

Introduction

Schizophrenia is a chronic disease that afflicts approximately 1% of the population worldwide (Freedman 2003). It usually afflicts people at a young age and, according to a report of the World Health Organization, it is among the seven most disabling diseases in the age group between 20 and 45, far surpassing diabetes, HIV or cardiovascular diseases (World Health Organization 2001). A number of reviews have shown that there is an excess mortality in people with schizophrenia, the overall mortality being twice as high as that in the general population (Allebeck 1989, Brown 1997, Colton and Manderscheid 2006, Harris and Barraclough 1998), so that schizophrenia has been called a 'life-shortening disease' (Allebeck 1989). Suicide and accidents account for about 40% of this excess mortality (Baxter and Appleby 1999, Black *et al.* 1985, Palmer *et al.* 2005, Tsuang *et al.* 1999); the rest is due to physical illness. Despite this excess mortality due to physical diseases, the concern for the somatic well-being of people with schizophrenia has been neglected for decades. A number of reasons account for this neglect, one of them being the stigma related to psychiatric disorders (Sartorius and Schulze 2005). A recent population-wide study in Australia (Lawrence *et al.* 2003) showed that although people with schizophrenia suffer more frequently from cardiovascular problems than the general population, they receive revascularization procedures less frequently than the general population. People with mental disorders were also reported to be less likely to be placed on HbA1c and cholesterol monitoring (Jones *et al.* 2004), to have a retinal examination if they have diabetes (Desai *et al.* 2002), to be treated for osteoporosis (Bishop *et al.* 2004) or to receive medical visits (Cradock-O'Leary *et al.* 2002, Folsom *et al.* 2002); and they are treated for a physical disease only if it is life-threatening (Munck-Jorgensen *et al.* 2000).

While the excess mortality of people with schizophrenia has been well established (Allebeck 1989, Brown 1997, Harris and Barraclough 1998), no comprehensive review of the comorbidity of schizophrenia with physical illness is available to date. Such data would be useful, because a review of the excess rates of *comorbidities* rather than excess *mortality* assesses the problem at a

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stage when interventions are still possible. The main aim of this book was to fill this gap by providing a comprehensive review of the epidemiological literature on the association between schizophrenia and comorbid medical illnesses. Hypotheses explaining excess or reduced rates are also listed. The review may thus serve as a basis for projects for improving the physical health of people with schizophrenia.

Method

A search in MEDLINE (1966 – last update May 2006) was made to find epidemiological studies on the association between schizophrenia and physical illnesses. A broad search strategy had to be used to ensure that no physical illness had been missed. For this reason the MeSH term for schizophrenia was combined with the 23 MeSH terms for the general disease categories of physical diseases. If the search had been performed for each individual physical disease alone, some diseases could have easily been missed. These MeSH terms were:

- Bacterial Infections and Mycoses
- Virus Diseases (+ HIV)
- Parasitic Diseases
- Neoplasms
- Musculoskeletal Diseases
- Digestive System Diseases
- Stomatognathic Diseases
- Respiratory Tract Diseases
- Otorhinolaryngologic Diseases
- Diseases of the Nervous System: autoimmune diseases of the nervous system, autonomic nervous system diseases, central nervous system diseases (*brain diseases, CNS infections, encephalomyelitis, high-pressure neurological syndrome, meningitis, movement disorders, ocular motility disorders, pneumocephalus, spinal cord diseases*), chronobiology disorders, cranial nerve diseases, demyelinating diseases, nervous system malformations, nervous system neoplasms, neurocutaneous syndrome, neurodegenerative diseases, neurologic manifestations, neuromuscular diseases, neurotoxicity syndromes, sleep disorders, trauma, nervous system
- Eye Diseases
- Urologic and Male Genital Diseases
- Female Genital Diseases and Pregnancy Complications
- Cardiovascular Diseases
- Hemic and Lymphatic Diseases

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- Congenital, Hereditary and Neonatal Diseases and Abnormalities
- Skin and Connective Tissue Diseases
- Nutritional and Metabolic Diseases
- Endocrine Diseases
- Immune System Diseases
- Disorders of Environmental Origin
- Animal diseases
- Pathological Conditions, Signs and Symptoms.

All abstracts found were read, and potentially relevant articles were ordered for more detailed inspection. The first search was made in autumn 2004; an update search was made in May 2006. The search was complemented by relevant articles mentioned in the studies and other reviews identified. In addition, the drafts of each thematic chapter were sent to experts with the request for information on studies that were missed by our search (see Acknowledgements).

At the beginning of each section we indicate how many references were found by the MEDLINE search and how many references were added from other sources (mainly cross-referencing). These numbers relate solely to the epidemiological studies included in the various sections, not to references for e.g. definitions, hypotheses etc. The aim of this description was to provide some information about the search and on how many studies were found for each category.

There was no restriction as to language.

The focus was on comorbidity studies rather than on mortality studies, since, on the one hand, mortality studies had already been well summarized in other reviews (Allebeck 1989, Brown 1997, Harris and Barraclough 1998). Furthermore, the interest in doing a review of comorbidity studies lies in these studies which assess the associations at a stage when interventions are still possible. Studies that were concerned with mere side-effects of antipsychotic drugs rather than true comorbid diseases were also excluded. Sometimes, however, this distinction was difficult. For example, weight gain is a side-effect of antipsychotic drugs, but the resulting obesity and its potential consequences are major health problems.

Given that the general quality of the studies identified varied substantially from one disease category to another, it was not possible to apply the same inclusion and exclusion criteria for all disease categories. For example, while there are many high-quality, population-based studies on the association between schizophrenia and cancer, the literature on bacterial infections in schizophrenia is much more limited. The aim of the review was not only to find out for which areas compelling evidence is already available, but also whether according to preliminary evidence there are areas of potential importance that could be the focus of future research. Therefore the inclusion criteria such as e.g. 'only population-based studies' or 'only controlled studies' could not be applied to all

chapters. Rather, in well-researched areas (such as that of comorbidity of cancer and schizophrenia), we included only the high-quality studies (in particular, population-based studies with a control group), whereas in areas where only very few studies were available, studies of lower quality such as case series were also included.

When the same study was found several times in different searches, it was described only once in the best fitting category. On the other hand, some studies examined more than one comorbid condition. They were then reported in different chapters. Due to the heterogeneity in terms of quality and designs, meta-analytic calculations were not possible, but rather the results were described in a narrative way. Potential explanations for increased or decreased rates of some physical illnesses are also summarized. Finally, informations on the country of origin of the studies are presented, so as to address the question of whether the results can be generalized to all patients with schizophrenia or are limited only to specific populations.

Results

Figure 3.1 shows the results of the MEDLINE search for the different MeSH terms. It yielded the greatest number of hits on *Diseases of the Nervous System*, followed by *Pathologic Signs and Conditions* and *Disorders of Environmental Origin*, but the latter two were supplemental categories that provided only few new data (see below). The following text addresses the results in the same sequence in which the MeSH terms are listed in MEDLINE.

3.1. Bacterial infections and mycoses

The MEDLINE search on *Bacterial Infections and Mycoses* yielded 277 hits. None of the reports was relevant. Five reports were added from other MEDLINE searches.

3.1.1. *Borrelia burgdorferi*

Brown (1996) identified geographical distributions of bacterial infections and schizophrenia. He found that areas in the United States with high rates of tick-borne encephalitis (TBE) correlated significantly with areas with high schizophrenia rates. He described a similar distribution and correlation in European countries (Croatia, Norway, Finland, Germany, Ireland and others). However, this was only a hypothesis-generating study with a line stating that ‘the opinion expressed in the article are solely those of the author . . .’. Brown also concluded that definite proof of an association could not be demonstrated because of incomplete epidemiological data.

3.1.2. Tuberculosis

Ohta *et al.* (1988) investigated the incidence of tuberculosis among 3251 Japanese patients with a diagnosis of schizophrenia. The incidence of

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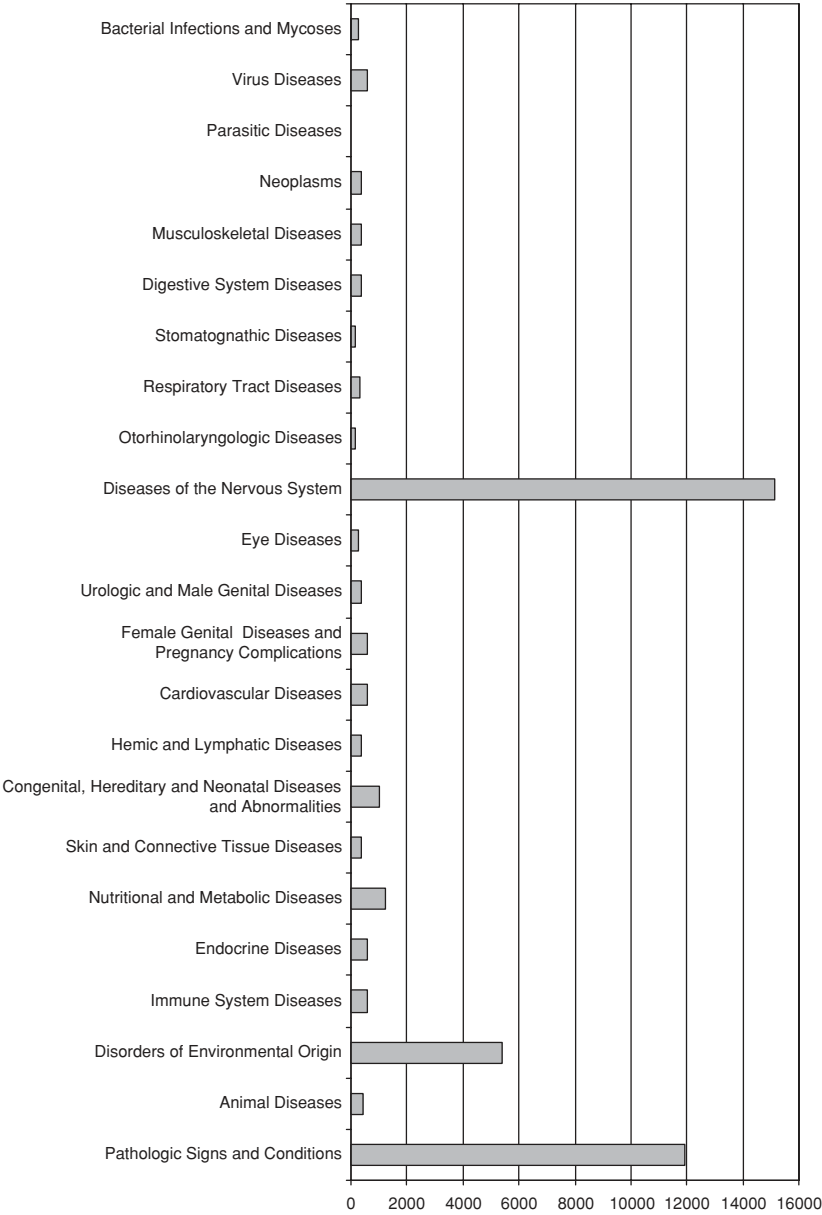


Figure 3.1 Number of hits for the different MeSH terms.

tuberculosis was significantly higher (3.04) in schizophrenic patients than in the general population. In addition to some mortality studies they quoted only the Oxford Record Linkage Study (Baldwin 1979), which also found an increased rate of tuberculosis in schizophrenia.

Fisher *et al.* (1996) examined 113 patients with severe mental illness for tuberculosis. Active respiratory tuberculosis were found in 4.4% of the cases, foci of indefinite activity were found in 3.5% and post-tubercular changes in the lungs and the pleura were found in 7.1% of the cases.

Zeenreich *et al.* (1998) found a prevalence of 5.4% cases of active pulmonary tuberculosis in 720 hospitalized patients during the period 1983–96 in Israel. There was no control group. Zeenreich and colleagues recommended routine screening of all new patients and control screenings to determine if there were cases of tuberculosis to prevent recurrent outbreaks of tuberculosis.

Lawrence *et al.* (2001) observed 3368 schizophrenic male patients and 1674 female schizophrenic patients in Western Australia from 1980 to 1998. They found a first-time hospitalization rate ratio for tuberculosis of 3.04 (n.s.) in male patients and of 2.26 (s.) in female patients.

In summary, it appears that the association between bacterial infections, mycoses and schizophrenia has been insufficiently studied in comorbidity studies. The only bacterial infection for which some evidence is available is tuberculosis. This contrasts with mortality studies in which increased rates of excess mortality due to infections has been demonstrated (Harris and Barraclough 1998). Alternative explanations are that the evidence is buried in old studies that can not be detected by MEDLINE (which starts in 1966), but the older studies would no longer necessarily be representative. Since in some countries, such as Romania, specific wards for people with both schizophrenia and tuberculosis exist, further analyses of these preventable causes of death are warranted.

3.2. Virus diseases

The MEDLINE search on *Virus Diseases* yielded 448 hits. Given the importance of the association between schizophrenia and HIV another MEDLINE search for *HIV* was added which yielded another 153 hits. A total of 62 reports were ordered, of which 14 were included; and 35 reports were added by cross-referencing. Many of the reports investigated the ‘viral hypothesis’ of schizophrenia, i.e. the question whether virus infections play an aetiological role in the development of schizophrenia, which is not within the scope of this review. Only the studies on HIV and hepatitis were related to physical comorbidity.

3.2.1. Influenza virus

Probably the best-studied association is that of maternal infection with the influenza virus during pregnancy as a risk factor for the later development of

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schizophrenia. Since by definition these studies considered the rates of influenza infection in mothers of people with schizophrenia rather than examining the prevalence of influenza in schizophrenia, these studies were excluded a priori. Nevertheless, a review on the topic has been provided by Ebert and Kotler (2005), in which 11 out of 19 studies showed a significant relationship between exposure to influenza virus in mid-pregnancy (second trimester) whereas eight did not. The authors concluded that the relationship between influenza virus and schizophrenia is still incompletely understood.

Lawrence *et al.* (2001) analysed 3368 schizophrenic male patients and 1674 female schizophrenic patients in Western Australia. They found a first-time hospitalization rate ratio for influenza of 1.35 (n.s.) in males and of 0.27 (s.) in females compared to the general population.

3.2.2. Herpes simplex type 1 and 2, rubella virus, measles virus, cytomegalovirus, Epstein-Barr virus

Halone *et al.* (1974) found increased rates of herpes simplex type 1 antibodies in 54 patients with schizophrenia, although the rates were higher in patients with psychotic depression. No differences in rubella virus titres compared to medical personnel were found, and measles virus titres were even slightly lower among the psychiatric patients.

Rimon *et al.* (1979) measured immunoglobulin G antibodies to herpes simplex type 1 virus in 16 patients with schizophrenia and found no significant differences in the antibody levels between the schizophrenic patients and normal controls.

Delisi *et al.* (1986) did not find significantly higher herpes simplex and cytomegalovirus titres in schizophrenics; Epstein-Barr virus titres were increased though not only in patients with schizophrenia but also in non-ill siblings and hospital staff.

Conejero-Goldberg *et al.* (2003) screened post-mortem orbital frontal brain samples from patients with schizophrenia and compared them with healthy controls. They found no evidence of herpesvirus DNA in the 24 psychiatric cases and the 25 normal controls. Other studies on the prevalence of herpes simplex type 1 antibodies in patients with schizophrenia have been mentioned. It seems that the results were conflicting, i.e. while several studies found increased levels of herpes simplex antibodies in schizophrenic patients, others found no differences between schizophrenics and controls.

3.2.3. Human T-cell lymphotropic virus type 1

Based on previous studies which reported an 18-fold higher incidence of schizophrenia among second-generation Afro-Caribbeans, especially in Jamaican males (Harrison *et al.* 1988, Harvey *et al.* 1990), Rodgers-Johnson *et al.*

(1996) were interested in the role of a novel virus as an aetiological agent for schizophrenia. They examined the retrovirus human T-cell lymphotropic virus type 1 (HTLV-1) as a possibility; because HTLV-1 is endemic in the Caribbean, it is known to be neuropathogenic and can be transmitted perinatally, by sexual contact, blood transfusion and intravenous drug abuse. The prevalence of HTLV-1 infection in 201 Afro-Caribbean psychiatric inpatients was compared with rates in a control hospital population and rates in the healthy Jamaican population. The prevalence was 10% in psychiatric patients and 7% in the control hospital population; the prevalence in the Jamaican population ranged from 1.7% to 17.4% depending on age, gender and social class. The results did not support an aetiological relationship between HTLV-1 and schizophrenia.

3.2.4. Borna disease virus

Taieb *et al.* (2001) reviewed 17 studies using serologic tests or polymerase chain reaction to detect Borna disease virus (BDV) in psychiatric patients. Most studies have sought BDV infection markers in patients with schizophrenia and mood disorders, but BDV may also be involved in other disorders such as autism. The reviewed data supported the assumption that BDV can infect humans and persist in the CNS. While some studies showed an increased prevalence of BDV in psychiatric samples, the contribution of BDV to the physiopathology of mental disorders is not proven by this association. They concluded that further research on the association of schizophrenia and Borna disease virus is warranted.

3.2.5. Human immunodeficiency virus

The association between serious mental illness and human immunodeficiency virus (HIV) serum positivity is well studied. A number of reviews on the prevalence of HIV in mental disorders are available (Cournos and McKinnon 1997, Gottesman and Groome 1997, Grassi 1996, Sewell 1996). Table 3.1 summarizes the results of these reviews as supplemented by further trials identified by our search. The prevalence of HIV among people with serious mental disorders varied quite substantially within a range of 1.30% to 22.9%. In contrast, the latest reported prevalence estimation of HIV in the general population of North America was 0.4% (World Health Organization 2004).

Although evidence clearly shows that rates of HIV infection are increased in schizophrenia, a number of methodological issues require a comment. A first problem is that many studies considered psychiatric patients in general so that those with a primary diagnosis of intravenous substance abuse were not excluded and may have increased the perceived risk. Almost no study exclusively examined the prevalence of HIV in schizophrenia. However, after schizophrenia has been differentiated from rates among other psychotic disorders, no significant differences emerge (Wainberg *et al.* 2003).