



Inbreeding depression for producer-recorded udder, metabolic, and reproductive diseases in US dairy cattle

Emmanuel A. Lozada-Soto,^{1*} Kristen L. Parker Gaddis,² Francesco Tiezzi,³ Jicai Jiang,¹ Li Ma,⁴ Sajjad Toghiani,⁵ Paul M. VanRaden,⁵ and Christian Maltecca¹

¹Department of Animal Science, North Carolina State University, Raleigh, NC 27607

²Council on Dairy Cattle Breeding, Bowie, MD 20716

³Department of Agriculture, Food, Environment and Forestry (DAGRI), University of Florence, 50144 Florence, Italy

⁴Department of Animal and Avian Sciences, University of Maryland, College Park, MD 20742

⁵Animal Genomics and Improvement Laboratory, Henry A. Wallace Beltsville Agricultural Research Service, USDA, Beltsville, MD 20705

ABSTRACT

This study leveraged a growing dataset of producer-recorded phenotypes for mastitis, reproductive diseases (metritis and retained placenta), and metabolic diseases (ketosis, milk fever, and displaced abomasum) to investigate the potential presence of inbreeding depression for these disease traits. Phenotypic, pedigree, and genomic information were obtained for 354,043 and 68,292 US Holstein and Jersey cows, respectively. Total inbreeding coefficients were calculated using both pedigree and genomic information; the latter included inbreeding estimates obtained using a genomic relationship matrix and runs of homozygosity. We also generated inbreeding coefficients based on the generational inbreeding for recent and old pedigree inbreeding, for different run-of-homozygosity length classes, and for recent and old homozygous-by-descent segment-based inbreeding. Estimates on the liability scale revealed significant evidence of inbreeding depression for reproductive-disease traits, with an increase in total pedigree and genomic inbreeding showing a notable effect for recent inbreeding. However, we found inconsistent evidence for inbreeding depression for mastitis or any metabolic diseases. Notably, in Holsteins, the probability of developing displaced abomasum decreased with inbreeding, particularly for older inbreeding. Estimates of disease probability for cows with low, average, and high inbreeding levels did not significantly differ across any inbreeding coefficient and trait combination, indicating that although inbreeding may affect disease incidence, it likely plays a smaller role compared with management and environmental factors.

Key words: dairy cattle, inbreeding depression, age of inbreeding, health traits

INTRODUCTION

A productive dairy cow must be able to become pregnant, give birth, and produce sufficient milk over a standard lactation period. The occurrence of disease can prevent the completion of these milestones, thereby affecting farm profitability and decreasing the health and welfare of the cow. Mastitis, the inflammation of the mammary gland due to infection, is by far the most impactful disease in dairy cattle, leading to significant economic losses due to decreased milk production in affected cows, as well as costs related to treatment, milk quality, and susceptibility to other diseases (Seegers et al., 2003; Halasa et al., 2007). Diseases of the reproductive tract (such as retention of the placenta and metritis) and metabolic diseases (such as ketosis, milk fever, and displaced abomasum) can also have a highly detrimental effect on the farm, causing decreased production, delays in reproductive benchmarks, and increasing the risk of other diseases (Raboisson et al., 2014; Gilbert, 2016).

These diseases also increase the likelihood that the animal will die or be removed from the farm through culling. Reproductive disorders and mastitis are the primary nondeath reasons for culling dairy cattle in the US (Pinedo and De Vries, 2010; De Vries and Marcondes, 2020). According to data for 2022 from the Council on Dairy Cattle Breeding (CDCB), the percentage of cows culled due to reproductive problems or mastitis was 21.14% when considering all termination codes and 28.45% when considering all termination codes excluding unspecified culling reasons (CDCB, 2022). Therefore, it is crucial to understand the factors that affect their incidence to improve the health and profitability of the herd.

Recent advances in reproductive technologies and genomic prediction have led to an apparent increase in the rate of inbreeding accumulation among dairy cattle populations (Doekes et al., 2018; Mekanjuola et al., 2020a; Lozada-Soto et al., 2022). For instance, in

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*Corresponding author: emmanuel.lozadasoto@usda.gov

our previous study, it was found that the annual rate of inbreeding determined by genomic runs of homozygosity for US Holstein (**HO**) dams grew from 0.21% for animals born between 2000 and 2009 to 0.66% per year for those born between 2015 and 2018 (Lozada-Soto et al., 2022). Similarly, Makanjuola et al. (2020a) found that the annual rate of inbreeding based on several inbreeding metrics for North American HO cattle exceeded 0.5% per year for animals born between 2010 and 2018. This increase in the rate of inbreeding not only jeopardizes the genetic diversity of cattle populations but can also increase the frequency of deleterious mutations affecting production and animal wellbeing.

Inbreeding can affect the performance of individuals in terms of fitness and production traits, leading to what is known as inbreeding depression. A recent meta-analysis of inbreeding-depression estimates for fitness and production traits in several livestock species found a median reduction in phenotype value of 0.13% of a trait's mean per a 1% increase in pedigree inbreeding (Doekes et al., 2021). Evidence of inbreeding depression in dairy cattle has been observed for traits such as milk yield and composition (Bjelland et al., 2013; Doekes et al., 2019; Makanjuola et al., 2020b), fertility (Pryce et al., 2014; Ferencaković et al., 2017), and conformation traits (Bjelland et al., 2013), among others. However, the challenges associated with collecting phenotypes for health traits have resulted in very few published estimates of the effect of inbreeding on the incidence of various dairy cattle diseases (Sørensen et al., 2006; Schneider et al., 2023). Sørensen et al. (2006) found evidence of inbreeding depression for clinical mastitis in different lactations associated with increased pedigree inbreeding. In a more recent study, Schneider et al. (2023) looked at the effect of genomic homozygosity levels on production traits and health traits related to the udder, hoofs, and the female reproductive tract but did not find significant estimates of inbreeding depression.

However, the effects of inbreeding on fitness can vary and are not always detrimental. The generational "age" of inbreeding plays a significant role in moderating its effect. Older inbreeding has more time and, therefore, a greater opportunity for purifying selection to eliminate harmful alleles from the population (Charlesworth and Willis, 2009). Several studies have suggested the presence of purifying selection for deleterious mutations affecting multiple traits in dairy cattle (Gulisija and Crow, 2007; McParland et al., 2009; Doekes et al., 2019; Makanjuola et al., 2020b). For instance, work done by Doekes et al. (2019) revealed that recent pedigree or genomic inbreeding reduced milk yield and components, increased calving and insemination intervals, and decreased conception rates. However, older inbreeding had

little to no effect on these traits. Interestingly, the same study provided mixed evidence regarding the purging of inbreeding depression for somatic cell score (Doekes et al., 2019), a milk-quality trait that indirectly reflects udder health and the incidence of mastitis.

Our study aims to build upon existing knowledge by investigating the relationship between pedigree and genomic estimates of inbreeding and the incidence of producer-recorded health events, specifically focusing on mastitis, ketosis, metritis, milk fever, displaced abomasum, and retained placenta. We conducted this analysis in the 2 largest US dairy breed populations: HO and Jersey (**JE**) cattle. Additionally, we aimed to investigate the effects of the generational age of inbreeding on producer-recorded diseases.

MATERIALS AND METHODS

Because no live animals were used in this study, Institutional Animal Care and Use Committee approval was not required.

Animals and Health Records

Phenotypic data for this study was obtained from the CDCB. Records for producer-recorded health data were obtained for 658,194 US HO and 107,069 US JE cows. Pedigree and genomic information were also available for each cow. Health data included records of the presence or absence of disease(s) within a given parity of a cow. Diseases studied included mastitis (**MAST**), metabolic diseases (**META**) such as ketosis (**KETO**), milk fever (**MFEV**), and displaced abomasum (**DA**), and reproductive diseases (**REPR**) such as metritis (**METR**) and retained placenta (**RETP**). Quality control of health data was done according to protocols outlined by Parker Gaddis et al. (2012). Disease data was excluded from health events not taking place within 365 d of calving in cows in parities 1 through 5 or for cows culled before the end of lactation. Data from herds that did not report a sick cow or exclusively reported sick cows was also excluded. Only records for herd-years with at least one reported health event and including more than 5 cows were used. Last, data from herd-years with a noticeably large reporting frequency, as defined by having a reporting frequency greater than 2 standard deviations above the mean for a particular disease, were excluded.

Genotypes comprising 76,389 previously imputed autosomal SNP were obtained for each animal. Details on variant selection and imputation can be found in the methodology described by VanRaden et al. (2017). To ensure genomic data quality, breed-specific genomic quality-control measures were performed using PLINK

1.9 (Chang et al., 2015). This involved removing animals with a call rate lower than 95% and SNP with a call rate below 95%, a minor allele frequency below 0.50%, or a Mendelian error rate exceeding 10%. A total of 71,858 and 65,955 markers passed genomic quality control for HO and JE cows, respectively. Pedigree information was also made available for each animal. Pedigree quality control was done as described in Lozada-Soto et al. (2022). After quality control, a total of 354,043 HO cows born between 2009 and 2020 and 68,292 JE cows born between 2010 and 2020 were retained for further analyses. The number of genotyped cows with producer-recorded health data can be found in Table 1.

Inbreeding Coefficients

The inbreeding coefficient of cows was calculated using several methods based on pedigree or genomic information. The total pedigree inbreeding coefficient (F_{PED}) was calculated using the tabular method proposed by VanRaden (1992) using PEDIG (v.5; Boichard, 2002). This method also enabled us to decompose F_{PED} by generation, allowing us to obtain inbreeding coefficients based on inbreeding up to 5 generations ago or more recently (F_{PED_REC}), as well as inbreeding from 6 generations ago or older (F_{PED_OLD}).

Genomic inbreeding coefficients were calculated using 3 different approaches: a marker-by-marker method (F_{GRM}), a segment-based method using runs of homozygosity (ROH ; F_{ROH}), and a segment-based method using homozygous-by-descent (HBD) segments derived from a hidden Markov model (F_{HBD}). The F_{GRM} coefficient for animal i was obtained as G_{ii}^{-1} , where G represents a genomic relationship matrix constructed using method 1 as described by VanRaden (2008). In the centering and scaling of the genotype matrix, allele frequencies were fixed at 0.5 (VanRaden et al., 2011). Runs of homozygosity were identified using a sliding-window approach in PLINK 1.9 (Chang et al., 2015). The specific parameters used to define an ROH are described in detail in Lozada-Soto et al. (2022). This included a window size of 20 SNP, a maximum of one heterozygote and 2 missing calls per window, a minimum physical length of an ROH of 2 Mb, a maximum gap of 500 kb between consecutive SNP, a minimum SNP density of 1 SNP per 100 kb, and a minimum number of 60 SNP to declare an ROH.

The F_{ROH} coefficient for each animal was calculated as the proportion of the autosomal genome covered by ROH. Additionally, inbreeding coefficients were generated based on the proportion of the genome covered by ROH of different lengths, where shorter segment lengths indicate older inbreeding and vice versa. These

Table 1. Number of genotyped cows with producer-recorded health data, proportion of cases and diseased cows, heritability, and repeatability for each disease trait¹

Trait	Acronym	Number of cows		Proportion of cases		Proportion of diseased cows ²		Heritability		Repeatability	
		HO	JE	HO	JE	HO	JE	HO	JE	HO	JE
Any disease	ANYD	354,043	68,292	0.16	0.12	0.25	0.20	0.04 (0.03, 0.05)	0.04 (0.02, 0.05)	0.07 (0.07, 0.08)	0.10 (0.08, 0.11)
Reproductive disease	REPR	305,424	41,331	0.07	0.04	0.12	0.06	0.05 (0.04, 0.06)	0.03 (0.01, 0.04)	0.08 (0.06, 0.08)	0.07 (0.04, 0.10)
Metabolic disease	META	299,014	56,816	0.05	0.03	0.08	0.05	0.06 (0.05, 0.07)	0.05 (0.03, 0.07)	0.07 (0.06, 0.08)	0.09 (0.06, 0.13)
Mastitis	MAST	249,516	52,848	0.12	0.11	0.18	0.18	0.08 (0.07, 0.09)	0.05 (0.03, 0.07)	0.16 (0.15, 0.17)	0.15 (0.13, 0.16)
Metritis	METR	213,256	29,631	0.08	0.04	0.12	0.07	0.05 (0.04, 0.06)	0.03 (0.01, 0.06)	0.07 (0.06, 0.08)	0.08 (0.05, 0.12)
Retained placenta	RETP	287,503	32,352	0.03	0.01	0.06	0.02	0.06 (0.05, 0.07)	0.03 (0.01, 0.05)	0.11 (0.10, 0.12)	0.09 (0.05, 0.15)
Ketosis	KETO	174,102	26,376	0.07	0.04	0.12	0.07	0.06 (0.05, 0.07)	0.04 (0.01, 0.07)	0.07 (0.06, 0.08)	0.11 (0.07, 0.15)
Milk fever	MFEV	228,692	51,336	0.01	0.01	0.01	0.01	0.10 (0.06, 0.14)	0.08 (0.04, 0.13)	0.19 (0.15, 0.24)	0.18 (0.10, 0.25)
Displaced abomasum	DA	221,213	16,631	0.01	0.01	0.02	0.01	0.17 (0.15, 0.19)	0.18 (0.07, 0.26)	0.17 (0.15, 0.19)	0.18 (0.07, 0.26)

¹HO = Holstein; JE = Jersey. The values in parentheses are the lower and upper bound of the 95% highest posterior density interval.

²Proportion of cows with at least one recorded health event across multiple lactations.

coefficients were derived from ROH segments measuring 2 to 4 Mb ($\mathbf{F}_{\text{ROH}_2-4}$), 4 to 8 Mb ($\mathbf{F}_{\text{ROH}_4-8}$), 8 to 16 Mb ($\mathbf{F}_{\text{ROH}_8-16}$), and 16 Mb or larger ($\mathbf{F}_{\text{ROH}_{16+}}$) in length.

The remaining inbreeding coefficients were obtained by using a model-based approach with the RZooROH package (v.0.3.1) to detect HBD segments (Bertrand et al., 2019). The methodology for detecting HBD segments using the hidden Markov model is detailed in Druet and Gautier (2017). Briefly, this approach models the probability of a marker belonging to a larger HBD segment, with the length of the HBD segment following an exponential distribution. The probability of continuing or stopping the segment between 2 markers is determined by e^{-Rd} , where R represents the rate of the exponential distribution and d is the distance in morgans separating the markers. Similar to the coefficients derived from ROH, the size of the HBD segment is correlated with the number of generations in the past when the inbreeding occurred. We modeled multiple HBD classes, where the rates used followed a power of 2 series (2^n ; $n = 1-7$), allowing us to obtain inbreeding coefficients from HBD segments acquired approximately 2, 4, 8, 16, 32, 64, and 128 generations in the past. The inbreeding coefficients from 2 to 8 and 16 to 128 generations in the past were grouped together to represent coefficients of recent ($\mathbf{F}_{\text{HBD_REC}}$) and old ($\mathbf{F}_{\text{HBD_OLD}}$) inbreeding, respectively.

Statistical Analysis

The effect of pedigree and genomic inbreeding on the incidence of various producer-recorded health traits was evaluated using a threshold-linear mixed model. This model incorporates all relevant effects currently used in US genetic evaluations for producer-recorded health traits calculated at the CDCB. The model is defined as follows:

$$\mathbf{y} = \mathbf{Xb} + \beta\mathbf{F} + \mathbf{Z}_h\mathbf{h} + \mathbf{Z}_s\mathbf{s} + \mathbf{Z}_a\mathbf{a} + \mathbf{Z}_p\mathbf{p} + \mathbf{e},$$

where \mathbf{y} is a vector of unobserved liabilities for a given health trait; \mathbf{b} is a vector of fixed effects that included the concatenation of season within a given year (year-season effect) and the concatenation of age and parity of cows (age-parity effect); \mathbf{F} is a vector of the inbreeding coefficients (\mathbf{F}_{PED} , \mathbf{F}_{GRM} , or \mathbf{F}_{ROH}); \mathbf{h} is the random effect of herd within year (herd-year effect), following $h \sim N(0, \mathbf{I}\sigma_{hy}^2)$, where \mathbf{I} is an identity matrix and σ_{hy}^2 is the herd-year variance; \mathbf{s} is the random effect of sire within herd (herd-sire effect) following $s \sim N(0, \mathbf{I}\sigma_{hs}^2)$, where σ_{hs}^2 is the herd-sire variance; \mathbf{a} is the random animal effect, following $a \sim N(0, \mathbf{A}\sigma_a^2)$, where \mathbf{A} is the numerator rela-

tionship matrix and σ_a^2 is the additive genetic variance; \mathbf{p} is the random permanent environmental effect, following $p \sim N(0, \mathbf{I}\sigma_{pe}^2)$, where σ_{pe}^2 is the permanent environmental variance; \mathbf{X} is the incidence matrix for the fixed effects; \mathbf{Z}_h , \mathbf{Z}_s , \mathbf{Z}_a , and \mathbf{Z}_p are the incidence matrices for the respective random effects; β is the linear regression coefficient for the inbreeding coefficient; and \mathbf{e} is the random residual, following $e \sim N(0, \mathbf{I}\sigma_e^2)$, where σ_e^2 is the residual variance. The number of records included in each breed and trait model and the corresponding number of levels for the year-season, age-parity, herd-year, and herd-sire effects can be found in Supplemental File S1 (<https://doi.org/10.6084/m9.figshare.23589078.v2>; Lozada-Soto et al., 2023). To examine the effect of recent and old inbreeding, we extended the previous model to simultaneously fit the inbreeding coefficients of a specific class.

Variance components were previously estimated using the same model and fixed at their respective values. Heritability and repeatability estimates for each trait were then derived from these variance components estimates. The models were run using the THRGIBBS1F90 program (v.2.116; Tsuruta and Misztal, 2006) for 200,000 iterations, with a burn-in period of 50,000 and a thinning parameter of 25.

We used the model estimates to compute least-squares estimates of disease liability at each model iteration for animals with low, average, and high levels of inbreeding. The inbreeding coefficients corresponding to the least and most highly inbred individuals were considered as the thresholds for low and high inbreeding, respectively. This analysis was conducted separately for each breed, inbreeding coefficient, and health trait combination. Posterior means and 95% highest posterior density intervals were obtained and subsequently transformed to the probability scale using a previously published method (Zwald et al., 2006). The function used to obtain probabilities was

$$P_{ijkl} = \phi(x_{ijkl}),$$

where P_{ijkl} is the probability of disease i ($i = \text{ANYD}$, REPR , META , MAST , METR , RETP , KETO , MFEV , or DA) in breed j ($j = \text{HO}$ or JE) for cows with the l th ($l = \text{low}$, average , or high) level of inbreeding coefficient k ($k = \mathbf{F}_{\text{PED}}$, $\mathbf{F}_{\text{PED_REC}}$, $\mathbf{F}_{\text{PED_OLD}}$, \mathbf{F}_{GRM} , \mathbf{F}_{ROH} , $\mathbf{F}_{\text{ROH}_{16\text{Mb}}}$, $\mathbf{F}_{\text{ROH}_{8-16\text{Mb}}}$, $\mathbf{F}_{\text{ROH}_{4-8\text{Mb}}}$, $\mathbf{F}_{\text{ROH}_{2-4\text{Mb}}}$, $\mathbf{F}_{\text{HBD_REC}}$, or $\mathbf{F}_{\text{HBD_OLD}}$); ϕ is the standard normal cumulative density function; and x_{ijkl} is the posterior mean, lower bound of the 95% highest posterior density interval, or the upper bound of the 95% highest posterior density interval for disease liability for disease i , breed j , inbreeding coefficient k , and inbreeding level l .

RESULTS

Characteristics of Health Data and Genetic Parameters

Table 1 provides information on the proportion of cases, proportion of diseased cows, heritability, and repeatability for each producer-recorded health trait. The proportion of diseased cows was determined by considering the proportion of cows that had at least one recorded disease event across multiple lactations for a specific disease. Approximately 25% of HO cows and 20% of JE cows had at least one recorded disease event when considering all diseases together (ANYD). Mastitis exhibited the highest proportion of cases (HO = 0.12; JE = 0.11) and proportion of diseased cows (HO = 0.18; JE = 0.18) among both breeds. In contrast, MFEV and DA had the lowest incidence in the dataset, with the proportion of cases and diseased cows ranging from 0.01 to 0.02 in both breeds. Estimates of the heritability and repeatability for each trait were low. Trait heritability ranged from 0.03 for all reproductive-disease traits in JE to 0.18 for DA in JE, and repeatabilities ranged from 0.07 for ANYD, META, METR, and KETO in HO, and REPR in JE, to 0.19 for MFEV in HO.

Measures of Inbreeding

The within-breed means for all estimates of the inbreeding coefficients can be found in Table 2, and the distribution of inbreeding and the Pearson correlations between inbreeding coefficient estimates are presented in Supplemental Files S2 and S3 (<https://doi.org/10.6084/m9.figshare.23589078.v2>; Lozada-Soto et al., 2023). Inbreeding using total pedigree and genomic inbreeding measures ranged from 7.18% (F_{PED}) to 25.23% (F_{GRM}) in HO cows and from 8.04% (F_{PED}) to 31.92% (F_{GRM}) in JE cows. These observed levels of inbreeding in phenotyped cows align with the average inbreeding of animals within the larger US population in both breeds (Lozada-Soto et al., 2022). The average pedigree inbreeding coefficient from the last 5 generations ($F_{\text{PED_REC}}$) was on average smaller than the older inbreeding in both breeds, with values of 2.28% and 5.34% in HO and 2.48% and 5.57% in JE, respectively. Similarly, the average $F_{\text{HBD_REC}}$, which accounted for inbreeding accumulated in the last 8 generations, was smaller than the coefficient for older inbreeding ($F_{\text{HBD_OLD}}$) in both breeds, with values of 2.15% and 14.19% in HO and 2.05% and 19.88% in JE, respectively. The average values of the ROH inbreeding coefficients were similar across segment-length categories, with values ranging from 1.96% for $F_{\text{ROH_2-4}}$ to 4.00%

Table 2. Within-breed means (\pm SD) of pedigree and genomic inbreeding coefficients (%) for cows with producer-recorded health data

Inbreeding coefficient ¹	HO	JE
F_{PED}	7.39 \pm 2.19	8.00 \pm 2.02
$F_{\text{PED_REC}}$	2.18 \pm 1.91	2.46 \pm 2.04
$F_{\text{PED_OLD}}$	5.20 \pm 0.86	5.53 \pm 0.94
F_{GRM}	24.93 \pm 2.84	29.97 \pm 2.76
F_{ROH}	12.77 \pm 3.32	17.92 \pm 3.16
$F_{\text{ROH_16+}}$	3.54 \pm 2.35	4.40 \pm 2.51
$F_{\text{ROH_8-16}}$	3.90 \pm 1.46	5.15 \pm 1.55
$F_{\text{ROH_4-8}}$	3.41 \pm 0.96	5.35 \pm 1.10
$F_{\text{ROH_2-4}}$	1.92 \pm 0.50	3.02 \pm 0.62
$F_{\text{HBD_REC}}$	2.15 \pm 3.21	2.02 \pm 3.30
$F_{\text{HBD_OLD}}$	13.88 \pm 3.10	19.71 \pm 3.19

¹ F_{PED} = total pedigree inbreeding; $F_{\text{PED_REC}}$ = pedigree inbreeding from the last 5 generations; $F_{\text{PED_OLD}}$ = pedigree inbreeding from 6 or more generations; F_{GRM} = genomic inbreeding from genomic relationship matrix; F_{ROH} = genomic inbreeding from runs of homozygosity (ROH) of 2 Mb or larger in length; $F_{\text{ROH_16+}}$ = genomic inbreeding from ROH of 16 Mb or larger in length; $F_{\text{ROH_8-16}}$ = genomic inbreeding from ROH 8 to 16 Mb in length; $F_{\text{ROH_4-8}}$ = genomic inbreeding from ROH 4 to 8 Mb in length; $F_{\text{ROH_2-4}}$ = genomic inbreeding from ROH 2 to 4 Mb in length; $F_{\text{HBD_REC}}$ = genomic inbreeding from model-based homozygous-by-descent (HBD) segments from approximately 2 to 8 generations in the past; $F_{\text{HBD_ANC}}$ = genomic inbreeding from model-based HBD segments from approximately 16 to 128 generations in the past; HO = Holstein; JE = Jersey.

for $F_{\text{ROH_8-16}}$ in HO and from 3.23% for $F_{\text{ROH_2-4}}$ to 5.31% for $F_{\text{ROH_4-8}}$ in JE.

Trends in the correlation between the different inbreeding coefficients were consistent in both breeds. The Pearson correlation estimates between F_{PED} and F_{GRM} or F_{ROH} were high (>50%) and between F_{GRM} and F_{ROH} were exceptionally high (>0.95) in both breeds. In general, the pedigree and genomic measures that represent more recent inbreeding showed moderate to strong correlations among themselves. In the best-case scenario, the Pearson correlation between $F_{\text{ROH_16+}}$ and $F_{\text{HBD_REC}}$ was 0.76 in HO and 0.70 in JE, indicating a reasonably strong correlation. However, the correlation among inbreeding coefficients representing older inbreeding was weaker. The Pearson correlation between $F_{\text{PED_REC}}$ and the ROH inbreeding coefficients (excluding $F_{\text{ROH_16+}}$) ranged from 0.27 to 0.32 in HO and from 0.15 to 0.18 in JE. Similarly, the correlation between $F_{\text{PED_REC}}$ and $F_{\text{HBD_REC}}$ was 0.43 in HO and 0.24 in JE.

Inbreeding Depression Using Pedigree and Genomic Approaches

Table 3 provides the regression coefficient estimates for the effect of a 10-percentage point (10%) increase in F_{PED} , F_{GRM} , and F_{ROH} on the presence or absence of each health trait in the liability scale. In the context of a threshold-linear model, a positive (negative) regression coefficient indicates an increase (decrease)

Table 3. Estimates of the regression coefficient of a 10% increase in F_{PED} , F_{GRM} , and F_{ROH} for health traits in Holstein and Jersey cows^{1,2}

Trait	Breed	F_{PED}		F_{GRM}		F_{ROH}	
		Estimate	95% HPDI	Estimate	95% HPDI	Estimate	95% HPDI
ANYD	HO	0.03	(−0.00, 0.06)	0.04	(0.02, 0.06)	0.03	(0.01, 0.05)
	JE	0.05	(−0.01, 0.10)	0.07	(0.03, 0.11)	0.05	(0.01, 0.08)
REPR	HO	0.05	(0.01, 0.09)	0.08	(0.06, 0.11)	0.06	(0.04, 0.09)
	JE	0.18	(0.08, 0.16)	0.18	(0.09, 0.26)	0.12	(0.06, 0.18)
META	HO	−0.01	(−0.06, 0.04)	−0.03	(−0.07, −0.01)	−0.03	(−0.05, 0.00)
	JE	−0.06	(−0.18, 0.06)	0.02	(−0.07, 0.11)	0.00	(−0.07, 0.09)
MAST	HO	0.01	(−0.03, 0.06)	0.02	(−0.02, 0.04)	0.01	(−0.01, 0.04)
	JE	0.03	(−0.04, 0.10)	0.04	(−0.01, 0.09)	0.03	(−0.01, 0.07)
METR	HO	0.07	(0.03, 0.12)	0.08	(0.06, 0.11)	0.07	(0.04, 0.09)
	JE	0.18	(0.08, 0.29)	0.19	(0.11, 0.27)	0.14	(0.08, 0.22)
RETP	HO	0.00	(−0.05, 0.05)	0.05	(0.02, 0.08)	0.04	(0.01, 0.07)
	JE	0.15	(−0.00, 0.29)	0.05	(−0.05, 0.18)	0.03	(−0.07, 0.13)
KETO	HO	−0.03	(−0.08, 0.06)	−0.03	(−0.06, 0.00)	−0.02	(−0.05, 0.01)
	JE	−0.09	(−0.24, 0.04)	−0.04	(−0.13, 0.06)	−0.04	(−0.13, 0.05)
MFEV	HO	0.02	(−0.13, 0.16)	0.03	(−0.07, 0.12)	0.01	(−0.07, 0.09)
	JE	−0.04	(−0.27, 0.21)	0.10	(−0.08, 0.26)	0.05	(−0.09, 0.20)
DA	HO	−0.11	(−0.20, −0.02)	−0.16	(−0.22, −0.10)	−0.12	(−0.17, −0.07)
	JE	0.05	(−0.19, 0.31)	0.06	(−0.12, 0.24)	−0.00	(−0.19, 0.16)

¹Estimates are presented in the liability scale.

²HPDI = highest posterior density interval; ANYD = any disease; REPR = any reproductive disease; META = any metabolic disease; MAST = mastitis; METR = metritis; RETP = retained placenta; KETO = ketosis; MFEV = milk fever (hypocalcemia); DA = displaced abomasum; HO = Holstein; JE = Jersey; F_{PED} = total pedigree inbreeding; F_{GRM} = genomic inbreeding from genomic relationship matrix; F_{ROH} = genomic inbreeding from runs of homozygosity (ROH) of 2 Mb or larger in length.

in the underlying probability of disease, assuming all other variables are held constant. The magnitude of the change in probability associated with an increase in inbreeding relies on the average probability of disease in the population and the specific values of all other variables in the model. Consequently, interpretation becomes more complex, and we will focus on the direction (positive, negative) and significance (if the estimate is different from 0) of estimates.

For ANYD, an increase in F_{GRM} and F_{ROH} was associated with a higher probability of disease in both breeds, but F_{PED} had no effect. In terms of REPR, higher inbreeding was linked to an increased likelihood of disease in both breeds. However, when considering specific reproductive disorders, we found that both pedigree and genomic inbreeding increased the probability of METR in both breeds, but only F_{GRM} and F_{ROH} affected RETP in HO. No significant effects of F_{PED} , F_{GRM} , or F_{ROH} were observed for MAST, KETO, or MFEV in either breed. However, in HO, we found that an increase in pedigree or genomic inbreeding decreased the probability of DA, and an increase in F_{GRM} decreased the probability of META.

With the use of model outputs, the least-squares estimates of the probability of disease were determined for animals at different inbreeding levels (minimum, average, and maximum) based on F_{PED} , F_{GRM} , and F_{ROH} in each breed and for each disease. These estimates are presented in Figures 1 and 2 for HO and JE, respectively. At a 95th percent confidence level, no significant

differences were observed in the probability of disease between animals, irrespective of their inbreeding level. Consistent with the liability-scale results, there was a clear yet nonsignificant trend of increasing probability from low to high inbreeding levels for ANYD, REPR, and METR in both breeds, as well as for RETP for genomic inbreeding coefficients in HO. For example, transitioning from the lowest to the highest inbreeding levels in JE resulted in an increased probability of METR from 0.53% (0.18%, 1.35%) to 2.96% (0.88%, 7.76%) for F_{PED} , from 0.46% (0.15%, 1.18%) to 2.36% (0.86%, 5.95%) for F_{GRM} , and from 0.49% (0.17%, 1.26%) to 2.06% (0.74%, 5.24%) for F_{ROH} . Conversely, increasing inbreeding levels in HO from the lowest to the highest observed values decreased the probability of DA from 0.40% (0.15%, 1.03%) to 0.06% (0.02%, 0.21%) for F_{GRM} and from 0.38% (0.14%, 0.98%) to 0.08% (0.02%, 0.28%) for F_{ROH} .

Effect of Recent and Old Inbreeding on Health

Figures 3 and 4 display the regression coefficient estimates in the liability scale, indicating the effect of a 10% increase in recent and older pedigree (F_{PED_REC} and F_{PED_OLD}) and genomic (F_{ROH_16+} , F_{ROH_8-16} , F_{ROH_4-8} , F_{ROH_2-4} , F_{HBD_REC} , F_{HBD_OLD}) inbreeding on the presence or absence of disease.

An increase in recent pedigree inbreeding (F_{PED_REC}) was associated with an increased probability of disease for ANYD in HO and for REPR and METR in both



Figure 1. Estimated probability of disease occurrence in Holstein cows based on their pedigree (F_{PED} ; total pedigree inbreeding) or genomic (F_{GRM} ; genomic inbreeding from genomic relationship matrix; F_{ROH} ; genomic inbreeding from runs of homozygosity of 2 Mb or larger in length) inbreeding levels. These are provided for 3 different inbreeding levels, low (the level of inbreeding of the least inbred cow with a health record), average (average inbreeding for cows with records), and high (the level of inbreeding of the most inbred cow with a health record) for each health trait. The text above an estimate shows the inbreeding level evaluated. The dots are the posterior means, and error bars represent the 95% highest posterior density intervals. ANYD = any disease; REPR = any reproductive disease; META = any metabolic disease; MAST = mastitis; METR = metritis; RETP = retained placenta; KETO = ketosis; MFEV = milk fever (hypocalcemia); DA = displaced abomasum.

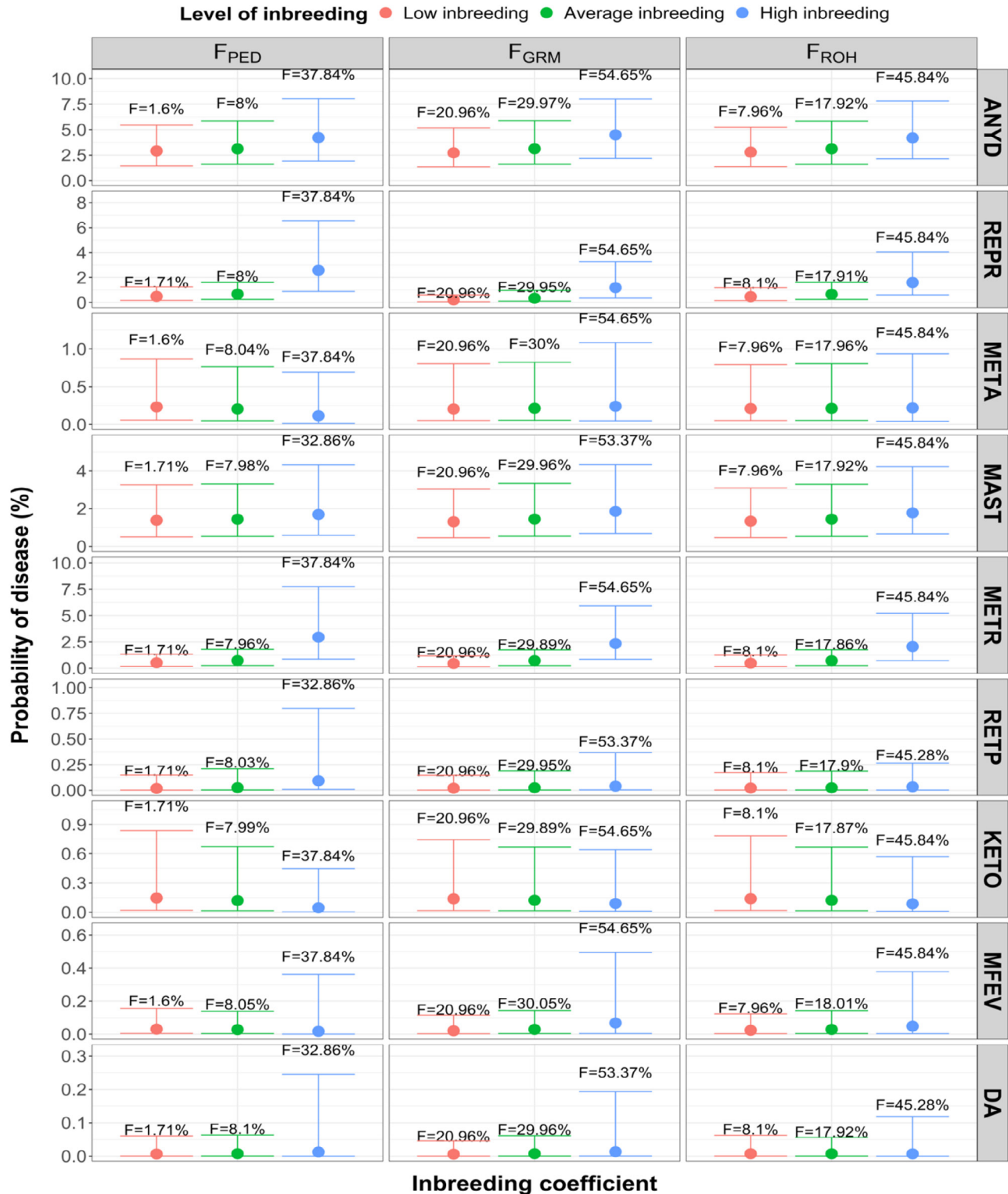


Figure 2. Estimated probability of disease occurrence in Jersey cows based on their pedigree (F_{PED} ; total pedigree inbreeding) or genomic (F_{GRM} ; genomic inbreeding from genomic relationship matrix; F_{ROH} , genomic inbreeding from runs of homozygosity of 2 Mb or larger in length) inbreeding levels. These are provided for 3 different inbreeding levels, low (the level of inbreeding of the least inbred cow with a health record), average (average inbreeding for cows with records), and high (the level of inbreeding of the most inbred cow with a health record) for each health trait. The text above an estimate shows the inbreeding level evaluated. The dots are the posterior means, and error bars represent the 95% highest posterior density intervals. ANYD = any disease; REPR = any reproductive disease; META = any metabolic disease; MAST = mastitis; METR = metritis; RETP = retained placenta; KETO = ketosis; MFEV = milk fever (hypocalcemia); DA = displaced abomasum.

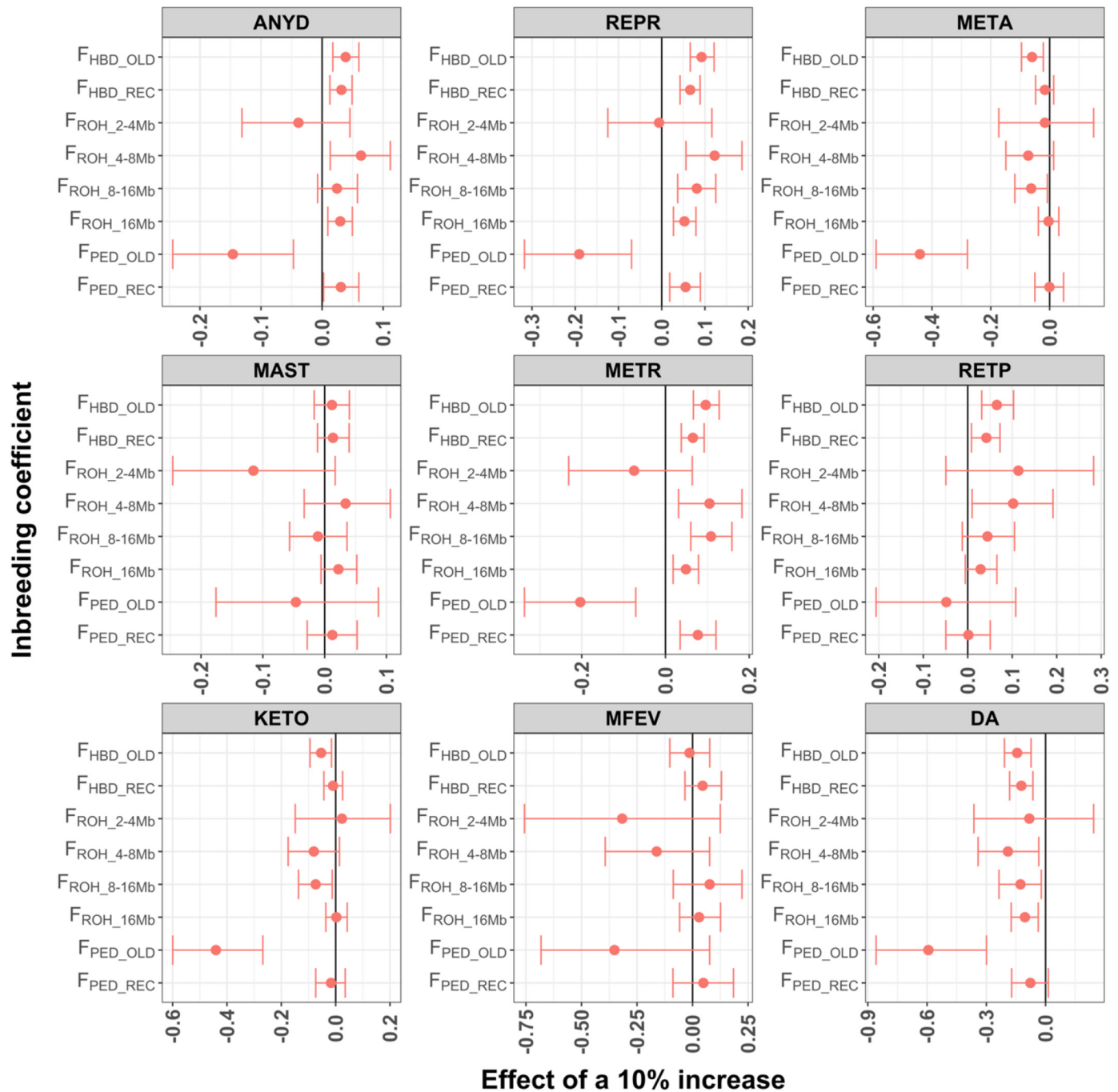


Figure 3. Estimates in the liability scale of the effect of a 10% increase in age-based pedigree (F_{PED_REC} , F_{PED_OLD}) and genomic (F_{ROH_16+} , F_{ROH_8-16} , F_{ROH_4-8} , F_{ROH_2-4} , F_{HBD_REC} , F_{HBD_OLD}) inbreeding on health traits in Holstein cows. F_{PED} = total pedigree inbreeding; F_{PED_REC} = pedigree inbreeding from the last 5 generations; F_{PED_OLD} = pedigree inbreeding from 6 or more generations; F_{ROH_16+} = genomic inbreeding from runs of homozygosity (ROH) of 16 Mb or larger in length; F_{ROH_8-16} = genomic inbreeding from ROH 8 to 16 Mb in length; F_{ROH_4-8} = genomic inbreeding from ROH 4 to 8 Mb in length; F_{ROH_2-4} = genomic inbreeding from ROH 2 to 4 Mb in length; F_{HBD_REC} = genomic inbreeding from model-based homozygous-by-descent (HBD) segments from approximately 2 to 8 generations in the past; and F_{HBD_OLD} = genomic inbreeding from HBD segments from approximately 16 to 128 generations in the past. The point is the posterior mean of the estimate of the effect of a 10% increase in inbreeding. The error bars are the 95% highest posterior density intervals. ANYD = any disease; REPR = any reproductive disease; META = any metabolic disease; MAST = mastitis; METR = metritis; RETP = retained placenta; KETO = ketosis; MFEV = milk fever (hypocalcemia); DA = displaced abomasum.

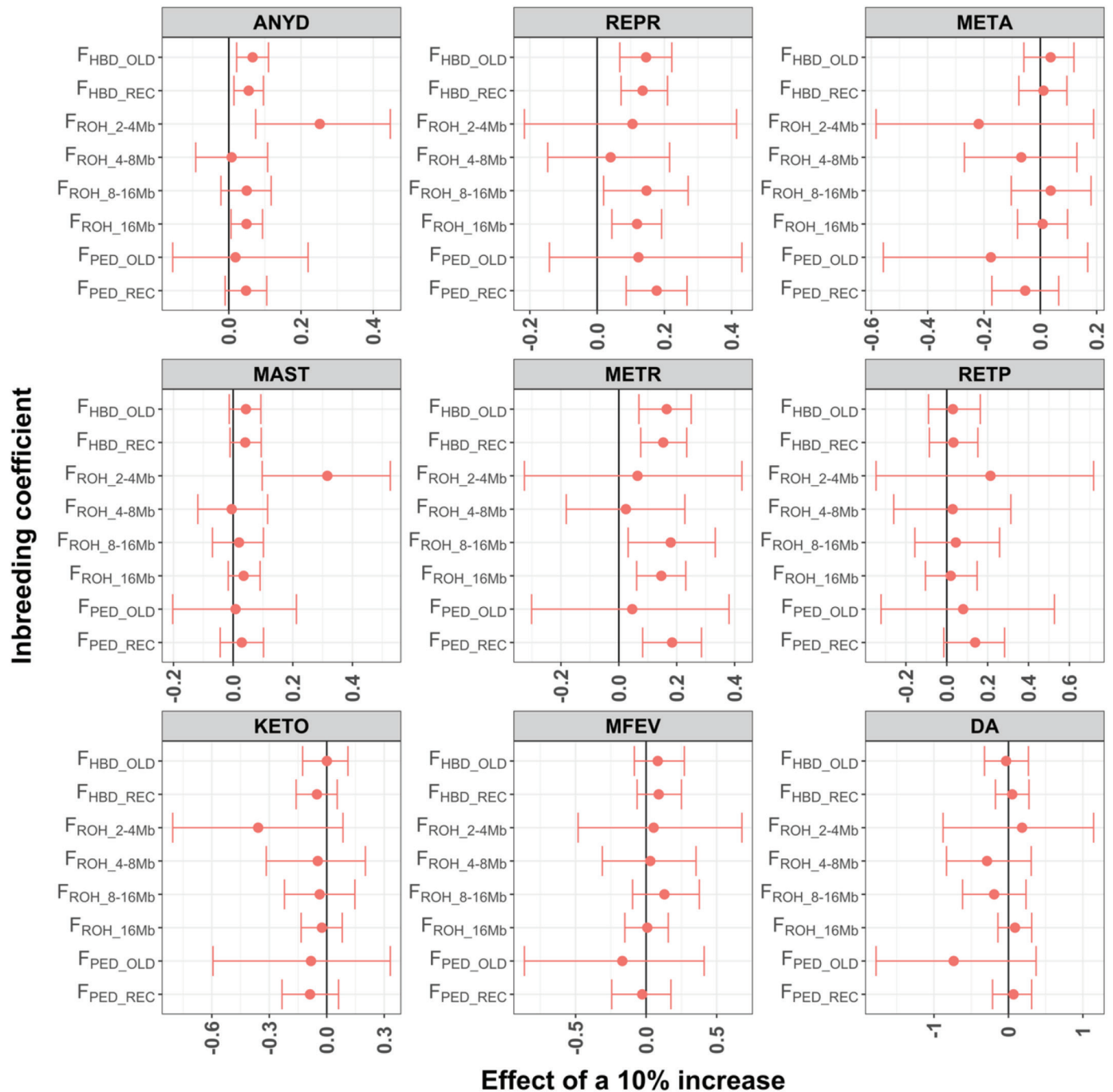


Figure 4. Estimates in the liability scale of the effect of a 10% increase in age-based pedigree (F_{PED_REC} , F_{PED_OLD}) and genomic ($F_{ROH_{16+}}$, $F_{ROH_{8-16}}$, $F_{ROH_{4-8}}$, $F_{ROH_{2-4}}$, F_{HBD_REC} , F_{HBD_OLD}) inbreeding on health traits in Jersey cows. F_{PED} = total pedigree inbreeding; F_{PED_REC} = pedigree inbreeding from the last 5 generations; F_{PED_OLD} = pedigree inbreeding from 6 or more generations; $F_{ROH_{16+}}$ = genomic inbreeding from runs of homozygosity (ROH) of 16 Mb or larger in length; $F_{ROH_{8-16}}$ = genomic inbreeding from ROH 8 to 16 Mb in length; $F_{ROH_{4-8}}$ = genomic inbreeding from ROH 4 to 8 Mb in length; $F_{ROH_{2-4}}$ = genomic inbreeding from ROH 2 to 4 Mb in length; F_{HBD_REC} = genomic inbreeding from model-based homozygous-by-descent (HBD) segments from approximately 2 to 8 generations in the past; and F_{HBD_OLD} = genomic inbreeding from HBD segments from approximately 16 to 128 generations in the past. The point is the posterior mean of the estimate of the effect of a 10% increase in inbreeding. The error bars are the 95% highest posterior density intervals. ANYD = any disease; REPR = any reproductive disease; META = any metabolic disease; MAST = mastitis; METR = metritis; RETP = retained placenta; KETO = ketosis; MFEV = milk fever (hypocalcemia); DA = displaced abomasum.

breeds. In contrast, $F_{\text{PED_OLD}}$ decreased ANYD, REPR, and METR in HO cows and had no effect on these traits in JE cows. In HO, an increase in older pedigree inbreeding ($F_{\text{PED_OLD}}$) decreased the probability of having general META or KETO and DA metabolic diseases. However, there was not any significant evidence that the level of recent pedigree inbreeding ($F_{\text{PED_REC}}$) influenced the probability of developing any metabolic diseases in either breed.

The estimates for the inbreeding coefficients obtained using the model-based HBD segments, $F_{\text{HBD_REC}}$ and $F_{\text{HBD_OLD}}$, showed minimal distinction between themselves. Generally, the coefficients for recent and old inbreeding had similar effects on the probability of disease. An increase in $F_{\text{HBD_REC}}$ and $F_{\text{HBD_OLD}}$ increased the probability of an animal being diseased for ANYD, REPR, METR, and RETP in HO, as well as ANYD, REPR, and METR in JE. Regarding metabolic diseases, $F_{\text{HBD_OLD}}$ was observed to decrease the probability of HO having META, KETO, or DA. Interestingly, for DA, $F_{\text{HBD_REC}}$ also reduced the probability of disease in HO. The estimates of the effects of $F_{\text{HBD_REC}}$ and $F_{\text{HBD_OLD}}$ on metabolic diseases did not significantly differ from zero in JE.

The results for the effect of inbreeding coefficients based on ROH length categories yielded mixed findings. For REPR and METR in both breeds, recent inbreeding ($F_{\text{ROH_16+}}$ or $F_{\text{ROH_8-16}}$) was associated with a higher probability of disease, but older inbreeding ($F_{\text{ROH_2-4}}$) showed no effect. Among the segment-length-based F_{ROH} coefficients, only $F_{\text{ROH_4-8}}$ in HO had an effect on the probability of having RETP, with higher levels of $F_{\text{ROH_4-8}}$ being associated with disease. In the case of ANYD, an increase in $F_{\text{ROH_16+}}$ was associated with disease in both breeds, and the same applied to $F_{\text{ROH_4-8}}$ in HO and $F_{\text{ROH_2-4}}$ in JE.

We found no evidence of any segment-length-based F_{ROH} coefficient affecting META in either breed. However, an effect was observed for specific metabolic disorders in HO. A higher level of $F_{\text{ROH_8-16}}$ was associated with a significant decrease in the probability of HO cows having KETO, and increased levels of $F_{\text{ROH_16+}}$, $F_{\text{ROH_8-16}}$ and $F_{\text{ROH_4-8}}$ decreased the probability of having DA in HO. Our results for MAST showed no clear trend in the effect of recent or old inbreeding on the incidence of this trait. No significant effect was found from ROH segment-length-based inbreeding for MAST in HO cows. In contrast, the results for JE showed a substantial and detrimental effect of increased levels of $F_{\text{ROH_2-4}}$ on the probability of MAST. However, the estimates for the effect of other coefficients representing older inbreeding, $F_{\text{PED_OLD}}$ and $F_{\text{HBD_OLD}}$, were not significant in this breed.

Similar to the results for the total inbreeding coefficients, the estimated probabilities of cows with low, average, and high inbreeding levels were not significantly different from each other for each combination of age-based inbreeding coefficient and trait. However, we did observe a clear trend of increased probability for high levels of recent inbreeding for reproductive-disease traits in both breeds. Complete results can be found in Supplemental Files S4 and S5 (<https://doi.org/10.6084/m9.figshare.23589078.v2>; Lozada-Soto et al., 2023).

DISCUSSION

The effects of inbreeding on traits important to livestock production are well known. In dairy cattle, inbreeding is known to affect traits related to milk production, reproductive performance, and conformation, among others (Bjelland et al., 2013; Pryce et al., 2014). However, there are limited published estimates on the effect of inbreeding on disease incidence in dairy cattle, with most studies focusing only on MAST and related milk-quality traits (Miglior et al., 1995; Sørensen et al., 2006). In this study, we investigated the effect of inbreeding depression on dairy-cattle health traits using a large dataset of producer-recorded health records in the US and used genomic tools to characterize inbreeding depression.

Effect of Total Pedigree and Genomic Inbreeding on Incidence of Producer-Recorded Health Traits

Results in the liability scale indicate clear evidence of inbreeding depression for ANYD. The ANYD trait was created to improve the statistical power of our analysis by combining disease records and provide a general sense of the effect of inbreeding on general disease occurrence. Our findings suggest that controlling the accumulation of inbreeding can reduce disease prevalence when all producer-recorded health traits are considered.

Furthermore, our study reveals that inbreeding depression significantly affects the reproductive health of dairy cattle. Specifically, both the pedigree and genomic inbreeding increased the probability of REPR, METR, and RETP in one or both breeds. Our observation that inbred HO cows are at a higher risk of developing RETP contrasts with recent findings in German Holsteins where observed homozygosity did not significantly affect the incidence of RETP (Schneider et al., 2023). The difference may be attributed to the larger sample size in our study, allowing for more precise estimates. Nevertheless, the observed inbreeding depression for

REPR, METR, and RETP is consistent with previous studies showing inbreeding depression for traits related to reproductive performance (Bjelland et al., 2013; Mäkanjuola et al., 2020b). For instance, Bjelland et al. (2013) reported an increase in days open of 1.72 and 1.06 d and a decrease in conception rate of 0.82% and 0.53%, for a 1% increase in F_{ROH} and F_{GRM} , respectively. Reproductive-tract diseases are known risk factors for reduced reproductive performance, as demonstrated by a study showing that cows with RETP had a 14% lower conception rate, and those with metritis had a 15% lower conception rate compared with disease-free cows (Gröhn and Rajala-Schultz, 2000). Therefore, the observed inbreeding depression for REPR, METR, and RETP may contribute to the overall negative effect of inbreeding on reproductive performance observed in other studies.

Liability estimates for the effect of inbreeding on MAST did not yield significant results in our study. However, all estimated effects were in the positive, indicating that inbreeding can increase the probability of MAST, which aligns with previous research. In German Holsteins, increased homozygosity showed a nonsignificant association with higher MAST incidence (Schneider et al., 2023), consistent with our findings using pedigree and genomic measures. A study by Sørensen et al. (2006) on Danish Holsteins reported that a linear increase in pedigree inbreeding was associated with an increased incidence of clinical MAST in the first 3 lactations. Nevertheless, comparing our results with the aforementioned studies (Sørensen et al., 2006; Schneider et al., 2023) is complicated due to differences in the statistical models used (threshold vs. linear) and potential variations in MAST definitions, diagnosis, and reporting protocols.

Our study indicated that inbreeding did not significantly increase the probability of having META. On the contrary, inbred HO cows showed a decreased probability of experiencing DA. This is, to our understanding, the first study to report estimates of inbreeding depression for META in any livestock species, making direct comparisons difficult. However, one possible explanation for this finding is the negative effect of inbreeding on milk production, as documented in previous studies (Bjelland et al., 2013; Pryce et al., 2014; Doekes et al., 2019). In US Holsteins, a 1% increase in genomic homozygosity or inbreeding decreased 205-d milk yield by up to 53 kg and decreased average daily milk by up to 0.28 kg (Bjelland et al., 2013). Previous research has shown that higher milk yield in the preceding lactation increases the risk of developing MFEV and KETO, but its effect on DA is less clear (Erb and Gröhn, 1988; Gröhn et al., 1989; Hamann et al., 2004). Hence, we speculate that the observed inbreeding depression for

production traits may indirectly contribute to the apparent “beneficial” effects of inbreeding observed for META.

Effect of Recent and Old Inbreeding on Incidence of Producer-Recorded Health Traits

This study also aimed to explore the relationship between the generational age of inbreeding and inbreeding depression for health traits. It is generally believed that older inbreeding is expected to be less harmful due to purifying selection against recessive deleterious mutations (Charlesworth and Willis, 2009). Previous studies have investigated the purging of inbreeding depression for production and reproduction traits in cattle populations (Ferenčaković et al., 2017; Doekes et al., 2019; Mäkanjuola et al., 2020b). In our study, we found that age-based pedigree (F_{PED}) and genomic (F_{ROH}) inbreeding coefficients provided the clearest distinction between the effects of recent and older inbreeding. Although there are no previous estimates for the effect of inbreeding age on inbreeding depression for reproductive diseases, several studies have investigated this relationship for reproductive performance. For instance, recent pedigree and genomic inbreeding were found to affect calving intervals and conception rates in Dutch Holstein-Friesian cattle (Doekes et al., 2019). Similarly, in Canadian Holsteins, a 1% increase in recent pedigree or genomic inbreeding was associated with delayed age at first service, increased number of services, and prolonging the time from first service to conception in heifers, as well as increased number of services and nonreturn rate in cows (Mäkanjuola et al., 2020b).

In JE cows, we found an association between increased F_{ROH1-2} and inbreeding depression for MAST and ANYD. This effect may be attributed to the high incidence of MAST in the dataset when compared with other disease traits. Although it is generally expected that shorter ROH are less detrimental, previous findings have demonstrated the significant inbreeding depression caused by shorter ROH segments. In Dutch Holsteins, milk yield was found to be most affected by inbreeding originating from short ROH segments, whereas protein yield was generally equally affected by ROH of all length classes (Doekes et al., 2019).

The effects of recent and old inbreeding on metabolic disease traits in JE cows were not found to be significant, which is consistent with the results obtained from the total pedigree and genomic coefficients (F_{PED} , F_{GRM} , and F_{ROH}). The low incidence of META in JE cows and the smaller number of records for this breed could explain the large confidence intervals attached to the inbreeding-depression estimates.

Although F_{PED} significantly decreased the probability of DA in HO, our findings suggest a more substantial and beneficial effect of F_{PED_OLD} . Furthermore, similar to what was found in JE, none of the estimates for the effect of the age-based inbreeding coefficients on MFEV were significant in HO. This can be attributed to the low proportion of cases, low proportion of diseased cows, and the low heritability of MFEV for both breeds (Table 1).

We also used a model-based method to generate inbreeding coefficients from HBD segments associated with specific past generations. Due to the highly skewed distribution of some resulting coefficients, we combined inbreeding from 2 and 8 generations in the past and referred to it as recent inbreeding (F_{HBD_REC}) and inbreeding from 16 to 128 generations in the past was termed old inbreeding (F_{HBD_OLD}). Previous estimates on the effect of HBD segment inbreeding coefficients revealed significant inbreeding depression for production and fertility from the F_{HBD} coefficients representing the most recent inbreeding, whereas older inbreeding did not have a significant effect (Makanjuola et al., 2020b). In our study, we found that most estimates of the effect of F_{HBD_REC} and F_{HBD_OLD} were not significantly different, and there was generally little distinction in the magnitude and direction of their effects.

Limitations of Assessing Inbreeding Depression for Producer-Recorded Health Traits

Although liability-scale estimates provided compelling evidence of the effect of inbreeding on certain health traits, we did not observe a statistically significant difference in the estimated mean probability of disease occurrence for any trait among cows with low, average, or high levels of inbreeding. This result can be due to several limitations and characteristics of the producer-recorded traits. First, all the studied producer-recorded health traits exhibit low heritability and repeatability. Except for REPR and DA, the heritability of the disease traits studied was very low, with values at or below 0.10 in both breeds. Similarly, the repeatability of the disease traits studied was at or below 0.25. A previous study on recorded health traits in US dairy cattle found low heritability values, with most traits having heritabilities below 0.10, and the highest heritability observed was 0.36 for RETP (Parker Gaddis et al., 2014). These values indicate that these traits are significantly influenced by environmental factors and that farm management likely plays a prominent role in disease incidence. Second, the phenotypes for these traits rely on producer-recorded information. Although efforts are made to ensure the quality of such

data through protocols (Parker Gaddis et al., 2012), it is important to acknowledge that the recorded information may only partially capture the true disease history of individual cows. Last, diseases like MAST are highly multifactorial, and the current definition of MAST used in recording may encompass MAST caused by different pathogens and of varying levels of severity (Zadoks et al., 2011). These complexities further complicate our analysis, and it is possible that the true impact of inbreeding on dairy udder, reproductive, and metabolic diseases is more substantial than what was estimated in our study.

CONCLUSIONS

In this study, we investigated the effect of inbreeding on disease status using a large dataset of producer-recorded phenotypes for MAST as well as various reproductive and metabolic diseases in US HO and JE cattle. Our findings revealed that higher levels of pedigree and genomic inbreeding in cows were associated with a higher probability of developing diseases, with the strongest evidence of inbreeding depression being for METR in both breeds. However, this was not true of all diseases; we found consistent evidence that the probability of developing DA decreased with increasing inbreeding levels in HO. Moreover, recent pedigree and ROH inbreeding were linked to an increased likelihood of developing reproductive diseases, particularly METR. In contrast, older inbreeding either had no effect or it reduced the probability of reproductive disease(s). These findings suggest that implementing informed cow management practices, such as breeding animals with lower levels of recent kinship, can help mitigate the effect of inbreeding on disease incidence.

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ORCIDS

- Emmanuel A. Lozada-Soto  <https://orcid.org/0000-0001-8381-7988>
- Kristen L. Parker Gaddis  <https://orcid.org/0000-0003-1234-1075>
- Francesco Tiezzi  <https://orcid.org/0000-0002-4358-9236>
- Jicai Jiang  <https://orcid.org/0000-0001-6890-7539>
- Li Ma  <https://orcid.org/0000-0003-1038-1081>
- Sajjad Toghiani  <https://orcid.org/0000-0002-5090-728X>
- Paul M. VanRaden  <https://orcid.org/0000-0002-9123-7278>
- Christian Maltecca  <https://orcid.org/0000-0002-9996-4680>