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Familial Aggregation of Survival and Late Female Reproduction

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Familial Aggregation of Survival and Late Female Reproduction

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Women in natural fertility conditions bearing children at advanced ages have been shown to have better post-menopausal survival (*1-3*) Women who reach advanced ages at natural menopause also experience significantly improved survival chances (*4*). Experiments that select for late reproduction in female mice (*5*) and *Drosophila melanogaster* (*6*) have generated longer-lived strains.

No studies have considered whether longevity is more frequent among relatives of late-fertile women. The hypothesis is that long life is partly attributable to genetic variants that slow the rate of aging in both sexes via a mechanism that also facilitates late female fertility. We compare the survival of men who have a late-fertile sister to men with sisters who were not fertile late. To evaluate possible socio-environmental explanations, we examine survival among wives married to brothers of late and non-late fertile women.

We use two historical sources of comprehensive data on sibships with complete survival and fertility information when little or no effective birth control existed. The first population is drawn from the Utah Population Database (UPDB) at the University of Utah. The full UPDB includes genealogical data on 1.6 million individuals who comprise the founding Utah population and their descendants. The second dataset is compiled by the Programme de recherche en démographie historique (PRDH) at the Université de Montréal and includes more than 400,000 individuals who lived in Québec between 1608 and 1850. For the UPDB, sibships are included in which all siblings were born before 1870 while PRDH siblings were born between 1670 and 1750. Both samples comprise extinct cohorts. We restricted the sample to once-married individuals and those who survived to age 50 to minimize variability in survival unrelated to aging. Requiring that individuals survive to 50 ensured that female fertility was largely complete.

We compared male survival classified according to the age-at-last-birth of their latest fertile sister: >=85th percentile, 50th-84th percentile, and the bottom 50th percentile (reference category). The longevity of the longest-lived sisters was also controlled using the same three-category scheme, along with other confounders. Given that selection for extreme values of traits is associated with larger sibships, we examined how the number of sisters affects the association between late female fertility and survival of brothers.

Mortality hazard rate ratios (HRR) associated with sisters' maximum age-at-last-birth are generated using Cox regression models. Statistical adjustments to account for correlated survival among brothers yielded results (not shown) quite similar to those in Figure 1.

Relative survival after age 50 was greater for men with a late-fertile sister ($\geq$85 percentile). The estimated male survival advantage increases with increasing numbers of sisters in the sample. Additional sisters provide more opportunities to detect sisters with slower reproductive senescence. Therefore, the probability that control sibships (sibships with sisters with only low ages-at-last-birth) will lack genes for slower reproductive senescence should rise with the number of sisters in those sibships. Specifically, men with a late-fertile sister (out of three sisters) had a mortality rate that was approximately 20% lower than for men without such sisters (HRR(Utah)=0.801, p=0.028; HRR(Québec)=0.776, p=0.030).

Survival benefits for brothers associated with late female fertility may arise for unmeasured social reasons. If true, and because spouses share environmental circumstances, wives of brothers of late-fertile women might also experience a survival advantage. However, the survival of wives was unaffected by whether their husbands had a late-fertile sister.

The association between increased male survival and late fertility in their sisters is consistent with the hypothesis that genetic variants exist that might simultaneously facilitate late fertility and slow somatic aging. Genetic analyses of longevity may be more powerful in families with late-fertile or late-menopausal women. Mapping such genes without long-lived research subjects is feasible, if heritable quantitative traits that are as good or better indicators of slow rates of aging can be measured in middle-aged individuals.

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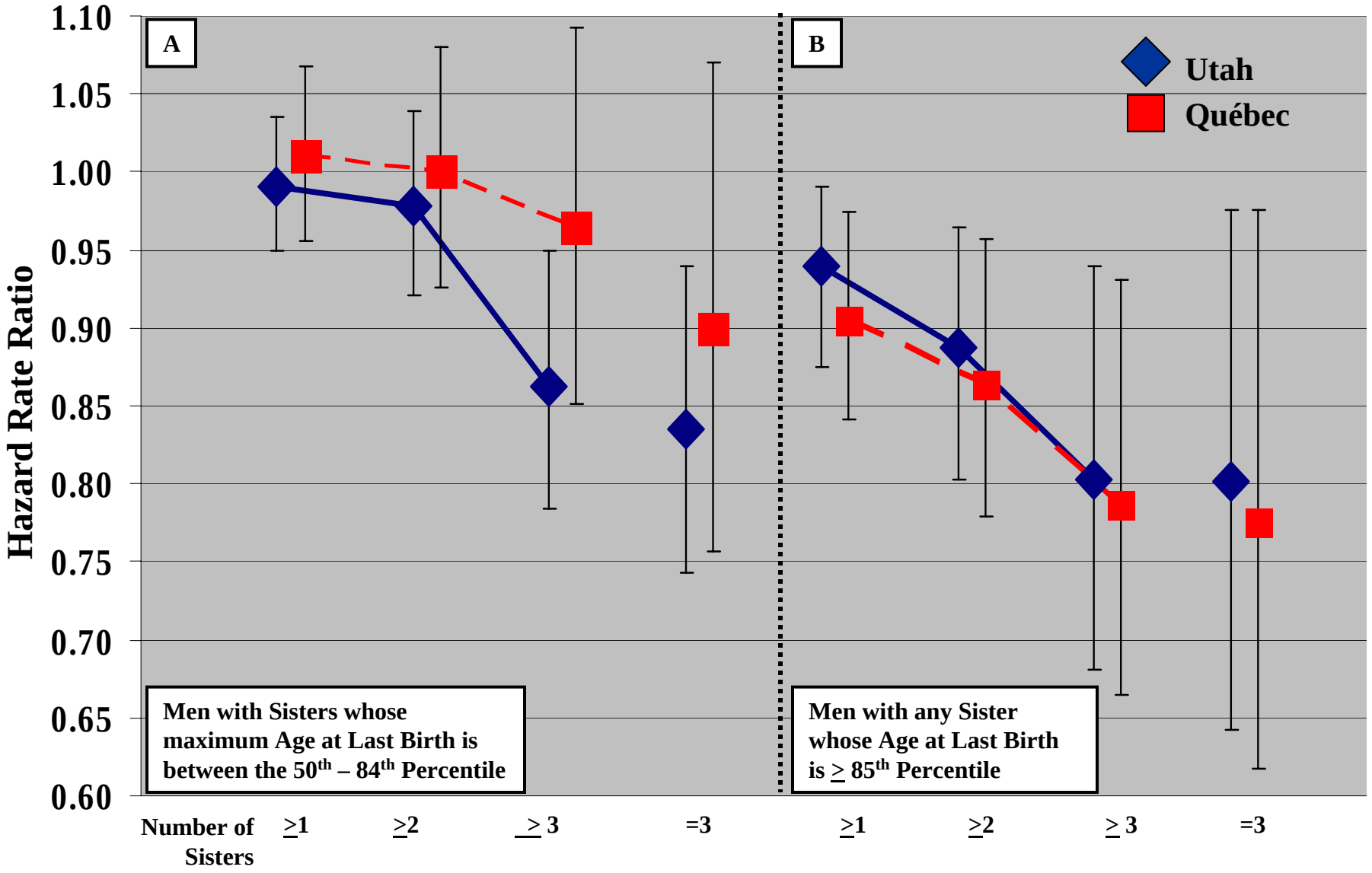
Fig. 1. Mortality hazard rate ratios (HRR) for brothers living to age 50 by age-at-last-birth of sisters who also survived to age 50. HRR were based on Cox proportional hazards models that adjust for affiliation with the Church of Jesus Christ of Latter-day Saints (Utah), whether in a settled colony (Quebec), sisters' maximum age-at-death, number of sisters, and mother's/father's age-at-death. HRR estimates are diamonds (♦) for Utah and squares (■) for Quebec. Vertical bars represent HRR 95% confidence intervals that adjust for familial clustering. The comparison group comprises brothers whose sisters are all in the bottom 50^{th} percentile. ***(A)*** Survival of men with sisters whose maximum age-at-last-birth was in the 50^{th}-84^{th} percentile of the female age-at-last birth distribution. For Utah, the 50^{th} percentiles are at ages 41.2, 42.4, and 43.1 for samples with $\geq$1, $\geq$ 2, and $\geq$3 sisters respectively. For Quebec, the 50^{th} percentiles are at ages 42.5, 43.2, and 43.8 for the comparable three samples. For these three sub-samples, the 85^{th} percentiles are at ages 44.4, 45.1, and 46.3 for Utah and at ages 44.9, 45.4, and 45.6 for Quebec. (***B***) Survival of men with a sister whose age at last birth is $\geq 85^{th}$ percentile of the female age-at-last-birth distribution.



Number of Sisters	≥1	≥2	≥ 3	=3
Utah N	11,604	5,784	2,430	1,596
Québec N	6,206	3,213	1,221	673