Genetic variability of functional longevity in five rabbit lines

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Short title: Genetic parameters of longevity in rabbits

Abstract

Longevity is a functional trait directly related to farm profitability. The objectives of this study were to analyze the differences in the genetic determination of functional longevity in five Spanish lines of rabbits, and to check how different systematic factors might affect this genetic determination. Four of the lines were maternal (line A, V, H and LP), these lines were established selecting base generation animals according to different criteria, but in the subsequent generations all of them were selected for litter size at weaning. The other is the paternal line R, this line was constituted by selecting animals with an outstanding daily growth rate and the same criterion was applied to the subsequent generations. The trait analyzed, length of productive life, was the time in days between the date of the first positive pregnancy test and the date of culling or death of a doe. Data analysis was performed by applying the survival analysis using a Bayesian approach. Four models extended from the Cox proportional hazard model were used to analyze data of each line separately and jointly. The complete model (Model 1) included the fixed effect of year-season combination, positive palpation order (OPP), i.e. reproductive cycle, physiological status of the doe at service (PS) and number of kits born alive at each kindling (NBA) as time-dependent factors. The inbreeding coefficient was fitted as a continuous covariate and the animal's additive genetic effect was also fitted to the model (Model 1). The other models were the same as Model 1 but excluding OPP (Model 2) or PS (Model 3) or NBA (Model 4), these alternative models were explored to assess the consequence on additive variance estimates of not correcting for these animal-dependent factors. Combined analysis using data from all lines was performed using the same model as Model 1 substituting the year-season combination for the line-year-season combination. Estimated effective heritabilities of longevity were 0.07±0.03, 0.03±0.02, 0.14±0.09, 0.05±0.04, 0.02±0.01

and 0.04±0.01 for lines A, V, H, LP, R and for the merged data set, respectively. Removing the PS from the model led to an increase in the estimated additive genetic variance in all lines (0.17±0.05, 0.05±0.03, 0.29±0.19, 0.29±0.20, 0.07±0.04 and 0.05±0.02 for lines A, V, H, LP, R and the merged data set, respectively), which could be an indication of the existence of a genetic correlation between longevity and physiological status, while discarding the OPP or NBA from the model was shown to be less important. The highest hazard of death and/or culling was observed during the first two parities and decreased as the order of parity progressed. Does non-pregnant-non-lactating had the highest risk of death or culling. The does that had zero kits born alive incurred the highest risk, and this risk decreased as the number of kits born alive increased. In conclusion, the consideration of longevity as selection criterion for the studied rabbit lines is not recommended.

Keywords: Rabbit does, length of productive life, genetic parameters, Cox proportional hazard model, survival analysis

Implications

Longevity in rabbits has a relatively low economic weight compared to other traits like, for example, efficiency in the use of feed or prolificacy. This is so because until now in the computation of this weight some relevant factors associated with management, welfare and ethics are not properly defined in the farm benefit function. The consideration of longevity in rabbit breeding programs is a fact and it is important to both properly assess the genetic determinism in the different populations considered in those programs and to know the role that systematic factors associated to management and animal-dependent factors have on the trait. In this study we report these estimates for the different rabbit lines involved in one of most influent rabbit breeding programs worldwide. From our results, it can be concluded that in the maternal lines a non-zero genetic correlation might exist between the longevity of the rabbit doe and its physiological status.

Introduction

The annual replacement rate in meat rabbits is about 120% (Ramon and Rafel 2002) with near 50% of the dead or culled does replaced during their first three parities (Rosell, 2003). The average pregnancy rate in the Spanish commercial farms is about 78.2% and the average number of parities per doe/year is 5.7 kindlings (BdCuni, http://www.ivia.es/bdcuni/Inicio/presentacionbdcuni.php, Valencian Institute of Agricultural Research). The main problems associated with this high replacement rate are the cost of the does, the greater proportion of less mature females, i.e. less productivity, and a higher incidence of management and pathological problems related to the continuous introduction of animals from other farms. Another important point regarding the replacement of an animal becoming ill or dead is its drop in production during the period between the moment the animal became sick and when it is eventually replaced. This point could be relevant and it was not considered in previous studies concerning longevity and its economic importance.

Given the aforementioned relevance of the longevity, it has been considered in different ways in two rabbit breeding programs. Sánchez *et al.* (2008) considered longevity of rabbit does as a criterion to recruit females from commercial farms used to constitute the LP line. A divergent selection experiment for functional longevity was carried out in the INRA 1077 rabbit line, estimating a difference of longevity between the two lines of 32 days (Larzul *et al.,* 2014). This second approach has a most experimental character but nonetheless exemplifies the consideration of the trait as selection criterion. In these breeding programs, additional lines participate, both maternal and paternal, and the available information recorded during their selection process would be highly valuable for further characterizing the longevity, both genetically and phenotypically, in the whole breeding program. Many generations of

115 records have been collected, usually having the different populations involved in the
116 breeding program in the same farm, and in that nucleus of selection a common practice
117 is not to cull females based on their production, so the available data permits us to
118 address directly a doe's functional longevity.

119 Therefore, the objective of this study was to phenotypically and genetically
120 characterize the longevity of the lines involved in the rabbit breeding program
121 coordinated by the Institute for Animal Science and Technology at the Polytechnic
122 University of Valencia (UPV). The different estimated parameters will be interpreted by
123 accounting for both the criteria used for selecting the founder animals of the lines and
124 for the selection criteria applied afterwards along the generations of selection. In
125 addition, for some systematic factors affecting longevity, which are intrinsic to the
126 animal, like prolificacy or fertility for example, will be explored for their genetic
127 association with functional longevity. The achievement of these objectives will allow for
128 a broader consideration of the functional longevity within the whole breeding program.
129
130 **Material and Methods**

131 *Animals and Management*

132 Data used in the present study were collected from five lines of rabbits. Four of them
133 are maternal lines (A, V, H and LP), and the other line is a paternal line (R). Animals
134 were reared at a selection nucleus located on the farm of the Institute for Animal
135 Science and Technology, Universitat Politècnica de València. The records used in this
136 study were collected from the initial foundation of these lines until March 2013.

137 The process of foundation of line A began in 1976 by sampling New Zealand White
138 (NZW) rabbits, reared by farmers near Valencia (Spain). After three generations
139 without selection, the line has since 1980 been selected by a family index based on

litter size at weaning (Estany *et al.,* 1989). Line V was founded in 1980 as a synthetic line, mating crossbred animals that were progeny of four specialized maternal lines. Since then, the line has been selected (Estany *et al.,* 1989) to increase litter size at weaning. Line H was founded by applying hyperprolific selection and embryo cryopreservation techniques (García-Ximénez *et al.,* 1996; Cifre *et al.,* 1998). Hyperprolific does were assembled from a large commercial population, spread over different Spanish farms. This line was housed from its foundation in 1996 at the nucleus of selection until May, 2004 (10^{th} generation of selection) when it was moved to another farm in Sant Carles de la Ràpita, Tarragona (Spain). The foundation of the line LP was started in 2003 by selecting females from commercial farms that showed extremely long productive lives and prolificacy near or above the average of the Spanish commercial rabbit population. This line has been selected since its foundation to increase litter size at weaning (Sánchez *et al.,* 2008). In V, H and LP, animals are selected based on BLUP breeding value predictions obtained with a repeatability animal model. Line R comes from the fusion of two paternal lines, one founded in 1976 with California rabbits reared by Valencian farmers and another founded in 1981 with rabbits belonging to specialized paternal lines (Estany *et al.,* 1992). The method of selection has always been by individual selection on post-weaning daily gain.

The last generations of selection considered in the present study were the 44^{th}, 39^{th}, 10^{th}, 8^{th} and 32^{nd} generations for lines A, V, H, LP and R, respectively. The mating system of the maternal lines is conducted in non-overlapping generations, i.e. mating males and females belonging to the same generation. Does for the next generations are selected from 25 – 30 % of the best-evaluated matings, i.e. based on parent average prediction, with a limit of four does per mating. The bucks were selected within sire families from their best mating, i.e. within family, one son from the mating female

with the best breeding value prediction. In order to minimize the increase of inbreeding, mating between close relatives was avoided, i.e. mates could not have common grandparents. In addition, the contribution of bucks to the next generation was equalized; thus, as it has been stated, males were selected within sire families.

The farm where the rabbits were housed had insolated roofs and had controlled ventilation, depending on the indoor temperature. The cages for does (90 cm long, 50 cm wide and 40 cm high) and progeny (80 cm long, 50 cm wide and 30 cm high) were standard flat deck. Management of animals in the different lines was the same, using natural mating; bucks and does began reproduction from 17 to 18 weeks of age. On day 12 post-mating, each doe was tested for pregnancy by abdominal palpation, and non-pregnant does were mated back. Does were mated 11 days after kindling, generally one female was always mated to the same buck, litters were examined each morning during the suckling period to remove the dead kits. Kits were reared by their own dams and weaned at 28 days. Then animals were individually identified by a number tattooed on the left ear and transferred to fattening cages (8-9 rabbits per cage) until marketing at 63 days. From weaning at 4 weeks to 9 weeks of age, rabbits were fed *ad libitum* with a commercial pelleted diet formulated for growing animals (14.5% crude protein, 16.7% crude fiber and 2.6% fat). During the subsequent production period, breeding animals were housed in individual cages and fed ad libitum with a commercial pelleted diet formulated for adults (17% crude protein, 15.5% crude fiber and 3.5% fat). The animals were kept under a controlled 16-h light / 8-h dark photoperiod. For a suitable genetic evaluation of animals in the nucleus, some common culling criteria in commercial farms were not considered; for example in the nucleus, does with low levels of production or with long kindling intervals were not culled. Thus, our longevity records directly represent measurements of functional

longevity, i.e. free from the effect of culling due to productive reasons. In commercial farms, however, it is common to cull females with two to three infertile cycles or a prolificacy clearly below the average of the farm.

Trait and Statistical Models

The longevity of a doe (length of productive life, LPL) was measured as the difference between the date of the first positive palpation test and the date of death or culling due to involuntary causes. In this context involuntary culling refers to culling due to pathological problems (i.e., snuffles, mastitis, sore hocks, diarrhea, etc.) or culling due to strong infertility (does with three consecutive non-fertile matings) were culled (Sánchez *et al.,* 2008). All of these reasons for culling are considered indicators of disease problems but not indicators of poor production of healthy animals. As has been already stated, does were never culled based on production results, therefore, LPL reflected a direct measurement of functional longevity. Date and reason for culling or death are systematically recorded, as well as all the information regarding mating and parturition dates, pregnancy status after the abdominal palpation and prolificacy. Records from females removed to free up cage space for animals of the next generation, or culled because of accidents or other technical reasons not related to health status, were treated as censored (Piles *et al.,* 2006). Thus, the record of each animal included a censoring code (0 = censored; 1 = uncensored) and all the information regarding physiological status of the female during its entire life (reproductive and lactation status), as well as all the prolificacy records and the line to which the animal belonged. The trait was analyzed using survival analysis methodology by modelling the risk of failure instead of the actual longevity of an animal. The model relies on the concept of hazard at a given time which is the limiting

probability of being culled among animals still alive at the specified time. The hazard can be modelled for all records, whether censored or not. The chosen models to perform the analyses were Cox proportional hazard models. A Weibull model was discarded because of its misfit due to the high proportion of does dying in the first parturition (Sánchez *et al.,* 2004; Piles *et al.,* 2006). The number of does with records was 15 670 and the pedigree involved 19 405 animals. Among the total number of females with records, 5775 were censored (Table 1).

A first analysis was performed with a model that was called Model 1 or complete model whose equation was:

$$h_i\left(\mathrm{t}|\mathbf{x'_i}(\mathrm{t})\right) = h_0\ (t)\exp\{\mathbf{x'_i}(\mathrm{t})_{\mathbf{YS}}\,\boldsymbol{\beta}_{\mathbf{YS}} + \mathbf{x'_i}(\mathrm{t})_{\mathbf{OPP}}\,\boldsymbol{\beta}_{\mathbf{OPP}} + \mathbf{x'_i}(\mathrm{t})_{\mathbf{PS}}\,\boldsymbol{\beta}_{\mathbf{PS}} + \mathbf{x'_i}(\mathrm{t})_{\mathbf{NBA}}\,\boldsymbol{\beta}_{\mathbf{NBA}} + \mathrm{F}_i\,\beta_{\mathrm{F}} + \mathbf{z'}_i\,\mathbf{u}\}$$

where $h_i(t|x'_i(t))$ is the hazard of animal i at time t, affected by covariates indicated by $x_i'(t)=\{x_i'(t)_{YS}, x_i'(t)_{OPP}, x_i'(t)_{PS}, x_i'(t)_{NBA}, F_i, z_i'\}$; $h_0(t)$ is the baseline hazard function at time t, defined by a step-wise function given by $h_0(t) = h_{0m}$ for t ∈ $[\tau_{m-1}, \tau_m]$, $m = 1, \ldots, M+1$, where $\tau_1, \ldots, \tau_M$ are the M different ordered survival times, $\tau_0 < \tau_1 < \cdots < \tau_M < \tau_{M+1}$; $\tau_0 = 0$ and $\tau_{M+1} = \infty$. $\boldsymbol{\beta}_{\mathbf{YS}}$ is a vector comprising the effects of year-season (YS) combinations. It was defined by intervals of 6 months and the number of levels was 63, 63, 17, 20 and 49 for the subsets of A, V, H, LP and R lines, respectively. This factor accounts for the effect acting over all the contemporary animals in the farm. When a joint analysis of all lines was conducted, YS was substituted by LYS (line-year-season combination) with 212 levels. The line effect comprised 5 levels (A, V, H, LP and R). $\boldsymbol{\beta}_{\mathbf{OPP}}$ is a vector including the effects of the three levels of the positive palpation order (OPP) (1, 2 and 3 or more positive palpation orders). The changes of level in this factor occurred after every pregnancy test. $\boldsymbol{\beta}_{\mathbf{PS}}$ is a vector including the effects of the physiological status of the female, which comprised 6 levels. This factor reflects

240 the combination between the reproductive status of the doe (pregnant, non-pregnant,
241 and unknown), and its lactation status (lactating and non-lactating) at the time of
242 mating. With regard to lactation status, changes of level occurred at parturition and at
243 weaning, while for reproductive status the levels might change at mating, after
244 pregnancy test and at parturition; the unknown level included does in the period
245 between mating and the pregnancy test. $\boldsymbol{\beta}_{\mathbf{NBA}}$ is a vector including the effects of 5
246 classes of number of kits born alive in each kindling (NBA); the first level corresponded
247 to does that had 0 NBA, the second level to does that had 1 to 4 born alive, the third
248 to 5 to 8 born alive, and so on until the fifth level which corresponded to does that had
249 at least 12 born alive. The changes of levels in this time-dependent factor occurred at
250 parturition. β_{F} is the time-independent linear regression coefficient on the inbreeding
251 coefficient of animal i ($\mathrm{F_i}$). Finally, $\mathbf{u}$ is the additive genetic effect of the animal i. This
252 factor was assumed to follow a priori a multivariate normal distribution with mean 0 and
253 (co)variance $A\sigma^2_a$, where A is the numerator relationship matrix and σ^2_a is the additive
254 genetic variance. Prior distributions for the parameters were defined in the same way
255 as in Sánchez *et al.* (2006b). Baseline hazard step-wise function elements h_{0m} for $m =$
256 $1, \ldots, M+1$ were assumed to be independent and identically distributed (i.i.d.) :
257 $p(h_{0m}) \sim \frac{1}{h_{0m}}$, where $0 < h_{0m} < \infty$. This is a long-uniform prior which supposes an
258 uniform distribution for the logarithm of h_{0m}. The elements of all $\boldsymbol{\beta}$ were assumed to
259 be i.i.d. following a uniform distribution and the additive genetic variance (σ^2_a) was also
260 assumed to follow a uniform distribution. The estimation of model parameters was
261 performed by a Bayesian approach, based on statistics of samples from the marginal
262 posterior distributions obtained using a Gibbs sampling algorithm. The Gibbs sampling
263 was programmed using Fortran 90, utilizing the subroutines by Gilks and Wild (1992)
264 for adaptive rejection sampling (Sánchez *et al.,* 2006b) and the program is available

upon request from the authors. The Gibbs sampler algorithm comprised 200 000 iterations, discarding the first 20 000. Afterwards, one sample in each 20 was saved and features of interest of the marginal posterior distributions were obtained with the coda package of the R program (Plummer *et al.,* 2006). Convergence of the chains of the parameters and contrasts of interest were assessed by using the Z-criterion of Geweke (Geweke, 1992). More details about this procedure can be found in Blasco (2001) and Sorensen and Gianola (2002).

Given the non-linear nature of the models used in the survival analysis, there is no heritability definition equivalent to that from linear models. One interesting definition of heritability, related to the computation of the accuracy of breeding values predictions, is the effective heritability (Yazdi *et al.,* 2002), $h^2_{\text{eff}} = \frac{\sigma^2_a}{\sigma^2_a + 1}$. This formula was developed by Yazdi *et al.* (2002) for a Weibull sire model. Its extension to a Cox model was validated by J.P. Sánchez for the Cox model through simulation (personal communication). To check the effects of the systematic factors on the genetic determination of longevity (additive variance estimate), three additional analyses were performed with the same Model 1 but discarding OPP (Model 2), or PS (Model 3), or NBA (Model 4).

Results

Descriptive statistics regarding longevity data of the lines are presented in Table 1. As shown in this table, the lines H and LP had the highest censoring rates. Percentage of the censored records in line R (19.3%) was markedly lower than those of the other lines. The Geweke test did not detect lack of convergence in any case. As shown in Table 1, LP line had a longer LPL compared to the other lines and followed by the line

289 V. Lines A and R had a similar LPL for both censored and uncensored records. The
290 paternal line in this study, line R, had the lowest estimate (0.02). Estimates of the
291 additive variance and the corresponding effective heritabilities were low and within the
292 range of the previous estimates as shown in Tables 2. Line H had the highest
293 heritability estimate (0.14) but with a very wide HPD95% (0.003, 0.292).

294 Results from models 1 and 3 are compared in Table 2, correcting for physiological
295 status of the female (model 1) removed about 51, 39, 38, 83 and 75% of the additive
296 variance in lines A, V, H, LP and R, respectively. Comparing results of Models 1 and 4
297 in Table 2, the effect of accounting for number born alive in the model slightly changed
298 the additive variance of longevity in all lines. The same trend was observed when
299 comparing the results from Models 1 and 2 (Table 2); there were no relevant changes
300 in the additive variance when correcting for positive palpation order.
301 Figure 1 shows genetic trends for the different lines. These trends were computed as
302 the posterior means of the estimated breeding values for the log hazard of the animals
303 born in a given generation. Animals with the more negative breeding values are those
304 with the higher longevity and vice versa. The highest genetic trends were observed for
305 lines H and A. The posterior means and standard deviations of the inbreeding
306 depression affecting the log hazard are presented in Table 2. Given the observed
307 uncertainty, it has not been possible to confirm that the inbreeding has an unfavorable
308 effect on longevity for any of the lines.
309 Posterior means and standard deviations of the contrasts of log-hazard between the
310 different levels of the positive palpation order are presented in Table 3. The differences
311 between the positive palpation orders were relevant. The probabilities of these
312 differences being greater than zero were between 99 and 100% in 12 out of 15
313 contrasts. The results showed that the hazard decreased as the parity order advanced.

The highest differences of hazard were observed between OPP1 and OPP3, followed by the contrasts between OPP2 and OPP3. The maximum difference of hazard between the first and third level of OPP was in LP line (1.30±0.34). The lowest risk was found for the third parity (1.00).

The posterior means and standard deviations of the contrasts of log-hazard between the different levels of the physiological status of the doe at mating are presented in Table 4. The PS reflects the combination between the reproductive and the lactation statuses of the doe. The results showed that the non-pregnant-non-lactating level (NP/NL) had higher risk than the other levels in all the five lines. The results in Table 4 showed that NP/NL level had higher risk than the other levels in each one of the five lines, showing that the low fertility of the does in this level is an indication of health and/or stress problems.

The posterior means and standard deviations of the contrasts of log-hazard between the different levels of the number of kits born alive are presented in Table 5. In line H the probabilities of the contrasts being higher (positive contrasts), or lower than zero (negative contrasts) were between 52 and 91%. Although the contrasts involving H line, in some cases, reached relevant magnitudes, given the reduced number of records of this line, the probability of them being greater than zero did not reach extreme values. In the other four lines, the level of zero born alive (Z) had a higher risk compared with the other levels. In addition, in line V the level of 1 to 4 born alive (B) had higher risk than the levels of 5 to 8 (C) and 9 to 12 (D) born alive.

Discussion

In the present study, the low censoring rate of line R may be attributed to the higher disease incidence in this line compared to the others. This result is in accordance with

Sánchez *et al.* (2012) who found that R line animals had mastitis prevalence and ulcerative pododermatitis of 10% and 23% while line V had 4% and 9%, respectively. They also stated that the overall disease index for the lines A, V and R was 32%, 20% and 42% respectively, with significant differences between them. The low precision associated with the high estimate of heritability for longevity in line H is a consequence of the low number of records in this line. The high longevity of line LP was expected, as a consequence of its foundation process (Sánchez *et al.,* 2008). The estimation error of the heritability estimate was lower in the case of lines A and V than in the other lines involved in the study. This is due to the larger number of records in these populations; in these cases around 40 generations of data were covered. In spite of the large variation of the heritability estimates, the corresponding HPD95% always overlapped and consequently we cannot discard that these lines might have the same heritability. Taking into account the low estimates of heritability for longevity in the five rabbit populations, including this trait as selection criterion in rabbit breeding programs is not recommended.

Accounting for physiological status in model 1 caused a significant decrease in the additive genetic variance of longevity of the five rabbit lines compared to the estimates of model 3. Hence, part of the genetic differences for functional longevity can be related to the way in which the risk of the females changed with the physiological status and to the genetic determination of the physiological status. These findings are in agreement with those reported by Piles *et al.* (2006) who found that in the Prat line the correction for physiological status removed about 40% of the additive variance. However, correcting for number born alive slightly changed the additive variance of longevity in all lines. This could be an indication of the low genetic correlation between prolificacy and functional longevity, previously estimated as very low and not

364 statistically significant different from zero (Sánchez *et al.,* 2006a). Sánchez *et al.*
365 (2006b) included a residual term in the model and reported an additive variance of 0.25
366 and a residual variance of 0.69 which corresponds to an effective heritability of 0.19 in
367 a replicate of line V. Effective heritabilities of longevity obtained in the Prat and A1077
368 lines were quite similar (Piles *et al.*, 2006), despite the differences in breeding
369 schemes, voluntary culling rules, definition of reproductive longevity and modeling of
370 the baseline hazard function. Using the model with the physiological status, these
371 estimates were 0.158 and 0.172 in Prat and A1077 lines, respectively, while using the
372 model without this factor; the corresponding estimates were 0.237 and 0.187. Larzul
373 *et al.* (2014), using a sire-maternal grandsire model, reported an effective heritability
374 of 0.185 for longevity in INRA 1077 line measured as the total number of artificial
375 inseminations. In pigs, Yazdi *et al.* (2000) found estimates of heritability for LPL varying
376 from 0.109 to 0.268. Serenius and Stalder (2004) reported heritabilities of 0.16 and
377 0.19 for LPL in Landrace and Large White pig populations. Other studies indicated that
378 the estimates of heritability ranged from 0.06 to 0.4 (Engblom *et al.,* 2009 and
379 Mészáros *et al.,* 2010).

380 The important increases in genetic variance in some lines when removing the
381 physiological status from the model could be an indication of the existence of a high
382 positive genetic correlation between longevity and physiological status in these lines.
383 A genetic correlation between longevity and physiological status could be expected if
384 it is taken into account that both are affected by the fertility and health of the does.
385 However, more studies are needed to check this speculation. In LP line, the change in
386 additive variance was about 83%, which could be related to the highest values in this
387 line of the contrasts between different levels of the physiological status. Additionally,
388 it is indicated that these highest values could be a consequence of the foundation

389 criterion of this line which increased the average longevity and could produce a scale
390 effect on other factors affecting the trait.
391 The differences in genetic trend between lines can be partly explained by the
392 differences of the heritability, as well as the differences in intensity of natural or
393 unintended selection for longevity in the different lines. Correlated response is not
394 expected to be responsible for the observed trend, since the genetic correlations with
395 the selection criteria are low (EL Nagar, 2015). Here, the importance of natural or
396 unintended selection in a line is clearly related to its longevity. Animals with lower
397 longevity have a higher probability of dying before leaving progeny to be selected as
398 reproducing animals for the next generation. Consequently, the high genetic trend
399 observed in lines A and H is due to their relatively high heritabilities and to their low
400 longevities. On the contrary, in line R, in spite of its low longevity we do not observe a
401 clear genetic trend because of its extremely low heritability value (0.02).
402 Concerning the inbreeding depression, it was not possible to confirm that inbreeding
403 has an unfavorable effect on longevity for any of the lines. The large errors of the
404 estimates could be due to the collinearity between the inbreeding and year-season
405 effects (Fernández *et al.,* 2017); it means that a group of does within the same year-
406 season tends to have the same inbreeding level. This collinearity makes the separation
407 of the two effects in the model of analysis difficult. In pigs, Casellas *et al.* (2008) studied
408 the founder-specific inbreeding depression effects (FSID) on the longevity of Landrace
409 sows and reported that all models of analysis were consistent with an overall negative
410 genetic effect of inbreeding on sow longevity. However, the analyses highlighted
411 considerable variability in FSID effects, with unfavorable, neutral and even favorable
412 influences on sow longevity. They added that the founders with the worst inbreeding

depression effect reduced sow longevity by 32 days for 1% or 167 days for 10% of partial inbreeding.

The hazard of culling or death decreases as the parity order advanced, the maximum difference between the 1st and 3rd order of positive palpation was observed for line LP. The selection conducted when founding this line, recruiting extremely long-lived animals, would promote survival ability at later ages rather than at early ages (Sánchez *et al.,* 2008). The hazard of death or culling was greater for the first two parities. This could be explained because in the first two parities does are still growing and kindling could be an important risk factor (Sánchez *et al.,* 2004). In line V, does in OPP1 always had the highest risk followed by does in OPP2 and OPP3 (Sánchez *et al.,* 2006b). The same trend was observed by Lenoir *et al.* (2013) in the Hycole line D, and reported that the hazard was greater for does in the first parity (1.47) than for those in the second parity (1.22). The results of the present study are in agreement with those by Rosell (2003) who indicated that 50% of the rabbit does die or are culled during the first three kindlings. In pigs, young sows are being removed at a higher rate for reproductive problems when compared with older sows (Lucia *et al.,* 1996; Boyle *et al.,* 1998). On the contrary, Tarrés *et al.* (2006) reported that the risk of sow removal increased with higher parity numbers as well as with decreasing litter size (Friendship *et al.,* 1986; Yazdi *et al.,* 2000).

Regarding the effect of physiological status on longevity, NP/NL had higher risk than the other levels, showing that the low fertility of the does in this level is an indication of health and/or stress problems. In addition, it seems that the lactation status of the doe at mating had relatively higher importance than reproductive status. The same pattern was observed by Sánchez *et al.* (2004) in a replicate of the V line who found that non-pregnant does at 28 days after kindling had a greater risk of culling than pregnant does

438 within 28 days after kindling. Similarly, Piles *et al.* (2006) in the A1077 rabbit line
439 reported that the relative risk increased for non-suckling does, which corresponded to
440 unsuccessful artificial insemination. Sánchez *et al.* (2006b) found that for a given level
441 of OPP (1st, 2nd or ≥3rd), the physiological state “Empty” was always the level with the
442 highest relative risk followed by “Pregnant”, “Lactating” and “Pregnant&Lactating”. The
443 same findings were reported by Lenoir *et al.* (2013) who stated that the risk of survival
444 was lower for non-lactating females at the time of artificial insemination than for the
445 lactating females of the commercial line D rabbits.
446 The association between litter size and doe longevity could be explained by the
447 practice in commercial farms of culling the does with small litters, but in the current
448 study no voluntary culling for productive reasons was practiced in the farm. Thus, the
449 greater risk of culling related to low litter sizes could be associated with underlying
450 pathological and/or stress disorders. In the present study, longevity of rabbit does of
451 the five lines were not unfavorably affected by the large number born alive, and the
452 risk of culling or death decreased with increasing the number born alive; the same
453 pattern was previously observed by Garreau *et al.* (2001), Sánchez *et al.* (2006b) and
454 Lenoir *et al.* (2013). Similarly, Tudela *et al.* (2003) reported that increasing litter size
455 by selection did not increase culling rate. In the same context, Sánchez *et al.* (2006a)
456 showed that in line V, longevity and litter size were not antagonistic traits and the
457 genetic correlations between longevity and number of born alive and number at
458 weaning were 0.16±0.09 and -0.17±0.11, respectively. In addition, in an experiment
459 comparing a rabbit line selected for litter size over seven generations with a control
460 line, no differences were found in longevity (Rinaldo and Bolet, 1988). In pigs, Serenius
461 *et al.* (2006) reported in six genetic lines that there was no clear association between
462 litter size and functional longevity. Analyzing the relative importance of the contrasts

between the different levels of the systematic effects considered is noticeable that the LP line had the maximum magnitude of the contrasts. This result could be considered as a scale effect due to the criterion of foundation of this line that increased its longevity and the range of the systematic effects of the factors affecting the trait.

Conclusions

The estimates of effective heritability for functional longevity in the five lines were low, thus the inclusion of this trait as selection criterion for these lines is not recommended. Despite the differences in the genetic variability across lines for LPL, the large estimation errors prevent rejection of the hypothesis of all the studied populations having the same heritability. By correcting for physiological status of the female, a relevant part of the additive variance for longevity was removed, particularly in line LP, and this result could be related to the foundation criteria of this line. However, discarding the positive palpation order or the number of kits born alive from the model of analysis affected the estimate of the additive variance only slightly. The lines that had relatively higher additive variance and lower longevity were those in which the genetic trend of longevity was the highest, most likely as a consequence of unintended or natural selection. The hazard decreased as the order of parity progressed, the highest during the first two parities. The NP/NL level of physiological status had the highest risk of death or culling compared with the other levels, which is an indication of diseases and/or pathological low fertility. The does that had zero born alive had the highest risk of dying or being culled, and the risk decreased as the number of kits born alive increased. This effect was not important for line H, and this could be associated with the hyperprolificacy criterion used to select the founder animals of this line.

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Declaration of interest

The authors declare no conflict of interest.

Ethics statement

All experimental procedures involving animals handling and treatment were approved by the Universitat Politècnica de València Research Ethics Committee, according to council directive 2010/63/EU (European Commission Directive, 2010).

Software and data repository resources

Data used and analyzed are available from the corresponding author upon reasonable request.

References

Blasco A 2001. The Bayesian controversy in animal breeding. Journal of Animal Science 79, 2023-2046.

Boyle L, Leonard FC, Lynch B and Brophy P 1998. Sow culling patterns and sow welfare. Irish Veterinary Journal 51, 354–357.

Casellas J, Varona L, Ibáñez-Escriche N, Quintanilla R and Noguera JL 2008. Skew distribution of founder-specific inbreeding depression effects on the longevity of Landrace sows. Genetics Research Cambridge 90, 499-508.

Cifre P, Baselga M, Gacia-Ximenez F and Vicente J 1998. Performance of hyperprolific rabbit line. I. Litter size traits. Journal of Animal Breeding and Genetics 115,131-138.

EL Nagar AG 2015. Genetic analysis of longevity in specialized lines of rabbits. Ph.D. thesis, Universitat Politècnica de València, Valencia, Spain.

Engblom L, Lundeheim N, Schneider Md, Dalin AM and Andersson K 2009. Genetics of crossbred sow longevity. Animal 3, 783-790.

Estany J, Baselga M, Blasco A and Camacho J 1989. Mixed model methodology for the estimation of genetic response to selection in litter size of rabbits. Livestock Production Science 21, 67–75.

Estany J, Camacho J, Baselga M and Blasco A 1992. Selection response of growth rate in rabbits for meat production. Genetics Selection Evolution 24, 527-537.

Fernández EN, Sánchez JP, Martíez R, Legarra A and Baselga M 2017. Role of inbreeding depression, non-inbred dominance deviations and random year-season effect in genetic trends for prolificacy in closed rabbit lines. Journal of Animal Breeding and Genetics 134, 441–452.

Friendship RM, Wilson MR, Almond GW, McMillan I, Hacker RR, Pieper R and Swaminathan SS 1986. Sow wastage: Reasons for and effect on productivity. Canadian Journal of Veterinary Research 50, 205-208.

García-Ximénez F, Vicente JS, Cifre P and Baselga M 1996. Foundation of a maternal rabbit line using hysterectomy and embryo cryopreservation. In Proceedings of the 6th World

Rabbit Congress, 9-12 July 1996, Toulouse, France, pp. 285-288. https://world-rabbit-science.com/WRSA-Proceedings/Congress-1996-Toulouse/Papers-pdf/05-Genetics/GARCIA-XIMENEZ.pdf.

Garreau H, Larzul C and Ducrocq V 2001. Analyse de longévité de la souche de lapins INRA 1077. In Proceedings of the 9émes Journées de la Recherche Cunicole, 28-29 Novembre 2001, Paris, France, pp. 217-220. http://pascal-francis.inist.fr/vibad/index.php?action=getRecordDetail&idt=14178974

Geweke 1992. Evaluating the accuracy of sampling-based approaches to the calculation of posterior moments In: Bernardo JM, Berger JO, Dawid AP and Smith AFM editors, Bayesian Statistics 4. Oxford University Press, Oxford, UK. pp. 169-193.

Gilks WR and Wild P 1992. Adaptive Rejection Sampling for Gibbs Sampling. Applied Statistics 41,337-348.

Larzul C, Ducrocq V, Tudela F, Juin H and Garreau H 2014. The length of productive life can be modified through selection: An experimental demonstration in the rabbit. Journal of Animal Science 92, 2395-2401.

Lenoir G, Maupin M, Leloire C and Garreau H 2013. Analyse de la longévité des lapines d'une lignée commerciale. In Proceedings of the 15èmes Journées de la Recherche Cunicole, 19-20 Novembre 2013, Le Mans, France, pp.181-184. http://www.cuniculture.info/Docs/Magazine/Magazine2013/fichiers-pdf-JRC/R07-Lenoir.pdf.

Lucia T, Dial GD and Marsh WE 1996. Patterns of female removal. I. Lifetime productivity for reproduction and performance-related culls. In Proceedings of the 14th International Pig Veterinary Society, 7-10 July 1996, Bologna, Italy, p. 540. https://lib.ugent.be/catalog/rug01:000400386

Mészáros G, Pálos J, Ducrocq V and Sölkner J 2010. Heritability of longevity in Large White and Landrace sows using continuous time and grouped data models. Journal of Genetics Selection Evolution 42, 1-13.

564 Piles M, Garreau H, Rafel O, Larzul C, Ramon J and Ducrocq V 2006. Survival analysis in two
565 lines of rabbits selected for reproductive traits. Journal of Animal Science 84, 1658-1665.
566 Plummer M, Best N, Cowles K and Vines K 2006. CODA: Convergence diagnosis and output
567 analysis for MCMC. R News 6, 7-11.
568 Ramon J and Rafel O 2002. Diez años de gestión global en España. In Proceedings of the 2th
569 Congreso Internacional de Producción y Sanidad Animal, 5-8 November 2002,
570 Expoaviga, Barcelona, Spain, pp. 113-117.
571 Rinaldo D and Bolet G 1988. Effect of selection for litter size at weaning on reproductive life of
572 female rabbits. In Proceedings of the 4th World Rabbit Congress, 10-14 October 1988,
573 Budapest, Hungary, pp. 269-275.
574 Rosell JM 2003. Health status of commercial rabbitries in the Iberian Peninsula. A practitioners
575 study. World Rabbit Science 11,157-169.
576 Sánchez JP, Baselga M, Peiró R and Silvestre MA 2004. Analysis of factors influencing
577 longevity of rabbit does. Livestock Production Science 90,227-234.
578 Sánchez JP, Baselga M and Ducrocq V. 2006a. Genetic and environmental correlations
579 between longevity and litter size in rabbits. Journal of Animal Breeding and Genetics
580 123,180-185.
581 Sánchez JP, Korsgaard IR, Damgaard LH and Baselga M 2006b. Analysis of rabbit doe
582 longevity using a semiparametric log-Normal animal frailty model with time-dependent
583 covariates. Genetics Selection Evolution 38, 281-295.
584 Sánchez JP, Theilgaard P, Mínguez C and Baselga M 2008. Constitution and evaluation of a
585 long-lived productive rabbit line. Journal of Animal Science 86, 515-525.
586 Sánchez JP, de la Fuente LF and Rosell JM 2012. Health and body condition of lactating
587 females on rabbit farms. Journal of Animal Science 90, 2353-2361.
588 Serenius T and Stalder KJ 2004. Genetics of length of productive life and lifetime prolificacy in
589 the Finnish Landrace and Large White pig populations. Journal of Animal Science 82,
590 3111–3117.

591 Serenius T, Stalder KJ and Puonti M. 2006. Impact of dominance effects on sow longevity.
592 Journal of Animal Breeding and Genetics 123, 355–361.
593 Sorensen D and Gianola D 2002. Likelihood, Bayesian, and MCMC Methods in Quantitative
594 Genetics. Springer Science and Business Media, New York, USA.
595 Tarrés J, Bidanel JP, Hofer A and Ducrocq V 2006. Analysis of longevity and exterior traits on
596 Large White sows in Switzerland. Journal of Animal Science 84, 2914-2924.
597 Tudela F, Hurtaud J, Garreau H and Rochambeau H 2003. Comparaison des performances
598 zootechniques de femelles parentales issues d'une souche témoin et d'une souche
599 sélectionnée sur la productivité numérique. In Proceedings of the 10émes Journées de
600 la Recherche Cunicole, 19–20 November, Paris, France pp. 53–56.
601 http://www.hypharm.fr/media/tudela_jrc_2003__056604300_1453_06092016.pdf.
602 Yazdi M, Rydhmer L, Ringmar-Cederberg E, Lundeheim N and Johansson K 2000. Genetic
603 study of longevity in Swedish Landrace sows. Livestock Production Science 63, 255–
604 264.
605 Yazdi MH, Visscher PM, Ducrocq V and Thompson R 2002. Heritability, reliability of genetic
606 evaluations and response to selection in proportional hazard models. Journal of Dairy
607 Science 85, 1563-1577.
608

609 ***Table 1*** *Summary statistics for longevity data in the different rabbit lines*

Line	N1[1]	Censored (%)	LPL (d)[3]		N2[2]
			Censored[4]	Uncensored[5]	
A	4986	35.9	238.0	151.6	6146
V	5275	35.7	284.6	175.7	6423
H	1156	55.2	235.3	138.4	1376
LP	1224	55.7	355.1	208.1	1425
R	3029	19.3	240.9	153.9	4035
All lines	15 670	35.6	268.1	162.6	19 405

610 [1] Numbers of does in data file.

611 [2] Number of animals in pedigree file.

612 [3] Length of productive life in days.

613 [4] Records from does that had not completed their productive life.

614 [5] Records from does that had completed their productive life.

615

616

Table 2 *Estimates of additive variance using different models, effective heritability and inbreeding depression for longevity in different rabbit lines*

Line	Additive variance				Effective heritability		Inbreeding depression	
	Model 1	Model 2	Model 3	Model 4				
	PM[1](PSD)[2]	PM[1](PSD)[2]	PM[1](PSD)[2]	PM[1](PSD)[2]	PM[1](PSD)[2]	HPD95%[3]	PM[1](PSD)[2]	HPD95%[3]
A	0.08(0.03)	0.07(0.03)	0.17(0.05)	0.07(0.03)	0.07(0.03)	0.024 , 0.130	-0.22(1.72)	-3.64 , 3.12
V	0.03(0.02)	0.03(0.02)	0.05(0.03)	0.02(0.02)	0.03(0.02)	0.003 , 0.066	0.41(1.67)	-2.77 , 3.69
H	0.18(0.13)	0.13(0.10)	0.29(0.19)	0.18(0.12)	0.14(0.09)	0.003 , 0.292	6.01(3.10)	-0.14 , 12.08
LP	0.05(0.05)	0.04(0.04)	0.29(0.20)	0.03(0.03)	0.05(0.04)	0.000 , 0.126	6.44(7.68)	-9.10 , 20.98
R	0.02(0.01)	0.01(0.01)	0.07(0.04)	0.02(0.01)	0.02(0.01)	0.000 , 0.043	-0.48(0.97)	-2.32 , 1.47
All lines	0.05(0.02)	0.04(0.01)	0.05(0.02)	0.05(0.02)	0.04(0.01)	0.013 , 0.066	-	-

Model 1 = YS + OPP + PS + NBA + F + animal; Model 2 = YS + PS + NBA + F + animal = (Model 1 – OPP); Model 3 = YS + OPP + NBA + F + animal = (Model 1 – PS); Model 4 = YS + OPP + PS + F + animal = (Model 1 – NBA).

YS = Year-season; OPP = Positive palpation order; PS = Physiological status of the doe; NBA = Number of kits born alive; F = Inbreeding coefficient.

[1] Posterior mean.

[2] Posterior standard deviation.

[3] Highest posterior density region at 95 % of probability.

Table 3 *Posterior means (posterior standard deviations) of the contrasts (log-hazard) between the levels of positive palpation orders affecting longevity in different rabbit lines*

Contrast \ Line	A	P(%)	V	P(%)	H	P(%)	LP	P(%)	R	P(%)
OPP1 – OPP2	0.26(0.08)	99	0.19(0.09)	99	0.30(0.19)	94	0.31(0.23)	91	0.24(0.08)	99
OPP1 – OPP3	0.56(0.13)	100	0.31(0.13)	99	0.84(0.29)	99	1.30(0.34)	100	0.61(0.12)	100
OPP2 – OPP3	0.31(0.08)	100	0.11(0.08)	92	0.54(0.18)	99	0.99(0.22)	100	0.38(0.08)	100

OPP1 = 1st order of positive palpation; OPP2 = 2nd order of positive palpation; OPP3 = 3rd order of positive palpation or more; P(%) = Probability of the difference being >0 when the contrast >0 and probability of the difference being <0 when the contrast <0.

631 **Table 4** *Posterior means (posterior standard deviations) of the contrasts (log-hazard) between the levels of physiological status*
632 *affecting longevity in different rabbit lines*

Contrast \ Line	A	P(%)	V	P(%)	H	P(%)	LP	P(%)	R	P(%)
					WITHIN LACTATIONAL STATUS					
U/NL – P/NL	0.76(0.07)	100	0.47(0.07)	100	0.29(0.18)	94	0.47(0.20)	99	0.89(0.08)	100
U/NL – NP/NL	-0.86(0.06)	100	-1.20(0.06)	100	-0.83(0.15)	100	-2.02(0.15)	100	-0.54(0.06)	100
P/NL – NP/NL	-1.63(0.06)	100	-1.67(0.06)	100	-1.12(0.15)	100	-2.50(0.15)	100	-1.43(0.07)	100
U/L – P/L	-0.55(0.11)	100	-0.32(0.13)	99	0.36(0.40)	81	1.02(0.85)	90	0.11(0.22)	70
U/L – NP/L	-0.68(0.08)	100	-0.58(0.08)	100	-0.45(0.19)	99	-0.78(0.24)	100	-0.18(0.10)	96
P/L – NP/L	-0.13(0.11)	89	-0.25(0.12)	99	-0.80(0.39)	99	-1.80(0.83)	100	-0.29(0.21)	70
					WITHIN REPRODUCTIVE STATUS					
U/NL – U/L	1.45(0.08)	100	1.43(0.09)	100	1.23(0.21)	100	1.28(0.26)	100	1.21(0.10)	100
P/NL – P/L	0.14(0.11)	91	0.63(0.12)	100	1.30(0.39)	100	1.83(0.83)	99	0.43(0.21)	98
NP/NL – NP/L	1.64(0.06)	100	2.05(0.06)	100	1.62(0.16)	100	2.53(0.15)	100	1.57(0.07)	100
P/L – NP/NL	-1.77(0.11)	100	-2.31(0.12)	100	-2.43(0.41)	100	-4.33(0.83)	100	-1.86(0.21)	100
P/L – U/NL	-0.91(0.12)	100	-1.11(0.13)	100	-1.59(0.42)	100	-2.30(0.84)	99	-1.32(0.22)	100
NP/L – P/NL	-0.02(0.06)	41	-0.38(0.06)	100	-0.50(0.15)	100	-0.03(0.17)	56	-0.14(0.08)	95
NP/L – U/NL	-0.78(0.07)	100	-0.85(0.07)	100	-0.79(0.18)	100	-0.50(0.20)	99	-1.03(0.08)	100
U/L – NP/NL	-2.32(0.08)	100	-2.63(0.08)	100	-2.07(0.19)	100	-3.30(0.23)	100	-1.75(0.10)	100
U/L – P/NL	-0.69(0.08)	100	-0.96(0.08)	100	-0.95(0.19)	100	-0.80(0.25)	100	-0.32(0.10)	100

633 U = Before palpation test; P = After positive palpation test; NP = After negative palpation test; L = Lactating; NL = Non-lactating; P(%) = Probability of the difference
634 being >0 when the contrast >0 and probability of the difference being <0 when the contrast <0.

Table 5 *Posterior means (posterior standard deviations) of the contrasts (log-hazard) between the levels of number born alive affecting longevity in different rabbit lines*

Contrast \ Line	A	P(%)	V	P(%)	H	P(%)	LP	P(%)	R	P(%)
B – Z	-0.28(0.10)	100	-0.16(0.09)	96	-0.04(0.27)	56	-0.83(0.25)	100	-0.55(0.08)	100
C – Z	-0.30(0.09)	100	-0.36(0.08)	100	-0.01(0.22)	53	-1.15(0.16)	100	-0.57(0.07)	100
D – Z	-0.30(0.09)	100	-0.42(0.07)	100	-0.15(0.20)	78	-1.21(0.14)	100	-0.48(0.07)	100
E – Z	-0.35(0.11)	100	-0.32(0.08)	100	0.01(0.21)	52	-1.40(0.17)	100	-0.43(0.15)	100
C – B	-0.02(0.07)	62	-0.20(0.08)	99	0.03(0.21)	54	-0.32(0.24)	91	-0.02(0.06)	65
D – B	-0.02(0.07)	62	-0.26(0.07)	100	-0.11(0.20)	72	-0.39(0.23)	95	0.07(0.06)	84
E – B	-0.07(0.10)	75	-0.15(0.08)	97	0.05(0.21)	59	-0.57(0.25)	98	0.12(0.15)	79
D – C	-0.01(0.04)	52	-0.06(0.04)	91	-0.14(0.12)	86	-0.07(0.13)	70	0.09(0.05)	95
E – C	-0.05(0.09)	72	0.04(0.06)	77	0.03(0.15)	57	-0.25(0.17)	93	0.14(0.15)	83
D – E	0.05(0.08)	72	-0.10(0.05)	98	-0.16(0.12)	91	0.18(0.14)	91	-0.05(0.15)	65

Z = Zero born alive; B = 1 to 4 born alive; C = 5 to 8 born alive; D= 9 to 12 born alive; E= More than 12 born alive; P(%) = Probability of the difference being >0 when the contrast >0 and probability of the difference being <0 when the contrast <0.

Figure captions

Figure 1 Genetic trend for hazard by line using the data analyses of A, V, H, LP and R rabbit lines separately.