

## **ABSTRACT**

DHAKAL, KUMUD. Phenotypic and Genetic Aspects of Health Events and Production Traits in Dairy Cattle. (Under the direction of Christian Maltecca and Joseph P. Cassady).

The overall objective of this study was to estimate causal relationships among common health disorder and production traits, and to estimate variance components of common health disorders and production measures. Two separate studies were conducted to identify causal relationships among health disorders and production traits using structural equation models (SEM) implemented in a Bayesian framework. In the first study, the dataset included traits like reproductive health disorders (retained placenta (RP); metritis (METR)), metabolic health disorders (ketosis (KETO); displaced abomasum (DA)), mean milk yield (MY) from early part of lactation (1-120 DIM), peak milk yield (PMY), day in milk of peak milk yield (PeakD), and lactation persistency (LP). Three different sets of traits were analyzed which included: recursive effect from each health disorder on culling reason; recursive effects of one health disorder on another health disorder and on MY, and recursive effects of each health disorder on production traits including PeakD, PMY and LP. The estimated structural coefficients of the recursive models revealed how the presence of health disorder increases culling frequency with stronger impact from DA, followed by RP, KETO, and METR. Positive recursive effects of RP to METR and of KETO on DA were estimated, while recursive effects from health disorders to production traits were negligible in all cases. The second study, included mastitis events of first and second lactation, LP, and test day milk yields recorded in three different periods; period 1 (5 to 60 DIM), period 2 (61 to 120 DIM) and period 3 (121 to 180 DIM), and total milk yield recorded for second lactation. The causal relationship between mastitis and milk yield found in this study suggests that mastitis results

in a direct decline in test day milk production. There is nonetheless little impact of mastitis on LP. The causal relationship among mastitis events in first and second lactation found in this study indicate that having a mastitis in first lactation is likely to increase the risk of a mastitis in later lactations. Based on the results it was concluded that a health disorder occurring in early lactation has a moderate causal effect on the health disorder occurring in later lactation. Causal links among mastitis events and test-day milk yields were detected that evolved over the course of lactation in the cow's life. Heritability estimates of health disorders ranged from 0.023 to 0.114, in accordance with previous studies. Similarly, genetic correlations obtained between health disorders and production measures were moderate. The SEM should be implemented in analyzing health traits in order to make better farm management decisions, because knowing causal relationships between health disorders will provide information on future health events. This information may then be used to reduce the likelihood of future health challenges via management intervention. In the third study, variance components and heritability of infectious and non-infectious hoof lesions were estimated using pedigree- and genomic-based analyses. In case of genomic-based analysis, a single-step procedure was conducted to estimate genomic variance components and heritability for hoof lesions. The pedigree based analysis produced heritability estimates of 0.11 ( $\pm$  0.05) for infectious hoof lesions and 0.08 ( $\pm$  0.05) for non-infectious hoof lesions. The single-step genomic analysis produced heritability estimates of 0.14 ( $\pm$  0.06) for infectious hoof lesions and 0.12 ( $\pm$  0.08) for non-infectious hoof lesions. Inclusion of genomic data substantially improved young sire reliabilities for hoof lesions. Genomic selection against the occurrence of hoof lesions should be incorporated into breeding programs to improve the health status of animal.

© Copyright 2014 by Kumud Dhakal

All Rights Reserved

Phenotypic and Genetic Aspects of Health Events and Production Traits in Dairy Cattle

by  
Kumud Dhakal

A dissertation submitted to the Graduate Faculty of  
North Carolina State University  
in partial fulfillment of the  
requirements for the degree of  
Doctor of Philosophy

Animal Science & Poultry Science

Raleigh, North Carolina

2014

APPROVED BY:

---

Christian Maltecca  
Co-Chair of Advisory Committee

---

Joseph P. Cassady  
Co-Chair of Advisory Committee

---

Steven P. Washburn

---

David A. Dickey  
Minor Representative

**DEDICATION**

To my parents

## **BIOGRAPHY**

Kumud Dhakal was born and raised on Kathmandu, Nepal. After graduating from high school, Kumud enrolled as a student at Tribhuvan University in the Institute of Agriculture and Animal science, Rampur campus, Chitwan, where he completed his undergraduate degree in Bachelor of Veterinary Science and Animal Husbandry (BVSc & AH). In fall of 2009, Kumud came to United States to pursue his further study on animal science and joined University of Nebraska-Lincoln. He conducted his research under the supervision of Dr. Jeffrey F. Keown in the area of dairy management and graduated with Masters of Science (MS) degree in Animal science in August 2011. After that, Kumud moved to Raleigh, NC, and joined North Carolina State University (NCSU) for PhD program in Animal breeding and genetics starting at fall of 2011. At NCSU, he has been working for his doctoral research in phenotypic and genetic relationships between health events and production traits in dairy cattle, under the supervision of Dr. Christian Maltecca and Dr. Joseph P. Cassady. His research interest includes using quantitative genetics, genomics, and statistics to predict behavior of complex traits.

## ACKNOWLEDGMENTS

First of all, I would like to express my gratitude to my supervisors Drs. Christian Maltecca and Joseph P. Cassady for their guidance, encouragement and excellent advice throughout my study. I acknowledge my committee members Drs. Steve Washburn and David A. Dickey for their suggestions and technical guidance.

I'm very thankful to Dr. Francesco Tiezzi for his guidance and expertise that he have shared with me during my research. I'm very thankful to my lab friends Kristen Parker Gaddis, Shuhui Jiao, Maria Arcero and Jeremy Howard for their help with the development of my research. I would also like to thank Marian Correll for all of her assistance.

I appreciate the support from the North Carolina Agriculture foundation for providing assistantship for this research. I would also like to thank Dairy Records Management Systems for providing the data necessary to make this project successful. It is my pleasure to thank those who made this dissertation possible, which would not have been completed without the valuable contributions and advice of many people.

I wish to thank my parents, Mr. Megh Raj Dhakal and Mrs. Tara Dhakal, for their love and encouragement. I am thankful to my brother, Mr. Kundan Dhakal, and sister-in-law, Mrs. Sonisa Sharma, for the guidance, love and encouragement.

Last, but not least, my wife Anita Panthi, for all the love, encouragement, moral and technical supports, and for being there for me throughout the dissertation project.

## TABLE OF CONTENTS

LIST OF TABLES .....	ix
LIST OF FIGURES .....	xii
CHAPTER1. LITERATURE REVIEW .....	1
INTRODUCTION .....	2
Common health disorders in dairy cattle .....	3
Mastitis .....	5
Lameness .....	8
Displaced Abomasum.....	11
Ketosis .....	12
Metritis.....	15
Retained Placenta .....	18
Selection of health traits in dairy cattle.....	20
Structural equation models .....	21
Genomic selection.....	23
On-farm producer recorded health data .....	25
CONCLUSION.....	26
Chapter 2.....	26

Chapter 3.....	27
Chapter 4.....	27
REFERENCES .....	28
CHAPTER 2. INFERRING CAUSAL RELATIONSHIPS BETWEEN REPRODUCTIVE AND METABOLIC HEALTH DISORDERS AND PRODUCTION TRAITS IN FIRST-LACTATION US HOLSTEINS USING RECURSIVE MODELS .....	
	42
ABSTRACT.....	43
INTRODUCTION .....	44
MATERIALS AND METHODS.....	47
Data description.....	47
Statistical Analyses.....	49
RESULTS AND DISCUSSION.....	55
Recursive effects.....	55
Health disorders and culling .....	55
Health disorders and production traits .....	57
Heritabilities and Genetic Correlations .....	60
CONCLUSION.....	62
REFERENCES .....	62

CHAPTER 3. CAUSAL RELATIONSHIPS BETWEEN CLINICAL MASTITIS EVENTS, MILK YIELDS AND LACTATION PERSISTENCY IN US HOLSTEINS.....	85
ABSTRACT.....	86
INTRODUCTION .....	87
MATERIALS AND METHODS.....	89
Data.....	89
Statistical Analysis .....	90
RESULTS AND DISCUSSION .....	95
Recursive effects.....	95
Heritabilities and genetic correlations .....	98
CONCLUSION.....	100
REFERENCES .....	101
CHAPTER 4. GENOMIC SELECTION FOR HOOF LESIONS IN US HOLSTEINS.....	113
ABSTRACT.....	114
INTRODUCTION .....	115
MATERIALS AND METHODS.....	116
RESULTS AND DISCUSSION .....	119
CONCLUSION.....	122

REFERENCES ..... 122

CONCLUSION..... 129

## LIST OF TABLES

### CHAPTER 2. Inferring Causal Relationships between Reproductive and Metabolic Health Disorders and Production Traits in First-Lactation US Holsteins using Recursive Models

Table 1 Descriptive statistics for metabolic (ketosis and displaced abomasum) and reproductive (retained placenta and metritis ) health disorders .....	67
Table 2 Descriptive statistics of production traits.....	68
Table 3 Posterior mean, standard deviation (SD), and 95% highest posterior density interval (95% HPD) of recursive effects from liability to health disorder (retained placenta (RP), metritis (METR), ketosis (KETO), and displaced abomasum (DA)) to culling from Health-Culling analyses.....	69
Table 4 Posterior mean, standard deviation (SD), and 95% highest posterior density interval (95% HPD) of recursive effects between liability to health disorders disorder (retained placenta (RP), metritis (METR), ketosis (KETO), and displaced abomasum (DA)) and between production traits (milk yield 1 (MY1) and milk yield 2 (MY2)) from Health-MY <sup>1</sup> analyses.....	70
Table 5 Posterior mean, standard deviation (SD), and 95% highest posterior density interval (95% HPD) of recursive effects from liability to health disorders ((retained placenta (RP), metritis (METR), ketosis (KETO), and displaced abomasum (DA)) to	

production traits (day in milk of peak milk yield (PeakD), peak milk yield (PMY), lactation persistency (LP)) from Health-Lactation <sup>1</sup> analyses .....	71
Table 6 Posterior mean, standard deviation (SD), and 95% highest posterior density interval (95% HPD) of heritability of liability a health disorders and production traits from Health-Culling, Health-MY, and Health-Lactation analyses. ....	72
Table 7 Posterior mean, standard deviation (SD), and 95% highest posterior density interval (95% HPD) of genetic correlations of health disorders and production traits from Health-Culling, Health-MY and Health-Lactation analyses .....	74
 CHAPTER 3. Causal Relationships between Clinical Mastitis events, Milk Yields and Lactation Persistency in US Holsteins	
Table 1 Descriptive statistics for mastitis events .....	105
Table 2 Descriptive statistics of production measures.....	102
Table 3 Posterior mean, standard deviation (SD), and 95% highest posterior density interval (95% HPD) of causal relationships between liability to mastitis, milk yields, and lactation persistency .....	103
Table 4 Posterior mean, standard deviation (SD), and 95% highest posterior density interval (95% HPD) of heritability of liability to mastitis, milk yields (MY), and lactation persistency, and total milk yield (TMY) of second lactation. ....	108

Table 5 Posterior mean, standard deviation (SD), and 95% highest posterior density interval (95% HPD) of genetic correlation between liability to mastitis, milk yields, and lactation persistency .....	109
--	-----

#### CHAPTER 4. Genomic Selection for Hoof lesions in US Holsteins

Table 1 Posterior mean, SD, and 95% highest posterior density (HPD) of variance components and heritability of infectious and non-infectious hoof lesions obtained from pedigree- and genomic-based analysis. ....	125
Table 2 Comparison of mean sire reliabilities from pedigree-and genomic-based analysis.	126
Table 3 Posterior mean, standard deviation (SD), and 95% highest posterior density (HPD) of heritability and genetic correlation from bivariate analysis of hoof lesions and lameness traits from both pedigree-and genomic based analysis. ....	127

## LIST OF FIGURES

### CHAPTER 2. Inferring Causal Relationships between Reproductive and Metabolic Health Disorders and Production Traits in First-Lactation US Holsteins using Recursive Models

Figure 1 Recursive threshold sire model was used in the analysis: (A) Possible relationship between retained placenta (RP) and culling, (B) Possible relationships between metritis (METR) and culling, (C) Possible relationships between ketosis (KETO) and culling, and (D) Possible relationships between displaced abomasum (DA) and culling. A single headed arrow ( $\rightarrow$ ) indicates a causal relationship. .... 76

Figure 2 Recursive Gaussian threshold sire model was used in the analysis: (A) Possible relationships between two reproductive health disorder traits, retained placenta (RP) and metritis (METR) along with production traits, milk yield 1 (MY1) and milk yield 2 (MY2), (B) Possible relationships between two metabolic health disorder traits, ketosis (KETO) and displaced abomasum (DA) along with production traits, MY1 and MY2, and (C) Possible relationships between reproductive health disorder traits (REPRO), metabolic health disorders (META) traits along with production traits, MY1 and MY2. A single headed arrow ( $\rightarrow$ ) indicates a causal relationship. 77

Figure 3 Recursive Gaussian threshold sire model was used in the analysis: (A) Possible relationships between retained placenta (RP) and production traits such as days in milk at peak milk yield (PeakD), peak milk yield (PMY), and lactation persistency of milk yield (LP), (B) Possible relationships between metritis (METR) and

production traits such as PeakD, PMY, and LP, (C) Possible relationships between ketosis (KETO) and production traits such as PeakD, PMY, and LP, (D) Possible relationships between displaced abomasum (DA) and production traits such as PeakD, PMY and LP. A single headed arrow ( $\rightarrow$ ) indicates a causal relationship.. 79

Figure 4 Posterior distributions of recursive effects from: (A) liability to health disorder (LDA, LKETO, LMETR, or LRP) to culling; (B) liability to one health disorder (LKETO, LRP, and LREPRO) to liability to another health disorder (LDA, LMETR, and LMETA); (C) liability to health disorders (LDA, LKETO, LMETR, LRP) to milk yield 1 (MY1); (D) liability to health disorders (LDA, LKETO, LMETR, LRP) to milk yield 2 (MY2); (E) liability to health disorders (LREPRO, LMETA) to MY1; (F) liability to health disorders (LREPRO, LMETA) to MY2. LDA= liability to displaced abomasum; LKETO = liability to ketosis; LMETR= liability to metritis; LRP= liability to retained placenta; LREPRO = liability to reproductive diseases; LMETA=liability to metabolic diseases. .... 81

Figure 5 Posterior distributions of recursive effects from: (A) liability to health disorders (LDA, LKETO, LMETR, or LRP) to day in milk of peak milk yield (PeakD); (B) liability to health disorders (LDA, LKETO, LMETR, or LRP) to peak milk yield (PMY); (C) liability to health disorders (LDA, LKETO, LMETR, or LRP) to lactation persistency. LDA= liability to displaced abomasum; LKETO = liability to ketosis; LMETR= liability to metritis; LRP= liability to retained placenta. .... 83

CHAPTER 3. Causal Relationships between Clinical Mastitis events, Milk Yields and  
Lactation Persistency in US Holsteins

- Figure 1 Recursive effects between milk yields and liability to mastitis in three different periods of first-lactation (5 – 60, 61 – 120, and 121 – 180 days in milk): (A) Recursive effects from liability to mastitis (LMAST1, LMAST2, LMAST3) to milk yields (MY1, MY2, MY3) of corresponding period of first -lactation; (B) Recursive effects from milk yields (MY1 and MY2) to liability to mastitis (LMAST2 and LMAST3) of corresponding period of first lactation; (C) Recursive effects from liability to mastitis (LMAST1, LMAST2, LMAST3) to lactation persistency of milk yield (LP)..... 110
- Figure 2 Recursive effects between liability to mastitis events between parity 1, 2 and total milk yield (TMY) of second parity: (A) Recursive effects from liability to mastitis in parity 1 (LM1) to liability to mastitis in parity 2 (LM2); (B) Recursive effects from milk yields LM1 and LM2 to TMY..... 112

## CHAPTER 4. Genomic Selection for Hoof lesions in US Holsteins

Figure 1 Increase in reliability trend with respect to number of daughters per sire in univariate single-step analysis for: (A) infectious hoof lesions, and (B) non-infectious hoof lesions.....	128
---	-----

CHAPTER 1  
**LITERATURE REVIEW**

## INTRODUCTION

Breeding healthier cattle is now a global demand of dairy producers and milk consumers. There has been an increasing interest in breeding dairy cows by dairy producers that will be healthier, produce optimum milk yields, and remain in the herd for a longer time (Maltecca, 2013). Direct and indirect costs associated with health events account for a large proportion of the expenses sustained by the producer (Kossaibati and Esslemont, 1997). Such costs can potentially be reduced significantly by performing selection on improved health status of dairy cows. Economic losses associated with poor health in dairy cows is an important concern to the US dairy industry (Wells et al., 1998). Despite the effort to control or prevent health disorders, problems associated with health disorders have been gradually increasing, especially in high producing dairy cows (Ingvarlsen et al., 2003).

Opinions among researchers differ on whether the continuous selection for milk yield is the leading cause of production-associated diseases. Oltenacu and Broom (2010) reported that before the mid-1980s, an increase in milk yield was mainly due to better management such as feed meeting nutritional standards and improvement in quality of roughages, and thereafter increased milk production can primarily be attributed to genetics. Continuous selection for milk yield in the US dairy cows, has tripled the amount of milk produced per cow since the 1950s (VanRaden, 2004). The emphasis on increased profit through high production in dairy cattle has resulted in negative associations between production measures and health traits (Rauw et al., 1998). Similarly, Ingvarlsen et al. (2003) concluded that continued selection for milk yield will continue to increase the incidence rate of health

disorders. Rauw (2009) concluded that continued selection for milk yield without providing proper nutrition, health management, and an energy balance will affect other biological functions such as immune functions, reproductive functions, and maintenance functions, which leads to poor welfare and increased health costs.

Studies by Dunklee et al. (1994) and Jones et al. (1994) found that higher health care costs were associated with high producing cows when compared with the control line of cows producing average milk yield. Other studies (Simianer et al., 1991; Van Dorp et al., 1998; Berry et al., 2004) have highlighted the correlation between high milk yield and incidences of health disorders. Nonetheless, causal relationships between these factors has often been overlooked. Different types of causal associations could be sources of correlation between milk yield and health disorders. For example, correlations between milk yield and health disorders could be due to the causal effect of milk yield on a health disorder or to a causal effect of a health disorder on milk yield. In addition, there could be another trait, for instance, the negative energy balance which could be affecting both milk yield and health disorder trait simultaneously. Thus, the knowledge regarding cause and effect relationships between phenotypes should be paramount in predicting the effect of management practices focused on traits like milk yield and health disorders (Rosa et al., 2011).

### **Common health disorders in dairy cattle**

Mastitis and lameness are the two most common disease in dairy cows worldwide. Beside these, globally other most frequent dairy herd diseases are metabolic diseases (e.g. milk fever, ketosis, displaced abomasum), and reproductive diseases (e.g. cystic ovaries,

retained placenta, metritis). The most common dairy cattle health disorders that have been studied in the United States are retained placenta, metritis, ketosis, displaced abomasum, mastitis and lameness (Kaneene and Hurd, 1990; Lyons et al., 1991; Zwald et al. 2004; Appuhamy et al, 2009; Parker Gaddis et al., 2012; 2014). Among these health disorders, mastitis and lameness are recognized as having significant negative impact on profitability of dairy enterprise worldwide (Berry et al., 2011). Several studies investigated the association between health disorders and production measures. Test day milk yields, peak milk yield, days in milk (DIM) at peak milk yield, and lactation persistency of milk yield are all production measures that help define the lactation curve of dairy cattle. These production measures are important because the amount of milk produced by cow is dependent on the shape of its lactation curve. Carlen et al (2004) reported that undesirable genetic relationship exists between health disorders and production measures. Heuer et al. (1999) raised concern on whether an increase in milk production is associated with certain diseases. Fleischer et al. (2001) reported that high metabolic priority is given for milk secretion at the expense of the other reproductive and metabolic process in dairy cattle. As a result, disease may develop (Bauman and Bruce Currie, 1980). Simianer et al. (1991) reported that high milk producing cows are more susceptible to disease than low milk producing cows due to the antagonistic relationship between disease resistance and total milk production. Wilson et al. (2004) reported that milk yield from high producing sick cows could still be better than or at least similar to that of their healthy, low-producing herd mates.

The effects of diseases on production measures varies according to when diseases occurred during a cow lactation period. Such as reproductive disease which normally appears in early lactation may reduce the milk yield in early period but may not affect the milk yield of late lactation, whereas mastitis occurrences has been observed throughout the cow lactation period and the overall mastitis effect would reflect declined lactation persistency. In this context, a general discussion of common health disorders of dairy cattle especially mastitis, lameness, metabolic health disorders (ketosis and displaced abomasum), reproductive health disorders (retained placenta and metritis), and their association with production measures is provided below. Health disorders are ordered according to their significant impact on profitability of the US dairy enterprise.

### **Mastitis**

Mastitis is defined as the inflammation of the mammary gland. Bovine mastitis is one of the highly prevalent, most costly disease to dairy producers (Bennett et al., 1999; Halasa et al., 2007), and is widely investigated disease worldwide. Literature on research about bovine mastitis is quite abundant and most of them mainly discussed about the incidence pattern of mastitis occurrence (Barkema et al., 1998; Olde Riekerink et al., 2008); risk factors of mastitis (Elbers et al., 1998; Peeler et al., 2000); economic aspects of mastitis in dairy industry (Blosser, 1979; Schakenraad and Dijkhuizen, 1990; Halasa et al., 2007); genetic studies of mastitis resistance (Heringstad et al., 2000; Rupp and Boichard, 2003; Østerås et al., 2007); relationship of mastitis with production traits and other health traits (Zwald et al.,

2004b, Appuhamy et al., 2007, Parker Gaddis et al, 2012; 2014). A concise summary of mastitis and its relationship with production traits is provided below.

Although there has been great advancement in treatment and care, mastitis is considered as a serious global issue due to the fact that the incidence of mastitis has increased in many countries over the past 30 years (Oltenacu and Broom, 2010). Loss due to mastitis mostly include veterinary and treatment costs, discarded milk following treatment, reduced milk production, and increased risk of culling (Shim et al., 2004; Hinrichs et al., 2005; Bar et al., 2008; Hertl et al., 2011; Koeck et al., 2012a). In addition, replacement costs, increased reproductive problems, increased future disease risk, and increased labor cost due to mastitis substantially impact the profitability of dairy enterprises (Moore et al., 1991; Huijps et al., 2008). Shim et al. (2004) reported mastitis is estimated to cost US dairy producers about \$1.2 to 1.7 billion per year. Wilson et al. (2004) estimated that the average cost of clinical mastitis within lactation per case to be between \$100 and \$200. Similarly, Bar et al. (2008) presented the average cost of clinical mastitis per case estimated at \$179 with \$115 from milk lost, \$14 due to increased mortality loss, and \$50 from treatment costs.

Risk factors for mastitis include exposure to microbes, poor immune mechanisms, and environmental and management factors. Bacteria and non-bacterial pathogens like fungi, yeasts, chlamydia, and virus are considered as the risk factors that causes mastitis (Bradley, 2002; Wellenberg et al., 2002). The reported frequency of mastitis ranged from 5% to 60% across 379 US Holstein herds with mean frequency of 20% (Zwald et al., 2004a). Kelton et al. (1998) summarized 62 reports of the incidence of mastitis and reported that the frequency

of mastitis ranged from a LIR of 1.7% to an annual incidence rate of 54.6%. In that study, the median LIR was 14.2%. Similarly, Parker Gaddis et al. (2012) summarized 29 reports of incidences of mastitis and reported that mean literature incidence of mastitis was 17.98% with 95% range from 0.96% to 39.13%.

Heritability of mastitis has been estimated by several authors using mostly first lactation data and estimates of heritability ranged from 0.02 to 0.16 (Zwald et al., 2004a; Zwald et al., 2004b; Abdel-Azim et al., 2005; Heringstad et al., 2005; Appuhamy et al., 2009; Parker Gaddis et al., 2014). Rajala-Schultz et al. (1999b) reported that total loss of milk production varied from 110 to 552 kg over the entire lactation depending on parity and the time of mastitis occurrence. A review by Ingvarlsen et al. (2003) found a strong evidence of positive association between high milk yields and increased mastitis occurrences. Dohoo et al. (1984) reported a small positive association between clinical mastitis and milk production while subclinical mastitis had larger negative association; suggesting small positive association between clinical mastitis and milk production is due to treatment involved. Simianer et al. (1991) reported that high milk yield is genetically associated with high susceptibility to mastitis. Bar et al. (2008) reported that greatest loss of milk production due to mastitis occurs in first weeks after the diagnosis; on average first lactation cows lost 181 kg of milk and older cows lost 236 kg of milk. Appuhamy et al. (2009) found that mastitis occurring before 100 DIM was associated with higher lactation persistency of milk yield and those mastitis events occurring after 100 DIM was associated with lower lactation persistency of milk yield.

## **Lameness**

Lameness is defined as any abnormality that causes the animal to change its gait or posture. Huxley (2013) reported that lameness is a symptom of a wide range of diseases. The primary cause of lameness in most dairy herds are hoof lesions (Oberbauer et al., 2013). Hoof lesions such as infectious hoof lesions (e.g. digital and interdigital dermatitis, and foot rot), horn lesions (e.g. sole hemorrhage, sole and toe ulcer, and white line disease), and other lesions (e.g. korn, fissures, thin soles, and corkscrew claw) are the major hoof lesions that causes lameness (Chapinal et al., 2013). In commercial dairy operations, lameness causes major economic losses due to its unfavorable effect on productivity and profitability of dairy industry. Several studies have reported how lameness causes weight loss and (Enting et al., 1997), reduced milk yield (Lucey et al., 1986; Warnick et al., 2001; Hernandez et al., 2005), reduced reproductive efficiency (Bicalho and Oikonomou, 2013), and premature culling (Booth et al., 2004). Lameness causes pain leading to a debilitating condition and distress in affected cows, which is considered as a serious animal welfare issue (Booth et al., 2004; Vermunt, 2007; Von Keyserlingk et al., 2009). Kelton et al. (1998) reported that lameness costs \$302 per case. Guard (1999) estimated direct cost due to lameness in 100-cow herds to be \$7,600. Cha et al. (2010) used a dynamic programming method and determined approximate cost per case for sole ulcer, digital dermatitis, and foot rot to be \$216, \$132, and \$121, respectively.

The risk factors for lameness mainly include design of floor and housing facilities as well as management practices (Barker et al., 2010). Lawrence et al. (2011) reported that

lameness is a persistent problem in dairy cows worldwide. Kelton et al. (1998) summarized the 39 lameness incidence report and reported mean annual incidence rate of lameness of 30%. Similarly, Parker Gaddis et al. (2012) calculated mean literature incidence of lameness of 9.27% from 17 citations.

Heritability of lameness has been estimated to be between 0.02 and 0.22 (Zwald et al., 2004a; Zwald et al., 2004b; Neuenschwander et al., 2012; Parker Gaddis et al., 2014).

Several studies have reported that cows producing higher amount of milk are more susceptible to lameness (Lyons et al., 1991; Van Dorp et al., 1998; Green et al., 2002; Espejo et al., 2006). Study by Lyons et al. (1991) and Van Dorp et al. (1998) reported a positive genetic relationship between milk production and lameness indicating that cows of higher genetic merit for milk production are more prone to develop lameness. Studies have found that lameness has a negative impact on milk production (Faust et al., 2001; Hernandez et al., 2002; Hernandez et al., 2005; Bicalho et al., 2008; Bicalho and Oikonomou, 2013). Dairy cows affected with lameness have reduced milk production and total losses in milk production reported were 270 to 440 kg (Coulon et al., 1996), 357 kg (Green et al., 2002), 370 to 570 kg (Amory et al., 2008), 314 to 424 kg (Bicalho et al., 2008), and 350 kg (Archer et al., 2010) per lactation. Study by Tranter and Morris (1991), Warnick et al. (2001), and Hernandez et al. (2002) reported that lame cows were reported to produce lower milk compared to healthy cows. Warnick et al. (2001) reported that lame cows with sole ulcers had the greatest loss of milk, followed by sole and white line abscesses. Sogstad et al. (2007) observed that cows with lameness yielded less milk than those without the defect. With so

many literature reports concluding that lameness is a cause for reduced milk yield, some scientists are reporting that high producing cows are predisposed for lameness (Barkema et al., 1994; Warnick et al., 2001; Ingvarlsen et al., 2003).

Lame cows producing higher amounts of milk raised concerns among researchers as to whether or not high milk production is associated with the occurrence of lameness. Some studies have been made to address this issue (Rowlands and Lucey, 1986; Deluyker et al., 1991; Barkema et al., 1994) and have reported that the relationship between high milk production and lameness supports the possibility that high milk production is a risk factor for lameness. Enevoldsen et al. (1991) found that a higher incidence of lameness was found in herds with higher milk production. Barkema et al. (1994) reported a positive correlation between milk yield and lameness in cows. Deluyker et al. (1991) found a positive association between lameness and milk yield on a 500-cow commercial dairy herd. The positive association between lameness and milk yield during early lactation suggested that high production was a risk factor for lameness. Rowlands and Lucey (1986) reported that the occurrence of lameness after peak yield was associated with high milk production. These studies indicated that high yielding dairy cows are at a greater risk of lameness (Rowlands and Lucey, 1986; Barkema et al., 1994; Green et al., 2002).

Some scientists had also indicated that high producing dairy cows tend to be at high risk of lameness due to the metabolic stress of high milk yield (Barkema et al., 1994; Warnick et al., 2001). Conversely, Gröhn et al. (1995) reported that high yielding cows are not necessarily more susceptible to disease provided better management including improved

nutrition and husbandry meet their increased biological needs. Ingvarlsen et al. (2003) concluded that there is an unfavorable genetic association between milk yield and incidence of ketosis, mastitis, ovarian cyst and lameness. Some studies have found that there is no such association of milk yield and lameness (Cobo-Abreu et al., 1979; Vaarst et al., 1998; Aeberhard et al., 2001; Haskell et al., 2006).

### **Displaced Abomasum**

Displaced abomasum is defined as the metabolic disorder in which the abomasum is floating in the dorsal part of the abdomen due to gas accumulation inside abomasum. Displaced abomasum can be both left sided and right sided but about 80 to 90% of displaced abomasum are left-sided (Shaver, 1997). Displaced abomasum results in decrease in appetite, reduced milk production, pain and discomfort of the cow and in extreme cases death of the cow (Van Winden and Kuiper, 2003). Kelton et al. (1998) reported that displaced abomasum costs approximately \$340 per case which included costs of surgery and lost milk production. Similarly, Zwald et al. (2004a) reported that displaced abomasum costs approximately \$312 per case.

Raizman and Santos (2002) reported that there is higher risk for a cow to develop displaced abomasum if the cow has previous history of one or more reproductive disorders (e.g. dystocia, stillbirth, retained placenta, metritis) and metabolic disorders (e.g. ketosis, milk fever). Kelton et al. (1998) summarized 22 incidence reports of displaced abomasum and reported the median displaced abomasum LIR of 1.7% ranging from 0.3% to 6.3%.

Similarly, Parker Gaddis et al. (2012) reported the mean literature incidence of displaced abomasum of 2.67 % calculated from 11 citations.

Heritability of displaced abomasum has been estimated to be between 0.05 and 0.32 (Zwald et al., 2004a; Zwald et al., 2004b; Neuenschwander et al., 2012; Parker Gaddis et al., 2014).

Cobo-Abreu et al. (1979) found that cows with displaced abomasum yielded on average 160 kg less milk per lactation than healthy cows. Similarly, Detilleux et al. (1997) found that displaced abomasum significantly decreased the amount of milk production; on average cows with displaced abomasum yielded 557 kg less milk than cows without displaced abomasum; and the loss of milk yield before diagnosis was about 167 kg. Fleischer et al. (2001) reported that high producing cows are likely to develop more incidences of displaced abomasum. In contrast to this, review by Ingvarsten et al. (2003) did not find any strong evidence that high yielding cows are linked with high incidences of displaced abomasum. Koeck et al. (2013) reported that displaced abomasum is genetically uncorrelated with milk yield in early lactation. Appuhamy et al. (2009) reported that displaced abomasum had a significantly positive relationship with lactation persistency of milk yield in both first and later lactations.

### **Ketosis**

Ketosis is defined as the metabolic disorder in which increased pathologic levels of circulating ketone bodies are found accumulating inside animal body. Ketosis occurs in high producing lactating cows when energy demands are greater than energy intake resulting in

negative energy balance (Herdt, 2000; McArt et al., 2012). Clinical signs of ketosis include decrease in appetite, weight loss, and decrease in milk production (Andersson, 1988).

Generally, ketosis is diagnosed through the detection of ketone bodies in milk, urine and breath. Kelton et al. (1998) reported that ketosis costs approximately \$145 per case which included treatments costs, lost from milk production, increased days open and increased culling. Similarly, Zwald et al. (2004a) reported that ketosis in US dairy cattle costs \$151 per case.

The risk factor of ketosis mainly include pervious disease, stage of lactation, parity, body condition score (BCS), season of calving, milk production, and nutritional management (Dohoo and Martin, 1984; LeBlanc, 2010). Duffield et al. (1997) reported that the prevalence of ketosis increases with an increase in parity level. Busato et al. (2002) reported that there is a higher risk of developing ketosis for cow with BCS higher than 3.5 on a 5-point scale at the time of calving. Moreover, Richert et al. (2013) found that farmer reported ketosis incidence increased when diet contained increased levels of concentrates. Similarly, Gustafsson et al. (1995) found that herds that had fewer meals throughout the day had higher chances of having ketosis especially with herds whose diets have high concentrate levels. Duffield et al. (1997) reported that subclinical ketosis usually occurs in the first two weeks of lactation and also reported that cows in early lactation were four times more likely to have subclinical ketosis than the cows in late lactation.

Duffield (2000) reported that on average cumulative lactational incidences of ketosis ranges from 40% to as high as 80% in some herds. Zwald et al. (2004a) found the mean

disease frequency of 10% for ketosis. Kelton et al. (1998) summarized 36 ketosis incidence reports and found that the median LIR was 4.8% with range from 1.3% to 18.3%. Likewise, Parker Gaddis et al. (2012) calculated mean literature incidence of ketosis from 21 reports of 5.07% with 95% range from 0.32% to 19.50%

Heritability of ketosis has been estimated to be between 0.06 and 0.16 (Zwald et al., 2004a; Zwald et al., 2004b; Heringstad et al., 2005; Parker Gaddis et al., 2014).

Rowlands and Lucey (1986) reported that ketosis is associated with drop in cumulative milk production over lactation. Deluyker et al. (1991) found that ketosis is associated with decreased peak yield and milk production losses both before and after the treatment. Rajala-Schultz et al. (1999a) found that milk yield started to decline 2 to 4 weeks before the diagnosis of ketosis. They also reported that milk yield continued to decline for a varying time period after the diagnosis of ketosis. Simianer et al. (1991) reported genetic association exists between high milk yield and high susceptibility to ketosis. Similarly, some studies found strong evidence of association between the occurrence of ketosis and high milk production (Rajala-Schultz et al., 1999a; Oltenacu and Algers, 2005). In contrast, Koeck et al. (2013) reported that ketosis is genetically uncorrelated with milk yield in early lactation. Fleischer et al. (2001) found that high milk yield in previous lactation is likely to increase occurrences of ketosis in later lactation. Appuhamy et al. (2009) reported that ketosis had positive relationships with lactation persistency in both first lactation and in later lactations.

## **Metritis**

Metritis is the inflammation of the uterus. Uterine diseases can be differentiated by the uterine infection site and causes of inflammation into puerperal metritis, clinical metritis, clinical endometritis and subclinical endometritis (Sheldon et al., 2006). Metritis is highly prevalent in high producing dairy cows and has been associated with reduced fertility, increased days open, increased culling and economic losses (Sheldon and Dobson, 2004; Gilbert et al., 2005; Dubuc et al., 2010). Fourichon et al. (2000) conducted a meta-analysis of reproductive health disorders from data available from different countries (Canada, Finland, Israel, Japan, Mexico, The Netherlands, New Zealand, Sweden, UK, USA) from 1960 until 1998 from seventy selected papers published in English in peer-reviewed journals, and reported that metritis affects a large proportion of dairy cattle and is associated with substantial productive loss as well as compromising reproductive efficiency. Uterine infection occurring in late gestation can negatively impact a cow or fetal health and infection happening after parturition has the largest effect on milk production and health of a cow (Sheldon et al., 2008). In addition to treatment costs, costs of metritis include increased chance of culling, milk discarded, and reproductive insufficiency (LeBlanc, 2008). Lewis (1997) estimated the average cost of metritis to be \$106 per each case of a lactating cow. Loss of milk production due to metritis per lactation on average was 300 l (Sheldon et al., 2008). The direct treatment cost per cow affected with metritis was \$134 and that of indirect costs which include increased costs due to longer calving interval, increased culling rate,

extra inseminations, and lower expressions of estrus were approximately \$150 (Sheldon et al., 2008).

Based on the previous studies it was suggested that risk factors of metritis which are consistent in the literature include retained placenta, type of calving environment, twins, diet, stillbirth, abortion, prolapsed uterus and dystocia (Correa et al., 1993; Kaneene and Miller, 1995; Sheldon et al., 2008). LeBlanc (2008) reported that the most important risk factor for metritis is retained placenta. In addition, other suggested risk factors in the literature include parity (Gröhn et al., 1990; Rajala and Gröhn, 1998), herd size (Kaneene and Miller, 1995), age of cow (Erb et al., 1981; Dohoo et al., 1984), and season of calving (Markusfeld, 1987; Gröhn et al., 1990). Correa et al. (1993) reported a path analysis for metritis that indicated that diseases inducing stress such as dystocia and retained placenta increased the likelihood that a cow will develop metritis. Other predictors of metritis include reduced feeding time and dry matter intake before parturition (Huzzey et al., 2007).

The reported incidence rate of metritis ranged from 7.8% to 51.3% in US dairy cows (Lewis, 1997). Bartlett et al. (1986) reported the incidence rate of metritis of 18% in twenty-two Michigan Holstein-Friesian dairy herds when metritis events was reported immediately following calving. In the study conducted by Gardner et al. (1990) in 43 randomly selected California dairy cattle farm from year 1986 and 1987, the incidence rate of metritis was 7.9%. The LIR of metritis was 0.107 when metritis was clinically diagnosed at the median time of 26 days in an observational study of 34 Holstein herds from Ontario (Bigras-Poulin et al., 1990). Kelton et al. (1998) reported LIR of metritis compiled from 43 citations, ranging from

LIR of 2.2% to a LIR of 37.3%. In a review by Ingvarlsen et al. (2003), they reported a LIR of metritis ranged from 2.2% to 43.8%. Similarly, Parker Gaddis et al. (2012) calculated the mean literature incidence rate of metritis compiled from 23 citations being 12.34% with 95% range from 1.77% to 39.13 %. Several other studies have reported that incidence rate of metritis ranging from 8 to greater than 40 % (LeBlanc et al., 2002; Hammon et al., 2006; Huzzey et al., 2007). Appuhamy et al. (2007) found that metritis incidences were higher in first lactations than in later lactations (19.1 vs 9.5 %). The wide range of incidence of metritis in literature could be, in part, due to the use of different definitions of metritis as some studies include only metritis whereas other studies include puerperal metritis, endometritis, retained placenta together with metritis; also some studies include early metritis events and others included all metritis events that occurred during lactation.

Heritability of metritis has been estimated by several authors using mostly first lactation data and estimates of heritability ranged from 0.009 to 0.14 (Lin et al., 1989; Zwald et al., 2004a; Zwald et al., 2004b; Appuhamy et al., 2009; Heringstad, 2010; Koeck et al., 2012b; Neuenschwander et al., 2012; Parker Gaddis et al., 2014).

Several studies have reported that metritis causes decreased milk yield (Deluyker et al., 1991; Rajala and Gröhn, 1998; Wittrock et al., 2011), however, some studies (Markusfeld and Ezra, 1993; Goshen and Shpigel, 2006) reported no effect of metritis on milk yield. Appuhamy et al. (2009) reported that no association was found between metritis and lower peak milk yield in both first lactation and later lactations, but found metritis event was associated with longer DIM at peak in later lactations. Østergaard and Gröhn (1999)

reported that multiparous cows affected by metritis produced less milk than healthy cows up to 6 week after diagnosis. Similarly, Wittrock et al. (2011) reported that multiparous cows affected with metritis produced approximately 4 kg/d less milk than healthy cows. Fleischer et al. (2001) found no associations between metritis occurrence and production measures. Appuhamy et al. (2009) reported that metritis had positive relationships with lactation persistency in both first lactation and in later lactations.

### **Retained Placenta**

Retained placenta is the clinical condition in which failure of the fetal placenta to separate from the maternal placenta occurs (Wetherill, 1965). Normally, if the retention of fetal membranes 24 hours or more postpartum occurs then the condition is called retained placenta (Esslemont and Peeler, 1993). Exact etiology of retained placenta is not known but based on extensive research it has been concluded that there is involvement of several risk factors such as breed, premature births, multiple calves, dystocia, abortion, still births, uterine infections, gestation length, age of cow, stress, antioxidant deficiency, calving season and hormone levels (reviewed in Joosten et al., 1987; Laven and Peters, 1996; Drillich, 2011). LeBlanc et al. (2004) reported that cows in negative energy balance pre-partum were 80% more likely to have retained placenta.

Retained placenta is considered as an economically important disease due to costs associated with the disease such as treatment costs, milk loss, increased days open, increased culling rates and increased incidence of other diseases (Qu et al., 2014). Kelton et al. (1998) summarized 50 reports on the incidence of retained placenta and reported that approximately

7.8% of US dairy cows were affected by retained placenta with the median lactational incidence risk (LIR) of 8.6%. The reported mean frequency of retained placenta from several studies as calculated by Parker Gaddis et al. (2012) was 8.02 % with 95% range from 2.33% to 17.94%. Kelton et al. (1998) estimated that the average cost of retained placenta (including associated costs such as treatment costs, milk loss, and increased days open) to be \$285 per case. Cows affected with retained placenta also have increased risk of displaced abomasum, ketosis and mastitis (Gröhn et al., 1990; Oltenacu et al., 1990). Fourichon et al. (2000) reported that cows affected with retained placenta reduced the pregnancy rate by approximately 15% relative to unaffected cows.

Several studies have reported heritability estimates for retained placenta which ranged from 0.08 to 0.22 ( Schnitzenlehner et al., 1998; Heringstad et al., 2005; Benedictus et al., 2013; Parker Gaddis et al., 2014).

Cobo-Abreu et al. (1979) found that retained placenta did not reduce the amount of milk production but was significantly associated with high culling risk. Bigras-Poulin et al. (1990) reported that retained placenta alone can decrease milk production by 360.2 kg over 305 DIM. Deluyker et al. (1991) reported that the reduction of milk production was found in lactation from 5 to 21 d postpartum. Similarly, Fleischer et al. (2001) reported that retained placenta decreased milk production. Dubuc et al. (2011) reported that retained placenta decreased milk production by 2.6 kg / day in multiparous cows while they didn't find any significant reduction of milk production in primiparous cows with retained placenta. In the

study they calculated the projected reduction of milk yield due to retained placenta to be of 753 kg over 305 DIM.

### **Selection of health traits in dairy cattle**

Improvement of health condition of dairy cattle has become primary concern to dairy producers because of its significant impact on other traits as well as on the overall productivity and profitability of dairy enterprise. Shook (1989) reported that due to greater economic importance of health traits, the inclusion of health traits would be justifiable in breeding goals. Jakobsen et al (2003) reported that improved health condition of animals can be achieved through genetic selection due to the presence of the underlying genetic components in health traits. In the review by Berry et al. (2011) they reported that improved health condition of animal can be achieved through genetic selection because of the fact that genetic gain is cumulative and permanent. Even though, health disorders phenotypic records are expensive to collect and record, Nordic countries are already implementing health data in their genetic evaluation of dairy cows (Philipsson and Lindhé, 2003; Heringstad and Østerås, 2013). In the study from Norway by Østerås et al. (2007), they reported that after 30 years of selection for mastitis resistance, they have been able to breed cows with improved mastitis resistance. Heringstad and Østerås (2013) have reported that health traits such as clinical mastitis and claw health are included in genetic evaluation of Norwegian Red cows.

In the United States few studies have been made in the area of genetic evaluation of health traits. Maltecca (2013) pointed that the reason for this is mainly due to unavailability

of health phenotypes because throughout the United States, there is no mandatory or consistent health recording system imposed. On-farm producer recorded health data have been used for genetic analysis by several authors (Zwald et al., 2004b; Appuhamy et al., 2009; Parker Gaddis et al., 2012; 2014).

### **Structural equation models**

Most of the analyses conducted and described in previous sections concerning common health disorders and production traits do not specifically assume a direct effect of health disorders on production (or on other health disorders) so that it is difficult to quantify the exact extent of the disease effect on the overall profitability of the cow. Furthermore, it is difficult to assess without a causal model the effect of external intervention, such as environmental factors, and management practices in culling or management decisions. Rosa et al (2011) reported that knowledge regarding the causal structure underlying phenotypic relationships is important to assess the direct effect of one variable to another variable. Due to these reasons different models such as structural equation models (SEM) and Bayesian networks, which can infer causal relationships between variables have become an appealing tool to analyze health disorders data.

Structural equation modeling is a powerful statistical modeling technique for studying relationships among variables, either measured or unmeasured (Wu et al., 2010), with causal assumptions assumed explicitly; and represents a class of statistical specifications (factor analysis, path analysis, and regression) where the main objective is to introduce causal pathways (Heringstad et al., 2009). Gianola and Sorensen (2004) extended mixed

models allowing for mutual or recursive relationships between phenotypes involved in a multivariate system in a quantitative genetics framework. The causal structure, which defines the simultaneous or recursive relationships in SEM, influences the interpretation of quantitative genetic parameters, such as heritability, offspring-parent regression, and genetic correlation (Wu et al., 2010).

One of SEM peculiar features is the ability of incorporating many response variables and allowing feedback systems, because SEM handles measurement error in both response and predictor variables, allowing multiple indicators of latent constructs, enabling the specification of causal structure among latent variables, and allowing the response variable in one regression equation to appear as a predictor in another response variable (Wu et al., 2010; Rosa et al., 2011). Structural equation models are used to study recursive and simultaneous relationships among phenotypes in multivariate systems such as multiple-trait models in quantitative genetics (Valente et al., 2010). Behavior of complex traits (e.g. diseases, growth, and reproduction) can be predicted if relationships (simultaneous and recursive) between phenotype network are assumed known (Rosa et al., 2011). Valente et al. (2013) also suggested that SEM allows dissecting the impact of external interventions on selection decisions particularly in cases where interventions dramatically modify how genetics affects such complex systems of traits.

Recently, there has been an increasing interest in applying SEM in animal breeding and genetics (de los Campos et al., 2006a; de los Campos et al., 2006b; Wu et al., 2008; Heringstad et al., 2009; Varona and Sorensen, 2014). In 2006, de los Campos et al. (2006a,

b) used SEM approaches to examine relationships between somatic cell score and milk yield in first-lactation dairy cows and dairy goats. Simultaneous effects between somatic cell score from the left and right halves of the udder was found in dairy goats (de los Campos et al., 2006a). In case of dairy cattle, unfavorable direct effects between somatic cell score and milk yield was observed (de los Campos et al., 2006b). Lagged relationships between clinical mastitis and milk yield in Norwegian dairy cows was explored by Wu et al. (2008) using SEM approaches. Unfavorable effects from clinical mastitis to milk yield and small positive recursive effects between milk yield and clinical mastitis were identified in the first 180 days of lactation (Wu et al., 2008). Relationships between health and fertility traits have been explored by Heringstad et al. (2009) using a recursive effects model. The causal effect identified indicated that the presence of ketosis or retained placenta increased the length of the interval from calving to first insemination Heringstad et al. (2009).

### **Genomic selection**

In comparison to production traits difficulty arises when doing genetic selection of health disorder traits, mostly because health traits are lowly heritable and at least in the case of the US for the lack of a unified recording system of health-related phenotypes. Traditional selection schemes with this limited availability of health traits phenotypes takes several years for breeding healthier cattle. Due to recent advancement in molecular methodologies and availability of dense molecular data, genomic selection seems to be an appealing tool to improve health status of dairy cattle. Most health-related phenotypes in the US are voluntarily recorded by dairy producers (Zwald et al., 2004a; Parker Gaddis et al., 2012); and

due to lack of proper identification of disease condition by dairy producers most of the different disease conditions are often characterized as a single health event. For instance, lameness is due to different hoof lesions conditions, some of them could be infectious hoof lesions and other could be non-infectious hoof lesions, but most of the time dairy producers records hoof lesions as only lameness. Nonetheless, if proper characterization of hoof lesions is possible, then with the help of genomic selection, we can perform selection on the particular category of hoof lesions to improve the health status of the animal, even though only a fraction of variability is heritable. It has been a proven fact that once selection has been practiced then the genetic gains obtained are permanent and cumulative in the population.

Traditional animal breeding programs were based on using phenotypic records and pedigree information. Genomic selection is a relatively new approach in which pedigree information, phenotypic records as well as a large number of genetic markers across the genome are utilized to estimate breeding values. The main advantages of genomic selection over traditional BLUP method are: i) increase in accuracy, ii) increase in selection intensity, and iii) shorter generation interval. This can be best demonstrated using breeder's equation:

$$\Delta G = \frac{\textit{intensity of selection} * \textit{accuracy of selection} * \textit{genetic standard deviation}}{\textit{generation interval}}$$

where  $\Delta G$  is genetic gain per year. In genomic selection, genetic gain is mainly increased due to increased accuracy of selection, increased selection intensity, and the shorter

generation interval. The rate of genetic progress can be achieved quickly for economically important traits through the application of genomic selection (Scheifers and Weigel, 2012). Recently, Parker Gaddis et al. (2014) estimated genomic variance components and heritability of common health disorders of US dairy cows using single-step method. An increase in reliabilities was observed when using genomic information in production traits (VanRaden et al., 2009) and in health disorders Parker Gaddis et al. (2014). Using single-step method, both pedigree relationship matrix and genomic relationship matrix are incorporated into a blended H matrix, making single-step method easier to implement (Legarra et al., 2009; Legarra et al., 2014). Gray et al. (2012) reported that single-step method yielded better accuracies than GBLUP for several milkability traits.

### **On-farm producer recorded health data**

There is a lack of health-related phenotypes in the US partly because of no mandatory or structured health recording system and partly because of farmer unwillingness to share data due to security concerns. Nonetheless, most of the dairy health data in the US is voluntarily recorded by producers in their on-farm computers and is provided to Dairy Records Management Systems. Such field data can provide a plethora of information about health related phenotypes which can be used extensively for genetic evaluation. Several authors (Bartlett et al., 1986; Zwald et al., 2004b; Appuhamy et al., 2009; Parker Gaddis et al., 2012; 2014) have confirmed the possibility of using on-farm producer-recorded health information for genetic improvement and to identify phenotypic relationships among health

disorders. In this dissertation, on-farm producer recorded health data were used for study purpose.

## **CONCLUSION**

Direct cost such as veterinary and treatment cost, and indirect costs such as decrease in milk production, increased labor costs and discarded milk due to health disorders can affect the profitability of dairy enterprise. Understanding causal relationship between health disorder and production measures is crucial because it will enhance our knowledge about the biological pathway of disease process and provide us guidance on future occurrence of disease incidences. This knowledge can be used to improve health status of cows which can be done by placing selection on optimum milk yield and disease resistance.

Health traits are normally lowly heritable and to make genetic process via selection will require good phenotypic records and considerable amount of time. Genomic selection appears as a promising tool for lowly heritable traits because through the use of genomic information it helps to increase the accuracy and also reduces the generation interval. In the following two chapters (2 and 3) causal relationships between health disorders and production measures were introduced. The genomic variance components and heritability of infectious and non-infectious hoof lesions were introduced in chapter 4.

### **Chapter 2**

The objective of this study was to estimate the causal effect among health disorders, production measures and culling reasons in first-lactation US Holsteins. The following steps were considered: i) estimation of causal effects between health disorders and culling reasons,

ii) estimation of causal effects among health disorders and milk yields records iii) estimation of causal effects between health disorders and production measures such as peak milk yield, day in milk at peak milk yield and lactation persistency of milk yield, and iv) estimation of heritabilities and genetic correlations among health disorders and production measures.

### **Chapter 3**

The aim of this study was to estimate the causal effects between test-day milk yields and clinical mastitis events that evolve during the course of lactation. The following steps were considered: i) estimation of causal effects between clinical mastitis events and test-day milk yields in first-lactation Holstein cows, ii) estimation of causal effects between clinical mastitis events and lactation persistency of milk yield of first-lactation Holsteins, iii) estimation of causal effects between mastitis event of first lactation and second lactation and causal effects were also estimated between total milk yield of second lactation and mastitis events from first and second lactation , and iv) estimation of heritabilities and genetic correlations between mastitis events and production measures.

### **Chapter 4**

The genomic information together with phenotypic records, and pedigree helps to estimate the accurate breeding value for traits which are difficult and expensive to observe. Genomic selection appears to be an appealing tool to analyze health traits. In this chapter, hoof lesions were categorized into infectious and non-infectious category and their genomic variance components and heritability were estimated. The aim of this study was to identify whether individual hoof lesions categories has a heritable component or not, and to compare the sire PTAs reliabilities of hoof lesions calculated from pedigree-based and genomic-based

relationship matrices. A bivariate analysis was also performed with each category of hoof lesions and a dataset where hoof lesions were categorized as a single health event ‘lameness’ to understand the producers preference on hoof lesions data recording.

## REFERENCES

- Abdel-Azim, G., A. Freeman, M. Kehrli Jr, S. Kelm, J. Burton, A. Kuck, and S. Schnell. 2005. Genetic basis and risk factors for infectious and noninfectious diseases in US Holsteins. I. Estimation of genetic parameters for single diseases and general health. *J. Dairy Sci.* 88:1199-1207.
- Aeberhard, K., R. Bruckmaier, U. Kuepfer, and J. Blum. 2001. Milk yield and composition, nutrition, body conformation traits, body condition scores, fertility and diseases in high-yielding dairy cows–Part 1. *J. Vet. Med. A.* 48:97-110.
- Amory, J., Z. Barker, J. Wright, S. Mason, R. Blowey, and L. E. Green. 2008. Associations between sole ulcer, white line disease and digital dermatitis and the milk yield of 1824 dairy cows on 30 dairy cow farms in England and Wales from February 2003–November 2004. *Prev. Vet. Med.* 83:381-391.
- Andersson, L. 1988. Subclinical ketosis in dairy cows. *Vet. Clin. North Am. Food Anim. Pract.* 4:233-251.
- Appuhamy, J., B. Cassell, and J. Cole. 2009. Phenotypic and genetic relationships of common health disorders with milk and fat yield persistencies from producer-recorded health data and test-day yields. *J. Dairy Sci.* 92:1785-1795.
- Appuhamy, J., B. Cassell, C. Dechow, and J. Cole. 2007. Phenotypic relationships of common health disorders in dairy cows to lactation persistency estimated from daily milk weights. *J. Dairy Sci.* 90:4424-4434.
- Archer, S. C., M. Green, and J. Huxley. 2010. Association between milk yield and serial locomotion score assessments in UK dairy cows. *J. Dairy Sci.* 93:4045-4053.
- Bar, D., L. Tauer, G. Bennett, R. Gonzalez, J. Hertl, Y. Schukken, H. Schulte, F. Welcome, and Y. Gröhn. 2008. The cost of generic clinical mastitis in dairy cows as estimated by using dynamic programming. *J. Dairy Sci.* 91:2205-2214.

- Barkema, H., J. Van der Ploeg, Y. Schukken, T. Lam, G. Benedictus, and A. Brand. 1999. Management style and its association with bulk milk somatic cell count and incidence rate of clinical mastitis. *J. Dairy Sci.* 82:1655-1663.
- Barkema, H., J. Westrik, K. Van Keulen, Y. Schukken, and A. Brand. 1994. The effects of lameness on reproductive performance, milk production and culling in Dutch dairy farms. *Prev. Vet. Med.* 20:249-259.
- Barker, Z., K. Leach, H. Whay, N. Bell, and D. Main. 2010. Assessment of lameness prevalence and associated risk factors in dairy herds in England and Wales. *J. Dairy Sci.* 93:932-941.
- Bauman, D. E., and W. Bruce Currie. 1980. Partitioning of nutrients during pregnancy and lactation: A review of mechanisms involving homeostasis and homeorhesis. *J. Dairy Sci.* 63:1514-1529.
- Benedictus, L., A. Koets, F. Kuijpers, I. Joosten, P. van Eldik, and H. Heuven. 2013. Heritable and non-heritable genetic effects on retained placenta in Meuse-Rhine-Yssel cattle. *Anim. Reprod. Sci.* 137:1-7.
- Bennett, R. M., K. Christiansen, and R. S. Clifton-Hadley. 1999. Estimating the costs associated with endemic diseases of dairy cattle. *J. Dairy Res.* 66:455-459.
- Berry, D. P., F. Buckley, P. Dillon, R. D. Evans, and R. F. Veerkamp. 2004. Genetic relationships among linear type traits, milk yield, body weight, fertility and somatic cell count in primiparous dairy cows. *Irish J. Agric. Food Res.* 43:161-176.
- Berry, D. P., M. L. Bermingham, M. Good, and S. J. More. 2011. Genetics of animal health and disease in cattle. *Ir. Vet. J.* 64:5.
- Bicalho, R., L. Warnick, and C. Guard. 2008. Strategies to analyze milk losses caused by diseases with potential incidence throughout the lactation: A lameness example. *J. Dairy Sci.* 91:2653-2661.
- Bicalho, R. C., and G. Oikonomou. 2013. Control and prevention of lameness associated with claw lesions in dairy cows. *Livest. Sci.* 156:96-105,
- Bigras-Poulin, M., A. Meek, and S. Martin. 1990. Interrelationships of health problems and age on milk production in selected Ontario Holstein cows. *Prev. Vet. Med.* 8:3-13.
- Blosser, T. 1979. Economic losses from and the national research program on mastitis in the United States. *J. Dairy Sci.* 62:119-127.

- Booth, C., L. Warnick, Y. Gröhn, D. Maizon, C. Guard, and D. Janssen. 2004. Effect of lameness on culling in dairy cows. *J. Dairy Sci.* 87:4115-4122.
- Bradley, A. J. 2002. Bovine mastitis: An evolving disease. *Vet. J.* 164:116-128.
- Busato, A., D. Faissler, U. Küpfer, and J. Blum. 2002. Body condition scores in dairy cows: Associations with metabolic and endocrine changes in healthy dairy cows. *J. Vet. Med. A.* 49:455-460.
- Bartlett, P. C., J. H. Kirk, M. A. Wilke, J. B. Kaneene, and E. C. Mather. 1986. Metritis complex in Michigan Holstein-Friesian cattle: Incidence, descriptive epidemiology and estimated economic impact. *Prev. Vet. Med.* 4:235-248.
- Cha, E., J. Hertl, D. Bar, and Y. Gröhn. 2010. The cost of different types of lameness in dairy cows calculated by dynamic programming. *Prev. Vet. Med.* 97:1-8.
- Chapinal, N., A. Koeck, A. Sewalem, D. Kelton, S. Mason, G. Cramer, and F. Miglior. 2013. Genetic parameters for hoof lesions and their relationship with feet and leg traits in Canadian Holstein cows. *J. Dairy Sci.* 96:2596-2604.
- Cobo-Abreu, R., S. Martin, R. Willoughby, and J. Stone. 1979. The association between disease, production and culling in a university dairy herd. *Can. Vet. J.* 20:191.
- Correa, M., H. Erb, and J. Scarlett. 1993. Path analysis for seven postpartum disorders of Holstein cows. *J. Dairy Sci.* 76:1305-1312.
- Coulon, J., F. Lescourret, and A. Fonty. 1996. Effect of foot lesions on milk production by dairy cows. *J. Dairy Sci.* 79:44-49.
- de los Campos, G., D. Gianola, P. Boettcher, and P. Moroni. 2006a. A structural equation model for describing relationships between somatic cell score and milk yield in dairy goats. *J. Anim. Sci.* 84:2934-2941.
- de los Campos, G., D. Gianola, and B. Heringstad. 2006b. A structural equation model for describing relationships between somatic cell score and milk yield in first-lactation dairy cows. *J. Dairy Sci.* 89:4445-4455.
- Deluyker, H., J. Gay, L. Weaver, and A. Azari. 1991. Change of milk yield with clinical diseases for a high producing dairy herd. *J. Dairy Sci.* 74:436-445.
- Detilleux, J., Y. Gröhn, S. Eicker, and R. Quaas. 1997. Effects of left displaced abomasum on test day milk yields of Holstein cows. *J. Dairy Sci.* 80:121-126.

- Dohoo, I. R., S. W. Martin, I. McMillan, and B. W. Kennedy. 1984. Disease, production and culling in Holstein-Friesian cows II. Age, season and sire effects. *Prev. Vet. Med.* 2:655-670.
- Dohoo, I. R., and S. W. Martin. 1984. Subclinical ketosis: Prevalence and associations with production and disease. *Can. J. Comp. Med.* 48:1-5.
- Dohoo, I. R., A. H. Meek, and S. W. Martin. 1984. Somatic cell counts in bovine milk: Relationships to production and clinical episodes of mastitis. *Can. J. Comp. Med.* 48:130-135.
- Drillich, M. 2011. Aetiology and therapy of retained fetal membranes in cattle-an overview on recent literature. *Wien. Tierarztl. Monatsschr.* 98:195-202.
- Dubuc, J., T. Duffield, K. Leslie, J. Walton, and S. LeBlanc. 2011. Effects of postpartum uterine diseases on milk production and culling in dairy cows. *J. Dairy Sci.* 94:1339-1346.
- Dubuc, J., T. Duffield, K. Leslie, J. Walton, and S. LeBlanc. 2010. Risk factors for postpartum uterine diseases in dairy cows. *J. Dairy Sci.* 93:5764-5771.
- Duffield, T. 2000. Subclinical ketosis in lactating dairy cattle. *Vet. Clin. North Am. Food Anim. Pract.* 16:231-53.
- Duffield, T. F., D. F. Kelton, K. E. Leslie, K. D. Lissemore, and J. H. Lumsden. 1997. Use of test day milk fat and milk protein to detect subclinical ketosis in dairy cattle in Ontario. *Can. Vet. J.* 38:713-718.
- Dunklee, J., A. Freeman, and D. Kelley. 1994. Comparison of Holsteins selected for high and average milk production. 2. Health and reproductive response to selection for milk. *J. Dairy Sci.* 77:3683-3690.
- Elbers, A., J. Miltenburg, D. De Lange, A. Crauwels, H. Barkema, and Y. Schukken. 1998. Risk factors for clinical mastitis in a random sample of dairy herds from the southern part of the Netherlands. *J. Dairy Sci.* 81:420-426.
- Enevoldsen, C., Y. Gröhn, and I. Thysen. 1991. Heel erosion and other interdigital disorders in dairy cows: Associations with season, cow characteristics, disease, and production. *J. Dairy Sci.* 74:1299-1309.
- Enting, H., D. Kooij, A. Dijkhuizen, R. Huirne, and E. Noordhuizen-Stassen. 1997. Economic losses due to clinical lameness in dairy cattle. *Livest. Prod. Sci.* 49:259-267.

- Erb, H., S. Martin, N. Ison, and S. Swaminathan. 1981. Interrelationships between production and reproductive diseases in Holstein cows path analysis. *J. Dairy Sci.* 64:282-289.
- Espejo, L., M. Endres, and J. Salfer. 2006. Prevalence of lameness in high-producing Holstein cows housed in freestall barns in Minnesota. *J. Dairy Sci.* 89:3052-3058.
- Esslemont, R., and E. Peeler. 1993. The scope for raising margins in dairy herds by improving fertility and health. *Br. Vet. J.* 149:537-547.
- Faust, M., M. Kinsel, and M. Kirkpatrick. 2001. Characterizing biosecurity, health, and culling during dairy herd expansions. *J. Dairy Sci.* 84:955-965.
- Fleischer, P., M. Metzner, M. Beyerbach, M. Hoedemaker, and W. Klee. 2001. The relationship between milk yield and the incidence of some diseases in dairy cows. *J. Dairy Sci.* 84:2025-2035.
- Fourichon, C., H. Seegers, and X. Malher. 2000. Effect of disease on reproduction in the dairy cow: A meta-analysis. *Theriogenology.* 53:1729-1759.
- Gardner, I. A., D. W. Hird, W. W. Utterback, C. Danaye-Elmi, B. R. Heron, K. H. Christiansen, and W. M. Sisco. 1990. Mortality, morbidity, case-fatality, and culling rates for California dairy cattle as evaluated by the national animal health monitoring system, 1986–87. *Prev. Vet. Med.* 8:157-170.
- Gianola, D., and D. Sorensen. 2004. Quantitative genetic models for describing simultaneous and recursive relationships between phenotypes. *Genetics.* 167:1407-1424.
- Gilbert, R. O., S. T. Shin, C. L. Guard, H. N. Erb, and M. Frajblat. 2005. Prevalence of endometritis and its effects on reproductive performance of dairy cows. *Theriogenology.* 64:1879-1888.
- Goshen, T., and N. Y. Shpigel. 2006. Evaluation of intrauterine antibiotic treatment of clinical metritis and retained fetal membranes in dairy cows. *Theriogenology.* 66:2210-2218.
- Gray, K. A., J. P. Cassady, Y. Huang, and C. Maltecca. 2012. Effectiveness of genomic prediction on milk flow traits in dairy cattle. *Genet. Sel. Evol.* 44:24-9686-44-24.
- Green, L., V. Hedges, Y. Schukken, R. Blowey, and A. Packington. 2002. The impact of clinical lameness on the milk yield of dairy cows. *J. Dairy Sci.* 85:2250-2256.

- Gröhn, Y., H. N. Erb, C. E. McCulloch, and H. S. Saloniemi. 1990. Epidemiology of reproductive disorders in dairy cattle: Associations among host characteristics, disease and production. *Prev. Vet. Med.* 8:25-39.
- Gröhn, Y., S. Eicker, and J. Hertl. 1995. The association between previous 305-day milk yield and disease in New York state dairy cows. *J. Dairy Sci.* 78:1693-1702.
- Guard, C. 1999. Control programs for digital dermatitis. In: *The tools for success in the new millennium*. Kennelly, J. (ed.). *Advances in Dairy Technology*, University of Alberta, Edmonton, Canada. 2:235-242.
- Gustafsson, A., L. Andersson, and U. Emanuelson. 1995. Influence of feeding management, concentrate intake and energy intake on the risk of hyperketonaemia in Swedish dairy herds. *Prev. Vet. Med.* 22:237-248.
- Halasa, T., K. Huijps, O. Østerås, and H. Hogeveen. 2007. Economic effects of bovine mastitis and mastitis management: A review. *Vet. Q.* 29:18-31.
- Hammon, D., I. Evjen, T. Dhiman, J. Goff, and J. Walters. 2006. Neutrophil function and energy status in Holstein cows with uterine health disorders. *Vet. Immunol. Immunopathol.* 113:21-29.
- Haskell, M., L. Rennie, V. Bowell, M. Bell, and A. Lawrence. 2006. Housing system, milk production, and zero-grazing effects on lameness and leg injury in dairy cows. *J. Dairy Sci.* 89:4259-4266.
- Herd, T. H. 2000. Ruminant adaptation to negative energy balance: Influences on the etiology of ketosis and fatty liver. *Vet. Clin. North Am. Food Anim. Pract.* 16:215-30.
- Heringstad, B. 2010. Genetic analysis of fertility-related diseases and disorders in Norwegian red cows. *J. Dairy Sci.* 93:2751-2756.
- Heringstad, B., G. Klemetsdal, and J. Ruane. 2000. Selection for mastitis resistance in dairy cattle: A review with focus on the situation in the Nordic countries. *Livest. Prod. Sci.* 64:95-106.
- Heringstad, B., and O. Østerås. 2013. More than 30 years of health recording in Norway. *ICAR Technical Series no.17.* 39.
- Heringstad, B., X. L. Wu, and D. Gianola. 2009. Inferring relationships between health and fertility in Norwegian red cows using recursive models. *J. Dairy Sci.* 92:1778-1784.

- Heringstad, B., Y. Chang, D. Gianola and G. Klemetsdal. 2005. Genetic analysis of clinical mastitis, milk fever, ketosis, and retained placenta in three lactations of Norwegian red cows. *J. Dairy Sci.* 88:3273-3281.
- Hernandez, J. A., E. J. Garbarino, J. K. Shearer, C. A. Risco, and W. W. Thatcher. 2005. Comparison of milk yield in dairy cows with different degrees of lameness. *J. Am. Vet. Med. Assoc.* 227:1292-1296.
- Hernandez, J., J. K. Shearer, and D. W. Webb. 2002. Effect of lameness on milk yield in dairy cows. *J. Am. Vet. Med. Assoc.* 220:640-644.
- Hertl, J., Y. Schukken, D. Bar, G. Bennett, R. González, B. Rauch, F. Welcome, L. Tauer, and Y. Gröhn. 2011. The effect of recurrent episodes of clinical mastitis caused by gram-positive and gram-negative bacteria and other organisms on mortality and culling in Holstein dairy cows. *J. Dairy Sci.* 94:4863-4877.
- Heuer, C., Y. Schukken, and P. Dobbelaar. 1999. Postpartum body condition score and results from the first test day milk as predictors of disease, fertility, yield, and culling in commercial dairy herds. *J. Dairy Sci.* 82:295-304.
- Hinrichs, D., E. Stamer, W. Junge, and E. Kalm. 2005. Genetic analyses of mastitis data using animal threshold models and genetic correlation with production traits. *J. Dairy Sci.* 88:2260-2268.
- Huijps, K., T. J. Lam, and H. Hogeveen. 2008. Costs of mastitis: Facts and perception. *J. Dairy Res.* 75:113-120.
- Huxley, J. 2013. Impact of lameness and claw lesions in cows on health and production. *Livest. Sci.* 156:64-70.
- Huzzey, J., D. Veira, D. Weary, and M. Von Keyserlingk. 2007. Prepartum behavior and dry matter intake identify dairy cows at risk for metritis. *J. Dairy Sci.* 90:3220-3233.
- Ingvarstsen, K. L., R. Dewhurst, and N. Friggens. 2003. On the relationship between lactational performance and health: Is it yield or metabolic imbalance that cause production diseases in dairy cattle? A position paper. *Livest. Prod. Sci.* 83:277-308.
- Jakobsen, J. H., R. Rekaya, J. Jensen, D.A. Sorensen, P. Madesen, D. Gianola, L.G. Christensen, and J. Pedersen. 2003. Bayesian estimates of covariance components between lactation curve parameters and disease liability in Danish Holstein cows. *J. Dairy Sci.* 86:3000-3007.

- Jones, W. P., L. Hansen, and H. Chester-Jones. 1994. Response of health care to selection for milk yield of dairy cattle. *J. Dairy Sci.* 77:3137-3152. Joosten, I., P. Van Eldik, L. Elving, and G. Van Der Mey. 1987. Factors related to the etiology of retained placenta in dairy cattle. *Anim. Reprod. Sci.* 14:251-262.
- Kaneene, J. B., and H. S. Hurd. 1990. The national animal health monitoring system in Michigan. I. Design, data and frequencies of selected dairy cattle diseases. *Prev. Vet. Med.* 8:103-114
- Kaneene, J., and R. Miller. 1995. Risk factors for metritis in Michigan dairy cattle using herd-and cow-based modelling approaches. *Prev. Vet. Med.* 23:183-200.
- Kelton, D. F., K. D. Lissemore, and R. E. Martin. 1998. Recommendations for recording and calculating the incidence of selected clinical diseases of dairy cattle. *J. Dairy Sci.* 81:2502-2509.
- Koeck, A., F. Miglior, D. Kelton, and F. Schenkel. 2012a. Short communication: Genetic parameters for mastitis and its predictors in Canadian Holsteins. *J. Dairy Sci.* 95:7363-7366.
- Koeck, A., F. Miglior, D. Kelton, and F. Schenkel. 2012b. Health recording in Canadian Holsteins: Data and genetic parameters. *J. Dairy Sci.* 95:4099-4108. Koeck, A., F. Miglior, J. Jamrozik, D. Kelton, and F. Schenkel. 2013. Genetic associations of ketosis and displaced abomasum with milk production traits in early first lactation of Canadian Holsteins. *J. Dairy Sci.* 96:4688-4696.
- Kossabati, M. A., and R. J. Esslemont. 1997. The costs of production diseases in dairy herds in England. *Vet. J.* 154:41-51.
- Laven, R. A., and A. R. Peters. 1996. Bovine retained placenta: Aetiology, pathogenesis and economic loss. *Vet. Rec.* 139:465-471.
- Lawrence, K., R. Chesterton, and R. Laven. 2011. Further investigation of lameness in cows at pasture: An analysis of the lesions found in, and some possible risk factors associated with, lame New Zealand dairy cattle requiring veterinary treatment. *J. Dairy Sci.* 94:2794-2805.
- LeBlanc, S., T. Duffield, K. Leslie, K. Bateman, G. P. Keefe, J. Walton, and W. Johnson. 2002. Defining and diagnosing postpartum clinical endometritis and its impact on reproductive performance in dairy cows. *J. Dairy Sci.* 85:2223-2236.

- LeBlanc, S., T. Herdt, W. Seymour, T. Duffield, and K. Leslie. 2004. Factors associated with peripartum serum concentrations of vitamin E, retinol, and  $\beta$ -carotene in Holstein dairy cattle, and their associations with periparturient disease. *J. Dairy Sci.* 87:609-619.
- LeBlanc, S. 2010. Monitoring metabolic health of dairy cattle in the transition period. *J.Reprod.Dev.* 56:S29-S35.
- LeBlanc, S. J. 2008. Postpartum uterine disease and dairy herd reproductive performance: A review. *Vet. J.* 176:102-114.
- Legarra, A., I. Aguilar, and I. Misztal. 2009. A relationship matrix including full pedigree and genomic information. *J. Dairy Sci.* 92:4656-4663.
- Legarra, A., O. F. Christensen, I. Aguilar, and I. Misztal. 2014. Single step, a general approach for genomic selection. *Livest. Sci.* doi: 10.1016/j.livsci.2014.04.029.
- Lewis, G. S. 1997. Uterine health and disorders. *J. Dairy Sci.* 80:984-994.
- Lin, H., P. Oltenacu, L. D. Van Vleck, H. Erb, and R. Smith. 1989. Heritabilities of and genetic correlations among six health problems in Holstein cows. *J. Dairy Sci.* 72:180-186.
- Lucey, S., G. J. Rowlands, and A. M. Russell. 1986. Short-term associations between disease and milk yield of dairy cows. *J. Dairy Res.* 53:7-15.
- Lyons, D., A. Freeman, and A. Kuck. 1991. Genetics of health traits in Holstein cattle. *J. Dairy Sci.* 74:1092-1100.
- Maltecca, C. 2013. Fitter happier: The never-ending quest for a better cow. *J. Anim. Breed. Genet.* 130:87-88.
- Markusfeld, O. 1987. Periparturient traits in seven high dairy herds: Incidence rates, association with parity, and interrelationships among traits. *J. Dairy Sci.* 70:158-166.
- Markusfeld, O., and E. Ezra. 1993. Body measurements, metritis, and postpartum performance of first lactation cows. *J. Dairy Sci.* 76:3771-3777.
- McArt, J., D. Nydam, and G. Oetzel. 2012. Epidemiology of subclinical ketosis in early lactation dairy cattle. *J. Dairy Sci.* 95:5056-5066.

- Moore, D., J. Cullor, R. Bondurant, and W. Sischo. 1991. Preliminary field evidence for the association of clinical mastitis with altered interestrus intervals in dairy cattle. *Theriogenology*. 36:257-265.
- Neuenschwander, T., F. Miglior, J. Jamrozik, O. Berke, D. Kelton, and L. Schaeffer. 2012. Genetic parameters for producer-recorded health data in Canadian Holstein cattle. *Animal*. 6:571-578.
- Oberbauer, A., S. Berry, J. Belanger, R. McGoldrick, J. Pinos-Rodriguez, and T. Famula. 2013. Determining the heritable component of dairy cattle foot lesions. *J. Dairy Sci.* 96:605-613.
- Olde Riekerink, R., H. Barkema, D. Kelton, and D. Scholl. 2008. Incidence rate of clinical mastitis on Canadian dairy farms. *J. Dairy Sci.* 91:1366-1377.
- Oltenacu, P., and D. Broom. 2010. The impact of genetic selection for increased milk yield on the welfare of dairy cows. *Anim. Welfare*. 19:39-49.
- Oltenacu, P. A., and B. Algers. 2005. Selection for increased production and the welfare of dairy cows: Are new breeding goals needed? *AMBIO*. 34:311-315.
- Oltenacu, P. A., A. Frick, and B. Lindhé. 1990. Epidemiological study of several clinical diseases, reproductive performance and culling in primiparous Swedish cattle. *Prev. Vet. Med.* 9:59-74.
- Østerås, O., H. Solbu, A. Refsdal, T. Roalkvam, O. Filseth and A. Minsaas. 2007. Results and evaluation of thirty years of health recordings in the Norwegian dairy cattle population. *J. Dairy Sci.* 90:4483-4497.
- Østergaard, S., and Y. Gröhn. 1999. Effects of diseases on test day milk yield and body weight of dairy cows from danish research herds. *J. Dairy Sci.* 82:1188-1201.
- Parker Gaddis, K., J. Cole, J. Clay, and C. Maltecca. 2012. Incidence validation and relationship analysis of producer-recorded health event data from on-farm computer systems in the United States. *J. Dairy Sci.* 95:5422-5435.
- Parker Gaddis, K. L., J. B. Cole, J. S. Clay, and C. Maltecca. 2014. Genomic selection for producer-recorded health event data in US dairy cattle. *J. Dairy Sci.* 97:3190-3199.
- Peeler, E., M. Green, J. Fitzpatrick, K. Morgan, and L. Green. 2000. Risk factors associated with clinical mastitis in low somatic cell count British dairy herds. *J. Dairy Sci.* 83:2464-2472.

- Philipsson, J., and B. Lindhé. 2003. Experiences of including reproduction and health traits in scandinavian dairy cattle breeding programmes. *Livest. Prod. Sci.* 83:99-112.
- Qu, Y., A. Fadden, M. Traber, and G. Bobe. 2014. Potential risk indicators of retained placenta and other diseases in multiparous cows. *J. Dairy Sci.* 97:41511-4165.
- Raizman, E., and J. Santos. 2002. The effect of left displacement of abomasum corrected by toggle-pin suture on lactation, reproduction, and health of Holstein dairy cows. *J. Dairy Sci.* 85:1157-1164.
- Rajala, P., and Y. Gröhn. 1998. Effects of dystocia, retained placenta, and metritis on milk yield in dairy cows. *J. Dairy Sci.* 81:3172-3181.
- Rajala-Schultz, P., Y. Gröhn, and C. McCulloch. 1999a. Effects of milk fever, ketosis, and lameness on milk yield in dairy cows. *J. Dairy Sci.* 82:288-294.
- Rajala-Schultz, P., Y. Gröhn, C. McCulloch, and C. Guard. 1999b. Effects of clinical mastitis on milk yield in dairy cows. *J. Dairy Sci.* 82:1213-1220.
- Rauw, W. M. 2009. Resource allocation theory applied to farm animal production. London: Cab International.
- Rauw, W., E. Kanis, E. Noordhuizen-Stassen, and F. Grommers. 1998. Undesirable side effects of selection for high production efficiency in farm animals: A review. *Livest. Prod. Sci.* 56:15-33.
- Richert, R., K. Cicconi, M. Gamroth, Y. Schukken, K. Stiglbauer, and P. Ruegg. 2013. Risk factors for clinical mastitis, ketosis, and pneumonia in dairy cattle on organic and small conventional farms in the United States. *J. Dairy Sci.* 96:4269-4285.
- Rosa, G. J. M., B. D. Valente, G. de los Campos, X. L. Wu, D. Gianola, and M. A. Silva. 2011. Inferring causal phenotype networks using structural equation models. *Genet. Sel. Evol.* 43:1-13.
- Rowlands, G., and S. Lucey. 1986. Changes in milk yield in dairy cows associated with metabolic and reproductive disease and lameness. *Prev. Vet. Med.* 4:205-221.
- Rupp, R., and D. Boichard. 2003. Genetics of resistance to mastitis in dairy cattle. *Vet. Res.* 34:671-688.
- Schakenraad, M., and A. Dijkhuizen. 1990. Economic losses due to bovine mastitis in Dutch dairy herds. *Neth. J. Agric. Sci.* 38:89-92.

- Schefers, J. M., and K. A. Weigel. 2012. Genomic selection in dairy cattle: Integration of DNA testing into breeding programs. *Anim. Front.* 2:4-9.
- Schnitzenlehner, S., A. Essl, and J. Sölkner. 1998. Retained placenta: Estimation of nongenetic effects, heritability and correlations to important traits in cattle. *J. Anim. Breed. Genet.* 115:467-478.
- Shaver, R. 1997. Nutritional risk factors in the etiology of left displaced abomasum in dairy cows: A review. *J. Dairy Sci.* 80:2449-2453.
- Sheldon, I. M., G. S. Lewis, S. LeBlanc, and R. O. Gilbert. 2006. Defining postpartum uterine disease in cattle. *Theriogenology.* 65:1516-1530.
- Sheldon, I. M., E. J. Williams, A. N. Miller, D. M. Nash, and S. Herath. 2008. Uterine diseases in cattle after parturition. *Vet. J.* 176:115-121.
- Sheldon, I., and H. Dobson. 2004. Postpartum uterine health in cattle. *Anim. Reprod. Sci.* 82:295-306.
- Shim, E., R. Shanks, and D. Morin. 2004. Milk loss and treatment costs associated with two treatment protocols for clinical mastitis in dairy cows. *J. Dairy Sci.* 87:2702-2708.
- Shook, G. E. 1989. Major advances in genetic evaluation techniques. *J. Dairy Sci.* 89(4):1337-1348.
- Simianer, H., H. Solbu, and L. Schaeffer. 1991. Estimated genetic correlations between disease and yield traits in dairy cattle. *J. Dairy Sci.* 74:4358-4365.
- Sogstad, Å., O. Østerås, T. Fjeldaas, and A. Refsdal. 2007. Bovine claw and limb disorders at claw trimming related to milk yield. *J. Dairy Sci.* 90:749-759.
- Tranter, W., and R. Morris. 1991. A case study of lameness in three dairy herds. *N. Z. Vet. J.* 39:88-96.
- Vaarst, M., J. Hindhede, and C. Enevoldsen. 1998. Sole disorders in conventionally managed and organic dairy herds using different housing systems. *J. Dairy Res.* 65:175-186.
- Valente, B. D., G. J. M. Rosa, G. de Los Campos, D. Gianola, and M. A. Silva. 2010. Searching for recursive causal structures in multivariate quantitative genetics mixed models. *Genetics.* 185:633-644.

- Valente, B. D., G. J. Rosa, D. Gianola, X. L. Wu, and K. Weigel. 2013. Is structural equation modeling advantageous for the genetic improvement of multiple traits? *Genetics*. 194:561-572.
- Van Dorp, T., J. Dekkers, S. Martin, and J. Noordhuizen. 1998. Genetic parameters of health disorders, and relationships with 305-day milk yield and conformation traits of registered Holstein cows. *J. Dairy Sci.* 81:2264-2270.
- Van Winden, S. C., and R. Kuiper. 2003. Left displacement of the abomasum in dairy cattle: Recent developments in epidemiological and etiological aspects. *Vet. Res.* 34:47-56.
- VanRaden, P. 2004. Invited review: Selection on net merit to improve lifetime profit. *J. Dairy Sci.* 87:3125-3131.
- VanRaden, P., C. Van Tassell, G. Wiggans, T. Sonstegard, R. Schnabel, J. Taylor, and F. Schenkel. 2009. Invited review: Reliability of genomic predictions for North American Holstein bulls. *J. Dairy Sci.* 92:16-24.
- Varona, L., and D. Sorensen. 2014. Joint analysis of binomial and continuous traits with a recursive model: A case study using mortality and litter size of pigs. *Genetics*. 196:643-651.
- Vermunt, J. J. 2007. One step closer to unravelling the pathophysiology of claw horn disruption: For the sake of the cows' welfare. *Vet. J.* 174:219-220.
- Von Keyserlingk, M., J. Rushen, A. M. de Passillé, and D. M. Weary. 2009. Invited review: The welfare of dairy cattle—Key concepts and the role of science. *J. Dairy Sci.* 92:4101-4111.
- Warnick, L., D. Janssen, C. Guard, and Y. Gröhn. 2001. The effect of lameness on milk production in dairy cows. *J. Dairy Sci.* 84:1988-1997.
- Wellenberg, G., W. Van Der Poel, and J. Van Oirschot. 2002. Viral infections and bovine mastitis: A review. *Vet. Microbiol.* 88:27-45.
- Wells, S. J., S. L. Ott, and A. H. Seitzinger. 1998. Key health issues for dairy cattle—New and old. *J. Dairy Sci.* 81:3029–3035.
- Wetherill, G. D. 1965. Retained placenta in the bovine. A brief review. *Can. Vet. J.* 6:290-294.

- Wilson, D. J., R. González, J. Hertl, H. Schulte, G. Bennett, Y. Schukken, and Y. Gröhn. 2004. Effect of clinical mastitis on the lactation curve: A mixed model estimation using daily milk weights. *J. Dairy Sci.* 87:2073-2084.
- Wittrock, J., K. Proudfoot, D. Weary, and M. Von Keyserlingk. 2011. Short communication: Metritis affects milk production and cull rate of Holstein multiparous and primiparous dairy cows differently. *J. Dairy Sci.* 94:2408-2412.
- Wu, X. L., B. Heringstad, and D. Gianola. 2010. Bayesian structural equation models for inferring relationships between phenotypes: A review of methodology, identifiability, and applications. *J. Anim. Breed. Genet.* 127:3-15.
- Wu, X. L., B. Heringstad, and D. Gianola. 2008. Exploration of lagged relationships between mastitis and milk yield in dairy cows using a bayesian structural equation gaussian-threshold model. *Genet. Sel. Evol.* 40:333-358.
- Zwald, N., K. Weigel, Y. Chang, R. Welper, and J. Clay. 2004a. Genetic selection for health traits using producer-recorded data. I. Incidence rates, heritability estimates, and sire breeding values. *J. Dairy Sci.* 87:4287-4294.
- Zwald, N., K. Weigel, Y. Chang, R. Welper, and J. Clay. 2004b. Genetic selection for health traits using producer-recorded data. II. Genetic correlations, disease probabilities, and relationships with existing traits. *J. Dairy Sci.* 87:4295-4302.

**CHAPTER 2****INFERRING CAUSAL RELATIONSHIPS BETWEEN REPRODUCTIVE AND  
METABOLIC HEALTH DISORDERS AND PRODUCTION TRAITS IN FIRST-  
LACTATION US HOLSTEINS USING RECURSIVE MODELS**

## ABSTRACT

Health disorders in dairy cows have a substantial impact on the profitability of a dairy enterprise due to loss in milk sales, culling of unhealthy cows, and increased replacement costs. Complex relationships exist between health disorders and production traits.

Understanding the causal structures among these traits may help us to disentangle those complex relationships. The principal objective of this study was to use producer-recorded data to explore phenotypic and genetic relationships among health disorders and production traits in first-lactation US Holsteins. A total of 77,004 first-lactation daughters' records of 2,183 sires were analyzed using recursive models. Health data contained information on reproductive health disorders (retained placenta (RP); metritis (METR)) and metabolic health disorders (ketosis (KETO); displaced abomasum (DA)). Production traits included mean milk yield (MY) from early part of lactation (1-120 DIM), peak milk yield (PMY), day in milk of peak milk yield (PeakD), and lactation persistency (LP). Three different sets of traits were analyzed which included: recursive effect from each health disorder on culling; recursive effects of one health disorder on another health disorder and on MY, and recursive effects of each health disorder on production traits including PeakD, PMY and LP. Different recursive Gaussian-threshold and threshold models were implemented in a Bayesian framework. The estimated structural coefficients of the recursive models revealed how the presence of health disorder increases the culling frequency with stronger impact from DA, followed by RP, KETO, and METR. Positive recursive effects of RP to METR and of KETO on DA were estimated, whereas recursive effects from health disorders to production traits

were negligible in all cases. Heritability estimates of health disorders ranged from 0.023 to 0.114, in accordance with previous studies. Similarly, genetic correlations obtained between health disorders were moderate. The results obtained suggest that reproductive and metabolic health disorder and culling due to metabolic and reproductive diseases have strong causal relationships with recursive effects from a health disorder to culling. Based on these results it was concluded that a health disorder occurring in early lactation has a moderate causal effect on another health disorder occurring in later lactation.

**Key words: causal effect, health, persistency, structural equation model**

## INTRODUCTION

Many health disorders in dairy cows have a substantial impact on the farm economy. The occurrence of a health disorder can cause economic losses due to increased culling and treatment costs. In addition, health disorders increase the number of potential replacements, impair reproductive efficiency, decrease longevity of cows, and also have an adverse effect on animal welfare (Congleton Jr and King, 1984; Britt, 1985; Jakobsen et al., 2003; Dhakal et al., 2013). Health disorders have a direct impact on culling and production traits (Duffield and Herdt, 2000; Drackley, 2006; Esposito et al., 2013). Dechow and Goodling (2008) reported that early culling were a reliable indicator of poor cow health. Rauw et al. (1998) further reported that there could be an antagonistic relationship between milk production and disease resistance.

Beaudeau et al. (2000) reported that metabolic disorders have effects on milk production, reproductive performance, and culling. Ketosis (**KETO**) and displaced abomasum (**DA**), were reported as the two most frequent metabolic diseases in first-lactation Canadian Holstein cows with disease frequencies of 4.09 % and 2.66 %, respectively (Koeck et al., 2013). In the US, Zwald et al. (2004a) reported disease frequencies of 10% for KETO and 3% for DA in dairy cows, from producer-recorded data. Similarly, Appuhamy et al. (2009) reported incidence rates of 5.2% for KETO and 4.1% for DA for first-lactation US dairy cows. More recently, Parker Gaddis et al. (2012) using producer-recorded health data reported lactational incidence rates of 3.42% for KETO and 1.29% for DA for first parity cows. Similarly, regarding reproductive efficiency, retained placenta (**RP**) and metritis (**METR**) have been reported as the disorders mostly affecting, culling risk and depressing the overall productivity of dairy cows by reducing milk yield (Rajala and Grohn, 1998). Lactational incidence rates of METR reported were 8.71% (Parker Gaddis et al. 2012), 21% including RP (Zwald et al. 2004a), and 17.7 % (Appuhamy et al. 2009) including RP and cystic ovaries in US dairy cows using producer-recorded data.

Production traits such as test day milk yields, day in milk of peak milk yield (**PeakD**), peak milk yield (**PMY**), and milk yield lactation persistency (**LP**) have been studied in the past in connection with health events (Muir et al., 2004; Appuhamy et al., 2009). However, there could be non-trivial relationships among health disorders and production traits (Heringstad et al., 2009). Inferring causal relationships between phenotypes could help disentangle the complex relationships between health disorders and production traits (Wu et

al., 2008; Valente et al., 2010; Rehbein et al., 2013). In the context of animal breeding, Gianola and Sorensen (2004) extended quantitative genetic models to infer recursive and simultaneous relationships between phenotypes in a multivariate system. In recent years, structural equation models (**SEM**) were applied to study recursive and simultaneous relationships among phenotypes in a multivariate system (Rosa et al., 2011).

Even though there is no mandatory or consistent recording of health disorders of dairy cows in the United States, previous studies by Zwald et al. (2004b), Apphuamy et al. (2009), and Parker Gaddis et al. (2014) have confirmed the possibility of using on-farm producer-recorded health information for genetic evaluation and to identify phenotypic relationships among health disorders. However, those previous studies have not explored the causal effect of health disorders on culling and production traits.

Causal relationships may exist between health disorders that evolve during the course of a cow's lactation. Identifying such causal relationships could help us better understand patterns of disease occurrence. Similarly, inferring the magnitude of causal effects between health disorders and culling could help improve management strategies. Finally, eliciting the magnitude of a causal effect from a health disorder (occurring in early lactation) to early and late lactation production measures could improve the understanding of both the immediate impact of a health disorder and the delayed effect on overall lactation yield. To identify the magnitude of these effects, separate analyses were conducted in the present study. Structural equation models were employed to infer causal relationships among binary (e.g. health

disorders, culling), and continuous (e.g. production) traits, particularly from health disorders to early and late lactation production measures and from health disorders to culling.

## **MATERIALS AND METHODS**

### **Data description**

Early lactation production measures such as test day milk yields were used to estimate the immediate impact of health disorders. Similarly, mid lactation production measures such as PeakD and PMY, and late lactation production measures such as LP were used to estimate the delayed impact of health disorders on production. Culling was considered to estimate the impact of health disorders on culling of cows.

The health disorder data, which represented on-farm producer recorded dairy herd records containing information about common health disorders of US dairy farms were available from Dairy Records Management Systems (**DRMS**) (Raleigh, NC) in “Format 6: Health” data exchange format (Animal Improvement Programs Laboratory, 2010) from year 1996 through June 2013. Among health disorders, metabolic (i.e. KETO and both right- and left-sided DA) and reproductive (i.e. RP and METR) were selected for analysis. Health disorders occurring in the early part of lactation - from date of calving to the first 30 d of lactation were considered. This value was chosen because the majority (92%) of health disorders considered in the current study occurred in the first 30 d of lactation. The mean ( $\pm$ SD) day of lactation to occurrence was 2.3 ( $\pm$ 1.1) d for RP, 9.1 ( $\pm$ 1.4) d for KETO, 11.7 ( $\pm$ 1.3) d for METR, and 18.5( $\pm$ 1.9) d for DA. Zwald et al. (2004a) had also found the majority of producer recorded health disorders occurred during the first 30 d of lactation. For

each of the health disorders, if a health disorder for a cow was recorded within 30 d of lactation, a score of 1 (diseased) was assigned to the cow; otherwise 0 (healthy) was assigned. Repeated cases of the same disorder were ignored. Reproductive disorders (RP and METR) were further combined to create a single measure termed REPRO. Similarly, metabolic disorders (KETO and DA) were further combined to provide a single measure termed META.

Health data were merged with test day milk yields provided by DRMS in “Format4: Lactation” data exchange format (Animal Improvement Programs Laboratory, 2006). The test day milk yields recorded during the first 120 d of lactation were divided into two 60 d periods such that 1 to 60 DIM was categorized as period 1 and 61 to 120 DIM was categorized as period 2. For each cow, mean milk yield (MY) records were obtained for each period, and referred as MY1 and MY2 for periods 1 and 2 respectively. The mid and late lactation production measures i.e. PeakD, PMY, and LP were obtained for each cow starting from individual test day yield using BESTPRED software (Cole and VanRaden, 2007). In this study, LP is defined as the ability of a cow to maintain milk production at a higher level after peak milk yield, which is independent of milk yield (Cole and VanRaden, 2007).

Culling was recorded in binary format such that, if a cow was culled, she received a score of 1 = culled; otherwise a score of 0 = not culled was assigned. Incidence of culling was based on termination codes 3 and 4 of “Format 4: Lactation” data exchange format (Animal Improvement Programs Laboratory, 2006). Termination code 3 was defined as “Cow sold for poor production” and termination code 4 was defined as “Cow sold because of

reproductive problems” (Animal Improvement Programs Laboratory, 2013); other termination codes were not included in the study because they were assigned to different health disorders such as locomotion problems, mastitis or high somatic cells, undesirable confirmation, aggressive behavior etc.

Health disorder data edits were applied as described in Parker Gaddis et al. (2012). Only records of disorders from years 2011 and 2012 were retained for analysis to ensure consistent incidences across all herds. After applying data quality edits, a total of 77,004 first parity Holsteins daughters from 2,183 sires across 553 herds were represented in the data. Data were retained for subsequent analyses and will be termed *Health-Culling-Prod* dataset hereafter. Within *Health-Culling-Prod*, the traits included were health disorders, culling, and MY. To identify the causal effect of health disorders on middle and late production measures, a subset of *Health-Culling-Prod* was formed and termed as *Health-Prod* dataset. Data editing constraints applied to *Health-Prod* was the same as that of *Health-Culling-Prod* except for the fact that only cows with complete lactations were retained for analysis. *Health-Prod* included 67,907 first parity records from 2,029 sires across 548 herds. Traits included in *Health-Prod* were health disorders, PeakD, PMY and LP.

### **Statistical Analyses**

Different series of analyses were defined to meet the objectives of the study. To identify the causal relationship of health disorders and culling (using *Health-Culling-Prod*) a bivariate threshold-threshold sire recursive SEM was used and will be termed as *Health-Culling* analyses hereafter. The threshold model assumes an underlying continuous variable,

liability ( $l_i$ ) for a binary trait that defines the observed binary variable into a value of 1 if liability is larger than a fixed threshold and 0 otherwise. A causal effect of health disorder on culling was considered between health disorders and culling trait as shown in Figure 1.

Threshold-Gaussian SEM were employed to elicit the causal relationships among health disorders and milk yields (using *Health-Culling-Prod*). Recursive causal structure was in this case from one health disorder to another health disorder and from health disorders to milk yields (MY1 and MY2) as shown in Figure 2. The one-way causal structure from one health disorder to another was considered on the basis of occurrence of the disorder from calving date. According to this definition, a disorder that occurred nearest to the calving date had an effect on a health event occurring later in a cow's lactation. This assumption was based on the study by Parker Gaddis et al. (2012), where they used path analysis to identify the effect of one health disorder to another health disorder. Using the causal structure defined above, three analyses were performed and will be termed as *Health-MY* analyses hereafter. Each one included two Gaussian traits, MY1 and MY2, and two health disorders, i.e. either RP and METR, KETO and DA, or REPRO and META and direct and indirect recursive effects were assumed from the first trait to MY1 and MY2. For example, direct and indirect recursive effects were assumed from RP to MY1. The direct recursive effect measured how much MY1 would be affected by the change in liability to RP. The indirect recursive effect measured how much MY1 would be affected by change in liability to RP through the mediating effect of the liability to METR. The indirect recursive effect can be calculated as the product of structural coefficients  $(RP \rightarrow METR) \times (METR \rightarrow MY1)$

(López de Maturana et al., 2008, Shipley, 2002). The overall causal effect of RP on MY1 can then be calculated as  $(RP \rightarrow MY1) + ((RP \rightarrow METR) \times (METR \rightarrow MY1))$ .

A threshold-Gaussian SEM was employed to explore the causal relationships between health disorders and production parameters describing lactation curve such as PeakD, PMY, and LP (using *Health-Prod*). Again, an acyclic causal structure was considered between health disorders and production traits (PeakD, PMY, and LP) as shown in Figure 3 and four analyses were performed using this causal structure. These analyses will be termed as *Health-Lactation* hereafter. Each one included three Gaussian traits (PeakD, PMY, and LP) and one binary health disorder trait, i.e. either RP, METR, KETO, or DA.

The equations used in all the above analyses can be represented as follows:

$$\text{Health} - \text{Culling: } \begin{cases} \mathbf{y}_1 = \mathbf{Xb}_1 + \mathbf{Z}_h \mathbf{h}_1 + \mathbf{Z}_s \mathbf{s}_1 + \mathbf{e}_1 \\ \mathbf{y}_2 = \lambda_{21} \mathbf{y}_1 + \mathbf{Xb}_2 + \mathbf{Z}_h \mathbf{h}_2 + \mathbf{Z}_s \mathbf{s}_2 + \mathbf{e}_2 \end{cases}$$

$$\text{Health} - \text{MY: } \begin{cases} \mathbf{y}_1 = \mathbf{Xb}_1 + \mathbf{Z}_h \mathbf{h}_1 + \mathbf{Z}_s \mathbf{s}_1 + \mathbf{e}_1 \\ \mathbf{y}_2 = \lambda_{21} \mathbf{y}_1 + \mathbf{Xb}_2 + \mathbf{Z}_h \mathbf{h}_2 + \mathbf{Z}_s \mathbf{s}_2 + \mathbf{e}_2 \\ \mathbf{y}_3 = \lambda_{31} \mathbf{y}_1 + \lambda_{32} \mathbf{y}_2 + \mathbf{Xb}_3 + \mathbf{Z}_h \mathbf{h}_3 + \mathbf{Z}_s \mathbf{s}_3 + \mathbf{e}_3 \\ \mathbf{y}_4 = \lambda_{41} \mathbf{y}_1 + \lambda_{42} \mathbf{y}_2 + \mathbf{Xb}_4 + \mathbf{Z}_h \mathbf{h}_4 + \mathbf{Z}_s \mathbf{s}_4 + \mathbf{e}_4 \end{cases}$$

$$\text{Health} - \text{Lactation: } \begin{cases} \mathbf{y}_1 = \mathbf{Xb}_1 + \mathbf{Z}_h \mathbf{h}_1 + \mathbf{Z}_s \mathbf{s}_1 + \mathbf{e}_1 \\ \mathbf{y}_2 = \lambda_{21} \mathbf{y}_1 + \mathbf{Xb}_2 + \mathbf{Z}_h \mathbf{h}_2 + \mathbf{Z}_s \mathbf{s}_2 + \mathbf{e}_2 \\ \mathbf{y}_3 = \lambda_{31} \mathbf{y}_1 + \mathbf{Xb}_3 + \mathbf{Z}_h \mathbf{h}_3 + \mathbf{Z}_s \mathbf{s}_3 + \mathbf{e}_3 \\ \mathbf{y}_4 = \lambda_{41} \mathbf{y}_1 + \mathbf{Xb}_4 + \mathbf{Z}_h \mathbf{h}_4 + \mathbf{Z}_s \mathbf{s}_4 + \mathbf{e}_4 \end{cases}$$

In the equations above,  $\mathbf{y}_1$  and  $\mathbf{y}_2$  are the vectors of liability to health disorder and observations of culling in *Health-Culling* analyses,  $\mathbf{y}_1$ , and  $\mathbf{y}_2$ , are the vectors of liability to health disorder, and  $\mathbf{y}_3$ , and  $\mathbf{y}_4$  are the vectors of observations of milk yields (health disorder 1, health disorder 2, MY1 and MY2, considered in this order) in *Health-MY* analyses, and the  $\mathbf{y}_1$  is the vector of liability to health disorder, and  $\mathbf{y}_2$ ,  $\mathbf{y}_3$ , and  $\mathbf{y}_4$  are the vectors of observations of production traits (health disorder, PeakD, PMY, and LP, considered in this order) for the *Health-Lactation* analyses. For all models,  $\lambda_{ij}$  is the structural coefficients describing the rate of change of trait  $i$  with respect to trait  $j$ . For *Health-Culling* analyses,  $\lambda_{21}$  is the response of culling with respect to health disorders. In the case of *Health-MY*, for example, in the analysis including RP, METR, MY1 and MY2 traits,  $\lambda_{21}$  is the response of METR with respect to RP. The rate of change in MY1 with respect to RP and METR is given by  $\lambda_{31}$  and  $\lambda_{32}$ . Similarly, the rate of change in MY2 with respect to RP and METR is given by  $\lambda_{41}$  and  $\lambda_{42}$ . For *Health-Lactation* analyses, the structural coefficients  $\lambda_{ij}$  describe, for example, the rate of change in PeakD with respect to RP given by  $\lambda_{21}$ . For all models,  $\mathbf{b}$  is a vector of systematic effects including the effect of year-season of calving;  $\mathbf{h}$  is a vector of herd effects,  $\mathbf{s}$  is a vector of sire effects, and  $\mathbf{e}$  is a vector of residuals;  $\mathbf{X}$ ,  $\mathbf{Z}_h$ , and  $\mathbf{Z}_s$  are the corresponding incidence matrices.

In matrix form, the general model for all three different analyses can be written as:

$$\mathbf{y} = (\mathbf{\Lambda} \otimes \mathbf{I})\mathbf{y} + \mathbf{X}\mathbf{b} + \mathbf{Z}_h\mathbf{h} + \mathbf{Z}_s\mathbf{s} + \mathbf{e}$$

where the  $\mathbf{\Lambda}$  structure for three different analyses can be written as follows:

$$\text{Health-Culling: } \Lambda_1 = \begin{bmatrix} 0 & 0 \\ \lambda_{21} & 0 \end{bmatrix}$$

$$\text{Health-MY: } \Lambda_2 = \begin{bmatrix} 0 & 0 & 0 & 0 \\ \lambda_{21} & 0 & 0 & 0 \\ \lambda_{31} & \lambda_{32} & 0 & 0 \\ \lambda_{41} & \lambda_{42} & 0 & 0 \end{bmatrix}$$

$$\text{Health-Lactation: } \Lambda_3 = \begin{bmatrix} 0 & 0 & 0 & 0 \\ \lambda_{21} & 0 & 0 & 0 \\ \lambda_{31} & 0 & 0 & 0 \\ \lambda_{41} & 0 & 0 & 0 \end{bmatrix}$$

Prior distributions for structural coefficients, systematic effects  $\mathbf{b}$ , sire genetic effects  $\mathbf{s}$ , effect of herd  $\mathbf{h}$ , and the corresponding (co)variance matrices were similar to those described by Heringstad et al. (2009). Structural coefficients and elements of  $\mathbf{b}$  were assigned multivariate normal prior distributions, with mean 0 and variance 10000. Sire effects were assigned a multivariate normal prior distribution  $\mathbf{s} \sim N(\mathbf{0}, \mathbf{G} \otimes \mathbf{A})$ , where  $\mathbf{G}$  is the sire covariance matrix for the traits involved and  $\mathbf{A}$  is the matrix of additive genetic relationships among sires. The prior distribution of the herd effects was  $\mathbf{h} \sim N(\mathbf{0}, \mathbf{H} \otimes \mathbf{I})$ , where  $\mathbf{H}$  is the (co)variance matrix and  $\mathbf{I}$  is an identity matrix. Independent inverse-Wishart prior distributions were used for  $\mathbf{H}$  and  $\mathbf{G}$ , the covariance matrices of  $\mathbf{h}$  and  $\mathbf{s}$ , respectively. Residual variances were fixed to 1 and residual covariances were assumed equal to 0. This is an assumption that is required for the identifiability of structural coefficients. In this case, the prior distribution of the matrix  $\mathbf{R}$  fixing the residual covariances was an inverse Wishart

distribution. The estimated covariance matrices for models from each series of analyses was transformed as:

$$\mathbf{G}^*_n = (\mathbf{I}-\mathbf{A})^{-1}_n \mathbf{G}_n (\mathbf{I}-\mathbf{A})'^{-1}_n$$

$$\mathbf{H}^*_n = (\mathbf{I}-\mathbf{A})^{-1}_n \mathbf{H}_n (\mathbf{I}-\mathbf{A})'^{-1}_n$$

$$\mathbf{R}^*_n = (\mathbf{I}-\mathbf{A})^{-1}_n \mathbf{R}_n (\mathbf{I}-\mathbf{A})'^{-1}_n$$

where the index  $n$  indicates the models used for Health-Culling, Health- MY, and Health-Lactation analyses,  $\mathbf{G}$ ,  $\mathbf{H}$ ,  $\mathbf{R}$ , and  $\mathbf{A}$  were as defined above, and  $\mathbf{I}$  is the identity matrix. Heritabilities and genetic correlations were then calculated in the usual manner from (co)variance components in  $\mathbf{G}^*_n$ ,  $\mathbf{H}^*_n$ , and  $\mathbf{R}^*_n$ .

Data analyses were conducted in a Bayesian framework using the SIR-BAYES package (Wu et al., 2007; Wu et al., 2008) in which all Bayesian models were implemented via Markov chain Monte Carlo (MCMC) methods. For each model, 100,000 iterations were run and posterior samples from each chain were thinned every 25 iterations after 20,000 iterations of burn-in. Posterior distributions of parameters of interest were inferred based on posterior samples after burn-in and thinning. Markov chains convergence was assessed by visual inspection of trace plots; in addition, Geweke's convergence statistic (Geweke, 1992) was obtained through the CODA package (Plummer et al., 2013) of R (<http://cran.r-project.org>).

For ease of interpretation estimates on the liability scale were converted to the observable scale following Wu et al. (2008). For example, the difference in the mean PMY between sick (1) cows due to RP and healthy (0) cows can be calculated as:

$$\Delta \approx \lambda(\bar{l}_1 - \bar{l}_0)$$

where  $\bar{l}_1$  and  $\bar{l}_0$  are averages of liabilities for sick cows due to RP and healthy cows, respectively, and lambda ( $\lambda$ ) is the same as described above .

## **RESULTS AND DISCUSSION**

Summary statistics of metabolic and reproductive health disorders along with the culling due to each health event of interest are shown in Table 1. The largest incidence of health disorder was for METR followed by RP and KETO. Most of the cow cullings were due to METR followed by KETO and DA. Summary statistics of production traits are shown in Table 2. Mean peak milk yield was 36.41 kg, which was slightly higher than reported by Muir et al. (2004) (31.35 kg) for first-lactation Canadian Holsteins.

### **Recursive effects**

#### **Health disorders and culling**

Structural coefficients  $\lambda$  measure recursiveness at the phenotypic level (Gianola and Sorensen, 2004). Posterior distribution of recursive effects from liability of health disorders to liability to culling are shown in Figure 4 (A) and their posterior mean, standard deviation (SD), and 95% highest posterior density interval (95% HPD) are shown in Table 3. Posterior means of recursive effects from health disorders to culling were positive and ranged from 0.93 to 1.59 on the liability scale. The SD of the structural coefficients was moderate ranging from 0.06 to 0.11. The 95% HPD did not include zero for any of the analyses with traits involving liability to health disorders and culling. The recursive effects indicates that each 1-

unit increase of liability for RP, METR, KETO and DA, would increase culling by 1.23, 0.93, 1, and 1.59 on the underlying liability scale, respectively. In the observable scale, the difference in mean culling between sick (due to RP, METR, KETO, and DA) and healthy cows is 3.48, 2.68, 3.99, and 7.85 units respectively. In general, strong causal relationships were identified between health disorders and culling.

Gröhn et al. (1998) reported the disease-specific risk of culling for Holstein cows, which were 26.9% for DA, 32.5% for KETO, 31.7% for RP and 17.1% for METR. The recursive effects obtained in our results also suggest a similar trend for culling cows with higher emphasis on metabolic health disorders than reproductive health disorders. Raizman et al. (2002) conducted a survival analysis and found that 8% of cows died and 27.7% of cows were sold out of 188 cows affected with DA. The structural coefficient for liability to DA to culling in our analysis indicates that cows affected with DA have higher culling risk. Similarly, Lewis (1997) reported that cows with METR had higher culling (26.6%) compared to cow without METR (20.5%). Posterior mean of recursive effect from METR to culling from our study suggests that an increase in incidence of METR would directly increase the culling. Cobo-Abreu et al. (1979) reported an odds ratio (OR) of 4.1 for METR and risk of culling and an OR of 2.3 for RP and risk of culling. Bigras-Poulin (1985) reported an OR of 1.8 for RP and risk of culling. Oltenacu et al. (1990) reported an OR of 1.4 for RP and risk of culling, and also reported an OR of 0.8 for KETO and risk of culling. The OR for disease and risk of culling mentioned above is a measure of association between disease exposure and culling outcome, and doesn't account for the causal relationships between traits. The causal

effect from diseases to culling found in our study is a strong proof of the causal relationships between diseases and culling.

### **Health disorders and production traits**

Recursive effects obtained from *Health-MY* analyses are given in Table 4. Posterior distributions of recursive effects (on the liability scale) of one health disorder on a second disorder are shown in Figure 4 (B), while recursive effects of health disorders on yield traits MY1 and MY2 are shown in Figure 4 (C, D, E, and F). Based on the results it was concluded that a positive recursive effect from liability of RP on METR (approximately 0.120 units increase of liability of METR for a 1-unit increase of liability of RP). Conversely, the posterior means of direct effect of liability of RP on MY1 and MY2 were negative, albeit small in magnitude (-0.025 and -0.002 on underlying liability scale, respectively). Similarly, the posterior means of the recursive effect of METR on MY1 and MY2 were -0.044 and 0.085 on underlying liability scale, respectively. The indirect recursive effect of liability to RP to MY1 and MY2 through the mediating effect of liability to METR was similar in magnitude to that of the direct recursive effect of liability to RP to MY1 and MY2. The overall causal effect of liability to RP to MY1 and MY2 was weak. The 95% HPD of structural coefficients of liability to health disorder (RP and METR) to MYs included zero in their credible region, except for structural coefficient obtained for liability to METR to MY2 (Table 4).

For metabolic diseases, the results showed a positive effect from KETO to DA with a posterior mean of the direct recursive effect of 0.122. The direct effects of liability to KETO and DA to MY1 and MY2 were in all cases weak (-0.007, 0.034, -0.025, and -0.003 on underlying liability scale, respectively). Magnitude of the indirect recursive effect of liability to KETO to MY1 and MY2 through the mediating effect of liability to DA was similar to that of the direct recursive effect of liability to KETO to MY1 and MY2 was similarly negligible. The recursive effect of REPRO on META was positive (approximately 0.112 unit increase of liability to META for a 1-unit increase of liability to REPRO), while direct effects REPRO and META on MY1 and MY2 were again small (-0.058, 0.082, -0.031, and 0.026 on underlying liability scale, respectively). Both direct and indirect (through the mediating effect of META) effects of REPRO on MY1 and MY2 were similar in magnitude and in all cases the 95% HPD of structural coefficients of liability to health disorders (KETO, DA, REPRO, and META) to MYs included zero.

The recursive effects obtained from the Health-MY analyses were converted to the observable scale. For reproductive health disorders, the difference in METR incidence, MY1, and MY2, between cows with and without RP were 0.34 units, -0.07 kg, and -0.01 kg respectively. Similarly, the difference in MY1 between cows with and without METR was 0.13 kg and the difference in MY2 was 0.25 kg. In case of metabolic health disorders, the difference in DA incidence, MY1, and MY2, between cows with and without KETO were of 0.63 units, -0.03 kg, and 0.14 kg respectively. Similarly, the difference in MY1 between cows with DA and without DA were -0.12 kg, and the difference in MY2 was -0.02 kg.

Likewise, the differences in META incidence, MY1, and MY2, between cows with and without REPRO were of 0.29 units, -0.15 kg, and 0.01 kg respectively. Difference in MY1 between cows with and without META was -0.11 kg and the difference in MY2 was 0.01 kg.

Magnitude of causal effects from one health disorder to another health disorder in either metabolic, reproductive or in combined (reproductive and metabolic) category was moderate (Table 4). Posterior means of inferred structural coefficients indicate that the occurrence of one health disorder would directly increase the liability to other health disorders.

Recursive effects obtained from Health-Lactation analyses (which included health disorders and production parameters describing the overall lactation curve (using *Health-Prod*)) are given in Table 5 and the posterior distributions are shown in Figure 5. The 95% HPD of all structural coefficients of liability of health disorders to production traits (PeakD, PMY, and LP) included zero in their credible interval, thus the interpretations of causal effects should be considered carefully. Possible explanations for this behavior could be that the causal effect of health disorders on production traits could be null or of relatively small magnitude or these results might be due to use of producer-recorded data, which may not reflect the “true” incidences of health disorders and also somewhat underestimate the sub-clinical states cases. Posterior mean of recursive effects obtained have small magnitude and are weak in strength. Recursive effects from health disorders to LP were between -0.002 to 0.001 on underlying liability scale. Similarly, recursive effects from health disorders to PeakD ranged from 0.018 to 0.095 on underlying liability scale. The recursive effects of

health disorders on PMY were between -0.001 and 0.003 on underlying liability scale. Weak recursive effects could be explained by the fact that experiencing a health event in the early part of lactation and could effectively leave enough time for the individual to recover from the disease resulting in negligible long term effects.

### **Heritabilities and Genetic Correlations**

Posterior mean, SD, and 95% HPD of heritabilities of liability of health disorders, culling and production traits, from all series of analyses conducted are shown in Table 6. The heritabilities of liability to RP (0.054), METR (0.023), KETO (0.041) and DA (0.114) were within the range of previous threshold model estimates of heritability for these health disorders (Zwald et al., 2004; Heringstad et al., 2005; Heringstad et al., 2009). Parker Gaddis et al. (2014) reported similar heritability estimates for health disorder using producer-recorded data. Heritability estimates of MY1 and MY2 were of 0.132 and 0.127 respectively. The heritability estimate obtained for PeakD was low (0.02). Muir et al. (2004) reported a comparable, albeit larger, estimated heritability of PeakD from first-lactation Canadian Holstein equal to 0.09. Heritability estimate of PMY was approximately 0.19, which was lower than reported by Zwald et al. (2003) (range between 0.27 to 0.37), and Rekaya et al. (2000) (0.26), and was slightly higher than Ferris et al. (1985) (0.16).

Heritability estimate of LP was approximately 0.34, which was similar to the estimates obtained in literature (Danell, 1982; Jamrozik and Schaeffer, 1997; Strabel et al., 2001; Jakobsen et al., 2002), but were higher than what obtained by Cole and VanRaden,

(2006) who estimated heritability of lactational persistency equal to 0.10. Additionally, Gengler (1996) reported heritability for LP of 0.14 for Holstein cows.

The posterior mean of genetic correlations, as well as 95% HPD interval, of health disorder traits and production traits from all series of analyses are given in Table 7. The strongest genetic correlation was found for KETO with DA, with genetic correlations of approximately 0.57. Similarly, a positive genetic correlation was found for RP with METR (0.49). The 95% HPD for genetic correlations of RP and METR with PeakD, PMY, and LP included zero in credible interval. Negative genetic correlation estimates was found for KETO and PeakD (-0.505). The 95% HPD for genetic correlations of KETO with PMY and LP, and DA with PeakD, PMY and LP included zero in the credible interval.

The posterior mean of genetic correlation for production traits including MY1 and MY2 was positive and strong (0.995) as expected. Similarly, the estimate of genetic correlation between PMY and LP was positive and strong (0.836). The 95% HPD for genetic correlation of PeakD with PMY and LP included zero in credible interval. However, the mean of genetic correlation of PeakD with LP suggests a positive genetic correlation higher than 0.5. Muir et al. (2004) reported a genetic correlation of PeakD with LP of approximately 0.54 for first-lactation Canadian Holstein cows. The genetic correlation results in our analysis indicate that there is evidence of a genetic correlation between RP and METR and also between KETO and DA, and most of the genetic correlations of health disorders with production traits included zero in 95% HPD credible interval.

## CONCLUSION

Understanding the relationships between reproductive and metabolic health disorders along with culling, and production traits in a phenotypic level could help us identifying the development of the disease process and its consequences in culling, and production traits. The causal relationship between metabolic and reproductive health disorders and culling found in this study suggest that with increases in the incidence of health disorders there would be an increase in culling. Similarly, the causal relationship among health disorders found in this study indicate that having one health disorder at an earlier time in a cow's productive life increases the risk of future health disorders. There is little to no impact on production traits from health disorders for cows who survived these health disorders

## REFERENCES

- Animal Improvement Programs Laboratory. 2006. Format 4: Lactation. Accessed Oct. 18 2013. <http://www.aipl.arsusda.gov/CF-RCS/GetRCS.cfm?DocType=formats&DocName=fmt4.html>.
- Animal Improvement Programs Laboratory. 2010. Format 6: Health records. Accessed Oct. 18 2013. <http://www.aipl.arsusda.gov/CF-RCS/GetRCS.cfm?DocType=formats&DocName=fmt6.html>.
- Animal Improvement Programs Laboratory. 2013. List of reference notes for format 4 as of: 2013-10-18. Accessed Oct. 18, 2013. <http://aipl.arsusda.gov/CF-RCS/GetAllRef.cfm?docname=fmt4.html&format=fmt4&title=List of Reference Notes for Format 4&NextChangeDate=2013-10-18>.
- Appuhamy, J. A. D. R. N., B. G. Cassell, and J. B. Cole. 2009. Phenotypic and genetic relationships of common health disorders with milk and fat yield persistencies from producer-recorded health data and test-day yields. *J. Dairy Sci.* 92:1785–1795.

- Beaudeau, F., H. Seegers, V. Ducrocq, C. Fourichon, and N. Bareille. 2000. Effect of health disorders on culling in dairy cows: a review and a critical discussion. *Ann. Zootech.* 49:293-311.
- Bigras-Poulin, M. 1985. Interrelationships among calving events, selected health problems, milk production, disposal and death in Ontario Holstein cows. Ph.D. Diss., Univ. Guelph, Guelph, ON, Canada.
- Britt, J. H. 1985. Enhanced reproduction and its economic implications. *J. Dairy Sci.* 68:1585-1592.
- Cobo-Abreu, R., S. Martin, R. Willoughby, and J. Stone. 1979. The association between disease, production and culling in a university dairy herd. *Can. Vet. J.* 20:191-195.
- Cole, J., and P. VanRaden. 2007. A manual for use of BESTPRED: A program for estimation of lactation yield and persistency using best prediction. Animal Improvement Programs Laboratory, Agricultural Research Service, Beltsville, MD.
- Cole, J., and P. VanRaden. 2006. Genetic evaluation and best prediction of lactation persistency. *J. Dairy Sci.* 89:2722-2728.
- Congleton Jr, W., and L. King. 1984. Profitability of dairy cow herd life. *J. Dairy Sci.* 67:661-674.
- Danell, B. 1982. Studies on lactation yield and individual test-day yields of Swedish dairy cows: II. Estimates of genetic and phenotypic parameters. *Acta Agric. Scand.* 32:83-92.
- Dechow, C., and R. Goodling. 2008. Mortality, culling by sixty days in milk, and production profiles in high- and low-survival Pennsylvania herds. *J. Dairy Sci.* 91:4630-4639.
- Dhakal, K., C. Maltecca, J. P. Cassady, G. Baloche, C. M. Williams, and S. P. Washburn. 2013. Calf birth weight, gestation length, calving ease, and neonatal calf mortality in Holstein, Jersey, and crossbred cows in a pasture system. *J. Dairy Sci.* 96:690-698.
- Drackley, J. 2006. Advances in transition cow biology: New frontiers in production diseases. *Production Disease in Farms Animals*. Wageningen Academic Publishers, Wageningen, The Netherlands. 24-34.
- Duffield, T., and T. Herdt. 2000. Subclinical ketosis in lactating dairy cattle. *Vet. Clin. North Am. Food Anim. Pract.* 16:231-253.

- Esposito, G., P. C. Irons, E. C. Webb, and A. Chapwanya. 2013. Interactions between negative energy balance, metabolic diseases, uterine health and immune response in transition dairy cows. *Anim. Reprod. Sci.* 144:60-71.
- Ferris, T., I. Mao, and C. Anderson. 1985. Selecting for lactation curve and milk yield in dairy cattle. *J. Dairy Sci.* 68:1438-1448.
- Gengler, N. 1996. Persistency of lactation yields: A review. *Proc. Int. Workshop on genetic improvement of functional traits in cattle. Gembloux, Belgium. Interbull Bull.* 12:87-96.
- Geweke, J. 1992. Evaluating the accuracy of sampling-based approaches to the calculation of posterior moments. Pages 169-193 in *Bayesian Statistics 4*. J. M. Bernardo, J. Berger, A.P. Dawid, and A. F. M. Smith, ed. Oxford University Press, Oxford, UK.
- Gianola, D., and D. Sorensen. 2004. Quantitative genetic models for describing simultaneous and recursive relationships between phenotypes. *Genetics.* 167:1407-1424.
- Gröhn, Y., S. Eicker, V. Ducrocq, and J. Hertl. 1998. Effect of diseases on the culling of Holstein dairy cows in New York State. *J. Dairy Sci.* 81:966-978.
- Heringstad, B., X. L. Wu, and D. Gianola. 2009. Inferring relationships between health and fertility in Norwegian red cows using recursive models. *J. Dairy Sci.* 92:1778-1784.
- Heringstad, B., Y. Chang, D. Gianola, and G. Klemetsdal. 2005. Genetic analysis of clinical mastitis, milk fever, ketosis, and retained placenta in three lactations of Norwegian red cows. *J. Dairy Sci.* 88:3273-3281.
- Jakobsen, J. H., P. Madsen, J. Jensen, J. Pedersen, L. Christensen, and D. Sorensen. 2002. Genetic parameters for milk production and persistency for Danish Holsteins estimated in random regression models using REML. *J. Dairy Sci.* 85:1607-1616.
- Jakobsen, J. H., R. Rekaya, J. Jensen, D. Sorensen, P. Madsen, D. Gianola, L. G. Christensen, and J. Pedersen. 2003. Bayesian estimates of covariance components between lactation curve parameters and disease liability in Danish Holstein cows. *J. Dairy Sci.* 86:3000-3007.
- Jamrozik, J., and L. Schaeffer. 1997. Estimates of genetic parameters for a test day model with random regressions for yield traits of first lactation Holsteins. *J. Dairy Sci.* 80:762-770.

- Koeck, A., F. Miglior, J. Jamrozik, D. Kelton, and F. Schenkel. 2013. Genetic associations of ketosis and displaced abomasum with milk production traits in early first lactation of Canadian Holsteins. *J. Dairy Sci.* 96:4688-4696.
- Lewis, G. S. 1997. Uterine health and disorders. *J. Dairy Sci.* 80:984-994.
- López de Maturana, E., X. L. Wu, D. Gianola, K. A. Weigel, and G. J. M. Rosa. 2008. Exploring biological relationships between calving traits in primiparous cattle with a Bayesian recursive model. *Genetics* 181:277–287.
- Muir, B., J. Fatehi, and L. Schaeffer. 2004. Genetic relationships between persistency and reproductive performance in first-lactation Canadian Holsteins. *J. Dairy Sci.* 87:3029-3037.
- Oltenacu, P. A., A. Frick, and B. Lindhé. 1990. Epidemiological study of several clinical diseases, reproductive performance and culling in primiparous Swedish cattle. *Prev. Vet. Med.* 9:59-74.
- Parker Gaddis, K. L., J. Cole, J. Clay, and C. Maltecca. 2014. Genomic selection for producer-recorded health event data in US dairy cattle. *J. Dairy Sci.* 97:3190-3199.
- Parker Gaddis, K.L., J. Cole, J. Clay, and C. Maltecca. 2012. Incidence validation and relationship analysis of producer-recorded health event data from on-farm computer systems in the United States. *J. Dairy Sci.* 95:5422-5435.
- Plummer, M., N. Best, K. Cowles, K. Vines, D. Sarkar, and R. Almond. 2013. Package ‘coda’. Accessed Jan. 12, 2014. <http://cran.r-project.org/web/packages/coda/coda.pdf>
- Raizman, E., and J. Santos. 2002. The effect of left displacement of abomasum corrected by toggle-pin suture on lactation, reproduction, and health of Holstein dairy cows. *J. Dairy Sci.* 85:1157-1164.
- Rajala, P., and Y. Gröhn. 1998. Effects of dystocia, retained placenta, and metritis on milk yield in dairy cows. *J. Dairy Sci.* 81:3172-3181.
- Rauw, W., E. Kanis, E. Noordhuizen-Stassen, and F. Grommers. 1998. Undesirable side effects of selection for high production efficiency in farm animals: A review. *Livest. Prod. Sci.* 56:15-33.
- Rehbein, P., K. Brügemann, T. Yin, X. Wu, and S. König. 2013. Inferring relationships between clinical mastitis, productivity and fertility: A recursive model application

including genetics, farm associated herd management, and cow-specific antibiotic treatments. *Prev. Vet. Med.* 112:58-67.

- Rekaya, R., M. Carabaño, and M. Toro. 2000. Bayesian analysis of lactation curves of Holstein-Friesian cattle using a nonlinear model. *J. Dairy Sci.* 83:2691-2701.
- Rosa, G. J. M., B. D. Valente, G. de los Campos, X. L. Wu, D. Gianola, and M. A. Silva. 2011. Inferring causal phenotype networks using structural equation models. *Genet. Sel. Evol.* 43:1-13.
- Shipley B. 2002. *Cause and correlation in Biology*. Cambridge University Press, Cambridge, UK.
- Strabel, T., W. Kopacki, and T. Szwaczkowski. 2001. Genetic evaluation of persistency in random regression test day model. *Interbull Bulletin.* 27:189-192.
- Valente, B. D., G. J. M. Rosa, G. de Los Campos, D. Gianola, and M. A. Silva. 2010. Searching for recursive causal structures in multivariate quantitative genetics mixed models. *Genetics.* 185:633-644.
- Varona, L., D. Sorensen, and R. Thompson. 2007. Analysis of litter size and average litter weight in pigs using a recursive model. *Genetics.* 177:1791-1799.
- Wu, X. L., B. Heringstad, Y. M. Chang, G. De los Campos, and D. Gianola. 2007. Inferring relationships between somatic cell score and milk yield using simultaneous and recursive models. *J. Dairy Sci.* 90:3508-3521.
- Wu, X. L., B. Heringstad, and D. Gianola. 2008. Exploration of lagged relationships between mastitis and milk yield in dairy cows using a Bayesian structural equation Gaussian-threshold model. *Genet. Sel. Evol.* 40:333-358.
- Zwald, N., K. Weigel, Y. Chang, R. Welper, and J. Clay. 2004a. Genetic selection for health traits using producer-recorded data. I. Incidence rates, heritability estimates, and sire breeding values. *J. Dairy Sci.* 87:4287-4294.
- Zwald, N., K. Weigel, Y. Chang, R. Welper, and J. Clay. 2004b. Genetic selection for health traits using producer-recorded data. II. Genetic correlations, disease probabilities, and relationships with existing traits. *J. Dairy Sci.* 87:4295-4302.

**Table 1** Descriptive statistics for metabolic (ketosis and displaced abomasum) and reproductive (retained placenta and metritis) health disorders

Traits	Number of records		Health Disorder frequency (%)	Disease-specific culling risk <sup>1</sup>
	Healthy	Diseased		
Retained placenta	75,245	1,759	2.28	5.00
Metritis	73,578	3,426	4.45	6.65
Ketosis	75,716	1,288	1.67	8.15
Displaced abomasum	76,821	183	0.24	7.65

<sup>1</sup>Percentage of cows with a particular disease that were culled.

**Table 2** Descriptive statistics of production traits

Traits	Number of records	Mean	SD	Minimum	Maximum
Milk yield 1 <sup>1</sup> (kg)	77,004	30.05	8.50	0	57.16
Milk yield 2 <sup>2</sup> (kg)	77,004	28.65	13.78	0	69.17
Peak milk yield (kg)	67,907	36.41	5.52	13.38	68.36
Day in milk of peak milk yield (d)	67,907	55.27	20.05	30	145
Lactation persistency	67,907	0.47	0.98	-5.31	5.49

<sup>1</sup>Mean milk yield obtained from test-day records from 1 to 60 DIM.

<sup>2</sup>Mean milk yield obtained from test-day records from 61 to 120 DIM.

**Table 3** Posterior mean, standard deviation (SD), and 95% highest posterior density interval (95% HPD) of recursive effects from liability to health disorder (retained placenta (RP), metritis (METR), ketosis (KETO), and displaced abomasum (DA)) to culling from Health-Culling analyses

Traits <sup>1</sup>	Recursive effects		
	Mean	SD	95% HPD
RP → Culling	1.226	0.078	[1.091; 1.385]
METR → Culling	0.929	0.045	[0.846; 1.018]
KETO → Culling	1.004	0.067	[0.889; 1.145]
DA → Culling	1.590	0.110	[1.379; 1.729]

<sup>1</sup> A single headed arrow (→) indicates causal relationship between traits listed where first trait affects second trait.

**Table 4** Posterior mean, standard deviation (SD), and 95% highest posterior density interval (95% HPD) of recursive effects between liability to health disorders disorder (retained placenta (RP), metritis (METR), ketosis (KETO), and displaced abomasum (DA)) and between production traits (milk yield 1 (MY1) and milk yield 2 (MY2)) from Health-MY analyses

Traits <sup>1</sup>	Recursive effects		
	Mean	SD	95% HPD
RP → METR	0.117	0.017	[0.084; 0.152]
RP → MY1	-0.025	0.033	[-0.092; 0.040]
RP → MY2	-0.002	0.046	[-0.092; 0.086]
METR → MY1	-0.044	0.033	[-0.109; 0.019]
METR → MY2	0.085	0.046	[0.001; 0.178]
KETO → DA	0.122	0.051	[0.022; 0.228]
KETO → MY1	-0.007	0.031	[-0.069; 0.051]
KETO → MY2	0.034	0.043	[-0.046; 0.117]
DA → MY1	-0.025	0.032	[-0.086; 0.040]
DA → MY2	-0.003	0.043	[-0.085; 0.082]
REPRO → META	0.112	0.022	[0.071; 0.156]
REPRO → MY1	-0.058	0.033	[-0.122; 0.004]
REPRO → MY2	0.082	0.046	[-0.007; 0.168]
META → MY1	-0.031	0.034	[-0.098; 0.034]
META → MY2	0.026	0.045	[-0.065; 0.111]

<sup>1</sup>A single headed arrow (→) indicates causal relationship between traits listed where first trait affects second trait.

**Table 5** Posterior mean, standard deviation (SD), and 95% highest posterior density interval (95% HPD) of recursive effects from liability to health disorders ((retained placenta (RP), metritis (METR), ketosis (KETO), and displaced abomasum (DA)) to production traits (day in milk of peak milk yield (PeakD), peak milk yield (PMY), lactation persistency (LP)) from Health-Lactation analyses

Traits <sup>1</sup>	Recursive effects		
	Mean	SD	95% HPD
RP → PeakD	0.095	0.146	[-0.177; 0.390]
RP → PMY	-0.011	0.038	[-0.084; 0.065]
RP → LP	-0.001	0.033	[-0.064; 0.062]
METR → PeakD	0.026	0.149	[-0.281; 0.295]
METR → PMY	-0.001	0.038	[-0.072; 0.077]
METR → LP	0.001	0.033	[-0.065; 0.063]
KETO → PeakD	0.020	0.145	[-0.237; 0.318]
KETO → PMY	-0.012	0.037	[-0.082; 0.063]
KETO → LP	-0.002	0.033	[-0.062; 0.062]
DA → PeakD	0.018	0.145	[-0.257; 0.297]
DA → PMY	0.003	0.037	[-0.064; 0.078]
DA → LP	0.001	0.032	[-0.060; 0.062]

<sup>1</sup>A single headed arrow (→) indicates causal relationship between traits listed where first trait affects second trait.

**Table 6** Posterior mean, standard deviation (SD), and 95% highest posterior density interval (95% HPD) of heritability of liability a health disorders and production traits from Health-Culling, Health-MY, and Health-Lactation analyses.

	Traits	Heritability		
		Mean	SD	95% HPD
Health-Culling	Displaced abomasum	0.10	0.04	[0.015; 0.147]
	Ketosis	0.04	0.01	[0.016; 0.065]
	Metritis	0.02	0.01	[0.010; 0.037]
	Retained placenta	0.05	0.01	[0.021; 0.070]
	Culling <sup>1</sup>	0.06	0.03	[0.012; 0.136]
Health-MY	Displaced abomasum	0.11	0.04	[0.031; 0.202]
	Ketosis	0.04	0.01	[0.017; 0.067]
	Metritis	0.02	0.01	[0.011; 0.036]
	Retained placenta	0.05	0.01	[0.029; 0.081]
	Metabolic	0.05	0.01	[0.022; 0.076]
	Reproductive	0.03	0.01	[0.014; 0.040]
	Milk yield 1 <sup>2</sup>	0.13	0.01	[0.112; 0.152]
Milk yield 2 <sup>2</sup>	0.13	0.01	[0.106; 0.147]	
Health-Lactation	Displaced abomasum	0.10	0.03	[0.039; 0.190]
	Ketosis	0.05	0.02	[0.020; 0.090]
	Metritis	0.02	0.01	[0.012; 0.038]
	Retained placenta	0.05	0.02	[0.024; 0.080]
	Day in milk of peak milk yield <sup>3</sup>	0.02	0.01	[0.011; 0.052]
	Peak milk yield <sup>3</sup>	0.19	0.06	[0.161; 0.208]
	Lactation Persistency <sup>3</sup>	0.34	0.01	[0.310; 0.380]

<sup>1</sup>Results from the 4 analyses of Health-Culling analyses were very similar and only results from the analysis with displaced abomasum are given.

**Table 6** Continued

---

<sup>2</sup>Results from the 3 analyses of Health-MY analyses were very similar and only results from the analysis with displaced abomasum are given.

<sup>3</sup>Results from the 4 analyses of Health-Lactation analyses were very similar and only results from the analysis with displaced abomasum are given.

**Table 7** Posterior mean, standard deviation (SD), and 95% highest posterior density interval (95% HPD) of genetic correlations of health disorders and production traits from Health-Culling, Health-MY and Health-Lactation analyses

		Genetic correlations		
Traits <sup>1</sup>		Mean	SD	95% HPD
Health-Culling	DA and Culling	0.80	0.20	[0.431; 0.993]
	KETO and Culling	0.76	0.17	[0.415; 0.974]
	METR and Culling	0.65	0.17	[0.317; 0.927]
	RP and Culling	0.69	0.19	[0.284; 0.955]
Health-MY	DA and KETO	0.57	0.20	[0.196; 0.901]
	METR and RP	0.49	0.16	[0.185; 0.774]
	META and REPRO	0.26	0.18	[-0.089; 0.596]
	DA and MY1	-0.28	0.26	[-0.735; 0.252]
	KETO and MY1	0.12	0.17	[-0.209; 0.463]
	METR and MY1	-0.02	0.18	[-0.365; 0.363]
	RP and MY1	-0.14	0.16	[-0.440; 0.160]
	META and MY1	0.01	0.02	[-0.311; 0.345]
	REPRO and MY1	-0.06	0.16	[-0.356; 0.244]
	DA and MY2	-0.28	0.26	[-0.781; 0.219]
	KETO and MY2	0.11	0.18	[-0.231; 0.450]
	METR and MY2	-0.03	0.19	[-0.396; 0.340]
	RP and MY2	-0.16	0.15	[-0.471; 0.134]
	META and MY2	-0.01	0.17	[-0.338; 0.339]
	REPRO and MY2	-0.07	0.16	[-0.390; 0.222]
	MY1 and MY2 <sup>2</sup>	0.99	0.01	[0.980; 0.999]

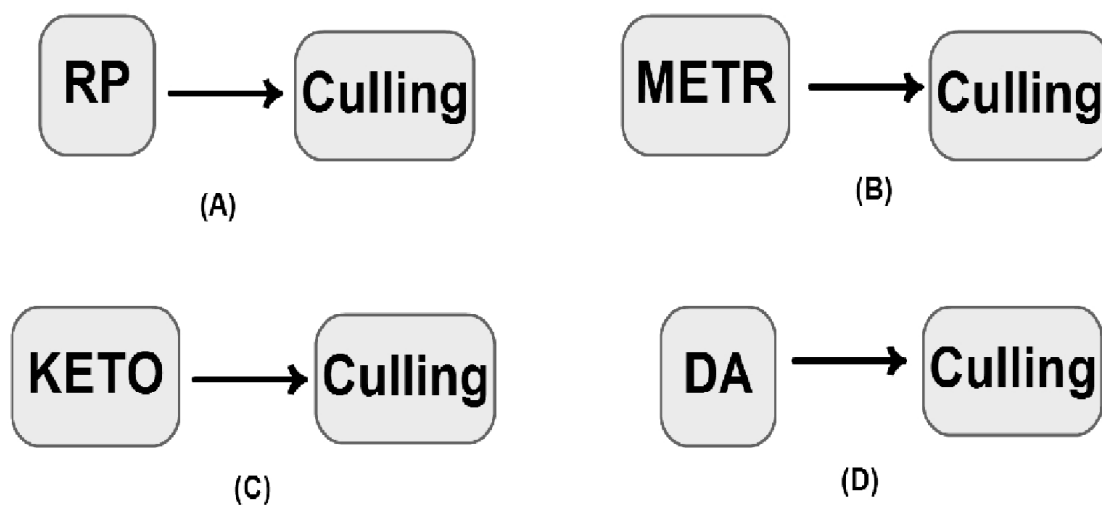
**Table 7** Continued

Health-Lactation	DA and PeakD	0.18	0.42	[-0.564;0.870]
	KETO and PeakD	-0.51	0.26	[-0.934; -0.013]
	METR and PeakD	0.02	0.02	[-0.013; 0.054]
	RP and PeakD	0.02	0.02	[-0.023; 0.059]
	DA and PMY	0.12	0.33	[-0.475;0.748]
	KETO and PMY	-0.20	0.19	[-0.592;0.206]
	METR and PMY	0.02	0.01	[-0.001;0.032]
	RP and PMY	0.02	0.01	[-0.008;0.033]
	DA and LP	0.12	0.29	[-0.413; 0.683]
	KETO and LP	-0.19	0.18	[-0.585; 0.186]
	METR and LP	0.01	0.01	[-0.004;0.02]
	RP and LP	0.01	0.01	[-0.003;0.02]
	PeakD and PMY <sup>3</sup>	0.72	0.34	[-0.111;0.983]
	PeakD and LP <sup>3</sup>	0.61	0.29	[-0.049; 0.908]
	PMY and LP <sup>3</sup>	0.84	0.04	[0.741 ; 0.906]

<sup>1</sup>Health disorders included were retained placenta (RP), metritis (METR), ketosis (KETO), displaced abomasum (DA), metabolic diseases (META), and reproductive diseases (REPRO); production traits included were milk yield 1 (MY1), milk yield 2 (MY2), day in milk of peak milk yield (PeakD), peak milk yield (PMY), and lactation persistency (LP).

<sup>2</sup>Results from the 3 analyses of Health-MY analyses were similar and only results from the analysis with displaced abomasum are given.

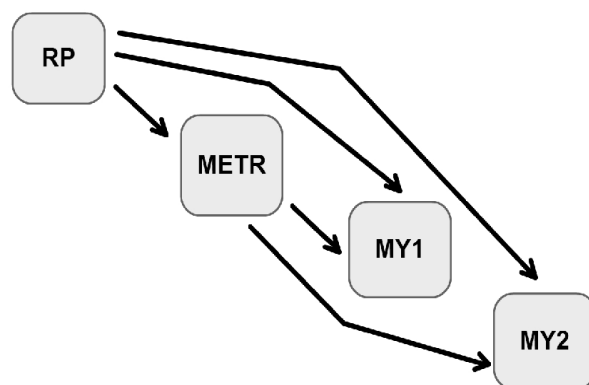
<sup>3</sup>Results from the 4 analyses of Health-Lactation analyses were very similar and only results from the analysis with displaced abomasum are given.



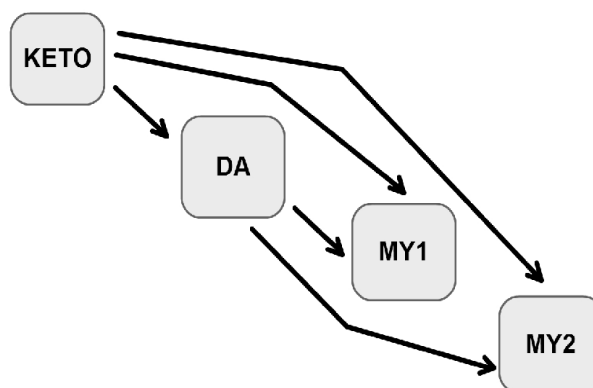
**Figure 1** Recursive threshold sire model was used in the analysis: (A) Possible relationship between retained placenta (RP) and culling, (B) Possible relationships between metritis (METR) and culling, (C) Possible relationships between ketosis (KETO) and culling, and (D) Possible relationships between displaced abomasum (DA) and culling. A single headed arrow ( $\rightarrow$ ) indicates a causal relationship.

**Figure 2** Recursive Gaussian threshold sire model was used in the analysis: (A) Possible relationships between two reproductive health disorder traits, retained placenta (RP) and metritis (METR) along with production traits, milk yield 1 (MY1) and milk yield 2 (MY2), (B) Possible relationships between two metabolic health disorder traits, ketosis (KETO) and displaced abomasum (DA) along with production traits, MY1 and MY2, and (C) Possible relationships between reproductive health disorder traits (REPRO), metabolic health disorders (META) traits along with production traits, MY1 and MY2. A single headed arrow (→) indicates a causal relationship.

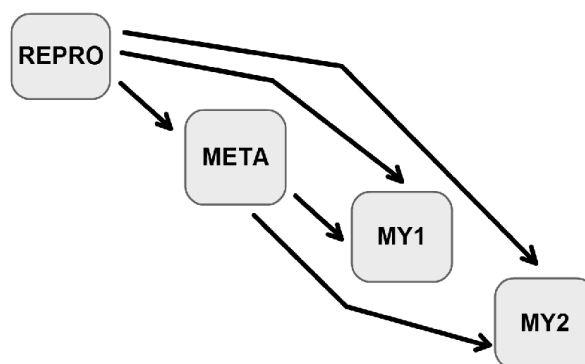
A



B

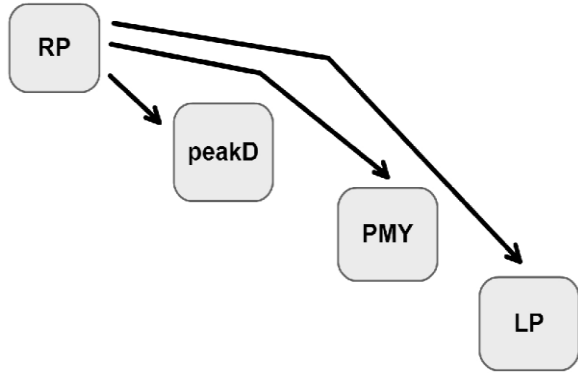


C

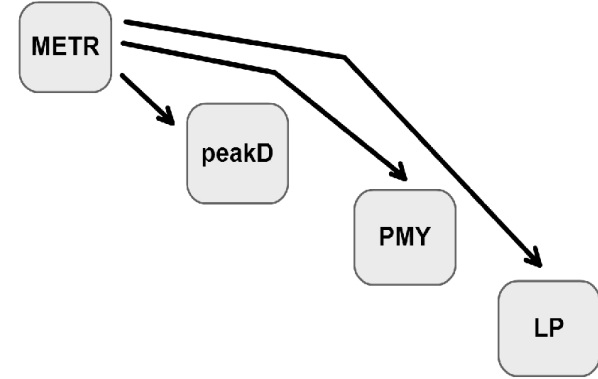


**Figure 3** Recursive Gaussian threshold sire model was used in the analysis: (A) Possible relationships between retained placenta (RP) and production traits such as days in milk at peak milk yield (PeakD), peak milk yield (PMY), and lactation persistency of milk yield (LP), (B) Possible relationships between metritis (METR) and production traits such as PeakD, PMY, and LP, (C) Possible relationships between ketosis (KETO) and production traits such as PeakD, PMY, and LP, (D) Possible relationships between displaced abomasum (DA) and production traits such as PeakD, PMY and LP. A single headed arrow ( $\rightarrow$ ) indicates a causal relationship.

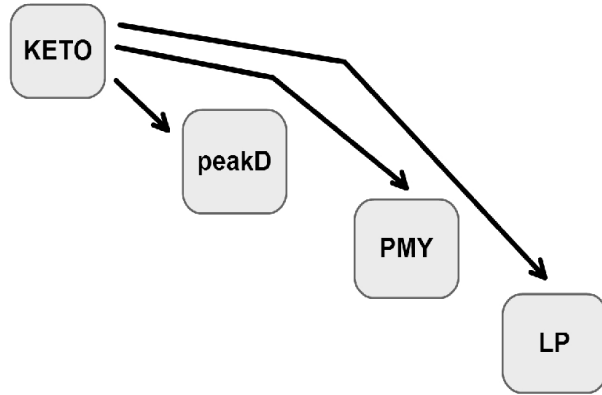
**A**



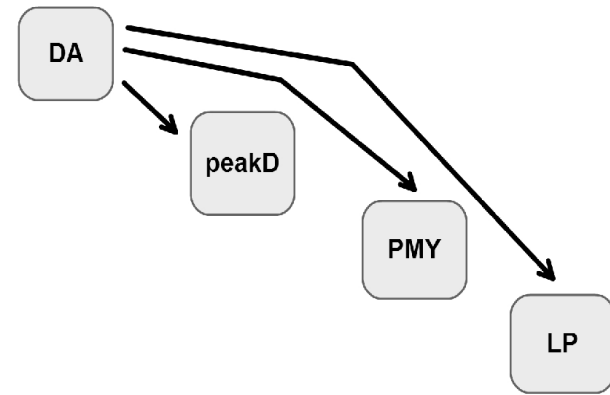
**B**



**C**

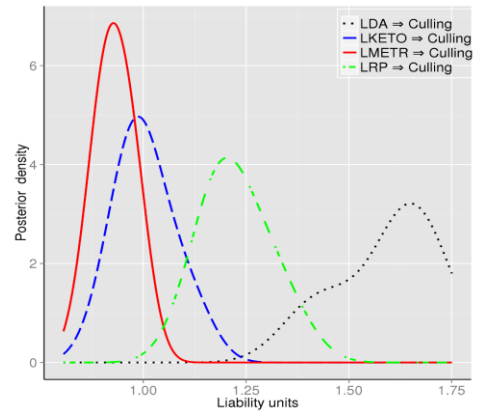


**D**

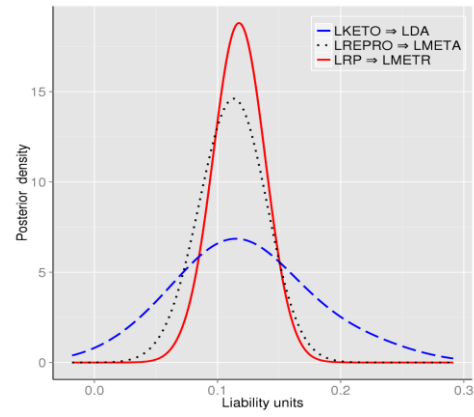


**Figure 4** Posterior distributions of recursive effects from: (A) liability to health disorder (LDA, LKETO, LMETR, or LRP) to culling; (B) liability to one health disorder (LKETO, LRP, and LREPRO) to liability to another health disorder (LDA, LMETR, and LMETA); (C) liability to health disorders (LDA, LKETO, LMETR, LRP) to milk yield 1 (MY1); (D) liability to health disorders (LDA, LKETO, LMETR, LRP) to milk yield 2 (MY2); (E) liability to health disorders (LREPRO, LMETA) to MY1; (F) liability to health disorders (LREPRO, LMETA) to MY2. LDA= liability to displaced abomasum; LKETO = liability to ketosis; LMETR= liability to metritis; LRP= liability to retained placenta; LREPRO = liability to reproductive diseases; LMETA=liability to metabolic diseases.

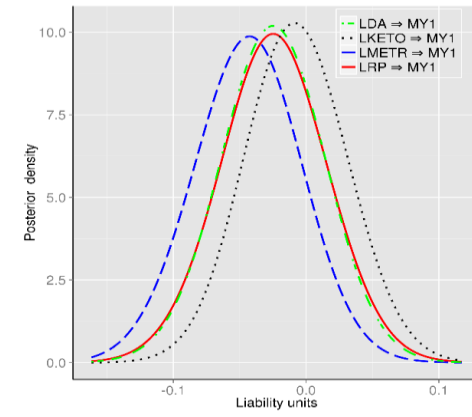
(A)



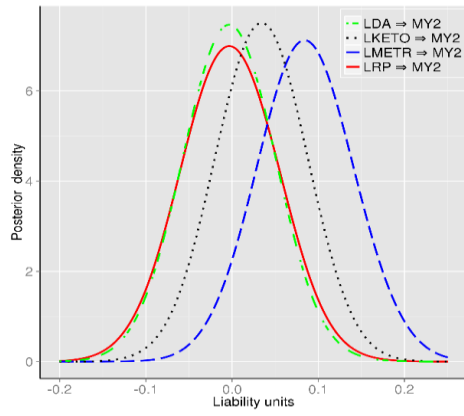
(B)



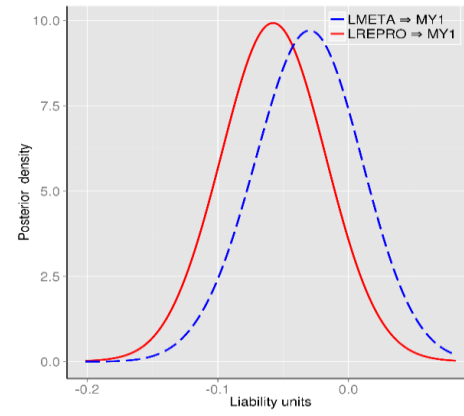
(C)



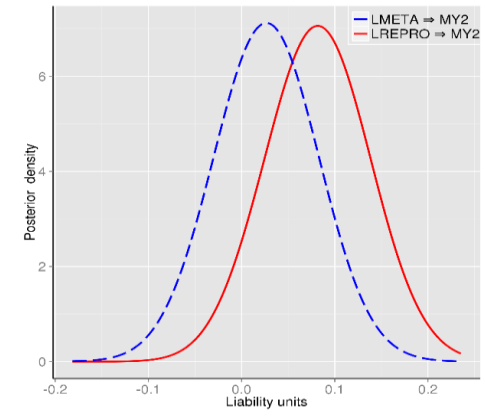
(D)



(E)

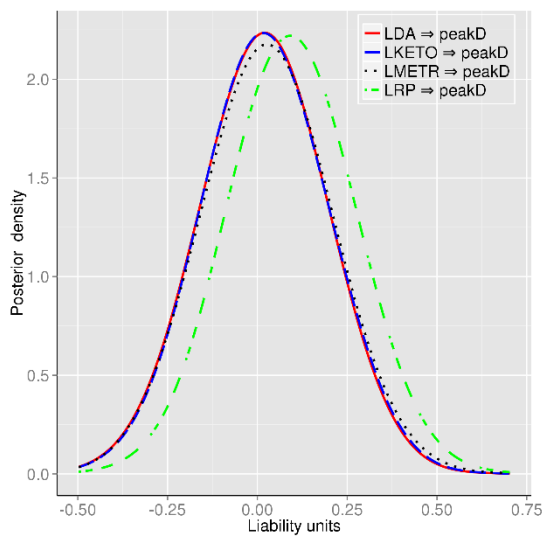


(F)

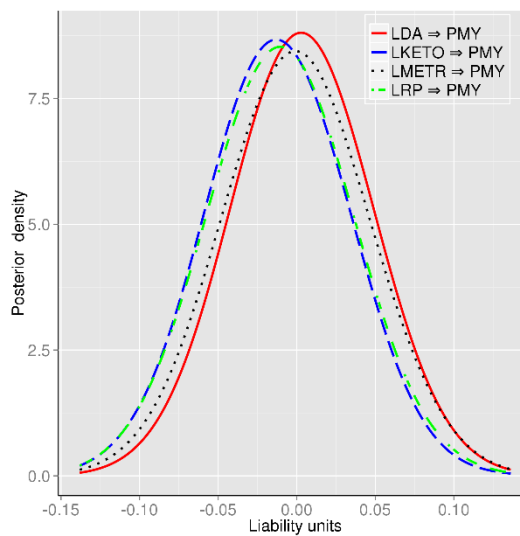


**Figure 5** Posterior distributions of recursive effects from: (A) liability to health disorders (LDA, LKETO, LMETR, or LRP) to day in milk of peak milk yield (PeakD); (B) liability to health disorders (LDA, LKETO, LMETR, or LRP) to peak milk yield (PMY); (C) liability to health disorders (LDA, LKETO, LMETR, or LRP) to lactation persistency. LDA= liability to displaced abomasum; LKETO = liability to ketosis; LMETR= liability to metritis; LRP= liability to retained placenta.

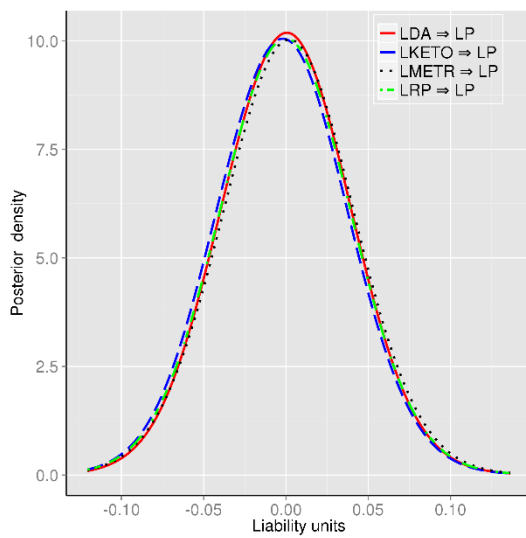
(A)



(B)



(C)



CHAPTER 3

**CAUSAL RELATIONSHIPS BETWEEN CLINICAL MASTITIS EVENTS, MILK  
YIELDS AND LACTATION PERSISTENCY IN US HOLSTEINS**

## ABSTRACT

Complex relationships exist between udder susceptibility to mastitis and milk production traits. Identifying causal association between these traits could help disentangle these complex relationships. The main objective of the study was to use producer-recorded health data to examine the causal relationship between mastitis events, milk yield, and lactation persistency. A total of 48,058 first lactation daughters of 2,213 Holstein sires across 207 herds were analyzed using structural equation models. Traits included in the dataset were mastitis events and test day milk yields recorded in three different periods; period 1 (5 to 60 DIM), period 2 (61 to 120 DIM) and period 3 (121 to 180 DIM). In addition, lactation persistency was also included. A subset including 28,867 daughters from 1,809 Holstein sires having both first and second lactation across 201 herds was further investigated. In this dataset, mastitis events were defined on a lactation basis as an all-or-none trait; either a cow was assigned a score of 1 (had a mastitis event in that lactation) or a score of 0 (healthy) for that particular lactation, regardless of the time of occurrence. Total milk yield from second lactation was also included in the dataset. Negative structural coefficient (-0.032) found in this study between clinical mastitis and test day milk production in early lactation period suggests that mastitis results in a direct decline in test day milk production in early lactation. There is nonetheless little impact of mastitis on test day milk production of mid and late lactation periods, and on milk yield lactation persistency. Likewise the positive structural coefficient (0.449) obtained among mastitis events in first and second lactation suggests an increased risk of mastitis in second lactation if a case of mastitis is present in the primiparous

cow. Heritability estimates obtained were low for mastitis (ranged 0.04 to 0.07), and negative genetic correlations were found between mastitis events and milk yield. The study illustrates how mastitis events and production traits are related through the use of structural equation models by pointing out the causal effect among mastitis events and production traits that evolve over the course of lactation in cow life.

Key words: **causal effects, mastitis, milk yield, structural equation models**

## INTRODUCTION

Mastitis is a mammary inflammation and is one of the most economically impacting health events in the dairy cattle industry. The losses due to mastitis are costly (Koeck *et al.*, 2012), mostly due to veterinary and treatment costs (Hinrichs *et al.*, 2005), discarded milk (Shim *et al.*, 2004), and reduced milk production (Bar *et al.*, 2008). But also due to increased risk of culling (Hertl *et al.*, 2011), and increased reproductive problems (Moore *et al.*, 1991). Moreover, replacement costs and increased labor cost due to mastitis substantially impact the profitability of dairy enterprises (Huijps *et al.*, 2008). The average cost of a clinical mastitis was estimated at \$179 with \$115 from milk lost per case, \$14 due to increased mortality loss, and \$50 from treatment costs (Bar *et al.*, 2008). The antagonistic relationship between health disorders and milk yield in dairy cows is generally accepted (Rauw *et al.*, 1998). In the past 50 years, there has been intensive selection for milk yield that has resulted in an increased genetic deterioration of dairy health (Miglior *et al.*, 2005). These problems in dairy cattle have pointed towards genetic selection for increased disease resistance and several researchers in the past decade have suggested inclusion of clinical mastitis in the overall

breeding goal of Holstein dairy cattle (Kadarmideen and Pryce, 2001; Ødegård *et al.*, 2003). Selection for mastitis resistance has been implemented in Nordic cattle (Heringstad *et al.*, 2003; Philipsson and Lindhé, 2003).

Several researchers in the past have used mixed models to compute genetic correlations between mastitis and milk yield. Results from those studies mostly revealed the unfavorable genetic correlations between mastitis events and milk yield traits. Because correlations do not imply causation, there is a lack of knowledge about the cause and effect between traits, which could be addressed using structural equation models (SEM). In the context of animal breeding, Gianola and Sorensen (2004) extended multivariate mixed model theory to infer recursive relationships between phenotypes by accounting for possible feedback situations. Several papers that have been published in the realm of animal breeding over the past few years used structural equation models (SEM) to infer causal relationships between traits. Wu *et al.* (2008) used a dataset of Norwegian Red cows to study the causal effect between mastitis and milk yield. To our knowledge, no study has been conducted to infer causal relationships between mastitis events and milk yield in the US Holstein cattle population. Similarly, there is a knowledge gap regarding the causal effect of mastitis occurring in first lactation and mastitis events occurring in later lactations. Thus, the objective of the current study was to explore phenotypic and genetic relationships among mastitis events and production traits (milk yield and lactation persistency of milk yield) in US Holsteins using recursive models.

## MATERIALS AND METHODS

### Data

Health information records were made available from Dairy Records Management Systems (Raleigh, NC) from US dairy farms from 1996 through June 2013. Holstein cows with mastitis records in first and second parity were retained for analysis. Health data quality edits were applied as described in detail in Parker Gaddis *et al.* (2012). In order to avoid herds that over or under reported mastitis events, maximum and minimum constraints were applied to the dataset. Only records of cows having lactation length less than or equal to 400 days in milk (DIM) were included. After applying data quality edits, a dataset was formed to identify causal effects between mastitis and production measures (test-day milk yields and lactation persistency) in first parity US Holsteins. This dataset included 48,058 first parity daughters of 2,213 Holstein sires across 207 herds and will be referred to as First-Lactation dataset.

The First-lactation dataset included test-day (TD) records for milk yield (MY) and lactation persistency of MY in addition to mastitis events. Test Day records from 5 to 180 days after calving were included and cows with missing TD records were removed from the original dataset in the process of forming the First-Lactation dataset. Days in milk up to 180 days after calving were divided into 3 lactation periods such that period 1 included 5 to 60 days, period 2 included 61 to 120 days, and period 3 included 121 to 180 days similarly to what was reported by Wu *et al.* (2008). Single MY TD records were assigned for each period that was closest in time to the midpoint of each lactation period and will be hereafter referred to

as MY1, MY2, and MY3, respectively. Cows were assigned a value of 0 (healthy) or 1 (mastitis) in each period. Only mastitis records that were prior and closer to the assigned TD for each period were considered. This definition implies that pre-existing mastitis events would affect the MY of the following TD. Lactation persistency of MY (LP), which describes the shape of the lactation curve after peak milk yield, was calculated for each cow using BESTPRED software (Cole and VanRaden, 2007).

A subset (First & Second-Lactation) dataset was formed to identify causal effects between mastitis in first lactation and second lactation and their effects on total milk yield of second lactation. The First & Second-Lactation dataset included 28,867 daughters from 1,809 sires having first and second lactation across 201 herds. Only cows showing records for both lactations were included in the dataset. Mastitis events were in this case defined on a lactation basis as an all-or-none trait; either a cow was assigned a score of 1 (had a mastitis event in that lactation) or a score of 0 (healthy) for that particular lactation, regardless of the time of occurrence. Total milk yield from second lactation was also included in the analysis.

### **Statistical Analysis**

Recursive Gaussian-threshold sire models were used for statistical analyses. The threshold model assumed an underlying continuous variable, liability ( $l_i$ ), for binary mastitis events that defines the observed binary variable into a value of 1 if liability is larger than a fixed threshold and 0 otherwise. Two different series of analysis (LAC1 and LAC12) were defined for the purpose of identifying causal relationship between mastitis events and production measures. The LAC1 series of analyses employed a SEM to find recursive

relationships between mastitis events, TD milk yields, and LP in first lactation. Four analyses were performed, which are as follows:

- LAC1.A: This analysis included two traits: liability to mastitis in the first period (LMAST1) and MY1. The direct recursive effect was assumed from LMAST1 to MY1.
- LAC1.B: This analysis included MY1, liability to mastitis in the second period (LMAST2) and MY2. The direct recursive effect was assumed from MY1 to LMAST2 and from LMAST2 to MY2.
- LAC1.C: This analysis included MY2, liability to mastitis in the third period (LMAST3) and MY3. The direct recursive effect was assumed from MY2 to LMAST3 and from LMAST3 to MY3.
- LAC1.D: Liability to mastitis of each period and LP were included in this analysis. The direct recursive effects were assumed from mastitis of each period (LMAST1, LMAST2, and LMAST3) to lactation persistency of milk yield.

Lastly, the LAC12 analysis (using First & Second-Lactation dataset) included direct recursive effects assumed from liability to first lactation mastitis (LM1) to liability to second lactation mastitis (LM2) and from LM2 to total milk yield of second parity (TMY). An indirect recursive effect was assumed from LM1 to TMY. A direct recursive effect measures how much TMY would be affected by changes in LM1. An indirect recursive effect measures how much TMY would be affected by changes in LM1 through the mediating effect of LM2. The indirect recursive effect can be calculated as the product of structural

coefficients  $LM1 \rightarrow LM2 \times LM2 \rightarrow TMY$ . The overall causal effect on TMY can be calculated as  $LM1 \rightarrow TMY + LM1 \rightarrow LM2 \times LM2 \rightarrow TMY$  (Lopez de Maturana *et al.*, 2009; Shipley, 2002).

The equations used in LAC1 and LAC12 analyses can be summarized as follows:

$$LAC1.A: \begin{cases} y_1 = Xb_1 + Z_h h_1 + Z_s s_1 + e_1 \\ y_2 = \lambda_{21} y_1 + Xb_2 + Z_h h_2 + Z_s s_2 + e_2 \end{cases}$$

$$LAC1.B / LAC1.C: \begin{cases} y_1 = Xb_1 + Z_h h_1 + Z_s s_1 + e_1 \\ y_2 = \lambda_{21} y_1 + Xb_2 + Z_h h_2 + Z_s s_2 + e_2 \\ y_3 = \lambda_{32} y_2 + Xb_3 + Z_h h_3 + Z_s s_3 + e_3 \end{cases}$$

$$LAC1.D: \begin{cases} y_1 = Xb_1 + Z_h h_1 + Z_s s_1 + e_1 \\ y_2 = Xb_2 + Z_h h_2 + Z_s s_2 + e_2 \\ y_3 = Xb_3 + Z_h h_3 + Z_s s_3 + e_3 \\ y_4 = \lambda_{41} y_1 + \lambda_{42} y_2 + \lambda_{43} y_3 + Xb_4 + Z_h h_4 + Z_s s_4 + e_4 \end{cases}$$

$$LAC12: \begin{cases} y_1 = Xb_1 + Z_h h_1 + Z_s s_1 + e_1 \\ y_2 = \lambda_{21} y_1 + Xb_2 + Z_h h_2 + Z_s s_2 + e_2 \\ y_3 = \lambda_{31} y_1 + \lambda_{32} y_2 + Xb_3 + Z_h h_3 + Z_s s_3 + e_3 \end{cases}$$

where, the  $y_1$  and  $y_2$  are vectors reporting LMAST1 and MY1 respectively in LAC1.A analysis. The  $y_1$ ,  $y_2$ , and  $y_3$  are the vectors reporting MY1, LMAST2, and MY2 respectively in LAC1.B analysis. Similarly, the  $y_1$ ,  $y_2$ , and  $y_3$  are vectors reporting MY2, LMAST3, and MY3 respectively in LAC1.C analysis. In case of LAC1.D analysis, the  $y_1$ ,  $y_2$ ,  $y_3$ , and  $y_4$  are vectors reporting LMAST1, LMAST2, LMAST3, and LP respectively. In equations

reported above for LAC12 analysis, the  $\mathbf{y}_1$ ,  $\mathbf{y}_2$ , and  $\mathbf{y}_3$  are vectors reporting LM1, LM2, and TMY respectively. The  $\lambda_{ij}$  is the structural coefficients describing the rate of change for trait  $i$  with respect to trait  $j$ ,  $\mathbf{b}$  is a vector of systematic effects including the effect of year-season of calving;  $\mathbf{h}$  is a vector of herd effects,  $\mathbf{s}$  is a vector of sire of cow effects, and  $\mathbf{e}$  is a vector of residuals;  $\mathbf{X}$ ,  $\mathbf{Z}_h$ , and  $\mathbf{Z}_s$  are the corresponding incidence matrices. In matrix form, the general model was:

$$\mathbf{y} = (\Lambda \otimes \mathbf{I})\mathbf{y} + \mathbf{X}\mathbf{b} + \mathbf{Z}_h\mathbf{h} + \mathbf{Z}_s\mathbf{s} + \mathbf{e}$$

where,  $\Lambda$  are lower triangular matrices with 1 on diagonal,  $\lambda_{ij}$  on off-diagonals representing the recursive effects from  $j$  to  $i$ , and 0 everywhere else.

Multivariate normal prior distributions were assigned to structural coefficients and elements of  $\mathbf{b}$ . Sire effects were assigned a multivariate normal prior distribution  $\mathbf{s} \sim N(0, \mathbf{G} \otimes \mathbf{A})$ , where  $\mathbf{G}$  is the sire covariance matrix for the traits involved and  $\mathbf{A}$  is the matrix of additive genetic relationships among bulls. The prior distribution of herd effects was  $\mathbf{h} \sim N(0, \mathbf{H} \otimes \mathbf{I})$ , where  $\mathbf{H}$  is the herd (co)variance matrix and  $\mathbf{I}$  is an identity matrix. Independent inverse-Wishart prior distributions were used for  $\mathbf{H}$  and  $\mathbf{G}$ , the covariance matrices of  $\mathbf{h}$  and  $\mathbf{s}$ , respectively. In order to achieve identifiability, residual variances of threshold traits were fixed to 1. Furthermore all residual covariances were forced to be equal to 0. In this case, the prior distribution of the  $\mathbf{R}$  matrix fixing the residual covariances was an inverse chi-square distribution. Transformation of the estimated covariance matrices for the SEM in multiple trait model scale was performed as:

$$\mathbf{G}^*_n = (\mathbf{I}-\mathbf{\Lambda})^{-1}_n \mathbf{G}_n (\mathbf{I}-\mathbf{\Lambda})'^{-1}_n$$

$$\mathbf{H}^*_n = (\mathbf{I}-\mathbf{\Lambda})^{-1}_n \mathbf{H}_n (\mathbf{I}-\mathbf{\Lambda})'^{-1}_n$$

$$\mathbf{R}^*_n = (\mathbf{I}-\mathbf{\Lambda})^{-1}_n \mathbf{R}_n (\mathbf{I}-\mathbf{\Lambda})'^{-1}_n$$

where the index  $n$  indicates the models used in first and second series of analyses , and  $\mathbf{G}$ ,  $\mathbf{H}$ ,  $\mathbf{R}$ , and  $\mathbf{\Lambda}$  were as defined above. Heritabilities and genetic correlations were then calculated in the usual manner from (co)variance components in  $\mathbf{G}^*_n$ ,  $\mathbf{H}^*_n$ , and  $\mathbf{R}^*_n$ .

Data analyses were conducted in Bayesian framework using the SIR-BAYES package (Wu *et al.*, 2008) in which all Bayesian models were implemented via Markov chain Monte Carlo (MCMC) sampling. For each model, 100,000 iterations were generated and the first 20,000 iterations were discarded as burn-in. Posterior samples from each chain were thinned every 25 iterations after burn-in and retained for analysis. Posterior distributions of parameters of interest were inferred based on posterior samples after burn in. Markov chain convergence was assessed by visual inspection of trace plots. Additional diagnostic tests such as Geweke's convergence statistic (Geweke, 1992) was obtained to confirm convergence through R (<http://cran.r-project.org>) with the CODA package (Plummer *et al.* 2013).

Transformation of lambda coefficients estimates from liability to observable scale was done following Wu *et al.* (2008). For example, the difference in mean peak milk yield between sick (1) cows due to MAST1 and healthy (0) cows can be calculated as

$$\Delta \approx \lambda(\bar{l}_1 - \bar{l}_0)$$

where  $\bar{l}_1$  and  $\bar{l}_0$  are averages of augmented liabilities for sick cows due to MAST1 and healthy cows, respectively.

## RESULTS AND DISCUSSION

The incidence of mastitis events in First-Lactation dataset were 6.58%, 4.13%, and 3.90% for lactation periods 5 to 60, 61 to 120, and 121 to 180 DIM respectively (Table 1). The TD MYs decreased over the three lactation periods. The mean (standard deviation) of TD MY was 34.66 (7.18) kg, 34.28 (7.92) kg, and 28.55 (7.32) kg at lactation periods 1, 2, and 3, respectively (Table 2). The mean (standard deviation) of LP was 0.38 (0.97) LP units. The mean of LP in our study was lower than that reported by Appuhamy *et al.* (2009). In their study, they reported a mean (standard deviation) 0.53 (1.19) LP units for first parity cows. Incidences of mastitis events in the First & Second-Lactation dataset were 10.87% and 14.05% for lactations 1 and 2, respectively (Table 1). Incidences of mastitis events in this study were slightly higher than those reported by Parker Gaddis *et al.* (2012) (9.53% and 10.24% in parities 1 and 2, respectively). The mean (standard deviation) of TMY in parity 2 was 10800.60 (1900.98) kg (Table 2).

### Recursive effects

Posterior distribution of recursive effects from liability to mastitis to TD milk yields of three lactation periods from LAC1 series of analyses (LAC1.A, LAC1.B, LAC1.C analysis using First-Lactation dataset) are shown in Figure 1 (A) and that of TD milk yields to liability to mastitis in the following lactation period are shown in Figure 1 (B); the posterior mean, standard deviation (SD) and 95% posterior density interval (95% HPD) are

shown in Table 3.

The recursive effects from liability to mastitis to milk yields were between -0.032 and -0.003. Among the recursive effects from liability from mastitis to milk yields, only the recursive effect from LMAST1 to MY1 did not include zero in 95% HPD credible interval. Posterior means of structural coefficients indicate a negative recursive effects of liability to mastitis to TD milk yields. An increase in one unit of liability to mastitis decreased TD milk yields by 0.032, 0.004, and 0.003 kg per day, in lactation period 1, 2, and 3, respectively. The decrease in TD milk yield was higher in period 1 but similar for period 2 and 3. Wu *et al.* (2008) reported similar decrease in TD milk yields in Norwegian Red cows with clinical mastitis. In the observable scale, the difference in mean MY1, MY2 and MY3 between the sick cows due to mastitis and healthy cows in our study were -0.24 kg, -0.09 kg and -0.08 kg per day for lactation periods 1, 2, and 3, respectively. Based on results, an increased liability to mastitis slightly reduces milk yield at the following TD. This result is in agreement with a study by Wu *et al.* (2008), in which they reported the presence of a causal relationship between mastitis incidence and milk yield production. Estimates of structural coefficients obtained were also similar. Several other authors have reported the causal relationship between somatic cell score (SCS) and milk yield (de los Campos *et al.*, 2006; Jamrozik *et al.*, 2010; Wu *et al.*, 2007) and found that increases in SCS decreased the milk yield production. These results were also reflected in our study because SCS can be considered as an indicator of udder infection (Jamrozik *et al.*, 2010) and high SCS is often associated with clinical mastitis cases (Shook and Schutz, 1994).

Based on the recursive effects from TD milk yields to liability to mastitis in the following lactation period (e.g. MY1  $\rightarrow$  LMAST2), it was concluded that a weak positive relationship exists, nonetheless zero was included in the 95% HPD credible region (Table 3). This may be an indication of the fact that the increase in TD milk production in lactation period 1 and 2 had no effect on occurrence of mastitis events. It is otherwise possible that our data (which included producer-recorded data) were insufficient to estimate the true recursive effects between TD milk yields and liability to mastitis.

Posterior distribution of recursive effects from liability to mastitis of lactation periods 1, 2 and, 3 to LP are shown in Figure 1 (C); the posterior mean, standard deviation (SD) and 95% HPD are shown in Table 3. The 95% HPD for the structural coefficients obtained in this analysis included zero in the credible interval. Posterior means of structural coefficients indicate a weak effect of liability to mastitis of each period to LP. An increase of one unit of liability to mastitis decreased LP by 0.002 (LMAST1  $\rightarrow$  LP) and 0.003 (LMAST2  $\rightarrow$  LP) LP units and increased LP by 0.006 (LMAST3  $\rightarrow$  LP) LP units, thus indicating that a mastitis event (LMAST1 and LMAST2) happening in a cow's early lactation period would subtly decline persistency while late mastitis (LMAST3) would slightly increase persistency. This could be due to the reason that in the beginning of the lactation cows with mastitis may compromise with the production more than with cows in late lactation, because cows at late lactation cows may have enough energy reserves which they utilize slowly and efficiently to maintain their production (Ferris *et al.*, 1985).

Posterior distribution of direct recursive effects from LM1 to LM2 are shown in

Figure 2 (A); from LM1 to TMY and from LM2 to TMY are shown in Figure 2 (B); the posterior mean, SD, and 95% HPD are shown in Table 3. Based on the results it was concluded that the recursive effect from LM1 to LM2 had a posterior mean with a large positive effect; approximately 0.449 liability unit increase of LM2 for a 1-unit increase of LM1. Cow with a mastitis infection in first parity have an increased risk of getting mastitis in second parity due to the direct causal effect of the first event on the second. The direct recursive effect from LM1 to TMY had a posterior mean with positive effect of approximately 0.493 kg per day increase of TMY for a 1-unit increase of LM1. The direct recursive effect from LM2 to TMY had a posterior mean with negative effect of approximately 1.280 kg per day decrease of TMY for a 1-unit increase of LM2. The indirect effect of LM1 to TMY through the mediating effect of LM2 had a negative posterior mean; approximately 0.570 kg per day decrease of TMY for a 1-unit increase of LM1. The overall recursive effect of LM1 to TMY was negative and was approximately 0.081 kg per day decrease for TMY for a 1-unit increase of LM1. This indicates that the overall recursive effect from LM1 to TMY is as expected, mainly indirect and exerted through an increased susceptibility to mastitis in second lactation. When recursive effects are converted to the observable scale, mean difference in TMY between sick cows and healthy cows from first lactation is 0.97 kg per day (direct LM1  $\rightarrow$  TMY), and mean difference in TMY between sick and healthy cows from second lactation is -3.16 kg per day (direct LM2  $\rightarrow$  TMY).

### **Heritabilities and genetic correlations**

Posterior mean, SD, and 95% HPD heritabilities of mastitis events and milk yields of

all three lactation periods of first lactation and LP are shown in Table 4. The posterior mean of heritabilities for LMAST1 (0.04), LMAST2 (0.07) and LMAST3 (0.04) were slightly lower than the study done by Wu *et al.* (2008) using recursive Gaussian threshold model for Norwegian Red cows. Heritabilities in that study of liability to clinical mastitis (LCM) for three periods of lactation were 0.067 (LCM1), 0.094 (LCM2) and 0.079 (LCM3), respectively. The lower heritabilities of mastitis in this study could be due to the fact that no selection was performed in respect to health-related traits in the US, and also may be due to the use of farm recorded data in estimating heritability. The posterior mean of heritabilities for MYs ranged from 0.12 to 0.24. These estimates of heritabilities for MYs were similar to those estimated by Wu *et al.* (2008). The posterior mean of heritability for LP was approximately 0.14 and falls within the range of previous estimates of heritability for LP. Gengler (1996) reported heritability for LP of 0.14 for Holstein cows. Cole and VanRaden (2006) estimated the heritability of LP equal to 0.10. Posterior mean, SD, and 95% HPD of heritabilities for mastitis events in first and second lactation and TMY are shown in Table 4. The posterior mean of heritabilities for LM1 and LM2 were 0.04. These estimates of heritabilities were lower than that reported by Zwald *et al.* (2006) using producer-recorded data where heritability of liability to mastitis for first parity was 0.12 and for second parity was 0.10. Heritability estimates of liability to mastitis in the present study were in agreement with Parker Gaddis *et al.* (2014) where they reported a heritability of 0.06 for mastitis in first parity cows and 0.03 for mastitis in later parity cows using producer-recorded dataset. The posterior mean of heritability for TMY was 0.14.

Posterior mean, SD, and 95% HPD genetic correlations between mastitis events; between mastitis event and milk yields; and between mastitis event and LP are shown in Table 5. Posterior means of genetic correlations among mastitis events in three lactation periods of first lactation were all positive. Genetic correlations between LMAST1 and LMAST2, LMAST1 and LMAST3, and LMAST2 and LMAST3 were 0.58, 0.45, and 0.59, respectively. These estimates of genetic correlations are moderate and were lower than those obtained by Wu et al. (2008). The genetic correlations between LMAST1 and MY1, LMAST2 and MY1, LMAST2 and MY2, LMAST3 and MY2, and LMAST3 and MY3 were 0.21, -0.14, -0.15, 0.44, and 0.43, respectively. Among these posterior means only genetic correlations between LMAST3 and MY2 and LMAST3 and MY3 were well defined and others include zero in their 95% HPD credible interval. The genetic correlations between LMAST1 and LP, LMAST2 and LP, and LMAST3 and LP were 0.008, 0.003, and 0.20, respectively, and included zero in the 95% HPD credible interval.

Posterior mean, SD, and 95% HPD genetic correlations between mastitis events of first and second lactation and TMY were shown in Table 5. The genetic correlation between LM1 and LM2 was 0.54. The genetic correlation between LM1 and TMY was 0.17 and that between LM2 and TMY was -0.75.

## **CONCLUSION**

Causal relationships between mastitis events along with production traits such as milk yields and lactation persistency can help us to identify the real biological pathway of disease

process and its consequences in production traits. The causal relationship between mastitis events and milk yields showed that with an increase in mastitis events there would be a decline in milk production. There is little to no impact of mastitis events on lactation persistency of milk yield. The causal relationship among mastitis events in first and second lactation found in this study indicate that having a mastitis event in first lactation is likely to increase the risk of a mastitis event in second lactation. Based on the causal relationships between clinical mastitis events and production traits, economic loss from clinical mastitis events can be mitigated by addressing proper disease management strategies such as providing proper vaccination to boost immunity, proper treatment of infected cows, feeding improved feed stuffs, having better nutritional standards to cope with disease, etc. Greater insight into relationships between mastitis and production traits could be achieved by incorporating other factors in a recursive model such as risk factors of mastitis, herd demographics, housing conditions, and feeding procedures.

## REFERENCES

- Appuhamy J., Cassell B., Cole J. (2009) Phenotypic and genetic relationships of common health disorders with milk and fat yield persistencies from producer-recorded health data and test-day yields. *J. Dairy Sci.*, 92, 1785-1795.
- Bar D., Tauer L., Bennett G., Gonzalez R., Hertl J., Schukken Y., Schulte H., Welcome F., Gröhn Y. (2008) The cost of generic clinical mastitis in dairy cows as estimated by using dynamic programming. *J. Dairy Sci.*, 91, 2205-2214.
- Cole J., VanRaden P. (2007) A Manual for Use of BESTPRED: A program for estimation of lactation yield and persistency using best prediction. Available: <http://aipl.arsusda.gov/software/brestpred/>. Accessed Nov. 14, 2013.

- Cole J., VanRaden P. (2006) Genetic evaluation and best prediction of lactation persistency. *J. Dairy Sci.*, 89, 2722-2728.
- de los Campos G., Gianola D., Heringstad B. (2006) A structural equation model for describing relationships between somatic cell score and milk yield in first-lactation dairy cows. *J. Dairy Sci.*, 89, 4445-4455.
- de Maturana E.L., Wu X. L., Gianola D., Weigel K. A., Rosa G. J. M. (2009) Exploring biological relationships between calving traits in primiparous cattle with a Bayesian recursive model. *Genetics*, 181, 277-287.
- Ferris, T. A., I. L. Mao, and C. R. Anderson. (1985) Selection for lactation curve and milk yield in cattle. *J. Dairy Sci.* 68:1438–1448.
- Gengler N. (1996) Persistency of lactation yields: A review. *Proc. Int. Workshop on Genetic Improvement of Functional Traits in Cattle*. Gembloux, Belgium. *Interbull Bull.* 12:87–96.
- Geweke, J. (1992) Evaluating the accuracy of sampling-based approaches to the calculation of posterior moments. Pages 169-193 in *Bayesian Statistics 4*. J. M. Bernardo, J. Berger, A.P. Dawid, and A. F. M. Smith, ed. Oxford University Press, Oxford, UK.
- Gianola, D., Sorensen, D. (2004) Quantitative genetic models for describing simultaneous and recursive relationships between phenotypes. *Genetics* 167, 1407–1424.
- Heringstad B., Klemetsdal G., Steine T. (2003) Selection responses for clinical mastitis and protein yield in two Norwegian dairy cattle selection experiments. *J. Dairy Sci.*, 86, 2990-2999.
- Hertl J., Schukken Y., Bar D., Bennett G., González R., Rauch B., Welcome F., Tauer L., Gröhn Y. (2011) The effect of recurrent episodes of clinical mastitis caused by gram-positive and gram-negative bacteria and other organisms on mortality and culling in Holstein dairy cows. *J. Dairy Sci.*, 94, 4863-4877.
- Hinrichs D., Stamer E., Junge W., Kalm E. (2005) Genetic analyses of mastitis data using animal threshold models and genetic correlation with production traits. *J. Dairy Sci.*, 88, 2260-2268.
- Huijps K., Lam T. J., Hogeveen H. (2008) Costs of mastitis: facts and perception. *J. Dairy Res.*, 75, 113-120.

- Jamrozik J., Bohmanova J., Schaeffer L. (2010) Relationships between milk yield and somatic cell score in Canadian Holsteins from simultaneous and recursive random regression models. *J. Dairy Sci.*, 93, 1216.
- Kadarmideen H., Pryce J. (2001) Genetic and economic relationships between somatic cell count and clinical mastitis and their use in selection for mastitis resistance in dairy cattle. 73, 19-28.
- Koeck A., Miglior F., Kelton D., Schenkel F. (2012) Short communication: Genetic parameters for mastitis and its predictors in Canadian Holsteins. *J. Dairy Sci.*, 95, 7363-7366.
- Miglior F., Muir B., Van Doormaal B. (2005) Selection indices in Holstein cattle of various countries. *J. Dairy Sci.*, 88, 1255-1263.
- Moore D., Cullor J., Bondurant R., Sisco W. (1991) Preliminary field evidence for the association of clinical mastitis with altered interestrus intervals in dairy cattle. *Theriogenology*, 36, 257-265.
- Ødegård J., Klemetsdal G., Heringstad B. (2003) Variance components and genetic trend for somatic cell count in Norwegian Cattle. *Livest. Prod. Sci.*, 79, 135-144.
- Parker Gaddis K., Cole J., Clay J., Maltecca C. (2012) Incidence validation and relationship analysis of producer-recorded health event data from on-farm computer systems in the United States. *J. Dairy Sci.*, 95, 5422-5435.
- Philipsson J., Lindhé B. (2003) Experiences of including reproduction and health traits in Scandinavian dairy cattle breeding programmes. *Livest. Prod. Sci.*, 83, 99-112.
- Plummer, M., N. Best, K. Cowles, K. Vines, D. Sarkar, and R. Almond. (2012) Package 'coda'. Available: <http://cran.r-project.org/web/packages/coda/coda.pdf>. Accessed Jan. 12 2014.
- Rauw W., Kanis E., Noordhuizen-Stassen E., Grommers F. (1998) Undesirable side effects of selection for high production efficiency in farm animals: a review. *Livest. Prod. Sci.*, 56, 15-33.
- Shim E., Shanks R., Morin D. (2004) Milk Loss and Treatment Costs Associated with Two Treatment Protocols for Clinical Mastitis in Dairy Cows. *J. Dairy Sci.*, 87, 2702-2708.
- Shipley B. (2002) Cause and correlation in biology: a user's guide to path analysis, structural equations and causal inference. Cambridge University Press.

- Shook G., Schutz M. (1994) Selection on somatic cell score to improve resistance to mastitis in the United States. *J. Dairy Sci.*, 77, 648-658.
- Wu X. L., Heringstad B., Chang Y. M., De los Campos G., Gianola D. (2007) Inferring relationships between somatic cell score and milk yield using simultaneous and recursive models. *J. Dairy Sci.*, 90, 3508-3521.
- Wu X. L., Heringstad B., Gianola D. (2008) Exploration of lagged relationships between mastitis and milk yield in dairy cows using a Bayesian structural equation Gaussian-threshold model. 40, 333-358.

**Table 1** Descriptive statistics for mastitis events

Traits <sup>1</sup>	Number of records		Mastitis event frequency (%)
	Healthy	Diseased	
MAST1	44,896	3,162	6.58
MAST2	46,073	1,985	4.13
MAST3	46,184	1,874	3.90
M1	25,729	3,138	10.87
M2	24,811	4,056	14.05

<sup>1</sup>MAST1 is the mastitis event occurring in 5 to 60 DIM in first lactation; MAST2 is the mastitis event occurring in 61 to 120 DIM in first lactation; MAST3 is the mastitis event occurring in 121 to 180 DIM in first lactation; M1 is the mastitis event occurring in first lactation; and M2 is the mastitis event occurring in second lactation.

**Table 2** Descriptive statistics of production measures

Traits <sup>1</sup>	Number of records	Mean	SD	Minimum	Maximum
MY1 (kg)	48,058	34.66	7.18	6.50	81.22
MY2 (kg)	48,058	34.28	7.92	9.64	79.34
MY3 (kg)	48,058	28.55	7.32	8.32	72.09
LP (units)	48,058	0.38	0.97	-3.12	4.86
TMY (kg)	28,867	10,800.60	1,900.98	3,094.00	17,470.00

<sup>1</sup> MY1 is the test-day milk yield of first period (5 to 60 DIM) of first lactation; MY2 is the test-day milk yield of second period (61 to 120 DIM) of first lactation; MY3 is the test-day milk yield of third period (121 to 180 DIM) of first lactation; LP is the lactation persistency of milk yield in first lactation; TMY is the total milk yield of second lactation.

**Table 3** Posterior mean, standard deviation (SD), and 95% highest posterior density interval (95% HPD) of causal relationships between liability to mastitis, milk yields, and lactation persistency

Traits <sup>1</sup>	Recursive effects			
	Liability scale			Observable scale
	Mean	SD	95% HPD	Mean
<i>LAC1.A</i>				
LMAST1 → MY1	-0.032	0.010	[-0.051; -0.013]	-0.24 kg
<i>LAC1.B</i>				
MY1 → LMAST2	0.005	0.008	[-0.011; 0.021]	
LMAST2 → MY2	-0.004	0.008	[-0.021; 0.010]	-0.09 kg
<i>LAC1.C</i>				
MY2 → LMAST3	0.001	0.008	[-0.015; 0.017]	
LMAST3 → MY3	-0.003	0.009	[-0.020; 0.016]	-0.08 kg
<i>LAC1.D</i>				
LMAST1 → LP	-0.002	0.005	[-0.013; 0.008]	-0.01 LP units
LMAST2 → LP	-0.003	0.005	[-0.015; 0.007]	-0.01 LP units
LMAST3 → LP	0.006	0.005	[-0.005; 0.016]	0.02 LP units
<i>LAC12</i>				
LM1 → LM2	0.449	0.031	[0.390; 0.512]	
LM1 → TMY	0.493	0.094	[0.303; 0.673]	0.97 kg
LM2 → TMY	-1.280	0.087	[-1.455; -1.115]	-3.16 kg

<sup>1</sup> Liability to mastitis in first parity divided into three periods (LMAST1, LMAST2, LMAST3); test-day milk yields (MY1, MY2, MY3); Lactation persistency of milk yield denoted as LP; liability to mastitis in lactation 1 and 2 denoted as LM1 and LM2. Total amount of milk yield in second lactation denoted as TMY.

**Table 4** Posterior mean, standard deviation (SD), and 95% highest posterior density interval (95% HPD) of heritability of liability to mastitis, milk yields (MY), and lactation persistency, and total milk yield (TMY) of second lactation.

Traits <sup>1</sup>	Heritability		
	Mean	SD	95% HPD
LMAST1 <sup>2</sup>	0.04	0.01	[0.020; 0.070]
LMAST2 <sup>2</sup>	0.07	0.02	[0.034; 0.104]
LMAST3 <sup>3</sup>	0.04	0.01	[0.017; 0.058]
MY1	0.12	0.01	[0.091; 0.141]
MY2 <sup>2</sup>	0.13	0.02	[0.104; 0.161]
MY3	0.24	0.02	[0.203; 0.281]
LP	0.14	0.02	[0.114; 0.172]
LM1	0.04	0.01	[0.018; 0.065]
LM2	0.04	0.02	[0.013; 0.075]
TMY	0.14	0.02	[0.081; 0.226]

<sup>1</sup> Liability to mastitis in first lactation divided into three periods (LMAST1, LMAST2, LMAST3); test-day milk yields (MY1, MY2, MY3); Lactation persistency of milk yield denoted as LP; liability to mastitis in lactation 1 and 2 denoted as LM1 and LM2. Total amount of milk yield in second lactation denoted as TMY.

<sup>2</sup> Heritability of liabilities of mastitis were reported from LAC1.D analysis.

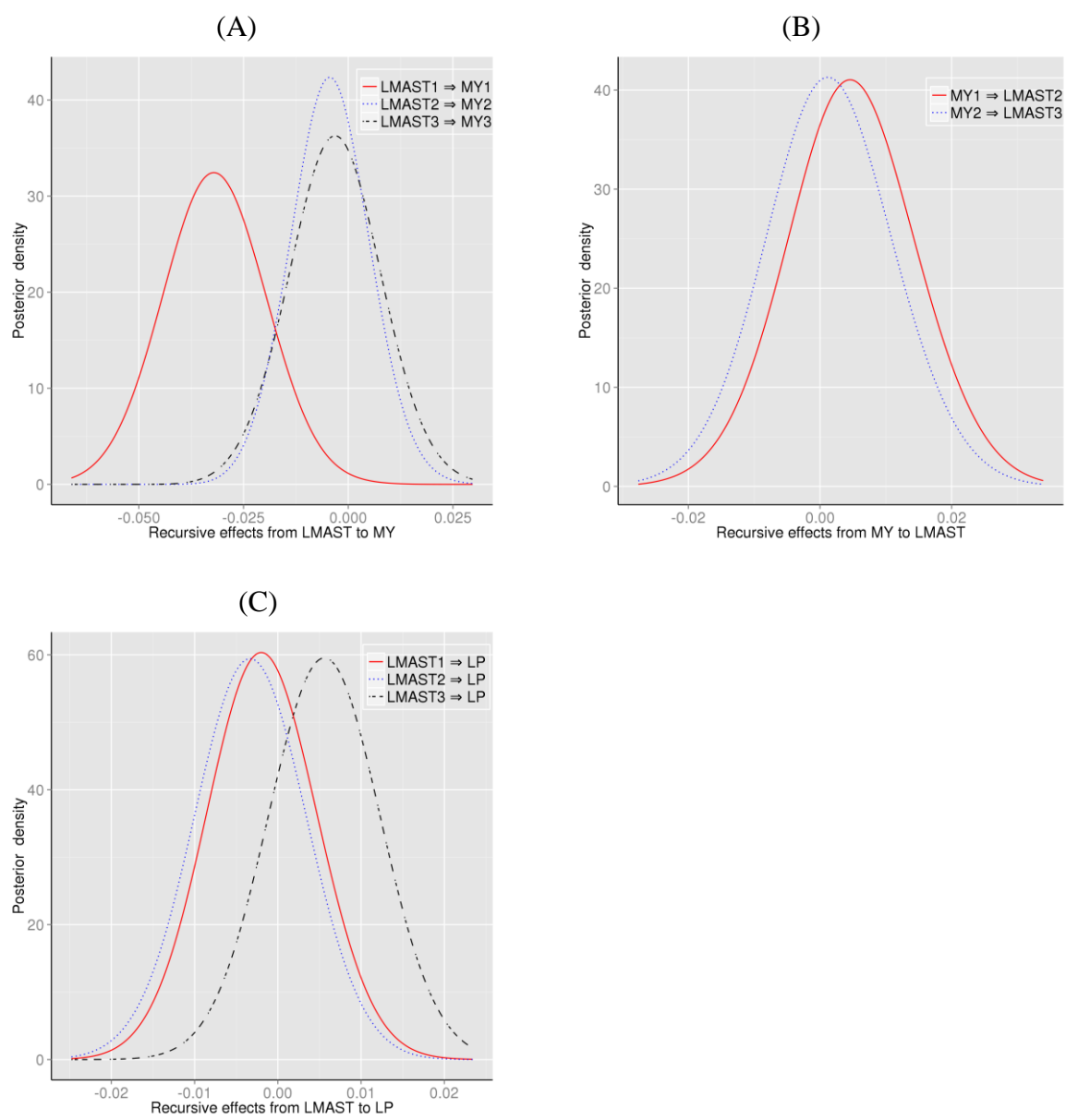
<sup>3</sup> Heritability of MY2 was reported from LAC 1.B analysis.

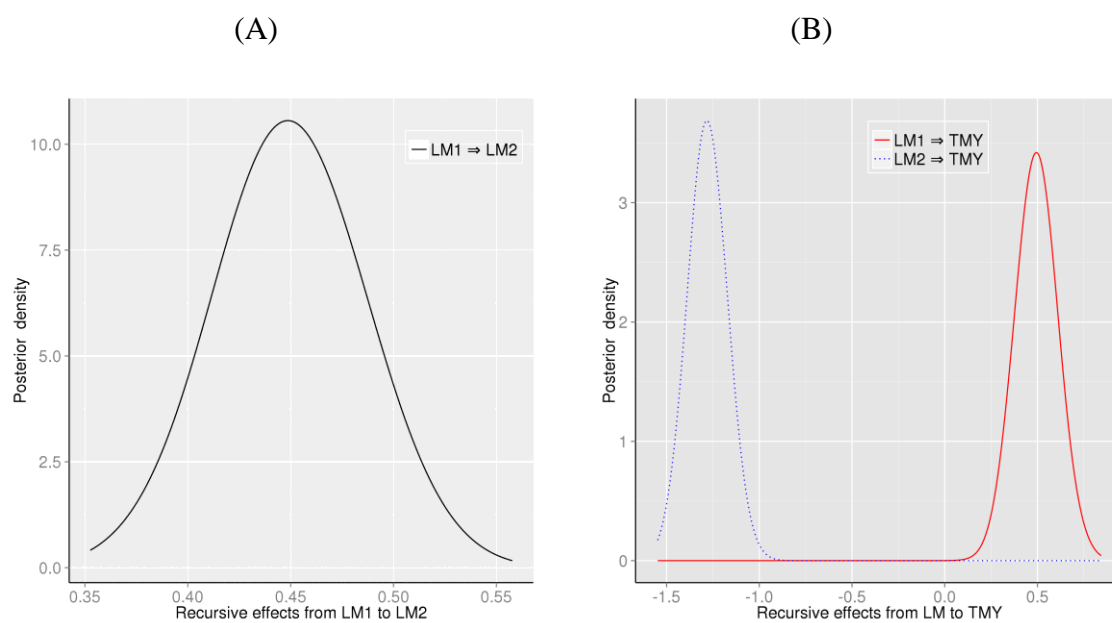
**Table 5** Posterior mean, standard deviation (SD), and 95% highest posterior density interval (95% HPD) of genetic correlation between liability to mastitis, milk yields, and lactation persistency

Traits <sup>1</sup>	Genetic Correlation		
	Mean	SD	95% HPD
LMAST1 and MY1	0.21	0.20	[-0.191; 0.612]
LMAST2 and MY1	-0.14	0.20	[-0.517; 0.260]
LMAST2 and MY2	-0.15	0.19	[-0.532; 0.237]
LMAST3 and MY2	0.44	0.20	[0.084; 0.816]
LMAST3 and MY3	0.43	0.20	[0.046; 0.780]
LMAST1 and LMAST2	0.58	0.15	[0.268; 0.814]
LMAST1 and LMAST3	0.45	0.16	[0.134; 0.745]
LMAST2 and LMAST3	0.59	0.13	[0.342; 0.820]
LMAST1 and LP	0.008	0.17	[-0.316; 0.355]
LMAST2 and LP	0.003	0.15	[-0.291; 0.289]
LMAST3 and LP	0.20	0.15	[-0.068; 0.502]
LM1 and LM2	0.54	0.32	[-0.249; 0.660]
LM1 and TMY	0.17	0.22	[-0.300; 0.673]
LM2 and TMY	-0.75	0.09	[-0.978; -0.596]

<sup>1</sup> Liability to mastitis in first lactation divided into three periods (LMAST1, LMAST2, LMAST3); test-day milk yields (MY1, MY2, MY3); Lactation persistency of milk yield denoted as LP; liability to mastitis in lactation 1 and 2 denoted as LM1 and LM2. Total amount of milk yield in second lactation denoted as TMY.

**Figure 1** Recursive effects between milk yields and liability to mastitis in three different periods of first-lactation (5 – 60, 61 – 120, and 121 – 180 days in milk): (A) Recursive effects from liability to mastitis (LMAST1, LMAST2, LMAST3) to milk yields (MY1, MY2, MY3) of corresponding period of first -lactation; (B) Recursive effects from milk yields (MY1 and MY2) to liability to mastitis (LMAST2 and LMAST3) of corresponding period of first lactation; (C) Recursive effects from liability to mastitis (LMAST1, LMAST2, LMAST3) to lactation persistency of milk yield (LP).





**Figure 2** Recursive effects between liability to mastitis events between parity 1, 2 and total milk yield (TMY) of second parity: (A) Recursive effects from liability to mastitis in parity 1 (LM1) to liability to mastitis in parity 2 (LM2); (B) Recursive effects from milk yields LM1 and LM2 to TMY.

## CHAPTER 4

**GENOMIC SELECTION FOR HOOF LESIONS IN US HOLSTEINS**

## ABSTRACT

Hoof lesions contributing to lameness are crucial economic factors that hinder the profitability of dairy enterprises. Producer-recorded hoof lesions data of US Holsteins were categorized into infectious (abscess, digital and interdigital dermatitis, heel erosion, and foot rot) and other (korn, corkscrew, sole and toe ulcer, sole hemorrhage, white line separation, fissures, thin soles, and upper leg lesions) categories of hoof lesions. Pedigree-based and genomic-based univariate analyses were conducted to estimate the variance components and heritability of infectious and non-infectious hoof lesions. A threshold sire model was used with fixed effects of year-seasons and random effects of herd and sire. In the case of genomic-based analysis, a single-step procedure was conducted incorporating a **H** matrix to estimate genomic variance components and heritability for hoof lesions. The pedigree based analysis produced heritability estimates of 0.11 ( $\pm$  0.05) for infectious hoof lesions and 0.08 ( $\pm$  0.05) for non-infectious hoof lesions. The single-step genomic analysis produced heritability estimates of 0.14 ( $\pm$  0.06) for infectious hoof lesions and 0.12 ( $\pm$  0.08) for non-infectious hoof lesions. Sire reliabilities increased with incorporation of genomic data. Inclusion of genomic data substantially improved young sire reliabilities for hoof lesions. Genomic selection for hoof lesions could be incorporated into breeding programs to improve the health status of the US Holsteins.

Key words: **genomic selection, hoof lesions, reliability**

## INTRODUCTION

Hoof lesions are a primary cause of lameness in most dairy herds (Oberbauer et al., 2013). Lameness is recognized as a major cause of economic loss in the dairy industry due to its unfavorable effect on productivity and profitability in commercial dairy operations. Several studies have reported lameness to cause weight loss (Enting et al., 1997), reduced milk yield (Lucey et al., 1986; Hernandez et al., 2005; Warnick et al., 2001), reduced reproductive efficiency (Bicalho and Oikonomou, 2013), and premature culling (Faust et al., 2001). Lameness causes pain leading to a debilitating condition and distress in affected cows, which is considered to be a serious animal welfare issue (Booth et al., 2004; Vermunt, 2007; Von Keyserlingk et al., 2009). A few decades ago, the incidence of lameness in dairy cattle in US was estimated at 15% (Wells et al., 1993) and a more recent study in 3 commercial California dairies performed by Oberbauer et al. (2013) reported that the prevalence of hoof lesions ranged from 2.2% (foot rot) to 17.1% (digital dermatitis). Guard (1999) estimated direct cost due to lameness in a 100-cow herd to be \$7,600. Cha et al. (2010) used a dynamic programming method and determined the approximate cost per case for sole ulcer, digital dermatitis and foot rot to be \$216, \$132 and \$121, respectively.

Genomic selection is an appealing tool for improvement of health traits. Several previous studies have reported the heritabilities of hoof lesions using pedigree relationship matrix. Recent advancements in genomics have made available dense molecular data that can be used for genomic selection. Recently, Parker Gaddis et al. (2014) estimated genomic variance components and heritabilities for various health events using producer-recorded

health data. However, previous studies have not evaluated specific categories of hoof lesion events using genomic information. The objectives of the current study were to (1) estimate the genomic variance components and heritability of hoof lesions in US Holsteins, (2) compare the sire PTA reliabilities between pedigree- and genomic-based analyses and (3) compare the genetic association between hoof lesions data coming from different sources and recorded in different formats.

## **MATERIALS AND METHODS**

In this study, hoof lesion records recorded voluntarily by dairy farmers were obtained from Dairy Records Management Systems (DRMS) from year 2007 to 2013, and subjected to a series of data quality edits following Parker Gaddis et al. (2012). Records on first-parity Holstein cows were retained and hoof lesions were categorized as infectious and non-infectious hoof lesions. Infectious hoof lesions included lesions such as abscess, digital and inter-digital dermatitis, heel erosion, and foot rot; non-infectious included lesions such as korn, corkscrew, sole and toe ulcer, sole hemorrhage, white line separation, fissures, thin soles, and upper leg lesions. After editing, 23,467 records were available for analysis. Hoof lesions were recorded in a binary format 0 = healthy and 1 = hoof lesion. Pedigree-based analyses were performed for each category of hoof lesion. A threshold sire model was used to estimate variance components and heritability using the THRS GIBBS1F90 program (version 2.104; Tsuruta and Misztal, 2006) and approximate reliabilities of estimated sire PTA were calculated using the ACCF90 program (version 1.67; Misztal et al., 2002). The model was

$$\lambda = X\beta + Z_h h + Z_s s + e$$

where  $\lambda$  represents a vector of unobserved liabilities to the given hoof lesion; is a vector of fixed effects including overall mean and year-season;  $\mathbf{h}$  represents the random herd effect, where  $\mathbf{h} \sim N(0, \mathbf{I}\sigma_h^2)$  with  $\mathbf{I}$  representing an identity matrix and  $\sigma_h^2$  representing the variance of herd;  $\mathbf{s}$  represents the random sire effect, where  $\mathbf{s} \sim N(0, \mathbf{A}\sigma_s^2)$ , with  $\mathbf{A}$  representing the additive genetic relationship matrix and  $\sigma_s^2$  representing the sire variance,  $\mathbf{X}$  represents the corresponding incidence matrix for the fixed effect,  $\mathbf{Z}_h$  and  $\mathbf{Z}_s$  represent the corresponding incidence matrices for the appropriate random effects; and  $\mathbf{e}$  represents random residuals following  $N(0, \mathbf{I})$  and fixing the variance equal to 1 to attain identifiability.

Genomic-based analysis was also conducted for infectious and non-infectious hoof lesions using genomic data. The preGSf90 software (version 1.142; Aguilar et al., 2011) was used to incorporate genomic data into a blended  $\mathbf{H}$  matrix in a single-step procedure (Legarra et al, 2012; Aguilar et al., 2010), the  $\mathbf{H}$  matrix was used instead of  $\mathbf{A}$  for the random sire effect  $\mathbf{s} \sim N(0, \mathbf{H}\sigma_s^2)$ . Genomic data quality control as implemented in software include exclusion of SNP with minor allele frequency below 0.05, exclusion of SNP with call rates below 0.90, exclusion of individuals with call rates below 0.90 and exclusion of SNP located in sex chromosomes. Before applying data quality edits, there were 876 sires with genomic information and the minimum number of daughters per sire was 3. After applying data quality edits, genomic data were available for 471 sires on 40,608 markers. The  $\mathbf{G}$  matrix

was calculated following VanRaden (2008), using allele frequencies calculated from the available genotypes.

A Monte Carlo Markov chain approach through Gibbs sampling was used to obtain estimates of variance components. A total of 300,000 iterations were completed with the first 50,000 discarded as burn-in, and storing every 100<sup>th</sup> sample. Convergence was assessed by visual inspection of trace plots and more additional diagnostic tests were carried out to confirm convergence such as obtaining estimates of autocorrelation and effective sample size through R (<http://cran.r-project.org>) with the CODA package (Plummer et al. 2013). Post-Gibbs analyses were completed using the POSTGIBBSF90 program (version 3.04; Misztal et al., 2002). Reliabilities of genomic PTA were estimated following Misztal et al. (2013).

After calculating variance components and heritabilities for infectious and non-infectious hoof lesions using the above-mentioned data set, we decided to include sires with low number of daughters (excluded in previous data editing process) and to calculate reliabilities both with pedigree and genomic information in order to assess the advantage of including genomic information on the sires with fewer daughters by comparing the reliabilities of pedigree- and genomic-based analysis of infectious and non-infectious hoof lesions. In the genomic-based analysis, the number of sires with both phenotyped daughters and genomic information was 876 and total number of records was 33,541. Variance components previously estimated were used to compute reliabilities.

A bivariate analysis was also performed using first parity US Holsteins hoof lesion records and producer recorded lameness data from the analysis conducted by Parker Gaddis

et al. (2014). Lameness and hoof-lesions data were assumed to be different traits because they are recorded in different formats in which hoof lesion data contain specific types of hoof lesions whereas in lameness all causes of lameness were recorded in a single category of lame or sound. Thus, it is reasonable to expect hoof lesions and lameness to be different traits as they would display different distributions, with distinct means and variances. Lameness data and hoof lesion data were merged by animal identification number, keeping both records that matched (i.e. cows phenotyped from both sources, n=12,881). Records that didn't match (i.e. cows that were phenotyped for hoof lesions n= 20,660 and lameness n=74,590) were assigned missing value for one of the two traits. A total of 108,131 records were used in the analysis. A bivariate threshold sire model with the same fixed and random effects as described in the univariate analysis was used for both pedigree- and genomic-based analysis and carried out using THRGIBBS1F90 program (version 2.104; Tsuruta and Misztal, 2006). Chains of 300,000 iterations were run with first 50,000 samples discarded as burn-in and thinning occurring every 100<sup>th</sup> sample. Convergence was assessed as described before.

## **RESULTS AND DISCUSSION**

The frequency of infectious and non-infectious hoof lesions in the edited dataset was 2.27% and 2.08% respectively. In a study conducted in Canada, Chapinal et al. (2013) reported that the incidence rates of front hoof lesions in first parity cows were 2.7%, 4.4%, and 0.9% for infectious, horn and other hoof lesions respectively and similarly incidence rates for rear hoof lesions in first parity cows were 23.8%, 13.1% and 2.9% for infectious, horn and other hoof lesions respectively. Infectious hoof lesions are the more common hoof

lesions in our study and are in agreement with other studies that classified lesions similarly (Somers et al., 2003; Holzhauer et al., 2006; Chapinal et al., 2013).

Posterior means of pedigree and genomic-based variance components and heritability of infectious and non-infectious hoof lesions are shown in Table 1. As expected sire variance components increased in genomic-based analysis as compared to pedigree-based analysis resulting in slightly larger heritability of hoof lesions. The heritability estimates of infectious hoof lesions from pedigree- and genomic-based analysis were  $0.11 (\pm 0.05)$  and  $0.13 (\pm 0.06)$  respectively and that of non-infectious hoof lesions were  $0.08 (\pm 0.05)$  and  $0.12 (\pm 0.08)$  respectively. The differences in heritability estimates between pedigree- and genomic-based analysis may be due to the differences in scale of the relationship matrices and also because different base populations were used in creating **A** and **H** matrices (Parker Gaddis et al., 2014). The heritability estimates for infectious hoof lesions were in agreement with a previous study conducted by Chapinal et al. (2013). It should be noted that most of the time the etiology remains unknown for non-infectious hoof lesions and thus, genetic variance obtained for non-infectious lesions may not reflect true genetic variance.

The comparison between sire PTA reliabilities from pedigree- and genomic-based reliabilities is shown in Table 2. The addition of genomic data improved the reliabilities for both infectious and non-infectious hoof lesions. The average increments in reliability using genomic data were 0.24 and 0.18 for infectious and non-infectious hoof lesions, respectively. The improvement trend of reliability based on number of daughters for each sire is shown in

Figure 1A for infectious, and Figure 1B for non-infectious hoof lesions. As expected, the use of genomic data mainly improved the reliabilities of young sires that have few daughters.

The posterior means, SD and 95% highest posterior density (95% HPD) of pedigree- and genomic-based heritabilities and genetic correlation from bivariate analyses are shown in Table 3. Heritability estimates were larger in genomic-based analysis and were also larger than univariate genomic-based analysis. Heritability estimates were 0.11 ( $\pm$  0.05), 0.10 ( $\pm$  0.05), and 0.04 ( $\pm$  0.01), for infectious, non-infectious and lameness respectively in pedigree-based analysis where as in genomic-based analysis heritability estimates are 0.17 ( $\pm$  0.07), 0.15 ( $\pm$  0.07), 0.06 ( $\pm$  0.02), for infectious, non-infectious and lameness traits. Most of the previous studies categorize all hoof lesions into single lameness event. Heritability of lameness has been estimated between 0.02 and 0.22 (Zwald et al., 2004; Neuenschwander et al., 2012; Parker-Gaddis et al., 2014). The posterior mean of genetic correlation between infectious and lameness is 0.51 (95% HPD: -0.098; 0.996) and genetic correlation between non-infectious and lameness is 0.91 (95% HPD: 0.636; 1.000). The posterior mean of genomic correlation between infectious and lameness is 0.44 (95% HPD: -0.048, 0.931) and genomic correlation between non-infectious and lameness is 0.74 (95% HPD: 0.305, 0.994). In this study, in both pedigree-and genomic-based analysis, genetic correlation between non-infectious and lameness did not include zero in their 95% HPD interval (Table 3). This indicates that most of the producer-recorded data in lameness trait were mainly non-infectious hoof lesions. The reason for this could be that because producers voluntarily record these records, there may be some bias in recording infectious hoof lesions.

## CONCLUSION

Based on heritability estimates obtained for infectious and non-infectious hoof lesions in this study it was concluded that genetic or genomic selection is possible due to the presence of a heritable component in producer-recorded hoof lesions. Nordic countries have already included hoof health in their index and have seen slow progress in reducing prevalence of lameness. Thus, genetic or genomic selection for hoof lesions should be incorporated into breeding programs to enable reasonable genetic improvement of cows' resistance to hoof lesions.

## REFERENCES

- Aguilar, I., I. Misztal, D. Johnson, A. Legarra, S. Tsuruta, and T. Lawlor. 2010. Hot topic: A unified approach to utilize phenotypic, full pedigree, and genomic information for genetic evaluation of holstein final score. *J. Dairy Sci.* 93:743-752.
- Aguilar, I., I. Misztal, A. Legarra, and S. Tsuruta. 2011. Efficient computation of the genomic relationship matrix and other matrices used in single-step evaluation. *J. Anim. Breed. Genet.* 128:422-428.
- Bicalho, R. C., and G. Oikonomou. 2013. Control and prevention of lameness associated with claw lesions in dairy cows. *Livestock Science.*
- Booth, C., L. Warnick, Y. Gröhn, D. Maizon, C. Guard, and D. Janssen. 2004. Effect of lameness on culling in dairy cows. *J. Dairy Sci.* 87:4115-4122.
- Cha, E., J. Hertl, D. Bar, and Y. Gröhn. 2010. The cost of different types of lameness in dairy cows calculated by dynamic programming. *Prev. Vet. Med.* 97:1-8.
- Chapinal, N., A. Koeck, A. Sewalem, D. Kelton, S. Mason, G. Cramer, and F. Miglior. 2013. Genetic parameters for hoof lesions and their relationship with feet and leg traits in Canadian Holstein cows. *J. Dairy Sci.* 96:2596-2604.

- Enting, H., D. Kooij, A. Dijkhuizen, R. Huirne, and E. Noordhuizen-Stassen. 1997. Economic losses due to clinical lameness in dairy cattle. *Livest. Prod. Sci.* 49:259-267.
- Faust, M., M. Kinsel, and M. Kirkpatrick. 2001. Characterizing biosecurity, health, and culling during dairy herd expansions. *J. Dairy Sci.* 84:955-965.
- Guard, C. 1999. Control programs for digital dermatitis. *The Tools for Success in the New Millennium*. Kennelly (Ed.). 2:235-242.
- Hernandez, J. A., E. J. Garbarino, J. K. Shearer, C. A. Risco, and W. W. Thatcher. 2005. Comparison of milk yield in dairy cows with different degrees of lameness. *J. Am. Vet. Med. Assoc.* 227:1292-1296.
- Holzhauser, M., C. Hardenberg, C. Bartels, and K. Frankena. 2006. Herd-and cow-level prevalence of digital dermatitis in the Netherlands and associated risk factors. *J. Dairy Sci.* 89:580-588.
- Legarra, A., and V. Ducrocq. 2012. Computational strategies for national integration of phenotypic, genomic, and pedigree data in a single-step best linear unbiased prediction. *J. Dairy Sci.* 95:4629-4645.
- Lucey, S., G. J. Rowlands, and A. M. Russell. 1986. Short-term associations between disease and milk yield of dairy cows. *J. Dairy Res.* 53:7-15.
- Misztal, I., S. Tsuruta, I. Aguilar, A. Legarra, P. VanRaden, and T. Lawlor. 2013. Methods to approximate reliabilities in single-step genomic evaluation. *J. Dairy Sci.* 96:647-654.
- Misztal, I., S. Tsuruta, T. Strabel, B. Auvray, T. Druet, and D. Lee. 2002. BLUPF90 and related programs (BGF90). Page 1-2 in *Proceedings of the 7th world congress on genetics applied to livestock production, Montpellier, France, August, 2002. Session 28.* Institut National de la Recherche Agronomique (INRA).
- Neuenschwander, T., F. Miglior, J. Jamrozik, O. Berke, D. Kelton, and L. Schaeffer. 2012. Genetic parameters for producer-recorded health data in Canadian Holstein cattle. *Animal.* 6:571-578.
- Oberbauer, A., S. Berry, J. Belanger, R. McGoldrick, J. Pinos-Rodriguez, and T. Famula. 2013. Determining the heritable component of dairy cattle foot lesions. *J. Dairy Sci.* 96:605-613.

- Parker Gaddis, K., J. Cole, J. Clay, and C. Maltecca. 2012. Incidence validation and relationship analysis of producer-recorded health event data from on-farm computer systems in the United States. *J. Dairy Sci.* 95:5422-5435.
- Parker Gaddis, K. L., J. B. Cole, J. S. Clay, and C. Maltecca. 2014. Genomic selection for producer-recorded health event data in US dairy cattle. *J. Dairy Sci.* 97:3190-3199.
- Somers, J., K. Frankena, E. N. Noordhuizen-Stassen, and J. Metz. 2003. Prevalence of claw disorders in dutch dairy cows exposed to several floor systems. *J. Dairy Sci.* 86:2082-2093.
- Tsuruta, S., and I. Misztal. 2006. THRGIBBS1F90 for estimation of variance components with threshold and linear models. Page 27-31 in *Proceedings of the 8th world congress on genetics applied to livestock production, Belo Horizonte, Minas Gerais, Brazil, 13-18 August, 2006*. Instituto Prociência.
- VanRaden, P. 2008. Efficient methods to compute genomic predictions. *J. Dairy Sci.* 91:4414-4423.
- Vermunt, J. J. 2007. One step closer to unravelling the pathophysiology of claw horn disruption: For the sake of the cows' welfare. *The Veterinary Journal.* 174:219-220.
- Von Keyserlingk, M., J. Rushen, A. M. de Passillé, and D. M. Weary. 2009. Invited review: The welfare of dairy cattle—Key concepts and the role of science. *J. Dairy Sci.* 92:4101-4111.
- Warnick, L., D. Janssen, C. Guard, and Y. Gröhn. 2001. The effect of lameness on milk production in dairy cows. *J. Dairy Sci.* 84:1988-1997.
- Wells, S. J., A. M. Trent, W. E. Marsh, and R. A. Robinson. 1993. Prevalence and severity of lameness in lactating dairy cows in a sample of Minnesota and Wisconsin herds. *J. Am. Vet. Med. Assoc.* 202:78-82.
- Zwald, N., K. Weigel, Y. Chang, R. Welper, and J. Clay. 2004. Genetic selection for health traits using producer-recorded data. I. Incidence rates, heritability estimates, and sire breeding values. *J. Dairy Sci.* 87:4287-4294.

**Table 1** Posterior mean, SD, and 95% highest posterior density (HPD) of variance components and heritability of infectious and non-infectious hoof lesions obtained from pedigree- and genomic-based analysis.

Trait	Sire Variance			Herd Variance			Heritability		
	Mean	SD	95% HPD	Mean	SD	95% HPD	Mean	SD	95% HPD
<i>Pedigree-based</i>									
Infectious	0.039	0.017	[0.008; 0.071]	0.325	0.066	[0.209; 0.462]	0.113	0.047	[0.024; 0.202]
Non-infectious	0.027	0.018	[0.001; 0.063]	0.344	0.077	[0.206; 0.500]	0.077	0.052	[0.001; 0.179]
<i>Genomic-based</i>									
Infectious	0.048	0.022	[0.008; 0.092]	0.325	0.066	[0.209; 0.457]	0.138	0.063	[0.021; 0.257]
Non-infectious	0.044	0.028	[0.001; 0.096]	0.346	0.078	[0.206; 0.499]	0.124	0.077	[0.001; 0.264]

**Table 2** Comparison of mean sire reliabilities from pedigree-and genomic-based analysis.

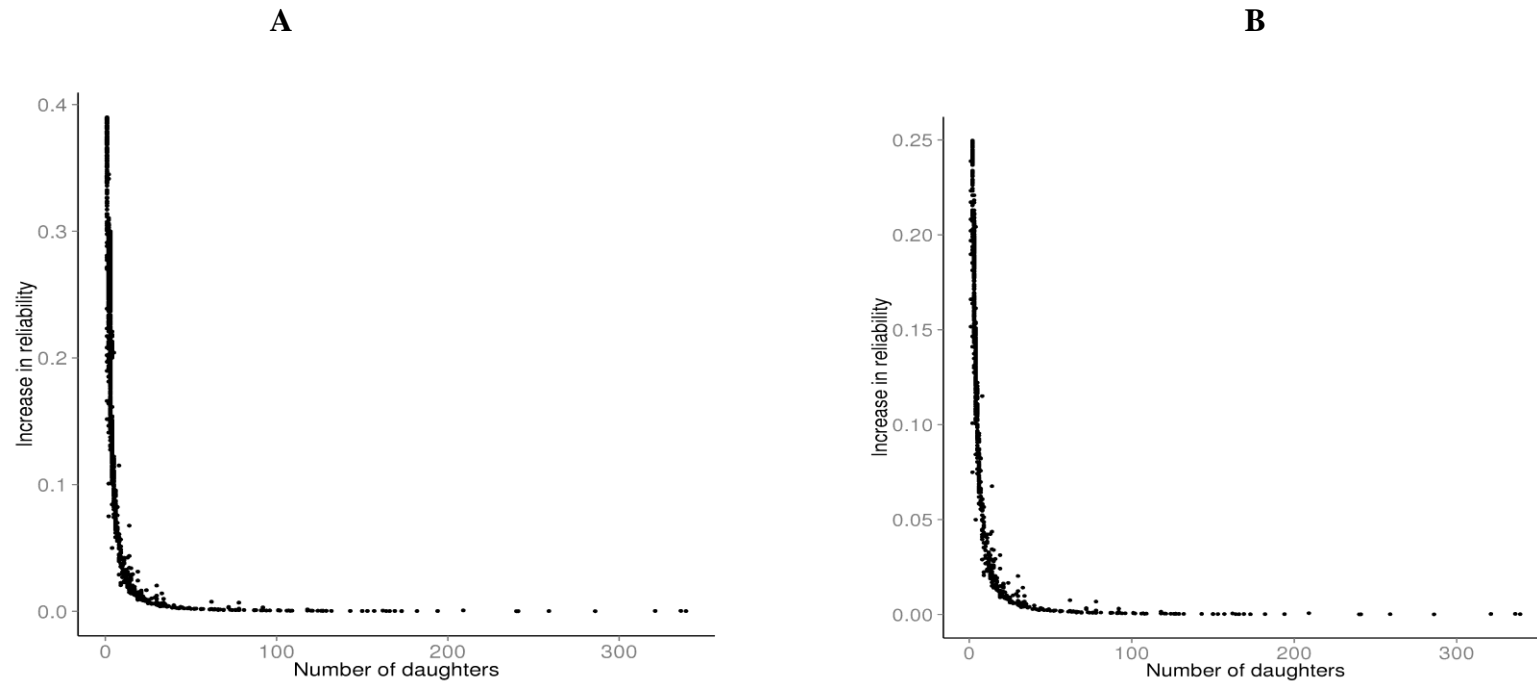
Trait	PTA <sup>1</sup> reliability	GPTA <sup>2</sup> reliability	Overall gain
Infectious	0.42	0.66	0.24
Non-infectious	0.30	0.48	0.18

<sup>1</sup>Predicted transmitting ability: PTA

<sup>2</sup>Genomic predicted transmitting ability: GPTA

**Table 3** Posterior mean, standard deviation (SD), and 95% highest posterior density (HPD) of heritability and genetic correlation from bivariate analysis of hoof lesions and lameness traits from both pedigree-and genomic based analysis.

Trait	Genetic correlation					
	Heritability			Lameness		
	Mean	SD	95% HPD	Mean	SD	95% HPD
<i>Pedigree-</i>						
<i>based</i>						
Infectious	0.11	0.05	[0.015; 0.207]	0.51	0.34	[-0.098; 0.996]
Non-infectious	0.10	0.05	[0.024; 0.197]	0.91	0.13	[0.636; 1.000]
Lameness	0.04	0.01	[0.020; 0.064]			
<i>Genomic-</i>						
<i>based</i>						
Infectious	0.17	0.07	[0.044; 0.295]	0.44	0.27	[-0.048; 0.931]
Non-infectious	0.15	0.07	[0.026; 0.300]	0.74	0.21	[0.305; 0.994]
Lameness	0.06	0.02	[0.021; 0.089]			



**Figure 1** Increase in reliability trend with respect to number of daughters per sire in univariate single-step analysis for: (A) infectious hoof lesions, and (B) non-infectious hoof lesions.

## CONCLUSION

Selection for milk yield in dairy has increased the amount of milk produced by dairy cows by 3 fold in about 60 years. This selective breeding for increased milk yield is accompanied by serious cost issues due to little to no selection emphasis on other important traits such as improved health status of cow, reproductive efficiency, longevity, and welfare.

Health events in dairy cattle are important traits to be considered not only because of the associated costs such as veterinary and treatment costs, discarded milk due to treatment, and lower production of milk during the illness timeframe etc; but also because of the animal welfare issues. Different studies have estimated the association between milk yield and health events. Most of these studies have reported genetic correlations among health events and production traits. Even though, having the knowledge about genetic correlations among traits is useful, it doesn't tell much about the causal relationships among traits.

Understanding the causal relationships among health and production traits could help us to disentangle the complex behavior of these traits.

The studies within this dissertation were conducted to increase our knowledge on the associations among health disorders and production measures that evolve during the course of lactation and to estimate variance components of these traits. In chapter 2 causal relationships between metabolic and reproductive health disorders along with production measures such as peak milk yield, days in milk in peak milk yield and lactation persistency of milk yield were investigated. In addition, causal relationships between health disorder and culling were also examined. This study revealed that causal link exists between health

disorders that evolve during the course of lactation. Stronger causal relationships were identified within each health disorder category. The causal relationship among health disorders found in this study indicate that having one health disorder at an earlier time in a cow's productive life increases the risk of future health disorders. Study also revealed that there was little to no impact on production traits from health disorders. Causal relationship between health disorders and culling found in this study suggest that with increases in the incidence of health disorders there would be an increase in culling. The knowledge regarding causal relationships among health disorders and production traits explored in this study could be implemented in genetic selection and management strategies to rule out the possible future health events and to place selection pressure on initial health events that occur in early lactation, so that cow health status can be improved.

In chapter 3, casual relationship among clinical mastitis events and test-day milk yields were explored. The causal relationship between clinical mastitis events and milk yields found in this study suggest that with an increase in clinical mastitis events there would be decline in milk production. There is little to no impact of mastitis events on lactation persistency of milk yield. The causal relationship among mastitis events in first and second lactation found in this study indicate that having a mastitis event in first lactation is likely to increase the risk of a mastitis event in second lactation. The knowledge obtained from this study can be used on understanding how the clinical mastitis and test-day milk yields are associated with each other and to implement improved management strategies to control clinical mastitis events after the disease appears early in the lactation period.

In chapter 4, genomic information was used to calculate genomic variance components and heritability of infectious and non-infectious hoof lesions. Single-step procedure was used to incorporate both pedigree and genomic information to analyze the data. The heritability estimates obtained for infectious and non-infectious hoof lesions in this study indicated that genomic selection is possible due to the presence of heritable components in hoof lesions. Infectious hoof lesions had higher heritability compared to non-infectious hoof lesions. It was also concluded that with the inclusion of genomic information, reliabilities of young sires were increased compared to reliabilities obtained from pedigree-based analysis.

An effort was made to use producer-recorded health data to provide evidence that data can be used to understand the complex behavior of health traits. Results of studies within this dissertation provide guidance to dairy cow breeders for identifications of the real pathway of the disease process and its consequences in culling and production traits based on the causal relationships among the traits. Moreover, it was concluded that there is a clear advantage to inclusion of genomic information in genetic evaluations of hoof lesions. In overall, information within this dissertation can be utilized in exploring complex relationships between health traits and production traits so that proper breeding and management strategy can be implemented for breeding healthier dairy cattle.