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REVIEW

# Demographic Evidence for Adaptive Theories of Aging

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**Abstract**—Pleiotropic theories for the evolutionary origins of senescence have been ascendant for forty years (see, for example, G. Williams (1957) *Evolution*, **11**, 398-411; T. Kirkwood (1977) *Nature*, **270**, 301-304), and it is not surprising that interpreters of demographic data seek to frame their results in this context. But some of that evidence finds a much more natural explanation in terms of adaptive aging. Here we re-interpret the 1997 results of the Centenarian Study in Boston, which found in their sample of centenarian women an excess of late childbearing. The finding was originally interpreted as a selection effect: a metabolic link between late menopause and longevity. But we demonstrate that this interpretation is statistically strained, and that the data in fact indicate a causal link: bearing a child late in life induces a metabolic response that promotes longevity. This conclusion directly contradicts some pleiotropic theories of aging that postulate a "cost of reproduction", and it supports theories of aging as an adaptive genetic program.

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Are our metabolisms able to flip a switch and extend life span at will, in response to an extended need to care for offspring? Certainly there is suggestive evidence for this hypothesis, in the fact that longevity is positively correlated with family ties [1] and number of children [2] and that mortality rises rapidly in the wake of a lost spouse [3]. But there may also be more direct evidence in the centenarian database compiled by Perls. Perls reported [4] that within his sample of centenarian women, there is a fourfold enhancement of late child-bearing. In his original article, Perls suggests a more conventional hypothesis concerning this correlation: that within the standing population diversity for rate of aging, the rate of mortality increase is metabolically linked to the rate of fertility loss. In this interpretation, Perls's finding would not represent an active metabolic response to pregnancy.

However, we show herein that the fourfold enrichment which Perls reports is too strong a correlation for the passive mechanism to account for. We show with demographic and actuarial statistics that even if 100% of potential centenarians had extended fertility, the enrichment would amount to less than a factor of two.

A possible mechanism for a pro-longevity effect of pregnancy is suggested by the recent findings that life span of aging mice can be prolonged by implantation of stem cells from younger mice [5]. Human fetal cells can be recruited by a pregnant mother, and remain active in her system for decades [6]. The hypothesis that childbearing can extend life span is both powerful evidence for the idea that aging is an active process under genetic control, and also evidence contradicting the popular Disposable Soma theory of aging, according to which pregnancy ought to shorten life span.

## THE CENTENARIAN STUDY

Perls et al. [4] report that 15 of 78 centenarian women in the Boston area (19.2%) had borne children after their fortieth birthdays, compared to 3 of 54 (5.5%) in a control group of women who died at age 73. Women in both groups were born in 1894-96, and data on the centenarian women was obtained from interviewing them in 1995-96, while data on the controls were derived from hospital records from the late 1960s when these women died.

Perls suggests as an explanation that the effect derives from a correlation in the individual variations of two biological aging rates: the overall senescence rate and the rate of fecundity decline. Thus the subset of women whose reproductive aging rates are sufficiently slow as to permit them to bear children after age 40 overlaps strongly with the subset whose metabolic aging rate is such as to permit them to live 100 years.

This hypothesis is consistent with prevailing theories for the evolution of senescence. He does not mention the alternative hypothesis that the act of bearing a child after 40, or of rearing a child thereafter, confers a protective

effect on the mother, enhancing her probability of survival to a great age. This latter explanation is presumably ruled out on theoretical grounds.

But, in fact, the centenarian results may be combined with previously compiled actuarial tables and data on fecundity decline to yield a fair comparison of the two hypotheses. For actuarial data, we rely on a cohort life table [7] for women born in 1900. Standard mortality tables are tabulated as a snapshot in time, so that the data for each age apply to persons who are currently that age; a cohort life table is appropriate for our purpose, because it applies across time to all persons born in a single year. Perls's subjects were born in 1894-96, and 1900 was the closest year for which such a table was available from the National Office of Vital Statistics. For fecundity data, we have consulted studies from the 1980s by Menken et al. [8, 9] of fecundity decline with age. Finally, we have consulted fertility tables [10] from the US Department of Health, Education, and Welfare (HEW) for women in the 1896 birth cohort.

In Menken's tables, 29% of women are reported to be infecund by age 40. In a separate category, which Menken et al. label "impaired fecundity", they estimate that 55% of women 35-44 experience some "difficulty in conceiving or delivering a baby". In the HEW birth cohort data, the total fertility rate during the era 1936-1945 (a time when fertility was suppressed by non-biological factors of economic depression and war) was 7.2%.

## ANALYSIS

Using these numbers, it is possible to assess the likelihood of Perls's preferred explanation: that infertility at 40 is a biomarker identifying women who are less likely to enjoy long lifespans. Among Perls's controls, who lived an average lifespan, 3 of 54 women bore children after age 40 (5.5%). For this small sample, the result is consistent with the national 7.2% rate from the HEW data ($p = 0.47$). The higher rate among centenarians (15 of 78 = 19.2%) stands out enough to command an explanation, despite the small sample size ($p = 0.0004$). This is the probability of choosing 15 or more from a sample of 78, when each individually has a chance 7.2% of being chosen.

Our model of the Perls hypothesis is that the demographic association between fertility decline and mortality increase with age is as strong as it can be: if this association is perfect, then the entire group of centenarians would be drawn not from the sample of all women born in 1896, but from the 71% of that group who remained fecund at age 40. The thrust of our result is that even this extreme assumption is insufficient to explain the strength of the effect, which Perls observed. Limiting the population entirely to the fecund 71% raises the expected number of late-childbearing women only by a factor of 100%/71% = 1.4; we should expect 1.4 times the 7.2% rate, which is 10.1% compared to the 19.2% observed. The likelihood of the observed result is $p = 0.011$, which is the probability of choosing 15 or more from a sample of 78 when each individually has a 10.1% chance of being chosen. With the added extreme assumption that none of the 55% of women with "impaired fertility" were either among those who conceived a child after 40 or those who survived to age 100, this probability rises to $p = 0.16$.

The greatest uncertainty in this analysis derives from assumptions about the decline of fecundity with age. The Menken studies on which we rely are state-of-the-art, however he revises downward earlier estimates of the rate at which senescence erodes fecundity. In our simple model, fecundity is either on or off; allowing for a gradual decline could weaken or strengthen the statistical case against the Perls hypothesis.

If the 29% figure quoted corresponds to an extreme of absolute sterility, then accounting for the impaired fecundity of some of the remaining 71% could help reconcile the hypothesis with the observations. On the other hand, if some women with impaired fecundity were included in the 29%, then compensatory measures that they took to achieve pregnancy could skew the results in the opposite direction. In all events, we believe the analysis using 55% infecundity is overly generous to the hypothesis.

We have used 7.2% total fertility 1936-1945 as a measure of the number of women in the 1896 cohort who actually bore children after age 40; this figure is a small overestimate, since it includes women who were born late in 1896 but who bore children early in 1936, and it double-counts those few women who had two children during this time. This overestimation can only make our conclusions more conservative.

For Perls's subjects, all drawn from the Boston area, the national fertility statistic, which we employed (7.2%), may not have been appropriate. We have assumed that the difference between his control group (3/54 = 5.5%) and the national average is due to sampling error; but alternatively if the 5.5% figure is taken as representative of the Boston sample, then our conclusion is strengthened from the range $p = 0.011$-$0.16$ reported above to the range $p = 0.0009$-$0.05$.

## AN ALTERNATIVE ANALYSIS

We consider here the alternative hypothesis that the act of bearing a child late in life confers some protection against aging. A standard technique for modeling any influence on the aging process is to apply setback or setforward years to the mortality table. A mortality table that applies to a control population may be modified so that it applies approximately to a test group by interpreting all ages in the table as if they were $s$ years younger or older, where $s$ is the setback or setforward. (For fractional $s$, lin-

ear interpolation may be applied to create the setback or setforward table.)

Modeling the alternative hypothesis, we applied an actuarial setback $s$ to the 7.2% of women in the cohort who actually bore children past age 40. A corresponding setforward $t$ was applied to all others; this adjustment was necessary to reproduce the standard table for the composite statistics from the two groups together. Perls's data were best reproduced for $s = 3.3$ years, corresponding to $t = 0.5$ years. With these parameters, both the 15/78 in the centenarian group and the 3/54 in the control group were reproduced with composite probability $p = 0.41$ for the data space $\geqslant 15/78$ for test and $\leqslant 3/54$ for control subjects. Thus our model predicts that women who bear a child past age 40 live an average 3.8 years beyond the life expectancy for women who do not.

If extended life is indeed a response to late childbirth, the effect might be an evolutionary adaptation permitting women to survive long enough to nurture their children and grandchildren. The phenomenon would be akin to the reason that women's lifespans extend beyond menopause, and the reason that, among primate species, those in which the male assumes a nurturing role for the young are also those in which the male's lifespan compares favorably to the female's [11].

## COMPARISON OF THE TWO MODELS

The explanation offered by Perls and the alternative suggested here have each been modeled with one free parameter. In the case of the Perls model, the observed result was still found to be unlikely, even when pushing that parameter to its logical limit (perfect association between fecundity decline and mortality increase with age). The alternative model handily explains the data with the assumption that late childbearing women add 3.8 years to their lives.

These results should be viewed in the context of a growing body of animal and human data, much of which suggests that the long-term cost of reproduction is absent, or negative. In his encyclopedic review of the literature, Finch reported [12] that there was considerable animal evidence for an immediate mortality cost of reproduction, but little evidence that reproduction affects the rate of aging. Stearns has appended a survey of animal tradeoff studies to his text on life histories [13], cataloging evidence for and against the existence of a tradeoff. Müller et al. [14] studied a French-Canadian cohort from the XVII and XVIII centuries, and concluded that late child-rearing adds several years to life expectancy, consistent with findings of the present analysis. Other relevant evidence from human demographic data is reviewed by Le Bourg [15]. Recent studies of Norwegian men and women [2] and of the North American Amish population [16] both conclude that the existence of offspring can lengthen life. Davey Smith et al. [17] report that sexual activity lengthens lifespan, and they note the consistency of their result with other studies of females [18] as well as males [19, 20].

Evolutionary theories of aging deserve a fair and robust examination, and their prediction of tradeoffs in fertility and longevity are subject to demographic verification. Evidence thus far is equivocal on the existence of such tradeoffs. But if we ask only whether tradeoffs can be detected, we are setting the bar too low; more to the point, we should be asking whether the tradeoffs we see are sufficiently robust and sufficiently ubiquitous to provide firm grounding for evolutionary theories that posit these tradeoffs as the primary reason for senescence. To this question, the answer is unambiguous.

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