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Original Article

Reproductive epidemiology

Time to pregnancy and life expectancy: a cohort study of 18 796 pregnant couples

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ABSTRACT

STUDY QUESTION: Is fecundity, measured as time to pregnancy (TTP), associated with mortality in parents?

SUMMARY ANSWER: Prolonged TTP is associated with increased mortality in both mothers and fathers in a dose–response manner.

WHAT IS KNOWN ALREADY: Several studies have linked both male and female fecundity to mortality. In women, infertility has been linked to several diseases, but studies suggest that the underlying conditions, rather than infertility, increase mortality.

STUDY DESIGN, SIZE, DURATION: A prospective cohort study was carried out on 18 796 pregnant couples, in which the pregnant women attended prophylactic antenatal care between 1973 and 1987 at a primary and tertiary care unit. The couples were followed in Danish mortality registers from their child's birth date until death or until 2018. The follow-up period was up to 47 years, and there was complete follow-up until death, emigration or end of study.

PARTICIPANTS/MATERIALS, SETTING, METHODS: At the first antenatal visit, the pregnant women were asked to report the time to the current pregnancy. Inclusion was restricted to the first pregnancy, and TTP was categorised into <12 months, ≥12 months, not planned, and not available. In sub-analyses, TTP ≥12 was further categorized into 12–35, 36–60, and >60 months. Information for parents was linked to several Danish nationwide health registries. Survival analysis was used to estimate the hazard ratios (HRs) with a 95% CI for survival and adjusted for age at the first attempt to become pregnant, year of birth, socioeconomic status, mother's smoking during pregnancy, and mother's BMI.

MAIN RESULTS AND THE ROLE OF CHANCE: Mothers and fathers with TTP >60 months survived, respectively, 3.5 (95% CI: 2.6–4.3) and 2.7 (95% CI: 1.8–3.7) years shorter than parents with a TTP <12 months. The mortality was higher for fathers (HR: 1.21, 95% CI: 1.09–1.34) and mothers (HR: 1.29, 95% CI: 1.12–1.49) with TTP ≥12 months compared to parents with TTP <12 months. The risk of all-cause mortality during the study period increased in a dose–response manner with the highest adjusted HR of 1.98 (95% CI: 1.62–2.41) for fathers and 2.03 (95% CI: 1.56–2.63) for mothers with TTP >60 months. Prolonged TTP was associated with several different causes of death in both fathers and mothers, indicating that the underlying causes of the relation between fecundity and survival may be multi-factorial.

LIMITATIONS, REASONS FOR CAUTION: A limitation is that fecundity is measured using a pregnancy-based approach. Thus, the cohort is conditioned on fertility success and excludes sterile couples, unsuccessful attempts and spontaneous abortions. The question used to measure TTP when the pregnant woman was interviewed at her first attended prophylactic antenatal care: 'From the time you wanted a pregnancy until it occurred, how much time passed?' could potentially have led to serious misclassification if the woman did not answer on time starting unprotected intercourse but on the start of wishing to have a child.

WIDER IMPLICATIONS OF THE FINDINGS: We found that TTP is a strong marker of survival, contributing to the still-emerging evidence that fecundity in men and women reflects their health and survival potential.

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Introduction

There is strong evidence of declining reproductive health in humans, which, together with behavioural factors, is contributing to the world's declining fertility (Skakkebæk et al., 2021) and thus also to the soon-expected decreasing world population (Vollset et al., 2020). This may be partially explained by the fact that an unhealthy person (i.e. having a disease) may experience fertility problems. As such, reproductive health measures, such as semen quality, ovarian reserve, or time to pregnancy (TTP), are also possible markers of health and later survival.

Here, we consider fertility as proven fecundity measured by births and fecundity as the individual's biological ability to reproduce irrespective of pregnancy intentions (Smarr et al., 2017). TTP is a commonly used population measure of fecundity, the final common path of numerous biological mechanisms in both sexes in the couple. TTP is defined as the time to success to conceive under unprotected intercourse and is generally a well recalled sensitive measure of fecundity in both women and men (Zielhuis et al., 1992; Joffe et al., 1995). Age is the single most important factor for fecundity in both women (Steiner and Jukic, 2016; Wesselink et al., 2017) and men (Ford et al., 2000; Hassan and Killick, 2003; Martins da Silva and Anderson, 2022). Environmental factors (including lifestyle factors) explain around 70% of impaired fecundity (defined as a TTP > 10 months) in women and 95% in men, leaving 30 and 5%, respectively, for genetic factors (Ahrenfeldt et al., 2020).

Reproductive health measures as possible markers of health and later survival are well-studied in men, where semen quality and infertility diagnosis (inability to conceive within 12 months of unprotected attempting (Smarr et al., 2017)), have been linked to both health and mortality (Jacobsen et al., 2000; Jensen et al., 2009; Walsh et al., 2010; Eisenberg et al., 2013, 2015; Latif et al., 2017). The phenomenon is less studied for women, most probably because suitable reproductive health measures comparable to semen quality are not readily available. Most studies have thus instead examined the effect of infertility, measured as the inability to conceive within 1 year of unprotected attempt (Smarr et al., 2017), on survival and health (Murugappan et al., 2021; Huttler et al., 2023). Of the few previous studies (Stentz et al., 2020; Ahrenfeldt et al., 2021; Wang et al., 2022) on the association between TTP and parental survival, most had a relatively short follow-up (Stentz et al., 2020; Wang et al., 2022), thus addressing premature deaths. Our previous study on survival (Ahrenfeldt et al., 2021) had 24 years of follow-up. Still, TTP was retrospectively reported in a twin survey, thus conditioning on survival to a mean age of 58.6 years, which also increased the risk of recall bias for TTP.

Here, we avoid the limitations of the previous studies by prospectively examining fecundity proxied by TTP for couples and its possible influence on overall and cause-specific mortality for up to 47 years of follow-up. This will reduce recall bias on TTP, remove survival bias and result in less selection for age-related causes of death, as seen in many other studies with shorter follow-ups.

Materials and methods

Setting and study population

The Odense Pregnancy Cohort contains information on all pregnant women who attended prophylactic antenatal care between 1973 and 1987 at the Department of Gynecology and Obstetrics at Odense University Hospital in Denmark (Jensen et al., 2000). Some women had multiple pregnancies during the study period. Still, only first-time pregnancies were included in the present study (N = 18 795) based on demographic parity information from the Danish Medical Birth Registry (Bliddal et al., 2018). Information on reproduction, including TTP and medical, occupational, and lifestyle information, was collected as a part of the first routine antenatal examination as described previously (Jensen et al., 2000). In short, the information was recorded at the first routine antenatal examination (at the 20th week of gestation) by a medical secretary. The medical secretaries were salaried staff at the hospital clinic. They interviewed the pregnant women and recorded the information on preprinted records. These records were later digitalized (Jensen et al., 2000).

In Denmark, all residents are assigned a unique personal identification number at birth (CPR), registered in the Danish Civil Registration System (Pedersen, 2011) that can be used to link to all other individual-level Danish registries. The CPR number of the mother was used to identify the biological father of the child by identifying children of the mothers in the Danish Medical Birth Registry, which contains information on all births in Denmark since 1973 and their biological parents (Bliddal et al., 2018). In the Danish Medical Birth Registry, the biological father is self-reported by the child's mother. The final dataset contained information on deaths and causes of death for mothers and fathers until and including January 2018 and December 2016, respectively.

Exposure assessment

The exposure of interest was fecundity, measured as TTP, restricted to the first pregnancy as found by linkage to the Danish Medical Birth Registry (Bliddal et al., 2018). TTP was based on the following question: 'From the time you wanted a pregnancy until it occurred, how much time passed?' and the answer was recorded in months (Jensen et al., 2000). In total, TTP was reported by 16075 mothers (85.5%). TTP was categorized as follows: <12 months, ≥12 months, 'not planned', and 'not available' (TTP not reported). The not planned group consisted of women who did not know their waiting time or became pregnant despite contraception. The 'not available' group was excluded from the analysis. In sub-analyses of dose–response relations, TTP ≥12 was further categorized into 12–35, 36–60, and ≥60 months.

Outcome assessment

The survey data from the Odense Pregnancy Cohort was linked with the Danish Civil Registration System to identify deaths and migrations and to the Danish Register of Causes of Death (Helweg-Larsen, 2011). It was possible to follow-up for total mortality from 1 January 1973 to 31 January 2018 and for causes of death from 1 January 1973 to 1 January 2017. To suggest possible risk factors influencing the association between TTP and survival, we subdivided the total mortality into causes of death. This approach has been widely used by calculating attributable risk factors for specific causes of death and especially for cancer-specific mortality, with the potential to bring new insight into risk factors acting (Brown et al., 2018; Islami et al., 2018; Tran et al., 2022; Tybjerg et al., 2022). In the cause of death analyses, 18 359 mothers and fathers were followed up, and the causes of death were categorized into seven groups based on a 49-item list of four-digit International Classification of Disease (ICD)8 and ICD10 from the Danish Register of Causes of Death (Helweg-Larsen, 2011). Neoplasms as the cause of death were further investigated by dividing the category into specific types of cancer.

Covariate assessment

All analyses were adjusted for available potential confounders, including age at the first attempt to become pregnant (Crawford and Steiner, 2015), year of birth, socioeconomic status (Schrager *et al.*, 2020), mother's smoking during pregnancy (Augood *et al.*, 1998), and mother's BMI (Wise *et al.*, 2010). The reason for adjusting for maternal factors when addressing paternal effects was the lack of information on these paternal factors and that partners are often similar in terms of their physical and behavioural traits (Sjaarda and Kutalik, 2023). Mothers smoking during pregnancy was used as a proxy for smoking behaviour prior to pregnancy as studies have shown that most of those women who smoked before pregnancy continue to smoke during pregnancy or quit smoking after becoming pregnant (Jaddoe *et al.*, 2008; Liu *et al.*, 2020). Age at first birth was divided into six groups: <20, 20–24, 25–29, 30–34, 35–39, and >40 years. The birth year was divided into <1939 followed by 5-year groups between 1940 and 1969. Both parents' socioeconomic status based on working codes from Statistics Denmark (Statistics Denmark, 2023) were categorized as the following positions: administration, farming, industry, office, research and technology, sale, service, and unemployed or housewife. Information on smoking status during pregnancy (yes/no) and pregestational BMI was self-reported. The BMI cut-off points were based on World Health Organization guidelines (WHO, 2023) and were categorized into <18.5 (underweight), 18.5–25 (normal weight), and >25 kg/m^2 (overweight/obese).

Statistical analysis

Follow-up of mothers and fathers started from the child's birth date until whichever came first: emigration, end of the study, or death. This was chosen rather than from the start of the pregnancy attempt as this would have induced immortality of the participants until the birth of the child, with more immortality time for those with a longer TTP. This approach compensated the potential older age of those with longer TTP by the age adjustment in all adjusted analyses. Absolute measures of years lost in survival were estimated using restricted mean survival time (RMST) (Tian *et al.*, 2013) for each TTP group. RMST corresponds to the area under each survival curve for each TTP and corresponds to the expected survival time. If all ages were included, RMST would correspond to life expectancy at birth, but here it corresponds to the years lost only within the examined age spans.

The relative associations between TTP and death or cause of death were addressed using Cox regression with adjustment for the available potential confounders. Missing values in each covariate were treated as a separate category in the analysis. This strategy was chosen given the low influence of the covariates on the association between TTP and mortality (Supplementary Fig. S1). Owing to a low number of cases in the sub-analysis of causes of death, these analyses could solely be adjusted for age and birth year. A score process test (Lin *et al.*, 1993) was used to test the Cox proportional hazard assumption of proportional hazards, which was fulfilled in all analyses. All hazard ratios (HRs) are presented with a 95% CI. Separate models were regressed for the groups with planned and unplanned pregnancies. Analyses were performed using SAS 9.4 (SAS Institute Inc, 2014).

Results

Baseline characteristics

A total of 18 795 mothers and fathers had their first child between 1973 and 1988 at Odense University Hospital. Among parents with a reported TTP, 14 530 (83%) reported that the child was conceived within the first 11 months and 3014 (17%) after (Table 1). During the 47-year follow-up period, 4445 (24%) deaths occurred, of which 1509 (34%) were in mothers and 2936 (66%) in fathers. The median time of follow-up was 38 years (interquartile range: 34 to 43 years). Compared to parents with a TTP <12 months, a larger proportion of mothers and fathers with a TTP ≥12 months died. There was an increase in the proportion of deaths by decreasing birth year and increasing age. A higher proportion of both mothers and fathers died if the mother smoked during pregnancy. In contrast, no systematic pattern was observed between working positions or BMI of the mother and mortality (Table 1).

Overall mortality

TTP was associated with both absolute and relative survival. The years lost in survival increased with TTP (Fig. 1, Supplementary Fig. S2). The largest difference in RMST for mothers was 3.5 years (95% CI: 2.6–4.2) between mothers with a TTP <12 months and mothers with a TTP >60 months. The corresponding number for fathers was 2.8 years (95% CI: 1.8–3.7). A longer TTP was associated with increased mortality (Fig. 2). Adjusted risk of all-cause mortality during the study period was higher for mothers and fathers with a TTP ≥12 months than for mothers and fathers with a TTP <12 months (Fig. 2A). Mortality for parents with not-planned pregnancies did not differ from those with a TTP <12 months, although parents with non-planned pregnancies had an increased mortality. The mortality increased with increasing TTP in a dose–response-like manner for both mothers ($P_{trend} < 0.001$) and fathers ($P_{trend} < 0.03$) (Fig. 2B). The highest mortality was observed for parents with TTP > 60 months: For mothers the HR was 2.03 (95% CI: 1.56–2.63) and for fathers the HR was 1.43 (95% CI: 1.15–1.77), when compared to mothers and fathers with a TTP <12 months. The effect of adjustment for covariates on the risk of all-cause mortality during the study period was minor (Supplementary Fig. S1).

Cause-specific mortality

Higher mortality risk during the study period was found for specific causes of death for a TTP ≥12 months compared to <12 months (Table 2). For mothers, positive associations between TTP and the specific cause of death were present for most causes of death (Table 2). Among these causes, the strongest positive associations were found for diseases in the digestive system: HR: 1.75 (95% CI: 1.07–2.84), and for other causes: HR: 1.56 (95% CI: 1.07–2.27). Less positive associations were present for diseases in the circulatory system: HR: 1.45 (95% CI: 1.00–2.12) and for neoplasms: HR: 1.19 (95% CI: 1.00–1.45). Fewer positive associations were found for fathers than mothers (Table 2). The causes in fathers with positive associations were diseases of the circulatory system: HR: 1.51 (95% CI: 1.21–1.89) and neoplasms: HR: 1.45 (95% CI: 1.23–1.70). For the remaining causes of death in fathers, the associations were weaker and closer to the null value of 1 (i.e. respiratory system, digestive system, symptoms/senile, external causes and other causes).

The sub-analysis of causes of death from neoplasms showed an increased risk for mothers and fathers with a TTP ≥12 months compared to mothers with a TTP <12 months (Table 2). For mothers, strong positive associations were present for malignant neoplasm of the larynx, trachea, bronchus, and lung: HR: 3.35 (95% CI: 2.30–4.89) and for malignant neoplasm of other and unspecified sites: HR: 2.40 (95% CI: 1.68 to 3.44). Positive but weaker associations and with less precise estimates were present for malignant neoplasms of bone and skin: HR: 2.1 (95% CI: 0.58–

Table 1. Characteristics of pregnancies and number of parental deaths among 18795 couples with a firstborn child at Odense University Hospital between 1972 and 1987.

	Mothers		Fathers	
Characteristics	N[1] (%) 18795	Deaths (%) 1509 (34.0)	N[1] (%) 18795	Deaths (%) 2936 (66.0)
Time to pregnancy, months				
0–11	13061 (69.5)	963 (7.4)	13061 (69.5)	1928 (14.8)
≥12	3014 (16.0)	315 (10.5)	3014 (16.0)	565 (18.8)
12–35	2050 (10.9)	170 (8.3)	2050 (10.9)	348 (17.0)
36–59	510 (2.7)	60 (11.8)	510 (2.7)	102 (20.0)
≥60	454 (2.4)	85 (18.7)	454 (2.4)	115 (25.3)
Not planned	1469 (7.8)	126 (8.6)	1469 (7.8)	241 (16.4)
Not available	1251 (6.7)	105 (8.4)	1251 (6.7)	202 (16.1)
Birth year, mean (SE)	***1954.94 (0.04)***		***1952.16 (0.05)***	
≤1939	–	–	881 (4.7)	273 (31.0)
1940–1944	615 (3.3)	142 (23.1)	1305 (7.0)	381 (29.2)
1945–1949	2619 (13.9)	296 (11.3)	4150 (22.1)	802 (19.3)
1950–1954	5478 (29.2)	519 (9.5)	5728 (30.5)	857 (15.0)
1955–1959	5848 (31.1)	374 (6.4)	4536 (24.1)	451 (9.9)
1960–1964	3479 (18.5)	155 (4.5)	1903 (10.1)	151 (7.9)
1965–1969	756 (4.0)	23 (3.0)	292 (1.6)	21 (7.2)
Age (y) at start of TTP, mean (SE)	***24.67 (0.03)***		***26.96 (0.04)***	
<20	2018 (10.7)	177 (8.8)	519 (2.8)	72 (6.4)
20–24	8845 (47.1)	635 (7.2)	5597 (29.8)	760 (11.2)
25–29	6065 (32.3)	438 (7.2)	7788 (41.4)	1041 (14.2)
30–34	1497 (8.0)	173 (11.6)	3111 (16.6)	593 (23.8)
35–39	322 (1.7)	67 (20.8)	967 (5.2)	253 (34.7)
≥40	48 (0.3)	19 (39.6)	433 (2.3)	217 (61.8)
Missing	–	–	380 (2.0)	–
Mothers smoking during pregnancy				
Yes	7524 (40.0)	900 (12.0)	7524 (40.0)	1430 (19.0)
No	10122 (53.9)	480 (4.7)	10122 (53.9)	1293 (12.8)
Missing	1149 (6.1)	129 (11.2)	1149 (6.1)	213 (18.5)
Working position during the pregnancy				
Administration	3302 (17.6)	243 (7.36)	1055 (5.6)	145 (13.7)
Farming	1803 (9.6)	202 (11.2)	4739 (25.2)	712 (15.0)
Industry	1599 (8.5)	132 (8.3)	435 (2.3)	78 (17.9)
Office	1327 (7.1)	109 (8.2)	767 (4.1)	106 (13.8)
Research and technology	5248 (27.9)	365 (7.0)	2637 (14.0)	362 (13.7)
Sale	1592 (8.5)	143 (9.0)	376 (2.0)	46 (12.2)
Service	243 (1.3)	12 (4.9)	496 (2.6)	58 (11.7)
Unemployed or housewife	1088 (5.8)	119 (10.9)	NA[a]	NA[a]
Missing	2593 (13.8)	184 (7.1)	8281 (44.1)	1429 (17.3)
Mother's BMI before pregnancy, kg/m^2 mean (SD)	***21.22 (0.02)***		***21.22 (0.02)***	
<18.5	1834 (9.8)	170 (9.3)	1834 (9.8)	308 (16.8)
18.5–25	11200 (59.6)	909 (8.1)	11200 (59.6)	1751 (15.6)
>25	1251(6.7)	121 (9.7)	1251(6.7)	227 (18.2)
Missing	4510 (24.0)	309 (6.9)	4510 (24.0)	650 (14.4)

[1] Analyses of 18795 couples with a firstborn child at Odense University Hospital between 1972 and 1987.
[a] Not available as the number is too low to report according to data protection rules in Denmark (number below 3).
TTP: time to pregnancy.

7,44), leukaemia and other neoplasms of lymph and haematoid tissue: HR: 1.6 (95% CI: 0.60–4.44), and malignant neoplasm of the breasts: HR: 1.54 (95% CI: 0.96–2.46). For the remaining cancer-specific causes in mothers, the estimates showed weaker associations and were closer to the null value (malignant neoplasm of buccal cavity and pharynx, malignant neoplasm of stomach, malignant neoplasm of intestine except rectum, malignant neoplasm of rectum and rectosigmoid junction, and malignant neoplasm of cervix uteri). For fathers, there were strong positive associations with malignant neoplasms of the buccal cavity and pharynx: HR: 2.25 (95% CI: 1.37–3.72), leukaemia and other lymph and haematology tissue: HR: 1.74 (95% CI: 1.03 to 2.92). Positive associations were also found for malignant neoplasm of the stomach: HR: 2.29 (95% CI: 0.98–5.38) and rectum and rectosigmoid junction: HR: 1.91 (95% CI: 0.96–3.81), but the estimates showed low precision. A weaker but more precise association was found for malignant neoplasms of other unspecified sites: HR: 1.47 (95% CI: 1.10–2.0). Weaker associations closer to the null value were present for fathers for the remaining cancer-specific causes, namely malignant neoplasm of the larynx, trachea, bronchus, and lung, malignant neoplasm of prostate and malignant and neoplasms of bone and skin.

Discussion

In this large population-based cohort study of mothers and fathers, prolonged TTP was associated with increased mortality in a dose–response-like manner. Taking more than 12 months to conceive (i.e. the cut-off point for clinical infertility) increased mortality in both fathers and mothers, and the explanatory causes of death were manifold. Prolonged TTP (i.e. a proxy for reduced fecundity) appears to be a general marker of survival.

Our findings validate our previous findings (Ahrenfeldt et al., 2021) and support the association between fecundability

(measured as TTP) and survival, with lower survival for lower fecundability. Contrary to the previous study, we followed the couples prospectively for mortality from the birth date of the child, whereas the former study was conditioned on survival and had a long recall time for TTP in the participants. However, despite the differences in the study designs, the consistency in findings between studies supports the hypothesis that reduced fecundity is a marker of general health and disease, and supports the validity of the present study.

Many factors may influence the observed positive association between TTP and mortality, including lifestyle, socioeconomic, and environmental factors. The causes of death analysis could suggest possible factors influencing the association between TTP and mortality observed in the present study. Overall, our results indicate that persons with TTP ≥12 die more often from lifestyle-related causes of death, clearly indicated by the stronger association with deaths from malignant neoplasm of the larynx, trachea, bronchus, and lung (smoking-related) in mothers and malignant neoplasm of buccal cavity and pharynx (alcohol) in fathers (Tybjerg *et al.*, 2022). Most lifestyle factors may influence TTP, including smoking (Radin *et al.*, 2014), alcohol (Fan *et al.*, 2017), physical activity (Russo *et al.*, 2018), and diet (Grieger *et al.*, 2018). Thus, lifestyle factors fulfil the criteria for influencing the association between longer TTP and mortality observed in the presented study. It is also well known that socioeconomic factors, with lifestyle factors as possible mediators (up to 66% of the effect is mediated by lifestyle factors in men and 80% in women (Puka *et al.*, 2022)), or the socioeconomic factors themselves (Stringhini *et al.*, 2017), can influence premature mortality and cause-specific mortality, including deaths from cardiovascular diseases (CVDs) and cancer. The studies on the association between socioeconomic factors and TTP are more limited but suggest an association (Rachootin and Olsen, 1982; Schrager *et al.*, 2020; Jørgensen *et al.*, 2023). As such, various socioeconomic factors could contribute to explaining the association found in the presented study for the increased risks of specific cause-specific deaths. Further, environmental factors influence fecundity (Skakkebæk *et al.*, 2021), cause-specific mortality, and total mortality (Prüss-Ustün *et al.*, 2006), thus additionally having a possible influence on the observed associations between TTP and mortality. Surely, temporality (e.g. we do not know if the factors causing an increased risk of death acted after the measure of TTP) is a problem for the causes of death analysis in our study. Also, it is impossible to pinpoint precisely which factors or combinations act on the specific cause of death. Therefore, the results should be viewed in this perspective.

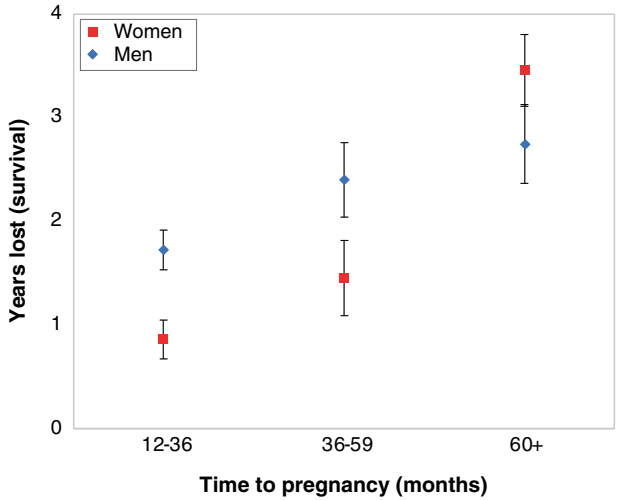

Figure 1. Years lost in survival for first-time mothers and fathers for categories of time to pregnancy (reference group <12 months). Error bars are 95% CIs.

Deaths from CVD have a strong lifestyle component (Colpani *et al.*, 2018; Zhang *et al.*, 2021), including smoking, diet, alcohol consumption, and inactivity (Zhang *et al.*, 2021) and are influenced by both socioeconomic factors (Stringhini *et al.*, 2017) and environmental factors (Prüss-Ustün *et al.*, 2006). In the present study, the causes-of-death analysis showed a positive association between prolonged TTP and cause-specific deaths related to diseases of the circulatory system in mothers (50% increased risk) and fathers (50% increased risk). We have only been able to find one study which examined an association between subfecundity, subfertility, or infertility and the risk of cardiovascular deaths (Stentz *et al.*, 2020), but several studies reporting on the risk of CVDs (Parikh *et al.*, 2012; Bosdou *et al.*, 2020; Magnus *et al.*, 2021; Skåra *et al.*, 2022). A US study found a 7% not significantly increased risk of CVD deaths among infertile women when they followed up with participants in a cancer screening programme for 10 years. In a Norwegian study, a weak association between TTP and the risk of early onset CVD (the average maximum age for follow-up was 51 years) was found (6–7% increased risk) and mainly from the category 'other causes of CVD' (Magnus *et al.*,

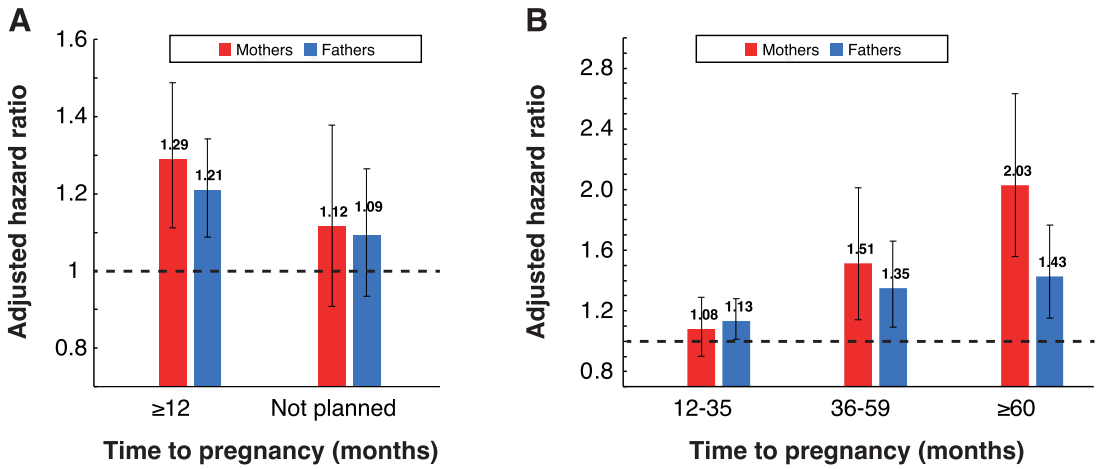

Figure 2. Adjusted hazard ratios for first-time mothers and fathers with time to pregnancy ≥12 months and with unplanned pregnancies (reference group <12 months). All hazard ratios were adjusted for age, birth year, working position, mother's smoking during pregnancy, and mother's BMI.

Table 2. Cause-specific risk of parental death and 95% CIs based on Cox regression analysis for 18 795 first-time mothers and fathers with >12 months time to pregnancy.*

Causes of death	Mothers		Fathers	
	Number of deaths	Adjusted Hazard ratio (95% CI)[1]	Number of deaths	Adjusted Hazard ratio (95% CI)[1]
Neoplasms	656	1.19 (0.97–1.45)	910	1.44 (1.23–1.70)
Malignant neoplasm of buccal cavity and pharynx	21	0.93 (0.20–4.15)	73	2.25 (1.37–3.72)
Malignant neoplasm of stomach	7	–	26	2.29 (0.98–5.38)
Malignant neoplasm of intestine, Except rectum	40	1.32 (0.56–3.11)	63	1.59 (0.88–2.87)
Malignant neoplasm of rectum and rectosigmoid junction	21	0.81 (0.18–3.56)	43	1.91 (0.96–3.81)
Malignant neoplasm of larynx, trachea, Bronchus and lung	161	3.35 (2.30–4.89)	247	1.15 (0.83–1.61)
Malignant neoplasm of bone and skin	18	2.08 (0.58–7.44)	38	0.98 (0.40–2.41)
Malignant neoplasm of breast	150	1.54 (0.96–2.46)	–	–
Malignant neoplasm of cervix uteri	14	0.73 (0.09–5.77)	–	–
Other malignant neoplasm of uterus	8	–	–	–
Malignant neoplasm of prostate	–	–	43	1.37 (0.66–2.87)
Malignant neoplasm of other and unspecified sites	176	2.4 (1.68–3.44)	272	1.47 (1.10–1.96)
Leukaemia and other neoplasms of lymphoid and haematopoietic tissue	34	1.6 (0.60–4.44)	88	1.74 (1.03–2.92)
Benign neoplasms and neoplasms of unspecific nature	6	–	17	0.26 (0.00–2.00)
Circulatory system	164	1.45 (0.99–2.12)	490	1.51 (1.21–1.89)
Respiratory system	77	1.49 (0.85–2.62)	122	0.96 (0.58–1.57)
Digestive system	97	1.75 (1.07–2.84)	217	1.13 (0.80–1.61)
Symptoms/senile	43	1.16 (0.51–2.61)	127	1.28 (0.81–2.00)
External causes	131	1.26 (0.80–1.99)	408	0.85 (0.64–1.13)
Other causes	166	1.56 (1.07–2.84)	333	0.82 (0.60–1.13)

[1] Adjusted for age at child's birth and year of birth.
* Compared to those with a time to pregnancy of <12 months.

2021). The differences between our results and those of other studies can be explained by the short follow-up in the previous studies capturing early onset CVD, in contrast to our study that also captured later onset CVD. The observed increased risk of death from CVD in the present study supports lifestyle factors (Colpani et al., 2018), socioeconomic factors (Stringhini et al., 2017), and environmental factors as possible causes for the observed association.

We have not found any studies examining the association between TTP and death from digestive diseases, or the incidence of digestive diseases. In the present study, mothers had an increased risk of death from diseases of the digestive system, suggesting a possible influence from lifestyle factors (Li et al., 2014; Corsello et al., 2020; Yuan et al., 2023), socioeconomic factors (Bytzer et al., 2001), and environmental factors (Ananthakrishnan et al., 2018).

The incidence of, and deaths from, many specific cancers have specific lifestyle and environmental components and are particularly useful for addressing these potential risk factors (Anand et al., 2008; Tybjerg et al., 2022). We found that increased mortality was related to cancers in both sexes. Even though our measure was the cause of death, this corresponds well with studies on the association between different measures of subfecundity and the risk of diagnosing a malignant neoplasm (Andarieh et al., 2019; Murugappan et al., 2019; Del Giudice et al., 2020a, 2020b). The previous studies suggest an association between infertility and hormone-related malignant neoplasms in women, including breast, ovarian, and endometrial cancers (Andarieh et al., 2019; Murugappan et al., 2019). In our study, the point estimate showed a 50% increased risk of mortality related to malignant neoplasm of the breast with prolonged TTP but with a low precision of the estimate, thus lending some support for the previous findings. Owing to low numbers, we were not able to address the relation to death with endometrial cancers and ovarian cancers. We also found a strong association with mortality for neoplasm of the larynx, trachea, bronchus, and lung in mothers, suggesting a role of smoking, as smoking explains the major fraction of lung cancers (Jassem et al., 2009; Tybjerg et al., 2022) and these are related to prolonged TTP (Bolumar et al., 1996; Hull et al., 2000; Sapra et al., 2016). Air pollution is potentially associated with TTP (Siegel et al., 2023) and explains a smaller fraction of lung cancer cases (Tybjerg et al., 2022) and may thus contribute to the observed association. The weaker association found for malignant neoplasm of the buccal cavity and pharynx suggest less influence of alcohol consumption on the association between TTP and mortality (Tybjerg et al., 2022). Similarly, the weaker associations found for malignant neoplasm of stomach and malignant neoplasm of cervix uteri suggest less influence of infections (Tybjerg et al., 2022), and the weak association with malignant neoplasm of rectum and rectosigmoid junction suggest less influence of diet in mothers (Tybjerg et al., 2022).

Two systematic reviews, Del Giudice et al. (2020a,b), have reported that male infertility may be associated with a future cancer risk. Most studies focus on male-related cancers, such as testicular and prostate cancer, and report an increased risk associated with male infertility. We found weak associations with cancers of the testicles or prostate, which is plausible given that we examine mortality rather than incidence (e.g. few die from testicular cancer). Yet, we found an association between prolonged TTP and increased risk of death related to malignant neoplasm of the buccal cavity and pharynx, leukaemia, and other neoplasms of lymphoid and haematopoietic tissue and malignant neoplasm of other and unspecified sites. In contrast to mothers, where only a weak association was found, the association in fathers with malignant neoplasm of the buccal cavity and pharynx indicates a role of alcohol (Tybjerg et al., 2022), as alcohol is also related to prolonged TTP (Finelli et al., 2022). Compared to mothers, only a weak association was found for malignant neoplasm of larynx trachea bronchus and lung in fathers, suggesting less influence of smoking and air pollution in fathers (Tybjerg et al., 2022; Siegel et al., 2023).

Based on prior research on the associations between TTP and the various possible causes of death, our results generally indicate that the underlying causes of the relation between fecundity

and survival may be multi-factorial. This is similar to the results of a previous study of TTP in a Danish twin cohort (Ahrenfeldt *et al.*, 2021) and what has been found for causes of death for men with impaired semen quality (Jensen *et al.*, 2009).

The major strengths of our study are the large population-based sample and the prospective design. The study population was linked to several Danish registries, which made it possible to obtain complete information on mortality with up to 47 years of follow-up. Also, our study period lies before the influence of ART as nearly all treatments until 1985 were unsuccessful in Denmark (Andersen, 2021). Our study has some limitations. The question used to measure the TTP, 'From the time you wanted a pregnancy until it occurred, how much time passed?', may have led to misclassification. Instead of interpreting the question as relating to the current pregnancy, the woman could have answered, for example, on the first time she wished to become pregnant during her life. Thus, the question does not differentiate 'trying' to get pregnant from 'wanting' to get pregnant and, as such, the assessment question for TTP itself is unreliable and has questionable validity; however, our results suggest that the former interpretation was given by the women based on the coherence between our TTP and those reported in other studies. Also, the misclassification would probably be random, thus biasing the relative risks towards their null value and reducing the risk of a type I error. Another significant limitation is that fecundity is measured using a pregnancy-based approach, where information on TTP is collected retrospectively among women who eventually conceived. Thus, the cohort is conditioned on fertility success and the results can, in principle, only be generalized to couples who succeeded. This selection may also have led to an underestimation of the association between prolonged TTP and increased mortality if mothers with more severe subfecundity have a higher mortality than those who conceive (Keiding *et al.*, 2012, 2021). To avoid such limitations in future studies, a current-duration design could be used to collect information on TTP among couples trying to conceive (Keiding *et al.*, 2012; Gasbarra *et al.*, 2015). In a current-duration design, information would be available for couples who conceive, those who do not conceive, those who have an abortion and those with unplanned pregnancies. When using TTP as a measure of fecundity, the inherent problem of not knowing the individual paternal and maternal factors for its value is another, not easily solved, major limitation. It is also possible that the mother has not reported on the actual biological father, which again would bias results for fathers towards null if non-differential across TTPs. A further limitation arises from the missing information on parental lifestyle factors prior to the pregnancy. For smoking, we attempted to correct for this by using mothers' smoking during pregnancy as a proxy for previous smoking behaviour (Jaddoe *et al.*, 2008; Liu *et al.*, 2020). Also, we did not have information on socioeconomic position and education from the Danish Registries, as this first became available in 1980. Therefore, we used instead the self-reported occupation of the parents, with the risk of misclassification and less social information represented by this variable. The suggested influence of lifestyle and socioeconomic factors on the association observed here further suggests that adjustment for these factors would have decreased the strength of the associations, as education and social factors are generally linked to lifestyle. Another significant limitation is reverse causality, as parents with long TTP may have poor health before the start of the attempt, leading to a prolonged TTP. Based on the findings in the present study, we cannot answer this question but only report the clear association between TTP and mortality.

In conclusion, in this large prospective cohort study of couples we found that prolonged TTP increased the overall mortality in both sexes. The findings of an association with several different diseases in the cause-of-death analyses indicate that the factors influencing the association between fecundity and survival are likely to be many and complex, in both men and women. Our results need confirmation and thus need to be repeated in other cohorts with lengthy follow-up and a better assessment of TTP.

Supplementary data

Supplementary data are available at *Human Reproduction* online.

Data availability

The data underlying this article cannot be shared publicly due to EU General Data Protection Regulation rules. The data are available by application to Statistics Denmark (fee payable) and the corresponding author.

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Authors' roles

R.L.-J. and T.K.J. conceptualized and designed the study. R.L.-J and M.T.P. conducted the data analyses. R.L.-J., M.T.P., and T.K.J. drafted all versions of the article. All authors revised the paper critically and approved the final version of the submitted article.

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Conflict of interest

M.L.E. is an advisor to Ro, VSeat, Doveras, and Next.

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