Late reproduction is associated with extended female survival but not with familial longevity

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ARTICLE

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BIOGRAPHY

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KEY MESSAGE

Longer living women or women with extremely long-living parents overall did not exhibit more favourable reproductive characteristics, and parental longevity was not related to a polygenic risk score for age at menopause. Reproductive success thus does not seem to be dependent on a genetic predisposition for DNA and soma maintenance.

ABSTRACT

Research question: Are age at last childbirth and number of children, as facets of female reproductive health, related to individual lifespan or familial longevity?

Design: This observational study included 10,255 female participants from a multigenerational historical cohort, the LINKing System for historical family reconstruction (LINKS), and 1258 female participants from 651 long-lived families in the Leiden Longevity Study (LLS). Age at last childbirth and number of children, as outcomes of reproductive success, were compared with individual and familial longevity using the LINKS dataset. In addition, the genetic predisposition in the form of a polygenic risk score (PRS) for age at menopause was studied in relation to familial longevity using the LLS dataset.

Results: For each year increase in the age of the birth of the last child, a woman's lifespan increased by 0.06 years (22 days; $P = 0.002$). The yearly risk for having a last child was 9% lower in women who survived to the oldest 10% of their birth cohort (hazard ratio 0.91, 95% CI 0.86–0.95). Women who came from long-living families did not have a higher mean age of last childbirth. There was no significant association between familial longevity and genetic predisposition to age at menopause.

Conclusions: Female reproductive health associates with a longer lifespan. Familial longevity does not associate to extended reproductive health. Other factors in somatic maintenance that support a longer lifespan are likely to have an impact on reproductive health.

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KEY WORDS
Ageing
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INTRODUCTION

Female reproductive health encompasses the evolution from being born with a complete set of oocytes, to fertility and pregnancy, then to the deterioration of ovarian quality and quantity, and ultimately to post-menopausal health. It is widely accepted that these milestones and transitions do not stand alone but may be subject to the same processes that govern overall somatic ageing and health (*Laven et al., 2016*). This relationship has not yet been fully clarified and it thus remains unknown to what extent the maintenance of somatic health is primarily essential to reproductive health or vice versa, and whether there is a genetic predisposition underlying both healthier somatic and reproductive ageing.

Over the past decades a plethora of studies have sought to determine and explain the relationship between ovarian and overall somatic ageing. Although there remains some dispute, several studies have observed that mothers who give birth to a child at an advanced age have a longer post-reproductive survival (*Brandts et al., 2019*; *Costanian et al., 2022*; *Gagnon, 2015*; *Gagnon et al., 2009*; *Jaspers et al., 2017*; *Shadyab et al., 2017*). Studies also suggested a familial or genetic component underlying both an increasing somatic lifespan and a longer reproductive period or reproductive lifespan (*Li et al., 2022*; *Perls et al., 1997*; *Shadyab et al., 2017*; *Smith et al., 2009*), while others have proposed a trade-off mechanism for an increasing lifespan and childbearing (*Westendorp and Kirkwood, 1998*). The latter results originate from studies with varying sample sizes and potential biases in the selection of their study population and await confirmation from well-defined, large-scale cohorts.

If longevity and late reproductive ageing coincide in families, the study of both traits in families with longevity may reveal shared genetic loci predisposing to a better maintenance of both somatic and reproductive cell functions. Thus, it can be postulated that long-living females or female members of long-living families are better at conserving their oocyte quality and can therefore conceive more easily and for a longer duration. Furthermore, the end-point of the reproductive lifespan, or age at menopause, has been found to be related to a polygenic risk score (PRS) involving loci of DNA repair processes, known as one of the hallmark mechanisms of ageing (*Ruth et al., 2021*). It is unknown whether the genetic component of age at menopause associates with that of familial longevity.

The current study addresses the relationship between somatic and reproductive ageing and health in both a large multigenerational historical cohort and a cohort of long-living families. The aim was to test whether individual and familial female longevity is associated with reproductive health and whether female members of exceptionally long-living families share genetic traits for menopause occurrence.

MATERIALS AND METHODS

LINKS study population

The study used data from the LINKing System for historical family reconstruction (LINKS), which is a historical cohort of inhabitants of the province of Zeeland, the Netherlands, from the early 19th century. The LINKS database contains demographic and genealogical information derived from the Netherlands linked vital event registration. In the Netherlands, birth, marriage and death certificates have been registered from the year 1812 onward. Currently, LINKS Zeeland contains 739,453 birth, 387,102 marriage and 641,216 death certificates that have been led together to reconstruct intergenerational pedigrees and individual life courses (*van den Berg et al., 2021*).

Two generations were identified in the dataset (Supplementary Figure 1), F_0 and F_1, of which the F_1 generation is the index generation comprising the study participants. The F_0 generation was selected by identifying couples who were married between 1812 and 1850 and had at least two children, ensuring that the F_1 individuals had at least one sibling. The families were mutually exclusive, meaning that a parent in the F_0 generation could only contribute data for a single family. From the F_1 generation, the LINKS research persons were selected using the following criteria: members of the female sex, with an age of death above 50 years and a single spouse who lived until the research person was at least 50 years old, and who delivered at least one child, ensuring high data quality. This selection made it possible to longitudinally study the reproductive outcomes in the study population throughout the entire fertile lifespan.

In both generations, a distinction was made between persons who belonged to the top 10% of survivors of their birth cohort, and those who did not. This calculation was based on Dutch life tables, nationally collected sex-specific and birth cohort-specific survival data of the entire Dutch population. These data are collected by Statistics Netherlands (CBS) and range from around 1800 until now, with yearly updates (*van den Berg et al., 2021*). The reproductive characteristics of the research persons were derived using information on their children (the F_3 generation). The reproductive characteristics that could reliably be extracted from the historical data were age at last childbirth and total number of children.

Leiden Longevity Study population

The Leiden Longevity Study (LLS) was initiated in 2002 to study the mechanisms that lead to exceptional survival in good health. The LLS currently consists of 651 three-generational families, defined by siblings who have the same parents. Inclusion took place between 2002 and 2006 and initially started with the recruitment of living nonagenarian sibling pairs of European descent (F_2 generation). Within a sibling pair, male individuals were invited to participate if they were 89 years or older and females if they were 91 years or older (n = 944 individuals, mean age 93 years); these represented less than 0.5% of the Dutch population in 2001 (*Schoenmaker et al., 2006*). Inclusion was subsequently extended to the offspring of the sibling pairs and the partners of these offspring (F_3 generation). This study focuses on all F_3 generation female members, who are henceforth denoted as LLS research persons (offspring and partners combined). For this study, 1,258 F_3 females with a mean age of 59 years were investigated.

The LLS DNA samples were genotyped using Illumina Infinium HD Human660W-Quad and OmniExpress BeadChips (Illumina, USA). DNA genotyping for the LLS was performed at baseline as described in detail by Beekman and colleagues (*Beekman et al., 2006*) using the Illumina Human660W and Illumina OmniExpress arrays (Illumina, USA). Genotype imputation was performed using 288,635 single-nucleotide polymorphisms (SNP) with a SNP-wise call rate (>95%), minor allele frequency (>1%) and no derivation from Hardy–Weinberg equilibrium (P-value $>1 \times 10^{-4}$) on the

Michigan Imputation Server (https://imputationserver.sph.umich.edu/index.html) with Haplotype Reference Consortium reference panels (HRC1.1) (*McCarthy et al., 2016*).

Mortality information was verified by birth or marriage certificates and passports whenever possible. Additionally, verification took place via personal cards that were obtained from the Dutch Central Bureau of Genealogy. In January 2021 all mortality information was updated through the Personal Records Database, which is managed by the Dutch governmental service for identity information (https://www.government.nl/topics/personal-data/personal-records-database-brp). The combination of officially documented information provides very reliable and complete ancestral as well as current mortality information.

Ethical approval was granted by the ethical committee of Leiden University Medical Center in August 2002 (reference number P01.113). In accordance with the Declaration of Helsinki, the LLS obtained informed consent from all participants prior to their entering the study.

Construction of the Longevity Relatives Count score in the LLS data

Familial longevity was quantified with the Longevity Relatives Count (LRC) score. The LRC score can be interpreted as a weighted proportion (ranging between 0 and 10) (*van den Berg et al., 2020*). For example, an LRC score of 5 for a research person indicates 50% long-lived family members, weighted by the genetic distance between the research persons and their family members. A long-living parent could provide 50% weight, while a grandparent could provide 25% weight, and so on.

Construction of the PRS of age at menopause in the LLS data

A recent large genome-wide association analysis for age at menopause resulted in a PRS (*Ruth et al., 2021*) that could be constructed from 290 SNP. After all T/A SNP, SNP with a minor allele frequency of <0.01 and Hardy–Weinberg equilibrium P-value of $<10^{-4}$, and an imputation quality <0.8 (*Choi et al., 2020*), were removed, and 195 SNP were used to construct the PRS for age at menopause in the LLS dataset.

Statistical analysis

All analyses were performed with R version 4.0.2 (The R Foundation, Austria). In the results 95% confidence intervals (95% CI) were reported and two-sided P-values were considered statistically significant at the 5% level ($\alpha = 0.05$). A list of used R-packages and version numbers will be made available on GitLab (see the Code Availability Statement). Random effects models were used to adjust for within-family relations, assuming family-specific random effects and defining research persons who share the same parents. The random effects models were designed with mixed-model linear regression using the lme4 and lmerTest packages. Confidence intervals were calculated with the confint function using the Wald method.

First, the results of the LINKS cohort were compared with the previous literature and historical cohorts. To this end, age at last childbirth and total number of offspring were included as independent variables, and individual lifespan as the dependent variable. Lifespan (age at death) was regressed on the following: (i) age at last childbirth (continuous and categorical, with a distinction between age at last childbirth of less than 40 or over 45 years, based on a distribution of age at childbirth (*Gottschalk et al., 2019*); and (ii) the number of children (continuous and categorical, making a distinction between a low and high number of children based on the authors' data); this involved using a linear mixed model with a random effect for the unique sibship ID to account for within-sibship correlation.

Second, individual longevity and familial longevity were included as independent variables with age at last childbirth as the dependent variable in a time-to-event survival analysis. Individual longevity was defined in terms of whether or not the research person belonged to the top 10% of survivors of her birth cohort. Familial longevity was defined by the number of long-lived parents (0, 1 or 2 parents who belonged to the top 10% of survivors of their birth cohort) (*van den Berg et al., 2019*). Age at last childbirth was defined as the event, with time in years as the time variable. The model was adjusted for maternal birth year and age at marriage, in order to account for temporal changes and exposure time for reproduction.

Third, individual longevity and familial longevity were included as independent variables, with the total number of offspring as the dependent variable. A Poisson mixed-model with a random effect for the unique sibship ID to account for within-sibship correlation was used, with adjustment for maternal birth year and age at marriage. Residuals were plotted in order to confirm a normal distribution (*van den Berg et al., 2019*).

Finally, the relationship of familial longevity to the genetic risk score for (early) menopause (the PRS) was studied in the LLS dataset. The standardized PRS, defined as the number of alleles associated with menopause, of the study participants was regressed on the number of long-lived family members, indicated by the LRC score. A linear mixed effects model with a random effect was used for family ID to account for within-family correlations. The models were adjusted for year of birth.

RESULTS

Study populations

In the LINKS data, 10,255 female research persons (the F_1 generation) were identified. Collectively, they were registered to 7664 mothers and 7636 fathers (the F_0 generation) and 72,895 children (the F_2 generation). In total, there were 7721 unique families, taking into account that the research person generation included siblings. The mean age at death of the research persons was 73.9 (SD ±10.4) years, and their mean number of children was 7.1 (±3.9). Further descriptive characteristics of the research persons group are described in detail in **TABLE 1**.

The LLS cohort included 1258 female participants with a mean age of 59 years.

Female participants giving birth to their last child at a higher age lived longer

To confirm in the LINKS dataset that mothers who give birth to a child at an advanced age have a longer post-reproductive survival, the relationship between age at last child and lifespan was investigated using linear mixed-model regression analysis. It was observed that for each year increase in the age at the birth of the last child, a woman had a 0.06 years (95% CI 0.02-0.10, 22 days) longer lifespan. In a comparison of the lifespan of female participants with a normal (≤40 years) versus high (≥45 years) age at last childbirth, it was observed that those who delivered their last child after the age of 45

TABLE 1 LINKING SYSTEM FOR HISTORICAL FAMILY RECONSTRUCTION STUDY POPULATION SELECTED FOR FEMALE PARTICIPANTS WHO GAVE BIRTH TO AT LEAST ONE CHILD

Parameter	Total number	Mean ± SD	Range
Number of F_1 RP (*n*, % female)	10,255 (100)	–	–
Top 10% survivors of their birth cohort	2241 (21.9)		
Number of unique sibships (*n*)	7721	–	–
Birth year (mean)	–	1839	1812–1873
Age at death in years (mean ± SD)	–	73.9 ± 10.4	50–104
Number of children (mean ± SD)	72,985	7.1 ± 3.9	1–24
Number of children ≤4 (*n*, %)	2990 (29.2)	2.6 ± 1.1	1–4
Number of children ≥10 (*n*, %)	2771 (27.0)	12.2 ± 2.1	10–24
Age at first child in years (mean ± SD)	–	26.9 ± 4.9	15–49
Age at last child in years (mean ± SD)	–	39.2 ± 5.0	18–51
Last childbirth ≤40 years (*n*, %)	5190 (50.6)	35.5 ± 4.4	18–40
Last childbirth ≥45 years (*n*, %)	981 (9.6)	45.8 ± 1.0	45–51
Age at marriage in years (mean ± SD)[a]	–	25.9 ± 4.6	16–46
Number of identified F_0 parents (*n*, %)	15,300 (99.7)[b]	–	–
RP with 0 long-lived parents (*n*, %)[c]	8293 (80.9)	–	–
RP with 1 long-lived parent (*n*, %)[c]	1849 (18.0)	–	–
RP with 2 long-lived parents (*n*, %)[c]	113 (1.1)	–	–

[a] In the case of multiple marriages, age at first marriage was considered.
[b] The denominator is the total number of parents (*n* = 15,442) for 7721 sibships. Of the total possible number of parents, 142 (0.3%) were not identified.
[c] Belonging to the top 10% survivors of their birth cohort; 15.3% (2344) of the identified parents have a missing age at death.
RP, research person.

TABLE 2 AGE AT LAST CHILDBIRTH AND NUMBER OF OFFSPRING ASSOCIATES WITH INDIVIDUAL LIFESPAN

Outcome and variable	*n* (mean/proportion)	β (95% CI)	*P*-value
Age at last child (years, continuous)	10,255 (39.23)	0.06 (0.02 to 0.10)	2.16×10^{-3}
Age at last child			
Group 0: ≤40 years	5190 (50.6)	REF	REF
Group 1: ≥45 years	981 (9.6)	1.41 (0.71 to 2.12)	9.07×10^{-5}
Number of children (continuous)	10,255 (7.12)	0.05 (−0.01 to 0.11)	7.63×10^{-2}
Number of children			
Group 0: ≤4	2990 (29.2)	REF	REF
Group 1: ≥10	2771 (27.0)	0.61 (−0.03 to 1.25)	6.25×10^{-2}

All analyses were adjusted for the maternal birth year and the research person's age at marriage. In addition, the research design accounted for the survival of research persons and their partners up to the age of 50 years and the number of marriages.

Analyses were carried out using mixed-model linear regression using the lme4 and lmerTest packages in R. Confidence intervals were calculated in R with the confint function using the Wald method.

Four separate analyses were undertaken with age at death as outcome; (i) with the age at last childbirth (quantitative definition) as the independent variable of interest; (ii) with the age at last childbirth (qualitative definition) as the independent variable of interest; (iii) with the number of children (quantitative definition) as the independent variable of interest; and (iv) with the number of children (qualitative definition) as the independent variable of interest.

REF, reference.

lived 1.41 years (17 months) longer than those who had their last child at less than 40 years of age (95% CI 0.71–2.12), after adjusting for the age at marriage and the mother's birth year (TABLE 2).

Although it was not statistically significant, it was observed that for each additional child the lifespan of female participants increased by 0.05 years (95% CI −0.01 to 0.11). Moreover, those who had 10 or more children (*n* = 2771), in comparison to those who had four or fewer children (*n* = 2990), lived on average 0.61 years longer, although again this effect did not reach statistical significance (95% CI −0.03 to 1.25; TABLE 2).

Long-living female participants gave birth to their last child at a later age

TABLE 3 displays the results of the survival and Poisson analysis for individual longevity. For each year, the top 10% survivors (*n* = 2241, 21.9%) were 9% less likely to have reached their 'reproductive stop', or age at last childbirth, than the remaining cohort (*n* = 8014, 78.1%) (hazard ratio 0.91, 95% CI 0.86–0.95). Of the long-lived research persons, 50% gave birth to their last child at age 41 years, in comparison to age 40 for the remaining cohort (FIGURE 1). There was no difference in the degree of familial longevity and age at last childbirth (TABLE 4).

Long-living females did not give birth to more children

Although it was not statistically significant, female research persons who survived to the top 10% of their birth cohort delivered on average 2% more children than other female participants (incidence rate ratio 1.02, 95% CI 0.99–1.04; TABLE 3). The number of offspring did not differ significantly between participants with 0, 1 or 2 long-lived parents, as displayed in TABLE 4.

Female participants with long-lived parents had a similar genetic predisposition to early menopause to others

The authors further studied the genetic component underlying both longevity and reproductive health in 1258 F_3 female participants from the LLS (see the Materials and Methods section for more details on the study). No statistically significant association was observed between an increasing number of long-lived family members (familial longevity; as captured by the LRC score) and the

TABLE 3 ASSOCIATION OF INDIVIDUAL LONGEVITY WITH AGE AT LAST CHILDBIRTH AND NUMBER OF OFFSPRING

Outcome and variable	*n* (mean/proportion)	HR/IRR (95% CI)	*P*-value
Age at last child (years)			
Top 10% survivor			
No	8014 (78.1)	REF	REF
Yes	2241 (21.9)	0.91 (0.86–0.95)[a]	3.86×10^{-5}
Number of children			
Top 10% survivor			
No	8014 (78.1)	REF	REF
Yes	2241 (21.9)	1.02 (0.99–1.04)[b]	9.19×10^{-2}

All analyses were adjusted for the maternal birth year and the research person's age at marriage. In addition, the research design accounted for the survival of research persons and their partners up to the age of 50 years and the number of marriages.

Analyses were carried out using mixed-model Poisson regression using the lme4 and lmerTest packages in R. Confidence intervals were calculated in R with the confint function using the Wald method.

[a] HR.

[b] IRR.

HR, hazard ratio; IRR, incidence rate ratio; REF, reference.

genetic score for age at menopause (PRS) ($\beta = 0.014$, % CI −0.01 to 0.04). The effect showed a trend towards the postulated direction: with every 10% increase in the LRC score, indicating greater familial longevity, the number of alleles associating with age at menopause was 0.014 SD higher.

DISCUSSION

The study showed that female participants who gave birth to their last child at a higher age, and with an increasing number of offspring, had a longer lifespan. Moreover, those who were among the top 10% survivors of their birth cohort delivered their last child at a higher age and overall may have had slightly more children. On the familial level, there was no association between the number of long-lived parents and the reproductive outcomes. Furthermore, no evidence was found for an association between a genetic predisposition to early or delayed menopause and familial longevity. Hence, it was concluded that a high age of last childbirth and the number of offspring are markers of good reproductive health and overall health supporting longevity. In the current study they were not, however, explained by the genetic component in longevity.

This study affirms previous research that supports a relationship between a later age at last childbirth and increased post-reproductive survival (*Brandts et al., 2019*; *Costanian et al., 2022*; *Gagnon, 2015*;

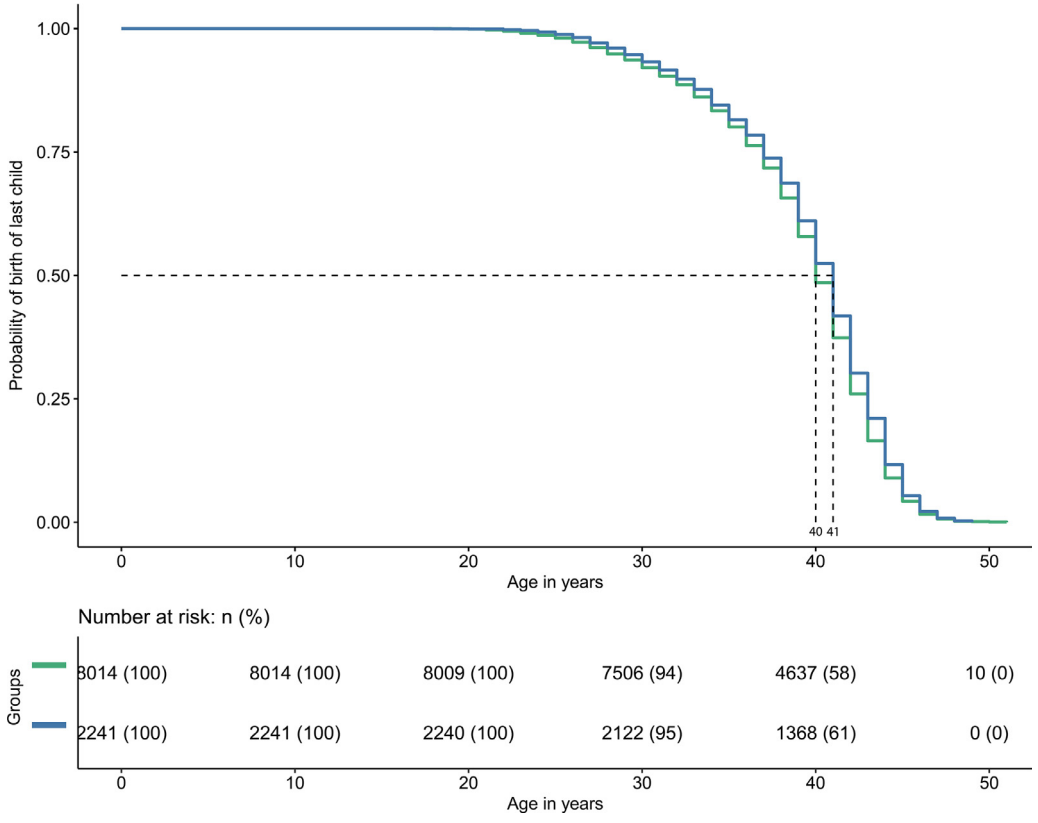

FIGURE 1 Survival plot of age at last childbirth for long-living females (blue) and the remaining cohort (green). The dashed line indicates the median age at childbirth (41 versus 40 years).

TABLE 4 ASSOCIATION OF FAMILIAL LONGEVITY WITH AGE AT LAST CHILDBIRTH AND NUMBER OF OFFSPRING

Outcome and variable	*n* (mean/proportion)	HR/IRR (95% CI)	*P*-value
Age at last child (years)			
Number of long-lived parents			
0 long-lived parents	8293 (80.9)	REF	REF
1 long-lived parent	1849 (18.0)	1.04 (0.99–1.09)[α]	1.30×10^{-1}
2 long-lived parents	113 (1.1)	1.15 (0.95–1.38)[α]	1.52×10^{-1}
Number of children			
Number of long-lived parents			
0 long-lived parents	8293 (80.9)	REF	REF
1 long-lived parent	1849 (18.0)	0.98 (0.96–1.01)[β]	1.62×10^{-1}
2 long-lived parents	113 (1.1)	0.98 (0.89–1.08)[β]	6.44×10^{-1}

All analyses were adjusted for the maternal birth year and the research person's age at marriage. In addition, the research design accounted for the survival of research persons and their partners up to the age of 50 years and the number of marriages.

Analyses were carried out using mixed-model Poisson regression using the lme4 and lmerTest packages in R. Confidence intervals were calculated in R with the confint function using the Wald method.

HR, hazard ratio; IRR, incidence rate ratio; REF, reference.

Gagnon et al., 2009; *Helle et al., 2005*; *Jaffe et al., 2015*; *Jaspers et al., 2017*; *McArdle et al., 2006*; *Müller et al., 2002*; *Shadyab et al., 2017*; *Sun et al., 2015*). In addition, the brothers of female participants who gave birth to their youngest child at a younger age lived significantly longer (*Smith et al., 2009*). Several underlying mechanisms have been proposed for this relationship.

On the genetic level, several genes and gene pathways have been identified that could play a role in both somatic and reproductive function (*Wainer-Katsir et al., 2015*). Profiles of SNP or genome copy number variant regions have furthermore been associated with risk of mortality and longevity and may be linked to reproduction, although the latter is predominantly assessed through proxy measures such as age at menopause (*Wainer-Katsir et al., 2015*). Gene variants in the DNA repair pathways strongly relate to age at menopause (*Ruth et al., 2021*), suggesting that the latter could be the result of overall somatic ageing (*Laven, 2022*). Although the genetic loci associated with age at menopause have not yet been directly correlated to human longevity or familial longevity, a meta-analysis relating SNP to exceptional human longevity (in single cases) reported a correlation with several of the same SNP that related to age at menopause (*Sebastiani et al., 2013*). Because the genetic predisposition for a late onset of menopause is not significantly associated with the familial component of human longevity in the current study, the health of female participants who reproduced late might also be affected by other factors that influence lifespan, such as good environmental circumstances, healthy lifestyles or favourable social factors.

Besides oocyte quantity, oocyte quality is a necessary factor for reproductive success and is thought to be a causal factor in the age-related decline of fertility (*Silber et al., 2017*). As women age, oocyte competence decreases, leading to an increased risk of aneuploidy and miscarriage, leading in turn to decreased fecundity. Suggested pathways for the decline in oocyte quality include a deterioration of the maintenance of mitochondrial function (*Chiang et al., 2020*) and the intrafollicular processes of DNA translation (*Llarena and Hine, 2021*). These processes are in turn thought to be subject to oxidative stress, to which the oocyte becomes more vulnerable with increasing age, as shown in animal models (*Sasaki et al., 2019*).

Fertility treatments such as IVF have previously, although not consistently, been linked to adverse cardiovascular outcomes in both the short and long term (*Bungum et al., 2019*; *Henriksson, 2021*; *Yiallourou et al., 2022*), which could suggest an adverse ageing profile for the subfertile population, but it is not clear whether this can be attributed to the effects of treatment or population risk. While it is possible that the influence of the DNA damage repair genes associated with age at menopause additionally extends to oocyte quality, this remains to be further determined (*Wainer-Katsir et al., 2015*). In oocytes, a group of cells that spend most of their life in senescence, it might be that the pathways for cell maintenance are regulated somewhat differently from those in somatic cells. This could be another explanation for the lack of association between familial longevity and the PRS for menopause as well as reproductive outcomes in the current study. It is also possible that fecundity, and thus oocyte quality, cannot be adequately measured through the proxies of age at childbirth and number of offspring. In addition, because this study involved a, by definition, relatively healthy group of women who lived to age 50 years and underwent at least one successful pregnancy and delivery, it precludes an in-depth enquiry into the association between infertility or involuntary childlessness and longevity.

It is challenging to put the effect sizes of the current results into clinical perspective. For the sake of comparison, the total effects of obesity-related disease in the USA are estimated to vary from 0.2 to 11.7 life−years lost (*Chang et al., 2013*). Considering the magnitude of possible morbidities in affecting the total lifespan, an average lifespan increase of 1.41 years for those with childbirth after 45 years may in fact hold significance.

The method of linkage of families in the historical cohort makes this study uniquely suited to investigating the familial effects of reproduction and longevity. The methodological selection of the study population, as well as the population size, adds to its strengths. Due to the historical nature of the data, the results are not influenced by the use of hormonal contraception or assisted reproductive techniques, therefore allowing for a reasonable assumption of unrestricted natural fertility. For this reason, the results cannot be directly applied to a contemporary population with access to family planning methods, but provide a unique insight into the underlying biology.

The results are limited by the obligatory use of a select number of proxy variables for fertility and reproductive success, as the study was limited to the data stored in governmental registries. Furthermore, as mentioned, it included a relatively healthy

group of individuals who lived to be at least 50 years old. It is possible that this selection excludes individuals with accelerated ageing genotypes or susceptibility to infectious or other diseases, and therefore attenuates any associations of reproduction with strong somatic maintenance or longevity.

The historical data furthermore preclude the correction for confounders such as smoking, or societal and socioeconomic effects. In a prior centenarian study of 197 female participants, a significant relationship between the total number of children and longevity was attenuated after adjusting for smoking (*Lockhart et al., 2016*). That being said, population studies from multiple countries have shown that the early 19th-century increase in lifespan preceded improvements in public health and diet (*Mourits, 2017*). It is therefore possible that lifestyle factors, socioeconomic status and societal class were less prominently associated with health and longevity than they are today. Finally, although it was possible to identify the associations between longevity and reproduction from different perspectives, it was not possible to remark on their causality.

In conclusion, it can be confirmed that a late age at last childbirth is associated with a longer lifespan and that traits of reproductive success seem to be markers of female health in middle age, probably acquired by good environmental circumstances. Furthermore, the authors conclude that neither parental nor more extended ancestral familial longevity is characterized by reproductive success.

Attestation statement: Data regarding any of the subjects in the study have not been previously published unless specified.

Code availability statement: the scripts containing the code for data pre-processing and data analyses can be freely downloaded at https://git.lumc.nl/publications/fertility-longevity.

SUPPLEMENTARY MATERIALS

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.rbmo.2024.104073.

DATA AVAILABILITY

The authors do not have permission to share data.

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