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Quantification of the effect of in-*utero* events on lifetime resilience in dairy cows

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ABSTRACT

Currently, the dairy industry is facing many challenges that could affect its sustainability, including climate change and public perception of the industry. As a result, interest is increasing in the concept of identifying resilient animals, those with a long productive lifespan, good reproductive performance and milk yield. There is much evidence that events in utero, i.e., the Developmental Origins of Health and Disease (DOHaD), alter life-course health of offspring and we hypothesized that these could alter resilience in calves, where resilience is identified using lifetime data.

The aim of this study was to quantify lifetime resilience scores (LRS) using an existing scoring system based on longevity with secondary corrections for age at first calving and calving interval and to quantify the effects of *in-utero* events on the LRS using 2 data sets. The first was a large data set of cattle in 83 farms in Great Britain born from 2006 to 2015 and the second was a smaller, more granular data set of cattle born between 2003 and 2015 in the Langhill research herd at Scotland's Rural College. Events during dam's pregnancy included health events (lameness, mastitis, use of an antibiotic or anti-inflammatory medication), the impact of heat stress as measured by temperature-humidity index and perturbations in milk yield and quality (somatic cell count, percentage fat, percentage protein and fat:protein ratio).

Daughters born to dams that experienced higher temperature-humidity indexes while they were *in-utero* during the first and third trimesters of pregnancy had lower LRS. Daughter LRS scores were also lower where milk yields or median fat percentages in the first trimester were low, and when milk yields were high in the third trimester. Dam LRS was positively associated with LRS of their offspring, however, as parity of the dam increased, LRS of their calves decreased. Similarly, in the Langhill herd, dams of a higher parity produced calves with lower LRS. Additionally, dams which recorded a high max locomotion score in the third trimester of pregnancy were negatively associated with lower calf LRS in the Langhill herd.

Our results suggest that events that occur during pregnancy have lifelong consequences for the calf's lifetime performance. However, experience of higher temperature-humidity indexes, higher dam LRS scores and mothers in higher parities explained a relatively small proportion of variation in offspring LRS, which suggests that other factors play a substantial role in determining calf LRS scores. While 'big data' can contain a considerable amount of noise, similar findings between the 2 data sets indicate it is likely these findings are real.
Key words: Dairy cow resilience, developmental origins of health and disease, heat stress

INTRODUCTION

In light of the current challenges facing the dairy industry, such as climate change and public perception, there is increasing interest in the concept of cow resilience as a way to increase sustainability of dairy farming. Resilience encompasses an animal's capacity to cope with environmental, social and disease challenges and cows that are considered resilient have a high probability of completing many lactations with a good reproductive performance and few health problems (Ahlman et al., 2011; Adriaens et al., 2020; Ouweltjes et al., 2021). Resilient cows therefore cope well with the

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farm's management and environmental conditions and avoid premature culling.

One factor that influences an individual's lifetime health (and by proxy their resilience) is the *in-utero* environment in which they were gestated – known as the Development Origins of Health and Disease (DOHaD). There is substantial evidence for this in humans, for example there are several epigenetic effects associated with prenatal exposure to hunger (Vaiserman and Lushchak, 2021). It has already been demonstrated in cattle that nutritional restriction can alter numbers of oocytes in an animals ovarian reserve (Mossa et al., 2009) and *in-utero* heat stressed heifers have mammary glands with smaller alveoli (Skibiel et al., 2018a). Being able to identify resilient animals based on the events experienced by their mother during pregnancy could help inform farm management decisions. In particular, the impact of heat-stress on fetus development is of interest to the dairy industry because climatic disturbances are likely to increase as a result of climate change (Hansen et al., 2012). When the impact of heat-stress on the fetus is known, the importance of preventing heat-stress is better substantiated.

To quantify resilience, indicative traits are used because resilience itself is difficult to measure directly. A definition of resilience agreed by the EU Horizon 2020 GenTORE consortium (Friggens and De Haas, 2019) is that resilience can be considered as the cumulative effect of good health and fertility, resulting in a long productive life span. Using this definition, quantitative lifetime resilience scores can be calculated by allocating points based primarily on the number of lactations completed, and the cow's productive performance relative to the rest of the herd (Adriaens et al., 2020; Ouweltjes et al., 2021). These scores allow resilience to be identified from commercially available data, but do not account for factors that may vary within farms, such as changes in management over time (Adriaens et al., 2020). While it is possible to quantify resilience using these scores, there is limited knowledge about factors associated with between-cow heterogeneity in resilience score.

Developmental Origins of Health and Disease (DOHaD) (Barker, 2007; Fleming et al., 2015) suggests that events experienced in very early life, from the peri-conception period to birth, have lifelong effects. In dairy cows, these environmental sources of stressors include disease events, metabolic and nutritional status or environmental disturbances, such as high environmental temperature or humidity. There is evidence that disease experienced by mothers during pregnancy is associated with performance of the offspring; daughters born to mothers that had experienced clinical health events around conception had fewer incidences of disease themselves as young heifers/first lactation animals (Carvalho et al., 2020) and those from dams with higher mean somatic cell counts had a greater age at first calving, increased first and second lactation mean somatic cell count, and reduced yield (Swartz et al., 2021). These changes may occur because the inflammatory response of the dam results in post-natal adaptations in the calf, which induce adaptive changes in the conceptus that may improve it's tolerance to postnatal health problems. This has been demonstrated in mouse models where adult offspring of mothers that experienced immune challenge while pregnant are hyper-sensitive to inflammatory stimuli (Williams et al., 2011). The exact mechanism for this in cattle is currently unknown, but possible pathways include a sub-optimal uterine environment (Aiken and Ozanne, 2014), inheritance of mitochondrial dysfunction (Igosheva et al., 2010) or epigenetic alterations (Ozanne and Constância, 2007).

In the UK, cattle currently experience relatively few days of heat-stress (Dunn et al., 2014) but by the end of the 21st century, heat-stress events are likely to increase (Fodor et al., 2018). Heat-stress experienced during gestation has been found to have detrimental effects, calves born to mothers that have experienced heat-stress in late gestation have lower birth and weaning weights (Collier et al., 1982; Tao et al., 2012), lower probability of survival and reduced lifetime performance (Monteiro et al., 2016; Weller et al., 2021). Some possible reasons for this could either be that heat stress alters maternal physiology resulting in increased maternal core body temperature and changes in placental mass and blood flow which leads to dysfunction (Reynolds et al., 1990, 2006; Van Eetvelde et al., 2016) or heat stress alters maternal behavior, for example heat-stressed mothers reduce their feed intake and alter their lying behavior (Mallonée et al., 1985; Allen et al., 2015; Kanjanapruthipong et al., 2015). These alterations in behavior can then lead to physiological changes, for example when heat-stressed animals take in less dry matter, protein reserves are mobilised to prioritise the fetus (Lamp et al., 2015). Effects of heat stress can persist long after the developmental insult occurs, exposure to heat-stress while *in-utero* results in alterations in mammary gland gene expression (Skibiel et al., 2018a) and these cows produce less milk as heifers (Monteiro et al., 2016).

The purpose of this research was to identify cow- and farm-level maternal stressors that may modify lifetime resilience in the offspring of dairy cows. Specifically, we aimed to investigate the effects of a variety of stressors experienced by the mother during specific stages of pregnancy on individual cow lifetime resilience scores in 2 data sets, one large data set consisting of cows born over a 10-year period from 83 farms and a smaller, more granular data set from 293 animals in the Langhill research herd at Scotland's Rural College over a 12-year period. These environmental stressors included health-related stress in the dam (mastitis, lameness, diseases requiring use of antibiotics/anti-inflammatories) and broader environmental stresses associated with heat-stress events defined from national weather stations.

MATERIALS AND METHODS

Data sources

Two different data sources were used. The first was a large data set which consisted of multiple herds with commercially recorded data (described below). 'Big data' has many advantages for creating meaningful insights into animal health (VanderWaal et al., 2017) but farmers differ in their observations of animal health and event recording. In particular, recording of treatments is often lower than the true on-farm use (Nobrega et al., 2017) while the ease of recording and storing data on farm, and the requirements for doing so have increased over time. Therefore, to further investigate our hypothesis, we also considered data from a research herd, where events were recorded with a high level of accuracy and consistency. The 2 data sets are described below:

Data set 1 Herds came from a convenience sample of 108 herds that supplied data to Quality Milk Management Services (QMMS Ltd.). Data were extracted from '*TotalVet*', a dairy herd analysis software (https://www.total-vet.co.uk/) into .csv files. The files contained 12,309,843 records from 108 farms dated from 15 to 07–1975 to 09–06–2022. Records included in the data set included calving events, milk recordings, health and treatment events.

Data set 2 Cows in the Langhill research herd, housed at the Crichton Royal Farm at the Dairy Research and Innovation Centre at Scotland's Rural College. Data were extracted from a Microsoft SQL Server for cows in the herd born between 01 and 01–2003 and 31–12–2015, giving records up to the year of data analysis (2022).

Data processing and sample selection

Selection of animals Cows were selected that were born between 01 and 01–2006 and 31–12–2015 to ensure lifetime data were available for each animal. Data cleaning took place in Python v3.10.5 using *pandas* (McKinney, 2010) and *numpy* (Harris et al., 2020) and a summary of the data cleaning steps is detailed in Table 1. In brief, cows were excluded when identification numbers were duplicated, ages at first calving were unrealistic (<15 mo or > 4.5 years), or they were not born on the farm where data were recorded (Table 1). Milk records were selected for each lactation (Table 1) and cows were excluded if milk records occurred before their first recorded calving date, indicating they were not first parity cows and therefore not all lifetime data were available. Milk records were excluded if the yield was unrealistic (>100kg/day). The 305-d milk yield for each lactation was calculated using the "*milkbot*" model, a nonlinear lactation model that uses 4 parameters to fit curves to the lactation (Ehrlich, 2010). LRS were then calculated (see section 2.3) for all cows that had calved at least once on the farm.

Due to variability in recording of treatments between herds and years within herds, herd-years were only included in the analysis when at least one "stressor" (lameness, mastitis, or treatment with antimicrobial or anti-inflammatory products) was recorded in the year. Once mother-daughter pairs had been matched up, the data set consisted of 15838 mother-daughter pairings, where the daughter had calved at least once and therefore had her own LRS. The first calves from each cow were excluded because the mother was not lactating during that pregnancy meaning the impact of production-related variables could not be assessed.

Selection of animals Cows were selected that were born between 01 and 01–2003 and 31–12–2015 to ensure lifetime data were available for each animal. The Langhill research herd contains with 2 genetic lines; a control genetic group (UK average production efficiency) and a select group (high production efficiency; (Pollott and Coffey, 2008). The herd continuously host feed trial research which occurs in 5-year cycles. During this research period, feed trials had cows grouped in either high-input, all-year-round housed systems or low-input, seasonal grazing systems and once assigned to a system, cows did not change system as feed trials changed.

Due to the smaller size of the initial data set, data were systematically assessed in Microsoft Excel (Microsoft Corporation, 2018). Criteria for selection were that cow service dates corresponded to the relevant calving date and that all milk recording data were available. Cows without these data were removed from the data set. The final data set consisted of 192 mother-daughter pairings and 74 mother-granddaughter pairings (Table 2).

Calculation of lifetime resilience score An LRS was calculated for cows as in Adriaens et al., (2020), where resilience is based on the cumulative result of the cow's ability to recalve (thereby extending her reproductive lifespan), with secondary corrections applied for age at first calving, 305-d milk yield and calving intervals. The score consists of a baseline interval

Table 1 Selection of cows and herds for inclusion in the final models of lifetime resilience score for Data set 1

Selection step	Number of animals	Number of records	Number of herds
Animal records	338,129	—	108
Cow identification number occurred on one farm only	336,423	—	
Cows entered herd on their date of birth	309,065	—	
Cow had not had a previous lactation on entry to herd	218,929	—	
Cows born 2006–2015	84,795	—	
Calving records	56,500	206,362	
Age at first calving > 458 d and < 1461 d	56,009	204,539	
Milk records	54,940	2,193,071	
Milk records selected between calving date$_j$ and calving date$_{j+1}$, or after the last calving date$_{jn}$	53,849	2,148,907	
Records with yield > 100kg removed	53,358	2,148,837	
milkbot model applied to records DIM ≥ 0 and ≤ 305 d and yield > 0	52,030	1,800,013	
Cows excluded if yield was 0 in any lactation but lactation *j*	45,425	159,744	
LRS scores calculated*	45,317	—	102
>1 stressor recorded in the year by the farm	43,500	149,351	101
LRS scores for years where there was recording and mother-daughter pairs could be matched	42,982	—	83
Mother-daughter pairs matched in recording years	15,838 daughters 12,125 mothers	—	83
First calves excluded	9292 daughters 7334 mothers	—	83

* LRS = lifetime resilience score, lactation j = the last lactation of the cow, DIM = days in milk.

*LRS scores not calculated for 127 animals that were first parity, with no milk data for the lactation.

equal to the calving interval of the herd and each newly started lactation gains a bonus of 300 points. Each cow then gains or loses points for the following components:

- For every day shorter or longer their date of first calving was from 730 d
- For the number of days the calving interval is shorter or longer than the herd average
- For the percentage that the 305-d milk yield is higher or lower than the herd average
- Points are lost if the cow exits the herd before 100 d in milk

The LRS was calculated as described by Adriaens et al., 2020:

$$LRS_i = \overline{CI} + 300\,x\,L_i + \left(730 - AFC_i\right) + \sum_{j=1}^{L_i-1}\left[\left(\overline{CI_j} - \overline{C_{i,j}}\right) + \sum_{j=1}^{L_i}\left[\frac{\sum_{k=1}^{\max(305,DIM_{i,j})} MY_{i,j,k}}{\sum_{k=1}^{\max(305,DIM_{i,j})} \overline{MY_{i,j,k}}} - 1\right]\right] \times 100 + \min\left[0,\left(DIM_{i,L_i} - 100\right)\right],$$

where LRS_i = lifetime resilience score for cow *i*. $\overline{CI}$ = average calving interval of the herd over all selected years, L_i = lactation number in which cow *i* exited the herd (last lactation number of a cow), AFC_i = age at first calving of cow *i* (in d), $CI_{i,j}$ = calving interval of cow *i* between the start of lactation *j* and (*j* + 1), $\overline{CI_{i,j}}$ = average calving interval between the start of lacta-

Table 2 Selection of cows for inclusion in the final models of lifetime resilience score for Data set 2

Selection step	Number of animals
Cows born 2003–2015	928
LRS scores calculated*	811
Mother-daughter pairs matched	390 daughters 293 mothers
Mother-daughter pairs with complete stressor data**	192 daughters 156 mothers
Mother-granddaughter pairs matched	158 granddaughters 105 mothers
Mother-granddaughter pairs with complete stressor data**	74 granddaughters 53 mothers

* LRS = lifetime resilience score, lactation j = the last lactation of the cow, DIM = days in milk.

*LRS scores not calculated for animals that had incomplete data.

** Body condition and Locomotion scores were not available for first parity births.

tion j and $(j + 1)$ of all cows in the herd, $MY_{i,j,k}$ = milk production (in kg) of cow i at day k of lactation j, $\overline{MY}_{i,j,k}$ = average milk production (in kg) at day k of all cows in the herd in lactation j, $DIM_{i,j}$ = DIM of cow i at the end of lactation j, DIMi,Li = DIM of cow i at the end of her last lactation L_i.

Explanatory variables Potential 'stressor' events that could be identified in both data sets came from records of lameness, mobility scores and treatments given. Climate data were obtained from the National Center for Environmental Information National Oceanic and Atmospheric Administration's Global Summary of the Day (National Centers for Environmental Information, 2022).

The explanatory variables used in both analyses are detailed below.

Health events, treatment records and milk quality records Health records included for Data set 1 were:

a) Clinical mastitis – the date the cow was recorded with a clinical case of mastitis.
b) Clinical lameness – the date the cow was recorded with a clinical case of lameness.
c) Mobility scores – the date when the cow was identified lame during at a routine herd mobility score. These were combined with the clinical lameness records to give records of any identified case of lameness.
d) Treatment, or other, records – these were recorded as free text, along with the date. A list of products registered as authorised on the Veterinary Medicines Directorate Product Information Database (https://www.vmd.defra.gov.uk/productinformationdatabase/current, accessed 19.10.2022) was downloaded, and filtered for whether the use category was marked as anti-microbial, anti-inflammatory (or both) or a vaccine. Records were matched to the products using partial ratio string joining with *fuzzywuzzy* (SeatGeek Inc., 2014). This method matches strings by calculating the ratio similarity measure (Levenshtein Distance) between strings x and y. Where the shorter string (x) is of length m, the measure is calculated between the shorter string and every substring of length m of the longer string, and the maximum of those similarity measures is returned. Records were manually checked following joining, and any incorrect matches removed.
e) Milk quality records included percentage fat, protein, lactose, and somatic cell count (SCC) at each recording.

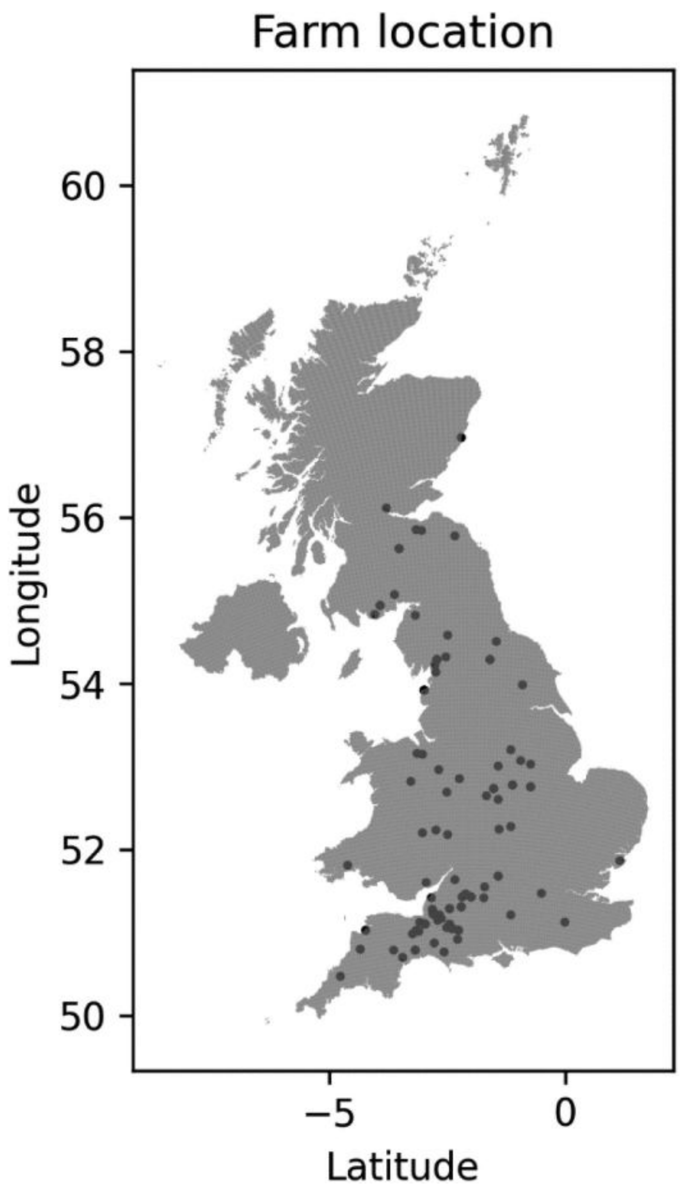

Figure 1. Point locations of the 'out' postcode for 108 farms

Farm location, climate records and calculation of a thermal discomfort index Farm locations were indicated by the 'outcode', the first 4 letters of the postcode which corresponds to the postcode area and district. Latitude and longitude were identified using the UK grid reference finder (https://gridreferencefinder.com/).

Climate data were obtained from the National Center for Environmental Information National Oceanic and Atmospheric Administration's Global Summary of the Day (National Centers for Environmental Information, 2022). Daily mean temperature, maximum temperature and dewpoint temperature from 263

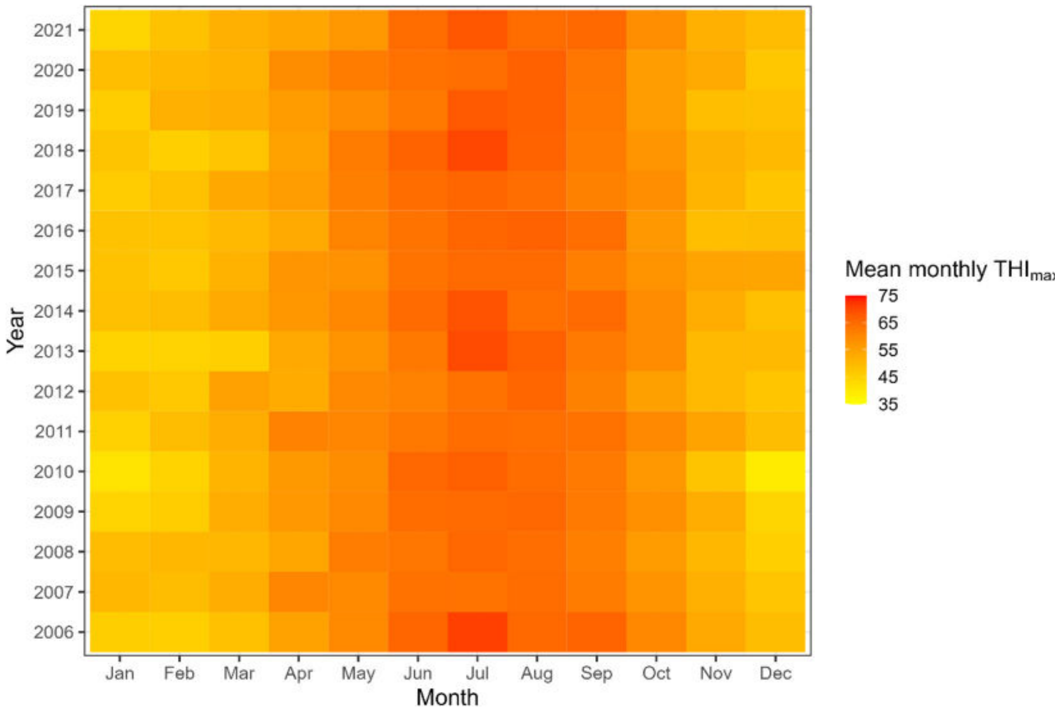

Figure 2. Summary of the mean monthly THI_{max} for 83 herds, from 627962 weather observations between 2006 and 2021

weather-stations across the United Kingdom between longitude 59.779–49.781 and latitude 7.910–2.201 were obtained from 2006 to 01–01 to 2021–12–31. Of the stations obtained, 177 had data from each year, and stations were excluded if > 10% of daily observations were missing in the year (1 station). Farms were matched to their nearest weather station based on distance from their point location (mean distance = 28.6km, range = 4.3–66.9km) using *geopandas* (Jordahl et al., 2020) in Python v 3.10.5.

A maximum thermal discomfort index (Thom, 1959) for each day was calculated as:

$$THI_{max} = 0.8 * T + (RH/100*(T - 14.4)) + 46.4$$

Where T was the daily maximum temperature of the day and RH was minimum relative humidity for the day.

The minimum relative humidity (RH) for the day was calculated as:

$$RH = 100 * \exp(17.625 * DP / (243.04 + DP)) / \exp(17.625 * T / (243.04 + T)))$$

Where DP is dewpoint temperature (∘C) and T is the maximum temperature (∘C) for the day.

A summary of mean THI_{max} summarized for each month and year is presented in Figure 2.

Health events, treatment records The Langhill research herd are regularly mobility scored on a scale of 1–5 (Manson and Leaver, 1988), and body condition scored on a scale of 0–5 from the National Institute for Research in Dairying (Mulvany, 1977) and have detailed health records for all health events and medicine use. The health records included for the Langhill herd in the current data set were as follows:

a) Health events – the date the cow was recorded as having a significant health event (see Supplementary Table 2 for comprehensive list and frequency of health events recorded)
b) Body Condition Scoring (BCS) – the dates and scores when the cow's BCS was recorded
c) Mobility scores – the dates and scores when the cow's mobility score was recorded
d) Treatment – the dates and products used to treat illness, which were then filtered for whether the use category was anti-inflammatory or antibiotic.

Climate records and calculation of a thermal discomfort index From the National Center for Environmental Information National Oceanic and Atmospheric Administration's Global Summary of the Day (National Centers for Environmental Information, 2022) database, climate data were obtained from

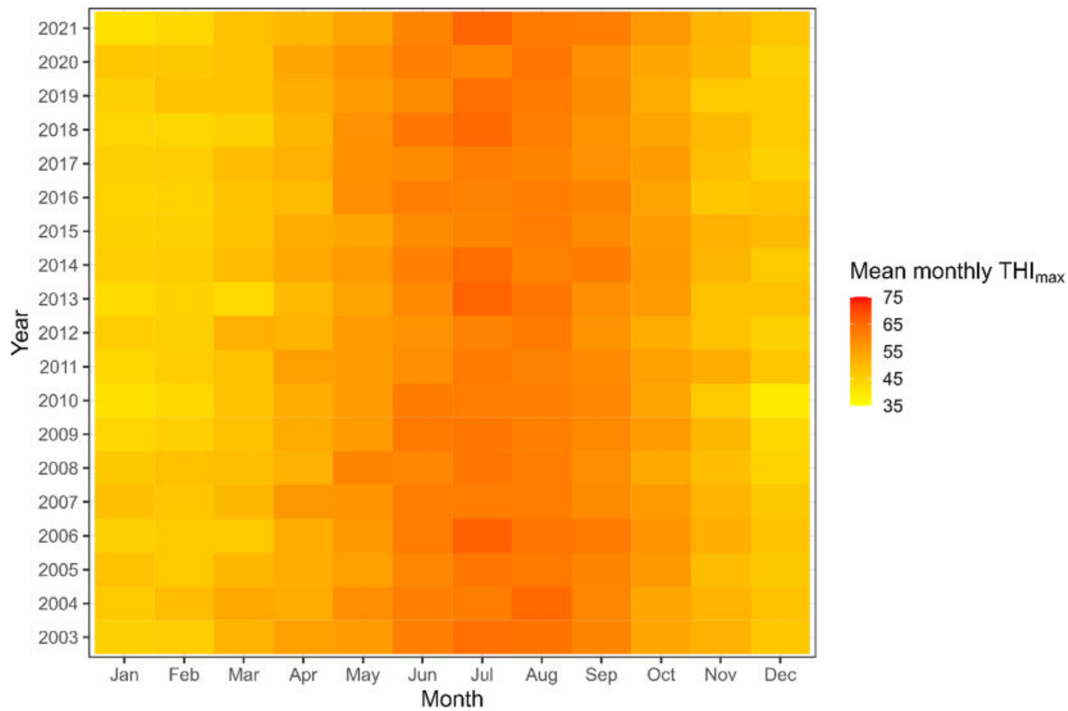

Figure 3. Summary of the mean monthly THI_{max} for the Langhill research herd, from 6809 weather observations between 2003 and 2021

the Dundrennan weather station (~38 km from the Langhill Herd). THI_{max} for each date was calculated as above. One year (2004) was missing > 10% of data (only 319/366 d with observations) daily observations but is still presented and included in the analysis below.

Datasets 1 and 2: Windows of events during pregnancy and potential for developmental programming For each pregnancy, an estimated date of conception was used for Data set 1 (283 d before the calving date) and date of a cow's last insemination before a pregnancy was considered the conception date for the Langhill cows. We also investigated 7 d before the estimated conception date because the pre-conception uterine environment can have lasting effects on health status of the offspring (Berry et al., 2008; Stephenson et al., 2018). Stressor events can have different effects on the fetus at different times during pregnancy and so several 'windows' for events were considered, these were:

- **Trimester 1 (T1):** 7 d pre-conception to 94 d of pregnancy

During T1, early embryonic development takes place. The body plans are established with the majority of the organs have started to develop by d 40 (Winters et al., 1942) and the fetus begins to increase in size (Eley et al., 1978).

- **Trimester 2 (T2):** 95 to 189 d of pregnancy

During T2, the fetus continues to grow (Reynolds et al., 1990) and structures begin to be established, such as the number of myocytes in muscle fibers (Du et al., 2010).

- **Trimester 3 (T3):** 190 – 283 d of pregnancy

During T3, the majority of increase in fetal tissue size takes place (Winters et al., 1942), as well as proliferation of immune cells (Higgins et al., 1983), adipogenesis (Fève, 2005), and muscular development, including myocyte size and intramuscular adipocyte formation (Du et al., 2010).

Within each trimester window, the following were summarized in both data sets:

- Presence or absence of each health event for each dam
- Mean THI_{max}: mean value of all the daily values of THI_{max} between the relevant dates

For Data set 1, since the majority of farms had monthly milk recordings, we considered the following milk quality variables within each trimester window:

- Fat: minimum, median and maximum percentage. This was categorized into > 0–3%, > 3–5%, > 5%

and missing, if there was no recording between the trimester window dates.

- Protein: minimum, median and maximum percentage. This was categorized into > 0–3%, > 3–4%, > 4% and missing.
- Fat/protein ratio: maximum ratio. This was categorized into > 0–1, > 1–1.2, > 1.2–1.4, > 1.4 and missing.
- SCC count: maximum SCC count (100,000 cell). This was categorized into > 0–50, > 50–100, > 100–200, > 200–400, > 400 and missing.
- Milk yield: minimum, median and maximum (liters). This was categorized into > 0–20, > 20–30, > 30–40, > 40, and missing.
- For the Langhill herd, we also considered:
- Average BCS: under (<1.5), normal (1.5–3.25), over (>3.25)
- Locomotion Score (LS): lame ($LS_{max} \geq 4$), not lame ($LS_{max} < 4$) – see section 2.4.2.1 for details of the scoring system

In the Langhill herd, the recording of BCS and LS begins when the cow first enters the herd, after giving birth to her first calf. Due to this, data for parity 1 cows was not available and therefore not included in the final model.

Shorter intervals of pregnancy were considered, but there were insufficient data per window for the health events to allow analysis, particularly in Data set 1.

Cow-level features

Features that were relevant to each calf were also included in the models, these were:

1) Their mother's LRS score, to provide a proxy for possible genetic effects since traits that make up the LRS score, e.g., milk yield are heritable. This predictor was centered around the mean mother LRS score for the entire data set
2) Season of birth: calf season of birth, based on date of birth, was included to account for any potential confounding influence of birth season (March–May: spring, June–August: summer, September–November: autumn, and December–February: winter).

For the Langhill herd, a fixed effect was tested for the genetic group and feed trial a cow was in.

Farm-level features

For Data set 1, where multiple herds were considered, farm-level features were included to determine if they impacted the LRS scores of calves born on that farm/ These were:

1) Mean 305-d yield: for each calf, the mean 305-d yield of the herd at the time of the calf's birth was calculated as the mean of all the 305-d yields from all lactations that had occurred before the day of birth of the calf in the past 12 mo from the selected subset of cows.
2) Mean parity structure: a yearly mean parity structure for each farm was calculated as a proxy for the expected survival of a cow. This was calculated as the mean of the parity of mothers on the farm in the year of birth of the calf, including those that were born before 2006.
3) Farm: farm was included as a random effect to account for other unknown farm factors that differed between farms, such as diet and housing.

Associations between explanatory variables

Correlations between explanatory variables were tested by calculation of the Spearman's rank correlation coefficient, using the *stats* package in R (R Core Team, 2022).

Modelling associations between explanatory variables and lifetime resilience score

For Data set 1, linear mixed effects models using the *lmer* package (Bates et al., 2015) in R v4.2.2 (R Core Team, 2022) were used to identify whether events that occurred while the calf was *in-utero* were associated with the lifetime resilience score of that calf.

The models took the form:

$$y_{ijk} = \beta_0 + \beta_1 x_{ijk} + \beta_2 x_{jk} + \beta_3 x_k + f_k + u_{jk} + e_{ijk},$$

where y_{ij} was the continuous outcome variable lifetime resilience score for calf i from dam j in herd k, b_0 was the model intercept, x_{ijk} is the matrix of the explanatory variables at calf level and β_1 their coefficients, x_{jk} is the matrix of the explanatory variables at dam level and β_2 their coefficients and x_k is the matrix of the explanatory variables at farm level and β_3 their coefficients. Residual error variance estimates were included at farm (f_k), dam (u_{jk}) and calf (e_{ijk}) level and assumed to be normally distributed with mean = 0 and variances σ_f, σ_u, and σ_e, respectively. Models were fitted using maximum likelihood.

Models were built using a forward stepwise selection process, adding variables where $P < 0.05$ (Wald's test

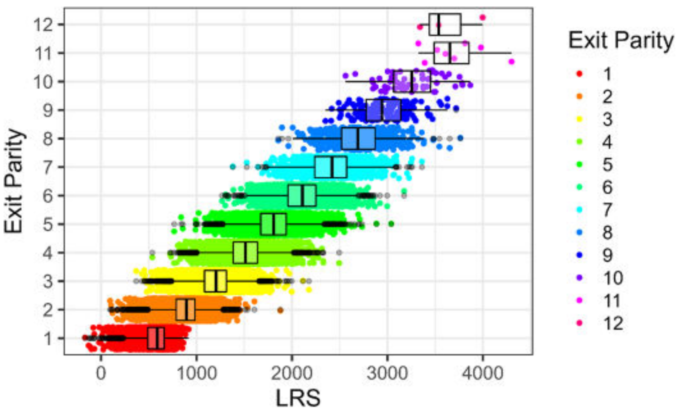

Figure 4. Distribution of lifetime resilience scores from 42982 cows from 83 herds by exit parity (the parity at which the cow left the herd)

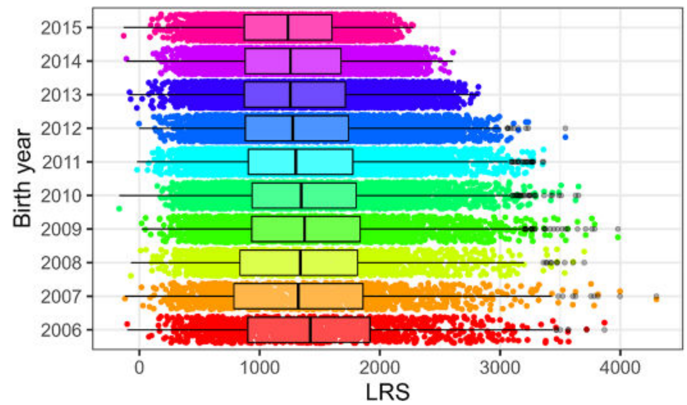

Figure 6. Lifetime resilience scores by year of birth for 42982 cows from 83 herds by year of birth

of significance). Milk quality and yield variables were grouped into subgroups consisting of the minimum/median/maximum for each variable, and if multiple were significant, the one with the lowest *P*-value was retained in the model and correlations between variables noted.

Polynomial terms (up to third degree) were tested in the final model for all continuous predictors. Interactions between biologically plausible variables were tested and were included if they were significant and improved model fit. Model fit was assessed using by calculation of the marginal and conditional R_2 for mixed effects models (Nakagawa et al., 2017) and by leave-one-out-cross validation (LOOCV), training the model on all but one farm, and predicting values for the omitted farm.

A further set of analyses were conducted to evaluate possible associations between potential stress events during pregnancy and lifetime resilience score

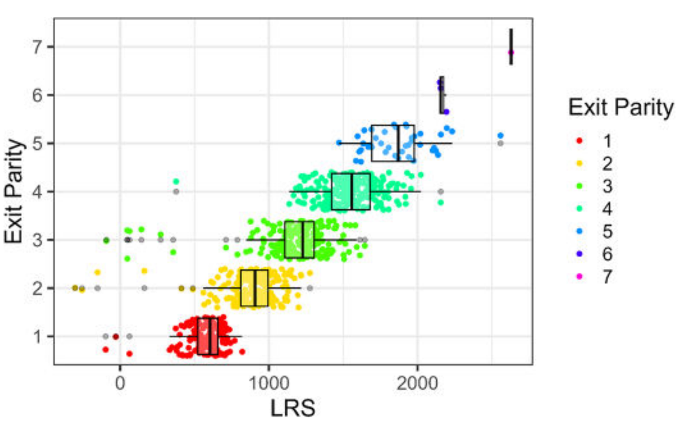

Figure 5. Distribution of lifetime resilience scores from 811 cows from the Langhill research herd (the parity at which the cow left the herd)

of granddaughters. That is, the outcome variable was the granddaughters LRS and the explanatory variables related to events during the pregnancy of the grandmother. The LRS of both the mother and grandmother were tested in the models as explanatory variables. The data set comprised 1586 granddaughters that could be matched to pregnancies of the original dams in the data set, from 65 farms and analyses were conducted as described above.

For data set 2, the models took the form:

$$y_{ij} = \beta_0 + \beta_1 x_{ij} + \beta_2 x_j + u_j + e_{ij},$$

where y_{ij} was the continuous outcome variable lifetime resilience score for calf i in from dam j, β_0 was the model intercept, x_{ij} is the matrix of the explanatory variables at calf level and β_1 their coefficients, x_j is the matrix of the explanatory variables at dam level and β_2 their coefficients. Residual error variance estimates were included at dam (u_j) and cow (e_{ij}) level and assumed to be normally distributed with mean = 0 and variances σ_j and σ_{ij}, respectively. Models were fitted using maximum likelihood.

The model fitting process was as described as above, with LOOCV validation performed by leaving out one genetic/feed trial 'group' at a time.

RESULTS

Descriptive statistics – Lifetime resilience scores and health events

We calculated 42982 resilience scores from the 83 herds with sufficient recording data and 811 resilience scores for cows with sufficient data from the Langhill research herd. As expected, cows which had completed more lactations tended to have higher scores (Data set

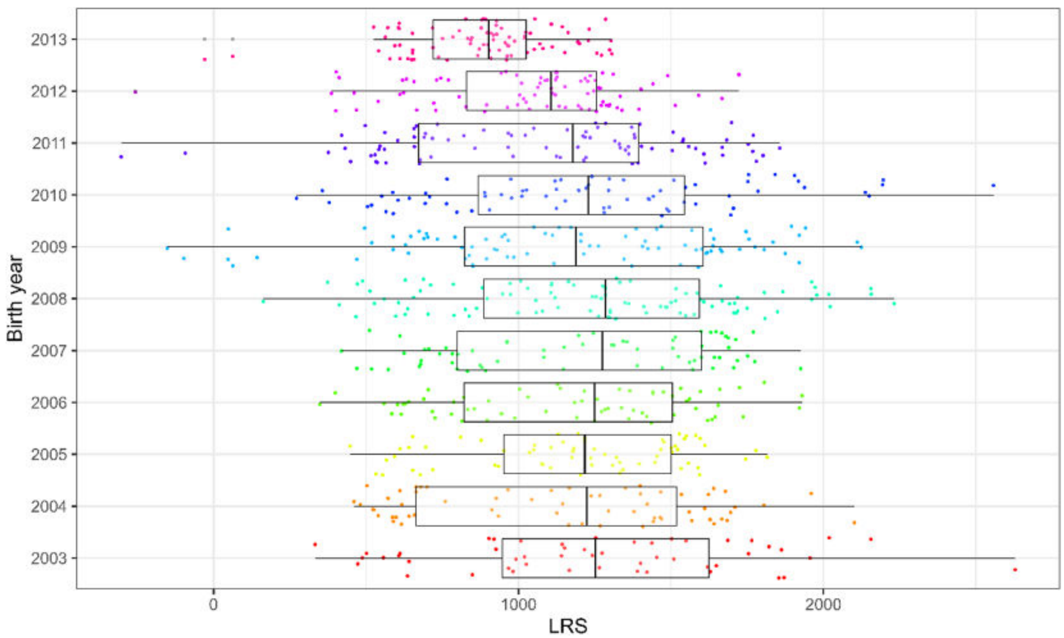

Figure 7. Lifetime resilience scores by year of birth for 811 cows from the Langhill research herd

1: Figure 4, Langhill: Figure 5). LRS ranged from −168 to 4300 in Data set 1, and from −303 to 2629 in Data set 2 and resilience scores did not appear to increase over time (Data set 1: Figure 6; Langhill: Figure 7).

Associations between events that occurred while the calf was in-utero and lifetime resilience scores of daughters

In Data set 1, a health event (excluding use of dry cow therapies) occurred in a mean 22% of the pregnan-

Table 3 Mean proportion of pregnancies with lameness, mastitis, antibiotic and anti-inflammatory usage from dams of calves born 2006–2015 in the recording years; 9292 calves from 7334 mothers that were in their second or greater pregnancy on 83 farms

Stressor type	N_{farms}	Mean	Median	Min	Max
Anti-inflammatory use	83	0.02	0.00	0	0.42
Antimicrobial use (excluding dry cow therapies)	83	0.13	0.00	0	0.75
Antimicrobial use (including dry cow therapies)	83	0.32	0.00	0	1.00
Lameness	83	0.02	0.00	0	0.37
Mastitis	83	0.11	0.09	0	0.32
Any stressor (including dry cow therapies)	83	0.39	0.23	0	1.00
Any stressor (excluding dry cow therapies)	83	0.22	0.16	0	0.76

[1]N_{farms} = number of farms, min = minimum, max = maximum.

Table 4 Mean proportion of pregnancies with anti-inflammatory usage, antibiotic usage, high locomotion score, low or high body condition score, and health event recorded from dams of calves born 2006–2013 that were included in the final model; 192 calves from 156 mothers

Stressor type	$Mean_{All}$	$Mean_{F25}$	$Mean_{T1}$	$Mean_{T2}$	$Mean_{T3}$
Anti-inflammatory use	0.02	0.00	0.01	0.01	0.02
Antibacterial use	0.70	0.13	0.41	0.33	0.19
High Locomotion Score*	0.77	0.21	0.51	0.51	0.39
Low/High Body Condition Score**	0.07	0.05	0.04	0.03	0.03
Health Event	0.52	0.12	0.35	0.21	0.19

[1]*High locomotion score based on average scores recoded (≥4).

[2]**Low/High body condition score based on average scores recorded (<1.5, > 3.5).

Table 5 Final model of calf lifetime resilience scores and *in-utero* events in the mother in Data set 1, model coefficients and Wald's confidence intervals and p-values

Predictors	N	β	LCI-UCI	P-value
Intercept		1915.00	1466.35 – 2363.65	<0.001
Fixed effects				
Mean THI_{max} – T1	9,292	−5.18	−9.21 – −1.16	0.012
Mean THI_{max} – T3	9,292	−5.76	−9.81 – −1.71	0.005
Pregnancy – 2	4,756	—		
Pregnancy - 3	2,684	−38.40	−62.70 – −14.10	0.002
Pregnancy - 4	1,852	−74.47	−104.26 – −44.68	<0.001
Mother - LRS	9,292	0.07	0.05 – 0.09	<0.001
$Yield_{min}$ > 20–30L – T1	3,753	—		
$Yield_{min}$ > 0–20L – T1	1,760	−54.65	−85.52 – −23.78	0.001
$Yield_{min}$ > 30–40L – T1	2,754	1.45	−24.72 – 27.61	0.914
$Yield_{min}$ > 40L – T1	715	−5.56	−50.37 – 39.25	0.808
$Yield_{min}$ Missing – T1	310	94.47	8.14 – 180.79	0.032
$Yield_{max}$ > 20–30L – T3	3,206	—		
$Yield_{max}$ > 0–20L – T3	3,555	4.79	−21.35 – 30.93	0.720
$Yield_{max}$ > 30–40L – T3	893	−4.73	−42.31 – 32.85	0.805
$Yield_{max}$ > 40L – T3	118	−104.20	−196.86 – −11.53	0.028
$Yield_{max}$ Missing – T3	1,520	5.83	−27.55 – 39.22	0.732
Fat_{median} > 3–5% – T1	6593	—		
Fat_{median} > 0–3% - T1	844	−44.09	−81.34 – −6.84	0.020
Fat_{median} > 5% - T1	823	14.79	−26.90 – 56.47	0.487
Fat_{median} Missing – T1	1,032	−121.48	−186.21 – −56.75	<0.001
Random Effects				
Residual – SD	—	477.17		
Dam – SD	7334	81.42		
Farm - SD	83	142.27		

[1]n = number of observations, β = model coefficient, LCI = lower confidence interval, UCI = upper confidence interval, T = trimester, Min = minimum, Max = max LRS = lifetime resilience score, SD = standard deviation, P-value = P-value from Wald's test of significance.

cies across the farms (Table 3), where cows were in either their second or subsequent pregnancies. Use of antimicrobial products was the most common health event (13% of pregnancies), followed by mastitis (11% of pregnancies). A summary of the milk quality variables over the pregnancies is in Supplementary Table 1 and correlations between all explanatory variables are in Supplementary Figures 1A-D.

In the Langhill herd, health events occurred in a mean of 52% of pregnancies, with the largest proportion of health events being recorded in trimester 1 of pregnancies (35%; Table 4). Use of antimicrobial products was common (70% of pregnancies) with the use of anti-inflammatories low (0.02% of pregnancies). Seventy 7 percent of cows were recorded as having a high locomotion score (≥4) at some point during pregnancy and just 0.07% of cows recorded as having a low or high body condition score (<1.5, > 3.5).

The final mixed effects model of calf lifetime resilience scores and *in-utero* events in the mother for Data set 1 is presented in Table 5. A higher mean daily THI_{max} in the first and third trimester of pregnancy was associated with lower lifetime resilience scores. Calves that were born to older dams (dams in their third or higher pregnancy compared with dams in their second pregnancy) had lower lifetime resilience scores. Higher

Table 6 Final model of calf lifetime resilience scores and *in-utero* events in the mother, model coefficients and Wald's confidence intervals and p-values for the Langhill research herd

Predictors	N	β	LCI-UCI	P-value
Intercept	—	1292.52	1209.11 – 1375.93	<0.001
Fixed effects	—	—	—	—
Pregnancy – 2	102	—	—	—
Pregnancy – 3	60	−22.40	−137.36 – 92.56	0.701
Pregnancy – 4+	30	−178.93	−329.75 – −28.12	0.020
Locomotion $Score_{max}$ < 4 – T3	118	—		
Locomotion $Score_{max}$ > 4 – T3	74	−151.12	−260.50 – −41.75	0.007
Random Effects	—	—	—	—
Residual – SD	—	324.77	—	—
Dam – SD	155	185.67	—	

Table 7 Final model of calf lifetime resilience scores and *in-utero* events in the grandmother, model coefficients and Wald's confidence intervals and p-values (65 farms, 1586 granddaughters)

Predictors	N	β	LCI-UCI	P-value
Intercept		1197.96	1138.63 – 1257.29	<0.001
Fixed effects				
Pregnancy – 2	987			
Pregnancy – 3	409	−57.37	−108.88 – −5.87	0.029
Pregnancy - 4+	190	−53.32	−125.53 – 18.89	0.148
Antimicrobial – T3 (no)	1502	—		
Antimicrobial – T3 (yes)	84	−106.29	−197.42 – −15.16	0.022
SCC_{max} 0–50 – T2	362	—		
SCC_{max} 51–100 – T2	375	56.22	−7.87 – 120.31	0.086
SCC_{max} 101–200 – T2	416	29.08	−34.02 – 92.18	0.366
SCC_{max} 201–400 – T2	221	87.88	12.52 – 163.25	0.022
SCC_{max} > 400 – T2	172	46.12	−37.91 – 130.14	0.282
SCC_{max} Missing – T2	40	−101.06	−246.35 – 44.22	0.173
Random Effects				
Residual SD	—	420.05		
Cow SD	1227	94.38		
Farm ID	65	126.85		

[1]n = number of observations, β = model coefficient, LCI = lower confidence interval, UCI = upper confidence interval, T = trimester, LRS = lifetime resilience score, min = minimum, max = maximum, SD = standard deviation, P-value = P-value from Wald's test of significance, SCC = somatic cell count (100,000).

mother LRS scores were associated with higher LRS scores of their calf (Table 5).

Milk yield and quality variables over the mother's pregnancy were associated with daughter LRS scores. Daughter LRS scores were lower where milk yields were low in trimester 1 (>0–20L compared with > 20–30L), where median fat percentages in trimester 1 were 0–3% compared with > 3–5%, and when milk yields were high (>40L compared with > 20–30L) in trimester 3 (Table 5).

Overall, the model explained a low proportion of the variation in lifetime resilience score (12%, conditional R_2 = 0.120), with the fixed effects explaining 1% of this (marginal R_2 = 0.0116. Plots of residuals vs fitted values (Supplementary Figure 2), and predictions from the LOOCV cross-validation (Supplementary Figure 3A and B) indicated a good model fit.

The final model of calf LRS and *in-utero* events in the mother for data set 2 is presented in Table 6. Calves that were born to older dams (dams in their fourth or greater pregnancy compared with their second pregnancy) had lower LRS. Calves whose mothers had a maximum locomotion score of ≥ 4 in the third trimester of pregnancy had lower LRS than calves whose mothers had maximum locomotion scores less than 4 in the third trimester of pregnancy.

Overall, the model explained a low proportion of the variation in lifetime resilience score (~30%, conditional R_2 = 0.298), with the fixed effects explaining about 7% (marginal R_2 = 0.069). Plots of residuals vs fitted values (Supplementary Figure 4), and predictions from the LOOCV cross-validation (Supplementary Figure 5A and 5B) indicated a good model fit.

Associations between events that occurred while the mother was in-utero and lifetime resilience of granddaughters

The final model for granddaughters in Data set 1 is presented in Table 7. Granddaughters had lower lifetime resilience scores when their grandmother was in their third pregnancy compared with their second and when their grandmother had received an antimicrobial treatment during T3. Granddaughters had higher resilience scores when SCC_{max} counts were 201–400,000 in T2 compared with 0–50,000.

Plots of residuals versus fitted values and predictions from LOOCV validation indicated good model fit (Supplementary Figure 6, Supplementary Figure 7A and 7B), however the fixed effects explained only a very small proportion of variation in lifetime resilience score (~1%, marginal R_2 = 0.014, conditional R_2 = 0.136). In the Langhill herd, no *in-utero* event predictor variables were significantly associated with LRS of granddaughters, however this data set was very small (74 granddaughters).

DISCUSSION

This is the first study to explore associations between lifetime resilience scores of dairy cows and events that occurred *in-utero* in a large longitudinal data set of dairy cattle. The importance of early life events in determining future performance of dairy cattle is becoming increasingly apparent and the key findings from our study were that cows that experienced higher THI_{max} values in the first or last trimester of pregnancy, cows that were born to multiparous dams compared with primiparous dams, calves from cows with the lowest milk yields and fat percentages in the first trimester, calves from cows with high milk yields in the third trimester, and those born to dams with high locomotion scores in the third trimester had lower lifetime resilience scores. This adds to the existing evidence base that the *in-utero* environment has lifelong implications on calf performance.

Currently, relatively little is known about the exact mechanisms of developmental programming events, but they tend to result in either structural alterations to tissue/organ structures, or functional alterations that arise from changes in gene expression (Reynolds and Caton, 2012). In laboratory animals, some specific links between maternal environment and offspring performance have been reported, for example in rats, maternal malnutrition is associated with the occurrence of prostatic disorders in the offspring (Portela et al., 2021) and in mice, depriving the mother of water during pregnancy is associated with dysregulation of plasma glucose levels and fatty liver in female offspring (Kondo et al., 2023). In our study, we have identified several potential effects, but additional research is required to elucidate underpinning mechanisms.

The effects of fetal heat stress in dairy cattle have been reported mostly in late gestation, and the results of our study are consistent with this (Table 5). Calves born to late gestation heat-stressed dams weighed less both at birth and up to one year of age (Collier et al., 1982; Monteiro et al., 2016; Laporta et al., 2017; Dado-Senn et al., 2020), have compromised metabolic and immune functions (Dado-Senn et al., 2020), and have poorer milk yield and shorter life spans (Monteiro et al., 2016; Laporta et al., 2018; Skibiel et al., 2018b; Weller et al., 2021). All of these factors potentially lead to lower lifetime resilience scores. Heat stress may be particularly detrimental in late gestation, when the majority of increase in fetal tissue size takes place (Winters et al., 1942). Additionally, the effects of heat stress on the mother can lead to behavioral and physiological changes that contribute to dysregulation in fetal growth by reducing the nutrition available to the fetus as nutrition is associated with growth (Funston et al., 2010). For example, increased maternal core body temperature leads to a reduction in dry matter intake (Lamp et al., 2015), and a redirection of blood from the gravid uterus to the periphery to limit the increase in temperature to the fetus (Reynolds et al., 1990).

We also identified that calves that experienced higher mean THI_{max} values in early gestation had lower lifetime resilience scores (Table 5). Further investigation is needed to determine exactly how heat-stress in early gestation is associated with lifetime performance of cattle, but embryos are known to be sensitive to heat-stress in the early stages of pregnancy. Changes that have been associated with heat stress during embryo development include changes in DNA methylation (Paula-Lopes and Hansen, 2002) and increased production of reactive oxygen species, leading to cellular damage (de Barros and Paula-Lopes, 2018). Many embryos do not survive early heat stress exposure in cattle, leading to pregnancy loss (García-Ispierto et al., 2006; Sakatani et al., 2008), however, in this study we were unable to assess any impact on early embryonic loss. We did not find any effect of THI_{max} in the Langhill herd, however this herd is housed in Scotland where the values of daily THI_{max} experienced did not reach what could be considered heat stress (Figure 3). The physiological effects of heat stress, such as decline in milk production are seen at THI values of ≥ 68 (Morton et al., 2007; Gantner et al., 2017). Most of the herds in Data set 1 were in Southern England (Figure 1) and herds in the South are more likely to experience temperatures that could lead to heat stress (Dunn et al., 2014). Due to the nature of the data available, there were limitations in the assessment of heat stress because farm specific information was not available and data from local weather stations were used. We acknowledge that these measurements are limited as they were not able to take into account factors such as air flow or availability of shade/ventilation/cooling equipment or factors such as photoperiod that may differ between farms or even between animals on farm. Therefore, animals may not have experienced the exact THI_{max} as measured, yet despite this source of random error, clear relationships were still identified in the final models.

The lower performance phenotype of calves that had experienced higher THI_{max} is likely because heat stress is known to affect several of the components that make up the LRS score. Age at first calving is lower for heifers born to mothers that were not cooled during pregnancy (Dahl et al., 2016) and these animals also produce less milk as heifers (Monteiro et al., 2016; Skibiel et al., 2018b). Lower milk yields likely come from that heat-stress while *in-utero* is associated with smaller alveoli and greater proportions of connective tissue in the mammary gland (Skibiel et al., 2018b). Many differentially methylated genes involved in processes such as cellular repair, oxidative defense and energy metabolism are found in calves which have experienced fetal heat stress (Skibiel et al., 2018a) and resulting epigenetic changes may contribute to the lower LRS scores seen for calves from mothers who had experienced higher THI_{max}, though this is still an emerging area of research. Another explanation is body weight, *in-utero* heat-stressed calves are lighter (Tao et al., 2012; Dahl et al., 2016; Monteiro et al., 2016) and since heavier heifers reach puberty faster (Archbold et al., 2012) and age at first calving is a component of the LRS score, body weight may partially explain the poorer performance of these calves.

Calves born to mothers of a higher parity and therefore older animals had lower lifetime resilience scores (Table 5, Table 6) and this effect was also seen for granddaughters in Data set 1 (Table 7). This aligns with a previous study that reported that the highest yielding daughters in a cohort were born to younger mothers (Astiz et al., 2014). In the current study, it was not possible to discriminate whether the effect of parity was due to the cow having had previous pregnancies or due to increased maternal age and possible epigenetic changes associated with aging. There are epigenetic effects associated with aging in cattle such as changes in DNA methylation (Ribeiro et al., 2022) but currently little is known about effects on the *in-utero* environment caused by epigenetic changes; our results suggest this area is worthy of future research in terms of its impact on lifetime resilience.

The mother's LRS was included in the models as a fixed effect on the basis that the traits that make up the LRS, particularly milk yield are heritable (Hill et al., 1983; Visscher and Goddard, 1995; Gudex et al., 2014), and therefore the mother's LRS would act as a proxy for genetic merit of the dam. Higher mother LRS was associated with higher LRS of the calf, suggesting a genetic component in resilience. There are genetic correlations between resilience indicators and health, fertility and longevity (Twomey et al., 2018; Poppe et al., 2020, 2021) although resilience is a composite trait not currently incorporated into breeding programs (Berghof et al., 2019). In calculating the LRS for the Langhill data set, the herd was split into "sub-herds" based on feed trial and genetic merit, with averages for each sub-herd contributing to the LRS equation. This was to take into account any effect feed-trial type or genetic merit may have had on LRS. Had the LRS of the Langhill herd been calculated without the categorisation of the herd into sub-herds, an effect of mother LRS may have also been found in this data set. We did not have sufficient data to examine the effect of sire on LRS although this would be of interest. There is evidence of sire effects on factors such as gestation length (Fang et al., 2019), which can be associated with performance of offspring since increased gestation lengths are associated with greater incidences of stillbirth, retained placenta, and metritis (Vieira-Neto et al., 2017). Sire effects could also affect resilience through genetic links between factors such as milk yield, age at first calving or susceptibility to foot lesions (Oikonomou et al., 2013; Konkruea et al., 2017).

In our study, there was no effect of health events in the mother on calf lifetime resilience score in Data set 1 (Table 5), however, there was a significant reduction in LRS when mothers were lame in T3 in the Langhill herd (Table 6). Lame cattle spend less time feeding and take in less feed (Miguel-Pacheco et al., 2014; Thorup et al., 2016) and since nutrition is associated with fetal tissue growth (Funston et al., 2010), this may cause alterations that lead to a reduced lifetime resilience score for these offspring. Lameness in the Langhill herd was assessed using a 5-point scale, with cows considered to have a lameness event if a max mobility score of 4 or greater was recorded within a window of events period during pregnancy. There is more uncertainty about lameness records in the large data set because farmers differ in what they recognize as lameness or determine as sufficient lameness to require treatment (Horseman et al., 2014).

Other studies have found links between clinical disease and performance of daughters (Carvalho et al., 2020). One limitation of Data set 1 is that we were not able to take into account the duration, frequency or severity of health events due to the inconsistences of records between farms; some treatment events included details of the treatment used such as drug dose and length while others did not. Additionally, some events may have been missed because of recording errors, leading to misclassification of cows. However, we were able to look at this in more detail with the Langhill research herd, where events were known to be recorded with a high level of consistency and accuracy, which overall resulted in a higher proportion of these events occurring. The only clinical disease associated with LRS of calves was lameness, as discussed above.

Milk quality factors were associated with lifetime performance. Milk quality variables were tested in the models for 2 reasons, first milk production is a major component of dairy cow energy balance and higher producing cows tend to be in greater negative energy balance (Berry et al., 2006) and second, perturbations in yield or quality could be indicative of disease or other metabolic or physiological disturbances that may not have been seen or recorded (Poppe et al., 2020; Kok et al., 2021). Our models revealed that the cows with low milk yields and fat percentages in T1 (Table 5) had calves with lower LRS, which could be because low yield and fat percentage is indicative of either increased metabolic stress or unrecorded/unseen health issues, which may have subsequent deleterious effects for progeny performance. Other studies have reported associations between yields of dams and yield of their offspring, as well as composition (Berry et al., 2008) where higher milk fat concentration was associated with greater milk yield, reduced survival and reduced somatic cell counts in the offspring. Using milk quality variables in our models did mean we were unable to assess the LRS of the calves from mothers in their first parity as they did not have milk quality information available.

Our analysis of the lifetime resilience score of granddaughters identified that LRS were lower in granddaughters of cows in their third pregnancy compared with their second and that received an anti-microbial treatment in T3. Currently, there is limited understanding of carryover effects of maternal exposures on subsequent generations, although recent studies have reported an association between late-gestation heat stress in the grandmother and reduced milk yield and survival of the F2 progeny to first lactation (Laporta et al., 2018). Again, this area warrants further research. We did not find any effects for granddaughters in the Langhill herd, which may be because the data set is much smaller (74 cows).

A limitation of our final models is that they explained a relatively small percentage of the total variation in lifetime resilience score (~1% explained by the fixed effects in Data set 1, and 3% in Data set 2). This is unsurprising since many events that happen to a calf after birth will affect lifetime performance, and we did not include these aspects in the analyses. In Data set 1, there was more variation in LRS between farms than between dams (Table 5). The random effect for farm was included to account for factors that differ between farms but cannot be measured directly, such as housing or diet. Other studies using the same resilience scoring system have also found that LRS are difficult to predict across different farms (Adriaens et al., 2020), suggesting that the unidentified farm factors are important in determining calf LRS, which is unsurprising. It is also possible that policies within each farm changed over time, for example changes in diet, housing or culling policies, all of which could contribute to changes in within-farm LRS policies, although most components of the score are measured relative to the herd average, therefore the one that would have the biggest impact would be a change in culling policy. However, we demonstrate that the *in-utero* environment has a lasting impact on calf lifetime performance, and these factors warrant further research, particularly in the context of the challenges such as climate change that are facing the dairy industry.

CONCLUSION

In conclusion, this research has demonstrated associations between events that occur during pregnancy and lifetime resilience scores in dairy cows. An increased temperature-humidity index during the first and the final trimester of pregnancy was associated with lower lifetime resilience scores and this may become of increasing importance in the face of global climate change.

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