

Archival Report

Heritability of Schizophrenia and Schizophrenia Spectrum Based on the Nationwide Danish Twin Register

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ABSTRACT

BACKGROUND: Twin studies have provided evidence that both genetic and environmental factors contribute to schizophrenia (SZ) risk. Heritability estimates of SZ in twin samples have varied methodologically. This study provides updated heritability estimates based on nationwide twin data and an improved statistical methodology.

METHODS: Combining two nationwide registers, the Danish Twin Register and the Danish Psychiatric Research Register, we identified a sample of twins born between 1951 and 2000 ($N = 31,524$ twin pairs). Twins were followed until June 1, 2011. Liability threshold models adjusting for censoring with inverse probability weighting were used to estimate probandwise concordance rates and heritability of the diagnoses of SZ and SZ spectrum disorders.

RESULTS: The probandwise concordance rate of SZ is 33% in monozygotic twins and 7% in dizygotic twins. We estimated the heritability of SZ to be 79%. When expanding illness outcome to include SZ spectrum disorders, the heritability estimate was almost similar (73%).

CONCLUSIONS: The key strength of this study is the application of a novel statistical method accounting for censoring in the follow-up period to a nationwide twin sample. The estimated 79% heritability of SZ is congruent with previous reports and indicates a substantial genetic risk. The high genetic risk also applies to a broader phenotype of SZ spectrum disorders. The low concordance rate of 33% in monozygotic twins demonstrates that illness vulnerability is not solely indicated by genetic factors.

Keywords: Censoring, Concordance, Heritability, Register, Schizophrenia, Twin study

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The risk of developing schizophrenia (SZ) is influenced by both genetic and environmental factors (1,2). Twin studies have provided important insight, with several reports indicating a strong genetic risk. Previous twin studies have varied methodologically, and there is a need for new studies that use current diagnostic practice and escape some of the methodological pitfalls. Twin studies are particularly powerful when estimating the proportion of genetic variance to disease susceptibility by modeling the variance of phenotypic concordance across monozygotic (MZ) and dizygotic (DZ) twin pairs (3). Importantly, twin concordance itself, while expressing the probability that a twin is affected given that the cotwin is affected, does not provide a quantification of the genetic influence (3). Modeling phenotypic concordance in quantitative genetics is based on the concept of disease liability, which is assumed to be a continuous metric that is normally distributed in the population. Individuals with a liability above a certain threshold will develop the disease (4). Heritability modeling includes the coefficient of the additive genetic relation between family members, which for MZ twins is $r = 1$ and for DZ twins is $r = 0.5$. The closer the relation between family members included in such analysis (highest for MZ twins), the better the

quantification of the genetic contribution to the liability of disease (4–6).

Liability threshold models usually define the outcome as having a diagnosis versus no diagnosis at the study end point. Thus, a large proportion of subjects are still at risk for disease at the end of the observation period. The lack of complete outcome information for these individuals results in what is referred to as censored data, a potential bias that has not been accounted for in previous SZ heritability studies. A more robust way of quantifying genetic influence on SZ can be obtained by extending the classic liability threshold model to include inverse probability weighting (IPW). This method takes the censoring of data into account, which possibly provides more accurate heritability estimates (7).

As outlined in an overview of the five most recent twin studies, SZ concordance rates are between 41% and 65% in MZ twins and 0% and 28% in DZ twins (8). A meta-analysis of 12 twin studies found evidence for large additive genetic effects with heritability estimates of 81% in liability to SZ (9). However, these results stem from distinct methodological differences across studies regarding factors such as diagnostic categories and sample selection procedures, which limit study comparability.

Two studies estimated heritability based on national twin samples. One study from Finland (10) covered same-sex twin pairs born between 1940 and 1954 and found that 83% of the variance in liability to SZ could be attributed to additive genetic effects. Another study from Sweden (11) included both same- and opposite-sex twin pairs born between 1926 and 1958 and estimated the gender-specific heritability for SZ spectrum disorders to be 67% in females and 41% in males. By including older cohorts, the studies may be biased by a truncation mechanism, because case status requires that the individual survive until initiation of the register. The Finnish Psychiatric Case Register was established in 1968 and the Swedish in 1987 (12,13). In addition, a censoring mechanism may have contributed to less accurate estimates, which if unaccounted for could result in downward-biased concordance rates and heritability estimates that are biased in both directions depending on the dependence structure and the censoring distribution (14).

It is important to refine the methodology when estimating the heritability for SZ because the total heritability can be interpreted as an upper limit for the variance in a phenotype, which is explained by the variance in genes (6). A genome-wide association study is one approach that estimates single nucleotide polymorphism heritability, which may account for around 30% of the heritability in SZ (15,16). The discrepancy between the single nucleotide polymorphism heritability estimated in genome-wide association studies and the heritability based on diagnostic outcome in population studies is referred to as “missing heritability,” with a large part of the heritability unexplained by estimates from the genetic studies. Rare variants, including copy number variants, such as deletions and duplications that affect large areas of the genome, can possibly explain a marked part of the missing heritability (17,18). An updated total heritability estimate is important for future genome-wide association studies because it reflects a theoretical maximum of the variance explained by the potential genetic factors in SZ.

We aim to estimate concordance rates and heritability of SZ in a twin cohort identified in the Danish Twin Register using diagnostic information in the Danish Psychiatric Central Research Register. The study examines two nested phenotypes. First, the narrow definition of SZ as defined in ICD-8 and ICD-10, and second, a broader diagnostic category of SZ spectrum disorders in ICD-8 and ICD-10 (see Methods and Materials for details).

METHODS AND MATERIALS

The study was approved by the Danish Data Protection Agency and the National Board of Health.

National Registers

In Denmark, each person is assigned a unique identification number at birth and registered in the Danish Central Civil Registration System, making it possible to identify each person in all registers (19). The Danish Twin Register, initiated in 1954, is population-based and includes twins born in Denmark since 1870. Ascertainment of the Danish Twin Register is complete from 1968, i.e., it covers all twins born in Denmark before 1968, and the ascertainment rate is 72% (20). Information on

zygosity is obtained from the register by questionnaire. The Danish Psychiatric Central Research Register was computerized in 1969 and contains information on all psychiatric admissions in Denmark. From 1995 onward, outpatient contacts were also included. This register differentiates between main and secondary diagnoses (21).

Disease Classifications

In Denmark, the ICD-8 classification system was used from 1969 to 1993; ICD-10 was put into use in 1994 (22,23). In this study, SZ was defined as a main or secondary lifetime diagnosis in the ICD-10 (F20.xx) and ICD-8 (295 [excluding 295.79, schizoaffective disorder]) and SZ spectrum disorders as a main or secondary lifetime diagnosis in the ICD-10 (F2x.xx) and ICD-8 (295, 297, 29829, 29839, 29889, 29899, 29905, 29909, 30109, and 30129). In this study, a lifetime diagnosis covers a diagnosis received at any time point during the observation period, i.e., births before June 1, 2011. For SZ, this is defined as the first date of diagnosis, thus ignoring a possible diagnosis in the SZ spectrum before this date. For SZ spectrum disorders, it is defined as the first date of diagnosis.

Statistical Analysis

The concordance rate is an estimate of probability that measures the proportion of affected twins given that the cotwin is also affected. It can be calculated in two ways: pairwise and probandwise. Both methods refer to conditional probabilities; however, probandwise rates are applicable to twin individuals, and not twin pairs, thus comparable with the incidence rate and prevalence in a nontwin population (24). In this study, we calculated the probandwise concordance rates with 95% confidence intervals (95% CIs).

Tetrachoric correlations among twin pairs are calculated to measure the degree of agreement in diagnostic status in the twin pairs. Structural equation and liability threshold models are applied to estimate the heritability of SZ.

The general assumptions for the structural equation modeling are 1) gene–environment interactions are minimal for the trait; 2) twins are comparable to the general population; and 3) mating in the population is random (5,25), while the specific assumptions are 4) MZ and DZ pairs share common environmental effects to the same extent 5) the additive genetic effects are shared with correlation equal to 1 between MZ pairs and correlation 0.5 between DZ pairs.

Liability threshold models estimate the heritability as the contribution to variance in liability of additive genetic effects (A), common environmental effects (C), and unique environmental effects (E). Because A is considered the most important component for the observable genetic properties in a population (4) and because SZ is a complex disorder assumed to be caused by many genes with small effects (15), we chose to apply ACE models (and submodels). The full ACE model is fitted to data on the two diagnostic groups and compared with the two nested AE and CE models using delta χ^2 goodness of fit statistics and Akaike information criterion (AIC) (5,25). In the AE model, C is set to 0 having no uncertainty. The likelihood ratio test statistic, with one degree of freedom, is used to compare models to the full (ACE) model resulting in a *p* value indicating if the model fit is significantly better according to the

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data. Traditionally, when C is estimated in the analyses to be equal to 0 in the ACE model, the CIs of the uncertainty are achieved and the ACE model is chosen as the best-fitting model.

A major issue when estimating heritability of SZ is that a large proportion of study participants are still at risk of developing the illness at the end of the observation period. This induces a bias referred to as censoring (in survival analysis), because there is a lack of complete outcome information. In this study, we attempt to overcome this censoring mechanism by using IPW (7). This means adding a weight to each complete observation (i.e., cases and deaths) based on the data from the censored observations. The IPW model, which estimates the weights, is adjusted for sex and stratified on zygosity. In practice, it is only possible to get reliable estimates of the dependence between twins on the part of the time scale where sufficient information is available. Therefore, to model the correct weights, the follow-up period needs to be the same in both zygosity groups. Consequently, this means we can estimate concordance rates and heritability until the age of the last observed concordant pair in both the MZ and DZ groups. This is up to 40 years of age in the present population, for both SZ and SZ spectrum disorders. Accordingly, heritability estimates in our study are only generalizable to a disease onset before 40 years of age.

Data analyses were carried out using Stata software (version 12; StataCorp LP, College Station, TX) and the Mets package (<https://cran.r-project.org/web/packages/mets/index.html>) in R (26).

RESULTS

All twin pairs born in Denmark between 1951 and 2000 ($N = 37,891$ pairs) were identified through the Danish Civil Register and coupled with 1) information on psychiatric hospital admissions and corresponding clinical diagnoses from the Danish Psychiatric Central Research Register, and 2) information on zygosity obtained from the Danish Twin Register (on the majority of twin pairs; $n = 31,524$ pairs). The twin pairs with unknown zygosity (UZ) ($n = 6367$ pairs) were excluded from subsequent analyses because liability threshold modeling cannot include UZ pairs. A flowchart describing the sample size in the main data and in the supplementary data is shown in Figure 1. Among UZ twins, 88 twins have SZ and 157 twins have SZ spectrum disorder. The concordance rate of SZ is 0.28 (95% CI: 0.16–0.45) and 0.22 (95% CI: 0.13–0.34) for SZ spectrum disorder in UZ twins.

Of the 31,524 twin pairs included, 448 twin pairs (corresponding to 472 twins) were affected with SZ and 788 twin pairs (842 twins) were affected with SZ spectrum disorder (Table 1). The mean age at onset of SZ and SZ spectrum disorder was 28.92 years (SD: 8.52 years) and 29.19 years (SD: 9.37 years), respectively, and the median age at onset was 27.69 and 27.85 years, respectively.

Table 1 shows the number of complete cases in MZ and DZ twins, diagnostic distribution, and the number of censored observations in the present analyses. As observed, most of the observations are censored, depicted in the category “censored, e.g., alive without diagnosis,” because this category covers the main proportion of the sample (91–95%). The follow-up period in both zygosity groups is specified. The

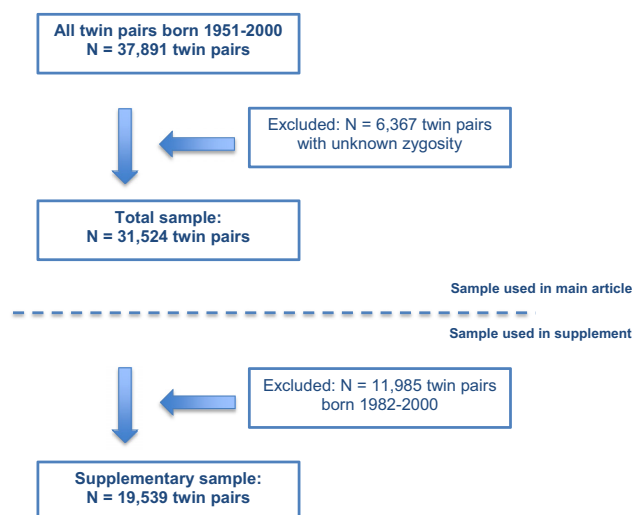


Figure 1. A flowchart describing the two samples included in this study, the main sample and the supplemental sample, identified by combining the Danish Twin Register and the Danish Psychiatric Central Research Register.

proportion of individuals with a SZ diagnosis is almost similar in the opposite sex and the same-sex DZ groups.

As shown in Table 2, the probandwise concordance rate and tetrachoric correlations are higher in MZ twins compared with DZ twins. Furthermore, both estimates are nearly identical for SZ and SZ spectrum disorders.

The probandwise concordance rate of SZ and SZ spectrum disorders as a function of years of follow-up (Figure 2) is higher in MZ and DZ twins than the overall cumulative incidence, indicating a familial risk for both conditions. In addition, in both conditions, the concordance rate is two- to threefold higher in MZ compared with DZ twins, with the DZ concordance rates being more stable across years of follow-up.

A liability threshold ACE model was initially fitted to SZ twin data (AIC = 14,031.65) (Table 3) and compared with a reduced AE model (AIC = 14,029.65), resulting in a nearly similar fit ($p = 1.0$). A CE model did not provide a better fit (AIC = 14,062.88, $p < .001$). We chose the AE model as the best-fitting model because it has the lowest AIC. The ACE model is not preferred because of the uncertain C and CI estimates (which are both set to 0). The same model-fitting procedure was applied to SZ spectrum disorder data and the AE model was selected as the best-fitting model (Table 3). For SZ, the dataset included 418 cases, 2534 deaths, and 60,096 censored individuals, of which the IPW weights are based on 34,423 whose follow-up time is under 40 years of age. For SZ spectrum disorders, the dataset included 721 cases, 2524 deaths, and 59,803 censored individuals, of which the IPW weights are based on 34,298 whose follow-up time is under 40 years of age.

The AE models estimated that the additive genetic effects accounted for 78.9% and 73.3% of the variance in liability to SZ and SZ spectrum disorders, respectively, while environmental effects accounted for 21.1% and 26.7% of the variance of the two diagnostic categories (Table 3).

For comparison with previous studies, the data for both SZ and SZ spectrum disorder were analyzed without consideration

Table 1. Number of Cases, Observations Followed Until Death, and Censored Observations in MZ and DZ Twins

	Schizophrenia			Schizophrenia Spectrum Disorder		
	MZ	DZ		MZ	DZ	
		Same Sex	Opposite Sex		Same Sex	Opposite Sex
Diagnosis, <i>n</i> (%)	93 (0.64)	173 (0.76)	206 (0.80)	181 (1.25)	317 (1.39)	344 (1.34)
Dead Without Diagnosis, <i>n</i> (%)	627 (4.32)	991 (4.33)	1839 (7.17)	617 (4.25)	974 (4.26)	1821 (7.09)
Censored (e.g., Alive Without Diagnosis), <i>n</i> (%)	13,794 (95.04)	21,704 (94.91)	23,621 (92.03)	13,716 (94.50)	21,577 (94.35)	23,501 (91.56)

DZ, dizygotic; MZ, monozygotic.

for censoring. When analyzing these data, a reduced twin sample consisting of $n = 19,539$ twin pairs born between 1951 and 1981 compared with twin pairs born between 1951 and 2000 in the adjusted analysis was included to ensure a minimum follow-up of 30 years. The results can be seen in [Supplemental Tables S1](#) and [S2](#). The analyses resulted in lower probandwise concordance rates for MZ twins (0.33) and heritability estimates (SZ = 75.5%; SZ spectrum disorder = 69.5%).

DISCUSSION

The present study is based on two nationwide registers in Denmark and provides the largest twin sample in SZ research to date. The key strengths in this study design are that censoring is adjusted for in the models for heritability estimates and that this improved method is applied to a nationwide twin sample. Our results show a substantial genetic component in liability to SZ, with a heritability estimate of 79%, and that the genetic effects seem to play a similar role in SZ spectrum disorders. The concordance estimates are moderately lower than generally indicated for MZ twins (0.33) and even lower with the standard method of concordance estimation (0.29) ([Supplement](#)).

We estimated the variance in liability according to additive genetic effects (the heritability) for SZ (79%) and for SZ spectrum disorders (73%). In general, our results are congruent with estimates found in previous twin studies of 83% and 82% ([10,27](#)) and in a meta-analysis of 12 twin studies of 81% ([9](#)). For both SZ and SZ spectrum disorders, the estimate is based on having an illness onset before 40 years of age, and large studies confirm that it is reasonable to assume that most cases of SZ will present before this age ([28–30](#)). SZ has been shown to have a higher heritability than most other psychiatric illnesses ([2](#)), and the strongest association with SZ risk in the general population is familial aggregation of SZ, although a diagnosis of SZ is associated with a wide range of

other psychiatric disorders ([31](#)). When expanding the outcome to SZ spectrum disorders, we expected to find a lower rate of genetic influence on the phenotype. We were not able to confirm this in our study because the heritability was similar for SZ and SZ spectrum disorders. This could reflect a robustness of the basic concept of the disorder despite observed heterogeneity in the clinical presentation across the spectrum of SZ. It may also suggest that the genetic risk for disease is not restricted to a narrow illness definition, but includes a broader phenotype, which supports the idea of a continuous illness spectrum.

In our model, we estimated C (common environmental effects) to be 0. In general, C may be confounded in the liability threshold models because of assumptions underlying the liability threshold models (see [Methods and Materials](#)). Another register-based study has also estimated C as being 0, while the meta-analysis estimated C as 11% (95% CI: 3–19%) across studies ([9,10](#)). Common environmental factors, such as urbanicity and social disadvantage, have been shown to have important impact on illness risk ([32](#)). Thus, these factors are shared by twins but do not necessarily affect both twins in a pair to the same extent. When C is estimated to 0 it can be an indication that C is intertwined with genetic factors and that C may be “hidden” in the estimate of A (additive genetic effects), which may contribute to an overestimation of the genetic liability to illness ([6,32](#)). Another consideration is that Denmark may be a homogenous society with relatively small variations in C compared to other countries.

We report a low concordance rate in MZ and DZ twins (0.33 and 0.07, respectively). This may seem to contradict a substantial heritability estimate. However, an explanation can be found in quantitative genetics and the general assumption that liability to disease is continuous and normally distributed, with disease becoming evident after passing a specific threshold ([4](#)). Looking at disease liability from this continuous perspective in a disorder like SZ with a low disease prevalence of 1%, it

Table 2. Probandwise CRs and TCRs for SZ and SZ+ in MZ and DZ Twins

	Zygosity	Concordant Pairs	Discordant Pairs	Healthy Pairs	Probandwise CR (95% CI)	TCR (95% CI)
SZ	MZ	12	69	7,176	0.33 (0.20–0.49)	0.78 (0.62–0.87)
	DZ	12	355	23,900	0.07 (0.04–0.13)	0.35 (0.21–0.48)
SZ+	MZ	23	135	7,099	0.32 (0.22–0.44)	0.73 (0.61–0.82)
	DZ	31	599	23,637	0.09 (0.06–0.13)	0.34 (0.23–0.44)

Probandwise CRs and TCRs are calculated for SZ and SZ+ using inverse probability weighting until 40 years of age.

CI, confidence interval; CR, concordance rate; DZ, dizygotic; MZ, monozygotic; TCR, tetrachoric correlation; SZ, schizophrenia; SZ+, SZ spectrum disorder.

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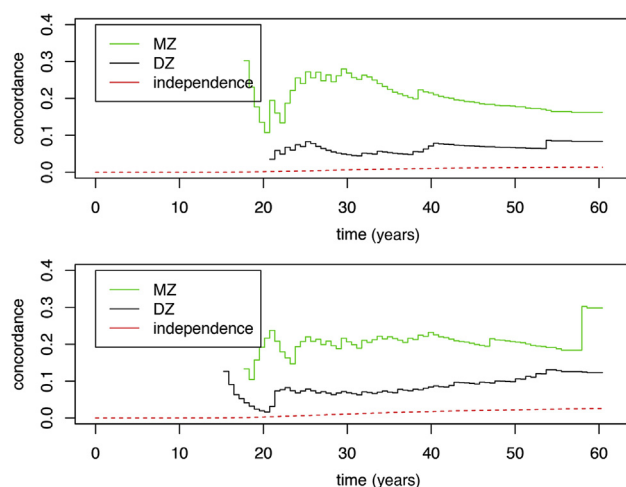


Figure 2. Probandwise concordance rates of schizophrenia (top) and schizophrenia spectrum disorder (bottom) as a function of years (i.e., time indicates the time from birth until the end of the study [age]). Independence indicates the marginal (i.e., prevalence) of disorder. DZ, dizygotic; MZ, monozygotic.

is possible even for MZ twin pairs to appear different clinically, and at the same time be similar in their underlying genetic disease liability (33). The estimation of concordance rates depends on disease prevalence. A low concordance rate does not directly imply a low contribution of genetic factors in disease liability (34). Twin studies have varied regarding methodological factors, e.g., illness severity, ascertainment procedures, and whether or not follow-up time is included in the studies. This limits the ability to compare concordance rates across studies. Two publications provide overviews of previous twin studies (8,35), and these include, among others, two early register-based studies reporting a low MZ concordance rate: 0.31 in Kendler and Robinette (36) and 0.36 in Fischer *et al.* (37). A low DZ concordance rate has also been reported previously, e.g., 0.07 in Kendler and Robinette (36), 0.09 in Cannon *et al.* (10), and 0.05 in Cardno *et al.* (27). One study has addressed to which extent methodological factors

may influence the estimate of concordance rates in twin studies and concluded that, among other factors, register-based sample selection procedures significantly lowered concordance rates in twins (38). We argue that our results are in line with findings in some earlier twin studies, which were mainly register based. We further argue that it may constitute a more accurate estimate because it is based on register data from a national twin sample, includes a follow-up period of 40 years, and features improved methodology. Our rates might be affected by the relatively low prevalence found (around 1% for SZ and 2% for SZ spectrum disorders) and reported in Supplemental Table S1. This is lower than the prevalence in another register-based twin study from Finland, reporting a prevalence of 2% for SZ and 3.4% for SZ spectrum disorders (10). In summary, our findings do indicate that genetic factors have a significant influence on the underlying illness susceptibility, but that an environmental trigger/interaction may be needed to affect illness penetrance, as previously described in a landmark twin study from 1989 (39).

Many factors, such as DNA sequence, epigenetic DNA modifications, differences in gene expression, and environmental factors, and the complex interaction between these are thought to act in concert to influence the outcome of a complex psychiatric phenotype like SZ (17). In general, heritability estimated from twin studies is precise because the pattern of correlation between family members is higher in twins than in other relatives (34); on the other hand, estimating heritability in closely related individuals can make it difficult to tease out possible confounding factors, such as nonadditive genetic combinations and environmental factors shared in the family (6,34). This may lead to an overestimation of the heritability (40). In addition, MZ and DZ twin pairs are assumed to share their environment to the same extent, but if MZ twins are exposed to more equal environments than DZ twins the heritability can be overestimated (5).

To estimate true concordance rates and heritability, a lifelong follow-up period for all individuals would be ideal. By applying IPW methodology we were able to overcome censoring mechanisms, and therefore we expect to observe changes in heritability estimates compared to previous studies and compared to our own data with standard methodology (Supplement). To

Table 3. Heritability Estimates for SZ and SZ+ in a National Cohort of Twin Pairs (N = 31,524 Twin Pairs)

Definition/Model	a2 (Heritability)		c2		e2		AIC	vs	df	χ^2	p Value
	%	95% CI	%	95% CI	%	95% CI					
SZ											
ACE	78.9	65.1–99.3	0.0	0.0–0.0	21.1	11.8–34.9	14,031.65	–	–	–	–
AE ^a	78.9	65.1–88.2	–	–	21.1	11.8–34.9	14,029.65	ACE	1	0.00	1.00
CE	–	–	47.0	37.3–57.0	53.0	43.0–62.7	14,062.88	ACE	1	33.23	<.001
SZ+											
ACE	73.3	62.5–81.9	0.0	0.0–0.0	26.7	18.1–37.5	21,545.74	–	–	–	–
AE ^a	73.3	62.5–81.9	–	–	26.7	18.1–37.5	21,543.19	ACE	1	0.00	1.00
CE	–	–	44.9	37.2–52.9	55.1	47.1–62.8	21,585.72	ACE	1	42.53	<.001

Liability threshold models adjusted for inverse probability weighting. These models estimate the following contributors to the variance in liability: A, C, and E. We used a cutoff at 40 years of age.

A, additive genetic effects; a2, variance of liability due to A; AIC, Akaike information criterion; C, common environmental effects; c2, variance of liability due to C; CI, confidence interval; E, unique environmental effects; e2, variance of liability due to E; SZ, schizophrenia; SZ+, SZ spectrum disorder.

^aIndicates the best fitting model.

minimize bias when IPW is not applied (i.e., censoring is not taken into account), we have only included twin pairs born between 1951 and 1981 in the supplement dataset in order to secure a minimum follow-up time of 30 years at the end of follow-up in June 2011. The main and supplementary data are not directly comparable because they are based on two differently defined samples and analysis approaches. Despite this limitation, the results are almost identical between the main data and the supplementary data, which indicates that if a sufficiently long follow-up period is included in the analyses, the bias may not have influenced the heritability estimates to a marked degree. By applying IPW, we were able to include a much larger twin sample ($N = 31,524$ pairs compared to $N = 19,539$ pairs), thereby contributing to further accuracy of the heritability estimate in the main data of our study. Furthermore, the apparent solidity of heritability estimates across previous studies and in the data presented here could reflect a relative stability in the diagnostic outcome in twin pairs over time, making bias less prominent (14). Although data were drawn from national registers, the number of concordant pairs is low, the last pair becoming concordant at 40 years of age. In this study, we estimate the heritability for an onset before 40 years of age. We do capture the majority of the cases, but including a wider age span would also increase the generalizability of our results. In addition, a large proportion of the sample is censored in 2012; with a longer (e.g., lifelong) follow-up time we could obtain more accurate estimates. The latter applies to all studies of heritability. We stipulate that addressing the censoring mechanism in the estimates as an improvement of methodology.

We estimated the mean age at SZ onset to 28.9 years of age. In our study, onset is defined as age at first contact to a psychiatric facility, which is considered a valid marker of illness onset (29). A Finnish twin study reports a similar mean age (10), and a recent study examining gender- and age-specific incidence rates and lifetime risks of psychiatric illness in the Danish population found a peak in age at onset of SZ in the early twenties and new cases diagnosed late in life (28).

Strengths and Limitations

This study examined a representative twin sample from comprehensive, nationwide registers, which is less liable to ascertainment bias. The Danish Psychiatric Research Register is highly representative of patients with SZ in Denmark because the number of privately treated patients is minimal (21). One concern might be that our approach is highly dependent on the consistency and validity of the clinical diagnoses drawn from health registers. However, a recent study demonstrated the high validity of the register diagnosis in SZ (41). Despite this, undiagnosed cases could exist. Because of reasons mentioned in the Methods and Materials section, our results cannot be generalized to disease onset after 40 years of age. All CIs were rather wide because the analysis only included complete observations (cases with disease onset before 40 years of age and observations followed until death).

In general, it is assumed that twins are representative of the general population, and as such these results are considered generalizable (5,42). The generalizability of our findings may be affected by the exclusion of UZ twins and by the use of a Danish twin sample.

In conclusion, we present SZ heritability estimates, which mirror previous reports and indicate solid findings across differences in diagnostic practice, ascertainment biases, and censored data. Our study suggests a robustness of the basic concept of SZ, including both narrow and broad definitions of illness.

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ARTICLE INFORMATION

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