Section 1

Epidemiology, Historical Background, Illness Phenomenology, and Diagnostic Issues

Chapter 1

Epidemiology of Psychotic Disorders: Methodological Issues and Empirical Findings

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Introduction

This chapter will begin with a discussion of several general topics regarding the study of psychiatric symptoms and disorders in older adults that are relevant to the research findings presented throughout this volume. This discussion will be followed by a review of the empirical findings on the epidemiology of psychotic disorders in older adults.

Epidemiology

The field of epidemiology includes studies of disease burden (as measured by prevalence and incidence), as well as studies of risk factors for diseases, their course and their consequences. Apart from being a way of understanding the etiology of disease, epidemiology is also of use in service planning and guidance of clinicians (for example in raising awareness of a disease that is common in a particular segment of the population). Since global and regional variations in living conditions influence exposures during the life-span, epidemiological studies of a particular disease may yield different results across societies over space and time. Thus, epidemiological studies must be conducted in different types of societies and conducted repeatedly to discover secular trends in the prevalence and incidence of diseases, their risk factors and their prognosis [1]. Epidemiological studies may utilize different data sources and different methods in this pursuit. Most epidemiological studies are observational, i.e., studied at the population or group level rather than the individual level, and without intervention. The observational epidemiology study designs commonly used in psychiatry are:

- *Longitudinal "cohort" studies*: one or more samples or "cohorts" are followed prospectively over time with respect to an outcome and associated risk factors.
- *"Case–control" studies*: retrospective examinations that compare patients or "cases" that have a disease or outcome of interest with patients who do not have the disease or outcome (controls) on various risk factors.
- *Cross-sectional studies*: examine data at one point in time. Cross-sectional studies can be distinguished from case–control studies in that they provide data on the entire population under study, whereas case–control studies usually focus on only people with a specific disease or disorder and compare them with those without the disease or disorder.

Case–control studies are more often used in psychiatric epidemiology because they are less expensive and time-consuming than prospective studies. For example, one frequently employed approach is to select a sample of the population in a catchment area and to define cases of a disorder on the basis of information gathered by interviews with participants or self-report questionnaires. Another approach is to utilize health care registers and/or hospital records to identify cases of a disorder within a catchment area; remaining inhabitants of the catchment area are assumed not to have the disorder. The strengths and weaknesses of these different designs will be reviewed with respect to the study of late-life psychosis.

General considerations when evaluating the observational epidemiological literature on psychoses

It is important to consider several general issues in evaluating the observational epidemiologic literature prior to a more specific discussion of psychotic disorders:

1. It is essential to define clinical outcome. As described in the next section, this is not a straightforward task with respect to psychosis. Consistently operationalized methods for defining symptoms and functioning, and making diagnoses across studies, are lacking in epidemiologic studies of psychosis. Comparison and replication of studies are, as a result, limited. However, when similar associations are observed despite differences in diagnostic criteria and/or operationalizing these criteria, this may denote a more robust association.
2. Overlap of psychiatric symptoms among disorders is known. For example, underlying dementia neuropathologies may induce psychotic symptoms, thereby confusing the diagnosis.
3. Socioethnodemographic characteristics of global populations at risk are important. Adequate descriptions of study samples are imperative for proper interpretation of the data, planning follow-up measures and ancillary studies, and identifying areas of intervention and ultimately prevention.
4. Age of exposure and age at which outcomes occur are critical in psychiatric epidemiology. Psychiatric outcomes have early-, mid- and later-life onsets and characteristics. Risk associations may differ depending on when an exposure is measured and when the outcome is manifest.
5. The timing of association between exposure and outcome is critical due to the influence of underlying neuropathological changes on physiological "exposures," as well as manifestation of intermediate and clinical phenotypes. For example, in the epidemiology of dementia, when measured in mid-life, body weight, blood pressure and blood cholesterol levels have been associated with increased late-onset dementia risk; however, when measured in late-life, they may not be risk factors, and are sometimes protective.
6. Duration of exposures may convey information regarding "load." Individual differences in susceptibility and length of exposure to stressors are linked to behavioral responses to environmental challenges that are coupled to physiologic and pathophysiologic responses.
7. Survival time of the population being studied is important in evaluating the population at risk for later-life psychiatric outcomes. Psychiatric outcomes in older ages are observed among survivors, i.e., those who have lived to old age.

8. Birth cohort is a primary consideration regarding the role of exposures, as well as outcome characteristics, not only based on neurodevelopmental hypotheses, but secular trends in exposures, such as diet and air pollution. In addition, birth cohort reflects rapid technological changes, as well as advancement of pharmacologic interventions for psychiatric disorders and comorbid conditions.
9. It is imperative to take note of the study design and the analysis strategy used to arrive at the conclusions of any research study. Longitudinal studies with comprehensive follow-up, adequate assessment of exposures and definitive outcomes data, including mortality, are the only ones whereby "true" risk can be calculated. Other study designs, e.g., case–control studies, provide provisional data on estimation of risks and correlations.
10. Competing risks are and will continue increasing in their importance with aging of the global population. Competing risk generally refers to the presence of multimorbidities, which increase with age, making it more difficult to identify the etiologic exposure or indicator.
11. The increasing availability of genetic or other biomarkers such as those provided by neuroimaging or fluid-based biomarkers will allow for novel approaches to risk stratification as well as refinement of both exposures and outcomes.

These points are summarized in Table 1.1.

Defining psychosis in epidemiological studies

It is fair to say that the epidemiology of late-life psychosis has been considerably less extensively studied than that of, for example, late-life depression. This may partly be explained by a long-prevailing lack of consensus on nomenclature and research diagnostic criteria for late-life psychosis [2]. Another explanation is that the study of psychosis is considered to present greater methodological challenges than the study of depression.

Measurement versus evaluation

Psychiatry is a "hybrid science" aiming at both explanation and interpretation. These aims have been in dialectic tension throughout its history [3,4]. Explanatory, quantitative

Table 1.1 General considerations when evaluating the observational epidemiological literature on psychoses

• Outcome definitions and measurements
• Overlapping symptoms across various psychiatric outcomes
• Age of exposure or onset of outcome
• Timing of exposure in relation to outcome, e.g., mid-life versus late-life exposure
• Exposure level ("load")
• Duration and persistence of exposure
• Survival factors
• Birth cohort
• Study design and analysis strategy
• Competing risks
• Biomarkers

research strives for objectivity by using methods of the natural sciences. However, psychiatric research is always dependent on interpretation of subjective experience, because psychiatric symptoms and signs are not objects ("things") that can be measured in the sense that, for example, blood levels of glucose are measured [5]. From this should follow that all data collection, whether it be via interviews or questionnaires, in routine health care or research contexts, includes evaluation or some kind of judgment, on the part of both the study participant and the interviewer [6–8].

Gathering information on psychotic symptoms

The problem of objectifying and quantifying subjective experiences is a problem of validity, i.e., whether a scientific method captures something that is relevant to the matter in question and is in concordance with reality [9]. A review of methods used in epidemiological studies of late-life psychosis suggests that assumptions about valid methods in the study of psychosis differ from the assumptions behind epidemiological studies of, for example, mood and anxiety disorders. Most of the epidemiological studies of psychosis rely on information gathered and/or reviewed by clinical experts. Thus, detection and evaluation of psychotic symptoms is considered to require the clinical skill to evaluate a person's beliefs and perceptions. This assumption does not seem to be made in most epidemiological studies of late-life depression, which often utilize structured interviews conducted by trained laypersons or even self-report symptom scales.

The basis of this methodological assumption may be as follows. Loss of contact with reality, or "lack of insight," is considered to be one important quality of psychosis. Thus, contrary to most individuals with depression or anxiety, most individuals with psychosis do not evaluate their beliefs and experiences as psychiatric symptoms per se. A question about whether they "have delusions or hallucinations" will obviously lead to "false negative" cases[1] [10]. To acquire valid information, questions about psychotic symptoms must be indirect, and there must be room for clarifying questions. This reduces the face validity of questions regarding psychotic symptoms, meaning that their intention should not be understood by study participants. However, beliefs and experiences similar to psychotic symptoms (such as beliefs in telepathic communication) are not uncommon in the population [11,12]. A poor conception of what kind of experiences are sought, either by the interviewer or by the interviewed, results in a rate of "false positive" cases that outnumbers the "true positives" [10,13–15]. Such psychosis-like experiences may be on a continuum with clinical psychotic disorders, so that research into the former may help to explain the latter [11,16–18]. However, if there are important qualitative differences between these phenomena, the psychosis-like experiences may blur the picture instead [19,20].

For other reasons, qualitative aspects of psychotic symptoms are of special importance in studies of older adults. In this age group, psychotic symptoms may often appear in the context of dementia, delirium, medication usage and/or physical disorders [21]. In fact, such conditions have been found to be the final diagnosis in a significant proportion of older patients presenting with new-onset psychotic symptoms, even in psychiatric settings [22–24]. Hallucinations and delusions due to, for example, medication or physical disorders are not by definition different from hallucinations and delusions due to a psychiatric disorder. An expert judgment of the quality (e.g., modality of hallucinations,

[1] These expressions are put between quotation marks since they are made with reference to a non-existent "gold standard" for when the symptoms actually are present. However, the expression is useful for the purposes of this discussion.

delusional content) and context of psychotic symptoms is crucial for studies aiming to report on psychotic symptoms that are primarily due to psychiatric disorders ("primary" psychotic disorders) and to study correlates of such symptoms. It is important to recognize that older persons may have two coexisting causes for psychotic symptoms that may affect their form and content, e.g., physical or neurological disease and schizophrenia.

Individuals with psychotic symptoms may be reluctant to reveal them because of previous negative experiences from doing so [26]. This may be of greater importance for a case finding of delusional disorder and isolated psychotic symptoms than for schizophrenia, since schizophrenia may be more likely to reveal itself by behavioral disturbances or signs of global functional impairment [27]. Thus, cases of psychosis may be missed if studies rely only on interviews with participants. Other important information sources are key informant interviews and medical records [28].

Apart from these problems with the detection of psychosis, individuals with psychosis may be more reluctant than others to participate in epidemiological studies [29]. Since the phenomenon studied is fairly rare, a selection bias involving a small number of individual non-participants can have a high relative impact on, for example, prevalence estimates [30].

Studies based on health care registers

Drawing information from health care registers and/or hospital records avoids the problem of non-participation. Many studies utilizing health care data use registered diagnostic codes to define a case of a disorder, while others add information by reviewing medical records of patients recorded to have a certain diagnosis. Since register studies require limited human resources to establish whether someone fulfills the diagnostic criteria for psychotic disorders or not, it is possible to obtain very large study samples, sometimes including the population of a whole country, which is a major advantage of this design. However, although researchers can expect an expert judgment to be involved in detection and diagnosis of psychosis in routine health care, and that the diagnosis is based on observations collected over an extended time period, they do not have control over the diagnostic process and have to rely on disorders being diagnosed adequately by clinicians within the health care system. Expert review of medical records avoids this problem, but requires more human resources and may limit the size of the catchment area. Another problem is that register studies only capture cases that have been identified by health care services. The magnitude of this bias is unknown, but may be significant, even for schizophrenia. A longitudinal study following a birth cohort with repeated examinations up to age 38 years identified a 2% cumulative incidence of schizophrenia that could be confirmed by pharmacological treatment or hospital records [31]. An additional 1.7% of this cohort formally met the diagnostic criteria for schizophrenia, but had not (yet) been diagnosed by health care services. Cases not (currently) identified by health care services may be less severe, but their identification is of importance for estimating the true disease burden and for studying the true risk factors and consequences of late-life psychosis [32].

Epidemiology of late-life psychosis

Prevalence

The prevalence of psychotic symptoms in older adults has been estimated to be between 1% and 13.4% [28,33–44]. The median prevalence in the included studies is 3%. One review study from Western Europe found increasing prevalence of psychotic symptoms

with advancing age, so that rates were under 2% in persons aged 65–74, but 4% and 7% in those aged 85–94 and 95–104, respectively [36].

The prevalence of non-affective psychotic disorders in older adults is reported to be between 0.1% and 4.7%. References are displayed in Table 1.2. The median prevalence of the reviewed studies is 1.2%. The majority of studies find schizophrenia to be the most common disorder. One study reported the prevalence of schizophrenia by age of onset, giving a prevalence of 0.35% for early-onset schizophrenia, 0.14% for late-onset schizophrenia (between the ages of 40 and 59 years) and 0.05% for very-late-onset schizophrenia-like psychosis (VLOSLP, onset at age 60 or older) [45]. Two studies reporting the current prevalence of delusional disorder in older adults found it to be very rare, 0.04% [26] and 0.03% [45]. Others found a life-time prevalence of 0.46% [46] and one study found it to be more common than schizophrenia (2.0%) [47]. The very low prevalence of delusional disorder reported by some studies may be due to underestimations related to methodological factors mentioned above.

Since psychotic disorders most often have an onset before age 40 and the mortality rate in the most common psychotic disorder, schizophrenia, is two to three times higher than in the general population [48], it might be expected that the point prevalence of psychotic disorders declines with age. Only one of the reviewed prevalence studies examined this and suggested schizophrenia to be slightly less common with increasing age among older adults [45]. Because of its rarity, age trends in the prevalence of delusional disorder are difficult to examine.

Incidence

The incidence of psychotic symptoms in older adults has been reported by few studies. The cumulative incidence has been found to be 6% with a follow-up duration of 3.6 years [33], 8% with a follow-up duration of 7 years [49], and 4.8% among 70 year olds followed until death or age 90 [50].

A meta-analysis of studies of the incidence of very-late-onset psychotic disorder (after 65 years) has been published [51]. It identified a total of 41 relevant studies between 1960 and 2016, of which 25 could be used to calculate a pooled incidence. Given this large time-span, the included studies were heterogeneous in important aspects such as diagnostic criteria, case definition and data sources. The study reported a pooled incidence of schizophrenia of 7.5 cases per 100 000 person-years. Of note, the incidence of affective psychosis was considerably higher (30.9 cases per 100 000 person-years), although this was based on a smaller number of studies.

Risk factors

The life-time risk for the most common psychotic disorder, schizophrenia, is higher in men than in women [52,53], but no significant gender differences were found in the prevalence of psychotic disorders in old age (Table 1.2). Women have been reported to have a later age at onset for schizophrenia [54]. One study [45] found the prevalence of schizophrenia in older adults to be two times higher in women than in men. This may partly reflect a higher likelihood of survival to old age in women with early-onset schizophrenia, but older women also seem to have higher incidence rates of psychosis than older men [51].

Table 1.2 Studies reporting prevalence estimates of psychotic disorders according to DSM criteria in old age

Study [Reference]	Year	Diagnostic instrument	Diagnostic criteria	Age
Gothenburg H85 [47]	1986	CPRS/expert judgment	DSM-III-R schizophrenia, delusional disorder, psychotic NOS	85
MRC ALPHA [26]	1986	GMS/expert judgment	DSM-III-R schizophrenia, delusional disorder, psychotic NOS	≥65
NCS-R [13]	2002	CIDI screen, SCID	DSM-IV non-affective psychosis	≥60
PIF Study[a] [46]	2002	CIDI screen, SCID, medical records, expert judgment	DSM-IV non-affective psychosis	≥65
ESPRIT [68][b]	2000	MINI, expert judgment	DSM-IV affective and non-affective psychosis	≥65
Amsterdam Study[c] [45]	2008	MINI-plus, expert judgment	DSM-IV schizophrenia spectrum	≥60

DSM: Diagnostic and Statistical Manual of Mental Disorders. CPRS: Comprehensive Psychopathological Rating Scale. NOS: N
State. CIDI: Composite International Diagnostic Interview. SCID: Structured Clinical Interview for DSM-IV-Axis-1 Disorders. M
All prevalence estimates are current to one year except ***a***, which is life-time prevalence estimate. Dementia was an exclusio
except ***b***. Prevalence figures include whole population including individuals with dementia except ***c*** which excluded indivi
study sample. Year denotes year in which study was initiated. ***d*** Case-register study of patients (numerator) in a catchment

Based on clinical experience, cross-sectional population studies and case–control studies, it is generally believed that sensory impairment (visual or hearing), social isolation and premorbid paranoid personality traits are risk factors for psychotic symptoms in old age [28,39,55]. Furthermore, there are reported associations between psychotic symptoms and structural brain pathology [55], for example basal ganglia calcification [56].

One systematic review of risk factors for late-onset psychosis has been published [57]. It included 11 studies, all with a longitudinal design. Temporal antecedence is one of the prerequisites for a causal relationship between a possible risk factor and a disease [58]. However, the review included studies that were very heterogeneous with respect to important factors such as study design, case definition, baseline age of the samples and length of follow-up. In this review, visual impairment, a history of psychotic symptoms, cognitive dysfunction, poor physical health and negative life events emerged as risk factors. Increasing age and female gender were not found to be risk factors for late-onset psychosis and results on social isolation were ambiguous.

Prognosis and consequences

Mortality

Psychotic disorder [59–63] and psychotic symptoms [28,33] have been associated with mortality in older adults. Thus, the well-known health gap between individuals with psychotic disorders and the general population persists into old age. However, the difference in mortality between individuals with and without schizophrenia may be smaller in older adults compared to younger age groups [62]. Excess mortality is higher among men than among women [59,61]. Physical disease dominates as cause of death in individuals with late-life psychosis, with circulatory diseases being the most common cause of death (as in the general population) [62]. Individuals with VLOSLP seem to have a higher mortality rate than age- and gender-matched individuals with early-onset schizophrenia [61], but disease duration seems to have little or no effect on mortality after adjustment for other variables [59,61]. Findings of higher mortality may, to an unknown extent, be explained by cases erroneously diagnosed as VLOSLP that may instead represent cases of dementia, which is strongly associated with mortality [61].

Association with dementia

Schizophrenia [64], as well as late-onset schizophrenia [65], has been associated with an increased risk for dementia. This association is likely to be multifactorial. Possible causes include higher rates of cerebrovascular disease and substance abuse compared to the general population [65]. An important etiological question is to what extent new-onset psychotic symptoms in later life represent prodromal symptoms of dementia. Several population studies, with a follow-up of between three and ten years, have reported an elevated relative risk for incident dementia among older individuals with prevalent [28,44,49] or first-onset [50] psychotic symptoms, late-onset delusional disorder [66] and VLOSLP [65]. In the studies of individuals with psychotic symptoms, the proportion who were later diagnosed with dementia varies widely (between 15% and 60%). To some extent, these findings corroborate an early clinical study of late-life psychosis which found that only a minority of these patients developed dementia within two years [67].

Conclusions

- Epidemiological studies of late-life psychosis pose several methodological challenges and there are relatively few high-quality studies regarding the risk factors and prognosis of late-life psychosis.
- Reports on the prevalence of late-life psychosis are highly variable, ranging from 1–13.4% for psychotic symptoms and 0.2–4.7% for non-affective psychotic disorders.
- Risk factors that have been found to be associated with late-life psychosis include sensory impairment, social isolation, paranoid personality, structural brain abnormalities, cognitive dysfunction, poor physical health and negative life events.
- Individuals with late-life psychosis have a markedly higher mortality rate than the general population and an increased risk for developing dementia.
- New-onset psychotic symptoms in older adults without dementia confer a greater risk for the subsequent development of dementia, but the proportion of persons at risk varies considerably between studies. Future investigations need to be undertaken to clarify those that are at greater risk for developing dementia.
- Some of the methodological goals for future research include: greater standardization of outcome definitions; increased inclusion of genetic and other biomarkers; improved understanding of critical exposures, their accumulation and duration over the life course; acknowledgment of multimorbidities accompanying aging and psychiatric disease; attention to the polypharmaceutical milieu and effects on psychiatric outcomes.

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