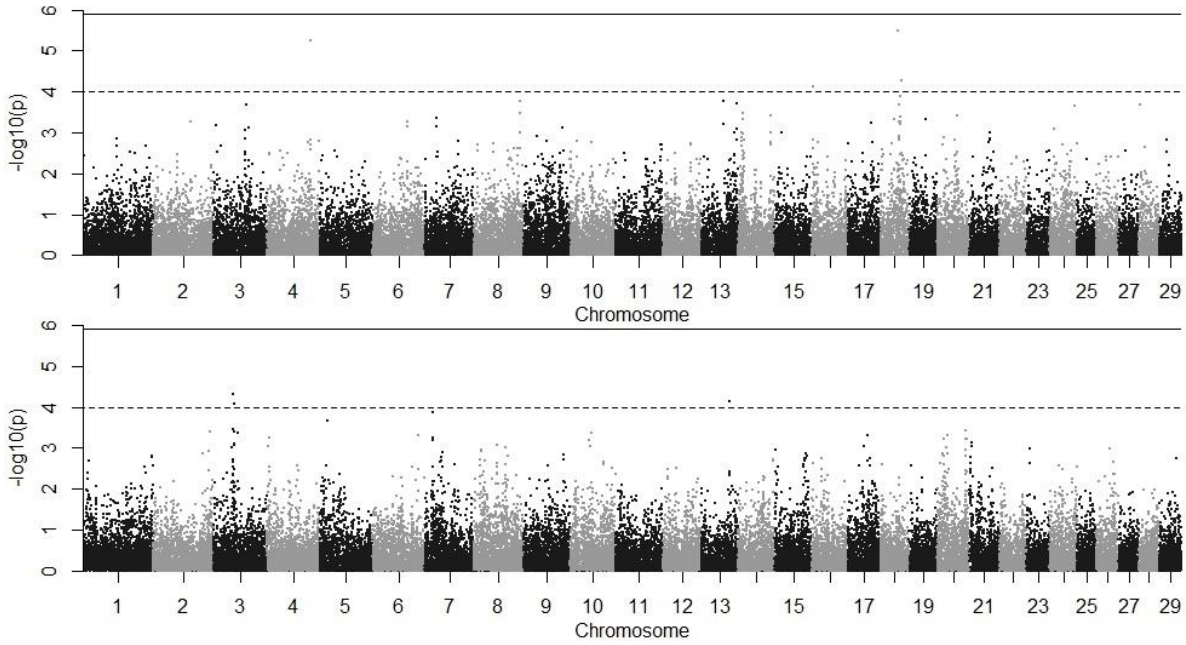

Figure 4.5: Manhattan plots from GWAS for ovarian cycle disorders in conventional (above) and organic (below) production systems. The solid line represents the Bonferroni-corrected threshold ($P_{Bonf} = 1.22 \times 10^{-6}$), the dashed line represents the potential candidate threshold ($P_{cand} = 1 \times 10^{-4}$)

Table 4.8: Significant SNP markers and annotated potential candidate genes influencing ovarian cycle disorders in conventional and organic herds

SNP	BTA[1]	SNP position (bp)[2]	-log$_{10}$(*P-value*)	Gene name	Gene position (bp)[2]
Conventional production system					
ARS-BFGL-NGS-77010	4	98,180,851	5.26	*AKR1B1* *AKR1B10*	98,115,288 - 98,132,148 98,217,455 – 98,239,457
Hapmap27200-BTA-154249	16	2,288,457	4.13	*MDM4*	2,255,641 - 2,292,885
ARS-BFGL-NGS-104890	18	39,636,977	5.50	*ZNF23* *CALB2*	39,613,326 - 39,627,072 39,673,114 – 39,702,531
ARS-BFGL-BAC-35026	18	47,927,237	4.27	*SIPA1L3*	47,786,571 - 48,022,839
Organic production system					
ARS-BFGL-NGS-4513	3	44,017,413	4.32	*PLPPR4*	43,921,627 - 43,976,646
BTA-20774-no-rs	3	46,986,210	4.09		
ARS-BFGL-NGS-70015	13	65,240,366	4.14	*EPB41L1*	65,221,138 - 65,353,703

[1]BTA = *Bos taurus* autosome;
[2]bp = Position in base pairs, according to bovine reference genome *Bos taurus* ARS-UCD1.2

For DD, no SNP surpassed the Bonferroni-corrected threshold for the conventional and organic populations (Figure 4.6). The significant SNP according to the less stringent candidate significance threshold and corresponding annotated potential candidate genes are listed in Table 4.9. The gene *BNC2* was associated with fertility traits in Brangus heifers (Peters et al., 2014), and *ARHGEF12* affected subclinical mastitis in Norwegian red cattle (Kirsanova et al., 2020). Interestingly, identified significant SNP from the present study were not detected in a previous GWAS for DD in German Holstein cows (Kopke, 2019). However, Kopke (2019) used an alternative scoring system considering different stages of DD. Sánchez-Molano et al. (2019) suggested *FPGT* and *TNNI3K* as potential candidate genes for DD. Both genes are located in close physical distance to the significantly associated SNP for organic DD in the present study. The correlation between SNP effects for conventional DD with SNP effects for organic DD was 0.04, indicating a different genetic background for the same health trait in the two different production systems.

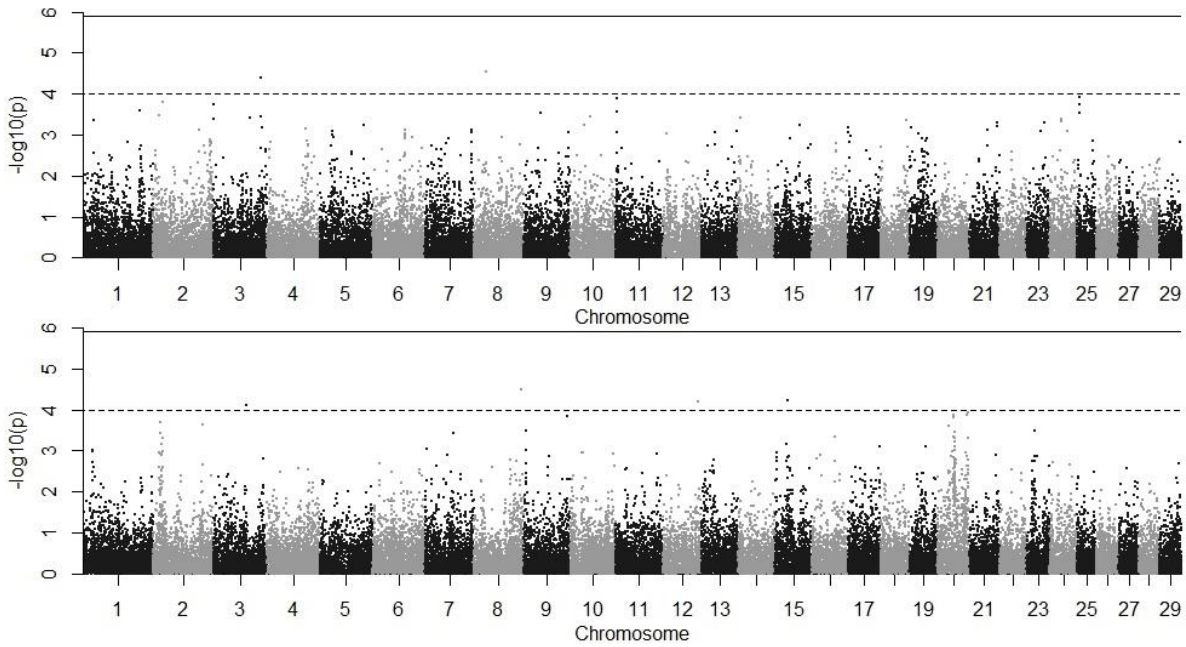

Figure 4.6: Manhattan plots from GWAS for digital dermatitis in conventional (above) and organic (below) production systems. The solid line represents the Bonferroni-corrected threshold ($P_{Bonf} = 1.22\times10^{-6}$), the dashed line represents the potential candidate threshold ($P_{cand} = 1\times10^{-4}$)

Table 4.9: Significant SNP markers and annotated potential candidate genes influencing digital dermatitis in conventional and organic herds

SNP	BTA[1]	SNP position (bp)[2]	-log$_{10}$(*P-value*)	Gene name	Gene position (bp)[2]
Conventional production system					
ARS-BFGL-NGS-87394	3	108,523,825	4.40		
BTB-01271445	8	27,700,660	4.55	*BNC2*	27,468,468 - 27,944,404
Organic production system					
Hapmap55103-rs29011390	3	74,438,439	4.10		
ARS-BFGL-NGS-884	8	107,482,423	4.49		
ARS-BFGL-NGS-118171	12	80,191,366	4.19		
BTB-00590347	15	31,026,940	4.22	*ARHGEF12*	30,922,864 - 31,090,062

[1]BTA = *Bos taurus* autosome;
[2]bp = Position in base pairs, according to bovine reference genome *Bos taurus* ARS-UCD1.2

For most of the traits considered in GWAS, the number of significantly associated SNP was larger in the conventional than in the organic dataset. A proper alternative for GWAS with a quite small number of genotyped cows, i.e. the organic sub-population, might be the application of single step GBLUP. In simulations, Wang et al. (2012) demonstrated increased

power and precision for estimation of genetic marker effects when including phenotypes from ungenotyped animals, and blending pedigree relationships with relationships derived from SNP markers.

CONCLUSION

Heritabilities for the production traits MY and FP were very similar in conventional and organic populations. This was the case for models with pedigree and genomic relationship matrices as well as in a single step approach. For functional health traits and LPL, smaller residual variances contributed to heritability increases in the organic population. Nevertheless, apart from DD, heritabilities for same health traits were in a narrow range. The genetic correlations between same traits recorded in the conventional or in the organic population were close to 0.80 for production traits. Genetic correlations substantially lower than 0.80 for all modelling approaches with **A**, **G** or **H** matrices indicated possible G×E for the low heritability traits DD, OCD, MAST, and for LPL when considering **A** or **H**. Nevertheless, especially for **G**, standard errors of genetic correlations were quite large due to the small organic reference population. For production traits with moderate to large heritabilities, there was a broad overlap of detected significantly associated SNP and annotated potential candidate genes in the two farming systems organic and conventional. Identified significantly SNP and potential candidate genes for LPL and health traits in the two systems were completely inconsistent. Results suggest different breeding indices for organic and conventional populations, but it is imperative to increase the organic cow reference population in order to improve the accuracies of genetic parameter estimates.

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Appendix

Supplementary table S4.1: Significant SNP markers and annotated potential candidate genes influencing milk yield in conventional and organic herds

Herd[1]	SNP	BTA[2]	SNP position (bp)[3]	-log$_{10}$(*P-value*) conv.	-log$_{10}$(*P-value*) org.	Gene name	Gene position (bp)[3]
C	ARS-BFGL-NGS-118182	6	86,860,291	6.36		*SLC4A4*	86,381,836 - 86,809,131
C	ARS-BFGL-NGS-17376	6	87,090,740	10.26		*GC*	86,953,984 - 87,007,062
C	BTB-01654826	6	87,156,735	8.82		*NPFFR2*	87,248,937 - 87,325,253
C	Hapmap38591-BTA-32800	13	45,859,677	6.69			
C	Hapmap30381-BTC-005750	14	279,949	7.54		*ZNF16*	261,621 - 275,771
B	Hapmap30383-BTC-005848	14	305,780	46.60	6.49	*C14H8orf33* *ZNF34*	303,633 - 305,704 309,282 - 313,478
B	ARS-BFGL-NGS-57820	14	465,742	91.39	14.80	*PPP1R16A* *FOXH1*	443,246 - 448,420 469,132 - 470,687
B	ARS-BFGL-NGS-34135	14	490,055	28.32	7.56	*CYHR1*	478,582 - 492,655
B	ARS-BFGL-NGS-94706	14	511,247	29.17	8.37	*VPS28*	508,418 - 512,819
B	ARS-BFGL-NGS-4939	14	609,870	103.73	16.67	*DGAT1*	603,813 - 612,791
C	ARS-BFGL-NGS-71749	14	762,253	6.77		*EXOSC4* *OPLAH*	755,134 - 757,010 765,421 - 774,581
B	UA-IFASA-6878	14	810,863	40.29	8.97	*SPATC1* *GRINA*	778,853 - 806,391 826,740 - 830,066
B	ARS-BFGL-NGS-107379	14	862,483	67.47	11.19	*PLEC*	839,972 - 896,647
C	Hapmap25384-BTC-001997	14	1,022,847	11.87	5.79	*IQANK1*	1,006,976 - 1,027,840
C	Hapmap24715-BTC-001973	14	1,044,777	10.12	5.51	*MAPK15*	1,040,716 - 1,066,536
C	ARS-BFGL-NGS-26520	14	1,184,910	7.68		*ZC3H3*	1,153,788 - 1,215,120
C	Hapmap30374-BTC-002159	14	1,265,916	15.13		*RHPN1*	1,262,194 - 1,269,340

Herd[1]	SNP	BTA[2]	SNP position (bp)[3]	-log$_{10}$(*P-value*) conv.	-log$_{10}$(*P-value*) org.	Gene name	Gene position (bp)[3]
C	Hapmap30086-BTC-002066	14	1,322,326	14.82		*GLI4*	1,323,954 - 1,335,463
C	Hapmap30646-BTC-002054	14	1,351,419	11.23		*LY6H*	1,359,669 - 1,363,525
						LY6E	1,422,652 - 1,426,356
C	ARS-BFGL-NGS-3122	14	1,520,054	6.08		*GML*	1,513,837 - 1,542,041
C	Hapmap25486-BTC-072553	14	1,567,838	9.89			
B	ARS-BFGL-NGS-103064	14	1,620,027	8.87	7.38		
C	ARS-BFGL-NGS-22866	14	1,681,783	6.53		*LYNX1*	1,669,738 - 1,672,645
						LYPD2	1,683,800 - 1,686,606
C	ARS-BFGL-NGS-18858	14	1,758,505	21.67	5.23	*ARC*	1,741,249 - 1,743,574
C	Hapmap24717-BTC-002824	14	1,799,618	7.39		*ADGRB1*	1,797,368 - 1,862,330
C	ARS-BFGL-NGS-59769	14	1,854,457	10.00			
C	Hapmap36620-SCAFFOLD50018_7571	14	2,142,001	10.99			

[1]C = SNP was significant associated with milk yield in conventional herds, B = SNP was significantly associated with milk yield in both systems;
[2]BTA = *Bos taurus* autosome;
[3]bp = Position in base pairs, according to bovine reference genome *Bos taurus* ARS-UCD1.2.

Supplementary table S4.2: Significant SNP markers and annotated potential candidate genes influencing fat percentage in conventional and organic herds

Herd[1]	SNP	BTA[2]	SNP position (bp)[3]	-log$_{10}$(*P-value*) conv.	-log$_{10}$(*P-value*) org.	Gene name	Gene position (bp)[3]
C	ARS-BFGL-NGS-64215	3	15,470,670	7.20		*EFNA1*	15,466,566 - 15,473,164
C	ARS-BFGL-NGS-100808	5	90,974,725	7.09			
C	Hapmap51546-BTA-109428	5	91,196,362	6.56			
C	ARS-BFGL-NGS-108617	5	91,393,516	8.16		*PLCZ1* *PIK3C2G*	91,335,807 - 91,384,524 91,399,521 - 91,842,738
C	ARS-BFGL-NGS-116999	5	92,796,641	19.92			
C	Hapmap36414-SCAFFOLD150043_20489	5	93,138,660	6.73			
C	Hapmap32415-BTA-74556	5	93,441,439	6.33		*MGST1*	93,497,064 - 93,521,047
C	ARS-BFGL-NGS-95906	5	93,490,294	12.80			
C	ARS-BFGL-NGS-111443	5	93,840,983	6.75		*DERA*	93,887,905 - 94,006,820
C	BTA-74585-no-rs	5	94,069,559	10.19		*STRAP*	94,018,317 - 94,039,904
C	Hapmap49734-BTA-74577	5	94,142,375	12.39			
C	Hapmap41349-BTA-74576	5	94,169,217	12.15		*EPS8*	94,125,186 - 94,321,587
C	Hapmap53294-rs29016908	5	94,217,230	11.92			
C	ARS-BFGL-NGS-20806	5	94,345,725	18.99		*PTPRO*	94,342,435 - 94,455,619
C	Hapmap60021-ss46526426	5	95,028,489	17.34		*MGP*	95,024,682 - 95,028,653
C	ARS-BFGL-NGS-15498	5	96,667,629	6.72		*EMP1*	96,633,068 - 96,654,177
C	ARS-BFGL-NGS-31097	11	103,243,510	6.20		*PAEP* *GSG1*	103,255,824 - 103,264,276 96,766,338 - 96,785,806
B	Hapmap30381-BTC-005750	14	279,949	13.70	11.23	*ZNF16*	261,621 - 275,771
B	Hapmap30383-BTC-005848	14	305,780	97.25	31.64	*C14H8orf33* *ZNF34*	303,633 - 305,704 309,282 - 313,478
B	ARS-BFGL-NGS-57820	14	465,742	234.89	58.12	*PPP1R16A* *FOXH1*	443,246 - 448,420 469,132 - 470,687

Herd[1]	SNP	BTA[2]	SNP position (bp)[3]	-log10(*P-value*) conv.	-log10(*P-value*) org.	Gene name	Gene position (bp)[3]
B	ARS-BFGL-NGS-34135	14	490,055	84.11	26.25	*CYHR1*	478,582 - 492,655
B	ARS-BFGL-NGS-94706	14	511,247	89.61	26.91	*VPS28*	508,418 - 512,819
B	ARS-BFGL-NGS-4939	14	609,870	250.48	63.16	*DGAT1*	603,813 - 612,791
B	ARS-BFGL-NGS-71749	14	762,253	15.60	7.84	*EXOSC4*	755,134 - 757,010
						OPLAH	765,421 - 774,581
B	UA-IFASA-6878	14	810,863	145.45	22.89	*SPATC1*	778,853 - 806,391
						GRINA	826,740 - 830,066
B	ARS-BFGL-NGS-107379	14	862,483	221.57	50.25	*PLEC*	839,972 - 896,647
B	Hapmap25384-BTC-001997	14	1,022,847	32.77	24.48	*IQANK1*	1,006,976 - 1,027,840
B	Hapmap24715-BTC-001973	14	1,044,777	23.11	21.85	*MAPK15*	1,040,716 - 1,066,536
B	ARS-BFGL-NGS-101653	14	1,119,139	15.25	8.89	*EEF1D*	1,113,551 - 1,126,356
B	ARS-BFGL-NGS-26520	14	1,184,910	34.25	11.70	*ZC3H3*	1,153,788 - 1,215,120
B	Hapmap30374-BTC-002159	14	1,265,916	48.85	24.58	*RHPN1*	1,262,194 - 1,269,340
B	Hapmap30086-BTC-002066	14	1,322,326	43.99	20.32	*GLI4*	1,323,954 - 1,335,463
B	Hapmap30646-BTC-002054	14	1,351,419	27.71	14.24		
O	ARS-BFGL-NGS-41248	14	1,403,386		6.34	*LY6H*	1,359,669 - 1,363,525
B	Hapmap25961-BTC-003785	14	1,440,024	9.67	7.07	*LY6E*	1,422,652 - 1,426,356
B	Hapmap29758-BTC-003619	14	1,472,679	10.32	11.87		
B	Hapmap25486-BTC-072553	14	1,567,838	17.75	18.15		
B	ARS-BFGL-NGS-103064	14	1,620,027	15.42	22.87		
B	ARS-BFGL-NGS-22866	14	1,681,783	14.96	12.55	*LYNX1*	1,669,738 - 1,672,645
						LYPD2	1,683,800 - 1,686,606
B	ARS-BFGL-NGS-18858	14	1,758,505	61.99	33.40	*ARC*	1,741,249 - 1,743,574
B	Hapmap24717-BTC-002824	14	1,799,618	14.31	9.56	*ADGRB1*	1,797,368 - 1,862,330

Herd[1]	SNP	BTA[2]	SNP position (bp)[3]	-log10(*P-value*) conv.	-log10(*P-value*) org.	Gene name	Gene position (bp)[3]
B	ARS-BFGL-NGS-59769	14	1,854,457	34.41	14.80		
C	Hapmap30375-BTC-003040	14	1,877,790	13.01			
C	ARS-BFGL-NGS-70821	14	1,926,589	7.32			
B	ARS-BFGL-NGS-32047	14	1,965,168	8.52	8.11	*TSNARE1*	1,902,552 - 2,019,963
C	ARS-BFGL-NGS-13653	14	1,985,112	10.86			
B	ARS-BFGL-NGS-85419	14	2,088,718	13.96	7.95		
B	ARS-BFGL-NGS-67477	14	2,120,416	11.56	7.90		
B	Hapmap36620-SCAFFOLD50018_7571	14	2,142,001	22.87	19.42		
C	UA-IFASA-5815	14	2,187,293	10.17			
O	ARS-BFGL-NGS-74378	14	2,616,322		7.68	*GPR20* *SLC45A4*	2,615,166 - 2,616,251 2,652,445 - 2,715,564
O	ARS-BFGL-BAC-1511	14	2,739,183		5.95	*DENND3*	2,711,735 - 2,775,154
O	UA-IFASA-9288	14	2,929,132		6.60	*PTK2*	2,844,134 - 3,037,063
O	Hapmap26527-BTC-005059	14	3,147,254		10.62	*CHRAC1*	3,153,138 - 3,156,593
B	ARS-BFGL-NGS-100480	14	3,336,128	12.89	6.52		
C	ARS-BFGL-NGS-102710	14	3,358,130	9.06		*TRAPPC9*	3,200,372 - 3,587,738
C	UA-IFASA-5765	14	3,491,977	9.93			
B	UA-IFASA-6329	14	4,059,754	6.43	7.76		
O	ARS-BFGL-NGS-56339	14	4,093,240		6.49		
O	ARS-BFGL-NGS-115947	14	4,459,231		7.82	*FAM135B*	4,388,017 - 4,643,810
C	UA-IFASA-7664	14	64,299,714	6.22		*RGS22*	64,289,853 - 64,398,324
C	UA-IFASA-7069	20	31,912,365	9.08		*GHR*	31,868,624 - 32,178,311
C	ARS-BFGL-NGS-118998	20	32,009,781	7.45			

[1]C = SNP was significant associated with fat percentage in conventional herds, O = SNP was significantly associated with fat percentage in organic herds, B = SNP was significantly associated with fat percentage in both systems,
[2]BTA = *Bos taurus* autosome;
[3]bp = Position in base pairs, according to bovine reference genome *Bos taurus* ARS-UCD1.2.

CHAPTER 5: GENERAL DISCUSSION

The research presented in this thesis is part of the "LongLife Project", which investigates breeding strategies to improve dairy cow longevity, with a focus on organic production systems. The present chapter discusses several important points that were not previously covered at length in this thesis. The first subsection of this chapter elaborates on the fundamental differences between longevity traits and the models used in Chapters 2 and 3. Furthermore, longevity in the total merit index is briefly considered. Next, choosing a model for estimating G×E and the effect of G×E on selection, is described. Then, breeding goals, programs, and appropriate dairy breeds for organic dairy production systems are discussed. Finally, future opportunities for the use of genomic selection to improve cattle longevity are proposed.

5.1 The effects of longevity

5.1.1 Comparison of longevity traits

As mentioned in the general introduction, there are various definitions of longevity. In Chapter 2, we estimated continuous traits – length of productive life (LPL) and the binary trait – stayability according to a certain lactation period. For LPL, we investigated the number of days that diseased cows could lose from LPL compared to healthy cows. For example, cows with mastitis at an early lactation stage are expected to have an LPL that is approximately 91 days shorter than that of healthy cows. For stayability, the output was the probability of survival in a specific lactation period. For example, if mastitis occurred at an early lactation stage, diseased cows would have a 1.66 % lower probability of survival compared to healthy cows. We found a similar heritability for LPL (0.05) and stayability in certain lactation periods (0.05-0.06). Additionally, we obtained high correlations between these traits (0.77 – 0.94). Thus, both LPL and stayability can be used to estimate longevity. Because of the early availability of stayability, this trait has been officially introduced in national genetic evaluations for longevity in German Holstein cattle (VIT, 2020).

Another longevity trait is the culling risk ratio, which was calculated with the proportional hazard model (Chapter 3). Results showed the relative risk of culling for cow groups compared to a reference group (in our case, healthy cows), in which the risk ratio was set to 1. For example, cows with mastitis that were in an early stage of first lactation had a lower risk ratio (1.29) compared to cows with mastitis in a late stage of first lactation (1.88). However, the results from the proportional hazard model were relative and difficult to explain in temporal terms. The heritability values of culling risk across models differed when the disease was separately or simultaneously considered at certain lactation stages. Thus, effective

heritability (ignoring the proportion of censoring) ranged from 0.01 to 0.36, and equivalent heritability (considering the proportion of censoring) ranged from 0.01 to 0.44. However, heritabilities significantly larger than from other models and extremely large shape parameter of the Weibull distribution from the model with health status considering nine stages from three lactations simultaneously indicating a potential bias. While ignoring diseases in survival analyses was lead to decline of culling risk heritabilities (see Chapter 3).

5.1.2 Choosing a model to estimate longevity traits

Because of its early availability, stayability could be more appropriate for estimating longevity, than LPL which is available after culling. Theoretically, threshold models are more suitable than linear models for analyzing categorical data such as stayability (Gianola and Foulley, 1983; Mäntysaari et al., 1991), as they account for non-normal distributions. However, several studies have reported minimal to no differences between threshold and linear models with regard to estimating cattle longevity (Holtsmark et al., 2009; van Pelt et al., 2015), mastitis (Carlén et al., 2006) and several binary reproductive traits (Vanderick et al., 2014; Silvestre et al., 2019). In addition, some researchers prefer using linear models because threshold models require more computing time (van Pelt et al., 2015).

In a linear model, the heritability of a binary trait should be transformed to the underlying normally distributed scale to facilitate comparison with heritability in a threshold model. The transformation of heritability was described by Robertson and Lerner (1949) and Dempster and Lerner (1950). Van Pelt et al. (2016) reported that the heritability values of binomial observations for stayability were lower when estimated with a linear model compared to a threshold model; however, after transformation to the underlying scale, the heritabilities were comparable between the models. However, van Vleck (1972) reported that heritability transformed to an underlying scale tended to be overestimate when normal heritability was large.

Through an analysis of survival to a certain endpoint, information on the length of life before or after the endpoint is ignored. An analysis of stayability at specific lactation stages does not consider how long the cow would live after its survival to a certain lactation stage. Thus, the accounting of censored records could be more appropriate for estimating longevity. These censored observations could be estimated with a proportional hazard model. However, Boettcher et al. (1999) and Lubbers et al. (2000) reported large correlations (0.72–0.97) between estimated breeding values (**EBV**) from linear and threshold models with EBV from proportional hazard models. In addition, Caraviello et al. (2004) reported stronger correlations

between estimates using proportional hazard models or linear models. The accuracy of reported EBV for longevity is controversial. Jamrozik et al. (2008) identified more accurate EBV from the Weibull model compared to the linear multiple-traits or random regression models, while Holtsmark et al. (2009) showed that linear multiple-traits models generated more accurate predicted sire breeding values than proportional hazards models.

The proportional hazard model requires much more computing memory (Boettcher et al., 1999), the transformation of heritability (Yazdi et al., 2002). In addition, it is difficult to compare effects from linear models and proportional hazard models (Jamrozik et al., 2008). In Chapter 3, we calculated the impacts of health traits on longevity using proportional hazard models and found that they required more time and computing memory compared to linear and thresholds models from Chapter 2.

In summary, we recommend the use of linear models to estimate the early available binary trait of stayability due to their shorter computing time compared to threshold or proportional hazard models. We also recommend avoiding transformation to an underlying scale due to the possibility of overestimating the transformed values.

5.2 The effects of genotype by environment interactions

In this study, the evaluation of genotype by environment interaction (**G×E**) was performed by estimating the genetic correlation of a trait expressed in different environments. The estimated effects of G×E were considered for yield, LPL, and health traits (Chapter 4) in organic and conventional production systems. Although there was no evidence of G×E for milk production traits, evidence of G×E was found for LPL and health traits.

5.2.1 Choosing a model to estimate genotype by environment interactions

There are two common methods for assessing the presence of G×E. The first is a multiple trait model in which each environment is considered as a separate trait (Falconer, 1952). A genetic correlation of less than 0.8 between traits expressed in different environments is an indication of G×E (Robertson, 1959). The second method is a reaction norm (**RN**) model in which phenotypes are described as a function of a continuous environmental gradient. In RN models, a difference in regression coefficients across environments is suggestive of G×E (Kolmodin et al., 2002). Fikse et al. (2003) concluded that multi-trait models perform better with regard to goodness of fit compared to RN models; however, it is important to note that this does not guarantee that the multi-trait model has greater accuracy. The advantage of the RN model is that environments can be easily defined as favorable or unfavorable (Kolmodin et al., 2002).

There are many possible environmental characteristics that could be defined in dairy cattle; however, they should effectively reflect the relevant environments and should not be strongly correlated with each other (Calus and Veerkamp, 2003). For example, a farm is simultaneously influenced by different environmental parameters; therefore, investigating the effects of only one environmental parameter would not accurately capture the environment of a herd. The disadvantage of the RN model is that environmental characteristics such as level of milk production, differences in feeding, or temperature cannot be simultaneously estimated.

Previously, Weigel and Rekaya (2000) proposed a "borderless clustering" approach, which suggested that herds in different countries may be more similar than herds within a country due to climate, herd management, genetic composition, and other factors. Thus, herds could be clustered by simultaneously considering different descriptors, and different production systems would be more accurately defined. For example, Ivemeyer et al. (2018) identified four types of organic dairy farms in Germany by performing cluster analysis according to herd size, milk yield, region, and housing system. These farm types were also found to be significantly different from each other with regard to feeding intensity and fertility traits. Given this evidence of diversity, organic farms could be considered different production systems with different breeding needs. However, cluster analysis is only possible with large amounts of data from organic farms. Due to the small number of organic herds examined in this study, multi-trait models and the correlation between same traits in different environments were used to examine G×E.

5.2.2 Genetic variance and heritability

In the present work, genetic variance and heritability were found to vary across environments, especially for traits with low heritability. For example, the heritability of mastitis was 0.11 in organic herds and 0.06 in conventional herds (see Chapter 4). Previous studies have reported differences in genetic variance and heritability between environments that were distinct with regard to productive and reproductive qualities (Kolmodin et al., 2002; Windig et al., 2006), herd sizes (Gernand et al., 2007), herd-year averages (Logar et al., 2007), production systems (extensive or intensive; Wahinya et al., 2020), housing systems (Lassen and Mark, 2008), and herd-test-day profiles (Huquet et al., 2012). This variation between environments can affect the accuracy of EBV in different environments (Hill et al., 1983). Thus, neglecting the effects of G×E could lead to biased EBV and suboptimal selection and breeding decisions (Meuwissen and van der Werf, 1993).

5.2.3 Considering selection response in light of genotype by environment interactions

It is important to consider that selection response may vary due to environmental differences between the environment in which the selection takes place and the production environment. Falconer (1952) identified that, if the environment in which animals were selected and the environment in which the products of selection will be used differ, the selection response in the production environment can be determined as a correlated response:

$$CR_Y = r_{XY} * \frac{\sigma_Y}{\sigma_X} * R_X,$$

where CR_Y is the correlated response in environment Y, r_{XY} is the genetic correlation between a trait expressed in different environments X and Y, σ_X and σ_Y are the genetic standard deviations in environments X and Y, and R_X is the response to selection in environment X.

Ignoring G×E can reduce selection response (Mulder and Bijma, 2005). Previous studies have reported low response to selection for sires that were selected and subsequently used in an extremely different environment. For example, selection response in the milk yield of sires evaluated in the UK and used in Kenya was 44% of the rate expected in the UK (Ojango and Pollott 2002). In addition, Mulder (2016) found that models that accounted for G×E were advantageous compared to conventional methods that ignored G×E in terms of accurately predicting both pedigree- and genomic-based breeding values in extreme environments. Furthermore, Yin et al. (2012) reported different genetic parameters between low- and high-input farming and underlined the importance of implementing organic breeding programs based on data from organic or low-input environments.

5.3 Improving longevity and health traits on organic dairy farms

5.3.1 Breeding goals, breeding program, and total merit index in organic production systems

Worldwide, breeding goals for dairy cattle have expanded beyond production traits to include functional traits such as health and longevity. However, the relative importance of these traits varies across production systems due to differing production conditions (Kargo et al., 2018) and economic weight of a trait (Groen et al., 1997). Organic dairy herds could be characterized by lower milk production levels and nutrition levels, smaller herd sizes, and restricted antibiotic use compared to conventional herds. The choices of organic farmers are often affected by these non-economic aspects and traits (Just et al., 2018). Some traits related to welfare and robustness can be difficult to measure in monetary terms. Nielsen et al. (2006) suggested defining the non-market value of these traits as a willingness to sacrifice milk yield.

Organic dairy farmers often emphasize disease resistance over milk production. In general, breeding goals tend to focus on functional traits due to the more limited medical treatment options available on organic farms, as preventive treatment with antibiotics is not permitted (EC, 2018). Another reason could be that the milk production potential of cows fed on grass cannot be as high as under conventional feeding, which uses more concentrate. In one study, Dutch organic dairy farmers were found to place more importance on functional traits such as udder health and fertility (Nauta et al., 2009). Similarly, Bapst et al. (2005) found that Swiss organic farms emphasized functional traits such as fertility, udder health, and longevity. In addition, Just et al. (2018) reported that organic farms in southern Germany weighted the fitness trait complex more than twice as heavily as conventional farms. Finally, another study found that Swedish organic dairy producers tended to desire a higher genetic gain in disease resistance than conventional producers (Ahlman et al., 2014). However, they reported that the development of special organic breeding goals was unreasonable, because differences between organic and conventional production environments were relatively small in Sweden and traits that were important to organic farms (e.g., longevity and disease resistance) were already considered in Nordic breeding goals at the time. Conversely, Slagboom et al. (2016) reported that Danish organic dairy farmers preferred more improvements in milk production traits than conventional farmers, which could be explained by farmers choosing to enhance weakly pronounced traits in their herds.

The organic dairy sector showed differences in breeding goals that varied according to farm management style. Ivemeyer et al. (2018) divided German organic farms by herd size, milk yield, region, and housing system and found a great diversity of breeding goals. For example, genetic hornlessness was identified as a priority breeding goal in one cluster but did not in the other clusters.

Currently, breeding bulls used in the organic production system are selected based on data that predominantly originates from conventional herds. According to Mulder et al. (2006), the development of a separate breeding program is needed when the genetic correlation is less than 0.61 and in the presence of moderate to severe G×E effects. Several studies have reported that a single breeding program for organic and conventional farms remains optimal (Nauta et al., 2006; Sundberg et al., 2010; Ahlman et al., 2014; Pfeiffer et al., 2017). However, the need for a unique breeding program may increase in the future with the growth of organic cattle populations (Liu et al., 2019). Nevertheless, a separate organic breeding program for organic dairy cow would likely be unsuccessful in Germany due to the low number of registered cows on organic farms.

An important tool in bull selection for organic farms is a separate total merit index (**TMI**) for organic production systems. The TMI is calculated by combining the EBV of economically important traits according to their weighting in the breeding goal. Therefore, it is important to consider the balance between production and functional traits. Categories of traits that have often been highlighted for dairy cattle include production, conformation, calving performance, female fertility, health, and longevity. Relative weights for categories of traits included in the TMI vary across countries, but the weight of functional traits in most countries has increased over the past few decades (Egger-Danner et al., 2015).

Table 5.1: The composition of total merit index in Holstein-Friesian cattle (according to EuroGenomics 2020)

Country[1]	Categories of traits					
	Production	Conformation	Calving	Fertility	Health	Longevity
DEU	45	15	3	10	7	20
DNK, SWE, FIN	29	15	13	12	21	4
ESP	49	20	0	8	12	11
FRA	35	15	0	22	18	5
NDL	26	30	5	14	14	11
POL	40	25	0	15	10	10

[1]Country ISO code: DEU = Germany, DNK = Denmark, ESP = Spain, FIN = Finland, FRA = France, NDL = Netherlands, POL = Poland, SWE = Sweden.

For Fleckvieh cattle, 65% of organic TMI comprises a fitness complex that includes longevity, udder health, fertility and conformation traits (LfL, 2020). In official TMI used in conventional farms, the weight of the fitness complex is lower and amounts to 44%. There is currently no organic selection index for German Holstein cows (VIT, 2020). However, the relative weight of functional traits amount to 55% of current TMI in conventional German Holstein farms. Furthermore, moderate to high genetic correlations between longevity and functional trait groups (0.20–0.45) can indirectly influence the improvement of longevity.

In summary, the development of separate breeding goals for organic dairy production systems could be appropriate when strong differences exist between organic and production environments or when conventional breeding goals do not consider traits that are important in organic herds, such as longevity and disease resistance. In addition, the diversity of organic farms should be taken into account. The development of a separate organic breeding program may not be appropriate when there is a low number of organic cows. However, the calculation

of separate organic TMI with a large proportion of functional traits could maximize genetic gain on organic farms.

5.3.2 Reproductive technology in organic production systems

Differences in acceptable reproductive technology between conventional and organic farming is worth noting. Currently, artificial insemination (**AI**) and multiple ovulation and embryo transfer (**MOET**) are broadly used in conventional cattle breeding. However, the use of MOET is not acceptable for breeding under organic standards (EC, 2018). These rules regarding organic cattle reproduction hinder the possibility of rapid genetic progress, as the MOET procedure would minimize the generation interval and increase the selection intensity of cows (Seidel and Seidel, 1991). Slagboom et al. (2020) presented a simulation study with different scenarios for organic breeding program implementation and found that banning MOET and using only organic bulls for breeding decreased genetic gain by more than 24%. Additionally, some organic farmers prefer to use natural mating rather than AI, because AI can conflict with natural mating behaviors. On German organic dairy farms, the percentage of cows subjected to natural mating ranges from 21% for large farms in northwest Germany to 49% for smaller farms in western Germany (Ivemeyer et al., 2018). In one simulation, Yin et al. (2014) found that the use of genotyped bulls from an organic population with AI ensured the greatest genetic gain compared to the natural breeding of genotyped bulls from an organic population. However, using genotyped organic bulls in natural breeding rather than implementing an AI program with conventional bulls is only suggested for traits with a strong G×E effect between conventional and organic farms and high reliability of genomic predicted EBV for organic bulls. Thus, we propose revising the ban on MOET and using AI from conventional bulls in order to maximize genetic gain in organic herds.

5.3.3 Selecting appropriate dairy breeds for organic production systems

For many years, genetic selection worldwide focused on American Holstein-Friesian cattle (Oltenacu and Broom, 2010; Rodríguez-Bermúdez et al., 2019), which demonstrated excellent milk production potential. However, this was only the case in comfortable environments in which they were fed high-quality diets. Accordingly, local European breeds such as the original Friesian cattle were replaced by American Holstein-Friesian cows (Brotherstone and Goddard, 2005). This selection for high milk production resulted in low disease resistance and more reproductive problems (Bjelland et al., 2011). However, the performance of Holstein cattle was not optimal under organic production conditions; therefore, their suitability for

organic milk production was uncertain (van Diepen et al., 2007; Horn et al., 2012). Despite these findings, previous studies have reported high proportions of Holstein breed cattle in Dutch (Nauta et al., 2006), Canadian (Rozzi et al., 2007), Spanish (Rodríguez-Bermúdez et al., 2017), and German organic dairy herds (excluding southern Germany; Ivemeyer et al., 2018). By contrast, Swedish Red cattle were found to be the most common breed on Swedish organic farms (Ahlman, 2010), and Brown Swiss and Fleckvieh cattle were the most common breeds on organic farms in Austria and Switzerland (Haas and Bapst, 2004; Roesch et al., 2005).

According to European Union organic regulations (EC, 2018), organic farmers should choose a breed that can adapt to local conditions. In contrast to conventional dairy herds, which generally feature purebred Holstein cows, many breeds can therefore be found in organic dairy herds. Organic farmers experiment with a variety of breeds, including Holstein cows from conventional selection, local breeds such as rustic Holstein, dual-purpose breeds, and crossbred cattle. Local breeds are generally more adaptable to local conditions but produce less milk than Holstein-Friesian cows. These breeds include Fleckvieh and Groningen White Headed cattle common to Dutch organic farms (Haas et al., 2013) and Normande and Montbeliarde cows adapted to the seasonal grass-based systems used in Ireland (Dillon et al., 2003). In Austria, Switzerland, Poland, and Sweden, Bieber et al. (2019) found that local breeds used in organic dairy systems had advantages with regard to longevity, fertility, and health traits compared to conventional commercial dairy breeds.

Generally, it would seem that the rustic Holstein-Friesian cattle gut has adapted to pasture-based feeding systems. In a review, Baudracco et al. (2010) demonstrated that Holstein-Friesian cows with a lower percentage of North American genes (New Zealand strain cattle) had greater pregnancy rates and achieved more economic profits in grazing dairy systems compared to those with a higher percentage of these genes. Furthermore, Irish strain of the Holstein-Friesian exhibited better survival and reproductive performance than American Holstein-Friesian cattle on grass-based farms (Dillon et al., 2003).

An example of a local German breed that contains Holstein-Friesian genes is the German Black and White dual-purpose cattle (Deutschen Schwarzbunten Niederungsrind; DSN). This breed has been characterized as a healthy cattle breed with good fertility and the ability to adapt to a wide variety of farming conditions (Brade and Brade, 2013). As a result, this breed is very common on organic farms.

Schäler et al. (2019) reported that the selection of cattle based on native uniqueness could lead to the production of more robust and functional individuals. Organic farmers frequently cross

Holstein-Friesian cattle with local breeds in order to create highly productive cattle (Rozzi et al., 2007). This crossbreeding strategy could improve fitness, as shown on Dutch organic farms, where crossbreeding Holstein cows with dual-purpose and local breeds improved fertility and udder health in most cases (Haas et al., 2013). In short, previous studies have indicated that there is no single breed that is best-suited to organic farming. However, the use of local breeds or rustic strains of Holstein-Friesian cattle is likely to be advantageous for organic farms.

5.3.4 Genomic selection for health traits and longevity in organic production systems

The use of genomic selection tools can minimize generation interval and increase prediction accuracy (Schaeffer, 2006). Currently, genomic breeding values (**GBV**) are widely used (Hayes et al., 2009, VanRaden et al., 2009). Increased accuracy and a reduced generation interval are especially important for traits with low heritability or that can only be effectively assessed at the end of an animal's life. The reliability of GBV depends on the level of linkage disequilibrium between markers and quantitative trait loci, the heritability of the trait, and the number of animals with known phenotypes and genotypes – the so-called "reference group" (Goddard, 2009; Hayes et al., 2009; Brito et al., 2011). Plieschke et al. (2018) and Thomasen et al. (2020) reported that adding more genotyped cows to a reference population has the potential to increase genetic gain and the reliability of GBV. Worldwide, approximately 3.5 million genotyped animals are available for Holstein cattle, and approximately 3.2 million of these animals are cows (CDCB, 2020). It is especially important to build a cow training set with traits for which assessment began more recently – such as the diagnosis of diseases – and only a few sires are available with high EBV reliability. For traits with low heritability, it is important to note that many cow genotypes are required to achieve high accuracy for sire GBV (Berry et al., 2019). However, it is also important consider that preselection would not represent a random sample and decreases the reliability of GBV (Plieschke et al., 2016). Therefore, it is more appropriate to randomly genotype groups of cows.

Currently, several research projects focus on the systematic genotyping of cows with certain phenotypes with the goal of building a cow training set. In Germany and Austria, projects with a focus on health traits include "FoKUHs", "Braunvieh Vision", "Fleckfficient" and "KuhVision" (Schwarzenbacher, 2019). The "LongLife Project" focused on the development of reference groups of cows from organic herds in order to analyze the association between genotypes and phenotypes of health traits and longevity and to compare these associations with cows from conventional herds. Due to the low number of genotyped organic dairy cattle

and the low heritability of longevity and health traits, extending the reference group for genomic predictions is especially important in organic production systems.

Despite the decreasing cost of genotyping chips, expenses can be a barrier for many farmers, especially if a large number of cows must be genotyped. However, using low-density panels and imputing missing genotype information from the high-density haplotypes of relatives offer a less costly option for genotyping a large number of animals. Therefore, combining markers with different densities can be used to balance the benefits of genomic selection and the cost of genotyping many animals (VanRaden et al., 2010). Pausch and Fries (2013) proposed the combination of genotype information from a large number of animals using DNA sequencing from so-called "key animals", which reflects a large proportion of a population's genetic diversity in order to explain a small proportion of the genetic variation. The re-sequencing of these key animals is a cost-effective approach for detecting causal trait variants in the entire population (Jansen et al., 2013; Daetwyler et al., 2014).

Thus, to increase the accuracy of breeding values for health traits and longevity, we suggest using genomic selection, low-density panels for the genotyping of cows, and the systematic collection of certain phenotypes, especially in organic herds.

5.4 General conclusion and recommendations

In summary, this work reached a number of main conclusions: there was disagreement between culling reasons provided by farmers and veterinary diagnoses. Therefore, we suggest including veterinary diagnoses rather than culling reasons when calculating EBV for disease resistance. High genetic correlations between length of productive life and stayability in different lactation periods (0.77–0.94) indicate similarities between these traits. Thus, both traits can be used to improve longevity. In addition, udder and metabolic diseases had a strong negative impact on the length of productive life and stayability; thus, these diseases could be used as indicator traits for longevity. Conversely, claw and female fertility disorders were found to have a minor impact on longevity. Due to the additional time and computing memory needed, the proportional hazard model is not recommended to predict longevity. Milk production traits in cattle from both conventional and organic farms showed similar heritability and high genetic correlations, and many significantly associated SNP markers and annotated potential candidate genes common to both production systems. These results indicate the absence of G×E. Unlike milk production traits, health traits and longevity showed variable heritability between organic and conventional farms, genetic correlations of substantially lower than 0.80, and a lack of common significantly associated single nucleotide polymorphisms. These results are consistent with the presence of G×E.

Based on our findings, we recommend the following measures:

- Veterinary diagnoses rather than culling reasons should be used to improve disease resistance. Therefore, uniform veterinarian diagnosis records should be considered across organic farms.
- Separate breeding goals and a corresponding organic merit index should be developed, with more weight placed on longevity and health traits. A separate breeding program for organic farms would fail due to the limited number of organic cows.
- The organic cow reference population should be expanded through the comprehensive genotyping of organic cows in order to increase the accuracy of genetic parameter estimates.

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FURTHER PUBLICATIONS

2020

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71th Annual Meeting of the European Federation of Animal Science, 01.-04. December 2020, Virtual meeting

Rolfes, A., T. Shabalina, H. H. Swalve, S. König (2020): Verbesserung der Langlebigkeit von Milchkühen unter besonderer Berücksichtigung ökologischer Zuchtstrategien. Final report of the project LongLife.

2019

Shabalina, T., T. Yin, K. May, S. König (2019): Genomische Charakteristika für Produktionsmerkmale und Langlebigkeit von Holstein Friesian Kühen unter Berücksichtigung ökologischer und konventioneller Haltungsumwelten.
Jahrestagung/Vortragstagung der DGfZ und GfT, 11. - 12. September 2019, Gießen

2018

Shabalina, T., T. Yin, S. König (2018): Survival analysis for health traits in German Holstein dairy cows.
69th Annual Meeting of the European Federation of Animal Science, 27. - 31. August 2018, Dubrovnik, Croatia

Shabalina, T., T. Yin, S. König (2018): Lebensdaueranalysen für Deutsche Holsteinkühe unter Berücksichtigung von Gesundheitsmerkmalen.
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2017

Shabalina T., T. Yin, S. König (2017): Einfluss der Tiergesundheit auf Merkmale der Langlebigkeit von Kühen der Rasse Holstein-Friesian.
Jahrestagung/Vortragstagung der DGfZ und GfT, 20. - 21. September 2017, Stuttgart

Der Lebenslauf wurde aus der elektronischen Version der Arbeit entfernt.

The curriculum vitae was removed from the electronic version of the paper.

FORMAL DECLARATION

Erklärung gemäß der Promotionsordnung des Fachbereichs 09 vom 07. Juli 2004 § 17 (2)

„Ich erkläre: Ich habe die vorgelegte Dissertation selbständig und ohne unerlaubte fremde Hilfe und nur mit den Hilfen angefertigt, die ich in der Dissertation angegeben habe.

Alle Textstellen, die wörtlich oder sinngemäß aus veröffentlichten Schriften entnommen sind, und alle Angaben, die auf mündlichen Auskünften beruhen, sind als solche kenntlich gemacht.

Bei den von mir durchgeführten und in der Dissertation erwähnten Untersuchungen habe ich die Grundsätze guter wissenschaftlicher Praxis, wie sie in der „Satzung der Justus-Liebig-Universität Gießen zur Sicherung guter wissenschaftlicher Praxis“ niedergelegt sind, eingehalten.“

Gießen, den 02. Februar 2021

Taisiia Shabalina