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Tykes, Toddlers, Teens, and Twins of Robust Mothers: Do the Offspring of Twinning Mothers Share in Their Mother's Robust Phenotype?

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Abstract

Women who bear twins may possess a robust phenotype compared to non-twinning mothers. We examine mortality patterns for the singleton offspring of mothers of twins compared to the offspring of non-twinning mothers to determine whether they share the hypothesized robust phenotype of their mothers. Using data from the Utah Population Database, we show that both male and female singleton offspring of twinning mothers experience a survival *disadvantage* prior to age 5, no survival benefit or penalty between ages 5 and 49, and – for males only – a statistically significant survival *advantage* after age 50. We further examine the survival effects on singletons born before and after a twinset. We observe a survival *disadvantage* in early life for singleton offspring of twinning mothers born after the twinset for both sexes. In addition, we find a significant survival *advantage* at older ages in certain categories of male singleton offspring – a likely reflection of mortality selection. The findings suggest that while bearing twins may reflect a robust maternal phenotype, the toll of bearing twins may disadvantage subsequent offspring, especially during infancy.

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Keywords

twins; siblings of twins; twinning mothers; survival; robust phenotype

BACKGROUND

Women who bear twins have been shown to exhibit a robust phenotype compared to their non-twinning counterparts. Twinning mothers are more likely to have longer reproductive spans, higher lifetime fertility, later ages at last birth and consequent longer post-menopausal lifespan, shorter interbirth intervals, and better anthropometric characteristics (Sear et al. 2001, Robson and Smith 2011, 2012, Gabler and Volland 1994, Campbell, Campbell, and MacGillivray 1974, Smith, Mineau, and Bean 2002, Basso et al. 2004). These characteristics suggest that a woman's ability to successfully complete a multi-fetal pregnancy, which results in live birth of twins, might be an indicator of her physical robustness, compared to women who do not bear twins. Although the high cost of twinning for a woman may outweigh the initial fitness advantage that allows her to bear twins successfully, we hypothesize that the survival benefits that have been reported for twinning women may be shared with their offspring, both twins and singletons. For example, a study by Rickard et al. (2012) demonstrates that singleton offspring of twinning women had greater birthweights compared to offspring of non-twinning women.

While women capable of bearing twins may be more robust, pregnancies leading to twin births are also associated with significant physical and psychological costs to the mother, leading to greater maternal depletion and nutrient deficiency, and increasing risks of maternal morbidity and mortality (Winkvist, Rasmussen, and Habicht 1992, Nwosu et al. 2008, Conde-Agudelo, Belizán, and Lindmark 2000). Thus, the offspring born immediately following the birth of twins – in a period we call the “twin shadow” – may suffer negative consequences associated with maternal depletion, likely made more severe by shorter interbirth intervals characteristic of twinning women (King 2003). Singleton siblings born after twin births may also bear the consequences of unsuccessful competition for parental time and resources required by the proximate twinset (Trivers 1972). Thus, genetic robustness that may be passed from a twin-bearing mother to her child may be overshadowed by factors associated with preceding twin pregnancy. Furthermore, increased lifetime fertility observed among twinning women and consequent larger sibship sizes among their offspring may result a mortality disadvantage for the offspring (Knodel and Hermalin 1984). Alternatively, offspring born in a twin shadow, as well as all offspring born after the twinset, may benefit from their position in the birth order, as suggested by Rickard et al. (2012), who found greater birthweights among singleton offspring born after the twinset, compared to those born before. This may be due to increased vascularization, which may be responsible for the positive association between birthweight and parity in non-twinning women (Khong, Adema, and Erwich 2003).

To investigate the influence of the hypothesized robust maternal phenotype, we examine the survival of singleton siblings of twins. Studies show that twins experience difficult conditions *in utero* and during the post-natal period, where they face increased mortality and

mortality risks throughout their lives (Barker 1995, Baird et al. 1998, Suri et al. 2001, Alam, Van Ginneken, and Bosch 2007, Ahrenfeldt et al. 2017). These adverse prenatal and neonatal conditions may obscure the influence of the robust maternal phenotype in that the twins themselves may not enjoy the survival and fitness benefits that exist for the twinning mother. However, twinning mothers still represent a subset of mothers who reflect a robust phenotype that might be shared with their singleton offspring.

In our first hypothesis, we predict that singleton offspring of twinning mothers will exhibit better survival outcomes throughout their lives than singletons born to mothers who do not bear twins. For our second hypothesis, we expect that survival outcomes for singleton offspring of twinning mothers will vary depending upon the timing of their birth relative to the twinset. Singletons born after the twinset face challenges associated with maternal depletion and parental resource divestment, with those *born immediately* following the twinset (during the interval we call the twin shadow) will be disproportionately affected by adverse factors faced by the mother associated with bearing twins.

MATERIALS & METHODS

We draw data from the Utah Population Database (UPDB) spanning years that include natural fertility conditions as well as years encompassing the demographic transition from the latter portion of the 19th to the beginning of the 20th century. The UPDB is one of the world's richest sources of linked population-based information for demographic, genetic and epidemiological studies. UPDB has supported biodemographic studies as well as numerous important epidemiological and genetic studies in large part because of its size, pedigree complexity, and linkages to numerous data sources. The complete holdings of the UPDB now contain data on over nine million individuals due to longstanding and on-going efforts to add new sources of data and by updating records as they become available. Because these records include basic demographic information on parents and their children, the data on fertility and mortality outcomes are extensive.

In our analyses, we compare all-cause mortality risks of singleton offspring of twin-bearing mothers to that of individuals born to non-twinning mothers in the same birth cohorts. We restrict the sample to offspring born before 1925 to guarantee at least 85 years of follow-up for mortality surveillance. With these restrictions, our final sample comprises 495,356 offspring. Approximately, 7.4 percent of these individuals were born to twinning mothers.

To test our first hypothesis, we estimate mortality hazard ratios for singleton offspring born to twinning mothers versus offspring born to non-twinning mothers, using Cox non-proportional hazard models controlling for birth year, birth order, sibship size and maternal mortality. *Birth years* range from 1768 to 1924. *Birth order* reflects the order in which a child is born to a mother and ranges from 1 to 22. *Sibship size* refers to the total number of children born to the mother during her lifetime, including multiple births. It is a continuous variable ranging from 3 to 20 for singleton offspring of twinning mothers, and from 1 to 23 for offspring of non-twinning mothers. Finally, *maternal mortality* is operationalized as dummy variable where we assigned a value of '1' when mother's year of death corresponds with the child's year of birth, and a value of '0' in all remaining cases. Controlling for

maternal mortality is important because twinning mothers have higher maternal mortality rates than non-twinning mothers.

In light of established differences in mortality between males and females, with females generally having better survival at all ages, our estimated models are sex-specific (Lindahl-Jacobsen et al. 2013). We also expect that relative survival between singleton offspring of twinning and non-twinning women to vary by age of the offspring. Singleton siblings of twins may be subjected to increased mortality risk during infancy compared to their counterparts born to non-twinning mothers, yet experience survival advantage during adulthood. Accordingly, we estimate non-proportional hazard ratios where hazard ratios can vary across five age intervals: up to age 1, age 1 to 4, age 5 to 17, age 18 to 49, and from age 50 and older. These age intervals were chosen to reflect the periods of infancy, the toddler years, childhood and adolescence, reproductive adulthood, and post-reproductive adulthood.

We include in our analysis the appropriate controls for mortality risk as a function of birth cohort. Accordingly, we estimate our Cox regression models that are stratified by birth year so that each birth cohort has its own baseline hazard. In order to adjust for cohort effects and potential differences between offspring of twinning mothers and non-twinning mothers, we group the latter to the former based on the birth cohort of the mother/offspring.

In the second set of models, we account for the timing of singleton births relative to the twin birth and differentiate between those born before and after the twins' births. We define the first singleton child born following the twinset as being born in the twin shadow. Furthermore, we separate those born in the twin shadow into early and late twin shadow births, with early twin shadow births occurring within 18 months of the twin birth. Late twin shadows are defined as the next singleton birth that follows the twinset but occurs after the 18-month threshold. We then estimate mortality hazard ratios for the four categories of singleton offspring of twinning mothers – pre-twins, offspring born in the early twin shadow, in the late twin shadow, and those born in the post-shadow period – in relation to the singleton offspring of non-twinning mothers. Figure 1 illustrates the four sibling categories used in the analysis.

We choose the 18-month cut-off point to differentiate between the early and late twin shadows to reflect a very short interbirth interval, in light of evidence suggesting that interbirth intervals of 18 months or less are associated with infant and child mortality risks markedly higher than those associated with longer intervals (Rutstein 2005). An 18-month birth interval corresponds to an interpregnancy interval of about 9–11 months, depending on the duration of pregnancy. Interpregnancy intervals lasting 11 months or less were shown to be linked with low birth weight and children small for gestational age (Conde-Agudelo, Rosas-Bermúdez, and Kafury-Goeta 2006). These adverse health outcomes are likely due to maternal depletion (Smits and Essed 2001), which would be even further exacerbated following a twin pregnancy. In our sample, interbirth intervals for twin shadows (mean = 32.65 months, median = 28.10 months) are, on average, slightly longer than those of offspring born to non-twinning women (mean = 31.13, median = 26.77 months), as well as for other categories of singleton offspring of twinning mothers. Thus, analyzing early twin shadows – those born within 18 months after the twinset – separately, enables us to consider

the more extreme cases, where the effects of maternal depletion attenuated by the preceding twin pregnancy is further amplified by the short birth interval.

RESULTS

Descriptive Characteristics of the Sample

Descriptive statistics are presented in Table 1. All categories of singleton offspring born to twinning women, regardless of the timing of birth relative to the twinset, have larger sibship sizes than those born to non-twinning women. Average sibship sizes for both male and female singleton offspring of twinning mothers are between 9.2 and 10.7, while singleton offspring of women who did not bear twins have an average sibship size of 7.9. Singleton offspring of twinning mothers – with the exception of singleton births occurring prior to the twinset – are more likely to experience the death of the mother during the first year of life than the offspring of non-twinning mothers. Over 2 percent of female singletons born in the early twin shadow, over 1 percent of those born in the late twin shadow, and over 1 percent of those born in the post-shadow period experienced the death of their mothers during the first year of life, compared to 0.7 percent of female offspring of women who did not bear twins. Among males, 1.5 percent of singletons born in the early twin shadow experienced the death of their mother during their first year of life, compared to 0.7 percent of offspring of non-twinning mothers. The percentage of male singletons born in the late twin shadow and during the post-shadow period whose mother died within their first year of life are 0.8 percent and 0.9 percent respectively. For both male and female singletons, the proportion of offspring experiencing maternal mortality is highest among those born in the early twin shadow.

Age-specific mortality risks vary by age between singleton offspring of twinning and non-twinning women, as well as by sex. The most pronounced differences are observed at the youngest ages. Mortality before age one is highest among singleton offspring born in the early twin shadow (within 18 months after the twinset) in relation to controls. Over 13 percent of female and 18.1 percent of male singletons born in the early twin shadow do not reach their first birthday, compared to 8.6 percent of females and 10.4 percent of males born to non-twinning mothers. Mortality for singletons born in the early twin shadow is higher than that for other categories of singleton offspring born to twinning women. Daughters born in the early twin shadow have mortality rates that are higher than that of other categories of singleton offspring of twinning mothers, as well as to offspring of women who did not bear twins after their first year of life. For males born in the early twin shadow period, mortality rates remain elevated, albeit less dramatically, throughout childhood. These mortality differences dissipate after age 18.

We test our first hypothesis that states that offspring of twinning women have lower hazard rates compared to offspring born to non-twinning mothers (Table 2). Based on Cox models, we find no evidence to support the hypothesis of a survival advantage for singleton offspring of twinning mothers. Indeed, the converse is found: both male and female singleton offspring of twinning mothers experience elevated all-cause mortality risks throughout early childhood. Female singleton offspring of twinning mothers have a mortality hazard rate that is 10 percent higher than daughters of non-twinning mothers during their first year of life

(HR=1.10, 95 percent CI 1.04–1.16). These singleton daughters have a mortality hazard that is 12 percent higher between ages one and five in relation to the reference category of daughters of non-twinning mothers (HR=1.12, 95 percent CI 1.01–1.23). Compared to male offspring of non-twinning mothers, mortality hazard ratios for singleton sons of twinning mothers are about 7 percent (HR=1.07, 95 percent CI 1.02–1.12) and 13 percent (HR=1.13, 96 percent CI 1.03–1.24) higher under age one and between ages one and five, respectively. At the same time, male but not female singleton offspring of twinning mothers experience a statistically significant survival advantage after age 50 (HR=0.96, 95 percent CI 0.94–0.98).

We test our second hypothesis by estimating all-cause mortality risks for the four categories of singleton offspring of twinning mothers, differentiated by the timing of their birth relative to the twinset (Table 3). The results reflect differential sex-specific mortality risk patterns for pre-twin, early and late twin shadow, and post-shadow offspring. Female singleton offspring born before the twinset have all-cause mortality risks similar to their counterparts born to non-twinning women. Male singleton offspring born before the twinset, on the other hand, experience a mortality advantage after the age of fifty, similarly to male singleton offspring of twinning mothers in the first set of models.

The nature of mortality risks for singleton offspring of twinning mothers born in the twin shadow vary as a function of the timing of the birth relative to the twinset. Singleton daughters born in the early twin shadow – within 18 months after the twinset – experience a significant survival disadvantage during the first year of life with a hazard rate that is nearly 50 percent higher than their counterparts born to non-twinning women. Daughters of twinning mothers born in the late twin shadow also experience a significant, albeit smaller, survival disadvantage (HR=1.18, 95 percent CI 1.02–1.36).

Males born in the early twin shadow experience significant survival disadvantage before the age of one and between the ages of one and five, with HR = 1.69 (95 percent CI 1.33–2.13) and HR = 1.90 (95 percent CI 1.13 – 3.21), respectively. The mortality penalty of being born in an early twin shadow on survival until age 1 and from age 1 to age 5 is larger for male offspring than the female offspring. However, male singletons born in the late twin shadow do not differ significantly from sons of non-twinning mothers.

Finally, both male and female singleton offspring born after the twin-shadow offspring are subject to significantly elevated mortality risks in early life. Recall that offspring born during the *post-shadow* are singletons whose births are separated from the twinset by another singleton birth. Female post-shadow offspring have mortality hazard rates of 1.24 (95 percent CI 1.13–1.35) during the first year of life and 1.30 (95 percent CI 1.10–1.53) between the ages of one and five. Male post-shadow offspring are also less likely to survive from birth to age one (HR=1.16, 95 percent CI 1.07–1.26) and from the age of one to the age of five (HR=1.19, 95 percent CI 1.00–1.41) compared to sons born to non-twinning women. Among the post-shadow sons, we can again observe a significant survival advantage after the age of 50.

DISCUSSION

Our analysis of mortality risks of individuals throughout the entire life course is based on the proposition that conditions early in life may play a central role in explaining variations in the age-specific risk of death. The focus of this paper relates to comparisons between mothers who bear twins and mothers who do not in terms of the survival prospects of their offspring. Here we examine offspring mortality as a function of their mothers twinning status that is not immediately confounded by the acute health effects of the twin births themselves. This strategy provided us with an opportunity to test whether the robust phenotype, as indicated by a woman's ability to bear twins, may be shared with her offspring as indicated by the offspring mortality risks. In our analyses, the singleton offspring of twinning women were compared to those born of mothers who bore only singleton births.

In general, our findings indicate that the hypothesized health advantages possessed by twinning mothers are not shared with their offspring and indeed these progeny may actually be disadvantaged because they are being reared by mothers who face significant challenges engendered by having borne twins (Winkvist, Rasmussen, and Habicht 1992, Nwosu et al. 2008, Conde-Agudelo, Belizán, and Lindmark 2000). Our analyses show that, on average, male and female offspring born to twinning mothers had elevated mortality risks throughout early childhood (before the age of 5). At the same time, a survival advantage is observed among male singleton offspring of twinning mothers during later life (after the age of 50). Given the excess mortality of sons of twinning mothers at young ages, we suggest that this *protective* effect observed past age 50 is a function of mortality selection: the most susceptible boys died at early ages, thereby leaving the more robust subset to live to later ages having been selected for better health.

When examining mortality risks for singleton offspring of twinning mothers by timing of their birth relative to the twinset, we find that offspring born prior to the twinset (where the immediate challenges engendered by maternal depletion and any other birth complications could not have arisen due to bearing twins) have mortality risks comparable to offspring of non-twinning mothers. This finding is inconsistent with our hypothesis that offspring of mothers who bear twins would possess the same robust phenotype that gave rise to the mother's ability to have twins. However, male singletons born prior to the twinset exhibit mortality advantage after the age of 50. Since these singletons do not experience excess mortality in early life, the later life mortality advantage is less likely a reflection of mortality selection. Instead, this specific finding may be one indication of the beneficial effects of being born to a twinning mother, which can be detected when not obscured by the immediate adverse effect of being born after the twinset. This interpretation is not universal given that daughters who were classified as pre-twins did not demonstrate a significant survival advantage after age 50 though the confidence interval suggests a similar reduction in mortality after midlife.

We demonstrate that offspring born immediately following the twinset, in the twin shadow, endure a decidedly disadvantaged mortality schedule. Those born in the early twin shadow have the greatest mortality disadvantage both for sons and daughters. Mechanisms that underlie this association are likely due to vascularization, maternal depletion and differential

allocation of parental resources (Rickard et al. 2012, Winkvist, Rasmussen, and Habicht 1992, Nwosu et al. 2008). The attenuated mortality risk for those born in the late versus early twin shadow indicates the importance that birth spacing has on offspring survival, echoing previous studies on interbirth intervals and offspring outcomes (Rutstein 2005, Wendt et al. 2012)

Singleton offspring born following the twin shadow period also appear to experience the detrimental effects faced by mothers who twin. We show that the post-shadow offspring face mortality penalties that are similar (though attenuated) to their siblings who are born in the twin shadow. The potential advantage possessed by the offspring of mothers with a robust phenotype appear to be either absent or overwhelmed by the proximate adverse influences encountered by mothers who bear twins.

Our models allow us to estimate the time-varying influences of being a singleton offspring of mothers who do or do not bear twins. This strategy helps isolate the profoundly elevated risks of mortality early in life particularly when those births occur on the heels of a pregnancy leading to twins. These models also demonstrate that the culling of arguably susceptible offspring from the population attributable to the strains brought about by the birth of twins is associated with lower mortality at older ages for offspring of mothers who twin. This we interpret as a classic example of mortality selection rather than support for the hypothesis that there is sharing of the robust phenotype between mothers who twin and their singleton offspring.

Although twinning among humans have occurred at persistently low rates under natural fertility conditions, twinning rates in contemporary populations are on the rise due increasing maternal age, and increasing use of medical interventions and reproductive technologies (Helle, Lummaa, and Jokela 2004, Aston, Peterson, and Carrell 2008, Beemsterboer et al. 2006). As the rate of live twin births worldwide increases, so does the importance of examining the effects of early life conditions on survival and other health outcomes of twins and their singleton siblings. While this study suggests some of the mechanisms that may be responsible for survival outcomes among singleton siblings of twins, these mechanisms warrant further examination. Future research should examine how health consequences of twinning for mothers may be linked to survival of their singleton offspring, as well as the effect of varying paternal features, such as age and health, on singleton offspring mortality outcomes. In addition, future research may consider potential differences in survival outcomes for offspring of mothers who gave birth to monozygotic or identical twins and offspring of mothers who gave birth to dizygotic twins, as these women's characteristics may have differential impact on offspring robustness. Furthermore, the conclusions drawn from this study can be strengthened through replication of the study procedures using comparable data from different historical populations worldwide.

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To understand the four different categories of singleton offspring of twinning mothers, consider three women.

Woman 1 gives birth to a singleton in 1890 and to twins in 1895. Her next child (*A*) is born in 1896, falling into the early twin shadow category. She then gives birth to three more children in 1898, 1900 and 1901. All three children fall into the post-shadow category.

Twinning woman 1

Woman 2 gives birth to singleton offspring who fall into the pre-twin category in 1890 and again in 1893. After giving birth to twins in 1895, this woman bears another singleton offspring (*B*) in 1898. Since the interbirth interval following the twinset is longer than 18 months, child *B* falls into the late twin shadow category. Offspring born after child *B* – in 1901 in this example – fall into the post-shadow category.

Twinning woman 2

Woman 3 gives birth to a singleton in 1890 and to twins in 1895. Her next child (*C*) is born in 1901, falling into the late twin shadow category. This woman does not bear any more offspring, thus never producing post-shadow children.

Twinning woman 3

Each of the four categories of the singleton offspring are then compared to a reference category – birth-cohort matched offspring of women who did not bear twins.

Figure 1.
Four categories of singleton offspring of twinning mothers.

Table 1.

Descriptive characteristics of the sample.

<i>Females</i>					
Singleton offspring of twinning mothers					
	Offspring of non-twinning mothers	Pre-twin	Early twin shadow	Late twin shadow	Post-shadow
Average birth year	1893 (23.0) [1768–1924]	1889 (22.8) [1775–1924]	1893 (23.6) [1805–1924]	1895 (22.8) [1803–1924]	1893 (21.6) [1781–1924]
Birth order	4.4 (2.9) [1–22]	3.6 (2.4) [1–15]	6.1 (3.0) [3–16]	6.7 (2.8) [3–17]	8.6 (2.7) [3–20]
Sibship size	7.9 (3.3) [1–23]	10.2 (2.9) [3–20]	9.6 (3.3) [3–20]	9.2 (2.9) [3–20]	10.7 (2.6) [4–20]
Maternal death (%)	0.7%	0.0%	2.3%	1.4%	1.1%
Mortality prevalence (%):					
0–1 years	8.6%	9.3%	13.2%	10.2%	10.9%
>1 & ≤5 years	2.4%	2.8%	2.0%	2.3%	3.2%
>5 & ≤18 years	3.2%	3.3%	1.7%	3.2%	3.5%
>18 & ≤49 years	9.5%	10.4%	6.9%	9.4%	9.7%
Sample size:	223,880	11,119	303	1,645	4,704
N censored:	49,969	2,001	59	373	1,008

<i>Males</i>					
Singleton offspring of twinning mothers					
	Offspring of non-twinning mothers	Pre-twin	Early twin shadow	Late twin shadow	Post-shadow
Average birth year	1893 (23.2) [1769–1924]	1888 (23.3) [1783–1924]	1893 (23.2) [1811–1924]	1894 (23.6) [1779–1924]	1893 (21.8) [1780–1924]
Birth order	4.4 (2.9) [1–22]	3.6 (2.4) [1–15]	6.4 (3.2) [2–15]	6.8 (2.8) [2–18]	8.6 (2.7) [3–19]
Sibship size	7.9 (3.3) [1–22]	10.2 (2.8) [3–20]	10.1 (3.1) [3–18]	9.3 (2.8) [3–19]	10.7 (2.6) [4–20]
Maternal death (%)	0.7%	0.0%	1.5%	0.8%	0.9%
Mortality prevalence (%):					
0–1 years	10.4%	11.1%	18.1%	11.4%	12.7%
>1 & ≤5 years	2.4%	3.1%	4.2%	2.7%	3.5%
>5 & ≤18 years	3.5%	3.7%	4.5%	3.3%	3.6%
>18 & ≤49 years	10.9%	11.4%	9.6%	10.5%	10.3%
Sample size:	234,905	11,839	332	1,754	4,875
N censored:	35,452	1,463	40	257	675

Note. Total N=495,356. Standard deviations for continuous variables are presented in parentheses; minimum and maximum values are presented in square brackets.

Table 2.

All-cause mortality hazards at different stages of life for singleton offspring of twinning mothers.

Parameter	Females				Males			
	Parameter Estimate	Hazard Ratio	95% Hazard Ratio Confidence Limits		Parameter Estimate	Hazard Ratio	95% Hazard Ratio Confidence Limits	
Birth year	-0.01 ***	0.99	0.99	0.99	-0.01 ***	0.99	0.99	0.99
Birth order	0.00 *	1.00	1.00	1.00	0.01 ***	1.01	1.00	1.01
Sibship size	0.01 ***	1.01	1.01	1.01	0.01 ***	1.01	1.01	1.01
Maternal death	0.55 ***	1.73	1.62	1.86	0.60 ***	1.83	1.70	1.97
<i>Singleton offspring of twinning mothers:</i>								
0–1 years	0.09 ***	1.10	1.04	1.16	0.07 **	1.07	1.02	1.12
>1 & ≤5 years	0.11 *	1.12	1.01	1.23	0.12 **	1.13	1.03	1.24
>5 & ≤18 years	-0.02	0.98	0.90	1.07	0.00	1.00	0.92	1.08
>18 & ≤49 years	0.03	1.03	0.98	1.08	-0.02	0.98	0.93	1.02
>49 years	-0.02	0.98	0.96	1.01	-0.05 ***	0.96	0.94	0.98

Note. Offspring of mothers who did not bear twins is a reference category. Significant results are indicated as follows:

*
p 0.05**
p 0.01***
p 0.001.

Table 3.

All-cause mortality hazards at different stages of life for singleton offspring of twinning mothers categorized by the timing of birth relative to the twinset.

Parameter	Females				Males			
	Parameter Estimate	Hazard Ratio	95% Hazard Ratio Confidence Limits		Parameter Estimate	Hazard Ratio	95% Hazard Ratio Confidence Limits	
Birth year	-0.01 ***	0.99	0.99	0.99	-0.01 ***	0.99	0.99	0.99
Birth order	0.00	1.00	1.00	1.00	0.01 ***	1.01	1.00	1.01
Sibship size	0.01 ***	1.01	1.01	1.01	0.01 ***	1.01	1.01	1.01
Maternal death	0.55 ***	1.73	1.62	1.85	0.60 ***	1.83	1.70	1.97
<i>Pre-twin:</i>								
0–1 years	0.02	1.02	0.96	1.09	0.02	1.02	0.96	1.08
>1 & ≤5 years	0.07	1.07	0.95	1.21	0.09	1.09	0.97	1.22
>5 & ≤18 years	-0.05	0.95	0.86	1.06	-0.00	1.00	0.91	1.10
>18 & ≤49 years	0.03	1.03	0.97	1.10	0.00	1.00	0.95	1.06
>49 years	-0.01	0.98	0.96	1.01	-0.04 **	0.96	0.94	0.99
<i>Early twin shadow:</i>								
0–1 years	0.40 **	1.49	1.11	2.00	0.52 ***	1.69	1.33	2.13
>1 & ≤5 years	-0.21	0.81	0.37	1.81	0.64 *	1.90	1.13	3.21
>5 & ≤18 years	-0.69	0.50	0.21	1.20	0.34	1.40	0.85	2.32
>18 & ≤49 years	-0.38	0.69	0.45	1.06	-0.03	0.97	0.69	1.38
>49 years	0.00	1.00	0.87	1.15	-0.13	0.88	0.76	1.01
<i>Late twin shadow:</i>								
0–1 years	0.16 *	1.18	1.02	1.36	0.07	1.07	0.93	1.22
>1 & ≤5 years	-0.05	0.95	0.69	1.31	0.12	1.12	0.85	1.49
>5 & ≤18 years	0.01	1.01	0.78	1.32	-0.09	0.92	0.71	1.19
>18 & ≤49 years	0.00	1.00	0.86	1.18	-0.07	0.93	0.81	1.08
>49 years	0.01	1.01	0.95	1.08	-0.04	0.96	0.91	1.03
<i>Post-shadow:</i>								
0–1 years	0.21 ***	1.24	1.13	1.35	0.15 ***	1.16	1.07	1.26
>1 & ≤5 years	0.26 **	1.30	1.10	1.53	0.17 *	1.19	1.00	1.41
>5 & ≤18 years	0.07	1.07	0.92	1.25	0.01	1.01	0.87	1.17
>18 & ≤49 years	0.04	1.05	0.95	1.15	-0.08	0.93	0.85	1.01
>49 years	-0.03	0.97	0.93	1.01	-0.06 **	0.94	0.91	0.98

Note. Offspring of mothers who did not bear twins is a reference category. Significant results are indicated as follows:

* p 0.05

** p 0.01

*** p 0.001.