CHAPTER 1

Epidemiology of Depression

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The first modern epidemiological surveys including information about depression were carried out in the late 1950s in the Midtown Manhattan (Srole, Langner, Michael, Opler, & Rennie, 1962) and the Stirling County (Leighton, Harding, & Macklin, 1963) studies. These studies used dimensional screening scales of nonspecific psychological distress to pinpoint respondents likely to have mental disorders and then administered clinical follow-up interviews to them. The outcome was a global measure of mental disorder rather than individual diagnoses, although the screening scales included questions that could subsequently be interpreted as part of the depressive syndrome to make rough post hoc estimates about prevalence and correlates of depressive disorders (Murphy, Laird, Monson, Sobol, & Leighton, 2000).

Later surveys up through the 1980s used variants on the Midtown Manhattan and Stirling County screening scales, but generally without clinical follow-up (see Link & Dohrenwend, 1980, for a review). Scale scores were sometimes dichotomized to define "cases" based on some standard clinical cut point, but there was controversy about the appropriate decision rules for defining cases (Seiler, 1973). To resolve this controversy, structured diagnostic interviews were developed for use in community surveys. The Diagnostic Interview Schedule (DIS; Robins, Helzer, Croughan, Williams, & Spitzer, 1981) was the first such instrument. Dimensional screening scales continued to be used to screen for mental illness in primary care (Goldberg, 1972) and to assess symptom severity and treatment effectiveness among patients in treatment for mental disorders (Derogatis, 1977). However, psychiatric epidemiologists, influenced by the widely published results of the first study to use the DIS, the Epidemiologic Catchment Area (ECA) study (Robins & Regier, 1991), largely abandoned dimensional distress measures in favor of dichotomous interview-based case classifications in general population surveys beginning in the late 1980s.

We now have over three decades of experience using fully structured diagnostic interviews such as the DIS and the more recently developed Composite International Diagnostic Interview (CIDI; Robins et al., 1988), the Primary Care Evaluation of Mental

Disorders (PRIME-MD; Spitzer et al., 1994), and Mini-International Neuropsychiatric Interview (MINI; Sheehan et al., 1998). It is clear from this experience that fully structured diagnostic interviews, although useful, are inadequate to provide complete information about the magnitude of the problem of mental illness, as DSM and ICD criteria are so broad that close to one-half of people in the general population receive one or more lifetime diagnoses (Kessler et al., 2007) and close to one-fifth carry a current diagnosis (Kessler et al., 2008). With prevalence estimates as high as these, the dichotomous case data provided in diagnostic interviews need to be supplemented with dimensional information on severity to be useful to health policy planners.

Only the most recent epidemiological data on the prevalence of major depression include dimensional measures of severity. This is an important expansion of previous research in light of the suggestion by some commentators that most untreated community cases of major depression are fairly mild cases (Regier, Narrow, Rupp, Rae, & Kaelber, 2000). The first part of this chapter presents the main findings in the literature on the descriptive epidemiology of major depression, including the most recent evidence on clinical severity. The second part of the chapter expands the discussion of severity by reviewing available data on the consequences of depression as assessed in community surveys.

Descriptive Epidemiology

Point Prevalence

Community surveys find that up to 20% of adults and up to 50% of children and adolescents report depressive symptoms during recall periods between 1 week and 6 months (Kessler & Bromet, 2013). Point prevalence estimates for DSM major depressive disorder (MDD) in surveys that use structured diagnostic interviews are considerably lower, with rates of current MDD typically less than 1% among children (reviewed by Merikangas & Angst, 1995), up to 6% among adolescents (reviewed by Kessler, Avenevoli, & Merikangas, 2001), and 2–4% among adults (reviewed by Kessler & Bromet, 2013).

The discrepancy between the high symptom prevalence and lower depressive disorder prevalence means that many people have subsyndromal depressive symptoms. Epidemiological studies investigating these symptoms have been hampered by inconsistent definitions of subsyndromal depression (Rodriguez, Nuevo, Chatterji, & Ayuso-Mateos, 2012) but have documented rates among both adolescents (Kessler & Walters, 1998) and adults (Judd, Akiskal, & Paulus, 1997) as high as, if not higher than, rates of MDD, with especially high relative rates among older adults (Meeks, Vahia, Lavretsky, Kulkarni, & Jeste, 2011). Longitudinal research shows that subsyndromal depression is a powerful predictor of subsequent MDD (Klein et al., 2013) and an important contributor to the persistence and severity of MDD (Altamura et al., 2011). The World Health Organization's (WHO) World Health Survey found that subsyndromal depression is quite common throughout the world, is associated with similar risk factors to MDD, and is associated with substantial decrements in health (Ayuso-Mateos, Nuevo, Verdes, Naidoo, & Chatterji, 2010).

12-Month Prevalence

Many community surveys focus on 12-month prevalence of MDD (i.e., the percentage of people with MDD at some time in the 12 months before interview) based on the fact that public health planning is typically made on an annual basis. The most recent such data

come from the WHO World Mental Health (WMH) surveys, which are large national general population epidemiological surveys in 18 countries with a combined sample of 89,037 respondents (Bromet et al., 2011). The average 12-month prevalence estimate of DSM-IV major depressive episodes is 5.5% in the 10 WMH surveys in high-income countries and 5.9% in the 8 surveys in low- to middle-income countries. These estimates are somewhat higher than the 3.2% 12-month prevalence of major depressive episodes *alone* found among 245,404 respondents in 60 countries in the World Health Surveys (Moussavi et al., 2007), but the World Health Surveys also showed that 9.3–23.0% of respondents with chronic physical conditions had *comorbid* major depressive episodes. The World Health Surveys also found that the impact of MDD on decrements in functioning is higher than that of virtually any other condition studied.

Lifetime Prevalence

Epidemiological surveys generally use retrospective reports to assess lifetime prevalence and age-of-onset (AOO) of MDD. Lifetime prevalence estimates in U.S. surveys have ranged widely, from as low as 6% (Weissman, Livingston, Leaf, Florio, & Holzer, 1991) to as high as 25% (Lewinsohn, Rohde, Seeley, & Fischer, 1991). The estimate in the National Comorbidity Survey Replication (NCS-R), the most recent validated U.S. epidemiological study, was 16.6% (Kessler, Berglund, Demler, Jin, & Walters, 2005). Clinical reappraisal data confirm the validity of the NCS-R estimate (Haro et al., 2006), suggesting that more than 30 million U.S. adults have met criteria for MDD at some time in their lives. The WMH surveys, which used the same diagnostic assessment as the NCS-R, estimated that lifetime prevalence of MDD was 14.6% in the 10 high-income and 11.1% in the 8 low- to middle-income countries studied (Bromet et al., 2011).

Age of Onset

Lifetime prevalence estimates represent cumulative prevalence *to date*. Some survey respondents who have never yet had MDD will have it later. Lifetime *risk* (as opposed to lifetime *prevalence*) can be estimated with actuarial methods that use retrospective AOO reports to predict subsequent risk for respondents who have not yet passed through the risk period. This type of analysis was carried out in the WMH surveys (Kessler et al., 2007). Median AOO of mood disorders across countries was in the age range of 29–43, with the AOO distributions across countries showing consistently low risk through the early teens, a roughly linear increase thereafter through late middle age, and a more gradual increase later in life. Projected lifetime risk by age 75 was 40–170% greater than the proportion of respondents with lifetime-to-date MDD at the time of interview.

In considering these results, it is important to recognize that the WMH lifetime risk projections assumed that conditional risk is constant across cohorts. This assumption is clearly incorrect, as shown by the fact that AOO curves differ substantially by cohort, with estimated risk successively higher in each younger cohort. This pattern of intercohort variation could be due to the risk of depression increasing in successively more recent cohorts, to various methodological possibilities involving cohort-related differences in willingness to admit depression or to recall past episodes of depression (Giuffra & Risch, 1994), or to some combination of substantive and methodological influences.

There is no way to adjudicate among these contending interpretations definitively with cross-sectional data of the sort available in the WMH surveys. Longitudinal data are needed. One published report with such data made a comparison of depression

prevalence estimates in two U.S. national surveys administered in 1991–1992 and 2001–2002 that used similar (but not identical) assessments of 12-month MDD (Compton, Conway, Stinson, & Grant, 2006). The comparison suggested that the prevalence of MDD increased significantly over the decade. However, this result can be called into question based on the baseline prevalence estimate (3.3%) being implausibly low due to methodological limitations in the assessment method. These limitations were corrected in the second survey, which would be expected to increase the prevalence estimate. However, the researchers failed to take this into consideration in their interpretation of the result, leading to the incorrect conclusion that prevalence increased substantially over time. Other longitudinal studies in the United States (Kessler, Demler, et al., 2005) and the Netherlands (de Graaf, ten Have, van Gool, & van Dorsselaer, 2012) failed to find evidence of significant time trends in prevalence.

Subtypes

A number of proposals have been made to subtype MDD based on symptom profiles (reviewed by Baumeister & Parker, 2012). The most consistent suggestion concerns a distinction between melancholic symptoms (e.g., weight loss, insomnia, appetite loss) and atypical symptoms (e.g., weight gain, hypersomnia, appetite increase), although many other distinctions have been proposed. A recent meta-analysis found little empirical support for these symptom-based subtyping distinctions (van Loo, de Jonge, Romeijn, Kessler, & Schoevers, 2012). That meta-analysis identified 34 studies of dimensions underlying depressive symptoms using cluster analysis, factor analysis, or latent class analysis to define subtypes. No symptom clusters emerged consistently across those studies other than a broad dimension for overall symptom severity.

Another way to define MDD symptom subtypes is in terms of synergistic effects among symptoms and/or comorbidities in predicting some outcome, such as differential treatment response or differential persistence and severity. Synergistic effects are typically examined by using some type of regression tree method (Berk, 2008; Breiman, Friedman, Olshen, & Stone, 1984; Hastie, Tibshirani, & Friedman, 2009). Although much less widely used than the internal-consistency subtyping approach described in the preceding paragraph, the few depression subtype studies using regression tree methods have yielded promising results (Joel et al., 2014; McKenzie et al., 2011; Nelson et al., 2012). However, these studies are too few and too inconsistent in outcomes to warrant synthesis. Given the high risks of overfitting in the stepwise data mining methods used in these analyses, it is especially important for future studies of this sort to use internal cross-validation methods and replication across multiple datasets before accepting results as reliable.

Another important subtyping distinction concerns cyclical depression. Two cycling MDD subtypes have been identified exclusive of those associated with bipolar disorder: seasonal affective disorder (SAD; Rosenthal et al., 1984) and premenstrual dysphoric disorder (PMDD; Halbreich, 1997). Community surveys find that 10% or more of people in the general population report seasonal variations in depressed mood and related symptoms (e.g., Booker & Hellekson, 1992). Seasonal depression is typically most common in the winter months and more prevalent in northern than in southern latitudes. However, the prevalence of DSM-5 SAD, which requires a lifetime diagnosis of recurrent episodes of mood disorder with regular onsets and offsets in particular times of the year, is much less common. Indeed, Blazer, Kessler, and Swartz (1998) found that only 1% of the population met narrowly defined criteria for MDD with a seasonal pattern, representing only about 5% of all people with MDD.

Community surveys show that most women report symptom changes associated with the menstrual cycle (Campagne & Campagne, 2007; Winer & Rapkin, 2006). Only between 4 and 6% of women, however, report what appears to be DSM-5 PMDD (Di Giulio & Reissing, 2006), which requires a clear recurring pattern of onset and offset of five or more mood and related symptoms at specific points in the majority of menstrual cycles over the course of a full year. Assessments with daily mood diaries over two or more menstrual cycles typically show only about half of women who report cyclical mood problems actually have PMDD, the others having more chronic syndromal or subsyndromal mood disorders that are exacerbated by menstrual symptoms (Freeman, DeRubeis, & Rickels, 1996). There is great interest in PMDD based on evidence of family aggregation with MDD and responsiveness to selective serotonin reuptake inhibitors but not tricyclic antidepressants (Freeman, Rickels, Sondheimer, & Polansky, 1999). There is also controversy, though, regarding appropriate diagnostic and assessment criteria (Campagne & Campagne, 2007). Community epidemiological data on PMDD are scant due to logistic complications in assessment. Given the existence of so many uncertainties about PMDD, a large, representative epidemiological survey using diary data would be very valuable.

Course

Little longitudinal research has studied the course of MDD in general population samples (but for important exceptions, see Gamma, Angst, Ajdacic, Eich, & Rossler, 2007; Yaroslavsky, Pettit, Lewinsohn, Seeley, & Roberts, 2013). However, cross-sectional surveys consistently find the ratio of 12-month to lifetime MDD to be in the range .5–.6 (Bromet et al., 2011), suggesting that between one-half and two-thirds of people with lifetime MDD will be in episode in any given year in the remainder of their lives. At least three separate processes contribute to the size of this ratio: probability of first episode chronicity, the probability of episode recurrence among people with a history of nonchronic MDD, and speed of episode recovery.

Epidemiological studies show the first of these three processes is quite small, with only a small fraction of people reporting a single lifetime depressive episode persisting for many years. Prevalence of dysthymia and chronic minor depression are somewhat higher but still only in the range of 3–4% of the population (Kessler & Bromet, 2013). Episode recurrence, in contrast, is very common, with the vast majority of people with lifetime MDD having recurrent episodes (Hardeveld, Spijker, De Graaf, Nolen, & Beekman, 2013; Pettit, Hartley, Lewinsohn, Seeley, & Klein, 2013). Finally, speed of episode recovery appears to be highly variable, although the epidemiological evidence on this issue is slim (Kendler, Walters, & Kessler, 1997; McLeod, Kessler, & Landis, 1992).

Comorbidity

Studies of diagnostic patterns in community samples document substantial comorbidity between MDD and other mental disorders (Kessler, Ormel, et al., 2011). Indeed, lifetime comorbidity is the norm among people with MDD. In the NCS-R, for example, nearly three-fourths of respondents with lifetime MDD also had at least one other lifetime DSM-IV disorder (Kessler et al., 2003), including 59% with anxiety disorders, 31.9% with impulse control disorders, and 24.0% with substance use disorders. Lifetime comorbidity is even higher among respondents with 12-month MDD, implying that comorbid MDD is more persistent. Comparison of retrospective AOO reports in the NCS-R

showed that MDD was reported to have started at an earlier age than all other comorbid disorders in only 12.4% of lifetime cases and 12.2% of 12-month cases, although temporal priority was much more common in cases of comorbidity with substance use disorders (41.3–49.2%) than with either anxiety disorders (13.7–14.6%) or impulse control disorders (17.9–20.9%).

Controversy exists about the extent to which this high comorbidity is an artifact of changes in the diagnostic systems used in almost all recent studies of comorbidity (Frances et al., 1992). Beginning with DSM-III, these systems dramatically increased the number of diagnostic categories and reduced the number of exclusion criteria so that many people who would have received only a single diagnosis in previous systems now receive multiple diagnoses. The intention was to retain potentially important differentiating information that could be useful in refining understanding of etiology, course, and likely treatment response (First, Spitzer, & Williams, 1990). However, it can also be argued that this had the unintended negative consequence of artificially inflating estimates of comorbidity. This uncertainty might be resolved in future attempts to determine the validity of diagnostic distinctions, based on the new National Institute of Mental Health (NIMH) Research Domain Criteria (RDoC) initiative (*www.nimh.nih.gov/research-priorities/rdoc/index.shtml*). The RDoC initiative will break down DSM diagnoses, which are currently based only on observable symptoms, into their underlying neural circuit-based domains and constructs. Identifying the common domains and constructs in which dysfunction is occurring may ultimately help to explain the high diagnostic overlap and comorbidity between depression and other DSM disorders. Until that time, though, we are left with a situation in which MDD appears to be highly comorbid with a number of other disorders.

As noted earlier, the majority of comorbid MDD is temporally secondary in the sense that first onset of MDD occurs subsequent to first onset of other comorbid disorders. Survival analysis of cross-sectional data in the WMH surveys using retrospective AOO reports to determine temporal priority shows that a wide range of temporally primary disorders predict subsequent MDD onset (Kessler, Ormel, et al., 2011). Most of these associations are confined to active, as opposed to remitted, primary disorders. The fact that remitted disorders generally do not predict MDD suggests indirectly that earlier disorders are (variable) risk factors rather than (fixed) risk markers (Kraemer et al., 1997).

The structure of comorbidity has been the subject of considerable interest over the past decade, beginning with an influential paper by Krueger (1999) that led to many other researchers using factor analysis to document associations among hierarchy-free anxiety, mood, behavior, and substance disorders associated with latent internalizing and externalizing disorders. The internalizing dimension is sometimes further divided into secondary dimensions of fear (e.g., panic, phobia) and distress (e.g., major depressive episode, generalized anxiety disorder) (Beesdo et al., 2009; Cox & Swinson, 2002; Krueger & Markon, 2006a; Lahey et al., 2008; Slade & Watson, 2006; Vollebergh et al., 2001). These results have been used to argue for a reorganization of the classification of mental disorders in the DSM and ICD diagnostic systems (Andrews et al., 2009; Goldberg, Krueger, Andrews, & Hobbs, 2009; Krueger & Markon, 2006b; Watson, 2005; Wittchen, Beesdo, & Gloster, 2009), although other data suggest that this theoretical structure might be insufficiently robust to serve as the basis for such a reorganization (Beesdo et al., 2009; Wittchen et al., 2009). For example, the distinction between fear and distress disorders does not emerge in all studies (Beesdo et al., 2009; Krueger, Caspi, Moffitt, & Silva, 1998; Krueger & Finger, 2001; Wittchen, Beesdo-Baum, et al., 2009), and model fit deteriorates when additional disorders are added or when the

model is estimated separately among people at different life-course stages (Watson, 2005; Wittchen, Beesdo-Baum et al., 2009).

Despite these inconsistencies, the general finding of strong comorbidity within the internalizing and externalizing domains has raised the question of whether common risk factors exist for disorders in these domains and, if so, whether risk factors for individual disorders in previous studies are actually risk factors for broader predispositions. This issue of specificity versus generality of risk factors is of considerable importance, as a number of hypotheses about causal pathways posit very specific associations between particular risk factors and particular outcomes. These interpretations would be called into question if empirical research showed that risk factors have less specific predictive effects (Green et al., 2010). In addition, evidence that a risk factor has a broad effect on a wide range of disorders would increase interest in that risk factor as an intervention target (Mrazek & Haggerty, 1994). It is noteworthy that not only environmental risk factors but also genes might be generalized risk targets of this sort, as recent studies suggest that some genes have pleiotropic effects that confer risk for a range of psychiatric disorders (Cross-Disorder Group of the Psychiatric Genomics Consortium, 2013).

Although use of latent variable models to study risk factor specificity is only in its infancy, research already has shown considerable value. For example, Kramer, Krueger, and Hicks (2008) found that the widely observed association of gender with MDD became insignificant when controls were included for latent internalizing and externalizing dimensions, arguing that gender is more directly associated with these overall latent dimensions than with MDD or any other disorder within these dimensions. In another example, Kessler and colleagues (2010) found that the effects of childhood adversities on onset of MDD and other individual mental disorders were largely mediated by more direct effects on predispositions for internalizing and externalizing disorders.

One special class of latent variable risk factor studies uses samples of twins to estimate effects of genetic factors on comorbidity. These studies suggest that much of the comorbidity between particular pairs of mental disorders in epidemiological samples, such as eating disorders and substance use disorders (Baker, Mitchell, Neale, & Kendler, 2010) or nicotine dependence and major depression (Lyons et al., 2008), can be explained by a latent variable model that assumes the existence of genetic influences. More elaborate studies have shown that much of the comorbidity among anxiety disorders (Tambs et al., 2009) and among personality disorders (Kendler et al., 2008) can be explained by similar models. Other studies have shown that intergenerational continuity of childhood-onset externalizing disorders can be explained by a similar genetic model (Bornovalova, Hicks, Iacono, & McGue, 2010) and that decomposition of factor analyses into separate additive genetic and environmental components results in stable internalizing and externalizing factors only for genetic, not environmental, influences (Kendler et al., 2011; Kendler, Prescott, Myers, & Neale, 2003).

It is important to note that the findings of strong genetic influences on comorbidity are constrained by the additivity (i.e., no interactions between genetic and environmental effects) and equal environment (i.e., comparability of environmental similarity between identical and nonidentical twins) assumptions needed to identify standard behavior genetic models. These assumptions have long been the subject of controversy. Caution is consequently needed in interpreting these results (Molenaar, 2010). An additional important implication is that the term *genetic* has a much broader meaning than typically appreciated. For example, as noted by Lewontin in 1974, a genetic effect on tryptophan metabolism mediated through "melatin deposition to skin color to hiring discrimination to lower income" would emerge in a standard twin analysis as documenting strong

"heritability for 'economic success,' " even if the true driving force behind the association was hiring discrimination based on skin color.

The risk factor studies described above treated latent measures of internalizing and externalizing predispositions as independent variables in causal models that predict individual disorders. Most of these studies used cross-sectional data assessing comorbidity at a point in time, although several studies used longitudinal data to determine whether the structure of internalizing and externalizing disorders is stable over time (Krueger et al., 1998). Other longitudinal studies examined temporal progression (Stein et al., 2001) or sequencing (Newman et al., 1996) between earlier and later disorders and documented strong persistence of disorders over time and predictive associations between some, but not other temporally, primary and later disorders. However, none of these studies investigated the extent to which associations of earlier disorders with later disorders were explained by latent internalizing or externalizing variables. For example, Fergusson, Horwood, and Ridder (2007) found that childhood conduct disorder but not attention-deficit/hyperactivity disorder (ADHD) predicted subsequent onset of substance disorders, whereas Beesdo and colleagues (2007) found that temporally primary social anxiety disorder predicted subsequent onset and persistence of MDD. However, they did not study whether these associations were due to effects of latent internalizing or externalizing predispositions.

More recent studies have examined the extent to which latent internalizing and externalizing predispositions might account for development of lifetime comorbidity between MDD and other disorders based on analysis of large-scale community epidemiological surveys that assess lifetime prevalence of mental disorders and use retrospectively reported information on AOO to study time-lagged associations (Kessler, Cox, et al., 2011; Kessler, Ormel, et al., 2011; Kessler, Petukhova, & Zaslavsky, 2011). These analyses find good fit of a latent variable model, suggesting that common causal pathways account for most comorbidities of MDD with other disorders, although evidence exists that MDD and generalized anxiety disorder (GAD) have significant residual associations. The latter might be due to symptom overlap between MDD and GAD (Cramer, Waldorp, van der Maas, & Borsboom, 2010). Thus far, though, all of these analyses have focused on predicting lifetime first onset of MDD using retrospective analyses. A new study based on a large multiwave longitudinal study is currently under way to determine whether the retrospective results can be replicated and extended to study onset and persistence of disorders over time (Beesdo et al., 2009; Beesdo, Pine, Lieb, & Wittchen, 2010).

Clinical Severity

The NCS-R is the only large U.S. national survey that assessed MDD clinical severity. Respondents who met criteria for 12-month MDD were administered the Quick Inventory of Depressive Symptomatology Self-Report (QIDS-SR; Rush, Carmody, & Reimitz, 2000) to assess symptom severity in the worst month of the past year. The QIDS-SR is strongly related to the Hamilton Rating Scale for Depression (HAM-D; Hamilton, 1960). Transformation rules converted QIDS-SR scores into clinical severity categories mapped to conventional HAM-D ranges of *none* (i.e., not clinically depressed), *mild, moderate, severe*, and *very severe*. Over 99% of respondents with 12-month MDD were independently classified by the QIDS-SR as being clinically depressed during the worst month of the year, with 10.4% having mild, 38.6% moderate, 38.0% severe, and 12.9% very severe depression. QIDS-SR mild through severe cases had average episode durations of

13.8–16.6 weeks, whereas very severe cases had average episode duration of 23.1 weeks during the year. Symptom severity was strongly related to role impairment and comorbidity. These results speak directly to the concern that prevalence estimates in community surveys might be upwardly biased due to the inclusion of clinically insignificant cases (Narrow, Rae, Robins, & Regier, 2002). The NCS-R results show this concern is not warranted with respect to MDD.

Consequences of Depression

Psychiatric epidemiologists have traditionally been much more interested in discovering modifiable risk factors (Eaton & Weil, 1955) than in documenting adverse consequences of mental illness (Faris & Dunham, 1939). This situation has changed in recent years, though, because the rise of evidence-based medicine has made it necessary to document societal costs of illness (Gold, Siegel, Russell, & Weinstein, 1996). MDD has emerged as an important disorder in this new work because MDD has been ranked as one of the most burdensome diseases in the world in terms of total disability-adjusted life years (Murray et al., 2012). This high ranking is due to a combination of high lifetime prevalence, early AOO, high chronicity, and high role impairment. Only a brief overview of the studies of impairment in MDD is presented here, with a focus on effects on role incumbency, role performance, morbidity, and mortality. A more detailed review is presented elsewhere (Kessler, 2012).

Life-Course Role Incumbency, Timing, and Transitions

Given its typically early AOO, MDD might be expected to have adverse effects on critical developmental transitions such as educational attainment and timing of marriage. Numerous epidemiological studies have examined these effects. These studies show that MDD and other early-onset mental disorders predict termination of education (Breslau, Lane, Sampson, & Kessler, 2008) and difficulties becoming married (Breslau et al., 2011). Other studies show that premarital MDD predicts divorce. Other studies have examined associations of MDD with employment emphasizing the impact of job loss on MDD rather than MDD as a risk factor for job loss (Dooley, Fielding, & Levi, 1996). However, a recent analysis from the WMH surveys documented the latter association by showing that history of MDD as of the age of completing schooling predicted current (at the time of interview) unemployment and work disability (Kawakami et al., 2012).

Role Performance

A considerable body of research shows that MDD predicts impaired role performance, with a special focus on marital quality and work performance. It has long been known that marital dissatisfaction and discord are strongly related to depressive symptoms (Culp & Beach, 1998; Whisman, 1999). Fewer studies have considered the effects of MDD (Coyne, Thompson, & Palmer, 2002), but the latter studies consistently document significant adverse effects. Considerable research documents that physical violence perpetration and victimization in marital relationships are both significantly associated with MDD (Stith, Smith, Penn, Ward, & Tritt, 2004). Although these studies have generally focused on adverse mental health *consequences* of relationship violence (Afifi et al., 2009), a growing body of research has more recently suggested that marital violence is partly a

consequence of preexisting mental disorders (Kessler, Molnar, Feurer, & Appelbaum, 2001). Indeed, longitudinal studies consistently find that premarital history of MDD predicts subsequent marital violence perpetration (Fang, Massetti, Ouyang, Grosse, & Mercy, 2010) and victimization (Stith et al., 2004).

Considerable research has examined days out of role associated with various physical and mental disorders (Alonso et al., 2004). These studies typically find MDD associated with one of the highest numbers of days out of role at the societal level of any physical or mental disorder due to its combination of high prevalence and strong individual-level effects. In the WMH surveys, for example, 62,971 respondents across 24 countries were assessed for a wide range of common physical and mental disorders, as well as for days out of role in the 30 days before interview (Alonso et al., 2011). MDD was associated with 5.1% of all days out of role, the fourth highest population attributable risk proportion of all disorders considered (exceeded only by headache/migraine, other chronic pain conditions, and cardiovascular disorders) and by far the largest among the mental disorders. A number of epidemiological surveys in the United States have estimated the workplace costs of MDD in absenteeism and low work performance (often referred to as *presenteeism*; Greenberg et al., 2003). These studies found that MDD significantly predicts overall lost work performance. Several studies attempted to estimate the annual salary-equivalent human capital value of these losses. These estimates were in the range of $30.1 billion (Stewart, Ricci, Chee, Hahn, & Morganstein, 2003) to $51.5 billion (Greenberg et al., 2003).

A number of community surveys, most of them carried out in the United States, examined comparative effects of diverse illnesses on various aspects of role functioning (Merikangas et al., 2007). Results typically showed that musculoskeletal disorders and MDD were associated with the highest levels of disability at the societal level among all commonly occurring disorders assessed. The most compelling study of this sort outside the United States was based on 15 national surveys carried out as part of the WMH surveys (Ormel et al., 2008). Disorder-specific disability scores were compared across people who experienced each of 10 chronic physical disorders and 10 mental disorders in the year before the interview. MDD and bipolar disorder were the mental disorders most often rated as severely impairing in both developed and developing countries. None of the physical disorders considered had impairment levels as high as these mood disorders despite the fact that the physical disorders included severe conditions such as cancer, diabetes, and heart disease. Nearly all the higher mental than physical ratings were statistically significant at the .05 level. Another set of surveys examined comparative decrements in perceived health associated with a wide range of disorders (Moussavi et al., 2007). MDD was one of the three disorders associated with the highest decrements in perceived health in these studies.

Morbidity and Mortality

It is well established that MDD is significantly associated with many chronic physical disorders, including arthritis, asthma, cancer, cardiovascular disease, diabetes, hypertension, chronic respiratory disorders, and a variety of chronic pain conditions (Baxter, Charlson, Somerville, & Whiteford, 2011). Although most data documenting these associations come from clinical samples, similar data exist in community epidemiological surveys. These associations have considerable individual and public health significance and can be thought of as representing costs of MDD in at least two ways. First, to the extent that MDD is a causal risk factor, it leads to increased prevalence of physical

disorders. Evidence about MDD as a cause is spotty, though, although we know from meta-analyses of longitudinal studies that MDD is a consistent predictor of subsequent first onset of coronary artery disease, stroke, diabetes, heart attacks, and certain types of cancer. A number of biologically plausible mechanisms have been proposed to explain the prospective associations of MDD with these disorders (de Jonge et al., 2010). Second, even if MDD is a consequence rather than a cause of chronic physical disorders, comorbid MDD is often associated with a worse course of the physical disorder (Gillen, Tennen, McKee, Gernert-Dott, & Affleck, 2001), possibly through nonadherence to treatment regimens (Ziegelstein et al., 2000). Based on these considerations, it is not surprising that MDD is associated with elevated risk of early death (Carney, Freedland, Miller, & Jaffe, 2002). This is true not only because people with MDD have high suicide risk but also because MDD is associated with elevated risk of many types of disorders and with elevated mortality risk among people with certain kinds of disorders.

Conclusions and Future Directions

Epidemiological evidence shows that MDD is a commonly occurring, seriously impairing, and often undertreated disorder. MDD occurs in the context of a very high prevalence of depressed mood and a high prevalence of subsyndromal depressive episodes. MDD is often recurrent and is typically comorbid with other mental disorders that are usually temporally primary in the sense that first lifetime onset of MDD usually occurs after the onset of at least one other lifetime comorbid disorder. Future efforts such as the NIMH RDoC initiative will be needed to identify the neural circuitry, disease mechanisms, and critical periods underlying depression—information essential to improving our current diagnostic, therapeutic, and prevention strategies. Progress in these areas is sorely needed, as evidenced by the structural impairments that occur subsequent to the onset of MDD, including low educational attainment, poor marital outcomes, and poor socioeconomic outcomes. The day-to-day role impairments that occur in conjunction with MDD include poor performance in both productive and social roles. Increased efforts are needed to document the cost-effectiveness of expanded depression treatment and of treatment-quality improvement initiatives. Because employers play such a large part in driving health insurance benefit design in the United States, it is especially important to document the return on investment of expanded depression outreach and treatment from the employer perspective. We also need to expand research on modifiable barriers to help seeking for depression and to evaluate the effectiveness of systematic depression screening and outreach programs designed to increase the proportion of people with depression who seek treatment.

ACKNOWLEDGMENTS

Preparation of this chapter was supported in part by Janssen Pharmaceutical Research and Development and the U.S. Public Health Service (Grant Nos. MH46376, MH49098, MH528611, MH061941, U01-MH060220, and R01-MH070884). Peter de Jonge is supported by a VICI grant (No. 91812607) from the Netherlands Research Foundation (NWO-ZonMW). Marsha A. Wilcox is an employee of Janssen. Portions of this chapter have appeared previously in Kessler et al. (2003), copyright 2003 by the American Medical Association; Kessler, Cox, et al. (2011), copyright 2011 by Wiley Periodicals, Inc.; and Kessler (2012), copyright 2012 by Elsevier. All used with permission. We appreciate the helpful comments of the editors.

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