

# The relationship between fertility and lifespan in humans

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**Abstract** Evolutionary theories of aging predict a trade-off between fertility and lifespan, where increased lifespan comes at the cost of reduced fertility. Support for this prediction has been obtained from

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various sources. However, which genes underlie this relationship is unknown. To assess it, we first analyzed the association of fertility with age at menarche and menopause, and with mortality in 3,575 married female participants of the Rotterdam Study. In addition, we conducted a candidate gene study where 1,664 single nucleotide polymorphisms (SNPs) in 25 candidate genes were analyzed in relation to number of children as a measure of fertility. SNPs that associated with fertility were analyzed for association with mortality. We observed no associations between fertility and age at menarche ( $p=0.38$ ) and menopause ( $p=0.07$ ). In contrast, fertility was associated with mortality. Women with two to three children had significantly lower mortality (hazard ratio (HR), 0.82; 95% confidence interval (95% CI), 0.69–0.97) compared to women with no children. No such benefit was observed for women with four or more children, who had a similar mortality risk (HR, 0.93; 95% CI, 0.76–1.13) as women with no children. The analysis of candidate genes revealed four genes that influence fertility after correction for multiple testing: *CGB/LHB* gene cluster ( $p=0.0036$ ), *FSHR* ( $p=0.023$ ), *FST* ( $p=0.023$ ), and *INHBA* ( $p=0.021$ ). However, none of the independent SNPs in these genes predicted mortality. In conclusion, women who bear two to three children live longer than those who bear none or many children, but this relationship was not mediated by the candidate genes analyzed in this study.

**Keywords** Fertility · Lifespan · Trade-off · Gene · SNP

## Introduction

Evolutionary theories of aging predict a trade-off between fertility and lifespan, where increased lifespan comes at the cost of reduced fertility (Kirkwood 1977; Williams 1957). Studies in model organisms have provided evidence for this prediction (Rose and Charlesworth 1980; Stearns and Partridge 2001). In humans, however, no convincing support for this hypothesis has been obtained when historical populations were studied. However, in contemporary populations, a trade-off between fertility and lifespan has been observed (Hurt et al. 2006; Le Bourg 2007). It is likely that genes underlie this relationship but the identity of these genes has largely remained unknown.

According to the antagonistic pleiotropy theory (Williams 1957) and the disposable soma theory (Kirkwood and Rose 1991; Kirkwood 1977) of aging, a trade-off between reproduction and lifespan exists. The disposable soma theory emphasizes energetic and metabolic costs associated with reproduction, which may lead to deterioration in maternal condition, increase risk of disease, and lead to higher mortality. The antagonistic pleiotropy theory, on the other hand, emphasizes a genetic trade-off, where genes that increase reproductive potential early in life increase risk of disease and mortality later in life. Such a trade-off would be expected even for women who have not given birth but who carry these gene variants. Several researchers have sought evidence for the trade-off between fertility and lifespan, with elusive results. In historical populations, negative (Korpelainen 2000; Penn and Smith 2007; Westendorp and Kirkwood 1998), positive (Korpelainen 2000; Le Bourg 2007; McArdle et al. 2006; Muller et al. 2002), and no relationship (Helle et al. 2004; Lycett et al. 2000) between fertility and lifespan have been reported. In contemporary populations, however, the results are more uniform. In several studies, it has been observed that women with no children and women with more than four children have the highest mortality (Doblhammer 2000; Hurt et al. 2006)

The increased mortality for women with no or with many children suggests that either the same or different genes are at play. To date, a number of genes have been identified to influence female

fertility. In addition, it has been estimated that the heritability of female lifetime reproductive success in a contemporary population is 22% (Kosova et al. 2010) whereas in a preindustrial population, it was estimated to reach 47% (Pettay et al. 2005). These estimates reflect an underlying genetic architecture of female fertility. According to the antagonistic pleiotropy theory of aging, the same genes should influence human lifespan.

Evidence suggests that age at menarche and menopause also influence female fertility. It has been found that women with earlier menarche have higher fertility (Borgerhoff Mulder 1989), but not all studies corroborate this finding (Helm et al. 1995; Sandler et al. 1984). Likewise, later age at menopause has been related to higher number of live births (Bromberger et al. 1997; Parazzini et al. 1992; Stanford et al. 1987; Whelan et al. 1990). In addition, later age at menopause has been associated with increased risk of breast and endometrial cancer, but with decreased risk of osteoporosis and cardiovascular diseases (Hu et al. 1999; Sowers and La Pietra 1995). These effects have been attributed to high lifetime exposure to estrogens. Given these associations, it is likely that age at menarche and at menopause could predict mortality at old age.

In this study, we set out to examine the relationship between fertility and lifespan and explore the influences of age at menarche and menopause on these phenotypes. In addition, we conducted a candidate gene study in order to identify genes that could influence both fertility and lifespan in an antagonistic manner. We expected that genetic variants that associate with increased fertility would result in higher mortality. The study was carried out in married female participants of the prospective Rotterdam Study.

## Methods

### Study population

This study is embedded in the Rotterdam Study, an ongoing population-based cohort on risk factors for chronic diseases in the elderly. Detailed information on design, objectives, and methods has been presented elsewhere (Hofman et al. 2009). For this study, data from the first (RSI) and second (RSII) cohort of

the Rotterdam Study were available. In RSI, all inhabitants aged over 55 years living in the Ommoord district of Rotterdam were invited to participate. Of these 7,983 (78%) agreed to participate. In 1999, 3,011 participants (out of 4,472 invitees) who had become 55 years of age or moved into the study district since the start of the study were added to the cohort (RSII). All participants of the Rotterdam Study were followed for mortality until January 1, 2009. The current study included 3,575 married female participants of the Rotterdam Study. The Medical Ethics Committee of the Erasmus Medical Center approved the Rotterdam Study, and written informed consent was obtained from all participants.

#### Fertility and age at menarche and at menopause

As a measure of fertility, data on self-reported number of children were used. Women were asked, “How many children do you have?” Fertility was analyzed linearly but also categorically, where women were categorized into the following groups: (1) childless vs. with children and (2) no children, one child, two to three children, and four or more children. Data on age at menarche were collected by asking women, “How old were you when you had your first menstrual period?”, and data on age at menopause were collected by asking women, “How old were you when you had your last menstrual period?” Self-reported age at menopause was defined as 12 months after periods had ceased. The retrospective data on self-reported number of children, age at menarche and at menopause were collected by a questionnaire during the first RSI interview (1990–1993) and during the first RSII interview (1999–2001).

#### Confounders

The following variables were considered as possible confounders: age at baseline, date of birth, smoking, and socioeconomic status. Smoking status was defined as having never smoked, being former or being current smoker. To correct for differences in socioeconomic status, data on education and household income were used. The participants were asked about their formal education, the number of years in each type of education, and whether education had been completed. Based on these data, education was divided into two levels: lower and higher education.

The lower education category included participants with primary, lower vocational, and lower secondary education. The high education category included participants with intermediate vocational, general secondary, higher vocational, and university education. Household income was classified into 13 pre-coded categories. Equivalent household income was defined as the midpoint of each income category divided by the number of persons living on that income raised to the power 0.36 (Buhmann et al. 1988).

#### Candidate genes and genotype data

Altogether, 25 candidate genes were selected based on their involvement in female fertility according to the published literature (Supplementary table 1). These genes function in hypothalamic–pituitary–ovarian (HPO) axis, folliculogenesis, and implantation processes. From these genes and within 10-kb vicinity 1,756 single nucleotide polymorphisms (SNPs) were selected for study. Genotype data for these SNPs were obtained from genome-wide genotyping data of the Rotterdam Study. The genome-wide genotyping was performed with Illumina 550K array (Illumina, San Diego, CA, USA) in self-reported Caucasian individuals (sample call rate,  $\geq 97.5\%$ ). Individuals with excess of autosomal heterozygosity, mismatch between genotypic and phenotypic gender, and outliers identified by the identity-by-state clustering analysis were excluded. This genotype data were used to impute 2.5 million autosomal SNPs described in HapMap’s Phase II European population panel with the imputation software MACH (<http://www.sph.umich.edu/csg/abecasis/MACH>). Such SNP imputation infers genotypes probabilistically according to shared haplotype stretches between the study samples and HapMap release 22 build 36 data. From the 1,756 SNPs in the candidate genes, 62 were excluded due to a minor allele frequency (MAF) of less than 1% and 30 SNPs due to the Hardy–Weinberg equilibrium  $p$  value lower than 1%, resulting in 1,664 SNPs for further analyses.

#### Statistical analysis

First, we analyzed the association between fertility and age at menarche and age at menopause with linear regression. Second, we assessed the relation of

fertility, age at menarche and at menopause with mortality using Cox proportional hazard regression. Third, the function- and gene-wide influence of SNPs on fertility was determined with a set-based test, implemented in PLINK (Purcell et al. 2007) (<http://pngu.mgh.harvard.edu/~purcell/plink/>). The default settings of PLINK were used ( $r^2=0.05$ ;  $p$  value < 0.05; max number of SNPs, 5). The significance of SNP combinations within a function or a gene was estimated using 10,000 permutations. Where a function or a gene met a significance threshold of  $p < 0.05$  after permutations, independently associated SNPs within these, as defined by PLINK, were analyzed further for association with fertility and mortality. Fourth, the association between SNPs and fertility was assessed with logistic regression. Finally, the association between SNPs and mortality was analyzed with Cox proportional hazard regression. All analyses were adjusted for birth year and education, except the mortality analyses which were additionally adjusted for age at baseline and education. All analyses were repeated with additional adjustment for household income and smoking status. Data were analyzed with SPSS version 17 (SPSS Inc, Chicago, IL, USA) and PLINK version 1.07 (Purcell et al. 2007) statistical software.

## Results

The characteristics of the 3,575 study participants are presented in Table 1. All women were born between 1893 and 1944, and their mean age at baseline was

**Table 1** Characteristics of the study participants

Number	3,575
Age at baseline (mean, SD)	68 (9.49)
Low education ( $n$ , %)	2,370 (67%)
Age at menarche (mean, SD)	13.6 (1.78)
Age at menopause (mean, SD)	48.8 (5.31)
Fertility	
0 children ( $n$ , %)	471 (13%)
1 child ( $n$ , %)	577 (16%)
2–3 children ( $n$ , %)	1,975 (55%)
$\geq 4$ children ( $n$ , %)	552 (16%)
Mortality ( $n$ , %)	1,116/3,238 (66%)
Follow-up (mean, SD)	12.1 (4.88)

68 years. Of the 3,575 participants, 2,370 (67%) had a lower education. The number of children in this population ranged from 0 to 16 (mean (SD), 2.22 (1.53)). Women with no children ( $n=471$ ) constituted 13% of the population. Data on mortality were available for 3,238 participants. Of these participants, 1,116 (66%) died during a mean follow-up period of 12.1 years.

In this study, age at menarche and at menopause had no pronounced influence on fertility, neither when analyzed linearly nor when categorizing women based on the number of children they have had (Table 2). The only trend observed involved women with two or three children who had later menopause compared to women with no children (estimate standard error (SE), 0.56 (0.29),  $p=0.06$ ). This trend was also reflected when fertility was analyzed by comparing women who have had children with women with no children (estimate (SE), 0.49 (0.28),  $p=0.07$ ). In contrast, mortality risks were not influenced by age at menarche (hazard ratio (HR), 0.99; 95% confidence interval (95% CI), 0.95–1.02) and at menopause (HR, 0.99; 95% CI, 0.98–1.00; Table 2).

Next, we assessed the association between fertility and all-cause mortality. We observed no linear relation between the number of children and mortality (HR, 0.99; 95% CI, 0.95–1.02; Table 2). But, when comparing women with two or three children with women with no children, it became apparent that they have significantly lower mortality (HR, 0.82; 95% CI, 0.69–0.97; Fig. 1). No such benefit was observed for women with four or more children, who had a similar mortality risk (HR, 0.93; 95% CI, 0.76–1.13) as women with no children (Table 2), but a higher mortality risk when compared to women with two to three children (HR, 1.13; 95% CI, 0.96–1.32).

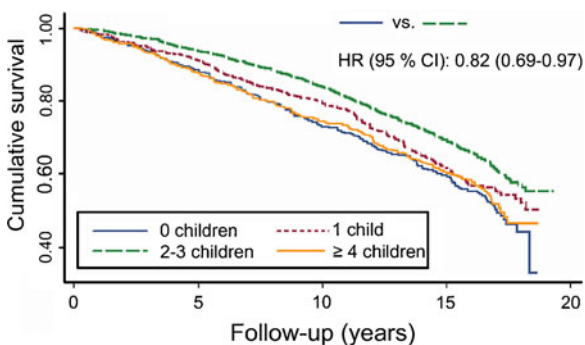
To explore the influence of genetic variation on fertility, we first assessed the combined effect of SNPs in folliculogenesis, HPO axis, and implantation on fertility. From these three functions, the combined effect of SNPs involved in HPO axis revealed a trend for association with fertility after permutations ( $p=0.09$ ; Supplementary table 2). To determine which of the 25 selected candidate genes contain SNPs that influence fertility the most, we performed a gene-wide association analysis. This approach revealed four genes that influence fertility after permutations: *CGB/LHB* (0 vs. 2–3 children,  $p=0.0036$ ), *FSHR* (0 vs.  $\geq 4$  children,  $p=0.023$ ), *FST* (0 vs.  $\geq 4$  children,  $p=0.023$ ), and

**Table 2** Association of fertility with age at menarche and menopause, and with mortality

	Menarche <sup>a</sup>		Menopause <sup>a</sup>		Mortality <sup>b</sup>
	Estimate (SE)	<i>p</i> value	Estimate (SE)	<i>p</i> value	HR (95% CI)
The number of deaths during follow-up in the different fertility categories: 0 children ( <i>n</i> =189), one child ( <i>n</i> =201), 2–3 children ( <i>n</i> =512), ≥4 children ( <i>n</i> =214)					
* <i>p</i> <0.05					
<sup>a</sup> Education- and birth year-adjusted linear regression					
<sup>b</sup> Cox proportional hazard model adjusted for education and age at baseline					
Fertility					
0 children	Reference	–	Reference	–	Reference
1 child	–0.18 (0.11)	0.10	0.31 (0.34)	0.37	0.96 (0.79–1.17)
2–3 children	–0.11 (0.09)	0.25	0.56 (0.29)	0.06	0.82 (0.69–0.97)*
≥4 children	0.13 (0.11)	0.27	0.49 (0.35)	0.16	0.93 (0.76–1.13)
Fertile (yes/no)	–0.08 (0.09)	0.38	0.49 (0.28)	0.07	0.87 (0.74–1.02)
Per child	0.02 (0.02)	0.21	0.10 (0.06)	0.09	0.99 (0.95–1.02)
Age at menarche	–	–	–	–	0.99 (0.95–1.02)
Age at menopause	–	–	–	–	0.99 (0.98–1.00)

*INHBA* (0 vs. 1 child,  $p=0.021$ ) (Supplementary table 2). Independent SNPs from these four candidate genes were further examined for their association with fertility and mortality.

The *CGB/LHB* gene cluster contained three SNPs, and *FSHR* contained five SNPs whereas *FST* and *INHBA* both contained one independent SNP. For all analyzed SNPs, a similar influence across the fertility categories was observed (Table 3). For instance, women carrying the rs1062708 SNP in *CGB/LHB* gene cluster had a high probability to have one child (OR, 1.20; 95% CI, 1.01–1.45), but lower probabilities to have two to three (OR, 1.13; 95% CI, 0.97–1.31) or four or more children (OR, 1.07; 95% CI, 0.89–1.27) when compared to women with no children. Finally, we tested the association of these SNPs with mortality. Despite their association with fertility, none of these SNPs directly predicted mortality (see also Table 3).



**Fig. 1** Kaplan–Meier survival curves for women with different numbers of children. The hazard ratio (HR) with 95% confidence interval (CI) for the comparison of women with no children and women with two to three children is adjusted for age at baseline and education

All reported analyses were repeated with additional adjustment for household income and smoking status, without leading to changes in results (data not shown).

## Discussion

In this study, we found that women with two or three children have lower mortality compared to women with no children. No such benefit was observed for women with four or more children, who had a similar mortality risk as women with no children. This relationship between fertility and lifespan was not mediated by the analyzed candidate genes. In addition, we found no pronounced influence of age at menarche and at menopause on fertility and lifespan.

The relationship between fertility and lifespan has previously been studied by a number of studies. Similar to other studies (Hurt et al. 2006), we found no linear relationship between number of children and lifespan. Instead, we observed that women with no children and with four or more children had the highest mortality. It has been hypothesized that with repeated pregnancies, women become depleted of resources that would otherwise be available for maintenance and repair of the body, and hence, lead to higher mortality (Kirkwood and Rose 1991; Winkvist et al. 1992). In addition, it has been suggested that repeated pregnancies result in permanent detrimental effects on lipid and glucose metabolism (Martin et al. 1999; Sattar and Greer 2002) and this way contribute to higher risk for coronary artery disease, stroke, diabetes (Lawlor et al. 2003; Qureshi



**Table 3** Influence of SNPs in candidate genes on fertility and mortality

Gene	MAF	Fertility			Mortality HR (95% CI)
		0 vs. 1 child OR (95% CI)	0 vs. 2–3 children OR (95% CI)	0 vs. ≥4 children OR (95% CI)	
<i>CGB/LHB</i>					
rs753308	0.41	0.70 (0.59–0.86)**	0.78 (0.67–0.91)**	0.74 (0.62–0.89)**	1.01 (0.93–1.10)
rs3752210	0.41	0.70 (0.61–0.89)**	0.78 (0.67–0.90)**	0.74 (0.62–0.89)**	1.03 (0.94–1.11)
rs1062708	0.49	1.20 (1.01–1.45)*	1.13 (0.97–1.31)	1.07 (0.89–1.27)	1.02 (0.94–1.11)
<i>FSHR</i>					
rs1277460	0.21	0.90 (0.70–1.07)	0.89 (0.75–1.06)	0.66 (0.52–0.83)**	0.95 (0.85–1.05)
rs6545094	0.42	1.20 (1.03–1.50)*	1.20 (1.03–1.40)*	1.35 (1.11–1.64)**	0.98 (0.90–1.06)
rs3913665	0.41	0.90 (0.71–1.02)	0.92 (0.79–1.07)	0.75 (0.62–0.91)**	1.03 (0.94–1.12)
rs971831	0.30	1.10 (0.90–1.34)	1.12 (0.95–1.32)	1.31 (1.06–1.60)*	1.00 (0.92–1.10)
rs2268360	0.22	0.90 (0.75–1.16)	0.90 (0.76–1.07)	0.76 (0.61–0.94)*	0.98 (0.89–1.08)
<i>FST</i>					
rs10080213	0.24	1.30 (1.03–1.58)*	1.15 (0.96–1.38)	1.37 (1.10–1.70)**	1.01 (0.92–1.12)
<i>INHBA</i>					
rs2237432	0.25	1.37 (1.10–1.71)**	1.24 (1.04–1.49)*	1.11 (0.89–1.38)	0.97 (0.88–1.07)

Association with fertility was analyzed with birth year- and education-adjusted logistic regression; association with mortality was analyzed with age at baseline and education-adjusted Cox proportional hazard model

MAF minor allele frequency, OR odds ratio, HR hazard ratio, CI confidence interval

\* $p < 0.05$ ; \*\* $p < 0.005$

et al. 1997), and to higher mortality later in life. On the other hand, the higher mortality among women with no children has probably different biological causes. It is likely that mechanisms that lead to infertility have also detrimental effects on other physiological processes, thereby contributing to higher mortality.

Female reproductive lifespan is determined by the onset and cessation of menstruation. It has been found that both the age at menarche and at menopause influence fertility (Borgerhoff Mulder 1989; Parazzini et al. 1992; Stanford et al. 1987; Whelan et al. 1990). In this study, we found no effects of age at menarche on fertility. For age at menopause, in contrast, we observed that women with children tended to have their menopause at later ages than women without children. Interestingly, it has been reported that women who have their menopause at later ages have decreased risk of having a heart attack, stroke, or other cardiovascular disease event, but increased risk of having breast or endometrial cancer (Hu et al. 1999; Sowers and La Pietra 1995). These associations are in an opposite direction than the disease risks

associated with higher fertility, which highlight the complex interactions between them. This might also explain why no association between age at menopause and mortality was observed in this study.

Over the years, a number of genes have been identified to influence fertility. In this study, we selected candidate genes that are involved in HPO axis, folliculogenesis, and implantation process. From these, three genes (*CGB/LHB* gene cluster, *FSHR*, and *INHBA*) involved in HPO axis and one gene (*FST*) involved in folliculogenesis were associated with fertility. The *CGB/LHB* gene cluster is located in a gene-rich region which is targeted by natural selection and gene conversion events (Nagimaja et al. 2010). Given the association of the *CGB/LHB* gene cluster with fertility and the fact that it is located in a region under natural selection, an influence of genetic variants in this gene cluster on lifespan would have been expected. This, however, was not the case. Likewise, an effect on mortality would have been expected for the *FSHR* gene variants since SNPs in *FSHR* have been associated with hypertension (Nakayama et al. 2006), bone mineral density

(Rendina et al. 2010), and ovarian cancer (Yang et al. 2006). In this study, however, genetic variants in *FSHR* gene influenced only fertility and not mortality, suggesting that the effect of *FSHR* gene variants on the other phenotypes is not fatal.

In exploring the relationship between fertility and lifespan, we selected candidate genes that have been shown to be involved in fertility. Another approach would be to select genes that have been associated with lifespan and assess their influence on fertility. This approach was recently applied in a study analyzing the influence of *ACE*, *PON1*, *PPARG*, and *APOE* genes on fertility in 151 healthy unrelated subjects in post-reproductive age (Corbo et al. 2008). It was found that *APOE*\*2 allele results in a trade-off with fertility whereas the *PPARG* Pro/Ala genotype contributes to beneficial effects both in early and in late life in a gender-specific way. These results warrant further research in analyzing candidate longevity genes in relation to fertility.

A strength of the current study is the large study population with a long follow-up time for mortality. In addition, the availability of genome-wide genetic data enabled us to investigate all to date known common genetic variants in the selected candidate genes. Another strength includes the fact that a contemporary population was analyzed, which is less selected than those used in historical studies (Hurt et al. 2006). Furthermore, in contemporary populations, data on birth and death dates and on the number of children are likely to be more accurate than for historical populations. On the other hand, the use of a contemporary population poses also a problem due to the use of birth control. Therefore, the reported fertility would not entirely reflect natural fertility. However, participants of this population were fertile before the use of oral contraceptives became widespread. In addition, we were able to adjust for the year of birth, which should account for the differences in fertility patterns over the years. A more likely source of bias would be the self-reported age at menarche and at menopause since older women may not accurately recall these ages.

In conclusion, in this study, we observed that women who bear fewer children are predicted to live longer than those who bear none or many children. In addition, we identified a number of SNPs that associate with fertility. Despite that, none of the identified SNPs associated with mortality. In this

study, we selected candidate genes based on their direct role in HPO axis, folliculogenesis, and implantation. It might be that genes influencing fertility indirectly, either through lipid or glucose metabolism, innate immunity, nutrition, or stress, are more likely candidates to affect human lifespan.

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**Competing interests** The authors declare that there are no competing interests associated with this study.

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