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Psychosis risk as a function of age at onset

A comparison between early- and late-onset psychosis in a general population sample

■ **Abstract** *Background* Little is known about late-onset psychosis (onset after the age 45 years) and how it relates to early-onset psychosis (before age 45 years). The aims of this study were to calculate the incidence of non-affective, non-organic psychotic symptoms across the life span and to explore the contribution of different sets of risk factors in relation to age at onset. *Methods* Data were obtained from the three measurements of the Netherlands Mental Health Survey and Incidence Study. Symptoms of psychosis were assessed in individuals aged 18–64 years using the Composite International Diagnostic Interview. All individuals reporting first-onset of psychotic symptoms within a three-year interval were included. The degree to which sets of risk factors affected the psychosis outcome similarly across age groups was assessed. *Results* The number of subjects displaying incident psychotic symptoms was similar across age groups. Cumulative incidence rates ranged from 0.3% to 0.4%. Age differences were found for life-time depressive symptoms (risk difference = 5%, 95% CI = 1%, 9%) and baseline neuroticism (risk difference = 3%, 95% CI = 0%, 6%), indicating that late-onset psychosis was less often preceded by these. In contrast, no effect modification by age was observed for female sex, hearing impairment, being single, or life-time cannabis use. *Conclusions* Onset of psychotic symptoms in late life is no rare event. Compared to early onset psychosis, the late-onset counterpart less often arises in a context of emotional dysfunction and negative affectivity, suggesting qualitative differences in aetiology and more effective premorbid coping styles.

■ **Key words** psychosis – late onset – risk factors – incidence – general population

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Introduction

Schizophrenia and related non-affective, non-organic psychotic disorders have predominantly been studied in adolescence and young adulthood (early-onset psychosis, EOP). Some individuals, however, experience psychotic symptoms for the first time after the age of 40 years (late-onset psychosis, LOP) [19, 29]. In LOP, the clinical picture is dominated by hallucinations in all modalities and systematic delusions that concern the patient's personal space and security like paranoid delusions or partition delusions [8, 26, 27], while disorganized and negative symptoms are uncommon [44, 53]. In 45% of subjects, the onset of LOP is preceded by a history of paranoid or schizotypic personality styles [31, 33, 45] which raises the question whether these cases constitute a group of schizophrenia with delayed expression of a latent disorder rather than truly late onset of a disorder de novo.

■ Incidence rates

Studies of first admission rates over the last four decades have consistently found low incidence rates

for LOP. Copeland et al. estimated an annual incidence of 3.0 per 100,000 for DSM-III-R schizophrenia and 16.6 per 100,000 for delusional disorder in those aged 65 years and over [11]. Castle and Murray, applying the same criteria, calculated a rate of 12.6 per 100,000 person-years [9]. Using the broader concept of late paraphrenia, Kay estimated the annual rate for those aged 55 years and older to be 10–15 per 100,000 for males and 20–25 per 100,000 for females [32]. In the general population aged 60 years or older, Van Os et al. showed an 11% increase in first admission rates for ICD-9 schizophrenia, paraphrenia, paranoid states and other non-affective, non-organic psychosis for each 5 year increase in age [64]. Incidence rates rose from 10 per 100,000 person-years in those aged 65 years to 19 per 100,000 in those aged 75 with further progression to 25 per 100,000 in the 90+ age group. Häfner et al. found an annual incidence rate of 13 per 100,000 for broadly defined schizophrenia-spectrum disorders within the age range of 50–59 years [18].

These figures match well with those reported for schizophrenia [20, 51]. Service-based studies, however, are likely to underestimate the frequency of the disorder, and community surveys independent of service use generally find higher rates, but researchers have been reluctant to carry out such studies with LOP [68]. Methodological obstacles in conjunction with the supposed infrequency of the disorder may explain this. For example, a diagnosis of LOP is difficult to make using lay interviews. Hence, an alternative approach is to collect data on the basis of presence of single functional psychotic symptoms without focussing on diagnostic categories. Using this strategy, Christenson and Blazer identified prevalent paranoid ideation in 4% of a sample of community living elderly [10]. Similar figures have been found among the non-institutionalized cognitively intact elderly [24], with prevalence rates as high as 10% among the non-demented very old (older than 84 years) [43]. Prevalence rates, however, cannot distinguish between persistence of psychosis with an early onset and psychosis with a true onset in old age.

■ Risk factors

If LOP constitutes a separate phenotype within the schizophrenia spectrum, it is attractive to hypothesize that there will be quantitative or qualitative differences between LOP and EOP with respect to risk factors associated with psychosis such as cannabis use [3, 25, 66], childhood trauma [30, 36], urbanisation [57, 58, 65], schizoid and paranoid premorbid personality [14], neuroticism [24, 34], depressive and other affective symptoms [35, 69] or social isolation [50]. Among the list of putative risk factors for LOP, female sex presents itself as the most prominent one, with women running a two to six times greater risk

than men [9, 18, 54], especially if only paranoid states are considered [1, 52]. It seems that men consume their lifetime risk more rapidly than women and are thus hardly found in late-onset pools [20]. A protective role for female sexual hormones in LOP has hence been suggested, as estrogens may decrease the risk in pre-menopausal women by virtue of their antidopaminergic effects [13, 18, 39, 55]. Another hypothesized age-related risk factor may be hearing impairment, particularly in patients aged 60 years and older [28, 46, 50, 62], although recent work suggests the effect of hearing impairment is not age specific [61].

■ Research questions and hypotheses

The present study calculates incidence rates for psychosis as a function of age in the general population of the Netherlands. It was hypothesized that onset of functional psychosis occurs less often in old age than in young and middle age. Second, possible effect modification by age of sets of known risk factors for psychosis was assessed, such as depression, neuroticism, urbanisation, cannabis use, sex, sensory impairment and family history of psychosis.

Method

■ Sample

This study made use of the data from the Netherlands Mental Health Survey and Incidence Study (NEMESIS), a longitudinal study of the prevalence, incidence, course and consequences of psychiatric disorders in the Dutch general population [5, 6, 16]. The study consists of three measurement points with a total duration of three years: at baseline (hereafter: T0), 1 year thereafter (hereafter: T1) and again 2 years after T1 (hereafter: T2). Participants were identified by means of a multistage, stratified, random sampling procedure in which 90 municipalities were sampled randomly. In a second step, random selections of addresses from private households were made. Thirdly, the person with the most recent birthday at the moment of selection and aged between 18 years and 64 years received an introductory letter form the Minister of Health. Not included were institutionalized individuals. At baseline, 7,076 subjects participated, which is a response rate of 69.7%. According to the General Health Questionnaire, 12 items (GHQ-12) [17] responders and non-responders did not differ with respect to psychiatric morbidity [5, 6]. At T1, 5,618 subjects (79%) participated, at T2, 4,848 subjects (69%) participated. The local ethics committee approved the study proposal.

■ Instruments

At T0 to T2, the Composite International Diagnostic Interview (CIDI) version 1.1 [56] was administered at home. The CIDI is a structured interview and is designed for the use by trained interviewers who are not clinicians. It has satisfactory inter-rater reliability [12] and test–retest reliability [67]. Ninety interviewers experienced in systematic data collection administered the interview after having received intensive training. In order to assess *psychotic symptoms*, ratings from the CIDI core psychosis section on delusions (13 items) and hallucinations (4 items) were used

(items G1–G13, G15, G16, G20, G21). These concern classic psychotic symptoms involving, for example, thought interference and passivity phenomena, persecution and auditory hallucinations. All these items can be rated in six ways: '1', no symptom; '2', symptom present but not clinically relevant (not bothered by it and not seeking help for it); '3', symptom result of ingestion of drugs/medication; '4', symptom result of a somatic disease; '5', true psychiatric symptom causing distress or help-seeking behaviour; '6', symptom may not really be a symptom because there appears to be some plausible explanation for it. In order to verify symptom presence and their clinical relevance, clinical re-interviews were conducted over the telephone by a senior registrar in psychiatry for all individuals who had at least one rating of 5 or 6, using single questions from the Structural Clinical Interview for DSM-III-R (SCID), an instrument with proven reliability and validity in diagnosing schizophrenia [59]. CIDI ratings of '5' and '6' were corrected on the basis of these clinical interviews. *Life-time depression* was assessed using the 28 items of the CIDI core depression section (E) with exclusion of four items related to dysthymia. *Life-time mania* was assessed using the 11 items of the CIDI core mania section (F). All these items can be rated as either 'yes' (1) or 'no' (0). Symptoms of depression (e.g., anhedonia) had to be present for at least 2 weeks, manic symptoms (e.g., persistently elevated, expansive or irritable mood) had to be present for at least two days. In order to make a DSM-III-R diagnoses, the CIDI assesses whether the mood symptoms and other symptoms were present within the same time period [48]. *Neuroticism* was assessed at baseline with the 14-item Groningen Neuroticism Scale [42]. *Family history* of depression and psychosis was examined at T1, by asking the subject whether any of his first degree biological relatives had ever experienced depressive symptoms and/or delusions or hallucinations, providing descriptions of these. Family history of treated depression and psychosis was examined at T1, by asking the subject whether the affected first degree biological relatives had ever received medical or psychological help for these symptoms. *Urbanicity* was coded as rural if a municipality had fewer than 500 addresses per square kilometre and urban otherwise. *Single living status* was assessed by asking the subject whether or not he permanently shares a household with someone else, irrespective of ownership. *Visual or auditory impairment* was scored as present if respondents self-reported such a condition being treated or monitored by a physician in the 12 months before T0.

■ Statistical analysis

For the current investigation, two outcome measures were created. First, all subjects with broadly defined psychosis-like experiences (CIDI ratings of '2', '3', '4', '5' and '6') at T1 or T2 were included in the analyses if they had not displayed such symptoms at T0 (hereafter: broad psychosis outcome). This outcome was rated as either present (='1') or absent (='0'). For the second outcome, only subjects who reported narrowly defined clinically relevant psychotic symptoms (CIDI ratings of '5') were included if they had had no evidence of psychosis at T0 (hereafter: narrow psychosis outcome). This outcome was similarly scored as either present (='1') or absent (='0'). Subjects were then divided into three age groups of young (18–34 years), middle (35–49 years) and old age (50–64 years). Contrasts were expected to show up most powerfully in the comparisons between the youngest and oldest age groups, thus the analysis has this contrast as its focus. In order to test for contributions of different sets of risk factors to the psychosis outcome, a general linear modelling (GLM) strategy was applied. Interaction effects were analysed using the BINREG procedure in STATA [60], a GLM extension for the binomial family. Interaction effects between age group and categorical or dummy coded exposure variables were estimated under an additive model [15] yielding risk difference effect sizes. Cumulative incidences of psychosis outcome at T1 and/or T2 were calculated in subjects with absence of the narrow psychosis outcome at baseline (risk set: $n = 4,637$) and in subjects with absence of the broad psychosis outcome (risk set: $n = 4,041$). Cumulative incidence rates across age groups were

Table 1 Characteristics of the NEMESIS sample at the one-year follow-up measure

	Age groups (%)			
	Young	Middle	Old	Total sample
Mean age	27.7	41.6	56.7	41.2
Female sex	55.6	50.8	54.7	53.5
Education (in years)				
0–11	17.1	25.2	37.0	25.7
12	40.4	35.8	33.1	36.6
13–15	9.2	7.3	5.9	7.6
16+	32.3	30.7	22.3	28.9
Single	56.4	14.9	6.2	26.5
Urban	83.4	81.4	83.4	82.6
Sensory deficits				
Hearing impairment	1.4	2.2	3.9	2.4
Visual impairment	0.7	1.2	2.5	1.4
Total number	1,891	2,198	1,527	5,616

compared by means of Pearson χ^2 tests. A post-hoc analysis was performed for first contact rates. All data were analysed using the STATA program, version 9.1 [60].

Results

Table 1 lists the demographic characteristics of the sample participating in the follow-up at T1 and/or T2. No differences existed for urbanicity ($\chi^2 = 3.78$, df = 2, $p = .151$) across groups. Differences emerged for level of education ($\chi^2 = 44.14$, df = 2, $p < .001$), single living status ($\chi^2 = 1300$, df = 2, $p < .001$), and visual and auditory impairment ($\chi^2 = 19.47$, df = 2, $p < .001$ and $\chi^2 = 24.34$, df = 2, $p < .001$, respectively) with older subjects having had less higher education than the young and the middle group, living alone more often and reporting sensory impairment more often. The male:female ratio also differed across groups with women being somewhat overrepresented in the young and old group ($\chi^2 = 10.92$, df = 2, $p = .004$).

■ Cumulative incidence

At T1 or T2, 56 out of 4,637 individuals with no psychosis at baseline had the narrow psychosis outcome. Of all these incident psychosis, 19 were in the young group (34%), 25 in the middle group (44%) and 12 in the old group (21%). The cumulative incidence of LOP was 0.3%. This rate was comparable to the cumulative incidence rate of EOP (0.4%) and MOP (0.4%) ($\chi^2 = 1.19$, df = 2, $p = .55$). Out of 4,401 subjects without any self-reported psychotic experiences in the past, 132 had developed the broad psychosis outcome at T1 or T2. Fifty-one of these were in the young group (38%), 54 were in the middle group (42%) and 27 (20%) were in the old group. The cumulative incidence for the broad psychosis outcome was 0.8% in the old group, 1.3% in the young group and 1.1% in the middle group ($\chi^2 = 4.66$, df = 2, $p = .097$).

Table 2 Risk increasing effect of the risk factors life-time depression and high neuroticism on the broad psychosis outcome for those with onset of first psychotic symptoms in young age (18–34 years), middle age (35–49 years) and old age (50–64 years)

	Age at onset	Risk factor		Risk differences	95% CI
		Yes	No		
Depression	Young	8.8%	2.3%	6.5%	3.3%, 9.7%
	Middle	5.1%	2.5%	2.5%	0.4%, 4.7%
	Old	3.7%	2.0%	1.7%	−0.7%, 4.1%
Neuroticism	Young	7.4%	2.1%	5.3%	2.9%, 10%
	Middle	5.2%	2.4%	2.8%	0.8%, 5%
	Old	3.8%	1.5%	2.2%	0.2%, 4.2%

Effect sizes are expressed as risk differences between those who had the risk factor and later on developed the psychosis outcome (yes) and those who did not have the risk factor but still developed the psychosis outcome (no).

■ **Risk factors**

Age effect modification

Main effects of risk factors on the broad psychosis outcome in NEMESIS have been described in other reports [4, 21, 30, 34, 35, 62, 66]. Significant interactions with age at onset were found for depression (Risk difference = −2.2%, 95% CI = −4.1%, −0.3%) and family history (FH) of treated delusions/hallucinations (RD = 3.3%, 95% CI = 0.3%, 6.2%), suggesting that the effects of both varied across age groups. The negligible prevalence, however, of FH treated delusions/ hallucinations in those having the broad psychosis outcome made further analysis impracticable (n = 3, all in the middle group). Statistical trends for interaction were observed for sex (RD = −1.3%, 95% CI = −0.8%, 2.7%), neuroticism (RD = −1.5%, 95% CI = −3.1%, 0.1%) and hearing impairment (RD = −5.9%, 95% CI = −12.1%, 0.2%). For the latter, the prevalence was too small to carry out stratified analyses, leaving depression, neuroticism and sex as targets for further analyses.

Age at onset and depression

Stratified comparisons (Table 2) demonstrated that baseline depressive symptoms significantly increased the risk for developing the broad psychosis outcome within a three-year interval in the young (RD = 6.5%, 95% CI = 3.3%, 9.7%) and middle group (RD = 2.5%, 95% CI = 0.4%, 4.7%), but not in the old group (RD = 1.7%, 95% CI = −0.7%, 4.1%) (Table 2). In the youngest group, 8.8% of those reporting life-time depressive symptoms at baseline had the broad psychosis outcome 3 years later as opposed to 2.3% of those reporting no depressive symptoms. In the old group, 3.7% of those reporting life-time depressive symptoms developed the broad psychosis outcome as opposed to 2.0% of those reporting no depressive symptoms. The absolute RD between the young and the old group was significant (RD = 4.8%, 95% CI = 0.8%, 8.8%). Thus, the risk-increasing effect of depression declined by a factor of 3.8 (6.5% / 1.7%) with age at onset.

Age at onset and neuroticism

A significant risk-increasing effect of neuroticism was observed for the young (RD = 5.3%, 95% CI = 2.7%, 7.9%), middle (RD = 2.8%, 95% CI = 0.8%, 4.9%) and old group (RD = 2.2%, 95% CI = 0.2%, 4.2%). In the young group, 7.4% of those with high neuroticism scores at baseline developed the broad psychosis outcome, versus 2.1% of those with low neuroticism scores. These figures dropped to 5.2 % vs. 2.4% in middle age with further progression to 3.8% vs. 1.5% in old age. The absolute RD between the young and the old group, however, did not reach significance (RD = 3.1%, 95% CI = −0.2%, 6.4%). Thus, the risk increasing effect of neuroticism declined by a factor of 2.4 (5.3%/ 2.2%) with age at onset.

Age at onset and sex

The overall interaction between sex and age showed a trend towards significance, but no clear effect was apparent after stratification for age at onset. No greater risk for female sex was found in the young (RD = 1.7%, 95% CI = −0.4%, 3.7%), the middle (RD = 0.4%, 95% CI = −1.4%, 2.1%) or the old group (RD = −0.9%, 95% CI = −2.7%, 0.9%).

Discussion

■ **Incidence**

With an annual incidence of 0.3%, the community rate for (clinically relevant, but mostly untreated) non-affective, non-organic psychotic symptoms with late-onset was twenty times higher than the rate of treated clinical disorders reported previously [9, 11, 18, 32, 64]. Of all new "cases", 21% were over 50 years of age at illness onset, which is in line with previous findings [27, 31]. Similar disparities between clinical and community levels have been published with regard to prevalence rates of psychotic symptoms among the cognitively intact old [10, 24] and very old [43]. Psychosis in old age seems much more common

than previously thought [7] and so does psychosis with late onset. The high incidence rate of psychotic symptoms as opposed to clinical disorder may not only be due to the fact that most of the sample with isolated psychotic symptoms would not have clinical needs, but may also be related to the argument that paranoid elderly often do not seek help [10, 47], and LOP, therefore, tends to be associated with longer community stays [49]. This lack of help-seeking behaviour may, in turn, be a direct reflection of persecutory ideation, illness behaviour or of social isolation in old age [49, 68]. In a post-hoc analysis for those with the broad psychosis outcome, however, we were unable to find any differences in first-contact rates as a function of age at onset (young versus middle: χ^2 = .61, df = 1, p = .435; young versus old: χ^2 = .08, df = 1, p = .777; middle versus old: χ^2 = .14, df = 1, p = .708).

It has to be noted that cell sizes for new psychosis were rather small and decreased even further by stratification for age groups. Hence, only 12 subjects out of 1,282 aged 50–64 years developed a recent-onset psychosis in the present study. This number may be considered too small to calculate reliable incidence rates. This finding, therefore, calls for replication, but echoes similar findings in the younger age groups [22].

■ Risk factors

Symptoms of depression and neurotic personality styles were found to have some association with age at onset. In young age, subjects reporting life-time depressive symptoms at baseline run a higher risk of developing psychotic experiences later on than those who do not report depressive symptoms. The risk-enhancing effect in young age decreased to a much lower level in middle and old age. Although effect sizes did not reach significance in those aged 50–64, a history of depressive symptoms went together with a two-fold increase in psychosis risk, which suggests that significance may have been reached with bigger cell sizes. Depression is known to be a common antecedent of psychosis in general [35, 69] and in late life [24], but it now seems that the strength of this relationship diminishes as the illness onset shifts towards later ages, pointing towards aetiological differences between LOP en EOP. This observation very nicely fits the repeated finding of less emotional comorbidity in LOP [31, 38, 49, 63].

In a similar fashion, the risk-enhancing effect of neuroticism has been studied previously [34], but its association with psychosis appears to be less strong with onset in old age [23]. Häfner et al. found that, although the severity of psychopathology decreased with age at first episode, this was not caused by a decrease in the severity of psychotic symptoms but by a decrease in neurotic syndrome levels [18]. Neurot-

icism is a personality trait related to stress reactivity, anxiety proneness and emotional instability in the context of daily stressors [40, 42]. In schizophrenic patients, high neuroticism levels are associated with avoidant coping styles and emotional discomfort [37], which might indicate that the diminishing effect of neuroticism in LOP reflects more adaptive coping skills in later adulthood. This lends further support to the notion of possible aetiological differences with psychosis in young age.

Men and women run an equal risk for LOP in the present study, which is at odds with earlier findings, but in line with the community-based study by Henderson and colleagues [24]. The authors explain their result by the higher refusal of women to take part in the study. This does not apply to NEMESIS. Alternatively, it may be that older men are less likely to come to professional attention and are for this reason missed in clinical studies. Although being highly speculative, it is compatible with the notion of profoundly lower symptom levels in males with LOP [18]. Unfortunately, we were unable to explore this issue in depth.

Sensory impairment was not found to increase the risk for psychosis in later life. The outcome measures of deafness and visual impairment appeared to be too stringent. In addition, the sample may have been too young for these variables to exert significant effects. Only two out of 132 subjects with recent-onset psychotic symptoms suffered from severe visual deficits and four reported severe auditory deficits. All were younger than 50 years.

No notable differences in risk profiles between groups were found for level of urbanisation, life-time cannabis use, life-time manic symptoms, family history of psychiatric treatment, family history of psychosis or single living status.

■ Limitations

Regrettably, NEMESIS does not provide information for those older than 64 years. One may expect (qualitative) differences in risk profiles with EOP to show up more profoundly in those aged 65 years and older including cognitive ageing, sensory loss, death of a spouse or retirement [2, 28, 29].

The reported differences between LOP and EOP might be considered an underestimation of true risk differences, because analyses of risk factors was based on the broad psychosis outcome. It has been shown previously that this outcome results in smaller effect sizes than narrowly defined psychosis [22, 41].

Further limitations include the use of lay interviewers and difficulties in excluding psychosis due to prodromal dementia. Although the CIDI is designed for the use by non-clinicians and interviewers underwent intensive training, these well-known problems cannot be completely solved in studies of this kind [68]. They were nevertheless minimized by

conducting re-interviews by an experienced psychiatrist to ascertain clinical relevance of psychotic symptoms using questions from the SCID.

Conclusion

This study fuels the finding that non-affective, non-organic psychotic symptoms arise more often in the second half of life than studies on a syndromal level have implied. LOP is less likely to be preceded by neuroticism and emotional disturbances, which suggests that those affected have learned to use more effective coping styles in daily life. Yet, the similarities in risk profiles across different ages at onset outweigh the differences.

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