Semen quality as predictor of mortality in a German andrology out-patient cohort: biomedical vs. life-with-children pathways of influence.

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Abstract

There are few studies on semen quality and survival, none of them having information on biological children. Such information is indispensible for distinguishing direct: semen quality may be a biomedical vitality marker - and indirect influences behind such an association: men with poor semen have fewer own children and may live riskier lives. Extending our previous database (Groos et al 2006) we have 2294 men born before 31.12.1941, without co-morbidity, undergoing semen analysis at the University Hospital in Marburg 1949-1995. Of 1397 we have the vitalstatus until 31.12.2010: 571 dead, 826 alive. Regional or semen parameter dependent selection of loss-to-follow-up was excluded. We compare mortality of normal-semen with subnormal- semen men, fitting a Gompertz-Gamma-Frailty Model, the standard parametrical model for advanced ages mortality, controlling for own children. We found semen quality, in particular concentration below 15 Mill/cm² independently of reproductive success being a marker of reduced survival.

Introduction:

Despite decades of research in male reproductive health, in one third of all cases the etiology of male fertility disorders remains unclear. Although new techniques of assisted reproduction help many of affected men to father children, the biomedical implications of poor semen quality remain an important issue. Particularly with regard to the hypothesis of declining sperm quality in Western countries (Shaw et al 2000, Jouannet et al 2001, Jørgensen et al 2002, Merzenich et al. 2010) and the debate on the testicular dysgenesis syndrome (Skakkebaek 2004, Akre and Richardi, 2009) further research on male reproductive disorders is necessary.

Longitudinal studies in Europe and the USA have identified the association between impaired fertility status and the increased prostate cancer risk (Jacobsen et al. 2000, Walsh et al. 2010).

Only three longitudinal studies, however, have analysed the association between post reproductive mortality and male fertility history. A previous paper of our group showed no significant mortality risks for oligospermic or azoospermic men between 1949 and 1985 (Groos et al. 2006). A Danish cohort study found increased mortality among Danish men with impaired Semen parameters between 1963 and 2001 (Jensen et al. 2009). A recent cohort study of subjects in California and Texas (Eisenberg et al. 2014) also found that men being evaluated of infertility had lower mortality risks in comparison to general population. Men with impaired semen parameters in the sample, however, had higher mortality risk in respect to men with normal semen parameters.

But these studies had information on semen quality only, not on subjects' actual reproductive success. Especially men who have their semen evaluated, may live in childless marriages, and may remain childless despite normal semen parameters. Men with compromised semen parameters, on the other hand, may still be lucky enough to father children with a fertile female partner.

For understanding any association between semen parameters and survival, it is essential to distinguish between a biomedical vs. life-with-children pathways of eventual causal influence: Men with subnormal semen parameters may live shorter lives because semen quality is a marker of a reduced vitality in general, or because the more often remain childless and, therefore, live riskier or otherwise unhealthier lives.

Here for the first time we can investigate both influence factors simultaneously, thereby making possible a decision between the two alternative causal pathways.

Based on these previous study results with higher mortality risk for subfertile men we reanalyzed the data by linking information from medical records on semen parameters with survey data to provide additional and detailed information about the fecundity for explaining that association.

Data and Methods

I.

Our database includes medical records of all 2265 born before 31 December 1941 married men who had their semen analyzed at the Department of Andrology at the University Hospital in Marburg during 1949 – 1995. Not included are few cases with foreign citizenship, missing values in sperm parameters as concentration, ejaculate volume, basic motility and morphology information, manifest co-morbidity with known effects on semen, and a voluntary vasectomy in the medical history. The documentation is quite complete.

Of these data, we analyze the 1397 cases with mortality-follow-up completed by 31.12.2010. Of these, 826 men were found alive and 571 cases had died.

Furthermore, from public registrar databases we sampled 569 pair-wise matched controls, ideally married men born in the same year as the case, and having their first child 9 months after the case's semen analysis date.

In 2010-2011 one of us (KB) for her PhD dissertation successfully contacted and interviewed 631 surviving men or surviving proxies of those 1397 with a complete mortality follow-up, obtaining information on biological, step- or adopted children.

II.

The stratification in fertile and subfertile subgroups followed the WHO Laboratory Manual for the Examination and Processing of Human Semen (Cooper et al. 2010, WHO, 2010).

Table 1 World Health Organization reference values for human semen characteristics (lower reference limits)

volume	1,5 ml
motility	40%
total number	39 x 10^6
sperm concentration	15x 10^6
morphology	4%

III.

Motivation for Using Gompertz-Gamma-Model:

As a very common used parametric model the Gompertz-Makeham specification describe the exponentially increase of death rates with age and a corresponding age-independent constant for the mortality section of those is not related to the aging process.

For human population the Gompertz-Makeham assumption leads to an overestimation of observed death rates at ages 80+ that makes the necessity to account for unobserved individual susceptibility more fundamental (Missov and Lenart, 2013). Otherwise ignoring such selective effects of heterogeneity among populations will often maintain the underestimation of the mortality rates at older ages.

Vaupel et al. 1979 introduced 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.

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 (Butt and Habermann, 2004).

The frailty concept requires, for the parametric paradigm, the specification of one statistical distribution. The most popular parametric specification for the frailty variance follows the gamma distribution (Balakrishnan and Peng, 2006). This is one of the most flexible statistical distributions and can be used as an approximation for any other parametric version.

The Gompertz-Gamma-Frailty Model (also known as Perks) with the characteristic asymptotically flat hazard rate is now the Standard Model for Mortality at advanced ages. The frailty is fixed, that means it remains constant over the life course (Finkelstein, 2012 ;Missov and Lenart, 2013).

Follow the Perks Model (Butt und 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 $\Lambda_0(t) = \frac{a}{b}\left(e^{bt} - 1\right)$

Results

Selectivities:

1.

Of those cases with a complete follow-up, 205 cases had a Marburg City address in the medical records, 542 a Marburg-Biedenkopf county address outside Marburg City, 670 an address outside the county. There were no differences in semen quality between the three groups.

2.

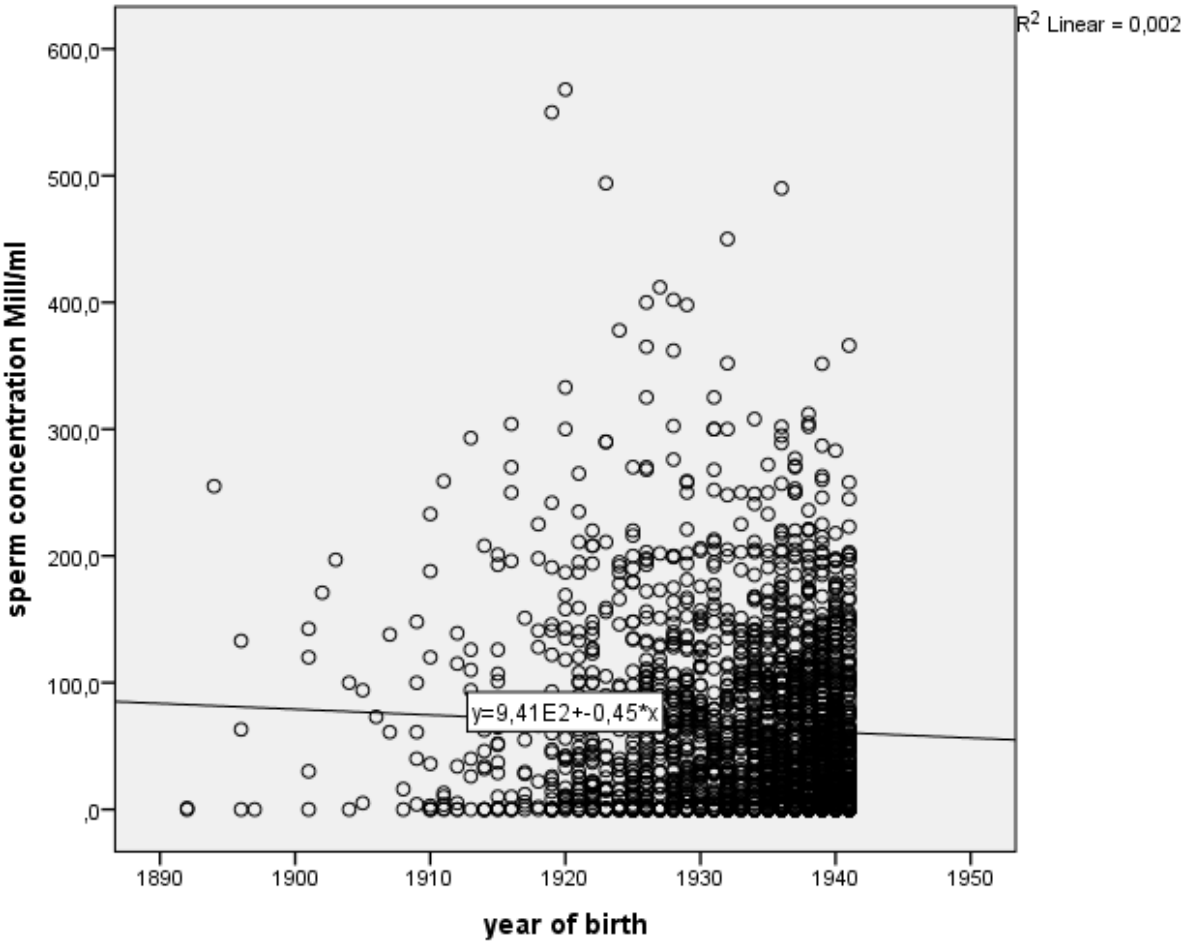
There was no loss-to-follow-up risk depending on semen quality.

Vitalstatus	Semen Status		
	fertile	subfertile	Total
known	976 (69,9%)	421	1397
lost	593 (66,1%)	304	897
Total	1569	725	2294

3.

There was no association between year of birth and semen quality (Figure 1)

Figure 1



Main Results:

1.

There were no difference in survival between men with normal semen parameters, with own biological or own social children and without, nor between these men and the fertile controls. (Figures 2 and 3)

Figure 2 Survival estimates for fertile and external controls

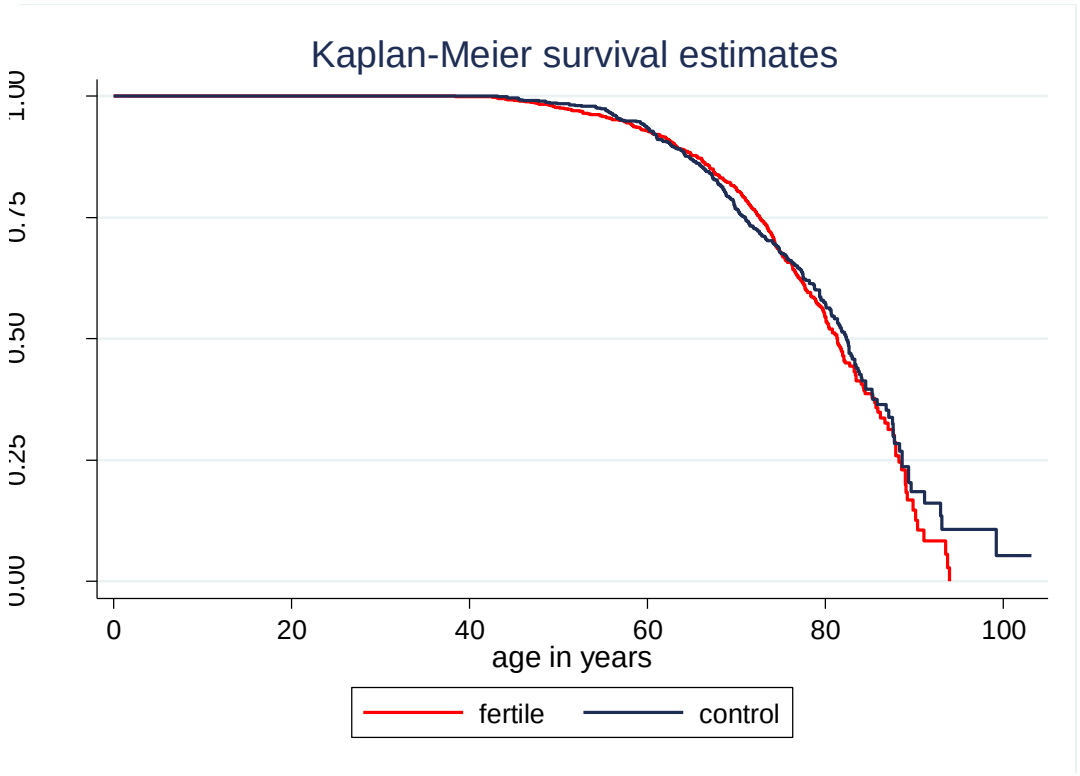
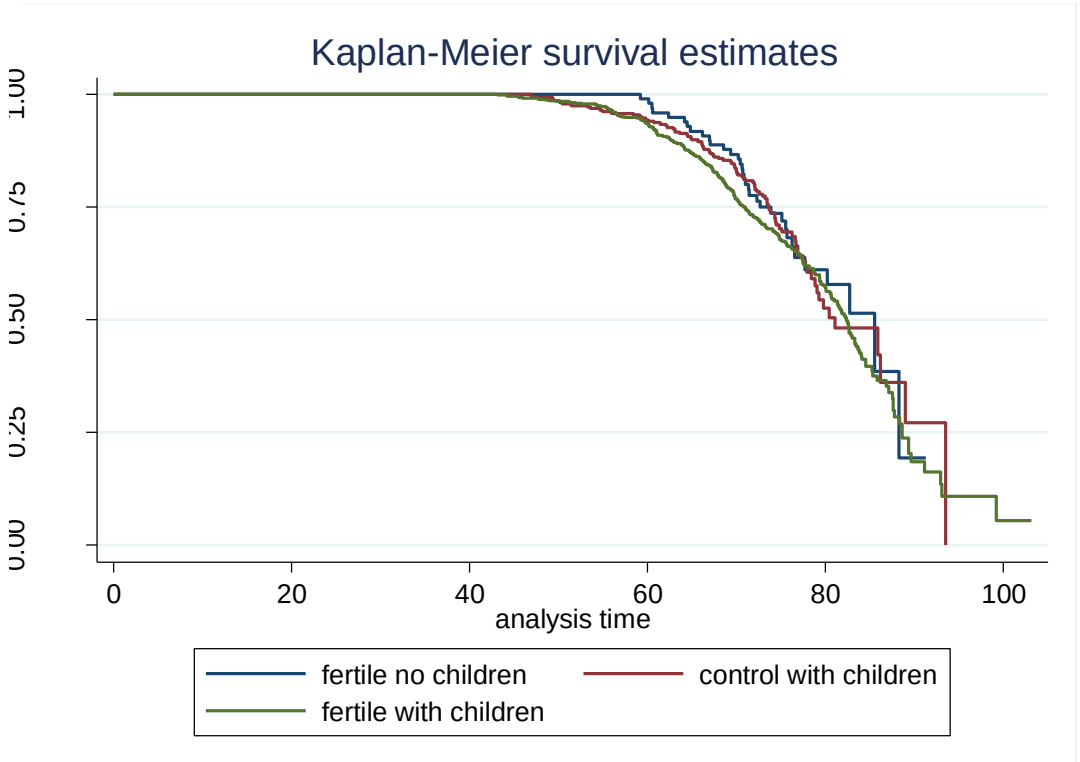


Figure 3 Survival estimates fertile and control under consideration of fatherhood

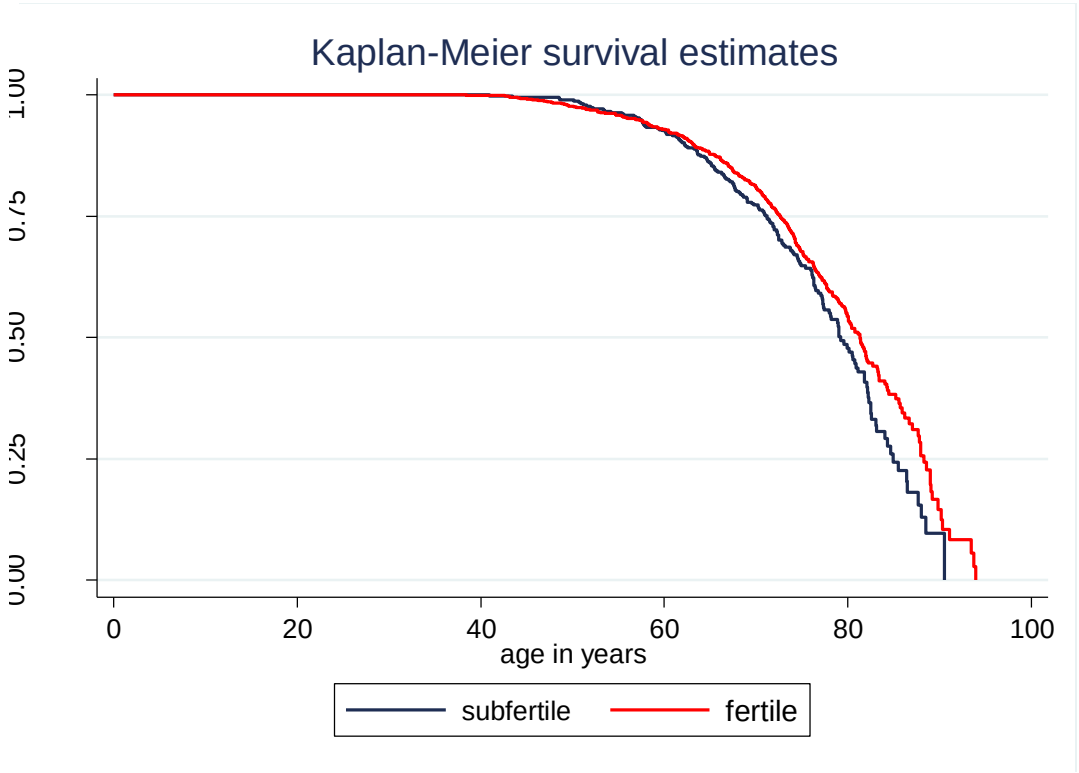


This finding was supported also with a pairwise comparison between fertile cases and controls: survival (dead or alive; among the dead average survival time) was not different between cases and controls.

2.

There was, however, a lower survival of cases with subnormal semen parameters, as compared with normal semen cases. This lower survival independent of whether these men had own biological or own social children or not. (Figure 4)

Figures 4: Survival estimates for subfertile and fertile



3.

One of us (HS) in her PhD dissertation had investigated cause of death of normal and subnormal cases as well as of controls, and had found no differences between these three groups.

Discussion

Here for the first time, we were able to show that the association between low semen quality and reduced survival is not mediated by a higher proportion of childlessness among men with low semen quality.

Limitations of this study.

The oldest cohorts in the study population may have experienced clinical mumps or gonorrhoea in the pre-antibiotics era or any other infection-caused damage to fertility. Therefore, some cohort effect cannot be excluded. Also, with the help of improved ART techniques men with lower and lower semen quality may father children today, which for those cases may improve survival. Again, these findings may not hold unaltered for future cohorts.

Conclusions

Semen quality, in particular sperm concentration below 15 Mill/cm² independently of realized reproductive success probably is a biomedical marker of reduced survival.

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