



The impact of a family history of psychosis on age-at-onset and positive and negative symptoms of schizophrenia: A meta-analysis

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ABSTRACT

The results of research on the relation of family history (FH) of psychosis with clinical presentation in schizophrenia have been mixed. To date, there have been no comprehensive reviews that have examined this body of research. The current review quantitatively evaluates research on the relation of FH with two aspects of schizophrenia, age-at-onset and symptom presentation. Studies investigating the influence of a FH on age-at-onset ($N = 15$ studies), age-at-onset and sex ($N = 12$ studies), and/or positive ($N = 11$ studies) and negative symptoms ($N = 12$ studies) in patients with schizophrenia were included in the meta-analyses. Results showed that FH has a small but significant impact on age-at-onset as well as negative symptoms. Of most interest was the finding that sex differences in age-at-onset are not observed in samples with a FH. Furthermore, there was a significant interaction between FH and sex with respect to negative symptoms. The findings of the current review are discussed in light of the diathesis-stress model. Theoretical assumptions and empirical research are reviewed to support the notion that FH influences susceptibility and presentation through similar mechanisms. Implications of the current findings, limitations of the review, and directions for future research are highlighted.

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1. Introduction

Affecting around 1% of the population over the course of a lifetime (Jablensky, 1997), schizophrenia is a heterogeneous and complex psychiatric disorder that is often chronic, severe, and disabling. Heterogeneity is observed in clinical characteristics such as age-at-onset and positive and negative symptoms. For example, although schizophrenia typically has an onset during late adolescence or early adulthood (Jablensky, 1997), research has shown consistent sex differences in age-at-onset, such that males display a significantly younger mean age-at-onset. Sex differences have also been reported in the symptoms of schizophrenia, with males showing more severe negative symptoms (Leung and Chue, 2000).

Fanous and Kendler (2005) point out that, across methodologies, research findings support the notion that familial factors not only influence illness liability but also clinical presentation. In line with this thinking, many studies have shown that a positive family history (FH+) is associated with some clinical characteristics of schizophrenia. For example, several researchers have shown that a FH+ of psychosis is associated with a younger age-at-onset (Alda et al., 1996; Ritsner et al., 2005, 2007); others suggest that the relation between FH and earlier age-at-onset is more pronounced for females, such that the well-established sex difference in age-at-onset may not hold for FH+ patients (Könnecke et al., 2000). Another line of investigation indicates that FH+ is linked with more severe symptoms, especially negative symptoms (Ara-järvi et al., 2006; Malaspina et al., 2000), although other studies do not support this (Feldmann et al., 2001).

To date, there have been no attempts to quantify the impact of FH by aggregating data across studies. A more accurate and

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comprehensive picture of the relation of FH with illness characteristics may emerge from a systematic analysis of the findings. Understanding this relation is important, because FH may be a marker for one or more etiologic subtypes that vary on clinical characteristics or course. Furthermore, while FH is not a modifiable prognostic factor, understanding its impact on clinical presentation could lead to earlier and improved intervention strategies for FH+ patients. Therefore, this meta-analytic review examines the impact of FH on two classes of variables for which there are accumulated bodies of literature: (1) variation in age-at-onset of psychosis, and (2) severity ratings of positive and negative symptoms. Furthermore, this review examines the impact of FH on sex differences in age-at-onset of schizophrenia.

2. Method

2.1. Study identification and inclusion

Several strategies were utilized to identify relevant published articles. First, English-language studies were identified through a search of computerized databases (i.e., *Medline* and *PsycINFO*), using keywords “schizophrenia,” “psychosis,” “family history,” “familial,” “sporadic,” “age-at-onset,” “symptoms,” and combinations of these terms. Second, reference sections were reviewed for relevant studies that were not identified in the initial database search. Finally, tables of contents from relevant journals (i.e., *Schizophrenia Research*, *Schizophrenia Bulletin*) were reviewed.

Studies were included in the meta-analysis if the following criteria were met: (1) the study assessed the presence (FH+) or absence (FH−) of a psychosis-related disorder in the pedigree of the patients; (2) the patient samples were diagnosed with a schizophrenia spectrum disorder; and (3) the study data were sufficient for calculating difference scores, such as mean scores, independent *t*-test values, probability values, and sample sizes for each group for either age-at-onset, positive symptoms, or negative symptoms for FH+ and FH− patients. Given these criteria, studies using indices such as familial loading or risk ratio scores were excluded, as these continuous measures are not readily amenable to dichotomization.

Several studies included samples of patients with other disorders, such as epilepsy-related psychosis (Adachi et al., 2008), in addition to patients with schizophrenia. Only those studies providing subgroup statistics were included in the meta-analysis. Additionally, age-at-onset was typically defined as *age at first psychotic symptom*, although several studies used *age-at-first-treatment* as a proxy for age-at-onset (Albus et al., 1994; Albus and Maier, 1995; Gorwood et al., 1995;). For these studies, the mean age provided was entered, and definition of age-at-onset was analyzed as a potential moderator. Finally, efforts were made to ensure that each study sample was independent, such that included studies from the same authors represented independent patient samples.

2.2. Statistical procedures

Because results from studies are reported as mean differences, the standardized mean difference (Cohen's *d*) was used as an effect size (ES) indicator. The magnitude of the weighted mean ES was interpreted utilizing Cohen's widely accepted conventions, in which $d \leq 0.20$ is considered small, $d \sim 0.50$ is

medium, and $d \geq 0.80$ is large. Standard calculation procedures outlined by Lipsey and Wilson (2001) and Cooper and Hedges (1994) were followed. Five meta-analyses were conducted.

Statistically independent ESs were calculated for each meta-analysis, with one ES per study that was weighted to account for differences in sample sizes. Hedges (1981) noted that the standardized mean difference ES tends to be upwardly biased when based on small sample sizes; thus, a correction for this bias was applied. Confidence intervals were calculated to evaluate the statistical significance of all individual study ESs and the weighted mean ESs from each meta-analysis. If the confidence interval (CI) did not contain zero, the mean ES was deemed statistically significant.

Given the relatively small number of studies included in each meta-analysis, fixed effects models were used, despite the limitations of these types of models (Hunter and Schmidt, 2000). However, if subsequent analyses for homogeneity of variance (*Q*-statistic, distributed as a chi-square with $k-1$ degrees of freedom, where k is the number of ESs) revealed significant variability among the ESs, moderator analyses were conducted to potentially explain any additional variability. Finally, publication bias was analyzed using Rosenthal's fail-safe *N* (Rosenthal, 1984).

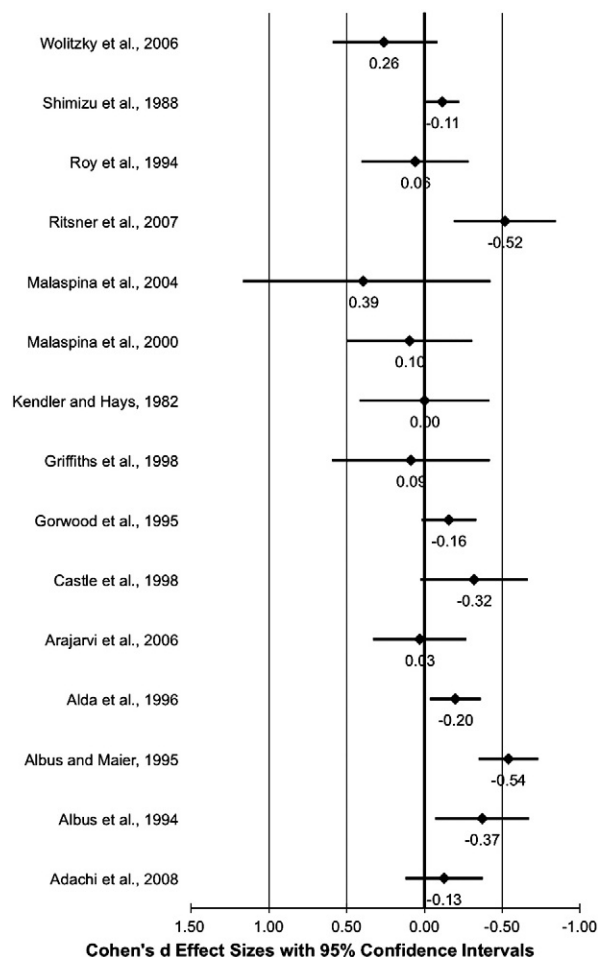


Fig. 1. Forest plot for ESs of studies of effect of family history on age-at-onset ($N = 15$).

2.3. Moderator analyses

Categorical moderators were examined using one-way Analyses of Variance (ANOVAs) and Student's *t*-tests, and continuous moderators were examined using least squares regression analyses. A priori moderators were: (1) diagnosis of the family members (*narrow* = schizophrenia or *broad* = any psychotic disorder), (2) degree of relation included in FH (*first*

degree only, *first and second degree*, or *any relation*), (3) sex (using separate meta-analyses for age-at-onset, and the *percentage of males* in the FH+ and FH− patient groups), (4) type of FH study (*family study* = diagnostic interviews conducted with all family members of the patient, or *family history study* = FH information collected via an interview with the patient and one or more informants), (5) definition of age-at-onset (*age at first psychotic symptom* or *age-at-first-treatment* or *-diagnosis*),

Table 1

Studies used in meta-analysis of effect of family history on age-at-onset of psychosis (*N* = 15).

Study	<i>n</i>	FH+	FH−	Family diagnosis	Degree of relation	Age-at-onset measure	Study type	Results	Effect size
Adachi et al. (2008) ^a	612	70	542	Psychotic disorder (ICD-10)	First	CASH; age at first psychotic symptom	Family history	Non-significant trend for FH+ patients to have a younger age-at-onset	−0.13
Albus et al. (1994) ^b	197	63	134	SZ or affective disorder or suicide	First	Interview; age at first psychotic symptom	Family history	FH+ patients had a significantly younger age-at-onset; no sex difference in age-at-onset in FH+ patients	−0.37
Albus and Maier (1995) ^c	618	137	481	SZ or SCAD (DSM-III-R)	First	Interview; age at first psychotic symptom	Family history	FH+ patients had a significantly younger age-at-onset; no sex difference in age-at-onset in FH+ patients	−0.54
Alda et al. (1996) ^d	1089	170	919	SZ or non-affective psychosis	First	Interview; no other info	Family history	FH+ patients had a significantly younger age-at-onset; no interaction between family history and sex	−0.20
Arajärvi et al. (2006) ^e	196	63	133	SZ or psychotic disorder (DSM-IV)	First	Register; no other info	Family history	No significant difference between FH+ and FH− patients for age-at-onset	0.03
Castle et al. (1998)	447	35	412	SZ (OCCPI)	No info	OCCPI; age first sought medical advice	Family history	Non-significant trend for FH+ patients to have a younger age-at-onset	−0.32
Gorwood et al. (1995)	663	165	498	SZ (DSM-III-R)	First and second	Interview; age at first diagnosis	Family history	FH+ patients had a significantly younger age-at-onset; significant interaction between FH and sex, such that FH− females showed oldest age-at-onset	−0.16
Griffiths et al. (1998)	60	32	28	SZ (DSM-III-R)	First and second	Interview; age-at-onset of symptoms	Family history	No significant difference in age-at-onset between FH+ and FH− patients	0.09
Kendler and Hays (1982)	113	30	83	SZ	First	Age-at-onset; no other info	Family history	No significant difference in age-at-onset between FH+ and FH− patients	0.00
Malaspina et al. (2000) ^f	99	39	60	SZ-related psychoses (DSM-III-R)	First and second	Interview; age-at-onset	Family history	No significant difference in age-at-onset between FH+ and FH− patients	0.10
Malaspina et al. (2004)	26	10	16	Chronic, non-affective psychoses	First and second	Interview; age-at-onset	Family history	Non-significant trend for FH+ patients to have an older age-at-onset	0.39
Ritsner et al. (2005, 2007)	148	69	79	SZ-related psychoses (DSM-IV)	First and second	Interview; age applying to mental health care	Family history	FH+ patients had a significantly younger age-at-onset	−0.52
Roy et al. (1994) ^g	130	68	62	SZ	First	CASH; age-at-onset of symptoms	Family history	No significant difference in age-at-onset between FH+ and FH− patients	0.06
Shimizu et al. (1988)	2417	371	2046	SZ	First	Interview and case review; Age at first symptoms	Family history	No significant difference in age-at-onset between FH+ and FH− patients; however, more FH+ patients became ill before 25 years of age	−0.11
Wolitzky et al. (2006)	154	51	103	Non-affective Psychosis (DSM-IV)	First and second	Age-at-onset of psychotic symptom	Family history	No significant difference in age-at-onset between FH+ and FH− patients; no significant interaction between FH and sex	0.26

ICD = International Classification of Diseases, CASH = Comprehensive Assessment of Symptoms/History, FH = family history, DSM = Diagnostic and Statistical Manual, RDC = research diagnostic criteria, SCAD = schizoaffective disorder, MDD = major depressive disorder, DD = delusional disorder, OCCPI = Operational Criteria Checklist for Psychotic Illness, and SSD = schizophrenia spectrum disorder.

^a Only used patient sample with schizophrenia (not epilepsy psychosis).

^b Used data for mean age-at-onset of first psychotic symptom (not mean age at ascertainment).

^c Did not use data from mixed male and female sibling pairs.

^d Use overall ANOVA results for three samples combined.

^e Only used data from isolate singleton patients and isolate multiplex patients.

^f Used data for mean age-at-onset (not mean age-at-first-treatment).

^g Used data for mean age-at-onset (not mean age-at-first hospitalization).

(6) age-at-onset measure (*standardized instrument or interview*), (7) symptom measure [*Positive and Negative Syndrome Scale (PANSS), Scale for the Assessment of Positive/Negative Symptoms (SAPS/SANS), or other*], (8) hospitalization status (*inpatient, outpatient, or mixed*), and (9) illness stage (*first-episode, chronic, or mixed*).

3. Results

3.1. Age-at-onset

The first meta-analysis examined the relation of FH with age-at-onset, and study ESs are presented in Fig. 1. Results from the meta-analysis of these studies ($N=15$ studies, Table 1) examining differences in age-at-onset between FH+ patients and FH− patients supported a small but statistically significant effect ($d = -0.17$; 95% CI = -0.14 to -0.20); the negative effect indicates that FH+ patients have a younger age-at-onset of psychosis. A subsequent test of homogeneity of variance was significant ($Q = 36.21$, $p < 0.05$); however, none of the moderators were significant (Table 2).

3.2. Age-at-onset and sex

Studies of the effect of FH and sex on age-at-onset (Table 3) were analyzed using two separate meta-analyses: (1) sex differences in age-at-onset for FH+ patients, and (2) sex differences in age-at-onset for FH− patients; these analyses utilized those studies that reported mean ages-at-onset separately for males and females in both FH+ ($N=12$ studies) and FH− ($N=10$ studies) groups. Results of the first meta-analysis showed that among FH+ patients, the ES for the age-at-onset difference between males and females was small and non-significant, suggesting that FH+ males and FH+ females do not differ in age-at-onset ($d = -0.07$; 95% CI = -0.20 to 0.06).

Results of the second meta-analysis showed that for FH− patients, the ES for the difference between males and females was moderate and significant ($d = -0.47$; 95% CI = -0.40 to -0.55), indicating that FH− males have a significantly younger

age-at-onset compared to FH− females. Tests for homogeneity of variance of the ESs were non-significant. In comparing the two ESs, results showed that the age-at-onset ES for FH+ patients was significantly smaller than the age-at-onset ES for FH− patients, suggesting that the difference in age-at-onset between female and male patients is significantly larger for FH− patients ($z = -4.41$, $p < 0.05$).

3.3. Positive and negative symptoms

The studies ($N=11$) included in the meta-analysis examining the effect of FH on positive symptoms are presented in Table 4, with study ESs shown in Fig. 2. Results showed a small and non-significant effect ($d = 0.11$; 95% CI = -0.01 to 0.24) for the difference in positive symptoms between FH+ and FH− patients. Studies ($N=12$) included in the meta-analysis of the effect of FH on negative symptoms are also presented in Table 4, with study ESs shown in Fig. 3. Results of this meta-analysis showed a small and significant effect ($d = 0.23$; CI = 0.11 to 0.35) for the difference between FH+ and FH− patients. The direction of the mean ESs (i.e., positive) indicates that FH+ patients had more severe negative symptoms than FH− patients. While a test for homogeneity of variance of the ESs of the studies of negative symptoms was non-significant ($Q = 13.05$, $p > 0.05$), potential moderators were nonetheless examined. Results pertaining to the literature on negative symptoms (Table 5) showed one significant finding: as the proportion of males in the FH− group increased, the mean ES for the overall difference for FH+ and FH− patients decreased ($r = -0.61$, $p < 0.05$).

3.4. Publication bias

Publication bias was assessed using the fail-safe N procedures of Rosenthal (1984). Results showed that 43 studies showing null findings would be needed to reduce the mean ES to zero for studies on the difference in age-at-onset between FH+ and FH− patients. Fifty-seven studies showing null findings would be needed to reduce the ES to zero for

Table 2

Results of moderator analyses for meta-analysis of age-at-onset literature.

Moderator	Level	<i>N</i>	Mean effect size	Standard deviation	<i>t</i> / <i>F</i>	<i>p</i>
Diagnosis of family members	Narrow	6	−0.07	0.15	0.05	0.82
	Broad	9	−0.11	0.33		
Relation of family members	First degree	8	−0.16	0.21	1.23	0.33
	First and second degree	6	0.03	0.33		
	Any relation	1	−0.32	–	0.69	0.52
Illness stage of patient sample	First episode	1	−0.32	–		
	Chronic	8	−0.13	0.33		
	Mix of both	6	−0.01	0.17		
Type of study	Family	5	−0.22	0.30	1.72	0.21
	Family history	10	−0.03	0.24		
Age-at-onset method	Instrument	9	−0.15	0.31	0.86	0.37
	Interview	6	−0.02	0.19		
Definition of age-at-onset	Age at first psychotic symptom	10	−0.03	0.28	2.15	0.17
	Age-at-first-treatment	5	−0.23	0.20		
Moderator correlating with mean effect size		<i>N</i>	<i>r</i>		<i>p</i>	
Percentage of males in overall sample		15	0.12		0.67	
Percentage of males in FH+ patient group		12	0.08		0.80	
Percentage of males in FH− patient group		12	−0.42		0.18	

Table 3Studies used in meta-analysis of effect of family history and sex on age-at-onset of psychosis ($N = 12$).

Study	<i>n</i>	FH+		FH–		Family diagnosis	Degree of relation	AOO measure	Study type	Results	FH+ ES	FH– ES
		M	F	M	F							
Adachi et al. (2008) ^a	612	36	34	274	268	Psychotic disorder (ICD-10)	First	CASH; age at first psychotic symptom	Family history	Males had younger age-at-onset overall, but no significant interaction between FH and sex	–0.25	–0.22
Albus et al. (1994) ^b	106	32	31	77	57	SZ or affective disorder or suicide (RDC)	First	Interview; age at first psychotic symptom	Family history	Males had younger age-at-onset overall and in FH– patients; no sex differences in age-at-onset in FH+ patients	–0.07	–0.70
Albus and Maier (1995) Sample 1 ^c	384	42	30	164	148	SZ or SCAD (DSM-III-R)	First	Interview; age at first psychotic symptom	Family	No significant sex differences in FH+ patients; FH– males had a significantly younger age-at-onset	0.06	–0.51
Albus and Maier (1995) Sample 2 ^c	234	36	29	96	73	SZ or SCAD (DSM-III-R)	First	Interview; age at first psychotic symptom	Family	No significant sex differences in FH+ patients; FH– males had a significantly younger age-at-onset	–0.06	–0.53
Alda et al. Sample 1 (1996) ^d	824	55	50	395	324	SZ or non-affective psychosis	First	Interview; no other info	Family history	Significant sex differences in age-at-onset in both FH+ and FH– patients	–0.42	–0.57
Alda et al. Sample 2 (1996) ^d	153	34	13	71	35	SZ or non-affective psychosis	First	Interview; no other info	Family history	Significant sex differences in age-at-onset in both FH+ and FH– patients	–0.37	–0.53
Alda et al. Sample 3 (1996) ^d	112	6	12	36	58	SZ or non-affective psychosis	First	Interview; no other info	Family history	Significant sex differences in age-at-onset in both FH+ and FH– patients	–0.98	–0.17
Arajärvi et al. (2006) ^e	196	44	19	88	45	SZ or psychotic disorder (DSM-IV)	First	Register; no other info	Family	Trends for males to have an older age-at-onset in FH+ patient group and younger age-at-onset in FH– patient group	0.33	–0.32
Gorwood et al. (1995) ^f	663	94	71	262	236	SZ (DSM-III-R)	First and second	Interview; age at first diagnosis	Family	Males had a significantly younger age-at-onset overall; no sex difference in age-at-onset in FH+ patients	0.08	–0.47
Könnecke et al. (2000)	151	7	19	60	65	SZ	First	IRAOS; age at first psychotic symptom	Family history	No sex difference in age-at-onset in FH+ patients	0.15	–0.47
LeBoyer et al. (1992) ^g	104	70	34	–	–	SZ	First	Age at first hospitalization	Family	Studied only FH+ patients; no sex difference in age-at-onset	–0.13	–
Murphy et al. (1994) ^g	166	–	–	–	–	SZ (DSM-III-R)	First	Age at first illness	Family	Studied only FH+ patients; no sex difference in age-at-onset	0.08	–

SZ = schizophrenia, ICD = International Classification of Diseases, CASH = Comprehensive Assessment of Symptoms/History, DSM = Diagnostic and Statistical Manual, SCAD = schizoaffective disorder, IRAOS = Interview for the Retrospective Assessment of the Onset of Schizophrenia, FH = family history, and RDC = research diagnostic criteria.

^a Only used patient sample with schizophrenia (not epilepsy psychosis).

^b Used data for mean age-at-onset of first psychotic symptom (no mean age at ascertainment).

^c Did not use data from mixed male and female sibling pairs; Albus and Maier (a) = data from Centre 1; Albus and Maier (b) = data from Centre 2.

^d Alda et al. Sample 1 = data from Berlin sample; Alda et al. Sample 2 = data from Ottawa sample; Alda et al. Sample 3 = data from Prague sample.

^e Only used data from isolate singleton patients and isolate multiplex patients.

^f Used data for mean age at first diagnosis (not mean age-of-first-treatment).

^g Study only included FH+ patients; no comparison sample of FH– patients.

studies on the difference in age-at-onset between FH– males and FH– females. Finally, 13 studies showing null findings would be needed for studies examining differences in negative symptoms between FH+ and FH– patients.

4. Discussion

Results of the review suggest that the presence of FH has a small but significant impact on several clinical features of schizophrenia, including age-at-onset of psychosis and negative symptoms. Age-at-onset and negative symptoms are important factors in the heterogeneity of schizophrenia. For example, Bellino et al. (2004) found that an earlier age-at-onset of schizophrenia is correlated with more severe negative

symptoms and poorer executive functioning. Thus, an understanding of the factors that contribute to heterogeneity in these clinical factors would be beneficial in that it could provide insight into etiologic mechanisms as well as guide possible intervention efforts. Results herein point to FH of psychosis as being a significant factor that contributes to age-at-onset and negative symptoms in schizophrenia, thus further describing one aspect of the heterogeneity of schizophrenia.

Perhaps the most compelling finding of the current review concerns the interaction between FH and sex. Sex differences in age-at-onset of psychosis are one of the most well-established findings in schizophrenia, with males typically showing a younger age-at-onset relative to females (Angermeyer and Kühn, 1988). It has been posited that estrogen, the primary

Table 4Studies used in meta-analyses of effect of family history on positive ($N = 11$) and negative ($N = 12$) symptoms.

Study	<i>n</i>	FH+	FH–	Family diagnosis	Degree of relation	Symptom measure	Study type	Results	Positive symptoms ES	Negative symptoms ES
Arajärvi et al. (2006) ^a	196	63	133	SZ or psychotic disorder (DSM-IV)	First	SAPS; SANS	Family	FH+ patients had significantly more severe positive and negative symptoms	0.44	0.16
Borkowska and Rybakowski (2002) ^b	50	24	26	Any psychiatric diagnosis	First and second	PANSS	Family history	FH+ patients had significantly more severe negative symptoms; no difference in positive symptoms	–0.14	0.53
Chen et al. (2005) ^c	123	31	92	Psychotic disorder (DSM-IV)	First and second	PANSS	Family history	No difference between FH+ and FH– patients on positive or negative symptoms	–0.11	–0.07
Feldmann et al., (2001) ^d	98	59	39	Any psychiatric diagnosis	Any	BPRS; SANS	Family history	No difference between FH+ and FH– patients on positive or negative symptoms	–0.14	0.02
Malaspina et al. (2000) ^e	99	39	60	SZ-related psychoses (DSM-III)	First and second	PANSS	Family history	FH+ patients had significantly more severe negative symptoms	–	0.57
Malaspina et al. (2004)	26	10	16	Non-affective psychoses	First and second	PANSS	Family history	FH+ patients had significantly more severe negative symptoms; no difference in positive symptoms	0.59	0.65
Martin Reyes et al. (2004)	150	62	88	SZ	Any	PANSS	Family history	FH+ patients had significantly more severe negative symptoms; no difference in positive symptoms	0.13	0.39
Norman and Malla (2001) ^f	24	12	12	SZ	First and second	SAPS; SANS	Family history	No difference between FH+ and FH– patients on positive or negative symptoms	0.49	0.49
Norman et al. (2007b)	56	28	28	SSD	First	SAPS; SANS	Family history	No difference between FH+ and FH– patients on positive or negative symptoms	0.06	0.27
Ritsner et al. (2005, 2007) ^g	148	69	79	SZ-related psychoses (DSM-IV)	First and second	PANSS	Family	FH+ patients had significantly more severe negative symptoms; no difference in positive symptoms	0.20	0.39
Roy et al. (1994)	130	68	62	SZ	First	CASH	Family history	FH– patients had significantly more severe positive symptoms; no difference on negative symptoms	–0.37	–0.07
Sautter et al. (1994)	72	37	35	SZ; SCAD; ADPF	First and second	SAPS; SANS	Family history	No difference between FH+ and FH– patients on positive or negative symptoms	0.15	–0.02

SZ = schizophrenia, DSM = Diagnostic and Statistical Manual, SAPS = Scale for the Assessment of Positive Symptoms, SANS = Scale for the Assessment of Negative Symptoms, PANSS = Positive and Negative Syndrome Scale, MDD = major depressive disorder, RDC = research diagnostic criteria, BPRS = Brief Psychiatric Rating Scale, SSD = schizophrenia spectrum disorder, CASH = Comprehensive Assessment of Symptoms/History, SCAD = schizoaffective disorder, ADPF = Affective Disorder with Psychotic Features, and DD = delusional disorder.

^a Only used data from isolate singleton patients and isolate multiplex patients.

^b Used baseline (before treatment) PANSS scores.

^c First author provided symptom data not published in manuscript; Used data from patients with family history of psychosis.

^d Used baseline (before therapy treatment) BPRS and SANS scores.

^e Used original subscale scores from the PANSS (not factor-derived scores).

^f Median and interquartile range values converted to mean and standard deviation values.

^g Used data for PANSS factor scores before adjustment for covariate variables.

female sex hormone, has protective effects that are similar to the benefits of antipsychotic medications (Häfner, 2003). In line with this, it has also been suggested that using hormone replacement therapy in combination with antipsychotic medication may help decrease the severity of negative symptoms in post-menopausal women with schizophrenia (Lindamer et al., 2001).

However, the current review presents evidence that the well-established sex difference in age-at-onset disappears in FH+ patients. In looking separately at FH+ and FH– patients, the difference in age-at-onset between males and females was non-existent in FH+ patients, indicating that FH has the potential to “override” the effects of sex hormones in females and act to significantly reduce females’ age-at-onset, making it more comparable to males’ age-at-onset (DeLisi et al., 1994; Gorwood

et al., 1995). These findings suggest that only the non-familial forms of schizophrenia are sexually dimorphic in terms of age-at-onset. Thus, non-familial forms of schizophrenia may largely represent nonhereditary etiologic factors, such as prenatal insults and acquired but not inherited genetic mutations, and these may differentially affect males and females.

Sex also played a role in the relationship between FH and negative symptoms; specifically, as the proportion of males in the FH– group increased, the mean study ES for the overall difference between FH+ and FH– patients decreased, suggesting that the difference in negative symptoms between FH+ and FH– patients is influenced by the proportion of males in the FH– patient group. However, the proportion of males in the FH+ patients group had no effect on the study

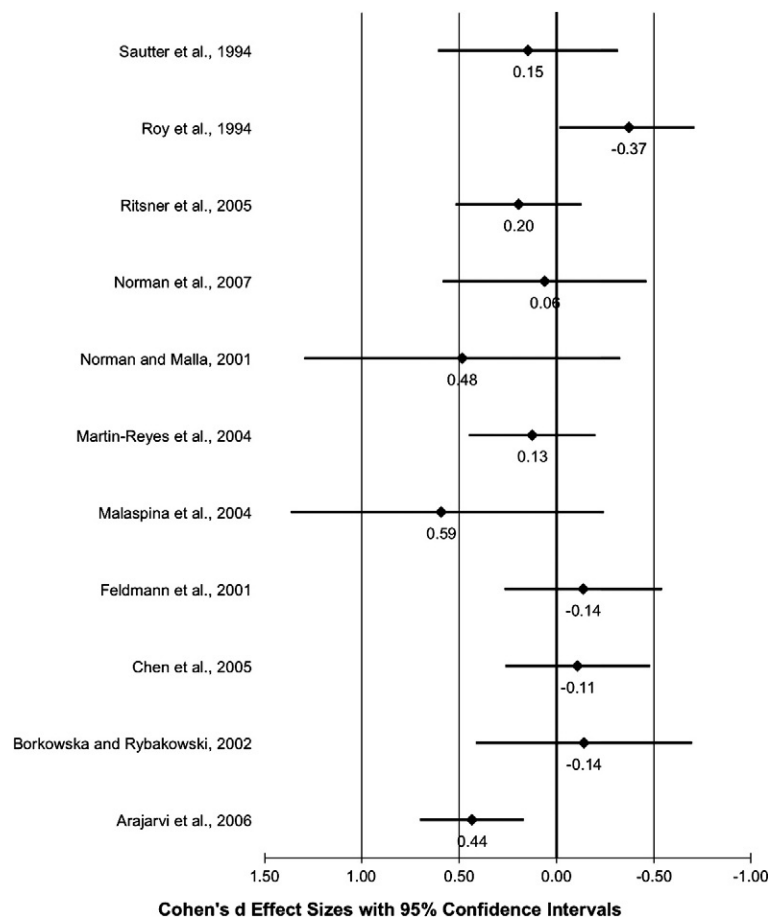


Fig. 2. Forest plot of ESs for studies of effect of family history on positive symptoms ($N = 11$).

ES, again suggesting that sex differences only manifest in the absence of a FH of psychosis. Sex differences in negative symptoms have also been documented, with males typically showing more severe symptomatology (Taylor and Langdon, 2006). It is possible that in the FH+ patient group, a decreased proportion of males, who in general tend to show more severe symptoms, results in a decreased mean of negative symptoms for the FH+ group. This likely leads to a greater difference between FH+ and FH- patients, which provides an explanation for sex being a significant moderator.

The diathesis-stress model posits that schizophrenia results from a complex interaction of genetic, biological, and environmental factors. In light of this model, it is hypothesized that FH can impact characteristics of schizophrenia through the same mechanisms that influence susceptibility. Joyce (2005) argued that research findings such as those reviewed herein provide strong evidence that there is a significant genetic contribution via inheritance to the variability in clinical features such as age-at-onset. One explanation for the influence of FH is the transmission of high-risk genotypes that are linked with severe clinical presentation, exemplified by the impact of DISC1 haplotypes on severity of positive symptoms (DeRosse et al., 2007). Alternatively, FH could influence presentation in schizophrenia through its impact on brain abnormalities. For instance, Zetzsche et al. (2008) found that FH+ patients

showed a significant reduction in right-hemisphere subcortical white matter, and that patients with this reduction displayed more severe negative symptomatology. Additionally, Goldstein et al. (2007) showed a higher prevalence of hypothalamic abnormalities in FH+ patients compared to FH- patients with schizophrenia.

Family history also could act as an environmental stressor, via conflictual interactions between an affected family member and the patient. Ritsner et al. (2007) found that the presence of a FH was associated with elevated emotional distress in patients, hypothesizing that this was due to the impact of FH on the emotional reactivity to stressful life events. Norman and Malla (2001) examined the relationship between stress reactivity and symptoms in FH+ and FH- patients; they showed that FH+ patients manifested a stronger relationship between stress reactivity and positive symptoms compared to FH- patients, indicating that FH acts as a potential influence on the stress response and subsequent symptom expression.

On the other hand, it is clear that FH has a relatively small impact on most characteristics of schizophrenia. It is likely that factors such as prenatal insults, and postnatal environmental stressors are also influencing the clinical characteristics of the disorder (Cannon et al., 2008; Walker and Tessner, 2008). Mutations and epigenetic processes are likely important as well. For example, a recent study found that rare

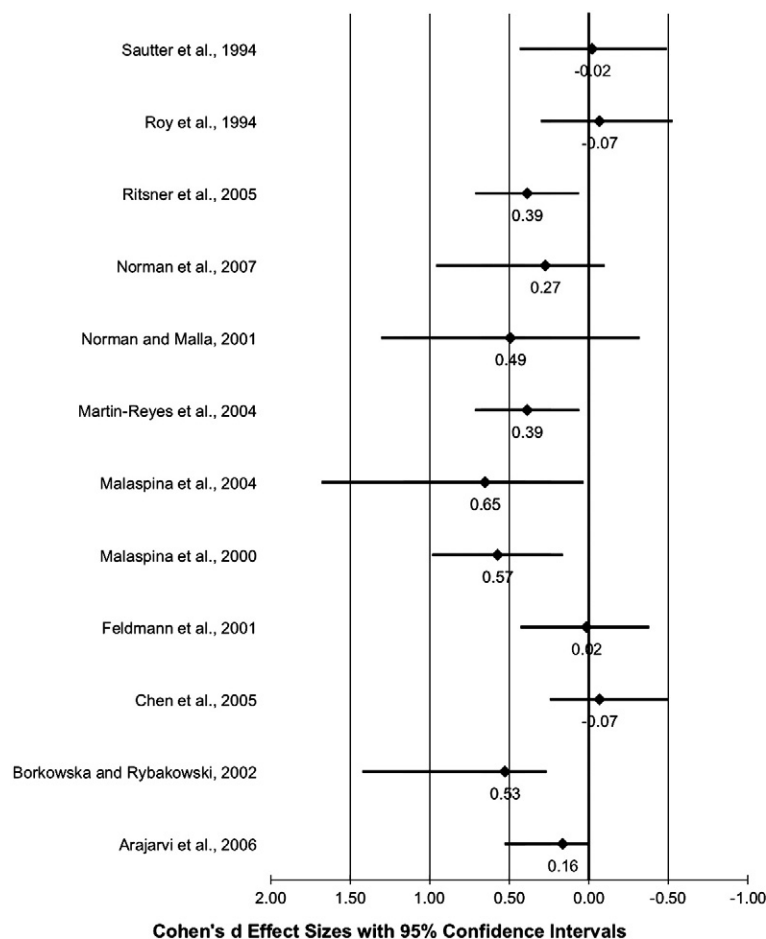


Fig. 3. Forest plot of ESs for studies of effect of family history on negative symptoms ($N = 12$).

de novo copy number variations (CNVs) were more frequent in affected individuals with a “sporadic” presentation in terms of FH compared to unaffected subjects (Xu et al., 2008). There was no difference in CNVs between FH+ and FH− patients, demonstrating that genetics factors operate outside the presence or absence of FH.

The findings herein underscore several directions for future research. First, there are inherent challenges in the classification of patients into FH+ and FH− subtypes (Roy and Crowe, 1994). It is not clear if a dichotomization is most appropriate, or whether future research should adopt continuous measures of FH, such as familial loading scores. Second, the interrelationships among the variables in the current meta-analysis are complex. For example, age-at-onset is related to a poorer course and outcome independent of FH (Rabinowitz et al., 2006); similarly, early onset of severe symptoms predicts poorer outcome (Milev et al., 2005). Thus, FH could have a direct influence on negative symptoms, or an indirect influence via its impact on age-at-onset, in which case age-at-onset would be a mediator in the relation between FH and symptom presentation.

Finally, when limited information is available in order to accurately date the age-at-onset, researchers often unfortunately rely on the age-at-first-treatment as a proxy for age-at-onset. The validity of this variable may be compromised by heterogeneity in the duration of untreated psychosis, or

the time period from the true onset of psychosis until initiation of adequate treatment. Thus, if age-at-first-treatment is an inappropriate proxy for age-at-onset, then earlier age-at-onset in FH+ patients may be a methodological artifact due to potential differences in treatment-seeking behavior. While we did not find that those studies that operationalized *age-at-onset* as *age-at-first-treatment* had larger effect sizes, future studies should nonetheless attempt to clarify the relative impact of FH on treatment-seeking behavior, especially in light of recent findings concerning the relationship between FH and duration of untreated psychosis (Norman et al., 2007a).

Several methodological limitations of these meta-analyses should be considered. First, the method of examining group differences in age-at-onset and symptoms precluded the inclusion of studies that have examined the influence of FH via risk ratios and familial loading scores. It has been argued that these methods offer a more accurate estimation of FH in patients with schizophrenia (Kendler and MacLean, 1990; Suvisaari et al., 1998; Van Os et al., 1997; Verdoux et al., 1996). However, the statistics employed in these studies do not lend themselves to meta-analysis, and therefore these studies were excluded from this report. Second, this meta-analysis focused largely on cross-sectional studies that examine the influence of FH on positive and negative symptoms. Research has shown

Table 5

Results of moderator analysis for meta-analysis of negative symptoms literature.

Moderator	Level	N	Mean effect size	Standard deviation	t/F	p
Diagnosis of family members	Narrow	3	0.27	0.30	0.01	0.97
	Broad	9	0.28	0.27		
Relation of family members	First degree	3	0.12	0.17	0.96	0.42
	First and second degree	7	0.36	0.29		
	Any relation	2	0.20	0.26		
Illness stage of patient sample	First episode	2	0.10	0.24	1.04	0.33
	Chronic	10	0.31	0.27		
Hospitalization status of patient sample	Inpatient	8	0.28	0.30	0.09	0.92
	Outpatient	3	0.30	0.25		
	Mix of both	1	0.16	–		
Type of study	Family	2	0.28	0.16	0.00	0.99
	Family history	10	0.28	0.29		
Method used to assess negative symptoms	Positive and Negative Syndrome Scale	6	0.41	0.26	2.39	0.15
	Scale for the Assessment of Negative Symptoms	5	0.18	0.21		
	Other	1	–0.07	–		
Moderator correlating with mean effect size		N	r		p	
Percentage of males in overall sample		11	0.28		0.40	
Percentage of males in the FH+ patient group		11	0.22		0.51	
Percentage of males in the FH– patient group		12	–0.61		0.03	

that while symptoms fluctuate over time, they are also correlated over time, and negative symptoms tend to be more stable than positive symptoms (Addington and Addington, 1991; Malla et al., 1993). However, this fluctuation presents difficulties in determining the true nature of the relationship between symptoms and trait predictors, such as FH, when using cross-sectional measurements. Finally, only a small number of studies have examined these phenomena in first-episode psychosis patients. In general, studies of first-episode psychosis may be less influenced by information bias (i.e., they more accurately estimate age-at-onset), and this should be taken into account when interpreting these findings, which were derived primarily from studies of chronic or mixed samples.

Despite these limitations, the current meta-analyses provide evidence of a small influence of FH on several clinical features of schizophrenia. Therefore, a large portion of the variance in presentation of illness remains to be explained, and a full understanding of predictors of clinical heterogeneity in schizophrenia remains to be realized. However, of most interest is the interaction between FH and sex and its impact on age-at-onset; it seems clear that FH plays a role in determining sex differences in age-at-onset of psychosis, and may also play a role in sex differences in negative symptomatology.

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Contributors

Michelle Esterberg served as the primary author of the meta-analysis study plan and manuscript, and conducted all data coding, statistical analyses, and wrote first draft of the manuscript.

Hanan Trotman assisted in the development of the initial meta-analysis study plan, assisted with literature review, and provided reviews of all drafts of the manuscript.

Carrie Holtzman served as a secondary, independent coder of all data included in meta-analyses and provided reviews of all drafts of the manuscript.

Michael Compton served as an advisor to the primary author and reviewed all drafts of the manuscript.

Elaine Walker served as mentor and advisor to the primary author, assisted in the development of the initial meta-analysis study plan, and provided critical reviews of the final drafts of the manuscript.

Conflict of interest

The authors have no conflicts of interest to report.

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References

- Adachi, N., Hara, T., Oana, Y., et al., 2008. Difference in age of onset of psychosis between epilepsy and schizophrenia. *Epilepsy Res.* 78, 201–206.
- Addington, J., Addington, D., 1991. Positive and negative symptoms of schizophrenia. Their course and relationship over time. *Schizophr. Res.* 5 (1), 51–59.
- Albus, M., Maier, W., 1995. Lack of gender differences in age-at-onset in familial schizophrenia. *Schizophr. Res.* 18, 51–57.
- Albus, M., Scherer, J., Hueber, S., et al., 1994. The impact of familial loading on gender differences in age-at-onset of schizophrenia. *Acta Psychiatr. Scand.* 89 132–134.
- Alda, M., Ahrens, B., Lit, W., et al., 1996. Age of onset in familial and sporadic schizophrenia. *Acta Psychiatr. Scand.* 93, 447–450.
- Angermeyer, M.C., Kühn, L., 1988. Gender differences in age-at-onset of schizophrenia. *Eur. Arch. Psychiatr. Neurol. Sci.* 37, 351–364.
- Arajärvi, R., Varilo, T., Haukka, J., et al., 2006. Affective flattening and alogia associate with the familial form of schizophrenia. *Psychiatry Res.* 141, 161–172.
- Bellino, S., Rocca, P., Patria, L., et al., 2004. Relationships of age-at-onset with clinical features and cognitive functions in a sample of schizophrenia patients. *J. Clin. Psychiatry* 65 (7), 908–914.
- Cannon, T.D., Cadenhead, K., Cornblatt, B., et al., 2008. Prediction of psychosis in youth at high clinical risk. *Arch. Gen. Psychiatry* 65 (1), 28–37.
- Cooper, H., Hedges, L.V., 1994. *The Handbook of Research Synthesis*. Russell Sage Foundation, New York, NY.
- DeLisi, L.E., Bass, N., Boccio, A., et al., 1994. Age of onset in familial schizophrenia. *Arch. Gen. Psychiatry* 51, 334–335.
- DeRosse, P., Hodgkinson, C.A., Lencz, T., et al., 2007. Disrupted in schizophrenia 1 genotype and positive symptoms in schizophrenia. *Biol. Psychiatry* 61, 1208–1210.
- Fanous, A.H., Kendler, K.S., 2005. Genetic heterogeneity, modifier genes, and quantitative phenotypes in psychiatric illness: searching for a framework. *Mol. Psychiatry* 10, 6–13.
- Goldstein, J.M., Seidman, L.J., Makris, N., et al., 2007. Hypothalamic abnormalities in schizophrenia: sex effects and genetic vulnerability. *Biol. Psychiatry* 61 (8), 935–945.
- Gorwood, P., Leboyer, M., Jay, M., Payan, C., Josue, F., 1995. Gender and age-at-onset in schizophrenia: impact of family history. *Am. J. Psychiatry* 152 (2), 208–212.

- Häfner, H., 2003. Gender differences in schizophrenia. *Psychoneuroendocrinology* 28, 17–54.
- Hedges, L.V., 1981. Distribution theory for Glass's estimator of ES and related estimators. *J. Educ. Stat.* 6, 107–128.
- Hunter, J.E., Schmidt, F.L., 2000. Fixed effects vs. random effects meta-analysis models: implications for cumulative research knowledge. *Int. J. Sel. Assess.* 8 (4), 275–292.
- Jablensky, A., 1997. The 100-year epidemiology of schizophrenia. *Schizophr. Res.* 28, 111–125.
- Joyce, E., 2005. Origins of cognitive dysfunction in schizophrenia: clues from age-at-onset. *Br. J. Psychiatry* 186, 93–95.
- 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. *Genet. Epidemiol.* 7, 409–417.
- Leung, A., Chue, P., 2000. Sex differences in schizophrenia: a review of the literature. *Acta Psychiatr. Scand. Suppl.* 401, 3–38.
- Lindamer, L.A., Buse, D.C., Lohr, J.B., Jeste, D.V., 2001. Hormone replacement therapy in postmenopausal women with schizophrenia: positive effect on negative symptoms? *Biol. Psychiatry* 49 (1), 47–51.
- Lipsey, M.W., Wilson, D.B., 2001. *Practical Meta-analysis*. Sage Publications, Inc., Thousand Oaks, CA.
- Malaspina, D., Goetz, R.R., Yale, S., et al., 2000. Relation of familial schizophrenia to negative symptoms but not to the deficit syndrome. *Am. J. Psychiatry* 157, 994–1003.
- Malla, A.K., Norman, R.M., Williamson, P., 1993. Stability of positive and negative symptoms in schizophrenia. *Can. J. Psychiatry* 38 (9), 617–621.
- Milev, P., Ho, B., Arndt, S., Andreasen, N.C., 2005. Predictive values of neurocognition and negative symptoms on functional outcome in schizophrenia: a longitudinal first-episode study with 7-year follow-up. *Am. J. Psychiatry* 162, 495–506.
- Norman, R.M.G., Malla, A.K., 2001. Family history of schizophrenia and the relationship of stress to symptoms: preliminary findings. *Aust. NZ J. Psychiatry* 35, 217–223.
- Norman, R.M.G., Malla, A.K., Manchanda, R., 2007a. Delay in treatment for psychosis: its relation to family history. *Soc. Psychiatry Psychiatr. Epidemiol.* 42 (6), 507–512.
- Rabinowitz, J., Levine, S.Z., Häfner, H., 2006. A population based elaboration of the role of age of onset on the course of schizophrenia. *Schizophr. Res.* 88 (1–3), 96–101.
- Ritsner, M.S., Ratner, Y., Gibel, A., Weizman, R., 2005. Familiality in a five-factor model of schizophrenia psychopathology: findings from a 16-month follow-up study. *Psychiatry Res.* 136, 173–179.
- Ritsner, M.S., Ratner, Y., Gibel, A., Weizman, R., 2007. Positive family history is associated with persistent elevated emotional distress in schizophrenia: evidence from a 16-month follow-up study. *Psychiatry Res.* 153, 217–223.
- Rosenthal, R., 1984. *Meta-analytic Procedures for Social Research*. Sage, Beverly Hills, CA.
- Roy, M.A., Crowe, R.R., 1994. Validity of the familial and sporadic subtypes of schizophrenia. *Am. J. Psychiatry* 151 (6), 805–814.
- Suvisaari, J.M., Haukka, J., Tanskanen, A., Lönnqvist, J., 1998. Age-at-onset and outcome in schizophrenia are related to the degree of familial loading. *Br. J. Psychiatry* 173 (6), 494–500.
- Taylor, R., Langdon, R., 2006. Understanding gender differences in schizophrenia: a review of the literature. *Curr. Psychiatr. Rev.* 2, 255–265.
- Van Os, J., Marcelis, M., Sham, P., Jones, P., Gilvarry, K., Murray, R., 1997. Psychopathological syndromes and familial morbid risk of psychosis. *Br. J. Psychiatry* 170 (3), 241–246.
- Verdoux, H., Van Os, J., Sham, P., Jones, P., Gilvarry, K., Murray, R., 1996. Does familiality predispose to both emergence and persistence of psychosis? A follow-up study. *Br. J. Psychiatry* 168, 620–626.
- Walker, E.F., Tessner, K.D., 2008. Schizophrenia. *Perspect. Psychol. Sci.* 3 (1), 30–37.
- Xu, B., Roos, J.L., Levy, S., van Rensburg, E.J., Gogos, J.A., Karayiorgou, M., 2008. Strong association of de novo copy number mutations with sporadic schizophrenia. *Nat. Genet.* 40 (7), 880–885.
- Zetzsch, T., Preuss, U.W., Frodl, T., et al., 2008. White matter alterations in schizophrenic patients with pronounced negative symptomatology and with positive family history for schizophrenia. *Eur. Arch. Psychiatry Clin. Neurosci.* 258 (5), 278–284.

The following references were included in the meta-analyses, but not cited in the text

- Borkowska, A., Rybakowski, J.K., 2002. Does risperidone act better in schizophrenic patients who have a family or obstetric history? *Prog. Neuropsychopharmacol. Biol. Psychiatry* 26 (7–8), 1349–1353.
- Castle, D., Sham, P., Murray, R., 1998. Differences in distribution of ages of onset in males and females with schizophrenia. *Schizophr. Res.* 33 (3), 179–183.
- Chen, E.Y., Dunn, E.L., Miao, M.Y., et al., 2005. The impact of family experience on the duration of untreated psychosis (DUP) in Hong Kong. *Soc. Psychiatry Psychiatr. Epidemiol.* 40, 350–356.
- Feldmann, R., Hornung, W.P., Buchkremer, G., Arolt, V., 2001. The influence of familial loading on the course of schizophrenia symptoms and the success of psychoeducational therapy. *Psychopathology* 4, 192–197.
- Griffiths, T.D., Sigmundsson, T., Takei, N., Rowe, D., Murray, R.M., 1998. Neurological abnormalities in familial and sporadic schizophrenia. *Brain* 121, 191–203.
- Kendler, K.S., Hays, P., 1982. Familial and sporadic schizophrenia: a symptomatic, prognostic, and EEG comparison. *Am. J. Psychiatry* 139 (12), 1557–1562.
- Könnecke, R., Häfner, H., Maurer, K., Löffler, W., an der Heiden, W., 2000. Main risk factors for schizophrenia: increased familial loading and pre- and peri-natal complications antagonize the protective effect of oestrogen in women. *Schizophr. Res.* 44, 81–93.
- LeBoyer, M., Filteau, M.J., Jay, M., Campion, D., Rochet, T., D'Amato, T., 1992. No gender effect on age-at-onset in familial schizophrenia? *Am. J. Psychiatry* 149 (10), 1409.
- Malaspina, D., Harkavy-Friedman, J., Corcoran, C., et al., 2004. Resting neural activity distinguishes subgroups of schizophrenia patients. *Biol. Psychiatry* 56, 931–937.
- Martin Reyes, M., Mendoza Quiñónez, R., Díaz de Villalvilla, T., Lomba, P., Padrón Fernando, A., Valdés Sosa, M., 2004. Family transmission of positive and negative symptoms in familial and sporadic schizophrenia. *Actas Esp. Psychiatr.* 32 (6), 353–357.
- Murphy, B.M., Burke, J.G., Bray, J.C., Walsh, D., Kendler, K.S., 1994. An analysis of the clinical features of familial schizophrenia. *Acta Psychiatr. Scand.* 89, 421–427.
- Norman, R.M.G., Manchanda, R., Malla, A.K., Harricharan, R., Northcott, S., 2007b. The significance of family history in first-episode schizophrenia spectrum disorder. *J. Nerv. Ment. Dis.* 195 (10), 846–852.
- Roy, M.A., Flaum, M.A., Gupta, S., Jaramillo, L., Andreasen, N.C., 1994. Epidemiological and clinical correlates of familial and sporadic schizophrenia. *Acta Psychiatr. Scand.* 89, 324–328.
- Sautter, F.J., McDermott, B.E., Cornwell, J., et al., 1994. Patterns of neuropsychological deficit in cases of schizophrenia spectrum disorder with and without a family history of psychosis. *Psychiatry Res.* 54, 37–49.
- Shimizu, A., Kurachi, M., Yamaguchi, N., Torii, H., Isaki, K., 1988. Does family history of schizophrenia influence age-at-onset of schizophrenia? *Acta Psychiatr. Scand.* 78, 716–719.
- Wolitzky, R., Goudsmit, N., Goetz, R.R., et al., 2006. Etiological heterogeneity and intelligence test scores in patients with schizophrenia. *J. Clin. Exp. Neuropsychol.* 28, 167–171.