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# Intergenerational cycle of disease: Maternal mastitis is associated with poorer daughter performance in dairy cattle

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## ABSTRACT

Adverse prenatal environments, such as maternal stress and infections, can influence the health and performance of offspring. Mastitis is the most common disease in dairy cattle, yet the intergenerational effects have not been specifically investigated. Therefore, we examined the associations between the dam's mammary gland health and daughter performance using somatic cell score (SCS) as a proxy for mammary health. Using data obtained from Dairy Records Management Systems (Raleigh, NC), we linked daughter records with their dam's records for the lactation in which the daughter was conceived. Linear and quadratic relationships of dam mean SCS with the daughter's age at first calving (AFC; n = 15,992 daughters, 4,366 herds), first- (n = 15,119 daughters, 4,213 herds) and second-lactation SCS (n = 3,570 daughters, 1,554 herds), first- and second-lactation mature-equivalent 305-d milk yield, and milk component yields were assessed using mixed linear regression models. We uncovered a phenomenon similar to those found in human and mouse models examining prenatal inflammation effects, whereby daughters born from dams with elevated SCS had poorer performance. Dam mean SCS was positively associated with daughter's AFC and first- and second-lactation mean SCS. Furthermore, for every 1-unit increase in dam mean SCS, daughter's first- and second-lactation mature-equivalent fat yield declined by 0.34% and 0.91% (−1.6 ± 0.49 kg, −4.0 ± 1.0 kg, respectively), although no effect was found on first- or second-lactation milk or milk protein yield. When accounting for genetics, daughter SCS, and AFC (first lactation only), dam mean SCS was associated with reduced second-lactation milk fat yield (−3.5 ± 1.8 kg/unit SCS), and a tendency was found for first-lactation milk fat yield (−1.9 ± 1.0 kg/unit SCS). Taken together, the association of greater dam mean SCS with lesser daughter milk fat yield is likely due to a few underlying mechanisms, in particular, a predisposition for mastitis and alterations in the epigenome controlling milk fat synthesis. As such, future studies should examine epigenetic mechanisms as a potential underpinning of this phenomenon.
**Key words:** mastitis, developmental programming, epigenetics, dairy cattle

## INTRODUCTION

The developmental origins of health and disease is an emerging field that evolved from numerous studies linking morbidity and mortality in adulthood with detrimental exposures that occurred during developmental periods in early life (Fleming et al., 2015). The Barker hypothesis established a causal relationship between early life stressors and the origins of coronary heart disease, hypertension, and diabetes (Barker, 2007), but has since been applied to numerous other diseases and developmental disorders in adults (Fleming et al., 2015). Indeed, this hypothesis has now been well-accepted and even extended into the preconception period as more epidemiological studies underscore the need to adjust preconception health and nutrition to improve birth outcomes and neonatal health (Stephenson et al., 2018).

Recent studies using rodent models demonstrate the imprinting of prenatal maternal infectious disease on the offspring's health and performance. For instance, acute prenatal inflammation induced by molecular mimetics of viral or bacterial pathogens impaired growth and development of the offspring (Arsenault et al., 2014). Moreover, prenatal maternal inflammation impaired the neonates' inflammatory responses to lipopolysaccharide (Hodyl et al., 2007; Lasala and Zhou, 2007; Beloosesky et al., 2010), which could result in a predisposition to infectious disease agents (Bengtson et al., 2010; Dauby et al., 2012). Although this concept has gained traction in human medicine, few studies have assessed the intergenerational associations in dairy cattle, most of which have focused on either milk production level (Berry et al., 2008; González-Recio et al., 2012; Gudex

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et al., 2014) or clinical disease incidence (Carvalho et al., 2020).

Mastitis is the most common disease in dairy cattle and is typically caused by bacterial infection. The annual incidence of clinical mastitis is approximately 25 cases per 100 cows (Erskine et al., 1988; Schukken et al., 1989; Olde Riekerink et al., 2008). More concerning, however, is the cow-level prevalence of subclinical mastitis infections, defined by SCS >4, which ranged from 26% in high-producing herds to 45% in low-producing herds (Ruegg, 2003). Furthermore, mastitis has numerous detrimental effects, including but not limited to reduced milk production (Gröhn et al., 2004; Wilson et al., 2004) and fertility (Barker et al., 1998; Schrick et al., 2001), impaired animal welfare (Petersson-Wolfe et al., 2018), and increased risk for herd removal (Erb et al., 1985). As such, intergenerational effects of mastitis, whether clinical or subclinical, could have substantial implications in the dairy industry.

Therefore, the objective of the present study was to explore whether an association existed between the dam's mean SCS during the lactation in which the daughter was conceived with the daughter's performance. We hypothesized that dams with greater SCS would have shorter gestation length, and the daughters would be older at first calving, have a greater first- and second-lactation SCS, and produce less milk and milk components.

## MATERIALS AND METHODS

### Data Acquisition and Management

To investigate intergenerational associations of mastitis with daughter performance, a large data set encompassing lactation records from 2009 to 2017 and from only United States herds was acquired from Dairy Records Management Systems (Raleigh, NC). Before linking dam and daughter records, all lactation records that began with an abortion were removed from the data set. A total of 33,260 dam-daughter records from 7,410 herds were linked. This was accomplished by merging dam and daughter records using 2 conditions: (1) matching the dam's identification denoted within the daughters' records with the identification of the dam's lactation records and (2) requiring that the dam's breeding date was 280 ± 20 d in advance of the daughter's birthdate to ensure that the daughter records were linked to the dam's lactation in which the daughter was conceived (INTNX function, SAS version 9.4; SAS Institute Inc., Cary, NC). Linking the daughter's records to the correct lactation of the dam's in which the daughter was conceived was quite challenging, particularly because we were dependent on the breeding date of the dam that resulted in the daughter's conception and this information was missing in many cases, which resulted in a smaller sample size than anticipated. To examine the association of dam mean SCS with dystocia incidence at the dam's calving resulting in the daughter's birth, we conducted a similar merge but matched the dam's calving date with the daughter's birth date instead. This was done to ensure that the calving difficulty score, as will be described, was correctly assigned to the daughter's birth. To remove daughters that were the result of embryo transfer (**ET**), records from dams with multiple daughters were removed from the analyses (n = 1,656 removed). Because we used the dam's mean lactation SCS [calculated as $\log_2(SCC/100{,}000) + 3$; Shook, 1993] to predict daughter performance, we used daughter records only if the dam's lactation record had at least 3 test days (n = 14,160 removed). To reflect standard dairy farm management, only daughters with an age at first calving (**AFC**) between 18 and 30 mo were allowed into the analyses related to heifer and first-lactation outcomes (n = 1,461 removed). This resulted in a final sample size of 15,992 daughter records (n = 4,366 herds; range, 1–496 daughters per herd) that were included in the daughter's gestation length and AFC analyses. Calving difficulty data (1–5 scale; eutocia = 1–2; dystocia = 3–5) were available for the calving resulting in the daughter's birth (n = 9,894, dystocia = 1,001) as well as for the daughter's first (n = 9,431, dystocia = 1,239) and second calving (n = 2,494, dystocia = 167).

We also examined the association of the dam's mean lactation SCS with the daughter's mature-equivalent (**305ME**) first- and second-lactation 305-d milk yield and milk component yields. We again allowed daughter records into the model only if the daughter had at least 3 test days, to improve the accuracy of the 305ME calculation (n = 873 removed for first lactation, 219 removed for second lactation). Our final sample sizes for models related to first- and second-lactation performance were 15,119 (n = 4,213 herds; range, 1–473 daughters per herd) and 3,570 (n = 1,554 herds; range, 1–204 daughters per herd) daughter records, respectively. To ensure that the stage of lactation did not skew the dam's mean SCS, we examined the number of test days between dams with a low SCS (mean SCS <4) with dams with a mean SCS ≥4. Dams with a low mean SCS had 7.8 ± 3.2 test days (mean ± SD), and dams with a mean SCS ≥4 had 7.9 ± 3.4 test days. Similarly, daughters born from dams with a low mean SCS had 9.2 ± 3.2 and 8.8 ± 3.2 test days, and daughters born from dams with a mean SCS ≥4 had 9.1 ± 3.4 and 8.6 ± 3.2 test days for their first and second lactations, respectively. Breed

breakdowns for first and second lactation, respectively, were as follows: Ayrshire, n = 77 and 22; Brown Swiss, n = 159 and 23; Crossbred, n = 882 and 271; Guernsey, n = 63 and 18; Holstein, n = 13,498 and 2,883; Jersey, n = 1,243 and 327; Milking Shorthorn, n = 42 and 18; Red and White, n = 28 and 8.

### Statistical Analysis and Model Building

Linear mixed models (PROC GLIMMIX, SAS) were used to evaluate the relationship of the dam's mean SCS with the daughter's gestation length and performance. The random effect of herd was included, and potential confounders (dam's lactation number and days in milk at pregnancy) were retained in the model if the variable made a 20% or greater change in the dam's mean SCS estimate in the final model (Dohoo et al., 2003). Variables retained in models are shown in results tables.

For the daughter's gestation length, fixed effects included the dam's mean SCS (linear and quadratic), breed, birth month, and birth year. For gestation length of the daughter's pregnancy occurring when the daughter was a heifer (pregnancy which ended with her first calving), fixed effects included dam's mean SCS (linear and quadratic), breed, calving type (heifer, bull, twin, or ET), calving month, and calving year. For gestation length of the daughter's pregnancy occurring during the daughter's first lactation (pregnancy that ended with her second calving), fixed effects included dam's mean SCS (linear and quadratic), daughter's first-lactation SCS (linear and quadratic), breed, calving type (heifer, bull, twin, or ET), calving month, and calving year. For the daughter's AFC, fixed effects included the dam's mean SCS (linear and quadratic), birth month, breed, and the calving year.

Two models were constructed to assess the association of the dam's mean SCS with the daughter's first- and second-lactation SCS. The initial models included the fixed effects of the dam's mean SCS (linear and quadratic), breed, calving month, daily milking frequency (2× or 3×), and calving year. If an association of the dam's mean SCS was found in the previous models for the daughter's gestation length, AFC, or first-lactation mean SCS models (used in the second-lactation SCS only), these variables were then tested in a broader model. Specifically, in the second model for daughter first-lactation SCS, fixed effects included the daughter's AFC (linear and quadratic), in addition to the dam's mean SCS (linear and quadratic), daughter's calving month, breed, milking frequency, and calving year. Similarly, in the second model for daughter second-lactation SCS, fixed effects included the dam's mean SCS (linear and quadratic), daughter's mean first-lactation SCS, daughter's calving month, breed, milking frequency, and calving year.

Multiple models were constructed to assess the association of the dam's mean SCS with the daughter's milk and milk component yields. The initial models included the fixed effects of the dam's mean SCS (linear and quadratic), breed, calving month, daily milking frequency (2× or 3×), and calving year. If an association of the dam's mean SCS was found in the previous models for the daughter's gestation length, AFC, or SCS models, these variables were then tested in a broader model. Specifically, in the second set of first-lactation milk and milk component yield models, fixed effects included the daughter's AFC (linear and quadratic) and daughter's mean first-lactation SCS in addition to the dam's mean SCS (linear and quadratic), breed, calving month, milking frequency, and calving year. Similarly, in the second set of second-lactation milk and milk component yield models, fixed effects included the dam's mean SCS (linear and quadratic), daughter's mean second-lactation SCS, breed, calving month, milking frequency, and calving year.

Finally, because only about 25% of the data set had PTA information available for milk and milk component yields (first lactation: n = 2,881 daughters, 1,315 herds; second lactation: n = 929 daughters, 456 herds), we constructed the models for a third time; however, this time we controlled for their respective genetic components. Therefore, in this third model for milk and milk component yields, fixed effects included the daughter's PTA for milk yield and milk protein and fat yields (PTAM, PTAP, or PTAF, respectively, depending on the model), the daughter's AFC (linear and quadratic), and daughter's mean first-lactation SCS, in addition to the dam's mean SCS (linear and quadratic), breed, calving month, milking frequency, and calving year. Similarly, in this third model for second-lactation milk and milk component yields, fixed effects included the daughter's PTA (PTAM, PTAP, or PTAF, depending on the model), the dam's mean SCS (linear and quadratic), daughter's mean second-lactation SCS, breed, calving month, milking frequency, and calving year.

Logistic models (PROC GLIMMIX, SAS) were used to assess the relationship of the dam's mean SCS with the incidence of dystocia at calving resulting in the daughter's birth as well as the daughter's first and second calving. These models included fixed effects of the dam's mean SCS (linear and quadratic), calving month, calving type (heifer, bull, twin, or ET; only used in daughter's first and second calving model), and calving year.

Backward elimination was used to remove terms until all remaining variables were significant at $P \leq 0.05$, except for the dam's mean SCS or if a confounder was

**Table 1.** Descriptive statistics of data from dam and daughter pairs used in subsequent analyses: intergenerational associations were assessed for the dam's mean SCS with the daughter's performance including the daughter's gestation length (n = 15,992 daughters, 4,366 herds), the daughter's gestation length for her first and second pregnancy, age at first calving (n = 15,992 daughters, 4,366 herds), first-lactation milk and milk component yields (n = 15,119, 4,213 herds), and second-lactation milk and milk component yields (n = 3,570 daughters, 1,554 herds)

| Variable | Mean | SD | IQR[1] |
|---|---|---|---|
| Dam SCS | 2.3 | 1.5 | 2.0 |
| Daughter's gestation length (d) | 279 | 6.6 | 7.0 |
| Daughter gestation length (d; 1st lact[2]) | 277 | 15 | 7.0 |
| Daughter gestation length (d; 2nd lact[2]) | 279 | 12 | 6.0 |
| Daughter AFC[3] (d) | 741 | 67 | 92 |
| Daughter 1st-lact SCS | 2.1 | 1.3 | 1.7 |
| Daughter 1st-lact 305ME[4] milk yield (kg) | 12,069 | 2,831 | 3,730 |
| Daughter 1st-lact 305ME protein yield (kg) | 369 | 80 | 104 |
| Daughter 1st-lact 305ME fat yield (kg) | 459 | 105 | 136 |
| Daughter 2nd-lact SCS | 2.3 | 1.4 | 1.8 |
| Daughter 2nd-lact 305ME milk yield (kg) | 11,559 | 2,864 | 3,750 |
| Daughter 2nd-lact 305ME protein yield (kg) | 355 | 79 | 101 |
| Daughter 2nd-lact 305ME fat yield (kg) | 439 | 106 | 136 |

[1]IQR = interquartile range.
[2]1st lact = first lactation; 2nd lact = second lactation.
[3]AFC = age at first calving.
[4]305ME = 305-d mature equivalent.

identified, in which case the variable was forced into the model regardless of significance. Data were checked to ensure that assumptions of the model were met (PROC UNIVARIATE, SAS). Outliers were removed if the absolute value of the Studentized residual was greater than 4. Significance was declared at $P \leq 0.05$ and statistical tendencies at $0.05 < P < 0.10$.

## RESULTS

### Association of Dam SCS With Gestation Length, Calving Difficulty, and AFC

Descriptive statistics are provided in Table 1. Dam mean SCS was not associated with the daughter's gestation length ($P = 0.44$; Table 2). Similarly, we did not

**Table 2.** Gestation length: association of the dam's mean SCS with the gestation length of the daughter (d; n = 15,992 daughters, 4,366 herds) and the daughter's gestation length for her pregnancies ending at her first (n = 15,992 daughters, 4,366 herds) and second calving (n = 3,570 daughters, 1,554 herds)

| Variable | Coefficient | SE | *P*-value | 95% CI |
|---|---|---|---|---|
| Daughter's gestation length | | | | |
| Dam mean SCS | −0.028 | 0.036 | 0.44 | −0.098, 0.043 |
| Dam lactation number | | | <0.01 | |
| Birth month | | | <0.0001 | |
| Breed | | | <0.0001 | |
| Year | | | <0.01 | |
| Intercept | 280 | 0.63 | <0.0001 | 279, 281 |
| Daughter gestation length for pregnancy ending at first calving | | | | |
| Dam mean SCS | 0.011 | 0.045 | 0.81 | −0.078, 0.099 |
| Breed | | | <0.0001 | |
| Calving month | | | <0.0001 | |
| Calving type[1] | | | <0.0001 | |
| Year | | | <0.01 | |
| Intercept | 277 | 0.32 | <0.0001 | 276, 278 |
| Daughter gestation length for pregnancy ending at second calving | | | | |
| Dam mean SCS | −0.10 | 0.077 | 0.19 | −0.25, 0.051 |
| Daughter 1st-lact SCS[2] (linear) | 0.58 | 0.30 | 0.06 | −0.019, 1.2 |
| Daughter 1st-lact SCS (quadratic) | −0.13 | 0.058 | 0.03 | −0.24, −0.013 |
| Breed | | | <0.01 | |
| Calving type | | | <0.0001 | |
| Intercept | 276 | 2.7 | <0.0001 | 271, 281 |

[1]Heifer, bull, twins, or embryo transfer.
[2]1st lact = first lactation.

find an association of dam mean SCS with the incidence of dystocia occurring at the calving that resulted in the daughter's birth (odds ratio, OR = 0.96, 95% CI = 0.91–1.0, $P = 0.09$). Dam mean SCS was not associated with the length of the daughter's first or second full gestation ($P = 0.81$ and 0.19, respectively), nor did we find an association with the incidence of dystocia occurring at the daughter's first calving (OR = 1.04, 95% CI = 0.99–1.1, $P = 0.15$; Table 3). Surprisingly, dam mean SCS was associated with a reduction in the odds of dystocia occurring at the daughter's second calving (OR = 0.88, 95% CI = 0.78–0.99, $P = 0.04$; Table 4). Furthermore, a quadratic relationship was found between the daughter's first-lactation SCS and the length of her second full gestation ($P = 0.03$). Interestingly, minimal changes in gestation length were found in daughters with a first-lactation mean SCS <4, the cut-off used to define subclinical mastitis; however, daughters with a first-lactation mean SCS >4 had a shorter second gestation (Figure 1). Dam mean SCS was positively associated with the daughter's AFC ($P < 0.01$; Table 5), but not with the daughter's age at second calving ($P = 0.95$; data not shown).

### Initial Model: Association of Dam SCS With the Daughter's First- and Second-Lactation SCS

Dam mean SCS had a linear relationship with the daughter's first-lactation mean SCS ($P < 0.0001$; Table 3) and a quadratic relationship with the daughter's second-lactation mean SCS ($P = 0.04$; Table 4).

### Second Model: Association of Dam SCS With the Daughter's First- and Second-Lactation SCS

Following evaluation for AFC, dam mean SCS remained strongly associated with daughter mean SCS ($P < 0.0001$; Table 6). We also found a positive relationship between AFC and first-lactation mean SCS ($P < 0.0001$). For the daughter's second-lactation mean

**Table 3.** Initial first-lactation models: association of the dam's mean SCS during the lactation in which the daughter was conceived with the daughter's first-lactation SCS, 305-d mature-equivalent milk and milk component yields (kg; n = 15,119 daughters, 4,213 herds), and dystocia incidence (n = 9,431, dystocia = 1,239)

| Variable | Estimate | SE | *P*-value | 95% CI |
|---|---|---|---|---|
| SCS | | | | |
| Dam mean SCS | 0.064 | 0.007 | <0.0001 | 0.050, 0.078 |
| Breed | | | <0.0001 | |
| Calving month | | | <0.0001 | |
| Milking frequency | | | <0.0001 | |
| Intercept | 1.8 | 0.043 | <0.0001 | 1.7, 1.9 |
| Milk yield (kg) | | | | |
| Dam mean SCS | −12 | 12 | 0.32 | −37, 12 |
| Breed | | | <0.0001 | |
| Calving month | | | <0.0001 | |
| Dam lactation number | | | <0.0001 | |
| Milking frequency | | | <0.0001 | |
| Year | | | <0.0001 | |
| Intercept | 12,615 | 98 | <0.0001 | 12,423, 12,806 |
| Protein yield (kg) | | | | |
| Dam mean SCS | −0.54 | 0.35 | 0.12 | −1.2, 0.14 |
| Breed | | | <0.0001 | |
| Calving month | | | <0.0001 | |
| Dam lactation number | | | <0.0001 | |
| Milking frequency | | | <0.0001 | |
| Year | | | <0.0001 | |
| Intercept | 382 | 2.8 | <0.0001 | 378, 388 |
| Fat yield (kg) | | | | |
| Dam mean SCS | −1.6 | 0.49 | 0.001 | −2.5, −0.62 |
| Breed | | | <0.0001 | |
| Calving month | | | <0.0001 | |
| Dam lactation number | | | <0.0001 | |
| Milking frequency | | | <0.0001 | |
| Year | | | <0.0001 | |
| Intercept | 471 | 3.9 | <0.0001 | 463, 478 |
| Daughter dystocia incidence at first calving | | | | |
| Dam mean SCS | OR[1] = 1.04 | | 0.15 | 0.99, 1.1 |
| Calving type[2] | | | <0.0001 | |
| Year | | | <0.0001 | |

[1]OR = odds ratio.

[2]Heifer, bull, twins, or embryo transfer.

SCS, dam mean SCS remained statistically significant ($P < 0.0001$; Table 6) following adjustment for the daughter's first-lactation mean SCS.

### Initial Models: Association of Dam SCS With the Daughter's Lactational Performance

Dam mean SCS was negatively associated with the daughter's first- and second-lactation fat yields (first lactation, $P = 0.001$; second lactation, $P < 0.0001$), but no association was found for first- ($P = 0.32$; Table 3) and second-lactation milk ($P = 0.10$; Table 4) and protein yields (first lactation, $P = 0.12$; second lactation, $P = 0.10$).

### Second Models: Association of Dam SCS With the Daughter's Lactational Performance

In our second models for first- and second-lactation daughter milk and milk component yields, we controlled for AFC and daughter mean SCS. In these models, we did not find an association of dam mean SCS with first- or second-lactation milk ($P = 0.97$ and 0.70, respectively; Table 7) or protein yields ($P = 0.52$ and 0.41, respectively; Table 8); however, the association between dam mean SCS and daughter fat yield remained statistically significant (both lactations $P = 0.02$; Table 9).

### Third Models: Association of Dam SCS With the Daughter's Lactational Performance

Following adjustment for genetic components, dam mean SCS was still associated with the daughter's second-lactation 305ME fat yield ($P = 0.05$; Table 10) and a tendency for first-lactation 305ME fat yield ($P = 0.06$) when using this smaller data set. No effect of dam mean SCS was detected for first- or second-lactation milk ($-4.44 \pm 27.45$ kg, $P = 0.87$; $-41.84 \pm 45.36$ kg, $P = 0.36$, respectively; data not shown) or protein yields ($-0.40 \pm 0.80$ kg, $P = 0.62$; $-1.41 \pm 1.27$ kg, $P = 0.27$, respectively; data not shown).

## DISCUSSION

Our study is the first to examine associations of the dam's mean SCS during the lactation in which the daughter was conceived with the daughter's performance. No association was seen between the dam's mean SCS and the daughter's gestation length or the

**Table 4.** Initial second-lactation models: association of the dam's mean SCS during the lactation in which the daughter was conceived with the daughter's second-lactation SCS, 305-d mature-equivalent milk and milk component yields (kg; n = 3,570 daughters, 1,554 herds), and dystocia incidence (n = 2,494, dystocia = 167)

| Variable | Estimate | SE | *P*-value | 95% CI |
|---|---|---|---|---|
| SCS | | | | |
| Dam mean SCS (linear) | 0.19 | 0.048 | <0.0001 | 0.096, 0.28 |
| Dam mean SCS (quadratic) | −0.015 | 0.0073 | 0.04 | −0.030, −0.00085 |
| Intercept | 2.1 | 0.068 | <0.0001 | 1.9, 2.2 |
| Milk yield (kg) | | | | |
| Dam mean SCS | −42 | 26 | 0.10 | −93, 8.0 |
| Breed | | | <0.0001 | |
| Calving month | | | <0.0001 | |
| Milking frequency | | | <0.0001 | |
| Year | | | 0.04 | |
| Intercept | 12,698 | 159 | <0.0001 | 12,385, 13,011 |
| Protein yield (kg) | | | | |
| Dam mean SCS | −1.2 | 0.74 | 0.10 | −2.7, −0.22 |
| Breed | | | <0.0001 | |
| Calving month | | | <0.001 | |
| Dam lactation number | | | 0.02 | |
| Milking frequency | | | <0.0001 | |
| Intercept | 377 | 4.9 | <0.0001 | 367, 387 |
| Fat yield (kg) | | | | |
| Dam mean SCS | −4.0 | 1.0 | <0.0001 | −6.0, −2.0 |
| Breed | | | <0.0001 | |
| Calving month | | | <0.001 | |
| Milking frequency | | | <0.0001 | |
| Intercept | 471 | 6.03 | <0.0001 | 459, 482 |
| Daughter dystocia incidence at second calving | | | | |
| Dam mean SCS | OR[1] = 0.88 | | 0.04 | 0.78, 0.99 |
| Calving type[2] | | | <0.0001 | |

[1]OR = odds ratio.

[2]Heifer, bull, twins, or embryo transfer.

**Table 5.** Age at first calving: association of the dam's mean SCS during the lactation in which the daughter was conceived with the daughter's age at first calving (d; n = 15,992 daughters, 4,366 herds)

| Variable | Coefficient | SE | *P*-value | 95% CI |
|---|---|---|---|---|
| Dam mean SCS | 0.91 | 0.32 | <0.01 | 0.27, 1.54 |
| Breed | | | <0.0001 | |
| Ayrshire | 31.00 | 7.77 | <0.0001 | 15.76, 46.23 |
| Brown Swiss | 26.53 | 5.35 | <0.0001 | 16.04, 37.01 |
| Guernsey | 32.14 | 8.83 | <0.001 | 14.84, 49.45 |
| Jersey | −15.12 | 2.47 | <0.0001 | −19.96, −10.28 |
| Milking Shorthorn | 28.39 | 10.32 | <0.01 | 8.16, 48.61 |
| Red and White | 6.21 | 11.43 | 0.59 | −16.20, 28.63 |
| Crossbred | −7.45 | 2.40 | <0.01 | −12.16, −2.74 |
| Holstein | Referent | — | — | — |
| Year | | | <0.0001 | |
| Intercept | 750.21 | 1.70 | <0.0001 | 746.89, 753.54 |

dam's calving difficulty, suggesting no obvious effect on the daughter in utero. Yet, daughters born from dams with greater mean SCS had a greater AFC, increased first- and second-lactation mean SCS, and reduced milk fat yield. These data, in general, suggest that maternal mastitis induced a developmental programming effect within the daughter that altered her lifelong performance.

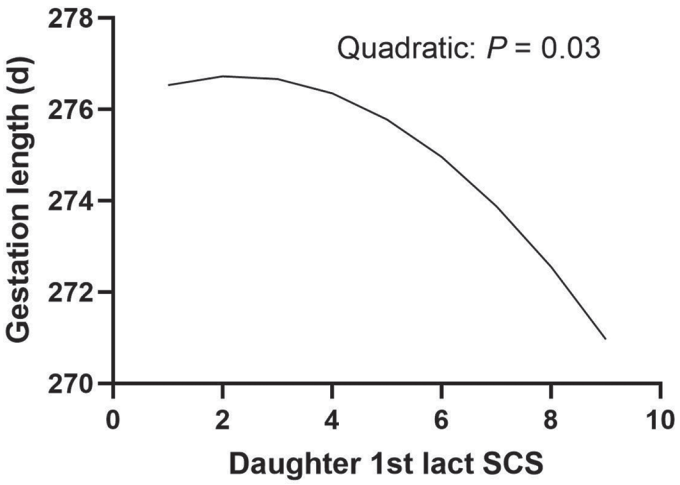


**Figure 1.** Quadratic relationship between the daughter's first-lactation (1st lact) SCS with the daughter's second gestation length. Data were acquired from US dairy herds using Dairy Records Management Systems (Raleigh, NC) from 2009 through 2017. To examine the association of the dam's mean SCS with daughter performance, daughter records (n = 15,992 daughters, 4,366 herds) were linked with the dam's records for the lactation in which the daughter was conceived. No association was found between the daughter's gestation length with the dam's mean SCS ($P = 0.44$); however, increased mean SCS during the daughter's first lactation was associated with a quadratic ($P = 0.03$) decrease in gestation length of the daughter's second pregnancy (n = 3,570 daughters, 1,554 herds). Minor changes in gestation length were found in daughters with a first-lactation mean SCS <4; however, daughters with a first-lactation mean SCS >4 (the cutoff for subclinical mastitis) had a shorter gestation.

### Association of Dam SCS With Gestation Length and Calving Difficulty

As previously mentioned, no association was observed between the dam's mean SCS and the daughter's gestation length or the dam's calving difficulty. We note that our data set is limited to gestations resulting in daughters who reached their first lactation. Therefore, gestations that terminated as abortions or resulted in stillborn calves, or live heifers that died or were culled before calving are not included. As such, our data set may be biased against dams with difficult calving events or dams with an altered gestation length. Because of this, our data set may not accurately reflect the association of maternal mastitis on the dam's gestation length, and likely resulted in underestimation. It does appear, however, that mastitis could influence gestation length. For instance, we found a quadratic relationship between the daughter's first-lactation mean SCS and the length of her second full gestation, where daughters with a first-lactation mean SCS >4 had a shorter gestation. These results parallel those found in humans, where inflammation is an underlying cause of preterm labor (Peltier, 2003).

### Association of Dam SCS With the Daughter's AFC

Dam mean SCS was positively associated with the daughter's AFC. Economically, the ideal AFC is between 23 and 24 mo (Ettema and Santos, 2004), and greater AFC has been associated with lesser first-lactation milk production (Heinrichs and Heinrichs, 2011). Although our study was not designed to determine causation, one possible mechanism behind this effect could be related to health. Reducing the incidence of disease in preweaned calves can improve average daily gain (Shivley et al., 2018) and subsequently reduce AFC (Waltner-Toews et al., 1986; Correa et al., 1988). Previous human studies suggest that prenatal inflam-

**Table 6.** Second model for daughter mean SCS: association of the dam's mean SCS during the lactation in which the daughter was conceived with the daughter's mean first- (n = 15,119 daughters, 4,213 herds) and second-lactation mean SCS (n = 3,570 daughters, 1,554 herds) when including age at first calving (first lactation only) and first-lactation mean SCS (second lactation only)

| Variable | Coefficient | SE | *P*-value | 95% CI |
|---|---|---|---|---|
| First lactation | | | | |
| Dam mean SCS | 0.063 | 0.0070 | <0.0001 | 0.049, 0.076 |
| Age at first calving (d) | 0.0016 | 0.00017 | <0.0001 | 0.0012, 0.0019 |
| Breed | | | <0.0001 | |
| Calving month | | | <0.0001 | |
| Milking frequency | | | <0.0001 | |
| Intercept | 0.67 | 0.13 | <0.0001 | 0.41, 0.93 |
| Second lactation | | | | |
| Dam mean SCS | 0.067 | 0.016 | <0.0001 | 0.035, 0.099 |
| Daughter mean SCS (1st lact[1]) | 0.37 | 0.019 | <0.0001 | 0.33, 0.41 |
| Intercept | 1.4 | 0.063 | <0.0001 | 1.3, 1.5 |

[1]First lactation.

mation predisposes the neonate to infectious disease agents (Bengtson et al., 2010; Dauby et al., 2012). Surprisingly, in dairy cattle, daughters born from diseased dams had a reduction in the incidence of clinical disease, particularly digestive disorders, during the preweaning period, but were also more likely to be sold before first calving (Carvalho et al., 2020). Prenatal inflammation is known to impair neonatal inflammatory responses (Hodyl et al., 2007; Lasala and Zhou, 2007; Beloosesky et al., 2010). For this reason, a reduction in clinical disease cases but increased incidence of subclinical diseases could occur due to less robust inflammatory responses and subsequent reductions in outward signs of illness. Consequently, these animals could be more difficult to identify during disease events, and lack of treatment could ultimately result in a greater AFC as well as poorer herd retention.

### Association of Dam SCS With the Daughter's Lactational Performance

Dam mean SCS was strongly associated with daughter mean SCS in both first and second lactation. Because this could be simply due to inheritance of mastitis-related genes (Thompson-Crispi et al., 2014; Martin et al., 2018), for the second-lactation SCS, we constructed

**Table 7.** Second model for daughter 305-d mature-equivalent (305ME) milk yield: association of the dam's mean SCS during the lactation in which the daughter was conceived with the daughter's first- (n = 15,119 daughters, 4,213 herds) and second-lactation (n = 3,570 daughters, 1,554 herds) 305ME milk yield (kg) including adjustment for age at first calving (first lactation) and the daughter's mean SCS (first or second lactation)[1]

| Variable | Coefficient | SE | *P*-value | 95% CI |
|---|---|---|---|---|
| First lactation | | | | |
| Dam mean SCS | −0.49 | 12 | 0.97 | −25, 24 |
| Age at first calving (linear) | 9.9 | 5.1 | 0.05 | −0.074, 20 |
| Age at first calving (quadratic) | −0.0092 | 0.0033 | <0.01 | −0.016, −0.0026 |
| Breed | | | <0.0001 | |
| Calving month | | | <0.0001 | |
| Dam lactation number | | | <0.0001 | |
| Daughter mean SCS (1st lact) | −171 | 14 | <0.0001 | −197, −144 |
| Dam DIM at conception | 0.30 | 0.22 | 0.17 | −0.12, 0.72 |
| Milking frequency | | | <0.0001 | |
| Year | | | <0.0001 | |
| Intercept | 9,471 | 1,920 | <0.0001 | 5,706, 13,236 |
| Second lactation | | | | |
| Dam mean SCS | −10 | 26 | 0.70 | −62, 41 |
| Breed | | | <0.0001 | |
| Calving month | | | <0.0001 | |
| Dam lactation number | | | 0.26 | |
| Daughter mean SCS (2nd lact) | −301 | 29 | <0.0001 | −358, −244 |
| Dam DIM at conception | 0.70 | 0.56 | 0.21 | −0.39, 1.8 |
| Milking frequency | | | <0.0001 | |
| Intercept | 13,020 | 195 | <0.0001 | 12,637, 13,402 |

[1]1st lact = first lactation; 2nd lact = second lactation.

**Table 8.** Second model for daughter 305-d mature-equivalent (305ME) milk protein yield: association of the dam's mean SCS during the lactation in which the daughter was conceived with the daughter's first- (n = 15,119 daughters, 4,213 herds) and second-lactation (n = 3,570 daughters, 1,554 herds) 305ME milk protein yield (kg) including adjustment for age at first calving (first lactation) and the daughter's mean SCS (first or second lactation)[1]

| Variable | Coefficient | SE | *P*-value | 95% CI |
|---|---|---|---|---|
| First lactation | | | | |
| Dam mean SCS | −0.22 | 0.35 | 0.52 | −0.91, 0.46 |
| Age at first calving (d) | −0.116 | 0.0085 | <0.0001 | −0.13, −0.099 |
| Breed | | | <0.0001 | |
| Calving month | | | <0.0001 | |
| Dam lactation number | | | <0.0001 | |
| Daughter mean SCS (1st lact) | −4.2 | 0.38 | <0.0001 | −5.0, −3.5 |
| Milking frequency | | | <0.0001 | |
| Year | | | <0.0001 | |
| Intercept | 476 | 6.9 | <0.0001 | 463, 489 |
| Second lactation | | | | |
| Dam mean SCS | −0.61 | 0.74 | 0.41 | −2.1, 0.85 |
| Breed | | | <0.0001 | |
| Calving month | | | <0.0001 | |
| Dam lactation number | | | <0.01 | |
| Dam DIM at conception | 0.024 | 0.016 | 0.13 | −0.0071, 0.055 |
| Daughter mean SCS (2nd lact) | −7.4 | 0.82 | <0.0001 | −9.0, −5.8 |
| Milking frequency | | | <0.0001 | |
| Intercept | 389 | 5.6 | <0.0001 | 379, 400 |

[1]1st lact = first lactation; 2nd lact = second lactation.

another model including the daughter's first-lactation SCS to account for at least part of this genetic influence as well as any carryover effects of mastitis from the previous lactation. In this model, dam mean SCS remained associated with the daughter's second-lactation SCS, suggesting that maternal mastitis predisposed the daughter to the same disease. Although no associations were found between dam mean SCS and daughter milk or milk protein yields, an association between dam mean SCS and daughter fat yield was apparent. Furthermore, this association remained statistically significant following adjustment for genetic parameters (PTAF), predisposition to mastitis, and AFC effects. Interestingly, the association between dam mean SCS and daughter milk fat yield found in the first lactation ($-1.9 \pm 1.0$) also carried into the second lactation,

**Table 9.** Second model for daughter 305-d mature-equivalent milk fat yield: association of the dam's mean SCS during the lactation in which the daughter was conceived with the daughter's first- (n = 15,119 daughters, 4,213 herds) and second-lactation (n = 3,570 daughters, 1,554 herds) 305-d mature-equivalent milk fat yield (kg) including adjustment for age at first calving (first lactation) and the daughter's mean SCS (first or second lactation)[1]

| Variable | Coefficient | SE | *P*-value | 95% CI |
|---|---|---|---|---|
| First lactation | | | | |
| Dam mean SCS | −1.1 | 0.49 | 0.02 | −2.1, −0.16 |
| Age at first calving | −0.15 | 0.01 | <0.0001 | −0.17, −0.13 |
| Breed | | | <0.0001 | |
| Calving month | | | <0.0001 | |
| Dam lactation number | | | <0.0001 | |
| Daughter mean SCS (1st lact) | −6.5 | 0.53 | <0.0001 | −7.6, −5.5 |
| Milking frequency | | | <0.0001 | |
| Year | | | <0.0001 | |
| Intercept | 595 | 9.5 | <0.0001 | 576, 613 |
| Second lactation | | | | |
| Dam mean SCS | −2.3 | 1.0 | 0.02 | −4.3, −0.29 |
| Breed | | | <0.0001 | |
| Calving month | | | <0.001 | |
| Dam lactation number | | | <0.01 | |
| Daughter mean SCS (2nd lact) | −11 | 1.14 | <0.0001 | −13, −8.9 |
| Milking frequency | | | <0.0001 | |
| Intercept | 485 | 7.13 | <0.0001 | 471, 499 |

[1]1st lact = first lactation; 2nd lact = second lactation.

and, in fact, the estimate was considerably larger in the daughter's second lactation (−3.5 ± 1.8). Inherently, these results suggest that maternal mastitis induced a developmental programming effect in the daughter, as the reduction in milk fat yield persisted over multiple lactations, and this reduction is only partly explained by some combination of genetic inheritance, the predisposition to mastitis, and AFC effects.

### Potential Mechanisms

Numerous mechanisms exist behind intergenerational effects of maternal disease, including a suboptimal uterine environment altering fetal development and growth (Aiken and Ozanne, 2014), inheritance of mitochondrial dysfunction (Igosheva et al., 2010), and alterations in the epigenome (Ozanne and Constância, 2007). Indeed, epigenetic epidemiology is an emerging area of research that describes the underlying molecular changes, providing a basis to the developmental origins of health and disease theory (Waterland and Michels, 2007). The term epigenetics was coined by Waddington many decades ago, and was defined as a "branch of biology which studies the causal interactions between genes and the products that bring their phenotype into being" (Waddington, 1942, 1968). Today, we have a sharper focus on epigenetics, and researchers have defined it as the heritable changes in gene expression potential that are not caused by changes in the DNA sequence (Riggs et al., 1996; Jaenisch and Bird, 2003). The mechanism behind these changes in gene expression include DNA methylation (Lande-Diner and Cedar, 2005), histone modifications (acetylation, methylation, phosphorylation, ubiquitination, and sumoylation; Peterson and Laniel, 2004), autoregulation of transcription factors (Riggs and Porter, 1996), and changes in microRNA expression (Hou et al., 2011). We propose that these epigenetic mechanisms, in addition to the other mechanisms previously mentioned, likely play a role in the present study. In particular, our data implies that maternal mastitis may exert an epigenetic modification dictating altered milk fat synthesis. Future studies should explore epigenetic regulation of gene expression to establish a causal link between maternal health and daughter performance.

### Limitations

One of the limitations with our study is that we used dairy records from numerous herds. Although we included the random effect of herd into our models, we acknowledge that we used data from herds with few observations, which could make it difficult to control for herd effects. This could be particularly limiting because herds with poor mastitis management may also have poor management as it relates to other outcomes. Because of this, we re-examined our initial analysis for the association of dam mean SCS with daughter first-lactation milk fat yield; however, this time we removed daughters if the herd had less than 4 daughters represented in the data set. This increased the number of daughters per herd from 3.6 in the original analysis to 12.2, although it substantially reduced the number of daughter records (n = 10,827 daughters from 889 herds versus 15,119 daughters from 4,213 herds in the original data set). Even in this smaller data set, dam mean SCS

**Table 10.** Third model for daughter 305-d mature-equivalent (305ME) milk fat yield following adjustment for genetics: association of the dam's mean SCS during the lactation in which the daughter was conceived with the daughter's first- (n = 2,881 daughters, 1,315 herds) and second-lactation (n = 929 daughters, 456 herds) 305ME milk fat yield (kg) including adjustment for genetics (PTA for fat, PTAF), age at first calving (first lactation only), and daughter's mean SCS (first or second lactation)[1]

| Variable | Coefficient | SE | *P*-value | 95% CI |
|---|---|---|---|---|
| First lactation | | | | |
| Dam mean SCS | −1.9 | 1.0 | 0.06 | −3.9, 0.11 |
| Age at first calving (d) | −0.12 | 0.025 | <0.0001 | −0.17, −0.070 |
| Breed | | | <0.0001 | |
| Calving month | | | <0.0001 | |
| Daughter mean SCS (1st lact) | −4.9 | 1.0 | <0.0001 | −7.0, −2.9 |
| Milking frequency | | | <0.0001 | |
| PTAF (kg) | 4.7 | 0.15 | <0.0001 | 4.4, 5.0 |
| Intercept | 532 | 20 | <0.0001 | 493, 570 |
| Second lactation | | | | |
| Dam mean SCS | −3.5 | 1.8 | 0.05 | −7.0, 0.033 |
| Breed | | | <0.01 | |
| Daughter mean SCS (2nd lact) | −11 | 2.0 | <0.0001 | −15, −6.9 |
| Milking frequency | | | <0.001 | |
| PTAF (kg) | 5.3 | 0.32 | <0.0001 | 4.6, 5.9 |
| Intercept | 477 | 9.0 | <0.0001 | 460, 495 |

[1]1st lact = first lactation; 2nd lact = second lactation.

was still associated with a reduction in the daughter's first-lactation milk fat yield, suggesting that herd effects likely did not have undue influence on the conclusions of this study. Finally, another major limitation to our study is the observational design; therefore, we can only speculate on causation. Although we propose an epigenetic mechanism, many other possibilities exist, and future studies should explore those prospects.

## CONCLUSIONS

Dam mean SCS was positively associated with daughter's age at first calving as well as first- and second-lactation mean SCS. Moreover, daughters born from dams with greater SCS produced less milk fat during their second lactation. Thus, an intergenerational association of maternal mastitis was found with poorer daughter performance. As such, these data provide a basis for future exploration in epigenetic mechanisms.

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