

Table 1. Positive and Negative Medical Comorbidities in Several Complex Disorders^a

Disorder	Positive Comorbidities	Negative Comorbidities
Schizophrenia	Cardiovascular diseases, hypothyroidism, diabetes, HIV infection, hepatitis, overweight, sexual dysfunction, altered pain sensitivity, middle ear disease, irritable bowel syndrome, acute intermittent porphyry, pulmonary infection, colon cancer	Lung and prostate cancer, rheumatoid arthritis
Bipolar disorder	Neck/back/spine problems, arthritis, stomach problems, migraines, cancer	Lymphoma, metastatic cancer
Depression	Diabetes, gastrointestinal diseases, stroke, musculoskeletal diseases, Parkinson's disease, obesity, migraines, arthritis	
Multiple sclerosis	Ulcerative colitis, Crohn disease	Rheumatoid arthritis, temporal arteritis
Diabetes	Type 1: celiac disease, Down syndrome, Addison syndrome, multiple sclerosis Type 2: non-Hodgkin lymphoma, psoriasis, Crohn disease	Type 1: Hodgkin lymphoma Types 1 and 2: prostate cancer
Metabolic syndrome		Prostate cancer

^aData were identified by a systematic review using the MEDLINE database, supplemented with a manual search of reference lists. The diagnostic terms *schizophrenia*, *bipolar disorder* or *manic-depression*, *depression*, *diabetes*, and *multiple sclerosis* were combined with keywords indicating a population-based register study.

Abbreviation: HIV = human immunodeficiency virus.

First, although a number of clinical and social factors probably account for the excess of comorbid somatic illnesses in patients with severe mental disorders (eg, symptoms, medication, lifestyle, and limited access to health care services), associations may also be partly due to specific biologic overlaps at the genetic and molecular level between disorders that at first instance are considered to be distinct. For example, underlying genetic vulnerabilities may explain the comorbidities of asthma with mental disorders² or migraine with other conditions such as endometriosis.^{3,4}

Second, in contrast with co-occurrence, few population-based studies have explored in detail the “negative” or “inverse” comorbidity in psychiatric and medical disorders (ie, a lower than expected probability of occurrence of diseases) (Table 1). It is intriguing that 2 rigorous population-based studies^{5,6} and the first meta-analysis of cancer incidence rates⁷ found a significantly lower risk of respiratory and prostate cancer in people with schizophrenia and their relatives compared with people without schizophrenia after adjusting for confounding variables. Moreover, schizophrenia is associated with tobacco smoking, the most studied risk factor for lung cancer. Lung and prostate cancers are associated with the highest numbers of deaths from cancer around the world, according to the World Health Organization.⁸ Although alternative explanations may be invoked (ie, biases arising from difficulties in adjusting for confounders or competing risks, cancer-protective effect of antipsychotic medications, obstetric complications, and lifestyle differences), we propose that the genetic predisposition toward schizophrenia might confer genetically reduced susceptibility to lung and prostate cancer.⁹ This is akin to the observation that individuals with young-adult-onset Hodgkin lymphoma are less likely to have a personal or family history of diabetes mellitus. Another finding is the reduced occurrence of rheumatoid arthritis in people with schizophrenia and in people with multiple sclerosis.

Comorbidity represents a significant opportunity to understand the biologic connections among disorders. Moreover, epidemiologic data suggest that negative comorbidity may be a valuable model for investigating common or related pathways or processes and testing new therapies. In fact, modulation of the dopaminergic system has been suggested as a new target for cancer therapy.¹⁰

The Importance of Negative Comorbidity

To the Editor: In their article “Comorbid Somatic Illnesses in Patients With Severe Mental Disorders: Clinical, Policy, and Research Challenges,” Fleischhacker et al¹ describe a plan of action to increase collaboration between Psychiatry and Medicine based on the fact that there are many patients with severe mental illnesses such as schizophrenia, depression, and bipolar disorder who have poor physical health and, consequently, a short life expectancy. The publication of the article signals opportunities for discussion. In this respect, we would like to make 2 contributions.

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