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Evidence that better outcome of psychosis in women is reversed with increasing age of onset: A population-based 5-year follow-up study

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ABSTRACT

Background: Female gender and later onset of psychosis are both associated with better outcome. However whether their effects are independent, is not known.
Method: In 379 incident cases of psychoses, from an epidemiologically defined catchment area, admixture analysis was employed to generate age of onset classes. Five year course and outcome measured across clinical and social domains were used as dependent variables in regression analyses, to estimate associations of outcomes with gender, age of onset and gender by age of onset interaction.
Results: Three age of onset classes were identified: early (14–41 years), late (42–64 years) and very late onset psychosis (65–94 years). Overall, women had better outcomes, including milder delusions, fewer negative symptoms, less deterioration from baseline functioning, fewer hospital readmissions and shorter psychotic episodes. Later age of onset was also associated with better outcome, although in the very late onset class the results were mixed. There was a statistically significant gender by age of onset interaction (in the ratio scale) within this sample with men displaying poorer outcome in the early/late onset class, whereas women tended to have a worse outcome in the very late onset class.
Conclusions: The favourable outcome in women becomes reversed in old age, suggesting gender-age-related differences in the distribution of aetiological factors for psychosis.

1. Introduction

Psychotic disorders show significant variation in their clinical presentation, course and outcome, probably reflecting aetiological and pathophysiological heterogeneity (Andreasen, 1995). Studying outcome can help elucidate the causes of such heterogeneity (Kendell, 1989; Robins and Guze, 1970). Several published studies suggest women have a better prognosis, including better global and psychosocial functioning, a less chronic course, fewer re-hospitalizations, shorter inpatients stays, reduced negative symptoms and significantly less disability (Goldstein, 1988; Leung and Chue, 2000). Furthermore, other putative differences have been reported such as fewer obstetric complications, less structural brain changes, less severe negative symptoms, more affective symptoms and better premorbid functioning in women (Leung and Chue, 2000). These differences suggest the distribution of aetiological factors may vary between the genders (Castle et al., 1995).

Yet the most consistent finding regarding gender differences in psychosis is the later age of onset in women and

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female overrepresentation in later onset samples (Angermeyer and Kuhn, 1988; Howard et al., 2000). As later age of onset is also associated with better outcome in schizophrenia and other psychoses (Haro et al., 1994; Malla et al., 2006; Rabinowitz et al., 2006), it can be hypothesised that gender and age of onset are not independent predictors of outcome.

The present study therefore reports the 5-year outcome, in a population of patients with first-episode psychoses, across the full adult age-range, and examines the effects of gender and age of onset (and their statistical interaction) on multiple clinical and social domains of outcome, while adjusting for factors known to potentially influence outcome, namely a positive family history for schizophrenia, a diagnosis of schizophrenia (as opposed to other psychoses), baseline symptoms and marital status (van Os et al., 1997).

2. Method

2.1. Participants

Case ascertainment has been described elsewhere (Allardyce et al., 2000). Briefly, all first contacts with an ICD-9 or ICD-10 diagnosis of schizophrenia, schizoaffective disorder, delusional disorder, mania, drug-induced psychotic disorder and acute, transient or unspecified psychotic disorder presenting to the psychiatric service (inpatients, day patients, outpatients, domiciliary assessments and informal out-of-hour contacts) of Dumfries and Galloway (D&G) between the years 1979 and 1998 were identified. Exclusions criteria were: no resident of D&G, psychotic symptoms prior to the study period, organic psychosis. This left a cohort of 464 patients for inclusion.

2.2. Baseline assessment

Demographic characteristics and the absence or presence of symptoms were extracted from the case records and ancillary documentation. Two experienced psychiatrists (JA, GM) completed The Operational Checklist for Psychotic Disorders (OPCRIT) (McGuffin et al., 1991). Good inter-rater agreement for both 1) individual symptom measures (kappa = .69–.92) and 2) DSM-IV diagnoses generated using OPCRIT 3.4 algorithm (kappa = .79) have been demonstrated (Allardyce et al., 2000). Age of onset was defined as age of first contact with psychiatric service. As described previously (Allardyce et al., 2007), an exploratory factor analysis of first year OPCRIT ratings identified five latent symptom dimensions, explaining 58% of the variance: mania, depression, disorganization, hallucinations, delusions. Factor scores were calculated for each individual for the five dimensions.

2.3. Outcome measures

The Local Regional Ethics Committee and the Privacy Committee of Information and Statistical Division in Scotland approved the follow-up study. Patients were traced between the years 2004 and 2005 using medical, regional and nationwide registers. Four-hundred-and-twenty-two (91%) patients were traced (median time from presentation to follow-up = 11.82 years, inter-quartile-range = 6.67–18.41). Where possible, multiple sources of information were used (systematic review of case notes, patient interviews, information from health professionals involved in day-to-day patient care and family members). All staff were formally trained and participated in regular review meetings and exercises from recorded interviews. Five-year outcome measures were created using items from the OPCRIT, WHO Life Chart Schedule (LCS) (World Health Organization, 1992) and Life Time Dimensions of Psychosis Scale (LTDS) (Levinson et al., 2002). The LCS was rated by research workers demonstrating good reliability (pairwise agreement >0.8 for all items used in the analyses) and the LTDS was completed by a single rater (JA). Outcomes included severity of delusions and hallucinations (both: 0 = mild/moderate, 1 = severe), presence of formal thought disorder, negative symptoms, first rank symptoms of Schneider and functional deterioration from levels at baseline/first admission (all: 0 = absent, 1 = present), course type (1 = one episode, 2 = multiple episodes, 3 = continuous symptoms), type of remission (1 = none, 2 = residual, 3 = complete), number of readmissions (1–5 or more), time of longest psychotic episode (in months), and time spent in supported residences (in months). The variables *longest psychotic episode* and *time spent in supported residency* suggested a skewed distribution. Therefore categories based on tertile cut-offs were generated and used in the analyses.

2.4. Statistical analysis

2.4.1. Admixture analysis of age of onset

Rather than using arbitrary age cut-offs to construct age of onset subgroups, we used admixture analysis in Mplus 4.0 (Muthen and Muthen, 2006). This method examines whether the observed continuous age of onset distribution could be better modelled as a mixture of two or more Gaussian distributions (McLachlan and Peel, 2000). It starts with the most parsimonious single-Gaussian distribution model and fits successive models with increasing numbers of distributions. Whether the model with $n+1$ distributions fits the observed distribution better than the model with only n distributions was compared using several model fit indices: 1) adjusted Lo–Mendell–Rubin likelihood ratio test (LRT) (Lo et al., 2001) 2) Akaike's information criterion (AIC) (Akaike, 1987) 3) Bayesian information criterion (BIC) (Schwartz, 1978). Subjects can then be classified into age of onset subgroups identified by the different underlying distributions. How well this classification fits the data is measured using standardised entropy scores (Ramaswamy et al., 1993).

2.4.2. Missing outcome data

Missing values are almost inevitable in epidemiological studies but most follow up studies ignore possible bias introduced by analyzing cases with complete information only. To deal with the missing data we used multiple imputation methods which assume data is missing at random (MAR) (Rubin, 1976). The method imputes several alternative versions of the complete dataset using the data that was not missing. These are then analyzed separately and the effect sizes and standard errors, which may vary, are combined using simple arithmetical procedures to obtain overall estimates. For follow-up measures with missing values, other than death, we imputed 20 datasets in STATA 9.2 (StataCorp, 2006) using the

ICE routine (Royston, 2005) without restriction to observed variable ranges.

2.4.3. Prediction of outcome

Using gender as the predictor variable, logistic regressions (presence of formal thought disorder, negative symptoms, first rank symptoms, deterioration) or ordinal logistic regressions (severity of delusions and hallucinations, course type, remission type, number of readmissions, longest episode, supported residency) were run adjusted for continuous age of onset. Next regression analyses were repeated using the age of onset subgroups from the admixture analysis as outcome predictors, adjusted for gender. However, as age of onset group membership is not deterministic but based on posterior probabilities, we weighted the analyses for probability of belonging to a particular age of onset group. We further included the following covariates in all analyses: diagnosis of schizophrenia (0 = other non-organic psychosis, 1 = DSM-IV schizophrenia), family history of schizophrenia (0 = absent, 1 = present), family history of other psychiatric disorders (0 = absent, 1 = present), marital status (0 = ever married, 1 = single) and the factor scores of the five symptom dimensions. The interaction between gender and indicator-coded age of onset classes was tested using the LINCOM procedure in STATA.

3. Results

3.1. Admixture analysis

The observed age of onset distribution (Fig. 1) suggests a major peak in young adulthood for both genders. A second and third peak appears to be primarily–but not exclusively–caused by a higher incidence in middle and old aged women. Admixture analysis was run in order to decompose the continuous age of onset distribution into age of onset classes. Model fit statistics and classification performance are shown in Table 1. A model with three Gaussian distributions showed superior model fit than the models with either two or four distributions. After class allocation based on posterior probability, these classes were called “early onset psychosis” (EOP), “late onset psychosis” (LOP) and “very late onset psychosis” (VLOP).

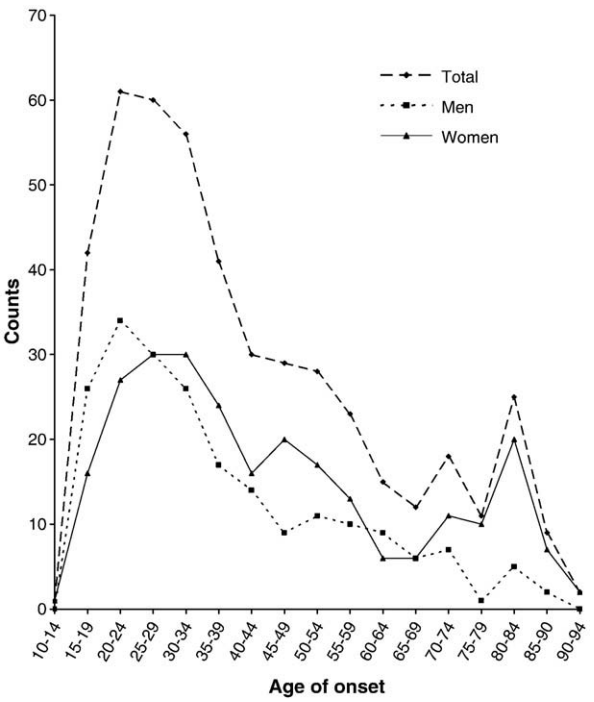

Fig. 1. The observed age of onset distributions for the total population, men and women.

Table 1
Goodness of model fit indices for the one to six class solution of the admixture analysis using age of onset as indicator.

Classes	Log-likelihood	AIC[a]	BIC[a]	Entropy	LMR LRT[a]	*p*
1	−2046.5	4097.0	4105.3			
2	−1983.3	3974.7	3991.2	0.844	116.8	<.0001
3	−1958.1	3928.1	3953.0	0.848	46.7	<.0001
4	−1953.3	3922.7	3955.8	0.786	8.7	.1505
5	−1947.9	3915.8	3957.2	0.810	10.1	.0615
6	−1947.9	3919.8	3969.4	0.822	0.0	.8313

[a] AIC = Akaike's information criterion, BIC = Bayesian information criterion, LMR LRT = adjusted Lo–Mendell–Rubin likelihood ratio test.

3.2. Gender differences at baseline

As shown in Table 2, women had a later mean age of onset and were married more often. No differences were found for family history of schizophrenia or other psychiatric disorders and diagnosis of schizophrenia between the genders, although there was a trend for men to be diagnosed with schizophrenia more often. The male-to-female ratio approached unity for EOP, but gradually shifted towards female preponderance in LOP and VLOP.

3.3. Loss to follow-up

At 5-year follow-up, information was obtained for 379 (82%) of the total inception cohort. Of these, 351 (93%) had continued contact with psychiatric services and 127 (34%) had a face-to-face interview. Eighty-five (18%) of the original cohort were lost to follow-up due to death in 56 and 29 were not traceable. Of those who had died, 32 were women and 24 were men ($\chi^2 = 0.09$, $df = 2/461$, $p = .766$). Causes of death were classified into circulatory system disease ($n = 25$, 45%), cancer ($n = 9$, 16%) respiratory system disease ($n = 7$, 12%), suicide ($n = 5$, 9%, all in EOP) and other reasons ($n = 10$, 18%). In VLOP, 34 (44%) of cases had died, 15 (13%) in LOP and 7 (3%) in EOP. The main cause of death in VLOP and LOP was circulatory system failure (50% and 53% respectively), whereas suicide accounted for most deaths in EOP (71%). There were no significant differences between those traceable and untraceable in age of onset, diagnosis of schizophrenia, gender, marital status, pre-morbid social adjustment and family history of schizophrenia or other psychiatric disorders. Missing values for untraceable patients were multiply imputed.

3.4. Gender, age of onset and 5-year outcome

When age of onset and other confounders were controlled for (Table 2), being female was associated with milder

Table 2
Differences between men and women in baseline characteristics and outcome of psychosis at 5-year follow-up.

		Men	Women	Total	T/χ^2	*df*	*p* [a]
		N = 207	*N* = 256	*N* = 463			
Baseline							
Age of onset, mean (s.d.)		37.6 (17.9)	45.3 (21.2)	41.8 (20.1)	2.86	2/461	<.001
EOP (age of onset: 14–41), *n* (%)		139 (67)	131 (51)	270 (58)	15.3	2/461	<.001
LOP (age of onset: 42–64)		47 (23)	69 (27)	116 (25)			
VLOP (age of onset: 65–94)		21 (10)	56 (22)	77 (17)			
Ever married, *n* (%)		97 (47)	175 (68)	272 (59)	21.83	2/461	<.001
Positive FH-s [b], *n* (%)		19 (9)	26 (10)	45 (10)	0.12	2/461	.724
Positive FH-p [b], *n* (%)		41 (20)	56 (22)	97 (21)	0.30	2/461	.587
DSM-IV schizophrenia [c], *n* (%)		59 (29)	54 (22)	113 (24)	2.86	2/461	.091
		Men	Women	Total			
		N = 183	*N* = 224	*N* = 407	OR	95%CI	*p*
Outcome [d]							
Severity of, *n* (%)							
Delusions	Mild/moderate	63 (37)	89 (43)	152 (40)	0.57	0.35/0.93	.024
	Severe	85 (50)	76 (37)	161 (43)			
Hallucinations	Mild/moderate	69 (41)	73 (35)	142 (38)	1.04	0.52/2.07	.911
	Severe	29 (17)	35 (17)	64 (17)			
Presence of, *n* (%)							
Formal thought disorder		48 (28)	42 (20)	90 (24)	0.66	0.33/1.31	.239
Negative symptoms		53 (31)	33 (16)	86 (23)	0.50	0.27/0.94	.031
First rank symptoms		75 (44)	83 (40)	158 (42)	0.85	0.52/1.40	.530
Deterioration from baseline, *n* (%)		84 (50)	69 (33)	153 (40)	0.56	0.35/0.90	.017
Course type, *n* (%)							
One episode		48 (29)	70 (34)	118 (31)			
Multiple episodes		58 (35)	83 (40)	141 (38)	0.75	0.48/1.15	.185
Continuous symptoms		62 (37)	53 (26)	115 (31)			
Remission type, *n* (%)							
None		61 (36)	55 (26)	116 (31)			
Residual		38 (23)	66 (31)	104 (28)	1.34	0.88/2.04	.168
Complete		69 (41)	89 (42)	158 (42)			
Number of readmissions							
0		19 (10)	52 (23)	71 (17)			
1–2		96 (52)	117 (52)	213 (52)			
3–4		40 (22)	33 (15)	73 (18)	0.59	0.40; 0.87	.009
5 or more		28 (15)	22 (10)	50 (12)			
Longest episode							
First tertile		56 (31)	80 (36)	136 (33)			
Second tertile		51 (28)	77 (34)	128 (31)	0.77	0.51; 1.18	.231
Third tertile		76 (42)	67 (30)	143 (35)			
Supported residency							
First tertile		52 (28)	83 (37)	135 (33)			
Second tertile		60 (33)	75 (33)	135 (33)	0.87	0.57; 1.31	.503
Third tertile		71 (39)	66 (29)	137 (34)			

[a] EOP = early onset psychosis, LOP = late onset psychosis, VLOP = very late onset psychosis.
[b] FH-s: family history of schizophrenia, FH-p: family history of other psychiatric disorders.
[c] Other non-organic psychosis: DSM-IV schizophreniform disorder, delusional disorder, and psychotic disorder NOS, major depression, bipolar disorder, and schizoaffective disorder.
[d] Corrected for age of onset, marital status, diagnosis of schizophrenia, FH-s, FH-p and baseline symptom factor scores.

delusions, less negative symptoms, lower risk of functional deterioration and less readmissions. When gender and other confounders were controlled for (Table 3), LOP was associated with a lower risk of first rank symptoms and risk of functional deterioration compared to EOP. VLOP was associated with milder delusions, a lower risk of having formal thought disorder, a lower risk of functional deterioration, less readmissions and less months spent in supported residences, but also with longer episodes and less likelihood of remission compared to EOP. Adjusted analyses further showed that worse outcome was seen in patients with a diagnosis of schizophrenia compared to other psychoses, including a higher likelihood of functional deterioration (OR = 2.37, 95% CI = 1.36; 4.07, $p = .002$), negative symptoms (OR = 2.22, 95% CI = 1.20;4.13, $p = .011$), longer episodes (OR = 4.87, 95% CI = 2.95;8.05, $p \leq .001$), more time spent in supported residency (OR = 2.21, 95%CI = 1.37;3.56, $p \leq .001$), less chance of remission (OR = 0.20, 95%CI = 0.11;0.37, $p \leq .001$) and higher risk of chronicity (OR = 4.12, 95%CI = 2.40;7.08, $p \leq .001$). Single living status was associated with longer episodes (OR = 2.13, 95%CI = 1.37;3.32, $p \leq .001$), higher risk of chronicity (OR = 1.76, 95%CI = 1.13;2.75, $p = .013$) but less severe delusions (OR = 0.54, 95%CI = 0.33;0.90, $p = .018$). A positive family history of schizophrenia related to the presence of formal thought disorders (OR = 2.56, 95%CI = 1.22;5.37, $p = .013$).

Table 3
Stratified comparisons of outcome across age of onset classes.

Outcome	LOP versus EOP [a]			VLOP versus EOP [a]		
	OR	95%CI	*p*	OR	95%CI	*p*
Severity of [b]						
Delusions	1.00	0.56; 1.79	.998	0.31	0.12; 0.82	.018
Hallucinations	0.92	0.41; 2.10	.845	1.07	0.26; 4.38	.903
Presence of [c]						
Formal thought disorder	0.63	0.27; 1.45	.278	0.14	0.03; 0.75	.022
Negative symptoms	0.46	0.20; 1.09	.078	Not observed in VLOP		
First rank symptoms	0.48	0.26; 0.88	.017	0.60	0.23; 1.58	.300
Deterioration [c]	0.54	0.29; 1.00	.049	0.41	0.17; 0.96	.041
Course type [d]	0.97	0.58; 1.61	.903	1.97	0.81; 4.79	.107
Remission type [e]	0.72	0.44; 1.17	.181	0.30	0.15; 0.60	.001
Longest episode [f]	1.27	0.74; 2.19	.390	3.82	1.76; 8.30	.001
Supported residency [f]	0.82	0.49; 1.38	.462	0.29	0.14; 0.61	.001
Number of readmissions	0.65	0.40; 1.06	.082	0.15	0.08; 0.27	<.001

[a] EOP: early onset psychosis, LOP: late onset psychosis, VLOP: very late onset psychosis.
[b] 1: mild/moderate, 2: severe.
[c] 0: absent, 1: present.
[d] 0: one episode, 1:multiple episodes, 2: continuous symptoms.
[e] 0: none, 1: residual, 2: complete.
[f] based on tertile cut-offs.

3.5. Interaction between gender and age of onset class

Significant gender by age of onset class interactions, in the ratio scale, were apparent for the outcomes of time of longest episode and course type, indicating the tendency for better outcome in EOP women to become inversed in VLOP, with psychosis becoming more persistent and chronic compared to men (Table 4). Thus, women in the EOP group were on average 0.63 times less likely to be in one of the higher tertiles of longest episode duration compared to men, which changing to 4.96 times more likely for women in the VLOP class. The same pattern was apparent for the outcome "course type", although the effect in the VLOP group was statistically inconclusive ($p = .075$). A similar pattern was apparent for remission type, although the interaction was inconclusive ($p = .167$). As formal thought disorders were virtually absent in VLOP men, this lead to a disproportional interaction effect.

4. Discussion

Consistent with the published literature, we found women to have a later age of onset and better outcome than men (Angermeyer and Kuhn, 1988; Leung and Chue, 2000). Later age of onset was also associated with better outcome, although in the VLOP class the result was mixed. Thus, VLOP patients' psychopathology was milder with decreased likelihood of functional deterioration, less readmission rates and more time spent living independently, while they were less likely to have complete remission and more likely to have long episodes. Estimating the joint effects of gender and age of onset strongly supports an effect measure modification with men displaying poorer outcome in the early age of onset class. However their prognosis improved as age of onset increased. In contrast, women had a more favourable outcome profile in young or middle age onset, but tended to have a poorer outcome in the very late onset cases, particularly in terms of course type, longest episode and remission type. The lack of published studies examining gender differences in outcome across the whole range of age of onset may in part explain why the idea that women have better outcome, regardless of age of onset interactions, has prevailed (Goldstein, 1988; Leung and Chue, 2000).

The gender differences in age of onset and clinical characteristics have been postulated to be due to an anti-psychotic effect of estrogens on dopamine-D2 receptors. This hypothesis suggests that the disorder only becomes apparent after menopause, for a proportion of women who have a psychosis liability (Häfner et al., 1998; Seeman and Lang, 1990). Although this "estrogen-hypothesis" may have some utility in explaining differences in mean age of onset and the second incidence peak in middle-aged women, it cannot explain gender differences in older age groups. Psychosis in the second half of life may represent a final common pathway of various disease processes of differing aetiology including hormonal changes, neurodegenerative conditions and gender-linked genetic effects (DeLisi, 1992). Therefore, women with a genetic vulnerability for psychotic disorder might be protected when they are younger, but develop psychotic disorder of a chronic type when their vulnerability becomes expressed later in life, under the influence of, for example, neurodegenerative mechanisms. On the other hand, genetically vulnerable men will be more likely to express their liability at an earlier age. Consequently, only men with lower levels of vulnerability develop psychotic disorders in old age, therefore displaying better outcome than their female counterparts.

Studies regarding the putative role of neurodegeneration in LOP/VLOP have so far been inconclusive, with some reporting transition to dementia rates of 13%–47% (follow-up ranging from 5 to 15 years) (Brodaty et al., 2003; Holden, 1987; Jorgensen and Munk-Jorgensen, 1985), while other studies, of comparable follow-up durations, do not find such high rates (Hymas et al., 1989; Rabins and Lavrisha, 2003). Likewise, neuropsychological testing and neuroimaging studies have generally failed to find clear evidence of accelerated cognitive decline (Barta et al., 1997; Lesser et al., 1993; Sachdev et al., 1999). However, none of these studies, to date, has examined the effect separately for gender or gender–age interactions. Interestingly, one study did find that elderly women with schizophrenia more often displayed neuropathological changes of Braak stages III and IV, indicative of possible Alzheimer disease, especially if onset was after 40 years of age (Casanova et al., 2002). Unfortunately, we do not have detailed neuropsychological testing on the current study sample, so were not able to investigate this important issue and potential cause for the observed inter-gender variation on outcome.

This paper should be interpreted in the light of its methodology. First, we assessed outcome retrospectively and mainly by chart review. Only one-third of the patients could be interviewed face-to-face, which may have resulted in incomplete and selective information. However, multiple information sources were used including high quality, complete case notes, and the WHO LCS and the LTDS are both standardized instruments designed for retrospective assessment of symptom course and disability. In addition, 93% of all live participants were still in contact with the clinical community services. As there is little staff turnover within the

Table 4
Comparison of the effect of gender (*M* = men, *W* = women) within the three age of onset classes (conditional OR estimates), and the interaction between age of onset class and gender for 5-year outcome with the gender-effect in the youngest age of onset class as the reference value.

Outcome	Age of onset [a]	Counts			Effect of gender			Age of onset × gender [b]		
		N	*M*	*W*	OR	95%CI	*p*	OR	95%CI	*p*
Severity of delusions [c]	EOP	215	119	96	0.80	0.44; 1.46	.463	–		
	LOP	86	33	53	0.35	0.13; 0.93	.036	0.43	0.14; 1.37	.154
	VLOP	32	9	23	0.27	0.04; 1.80	.176	0.34	0.05; 2.51	.288
Severity of hallucinations [d]	EOP	147	79	68	1.24	0.56; 2.72	.592	–		
	LOP	47	18	29	0.92	0.23; 3.64	.903	0.74	0.15; 3.56	.707
	VLOP	16	4	12	0.39	0.02; 6.31	.505	0.31	0.02; 5.59	.429
Formal thought disorder [d]	EOP	263	133	130	0.58	0.27; 1.26	.171	–		
	LOP	101	39	62	0.96	0.22; 4.20	.960	1.65	0.32; 8.36	.547
	VLOP	43	11	32	[e]	[e]	<.001	[e]	[e]	<.001
Negative symptoms [d]	EOP	263	133	130	0.55	0.27; 1.09	.087	–		
	LOP	101	39	62	0.47	0.10; 2.15	.329	0.86	0.16; 4.52	.857
	VLOP	43	11	32	[f]	[f]	[f]	[f]	[f]	[f]
First rank symptoms [d]	EOP	263	133	130	0.92	0.51; 1.68	.796	–		
	LOP	101	39	62	0.71	0.26; 1.95	.501	0.76	0.24; 2.46	.652
	VLOP	43	11	32	0.69	0.11; 4.49	.695	0.74	0.10; 5.50	.772
Deterioration [d]	EOP	263	133	130	0.55	0.31; 0.95	.035	–		
	LOP	101	39	62	0.63	0.23; 1.68	.351	1.14	0.37; 3.52	.816
	VLOP	43	11	32	0.58	0.10; 3.39	.542	1.05	0.16; 6.80	.957
Course type [g]	EOP	263	133	130	0.63	0.38; 1.04	.071	–		
	LOP	101	39	62	0.58	0.24; 1.40	.226	0.93	0.34; 2.49	.880
	VLOP	43	11	32	5.80	0.84; 40.19	.075	9.23	1.21; 70.40	.032
Remission type [h]	EOP	263	133	130	1.55	0.90; 2.66	.111	–		
	LOP	101	39	62	1.40	0.63; 3.13	.413	0.90	0.34; 2.38	.837
	VLOP	43	11	32	0.60	0.17; 2.06	.415	0.39	0.10; 1.49	.167
Number of readmissions [i]	EOP	263	133	130	0.71	0.43; 1.16	.169	–		
	LOP	101	39	62	0.52	0.24; 1.15	.107	0.74	0.30; 1.83	.516
	VLOP	43	11	32	0.31	0.12; 0.80	.015	0.43	0.15; 1.30	.136
Longest episode [j]	EOP	263	133	130	0.63	0.38; 1.06	.082	–		
	LOP	101	39	62	0.67	0.29; 1.58	.362	1.06	0.39; 2.90	.902
	VLOP	43	11	32	4.96	1.08; 22.82	.040	7.85	1.55; 39.66	**.013**
Supported residency [j]	EOP	263	133	130	0.77	0.46; 1.27	.303	–		
	LOP	101	39	62	1.05	0.45; 2.48	.902	1.38	0.51; 3.75	.531
	VLOP	43	11	32	1.12	0.26; 4.81	.881	1.46	0.31; 6.96	.635

[a] EOP: early onset psychosis, LOP: late onset psychosis, VLOP: very late onset psychosis.
[b] Interactions were tested additively as differences across classes with early onset as the reference class.
[c] 1: mild/ moderate, 2: severe.
[d] 0: absent, 1: present.
[e] Formal thought disorders were absent in very late onset men, resulting in extreme odds ratio.
[f] negative symptoms were not observed in the very late onset class and analyses could not be performed.
[g] 0: one episode, 1:multiple episodes, 2: continuous symptoms.
[h] 0: none, 1: residual, 2: complete.
[i] coded as: 1, 2, 3, 4, "5 or more".
[j] based on tertile cut-offs.

region of D&G, this facilitated more consistent long term documentation. Secondly, the LTDS was completed by a single rater, which ensures consistency of rating, but can also potentially introduce bias if the rater had preconceptions when assessing outcome (e.g. male gender and earlier age of onset go together with worse outcome). It seems unlikely however that such a bias has driven our main finding, i.e. the reversed prognosis in older psychotic women. Thirdly, we present data on a heterogeneous sample of psychosis patients because it has been previously shown that a priori restriction to a certain diagnostic subgroup in the study of later onset psychosis is likely to introduce bias (Riecher-Rössler et al., 2003). Fourthly, we defined onset as first contact with psychiatric services. The advantage of this measure is that it constitutes a precise datable event and is generally regarded as suitable proxy for age of onset (DeLisi, 1992). Still, first signs of psychosis may arise many years before a person comes in contact with psychiatric services and some later onset patients might represent long term "silent sufferers". While this cannot be ruled out for some cases, it seems unlikely that it accounts for the majority. Fifthly, some of the more borderline statistically significant effects should be interpreted with some caution as we tested multiple associations. However, there was a consistent pattern of change in effect size as a function of age of onset and gender across conceptually related outcome measures.

This study has significant strengths, including the complete case ascertainment of all first ever psychotic disorder presenting to a geographically well-defined catchment area, which included not only inpatients but all outpatient and informal contacts to psychiatric services, for all psychotic disorders; the careful tracing of patients using several local and national registrars; assessment of outcome across a wide range of domains (symptomatic, functional, psychosocial); attempt to derive natural classes of age of onset in order to increase the sensitivity to non-linearity in associations

between age of onset and course. Taken together, to the best of our knowledge, this makes it the most detailed study on the influence of age of onset and gender on (mid-term) outcome of psychotic disorders.

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Contributors

Sebastian Köhler, Jim van Os and Judith Allardyce formulated research questions, searched the literature, undertook the statistical analyses, data interpretation and wrote the first draft of the manuscript. Brian Hart, Gary Morrison, Robin McCreadie, Brian Kirkpatrick and Judith Allardyce were involved in study design and/or data collection of the 464 study. Margriet van der Werf, Mike Verkaaik, Lydia Krabbendam and Frans Verhey provided background information and critical comments. All authors contributed to and have approved the final manuscript.

Conflict of interest

Jim van Os is an unrestricted research grant holder with, or receives financial compensation as an independent symposium speaker from Eli Lilly, BMS, Lundbeck, Organon, Janssen-Cilag, GSK, AstraZeneca, Pfizer and Servier. Dr. Kirkpatrick received consulting and/or speaking fees from Pfizer, Organon, AstraZeneca, Wyeth, Eli Lilly, Bristol Myers Squibb, Cephalon, and Solvay. All other authors declare that they have no conflicts of interest.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.schres.2009.05.017.

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