

Reproductive History, Fertility and Morbidity

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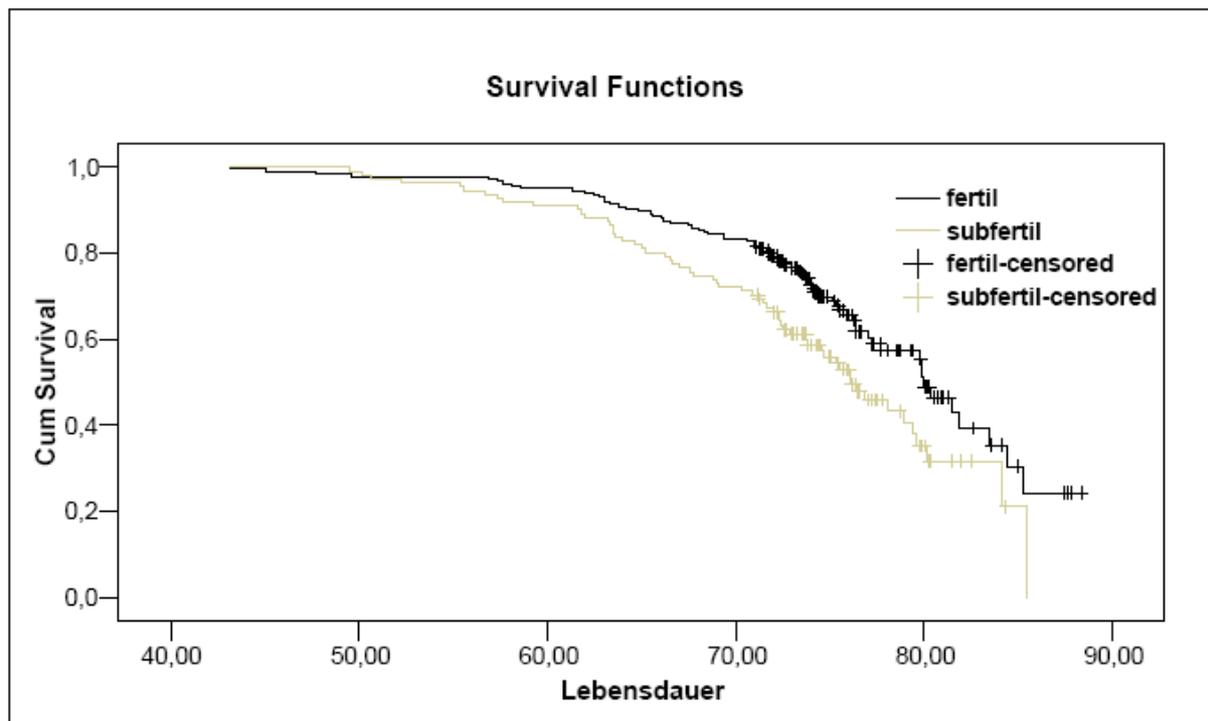
## **Abstract**

Based on the results of a recent study in which a higher mortality rate was found for subfertile men without a specific co-morbidity or previous illness over all age groups in comparison to fertile men, the objective of the current retrospective cohort study is to further explore the association between male fertility and life time morbidity. Based on semen analysis of men with fertility problems the reproductive history (i.e. number of children, type of fertility, forms of paternity), marital status and health related life style in the adulthood will be considered in consequence of the fertility diagnosis to explain the association between male fertility and morbidity. For this reason 1264 men who had a semen analysis done between 1949 and 1985 and which were born before 1938 will be interviewed on the basis of a modified version of the standardized questionnaire of the German Lebenserwartungssurvey of 1998 with main focus on health related variables.

## **Introduction**

Male infertility is a frequent problem with a complex aetiology. In many industrialized countries about 15% of all couples trying to become pregnant are infertile giving a waiting time of 12 month.<sup>i</sup> Although the research on reproductive health gains in importance one third of the aetiology of fertility disorders remains unclear. Particularly with regard to the hypothesis of declining sperm quality in Western countries<sup>ii</sup> the research on determinants of reproductive failures is receiving increasing attention. Thus there are a lot of studies which investigate the relationship between risk factors and male infertility. In most of these studies infertility is referred to as a multifactorial disease and the research interest is on investigating risk factors causing infertility/subfertility. There are four basic groups of factors which can exert a negative influence on men's reproductive potential. Aside from the typical andrological diseases like varicocele, viral diseases, congenital disorders or antisperm antibodies<sup>iii</sup> there are genetic factors which include abnormalities in the number and structure of chromosomes.<sup>iv</sup> Another group of factors with adverse effect on fertility are exposures to environmental agents like xeno-oestrogens or antiandrogens which are disrupting the hormonal balance and to occupational agents like toxic substances and high temperature which are suppressing spermatogenesis.<sup>v</sup> The fourth group of factors can be referred to as life style factors include nutrition, abuse of alcohol and tobacco, regular use of hot baths and severe stress.<sup>vi</sup> Furthermore there is a cumulative effect of different factors on sperm production. Whereas the most studies are concerned with the causes of male infertility/subfertility there are only a few studies which investigate the outcomes of male infertility/subfertility on morbidity and/or mortality. Most of them however refer to Third World Countries like Africa, Asia and South America, where infection diseases, poverty and risky sexual behaviour are prevalent.<sup>vii</sup> The target of the current study is to investigate the association between fertility and morbidity. The exploration is based on the results of a recently published study<sup>viii</sup> in which surprisingly a higher mortality risk was found for subfertile men without a specific co-morbidity or previous disease in comparison to fertile men over all age groups (see Figure 1). The underlying assumption of that study was that disorders of spermatogenesis are an indication of an exposure of the male organism to noxious agents and

therefore could serve as an indicator for their general state of health. From this it follows that men with worse general state of health has a shorter life expectancy than men without such a disorder.



**Figure 1:** Survival functions of fertile and subfertile men; early natal-cohorts (In: Groos S: Lebenszeit-Mortalität von Männern mit normalen und subnormalen Spermienkonzentrationen. Diss., Marburg 2005 (p. 60))

By investigating the association between fertility and life time morbidity two possibilities should be taken into consideration, i.e. the direct and indirect effects of involuntary childlessness on male morbidity. In the first case infertility/subfertility can be considered as a disease per se with objective physical symptoms (abnormal semen characteristics) which manifest in higher morbidity resulting in higher mortality risk. As an example we can take studies on the association between semen characteristics and testicular cancer in which a higher risk of testicular cancer could be found for men with abnormal semen characteristics.<sup>ix</sup>

In the second case infertility/subfertility can be considered as an exposure factor which in consequence of the infertility diagnosis is a stressful life event for the men involved and thus has negative indirect implications for the morbidity by influencing other areas of life associated with ill health. In this context the investigation of the history of the patients after the infertility diagnosis is of great importance. Aspects like paternity and their alternative forms, marital status, type of infertility (primary and secondary) should be taken into consideration by exploring the relationship between fertility status and morbidity. There is a plenty of studies about the association between marital status and morbidity and/or mortality which have provided evidence for a protective effect of marriage and paternity on the psychological and physical wellbeing of individuals and thus mortality.<sup>x</sup> As a result of this separation, divorce or the fact having no children in consequence of the infertility diagnosis may have negative effects on the health status of the affected men.

## **Conceptual Framework**

### **Objectives**

Based on the finding that subfertile men without a specific co-morbidity or previous disease have a higher mortality risk and thus a shorter life expectancy over all age groups than fertile men, we want to explore the association between fertility status and life time morbidity for that study population and clarify the mechanism responsible for the association between fertility and morbidity. A plausible biological mechanism as an explaining factor for the higher mortality and shorter life span could not be found yet by the literature review. Thus to explore the association between fertility, life time morbidity and mortality the following possibilities should be considered:

- a specific comorbidity or specific noxious agents with unfavourable influences on the spermatogenesis were already existing by the investigation for a number of cases with subnormal sperm findings but were not diagnosed or documented (confounder);
- men with subnormal sperm findings had a different life course: because of the higher prevalence of childlessness more unstable partnerships, more frequent changes of employment and residence and a more risky behavior (drift);
- intact fertility is per se a life prolonging specific disposition (direct specific causation);
- intact fertility is – because of a more frequent successful reproduction - a life prolonging specific disposition (indirect specific causation).

### **Hypotheses**

To explain which of the possibilities come into question, we do not only consider the cumulative mortality in dependence of the sperm concentration but also

- the life time morbidity of the survivor and the deceased cases and
- the reproductive biography of these cases: low sperm density does not exclude reproduction as well as intact fertility is only one of many conditions of actual reproduction.

For this reason we want to test the following hypotheses:

- The morbidity profile of men with oligozoospermia and azoospermia is different from that of men with normozoospermia.
- The prevalence of morbidity of men with oligozoospermia and azoospermia is different from that of men with normozoospermia. The latter will be rarely and less (critically) ill.
- Fertility and fecundity interact with morbidity: by the same fertility status childless men will have a higher and/or a different morbidity as men with children.
- The life course trajectory has an impact on morbidity/mortality. Stresses and strains in marriage/partnership in consequence of fertility disorders are the real cause.
- Fertility and fecundity interact with mortality: by the same fertility status childless men will have a higher mortality than men with children.

## **Materials and Methods**

### **Study population**

Database are medical records of 1461 men in couples with fertility problems who had a semen analysis done at the fertility and sterility office of the department of andrology at the University Hospital in Marburg during 1949 and 1985 and which were born before 1938. Following information was recorded in nearly all cases:

- name
- birth date/age,
- ejaculate volume,
- pH-value,
- sperm motility and sperm morphology,
- sperm concentration,
- co-morbidity with known effects on the spermatogenesis.

Assuming another health biography and other expositions by foreign-born patients and therefore uncontrollable selectivity, we only analyze cases that did not have a foreign citizenship. In 18 cases there was a missing value of sperm concentration in the semen analysis. Furthermore 170 cases were excluded from the analysis for which the following diseases were identified that might cause infertility:

- bilateral vasectomy
- current or previous orchitis, epididymitis and epididymo-orchitis
- current or previous mumps-disease; can/may cause an orchitis
- gonorrhoea
- infection with Marburg-Virus; can/may cause an orchitis
- urogenitale form of tuberculosis; can/may include orchitis, epididymitis and vesiculitis
- testis-malposition: maldescensus testis, cryptorchism, groin-testis (?) as well as with these diagnoses associated orchidopexia
- hydroceles
- previous testosterone-supplementation
- current or previous swelling of testis or epididymis
- testicular hypoplasia and atrophy

Further 9 cases were excluded because of both missing values in sperm concentration and pre-existing diseases. After applying these excluding criteria we have a study population of 1264 cases. Based on this sample size, information of the vital status through the registration office was collected. For 584 cases the vital status could be found out. Thereof 109 cases were from the city of Marburg, 201 from the district Marburg Biedenkopf, 274 were out of the district Marburg Biedenkopf. 349 cases were identified as being alive and 235 cases as deceased. For 680 cases the vital status could not be investigated because of missing address in the medical record and because of the fact that the

relevant cases could not be identified as residents of Marburg at the time of the sperm analysis or at a later date.

In a test for selectivity we could further demonstrate that patients living at an address in the city of Marburg do not differ from patients resident in the district Marburg Biedenkopf and out of the district Marburg Biedenkopf in terms of the distribution of sperm concentration or of the prevalence of normo-, oligo- und azoospermia and thus there is no difference between patients with and without a known address with regard to the fertility status. We could provide evidence against the possibility that among cases outside of Marburg there are more pathological findings as they are usually referred by a dermatologist to venereal disease clinic whereas residents of the city of Marburg more frequent are referred directly by the gynaecologist of the partner to the clinic for conducting a sperm analysis.

### **Study Design**

In our study we conceptualize fertility not as a typical andrological disease for which risk factors should be identified but rather as a risk factor for male life time morbidity. We assume that the diagnosis of infertility/subfertility has indirect negative implications on male morbidity in so far as it has an unfavourable influence on the further course of life regarding partnership and health related life style, factors having influence on health related variables. According to the determination of fertility status as exposure variable and life time morbidity as outcome variable we conduct a retrospective cohort study. In this context we refer to the term exposure "as a contact of an individual with an agent through any medium or environment."<sup>xi</sup> Referring to a concept of exposure applying to external and internal agents, fertility status can be considered as both - a biologic agent in the body (disorders of the spermatogenesis) as well as a societal agent - an incriminatory event in the live time.

### **Study variables**

To asses the association between fertility and life time morbidity the following variables will be considered:

#### **Independent variable**

##### **Fertility status**

For exposure assessment we use medical records which are available for nearly each subject in the study population. The medical records contain information on semen characteristics obtained by a semen analysis which allows the male reproductive function to be evaluated directly. The primary advantage of medical records is that they provide prospectively recorded information. Thus the exposure assessment based on historical records is immune to recall bias and the standardized recording of laboratory data provides valid information.<sup>xii</sup> For the assessment of the exposure variable we choose sperm concentration. The assignment to both groups, the exposed and non exposed subjects, was carried out by the analysis of the sperm concentration which according to the WHO declaration allows a classification to normozoospermia by a sperm concentration  $\geq 20$  Mio./ml, to

oligozoospermia by a sperm concentration <20 Mio. /ml and to azoospermia by 0 Mio./ml. Men with normozoospermia are referred to as fertile and men with oligo- and azoospermia as subfertile.<sup>xiii</sup> The decision to include only the sperm concentration in the analysis of the association between fertility status and morbidity is founded by the development of methods for the assessment of the semen related parameters. Compared to sperm morphology and sperm motility the methods for the assessment of sperm concentration remain the same during the investigation period, while for the measure of sperm morphology and sperm motility different criteria were applied.<sup>xiv</sup>

## **Dependent variable**

### **Morbidity**

For measuring life time morbidity as the outcome variable we use a modified and validated version of the standardized questionnaire of Lebenserwartungssurvey of 1998 with main focus on health related variables.<sup>xv</sup> For cases which already died a proxy interview with surviving members of the family, i.e. wife or children will be conducted. Thus the measurement of health outcomes is based on the self-assessment of health status by the interviewed persons. The indicators introduced to measure self rated health were account in many studies as strong predictors for future morbidity and mortality.<sup>xvi</sup> To measure self reported morbidity amongst others the following health indicators are applied:

- perceived general health by the question: "How would you describe your present health status?"
- health satisfaction by the question: "How satisfied are you with the following aspects of life?"
- functional health restrictions by the Activities of Daily Living (ADL)-Scale
- disorders or their absence by a list of symptoms
- diseases or disabilities or their absence by a list of diseases
- psychosocial disorders or well-being based on a list with psychosocial symptoms

Furthermore the following health indices are included:

- body mass index BMI by information on height and weight
- number of consultation and stay in hospital over night during the last 12 month
- frequency of intake of drugs by a list

## **Intermediating variables**

### **Marital status and partnership history**

In a multitude of studies evidence could be provided for the association between marital status and morbidity/mortality.<sup>xvii</sup> There are also investigations on the impact of infertility on marital status. To explore the influence of marital status in general and the partnership biography in particular on the association between fertility status and morbidity the following items are used:

- actual marital status by using the categories married and living with partner, not married living with partner, married living separated, divorced, widowed, never married, living alone

- date of birth of the spouse/partner
- number of previous spouses/partners
- duration/date of marriage/partnership
- marriage/partnership satisfaction
- coping with losing the spouse/partner

### **Paternity and reproductive history**

As an effect of marital status could be proven on morbidity/mortality we are also interested in the effect of paternity and its alternative forms on the association between fertility status and morbidity.

Thus we want to consider the following variables:

- number of children
- relationship of children to parents (biological, step- and adopted children)
- date of birth/death of children
- gender of children
- frequency and intensity of the contact with children

Another related variables we want to survey for further investigation of the association between fertility status, fecundity and inheritance are:

- marital status of (own) children
- form/mode of parenthood of (own) children to their children (social/biological)
- number of grandchildren
- date of birth/death of grandchildren
- gender of grandchildren
- number of great grandchildren
- number of (own) siblings
- gender of siblings
- date of birth/death of siblings
- marital status of siblings
- number of children of siblings
- form/mode of parenthood of siblings to their children (social/biological)
- number of grandniece/grandnephew

### **Health related life-style**

#### **Health related behavior and attitudes**

On the one hand there is much literature about the impact of life style on fertility<sup>xviii</sup>, on the other hand about the impact of life style on morbidity/mortality<sup>xix</sup>. Nevertheless there is no literature explicitly investigating the association between life style, fertility and morbidity. For this reason we want to investigate the influence of life style on the relationship between fertility and morbidity.

The concept of life style is often used to explain differences in morbidity and mortality by including the variable health related behavior into the exploration which is according to the two-dimensional concept of health related life-style<sup>xx</sup> one of its constituting elements. In the literature there is a clear agreement about health related behaviors that are of great importance for the health status and thus adopted by us. These are primarily the following:

- nutrition based on eating habits and frequency of healthy and unhealthy foods
- smoking based on frequency and amount of cigarettes
- physical activity based on frequency of sport activities
- regular alcohol consume based on the frequency and amount of the consumption of alcoholic beverages
- overweight based on BMI by height and weight
- utilization of health care and preventive measures

In addition to health related behavior we also factor health related attitudes as the second constitutive element of life style into the explanation of morbidity because they have an impact on health related behavior. In the literature there are mainly three models explaining the association between health-related attitudes and health-related behavior: "Sense of Coherence"<sup>xxi</sup>, "Health Belief Model"<sup>xxii</sup> and "Locus of Control Model"<sup>xxiii</sup>. We consider the following health related attitudes:

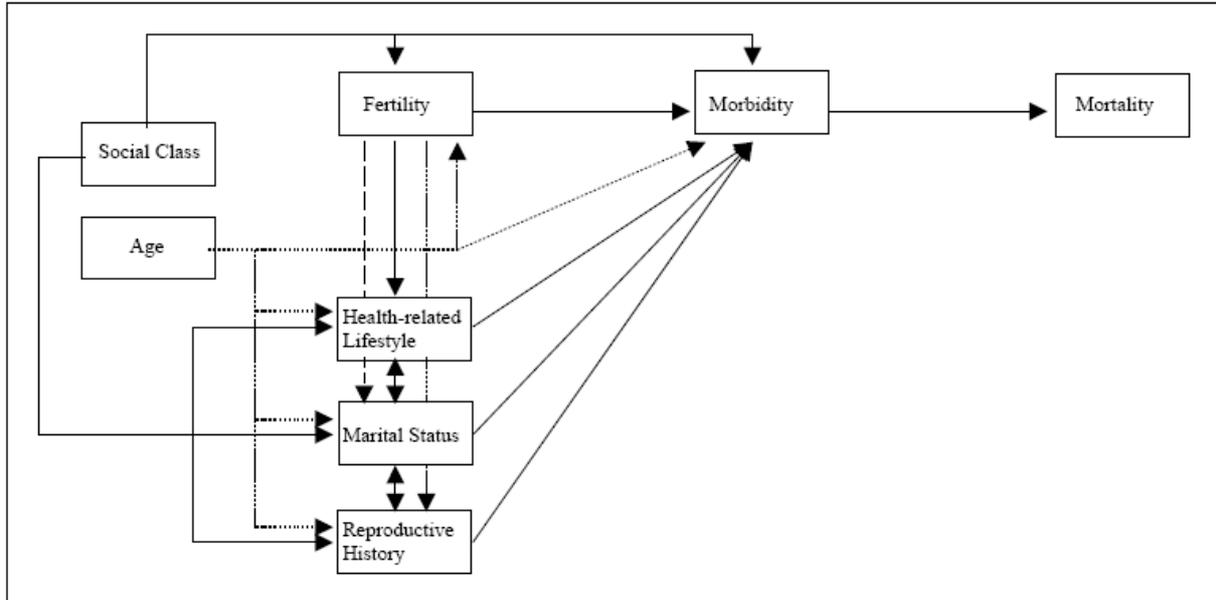
- belief in influencing the own state of health
- list of statements about how to behave in the case of disease

Regarding the relationship between health-related life style and morbidity it should be considered that the current health status can determine the health-related life style as well as be the consequence of it.

### **Social class**

Because not only health related life style is determined by external circumstances<sup>xxiv</sup> we want to investigate the influence of the variables income, education and occupation as the classical indicators for social class on the relationship between fertility and morbidity by using the already available finding about the effect of social class on fertility<sup>xxv</sup> on the one hand and on morbidity<sup>xxvi</sup> on the other hand. For this purpose we measure the variable social class by the following indicators:

- graduation
- professional education or tertiary education
- last practiced occupational activity
- last occupied position



**Figure 2:** Causal model about the association between fertility and morbidity

## Methods

### 1. The Estimation of Odds Ratios

In a first step we want to estimate the Odds for fertile and subfertile men according their risks in morbidity. For locating the overestimation of the truth OR therefore two different methods are used for approximating the KI.

Approximative KI of Woolf (1955)

$$KI(OR) = \left[ OR_{est} \cdot \exp \left\{ \pm u_{1-\alpha/2} \cdot \sqrt{\frac{1}{n_{11}} + \frac{1}{n_{10}} + \frac{1}{n_{01}} + \frac{1}{n_{00}}} \right\} \right] \quad (1)$$

if estimation is incumbent on Gaussian distribution.

In using the difference of two Logits this interval is also called as Logit-Limits. The most disadvantage of Woolf's approximation is that in cases with small cell frequencies it can't be expected that the estimation for KI leads to biases results.

Alternative in context to small epidemiological studies it's possible to use the asymptotic KI of Miettinen (1976). This method is a combination of the approximation of  $\chi^2$  and the quadratic approximation of log Odds Ratios

$$KI_{Miettinen}(OR) := \left[ OR_{est} \frac{1 \pm \frac{u_{1-\alpha/2}}{\sqrt{\chi^2}}}{\sqrt{\chi^2}} \right] \quad (2)$$

Under the assumption of Odds Ratios = 1 or  $\approx 1$  the KI of small epidemiological studies can be used for the estimation of Relative Risks.

## 2. Adjusting age-specific effect as confounder

For generating successive regression models it's indispensable to test the data set on homogeneity. We can suppose diversely likelihoods or Odds for fertility and morbidity status because of different age-specific composition. To avoid a confounding effected overestimation of the truth association it is common to use the Mantel-Haensel-Estimator. Our probands are divided in two different age groups.

$$OR_{est} = \sum_{k=1}^I W_k \cdot OR_{est,k}, \text{ then } W_k := \frac{\frac{n_{10k} \cdot n_{01k}}{n_{\bullet\bullet k}}}{\sum_{k'=1}^I \frac{n_{10k'} \cdot n_{01k'}}{n_{\bullet\bullet k'}}}, k = 1, \dots, I. \quad (3)$$

The stratified analysis is suited because of the adjustments for confounding. The Mantel-Haensel-Estimator is a weighted mean of the estimators for every stratum. The weights are the approximation for the reciprocal of the variances of the estimator  $OR_{est}$ .

Under the hypothesis  $H_0$  Odds Ratio =1 is  $OR_{est,ko}$  a combined estimator of the stratified results for the common OR following the  $\chi^2$  statistics

$$\text{with } X^2_{Hom-1} = \sum_{k=1}^I \frac{(\ln(OR_{estk}) - \ln(OR_{est,ko}))^2}{\text{Var}(\ln(OR_{estk}))} \quad (4)$$

$$\text{then } \text{Var}(\ln(OR_{estk})) = \left( \frac{1}{n_{11k}} + \frac{1}{n_{10k}} + \frac{1}{n_{01k}} + \frac{1}{n_{00k}} \right) = vk^{-1}, k = 1, \dots, I.$$

By comparing the quadratic differences of log Odds-Ratio-Estimator (observed) in the strata to the combined estimator (expected in case of homogeneity) their distance is supposed to be small in case of homogeneous strata. Following to our context if the distance of the observed Odds for the younger and older cohort and the expected combined Odds containing both subgroups is very small then the strata will be homogeneous.

Then follow  $\chi^2_{Hom-1}$  with hypothesis  $H_0$   $\chi^2$ - distributed with  $(I-1)$  degree of Freedom, the decision  $(1-\alpha)$  has to be denied, if

$$\chi^2_{Hom-1} > \chi^2_{t-1; 1-\alpha}$$

After the test-statistics on homogeneity are already done we want to focus on the generation of four logistic models. To avoid inconsistent results we use age-standardized variables for fertility and morbidity status because both are effected by events and changes over the life course.

Not only the age-specific variation in fertility and morbidity has to be examined, the fertility and morbidity status also might have changed according the cohorts. Hence we are also generating dummies for cohorts to control the cohort-specific variation for our regressors.

$$\text{logit}(P) = a + b_1 \cdot X^{(1)} + b_2 \cdot X^{(2)} + b_3 \cdot X^{(3)}, X^{(1)} X^{(2)} X^{(3)} = 0, 1 \quad (4)$$

P - probability for being infertile/fertile with interval (0,1)

$$\text{OR}_1 - \exp(b_1)$$

$$\text{OR}_2 - \exp(b_2)$$

$$\text{OR}_3 - \exp(b_3)$$

$$X^{(1)} = 1, \text{ if cohort, cohort1; } 0 \text{ if cohort, not cohort 1}$$

$$X^{(2)} = 1, \text{ if cohort, cohort2; } 0 \text{ if cohort, not cohort 2}$$

$$X^{(3)} = 1, \text{ if cohort, cohort3; } 0 \text{ if cohort, not cohort}$$

### 3. Maximum-Likelihood-Estimation

In previous analysis the logistic models couldn't regard definitively the estimations of the probabilities of disease for the total study population. The Maximum-Likelihood-techniques don't consider the individual probabilities, but rather the total probability of disease for all probands.

Referring to the assumption of statistical independency between exposure and non-exposure we are formulating the following. To simplify the maximisation of function L habited by the parameters of the model we use the logarithm of the Log-Likelihood-Function.

$$\begin{aligned} l(a, b_1, \dots, b_m) &= \ln[L(a, b_1, \dots, b_m)] = \sum_{i=1}^n \ln[P(K_i = j | X_i^{(1)}, \dots, X_i^{(m)})] \\ &= \sum_{\text{invalid}} \ln[1 + \exp\{-a - b_1 \cdot X^{(1)} \dots - b_m \cdot X^{(m)}\}]^{-1} \\ &= \sum_{\text{healthy}} \ln(1 - [1 + \exp\{-a - b_1 \cdot X^{(1)} \dots - b_m \cdot X^{(m)}\}]^{-1}). \end{aligned} \quad (5)$$

The Wald-Test is a convenient statistic for simultaneously tests for more than one parameter. This method gives information about the consistence and the real relationship of every regressor and dummy.

$$\begin{aligned} Z_j^2 &= \frac{b_{estj}^2}{\text{Var}(b_{estj})}, j = 1, \dots, m, \\ \text{with } Z^2 &= (b_{est1}, \dots, b_{estm})^T \cdot K^{-1} \cdot (b_{est1}, \dots, b_{estm}), \\ K' &= \text{Cov}(b_{est1}, \dots, b_{estm}) \end{aligned}$$

### **Expected Results**

Because the study is not finished i.e. the results of the standardized interview are not available yet no results can be presented until now. With regard to the association between fertility status and morbidity it is expected that differences in life time morbidity between fertile and infertile men with higher morbidity risk for subfertile men are not the result of a direct causation of fertility on life time morbidity in the sense of a biological mechanism. Differences in morbidity between the two groups, i.e. infertile and fertile men could then be attributed to differences in the reproductive history, in health related life style and marital status in the adulthood which depend on the fertility diagnosis. Thus there should be no differences in morbidity between subfertile and fertile men under the same reproductive conditions.

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