


The Influence of Female Reproductive Factors on Longevity: A Systematized Narrative Review of Epidemiological Studies

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Christy Costanian, PhD^{1*} , Raymond Farah, MSc^{2*},
Ray Salameh, BSc³, Brad A. Meisner, PhD¹,
Sola Aoun Bahous, MD, PhD⁴, and Abla M. Sibai, PhD⁵

Abstract

Purpose: This systematized review presents a synthesis of epidemiological studies that examine the association between female reproductive factors and longevity indicators. **Methods:** A comprehensive literature search was conducted using four bibliographic databases: OVID Medline, Web of Science, PubMed, and Google Scholar, including English language articles published until March 2022. Results from the search strategy yielded 306 articles, 37 of which were included for review based on eligibility criteria. Results were identified within the following nine themes: endogenous androgens and estrogens, age at first childbirth, age at last childbirth, parity, reproductive lifespan, menopause-related factors, hormone therapy use, age at menarche, and offspring gender. **Results:** Evidence that links reproductive factors and long lifespan is limited. Several female reproductive factors are shown to be significantly associated with longevity, yet findings remain inconclusive. The most consistent association was between parity (fertility and fecundity) and increased female lifespan. Age at first birth and parity were consistently associated with increased longevity. Associations between age at menarche and menopause, premature menopause, reproductive lifespan, offspring gender and longevity are inconclusive. **Conclusion:** There is not enough evidence to consider sex a longevity predictor. To understand the mechanisms that predict longevity outcomes, it is imperative to consider sex-specific within-population differences.

Keywords

reproductive factors, longevity, female reproductive factors, lifespan

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Introduction

Aging is a natural multidimensional process involving physical, psychological, and social changes, which ultimately affect one's longevity. Intraindividual and inter-individual differences in longevity outcomes can be attributed to the continuous and dynamic process through which a person's biological conditions interact with internal and external factors (Fernández-Ballesteros & Sánchez-Izquierdo, 2019). Women generally have a higher life expectancy than men, on average by 6 to 8 years. In fact, women are more likely to reach age 90 years than men (Austad & Bartke, 2015). Estrogen exposure can explain women's longer survival (Horstman et al., 2012; Muka et al., 2016), as it is

hypothesized that exposure to endogenous hormones reduces overall mortality (Horstman et al., 2012). However, evidence that links reproductive factors and long lifespan remains limited.

¹Faculty of Health, York University, Toronto, ON, Canada

²Lebanese University, Beirut, Lebanon

³University of Balamand, Beirut, Lebanon

⁴Lebanese American University, Beirut, Lebanon

⁵Faculty of Health Sciences, American University of Beirut, Beirut, Lebanon

*These authors contributed equally to this work.

Corresponding Author:

Christy Costanian, Faculty of Health, York University, 4700 Keele Street, Toronto, ON M3J 1P3, Canada.
Email: christycostanian@gmail.com



Female reproductive factors are currently relevant and important given the growing aging population, most of which are female (United Nations, Department of Economic and Social Affairs Population Division, 2015). Moreover, changing trends such as decreasing fertility at younger ages while increasing at older ages are recorded (Beaujouan & Toulemon, 2021). Several reproductive factors, such as a woman's age at first childbirth, parity, age at last reproduction, and ages at menarche and menopause are shown to be associated with longevity (Brandts et al., 2019; Gagnon, 2015; Leridon, 2007; Shadyab, Gass, et al., 2017; Shadyab, Macera, et al., 2017; Tavares, 2017; Wainer-Katsir et al., 2015; Zhang et al., 2019). However, results on these associations remain inconclusive given differences in study design, socio-demographic characteristics of samples used, and confounding factors considered. While animal studies have proven that reproduction is linked to survival (Flatt, 2011), focus on epidemiological literature has been scant and with results inconsistent. As such, this review systematically synthesized and summarized existing epidemiological evidence to elucidate associations between female reproductive factors on longevity outcomes from population-based observational studies.

Methods

Search Strategy

A comprehensive systematic literature search was conducted using four major electronic databases: OVID Medline, Web of Science, PubMed, and Google Scholar. The following combination of key terms were employed: ("longevity" OR "healthy ageing" OR "successful ageing" OR "healthy aging" OR "successful aging" OR "advanced old age" OR "reaching the age of 90" OR "survival to age 90" OR "Age \geq 90" OR "Age \geq 95" OR "Age \geq 85" OR "Age \geq 100" OR "time to death" OR "telomere length" OR "familial longevity") *joined by* "AND" ("female reproductive" AND ("factors" OR "predictors" OR "risk factors" OR "factors associated" OR "determinants" OR "correlates") OR "age at menopause" OR "age at natural menopause" OR "age at surgical menopause" OR "age at menarche" OR "parity" OR "gravidity" OR "age at childbirth" OR "reproductive lifespan" OR "oral contraceptive use" OR "hormone therapy use" OR "hysterectomy" OR "oophorectomy") "NOT" "treatment." Results from the search engines and bibliographic search yielded 306 articles.

Eligibility Criteria

Studies eligible for inclusion were from English language articles with any publication date up until March 2022 that directly and specifically examined the association of one or more female reproductive factors on a

longevity indicator. References lists of relevant studies were hand searched. Studies that evaluated treatment options in relation to lifespan or mortality, assessed the impact of longevity and successful aging on reproductive factors, examined the relationship between comorbidities such as breast cancer or osteoporosis on survivorship, or assessed the quality of life of older women, and anthropological studies were excluded. Also excluded were case series, case reports, and pre-clinical or biomedical studies.

Data Extraction and Analysis

Two authors (CC and RF) performed title/abstract screening and full-text data extraction. An abstraction form was prepared and calibrated between the authors performing the extraction to ensure consistency in pooling these data. Discrepancies regarding the inclusion or exclusion of articles were resolved by discussion until consensus was reached. A total of 37 articles warrant inclusion.

Results

Results of studies found are reported below, in Supplemental Table 1, and organized by nine themes, as follows: endogenous androgens and estrogens, age at first childbirth, age at last childbirth, parity (fertility and fecundity), reproductive lifespan, menopause-related factors, hormone therapy use, age at menarche, and offspring's gender.

Endogenous Androgens and Estrogens

Two papers focused on endogenous hormones' role in female longevity. First, Nieschlag et al. (2003) evaluated androgens and estrogens' role on lifespan beyond age 80 years in a cohort of 292 female singers from North America and Central Europe (Nieschlag et al., 2003). It was found that those with body features mirroring higher testosterone levels (i.e., deeper singing voice, taller height, and increased muscle mass) had a shorter lifespan than women with estrogen-influenced features (i.e., higher singing voice, shorter height, and decreased muscle mass; Nieschlag et al., 2003). However, no information on whether women were receiving any hormone therapy or had taken oral contraceptives was given (Nieschlag et al., 2003). Second, Jaspers et al. (2017) analyzed data from 4,076 postmenopausal women enrolled in the Rotterdam Study and showed that women with longer unopposed endogenous estrogen duration had a 4% increased hazard for all-cause mortality compared to women with shorter exposure to unopposed estrogen (Jaspers et al., 2017). It is worth noting that both studies had small sample sizes and inaccurate methods of measuring estrogen levels, which may have resulted in contradictory findings.

Age at First Childbirth

Most studies reported increased longevity with increased age at first childbirth (Brandts et al., 2019; Grundy, 2009; Jaspers et al., 2017; McArdle et al., 2006; Mirowsky, 2005; Poulain et al., 2016; Shadyab, Gass, et al., 2017; Tabatabaie et al., 2011). However, two studies reported no association between age at first childbirth and longevity (Gagnon et al., 2009; Helle et al., 2005). McArdle et al. (2006), using data from 937 Amish mothers, demonstrated that with every additional year of age at first childbirth a 0.29-year increase in maternal lifespan was attained (McArdle et al., 2006). Further, data from the Women's Health Initiative (WHI) indicated that later age at first childbirth was associated with increased maternal survival among women who had their first birth at 25 or older compared to those with a first birth before 25 (Shadyab, Gass, et al., 2017). Similarly, data from four cohorts of mothers from Norway, USA, England, and Wales, who experienced first childbirth before age 20, found an increased mortality risk (Grundy, 2009). These findings were corroborated by Brandts et al. (2019) in the Netherlands Cohort Study (NLCS), where mothers who gave birth to their first child after age 30, had greater longevity compared to those who gave birth before age 25 (Brandts et al., 2019). Similarly, data from 4,076 postmenopausal women in the Rotterdam Study showed that a later age at first birth (≥ 35 years) was associated with a 1% decrease in mortality risk (Jaspers et al., 2017). Hayward et al. (2015) reported similar findings where earlier age at first childbirth was associated with an increased mortality risk (Hayward et al., 2015). Evidence suggests that delaying childbirth to age 34 might prolong longevity, compared to teenage childbirth, earlier childbirth (before age 25), and childbirth after the age of 40 (Mirowsky, 2005). However, it is important to note that infertility might have led to a delay in first childbirth age and therefore, the independent effect of age at first childbirth cannot be elucidated fully without more information on mothers' fertility.

Age at Last Childbirth

A consistent positive association between later age at last childbirth and longevity was indicated across studies (Brandts et al., 2019; Grundy, 2009; Jaspers et al., 2017; McArdle et al., 2006; Mirowsky, 2005; Poulain et al., 2016; Shadyab, Gass, et al., 2017; Tabatabaie et al., 2011). Jaffe et al. (2015) showed that long-term mortality rates dropped by 16% for last births at ages 40 to 44 and by 42% at age 45 and greater (Jaffe et al., 2015). Similarly, in the Long-Life Family Study cohort on American and Danish women, age at last childbirth after 33 was associated with extended longevity (OR=2.08; 95% CI [1.13, 3.92]) compared to before age 29 (F. Sun et al., 2015). McArdle et al. (2006) found that every 1-year delay in age at last childbirth resulted

in a 0.29-year increase in average maternal lifespan ($p=.001$; McArdle et al., 2006). Moreover, women attaining longevity beyond age 95 was significantly associated with delaying last childbirth to an average age of 32.4 ($p < .0001$; Fagan et al., 2017; Tabatabaie et al., 2011).

Parity (Fertility and Fecundity)

Evidence on the association between parity and longevity is inconsistent. Some studies found that higher parity was associated with decreased longevity (Doblhammer & Oeppen, 2003; Gagnon et al., 2009; Jaspers et al., 2017; Penn & Smith, 2007); other studies showed that any or higher parity was associated with increased lifespan (Kuningas et al., 2011; Lycett et al., 2000; McArdle et al., 2006; Modig et al., 2017; Shadyab, Gass, et al., 2017; Tabatabaie et al., 2011). Yet, other studies did not detect an association (Brandts et al., 2019; Helle et al., 2002, 2005). Using three large cohorts, Gagnon et al. (2009) reported that having an additional child, offered a 1.6%, 3.2%, and 3.1% increase in maternal mortality (Gagnon et al., 2009). Further, a North American cohort study ($N=21,684$) reported that for every added childbirth, there was a 16% increased risk of a reduced lifespan for mothers (HR=1.16; $p < .0001$; Penn & Smith, 2007). Similarly, Doblhammer and Oeppen (2003) showed that with every added child, mothers suffer a 3.8% increase in mortality risk (Doblhammer & Oeppen, 2003). However, Kuningas et al. (2011) showed that women with two to three children had a significantly decreased mortality risk (HR=0.82; 95% CI [0.69, 0.97]) compared to nulliparous women or women with four or more children (Kuningas et al., 2011). Additionally, data from 8,805 participants in the Chinese Longitudinal Survey on Healthy Longevity demonstrated that staying alive above 90 was significantly associated with more late childbirths (Yi & Vaupel, 2004). Also, Shadyab et al. (2017) reported that multiracial women in the WHI with a parity of 2, had increased longevity odds (OR=1.15; 95% CI [1.00, 1.32]) compared to nulliparous women. Specifically, white women with two or more children had increased odds of reaching longevity compared to women with single births (Shadyab, Gass, et al., 2017). Conversely, Jaspers et al. (2017), using data from 4,076 women enrolled in the Rotterdam study, showed that women with one child had a 12% higher mortality risk compared to women with two to three children (HR=1.12; 95% CI [1.01, 1.24]) in the unadjusted analysis (Jaspers et al., 2017). However, after adjusting for multiple confounders, this association disappeared. The relationship between parity and longevity is perplexing without mentioning the effect of socio-economic dimensions such as income, education, and occupation. Evidence showed that wealthier mothers with more children are more likely to live longer than their less wealthy counterparts (Iacobucci, 2019;

Meara et al., 2008; Montez & Zajacova, 2014). Therefore, future studies should incorporate socio-economic fertility into their analyses.

Reproductive Lifespan

Reproductive lifespan is defined as age at menopause minus age at menarche. Data from the WHI revealed a significant positive association between a prolonged reproductive lifespan and longevity (Shadyab, Macera, et al., 2017). Compared to a reproductive lifespan of <33 years, women with reproductive lifespans of 33 to 37, 38 to 40, and >40 years had the following odds of attaining longevity: OR=1.09 (95% CI [0.99, 1.20]); OR=1.17 (95% CI [1.06, 1.29]); and OR=1.12 (95% CI [1.02, 1.24]), respectively (Shadyab, Macera, et al., 2017). However, in a Chinese cohort, women with a reproductive lifespan of <27.11 years had a reduced risk of developing gynecologic cancers (HRs=0.66; 95% CI [0.4, 1.11] and HR=0.84; 95% CI [0.52, 1.35]), compared to women with a reproductive lifespan between 32.46 to 34.86 and \geq 34.87 years (Wu et al., 2014). It is noteworthy that the effect of childbearing on lifespan might be inaccurately reported or underestimated in the studies reported here as none accounted for pregnancy losses (stillbirths, abortions, or miscarriages) experienced by some women, except (Shadyab, Macera, et al. (2017; Shadyab, Gass, et al., 2017). Nonetheless, in a case-control study on Canadian women, Hanna et al. (2009) showed that women with three miscarriages had shorter telomere length compared to healthy women ($p=.0004$) and women with successful pregnancies after age 37 ($p=.02$; Hanna et al., 2009). Telomeres are repetitive DNA sequences that cap the ends of the short and long arms of chromosomes and stabilize DNA. Telomeres predict aging of somatic cells whereby the length of the telomere shortens with each round of replication which progressively destabilizes the chromosome of a cell, leading to apoptosis and senescence (Aubert & Lansdorp, 2008; Shay, 2018; Turner et al., 2019). The rate of reproductive aging in women is determined by telomere length, which has also been linked to multiple psychological and physiological stress factors, that will influence longevity (Shammas, 2011; Starkweather et al., 2014; Q. Sun et al., 2012).

Menopause-Related Factors

Available literature indicates that menopause at a later age increases longevity (Jacobsen et al., 2003; Ossewaarde et al., 2005; Shadyab, Gass, et al., 2017; Shadyab, Macera, et al., 2017; Wu et al., 2014), except the Netherlands cohort study that reported no association (Brandts et al., 2019). Nilson et al. (2003) found that healthy females and females who underwent early (age 20–30 years) surgical menopause in Sweden, had the same life expectancy (until age 75), concluding that longevity was not impacted by the earlier loss of sexual hormones and fertility (Brandts et al., 2019). However,

women in the WHI who experienced later surgical and natural menopause had longevity beyond 90 years (Brandts et al., 2019). Specifically, when compared to women who attained menopause before age 40, women who had their natural menopause at the ages of 50 to 54 and \geq 55 had increased odds of attaining longevity with (OR=1.19; 95% CI [1.04, 1.36]) and (OR=1.18; 95% CI [1.02, 1.36]), respectively. Later age at natural menopause was also found to be associated with longevity past 90 ($p=.02$; Shadyab, Macera, et al., 2017). Similarly, data from 12,000 Dutch women revealed that with every 1-year delay in natural and surgical menopause resulted in a 2% decrease in mortality risk (OR=0.98 per year; 95% CI [0.97, 0.99]; Ossewaarde et al., 2005). Moreover, a 37-year follow-up study on 19,731 Norwegian women revealed a 1.6% reduction in mortality for every 3-year increase in the age of menopause (Jacobsen et al., 2003). This protective effect of later age at menopause diminished with age, as the mortality risk was reduced by 3.7% in women aged less than 70 while only decreased by 1% for women aged 80 or more (Brandts et al., 2019). This finding could be related to the increased age-related mortality risk incurred with advanced age (Jacobsen et al., 2003). Wu et al. (2014) reported similar findings among 31,995 Chinese women, where an earlier age at natural menopause (age < 46.64) was associated with increased mortality risk (HR=1.16; 95% CI [1.04, 1.29]) compared to a later age at natural menopause (Wu et al., 2014). Premature ovarian failure, conversely, was linked with an increased telomere length (Hanna et al., 2009). Meanwhile, in the Shanghai Women's Health Study, Wu et al. (2014) concluded that women with POF had an increased risk of mortality (Wu et al., 2014). Further investigation of the association between POF and longevity is recommended.

Hormone Therapy Use

Hormone therapy (HT) is indicated for women in the menopause transition to relieve vasomotor symptoms (Santen et al., 2010; Stuenkel et al., 2015). HT's role in women's longevity remains unclear (Canderelli et al., 2007; Rozenberg et al., 2013). Studies from Netherlands (Brandts et al., 2019) and California (Paganini-Hill et al., 2006) reported positive associations between HT use and longevity, while the WHI found no association after an 18-year follow-up (Manson et al., 2017). Studies in this review reported that HT use that starts at menopause and extends at least 5 years after menopause onset was associated with greater odds of survival past age 90 (Brandts et al., 2019; Paganini-Hill et al., 2006). A prospective study from the Leisure World Cohort demonstrated that long-term estrogen use exceeding 15 years significantly reduced risk of all-cause mortality (RR=0.83) except in women aged 95 years or more (Paganini-Hill et al., 2006). However, results from the WHI revealed that estrogen and/or progesterone therapies were not significantly associated with all-cause mortality (Manson et al., 2017). These results could be due to the healthy user effect,

whereby samples include individuals who usually adhere to long-term therapies and maintain a healthy lifestyle. Further, most studies in this review did not specify the type or formulation of estrogen or progesterone therapies used.

Age at Menarche

The relationship between age at menarche and longevity in women is inconclusive. Some studies show that menarche at 13.2 years on average live more than 95 years (Tabatabaie et al., 2011), while others reported weak associations between early menarche and longevity (Shadyab, Macera, et al., 2017; Wu et al., 2014), or no association (Brandts et al., 2019). However, earlier age at menarche (<14 years) was associated with increased mortality risk from stroke and diabetes (OR = 1.23; 95% CI [0.93, 1.62]) and (OR = 1.27; 95% CI [0.81, 1.99]), respectively (Wu et al., 2014).

Gender of Offspring

Several studies reported inconclusive results on the association between offspring gender and maternal longevity (Beise & Volland, 2002; Cesarini et al., 2007; Helle et al., 2002; Jasienska et al., 2006; McArdle et al., 2006; Modig et al., 2017; Pham-Kanter & Goldman, 2012; Poulain et al., 2016). Analyses conducted on an Amish cohort ($N=937$), a Swedish-Nordic cohort ($N=725,290$), the Chinese Longitudinal Healthy Longevity Survey (CLHLS), and the Taiwan Longitudinal Study of Aging (TLISA) indicated no association between offspring gender and maternal longevity (McArdle et al., 2006; Modig et al., 2017; Pham-Kanter & Goldman, 2012). Yet, data from Krummhorn and Quebec pre-modern cohorts revealed no association between male offspring number and decreased maternal lifespan in the Krummhorn cohort, whereas female offspring number extended maternal lifespan in the Quebec cohort (Beise & Volland, 2002). Cesarini et al. (2007) studied a pre-modern Swedish cohort of 3,549 families and found no association between offspring gender and maternal lifespan (Cesarini et al., 2007). However, Helle et al. (2002) reported a 34-week reduction in lifespan per son born only. Meanwhile, in a cohort of women in Sardinia ($N=539$), sons born to mothers after age 35 years were associated with higher survival (Poulain et al., 2016). Jasienska et al. (2006) was the only study to find that having both sons and daughters was associated with a decrease in maternal lifespan (Jasienska et al., 2006).

Commentary

Age at first birth and parity were consistently associated with increased longevity. Future studies on the role of ages at menarche, premature menopause, and reproductive lifespan on maternal longevity are warranted

given inconsistent findings. Nevertheless, the evidence presented here showed consistent associations between age at menopause, age at first childbirth, and parity with longevity outcomes. Delayed menopause's procreative benefits provide the mother with the ability to carry a child to term at a later age, representing good maternal health. Thus, delayed childbearing and extended fertility might reflect a healthier mother leading to increased longevity. Additionally, the relationship between reproductive factors and telomere length has not been fully investigated. Whether offspring gender is related to maternal lifespan also remains equivocal. Further studies are also needed to examine the relationship between endogenous and exogenous hormones and longevity. It is important to mention that the total number of children may not truly describe fertility given that whether a woman is multiparous or nulliparous does not reflect her biological fertility, especially with the advent of assisted reproductive technology (ART). ART use among women might confound gravidity and parity in the relation with longevity since infertile women are at a higher risk of adverse health conditions (Braat et al., 2010; Gelbaya, 2010; Venn et al., 2001; Zollner & Dietl, 2013). Therefore, future studies examining the association between fecundity and longevity should consider ART's role. The disposable soma theory posits that high fertility is associated with decreased lifespan, since reproduction deprives organisms of resources required for self-maintenance. Female reproductive factors with their physical stressors, have a consistent impact on longevity as demonstrated by this review's results. However, longevity is a multifactorial and pleiotropic trait and so, unrecognized genetic factors such as accumulation of mutations may also be responsible for increased maternal longevity (Cawthon et al., 2020). Therefore, both theories and other theories may offer potential explanations to findings reported here. Results presented here should be considered with some limitations and strengths. Retrospective cohorts could be problematic due to recall bias. Additionally, studies employed different longevity definitions, or different intervals and cut-offs for parity and ages at last birth, first birth, menopause and menarche, therefore making decreasing comparability across studies. Most studies in this review were based on Western and Caucasian samples hence, more research using multi-national and multiethnic samples from Asia, Africa, and Latin America is needed. The main strengths include prospective designs, large samples, and adjustment for potential confounders.

In conclusion, since longevity might be linked to different reproductive factors that in turn, are influenced by health behaviors and socioeconomic dimensions, future research must consider context when assessing factors associated with longer maternal lifespan. Associations between age at menarche and menopause, premature menopause, reproductive lifespan, offspring gender, and longevity outcomes are inconclusive (Figure 1).

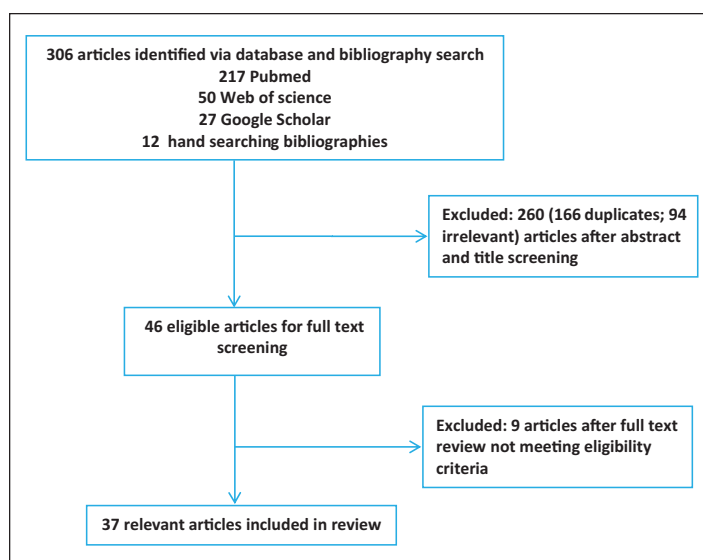


Figure 1. Study flow chart.

Author Contributions

CC was responsible for the conception of the study, conducted the literature search and review and revised the manuscript for critical content. RF conducted the literature search and review and drafted and revised the manuscript. RS, SAB, BM, and AMS contributed to the critical revision of the manuscript for important intellectual content. All authors have read and approved the final manuscript.

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ORCID iD

Christy Costanian  <https://orcid.org/0000-0003-4395-7278>

Supplemental Material

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