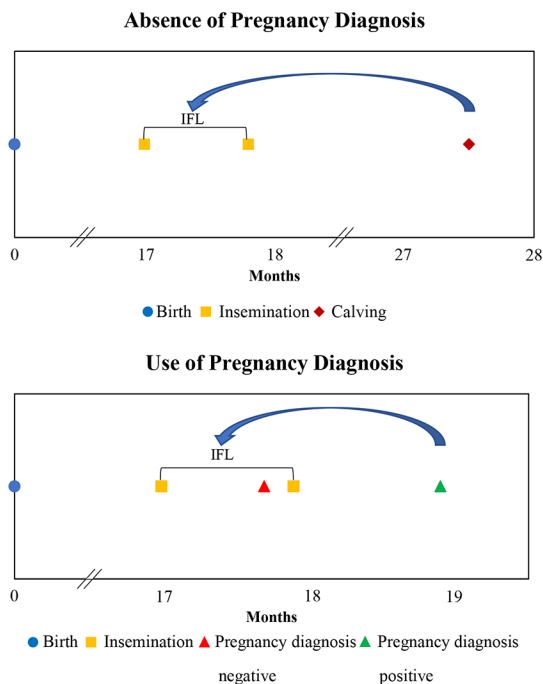


# Genetic and nongenetic variation of heifer fertility in Italian Holstein cattle

V. Ferrari,<sup>1,2\*</sup> G. Visentin,<sup>3\*</sup> J. B. C. H. M. van Kaam,<sup>1</sup> M. Penasa,<sup>2</sup> M. Marusi,<sup>1</sup> R. Finocchiaro,<sup>1†</sup> and M. Cassandro<sup>1,2</sup>

## Graphical Abstract

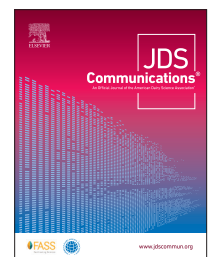


## Summary

Pregnancy diagnosis is important to characterize fertility earlier and on a larger proportion of individuals. In the present study, such information was exploited to derive genetic parameters for fertility in nulliparous Italian Holstein heifers. A selection index for heifer fertility was developed using selection index methodology, and phenotypic variation of heifer fertility traits across systematic environmental effects was estimated. The present study demonstrated that although lowly heritable, heifer fertility manifested ample and exploitable genetic variation for selective breeding. The derived selection index can be included in the national breeding objective as an additional source of information for fertility. Efforts should be made on the collection of pregnancy diagnosis to improve the genetic evaluation of fertility.

## Highlights

- Pregnancy diagnosis allows determination of heifer fertility traits earlier.
- Reduction of censored data is achievable by exploiting pregnancy diagnosis.
- Exploitable additive genetic variation exists for heifer fertility.
- Heifer ability to conceive at first service can be improved by selective breeding.



<sup>1</sup>Associazione Nazionale Allevatori della Razza Frisona, Bruna e Jersey Italiana, Via Bergamo 292, 26100, Cremona (CR), Italy, <sup>2</sup>Department of Agronomy, Food, Natural Resources, Animals and Environment, University of Padova, Viale dell'Università 16, 35020, Legnaro (PD), Italy, <sup>3</sup>Department of Veterinary Medical Sciences, Alma Mater Studiorum, University of Bologna, Via Tolara di Sopra 50, 40064, Ozzano dell'Emilia (BO), Italy. \*These authors contributed equally to this work. †Corresponding author: [raffaellafinocchiaro@anafi.it](mailto:raffaellafinocchiaro@anafi.it). © 2023, The Authors. Published by Elsevier Inc. and FASS Inc. on behalf of the American Dairy Science Association®. This is an open access article under the CC BY license (<http://creativecommons.org/licenses/by/4.0/>). Received June 08, 2022. Accepted August 29, 2022.

# Genetic and nongenetic variation of heifer fertility in Italian Holstein cattle

V. Ferrari,<sup>1,2\*</sup> G. Visentin,<sup>3\*</sup> J. B. C. H. M. van Kaam,<sup>1</sup> M. Penasa,<sup>2</sup> M. Marusi,<sup>1</sup> R. Finocchiaro,<sup>1†</sup> and M. Cassandro<sup>1,2</sup>

**Abstract:** Excellent fertility performance is important to maximize farmers' profit and to reduce the number of culled animals. Although female fertility of adult cows has been included in Italian Holstein breeding objectives since 2009, little has been done to quantify genetic variation of heifer fertility characteristics so far. The aim of the present study was to estimate genetic parameters of 4 fertility traits in nulliparous Italian Holstein heifers and to develop an aggregate selection index to improve heifer fertility. Data were retrieved from the national fertility database and included information on insemination, calving, and pregnancy diagnosis dates. The investigated phenotypes (mean  $\pm$  standard deviation) were age at first insemination (AFI, mo;  $17.25 \pm 2.89$ ), nonreturn rate at 56 d from the first insemination (NRR56, binary;  $0.78 \pm 0.41$ ), conception rate at first insemination (CR, binary;  $0.61 \pm 0.49$ ), and interval from first to last insemination (IFL, d;  $26.09 \pm 51.85$ ). Genetic parameters were estimated using a 4-trait animal model that included the following fixed effects: herd-year of birth and month of birth for AFI, and herd-year-season of birth and month-year of insemination for IFL, NRR56, and CR; the animal additive genetic effect (fitted to the pedigree-based relationship matrix) was considered as a random term. An aggregate index was developed from the estimated additive genetic (co)variance matrix by considering CR as the breeding goal and AFI, NRR56, and IFL as selection criteria. Heritability estimates from average covariance matrices ranged from 0.012 (CR) to 0.015 (IFL), with the exception of AFI (0.071). Conception rate at first insemination was strongly correlated with both IFL ( $-0.730$ ) and NRR56 (0.668), and weakly to AFI ( $-0.065$ ), and the relative emphasis placed on each selection criteria in the aggregate index was 10%, 47%, and 43% for AFI, IFL, and NRR56, respectively. The results of the present study suggest that heifer fertility should be considered as an additional trait in the breeding objectives of Italian Holstein.

Fertility is essential for dairy farmers to sustain and maximize annual farm profit. In young stock, poor fertility increases the non-productive period and increases costs, leading to reduced longevity and lifetime milk production (VanRaden et al., 2004; Wathes et al., 2014). Although lowly heritable, fertility exhibits exploitable additive genetic variation and is negatively genetically correlated with production performances (Wall et al., 2003; VanRaden et al., 2004; Berry et al., 2014). For these reasons, female fertility has become an important driver of breeding decisions in the dairy industry and is nowadays included in merit indices worldwide (Cole and VanRaden, 2018). In general, the main goal is to improve conception and daughter pregnancy rates, favor shorter calving intervals in lactating cows, and reduce the number of heifers that fail to conceive. The advantages of heifer fertility traits are that they are available early in life (before 18 mo of age) and they are genetically correlated with fertility of lactating cows (Tiezzi et al., 2012). Subsequently, some countries also include heifer fertility traits in their genetic evaluations and most of them consider only conception rate at first insemination (CR) or nonreturn rate at 56 d (NRR56; Fleming et al., 2019).

In Italy, heifer fertility data for dairy and dual-purpose cattle breeds, including inseminations and calving dates, have been stored nationally for a long time, and since 2015, pregnancy diagnoses have also been routinely collected and stored. These data

are important from different points of view. For example, early information on pregnancy status is helpful to improve reproductive efficiency and pregnancy rate in cattle (Fricke, 2002), and it can reduce the amount of censored data on traits such as days open and interval from first to last insemination (IFL; Wiggans and Goodling, 2005). Therefore, information on heifer fertility, combined with pregnancy status data, can be exploited to support farmers in their breeding decision process. The objective of the present study was to quantify genetic and nongenetic variation of fertility in nulliparous Italian Holstein heifers.

Data used in the present study were retrieved from the national fertility database managed by the National Breeders Association of Italian Holstein, Brown, and Jersey (ANAFIBJ, Cremona, Italy) for the national genetic and genomic evaluation and thus did not involve animals; prior ethical approval was deemed not to be required. The data set contained information on first inseminations ( $n = 5,596,046$ ), pregnancy diagnosis ( $n = 1,561,743$ ), and calving events ( $n = 4,863,802$ ) recorded since 1994. Furthermore, animal ID, event date, service sire, service code (e.g., AI, natural service), and service sire code (e.g., national or foreign daughter proven or genomic bull) were available for each event. A detailed description of the data quality assessment and editing procedures can be retrieved from Biffani et al. (2003).

<sup>1</sup>Associazione Nazionale Allevatori della Razza Frisona, Bruna e Jersey Italiana, Via Bergamo 292, 26100, Cremona (CR), Italy, <sup>2</sup>Department of Agronomy, Food, Natural Resources, Animals and Environment, University of Padova, Viale dell'Università 16, 35020, Legnaro (PD), Italy, <sup>3</sup>Department of Veterinary Medical Sciences, Alma Mater Studiorum, University of Bologna, Via Tolara di Sopra 50, 40064, Ozzano dell'Emilia (BO), Italy. \*These authors contributed equally to this work. †Corresponding author: [raffaellafinocchiaro@anafifi.it](mailto:raffaellafinocchiaro@anafifi.it). © 2023, The Authors. Published by Elsevier Inc. and FASS Inc. on behalf of the American Dairy Science Association®. This is an open access article under the CC BY license (<http://creativecommons.org/licenses/by/4.0/>). Received June 08, 2022. Accepted August 29, 2022.

Briefly, the aim of the quality control process was to identify the most reliable information to be retained for genetic and genomic evaluations by identifying calving events within an appropriate biological gestation range (i.e., 240 to 300 d), and in which the service sire of the successful insemination is effectively the sire of the newborn animal registered in the herdbook. Only fertility-related events collected on nulliparous heifers were extracted from the national database and used in the present study. Traits considered for subsequent genetic analysis were age at first insemination (AFI, mo) restricted to be between 9 to 27 mo, IFL (d), NRR56, and CR. For IFL, a value of 1 was attributed when only one insemination occurred and it was followed by a subsequent calving or confirmed by pregnancy diagnosis. When more than one insemination was necessary to achieve pregnancy, IFL was calculated as the difference between the first and the last insemination if followed by a calving, or if pregnancy was confirmed on the last insemination. When IFL was >230 d and conception was confirmed (or calving occurred), IFL was set to 230 d. Moreover, if the last insemination occurred less than 300 d from the first insemination (and conception was not confirmed nor calving occurred), IFL was set to missing. Otherwise, IFL was calculated as the difference from the first to the last insemination but with a penalty of 64 d (i.e., 3 estrous cycles). All these steps allowed us to reduce the proportion of censored records and therefore to also include phenotypic information on the least fertile animals. Regarding NRR56, 0 was attributed only to heifers for which the second insemination occurred within 56 d from the first insemination and 1 otherwise. Moreover, NRR56 was set to missing if the second insemination was within 14 d from the first service. Finally, CR was set to 1 if the first and only insemination was followed by a calving or a positive pregnancy diagnosis.

Fertility traits were first analyzed through a univariate linear animal model to estimate variance components, which were then used as starting values in a 4-trait animal model to estimate additive genetic and residual covariances among traits. (Co)variance components were estimated using the software AIREMLF90 (Misztal, 2008). To reduce computational time, 10 random subsets of 100 herds each were extracted from the entire fertility data set. This generated 10 data samples on which (co)variance components were estimated. Each herd (and related heifer fertility observations) was represented only once across the 10 generated data samples. Additive genetic (**G**) and residual (**R**) (co)variance matrices estimated in each of the 10 different subsets were then averaged; phenotypic (**P**) (co)variance matrix was calculated as the sum of **G** and **R**. Pedigree of animals in each subset was traced back up to 6 generations, when available. In case of 1 or 2 missing parents, unknown ancestors were assigned to genetic groups based on animal origin and year of birth. The multivariate linear mixed model in matrix notation was as follows:

$$\begin{bmatrix} \mathbf{y}_1 \\ \mathbf{y}_2 \\ \mathbf{y}_3 \\ \mathbf{y}_4 \end{bmatrix} = \begin{bmatrix} \mathbf{X}_1 & 0 & 0 & 0 \\ 0 & \mathbf{X}_2 & 0 & 0 \\ 0 & 0 & \mathbf{X}_3 & 0 \\ 0 & 0 & 0 & \mathbf{X}_4 \end{bmatrix} \begin{bmatrix} \mathbf{b}_1 \\ \mathbf{b}_2 \\ \mathbf{b}_3 \\ \mathbf{b}_4 \end{bmatrix} + \begin{bmatrix} \mathbf{Z}_1 & 0 & 0 & 0 \\ 0 & \mathbf{Z}_2 & 0 & 0 \\ 0 & 0 & \mathbf{Z}_3 & 0 \\ 0 & 0 & 0 & \mathbf{Z}_4 \end{bmatrix} \begin{bmatrix} \mathbf{a}_1 \\ \mathbf{a}_2 \\ \mathbf{a}_3 \\ \mathbf{a}_4 \end{bmatrix} + \begin{bmatrix} \mathbf{e}_1 \\ \mathbf{e}_2 \\ \mathbf{e}_3 \\ \mathbf{e}_4 \end{bmatrix},$$

where **y** is the vector of phenotypic observations (AFI, IFL, NRR56, and CR), **b** is the vector of fixed effects (herd-year of birth

and month of birth for AFI, and herd-year-season of birth and month-year of insemination for IFL, NRR56, and CR), **a** is the vector of random additive genetic effects, **e** is the vector of random residuals, and **X** and **Z** are incidence matrices relating the corresponding fixed or random effects, respectively, to the dependent variable. Variances of the random effects were assumed to be equal to  $var(a) = \mathbf{A}\sigma_a^2$  and  $var(e) = \mathbf{I}\sigma_e^2$ , where  $\sigma_a^2$  and  $\sigma_e^2$  are the additive genetic and residual variances, respectively, **A** is the pedigree-based relationship matrix, and **I** is an identity matrix of appropriate order. Genetic parameters were calculated on the average **G** and **R** matrices of the 10 subsets. Heritability was calculated as  $\sigma_a^2 / (\sigma_a^2 + \sigma_e^2)$ , and genetic ( $r_a$ ) and phenotypic ( $r_p$ ) correlations were assessed as  $cov_{a(x,y)} / \sigma_{a(x)}\sigma_{a(y)}$  and  $cov_{p(x,y)} / \sigma_{p(x)}\sigma_{p(y)}$ , respectively, where  $cov$  denotes the genetic (*a*) or phenotypic (*p*) covariance between trait *x* and *y*, and  $\sigma$  denotes the genetic (*a*) or phenotypic (*p*) standard deviation of trait *x* or *y*, respectively. The use of a linear animal model was preferred over the use of threshold animal models for NRR56 and CR. Indeed, linear animal models, applied also to binary traits, produce EBV that are strongly correlated with EBV generated from threshold animal models, and are much easier to be implemented in routine genetic evaluation and less computationally demanding (Malchiodi et al., 2017). Finally, least squares means of the fixed effects were estimated using a univariate linear mixed model by including the aforementioned fixed effects (fitted separately and not as interactions) for AFI, IFL, NRR56, and CR, and by adding herd as a random effect. The analysis was performed using the software Echidna (Gilmour, 2020) on the entire national heifer fertility database.

To generate individual weights for EBV to be combined in the aggregate index (**I**) for heifer fertility, CR was considered as the sole breeding goal and AFI, IFL, and NRR56 were considered as selection criteria. The **I** can be calculated as  $\mathbf{I} = \mathbf{b}'\mathbf{EBV}$ , where **b** is the vector of selection criteria individual weights and **EBV** is the vector of selection criteria EBV (Dekkers and Gibson, 1998). According to Schneeberger et al. (1992), **b** can be derived as  $\mathbf{b} = \mathbf{G}_I^{-1}\mathbf{G}_{IT}\mathbf{v}$ , where  $\mathbf{G}_I$  is the matrix with genetic (co)variances between traits in **I** (AFI, IFL, NRR56),  $\mathbf{G}_{IT}$  is the matrix with genetic covariances between traits in **I** and the breeding goal (CR), and **v** is the vector of economic values which were assumed to be 1 for all traits. Relative emphasis placed on each individual selection criterium *i* was calculated through the following equation (Berry, 2015):

$$\text{Relative emphasis} = \frac{|b_i\sigma_i|}{\sum_{j=1}^n |b_j\sigma_j|},$$

were  $\sigma_i$  and  $\sigma_j$  are the genetic standard deviations of the trait *i* and *j*, respectively. The **I** was then standardized to mean 100 and standard deviation 5 for proof publication within the national genetic and genomic evaluation.

Descriptive statistics of AFI, IFL, NRR56, and CR, as well as the heritability, and genetic and phenotypic correlations from average **G** and **P** (co)variance matrices are presented in Table 1. Mean  $\pm$  standard deviation of AFI, IFL, NRR56, and CR were  $17.25 \pm 2.89$  mo,  $26.09 \pm 51.85$  d,  $0.78 \pm 0.41$ , and  $0.61 \pm 0.49$ , respectively. Heritability was the greatest for AFI (0.071) and it ranged from 0.012

**Table 1.** Descriptive statistics, heritability (in bold, on the diagonal), genetic correlations (below the diagonal), and phenotypic correlations (above the diagonal) of heifer fertility traits

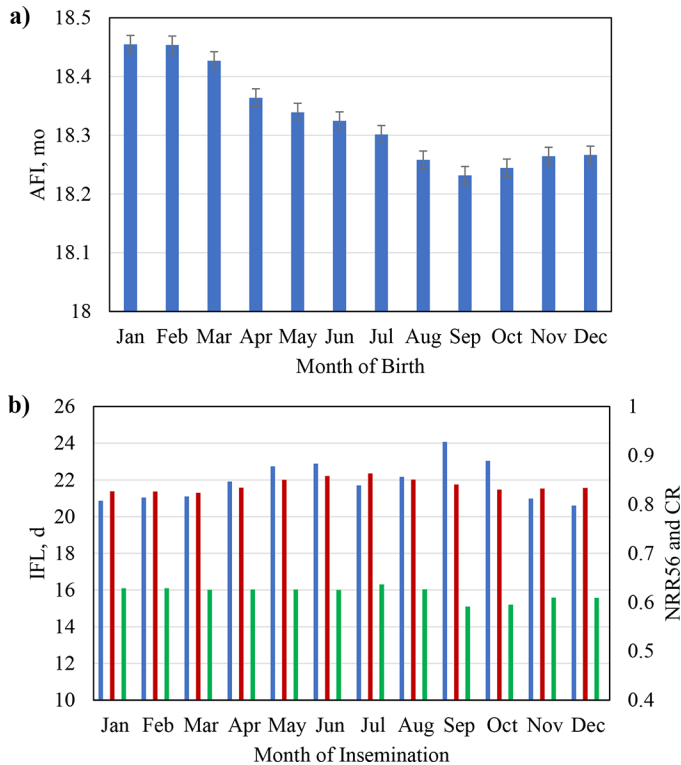
Trait <sup>1</sup>	Descriptive statistics				Genetic parameter			
	Mean	SD	Minimum	Maximum	AFI	IFL	NRR56	CR
AFI, mo	17.25	2.89	9	27	<b>0.071</b>	-0.089	0.006	0.048
IFL, d	26.09	51.85	1	294	0.050	<b>0.015</b>	-0.309	-0.729
NRR56	0.78	0.41	0	1	0.152	-0.256	<b>0.013</b>	0.763
CR	0.61	0.49	0	1	-0.065	-0.730	0.668	<b>0.012</b>

<sup>1</sup>AFI = age at first insemination; IFL = interval from first to last insemination; NRR56 = nonreturn rate at 56 d; CR = conception rate at first insemination.

(CR) to 0.015 (IFL) for the other traits. However, the coefficient of genetic variation ( $CV_a$ ) was the lowest for AFI (2.75%) and the greatest for IFL (21.22%). The  $CV_a$  for NRR56 and CR was 5.88% and 9.99%, respectively. Conception rate was weakly genetically correlated with AFI (-0.065) and strongly correlated with both IFL (-0.730) and NRR56 (0.668); these latter 2 correlations were very close, in magnitude and direction, to their phenotypic counterparts (Table 1). Age at first insemination was also weakly correlated with IFL ( $r_p = -0.089$ ;  $r_a = 0.050$ ) and NRR56 ( $r_p = 0.006$ ;  $r_a = 0.152$ ). The standard errors of heritability estimates of the 4 heifer fertility traits at each run ranged from 0.01 to 0.03, and standard errors of genetic and phenotypic correlations from 0.01 to 0.08. The low heritabilities estimated in the current study were expected and consistent with those reported for Canadian Holstein nulliparous heifers (Jamrozik et al., 2005). Results were also in agreement with Liu et al. (2008), who estimated heritability of 0.012 and 0.015 for heifer and cow NRR56, respectively, and 0.014 for heifer IFL in a joint genetic evaluation using Holstein, Red dairy cattle, and Jersey data from Germany, Austria, and Luxemburg. Muir et al. (2004) reported higher heritability estimates for NRR56 (0.030) and AFI (0.190). The present study on heifer fertility is the first one carried out in Italian Holsteins. Indeed, Tiezzi et al. (2012) investigated genetic variation of these traits in Italian Brown Swiss dairy cattle, with heritability estimates that agreed with those of the present study. Genetic correlations estimated in the present study corroborate those reported in previous studies (Jamrozik et al., 2005; Liu et al., 2008) in terms of both direction and magnitude, with AFI being only weakly genetically correlated with other heifer fertility traits (Muir et al., 2004; Jamrozik et al., 2005). The relative emphasis, in absolute value, of the traits included for the calculation of I was 10%, 47%, and 43% for AFI, IFL, and NRR56, respectively, and reflects the genetic correlations between the selection criteria (AFI, IFL, and NRR56) and the breeding goal (CR). The exclusion of CR from I was because CR is measurable only once calving has occurred, or after a positive pregnancy diagnosis, therefore CR is not measurable in some individuals and could also create a bias in genetic and genomic evaluations, as CR information would not be available for the least fertile daughters. In light of this, encouraging the collection of pregnancy check can be a viable solution to overcome this issue. Although data on pregnancy diagnosis are currently available at the national level, this source of information is not routinely collected by all farmers, and it has been introduced recently in the national fertility database. However, the number of registered pregnancy diagnoses on heifers increased from 180,779 in 2015 to 264,700 in 2021, with northern regions contributing the largest proportion (77.90%), followed by southern (13.60%) and central regions (8.50%). This reflects the national distribution of

Holstein herds, which are mainly located in the Po valley (Northern Italy; i.e., the area more suited to intensive dairy farming). The results of the present study are of great importance for the national Holstein breeding program not only to provide the farmers with useful information to optimize breeding decisions to improve fertility, but also because genetic proofs of heifer NRR56 can be used to participate in Interbull (2022) Multiple Across Country Evaluation (MACE) for the trait “maiden heifer ability to conceive” (T1). Proofs of this trait differ among countries participating in MACE, yet the genetic correlation between Holstein T1 of Italy and T1 of other countries ranges from 0.808 to 0.924, and this correlation is, as expected, stronger with countries that have defined T1 as in the current study (April 2022 evaluation run).

Figure 1a depicts the least squares means of AFI across months of birth. Although the effect was statistically significant, differences across months of birth are of little biological impact. Indeed, AFI was the largest for animals born in January and February (18.45 mo; SE = 0.15) and the smallest for animals born between August and October, with the minimum in September (18.23 mo; SE = 0.15). Least squares means across years of birth indicated that AFI progressively shortened from 19.16 mo (SE = 0.15) in 1994 to 17.17 mo (SE = 0.15) in 2018. Raising young stock is a significant cost for farmers (up to 15–20% of total milk production costs; Hutchison et al., 2017), and therefore farmers might prefer to voluntarily anticipate animals’ productive life. The reduction of AFI across calendar years is consistent with previous studies in US (Hare et al., 2006) and Canadian heifers (Duplessis et al., 2015), and could therefore be related to management (e.g., better calf-raising practices) but also to genetic factors. For example, intense selection for higher milk production may have increased the need for replacement heifers due to unfavorable genetic correlations to other functional traits (Brito et al., 2021). Figure 1b depicts the least squares means of IFL, NRR56, and CR across months of insemination. All traits had an erratic and similar trend and denoted poorer fertility performances (i.e., high IFL, and low NRR56 and CR) in September compared with the remaining calendar months of the year. The similarity of the trend among these traits is likely related to the strong genetic and phenotypic correlations between IFL, NRR56, and CR. Although differences among least squares means of months of insemination within traits were significant, their biological impact was negligible. An indefinite pattern of the month of insemination effect has been observed also by Kuhn et al. (2006), who reported higher CR in April and July and lower in September, October, and November. Regarding the year of insemination, results from the linear mixed models indicated that IFL, NRR56, and CR deteriorated. In particular, IFL changed from 21.23 d (SE = 0.19) in 1994 to 24.28 d (SE = 0.15) in 2020. Similarly, in the same



**Figure 1.** Least squares means of (a) age at first insemination (AFI) across months of birth (SE = 0.15) and (b) interval from first to last insemination (IFL; blue bar, SE = 0.10), nonreturn rate at 56 d (NRR56; red bar, SE = 0.001), and conception rate at first insemination (CR; green bar, SE = 0.001).

time span, NRR56 decreased from 0.88 (SE = 0.001) to 0.78 (SE = 0.001), and CR from 0.68 (SE = 0.001) to 0.63 (SE = 0.001), suggesting that, although EBV for cow fertility, as an aggregate index, has been included in the national Holstein selection index since 2009, little benefit has been achieved for heifer fertility. Although within trait genetic correlations between heifer and adult cows fertility attributes have never been estimated in Italian Holstein so far, Tiezzi et al. (2012) demonstrated that the genetic correlations between fertility traits measured in Brown Swiss lactating cows and maiden heifers was moderate to weak (0.348 for CR and 0.349 for NRR56 between heifers and first-parity cows, and 0.637 and 0.636 for CR and NRR56 between heifers and second-parity cows). Therefore, the correlated response to selection may prove insufficient. This evidence justifies the inclusion and subsequently the direct selection also for heifer fertility traits in the national breeding program, as currently done in other countries (Miglior et al., 2017). Indeed, heifer fertility traits have gained more relevance into selection indices worldwide (Miglior et al., 2017) and, for example, since 2014 heifer CR has been included in the US selection indices (Cole and VanRaden, 2018).

The present study supports that, as heifer fertility traits are available early in life, their inclusion into the genetic evaluation would be beneficial to improve the overall fertility of the dairy herd. Moreover, new available information on pregnancy diagnoses allows new traits to be collected early in life, such as IFL. The aggregate heifer fertility index calculated in the present study can

be included in the aggregate index of cow fertility, which is already published within the national genetic and genomic evaluation and has been included in the Italian Holstein breeding objective since 2009. Moreover, results of the present study can be useful to provide farmers with more detailed information on foreign AI bulls without daughters in Italy but available for the national market thanks to the participation in Interbull MACE for the trait dairy heifers' ability to conceive (T1 trait) as well as due to genomic evaluation.

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## Notes

- V. Ferrari  <https://orcid.org/0000-0002-7774-4388>
- G. Visentin  <https://orcid.org/0000-0003-0869-5516>
- J. B. C. H. M. van Kaam  <https://orcid.org/0000-0002-2592-2461>
- M. Penasa  <https://orcid.org/0000-0001-9984-8738>
- M. Marusi  <https://orcid.org/0000-0002-2359-3633>
- R. Finocchiaro  <https://orcid.org/0000-0002-9058-9992>
- M. Cassandro  <https://orcid.org/0000-0002-8709-2870>

This study was supported by “Latteco2 project, sottomisura 10.2 of the National Rural Development Program (PSRN) - Biodiversity 2020–2023” [Ministero delle politiche agricole, alimentari e forestali (MIPAAF). D.M. no. 465907 del 24/09/2021, project unique code J12C21004080005], National Breeders Association of Italian Holstein, Brown, and Jersey (ANAFIBJ, Cremona, Italy).

Because no live human or animal subjects were used for this study, no IRB or IACUC approval was required.

The authors have not stated any conflicts of interest.