FERTILITY AND LIFESPAN: LATE CHILDREN ENHANCE FEMALE LONGEVITY

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ABSTRACT

The relation between fertility and post-menopausal longevity is investigated for a sample of 1635 women from a historical French-Canadian cohort who lived past age 50. We find that increased fertility is linked to increased rather than decreased post-reproductive survival. Post-reproductive life expectancy extension is found to be tied to late births. This finding sheds new light on the cost of reproduction and may be viewed as supporting a new paradigm which states that reproductive potential drives remaining longevity [1]. The emerging reproductive potential concept complements the well-established cost of reproduction hypothesis [2]-[5]. Alternative explanations for the observed association are also explored.

A specific finding is that the degree to which mortality increases for 50 year old mothers due to senescence is closely tied to the logarithm of the age of their youngest child. For example, 50 year old mothers experience a mortality decrease of 38% and an increase of remaining lifetime of 3.93 years for every 10-fold decrease in the age of their youngest child. This amount of gain in remaining life expectancy would apply to a mother with a two-year old child as compared to a mother with a 20 year old offspring. We also find evidence for the existence of vulnerable periods in human life history that are characterized by phases of heightened mortality and are found to be tied to reproduction and senescence.

1. INTRODUCTION

An increase in the number of offspring has been traditionally associated with decreased longevity. The cost of reproduction hypothesis postulates that a trade-off occurs between resources available for reproduction on the one hand and for maintenance and life extension on the other [3],[4]. Extensive reproductive activity drains resources that would otherwise be available for maintenance and as a consequence increased reproduction is assumed to be associated with shortened lifespan according to this hypothesis. The cost of reproduction concept is by now well established and it was for example applied to an analysis of fertility data for the British royalty [5].

Recent studies of individual mortality and reproduction in the Mediterranean fruit fly (medfly) provided evidence for the existence of alternative mechanisms that lead to associations between reproduction and longevity. Medflies were found to regulate their remaining lifespan based on future reproductive potential on an individual basis. Such a strategy tends to maximize overall reproductive success [1],[6]. These findings are related to the concept of reproductive determinism [7] and prompted the present investigation. In this paper we take another look at the relationship between fertility and longevity for human cohorts in the light of these recent developments. For an overview on data and studies on the cost of reproduction for human longevity we refer to [8] and [9]. We note that [8] provides an alternative perspective for the data analysis presented in [3].

Specifically, we examine the relationship of women's fertility and longevity in a historical cohort of French-Canadian women of the 17th/18th century. This cohort is characterized by high average fertility. We find that increased female fertility is associated with increased rather than decreased post-reproductive survival. The latter would have been predicted by the cost of reproduction hypothesis. In order to explain this finding, we postulate that

post-reproductive life extension is triggered by late births and the associated presence of young children in the post-reproductive period. We show that the data in fact confirm that specifically the presence of young children, or equivalently, late timing of the last birth, is associated with increased post-reproductive longevity. Our findings thus support the reproductive potential hypothesis which holds that lifespan regulation has evolved in such a way as to maximize individual reproductive success.

2. DATA AND METHODS

When investigating the relations between fertility and longevity for women it is desirable to study cohorts with high average fertility. This excludes many modern cohorts but is an important prerequisite when studying the upper ranges of human fertility. Highly fertile cohorts will allow to observe a larger range of variation in individual fertility, especially late fertility, and will bring the observations closer to presumed pre-contraceptive patterns. For these reasons, it is preferable to use well-documented data on a historical cohort. An ideal cohort would be narrowly positioned in space and time so as to minimize confounding and biases caused by changes in reproductive patterns that may occur over time or space. Such changes are notoriously hard to control and may have contributed to methodological problems in previous reports on the relation between fertility and longevity, for example in [3].

Accordingly, we use data from a well-documented 17/18th century pre-birth control cohort of native born French-Canadian women. Dates of birth and death of the women and birth dates of children are based on church records and are deemed reliable. Further details on this cohort and the nature of the data can be found in [10], see also [11]. For other examples detailing the demography and interpretation of historical cohorts, we refer

to [12] and [13].

In order to avoid confounding of mortality by birthing which was associated with heightened mortality in the 17/18th century and to also avoid confounding with marriage status, we base our analysis on the $n = 1635$ women in the cohort, who were married, parous and lived to at least age 50. Mortality and longevity are studied exclusively in the post-reproductive period past age 50. Post-reproductive longevity is defined as remaining life expectancy past age 50. Some characteristic features of this sample are described in the next section.

The statistical methods used include Cox proportional hazards regression for remaining lifetimes [14]. In addition, we use nonparametric curve estimation techniques. These are based on the kernel method [15] for the nonparametric estimation of probability density functions with the aim of describing distributions of age-at-death, and on transformation methods for nonparametric hazard function estimation as described in [16]-[18]. Such methods let "the data speak for themselves" and do not impose requirements and shape restrictions typically needed for parametric modelling. Such restrictions would be difficult to meet given the complex structure of density and hazard functions (mortality rates) that we observe for these data.

3. RESULTS

It is remarkable that of the 1635 women in this cohort 78.3% have at least 4, 54.5% have at least 8, and 21.6% have at least 12 children. These numbers clearly demonstrate that this cohort is useful for studying the effects of higher end fertility on longevity. A bar chart demonstrating the distribution of the number of births in this cohort can be found in Fig. 1(a). The distribution of fertility for this cohort can be ascertained from Fig. 1(b).

The histogram presented there indicate that numbers of births as a function of the age of the mother increase rapidly from age 14 to 26 where they reach a sustained high level plateau that extends to age 35, declining rapidly over the next 11 years, and tapering off to 0 at age 49.

To investigate the association between fertility and longevity, we apply a Cox regression model with number of births as predictor. We find that increased fertility predicts significantly lower post-menopausal mortality, with $p = .0381$. The fitted Cox model is $\lambda(t) = \lambda_0(t)exp(-.0136NB)$, where $\lambda(t), \lambda_0(t)$ are hazard respectively baseline hazard functions, and NB denotes the number of births. The std.dev. of the slope for NB is .00657. According to this model, the relative mortality risk declines by 1.4% per additional birth. For example, the relative risk declines to .868 for 10+ births, meaning that post-menopausal mortality for women with 10+ births is 13.2% lower than that of women with one birth.

In an additional analysis, we compare a group of women with lower fertility (1-7 births) with a group with higher fertility (8+ births), dividing the cohort into two about equally large groups. Then the average odds ratio for the probability of dying in a given year within the age range 50-80 was found to be 1.22 ($st.dev. = 0.34$, $n = 31$, $p = .00012$) for women who had 1-7 children as compared to women who had 8+ children, confirming the findings obtained with the Cox model.

Nonparametric estimates of the probability densities of remaining lifetimes after age 50 for the low and high fertility groups are provided in Figure 2(a). These estimates provide valuable information about the distribution of remaining lifetime (or remaining life expectancy). The shift towards longer remaining lifetimes for the higher fertility group is

quite obvious. Remaining lifetimes are shifted towards higher ages; this effect tapers off for the oldest-old, where beginning at remaining lifetimes of 35+ (or ages of 85+) the two densities overlap. These results clearly imply that very high fertility is associated with overall lower late-life mortality.

One possible hypothesis to explain this shift towards increased remaining life expectancy for the more fertile group is that extended remaining life expectancy for mothers with many children confers an evolutionary advantage. Highly fertile women will tend to have small children at age 50, and their increased longevity is likely to improve the chances of survival for their offspring. A consequence of this hypothesis is the prediction that, for women aged 50, remaining life expectancy increases specifically with decreasing age of the youngest child.

Testing this prediction, we find that indeed mortality increases by 38% as $\log_{10}(age)$ of the youngest child increases by 1 ($p < 0.005$ in a Cox model). This means that as the age of the youngest child decreases by a factor of 10, mortality declines by 38%. For example, a mother with a 2 year old child at age 50 will have 18% less mortality than a mother with a 6 year old child. The slope of the predictor $\log_{10}(age)$ in the Cox model is .327 with standard deviation .116.

If both $\log_{10}(age)$ and number of births are considered as predictors, only $\log_{10}(age)$ remains significant, indicating that the effect of increased fertility on reducing post-menopausal mortality is indeed mediated by a late birth of the last child. A simple linear regression analysis of remaining lifespan versus $\log_{10}(age)$ of the youngest child shows that lifespan increases by 3.93 years on the average per $\log_{10}$-year decrease in the age of the last child ($p = 0.002$; the fitted regression line is $y = 23.79 - 3.93x$, with st.dev. 1.27 for the slope). For example, a mother with a child of 1 year at age 50 will live 2.75 years longer as com-

pared to a mother with a child of 5 years.

These analyses point to a protective effect of a late birth for the mother. This protective effect is illustrated in Fig. 2(b). One notices an obvious shift in the distribution of remaining life expectancy towards higher ages for the group of women with children of age 6- (less than 6) as compared to women with children of age 6+ at age 50.

4. FURTHER RESULTS ON OVERALL MORTALITY AND DISCUSSION

On the methodological level, it is relevant to note that we restrict our study of remaining lifetime to women who are 50 years old and who are thus past the period of increased mortality that is associated with the reproductive phase. This restriction is necessary in order to avoid confounding deaths caused by child bearing with post-reproductive mortality. Women that live longer have the opportunity to bear more children and a direct analysis of the association between overall lifetime and number of offspring will lead to a correlation between these quantities which is purely an artefact and results from confounding.

A cost of reproduction is indeed manifesting itself during the time of reproduction, as is clearly evidenced in Fig. 3. In Fig. 3(a) the nonparametric density function estimates of lifetime or age-at-death for all $n = 3055$ women in the study is provided. This sample is much larger than the one considered above as it also includes the nulliparous women and in particular women that did not live to age 50. Here, the densities of the distribution of lifetime (age-at-death) are shown for three fertility groups of women in the overall sample, irrespective of whether they survived to age 50 or not. The densities are shown for the three groups of women with no off-spring ($n = 244$), with 1-7 births ($n = 1218$) and 8+ births ($n = 1593$). The corresponding hazard rate estimates (smoothed and transformed

mortality rates, also known as trajectories of mortality) are displayed in Fig. 3(b).

It is obvious that there is a large death toll directly associated with child bearing in this historical cohort. For example, we find that nulliparous women with no off-spring happen to be in the nulliparous group to a large extent because they die during the beginning of the child-bearing period. The strongly evident early peak in mortality in this group that is particularly standing out in the density estimates is likely due to death during a first pregnancy or delivery. The more children a women has, the later her mortality starts to rise, illustrating the statistical selection effect this type of cost of reproduction is associated with. In order to bear more children, a woman needs to survive the first pregnancies in the first place. The restriction to consider women who reach the post-reproductive period is therefore well justified.

We note that Fig. 3 also reveals a striking bimodality in the distribution of age-at-death. While this is more evident in the density graphs of Fig. 3(a), it is also a clear pattern in the hazard rates of Fig. 3(b). A plethora of early deaths is likely caused by the challenges of reproduction and the surge in late deaths is caused by senescence. This bimodality is particularly strongly expressed for the groups with lower reproduction. The left "reproduction" mode shifts to the right for women with higher number of off-spring while the location of the right "senescence" mode remains surprisingly stable, irrespective of fertility level. Interestingly, bimodality in the distribution of age-at-death was also observed for medflies [6] and thus may point to a more general phenomenon occurring for various species.

These facts illustrate and corroborate two central notions: First, that increasing lifetime primarily has an *enabling* effect for reproduction; compare [1] for further details on the relationship between remaining reproductive potential and mortality. If a woman dies

early in life she is not provided with the opportunity to have any or more children. Secondly, there exist two clearly distinguished *vulnerable periods* in regard to mortality: The first vulnerable period occurs at the time of reproduction; a second vulnerable period occurs around 80 years for this historical sample. Such vulnerable periods were established as mortality patterns occurring in medflies [18] and our analysis shows that they are not limited to that species. Such vulnerable periods would primarily be observable in a "more natural" reproductive setting as provided by the historical French-Canadian cohorts but would less likely be observable in a modern cohort under the conditions of birth control and largely improved medical care.

5. FURTHER DISCUSSION AND CONCLUDING REMARKS

Our findings of a positive association of high fertility with lower post-reproductive mortality are in line with recent work [19] concerning an abundance of late births among centenarian women; see also [20]. They are compatible with the reproductive potential hypothesis, namely that increased reproductive potential is associated with prolonged life [1]. A mother who has late children would be associated with higher reproductive potential.

An evolutionary explanation for this positive association is provided by the hypothesis that the presence of a young child has a life-prolonging effect on the mother. We have shown here that indeed the post-menopausal mortality declines with declining age of the youngest child. Moreover, age of the youngest child was identified as the primary predictor for the decline in post-menopausal mortality.

A plausible explanation is that a high level of fertility increases the chance that young off-spring need to be cared for after menopause, and that the probability of their survival is likely to be linked to the presence of the mother as a care-giver. This outlines a possible

pathway of how the positive association of post-menopausal longevity with fertility has evolved, essentially through enhancing the likelihood for the presence of a care-giver for late children. Thus, it is plausible that extended longevity confers a selective evolutionary advantage to women with late children. This hypothesis is in accordance with recent findings of an inter-species analysis for primates regarding the relationship between the period of care giving required to raise offspring and longevity, where it was found that increased care giving requirements are indeed associated with extended lifespan [21].

An alternative explanation could be that both longevity and increased fertility as well as late births are associated with a third factor that influences both simultaneously in such a way as to create a positive association. This could be a genetic, socio-economic or environmental factor or a combination of these. That certain longevity genes may extend both child-bearing period and longevity of individual women has been suggested before in [22].

More specifically, one could think of a subject-specific frailty that is randomly assigned to each woman, based on biological or environmental factors. Increased frailty of a woman would decrease the chance to survive a given birth. If surviving any birth is the outcome of an independent Bernoulli trial with the probability of survival depending on a random frailty as above, then a mathematical consequence is that the conditional expected frailty of 50 year old women with many births is lower than that of women with fewer births. Assuming that lower frailty is then also associated with increased remaining lifespan, a positive association between number of births and remaining lifespan may result. There exists also some evidence that early life events have an impact on late life mortality [23]. It is here of interest to note that age of the last child is a more significant predictor of remaining lifetime than the number of births, a fact which may slightly favor the care-giver hypothesis of post-menopausal life extension.

Our findings point to a life-prolonging effect for women with late children under conditions of naturally regulated and quite high baseline fertility, coupled with historic conditions of health care. The observed association leads to several interesting questions. First of all, does the association hold under modern conditions with increasingly late child-bearing which occurs under birth control conditions and an altered environment that includes largely improved health care in comparison to the historical cohorts? If this were the case, late child bearing in modern women would still serve as a pointer towards extended remaining lifetime, irrespective of whether late child bearing is causal for the observed lifespan extension.

A second question that looms large is indeed that of causality. An association exists, as we have demonstrated in this article, but the fact remains that this finding is derived from an observational study, and thus subject to all the caveats that one must entertain in the interpretation of such studies. In particular, causality cannot be established from such data. The care-giver hypothesis provides a plausible causative mechanism, within the intriguing framework of the reproductive potential hypothesis. However, alternative models such as the above described selection through frailty also may explain the observations. One suggestion would be to seek experimental evidence from animal studies that could shed further light on some of these issues.

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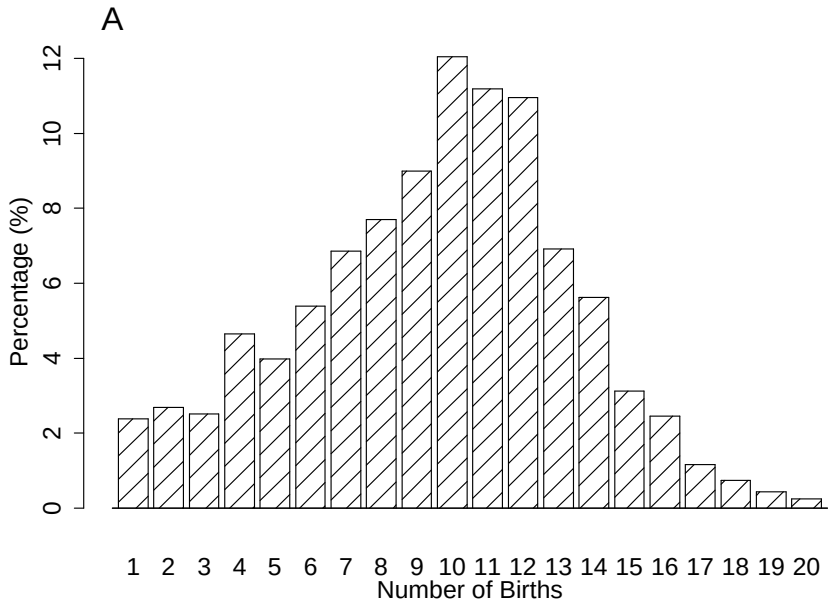
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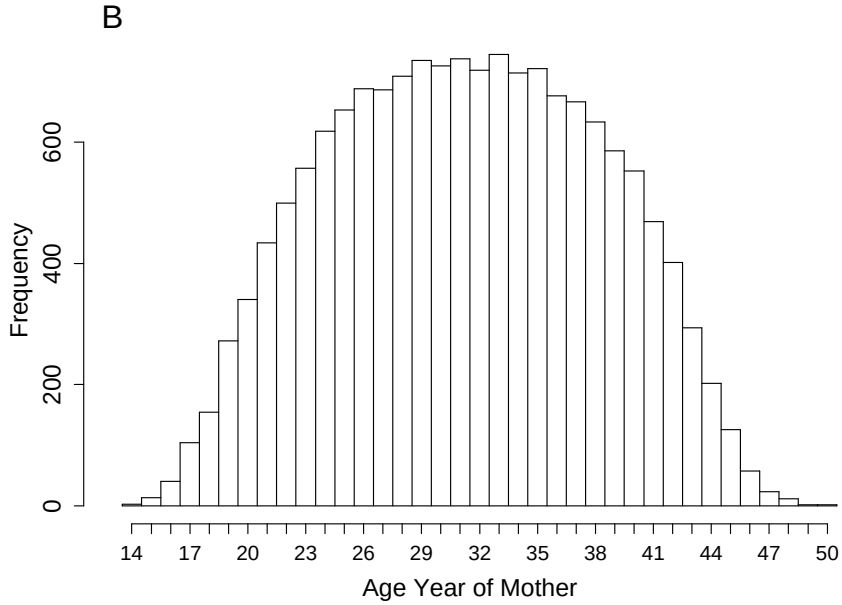
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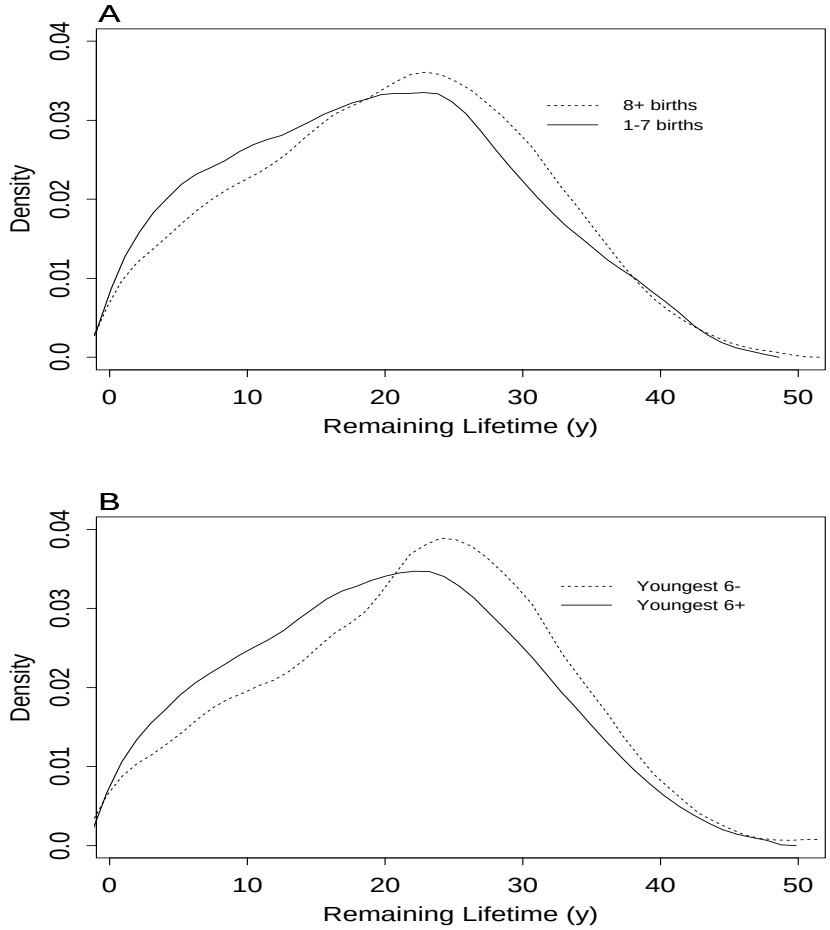
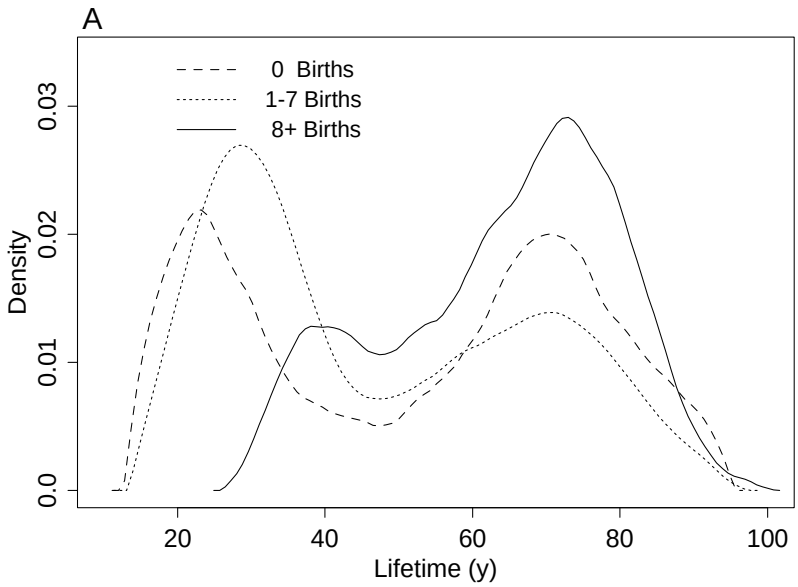


Figure 2. *Nonparametric density function estimates of age-of-death for women with one marriage (n =3055) sorted into 3 groups with 0, 1-7 and 8+ children. (Sample sizes, mean lifetimes and standard deviation) are (244, 53.50, 23.59), (1218, 48.76, 21.62) and (1593, 64.38, 15.37), respectively, for the 3 groups.*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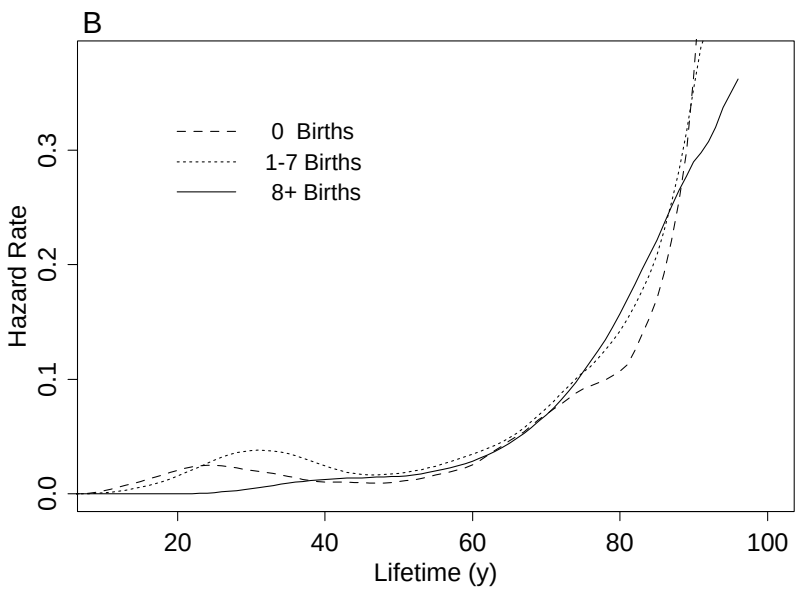
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0 Births
1-7 Births
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Lifetime (y)