Chapter 3

Excess Mortality from Mental, Neurological, and Substance Use Disorders in the Global Burden of Disease Study 2010

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INTRODUCTION

Findings from the Global Burden of Disease Study 2010 (GBD 2010) have reinforced the understanding of the significant impact that mental, neurological, and substance use disorders have on population health (Murray and others 2012; Whiteford and others 2013). One key finding was the health transition from communicable to noncommunicable diseases across all regions. This transition was particularly evident in low- and middle-income countries (LMICs) (Murray and others 2012), where the proportion of burden attributable to noncommunicable disease increased from 36 percent in 1990 to 49 percent in 2010, compared with an increase from 80 percent to 83 percent in high-income countries (HICs) (IHME 2013).

GBD 2010 estimates that the majority of disease burden caused by mental, neurological, and substance use disorders is from nonfatal health loss; only 15 percent of the total burden is from mortality in years of life lost (YLLs) (IHME 2013). This finding may erroneously lead to the interpretation that premature death in people with mental, neurological, and substance use disorders is inconsequential. A recent review has shown higher mortality risks than the general population for a range of mental disorders, with a standardized mortality ratio (SMR) as high as 14.7 for opioid use disorders (Chesney, Goodwin, and Fazel 2014). Excess mortality in people with epilepsy is reported to be two- to three-fold higher than that of the general population, with an increased risk up to six-fold higher in LMICs (Diop and others 2005). A significant proportion of these deaths is preventable (Diop and others 2005; Jette and Trevathan 2014).

There are multiple causes for lower life expectancy in people with mental disorders (Chang and others 2011; Crump and others 2013; Lawrence, Hancock, and Kisely 2013). Self-harm is an important cause of death, but the majority of premature deaths are caused by chronic physical disease, particularly ischemic heart disease (IHD), stroke, type II diabetes, respiratory diseases, and cancer (Crump and others 2013; Lawrence, Hancock, and Kisely 2013). Dementia is an independent risk factor for premature death; and patients with physical impairment, inactivity, and medical comorbidities are at increased risk (Park and others 2014).

In many HICs, the life expectancy gap between those with mental disorders and the general population is widening. The general population enjoys a longer life, while the lifespan for those with mental, neurological, and substance use disorders remains significantly lower and unchanged (Lawrence, Hancock, and Kisely 2013). Information on the extent and causes of premature mortality in people with mental, neurological, and substance

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use disorders in LMICs is sparse, but these groups are understood to experience reduced life expectancy, although causes of death may vary across regions.

This chapter explores the cause-specific and excess mortality of individual mental, neurological, and substance use disorders estimated by GBD 2010 and discusses the results. We present the additional burden that can be attributed to these disorders, using GBD results for comparative risk assessments (CRAs) assessing mental, neurological, and substance use disorders as risk factors for other health outcomes. We focus on the following mental, neurological, and substance use disorders:

- Mental disorders, including schizophrenia, major depressive disorder, anxiety disorders, bipolar disorder, autistic disorder, and disruptive behavioral disorders (attention-deficit hyperactivity disorder [ADHD] and conduct disorder [CD])
- Substance use disorders, including alcohol use disorders (alcohol dependence and fetal alcohol syndrome) and opioid, cocaine, cannabis, and amphetamine dependence
- Neurological disorders, including dementia, epilepsy, and migraine.

For the purposes of GBD 2010, countries were grouped into 21 regions and 7 super-regions based on geographic proximity and levels of child and adult mortality (IHME 2014; Murray and others 2012). Regions were further grouped into developed and developing categories using the GBD 2010 method. Details of countries in each region and super-region can be found on the Institute for Health Metrics and Evaluation (IHME) website (IHME 2014).

The mortality associated with a disease can be quantified using two different, yet complementary, methods employed as part of the GBD analyses. First, cause-specific mortality draws on vital registration systems and verbal autopsy studies that identify deaths attributed to a single underlying cause using the International Classification of Diseases (ICD) death coding system. Second, GBD creates natural history models of disease, drawing on a range of epidemiological inputs, which ultimately provide epidemiological estimates for parameters including excess mortality—that is, the all-cause mortality rate in a population with the disorder above the all-cause mortality rate observed in a population without the disorder. By definition, the estimates of excess deaths include cause-specific deaths.

Although arbitrary, the ICD conventions are a necessary attempt to deal with the multi-causal nature of mortality and avoid the double-counting of deaths. Despite the system's clear strengths, cause-specific mortality estimated via the ICD obscures the contribution of other underlying causes of death—for example, suicide as a direct result of major depressive disorder—and likely underestimates the true number of deaths attributable to a particular disorder. However, the estimation of excess mortality using natural history models often includes deaths from causal and noncausal origins and likely overestimates the true number of deaths attributable to a particular disorder. The challenge is to parse out causal contributions to mortality, beyond those already identified as cause-specific, from the effects of confounders.

The quantification of the burden attributable to risk factors requires approaches such as CRA, which is now an integral part of the GBD studies. The fundamental approach is to calculate the proportion of deaths or disease burden caused by specific risk factors—for example, lung cancer caused by tobacco smoking—while holding all other independent factors constant. A counterfactual approach is used to compare the burden associated to an outcome with the amount expected in a hypothetical situation of ideal risk factor exposure, for example, zero prevalence. This provides a consistent method for estimating the changes in population health when decreasing or increasing the level of exposure to risk factors (Lim and others 2012).

METHODOLOGY

Years of Life Lost and Cause of Death

The GBD uses YLLs to quantify the fatal burden due to a given disease or injury (Lozano and others 2012). YLLs are computed by multiplying the number of deaths attributable to a particular disease at each age by a standard life expectancy at that age. The standard life expectancy represents the normative goal for survival; for GBD 2010, it was computed based on the lowest recorded death rates in any age group in countries with populations greater than five million (Salomon and others 2012).

Cause-specific death estimates in GBD 2010 were produced from available cause-of-death data for 187 countries from 1980 to 2010. Data sources included vital registration, verbal autopsy, mortality surveillance, censuses, surveys, hospitals, police records, and mortuaries (Lozano and others 2012). Because cause-of-death data are often not available or are subject to substantial problems of comparability, a method of modeling cause-of-death estimates and trends was developed. Cause of Death Ensemble Modeling (CODEm) was used for all mental, neurological, and substance use disorders (Foreman and others 2012). CODEm uses four families of statistical models testing a large set of different models using different permutations of covariates. Model

ensembles were developed from these component models, and model performance was assessed with rigorous out-of-sample testing of prediction error and the coverage of 95 percent uncertainty intervals. Details relating to CODEm and the method for how these models were used in calculating YLLs are described in detail elsewhere (Foreman and others 2012; Lozano and others 2012).

Ultimately, YLLs for GBD 2010 were computed from cause-specific mortality estimates for only 7 of the 15 mental, neurological, and substance use disorders investigated in this chapter (Lozano and others 2012):

- Dementia
- Epilepsy
- Schizophrenia
- Alcohol use disorders (including alcohol dependence and fetal alcohol syndrome)
- Opioid dependence
- Amphetamine dependence
- Cocaine dependence.

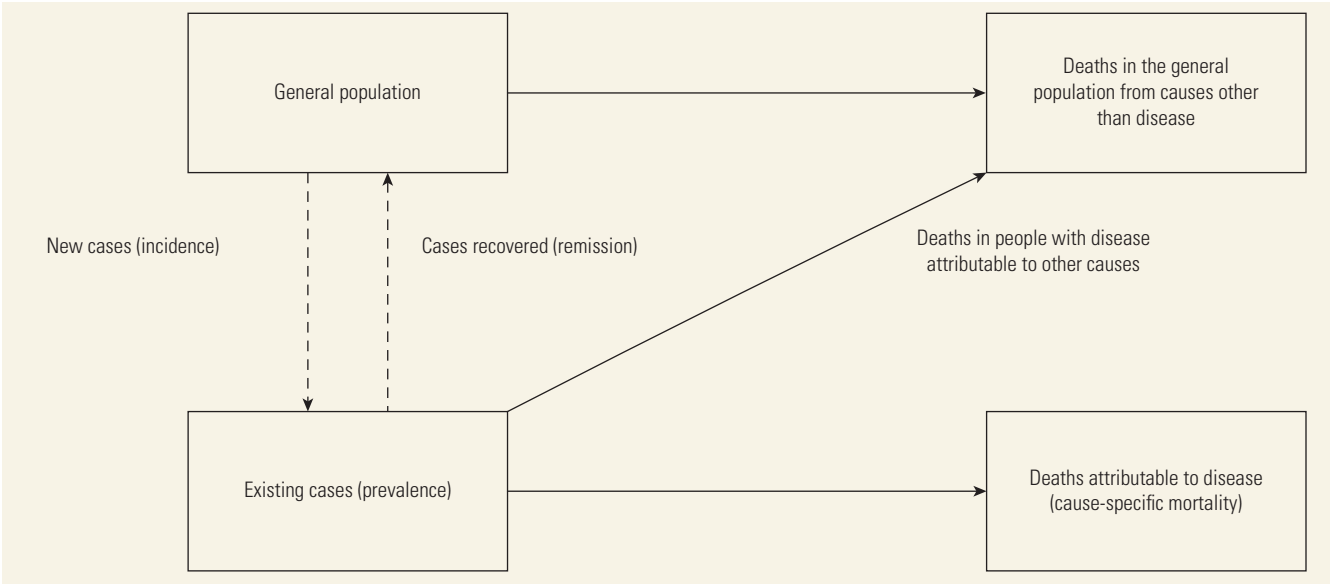
The justification for this selection lies in the rules of the ICD, which specify that the recorded cause of death should be the primary or direct cause of death, resulting in several important disorders being absent from the ICD cause-of-death list (Lim and others 2012; WHO 1993). For example, a person dying from endocarditis caused by injecting drug use is likely to have the cause of death coded to endocarditis rather than the substance use disorder.

Excess Mortality from Natural History Models

The GBD 2010 methods for developing a natural history model of disease using DisMod-MR are discussed in chapter 2 in this volume (Whiteford and others 2015) and in detail elsewhere (Ferrari and others 2013; Murray and others 2012). DisMod-MR is a Bayesian meta-regression tool that estimates a generalized negative binomial model for all epidemiological data (Murray and others 2012). The primary role of this modeling is to derive internally consistent models of prevalence that are used to produce burden of disease estimates—years lived with disability (YLDs) and disability-adjusted life years (DALYs). The models also provide estimates of other epidemiological parameters, utilizing the relationship described in figure 3.1 (Murray and others 2012). Excess mortality estimates for mental, neurological, and substance use disorders were made available through this process.

Cause-specific mortality estimated using ICD coding rules does not consider the contribution of underlying causes of death. However, estimates of excess deaths produced by DisMod-MR include deaths from causal and noncausal origins and therefore overestimate the true number of deaths attributable to a particular disorder. In this chapter, although we compare GBD 2010 estimates from both of these data sources and discuss the discrepancies between the two, caution should be exercised in interpreting the excess mortality data attributable to mental, neurological, and substance use disorders.

Figure 3.1 Generic Disease Model



Source: Adapted from Barendregt and others 2003, figure 1.

Counterfactual Burden and Comparative Risk Assessment

Using counterfactual analysis, the effect of a risk factor can be quantified by comparing the burden associated with an outcome with the amount expected in a hypothetical situation of ideal risk factor exposure. Prince and others (2007) have summarized the evidence where causal relationships between mental and substance use disorders and other health outcomes have been proposed. In GBD 2010, reviews were conducted to assess the strength of evidence for mental, neurological, and substance use disorders as independent risk factors for other health outcomes (Charlson and others 2011; Degenhardt and Hall 2012; Degenhardt, Hall, and others 2009; Rehm, Baliunas, and others 2010). Risk factor studies were identified through systematic searches of published and unpublished data, and information on effect sizes and study characteristics was extracted and collated (Charlson and others 2013; Degenhardt, Whiteford, and others 2013; Ferrari and others 2014).

Data were metasynthesized to calculate relative risks (RR) for mental and alcohol use disorders (the exposures) as risk factors for other health outcomes. These included mental and substance use disorders collectively as risk factors for suicide, alcohol use as a risk factor for a range of health outcomes, and injecting drug use as a risk factor for blood-borne viruses. The RR was applied to prevalence distributions of the specific exposures by gender and age group for each region to derive population attributable fractions (PAFs). The additional burden (YLLs and YLDs) attributable to mental, neurological, and substance use disorders is the product of the PAFs and the burden for the health outcome as estimated in GBD 2010. More detail on the calculation of PAFs in GBD 2010 is provided by Lim and others (2012).

MORTALITY AND MENTAL, NEUROLOGICAL, AND SUBSTANCE USE DISORDERS

Causal Mortality and Years of Life Lost

The seven disorders for which YLLs were estimated in GBD 2010 were directly responsible for 840,000 deaths in 2010, or approximately 20 million YLLs (figure 3.2). Online annex 3A further summarizes the YLLs allocated to mental, neurological, and substance use disorders by disorder, age, and gender. The YLLs attributable to each disorder as a proportion of total YLLs caused by mental, neurological, and substance use disorders highlight several key points. Globally, epilepsy contributed the greatest proportion of YLLs within this group, followed by dementia. Although the impact of substance use disorders, specifically alcohol and opioid dependence, is evident, the comparatively smaller contribution of several mental disorders is a finding that requires further explanation.

Examination of age-standardized YLL rates indicates large variations across the seven GBD 2010 geographical super-regions, primarily because of differences in patterns of alcohol use disorders, drug dependence, and mental and neurological disorder prevalence. Several regions have significant deviations from the global average YLL rates (figure 3.3).

In figure 3.3, amphetamine and cocaine dependence have been aggregated under psychostimulant dependence. Details of which countries are in each super-region can be found on the IHME website (IHME 2014).

In 2010, YLL rates were highest in Sub-Saharan Africa (604 YLLs per 100,000 population) and Central/Eastern Europe and Central Asia (593 YLLs per 100,000); the causes of these high fatal burden estimates vary considerably (figure 3.3). In Sub-Saharan Africa, the YLL burden was driven by epilepsy, which accounted for 511 YLLs per 100,000 population. This rate is fourfold higher than the global average and approximately 85 percent of all YLLs attributed to mental, neurological, and substance use disorders in the region. Sub-Saharan Africa has comparatively lower YLL rates for substance use disorders; however, illicit drug dependence YLLs increased by 3.0 percent from 1990 to 2010, almost double the average global increase and the highest of all regions. The Middle East and North Africa follows with a 2.6 percent increase (Degenhardt, Whiteford, and others 2013).

The high fatal burden in Central/Eastern Europe and Central Asia was largely caused by deaths attributed to alcohol use disorders. These disorders accounted for 331 YLLs per 100,000 population, compared with a global average of 57 YLLs per 100,000 population. High mortality caused by illicit drug use disorders also contributed to the YLL rate in Central/Eastern Europe and Central Asia, with all substance use disorders together explaining 73 percent of YLLs in the region.

Substance use disorders also explained a high proportion of total mental, neurological, and substance use YLLs in Latin America and the Caribbean and in HICs. In Latin America and the Caribbean, substance use disorders accounted for 142 YLLs per 100,000 population (54 percent of the region's mental, neurological, and substance use YLLs). In HICs, substance use disorders accounted for 151 YLLs per 100,000 population (49 percent of the region's mental, neurological, and substance use YLLs). Countries in East Asia and Pacific exhibit very low YLL rates across all mental, neurological, and substance use disorders, with little change observed between 1990 and 2010.

Globally, neurological disorders accounted for 58 percent of all mental, neurological, and substance use disorder YLLs in men, and 81 percent in women. Substance use disorders explained 39 percent of YLLs in men and 16 percent in women. The contribution of schizophrenia to total mental, neurological, and substance use disorder YLLs was similar for both genders, at 3 percent each.

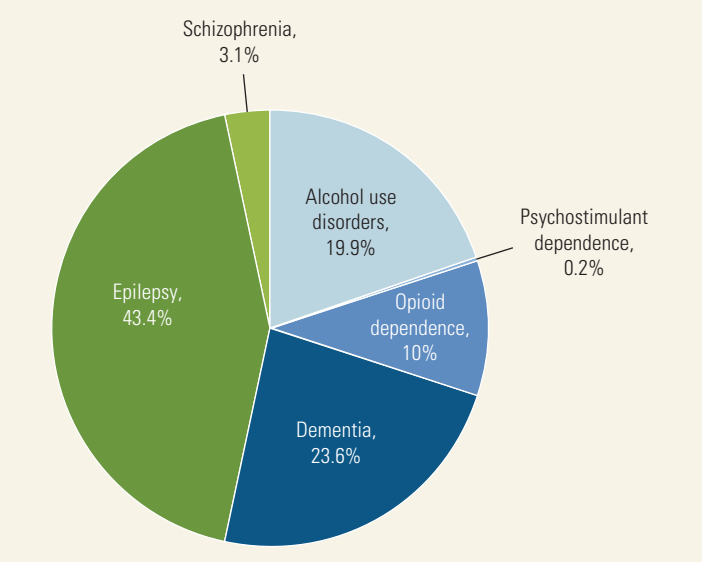
Differences in YLL patterns between the genders were influenced in part by the differing contribution to YLLs of substance use disorders compared with neurological disorders across regions. Where substance use disorders dominated YLLs, their higher prevalence in men drove up the overall YLL rates in men, compared with women. Interestingly, the gender differential was not stable across regions: in Central/Eastern Europe and Central Asia, there was a smaller gender difference in the proportion of YLLs caused by alcohol use disorders (61 percent of mental, neurological, and alcohol use disorder YLLs in men and 40 percent in women). A much larger gender differential exists in Latin America and the Caribbean, where 57 percent of YLLs were caused by alcohol use disorders in men and 15 percent in women. The gender differential for YLLs caused by alcohol use disorders was comparatively smaller in HICs: 28 percent of YLLs in men and 13 percent of YLLs in women, compared with the global mean of 27 percent and 9 percent, for men and women, respectively.

In those regions where neurological disorders contribute the greater proportion of YLLs, the gender differential was considerably smaller, as shown in figure 3.4. In Sub-Saharan Africa, for example, where epilepsy deaths were very high, there was less of a gender difference: epilepsy explained 84 percent of mental, neurological, and substance use disorder YLLs in men, compared with 86 percent in women. In South Asia, epilepsy contributed 60 percent of YLLs in men and 65 percent in women.

Excess Mortality from a Natural History Model

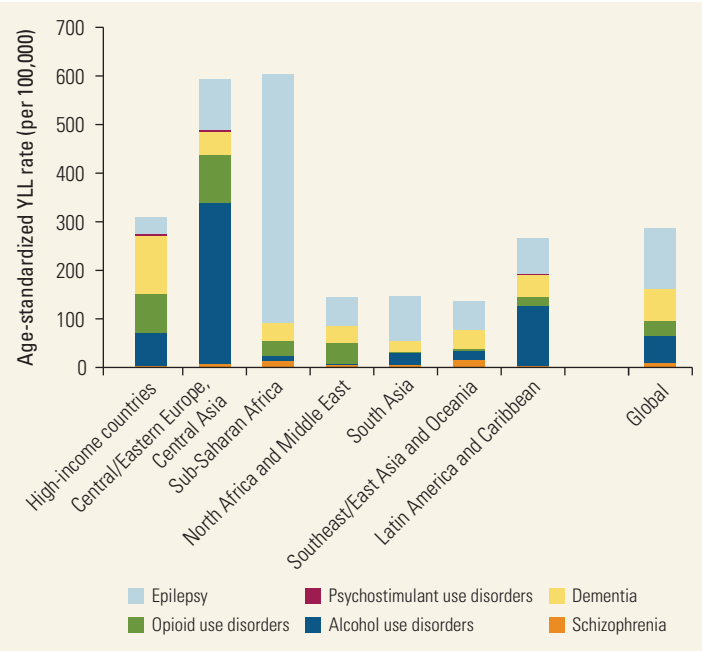
The GBD cause-of-death modeling translates to a relatively small YLL burden attributable to mental, neurological, and substance use disorders; however, to conclude that mental disorders are not associated with premature death would be misleading. The mental disorders for which cause-specific deaths and YLLs were estimated in GBD 2010 were schizophrenia and anorexia nervosa (the latter is not considered in this chapter). Several other mental disorders, such as major depressive disorder and bipolar disorder, exhibit significant and documented excess mortality (Baxter, Page, and Whiteford 2011; Roshanaei-Moghaddam and Katon 2009) (table 3.1).

Figure 3.2 Age-Standardized YLL Rates by Disorder, as a Proportion of Global YLL Rates for Mental, Neurological, and Substance Use Disorders, per 100,000 Population, 2010



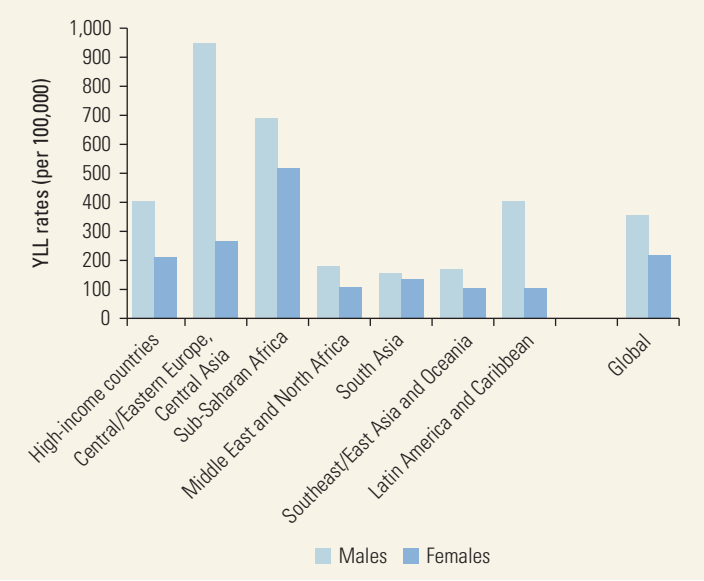
Source: IHME 2013.
Note: For the purposes of this graph, amphetamine and cocaine dependence have been aggregated under psychostimulant dependence. The individual disorder proportions are amphetamine dependence (0.1 percent) and cocaine dependence (0.1 percent). YLLs = years of life lost.

Figure 3.3 Age-Standardized YLL Rates for Mental, Neurological, and Substance Use Disorders, by GBD 2010 Super-Region and Disorder, per 100,000 Population, 2010



Source: IHME 2013.
Note: GBD = Global Burden of Disease; YLL = year of life lost.

Figure 3.4 Age-Standardized YLL Rates for Mental, Neurological, and Substance Use Disorders, by GBD 2010 Super-Region and Gender, per 100,000 Population, 2010



Source: IHME 2013.
Note: GBD = Global Burden of Disease; YLL = year of life lost.

These were not included in the estimated cause-specific deaths and YLLs, because the method for cause-of-death estimation, where death counts are used to calculate YLLs, can only be attributed to the primary ICD cause of death.

Examination of excess mortality derived from natural history models of disease allows for a better appreciation of the contribution of underlying diseases to poor health outcomes. There were five disorders for which sufficient evidence of excess all-cause mortality could not be found in the literature—anxiety disorders, ADHD, CD, cannabis dependence, and migraine—and no estimations of excess mortality were made.

Mental Disorders

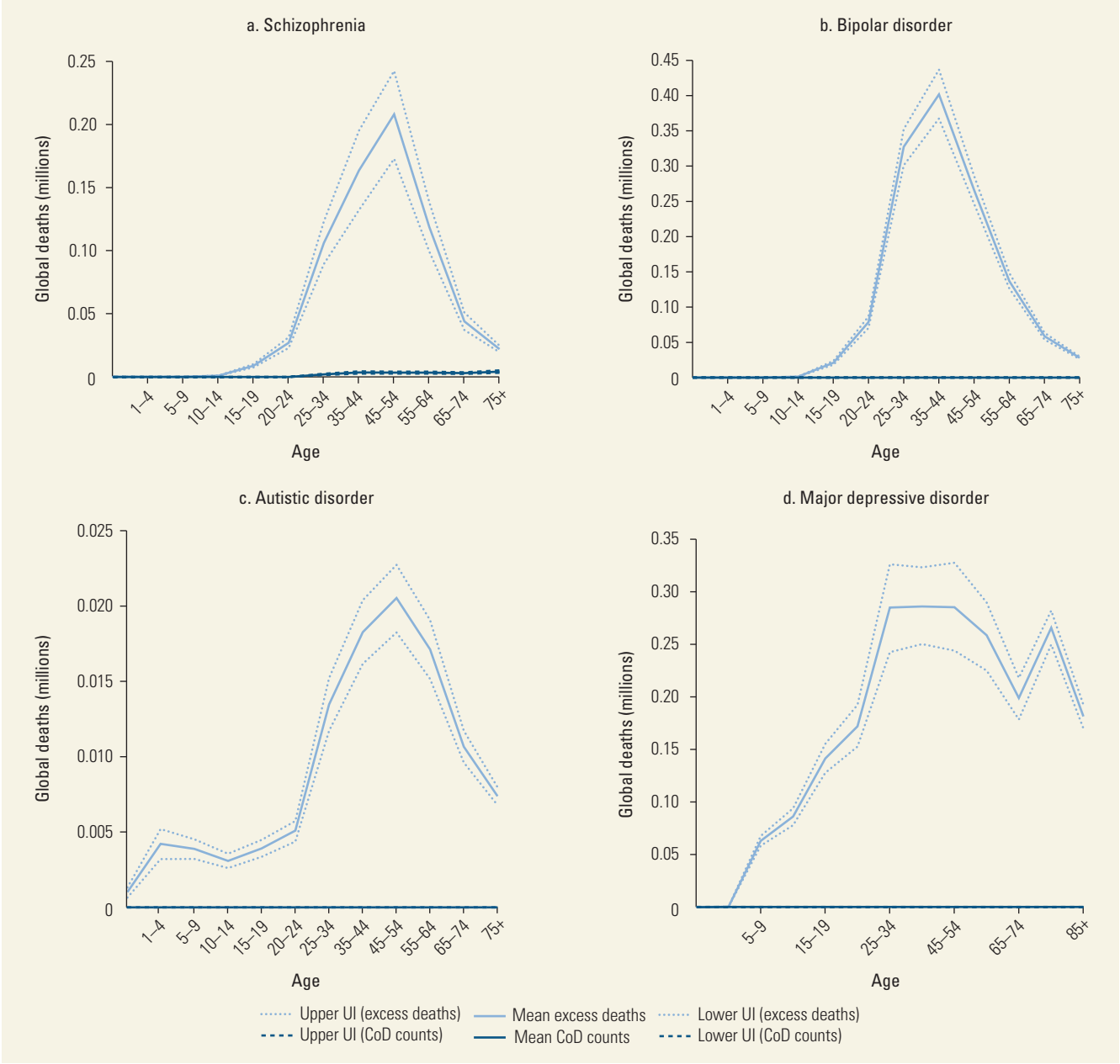
Figure 3.5 shows the estimated number of cause-specific and excess deaths for each of the five mental disorders, with estimated excess mortality by age and uncertainty bounds. Inspection of excess deaths suggests that schizophrenia, major depressive disorder, bipolar disorder, and autistic disorder are all associated with significant premature mortality not reflected in YLL calculations. This work should be interpreted with caution, given that not

Table 3.1 Presence of Cause-Specific Mortality and Excess Mortality Attributed to Mental, Neurological, and Substance Use Disorders in GBD 2010

Disorders	Cause-specific mortality attributed to disorders in GBD 2010	Excess mortality attributed to disorders in GBD 2010
Mental disorders		
Major depressive disorder	No	Yes
Anxiety disorders	No	No
Schizophrenia	Yes	Yes
Bipolar disorders	No	Yes
Disruptive behavioral disorders: ADHD and CD	No	No
Autistic disorder	No	Yes
Substance use disorders		
Alcohol use disorders[a]	Yes	Yes
Opioid dependence	Yes	Yes
Cannabis dependence	No	No
Amphetamine dependence	Yes	Yes
Cocaine dependence	Yes	Yes
Neurological disorders		
Epilepsy	Yes	Yes
Migraine	No	No
Dementia	Yes	Yes

Note: ADHD = attention-deficit hyperactivity disorder; CD = conduct disorder; GBD = Global Burden of Disease study.
a. Cause-specific deaths for alcohol use disorders include those from alcohol dependence and fetal alcohol syndrome; differentially, excess deaths represent those from alcohol dependence only.

Figure 3.5 Cause-Specific and Excess Deaths Attributed to Mental Disorders, by Age, with 95 percent Uncertainty, 2010



Source: IHME 2013.
Note: CoD = cause-specific deaths; UI = uncertainty interval. Disruptive behavioral disorders (attention-deficit hyperactivity disorder and conduct disorder) and anxiety are not shown, as cause-specific and excess mortality were not estimated.

all the excess deaths estimated by DisMod-MR will be causally attributable to the disorder. A complex interplay of risk factors will typically contribute to the high rates of all-cause mortality in people with mental disorders.

Mental disorders can directly impact the risk of chronic disease through underlying biochemical mechanisms (Stapelberg and others 2011). For example, major depression is linked to higher rates of coronary heart disease (Charlson and others 2011). Lifestyle risk factors and the use of medications in the treatment of some mental disorders contribute to higher morbidity and mortality rates through increased risk of obesity and metabolic dysfunction. Smoking rates are significantly higher in people with mental disorders (Lasser and

others 2000); this group experiences disproportionate tobacco-related harm.

Despite their increased exposure to chronic disease risk factors, people with mental disorders have inequitable access to health care, with less opportunity for metabolic risk factor screening (Crump and others 2013) and early cancer detection (Kisely, Campbell, and Wang 2009) and lower rates of common prescriptions and procedures (Kisely and others 2007; Laursen and others 2009), even in HICs.

Schizophrenia. People with schizophrenia have well-documented premature mortality (Laursen 2011), but very few YLLs in GBD 2010. Although schizophrenia is one of the few mental disorders with cause-specific deaths permissible by ICD, the number of cause-specific deaths globally (approximately 20,000) is noticeably lower compared with the number of all-cause deaths (approximately 700,000) ascribed by the disorder's natural history.

Research from HICs suggests that men with schizophrenia die about 15 years earlier than men without schizophrenia; women with schizophrenia die, on average, 12 years earlier than women without schizophrenia (Crump and others 2013; Lawrence, Hancock, and Kisely 2013). The majority of these deaths is due to chronic disease; cardiovascular disease accounts for more than 33 percent of all premature deaths in those with schizophrenia (Crump and others 2013; Lawrence, Hancock, and Kisely 2013). Suicide, homicide, and accidents account for less than 15 percent of excess deaths (Crump and others 2013; Lawrence, Hancock, and Kisely 2013).

The side effects of antipsychotic medications, particularly weight gain and impaired glucose tolerance, increase the risk of excess mortality in people regularly taking these medications. Despite concerns over the side effects of antipsychotic medication, the lack of antipsychotic treatment has been linked with higher all-cause mortality rates (hazard ratio [HR] 1.45; 95% confidence interval [CI], 1.20-1.76), with the highest risks attributed to suicide (HR 2.07; 95% CI, 0.73-5.87) and cancer (HR 1.94; 95% CI, 1.13-3.32) (Crump and others 2013). Research shows that although cancer-related death rates are higher in this group, people with schizophrenia are at lower risk of developing cancer (Grinshpoon and others 2005). High mortality rates therefore likely reflect inadequate and unequal access to health care and lower rates of diagnostic screening. Multiple medications and discontinuation of medication also appear to increase the risk of all-cause death (Haukka and others 2008; Joukamaa and others 2006).

Research suggests that the majority of excess mortality in people with schizophrenia could be directly attributable to their condition: a strong and consistent relationship between schizophrenia and higher death rates has been shown; the onset of schizophrenia generally precedes the physical health condition causally associated with their death; and plausible biological pathways exist through the side effects of medication and unhealthy behaviors directly related to the condition (Laursen, Nordentoft, and Mortensen 2014). Although poverty may be a confounding factor, with schizophrenia more prevalent in low socioeconomic populations that tend to experience poorer health outcomes, evidence indicates that people with schizophrenia move to these populations because of the impact of their disorder, such as difficulty in securing education and employment because of cognitive and social problems (Lambert, Velakoulis, and Pantelis 2003). Accordingly, schizophrenia can be the mediating factor for poorer socioeconomic and health outcomes.

Bipolar Disorder. Approximately 1.3 million excess deaths were estimated in the natural history model of bipolar disorder. However, in contrast to schizophrenia, no cause-specific deaths are attributed to the disorder. The natural history of the disease suggests that bipolar disorder is associated with more excess deaths globally than schizophrenia. Research from the United Kingdom suggests that the excess mortality rates in schizophrenia and bipolar disorder are comparable (Chang and others 2011); the higher number of deaths is likely explained by the higher population prevalence of bipolar disorders (58.9 million cases in 2010, compared with 23.8 million cases for schizophrenia) (Whiteford and others 2013). An estimated 80 percent of premature deaths in people with bipolar disorder is caused by physical disease, almost 50 percent of which is cardiovascular disease (Westman and others 2013). Unnatural causes account for nearly 20 percent of premature deaths (Westman and others 2013).

Autistic Disorder. GBD 2010 estimated that more than 100,000 excess deaths were caused by autistic disorder. There is clear evidence of premature mortality in the natural history of autistic disorder, despite lack of disorder-specific deaths registered using ICD codes. People with developmental disorders are at twice the risk of premature death compared with the general population (Mouridsen and others 2008). There are several causes of elevated death rates in autistic disorder, including accidents, respiratory diseases, and seizures (Mouridsen and others 2008; Shavelle, Strauss, and Pickett 2001). Autism spectrum disorders are highly comorbid, with a range of potentially life-limiting physical conditions, including epilepsy and chromosomal disorders such as fragile X

syndrome (Gillberg and Billstedt 2000), which suggest shared underlying pathophysiology. Without an identified temporal sequence in onset of these comorbid disorders and a plausible biological pathway, it is likely that the causal relationship between autistic disorder and elevated mortality may be due more to the presence of comorbid conditions rather than autistic disorder itself (Bilder and others 2013; Lee and others 2008).

Major Depressive Disorder. No deaths were coded to major depressive disorder in GBD 2010, because the disorder was absent from the list of ICD cause-of-death codes. Natural history models of major depressive disorder suggest that more than 2.2 million excess deaths occurred in this group. In GBD 2010, no YLLs and no excess all-cause mortality were found for dysthymic disorder, consistent with previous findings (Baxter, Page, and Whiteford 2011).

As is the case for other disorders, YLL calculations based on cause-of-death estimates for major depressive disorder highlight the gap between those deaths that can be causally attributed to a disorder and excess deaths, some of which will not be directly attributable to the disorder. More than two million excess deaths produced by DisMod-MR in 2010 is high, and likely to be an overestimate of directly attributable deaths when considered in a strict cause-and-effect framework, but this finding highlights the importance of deciphering the complex interplay of factors linking major depressive disorder with other health outcomes.

Anxiety Disorders. The information on excess mortality in anxiety disorders is inconsistent. Some anxiety disorders, especially severe presentations of post-traumatic stress disorder, have been associated with increased deaths caused by IHD, neoplasms, and intentional and unintentional injuries (Ahmadi and others 2011; Lawrence, Hancock, and Kisely 2013). There is insufficient information, however, to determine whether premature mortality is significantly raised across the entire spectrum of anxiety disorders (Baxter and others 2014). In GBD 2010, no YLLs or excess mortality were associated with the natural history of disease applied to the broad category of anxiety disorders.

Disruptive Behavioral Disorders. Disruptive behavioral disorders are associated with poor health outcomes across the lifespan. Research shows that children with ADHD or CD are two to three times more likely to experience unintentional injuries requiring medical attention than children without behavioral disorders (Lee and others 2008; Rowe, Maughan, and Goodman 2004). The most commonly reported injuries included burns, poisoning, and fractures (Rowe, Maughan, and Goodman 2004). Adolescents and young adults with inattention disorders are more likely to be involved in traffic accidents (Jerome, Segal, and Habinski 2006). Adults who were identified with behavioral disorders in childhood are at higher risk of cigarette smoking, binge drinking, and obesity (von Stumm and others 2011).

Despite the strong evidence of an association between childhood behavioral disorders and poorer health outcomes, insufficient data are available to model the natural history of disease; accordingly, no estimates quantify excess mortality in this group at the population level. However, it is likely that a significant proportion of excess mortality is causally attributable to these conditions. There is not only an implicit temporal relationship between onset of ADHD (that is, several symptoms must be present prior to age 12) and dangerous driving, but also a plausible biological mechanism in the relationship, specifically, the characteristic pattern of inattention and impulsivity of ADHD that leads to dangerous driving.

Substance Use Disorders

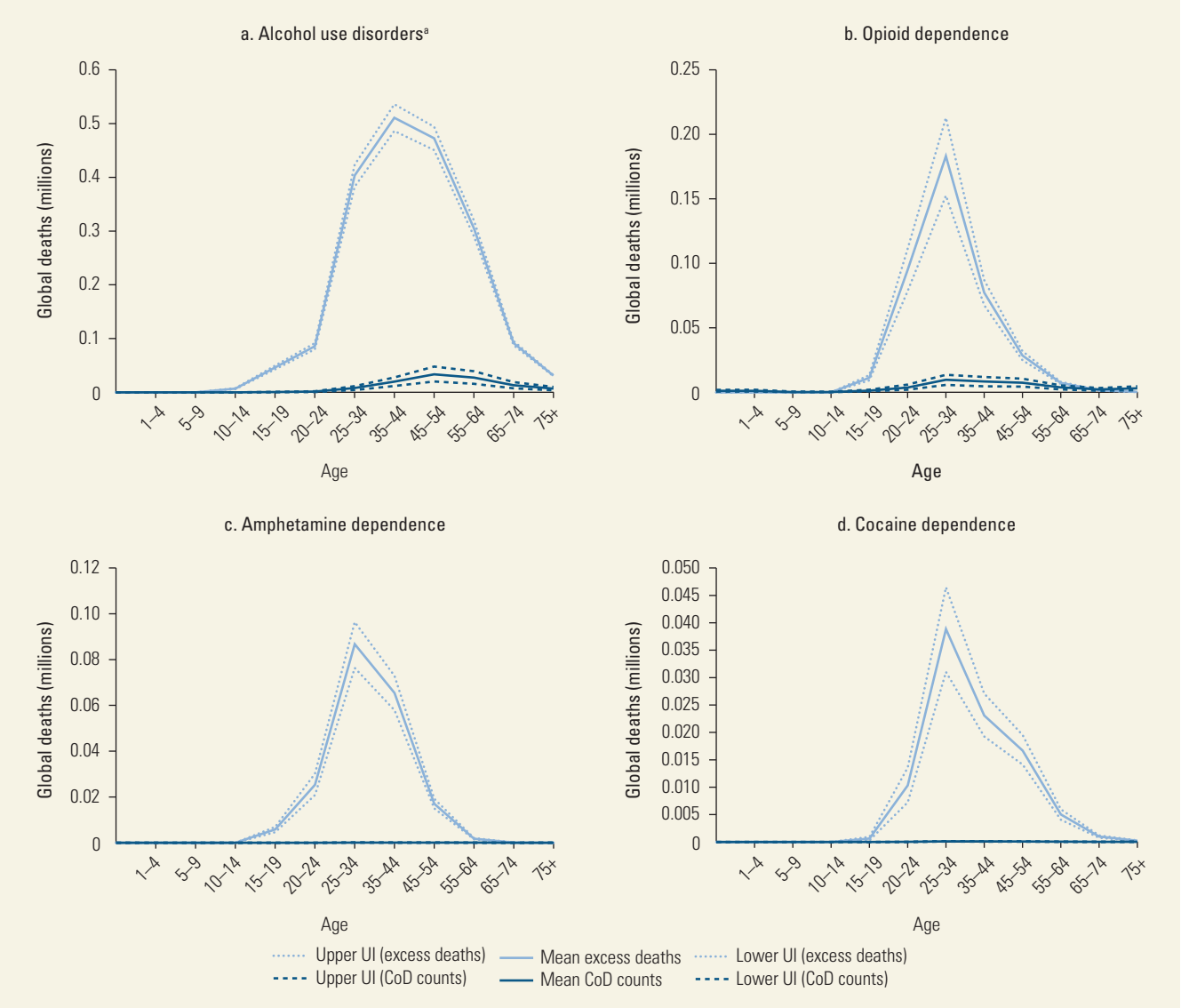
Figure 3.6 shows the estimated number of cause-specific and excess deaths for each substance use disorder, with estimated excess mortality by age and uncertainty bounds.

Alcohol Use Disorders. The number of cause-specific deaths attributed to alcohol use disorders in 2010 (111,000) was substantially lower than the number of excess deaths (1.95 million) calculated using natural history models.

Light to moderate alcohol consumption has been associated with lower rates of some diseases, such as diabetes mellitus and coronary heart disease. However, heavy consumption has been associated with increased rates of chronic diseases, including cancer; mental, neurological, and substance use disorders; cardiovascular disease; and liver and pancreas diseases (Rehm, Baliunas, and others 2010):

- Evidence suggests that alcohol may be a carcinogen in humans, with particularly strong causal links established between alcoholic beverage consumption and oral cavity, pharynx, larynx, esophagus, liver, colorectal, and female breast cancers (Rehm, Baliunas, and others 2010).
- A consistent relationship has been found between heavy alcohol consumption and epilepsy (Rehm, Baliunas, and others 2010).
- Alcohol has been implicated in the development of depression and personality disorders, although the

Figure 3.6 Cause-Specific and Excess Deaths Attributed to Substance Use Disorders, by Age, with Uncertainty, 2010



Source: IHME 2013.

Note: CoD = cause-specific deaths; UI = uncertainty interval. Cannabis is not shown, as there was no cause-specific or excess mortality.

a. Cause-specific deaths for alcohol use include those from alcohol dependence and fetal alcohol syndrome; differentially, excess deaths represent those from dependence only.

direction of causality and the effects of confounding factors remain uncertain (Rao, Daley, and Hammen 2000; Rohde and others 2001).

- The relationship between alcohol consumption and liver cirrhosis is well recognized, but alcohol use disorders appear to be more strongly related to cirrhosis mortality versus morbidity, as it negatively affects the course of existing liver disease (Rehm, Baliunas, and others 2010).
- Heavy alcohol use is related to higher rates of infectious diseases, such as tuberculosis, and unintentional and intentional injuries, with strong evidence for a dose-response relationship (Rehm, Baliunas, and others 2010).
- The risk of death through injuries and self-harm is elevated, accounting for approximately 30 million YLLs globally.

The elevated risks in those with alcohol use disorders appear to be mediated by the quantity of alcohol consumed and the drinking pattern (Rehm, Baliunas, and others 2010).

Illicit Drug Use Disorders. Between 95,800 (in cocaine dependence) and 404,000 (in opioid dependence) excess deaths occurred in dependent illicit drug users in 2010, compared with 78,000 deaths in which illicit drug use was identified as the explicit cause. The majority of these cause-specific deaths—43,000—are attributable to opioid dependence (Degenhardt, Whiteford, and others 2013).

Excess and premature deaths in illicit drug users occur in several ways, including the acute toxic effects of illicit drug use that may lead to overdose, specifically, the cause-specific deaths captured by the ICD coding system. In addition, substantial numbers of deaths are likely to be caused by the more indirect effects of intoxication that result in accidental injuries and violence, cardiovascular disease, liver disease, and a range of mental disorders. Suicide is an important outcome, particularly for opioid users, where an SMR of approximately 14 has been reported in two separate reviews (Chesney, Goodwin, and Fazel 2014; Degenhardt and others 2011). The injection of drugs carries a high risk of blood-borne bacterial and viral infections, notably, human immunodeficiency virus and acquired immune deficiency syndrome (HIV/AIDS), hepatitis B, and hepatitis C (Mathers and others 2010; Nelson and others 2011).

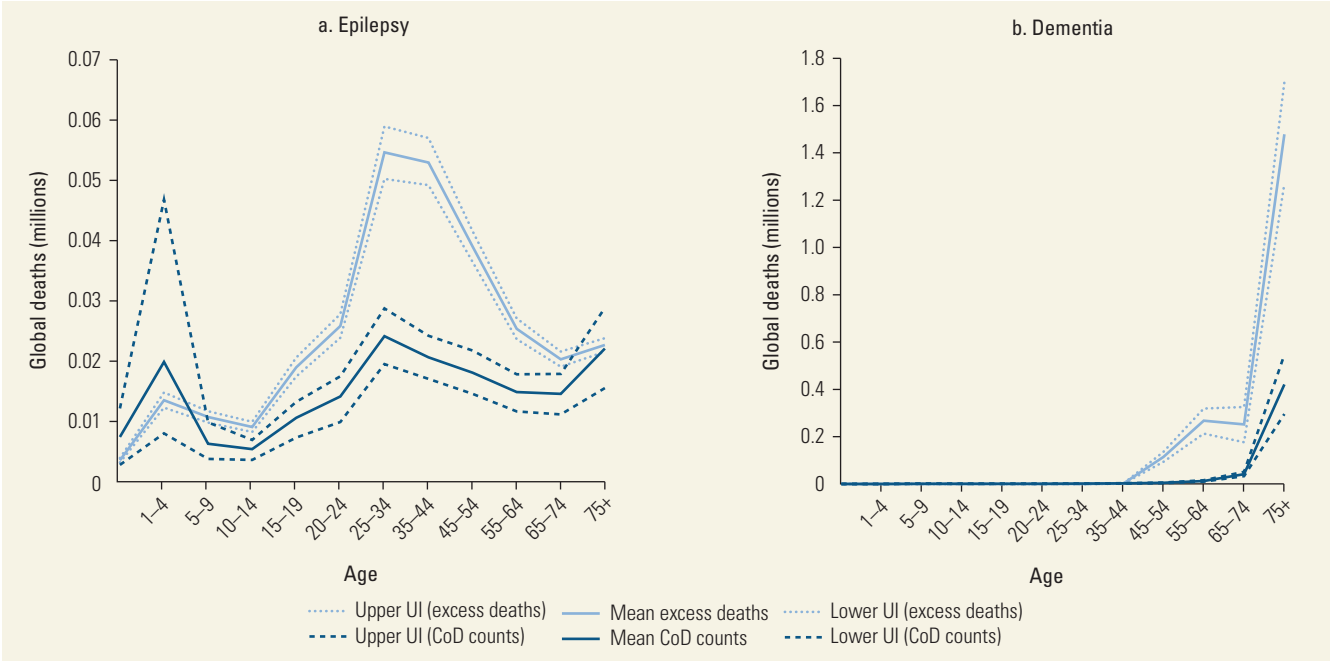
Neurological Disorders

Cause-specific death estimates are more substantial for neurological disorders (figure 3.7), resulting in a smaller gap between cause-specific and excess deaths. This finding may reflect the increasing recognition of neurological disorders as the primary cause of death.

Epilepsy. Epilepsy was modeled as an envelope condition in GBD 2010; idiopathic epilepsy and epilepsy were secondary to a range of causes, including meningitis, neonatal tetanus, iodine deficiency, and a variety of birth complications modeled as one disorder. Cause-of-death modeling estimated nearly 200,000 deaths caused by epilepsy in 2010; natural history models show approximately 300,000 excess deaths. The high number of deaths in young children is clear in figure 3.7.

Mortality in people with epilepsy is generally two- to three-fold higher than mortality in the general community (Preux and Druet-Cabanac 2005; Trinka and others 2013). The relative mortality in those with epilepsy in LMICs is significantly higher than in HICs (Carpio and others 2005; Diop and others 2005), particularly in poorer, rural populations (Carpio and others 2005). Mortality data from HICs show that most deaths are caused by underlying conditions, such as neoplasms, cerebrovascular diseases, and cardiac disease (Spencer 2014); a greater proportion of deaths in LMICs appears to be related to epilepsy (Carpio and others 2005; Diop and others 2005) or to accident or injury (Carpio and others 2005; Kamgno, Pion, and Boussinesq 2003;

Figure 3.7 Numbers of Cause-Specific and Excess Deaths Attributed to Neurological Disorders, by Age, with Uncertainty, 2010



Source: IHME 2013.
Note: CoD = cause-specific deaths; UI = uncertainty interval. Migraine is not shown, as there was no cause-specific or excess mortality.

Mu and others 2011). These differences could be due partly to methodological differences or to genuine differences caused by the etiology of the disease and environmental risk factors.

The proportion of deaths attributable to epilepsy differs by region. In GBD 2010, Sub-Saharan Africa had the highest death rates caused by epilepsy (Murray and others 2012). Importantly, studies have shown that a large proportion of these deaths—those attributable to falls, drowning, burns, and status epilepticus—is preventable (Diop and others 2005; Jette and Trevathan 2014). In a large cohort of people with active convulsive epilepsy in rural Kenya, 38 percent of epilepsy-related deaths were caused by status epilepticus. Mortality in this cohort was more than six-fold greater than expected and associated with nonadherence to (or unavailability of) anti-epileptic drugs, cognitive impairment, and age (Ngugi and others 2014).

Kamgno, Pion, and Boussinesq (2003) found similarly high mortality rates in Cameroon, associated with poor access to or compliance with medical treatment. In a study of 164 patients with epilepsy followed for 30 years in Tanzania and treated with phenobarbital, 67.1 percent of the patients died, a mortality rate twice that of the rural Tanzanian population. The causes of death were related to epilepsy in more than 50 percent of the patients and included status epilepticus, drowning, and burns (Jilek-Aall and Rwiza 1992).

In other LMICs outside Sub-Saharan Africa, the preventable causes of death in epilepsy patients are also a significant factor. Drowning is the most common cause of premature death in rural China (proportional mortality ratio = 82.4 percent). This finding is attributed in part to geographic and occupational risk hazards that include living and working around ponds, paddy fields, cesspits, and wells (Mu and others 2011).

Epilepsy is associated with premature mortality, with the highest SMR in the first one to two years following diagnosis (Neligan and others 2010). Common causes of premature mortality in epilepsy include acute symptomatic disorders, such as brain tumor or stroke; sudden unexpected death in epilepsy; suicides; and accidents (Hitiris and others 2007). The epidemiology of premature mortality is very relevant in LMICs, where 85 percent of those with epilepsy live and where the risk of premature mortality is highest (Diop and others 2005; Jette and Trevathan 2014; Newton and Garcia 2012). Particularly concerning is the risk of premature mortality in childhood onset epilepsy. In a prospective trial in Finland of patients with childhood onset epilepsy followed for 40 years, 24 percent of the patients died. This rate is three times higher than the expected age- and gender-adjusted mortality in the general population (Sillanpää and Shinnar 2010); 55 percent of the deaths in the cohort were directly related to epilepsy, including sudden, unexplained death in 30 percent, definite or probable seizure in 15 percent, and accidental drowning in 10 percent.

Another important risk factor for premature mortality is comorbid mental illness. Most studies of mortality risk in this population have been conducted in HICs, and the extent of this risk factor in resource-limited settings is largely unknown. In a Swedish retrospective study, 75 percent of epilepsy patients dying from an external cause had comorbid psychiatric illness, most commonly depression and substance abuse (Fazel and others 2013). In a population-based study in the United Kingdom, mortality among epilepsy patients was associated with alcohol use and depression (Ridsdale and others 2011). In a meta-analysis of studies on suicide in epilepsy patients, Pompili and others (2005) found that the incidence of suicide was significantly higher among epilepsy patients than the general population. This striking mortality risk in epilepsy patients with mental disorders requires further study and intervention in LMICs, where the burden of epilepsy is highest.

Dementia. Our natural history model attributed more than two million excess deaths worldwide to dementia in 2010, compared with 500,000 cause-specific deaths derived from ICD records. Figure 3.7 shows that the majority of deaths caused by dementia, as expected, occur in the elderly.

Excess mortality in dementia has been associated with functional disability leading to unhealthy lifestyle factors and comorbid physical conditions (Guehne, Riedel-Heller, and Angermeyer 2005; Llibre and others 2008). Midlife cardiovascular risk factors have been associated with later mortality in patients who develop dementia. In a Norwegian prospective study following patients for 35 years, dementia mortality was associated with increased total cholesterol levels, diabetes mellitus, and low body mass index in midlife (Strand and others 2013). A study in seven countries found that smoking, hypercholesterolemia, high blood pressure, low forced vital capacity, and previous history of cardiovascular disease at baseline were associated with a higher risk of death from dementia (Alonso and others 2009).

Dementia shows an increased mortality risk. In a study of male civil servants who participated in the Israel Heart Disease study, patients with dementia had a hazard ratio for mortality of 2.27 compared with patients without dementia (95% CI, 1.92–2.68) (Beeri and Goldbourt 2001).

The severity of disease is one of the most significant predictors of premature death in individuals with dementia after controlling for other factors, with an HR

for moderate cases of 2.0 (95% CI, 0.1-4.1) compared with mild cases, and an HR of 3.8 (95% CI, 2.7-3.4) for severe cases compared with mild cases (Gühne and others 2006). In a cohort of 15,209 patients in the Swedish Dementia Registry, lower scores on the mini-mental status examination, male gender, higher number of medications, institutionalization, and age were associated with increased death risk after dementia diagnosis (Garcia-Ptacek and others 2014).

Infections, particularly pneumonia, frequently lead to death in people with dementia (Mitchell and others 2009). Urinary tract infections caused by incontinence, as well as bedsores and deep venous clots caused by immobility, can lead to systemic bloodstream infections and death. Psychological agitation and aggression are frequent symptoms in patients with dementia, and antipsychotics are frequently prescribed, although significant increased mortality risk odds ratio (OR 1.7) is associated with typical and atypical antipsychotics. This practice has resulted in a formal black box warning by the United States Food and Drug Administration (U.S. FDA 2008). An independent, systematic review of 15 randomized control trials (RCTs) of atypical antipsychotics confirmed the significant increased risk (OR 1.54) for all antipsychotics (Schneider, Dagerman, and Insel 2005). The dementia antipsychotic withdrawal trial (DART-AD) trial reported increased mortality in patients who were prescribed agents in the long term and likely related to oversedation, dehydration, and prolongation of QT interval corrected for heart rate on electrocardiogram (Ballard and others 2009).

A clear causal relationship exists between dementia and premature death; however, other environmental factors can precede both outcomes and independently increase the risk of dementia and excess mortality. For example, education and literacy may confer a degree of protection against dementia and excess mortality (Prince and others 2012). Thus, these factors, which are already high on the agenda for LMICs, may be considered independent, modifiable risk factors in reduced life expectancy, explaining a portion of the excess mortality currently associated with dementia.

Deaths across the Lifespan

Cause-specific deaths from mental, neurological, and substance use disorders increase steadily across the lifespan, with the exception of a peak at ages one to four years caused by epilepsy-related deaths. The greatest number of deaths occurs in the oldest group (ages 75 years and older). This finding is explained almost entirely by dementia, including Alzheimer's disease, although it may, at least in part, be caused by the broad age-grouping at this age (table 3.2). If dementia deaths are excluded, the number of deaths attributable to mental, neurological, and substance use disorders is highest between ages 35 and 54 years; most are caused by epilepsy and alcohol use disorders.

Table 3.2 shows that the cause-specific deaths and excess deaths directly coded to mental, neurological, and substance use disorders are relatively similar up to age four years. After this age point, excess deaths rise sharply in relation to cause-specific deaths. As with cause-specific deaths, the greatest number of excess deaths occurs at ages 75 years and older due to dementia. If dementia deaths are excluded, excess deaths would peak between 25 and 54 years of age; the majority is attributable to alcohol use disorders.

Counter-Factual Burden and Comparative Risk Assessment

In GBD 2010, literature investigating mental, neurological, and substance use disorders as risk factors for other health outcomes was reviewed. Because of data limitations, only a few risk factor–outcome pairings could be established and assessed in the study's CRA analysis (Baxter and others 2011; Lim and others 2012). These risk factors are summarized in table 3.3. There were insufficient data to assess neurological disorders as risk factors in GBD 2010. From the data that were available for selected mental and substance use disorders, we can begin to appreciate the impact these disorders have on other health outcomes in the GBD cause list.

Online annex 3A summarizes the YLLs allocated to mental, neurological, and substance use disorders as direct causes of death; these were estimated using previously reported cause-specific death estimates. In addition to these cause-specific YLLs, mental and substance use disorders are responsible for 22.5 million YLLs caused by deaths from suicide; major depression is responsible for 3.5 million YLLs caused by deaths from IHD; injecting drug use is responsible for 7.2 million YLLs caused by deaths from blood-borne viruses and liver disease; and alcohol use is responsible for 78.7 million YLLs from death caused by various additional outcomes. Regular cannabis use as a risk factor for schizophrenia accounted for an estimated 7,000 DALYs globally, all of which were YLDs given that there was no evidence to suggest an elevated risk of mortality in cannabis users (Charlson and others 2013; Degenhardt, Ferrari, and others 2013; Ferrari and others 2014; Lim and others 2012).

Figure 3.8 shows the additional YLLs attributable to mental, neurological, and substance use disorders as risk factors for other health outcomes by region; these are

Table 3.2 Number of Cause-Specific and Excess Deaths, by Age, 2010

Cause-specific deaths	0–1 years	1–4 years	5–9 years	10–14 years	15–19 years	20–24 years	25–34 years	35–44 years	45–54 years	55–64 years	65–74 years	75+ years	Total
Alzheimer's disease and other dementias	-	-	869	605	578	642	1,259	2,302	4,575	12,559	41,622	420,710	485,721
Epilepsy	7,388	19,819	6,255	5,351	10,562	14,101	24,107	20,605	18,038	14,826	14,522	22,054	177,627
Schizophrenia	-	-	-	-	-	-	2,003	3,610	3,429	3,440	3,035	4,246	19,763
Alcohol use disorders	-	-	-	-	464	1,311	7,937	20,044	33,613	27,446	13,295	7,024	111,134
Opioid dependence	1,231	1,217	288	260	1,350	3,745	9,736	8,446	7,432	3,846	2,319	3,171	43,040
Cocaine dependence	13	12	3	3	16	47	120	107	96	53	33	44	549
Amphetamine dependence	13	11	3	3	14	40	102	88	75	44	30	41	465
Excess deaths	**0–1 years**	**1–4 years**	**5–9 years**	**10–14 years**	**15–19 years**	**20–24 years**	**25–34 years**	**35–44 years**	**45–54 years**	**55–64 years**	**65–74 years**	**75 + years**	**Total**
Alzheimer's disease and other dementias	-	-	-	-	-	-	-	1,160	114,334	267,613	251,719	1,478,957	2,113,783
Epilepsy	3,513	13,486	10,680	9,050	18,957	25,784	54,590	52,928	38,961	25,330	20,276	22,647	296,201
Schizophrenia	-	-	-	816	8,758	26,990	106,121	163,634	208,056	118,828	43,846	21,945	698,993
Alcohol use disorders	-	-	-	6,868	46,164	85,768	403,572	510,864	472,712	304,907	91,601	31,046	1,953,502
Opioid dependence	-	-	-	-	11,268	94,748	183,102	77,352	28,489	7,350	1,498	319	404,125
Cocaine dependence	-	-	-	-	638	10,334	38,838	23,083	16,682	5,023	984	237	95,818
Amphetamine dependence	-	-	-	-	5,856	25,306	86,702	65,420	17,058	1,765	101	11	202,219
Major depressive disorder	-	239	63,015	86,160	141,417	171,916	284,968	286,056	285,313	258,639	198,975	447,142	2,223,840
Bipolar disorder	-	-	-	1,337	21,063	78,773	327,425	401,817	266,179	136,888	58,706	28,204	1,320,391
Autistic disorder	963	4,220	3,883	3,087	3,918	5,102	13,468	18,276	20,536	17,133	10,675	7,384	108,645

Source: Lozano and others 2012.
Note: Larger than expected numbers in the 75+ age group may be an artefact of the age groupings. - = nil.

Table 3.3 Mental, Neurological, and Substance Use Disorders Included as Risk Factors in the GBD 2010 Comparative Risk Assessments and Attributable YLLs for Health Outcomes, 2010

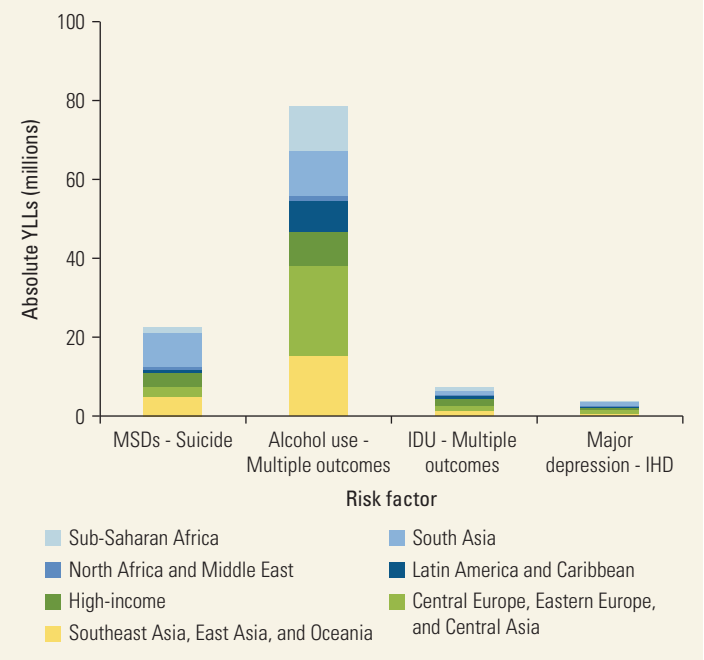
Risk	Outcome	Millions of YLLs (95% uncertainty)
Alcohol use	Alcohol use disorders, tuberculosis, lower respiratory infections, multiple cancers, cardiovascular and circulatory diseases, cirrhosis of the liver, pancreatitis, epilepsy, diabetes mellitus, injuries, and interpersonal violence	78.7 (70.9–86.8)
Injecting drug use	HIV/AIDS, hepatitis B and C, liver cancer, and cirrhosis of the liver secondary to hepatitis	7.2 (5.6–9.7)
Mental and substance use disorders	Suicide	22.5 (14.8–29.8)
Major depression	Ischemic heart disease	3.6 (1.8–5.4)
Regular cannabis use[a]	Schizophrenia	0

Sources: Estimates based on Charlson and others 2013; Degenhardt, Ferrari, and others 2013; Ferrari and others 2014; Lim and others 2012.
Note: DALYs = disability-adjusted life years; HIV/AIDS = human immunodeficiency virus and acquired immune deficiency syndrome; YLD = years lived with disability; YLL = years of life lost.
a. Regular cannabis use as a risk factor for schizophrenia accounted for an estimated 7,000 DALYs globally, all of which were YLDs.

over and above cause-specific YLLs directly attributable to these disorders. Variation in absolute YLLs among regions is explained not only by population size, but also the distribution of the risk factors and outcomes in each region. For example, YLLs attributable to alcohol use as a risk factor are greatest in Central Europe, Eastern Europe, and Central Asia—rather than South Asia, which has the largest population size—because of high rates of alcohol use disorders in this region. In contrast, the lower contribution of attributable YLLs in Sub-Saharan Africa likely reflects the lower rates of alcohol use disorders in this region. Had there been sufficient data to estimate YLLs caused by neurological disorders as risk factors for other health outcomes, estimates of attributable YLLs may have been higher in Sub-Saharan Africa, where cause-specific deaths from neurological disorders are highest.

The attributable YLLs presented provide more comprehensive insight into the magnitude of the burden of mental, neurological, and substance use disorders. For example, the addition of attributable suicide YLLs would have changed total YLLs caused by mental and substance use disorders combined from 0.5 percent (allocated to them as a direct cause) to 1.8 percent of global YLLs, elevating them from the fifth to the third leading disease category of global burden (DALYs) in 2010 (Charlson and others 2013; Degenhardt, Ferrari, and others 2013; Ferrari and others 2014; Lim and others 2012). Attributable YLLs estimated for each risk factor–outcome pairing are not mutually exclusive of contributions of other risk factors; consequently, they cannot be aggregated to estimate the overall YLLs attributable

Figure 3.8 Absolute YLLs Attributable to Mental, Neurological, and Substance Use Disorders as Risk Factors for Other Health Outcomes, 2010



Source: IHME 2013.
Note: Risk factor–outcome pairings are defined in table 3.3. IDU = injecting drug use; IHD = ischemic heart disease; MSDs = mental and substance use disorders; YLLs = years of life lost to premature mortality.

to all mental, neurological, and substance use disorders combined. Nevertheless, presenting attributable YLLs is another example of the deaths and YLLs caused by these disorders, over and above the direct cause-specific deaths and YLLs allocated to each disorder in GBD 2010. It is clear that the mortality-associated disease is significant.

DISCUSSION AND IMPLICATIONS

Mental Disorders

The GBD findings of elevated rates of excess mortality across most mental and substance use disorders are supported by the findings of a recent meta-analytic review (Walker, McGee, and Druss 2015). Moreover, recent studies suggest that the majority of excess deaths are caused by preventable diseases, with a smaller proportion attributed to unnatural or unknown causes (Fekadu and others 2015; Lawrence, Hancock, and Kisely 2013). The question remains as to what proportion of these deaths can be directly attributed to mental disorders and how much to subsequent confounding factors.

Despite the existence of complex relationships between mental disorders and premature mortality, some relationships, such as that between mental disorders and suicide, are well-established (Li and others 2011). Mental disorders have also been linked to higher rates of death caused by cardiovascular disease, stroke, diabetes mellitus, respiratory diseases, and some cancers (Crump and others 2013; Hoyer, Mortensen, and Olesen 2000). The relationship between mental disorders and a specific physical disease, leading to premature death, is also complex. People with major depression are more likely to develop cardiovascular disease (Charlson and others 2011). Psychotropic medications can negatively impact cardiovascular and metabolic health (De Hert and others 2012). Obesity and metabolic disturbances are primary risk factors for cardiovascular disease and type II diabetes, and these are two- to three-fold more common in people with mental disorders, compared with the general population (Scott and Happell 2011). Major modifiable risk factors for chronic disease, such as smoking (Lawrence, Mitrou, and Zubrick 2009), poor diet, physical inactivity (Kilbourne and others 2007; Shatenstein, Kergoat, and Reid 2007), and substance abuse (Scott and Happell 2011), are overrepresented in people with mental disorders. These risk factors may be the consequences of symptoms of mental, neurological, and substance use disorders; medication effects; and poor emotional regulation (Scott and others 2013).

Mental disorders are associated with poorer clinical management of comorbid conditions. People with severe and persistent mental disorders may be less likely to receive a timely diagnosis of physical illness because of diagnostic overshadowing, that is, physical complaints may be overlooked and attributed to psychological and psychiatric factors (Bailey, Thorpe, and Smith 2013). A review by Happell, Scott, and Platania-Phung (2012) found a reduced likelihood for people with mental disorders to receive screening for breast, cervical, and colorectal cancer or immunizations for influenza and pneumonia, compared with the rest of the population. Even in countries with well-established health care systems, people with mental disorders receive lower-than-average prescriptions for medication treating cardiovascular disease (Kisely, Campbell, and Wang 2009; Mitchell and Lord 2010) and are less likely to receive coronary artery bypass grafting, cardiac catheterization, or cerebrovascular arteriography (Kisely, Campbell, and Wang 2009; Mitchell and Lawrence 2011).

Strategies for reducing mortality associated with mental and substance use disorders primarily target preventing onset, reducing case fatality, and preventing the development of fatal sequela. Growing evidence indicates that excess mortality in people with these disorders can be reduced through established evidence-based treatments and improved screening and treatment for chronic disease.

Psychiatric treatments, specifically pharmacotherapies, may have some protective effect against excess mortality (Weinmann, Read, and Aderhold 2009), although evidence suggests that this depends on the use of medications according to best practice guidelines (Cullen and others 2013). However, some antidepressants and second-generation antipsychotics may actually pose an elevated risk mediated by metabolic side effects (Newcomer 2005; Rummel-Kluge and others 2010; Smith and others 2008).

Collaborative care by community-based health teams has the potential to reduce overall mortality, as well as suicide deaths (Dieterich and others 2010; Malone and others 2007). The use of collaborative care models to improve physical health in people with mental, neurological, and substance use disorders is growing in HICs; these models have demonstrated a range of positive health outcomes, including reduced cardiovascular risk profiles (Druss and others 2010). The effectiveness of these strategies in preventing premature mortality in LMICs has yet to be tested, but this may be a cost-effective approach to treatment in settings in which trained mental health clinicians are scarce.

Known chronic disease risk factors, such as smoking and obesity, are potentially modifiable. Lifestyle interventions comprising a psycho-educational or

behavioral approach can achieve modest but significant improvements, such as reduced smoking (Kisely and Campbell 2008; van Hasselt and others 2013), increased physical activity, and improved eating habits (Verhaeghe and others 2011), resulting in reduced body mass index and improved metabolic profiles (Gierisch and others 2013).

Screening, prevention of metabolic risk factors, and proactive provision of basic health care services are essential to improve life expectancy in people with comorbid mental and physical health issues. Strategies for early cancer detection need to be prioritized, and models of care need to be developed to ensure that people with these disorders receive the same level of physical health care and treatment as the rest of the population.

Several guidelines address the management of mental, neurological, and substance use disorders. The World Health Organization (WHO), for example, has developed specific strategies in its Mental Health Gap Action Programme, which aim to scale up services in LMICs (http://www.who.int/mental_health/mhgap/en/). The WHO has also developed guidelines for other related health priorities, such as suicide, which draws attention to the pivotal role that mental health care plays in suicide prevention (http://www.who.int/mental_health/prevention/suicide/suicideprevent/en/index.html).

Strategies to address self-harm remain critical, as evidence shows that a proportion of suicide deaths can be averted through public health measures. Policies that address restriction of access to common methods of suicide are effective in reducing suicide risk (WHO 2012). Strong evidence indicates that improved prevention and treatment of major depression and alcohol and substance abuse can reduce suicide rates.

The continuing life expectancy gap in persons with mental disorders is a clear example of discrimination and lack of parity between this portion of the population and the community in general (Thornicroft 2013). Differential access to usual care for this group leads to poorer outcomes in terms of health loss and mortality (Liao and others 2013) and incurs high costs in health care provision (Centre for Mental Health 2010). Accordingly, identification of physical health issues and equitable access to health care are essential to improve long-term health outcomes and reduce excess mortality among people with mental disorders (Bass and others 2012).

Substance Use Disorders

Opioid dependence and injecting drug use are significant contributors to the global burden of mental, neurological, and substance use disorders. Much of this burden could be averted by scaling up needle and syringe programs, opioid substitution treatment (OST), and HIV antiretroviral therapy (Degenhardt and others 2010; Turner and others 2011). Increasing evidence indicates that needle and syringe programs can reduce the burden of HIV/AIDS (Degenhardt and others 2010) and hepatitis C virus (HCV) (Turner and others 2011). The HCV burden can also be decreased by effectively treating chronic HCV (Turner and others 2011). The release of more effective and less toxic HCV drugs is expected to result in dramatic improvement in what have been extremely low rates of treatment uptake by people who inject drugs (Swan 2011).

More effective strategies to reduce the burden of disease attributable to opioid dependence include maintenance OST and HIV antiretroviral therapy (Degenhardt and others 2010; Turner and others 2011). The two most commonly used medications, methadone and buprenorphine, are on the *List of Essential Medicines* (WHO 2005) as core medications for the treatment of opioid dependence (Mattick and others 2008, 2009). OST reduces mortality among opioid dependent people (Brugal and others 2005; Caplehorn and Drummer 1999; Darke, Degenhardt, and Mattick 2006; Davoli and others 1994; Degenhardt, Randall, and others 2009; Gibson and others 2008), with time spent in treatment halving mortality compared with that of time spent not in treatment (Degenhardt and others 2011). A large evaluation study in multiple countries, including LMICs, demonstrated that OST is effective in reducing opioid use and injecting risk behaviors and improving physical and mental well-being (Lawrinson and others 2008).

There is scope for reducing the risk of overdose among people who continue to use opioids, particularly in countries with high injecting drug use rates but a low emphasis on harm reduction measures, such as the Russian Federation and the United States. Increasing evidence indicates that the provision of the opioid antagonist naloxone to users enables peers to intervene effectively if overdoses occur (Galea and others 2006; Sporer and Kral 2007). Additional strategies may include educating users about the risks of overdose and conducting motivational interviews with users who have recently overdosed (Sporer 2003). Safe injecting rooms have been proposed as an additional strategy to reduce overdose, although their population reach is likely to be more limited (Hall and Kimber 2005).

Psychosocial interventions, including self-help programs and cognitive behavioral therapy, can be effective (Baker, Lee, and Jenner 2005; Knapp and others 2007). There is no evidence to date that pharmacotherapies, such as mood stabilizers, antidepressants, or antipsychotics, are effective for the treatment

of stimulant dependence (Srisurapanont, Jarusuraisin, and Kittirattanapaiboon 2001). The RCTs of prescribed psychostimulants in cocaine dependence have not found that they lead to greater abstinence or retention in care (Castells and others 2010).

In some regions, notably Asia, there is also widespread delivery of non-evidence-based responses to psychostimulant dependence (Degenhardt and others 2010, 2014). Illicit drug users may be detained in closed settings, typically operated by military, government security, or police for what is claimed to be treatment, most often for psychostimulant use (IHRD 2009; Pearson 2009; UNODC Regional Centre for East Asia and the Pacific 2006; WHO 2009). Detainees are often forced to comply with the interventions; evidence-based, effective drug treatment and HIV prevention are rarely delivered (General Department for Social Evils Prevention, Constella Group, and DFID 2008; IHRD 2009; UNODC Regional Centre for East Asia and the Pacific 2006; WHO 2009). External evaluations have concluded that there may be adverse impacts on drug use and HIV risk (Pearson 2009), in addition to human rights violations (Human Rights Watch 2004; IHRD 2009; Pearson 2009; Rehm, Csete, and others 2010; WHO 2009).

Although cannabis dependence had no YLLs, two million YLDs were attributed to the disorder. Behavioral interventions are effective in the treatment of cannabis dependence (Denis and others 2013; Knapp and others 2007); cognitive behavioral therapy and contingency management show the greatest promise. Public health campaigns may be necessary to advise young people of the risks of developing dependence on cannabis, because many users fail to appreciate this risk. More research is needed, however, into how to scale up these behavioral approaches to reduce the population prevalence of these disorders (Knapp and others 2007).

Neurological Disorders

As the incidence of neurological disorders, including epilepsy and dementia, grows in many resource-limited settings, strategies to decrease mortality rates in these regions in particular must be addressed. Improvements in access to medical treatment, patient and clinician education, and a focus on preventable causes of death can substantially decrease mortality rates.

In resource-constrained settings, the mortality risk in epilepsy patients is up to six times higher than in HICs and largely due to preventable causes (Kamgno, Pion, and Boussinesq 2003; Ngugi and others 2014). The epilepsy treatment gap is more than 75 percent in low-income countries, and more than 50 percent in many LMICs and upper-middle-income countries (Jette and Trevathan 2014). Legislation to ensure the availability of affordable and efficacious anti-seizure medications, clinician education in prescribing anti-epileptic medications, and patient education on the importance of medical adherence is critical to alleviate the epilepsy treatment gap. Cost-effective epilepsy treatments are available, and accurate diagnosis can be made without costly technical equipment. Targeting epilepsy risk factors, including more common structural and metabolic causes of epilepsy, can decrease mortality risk. Education and information on safe lifestyle habits in epilepsy patients will benefit populations in LMICs, as will education initiatives targeted to employers and teachers to dispel the myths associated with epilepsy.

The mortality risk of dementia in many LMICs is poorly known. Studies on the mortality rates due to dementia and the incidence of preventable risk factors in these regions are critical to develop strategies to alleviate mortality in this fragile patient population. Mortality in dementia patients is commonly caused by preventable medical conditions. Caregiver education and support services regarding proper care of patients with cognitive decline will likely decrease infection rates and mortality. Government financial support for health care services and caregiver support would benefit this population. Strategies to enhance nutrition, as well as monitoring and treatment of vascular risk factors, are important measures. Raising awareness of the mortality risk among the public, caregivers, and health workers can lead to increased demand for services.

CONCLUSIONS AND LIMITATIONS

Quantifying mortality presents several challenges. The cause-of-death data are affected by multiple factors, including certification skills among physicians, diagnostic and other data available for completing the death certificate, cultural variations in choosing and prioritizing the cause of death, and institutional parameters governing mortality reporting (Lozano and others 2012). In LMICs, where many deaths are not medically certified, different data sources and diagnostic approaches are used to derive cause-of-death estimates (Lozano and others 2012). Overall, improving and expanding sources of national mortality estimates is imperative.

Mortality directly related to mental, neurological, and substance use disorders is particularly difficult to capture in cause-of-death data because of the complex web of causality that links these disorders with other physical disorders. It is important to identify and quantify the

excess premature mortality in people with these disorders by elucidating the pathway between the disorders and fatal sequelae. The estimates of excess mortality presented in this chapter include deaths from causal and noncausal origins and therefore cannot be interpreted as the number of deaths directly attributable to a particular disorder. In addition, DisMod-MR natural history models do not adjust for co-occurrence between disorders. Thus, it is important to note that excess deaths and YLLs (as is the case for estimates from risk factor analyses) cannot be aggregated across disorders.

Although valuable, the CRA undertaken as part of GBD 2010 also provides an incomplete picture. Given the lack of available data, we are not able to estimate and reassign all deaths attributable to mental, neurological, and substance use disorders. Assuming multiple risk factors are independent of each other is also a limitation. A more accurate quantification of the joint effects of multiple risk factors, that is, what explains the difference between excess and cause-specific deaths, is an important area for future research.

Our analysis of the excess and attributable deaths caused by mental, neurological, and substance use disorders demonstrates the elevated risk of mortality associated with these disorders, over and above what is captured in GBD 2010's estimation of cause-specific YLLs. Prevention of excess mortality in people with these disorders should be considered a high priority in the reform of health systems. A key step in the identification and treatment of comorbid health issues is to ensure equitable access to health care, thereby improving long-term health outcomes and reducing premature mortality among people with these disorders.

ANNEX 3A

The annex to this chapter is as follows. It is available at www.dcp-3.org/mentalhealth.

- Annex 3A. Cause-Specific Years of Life Lost as a Percentage of All-Cause Years of Life Lost, 2010

NOTE

A version of this chapter appeared in an article by F. J. Charlson, A. J. Baxter, T. Dua, L. Degenhardt, H. Whiteford, and T. Vos, titled "Excess Mortality from Mental, Neurological, and Substance Use Disorders in the Global Burden of Disease Study 2010." *Epidemiology and Psychiatric Sciences*, 2015: 24 (2): 121–40. doi:10.1017/S2045796014000687. <http://journals.cambridge.org/action/displayJournal?jid=EPS>.

World Bank Income Classifications as of July 2014 are as follows, based on estimates of gross national income (GNI) per capita for 2013:

- Low-income countries (LICs) = US$1,045 or less
- Middle-income countries (MICs) are subdivided:
  a) lower-middle-income = US$1,046 to US$4,125
  b) upper-middle-income (UMICs) = US$4,126 to US$12,745
- High-income countries (HICs) = US$12,746 or more.

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