Comparing the survival outcomes for the siblings of twins

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Abstract (150 words max)

We have shown that twinning is a marker of a robust maternal phenotype. Here we examine mortality patterns of the singleton offspring of mothers of twins compared to the offspring of non-twinning mothers to determine whether the siblings of twins possess the enhanced phenotype of their mothers. From the Utah Population Database (UPDB) we compared the survival of 463,438 offspring of singleton-only bearing mothers and singleton siblings of twin-bearing mothers. Using survival analyses we found that males had higher mortality at all ages but experience a protective effect if an offspring of a twinning mother. Singleton offspring immediately following a twinset did not suffer significant survival disadvantages. However, subsequent male siblings who survive to age 18 experience an improvement in survival. No survival benefits were detected for singleton sisters of twins. Further work will explore the fitness implications of being born to a twinning mother.

Introduction and Aims

Twinning varies between women and mothers of twins in the UPDB sample exhibit a robust phenotype compared to their singleton-only bearing counterparts by living longer past menopause, having higher overall parity, shorter average interbirth intervals, longer reproductive spans and later ages at last birth than non-twinning mothers (Robson and Smith 2011, 2012). Here we investigate the influence of this robust maternal phenotype on her offspring by comparing the pattern of survival in her offspring to those offspring of non-twinning mothers in this cohort.

Aim 1: The survival of the siblings of twins

We expect the benefits of this maternal robusticity will be translated to offspring, both twin sets and their siblings. Among twins, however, the heritable benefits gained by having a mother who bore twins could be difficult to measure due to the gestational and neonatal liabilities of being a twin. Studies have shown that twins suffer difficult early life conditions and increased mortality risk (Baird et al 1998, Suri et al 2001). Therefore, we look to the singleton siblings of twins to examine these maternal effects by comparing their pattern of survival to the offspring of non-twinning mothers. We control for material mortality to see if the effect of twinning persists.

Aim 2: Survival difference by sex

Males are more frail than females and females tend to live longer so we expect less of a survival advantage will be gained by a singleton offspring of a twinning mother. Correspondingly, we expect a greater gain in survival among male siblings of twins because there is greater room for improvement. We control for birth year to account for shifts in fertility and mortality patterns by era.

Aim 3: Sibling birth order

We examine the survival of siblings of twins by their proximity to the twin set in their birth order suspecting that twins have an influence on the survival of the immediately following offspring. In our analysis we refer to these individuals as being in the "twin shadow".

- Option 1: Subsequent offspring are at an advantage
  Rickard et al (2012) suggest that twinning propensity in women could be mediated by IGF-I system which also influences in utero fetal growth. They examined the weights of singleton offspring born to rural Gambian women before or after a twin pregnancy and found that singletons after a twin birth were significantly heavier than the offspring of non-twinning women. There is a parity progression effect on birthweight where subsequent offspring are heavier than firstborns (Khong et al 2003). Rickard et al (2012) posit that increased vascularization during a twin pregnancy may account for the additional weight gain among post-twin singleton offspring which could provide them with a survival advantage.

- Option 2: Subsequent offspring are at a disadvantage
  Alternatively, we could also expect that offspring immediately following a twin set to suffer mortality effects due to maternal depletion and the diversion of time and investment costs required by the proximate twin set. We examine the survival of siblings following a twin set expecting that twinning mothers suffer a depletion effect after a multiple pregnancy.

Sample and methods

We compared the mortality of 458,788 offspring of the singleton-only bearing mothers and singleton offspring of the twin-bearing mothers examined in Robson and Smith 2011, 2012. Twins were excluded from these analyses. These data are drawn from the vast natural fertility data in the Utah Population Database (UPDB). The UPDB is one of the world's most comprehensive computerized genealogies collating the vital records of migrants to Utah and their Utah descendants for more than 1.6 million individuals born from the early 1800s to mid-1970s (see http://www.huntsmancancer.org/groups/ppr/). Because these records include basic demographic information on parents and their children, fertility and mortality data are extensive.

Using survival analysis in SAS software we analyzed the survival results for each of the project aims. All analyses control for sibling of a twin, birth year, number of siblings (maternal parity), birth order, and maternal mortality. Aims 2 and 3 are further separated by sex. In aim three we categorize siblings of twins as 'twin shadow', or birth directly following the birth of twins, and other siblings of twins and compare them to children of non-twinning mothers.

Preliminary Results

Aim 1 (Table 1): Survival among siblings of twins

Using survival analyses and using a male-female combined sample, we find a protective effect of being an offspring of a twinning mother for survival to age 18, however this effect is loses significance for survival after age 50.

Aim 2 (Table 2): Sex differences in survival

Singleton brothers of twins enjoyed a small but significant survival advantage at all ages but especially after age 18. No survival benefits were detected for singleton sisters of twins. Further work will explore the basis for this gender difference and the fitness implications of being born to a twinning mother.

Aim 3 (Table 3): Sibling birth order on survival

Sons **of** twinning mothers, after excluding twin shadows, have a survival advantage. Male twin shadows, unlike their other singleton-birth brothers, do not realize this same benefit. The adverse survival consequences of being a twin shadow appear to attenuate the benefits of having a twinning mother.

Future Investigations:

Future investigations will examine whether that the timing of a twin set during the reproductive span could be an additional indicator of heterogeneity among this especially robust subset of parous women. Bearing twins at the end of the reproductive span when parity is high, may identify those women who are the "most" robust among twinning mothers (Lummaa et al 1998, Helle et al 2004, Helle 2008). It is well documented that women at advanced maternal ages bear multiples at higher rates (Bulmer 1970, Bortolus et al 1999, Hoekstra et al 2008). Twinning at the end of the reproductive span could be a marker of those women with of a large residual energy reserve – women who are able to bear singletons in succession and yet have a reproductive reserve remaining. Despite the reproductive advantage of this strategy, however, multiple births remain rare events, even among older mothers – highlighting the value of the vast Utah Population Database for this type of restrictive research (Wyshak 1975, 1978).

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Table 1: Results for Aim 1. Survival of the siblings of twins compared to offspring of non-twin mothers in the UPDB.

	Likelihood ratio=23109.0366 **Pr>Chisq=<.0001** **DV: lifespan** All, n=463438			**Likelihood ratio=5253.2518** **Pr>Chisq=<.0001** **DV: surival to age 5** <5, n=463438			**Likelihood ratio=6296.5023** **Pr>Chisq=<.0001** **DV: surival to age 18** <18, n=463438			**Likelihood ratio=19289.0607** **Pr>Chisq=<.0001** **DV: survival past age 18** >18, n=463438			**Likelihood ratio=16294.3377** **Pr>Chisq=<.0001** **DV: survival past age 50** >50, n=463438		
		95% Confidence Limits			95% Confidence Limits			95% Confidence Limits			95% Confidence Limits			95% Confidence Limits	
Variable	**HRR**	**Lower CI**	**Upper CI**	**HRR**	**Lower CI**	**Upper CI**	**HRR**	**Lower CI**	**Upper CI**	**HRR**	**Lower CI**	**Upper CI**	**HRR**	**Lower CI**	**Upper CI**
Mother had Twins	0.988	0.974	1.002	0.966	0.933	1.001	0.971	0.941	0.992	0.992	0.976	1.007	0.995	0.979	1.012
Birth year	0.992	1.308	1.300	0.993	0.992	0.993	0.992	0.992	0.922	0.992	0.992	0.992	0.992	0.992	0.922
Male	1.308	1.009	1.008	1.14	1.12	1.16	1.122	1.105	1.139	1.349	1.339	1.359	1.396	1.385	1.406
Number of Siblings	1.009	1.004	1.003	1.067	1.063	1.071	1.057	1.054	1.061	1	0.999	1.002	0.997	0.995	0.998
Birth order	1.004	1.003	1.005	1.001	0.997	1.004	1.001	0.998	1.004	1.005	1.003	1.006	1.005	1.004	1.007
Maternal Death	1.503	1.428	1.581	4.666	4.375	4.976	3.729	3.493	3.98	1.062	1.008	1.119	1.071	1.011	1.134

Table 2: Results for Aim 2. Survival by sex of the siblings of twins compared to offspring of non-twin mothers in the UPDB.

A. Females	**DV: lifespan**			**DV: (<5) Survival to age 5**			**DV: (<18) Survival to age 18**			**DV: (>18) Survival past age 18**			**DV: (>50) Survival past age 50**		
	Likelihood ratio=11206.0331			**Likelihood ratio=2507.1860**			**Likelihood ratio=3250.6212**			**Likelihood ratio=8805.3086**			**Likelihood ratio=5691.0475**		
	Pr>Chisq=<.0001			**Pr>Chisq=<.0001**			**Pr>Chisq=<.0001**			**Pr>Chisq=<.0001**			**Pr>Chisq=<.0001**		
	Females			**Females**			**Females**			**Females**			**Females**		
	All, n=225434			<5, n=225434			<18, n=225434			>18, n=225434			>50, n=225434		
		95% Confidence Limits			95% Confidence Limits			95% Confidence Limits			95% Confidence Limits			95% Confidence Limits	
Variable	**HRR**	**Lower CI**	**Upper CI**	**HRR**	**Lower CI**	**Upper CI**	**HRR**	**Lower CI**	**Upper CI**	**HRR**	**Lower CI**	**Upper CI**	**HRR**	**Lower CI**	**Upper CI**
Mother had Twins	0.999	0.98	1.018	0.966	0.92	1.014	0.968	0.928	1.011	1.005	0.984	1.026	1.009	0.987	1.032
Birth year	0.989	0.989	0.99	0.992	0.991	0.992	0.99	0.99	0.991	0.989	0.989	0.989	0.99	0.99	0.99
Number of Siblings	1.009	1.007	1.011	1.066	1.06	1.071	1.055	1.051	1.06	1	0.998	1.002	0.996	0.993	0.998
Birth order	1.003	1.001	1.004	0.999	0.994	1.004	1	0.996	1.005	1.003	1.001	1.005	1.004	1.002	1.006
Maternal Death	1.493	1.393	1.601	4.476	4.073	4.919	3.555	3.234	3.907	1.103	1.027	1.185	1.109	1.026	1.199

B. Males	**DV: lifespan**			**DV: (<5) Survival to age 5**			**DV: (<18) Survival to age 18**			**DV: (>18) Survival past age 18**			**DV: (>50) Survival past age 50**		
	Likelihood ratio=5579.3329			**Likelihood ratio=2586.1154**			**Likelihood ratio=2923.2644**			**Likelihood ratio=3839.1725**			**Likelihood ratio=3134.0688**		
	Pr>Chisq=<.0001			**Pr>Chisq=<.0001**			**Pr>Chisq=<.0001**			**Pr>Chisq=<.0001**			**Pr>Chisq=<.0001**		
	Males			**Males**			**Males**			**Males**			**Males**		
	All, n=238004			<5, n=238004			<18, n=238004			>18, n=238004			>50, n=238004		
		95% Confidence Limits			95% Confidence Limits			95% Confidence Limits			95% Confidence Limits			95% Confidence Limits	
Variable	**HRR**	**Lower CI**	**Upper CI**	**HRR**	**Lower CI**	**Upper CI**	**HRR**	**Lower CI**	**Upper CI**	**HRR**	**Lower CI**	**Upper CI**	**HRR**	**Lower CI**	**Upper CI**
Mother had Twins	0.978	0.96	0.996	0.967	0.925	1.012	0.973	0.935	1.013	0.98	0.961	1	0.984	0.964	1.005
Birth year	0.994	0.993	0.994	0.994	0.993	0.994	0.993	0.993	0.994	0.994	0.993	0.994	0.994	0.993	0.994
Number of Siblings	1.01	1.009	1.012	1.067	1.062	1.072	1.059	1.054	1.063	1.001	0.999	1.003	0.998	0.996	1
Birth order	1.005	1.003	1.007	1.002	.997	1.006	1.001	.997	1.005	1.006	1.004	1.008	1.006	1.004	1.008
Maternal Death	1.516	1.407	1.634	4.847	4.44	5.29	3.903	3.566	4.271	1.022	0.947	1.104	1.032	0.948	1.123

Table 3: Results for Aim 3. Survival of the siblings immediately following twins (twin shadow) compared to offspring of non-twin mothers in the UPDB.

A. Females	**DV: lifespan**			**DV: (<5) Survival to age 5**			**DV: (<18) Survival to age 18**			**DV: (>18) Survival past age 18**			**DV: (>50) Survival past age 50**		
	Likelihood ratio=11211.4083 **Pr>Chisq=<.0001** **Females** All, n=225366			**Likelihood ratio=2508.1594** **Pr>Chisq=<.0001** **Females** <5, n=225366			**Likelihood ratio=3255.0831** **Pr>Chisq=<.0001** **Females** <18, n=225366			**Likelihood ratio=8807.4147** **Pr>Chisq=<.0001** **Females** >18, n=225366			**Likelihood ratio=5692.5941** **Pr>Chisq=<.0001** **Females** >50, n=225366		
		95% Confidence Limits			95% Confidence Limits			95% Confidence Limits			95% Confidence Limits			95% Confidence Limits	
Variable	**HRR**	**Lower CI**	**Upper CI**	**HRR**	**Lower CI**	**Upper CI**	**HRR**	**Lower CI**	**Upper CI**	**HRR**	**Lower CI**	**Upper CI**	**HRR**	**Lower CI**	**Upper CI**
Offspring of A Twinning Mother, not a Twin Shadow	0.996	0.976	1.016	0.957	0.909	1.008	0.960	0.918	1.005	1.003	0.981	1.025	1.006	0.983	1.029
Twin shadow	1.026	0.979	1.077	1.040	0.917	1.180	1.035	0.929	1.154	1.024	0.972	1.079	1.037	0.980	1.096
Birth order	1.002	1.001	1.004	0.999	0.994	1.004	1.000	0.996	1.004	1.003	1.001	1.005	1.004	1.002	1.006
Birth year	0.989	0.989	0.990	0.992	0.991	0.992	0.990	0.990	0.991	0.989	0.989	0.989	0.990	0.990	0.990
Number of siblings	1.009	1.007	1.011	1.066	1.061	1.072	1.056	1.051	1.060	1.000	0.998	1.002	0.996	0.993	0.998
Maternal Death	1.493	1.393	1.601	4.476	4.073	4.919	3.556	3.236	3.908	1.103	1.027	1.185	1.109	1.025	1.198

B. Males	**DV: lifespan**			**DV: (<5) Survival to age 5**			**DV: (<18) Survival to age 18**			**DV: (>18) Survival past age 18**			**DV: (>50) Survival past age 50**		
	Likelihood ratio=5583.2048 **Pr>Chisq=<.0001** **Males** All, n=237943			**Likelihood ratio=2594.4195** **Pr>Chisq=<.0001** **Males** <5, n=237943			**Likelihood ratio=2932.6594** **Pr>Chisq=<.0001** **Males** <18, n=237943			**Likelihood ratio=3841.3950** **Pr>Chisq=<.0001** **Males** >18, n=237943			**Likelihood ratio=3135.0118** **Pr>Chisq=<.0001** **Males** >50, n=237943		
		95% Confidence Limits			95% Confidence Limits			95% Confidence Limits			95% Confidence Limits			95% Confidence Limits	
Variable	**HRR**	**Lower CI**	**Upper CI**	**HRR**	**Lower CI**	**Upper CI**	**HRR**	**Lower CI**	**Upper CI**	**HRR**	**Lower CI**	**Upper CI**	**HRR**	**Lower CI**	**Upper CI**
Offspring of A Twinning Mother, not a Twin Shadow	0.978	0.960	0.996	0.955	0.911	1.001	0.962	0.923	1.002	0.983	0.963	1.003	0.986	0.964	1.007
Twin shadow	0.976	0.934	1.021	1.049	1.058	0.944	1.062	0.962	1.173	0.961	0.916	1.008	0.973	0.924	1.025
Birth order	1.005	1.003	1.007	1.001	0.997	1.006	1.000	0.996	1.005	1.006	1.004	1.008	1.006	1.004	1.008
Birth year	0.994	0.993	0.994	0.994	0.993	0.994	0.993	0.993	0.994	0.994	0.993	0.994	0.944	0.993	0.994
Number of siblings	1.010	1.009	1.012	1.068	1.062	1.073	1.059	1.055	1.063	1.001	0.999	1.003	0.998	.996	1.000
Maternal Death	1.516	1.407	1.634	4.851	4.444	5.295	3.906	3.570	4.275	1.022	0.947	1.104	1.032	0.949	1.123