AALBORG UNIVERSITET

Test of sperm DNA integrity and the development of mental illness in the offspring, a preliminary cost-effectiveness analysis.

Medical Market Access - Master's thesis project

Date 27/5-2020

Adrian M. Udesen - 20125755

Nicklas S. Poulsen - 20153386

Vejleder: Louise Hansen

Physical pages: 27

Normal pages: 20.19

Abstract

Nowadays sperm assessment has only been based upon parameters such as sperm count, morphology and motility, however, recent evidence suggests that sperm DNA assessment can be used to determine overall sperm quality and could be a predictor of general health. Additionally, the assessment of the sperm DNA integrity could also be a predictor of the future health of the offspring since it has been discovered that increased paternal age increases the risk of the offspring becoming diagnosed with a mental disease such as schizophrenia or bipolar disorder. This, together with the fact that increased paternal age results in decreased DNA integrity of the sperm, forms the basis of this cost-effectiveness analysis. This study aims to investigate the potential economic benefit if the assessment of sperm DNA integrity could result in a lower incidence of schizophrenia and bipolar disorder. However, since the data is scarce, a hypothetical difference in the risk of the offspring developing either schizophrenia or bipolar disorder of 1% will be investigated. Additionally, this paper utilises a decision-analytic model created in TreeAge Pro 2019 resulting in an ICER for both schizophrenia and bipolar disorder. Furthermore, both a probabilistic sensitivity analysis (PSA) and a tornado diagram is performed. The results showed a dominating result in favour of the sperm DNA test both regarding schizophrenia and bipolar disorder without discounting. In conclusion, this preliminary economic evaluation indicates a significant health economic benefit if the sperm DNA test can be used to decrease the risk of an offspring becoming diagnosed with either schizophrenia or bipolar disorder with 1%.

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Introduction

Since the 1970s, men's sperm count has been reduced by approximately 50% (1). This trend was confirmed in a large study in which 40,000 men participated. Additionally, another study showed similar results, indicating that sperm quality had a downwards trajectory dating back to the 1940s (2). The changes in men's sperm quality can be contributed to both environmental and lifestyle factors since the changes have occurred rapidly. The overall lowering of men's sperm quality corresponds well to the fact that more and more couples require fertility treatment, which presents a burden to both society and the couples themselves. The increase in the demand for fertility treatments can either be contributed to the fact that better treatments exist nowadays than in the past, but it can also be because more men have fertility problems (2).

The declining sperm count also appears to be an indicator of the general health of the men. Studies have shown that lower sperm count observed in the young age may be correlated with long term health of the man (3). A Danish study from 2017 conducted on 5,370 men showed that men with a sperm count less than 5 million sperm cells pr. millilitre would be in contact with the healthcare system 6-7 years earlier in comparison to men with a sperm count of about 200 million pr. millilitre. The most frequent reasons for contacting the healthcare system was cardiovascular diseases, diabetes, cancer among other chronic diseases (4).

Since 2000, testing of sperm DNA integrity has become more accepted as a new sperm parameter which is closely linked with male fertility (5). Baumgartner et al. (6) showed a link between DNA damage in sperm and DNA damage in somatic cells. According to Baumgartner et al. (6), a clear link exists between reduced fertility, increased disease risk in the male and increased risk of de novo mutations in the offspring. Interestingly, Kong et al. (7) demonstrated that new cases of schizophrenia appear to be caused by a high number of new mutations in the offspring which almost exclusively is of parental origin. Studies of various mental diseases in the offspring (schizophrenia, autism and bipolar disorder) had already been linked with increasing age of the parent (8)(9)(10). One hypothesis is that the new mutations originate from DNA damage and inefficient repair in the testicular stem cells which then accumulate with increasing age of the male (11). This theory was challenged by Marchetti and Wyrobek (12) who demonstrated that DNA damage in sperm cells may occur during the late phases of spermatogenesis as a result of declining capability of the mature sperm cell to repair DNA. Various environmental, as well as lifestyle factors, may be responsible for the increase in DNA damage which after fertilization is incorrectly repaired by the oocyte leading to new mutations. A good example is tobacco smoke which has been directly linked with an increased level of DNA damage in the sperm cells as well and new mutations in the cord blood (13).

It appears from the above that improving environmental and especially lifestyle factors in the male may lead to better fertility as a result of a reduced level of sperm DNA damage. One of the first studies to demonstrate this effect was Håkonson et al. (14) who showed that loss of weight led to improved sperm DNA integrity. This effect may be due to a reduction in insulin resistance (15). Another study has focused on improvement in DNA integrity after an

intervention which was individually designed and focused on diet, weight loss, exercise, intake of vitamins and minerals and cessation of smoking (16).

In the present paper, we have focused on the potential beneficial effect on the risk of developing mental disorders in the offspring of the man improves sperm DNA integrity before conception. We have limited this to only focus on bipolar disorder and schizophrenia. We have chosen not to look at long term effects for the male such as lower incidence of various cancers, diabetes and cardiovascular disease. Although a positive effect may be observed, it is still possible that the men revert to a less healthy lifestyle once the desired pregnancy is achieved, meaning that the potential health benefit of increasing sperm DNA integrity only applies to the offspring.

Several different methods have been described concerning the assessment of sperm DNA integrity. In this report, we focus only on results achieved with Sperm Chromatin Structure Assay and other methods based on this protocol. This method is using flow cytometry which makes results objective and with appropriate quality control also has a very high precision which is essential for correctly diagnosing the level of DNA integrity/damage. The outcome of the afore-mentioned sperm DNA test is expressed as a DFI value, which expresses the percentage of sperm cells which have double-stranded DNA breaks (5).

A DFI value below 15% is categorized as normal DNA integrity, while a DFI value between 15% and 25% are categorized as suboptimal and lastly, a DFI value above 25% is categorised as poor (5). Additionally, it has been suggested that increased paternal age is positively correlated with an increased DFI value (17). This could, together with the indication that increased paternal age results in a higher risk of the offspring developing various mental diseases, (8)(9)(10)(18) indicate that an increased DFI value might be positively correlated with the risk of the offspring developing a mental disease. The mental diseases include, as mentioned earlier, ADHD, Bipolar disorder, autism and schizophrenia (5).

However, since there is no evidence that there is a direct link between increased DFI and the risk of developing a mental disease, this preliminary cost-effectiveness analysis will be carried out under the assumption that there is a direct link between elevated DFI and the development of mental disease in the offspring. Additionally, another important assumption made in this study is that only a very low difference in the risk of the offspring becoming diagnosed with a mental disease is assumed since the evidence available is scarce. The aim of the study, therefore, is to investigate the potential economic benefit if the sperm DNA test can be related to a decrease in the incidence of mental diseases in the offspring. This is important to be able to determine if more research funding should be invested into the area of investigating the possible correlation between sperm DNA integrity and the risk of the development of a mental disease in the offspring.

Lastly, the authors of this paper have to stress the fact that the sperm DNA test is only a test to assess the integrity of the DNA in the sperm cells. It is not a cure, nor a treatment since the male have to change his lifestyle, such as losing weight (5), to positively change his DFI value.

1 Background

1.1 Mental diseases

As mentioned before, the assumption that DFI is positively correlated with the development of different mental diseases is in this paper assumed. Two of the mental diseases that has the largest interest is schizophrenia and bipolar disorder because of their incurable nature and persisting symptoms (19)(20). Because of their incurable nature and persistent symptoms, it makes the costing more equal throughout all patients as compared to autism or ADHD. Patients with ADHD and autism differ within a spectrum of severeness, which therefore makes costing per patient difficult, which is why this study will investigate only schizophrenia and bipolar disorder (21).

1.1.1 Schizophrenia

The risk of developing schizophrenia has been shown to increase in the offspring with increased paternal age (8) since one study has estimated that about 26,6% of schizophrenia cases could be linked to increased paternal age (22). Malaspina et al. (22) investigated the link between paternal age and the development of schizophrenia with the theory that mutation rates within the sperm DNA increase with the age of the father. 87,907 participated in the study and out of the 87,907 participants, 1,337 were admitted to psychiatric units, whereas 658 were diagnosed with schizophrenia. After checking for confounders such as socioeconomic status and ethnicity, the study found that paternal age was a strong predictor of the development of schizophrenia. The study concluded that compared to men aged younger than 25 years, the relative risk of the offspring developing schizophrenia increased stepwise every five years. This meant that the relative risk was 2.02 (95% CI: 1.17-3.51) from age 45-49 and 50+ reaching 2.96 (95% CI: 1.60-5.47). After adjusting for paternal age, the age of the mother had no significant effect (22). The findings in the study support the hypothesis that the development of schizophrenia could be associated with paternal age (22).

In Denmark, there are 3,500 new cases of schizophrenia every year (23). This corresponds to approximately 16,000 psychiatric admissions, which equals to 32% of all psychiatric admissions (23). 280,000 outpatient hospital visits were because of schizophrenia (23), which equals to 30% of all psychiatric outpatient visits. Furthermore, 6% (560) of all early retirements is due to schizophrenia (23). People diagnosed with schizophrenia, who are working, have 280,000 more sick days from work than people without schizophrenia. This equals to 1% of all sick days in Denmark (23). All in all, schizophrenia costs approximately 2,610 Mio. Danish kroner in treatment and 5,650 Mio. DKK in lost productivity every year (23).

1.1.2 Bipolar Disorder

Bipolar is another mental disease which represents a great burden on society. Prevalence of this disease is estimated to be between 1.2% and 1.6% (24). Wyatt and Henter conducted a study in 1991 (25) estimating that the costs of bipolar disorder in the US was around 45 million dollars,

which exceeds the total costs for depression or diabetes alone(26), which indicates that bipolar disorder also represents a high burden on societies.

It is due to these before-mentioned numbers that the authors of this paper take these two mental disorders into account when creating the decision-analytic model.

2 Methods

In this paper, a preliminary cost-effectiveness analysis has been conducted. This preliminary cost-effectiveness analysis is based on two separate decision-analytic models since two distinct mental illnesses, namely schizophrenia and bipolar disorder was selected to investigate the economic impact if a theoretical difference of 1% was to occur with the use of the sperm DNA test. The rationale for selecting a simple decision tree is because this preliminary economic evaluation is only meant to investigate whether there is an economic incentive to launch further clinical research into the long-term effects of increased sperm DNA damage, which is also why a cost-effectiveness analysis has been chosen. Additionally, since there is scarce evidence in this field, creating a more advanced model, such as the Markov model would not be possible as of 2020. The decision-analytic models were created in TreeAge Pro 2019.

2.1 Perspective and time horizon

A societal perspective with a lifetime horizon was desired in this paper for both schizophrenia and bipolar disorder, however, it was only possible to achieve a societal perspective concerning schizophrenia since a general lack of Danish representable cost data about bipolar disorder exists. Therefore, only a healthcare perspective to cost data of bipolar disorder was adopted. Yet, it was possible to find costs related to lost productivity regarding bipolar disorder, but only in an American setting, and since the Danish and American societies are so very different, the authors chose to not include the American data. However, this means that a conservative approach in terms of estimating costs associated with bipolar disorder was made.

Lifetime is in this paper defined as from onset of mental disease until death. The average onset of schizophrenia is at the age of 20 (27), while average onset of bipolar disorder is at the age of 21(28) . Furthermore, the average life expectancy for schizophrenia patients is 66.25 years (29), while the average life expectancy for patients suffering from bipolar disorder is 63.75 years (30). The lifetime horizon used in this paper thereby becomes 66.25 years for schizophrenia patients and 63.75 years for patients diagnosed with bipolar disorder.

2.2 Design

The decision-analytic models created to investigate the aforementioned difference of 1% is created in the software TreeAge Pro and consists of a simple decision tree with an intervention arm and a baseline arm. In the intervention arm, males have taken the sperm DNA test with the assumption that there is a only 1% risk of their produced offspring will become diagnosed with

schizophrenia or bipolar disorder. However, in the baseline arm where males do not take the sperm DNA test, a theoretical assumption stating that there is a risk of 2% that the produced offspring will become diagnosed with schizophrenia or bipolar disorder has been made. This means that a theoretical difference of only 1% in this risk of an offspring becoming diagnosed with either bipolar disorder or schizophrenia, has been investigated.

The decision-analytic model used in this paper is illustrated in illustration 1 just below, however, it should be noted that the model just represents the scaffolding of both the decision-analytic model used in this paper.

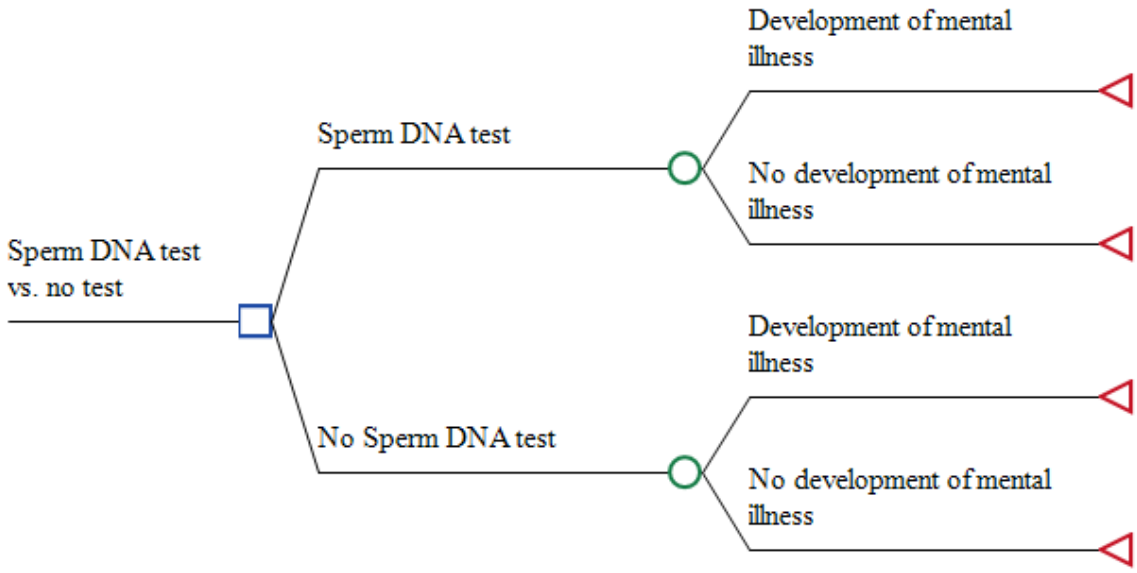

Illustration 1: Shows an illustration of the decision-analytic models used in this paper.

2.3 Study population

2.3.1 Schizophrenia

The included schizophrenia population was discovered through the website of the Danish health department where the yearly incidence rate of schizophrenia was 3,500 (23), however, the literature suggests that only 26.6% (22) of schizophrenia cases could be attributed to increased paternal age, and thereby increased DFI values. This means that the average total amount of new cases of schizophrenia in Denmark had to be multiplied by 0.266 which equals 931 new cases each year. This was done since it is only 26.6% of the total amount of cases which theoretically could be impacted by the use of the sperm DNA test method.

2.3.2 Bipolar Disorder

In terms of estimating the included population of bipolar disorder, the total yearly incidence in Denmark is between 10-30 people pr. 100,000 a year, which has to be multiplied by 0.226

resulting in a total included population of 10,000 (31). The incidence number chosen was 20 since it is the average value. Discovering the population which could be impacted by the use of the sperm DNA test is important to obtain knowledge about the number of potential individuals who might be benefited if the use of the sperm DNA test was to be implemented in Denmark. The rationale for also using 26.6% in terms of estimating the valid target population of patients suffering from bipolar disorder, is because both schizophrenia and bipolar disorder might share many of the same genetic defects (21).

2.4 Cost and resource consumption

In terms of estimating the costs for both mental diseases, schizophrenia and bipolar disorder respectively, different data was needed.

2.4.1 Schizophrenia

The total costs of schizophrenia include the treatment cost for schizophrenia and lost productivity cost. However, the incidence rate and prevalence of schizophrenia were also needed to create a cost estimate of schizophrenia. Furthermore, also the average life expectancy and the average age of disease debut was needed. Both the total costs, the incidence and prevalence was found through "sundhedsstyrelsen.dk" (23). The estimate on the average life expectancy of a patient diagnosed with schizophrenia was found on through videnskab.dk which lead to the article by Laursen et al. (29), while the average age of disease debut has been extracted from "psykiatrifonden" (27). Lastly, the average life expectancy, for a person who is not mentally ill in Denmark has been found though Danish statistics (32). The above-mentioned information has then been used to estimate the total costs of schizophrenia per patient, which was then computed into the decision-analytic model in this paper. The calculation is: Schizophrenia costs approximately 2,612,000,000 in treatment and care + 5,650,000,000 in productivity loss, which equals 8,262,000,000 DKK each year, which has to be allocated to 42,852 patients, this equals 192,803.13 DKK a year pr. patient. The cost of 192,803.13 DKK a year is then to be multiplied with 81.25-(20+15) which equals 46.25 years, which is the total amount of years schizophrenia patients accumulate costs. The total amount of 46.25 years have been found since schizophrenia patients have their debut at around 20 years of age and that patients diagnosed with schizophrenia have a 10-20 years shorter lifespan than the general population which in 2018/2019 was 81.25 (32) across gender. 15 was selected since it is the average value. The total cost estimate of schizophrenia used in this paper thereby becomes 192,803.13 * 46.25 which equals to 8,917,144.7625 DKK per patient in an approximate life span.

2.4.2 Bipolar Disorder

The total cost for bipolar disorder includes only the cost of treatment and care. The numbers have been extracted from an international review of cost of illness studies of bipolar disorder since the research done by the authors did not reveal any Danish costs. The incidence rate and

the prevalence of bipolar disorder, the average life expectancy and the average time of disease debut were needed as well to make the decision-analytic modelling.

The costs where, as mentioned earlier extracted from an international systematic review with an estimate of the total cost of bipolar disorder from Australia, the costs, however, did not reflect productivity loss, but only the costs of treatment and care (33). The costs have been estimated in the study with the same top-down approach as seen in Denmark. The estimation of the life expectancy of patients suffering from bipolar disorder as well as the average age of disease debut has been discovered through bedrepsykiatri.dk (30)(28). Lastly, the average life expectancy for a person who does not have a mental disease has been found on "Danmarks Statistik"(32).

The above-mentioned information has been used to make the cost estimate in the decision-analytic model. The calculation is as follows: The total cost of treatment for a patient with bipolar disorder was estimated to 2,855 Australian dollars annually pr. patient. This equals to 12,369 DKK, which was discovered through valutakurser.dk (34), with the exchange rate from the 3. of May 2020. The 12,369 DKK was then multiplied with the years from disease debut until death. The average time of debut is around 21 years of age, and the average time of death is 17.5 years before the general population. This equals to 81.25-(21+17,5) = 42.75 years. The total cost of bipolar disorder in a life perspective is then 42.75 multiplied by 12,369 DKK, which equals 528,775 DKK.

2.5 Discounting

In this paper discounting has not been applied to either costs nor effects. The rationale for not applying discounting to effects is due to the fact that the effects arguably occur almost instantaneously since a reduction in the DFI value can be detected after as little as three (35) meaning that the positive effects a reduction in DFI value might have, will affect the genetics of the produced offspring at the time of conception.

The justification for not applying discounting to the costs, however, is because of the very preliminary nature of this study and the aim of the study. However, the ICER, if the costs were to be discounted, have been investigated in a separate decision-tree as a different kind of sensitivity analysis. The applied discounting rate used is 4% since this is the same discount rate used by Amgros Denmark (36). The discounted costs can be seen in appendix 1.

2.6 Costs associated with the sperm DNA test

According to the CEO of SPZ Labs in Copenhagen, the costs associated with the sperm DNA test is 1500 DKK (37).

2.7 Outcome measures

The effect measure used in this study is expressed as becoming diagnosed with a mental disease versus to not become diagnosed with a mental disease.

2.8 Incremental cost-effectiveness ratio

An ICER calculation was made in this paper. The ICER is a mathematical equation used to investigate the difference in costs and effects between two different alternatives. The ICER thereby serves as a major analytical tool in health economics. The ICER equation subtracts the cost of a new intervention with the cost of an existing alternative in the numerator. This is then divided with the effect of the new intervention subtracted from the existing alternative in the denominator. The expression of an ICER becoming negative thereby means that the new intervention is less costly and have a higher effect, however, if the ICER is positive it should be interpreted as how much more money one should pay per extra measure of effect (38). In this paper, the ICER is calculated based on the following: (costs mental disease a patient with sperm DNA test - cost mental disease a patient with no sperm DNA test)/(no metal disease with sperm DNA test - no metal disease with no sperm DNA test). The ICER is expressed in Danish crowns (DKK) for an avoided case of mental disease.

2.9 Sensitivity analysis

In this paper, both a probabilistic sensitivity analysis (PSA) and a tornado diagram are created. Additionally, the ICER for the discounted costs have been calculated as a different kind of sensitivity analysis as well.

2.9.1 Probabilistic sensitivity analysis

The PSA has been set to trial 5,000 samples. Additionally, in terms of probabilities, beta distributions have been selected while gamma distributions have been applied to the costs related to schizophrenia and bipolar disorder. The mean approximate cost for a schizophrenia patient in a life span was estimated to be 8,917,144.7625 DKK, however, since the rather large uncertainty related with the costs of schizophrenia, an implemented standard error of 4,500,000 DKK was selected. Concerning bipolar disorder, the mean approximate lifetime cost a patient was found to be 528,775 DKK, but due to the fact that the numbers originate from Australia, a standard error of 500,000 DKK was selected. In terms of selecting standard error for the probabilities, a natural mathematical limitation exists since probabilities are based on beta distributions which cannot sample numbers below 0 (38). Therefore, since the modelled probabilities are 0.01 and 0.02 for schizophrenia and bipolar disorder respectively, a standard error of 0.01 and 0.02 represent the utmost possible extremes.

Lastly, the mean cost related to the sperm DNA test was found to be 1,500 DKK. The standard error has been selected to be 1,500 DKK since the authors sought to include one flawed test as uncertainty.

2.9.2 Tornado diagram

The high value of the probability an offspring catches either schizophrenia or bipolar disorder have been adjusted to be 30% since the literature suggests that 26.6% of cases can be attributed to the father's genetics (22). Additionally, the low values have been selected to be 0.01% for both schizophrenia and bipolar disorder. In terms of the selected high values, 20,000,000 DKK has been selected for both schizophrenia and bipolar disorder to be able to detect significant alterations in the ICER. The low values have been selected to be 5,000 DKK for both schizophrenia and bipolar disorder as well.

In table one and two below, the different included parameters and types of distribution concerning the probabilistic sensitivity analysis are shown, while table three and four display the different parameters and their low and high values concerning the tornado diagram.

Parameter name	**Type of distribution**	**Mean and SE's used**	**Definition of parameter**
P_dev_schiz_sperm_DNA_test	Beta	Mean: 0.01 (1%) SE: 0.01(1%)	The probability of an offspring becomes diagnosed with schizophrenia when the sperm DNA test has been taken
P_dev_Schiz_sandard	Beta	Mean: 0.02 (2%) SE: 0.02 (2%)	The probability of an offspring becomes diagnosed with schizophrenia when the sperm DNA test has not been taken
C_Schizophrenia	Gamma	Mean: 8,917,144.7625 DKK. SE: 4,500,000 DKK.	The total estimated costs of schizophrenia
C_Sperm_DNA_test	Gamma	Mean: 1,500 DKK. SE: 1,500 DKK	The total costs associated with taking the sperm DNA test

Table 1: Shows the types of used distributions with short explanations of each parameter and used means and standard errors (SE) typed into the decision-analytic model regarding schizophrenia.

Parameter name	Type of distribution	Mean and SE's used	Definition of parameter
P_dev_Bipolar_sperm_DNA_test	Beta	Mean: 0.01 (1%) SE: 0.01 (1%)	The probability of an offspring becomes diagnosed with Bipolar disorder when the sperm DNA test has been taken
P_dev_Bipolar_standard	Beta	Mean: 0.02 (2%) SE: 0.02 (2%)	The probability of an offspring becomes diagnosed with schizophrenia when the sperm DNA test has not been taken
C_bipolar_disorder	Gamma	Mean: 528,775 DKK SE: 500,000 DKK	The total estimated costs of Bipolar disorder
C_Sperm_DNA_test	Gamma	Mean:1,500 DKK. SE: 1,500 DKK	The total costs associated with taking the sperm DNA test

Table 2: Shows the types of used distributions with short explanations of each parameter and used means and standard errors (SE) typed into the decision-analytic model regarding bipolar disorder.

Parameter name	High and low values	Definition of parameter
P_dev_schizophrenia_DNA_test	High value: 0.3 (30%) Low value: 0.01 (1%)	The probability of an offspring becomes diagnosed with schizophrenia when the sperm DNA test has been taken
P_dev_schrizophrenia_standard	High value: 0.3 (30%) Low value: 0.001 (1%)	The probability of an offspring becomes diagnosed with schizophrenia when the sperm DNA test has not been taken
C_Schizphrenia_	High value: 20,000,000 DKK Base value: 8,917,144.7625 DKK Low value: 5,000 DKK	The total estimated costs of schizophrenia
C_Sperm_DNA_test_schiz	High value: 5,000 DKK Base value: 1,500 Low value: 250 DKK	The total costs associated with taking the sperm DNA test

Table 3: Shows the names of the different included parameters and their high and low values typed into the TreeAge software, which is then used to create the tornado diagram in this paper. A brief description of the different parameters is shown in the far-right.

Parameter name	High and low values	Definition of parameter
P_dev_Bipol_Sperm_DNA_test	High value: 0.3 (30%) Low value: 0.001 (0,1%)	The probability of an offspring becomes diagnosed with Bipolar disorder when the sperm DNA test has been taken
P_dev_Bipol_standard	High value: 0.3 (30%) Low value: 0.001 (0,1%)	The probability of an offspring becomes diagnosed with schizophrenia when the sperm DNA test has not been taken
C_Bipolar_Disorder_	High value: 20,000,000 DKK Base value: 528,775 DKK Low value: 5,000 DKK.	The total estimated costs of Bipolar disorder
C_Sperm_DNA_test_Bipol	High value: 5,000 DKK Base value: 1,500 DKK Low value: 250 DKK	The total costs associated with taking the sperm DNA test

Table 4: Shows the names of the different included parameters and their high and low values typed into the TreeAge software, which is then used to create the tornado diagram in this paper. A brief description of the different parameters is shown in the far-right.

2.9.3 Discounted costs

The total discounted costs for schizophrenia are calculated to be 2,120,541.42 DKK with a discount rate of 4% and a total time span of 46.25 years while the total discounted costs regarding bipolar are calculated to be 136,040,20 DKK with the same discount rate of 4%, but with a total time span of 42.75 years.

3 Results

3.1 Schizophrenia

The results regarding schizophrenia demonstrated an ICER of: $\frac{(90{,}656.45\ \text{DKK} - 178{,}342.90\ \text{DKK})}{(0.99 - 0.98)} = -8{,}768{,}630\ \text{DKK}$, which thereby indicates that the sperm DNA test is dominating the scenario where no sperm DNA test has been taken.

Additionally, the results of the different sensitivity analyses regarding Schizophrenia are explained below, first, the results regarding the probabilistic sensitivity analysis will be shown followed by the result of the tornado diagram.

3.1.1 Probabilistic sensitivity analysis

The results of the Cost-effectiveness acceptability curve (CEAC) shows an approximate chance of 85% that the sperm DNA-test is cost-effective with a willingness to pay at 0 DKK. Furthermore, it should be noted that the cost-effectiveness iteration does not change with the increasing willingness to pay threshold indicating that only situations where the Sperm DNA test is either dominating or is being dominated occur, based on the PSA of this paper. Illustration 2 and 3 below show the ICE scatter plot and the CE acceptability curve.

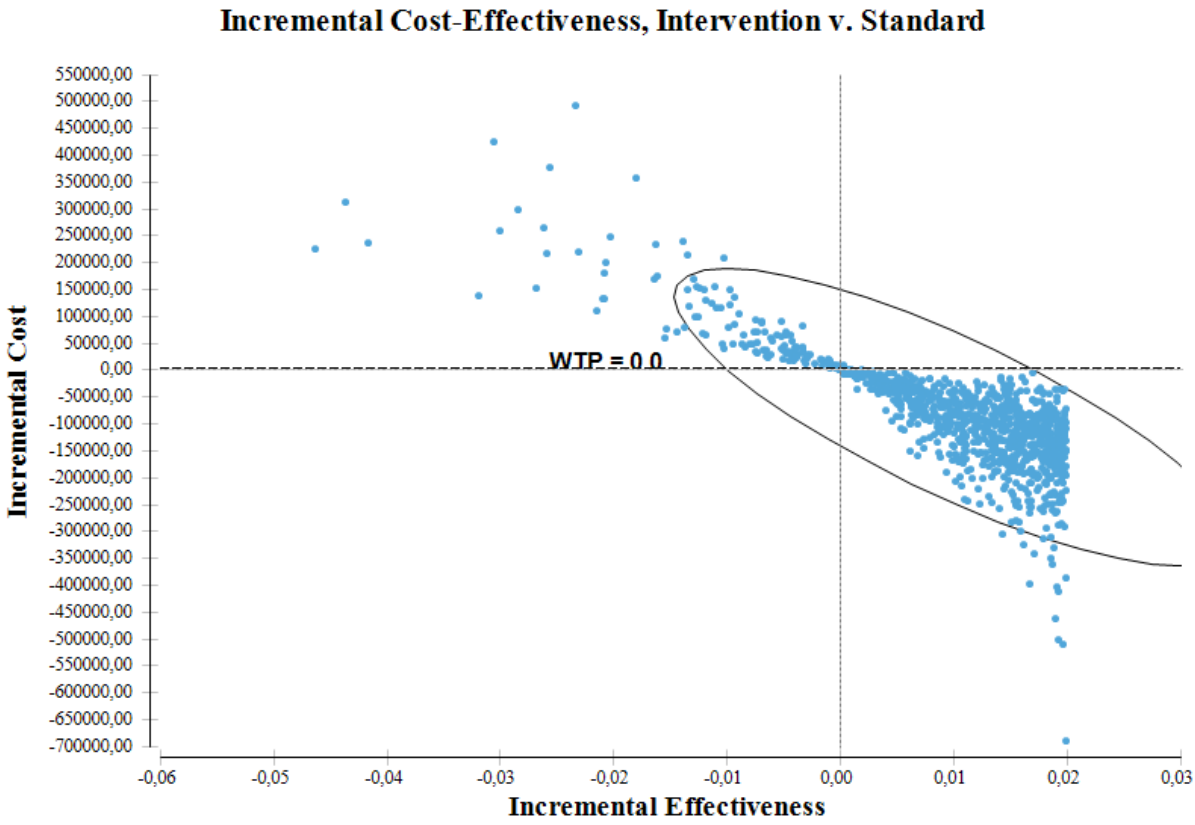

Illustration 2: Shows the ICE scatter plot which is used in order to create the CEAC above. The ICE scatter plot illustrates that the main part of dots is concentrated in the south east quadrant.

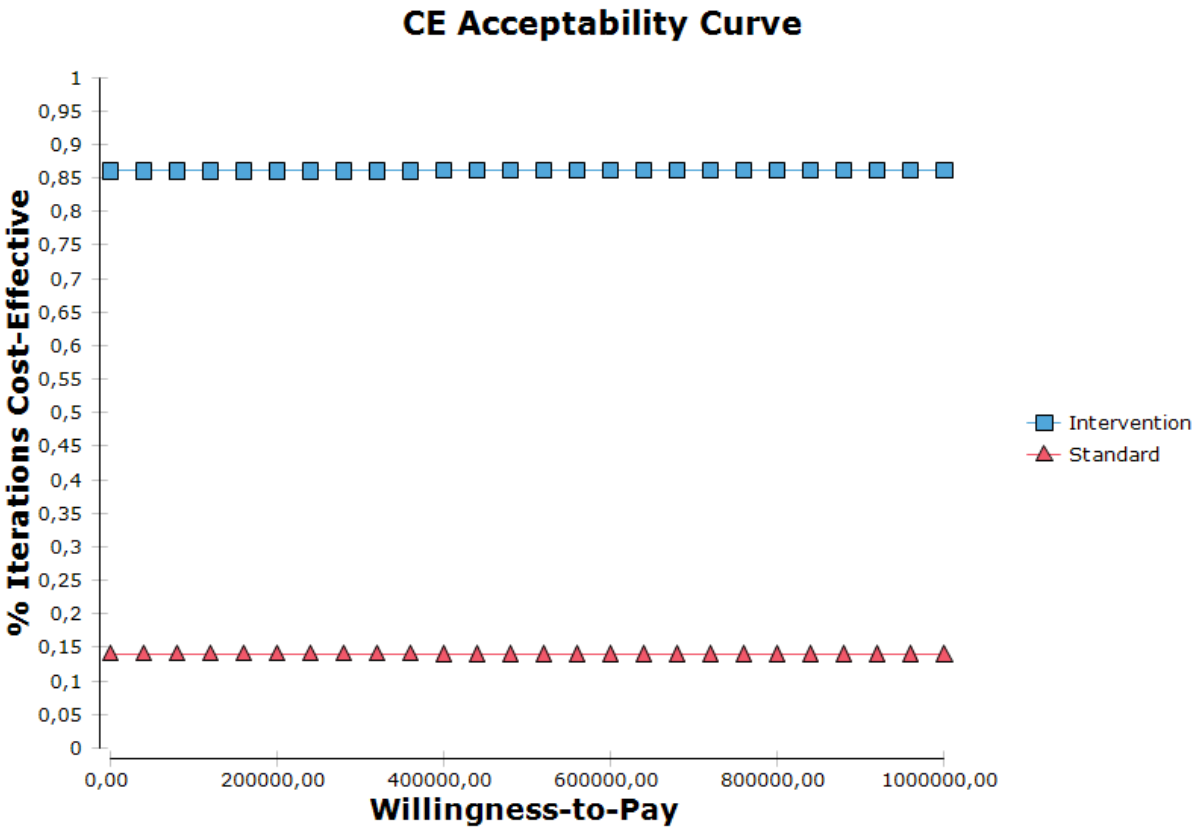

Illustration 3: Shows the Cost-effectiveness acceptability curve. The CEAC shows that there is an approximate chance of 87% that the Sperm DNA test being cost-effective when the willingness to pay threshold is 0 DKK.

3.1.2 Tornado diagram

The result of the tornado diagram shows that the parameter which has the greatest impact upon the ICER is the total accumulated lifetime cost associated with schizophrenia. The parameter which showed the second-highest impact on the ICER is the probability of which an offspring becomes diagnosed with schizophrenia when the sperm DNA test has not been taken. Lastly, the parameter which has the lowest impact upon the ICER is the price associated with the sperm DNA test. The tornado diagram is shown in illustration 4 below.

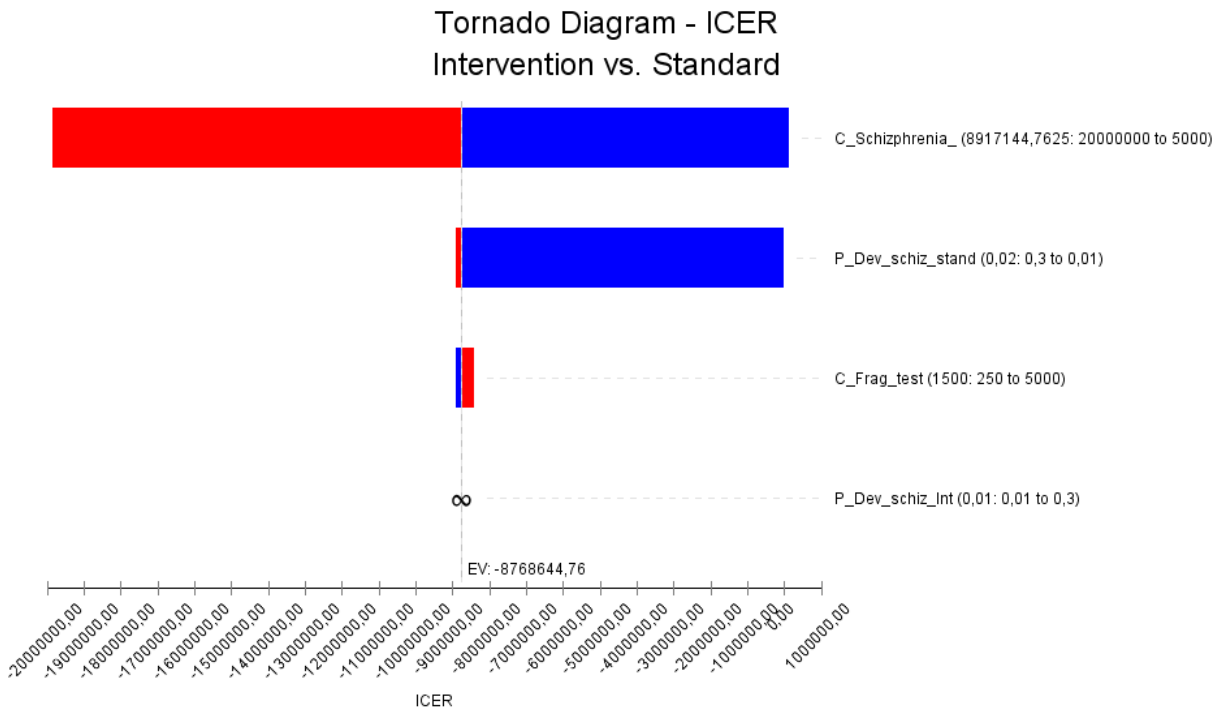

Illustration 4: Shows the result of the tornado-diagram regarding the schizophrenia decision tree. The parameter which has the greatest impact upon the ICER is the cost of schizophrenia followed by the probability an offspring becomes diagnosed with schizophrenia when no Sperm DNA test has been performed. The parameter which showed to have the smallest impact upon the ICER showed to be the cost of the Sperm DNA test. Lastly, the unlimited sign shown at the bottom of the tornado diagram means that with the selected range of the given parameter, the decision changes.

3.1.3 Result when discounting is applied to the total costs

The result if the costs regarding schizophrenia were to become discounted demonstrated an ICER of: $\frac{(20{,}741.92\ DKK - 38{,}513.85\ DKK)}{(0.99-0.98)} = -1{,}777{,}193$ DKK, which means that the sperm DNA test is dominating the scenario where no sperm DNA test has been taken.

3.2 Bipolar Disorder

The results regarding bipolar disorder demonstrated an ICER of: $\frac{(6{,}772.75\ \text{DKK} - 10{,}575.50\ \text{DKK})}{(0.99-0.98)} = -380{,}275$ DKK, which thereby indicates that the sperm DNA test is dominating the scenario where no sperm DNA test has been taken.

Furthermore, the results of the different sensitivity analyses regarding Bipolar disorder are explained below, first, the results regarding the probabilistic sensitivity analysis will be shown followed by the result of the tornado diagram.

3.2.1 Probabilistic sensitivity analysis

The results of the Cost-effectiveness acceptability curve (CEAC) shows an approximate chance of 70% that the sperm DNA-test is cost-effective with a willingness to pay at 0 DKK. Furthermore, it should be noted that the cost-effectiveness iteration changes slightly as the willingness to pay threshold increases indicating that situations where the Sperm DNA test have a higher effect, but at a higher cost might occur according to the PSA performed in this paper. Illustration 5 and 6 below show the ICE scatter plot and the CE acceptability curve.

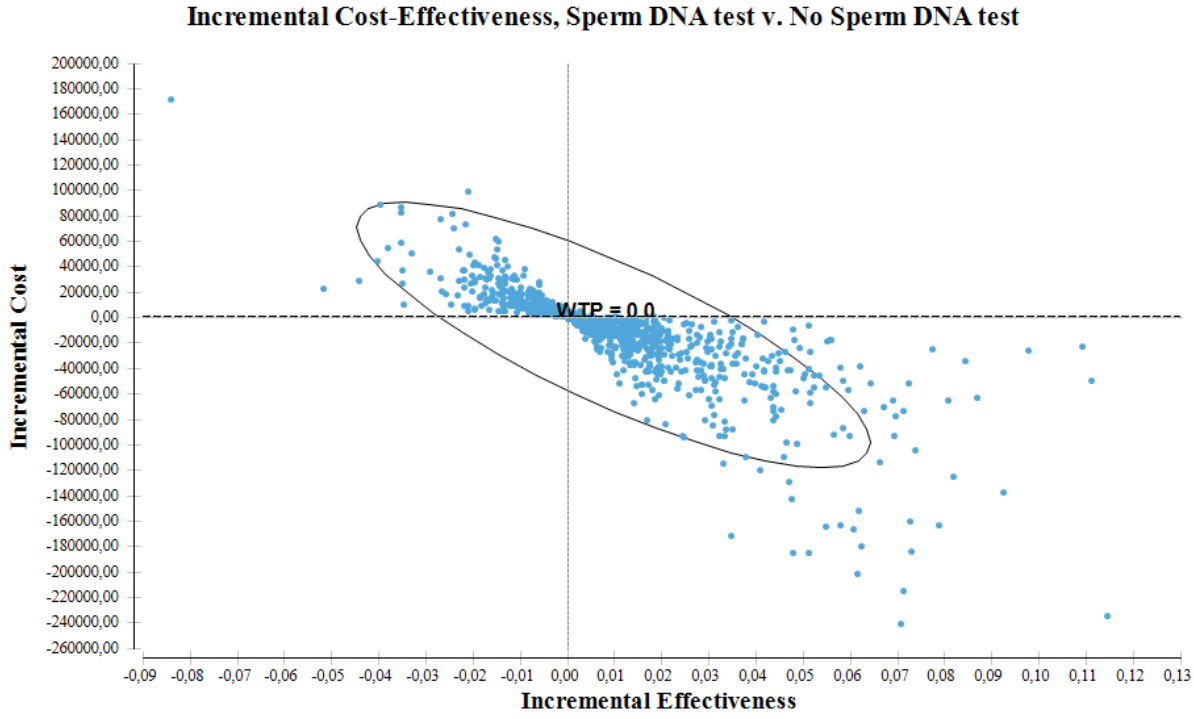

Illustration 5: Shows the ICE scatter plot which is used in order to create the CEAC above. The ICE scatter plot illustrates that the main part of dots is concentrated in the south east quadrant.

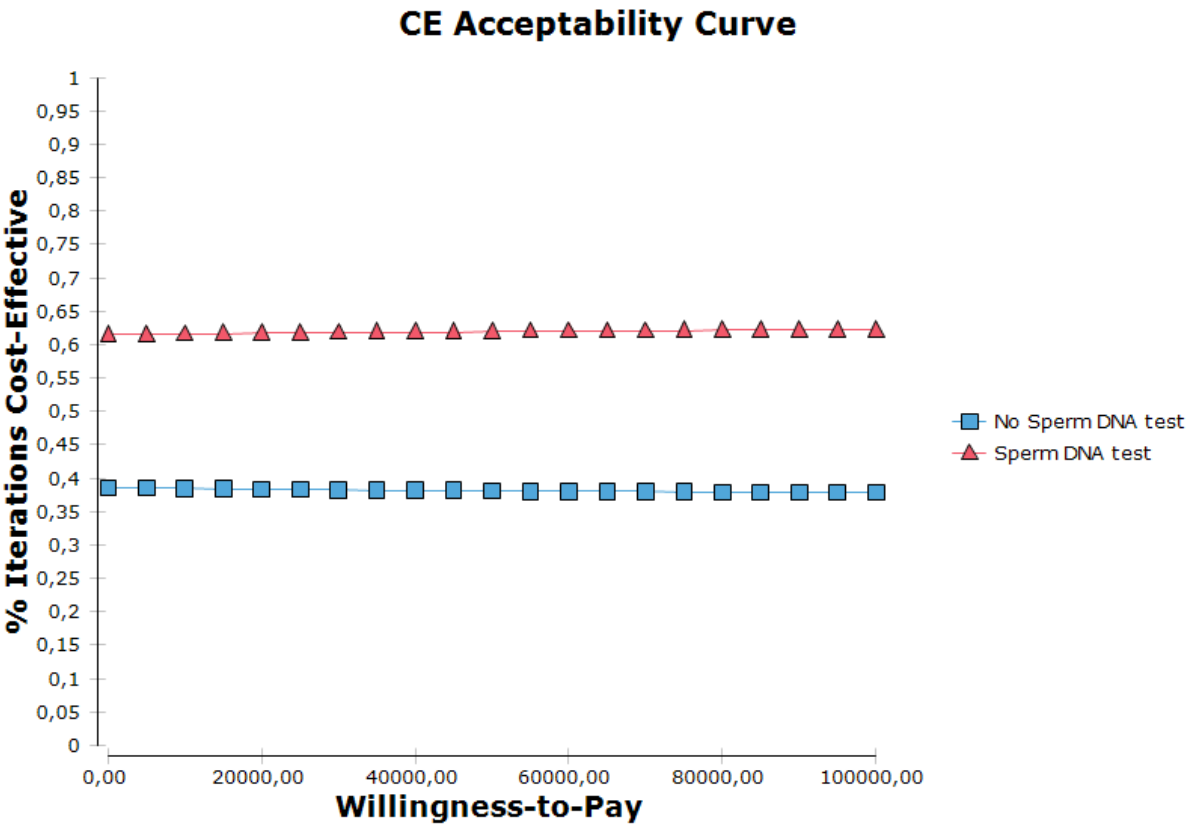

Illustration 6: Shows the Cost-effectiveness acceptability curve. The CEAC shows that there is an approximate chance of 63% that the Sperm DNA test being cost-effective when the willingness to pay threshold is 0 DKK.

3.2.2 Tornado diagram

The result of the tornado diagram shows that the parameter which has the greatest impact upon the ICER is the total accumulated lifetime cost associated with bipolar disorder. The parameter which showed the second-highest impact the ICER is the probability of which an offspring becomes diagnosed with bipolar disorder when the sperm DNA test has not been taken. Lastly, the parameter which has the lowest impact upon the ICER is the price associated with the sperm DNA test. The tornado diagram is shown in illustration 7.

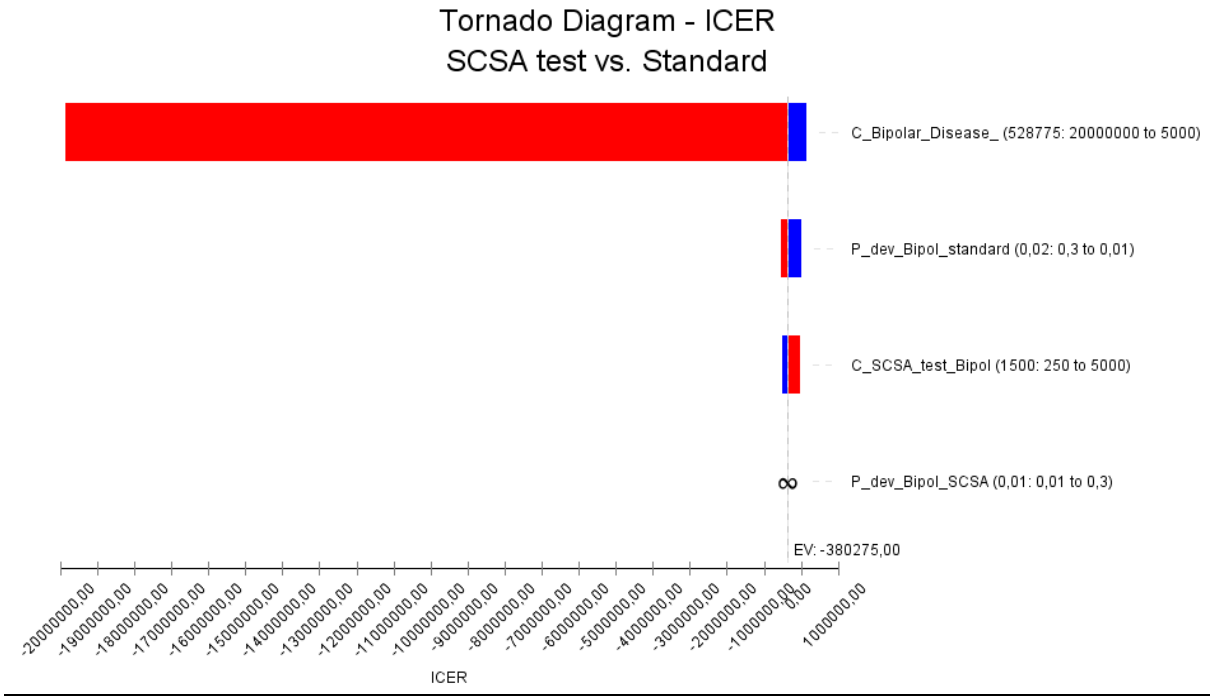

Illustration 7: Shows the result of the tornado-diagram regarding the bipolar disorder decision tree. The parameter which has the greatest impact upon the ICER is the cost of bipolar disorder followed by the probability an offspring becomes diagnosed with bipolar disorder when no sperm DNA test has been performed. The parameter which showed to have the smallest impact upon the ICER showed to be the cost of the sperm DNA test. Lastly, the unlimited sign shown in the bottom of the tornado diagram means that with the selected range of the given parameter, the decision changes.

3.2.3 Result when discounting is applied to the total costs

The result if the costs regarding bipolar disorder were to become discounted demonstrated an ICER of: $\frac{(2644.99\ DKK - 2319.98\ DKK)}{(0.99-0.98)} = 32{,}501$ DKK, which means that the sperm DNA test is no longer dominating the scenario where no sperm DNA test has been taken.

4 Discussion

The results of this preliminary economic evaluation suggest that the sperm DNA test is cost-effective for both schizophrenia and bipolar disorder suggesting that it could prove viable to fund more money into the research area. The results regarding schizophrenia demonstrated a

negative ICER, which means that the sperm DNA test is dominating the scenario where no sperm DNA test has been taken. The ICER in regard to bipolar disorder also demonstrated a dominating result in favour of the sperm DNA test. Both dominating results were demonstrated with a willingness to pay at 0 DKK.

Additionally, the demonstrated ICER, if the costs regarding schizophrenia were to become discounted, also showed to demonstrate a dominating result in favour of the sperm DNA test. This fact can arguably further support the fact that, in regard to schizophrenia, the sperm DNA test might have a substantial economic benefit, however, the results regarding bipolar disorder if the costs were to become discounted showed an ICER of 32,501 DKK, which means that the sperm DNA test is no longer cost-effective with a willingness to pay at 0 DKK. Yet, it is important to note that the estimated costs regarding bipolar disorder did not reflect lost productivity costs, which might indicate that the total costs regarding bipolar disorder are in fact underestimated, and as illustrated in the tornado diagram, the parameter with the highest impact on the ICER was, in fact, the costs related to the mental disease, both in the case of bipolar disorder, but also in regard to schizophrenia.

The probabilistic sensitivity analysis in regard to schizophrenia showed the highest concentration of dots in the southeast quadrant with an approximate chance of 86% that the sperm DNA test is cost-effective at a willingness to pay at 0 DKK. In regard to bipolar disorder, the probabilistic sensitivity analysis indicated an approximate change of the sperm DNA test being cost-effective of 63% with a willingness to pay at 0 DKK. This means that with the incorporated uncertainty modelled into the probabilistic sensitivity analysis, scenarios in where the sperm DNA test would have lower effect at a higher cost might occur. This applies to both schizophrenia and bipolar disorder.

The unlimited sign, which is seen in both the tornado diagram regarding schizophrenia and bipolar disorder shown next to the probability of a patient becoming diagnosed with a mental disease after taking the sperm DNA test, indicates that with the giving range of the parameter, the decision becomes dominated. However, since this study aims to investigate the potential economic benefit with only a hypothetical difference of 1% that the offspring are becoming diagnosed with a mental disease, the results of the tornado diagram regarding the probability that a patient becomes diagnosed with a mental disease after taking the sperm DNA test should be ignored. This is because it is not deemed relevant for the aim of this study to investigate how the change in the probability of an offspring becoming diagnosed with schizophrenia or bipolar disorder after taking the Sperm DNA test would reflect upon the results since it should be kept on a fixed value.

The preliminary indication of this study suggests that there is a potential economic benefit in undertaking the Sperm DNA test upon males in couples who are trying to conceive a child, however, the results of this study should only be used as a first preliminary hypothetical guess to investigate if more research into the area should be invested.

4.1 Quality of life and future research aspects

An additional topic worth discussing is the fact that this study only aims to investigate the potential economic benefit if the Sperm DNA test were to be able to lower the risk of an offspring becoming diagnosed with either schizophrenia or bipolar disorder. This, however, entails that only the economic implications will be investigated, and not the potential rather high increase in quality of life to the offsprings. More studies (39)(40)(41) have demonstrated that individuals suffering from either schizophrenia or bipolar disorder have decreased health-related quality of life, which is due to a variety of factors such as the fact that many individuals suffering from one of the aforementioned mental conditions, also suffer from a broad spectrum of different comorbidities. It thereby becomes predictable that there is a huge potential benefit in terms of evaded decreased health-related quality of life. The rationale for this is the fact that if the Sperm DNA test can be used completely to avoid that an individual becomes diagnosed with either schizophrenia or bipolar disorder, the hypothetical gain in health-related quality of life could be complete since the individual would be completely healthy and never have experienced a reality in where he or she would have been diagnosed with either schizophrenia or bipolar disorder. The point here is that there might be, strictly hypothetical, a huge gain in health-related quality of life, which is of large importance in terms of future research. Additionally, when addressing possible future research elements to this paper, the first and probably the most vital gap in the literature to date, is the fact that no direct link between increased DFI value and the risk of becoming diagnosed with schizophrenia or bipolar disorder exist.

4.2 Missing data

There has been a lot of assumptions in this paper to make an economical analysis possible. Some of the reasons for this, is among others, the fact that sperm DNA integrity has not yet been fully recognized as being a factor for mental diseases in the medical community. So far, it has been perceived that it is the woman's responsibility to live a healthy lifestyle throughout the pregnancy to avoid abortion or any anomalies to the embryo. Because of this perception, there has not been conducted many studies on the correlation between sperm DNA damage and the development of mental disease. Some of the studies referred to in this paper were conducted back in 1996. Besides that, the idea in Denmark came about since it was originally tested on cattle whether the sperm DNA integrity had something to do with how successful the insemination was. Because the test showed that there was a correlation between sperm DNA integrity and the success rates of cattle inseminations, the speculation came that maybe the same correlation could exist in humans. As of now, there are some individuals in the medical community who advocate this correlation acknowledging the fact that conception and sperm DNA integrity has a connection. However, it is not yet fully investigated whether or not mental diseases are connected with sperm DNA integrity. So far the thesis is that it is correlated because of the de novo mutations in the sperm cell that makes it more fragile. On the other hand, however, poor DNA quality can also originate from oxidative stress and a lack of vitamins and minerals such as D3 and selenium. Either way, it has been proven that up to 94%

(kilde:Assessment of Sperm DNA Integrity and Implications for the Outcome of ICSI Treatments. Preben Christensen and Anders Birck) of cases of mental diseases can be traced back to the father.

Therefore, the hypothesis that there is a correlation between the sperm DNA integrity and the risk of developing schizophrenia or bipolar disorder was deemed realistic enough to be the main hypothesis of which this paper has been based upon.

4.3 Sources and study population

To estimate costs correlated with schizophrenia and bipolar disorder as valid data as possible was needed. For the more severe mental disease, namely schizophrenia, quite good data from Danish databases exist. In the case of schizophrenia, the authors found The Danish Healthcare department as a valid source of data in terms of constructing a plausible cost estimate related to schizophrenia. The Danish Healthcare department had good data on both population size, prevalence rates, incidence rates and cost estimates. With bipolar disorder, however, it was quite another case. When it comes to bipolar there is a lot of unreported cases since the disorder has two variants, type 1 and type 2. The exact number of cases registered with bipolar disorder type 1 could therefore potentially be much higher than the number used in this paper. The reason why type 1 is the preferred type to investigate, is the fact that type 1 is characterized by having the more severe hyper mania and depressions, which therefore makes the disorder require treatment. The type 2 bipolar disorder is often overlooked because of the absence of the manic episode (42). The sources found to estimate incidence, prevalence and population size were only based on estimates. It seemed that even in the medical literature there were no specific numbers available.

The same applies to the costs correlated with bipolar disorder. With the research done by the authors, it was not possible to find data on how much bipolar disorder costs in a danish setting. With research on PubMed and google scholar, it was only possible to find cost data from Australia and the United States. The authors chose to go with the costing from Australia since the study found had the same top-down approach to the healthcare system as known in Denmark.(43)

The correlation between DFI and bipolar disorder also had to be estimated roughly. The correlation of 26.6% between DFI and bipolar came about because the authors did not succeed in finding data that suggested a percentage correlation between DFI and bipolar disorder. To make some economical assumptions, the authors, therefore, choose to use the same percentage as with schizophrenia. The reasoning for this was that sources suggested a genetic correlation between schizophrenia and bipolar disorder, meaning that the same de novo mutations are shared among those two disorders. Because of data suggesting the two disorders sharing the same genetic pool and studies backing up that patients seem to become diagnosed with both diseases, the authors found it plausible that the same de novo mutations in sperm cells would cause either one of these disorders with the same probability for each of them.

4.4 Strengths and weaknesses

The most significant weakness of this paper is probably the fact that the overall medical assumption that there is a direct correlation between the increased DFI value and the development of mental illness in the offspring is practically undocumented. This correlation had to be drawn hypothetically to be able to perform this preliminary economic evaluation. This is also why this paper is based on a very simple decision-tree since it is not possible to make plausible assumptions in terms of relative risk differences between different DFI value intervals. If a study were to be performed and was able to demonstrate that men within different DFI value intervals had different risks of their offsprings becoming diagnosed with a mental illness, a much more advanced, and representable decision-analytic model could be created. For instance, a decision-analytic model with multiple arms representing different DFI value intervals could be created. Additionally, it would also be of high interest to discover the true absolute risk related to increased DFI value and the development of mental illness in the offsprings. Moreover, the fact that the lifetime costs calculated for both schizophrenia and bipolar disorder are based on a total cost estimate of one year alone, represents a limitation in itself since it is possible that the costs might differ on a yearly basis.

A clear strength, however, is the fact that when determining the difference in the risk of an offspring becoming diagnosed with a mental illness, a very conservative approach was used since only a 1% difference was modelled into the decision-analytic model. Additionally, another strength is the fact that very broad standard errors were computed into the probabilistic sensitivity analysis to include a large degree of uncertainty. In terms of the probabilities of an offspring becoming diagnosed with either schizophrenia or bipolar disorder, the maximum standard error was used in order to capture as much parameter uncertainty as possible. Also, when the tornado diagrams of this paper were created, a very broad range of variability was taken into account, which also represents a strength of this paper.

4.5 Adherence to lifestyle changes

A large factor for this preliminary economic evaluation to play a role is whether or not the male subjects are willing to undergo the lifestyle changes that it requires in order to achieve the desired effect on the sperm DNA integrity. In a study relating lifestyle-related factors with reproductive health, they found that out of 28 men, 7 of the men did not start the lifestyle change even though they complied, to begin with, 5 were obese and 6 had abdominal obesity. 23 men were still drinking alcohol by the end of the trial period. 2 were smoking, and both reported smoking marijuana too. All in all the study suggests that it is difficult to make people adhere to lifestyle changes which could represent a challenge to the beneficial effects of the sperm DNA test (44). When discussing the topic of improving the DNA integrity in sperm cells, the test is only a test that results in a value. The work has to be done at home with lifestyle changes, and the duration of the lifestyle changes has to of a minimum of 76 days, which is the time of spermatogenesis (45). The preliminary economical results are very conservative, but even the 1% difference would still not be achieved if no male would be willing to change their lifestyle.

5 Conclusion

The conclusion of this preliminary cost-effectiveness analysis suggests that if the sperm DNA test can be used to reduce the risk of an offspring becoming diagnosed with either schizophrenia or bipolar disorder by 1%, the potential economic benefit seem to be rather large. Therefore, based on the ICER, it seems like a viable idea to fund more resources into the area of finding a clinical connection between DFI and the development of mental diseases in the offspring. The ICER demonstrated a dominating result in favour of the sperm DNA test with an approximate chance of 85% at a WTP of 0 of being cost-effective. With bipolar disorder, the ICER also demonstrated a dominating result in favour of the sperm DNA test with an approximate chance of 63% at a WTP of 0 of being cost-effective. However, much more research in the field of DFI and its relation to mental diseases is needed to construct a more realistic and representable economic analysis in this field.

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