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Semen Quality as Predictor of Mortality in a Cohort of Out-Patients of a German Andrology Clinic: Biomedical vs. Life with-children Pathways of Influence

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Historical populations

- **Positive association between fertility and postreproductive survival (Lycett et al. 2000, Müller et al. 2002; Sear 2007)**
- **Negative association between fertility and postreproductive survival (Doblhammer & Oeppen, 2003; Dribe 2004, Smith et al. 2002, Gagnon et al. 2005, 2008)**
- **None-significant (Le Bourg 1993; Helle et al. 2005)**

Studies with Sperm counts as biomarker

- Groos S, Mueller UO, Krause W. Men with subnormal sperm counts live shorter. Soc Biol 2006; 53:46-60.

- Eisenberg ML, Li S, Behr B, Cullen MR, Galusha D, Lamb DJ, Lipshultz LI. Semen quality , infertility and mortality in the USA. Hum Reprod 2014b; 29: 1567-1574.

- Jensen TK, Jacobsen R, Christensen K, Nielsen NC, Bostofte E. Good semen quality and life expectancy: a cohort study of 43,277 men. Am J Epidemiol 2009; 170: 559-565.

Study Profile

- Update from Groos et al. inclusion of birth cohorts 1938-1941
- Mortality-Follow-up through 31.12.2010
- Sperm count analysis followed the guidelines from the WHO Laboratory Manual for the Examination of Human Semen and Sperm-Cervical Mucus Interaction
  5th Edition, 2010
- External Controls
- Survey information on reproductive biography

- **Is there any association between male fertility status and their post-reproductive survival?**
- **Is there any association between fecundity and mortality?**
- **Are the differences in survival and morbidity due to diversity in sperm counts ? – OR only selective effects**

Fathered 11 children

died with 88 years

Fathered 7 children
(2 grandchildren)

72 years old

2012: 50th Anniversary of the Rolling Stones

Biology of Male Infertility

- **Menopause: N95. Menopausal and other perimenopausal disorders (ICD 10, WHO, 2013)**

- **Andropause: No specific ICD-Code, not clinical relevant**

Causes of Male Infertility, (Andrology Australia, 2015)

Sperm production problems	• Chromosomal or genetic causes
	• Undescended testes (failure of th testes to descend at birth
	• Infections
	• Torsion (twisting of the testis in scrotum)
	• Heat
	• Varicocele (varicose veins of the testes)
	• Medicines and chemicals
	• Radiation damage
	• Unknown cause
Blockage of sperm transport	• Infections
	• Prostate related problems
	• Absence of vas deferens
	• Vasectomy
Sperm antibodies	• Vasectomy
	• Injury or infection in the epididymis
	• Unknown cause
Sexual problems (erection and ejaculation problems)	• Retrograde and premature ejaculation
	• Failure of ejaculation
	• Infrequent intercourse
	• Spinal cord injury
	• Prostate surgery
	• Damage to nerves
	• Some medicines
Hormonal problems	• Pituitary tumours
	• Congenital lack of LH/FSH (pituitary problem from birth)
	• Anabolic (androgenic) steroid abuse

Risk factors of male infertility

Risk factors for male infertility include:

- Varicocele, an enlarged varicose vein in the spermatic cord that connects to the testicle
- Aging, which can reduce sperm counts and motility and decrease the genetic quality of sperm
- Sexually transmitted diseases, which can cause scarring in the male reproductive system or impair sperm function
- Lifestyle factors such as smoking and substance abuse
- Long-term or intensive exposure to certain types of chemicals, toxins, or medications

Diagnosis of Male infertility

- Semen analysis to evaluate the quantity and quality of sperm
- Blood tests to evaluate hormone levels
- Imaging tests to look for structural problems
- Genetic testing to identify sperm DNA fragmentation, chromosomal defects, or genetic diseases

Relevance of male infertility

- About 15% of all couples in reproductive age being infertile or not able to induce pregnancy
- 3-4% of all couples remain involuntarily childless at the end of their reproductive life phase
- Infertility: inability to induce a pregnancy or conceive within one year of regular unprotected intercourse (Nieschlag, Andrology 2010)
- Most studies according to infertility are focusing on the causes affecting females
- But in 46% of all cases the male factor being the cause of infertility

Medical records (spermiograms) from the Department of Andrology at University Hospital Marburg

- **Semen samples taken between 1949 and 1998 from men born before 1942 (n=2294)**
- **Two subgroups: fertile and subfertile men**
- **WHO-Classification (2010):**

  abnormal sperm counts: sperm concentration < 15 Mio. per mL

  normal sperm counts: sperm concentration ≥ 15 Mio. per mL

Study sample

dead by 31.12.2010		572
alive by 31.12.2010		826
interviewed 2010-2011 (index or proxy)		631
of those with normal sperm counts		396
of those with abnormal sperm counts		235
mortality-follow-up complete by 31.12.2010		1398
lost-to-follow-up		896
total cases in clinical documentation		2294

Study sample

	Marburg city + county	outside Marburg county	
pathozoospermic observed	218	203	421
expected	223,1	197,9	
normozoospermic observed	523	454	977
expected	517,9	459,1	
Total	741	657	1398

Statistical Model

Motivation for the Gamma-Gompertz-Model:

- The extension of the Standard parametric model the Gompertz-Makeham
- Gompertz-Makeham assumption leads to an overestimation of observed death rates at ages 80+
- (gamma-Gompertz) multiplicative frailty model was introducedby Vaupel, Manton, and Stallard (1979)
- Main purpose to capture the human mortality rates at older ages under the consideration of unobserved heterogeneity

Gamma-Gompertz Model

- a positive random variable Z, the frailty that accounts for the individual hazard. The frailty concept implies a mixture of individuals in populations varying in their susceptibility to common risks.

$$\mu(x \mid Z) = Z\mu(x)$$

- μ(x) is the baseline force of mortality and follows the Gompertz distribution

- In homogeneous populations the frailty variance is small, the value for the frailty Z converges to 1, so called “standard individual” with the standard hazard function.

- But in the case of the increasing frailty variance the frailty variable Z also increases and becomes more relevant for affecting the individual hazard intensively by unobserved heterogeneity

Gamma-Gompertz Model

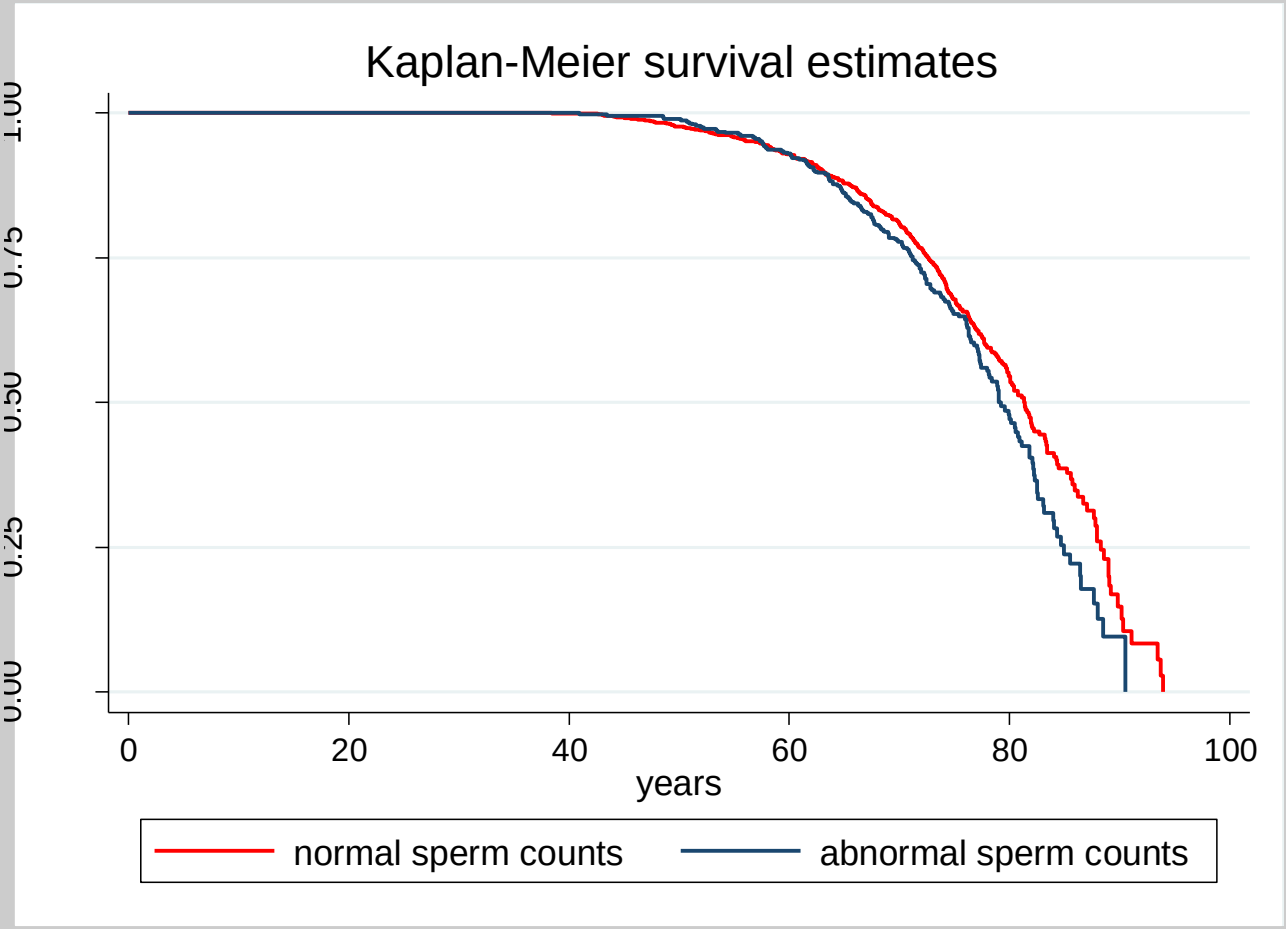
- Follow the Perks Model (Butt and Habermann, 2004) we estimate a parametric frailty model, with Gompertz-specification for the baseline and gamma for the frailty

$$\lambda(t) = a + \frac{ae^{bt}}{1 + \frac{\sigma^2 za}{b}(e^{bt} - 1)}$$

- with $\lambda_0(t) = ae^{bt}$ and $\Lambda_0(t) = \frac{a}{b}\left(e^{bt} - 1\right)$

- The application for the Gamma-Gompertz life expectancy at birth can be found in Missov, 2013

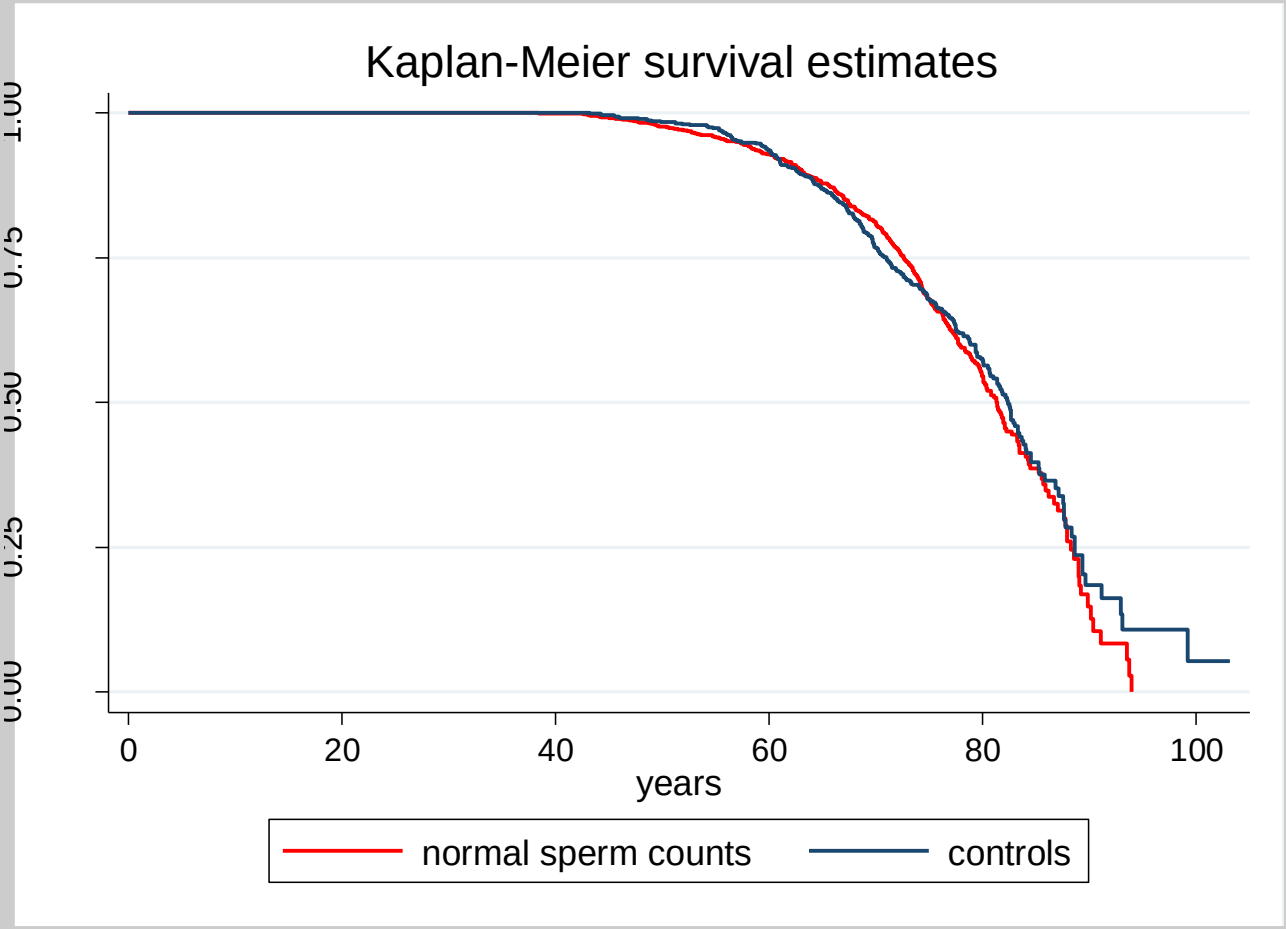
Results I


Kaplan-Meier survival estimates
1.00
0.75
0.50
0.25
0.00
0
20
40
60
80
100
years
normal sperm counts
abnormal sperm counts

Model I

	HR	SE	z	P>IzI	95 % CI	
normal vs. abnormal sperm count	0.7947337**	0.0719468	-2.54	0.011	0.6655226	0.949031
age at examination	0.9939139	0.0357351	-0.17	0.865	0.9262851	1.06648
life expextancy	0.98949	0.0366753	-0.29	0.776	0.9201567	1.064048
Log likelihood	-292.71951	LR chi² 6.70	Prob > chi²	0.0822		
theta	5.27 e-07	chi2 0.00	Prob > chi²	1.000		

Modell II


Kaplan-Meier survival estimates
1.00
0.75
0.50
0.25
0.00
0
20
40
60
80
100
years
normal sperm counts
controls

Modell II

	HR	SE	z	P>IzI	95% CI	
case vs control	0.950207	0.0855595	-0.57	0.571	0.7964773	1.133608
_cons	0.0000174	5.35e-06	-35.49	0.000	9.49e-06	0.000138
Log likelihood	-242.29776	LR chi² 0.32	Prob > chi²	0.5707		
theta	4.64e-06	chi2 0.00	Prob > chi²	1.000		

Results

- Cases with normal sperm count as young or middle-aged adults had a lower mortality than men with abnormal sperm counts, and also a higher survival well into old age.

- Cases with normal sperm count had the same mortality as age-matched fathers of a first legitimate child, drawn from the general population, who had fathered the child at the time when the case had its semen examined.

Discussion

- Statistical association between sperm count and survival correspond to the estimates in Groos et al. 2006, Jensen et al. 2009 and Eisenberg et al. 2014
- For external controls: having children does not result in better survival
- Some biological mechanism could explain our findings
- Analysis was limited to sperm concentration as indicator for fertility
- Sperm morphology, Sperm motility and total count not considered for analysis

Limitation of the study

- Potential Cohort effects can not be excluded
- No differentiation between primary or secondary sperm abnormalities
- 30-50% of all male infertility problems no causes can be established
- Those individuals receiving infertility therapy are known to be healthier and to live longer than an age-stratified sample of the normal population
- No lifestyle information was available for the baseline

Conclusion

- The association between sperm count and mortality is not mediated by the higher proportion of childlessness among men with low semen quality.

- Semen quality, in particular sperm concentration below 15 Mill/ml independently of realized reproductive success probably is a biomedical predictor of reduced survival in the next decades to come.

- Neither biological nor social paternity may have a protective effect, here.

Thank you for your attention !!!!!