Epidemiology of Psychiatric Disorders

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W. Ahrens, I. Pigeot (eds.) *Handbook of Epidemiology, 2nd edition*,
DOI 10.1007/978-0-387-09834-0_64,

59.1 Introduction

59.1.1 History of Psychiatric Epidemiology

The history of epidemiological approaches to the study of mental illness spans over 150 years. A classic paper by Dohrenwend and Dohrenwend (1982) proposed the division of psychiatric epidemiological studies into three time periods: first generation, second generation, and third generation. First-generation studies were those conducted from the end of the nineteenth century through the first half of the twentieth century. These studies relied mainly on official records and key informants to identify persons with mental disorders and, accordingly, were limited by a lack of clear operational criteria for the classification and assessment of psychiatric conditions. Although the Dohrenwends were mainly discussing prevalence studies, the historical division into these three generations is used here to describe a broader range of studies.

The first study that attempted to quantify mental illness for public health purposes was conducted in Massachusetts in 1855 by Edward Jarvis (1971). Jarvis located cases with mental disorders through the use of key informants, for instance, general practitioners and hospital records. He identified 2,632 "lunatics" and 1,087 "idiots" and analyzed the data according to demographic variables such as sex, place of birth, and economic status. A more comprehensive study was done by Arthur Mitchell in Scotland later in the nineteenth century (Susser et al. 2010).

Later in this "first generation," a landmark series of studies were led by Goldberger and Sydenstricker in the 1920s. These studies demonstrated the association between nutritional deficiency and the presence of psychosis secondary to pellagra and, moreover, went on to describe how the ecology and social inequalities of mill towns in Southern states fostered this type of nutritional deficiency (Terris 1964). In a subsequent major study of this time period, Faris and Dunham examined the geographical distribution of psychiatric patient hospitalizations in Chicago from 1922 to 1934. They found that admissions for schizophrenia were related to the ecology of urban and suburban areas, typically with higher rates reported in urban areas (Faris 1939).

During this initial period, there was also growing interest in the role of social factors in the etiology of psychiatric disorders. This idea was first introduced in the foundational work of the French scientist Émile Durkheim. In the classic text *"Le Suicide,"* published in 1897, Durkheim sought to explore the social correlates of suicide (Durkheim 1951). He explored the roles of social isolation and control among different groups and concluded that the higher rates of suicide observed among Protestants compared to Catholics and Jews and among single persons as compared to married, resulted from social isolation and deficits in social control.

In regard to prevalence, in the Dohrenwends' review of first-generation studies, they found a median prevalence rate for any psychiatric disorder of around 3.6%. These low rates, as compared to future studies, are likely due to major changes in

nomenclature following World War II that broadened the definition of mental disorders, resulting in higher prevalence rates (Dohrenwend and Dohrenwend 1982).

The second generation of psychiatric epidemiological studies occurred after World War II. The community became the focus of renewed attention for both the field of psychiatry and policy makers. Several factors occurred before, during and after the war that played a role in the development of a new complement of epidemiological studies. In World War II, the diagnosis of a psychiatric disorder was the leading cause of men being rejected from military service, and after the war, more than half of all hospital beds were occupied by patients with mental conditions (Tohen et al. 2000). The National Mental Health Act of 1946 initiated a cascade of funding for psychiatric education and research that resulted in the establishment of the National Institute of Mental Health (NIMH) in 1949 and financial support for epidemiological research in service of community psychiatry.

Major improvements occurred in the second-generation psychiatric epidemiological studies: mainly (1) that study participants were interviewed directly and (2) that well-defined, large populations were studied. However, these studies continued to be limited by some of the challenges of the first-generation studies, specifically, the lack of structured diagnostic instruments and an often unclear definition of diagnostic criteria (Tohen et al. 2000). Several well-known population-based studies were conducted during this period – most notably the Midtown Manhattan (Srole et al. 1962) and Stirling County (Leighton et al. 1963) studies. Both of these used highly trained non-professional interviewers to conduct standardized interviews with study participants. This second generation of studies also began to utilize more objective measures of psychopathology as opposed to clinical judgments. The measure most often used was a 22-item questionnaire called the Langner Index developed in connection with the Midtown Manhattan Study (Langner 1962). It is widely regarded as an index of psychophysiological symptomatology and general malaise (Seiler 1973). For purposes of epidemiological studies, the questionnaire is a non-specific measure of psychological distress (Dohrenwend and Dohrenwend 1982) and did not generate psychiatric diagnoses. The Midtown Manhattan Study, initiated in 1954, had three primary objectives: to canvass the community for variations in mental health, to examine sociocultural determinants of mental health, and to establish the need for psychiatric services in the community. The Midtown Manhattan Study examined mental health in 1,660 adults culled from 1,911 Midtown dwellings, selected as a probability sample. Investigators, comprising psychiatrists and social scientists, devised a composite classification of mental health, which they called the Global Judgment of Mental Health. By and large, the same approach and set of methods employed by the Midtown Manhattan Study were used in the non-urban context of Stirling County, Nova Scotia, conducted in 1952.

These two studies reflected the recognition that the local context influenced the occurrence, expression and distribution of psychopathology – a hallmark of early epidemiological studies informing community psychiatry. The results of the Midtown Manhattan Study estimated that over 80% of those surveyed had some form of current psychopathology. However, only a quarter (23.4%) were

classified as impaired, signifying the presence of marked, severe, or incapacitating symptoms – mostly anxiety. Moreover, about three quarters of those who were impaired had never sought help for their symptoms (Srole et al. 1962). In Stirling County, lifetime prevalence of any DSM-I (first edition of Diagnostic and Statistical Manual: Mental Disorders) mental disorder was about 20% (Leighton et al. 1963).

Clinical studies were also conducted during this second generation of epidemiological research. Unlike population-based studies, which surveyed community participants, these studies investigated treated populations. For example, one classic clinical study (Hollingshead and Redlich 1958) investigated the association between social class and mental illness among patients in New Haven, Connecticut, and reported higher rates of psychopathology among patients of lower social class and differences in the type of treatment received by social class. A landmark clinical study by Tsuang and Dempsey (1979) used a historical cohort design to compare patients with a diagnosed mental disorder to a surgical control group on various outcomes including patients, marital, residential, occupational, and psychiatric status. They found that, after a 30- to 40-year follow-up, patients with psychiatric disorders had worse outcomes, specifically those with schizophrenia.

The first- and second-generation studies had an important impact on the field of psychiatric epidemiology. They showed that mental illness was a substantial public health problem, that treatment service availability was lacking, and that the prevalence of psychiatric disorders varied consistently by gender, socioeconomic status, and locale (urban vs. rural) (Dohrenwend 1997). However, these studies suffered from design limitations, most notably the lack of reliable and valid assessment tools to identify cases, which impeded the quest for data on the distribution of mental disorders and potential causal factors (Tohen et al. 2000).

The third generation of epidemiological studies was marked by the development of standardized measures of mental disorders. In the late 1980s the NIMH Diagnostic Interview Schedule (DIS), a lay-administered, standardized diagnostic interview, was developed for use in the Epidemiological Catchment Area (ECA) Study (discussed in more detail below). Subsequently, a similar instrument, the Composite International Diagnostic Interview (CIDI), was used in the National Comorbidity Study (NCS) (discussed in more detail below). The creation of structured diagnostic interview instruments allowed for the reliable estimation of the prevalence of mental disorders (Tohen et al. 2000). This was the single most important contribution of the third-generation studies and resulted in the two largest population-based studies on psychiatric disorders conducted in the USA, the ECA and NCS. (Similar developments outside of the United States are discussed below.) In addition to estimates of the current prevalence of mental disorders, these instruments also collected data on lifetime prevalence and risk factors. Short-term follow-up interviews of samples from the ECA have subsequently been conducted to provide estimates of incidence (Dohrenwend 1997). These studies also examined utilization of health services, confirming prior reports that the majority of persons with mental disorders do not receive adequate treatment. The development of more

accurate diagnostic instruments and symptom scales in the third generation has also resulted in better research into the natural history of psychiatric disorders (Tohen et al. 2000). For instance, the Suffolk County Study (Bromet et al. 1992) provided new insights on the time of onset of schizophrenia. And the NIMH Collaborative Depression Study focused on recovery and relapse in major depressive disorder and bipolar disorder (Keller et al. 1992, 1993).

While the above focuses on epidemiological studies in North America, similar studies have been conducted in other regions of the world. Examples include those conducted in Taiwan (Hwu et al. 1989), Brazil (Almeida-Filho et al. 1997), and India (Mehta et al. 1985). In the 1960s, the International Pilot Study of Schizophrenia (IPSS), sponsored by the World Health Organization (WHO), set out to determine if it was feasible to engage in large-scale epidemiological research of psychiatric disorders, specifically schizophrenia, with comparable methods across different contexts, and to determine what, if any, differences existed in the incidence of schizophrenia across contexts (Sartorius et al. 1974). Indeed, the IPSS, which included 1,202 participants in its initial assessment, showed that this type of study was feasible. The IPSS also demonstrated that when schizophrenia was defined as a construct with extensively tested instruments, rates were fairly consistent across contexts and nations (Sartorius et al. 1974).

Later, the WHO sponsored the Determinants of Severe Mental Disorders (DOSMeD), also known as the Ten-Country Study, which built on the work of the IPSS to study the variation in incidence and course of severe mental illness, particularly schizophrenia, across countries and cultures. The DOSMeD included sites in Denmark, India, Colombia, Ireland, the USA, Nigeria, the USSR, Japan, the United Kingdom, and the Czech Republic. The study showed that the prevalence of schizophrenia was fairly constant across countries and that schizophrenia had a better course in developing versus developed countries over a period of 2 years (Jablensky et al. 1992), which gave rise to a long debate over potential factual and artifactual explanations for these findings (Hopper and Wanderling 2000).

With recent advances in neuroscience, brain imaging, genetics, and other related fields, it is fair to say that the field of psychiatric epidemiology has, in the past decade or so, entered a new fourth generation of discovery. This includes new study designs (including family, sibling, high-risk designs, and others), new statistical methods, new diagnostic assessment techniques, and an array of new approaches to assess exposures that may reflect potential causes and mechanisms resulting in mental disorder.

59.1.2 Overview of the Chapter

In this chapter, we summarize in considerable detail what we view as both some of the major achievements of the generation of epidemiological research recently completed (e.g., the third generation of community prevalence studies) and highlight some of the exciting new approaches currently under investigation with the present

generation of research. We start with a general description of the major classes of psychiatric disorders, the major classification systems used to diagnose these conditions, and summary statements regarding the global burden of mental illness. We then summarize major work in the USA and abroad on the prevalence and distribution of major psychiatric disorders and highlight two particular conditions (autism and schizophrenia) to demonstrate some of the approaches and discoveries from the current era of psychiatric epidemiology.

59.2 Overview of Major Mental Disorders

While there has been considerable change and refinement in the taxonomy and nosology of mental disorders, there is general consensus on the major categories of conditions studied in psychiatric epidemiology.

Psychotic Disorders are among the most debilitating and persistent diseases in humans. These disorders include schizophrenia, schizoaffective disorder, psychotic depression, bipolar disorder with psychotic features, and delusional disorder. Schizophrenia is the most common of the psychotic disorders and is characterized by a breakdown of thought processes and by poor emotional responsiveness. It commonly manifests as auditory hallucinations, paranoid or bizarre delusions, disorganized speech and thinking, and is accompanied by significant social or occupational dysfunction.

Mood Disorders are characterized by a disturbance in the regulation of mood, behavior, and affect. Major mood disorders include depressive disorders and bipolar disorder. One of the more common mood disorders is major depression, defined as a persistent period of dysphoric mood or loss of interest or pleasure, along with other symptoms. Bipolar disorder (also known as manic depressive illness) is a cyclical mood disorder in which episodes of major depression are interspersed with episodes of mania or hypomania.

Anxiety Disorders are disorders characterized by abnormal and pathological fear and anxiety. Anxiety disorders include generalized anxiety disorder, phobic disorders, and panic disorder. Generalized anxiety disorder is characterized by unrealistic or excessive anxiety and worry. A phobia is defined as an irrational fear that produces a conscious avoidance of the feared subject, activity, or situation. And panic disorder is a type of anxiety disorder characterized by recurring, unexpected panic attacks.

Personality Disorders are defined as inflexible and maladaptive personality traits that cause either substantial functional impairment or subjective distress. They are conceptualized as long-term characteristics of individuals that are likely to be evident by adolescence and continue throughout adulthood.

59.2.1 Refinements in the Definition and Classification of Mental Disorders: Growth of the Diagnostic and Statistical Manual of Mental Disorders (DSM) and International Classification of Diseases (ICD)

The goal of psychiatric epidemiology is to systematically study the distribution and determinants of psychiatric disorders in the population. This goal can only be obtained if there is a classification system that allows for a standardized method of collecting data on psychiatric disorders. This goal was advanced when the World Health Organization (WHO) published the sixth edition of *International Classification of Diseases* (ICD) in 1949, which included mental disorders for the first time. The American Psychiatric Association Committee on Nomenclature and Statistics developed a variant of the ICD-6 that was published in 1952, the first edition of the *Diagnostic and Statistical Manual: Mental Disorders* (DSM-I). The purpose of DSM-I was to create a common nomenclature based on a consensus of the contemporary knowledge about psychiatric disorders. These developments came in the post-World War II era (or "second generation" of psychiatric epidemiology research) to better incorporate the outpatient presentations of servicemen and veterans. DSM-I included three categories of psychopathology and was the first official manual of mental disorders to focus on clinical utility. The manual was developed to be both useful to those who diagnose and treat patients with mental illness and to provide a statistical classification to facilitate the collection of statistics on mental disorders. DSM-II was published in 1968 and had 11 major diagnostic categories and 185 diagnoses. DSM-I and DSM-II included only brief definitions of disorders which were not sufficiently operationalized to allow for reliable diagnostic judgments.

DSM-III, published in 1980, improved on previous editions by applying a descriptive approach and including diagnostic criteria. It included 265 diagnoses. The explicit diagnostic criteria in DSM-III provided the foundation for measurement of mental disorders at the population level (Eaton 2012). The emphasis on descriptive features of disorders, generally without regard for presumed etiology, allowed DSM-III to be largely embraced across disciplines. DSM-IV was published in 1994 and included 365 diagnoses. A major revision from previous versions was the inclusion of a clinical significance criterion to many of the categories, which required that symptoms cause "clinically significant distress or impairment in social, occupational, or other important areas of functioning."

A major component of psychiatric epidemiology studies is accurate psychiatric diagnosis of a clearly defined study population. Determining the prevalence of mental illness in a population requires reliable well-operationalized definitions of the disorders. There are three aspects of the DSM that have proved most valuable in the field of psychiatric epidemiology. First is the widespread acceptance of the DSM across psychiatry and related fields. This has enabled a common language for classifying mental disorders allowing for comparisons of data across studies. Second is the use of symptomatic descriptions in the DSM rather than hypothesized etiological assumptions. And third is the provision of operationalized definitions.

The introduction of DSM-III in 1980 and the subsequent development of a fully structured diagnostic interview based on it, the Diagnostic Interview Schedule (Robins et al. 1981), were critical to major population-level epidemiological studies.

One of the main questions in psychiatric epidemiology is whether the prevalence of mental disorders has been increasing over time. We have seen a clear increase in the number of persons meeting criteria for mental disorders, but this does not prove that the prevalence is increasing, as this may be due to changes in diagnostic criteria. Specifically, the DSM has expanded and the number of disorders has increased over time, which may result in an increased number of persons meeting criteria for psychiatric disorders. Researchers have questioned whether the DSM criteria are too inclusive such that we are diagnosing people with mild severity, which may not have clinical utility. This is one of the reasons that DSM-IV requires the presence of clinically significant distress or impairment to qualify for a diagnosis. As we move into the current, fourth generation of psychiatric epidemiology, there are plans for dramatic modifications to prior classification systems – both dimensional approaches based on presumed neurocognitive substrates which may cut across current diagnoses, as well as new categorical diagnoses based more on empirical data than clinical consensus.

59.2.2 Public Health Burden of Mental Disorders

Research has shown that mental disorders have a high public health burden. A global study by the World Health Organization (WHO), the so-called World Mental Health (WMH) Survey, estimated the prevalence, severity, and treatment of DSM-IV mental disorders in 14 countries (Demyttenaere et al. 2004). The findings showed a consistently high overall prevalence of mental disorders across the globe. The Global Burden of Disease (GBD) Study (Murray and Lopez 1996) found that mental disorders were responsible for 21% of the total disease burden in the world. Mental disorders ranked almost as high as cardiovascular diseases and respiratory diseases, and surpassed all different types of cancer and HIV, in Disability Adjusted Life Years (DALYs) (Ustun 1999). Specifically, depression was the fourth leading cause of disease burden, accounting for 4.4% of total DALYs (Ustun et al. 2004). Depression was reported to cause the largest amount of non-fatal burden, accounting for almost 12% of all total years lived with disability worldwide. Furthermore, WHO has projected that depression will be the second leading cause of disability by the year 2020. The DALYs are particularly high for mental disorders in part because these are non-fatal conditions of long duration, most of which have their onsets in childhood or young adulthood (Eaton 2012).

The European Study of the Epidemiology of Mental Disorders (ESEMeD) examined the impact of mental and physical disorders on work role disability and quality of life in six European countries (Alonso et al. 2004). The study showed that in each country, mental disorders resulted in loss of work and loss of quality of life.

The results suggested that mental disorders are important determinants of work role disability and quality of life, often having a greater impact than chronic physical disorders.

Studies have also shown the high cost of mental illness to individuals and society. Kessler and colleagues (2008) found that respondents with a serious mental illness in the past 12 months had earnings averaging $16,306 less than those without a mental illness, for a societal-level total of $193.2 billion. The authors used statistical modeling to show that the mean expected annual earnings of respondents with a serious mental illness in the absence of that illness were estimated at $38,851 compared to the mean observed earnings of $22,545. This difference, of approximately $16,000 (or 42%), is the estimated mean impact of serious mental illness on earnings. This study provides evidence that mental disorders are associated with substantial societal-level impairments that should be taken into consideration when making decisions about the allocation of treatment and research resources.

59.3 Summary of Findings from Major Population-Based Studies of Mental Illness

59.3.1 Major Epidemiological Studies of Psychiatric Disorder Among Adults

A number of major psychiatric epidemiological studies from the late twentieth century have helped establish methods for contemporary psychiatric epidemiology. Two classic studies in the USA include the Epidemiological Catchment Area (ECA) study and the National Comorbidity Survey (NCS). The ECA and NCS, discussed in more detail below, used reliable lay-administered structured diagnostic assessments to obtain standardized diagnostic criteria based on the DSM. The studies also compared clinical interviews with lay interviews to evaluate diagnostic validity and used advanced sampling strategies to identify nationally representative samples.

The Epidemiological Catchment Area (ECA) Study was initiated in response to the 1977 Report of the President's Commission on Mental Health, which described the state of American mental health research and services (Grob 2005). NIMH needed to provide descriptive psychiatric epidemiological data to the President's Commission, since the clinical picture of community mental health was incomplete (Regier et al 1978; Robins 1978). The ECA, therefore, sought to address the gaps identified in the President's commission report (Robins and Regier 1991).

The ECA, which commenced in 1980, was a collaborative effort between NIMH and a group of established psychiatric epidemiologists that surveyed the prevalence of mental disorders and service need and use in five US communities that had been designated Community Mental Health Center catchment areas – Baltimore, New Haven, St. Louis, Durham, and Los Angeles. Each site collected data on a common set of core questions and sample characteristics and sampled over 3,000

community residents and 500 institutionalized residents. Together, the 5-site ECA collected diagnostic service need and use data on 20,861 adults, aged 18 and over. An important innovation of the ECA was the use of a fully structured research diagnostic interview known as the Diagnostic Interview Schedule (DIS), which was shown to yield reliable and valid diagnoses of mental disorders (Helzer et al. 1985).

The ECA was the first study to document the prevalence of DSM-III disorders. While the ECA determined the epidemiological burden and service use patterns in these five communities, it also provided the indices of success of community-based treatment programs for mental illness. The ECA was critical in determining the prevalence of specific psychiatric disorders, as well as service needs and use patterns in the five communities studied. The rich information provided by the study once again supported the notion that services were inadequate relative to need; under 20% of respondents with recent mental disorders accessed services in the year prior to study participation (Robins and Regier 1991; Regier et al. 1993a). However, because the samples in the ECA were not collected to be nationally representative, there was an imperative to address epidemiological gaps regarding the prevalence and distribution of psychiatric disorders throughout the United States. Moreover, the ECA could only provide basic information regarding the comorbidity of psychiatric disorders; it was therefore necessary to determine patterns of comorbidity and the complexities of the affiliated need for services and their use.

Some of the limitations of the ECA influenced considerably the origins of the *National Comorbidity Survey (NCS)*, a truly national study of the prevalence, causes, and consequences of comorbidity between psychiatric and substance use disorders (Kessler 1994). The NCS, which began in 1990, was the first nationally representative survey of mental and substance use disorders in the United States. This study developed a new measure, the Composite International Diagnostic Interview (CIDI), to determine the prevalence and correlates of DSM-III-R (Diagnostic and Statistical Manual of Mental Disorders, third and revised edition) disorders in a nationally representative sample of 8,098 individuals, aged 18–54. The NCS was a face-to-face household survey.

The NCS found that DSM-III-R disorders are more prevalent than previously thought. The prevalence estimates of lay-administered CIDI-diagnosed psychiatric disorders were higher than those reported by the ECA, with the exception of psychotic disorders and lifetime anxiety disorders. Like the ECA, the NCS reported underuse of mental health services – about 13% of respondents accessed outpatient services in the prior 12 months. One of the most striking findings of the NCS indicated a problem with "met unneed" – that is, people with low levels of need had a higher probability of accessing treatment (Kessler et al. 1997; Mojtabai et al. 2002), with implications for policies affecting the distribution of community-based mental health services.

Similar prevalences of DSM-IV disorders and service use patterns were observed in the *NCS Replication Study (NCS-R)*, conducted about a decade later in 2001–2002 with a nationally representative sample of 9,282 respondents, aged 18–54 (Kessler et al. 2005a, b). Harkening to the results of the Midtown Manhattan Study, 26.2% of respondents reported a past-year psychiatric disorder; nearly a quarter of those with a past-year psychiatric disorder were classified as serious (Kessler et al. 2005b).

Significant unmet need for services was observed in the NCS-R; nearly 60% of those endorsing a serious past-year psychiatric disorder remained untreated (Kessler et al. 2001).

Among other large-scale epidemiological efforts, *The National Epidemiological Survey on Alcohol and Related Conditions (NESARC)* was a nationally representative United States sample of 43,093 adults aged 18 or older conducted in 2001–2002 by the National Institute on Alcohol Abuse and Alcoholism (NIAAA) (Grant et al. 2004). This face-to-face household survey demonstrated a high degree of comorbidity between DSM-IV substance use disorders and mood and anxiety disorders.

The National Longitudinal Alcohol Epidemiological Survey (NLAES) was a nationally representative household study conducted in the United States in 1992 sponsored by NIAAA (Grant and Harford 1995). The survey consisted of face-to-face interviews with 42,862 respondents aged 18 or older. DSM-IV diagnoses were made using the Alcohol Use Disorders and Associated Disabilities Interview Schedule (AUDADIS), a fully structured psychiatric interview administered by lay interviewers. The AUDADIS was designed to determine diagnoses of alcohol abuse and dependence over the course of the previous year or over a person's lifetime, other drug use and associated disorders, and the incidence of major depression.

The Christchurch Psychiatric Epidemiology Study (Oakley-Browne et al. 1989) was conducted in 1986 as a random survey of 1,498 adults aged 18–64 years living in the Christchurch area of New Zealand. The Diagnostic Interview Schedule (DIS) was used to make DSM-III diagnoses through in-person interviews. The study used similar methods as the NIMH ECA study to allow for comparisons.

A well-known prospective, longitudinal study is the *Dunedin Multidisciplinary Health and Development Study* which has followed 1,037 babies born in Dunedin, New Zealand, between 1972 and 1973 from birth until age 38 (Silva 1990). The study has very high retention rates (96%) and has collected a wealth of information on physical and mental health across the life span, including estimates of the prevalence and incidence of psychiatric disorders from childhood through adulthood (Newman et al. 1996).

These epidemiological studies provided valuable information on the occurrence of mental disorders. All of the studies revealed that psychiatric disorders are highly prevalent in the general population, with onset often beginning in early life and with subsequent high rates of comorbidity (Insel and Fenton 2005). There is also evidence that prevalence rates may be considerably higher than reported in many prior studies. Specifically, lifetime prevalence rates have been shown to be much greater in prospective versus retrospective studies, suggesting that asking participants to recall if they have ever experienced mental disorder symptoms leads to an under-reporting (Moffitt et al. 2010). Given that most of the information about lifetime prevalence of psychiatric disorders comes from retrospective surveys, mental disorders may be far more common than previously thought (Susser and Shrout 2010).

Importantly, the high prevalence of mental disorders found in these studies led to questions about the severity of the conditions diagnosed. More recent studies have attempted to address this concern by examining the severity of diagnosed conditions.

Table 59.1 Prevalence estimates from major psychiatric epidemiology surveys in adult populations

	Study							
	ECA	NCS	NCS-R	Christchurch	NESARC	NLAES	Dunedin	World Mental Health Surveys
Any Disorder								
12 months	28.1	29.5	26.2	31.3	–	–	–	–
Lifetime	43.7	48.0	46.4	50.7	–	–	–	–
Anxiety Disorders								
12 months	11.8	17.2	18.1	9.1	11.1	–	22.8	2.4–18.2
Lifetime	19.2	24.9	28.8	10.5	–	–	49.5	4.8–31.0
Mood Disorders								
12 months	10.1	11.3	9.5	10.4	9.2	3.3	16.7	0.8–19.6
Lifetime	14.9	19.3	20.8	14.7	–	9.9	41.4	3.3–21.4
Psychotic Disorders								
12 months	1.1	0.5	–	0.2	–	–	–	–
Lifetime	1.4	0.7	–	0.4	–	–	–	–

Abbreviations: ECA, Epidemiological Catchment Area Study; NCS, National Comorbidity Survey; NCS-R, National Comorbidity Replication Survey; Christchurch, Christchurch Psychiatric Epidemiology Study; NESARC, National Epidemiological Survey on Alcohol and Related Conditions; NLAES, National Longitudinal Alcohol Epidemiological Survey; Dunedin, Dunedin Multidisciplinary Health and Development Study.

Notes: NLAES mood disorder includes major depression only; Dunedin mood disorder includes depression only. ECA and Christchurch psychotic disorders refer to schizophrenia/schizophreniform disorders only.

The values presented for the World Mental Health Surveys represent the range of prevalence estimates across the 14 countries studied.

For example, findings from the NCS-R showed that 22.3% of individuals with a disorder in the past 12 months were reported to be "serious," 37.3% were reported to be "moderate," and 40.4% mild (Kessler et al. 2005b). These results suggest that over half of diagnosed cases of mental illness are moderate or severe, but a substantial portion are mild.

59.3.2 Prevalence and Incidence of Major Adult Psychiatric Disorders

The major epidemiological studies discussed above have provided a wealth of information on the prevalence and incidence of psychiatric disorders in the general adult population. While recent developments in the field have moved far ahead in insights regarding risk factors, causes, and mechanisms related to the etiology of these disorders, it is valuable to summarize some of these foundational elements of the field of psychiatric epidemiology. Table 59.1 provides a summary of the

prevalence estimates described below – some of the major products of the "third generation" of psychiatric epidemiology research.

Any Disorder The prevalence of any psychiatric disorder provides information on the overall burden of mental disease in the population. Prevalence estimates have been consistently high across studies. The ECA reported a 12-month prevalence of 28.1%. The NCS and NCS-R reported similar 12-month estimates at 29.5% and 26.2%, respectively. The Christchurch study reported somewhat higher rates with 31.3% of the respondents having any disorder in the past 12 months. Lifetime prevalence of any disorder is also high, with approximately half of the respondents reporting a lifetime disorder (48% in the NCS, 46.4% in the NCS-R, and 50.7% in the Christchurch study). The NCS-R also found that psychiatric disorders generally had an early onset with half of all cases reporting onset by age 14 and three quarters by age 24.

Anxiety Disorders Anxiety disorders are the most common group of disorders to occur in the general population. The ECA, NCS, and NCS-R all showed anxiety disorders to be more prevalent than mood disorders. The ECA found that 11.8% of the respondents had an anxiety disorder diagnosis in the past 12 months. Estimates in the NCS and NCS-R were similar with 12-month rates of 17.2% and 18.1%, respectively. The Christchurch study reported somewhat lower estimates of 9.1% for past 12-month diagnoses, and the NESARC found that 11.1% of the respondents had an anxiety disorder in the past 12 months. The lifetime prevalence of anxiety disorders is around one quarter. The ECA found that lifetime diagnoses of anxiety disorders occurred in 19.2% of the respondents, the NCS found a lifetime rate of 24.9%, and the NCS-R 28.8%. The Christchurch study reported a lower estimated rate of 10.5%.

Phobias have been found to be the most common anxiety disorder. The NCS-R reported that 8.7% of the respondents reported a phobia in the past 12 months with social phobia being the most common type. The NCS-R also reported on the prevalence of panic attacks, a subtype of anxiety disorder, with a lifetime prevalence of 28.3% and 12-month prevalence of 11.2% (Kessler et al. 2006). This rate is somewhat higher than that of the NCS (7.3%).

Mood Disorders Mood disorders are the second most prevalent class of disorders. The ECA found that 10.1% of the respondents had a mood disorder diagnosis in the past 12 months. Estimates in the NCS, NCS-R, and Christchurch study were comparable at 11.3%, 9.5%, and 10.4%, respectively. The NESARC found that 9.2% of the respondents had a mood disorder in the past 12 months, while the NLAES found a considerably lower prevalence of 3.3% (which is likely due to the fact that they only measured major depression).

The ECA found that lifetime diagnoses of mood disorders occurred in 14.9% of the respondents, while estimates in the NCS and NCS-R were higher at 19.3% and 20.8%, respectively. The Christchurch study found a prevalence of 14.7% for lifetime diagnosis, and the NLAES reported that 9.9% of the respondents had a lifetime diagnosis.

Psychotic Disorders Psychotic disorders are less common than mood and anxiety disorders and are less often studied in epidemiological surveys of the general population. The ECA found a lifetime prevalence of psychotic disorders of 1.4%, while the NCS reported lower estimates at 0.7% lifetime and 0.5% in the past 12 months. The Christchurch estimates were even lower at 0.2% lifetime and 0.4% past 12 months (which is likely explained by the fact that only schizophrenia/schizophreniform disorders were diagnosed).

Comorbidity of Psychiatric Disorders The ECA was among the first studies to show how common psychiatric comorbidity of psychiatric disorders is in the general population. Over 54% of the ECA respondents with a lifetime history of a disorder were found to have a second diagnosis. Similarly the NCS found that over 50% of all lifetime disorders occurred in a small proportion of the respondents with a history of three or more comorbid psychiatric disorders (Kessler et al. 1994). And the NCS-R also found high rates of psychiatric comorbidity; nearly 30% of the people surveyed had two disorders, and almost 20% had three (Kessler et al. 2005a, b).

Sociodemographic Risk Factors for Adult Psychiatric Disorders Studies have consistently shown that women have higher rates of mood and anxiety disorders, while men have higher rates of substance use disorders (Wells et al. 1989; Kessler et al. 1994). The prevalence of most disorders has been shown to decline with age and higher socioeconomic status (Regier et al. 1993b; Kessler et al. 1994). A family history of mental illness consistently elevates the risk for psychiatric disorder (Kendler et al. 1997).

Prior studies have also shown that persons who are separated or divorced are more likely to have a psychiatric disorder than those who are married (Regier et al. 1993b; Bjorkenstam et al. 2012). For instance, the National Survey of Mental Health and Wellbeing of Adults, a random sample of adults in Australia, found that married people were the least likely to suffer from a mental disorder, while divorced and separated adults were the most prone to mood and anxiety disorders and never-married adults were the most at risk for drug and alcohol disorders (Andrews et al. 1999). The nature of this association is complicated and may vary by sex and type of mental disorder (Fox 1980). It remains unclear whether the protective effect of marriage is due to the social role of being married (social causation) or characteristics of the individuals who get married (social selection). Persons with mental disorders may be less likely to marry and more likely to divorce; and separation and divorce or the death of a spouse may adversely affect a person's mental health. A study by Bjorkenstam et al. (2012) supported both the selection hypothesis, linking healthy individuals to long and stable marriages, and the social causation hypothesis, linking the stress of recent divorce to increased psychiatric disorder for both women and men. In a study of women, Afifi et al. (2006) found that never-married mothers from the NCS were similar to married mothers in lifetime prevalence rates of mental disorders. However, separated/divorced mothers had increased odds of various disorders such as depression and anxiety, as compared to married mothers.

59.3.3 Major Epidemiological Studies of Children and Adolescents

There has also been substantial epidemiological research on the occurrence of mental disorders among children and adolescents. The global burden of mental illness in young people is significant; the WHO predicts that by 2020, childhood neuropsychiatric disorders will become one of the leading causes of morbidity, mortality, and disability among children worldwide (USDHHS 1999). This age group is also important in light of the findings that many psychiatric disorders have their onset in early life (Kessler et al. 2007). Most major epidemiological studies, such as the National Comorbidity Survey Replication (NCS-R), indicate that many individuals with mental illness report onset of their disorders in adolescence or early adulthood. Mental disorders, particularly if left untreated, are likely to persist into adulthood. According to the 2001 Surgeon General's Conference on Children's Mental Health, approximately 74% of 21-year olds with mental disorders had prior mental health problems. Furthermore, researchers are interested in examining early risk and protective factors for psychiatric disorders in the hopes that early intervention can reduce the burden of disease in children, adolescents, and adults. Considerable scientific ground has been covered regarding the epidemiological study of child and adolescent psychopathology in the past 30 years. Most notably, much more is now known about the measurement, community study, prevalence, and risk factors for psychiatric disorders, particularly those of older children and adolescents. Epidemiological data suggests that roughly 20% of children aged 1–18 years are in need of mental health services (Burns et al. 1995; Shaffer et al. 1996).

A number of important epidemiological studies have been conducted in child and adolescent populations. One of the first major studies was the *Isle of Wight/Inner London Borough Study* (Rutter et al. 1975). The study reported on the prevalence of psychiatric disorders, measured by parent interviews, in a sample of 10-year-old children from inner city London ($n = 1{,}689$) and the Isle of Wight ($n = 1,279$). *The Ontario Children's Study* (Offord et al. 1987) studied the 6-month prevalence of four child psychiatric disorders (conduct disorder, hyperactivity, emotional disorder, and somatization) among approximately 2,670 children 4–16 years of age residing in Ontario, Canada.

The Great Smoky Mountains Study (GSMS) was a population-based study of 1,420 children aged 9–13 years in North Carolina that began in 1992 (Costello et al. 2003). The study was a longitudinal design in which three cohorts of children were examined at age 9, 11, and 13 years at intake. The children were assessed annually through age 16 years for DSM-IV disorders using the Child and Adolescent Psychiatric Assessment (CAPA), an in-person diagnostic interview. Both parents and children were interviewed, leading to one of the major methodological challenges in the field of child psychiatric epidemiology – namely, how to treat the large number of families in which child and parent diagnostic reports are inconsistent. *The Puerto Rico Community Study* examined DSM-IV disorder in 1,886 children aged 4–17 years using the Diagnostic Interview Schedule for Children (DISC) (Canino et al. 2004).

The National Comorbidity Survey Adolescent Supplement (NCS-A) (Merikangas et al. 2009b) was a nationally representative face-to-face survey of 10,148 adolescents aged 13–18 years in the United States conducted from 2001 to 2004. The purpose of the survey was to provide the first nationally representative estimates of the prevalence, correlates, and risk and protective factors of mental disorders in US adolescents. DSM-IV diagnoses were made based on a modified version of the Composite International Diagnostic Interview (CIDI), a fully structured research diagnostic in-person interview designed for use by trained lay interviewers. In addition to in-person interviews with adolescents, there was also a parent self-report questionnaire.

59.3.4 Prevalence and Incidence of Major Child and Adolescent Psychiatric Disorders

As discussed previously, psychiatric disorders among children and adolescents are widespread. Previous summaries of the prevalence of mental disorders in population surveys of US youth conclude that about one out of every four youth meet criteria for a DSM disorder (Costello et al. 2004). A review by Merikangas et al. (2009a) found that about one third of youth experience a mental disorder in their lifetime; and fewer than half with a current disorder receive mental health treatment (Merikangas et al. 2009a). Angold and Costello (1995) summarized findings from previous studies and found that the 6-month prevalence rate for any psychiatric disorder ranged from 17% to 27%. The most common forms of psychopathology were anxiety disorders, behavior disorders, and mood disorders, in that order.

In a review of 52 studies of psychopathology in children and adolescents, Roberts et al. (1998) found that prevalence estimates of psychopathology ranged from 1% to nearly 51%, with a mean prevalence of any mental disorder of 15.8%. In a similar review by Costello et al. (2005), the median prevalence estimate of psychiatric disorders was 12%. Importantly, the authors noted that disorders that often appear first in childhood or adolescence are among those ranked highest in the World Health Organization's estimates of the global burden of disease.

The Ontario Children's Study found that among children 4–16 years of age, the 6-month prevalence rate of any disorder was 18.1%. The Quebec Child Mental Health Survey (QCMHS) was conducted in 1992 on a representative sample of 2,400 children and adolescents aged 6–14 years in Quebec (Breton et al. 1999). The 6-month prevalence of any disorder was 19.9% according to parent report and 15.8% according child report. The rates of one or more anxiety disorders ranged from 58% to 17.5%, while rates of depressive disorders ranged from 1.1% to 3.5%.

The GSMS found a 3-month prevalence of any disorder of 13.3%; but by age 16 years, 36.7% (lifetime prevalence) of children had met DSM-IV criteria for one or more disorders. The authors concluded that while the proportion of children with a diagnosis at a given time was small, almost three times this number had one or more disorders over the entire study period suggesting that cross-sectional studies may underestimate the prevalence of psychiatric disorders among children.

Furthermore, 25.5% of children with a mental disorder diagnosis had two or more conditions. There was significant comorbidity among the behavioral disorders and between anxiety and depression. In particular, there was a strong association between oppositional defiant disorder and depression, and depression and anxiety.

The Puerto Rico Community Study found that 16.4% of children aged 4–17 years had a DSM-IV diagnosis in the past year. The most prevalent disorder was attention deficit/hyperactivity disorder (ADHD) occurring in 8% of children. They also found that 6.9% of children had an anxiety disorder and 3.4% of children had a depressive disorder.

The NCS-A showed high rates of mental disorders among adolescents; 40% of adolescents had a DSM-IV disorder in the past year (Kessler et al. 2012) and approximately one in every 4–5 youth met criteria for a mental disorder with severe impairment across their lifetime (Merikangas et al. 2010). Anxiety disorders were found to be the most prevalent mental disorder (24.9% 12-month prevalence and 31.9% lifetime prevalence), followed by behavior disorders (16.3% 12-month prevalence and 19% lifetime prevalence) and mood disorders (10% 12-month prevalence and 14.3% lifetime prevalence). Comorbidity was common with approximately 40% of those with one class of disorder also meeting criteria for another disorder. The median age of onset was earliest for anxiety disorders (6 years), followed by 11 years for behavior disorders, and 13 years for mood disorders.

Table 59.2 provides a summary of the prevalence estimates described above.

Risk Factors for Child and Adolescent Psychiatric Disorders A number of risk factors for child and adolescent psychiatric disorders have been identified. Findings from twin and adoption studies have firmly established the contribution of genetics to the occurrence of disorders in children. However, the mechanism of inheritance is complex (State and Dykens 2000) and the heritability estimate of each childhood psychiatric disorder is typically considerably less than 100%. Psychopathology in parents has also consistently been shown to be associated with mental disorders in offspring (Angold and Costello 1995).

Variation in rates of mental disorders by sex has been observed in child and adolescent populations. Most studies have found that behavior disorders are more common in boys and depressive and anxiety disorders are more common in girls (Offord et al. 1987; Costello et al. 2003; Canino et al. 2004; Merikangas et al. 2010; Kessler et al. 2012). The GSMS found that overall psychiatric disorders were more prevalent in boys aged 9–16 years than in girls as a result of the much higher rate of conduct disorder and attention deficit-hyperactivity disorder (ADHD) in boys.

Sex differences in developmental trajectories for mental disorders have also been observed. For example, the Ontario Children's Study found that rates of emotional disorders in boys and girls were similar in the 4- to 11-year-old age group at around 10%. However, by ages 12–16 the rate had dropped to 4.9% in males but increased to 13.6% in females. With regard to depression, among preadolescents, studies have shown either no sex differences in rates of depression or even higher rates in preadolescent boys (Merikangas and Avenevoli 2002). During adolescence,

Table 59.2 Prevalence estimates from major psychiatric epidemiology surveys of child and adolescent populations

	Study				
	Great Smokey Mountain Study (GSMS)	Ontario Children's Health Study	Quebec Child Mental Health Survey (QCMHS)	The Puerto Rico Community Study	NCS-A
Age of sample	9–16 years	4–16 years	6–14 years	4–17 years	13–18 years
Any disorder					
3 months	13.3	–	–	–	–
6 months	–	18.1	15.8 (child) 19.9 (parent)	–	–
12 months	–	–	–	16.4	40.3
Lifetime	36.7	51.3	–	–	–
Mood disorder					
3 months	2.2	–	–	–	–
6 months	–	–	3.4 (child) 1.7 (parent)	–	–
12 months	–	–	–	3.4	10.0
Lifetime	–	–	–	–	14.3
Anxiety disorder					
3 months	3.4	–	–	–	–
6 months	–	–	9.1 (child) 14.7 (parent)	–	–
12 months	–	–	–	6.9	24.9
Lifetime	–	–	–	–	31.9
Behavior disorder					
3 months	7.0	–	–	–	–
6 months	–	–	–	–	–
12 months	–	–	–	11.1	16.3
Lifetime	–	–	–	–	19.1

Abbreviations: NCS-A, National Comorbidity Survey Adolescent Supplement.
In the QCHMS, 'child' refers to diagnosis based on child report and 'parent' refers to diagnosis based on parent report.

however, rates of depression are higher among girls than boys (Cohen et al. 1993; Kessler and Walters 1998).

Overall psychiatric disorders have been shown to become more prevalent as children age. The NCS-A found that the lifetime prevalence was 8.4% in those 13–14 years versus 15.4% in those 17–18 years. However, there is variation in age-related rates by specific disorder. For example, prevalence rates of depressive disorders and anxiety disorders have been shown to increase with age, while prevalence rates of ADHD decrease with age (Breton et al. 1999; Canino et al. 2004).

Higher prevalence rates of child mental disorders have been found in urban versus rural areas (Offord et al. 1987; Costello et al. 1996; Canino et al. 2004). This was shown in the Isle of Wight/Inner London Borough Study in which the prevalence of any psychiatric disorder was higher in the London borough (25.4%), an urban area, than the Isle of Wight (12%), a rural area. Other risk factors for psychiatric disorders include lower socioeconomic status (SES) (Rutter et al. 1975; Costello et al. 1996; Merikangas et al. 2010), having unmarried parents (Canino et al. 2004; Merikangas et al. 2010), and a variety of exposures and complications during the prenatal period (Buka et al. 1993).

59.4 The Fourth Generation of Psychiatric Epidemiology: Examples of Specific Disorders

The material described thus far summarizes some of the major accomplishments of what we characterize as the "third generation" of psychiatric epidemiology research – largely conducted between 1980 and 2000. These large-scale community studies have solidified epidemiological knowledge of the prevalence, incidence, risks, and course of major disorders of children, youth, and adults. Since the turn of the century, there has been rapid expansion in the number and variety of epidemiological investigations pursued worldwide. With recent advances in neuroscience, brain imaging, genetics, and other related fields, the field of psychiatric epidemiology has entered a new fourth generation of research. This includes more extensive and sophisticated use of certain study designs (including family, sibling, high-risk designs, nested case-control studies, and others), new statistical methods, new diagnostic assessment techniques, and an array of new approaches to assess exposures that may reflect potential causes and mechanisms resulting in mental disorder. While space does not permit us to describe the full array of exciting work conducted over the past 10–20 years, we highlight two specific disorders to give some sense of these recent developments. We highlight two of the more severe and persistent mental disorders – autism and schizophrenia.

59.4.1 Autism Spectrum Disorders

Autism spectrum disorders (ASD) are a heterogeneous group of neurodevelopmental disorders characterized by deficits in social interaction and communication and the presence of restricted and repetitive behavior (Diagnostic and Statistical Manual of Mental Disorders, fourth edition, text revision). These core characteristics are frequently accompanied by impairments in cognition, learning, attention, and sensory processing. ASDs include three main conditions classified as pervasive developmental disorders in the DSM: autistic disorder, Asperger syndrome, and pervasive developmental disorder not otherwise specified (PDD-NOS). ASDs are typically diagnosed in early childhood and remain lifelong conditions. Symptoms are usually present before 3 years of age, but most individuals are now diagnosed

between 3 and 4 years of age, with boys being diagnosed, on average, earlier than girls (Chakrabarti and Fombonne 2001; Yeargin-Allsopp et al. 2003).

Autism was first described in the US and European medical literature in the 1940s. Through the 1980s, it was believed to be rare, with an estimated prevalence of 5 per 10,000 persons. The estimated prevalence has increased dramatically over the past 30 years, and at the present ASDs are estimated to occur in 110 in 10,000 children in the United States (Kogan et al. 2009; Principal Investigators 2012). Prevalence estimates in Europe are similar to the USA (Baron-Cohen et al. 2009), while prevalence rates in other parts of the world are somewhat lower. For example, a study conducted in Japan found a prevalence of 27.2 per 10,000 individuals (Honda et al. 2005).

A steady increase in ASD prevalence has been consistently shown in the USA and globally. In the USA, the prevalence of ASD in 8-year-old children increased by 78% between 2002 and 2008, with larger increases seen in children of borderline and average or above-average intellectual functioning (Principal Investigators 2012). A study of time trends in ASD diagnoses among children aged 36 months and younger in Massachusetts found that ASD incidence increased from 56 per 10,000 among the 2001 birth cohort to 93 per 10,000 in 2005 (Manning et al. 2011).

A little less than half of the considerable increase in the prevalence of ASD is best explained by broadening diagnostic criteria and increased awareness. Significant changes occurred in the diagnostic criteria from the DSM-III to DSM-IV, during which time increases in prevalence were observed (King and Bearman 2009). Furthermore, studies have shown that diagnostic substitution, which occurs when children with another diagnosis have their diagnosis changed to ASD, also explains some of the rise in ASD prevalence. One study found that 26.4% of the increased autism caseload in California was associated with diagnostic change (specifically, children previously diagnosed with only intellectual disability) (King and Bearman 2009). A large part of the increase remains unexplained, however, by any of these factors. Therefore, we must leave open the possibility that there has actually been an increase in prevalence due to a true increase in incidence.

There has been a particularly large increase in children meeting criteria for ASD who do not have cognitive delay. The inclusion of Asperger disorder in DSM-IV is likely to have contributed to the increased prevalence of ASDs by encouraging identification of high-functioning children with social problems but no language delay (McPartland et al. 2012). Furthermore, DSM-III applied a monothetic approach (i.e., an individual must meet all diagnostic criteria), while DSM-III-R used a set of polythetic criteria (i.e., individuals must meet only a subset of a range of criteria), which also broadened the diagnostic concept. A recent study revisited a sample of children diagnosed with ASD by DSM-III-R to determine how many would meet criteria under DSM-IV (Miller et al. 2013). The results showed that 91% of participants met both criteria and a large number of participants who did not meet criteria under DSM-III (59%) did meet DSM-IV-TR criteria. Similar retrospective studies that have applied current ASD diagnostic criteria to samples diagnosed in the past show that prior studies may have underestimated prevalence

(Heussler et al. 2001; Charman et al. 2009). Finally, recommendations from the American Academy Pediatrics to screen all children for ASD, and increased public awareness, have helped to improve diagnosis and treatment and may explain increases in prevalence (Duchan and Patel 2012).

Innovative epidemiological methods have been used in the field of autism epidemiology in recent years to better understand the distribution and determinants of ASD. Researchers have used new study designs and methods to obtain more accurate prevalence estimates and to attempt to explain increases in prevalence over time. Various epidemiological studies have been conducted to examine time trends in the prevalence of ASD. To study trends, repeated surveys in defined geographical areas at different points in time can be used, provided that methods are kept relatively constant (Fombonne 2009). These studies have generally shown increases in prevalence over time (Gillberg 1984; Kawamura et al. 2008). Also, age-period-cohort analyses of time trends in California have established that the increased prevalence of ASD in that state is primarily a birth cohort effect, which limits the possible explanations to some degree (Keyes et al. 2012).

Many studies have relied on public records (medical and educational) to obtain prevalence estimates in large population-based samples (Croen et al. 2002; Principal Investigators 2012). The most prominent ongoing population-based surveillance program is the Autism and Developmental Disabilities Monitoring (ADDM) Network conducted in the United States by the Centers for Disease Control (CDC) (Principal Investigators 2012). The ADDM uses a standardized protocol across various study sites in the USA to examine medical and educational records of 8-year-old children to diagnose ASD. The ADDM studies have been valuable in providing data on the prevalence of ASDs, describing the population of children with ASD, and identifying changes in prevalence over time.

Recent studies have challenged the diagnostic criteria for ASD outlined in the DSM. For example, Lord and colleagues (2012) found that clinical distinctions among categorical diagnostic subtypes of ASD (autistic disorder, Asperger disorder, and pervasive developmental disorder not otherwise specified) were not reliable across multiple study sites and concluded that dimensional descriptions of core features, along with language and cognitive function, would be more useful. Studies like this one provide support for the diagnostic changes proposed for DSM-V, which will eliminate subgroups in favor of one overall diagnosis – autism spectrum disorder.

A consistently shown risk factor for ASD is male sex. Studies show that the odds of having ASD are approximately four times greater for boys than girls (Kogan et al. 2009). However, when females are affected, they generally have lower functioning (Rivet and Matson 2011). Comorbid conditions are common in individuals with ASD. Kogan et al. (2009) found that 87.3% of children with ASD also had attention deficit disorder or attention deficit/hyperactivity disorder (ADHD), anxiety problems, behavioral or conduct problems, depression, or developmental delay. Among these conditions, the most common was ADHD, with an estimated prevalence of 47.2 per 100 among individuals with ASD. Psychiatric disorders in family members

are also more frequent in individuals with ASD (Duchan and Patel 2012). Recent studies have shown that schizophrenia coaggregates with ASD in many families (Sullivan et al. 2012).

Another common condition associated with ASD is intellectual disability (ID), defined as IQ at or below 70. Current estimates are that around 40% of children with ASDs have ID (Principal Investigators 2012). Epilepsy is also known to be comorbid with ASD and occurs in approximately 14% to 16% of individuals with ASD (Tuchman et al. 1991; Levy et al. 2010), a greater proportion of whom also have ID. Longitudinal studies that follow persons with ASD into adulthood have reported higher epilepsy rates (Danielsson et al. 2005). Genetic and medical problems are also common; one study found that 15% of individuals with pervasive developmental disorder had a known genetic disorder (Chudley et al. 1998).

Outcomes in persons with ASD vary greatly depending on the type of ASD, severity of symptoms, and presence of comorbid conditions. Individuals with ASD have higher mortality rates as compared to the general population (Gillberg et al. 2010), in particular persons with ASD and epilepsy (Pickett et al. 2011). While ASD can improve through treatment, in particular through behavioral therapies implemented in early childhood (Smith et al. 2000; Dawson et al. 2010), for most individuals the condition remains a significant lifelong impairment. Much of the epidemiological research on autism has focused on children. Very little is known about adults with ASD. However, it is critical to know more about this population because, at present, many adults with ASD were misdiagnosed or undiagnosed as children and there is a large number of children with autism who will soon become adults (Bresnahan et al. 2009). Furthermore, addressing the needs of adults with autism is a major public health concern. As the number of adults with ASD increases, there is a growing need for expanded services and an improved understanding of the types of services and treatment needed for adults. Epidemiologists must employ a life course approach to autism, which will improve our understanding of the disorder (Bresnahan et al. 2009).

The use of new study designs has moved the field of autism epidemiology forward. Infant sibling studies have played an important role in ASD research over the past decade. These studies have provided important new knowledge about the early signs of ASD, have improved our understanding of the developmental course of autism, and are useful methods to identify risk factors for autism. The use of infant sibling designs is effective because of the increased recurrence rate of autism in siblings and the opportunity to observe early behavioral markers of autism (Newschaffer et al. 2012). Furthermore, the enrollment of participants during pregnancy allows for prospective research on risk factors occurring during the perinatal period. This type of study has been labeled as an enriched-risk pregnancy cohort study and has been applied in studies such as the Early Autism Risk Longitudinal Investigation (EARLI) (Newschaffer et al. 2012). Large birth cohorts have also been employed in the research of ASD. For example, the Autism Birth Cohort (ABC) identifies cases of autism through population screening of participants from the Norwegian Mother and Child Cohort, a large, randomly selected birth cohort in Norway (Stoltenberg et al. 2010). More than 107,000

children have been screened for autism. Cases are compared to controls from the same cohort in a nested case-control design to identify genetic and environmental risk factors for autism.

There is a clear genetic risk for ASD as evidenced by twin and family studies. The relative risk of ASD is 22 times greater in individuals who have a sibling with ASD autism (Lauritsen et al. 2005), and there is a higher concordance rate in monozygotic (MZ) than dizygotic (DZ) twins (Lichtenstein et al. 2010). Based on twin studies, the heritability of ASD is estimated to be between 60% and 90%, making autism one of the most genetic of all developmental neuropsychiatric disorders (Kumar and Christian 2009). While prior studies showed significantly higher concordance rates in MZ twins (Steffenburg et al. 1989; Bailey et al. 1995), more recent studies have provided evidence of a greater role for environmental factors. Rosenberg and colleagues (2009) found a higher concordance rate in DZ twins than previously reported (31%), and Hallmayer et al. (2011) found a rate of concordance in DZ twins of 31% to 36%, concluding that environmental factors explain about 55% of the liability to autism. These studies have increased interest in research on environmental risk factors for ASD, in particular those occurring during the prenatal period. Environmental risk factors that have been identified include perinatal complications (Hultman et al. 2002; Gardener et al. 2009) and increased maternal (Manning et al. 2011) and paternal age (Durkin et al. 2008). In a meta-analysis, Gardener and colleagues (2009) reported that advanced parental age at birth, maternal prenatal medication use, bleeding, gestational diabetes, being firstborn, and having a mother born abroad were associated with increased risk of autism. Durkin et al. (2008) showed that both maternal and paternal age were independently associated with autism.

The recent interest in environmental risk factors for ASD has resulted in the identification of potential protective factors that reduce ASD risk. For example, in a Norwegian cohort of mothers and children, maternal use of folic acid supplements in early pregnancy was associated with a reduced risk of severe language delay, a condition associated with ASD, in children at age 3 years (Roth et al. 2011). And Schmidt and colleagues (2011) found that mothers of children with autism were less likely than those of typically developing children to report having taken prenatal vitamins before or in early pregnancy. The use of folic acid supplements and prenatal vitamins may reduce the risk of having a child with autism.

Exciting research investigating genetic risk factors for ASD has also been conducted in recent years. The advent of microarray technology has led to a revolution in the discovery of copy number variants (CNVs) in autism. A number of CNVs have been identified that occur more frequently in persons with ASD than controls (Morrow 2010). Curiously, many of these same CNVs are also related to other psychiatric disorders, such as schizophrenia (Sanders et al. 2012). Recently, genome-wide association studies (GWAS) of autism have been conducted that have found chromosomal deletions (Kumar et al. 2008) and copy number variants (Marshall et al. 2008) associated with autism. Currently ongoing are "next-generation" genomic studies, which use approaches such as whole genome sequencing that are far more comprehensive than GWAS approaches. One of the

earliest to be published showed that paternal age is associated with increased risk of de novo SNP mutations (not just CNVs) and suggested that some of these mutations were related to autism and/or schizophrenia (Kong et al. 2012). While these studies have yielded important findings, they have also underscored the complexity of autism inheritance.

Finally, recent advances in neuroscience and brain imaging have resulted in a better understanding of the brain development of persons with ASD. For example, a longitudinal study of brain growth by Schumann and colleagues (2010) found an abnormal growth rate of multiple areas of the brain among children with autism. The widespread use of standardized diagnostic instruments in the autism epidemiology field, in particular the Autism Diagnostic Interview Revised (ADI-R) (Rutter et al. 2003) and the Autism Diagnostic Observation Schedule (ADOS) (Lord et al. 2000) has allowed for better ascertainment of cases and the ability to make comparisons across studies. As DSM criteria for ASD continue to change (Wing et al. 2011), there will remain challenges in studying the incidence, prevalence, and risks for the disorder. While several risk factors have been identified, the exact cause or causes of ASD are still unknown. Further research on risk factors for ASD is needed, in particular those that occur during the perinatal period or which may be involved in the interplay of genes and environment. There also continues to be a need for studies examining the diagnostic criteria for ASD to better refine case identification.

59.4.2 Schizophrenia

Schizophrenia is a psychotic disorder characterized by a breakdown of thought processes and poor emotional responsiveness. The essential features are the presence of specific psychotic symptoms (delusions, hallucinations, etc.), social or occupational dysfunction, and a 6-month duration of illness (Tsuang and Tohen 2002).

In a review of 188 studies, McGrath et al. (2008) found a median point prevalence of schizophrenia of 4.6 per 1,000 and lifetime prevalence of 7.2 per 1,000. The risk of developing the illness over the life course was 0.7%. The Dutch national morbidity survey reported a lifetime prevalence of 3.7 per 1,000 (van Os et al. 2001).

Several studies have estimated the incidence of schizophrenia. A systematic review of 158 incidence studies reported a median annual incidence of 15.2 per 100,000 (McGrath et al. 2008). In a global study (WHO ten-country study, Jablensky et al. 1992), the estimated annual incidence of schizophrenia ranged from 16 to 40 per 100,000 using broad diagnostic criteria and 7 to 14 per 100,000 using narrow criteria. Eaton et al. (1998) reviewed incidence studies and reported a median annual incidence rate of 0.20 per 1,000. Currently many investigators question whether narrowly diagnosed schizophrenia is clearly separable from other psychotic disorders, at least in terms of genetic and early environmental causes. The overall incidence of psychoses varies, of course, but most studies suggest that the proportion of people who develop psychoses in high-income countries is similar to the proportion who develop ASD. Studies of incidence and prevalence for autism and schizophrenia from low-and middle-income countries (LMIC) are not yet

sufficient to draw general conclusions that pertain beyond high-income countries, although LMIC represent ∼90% of the world's population. With the growth of research capacity in LMIC, recent pioneering studies of incidence (Menezes et al. 2007) and prevalence (Kebede et al. 2003; Kim et al. 2011; Phillips et al. 2004) are now emerging for both ASD and schizophrenia, and we should soon have enough data to paint a broader, global picture for these disorders.

Although schizophrenia has been studied over the past century, its causes remain largely unknown. Among the reasons are the inherent etiological heterogeneity of schizophrenia as a "syndrome" defined by a confluence of symptoms, and the related historical practice of assigning a different diagnosis than schizophrenia once a specific cause of the syndrome is identified (e.g., pellagra, syphilis, drug-induced psychosis). There are clearly both environmental and genetic causes, and the interplay among these causes is likely to be important.

Schizophrenia has been shown to run in families (Jones and Cannon 1998; Gottesman and Shields 1982); heritability estimates range widely with an upper bound of ∼80% (Sullivan et al. 2003; Gottesman and Shields 1982). Individuals are at higher risk if a biological parent or sibling had the disease, and intriguingly, the increased risks related to parents and siblings are somewhat different despite the fact that parents and siblings share about 50% of their genes with an index individual (Heston 1966; Jones and Cannon 1998; Gottesman and Shields 1982). Twin studies show a substantially greater concordance in monozygotic as compared to dizygotic twins (Cannon et al. 1998; Sullivan et al. 2003).

In recent years, major advances have been made in identifying specific genetic mutations related to schizophrenia. About 5 years ago, we argued that individually rare mutations would turn out to be important causes (McClellan et al. 2007), and since then, a large number of studies have been published that identify rare mutations as strong causes (e.g., Gilman et al. 2012). However, it is still not known whether these individually rare mutations will be related to a very large proportion of cases. Thus, the counterargument that schizophrenia is related to multiple common genetic variants, each with a weak effect, could also be true for a proportion of cases (Owen et al. 2009). A very large number of common polymorphisms have been related to schizophrenia in GWAS studies (with weak effects as would be expected). Overall, with a few notable exceptions (e.g., 22q deletions), results across studies are not yet consistent enough to draw definitive conclusions about specific genes or gene regions, but do suggest that both rare mutations and common variants within pathways relating to neuronal (especially synaptic) development play a role. An intriguing recent paper reports that genes within these pathways are important for both ASD and schizophrenia and that there is substantial overlap for these two disorders (Xu et al. 2012). Finally, we note that genetic studies of both rare and common genetic variants are frequently subject to potential bias due to overlooking basic epidemiological precepts (e.g., Schwartz and Susser 2010), although we do not think such potential bias has altered the overall pattern of results described here.

A number of environmental risk factors for schizophrenia have also been identified. With regard to demographic factors, one of the most consistent findings

is the lower socioeconomic level of persons with schizophrenia compared to unaffected individuals A large body of research has addressed various hypotheses for this association, ranging from theories of social selection/social drift in which individuals who have or are prone to schizophrenia "drift" progressively downwards in social class as a result of the disorder and/or are prevented from attaining higher social class levels, to theories of social causation involving environmental conditions occurring among persons of lower SES. Both earlier (Dohrenwend et al. 1992) and recent cohort studies tend (Corcoran et al. 2009) to support the social selection view, with only children of the lowest social classes at elevated risk to develop schizophrenia. By contrast, there has been a large recent body of work indicating that ethnic minorities migrating to developed countries are at increased risk for developing schizophrenia and psychotic symptomatology, due to presumed (and yet unexplained) mechanisms of social causation (Morgan and Fearon 2007; Veling et al. 2011). There is also evidence that schizophrenia is more common among males than females (McGrath et al. 2004). McGrath et al. (2008) reported a relative risk in males versus females of 1.4. Higher rates of schizophrenia are also seen among persons who are unmarried (Eaton et al. 1998). It has been hypothesized that this may be due to reverse causation, such that individuals at risk for schizophrenia are less likely to become married or more likely to divorce. The evidence is mixed; van Os et al. (2000) found that the incidence of schizophrenia was higher in single people than married people.

There is also strong evidence for a role of perinatal risk factors in the etiology of schizophrenia. In a meta-analysis of 18 studies, the risk for schizophrenia approximately doubled (odds ratio of 2) for infants born with obstetric complications of all kinds (Geddes and Lawrie 1995). Susser and Lin (1992) showed that nutrition deprivation during pregnancy was associated with increased risk of schizophrenia in offspring. Other risk factors include being born in the winter (Torrey et al. 1993), urbanicity (McGrath et al. 2004), and older paternal age (Byrne et al. 2003). With regard to course and prognosis, many studies find that younger patients, males, and those with a family history have worse outcomes (Tsuang and Tohen 2002).

Current epidemiological investigations regarding the etiology of schizophrenia, as reflected by the work of two of the current authors, demonstrate the range of interdisciplinary approaches used in contemporary psychiatric epidemiology. A series of cohort studies dating back to a paper by Susser and Lin (1992), conducted first in the Netherlands (Susser et al. 2012) and later in China (St Clair et al. 2005) have identified periconceptional maternal nutritional deprivation (approximately 4 weeks before to 8 weeks after conception) as a risk factor for subsequent schizophrenia. Susser and colleagues are pursuing a program of epigenetic research linking maternal prenatal nutrition, DNA methylation and schizophrenia (Kirkbride et al. 2012). Several studies in humans now suggest that prenatal nutritional exposures can influence DNA methylation, in offspring, although the evidence is considerably more scant than that provided by animal studies. A follow-up study of persons exposed and unexposed to famine during the Dutch Hunger Winter of 1944–1945 (not focused on schizophrenia) reported

epigenetic changes among the offspring of women exposed to periconceptional starvation. The "sensitive" period for these epigenetic changes was very similar to the "sensitive" period identified in the schizophrenia studies described above (Heijmans et al. 2008). At approximately 60 years old, these offspring exhibited less methylation of the IGF2 locus in whole-blood samples than offspring of women who were unexposed or exposed later in gestation. IGF2 is an imprinted gene that plays a crucial role in early development and continues to play a role in cognitive and other brain processes over the life course (Chen et al. 2011). If genuine, it suggests that periconceptional maternal famine exposure can have a lasting effect on offspring DNA methylation over the life course. More recent analysis of global methylation patterns in this cohort have demonstrated no discernible difference in global DNA methylation patterns between offspring of exposed and unexposed mothers (Lumey et al. 2012), perhaps highlighting the complexity and potentially target-specific nature of prenatal exposures upon the fetal epigenome. A further important question now being examined is whether or not the effects of prenatal nutritional deficiency are transmitted across generations (Susser et al. 2012).

Buka and colleagues (1999) are also engaged in a wide array of epidemiological studies investigating the direct and interactive effects of conditions during pregnancy and familial and genetic risks in the etiology of schizophrenia. These involve a number of study designs, high-dimensional measurement, and statistical approaches. Study designs include basic cohort, nested case-control, sibling, high-risk, and multistage approaches where participants receive greater or lesser intensity of assessment based upon their risk profiles. Study measures reflect the influence of previous generations of epidemiological research (e.g., sociodemographic factors) as well as influences from related disciplines including neuropsychology, neuroscience, genetics, and immunology. Assessments include traditional diagnostic procedures, but also more fine-grained assessments of presumed related endophenotypes, including neuropsychological testing, functional and structural brain imaging, molecular genetics, and immune function. Following decades of research suggesting prenatal risks for schizophrenia, these and other investigators have used archived maternal serum samples from long-running pregnancy cohort studies to confirm the association between maternal infections, exposure to inflammatory cytokines during pregnancy, and subsequent schizophrenia (Buka et al. 2001a, b; Brown et al. 2004a, b). Subsequent work has incorporated molecular genetic methods, investigating the combined influences of prenatal complications, prenatal neurotrophic factors which are stimulated as part of a neuroprotective response to fetal distress (e.g., brain-derived neurotrophic factor), and related polymorphisms which have been associated with schizophrenia (Cannon et al. 2008). Other work motivated by this combined neurodevelopmental, neuroscience, and epidemiological orientation has focused on established gender differences in the phenomenology of schizophrenia and fetal brain development (Goldstein et al. 2011). New analyses move beyond traditional diagnostic classifications of psychotic disorders to dimensional approaches characterized by level

and severity of dysfunction in multiple domains (Goldstein et al. 2001; Seidman et al. 2006, 2012). This is in line with recent developments at the National Institute of Mental Health calling for new Research Domain Criteria (RDoC) with efforts to integrate genetic, neurobiological, imaging, behavioral, and clinical data. Modern epidemiological approaches require such integration of new disciplines, designs, and analyses to continue to advance understanding of the epidemiology of schizophrenia.

Prevention Although preventive interventions are beyond the scope of this chapter, we believe it important to note that there are already examples of successful public health prevention efforts for mental disorders, and promising initiatives that may lead to discovery of others. To illustrate, we use the example of nutritional interventions.

We offer two examples of nutritional interventions already implemented and proven effective. Pellagra was once a major cause of mental disorder, especially psychosis (Susser et al. 2006). After public health programs addressed the micronutrient deficiency underlying pellagra, it became a rare cause, almost nonexistent in high-income countries. Similarly, and equally dramatic, prenatal iodine deficiency was shown to be a cause of intellectual disability, mild cognitive impairment, and behavioral problems (Zimmermann 2012). Public health interventions such as iodized salt have dramatically reduced mental impairments related to iodine deficiency, in most though unfortunately still not all parts of the globe.

With regard to promising initiatives, we offer an example that follows on the studies linking periconceptional starvation and schizophrenia described above. Since neural tube defects are related to periconceptional folic acid intake and peaked in the same birth cohort as schizophrenia in the Dutch Famine studies, it is natural to consider whether folic acid deficiency also played a role in schizophrenia. This hypothesis is being explored in a variety of ways, one of which is the ongoing follow-up of a large Norwegian cohort comprising more than 100,000 pregnancies (Magnus et al. 2006; Stoltenberg et al. 2010). Studies from the Norwegian cohort have found that maternal use of periconceptional folic acid supplements (from 4 weeks before to 8 weeks after the last menstrual period) is associated with a reduced risk of child neurodevelopmental disorders such as autism and severe language delay (Surén et al. 2013). Moreover, as noted earlier, converging lines of evidence suggest substantial overlap in the causes of autism and schizophrenia. Within the next decade, the ongoing follow-up of this Norwegian cohort will make it possible to directly test whether these supplements are related to reduced risk of schizophrenia and, if so, to examine potential mechanisms (Kirkbride et al. 2012). We only consider this a promising initiative because we do not yet know whether periconceptional folic acid supplements will ultimately be proven to reduce the risk of autism, schizophrenia, and/or other neurodevelopmental disorders after birth (they are already proven to reduce the risk of neural tube defects at birth). Thus far, however, the evidence for this hypothesis is promising, and if it is ultimately proven true, it will add substantially to examples of successful prevention efforts achieved through public health initiatives.

59.5 Conclusions

Based on generations of studies, it is quite clear that the burden of mental disorders is very high across the globe, in LMIC as well as in high-income countries. Indeed, for several reasons, the burden is likely to increase substantially in the coming decades. For example, as we continue recent progress in reducing child mortality in LMIC, a large population of "child survivors" emerges, who often have neurodevelopmental delays and disabilities (Scherzer et al. 2012). Yet the resources devoted to research and treatment of mental disorders remains minimal in comparison with the resources devoted to other disorders, which make a smaller contribution to burden of disease (Prince et al. 2007; Saxena et al. 2007). The reasons for this discrepancy are not fully understood, but surely one is the stigma associated with mental illness. Since the shortage of resources is most pronounced in LMIC, a current focus of WHO, NIMH, and other leading organizations is to identify strategies to "close the treatment gap" in LMIC (Collins et al. 2011). A related problem is that services that do exist are not well distributed within countries; at times, those with no diagnosis of a mental disorder are more likely to access psychiatric treatment than those with severe mental illness.

We propose that we are now at a critical moment of transformation in psychiatric epidemiology. In recent years, epidemiological investigations of the causes of mental disorders have grown exponentially, and the nature of these investigations has changed. We are now studying specific genetic and epigenetic causes and their relationship to environmental exposures, using large population registries that provide data over long time periods, employing new technologies to examine neighborhood and societal-level effects, and transforming the use of high-risk and other designs that previously existed but could not be applied with the same sophistication. This kind of research entails interdisciplinary collaboration (and training to facilitate this), refined assessment of potential etiological factors, and more attention to potential mechanisms. It also entails the acknowledgement that factors at multiple levels, from cell to society, contribute to these disorders. This broader framework is important for the design of all studies; even though a single study will likely address questions at only one or two levels, the framework helps in the selection of the appropriate level and the understanding of the limitations inherent in studying only one level (Susser and Susser 1996; Susser et al. 2006).

The recognition that mental disorders should be a priority in all populations has also grown exponentially. Although the United Nations in 2011 did not include mental disorders among non-communicable disease priorities, there was considerable controversy about this exclusion, and soon afterward many international funding agencies added mental disorders to their list of priorities. The 2011 decision by the UN is already being seen as a mistake by many leaders in public health. We think it highly unlikely that by the end of this decade, the exclusion of mental disorders will still be considered acceptable in any broad public health initiative.

The magnitude of the global public health burden associated with mental disorders also highlights the need for additional applied research related to the

organization, financing, and delivery of mental health services. Throughout the past 100 years of research, there has been consistent evidence of the sizable proportion of persons with diagnosable mental disorders who receive no or limited treatment. At the same time, more recent epidemiological surveys reflect a high level of "met unneed" where individuals with low levels of need had a higher probability of accessing treatment than those with more severe conditions (Kessler et al. 1997; Mojtabai et al. 2002). There is an urgent need to increase both research and mental health services throughout the continuum of prevention and treatment, to increase availability in LMIC, and to better align service receipt with treatment need. As highlighted in this chapter, the field of epidemiology has advanced our knowledge of the forms and prevalence of major psychiatric conditions and is contributing to new discoveries regarding etiology. Parallel emphasis is needed on the applied side of psychiatric epidemiology, around the distribution and evaluation of population-level resources to reduce the burden of these highly prevalent and debilitating set of disorders.

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