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Late-gestation heat stress impairs daughter and granddaughter lifetime performance

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ABSTRACT

Records of late-gestation heat stress studies conducted over 10 consecutive years in Florida were pooled and analyzed to test the hypothesis that maternal hyperthermia during late gestation impairs performance of the offspring across multiple generations and lactations, ultimately impeding the profitability of the US dairy sector. Dry-pregnant multiparous dams were actively cooled (CL; shade of a freestall barn, fans and water soakers, n = 196) or not (HT; shade only, n = 198) during the last 46 d of gestation, concurrent with the entire dry period. After data mining, records of 156 daughters (F_1) that were born either to CL (CL_{F1}, n = 77) or HT dams (HT_{F1}, n = 79) and 45 granddaughters (F_2) that were born either to CL_{F1} (CL_{F2}, n = 24) or HT_{F1} (HT_{F2}, n = 21) were used in the analysis. Life events and daily milk yield for 3 lactations of daughters and granddaughters were obtained. Milk yield, reproductive performance, and productive life data were analyzed using MIXED and GLIMMIX procedures, and lifespan was analyzed using PHREG and LIFETEST procedures of SAS (SAS Institute Inc., Cary, NC). Milk production of HT_{F1} was reduced in their first (2.2 kg/d), second (2.3 kg/d), and third lactations (6.5 kg/d) compared with CL_{F1}. More HT_{F1} were culled before first calving, and the productive life and lifespan of HT_{F1} were reduced relative to CL_{F1} (4.9 and 11.7 mo, respectively). The granddaughters (HT_{F2}) born to HT_{F1} produced less milk in their first lactation (1.3 kg/d) relative to granddaughters (CL_{F2}) born to CL_{F1}. More HT_{F2} were culled before first breeding relative to CL_{F2}; however, productive life and lifespan were not different between HT_{F2} and CL_{F2} animals. An economic analysis was then performed based on the number of heat stress days, dry cows per state, and the aforementioned impairments on daughters' lifespans and milk production. Collectively in the United States, the economic losses for additional heifer rearing cost, reduced productive life, and reduced milk yield of the F_1 offspring were estimated at \$134, \$90, and \$371 million per year, respectively. In summary, late-gestation heat stress exerts carryover effects on at least 2 generations. Providing heat abatement to dry-pregnant dams is important to rescue milk loss of the dam and to prevent losses in their progeny.
Key words: dry cow, heat stress, in utero programming

INTRODUCTION

It is estimated that in the United States alone, environmental heat stress costs the dairy industry more than \$1.5 billion in annual losses due to decreased productive and reproductive performance and increased morbidity and mortality of lactating cows (St-Pierre et al., 2003; Collier et al., 2006). To alleviate heat stress impairments, advanced heat-abatement technologies such as fans, soakers, and misters are commonly employed on US dairies (Spiers et al., 2018; Dado-Senn et al., 2019a). In addition to detriments during lactation, heat stress during the dry period, a nonlactating period between lactations, also negatively affects milk yield in the subsequent lactation (do Amaral et al., 2009; Tao et al., 2012; Fabris et al., 2019). This reduction in milk yield is due, in part, to the abnormal mammary development that takes place in the dry period. Specifically, exposure to dry-period heat stress delays early mammary gland involution by blunting autophagy and impairing mammary gland proliferation during the redevelopment phase (Tao et al., 2011; Wohlgemuth et al., 2016). More recently, histological examination of the mammary gland microstructure during the subsequent lactation revealed reduced alveoli number, and consequently less secretory capacity in cows exposed to heat stress during the dry period (Dado-Senn et al., 2019b). Despite the impairments associated with dry-period heat stress, dry cows are less frequently considered for heat abatement relative to their lactating

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counterparts (Dado-Senn et al., 2019a; Negrón-Pérez et al., 2019).

Maternal circumstances during conception and gestation are determinant for the phenotype of the offspring at adulthood. For example, nutrition, concurrent lactation, milk yield level, and occurrence of disease during embryogenesis may preclude the offspring to fully express their genetic potential (Bach, 2012; González-Recio et al., 2012). In dairy cows, the dry period occurs during the last trimester of gestation, a critical period for fetal growth. Consequently, late-gestation exposure of the fetus to hyperthermia through the intrauterine environment may derail prenatal programming and affect the next generation of replacement heifers (first set of offspring; $\mathbf{F_1}$). Indeed, heifers born to heat-stressed dams during late gestation were smaller and produced 5.1 kg/d less milk in their first lactation relative to heifers born to cooled dams, despite their similar age and weight at calving (Monteiro et al., 2016; Skibiel et al., 2018a). This evidence is suggestive of a permanent effect of fetal environment on phenotype at adulthood. Further, in utero programing of the gametes that will form the granddaughters (offspring from the F_1 generation; $\mathbf{F_2}$) may alter developmental trajectories and lead to transgenerational inheritance in domesticated farm animals (Feeney et al., 2014). Thus, it is possible that late-gestation heat stress affects the developmental trajectory of fetal gametes and determine, in part, phenotype expression of the granddaughters.

Heat stress exposure during the dry period of the dam is estimated to cause $810 million in milk losses annually in the United States (Ferreira et al., 2016). Further, cooling dry cows was demonstrated to be profitable for 89% of the cows in the United States (Ferreira et al., 2016). However, this figure does not account for the economic impact of late-gestation heat stress on the future productivity of the offspring. To date, the effect of late-gestation heat stress on offspring survival, reproduction, and milk production across multiple generations and lactations has not been quantified. We hypothesized that exposure of pregnant Holstein cows to hyperthermia during late gestation will impair daughters' and granddaughters' lifetime performances. Our first objective was to quantify the carryover effects of maternal exposure to heat stress during late gestation on milk yield, reproductive performance, and survival of daughters and granddaughters. Our second objective was to estimate the economic losses related to those outcomes across the United States.

MATERIALS AND METHODS

Records from dams (n = 394), daughters (F_1; n = 156), and granddaughters (F_2; n = 45) used in this study were obtained from 9 experiments conducted in 2008, 2009, 2010, 2011, 2012, 2014, 2015, 2016, and 2018 at the Dairy Unit of the University of Florida, located in Hague, Florida. Data collected over a 10-yr period were pooled together and analyzed. All treatments and procedures of the experiments were approved by the Institutional Animal Care and Use Committee of the University of Florida.

Dam Treatments During Late Gestation

Pregnant multiparous (parity 2.25 ± 0.44) Holstein dams, blocked by mature-equivalent milk production of the previous lactation and parity, were dried off approximately 46 d before expected calving date (~234 d of gestation) according to standard operating procedures of the University of Florida Dairy Unit. Dry-pregnant multiparous dams were either actively cooled (**CL**; n = 196) by the shade of a freestall barn, fans that ran continuously, and water soakers that turned on for 1.5 min duration at a 6-min interval when ambient temperature exceeded 21°C, or not (**HT**; shade only, n = 198) during the last 46 d of gestation, concurrent with the entire dry period. All cows remained in their treatments until calving. All experiments were conducted from June to October with a targeted 46-d dry period occurring between June and September. The average rectal temperature and respiration rates of HT dams during the dry period were 39.4 ± 0.1 °C and 77 ± 1.8 breaths per minute (**bpm**), respectively; compared with 39.1 ± 0.1°C and 51 ± 1.9 bpm for CL dams. A respiration rate over 61 bpm is associated with heat stress in dry cows, indicating that treatments were successfully induced in the dams (Toledo et al., 2019). Studies from do Amaral et al. (2009), Tao et al. (2012), and Fabris et al. (2019) may be referred to for dry and lactating diet composition, feed intakes, and physiological traits of the dams.

Management of Daughters and Granddaughters

Management and environmental conditions were identical for all F_1 and F_2 cows from birth through third lactation. Within 4 h of birth, all female calves (F_1) born to HT or CL dams were fed 3.8 L of high-quality colostrum and housed in a shaded barn in individual wired hutches with access to fans. Thereafter, 1.9 L of pasteurized milk was fed twice a day up to 29 d, and then 3.8 L per feeding to 41 d. Heifers were gradually weaned from 42 to 49 d. Water and starter grain were provided ad libitum. After weaning, heifers were housed in group pastures of 8 to 10 heifers with access to supplemental shade (2.1 × 2.7 m shade cloth) and fed ~3 kg/d of calf starter and hay ad libitum. From d

75 to 130, heifers were fed a mixture of TMR (~4 kg/d) and calf starter (~3 kg/d). At about d 130, heifers were moved to larger group pens and fed ~10 kg/d of TMR until 1 yr of age. Heifers at least 1.3 m tall, more than 340 kg, and over 13 mo of age started the synchronization and AI protocols, which were performed according to Dairy Unit standard operating procedures. Heifers confirmed pregnant were kept on pasture with access to artificial shade (2.1 × 2.7 m shade clothes) and water, and were moved to maternity freestall barns at approximately 2 wk before expected calving day. Upon calving, all dams were fed a TMR and milked twice a day. For all lactations the animals were housed in sand-bedded freestall barns and actively cooled with fans and soakers. At dry-off, all cows were relocated to open pasture with access to artificial shade and water until 2 wk before their expected calving date, when they were moved back to freestall barns. Management and housing conditions of the granddaughters (F_2) were identical to that described for daughters (F_1).

Semen used in dam and daughter fertilization procedures across the 9 experiments was from 78 and 53 different sires, respectively. The PTA for milk production for the sires used to generate daughters (F_1: $\mathbf{CL_{F1}}$ daughters, 591 kg ± 52.3 vs. $\mathbf{HT_{F1}}$ daughters, 551 kg ± 51.6 kg; P = 0.58) and granddaughters (F_2: $\mathbf{CL_{F2}}$ granddaughters, 633 ± 79.9 kg vs. $\mathbf{HT_{F2}}$ granddaughters, 601 ± 83.1 kg; P = 0.78) was similar between treatments across all years.

Retrospective Assessment of Records

Records of dams that were used in more than one experiment, or daughters that were used as dams, were excluded from the current analysis. After data mining, records from 156 daughters that were either exposed (F_1; HT_{F1} n = 79) or not (F_1; CL_{F1} n = 77) to heat stress while developing in utero and 45 granddaughters that were born to F_1 daughters (F_2; CL_{F2} n = 24, HT_{F2} n = 21) were used in the current study.

Milk yield, fat, and protein (yield and %) were measured using Afimilk meters and AfiLab milk analyzers (Afikim Ltd., Kibbutz Afikim, Israel) at each milking and retrieved up to 35 wk in milk (**WIM**). Energy corrected milk was calculated as follows: ECM = [(0.3246 × kg of milk) + (12.86 × kg of fat) + (7.04 × kg of true protein)] (NRC, 2001). Reproductive performance (i.e., conception risk), productive life, lifespan, and culling rates (1/productive life in months) were calculated. Length of productive life (**PL**) was defined as the number of days between date of first calving and date at culling or censoring, and lifespan was defined as the number of days between dates of birth and culling or censoring.

Statistical Analyses of Records

All statistical analyses were conducted in SAS 9.4 (SAS Institute Inc., Cary, NC). Repeated measures of milk yield and components were analyzed by ANOVA using the MIXED procedure. Only milk records from animals that were born in years with 2 or more animals were included in the analysis. The model included fixed effects of treatment (**TRT**) of the dam during the dry period (CL or HT), year of birth (year), WIM, dam's calving season (F_1 only) and TRT by WIM interaction, and animal within TRT as a random effect. Two calving seasons were defined with dams calving from April to September defined as calving during warm season, while dams calving from October to March were defined as calving during cool season. For all lactations, calving season was balanced between groups with 68 and 32% of CL_{F1} born during the warm and cool season, respectively, compared with 74 and 26% for the HT_{F1}. For granddaughters (F_2), the effect of calving season was not included in the model because only records from animals that were born during the warm season (April to September) were kept in the analysis. Given the low number of records of granddaughters (F_2) for second (n = 15) and third lactations (n = 4), only descriptive statistics were analyzed using PROC MEANS.

For the lifespan analysis, time to event data were analyzed using Cox regression model (PROC PHREG) with a fixed effect of TRT and a random effect of year, using the Kaplan-Meier method (PROC LIFETEST). Fertility data were analyzed using the GLIMMIX procedure (fixed effect of TRT and random effect of year). Age at first calving, at first breeding, and PL were analyzed by a MIXED procedure with TRT as fixed effect and year as random effect. Least squares means ± standard error is presented unless otherwise noted. Differences with P-values ≤0.05 were considered statistically significant, and those with P-values >0.05 and ≤0.10 were considered trends.

Economic Loss Associated with Milk Production, Heifer Rearing, and Productive Life

Milk Production. Differences in milk production (kg/d) of CL_{F1} and HT_{F1} measured in the first, second, and third lactations from the 10-yr data set were used to calculate the economic loss related to milk production. Only the daughters (F_1) were included for this analysis. Following the methodology from Ferreira et al. (2016), the average daily temperature-humidity index (**THI**) was calculated per state using daily weather data provided by the National Oceanic and Atmospheric Administration from 2008 to 2013. The data set contained weather data, including average daily temperature (**T**,

°F) and dewpoint (°F), and relative humidity (**RH**) was calculated as follows (Ferreira et al., 2016):

$$\mathrm{RH} = [(173 - 0.1 \times \mathrm{T°F}) + \mathrm{dewpoint}]/ 173 + (0.9 \times \mathrm{T°F}).$$

Data from 50 states was averaged from all available weather stations within each state. Daily temperature was converted from °F to °C. The THI was calculated as follows (Schüller et al., 2014):

$$\mathrm{THI} = (1.8 \times \mathrm{T°C} + 32) - [(0.55 - 0.0055 \times \mathrm{RH}) \times (1.8 \times \mathrm{T°C} - 26)].$$

A heat-stress day was defined as a day in which the average THI ≥68 (Zimbelman et al., 2009), and the number of heat-stress days per state was averaged across years.

Following Ferreira et al. (2016), no seasonality of calving was assumed, and 15% of the cows were assumed to be dry each month. Calving interval was 400 d and all lactations lasted 340 d. Assuming an average cull rate of 35%, and that only conventional semen was used, the distribution of heifers entering the herd based on the lactation number of their dams is similar to the distribution of cows in the herd by lactation number. Therefore, the herd composition structure was set as 35% primiparous, 20% second lactation, and 14% third lactation, and milk losses were only assumed in first, second, and third lactations. In addition, it was assumed that cows were not cooled during the dry period, but they were actively cooled during all lactations. The total number of dairy cows for each of the 50 states in the United States in 2018 were obtained from USDA-ERS (2019).

The economic loss related to decreased milk production (kg/cow per year) were calculated by multiplying the estimated difference in milk production between the 2 treatments ($\mathrm{CL_{F1}}$ vs. $\mathrm{HT_{F1}}$) by the percentage of heat stress days per state, the lactation length (340 d), and the composition of the herd (35% primiparous, 20% second lactation, and 14% third lactation), and adjusted for 365 d. Milk loss (kg/cow per year) was then multiplied by the number of cows in each state to calculate the total milk loss per state per year. A default milk price of $0.44/kg of milk was used, based on the average of the all-US milk prices reported for 2010 to 2015 (Gould, 2016). Feed cost was assumed to be $0.11/kg of milk produced; therefore, the default milk revenue minus feed cost was $0.33/kg of milk (income over feed cost, **IOFC**). Ultimately, the IOFC was multiplied by the average milk loss per state to calculate the economic milk loss per state.

Heifer Rearing. The daily cost of rearing heifers was set as $2.68/d (Tranel, 2019). To estimate the cost associated with heifers leaving the herd before their first lactation, we used (from the 10-yr data set) lifespan estimations and the average age at which the animal left the herd. An interest rate of 5% and a weaning period of 60 d were assumed. First calving age was set at 24 mo.

Total costs of rearing a $\mathrm{HT_{F1}}$ or a $\mathrm{CL_{F1}}$ heifer was calculated as the sum of the costs of heifers that left the herd at the average age (24 mo) plus the sum of costs of rearing heifers that had a first calving. The total cost was divided by the proportion of heifers that calved to obtain the final cost of rearing heifers. The extra costs of raising a $\mathrm{HT_{F1}}$ heifer relative to a $\mathrm{CL_{F1}}$ heifer per state were calculated in a similar fashion as described for milk production.

Productive Life. Differences in PL of $\mathrm{CL_{F1}}$ and $\mathrm{HT_{F1}}$, previously obtained with the 10-yr data set, were used to calculate the economic loss associated with PL. The cost of a 1-mo difference in PL was set at $19 (USDA-AIPL, 2018), which is an estimate of the monthly depreciation in the value of a cow. The difference in PL (in mo) obtained from the 10-yr data set was then multiplied by the percentage of heat stress days per state and by the cost associated with shorter PL. To calculate the cost per year, the final value was multiplied by the percentage of the PL represented by one year.

RESULTS

Lifespan, Productive Life, and Reproductive Performance

Daughters. Daughter ($\mathrm{F_1}$) lifespan differed between groups; the time elapsed between birth and the moment the animal left the herd was reduced by 356 d (11.7 mo) in $\mathrm{HT_{F1}}$ relative to $\mathrm{CL_{F1}}$ (Figure 1a; 1,113 ± 77 vs. 1,469 ± 94 d; $P = 0.01$). The stillborn rate was 3.8% among $\mathrm{HT_{F1}}$, whereas no stillborn cases occurred among $\mathrm{CL_{F1}}$; however, this difference was not significant ($P = 0.32$). In addition, there was no difference in the probability of an animal to leave the herd before reaching weaning age between groups (95 vs. 89% for $\mathrm{CL_{F1}}$ and $\mathrm{HT_{F1,}}$ respectively; $P = 0.16$), with 4 CL and 9 HT daughters leaving the herd before 60 d of age. No difference between groups was observed in the probability of surviving until first breeding (87 vs. 80% for $\mathrm{CL_{F1}}$ and $\mathrm{HT_{F1}}$, respectively; $P = 0.17$), while chances of surviving to first calving tended to be higher in $\mathrm{CL_{F1}}$ relative to $\mathrm{HT_{F1}}$ daughters (82 vs. 71%, respectively; $P = 0.09$). However, the average age at which the animals left the herd before their first calving ($\mathrm{CL_{F1}}$: 322 ± 77,

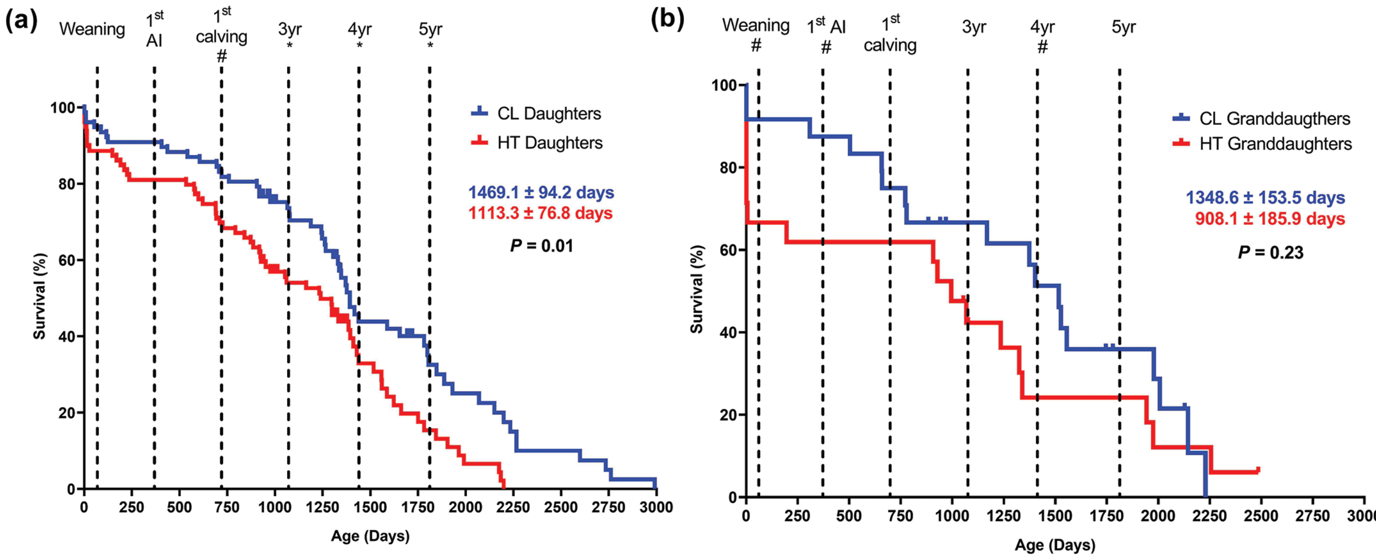

Figure 1. Survival (%) of F_1 daughters (a; n = 156) born to dams under cooling (CL; access to fans, shade, and water soakers) or heat stress (HT; only access to shade) during late gestation (~46 d) and granddaughters (b; n = 45) born to F_1 daughters through weaning (~60 d); first AI (~390 d); first calving (~730 d); and 3 (1,095 d), 4 (1,460 d), and 5 yr (1,825 d) of age. Daughters born to HT dams had a lower longevity ($P = 0.01$) compared with CL daughters. There was no difference between treatments in granddaughters' longevities. * indicates a hazard ratio with $P < 0.05$, # indicates $0.10 \geq P > 0.05$.

vs. HT_{F1}: 272 ± 57 d; $P = 0.56$) was similar between groups. The probability for the animals that made it to lactation to survive through 3, 4, and 5 yr was reduced in HT_{F1} compared with CL_{F1} ($P = 0.02$; Figure 1a). Altogether, once they entered the lactating herd, the PL of HT_{F1}, which represents the number of days between date of first calving and date when the animal left the herd, was reduced by 4.9 mo relative to CL_{F1} (20.9 vs. 25.8 ± 2.4 mo, respectively; $P = 0.05$). Reproductive performance did not differ between treatments; the age at first artificial insemination, the age at first calving, and the conception risks for the heifers' first, second, and third lactations were similar between HT_{F1} and CL_{F1} (Table 1).

Granddaughters. Although reduced by 14.5 mo in HT_{F2} granddaughters, lifespan did not statistically differ between groups (Figure 1b; HT_{F2}: 980 ± 186, vs. CL_{F2}: 1,349 ± 154 d; $P = 0.23$). Stillborn rate, although not statistically significant, was numerically greater for HT_{F2} compared with that for CL_{F2} (28 vs. 8%, respectively; $P = 0.13$). Consistent with the higher stillborn rate, the probability of surviving until weaning age (92 vs. 67%, respectively; $P = 0.06$), and puberty (88 vs. 62%, respectively; $P = 0.08$, Figure 1b) tended to be greater in CL_{F2} relative to HT_{F2}. However, the percentage of heifers leaving the herd before first calving did not differ between groups ($P = 0.26$). The percentage of granddaughters reaching 3 and 5 yr of age was similar between treatments, whereas the percentage of animals reaching 4 yr of age tended to be higher in CL_{F2} relative to HT_{F2}. Ultimately, the PL was similar between treatments (24.1 vs. 27.4 ± 6.0 mo; $P = 0.60$). The age at

Table 1. Reproductive performance of daughters (F_1) and granddaughters (F_2) of cows under cooling (CL, shade of a freestall barn, fans, and soakers) or heat stress (HT, only shade of the barn) during the last 46 d of gestation

	Daughters		Granddaughters	
Item	CL_{F1} vs. HT_{F1} ± SEM	*P*-value	CL_{F2} vs. HT_{F2} ± SEM	*P*-value
Age at first AI (mo)	12.9 vs. 12.8 ± 0.17 (n = 119)	0.79	12.8 vs. 12.4 ± 0.26 (n = 34)	0.05
Conception risk[1] for heifers	0.43 vs. 0.44 (n = 107)	0.97	0.63 vs. 0.53 (n = 31)	0.36
Age at first calving (mo)	23.8 vs. 24.2 ± 0.47 (n = 113)	0.56	22.9 vs. 23.0 ± 1.33 (n = 32)	0.78
Conception risk at first lactation	0.31 vs. 0.40 (n = 105)	0.17	0.33 vs. 0.18 (n = 29)	0.13
Conception risk at second lactation	0.31 vs. 0.21 (n = 53)	0.14	—	—
Conception risk at third lactation	0.15 vs. 0.27 (n = 16)	0.33	—	—

[1]Conception risk was calculated as 1/[1 + exp(estimate from GLIMMIX model)]. GLIMMIX model, SAS Institute Inc. (Cary, NC).

first AI was 0.3 mo earlier for CL_{F2} than for HT_{F2} ($P < 0.01$), but the age at first calving was similar between HT_{F2} and CL_{F2} ($P = 0.36$, Table 1).

Milk Losses Across Generations and Lactations

Daughter Milk Yield and Milk Components. Compared with CL_{F1}, HT_{F1} produced less milk up to 35 wk of the first, second, and third lactations (Figure 2a-c). In the first lactation, milk production of HT_{F1} was reduced by 2.2 kg/d across the 35 WIM compared with CL_{F1} (29.2 and 31.4 ± 0.08 kg/d, respectively; $P < 0.001$; Figure 2a). Relative to CL_{F1}, HT_{F1} produced 1.8 kg/d less during the first WIM. The highest yield for CL_{F1} was achieved at 11 wk with 33.8 kg, whereas HT_{F1} achieved peak yield at 13 wk with 31.2 kg (Figure 2a). In the second lactation, milk production of HT_{F1} was reduced by 2.3 kg/d compared with CL_{F1} (34.4 vs. 36.7 ± 0.13 kg/d, respectively; $P = 0.001$). Specifically, both groups achieved peak milk yield at 6 WIM, with HT_{F1} producing 3.9 kg less milk relative to CL_{F1}, which produced 45.4 kg/d of milk at peak (Figure 2b). In the third lactation, milk production of HT_{F1} was reduced by 6.5 kg/d compared with CL_{F1} (33.1 vs. 39.6 ± 0.22 kg/d, respectively) and there was a treatment by WIM interaction ($P < 0.001$) in which milk yield was lower for HT_{F1} for all WIM, except for the first 6 WIM compared with CL_{F1} (Figure 2c). Peak yield for CL_{F1} was achieved at 12 WIM with 47.4 kg/d, whereas HT_{F1} peak yield was 40.5 kg/d at 6 WIM with yield decreasing gradually thereafter. Table 2 depicts milk and ECM yields and milk components (fat and protein percentage and yield) of CL_{F1} or HT_{F1} for lactations 1, 2, and 3. Briefly, ECM yield was consistently higher across all lactations in CL_{F1} relative to HT_{F1} ($P < 0.001$). Fat and protein yields were lower for HT_{F1} compared with CL_{F1} across all 3 lactations ($P < 0.001$). There was an interaction between treatment and WIM for protein yields in third lactation ($P < 0.001$) and for fat yield in lactations 2 and 3 ($P < 0.05$). Overall, protein percentage was similar between groups in first lactation ($P = 0.66$), whereas it was higher for HT_{F1} in second lactation, and higher for CL_{F1} in third lactation. Fat percentage was higher for HT_{F1} in first lactation, but lower in second and third lactations compared with CL_{F1}.

Granddaughter Milk Yield and Milk Components. Compared with CL_{F2}, HT_{F2} produced less milk during the first ($P < 0.001$; Figure 3), second, and third lactations (Table 2). More specifically, in the first lactation depicted in Figure 3, there was an interaction between groups (HT_{F2} vs. CL_{F2}) and WIM ($P < 0.001$), with HT_{F2} producing less ($P < 0.001$) milk relative to CL_{F2} for 15 out of 35 WIM, and overall producing 1.3 kg/d less milk than CL_{F2} (29.9 vs. 31.2

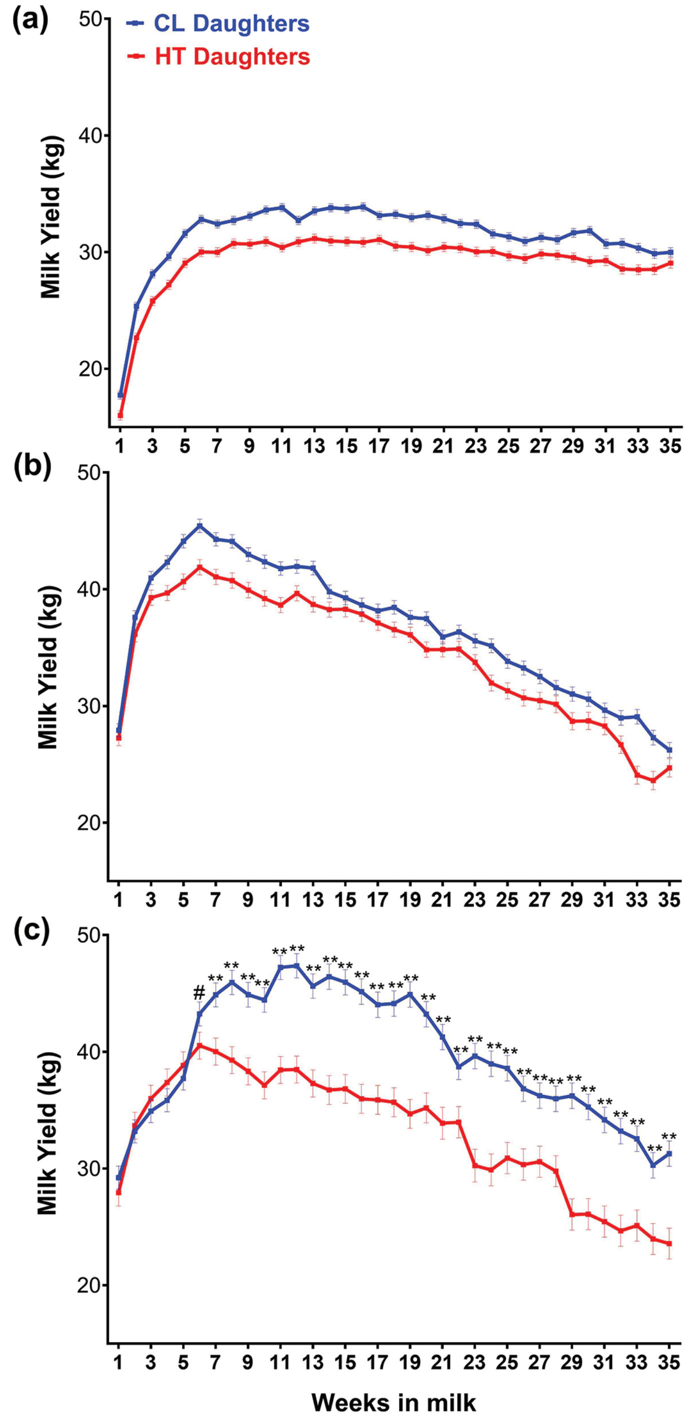

Figure 2. Milk yield in the first (a; n = 108), second (b; n = 54), and third (c; n = 19) lactation of daughters (F_1) born to dams under cooling (CL; access to fans, shade, and water soakers) or heat stress (HT; only access to shade) during late gestation (~46 d). All daughters had access to active cooling (e.g., shade of a freestall barn, fans, and water soakers) during their first, second, and third lactations. Data from daughters born from 10 different experiments were analyzed. Daughters born to HT dams produced less milk up to 35 wk postpartum in all 3 lactations compared with those born to CL dams ($P < 0.001$). All data are presented as LSM ± SEM. For third lactation daughters, ** indicates $P < 0.01$ and # indicates $0.10 \geq P > 0.05$.

Table 2. Milk yield and composition in the first (n = 108), second (n = 54), and third (n = 19) lactations of daughters (F_1) born to dams exposed to cooling (CL, access to fans, shade, and water soakers) or heat stress (HT, only access to shade) during pre-calving (~last 46 d of gestation)[1]

				P-values				
Item	CL_{F1}	HT_{F1}	SEM	TRT[2]	WIM[3]	Year[4]	Season[5]	TRT × WIM[6]
Daughters' 1st lactations								
Milk (kg/d)	31.4	29.2	0.08	<0.001	<0.001	<0.001	<0.001	0.19
ECM[7] (kg/d)	31.6	29.3	0.08	<0.001	<0.001	<0.001	<0.001	0.99
Fat (%)	3.67	3.69	0.005	0.03	<0.001	<0.001	<0.001	<0.001
Fat (kg/d)	1.14	1.07	0.003	<0.001	<0.001	<0.001	<0.001	0.89
Protein (%)	3.00	3.00	0.003	0.66	<0.001	<0.001	<0.001	<0.001
Protein (kg/d)	0.94	0.87	0.002	<0.001	<0.001	<0.001	<0.001	0.17
Daughters' 2nd lactations								
Milk (kg/d)	36.7	34.4	0.13	<0.001	<0.001	<0.001	<0.001	0.19
ECM (kg/d)	36.9	34.5	0.14	<0.001	<0.001	<0.001	<0.001	0.44
Fat (%)	3.66	3.64	0.008	0.008	<0.001	<0.001	0.02	<0.001
Fat (kg/d)	1.33	1.24	0.005	<0.001	<0.001	0.23	<0.001	0.03
Protein (%)	3.05	3.08	0.006	0.001	<0.001	<0.001	0.04	<0.001
Protein (kg/d)	1.11	1.05	0.005	<0.001	<0.001	<0.001	<0.001	0.35
Daughters' 3rd lactations								
Milk (kg/d)	39.6	33.1	0.22	<0.001	<0.001	<0.001	<0.001	<0.001
ECM (kg/d)	39.4	31.9	0.23	<0.001	<0.001	0.006	<0.001	<0.001
Fat (%)	3.67	3.45	0.01	<0.001	<0.001	<0.001	0.55	<0.001
Fat (kg/d)	1.44	1.14	0.01	<0.001	<0.001	0.23	<0.001	0.003
Protein (%)	2.86	2.78	0.008	<0.001	<0.001	<0.001	<0.001	0.0014
Protein (kg/d)	1.13	0.92	0.007	<0.001	<0.001	<0.001	<0.001	<0.001

[1]All daughters had access to cooling during their first, second, and third lactations.

[2]TRT = dam's treatment (CL vs. HT).

[3]WIM = weeks in milk (1–35 wk).

[4]Birth year (2008–2016).

[5]Season of calving (April–September; October–March).

[6]Interaction TRT × WIM.

[7]Value corrected for 3.5% fat and 3.2% true protein using formula from NRC (2001): ECM = [(0.3246 × kg of milk) + (12.86 × kg of fat) + (7.04 × kg of true protein)].

± 0.22 kg/d, respectively; $P < 0.001$) across the 35 WIM. In addition, descriptive statistics indicated that HT_{F2} overall produced 8.0 and 4.9 kg/d less relative to CL_{F2} during second (27.8 vs. 39.8 kg/d) and third (33.7 vs. 38.6 kg/d) lactations, respectively (Table 3). Results for granddaughters' milk and ECM yields and milk components (fat and protein percentage and yield) are summarized in Table 3. Briefly, ECM yield was consistently higher across first ($P < 0.001$), second, and third lactation in CL_{F1} relative to HT_{F1}. In addition, there was an interaction between groups (HT_2 vs. CL_{F2}) and WIM for ECM, fat and protein yields, and fat and protein percentages in first lactation ($P < 0.001$).

Economic Losses Associated with Late-Gestation Heat Stress

Heat Stress Days and Cow Demographics by State. The number of cows per state in the United States in 2018 and the calculated number of heat stress days per state are depicted in Figure 4. According to the USDA-ERS (2019), there were 9,396,800 dairy cows present in the United States in 2018. Of these, 1,409,520 (15%) were assumed to be dry at any point in time. Although the weighted average of number of heat stress days in the United States per year was 66, California, New Mexico, and Texas (that house 28% of all US dairy cows) had 69, 48, and 164 heat stress days per year, respectively. Florida had the greatest number of heat stress days per year with 219 d, which means that on average 60% of the cows in Florida would experience heat stress during their dry periods if not cooled. In cooler northern states; for example, Iowa and Ohio, 20% of the dry cows would experience heat stress if not cooled. In 17 out of 50 states, at least 25% of the dry-pregnant cows would experience heat stress during the year if not cooled.

Economic Loss Associated with Rearing of the Daughters. Given that less HT_{F1} survived until first calving relative to CL_{F1} (71 vs. 82%) and that there was no difference in the age at which the animals left the herd before first calving between HT_{F1} and CL_{F1} (322 ± 77 vs. 272 ± 57 d), the cost of rearing a heifer from birth to first calving would be \$157.49 greater if the heifer is born from a HT dam. Therefore, when accounting for the percentage of HT days per year per state, an average US dairy farm would have an extra heifer rearing cost of $14.26/cow per year. Extra rearing costs per cow per year were $47.25 in Florida, representing losses of $5.7 million. Collectively, the total losses associated with extra rearing costs of heifers in the United States would sum to $134 million per year (Figure 5).

Economic Loss Associated with Reduced Productive Life of the Daughters. Reduced number of days between first calving and date at death or culling has a negative impact on profitability. An average US dairy farm would have an extra loss associated with a shorter PL due to heat stress of $9.61 per cow per year, which collectively in the United States would represent losses of up to $90 million if dry cows were not cooled (Figure 5).

Economic Loss Associated with Reduced Milk Yield of the Daughters. An average US dairy farm with daughters (35% primiparous, 20% second lactation, and 14% third lactation) born to dams that experienced heat stress during the dry period (i.e., not cooled at least during the last 46 d of gestation) would lose 120 kg of milk per daughter per year. This estimation assumes that all dry cows at risk of heat stress per state are not cooled and that cows beyond their third lactation have no milk losses. Figure 5 summarizes the annual economic loss associated with supplemental heifer rearing costs, reduced PL length, and milk yield of the daughters born to dams exposed to heat stress during late gestation per state for the 24 states with the most dairy cows, and for Florida with the highest days of heat stress per year.

These milk losses associated with the reduced milk yield of daughters born to dams exposed to heat stress during late gestation translates to substantial economic losses nationally. For the top 3 states with the most dairy cows (California, Wisconsin, and New York) and the 2 states with the greatest number of heat stress days per year (Florida and Texas), the average milk losses per year of the daughter lactations were 125, 88, 94, 398, and 299 kg, respectively. Collectively in the US, weighted by the number of cows in each state, annual losses of the daughters would be $371 million ($39/daughter/year) if the milk price is $0.44/kg of milk and IOFC is $0.33/kg of milk. In California, Wisconsin, New York, Florida, and Texas, the total economic losses of the daughters would be approximately $71, $37, $16, $19, and $53 million per year, respectively, and the average annual losses per cow per year for those states would be $41, $29, $31, $155, $98, respectively. When the milk price is reduced from $0.44 to $0.33 per kg, total weighted annual losses in the United States would be $246 million, and the average loss per cow per year would be $26. Economic losses associated with reduced survival, PL, and milk yield of F_1 born to dams under heat stress when dry for all 50 states are presented in Appendix Table A1.

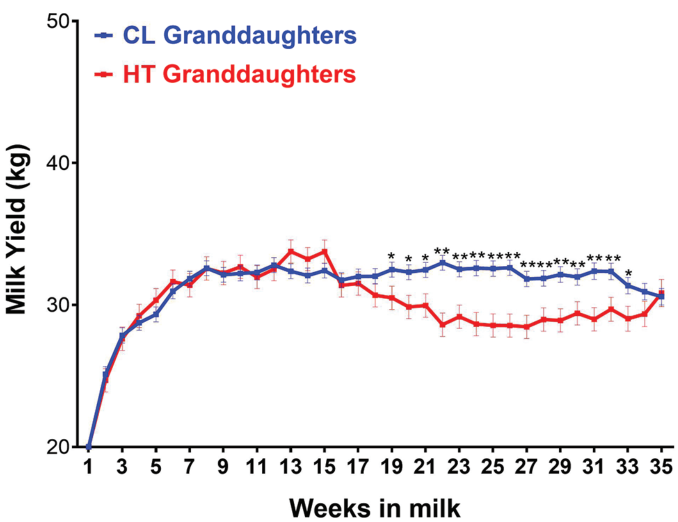

Figure 3. Milk yield in the first lactation of granddaughters (n = 23) of cows that were exposed to cooling (CL; access to fans, shade, and water soakers; n = 16) or heat stress (HT; only access to shade; n = 7) while pregnant (~last 46 d) with their mothers. Thus, the mothers experienced heat stress or cooling through the intrauterine environment the last 46 d of gestation. Data from granddaughters born from 10 different experiments were analyzed. All granddaughters had access to active cooling (e.g., shade of a freestall barn, fans, and water soakers) during their first, second, and third lactations. The HT granddaughters produced less milk postpartum in the first lactation compared with CL granddaughters. Data are presented as LSM ± SEM, and ** indicates $P < 0.01$ and * indicates $P < 0.05$.

DISCUSSION

Understanding of the carryover effects of late-gestation maternal exposure to heat stress on subsequent generations is relatively limited. Moreover, past economic analyses aiming at quantifying economic losses from heat stress were restricted to immediate effects during lactation and on young stock (St-Pierre et al., 2003), or to delayed effects observed in the subsequent lactation when heat stress occurs during the dry period without accounting for carryover detriments for the next generation (Ferreira et al., 2016). Herein, we quantify the long-lasting effects of maternal exposure to heat stress during late gestation on milk yield, reproductive performance, and survival of daughters and granddaughters, and estimate the economic losses associated with those outcomes across the United States.

First, we showed that maternal late-gestation heat stress negatively affected daughter survival from birth to first calving, length of PL, and milk performance, including milk and ECM yields. Carryover effects of maternal heat stress is not restricted to dairy cows; a previous study conducted in sows also reported that in utero heat stress impeded lactation performance (Wiegert et al., 2015). Further, lifelong consequences of in utero heat stress were previously reported in a companion study that used an experimental design comparable to the present analysis, but included fewer records and was of animals that were only followed until first lactation (Monteiro et al., 2016). These authors reported that heifers exposed to heat stress in utero had a lower survival rate and produced 5.1 kg/d less in the first lactation compared with heifers not exposed to heat stress through the intrauterine environment. In the present study, we included records from 9 experiments with data collected over the course of 10 yr, which allowed us to follow the animals for 3 lactations, and we ensured that offspring records included in the analysis were not from dams exposed to multiple treatments or used in different years. Ultimately, our results suggested that in utero heat stress exerts negative effects on a daughter's longevity and milk production that will persist through 3 lactations.

A variety of factors can potentially explain the lower survivability and milk output in HT_{F1} daughters relative to CL_{F1} daughters that were not exposed to heat stress while developing in utero. Late-gestation heat stress may alter the intrauterine environment, which might, in turn, exert epigenetic changes on the fetal genome (i.e., fetal programming) and result in different immune, metabolic, and mammary phenotypes at adulthood. For instance, dairy calves exposed to heat stress in utero have impaired passive immune transfer due to lower apparent IgG absorption (Tao et al., 2012; Laporta et al., 2017), decreased total plasma protein and hematocrit, and compromised cellular immune function compared with daughters born to cool dams (Tao et al., 2012). In addition, in utero heat stress can result in a metabolically inefficient phenotype, with calves born to late-gestation heat-stressed dams having higher plasma insulin concentration at d 1 after birth (Tao and Dahl, 2013) and faster glucose clearance during a glucose tolerance test and an insulin challenge (Tao et al., 2014). In utero heat-stressed heifers were also reported to have smaller mammary alveoli comprised of fewer milk secretory cells during their first lactation relative to heifers born to cooled dams (Skibiel et al., 2018a). Further, intrauterine heat stress exerts

Table 3. Milk yield and composition in the first (n = 23), second (n = 11), and third lactations (n = 4) of granddaughters (F_2) of cows exposed to cooling (CL, access to fans, shade, and water soakers) or heat stress (HT, only access to shade) while pregnant (~last 46 d) with their daughters

				P-values			
Item	CL_{F2}	HT_{F2}	SEM or SD[1]	TRT[2]	WIM[3]	Year[4]	TRT × WIM[5]
Granddaughters' 1st lactations							
Milk (kg/d)	31.2	29.9	0.22	<0.001	<0.001	<0.001	<0.001
ECM[6] (kg/d)	31.3	30.2	0.15	<0.001	<0.001	<0.001	<0.001
Fat (%)	3.69	3.69	0.008	0.91	<0.001	<0.001	0.0004
Fat (kg/d)	1.14	1.10	0.007	<0.001	<0.001	<0.001	<0.001
Protein (%)	2.98	3.04	0.008	<0.001	<0.001	<0.001	<0.001
Protein (kg/d)	0.92	0.91	0.006	0.03	<0.001	<0.001	<0.001
Granddaughters' 2nd lactations							
Milk (kg/d)	39.8	27.8	8.3	—	—	—	—
ECM (kg/d)	39.6	29.2	7.7	—	—	—	—
Fat (%)	3.67	3.77	0.58	—	—	—	—
Fat (kg/d)	1.45	1.06	0.32	—	—	—	—
Protein (%)	2.85	3.19	0.37	—	—	—	—
Protein (kg/d)	1.45	1.06	0.32	—	—	—	—
Granddaughters' 3rd lactations							
Milk (kg/d)	38.6	33.7	12.0	—	—	—	—
ECM (kg/d)	39.2	34.7	10.9	—	—	—	—
Fat (%)	3.76	3.92	0.56	—	—	—	—
Fat (kg/d)	1.45	1.31	0.42	—	—	—	—
Protein (%)	2.94	2.90	0.48	—	—	—	—
Protein (kg/d)	1.13	0.97	0.33	—	—	—	—

[1]Least squares means and standard error of the mean for the main effect of treatment (TRT).

[2]TRT = dam's treatment (CL vs. HT).

[3]WIM = weeks in milk (1–35 wk).

[4]Birth year (2008–2016).

[5]Interaction TRT × WIM.

[7]Value corrected for 3.5% fat and 3.2% true protein using formula from NRC (2001): ECM = [(0.3246 × kg of milk) + (12.86 × kg of fat) + (7.04 × kg of true protein)].

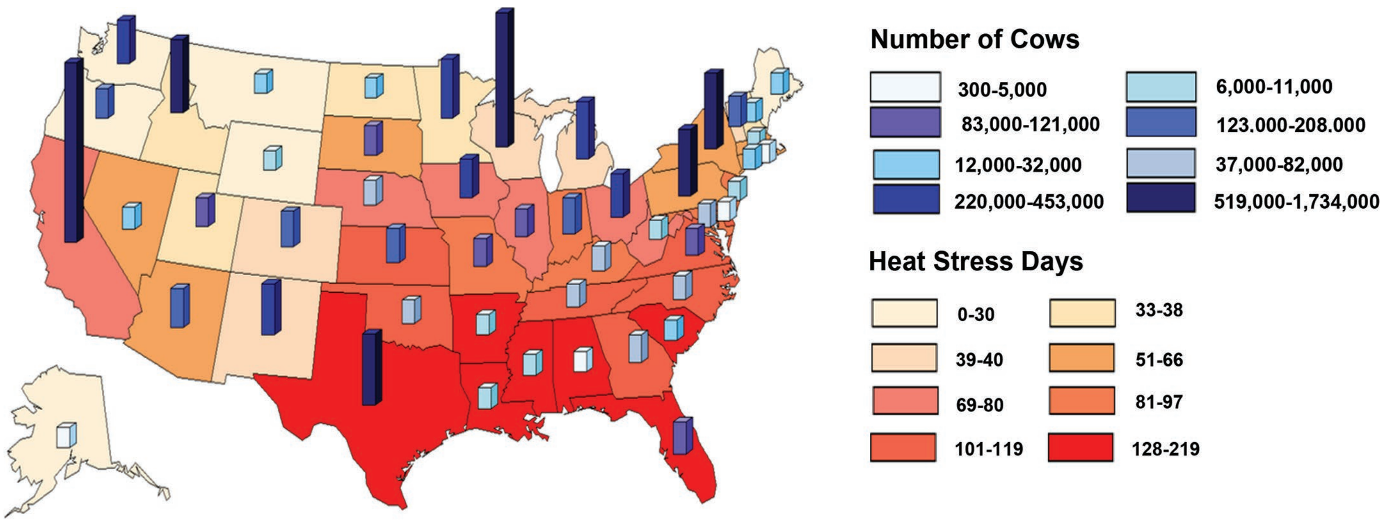

Figure 4. Number of dairy cows (dry and milking) per state (USDA-ERS, 2019) and number of heat stress days per state (NOAA, 2019). Taller bars represent more cows within each cow number range. A heat stress was declared when average daily temperature-humidity index was equal to or greater than 68. The number of heat stress days per state in each year from 2007 to 2013 was calculated and averaged across the years.

epigenetic changes in the mammary gland of heifers in their first lactation, 3 years after in utero exposure occurred (Skibiel et al., 2018b). Our results indicate that indirect intrauterine exposure to heat stress may alter developmental trajectories and initiate a combination of inefficient phenotypes that will ultimately contribute to the poorer lifetime performance of in utero heat-stressed daughters compared with their counterparts born to cooled dams.

Second, we demonstrated that reduced milk production through first, second, and third lactation, survivability through first calving, and reduced PL of HT_{F1} daughters could substantially impact the profitability of the US dairy sector with estimated losses up to $595 million per year. When considering heat stress related effects on the DMI, growth, and survival of dairy heifers and on the DMI, health, and performance of lactating cows, St-Pierre et al. (2003) reported annual losses of $1.507 billion in the absence of heat abatement. When only accounting for losses from subsequent milk production in multiparous cows that were heat stressed during the entire dry period (60 d before calving), Ferreira et al. (2016) reported annual losses of $810 million dollars for the US dairy sector, and showed that cooling dry cows is profitable in most states, even when building infrastructure is necessary. Therefore, in the United States , the total annual economic losses from dry cow heat-stress could increase to $1.405 billion from losses in subsequent milk production of the dam ($810 million from Ferreira et al., 2016) and financial damage from in utero heat stress ($595 million, calculated in the current study), which is similar in magnitude to those previously calculated for dairy heifers (from 0–1 yr and 1–2 yr) and lactating cows ($1.507 billion by St-Pierre et al., 2003). Ultimately, the present work reinforces the necessity of cooling dry cows to optimize profitability. Given the observed detriments for multiparous cows, cooling late-gestation heifers may also be of interest for dairy producers and warrants further research.

The economic analysis of in utero heat stress presented in the current study relies on a series of assumptions that may have affected the results in different ways. When calculating the costs associated with heifer rearing, we assumed a difference in the survivability of the heifers, even though in the present study only a tendency was found ($P = 0.09$). In addition to this type I error, we might be incurring a type II error. We therefore used the numerical differences for the economic analysis (Galligan et al., 1991). Additionally, we assumed an average 35% annual cow cull rate. However, cull rates across the United States vary, and this variation might affect the distribution of cows by lactation number in a herd (Pinedo et al., 2010), which may affect the economic losses associated with late-gestation in utero heat stress. Given that the exact number of dry cows experiencing heat stress (or actively cooled) in the United States is currently unknown, estimates presented in the current study likely represent an upper bound of the economic losses from the carryover effects of maternal heat stress exposure. Relative to their lactating counterparts, dry cows are less frequently considered for heat abatement as detriments are not as readily apparent and are only observed in the subsequent lactation (Negrón-Pérez et al., 2019). However, in practice, a growing proportion of US dairies, especially in the southern part of the country, are providing heat-abatement technologies for dry cows (Dado-Senn et al., 2019a). The assumption that no dry cow is provided heat stress abatement may cause overestimation of the proportion of dry cows experiencing heat stress per year, thereby overestimating overall economic losses of in utero heat stress. Moreover, the number of hours per day during which the animals were exposed to heat stress versus exposed to conditions that could alleviate accumulated heat load were not accounted for in the present calculations, and is presumably different for each state. This could shift the number of heat stress days across the United States . In contrast, it is likely that the total number of heat stress days will increase across the United States as average temperatures rise with climate change (Key and Sneeringer, 2014). Thus, more regions of the United States are likely to experience significant heat stress events in the future.

An average THI ≥68 was used to determine whether or not a dry cow is exposed to conditions susceptible to cause heat stress (Zimbelman et al., 2009). This threshold was developed for lactating dairy cows producing more than 35 kg/d and ignores the severity of heat stress and the fact that heat tolerance may vary depending on the climate where the animal was reared (Kadzere et al., 2002). Dry cows generate less metabolic heat relative to lactating cows, and are theoretically less sensitive to heat stress. However, the dry cow's endocrine system was shown to be more sensitive to moderate heat stress because heat stress reduces the concentrations of plasma thyroxine and placental estrogen, in turn leading to an impairment in growth and postpartum function of maternal tissues (Collier et al., 1982). Therefore, a THI ≥68 might only be proposed as a potential indicator of heat stress in dry cows as previously stated by Ferreira et al. (2016). Lastly, seasonality in reproductive performance was not considered in the current study, as 15% of the herd was assumed to be dried off throughout the year, regardless

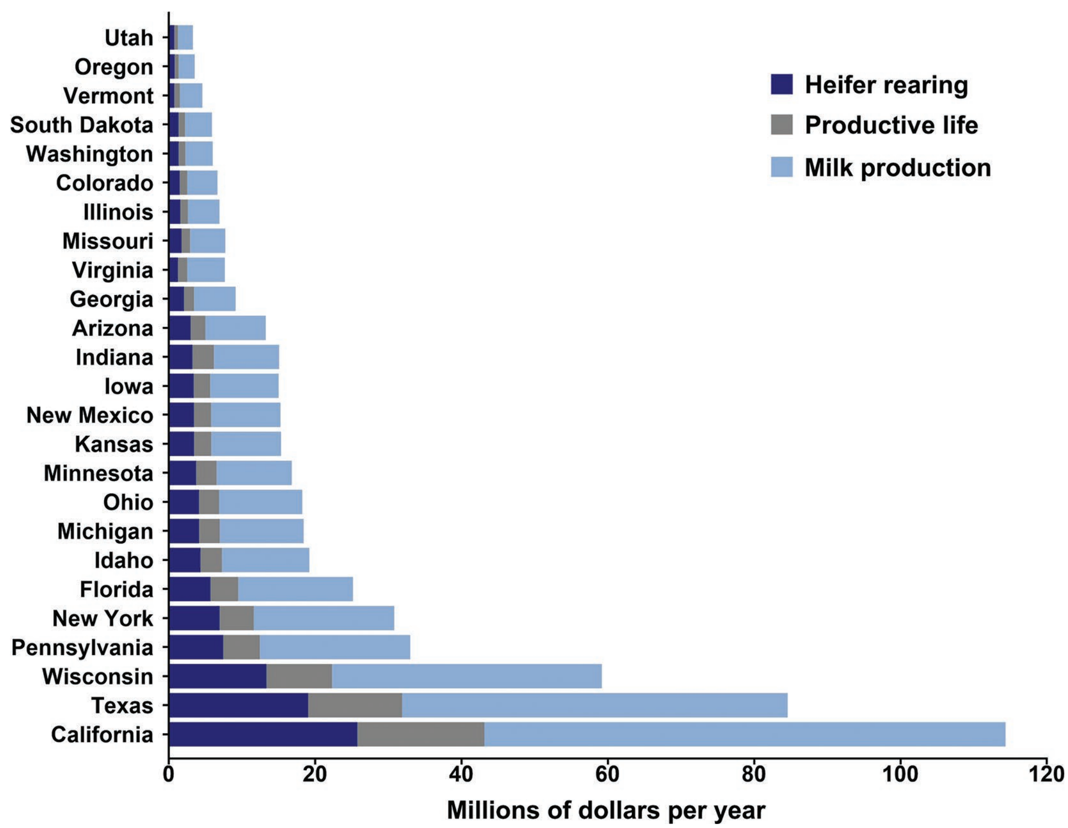

Figure 5. Annual economic loss (millions of dollars) associated with extra heifer rearing costs, reduced productive life length, and milk yield of daughters born to dams exposed to heat stress during late gestation (F_1) for the top 24 states with the most dairy cows, and Florida, the state with the most heat stress days per year. We assumed an additional rearing cost of $157.49 per heifer, reduced productive life length of 4.9 mo, and an average loss of 2.2, 2.3, and 6.5 kg/d per 340 d for lactations 1, 2, and 3, respectively. Collectively, in the United States, the economic losses for additional heifer rearing cost, reduced productive life, and reduced milk yield of the F_1 offspring were estimated at $134, $90, and $371 million per year, respectively.

of the season. However, more cows are dried off in the warmer season than the cooler season in the southeastern United States (de Vries and Risco, 2005), which can lead to an increase in the estimated total loss of milk not produced due to in utero heat stress.

In addition to effects on the F_1 daughters, our results indicated that effects of late-gestation heat stress may persist through multiple generations. Our data show that fewer HT_{F2} granddaughters survive through puberty, and those that survive produce less milk, at least during their first lactation, relative to CL_{F2}. These results are consistent with evidence suggesting that heat stress exposure during in utero development may have direct effects on the germ cells of the developing fetus, potentially leading to phenotype alteration of the daughters, and possibly granddaughters (Skinner, 2011; Feeney et al., 2014). Further studies with a larger number of animals are warranted to determine if these effects in granddaughters persist into subsequent lactations and to unravel the underlying mechanisms that might explain the observed outcomes.

CONCLUSIONS

Maternal heat stress during late gestation reduces daughter survivability and milk production for up to 3 lactations. Consequently, the average US dairy cow would have a 5 mo shorter PL, and lose an average of 120 kg of milk per year if exposed to heat stress while developing in utero. Annual losses for the dairy sector arising from in utero heat stress, including milk loss in multiple lactations, reduced PL, and additional heifer rearing costs, would be $595 million if dry cows were not cooled. Additionally, dry-period heat stress seems to exert carryover effects on the survivability and the productivity of the second-generation offspring. Cooling dry-pregnant cows is not only crucial to rescue dam subsequent lactation milk loss, but also to ensure optimal survivability and productivity of their daughters and granddaughters.

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APPENDIX

Table A1. Summary of number of dry cows, heat stress days, and annual economic loss (millions of dollars) associated with supplemental heifer rearing costs, reduced productive life length, and milk yield of daughters born to dams exposed to heat stress during late gestation (F_1) for 49 US states

State	Dry cows (no.)	Annual heat stress (d)	Heifer rearing cost (million $)	Productive life cost (million $)	Milk loss (million $)	Total loss (million $)
Alabama	750	139	0.15	0.10	0.42	0.67
Alaska	45	0	0.00	0.00	0.00	0.00
Arizona	31,200	66	2.98	2.01	8.25	13.24
Arkansas	900	132	0.17	0.12	0.47	0.76
California	260,100	69	25.76	17.36	71.24	114.36
Colorado	26,400	39	1.49	1.01	4.13	6.62
Connecticut	2,850	58	0.24	0.16	0.65	1.05
Delaware	720	101	0.10	0.07	0.29	0.47
Florida	18,000	219	5.67	3.82	15.68	25.17
Georgia	12,300	116	2.06	1.39	5.69	9.14
Idaho	91,350	33	4.33	2.92	11.96	19.21
Illinois	13,500	80	1.56	1.05	4.30	6.91
Indiana	27,600	81	3.23	2.18	8.94	14.36
Iowa	33,000	71	3.38	2.28	9.35	15.01
Kansas	23,850	101	3.45	2.33	9.55	15.33
Kentucky	8,250	96	1.14	0.77	3.15	5.05
Louisiana	1,650	165	0.39	0.26	1.08	1.74
Maine	4,500	24	0.15	0.10	0.42	0.68
Maryland	6,750	97	0.94	0.63	2.60	4.18
Massachusetts	1,650	54	0.13	0.09	0.35	0.57
Michigan	63,600	45	4.15	2.80	11.48	18.43
Minnesota	67,950	38	3.72	2.51	10.29	16.52
Mississippi	1,350	150	0.29	0.20	0.80	1.29
Missouri	12,450	97	1.74	1.17	4.81	7.73
Montana	1,800	29	0.07	0.05	0.21	0.33
Nebraska	9,000	72	0.94	0.63	2.59	4.16
Nevada	4,800	51	0.35	0.24	0.97	1.56
New Hampshire	1,800	38	0.10	0.07	0.27	0.44
New Jersey	900	86	0.11	0.07	0.31	0.49
New Mexico	49,500	48	3.44	2.32	9.51	15.26
New York	93,450	52	6.94	4.68	19.19	30.81
North Carolina	6,600	118	1.12	0.76	3.10	4.98
North Dakota	2,250	35	0.11	0.08	0.32	0.51
Ohio	38,850	74	4.11	2.77	11.37	18.25
Oklahoma	6,000	119	1.03	0.69	2.84	4.56
Oregon	18,450	30	0.80	0.54	2.21	3.55
Pennsylvania	77,850	66	7.43	5.01	20.56	33.00
Rhode Island	105	37	0.01	0.00	0.02	0.03
South Carolina	2,100	128	0.39	0.26	1.07	1.72
South Dakota	18,150	51	1.33	0.89	3.67	5.88
Tennessee	5,550	117	0.93	0.63	2.58	4.14
Texas	80,550	164	19.05	12.84	52.69	84.59
Utah	15,000	34	0.74	0.50	2.05	3.29
Vermont	19,050	41	1.11	0.75	3.07	4.93
Virginia	12,450	104	1.86	1.25	5.14	8.24
Washington	41,550	23	1.35	0.91	3.74	6.01
West Virginia	1,050	75	0.11	0.08	0.31	0.50
Wisconsin	191,100	49	13.33	8.98	36.87	59.18
Wyoming	900	28	0.04	0.02	0.10	0.16