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ASSOCIATIONS BETWEEN RISK FACTORS FOR SCHIZOPHRENIA AND CONCORDANCE IN FOUR MONOZYGOTIC TWIN SAMPLES

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ABSTRACT

Concordance for schizophrenia is high in monozygotic twins but the extent to which concordance varies according to the presence of other schizophrenia risk factors is not well established. We aimed to investigate this in systematically-ascertained twin samples. DSM-III-R/DSM-IV diagnoses were made from original data or published case histories from four systematically-ascertained monozygotic twin samples. Probandwise concordance for schizophrenia was calculated according to the presence of psychotic disorder in first-degree relatives, birth order, gender and age-at-onset. Logistic regression analysis was also performed to adjust for potential confounders. Psychotic disorder in parents and earlier age-at-onset were significantly associated with higher probandwise concordance for schizophrenia, including after adjustment for potential confounders. For example, when no parents had a psychotic disorder concordance was 34/88 (38.6%) versus 10/16 (62.5%) when one parent was affected; and for age-at-onset <23 years concordance was 25/46 (54.3%), declining to 13/44 (29.5%) for age-at-onset >30 years. These results are consistent with psychotic disorder in parents and age-at-onset being markers of the level of familial liability to schizophrenia and these factors may be useful in genetic counselling of monozygotic twins and in identifying and managing those at particularly high risk, if these findings are further replicated.

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1 INTRODUCTION

Concordance for schizophrenia is high in monozygotic twins (probandwise concordance usually 40-50% for operational diagnoses) (Cardno & Gottesman, 2000) but the extent to which concordance varies according to the presence or absence of other schizophrenia risk factors is not well established. Understanding this better could give further insights into the aetiology of schizophrenia and could be useful in genetic counselling and in identifying and proactively managing those at particularly high risk.

There is evidence from meta-analysis of twin studies that schizophrenia has a substantial heritability of 81% and a modest contribution from common environmental effects of 11% (Sullivan, Kendler, & Neale, 2003), with the remaining 8% of variance in liability due to individual-specific environmental effects. Risk factors for schizophrenia that act predominantly through familial effects (genetic or common environmental) are expected to increase monozygotic (MZ) concordance for schizophrenia, while risk factors that act predominantly through individual-specific effects are expected to decrease concordance.

Regarding familial risk factors, the presence of schizophrenia or a related psychotic disorder in a first degree relative is a well-established risk factor for schizophrenia (Gottesman, 1991; Gottesman, Laursen, Bertelsen, & Mortensen, 2010; Kendler et al., 1993; Lichtenstein et al., 2009; Mortensen, Pedersen & Pedersen, 2010), and is likely to be predominantly due to genetic influences (Hilker et al., 2018; Kläning et al., 2016; Sullivan et al., 2003). It might therefore be expected that concordance for schizophrenia in monozygotic twin pairs would be higher if a first degree relative is also affected.

Regarding individual-specific environmental risk factors, obstetric complications are a well-established risk factor for schizophrenia (Byrne, Agerbo, Bennedsen, Eaton, & Mortensen, 2007; Cannon, Jones, & Murray, 2002; Jablensky, Morgan, Zubrick, Bower, & Yellachich,

2005) not associated with family psychiatric history (Byrne et al., 2007) and, within a twin pair, the second born twin is at notably higher risk of obstetric complications/perinatal morbidity (Rossi, Mullin, & Chmait, 2011). Since twins within a pair must be different in birth order (i.e. this is a non-shared environmental factor), if being second born increases the risk of obstetric complications relevant to schizophrenia, we would expect that in monozygotic twin pairs discordant for schizophrenia the affected twin would be second born in more than 50% of pairs.

Against the above expectations, a Norwegian systematically-ascertained twin study employing DSM-III-R operational diagnoses found no association between monozygotic twin concordance and the presence of schizophrenia in a first degree relative, and no excess of second born affected twins among monozygotic pairs discordant for schizophrenia (Onstad, Skre, Torgersen & Kringlen, 1992). Also, earlier twin studies based on clinical diagnoses have not found clear and consistent evidence supporting these expectations (Fischer, 1973; Gottesman & Shields, 1972; Kringlen, 1967a,b; Slater & Shields, 1953). However, when each study is considered individually, sample size issues limit the conclusions that can be drawn.

We therefore decided to investigate these associations in all the available systematically-ascertained twin samples of schizophrenia where a) there was sufficient clinical information from primary sources or published case vignettes to make operational research diagnoses; and b) family psychiatric history and birth order were documented in most of the twins. All of the studies ascertained also included information on twins' gender and age at onset and, as female gender (Goldstein, Cherkerzian, Tsuang, & Petryshen, 2013; Goldstein, Faraone, Chen, Tolomiczencko, & Tsuang, 1990; Goldstein, Tsuang, & Faraone, 1989; Sham et al., 1994a) and younger age at onset of schizophrenia (Dworkin, Lenzenweger, Moldin, Skillings, & Levick, 1988; Esterberg, Trotman, Holtzman, Compton, & Walker, 2010; Hilker et al., 2017; Kendler & MacLean, 1990; Kendler, Tsuang, & Hays, 1987; Pulver & Liang, 1991;

Suvisaari, Haukka, Tanskanen, & Lönnqvist, 1998; Svensson et al., 2012) have been associated with increased familial risk of psychosis in some, although not all, studies (Cannon, Kaprio, Lonnqvist, Huttunen, & Koskenvuo, 1998; Kendler et al., 1987; Kendler, Karkowski-Shuman, & Walsh, 1996; Kendler & Walsh, 1995; Sham, Gottesman, MacLean, & Kendler, 1994b), we investigated these variables too.

1.1 Aims of the study

We aimed to investigate the extent to which family history of psychotic disorder, birth order, gender and age at onset of probands predicted twin concordance for DSM schizophrenia.

2 MATERIALS AND METHODS

2.1 Samples

The twin samples that were included are shown in Table 1. There were 134 probandwise pairs in total. Information from the Maudsley twin register study (Cardno et al., 1999; Gottesman & Shields, 1972) was derived from all available clinical information, including research interviews, case record reviews and detailed case vignettes. Information from the other three studies was based on the publications cited in Table 1 (Fischer, 1973; Kringlen, 1967a,b; Slater & Shields, 1953), which included case histories for monozygotic (MZ) twins. Therefore only risks in MZ pairs were analysed in the current study. A further study with published case histories (Tienari, 1963) was considered, but excluded from analysis because there were no concordant MZ pairs at the time of publication and, although some co-twins became ill on further follow-up (Tienari, 1975), published case histories relating to them are not available to our knowledge. Ethical approval was not obtained for this analysis: the Maudsley register was set up prior to the establishment of research ethics committees but was based on consistent principles, and the information for the other studies was based on published sources.

2.2 Diagnoses

The primary diagnosis was schizophrenia according to DSM criteria. In the Maudsley register study the original DSM-III-R diagnoses (APA, 1987) were employed and in the other studies we made DSM-IV diagnoses (APA, 1994) by performing new evaluations of the published case histories. Diagnoses in the Maudsley register sample were made by independent raters for members of each pair where there was any suggestion of concordance. Raters were psychiatrists or psychologists experienced in making research diagnoses. Inter-rater reliability was taken as the mean kappa between the three pairs of raters, based on 30 cases from the sample. Kappa for DSM-III-R schizophrenia was 0.73. Diagnoses in the other samples were made by one of the raters of the Maudsley register sample (AGC) blind to information relating to pair membership and to the original study diagnoses. An inter-rater reliability assessment was also undertaken, in which another psychiatrist also rated the twins in the sample. Kappas for DSM-IV schizophrenia were: Slater & Shields 0.76; Fischer 0.71; Kringlen 0.66. All inter-rater reliability results were above Landis and Koch's (1977) threshold for substantial agreement.

2.3 Analysis

We investigated probandwise concordance for DSM schizophrenia in MZ pairs in each sample and in the samples combined. For the investigation of family history, we divided the twin pairs according to the presence or absence of a psychotic disorder in a parent or full sibling. We excluded half-siblings and siblings where it was noted that they had died before the age of 15 years. The definition of psychotic disorder included diagnoses listed as schizophrenia, ?schizophrenia, schizoaffective disorder, schizophreniform disorder, catatonia, delusional disorder, paranoia, bipolar disorder, mania, depressive disorder with delusions or hallucinations, reactive psychosis, psychosis and psychotic disorder, and excluded oligophrenia (as the description of this term appeared to be closer to current definitions of intellectual disability than psychotic disorder) and epileptic psychosis.

Our primary analysis was of probandwise concordance for DSM schizophrenia in the four samples combined according to the presence vs absence of psychotic disorder in a parent or sibling. We undertook chi-square tests and binary logistic regression analysis with presence/absence of schizophrenia in co-twins as the dependent variable, and presence/absence of psychotic disorder in parents/sibs as the independent variable, and also with adjustment for sample, number of parents/sibs in the family, gender, and age of co-twin at last follow-up. As risks of psychotic disorders may be notably different in parents and siblings of affected probands (Gottesman, 1991; Kendler et al., 1993), we also performed analyses of parents and siblings separately.

For the primary investigation of birth order, we restricted the analysis to pairs discordant for DSM schizophrenia, and determined whether the affected proband was second-born more frequently than the expected 50%, calculating p-values using the one-sample binomial test. There was sufficient information in the paper by Onstad et al. (1992), to include the data from this study in a secondary analysis combined with the other samples. We also investigated the relationship between proband birth order and concordance in the samples combined, using chi-square tests and logistic regression analysis, the latter including adjustment for sample, gender and age of co-twin at last follow-up.

We analysed the relationship between gender and concordance using chi-square tests and logistic regression analysis, the latter including adjustment for study and age of co-twin at last follow-up.

We defined age at onset as age at first contact with psychiatric services. We compared the mean age at onset of concordant versus discordant twin pairs using independent t-tests. We also investigated the relationship between age at onset and concordance using logistic regression analysis, including with adjustment for sample, gender and age of co-twin at last follow-up.

Where more than one variable was a significant predictor of concordance, we also investigated their combined effects.

Statistical analyses were undertaken using SPSS version 21 (www.ibm.com/products/spss-statistics) or OpenEpi (Dean, Sullivan, & Soe, 2013). Results were considered statistically significant at $p<0.05$, two-tailed, without adjustment for multiple statistical tests as the study was exploratory.

3 RESULTS

3.1 Family history of psychotic disorder

Table 2 shows the probandwise concordance for DSM schizophrenia according to the absence/presence of psychotic disorder in a parent or sibling. For the samples combined (133 pairs), there was a non-significant trend towards higher concordance when a parent or sibling had a psychotic disorder: 39.4% versus 48.7% (χ^2=0.99, df=1, p=0.32). Three of the individual samples supported this trend (Maudsley register, Slater & Shields, Kringlen), while there was an opposite trend in the fourth sample (Fischer). Similarly, by logistic regression analysis with concordance as the dependent variable and absence/presence of psychotic disorder in a parent or sibling as the independent variable, n=133, p=0.32, OR=1.46 (95%CI 0.69 to 3.10), and adjusted for sample, family size, gender, and age of co-twin at last follow-up, n=132, p=0.26, OR=1.60 (95%CI 0.71 to 3.63).

However, the results were notably different for illness in parents and siblings considered separately, which could be analysed in the Slater & Shields, Fischer, Kringlen and earlier part of the Maudsley register sample investigated by Gottesman & Shields (1972) (106 pairs). Twin concordance significantly increased with the number of parents who had a psychotic disorder: 34/88 (38.6%) with no affected parents; 10/16 (62.5%) with one affected parent; and 2/2 (100%) with two affected parents (Mann-Whitney U p=0.026). Although

concordance was complete for pairs with two affected parents, it should be noted that this was based on only two twins, who came from a single doubly-ascertained pair. By logistic regression analysis, again twin concordance was significantly predicted by the number of affected parents (n=106, p=0.025, OR=3.13 (95%CI 1.16 to 8.46)) and also after adjustment for sample, gender and age of co-twin at last follow-up (n=106, p=0.018, OR=3.64 (95%CI 1.25 to 10.62)). Among the individual samples, the association was significant for the Kringlen sample (concordance 8/29 (27.6%) with no affected parents, 6/9 (66.7%) with one affected parent, and 2/2 (100%) with two affected parents; Mann-Whitney U p=0.039) and by logistic regression analysis adjusted for gender and age of co-twin at last follow-up, n=40, p=0.018, OR=8.44 (95%CI 1.45 to 49.01).

It was possible to investigate risk of psychotic disorder in siblings in the Slater & Shields, Fischer, Kringlen and earlier part of the Maudsley register samples in families where there was at least one full sibling. Unexpectedly, twin concordance for DSM schizophrenia was significantly lower when one or more siblings had a psychotic disorder (concordance 34/77 (44.2%) with no affected siblings, and 3/17 (17.6%) with 1 or more affected siblings; χ^2=4.1, df=1, p=0.042). Taking account of family size, the results were similar: in families of twin pairs concordant for DSM schizophrenia, 3/145 (2.1%) of their siblings had a psychotic disorder; while in families of discordant twin pairs, 19/230 (8.3%) of their siblings had a psychotic disorder (χ^2=6.17, df=1, p=0.013). None of the individual samples showed a significant association on their own. By logistic regression analysis, twin concordance was significantly predicted by having fewer affected siblings (n=94, p=0.042, OR=0.30 (95%CI 0.09 to 0.96)), but the association became non-significant after adjustment for sample, gender, age of co-twin at last follow-up and size of sibship (n=94, p=0.060, OR=0.31 (95%CI 0.09 to 1.05)). When the covariates were examined individually, the association was non-significant after adjustment for sample (p=0.063, OR=0.32), but significant after adjustment for each of the other covariates.

3.2 Birth order

Table 3 shows how frequently the proband was second born in pairs discordant for DSM schizophrenia. In the samples combined (73 pairs), 54.8% of probands were second born, which is non-significantly greater than the null expectation of 50% (one-sample binomial test p=0.48). Three of the individual samples supported this trend (Maudsley register, Fischer, Kringlen), while there was an opposite trend in the fourth sample (Slater). Adding the data from the Onstad et al. (1992) study (9/16 (56.7%)) gave similar overall results (49/89 (55.1%); 5 missing; p=0.40).

For the samples combined (excluding Onstad et al. (1992)), twin concordance was non-significantly higher when the proband was first born compared to second born (23/56 (41.1%) versus 25/65 (38.5%)). By logistic regression analysis, n=121, p=0.77, OR=1.12 (95%CI 0.54 to 2.31), and adjusted for sample, gender and age of co-twin at last follow-up, n=121, p=0.87, OR=1.07 (95%CI 0.50 to 2.26).

3.3 Gender

In the samples combined (134 pairs), there was a non-significant trend towards higher concordance for DSM schizophrenia in female than male pairs (27/61 (44.3%) and 29/73 (39.7%), respectively; χ^2=0.28, df=1, p=0.60), which was statistically significant for the Fischer sample (7/14 (50%) and 0/10 (0.0%), respectively; Fisher's exact test p=0.019). Similarly, by logistic regression analysis in the samples combined, with concordance as the dependent variable and gender as the independent variable, n=134, p=0.60, OR=1.21 (95%CI 0.61 to 2.40), and adjusted for sample and age of co-twin at last follow-up, n=134, p=0.49, OR=1.28 (95%CI 0.64 to 2.58). Logistic regression analysis of the Fischer sample alone did not give meaningful results due to the zero male concordance.

3.4 Age at onset

In the samples combined (134 pairs), mean age at onset was significantly lower in probands of concordant than discordant pairs (25.4 years versus 29.4 years: Table 4), and the difference was also statistically significant in the Maudsley register and Slater & Shields samples. Similarly, by logistic regression analysis in the combined samples, concordance was significantly predicted by earlier age at onset (n=134, p=0.016, OR=0.95 (95%CI 0.91 to 0.99), and after adjustment for sample, gender and age of co-twin at last follow-up (n=134, p=0.011, OR=0.94 (0.90 to 0.99). Looking at effects across the age range, in the samples combined divided into three age at onset groups (by tertiles to achieve approximately equal numbers in each group), concordance was 25/46 (54.3%) in the youngest group (age at onset below 23 years), 18/44 (40.9%) in the middle group (age at onset 23 to 30 years), and 13/44 (29.5%) in the oldest group (age at onset over 30 years).

Age at onset in twin probands was uncorrelated with the number of parents with psychotic disorder (the other variable that significantly predicted twin concordance after adjustment for covariates) (Spearman rho=-0.04, p=0.69). They could only be jointly analysed in the samples that included information on parental illness (Slater & Shields, Fischer, Kringlen and the earlier part of the Maudsley register sample), and with the reduction in sample size the association with age at onset became non-significant: by logistic regression analysis, with adjustment for sample, gender and age of co-twin at last follow-up (n=106), for number of parents with psychotic disorder (p=0.016, OR=3.55 (95%CI 1.27 to 9.93) and for age at onset (p=0.052, OR=0.95 (95%CI 0.90 to 1.00).

4 DISCUSSION

4.1 Family history of psychotic disorder

While there was only a trend towards higher twin concordance for DSM schizophrenia when a parent or sibling had a psychotic disorder, when parental illness was analysed separately this significantly predicted concordance. Compared with having no parents who had a

psychotic disorder, twins with one affected parent had a 24% higher concordance, and this is consistent with parental illness being a marker of level of familial liability to schizophrenia in MZ twin pairs, as has previously been found in family study data (Gottesman, 1991; Gottesman et al., 2010; Kendler et al., 1993; Lichtenstein et al., 2009; Mortensen et al., 2010). It also reinforces the value of analysing familial risks of schizophrenia separately in parents and siblings (or other relatives). Although there was complete concordance when both parents were affected, this result should be viewed with caution as it was only based on two twins from a single doubly-ascertained pair.

In contrast, the number of siblings with psychotic disorder predicted lower twin concordance for schizophrenia, although the result became non-significant by logistic regression analysis when adjusted for potential confounders, notably sample. In view of this, and the unexpected nature of the result given that evidence from family studies (Gottesman, 1991; Kendler et al., 1993; Lichtenstein et al., 2009; Mortensen et al., 2010) suggests that having an affected sibling should, if anything, be associated with higher concordance, the trend is most likely to be artefactual.

4.2 Birth order

In the primary analysis of the combined samples there was a modest non-significant trend towards the proband from discordant pairs being relatively likely to be second born. This result is similar to the finding of Onstad et al. (1992), but when we added the data from the Onstad et al. (1992) study to the analysis, the result in the enlarged combined sample remained at the non-significant trend level. In view of this, there may be no meaningful association between birth order and concordance, and the birth complications linked to being a second born twin are of minimal relevance to risk of developing schizophrenia. On the other hand, the trends shown by this study and the Onstad et al. (1992) study could be statistically significant in a larger sample which, if found, would bolster the argument for further investigation.

4.3 Gender

In the samples combined, there was a modest non-significant trend towards higher concordance in female twin pairs. It may be that gender is not a useful marker of familial liability to schizophrenia. Consistent with this, a range of family and twin studies have found no gender effects (Cannon et al., 1998; Kendler & Walsh, 1995; Sham et al., 1994b). However, a meaningful effect cannot be excluded because where an effect has been found it has been for higher familial risk when probands are female (Goldstein et al., 1989, 1990, 2013; Sham et al., 1994a), as with the trend in the current study. The significant result for the Fischer sample could be a chance finding or due to some unknown characteristic of the study that led to a relatively pronounced gender effect.

4.4 Age at onset

Concordance was significantly higher with younger age at onset, and the graded increase in concordance across the three age bands suggests that the effect is probably not confined only to a particular age range, e.g. early onset schizophrenia. In previous family and twin studies, where an association has been found it has also been between younger age at onset and higher familial risk (Esterberg et al., 2010; Hilker et al., 2017; Kendler et al., 1987; Kendler & MacLean, 1990; Pulver & Liang, 1991; Suvisaari et al., 1998; Svensson et al., 2012), including in a study that partly overlapped with the samples investigated here and that was based on clinical diagnoses (Dworkin et al., 1988). However, not all studies have found an association (Kendler et al., 1987, 1996), perhaps because the effect is too modest to always be detected. Although the association became non-significant when combined with analysis of psychosis in parents, this is most likely to be due to the reduction in sample size for this analysis. Age at onset can be defined in other ways, e.g. as age at first symptoms or first hospital admission, but they tend to be highly correlated (Sham et al., 1994a) so employing an alternative definition would be unlikely to notably affect the results.

4.5 Limitations

In three of the four samples, DSM diagnoses were based on published case histories rather than the full clinical information available to the original studies. However, the case histories focused on features relevant to making a diagnosis of schizophrenia, including those in DSM-III-R and DSM-IV. Additionally, MZ concordances across a broader range of operational definitions of schizophrenia are similar (Cardno et al., 1999; Cardno & Gottesman, 2000), so the more modest differences between DSM-III-R and DSM-IV are unlikely to have made a substantive difference to the results. In the investigation of familial risks, we did not adjust for age of siblings as this was often not documented, but as most co-twins (mean age 47.8 years) and hence most siblings were well through the period of risk for onset of schizophrenia, we would not expect this to notably affect the results. We were able to adjust for age at last follow-up of co-twins, which is also a rough proxy for age of other siblings. It is possible that additional co-twins could become ill with further follow-up, but as each study already included lengthy follow-up and age at onset in MZ twins is highly correlated (Allan et al., 2009) we would expect this to be rare.

Most of the data for analysis was based on fieldwork carried out in the mid-twentieth century. It is unlikely that genetic effects (i.e. DNA variants) would have notably altered since then, but it is possible that there have been notable changes in environmental factors. However, we did not observe clear trends towards greater or lesser strengths of association based on when the samples were ascertained. There were methodological differences between the studies, for example, in location and method of ascertainment (see Table 1), but we did not observe clear differences in results according to these factors. The analysis was confined to MZ twins. While most studies have found that the risk of schizophrenia is similar in twins or MZ twins and singletons (Fischer, 1973; Kendler, Pedersen, Farahmand, & Persson, 1996; Kläning, 1999; Kleinhaus et al., 2008), it is possible that some twin-specific factors could have influenced the results. Finally, the results of this study are consistent with psychotic disorder in parents and age at onset being markers of the level of familial, and probably

genetic, liability to schizophrenia. Information about these factors may be useful in genetic counselling of MZ twins, and in identifying and proactively managing those at particularly high risk. However, it would be valuable to further replicate these findings, and to ascertain whether trends found in the current study strengthen or weaken in studies with larger samples, where these are available.

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CONFLICTS OF INTEREST

All authors declare that they have no conflicts of interest.

REFERENCES

Allan, C. L., Cardno, A. G., Rijsdijk, F. V., Kalidindi, S., Farmer, A., Murray, R. M., & McGuffin, P. (2009). Twin study of illness history variables in psychosis. *Schizophrenia Research*, *115*, 237-244. doi: 10.1016/j.schres.2009.09.002

APA. (1987). *Diagnostic and statistical manual of mental disorders* (3rd ed rev). Washington: American Psychiatric Association.

APA. (1994). *Diagnostic and statistical manual of mental disorders* (4th ed). Washington: American Psychiatric Association.

Byrne, M., Agerbo, E., Bennedsen, B., Eaton, W. W., & Mortensen, P.B. (2007). Obstetric conditions and risk of first admission with schizophrenia: a Danish national register based study. *Schizophrenia Research*, *97*, 51-59. doi: 10.1016/j.schres.2007.07.018

Cannon, M., Jones, P. B., & Murray, R. M. (2002). Obstetric complications and schizophrenia: historical and meta-analytic review. *American Journal of Psychiatry*, *159***,** 1080-1092. doi: 10.1176/appi.ajp.159.7.1080

Cannon, T. D., Kaprio, J., Lonnqvist, J., Huttunen, M., & Koskenvuo, M. (1998). The genetic epidemiology of schizophrenia in a Finnish twin cohort: a population-based modeling study. *Archives of General Psychiatry*, *55*, 67-74.

Cardno, A. G., & Gottesman, I.I. (2000). Twin studies of schizophrenia: from bow-and-arrow concordances to star wars Mx and functional genomics. *American Journal of Medical Genetics Part C: Seminars in Medical Genetics*, *97*, 12-17.

Cardno, A. G., Marshall, E. J., Coid, B., Macdonald, A. M., Ribchester, T. R., Davies, N. J., … Murray, R. M. (1999). Heritability estimates for psychotic disorders: the Maudsley twin psychosis series. *Archives of General Psychiatry*, *56*, 162-168.

Dean, A. G., Sullivan, K. M., & Soe, M. M. (2013). *OpenEpi: open source epidemiologic statistics for public health* (version 3.01). Retrieved from http://www.openepi.com 14 February 2018.

Dworkin, R. H., Lenzenweger, M. F., Moldin, S. O., Skillings, G. F., & Levick, S. E. (1988). A multidimensional approach to the genetics of schizophrenia. *American Journal of Psychiatry*, *145*, 1077-1083.

Esterberg, M. L., Trotman, H. D., Holtzman, C., Compton, M. T., & Walker, E.F. (2010). The impact of a family history of psychosis on age-at-onset and positive and negative symptoms of schizophrenia: a meta-analysis. *Schizophrenia Research*, *120*, 121-130. doi: 10.1016/j.schres.2010.01.011

Fischer, M. (1973). Genetic and environmental factors in schizophrenia: a study of schizophrenic twins and their families. *Acta Psychiatrica Scandinavica*, *suppl 238*.

Goldstein, J. M., Cherkerzian, S., Tsuang, M. T., & Petryshen, T. L. (2013). Sex differences in the genetic risk for schizophrenia: history of the evidence for sex-specific and sex-dependent effects. *American Journal of Medical Genetics Part B: Neuropsychiatric Genetics*, *162B*, 698-710. doi: 10.1002/ajmg.b.32159

Goldstein, J. M., Faraone, S. V., Chen, W. J., Tolomiczencko, G. S., & Tsuang, M. T. (1990). Sex differences in the familial transmission of schizophrenia. *British Journal of Psychiatry*, *156*, 819-826.

Goldstein, J. M., Tsuang, M. T., & Faraone, S. V. (1989). Gender and schizophrenia: implications for understanding the heterogeneity of the illness. *Psychiatry Research*, *28*, 243-253.

Gottesman, I. I. (1991). *Schizophrenia genesis: the origins of madness*. New York: Freeman.

Gottesman, I. I., Laursen, T. M., Bertelsen, A., & Mortensen, P. B. (2010). Severe mental disorders in offspring with 2 psychiatrically ill parents. *Archives of General Psychiatry*, *67*, 252-257. doi: 10.1001/archgenpsychiatry.2010.1

Gottesman, I.I., & Shields, J. (1972). *Schizophrenia and genetics: a twin vantage point*. New York: Academic Press.

Hilker, R., Helenius, D., Fagerlund, B., Skytthe, A., Christensen, K., Werge, T. M., … Glenthøj, B. (2017). Is an early age at illness onset in schizophrenia associated with increased genetic susceptibility? Analysis of data from the nationwide Danish twin register. *EBioMedicine*, *18*, 320-326. doi: 10.1016/j.ebiom.2017.04.002

Hilker, R., Helenius, D., Fagerlund, B., Skytthe, A., Christensen, K., Werge, T. M., … Glenthøj, B. (2018). Heritability of schizophrenia and schizophrenia spectrum based on the nationwide Danish twin register. *Biological Psychiatry*, *83*, 492-498. doi: 10.1016/j.biopsych.2017.08.017

Jablensky, A. V., Morgan, V., Zubrick, S. R., Bower, C., & Yellachich, L. A. (2005). Pregnancy, delivery, and neonatal complications in a population cohort of women

with schizophrenia and major affective disorders. *American Journal of Psychiatry*, *162*, 79-91. doi:10.1176/appi.ajp.162.1.79

Kendler, K.S., Karkowski-Shuman, L., & Walsh, D. (1996). Age at onset in schizophrenia and risk of illness in relatives: results from the Roscommon family study. *British Journal of Psychiatry*, *169*, 213-218.

Kendler, K. S., & MacLean, C. J. (1990). Estimating familial effects on age at onset and liability to schizophrenia I: results of a large sample family study. *Genetic Epidemiology*, *7*, 409-417.

Kendler, K. S., McGuire, M., Gruenberg, A. M., O'Hare, A., Spellman, M., & Walsh, D. (1993). The Roscommon family study I: methods, diagnosis of probands, and risk of schizophrenia in relatives. *Archives of General Psychiatry*, *50*, 527-540.

Kendler, K.S., Pedersen, N. L., Farahmand, B. Y., & Persson, P.-G. (1996). The treated incidence of psychotic and affective illness in twins compared with population expectation: a study in the Swedish twin and psychiatric registries. *Psychological Medicine*, *26*, 1135-1144.

Kendler, K. S., Tsuang, M. T., & Hays, P. (1987). Age at onset in schizophrenia: a familial perspective. *Archives of General Psychiatry*, *44*, 881-890.

Kendler, K. S., & Walsh, D. (1995). Gender and schizophrenia: results of an epidemiologically-based family study. *British Journal of Psychiatry*, *167*, 184-192.

Kläning, U. (1999). Greater occurrence of schizophrenia in dizygotic but not monozygotic twins: register-based study. *British Journal of Psychiatry*, *175*, 407-409.

Kläning, U., Trumbetta, S. L., Gottesman, I. I., Skytthe, A., Kyvik, K. O., & Bertelsen A. (2016). A Danish twin study of schizophrenia liability: investigation from interviewed twins for genetic links to affective psychoses and for cross-cohort comparisons. *Behavior Genetics*, *46*, 193-204. doi: 10.1007/s10519-015-9765-z

Kleinhaus, K., Harlap, S., Perrin, M. C., Manor, O., Calderon-Margalit, R., Friedlander, Y., & Malaspina, D. (2008). Twin pregnancy and the risk of schizophrenia. *Schizophrenia Research*, *105*, 197-200. doi: 10.1016/j.schres.2008.06.017

Kringlen, E. (1967a). *Heredity and environment in the functional psychoses: an epidemiological-clinical twin study*. London: William Heinemann.

Kringlen, E. (1967b). *Heredity and environment in the functional psychoses: case histories*. Oslo: Universitetsforlaget.

Landis, J.R., & Koch, G.C. (1977). The measurement of observer agreement for categorical data. *Biometrics*, *33*, 1089-1091.

Lichtenstein, P., Yip, B. H., Björk, C., Pawitan, Y., Cannon, T. D., Sullivan, P. F., & Hultman, C. M. (2009). Common genetic determinants of schizophrenia and bipolar disorder in Swedish families: a population-based study. *Lancet*, *373*, 234-239. doi: 10.1016/S0140-6736(09)60072-6

Mortensen, P. B., Pedersen, M. G., & Pedersen, C. B. (2010). Psychiatric family history and schizophrenia risk in Denmark: which mental disorders are relevant? *Psychological Medicine*, *40*, 201-210. doi: 10.1017/S0033291709990419

Onstad, S., Skre, I., Torgersen, S., & Kringlen, E. (1992). Birthweight and obstetric complications in schizophrenic twins. *Acta Psychiatrica Scandinavica*, *85*, 70-73.

Pulver, A. E., & Liang, K. -Y. (1991). Estimating effects of proband characteristics on familial risk II: the association between age at onset and familial risk in the Maryland schizophrenia sample. *Genetic Epidemiology*, *8*, 339-350.

Rossi, A., Mullin, P., & Chmait, R. (2011). Neonatal outcomes of twins according to birth order, presentation and mode of delivery: a systematic review and meta-analysis. *British Journal of Obstetrics and Gynaecology*, *118*, 523–532. doi: 10.1111/j.1471-0528.2010.02836.x

Sham, P. C., Gottesman, I. I., MacLean, C. J., & Kendler, K. S. (1994b). Schizophrenia: sex and familial morbidity. *Psychiatry Research*, *52*, 125-134.

Sham, P. C., Jones, P., Russell, A., Gilvarry, K., Bebbington, P., Lewis, S., … Murray R. (1994a). Age at onset, sex, and familial psychiatric morbidity in schizophrenia: Camberwell collaborative psychosis study. *British Journal of Psychiatry*, *165*, 466-473.

Slater, E., & Shields, J. (1953). *Psychotic and neurotic illnesses in twins*. London: H.M.S.O.

SPSS. Retrieved from https://www.ibm.com/products/spss-statistics 14 February 2018.

Sullivan, P. F., Kendler, K. S., & Neale, M. C. (2003). Schizophrenia as a complex trait: evidence from a meta-analysis of twin studies. *Archives of General Psychiatry*, *60*, 1187-1192. doi: 10.1001/archpsyc.60.12.1187

Suvisaari, J. M., Haukka, J., Tanskanen, A., & Lönnqvist, J. K. (1998). Age at onset and outcome in schizophrenia are related to the degree of familial loading. *British Journal of Psychiatry*, *173*, 494-500.

Svensson, A. C., Lichtenstein, P., Sandin, S., Öberg, S., Sullivan, P. F., & Hultman, C. M. (2012). Familial aggregation of schizophrenia: the moderating effect of age at onset, parental immigration, paternal age and season of birth. *Scandinavian Journal of Public Health*, *40*, 43-50. doi: 10.1177/1403494811420485

Tienari, P. (1963). Psychiatric illnesses in identical twins. *Acta Psychiatrica Scandinavica*, *39*, suppl 171.

Tienari, P. (1975). Schizophrenia in Finnish male twins. In Lader, M.H., Editor. Studies of schizophrenia. *British Journal of Psychiatry*, [Special publication] *10*, 29-35.