

MEETING REPORT ON

EXCESS MORTALITY IN PERSONS WITH SEVERE MENTAL DISORDERS

WHO Headquarters, Geneva, 18-20 November 2015

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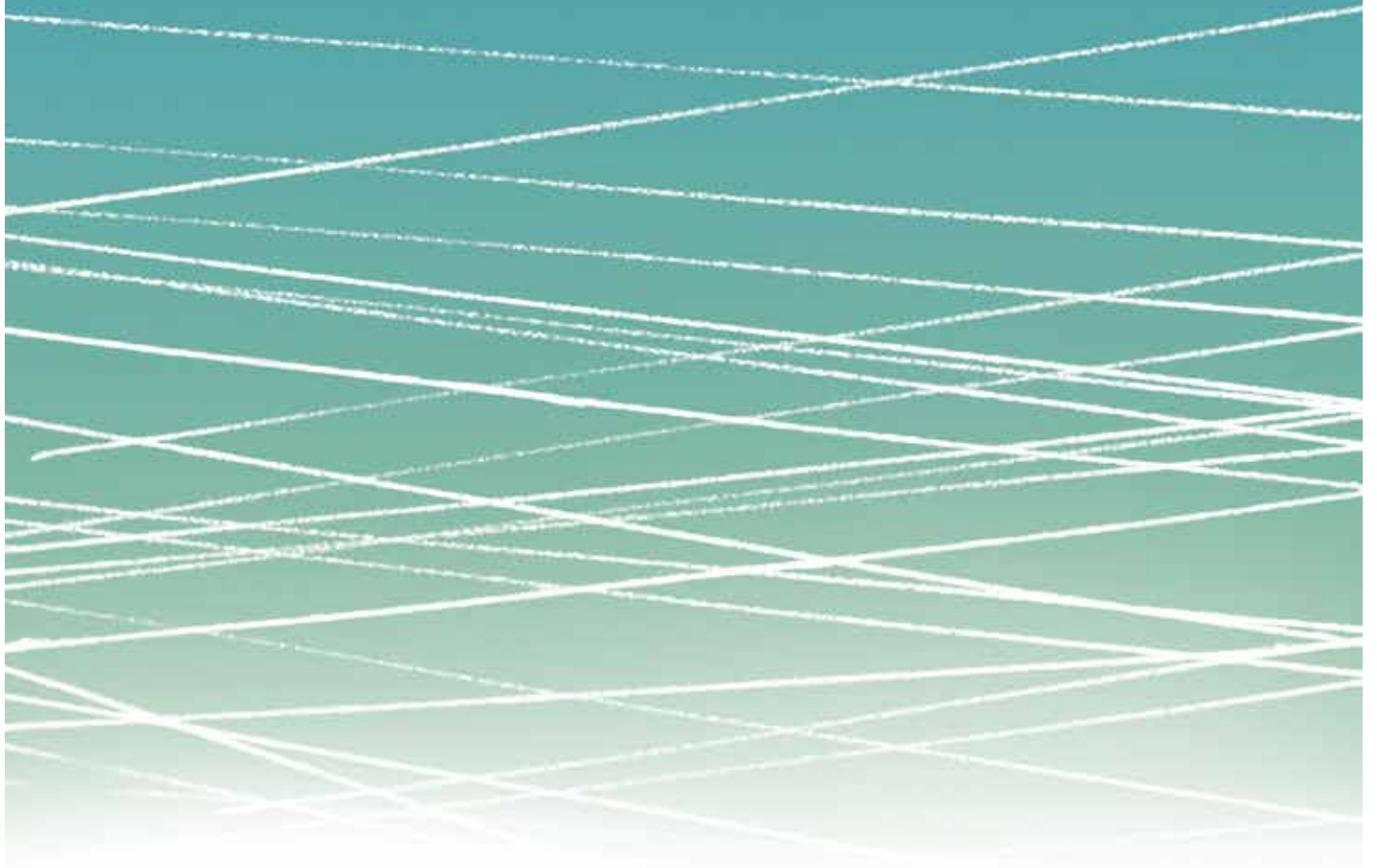
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ACRONYMS & ABBREVIATIONS

aHR	adjusted hazard ratio
aOR	adjusted odds ratio
BAD	bipolar affective disorder
DEP	moderate to severe depression
HIC	high-income countries
HR	hazard ratio
LAMIC	low- and middle-income countries
NCD	non-communicable disease
OR	odds ratio
PAR	population attributable risk
RR	relative risk
sDEP	sub-threshold depression
SCZ	schizophrenia and other psychotic disorders
SMD	severe mental disorders
SMR	standardized mortality ratio

MEETING REPORT

EXCESS MORTALITY IN PERSONS WITH SEVERE MENTAL DISORDERS



1. BACKGROUND & RATIONALE FOR MEETING

Excess mortality in persons with severe mental disorders (SMD) is a major public health challenge that warrants action. Persons with SMD (i.e., schizophrenia and other psychotic disorders, bipolar affective disorder, and moderate-to-severe depression) die about 10 to 20 years earlier than the general population, mostly from preventable physical diseases (Colton & Mandersheid, 2006; Laursen, 2011). The physical health of people with SMD is commonly ignored not only by themselves and people around them but also by health systems. Resulting physical health disparities that lead to premature mortality have been rightfully stated to be contravening international conventions for the 'right to health' and has been considered a 'scandal.' (Thornicroft, 2011).

Persons with schizophrenia have mortality rates that are 2 to 2.5 times higher than the general population. Those with bipolar mood disorders have high mortality rates ranging from 35% higher to twice higher than the general population (Chesney, Goodwin, & Fazel, 2014; Hayes, Miles, Walters, et al., 2015). Persons with depression have higher mortality rates (about 1.8 times) that is not limited to severe cases or to suicide (Cuijpers & Schoevers, 2004).

Our knowledge about mortality among people with severe mental disorders and its correlates in low- and middle-income countries (LAMICs) is limited. The figures mentioned above are drawn from studies coming from high income countries (HICs) where health literacy is higher, better quality services are available, and there is overall better monitoring of the institutions and more regular check-ups for physical health of persons with SMD. The situation might be much worse in LAMICs where the resources are scarce, the institutions are not well managed and access to quality mental health care and physical care is limited.

In order to better understand the scope of excess mortality in persons with SMD, its major causes and correlates, and the best next steps to set the World Health Organization (WHO) research and policy agenda in this area, a consultation was convened by the Department of Mental Health and Substance Abuse with key international experts at the WHO Headquarters in Geneva ([Appendix 1](#)).

2. OBJECTIVES & EXPECTED OUTCOMES

The objectives and expected outcomes of the November 2015 Consultation on Excess Mortality in Persons with Severe Mental Disorders were as follows:

- To review the epidemiology and risk factors on excess mortality among persons with SMD, with special attention to information from LAMICs.
- To review existing guidelines and best practices in this area and to develop an intervention framework.
- To advise WHO on the next steps for the development of a policy and research agenda to decrease excess mortality among persons with severe mental disorders.

Once the plan has been approved, implementation can start, ideally in phases. A pilot phase can be undertaken in a limited population or geographical area. On the basis of feedback, changes can be made and other interventions added in the expansion phase. Human and financial resources need to be carefully managed throughout.

3. DECLARATIONS OF INTEREST

Invited experts to the consultation completed the WHO standard form for declaration of interest prior to the meeting. At the start of the meeting, the secretariat reported that Dr Ulrich Hegerl was an advisory board member for pharmaceutical companies and received honorarium amounting to 45,050 from 2011 to 2015 from the following companies: Lilly, Lundbeck, Takeda, Servier and Otsuka Pharma. Conflict of interest was assessed to be significant and the participant acted as an observer during the meeting.

4. LANDSCAPE ANALYSIS: EPIDEMIOLOGY & CORRELATES – SUMMARY

This session began with a presentation of a landscape analysis of the epidemiology and risk factors for excess mortality in persons with SMD, with special attention to information from low-resource settings (see [Appendix 2](#)). This included a quantitative summary of excess mortality in persons SMD, such as standardised mortality ratios (SMR) of the major natural and unnatural causes of death, in both HICs and LAMICs. Key risk factors and correlates of excess mortality were presented (e.g., individual factors, health system factors, and social factors), along with an initial risk factor model.

The first panel presentations and subsequent discussions focused on identifying the major methodological and research challenges to gaining a clearer understanding about excess mortality, risk and protective factors, and challenges to intervention research in persons with SMD. Panellists highlighted our current knowledge along with gaps and provided suggestions for potential ways to overcome these challenges. Presentations covered systematic reviews on the topic, registry-based data, international consortia and data sharing platforms, information from the International Health Surveys, the types of indicators that have been collected in each, and the impact of interventions using both mental health and physical health as outcome variables. The subsequent discussion focused on how to monitor this globally, e.g., the minimum indicators necessary to provide meaningful data, despite barriers of diagnostic validity and reliability and complex interrelationships among risk factors.

The second panel presentations focused on developing a risk factor model, particularly identifying the key modifiable risk factors and interactions among these factors. Several major themes arose in the presentations, including disentangling risk factors versus correlates and the role of environmental factors over and above genetic factors in excess mortality. Another major theme included reduced access to health services and critical time points of risk, especially the first year following discharge or diagnosis. Health behaviours emerged as a major risk factor including, tobaccos use, substance use and suicide risk. The discussion focused on developing a model for understanding complex and interacting risk factors (Table 1).

5. RISK FACTOR MODEL

The multilevel model of risk (Table 1) highlights risk factors for excess mortality in persons with SMD at the individual, health system and socio-environmental levels. Risk factors at the *individual level* include characteristics inherent to SMD or an individual's health-related behaviours. These can be related to the severity of the SMD (e.g., symptoms, hospitalizations, impulsivity, physiological and emotional dysregulation), affect the engagement or interaction of the person with the health care system (e.g., cognitive deficits, social skills deficits, low motivation or mistrust of providers), or include behaviours that lead to or exacerbate health problems.

Health system factors include treatments, delivery of services, and organizational characteristics such as the workforce or information systems infrastructure. For example, persons with SMD often receive poor quality of physical health care, spanning from health promotion and disease prevention to intervention. When hospitalized for medical care, persons with SMD often have poor outcomes. Providers may have negative beliefs or attitudes about persons with SMD or may lack the skills necessary. Dichotomized or fragmented mental and physical health care may further challenge the ability for systems to meet the complex physical and mental health needs of persons with SMD.

Social determinants of health include, but are not limited to, public policies, an individual's socio-economic position, cultural and societal values, environmental vulnerabilities and social support. For example, persons with SMD are more likely to be socially isolated and more likely to be poor and at risk for homelessness. They are often denied care or coverage for health problems. Persons with SMD also tend to live in less safe neighbourhoods, have less access to healthy foods, and have less opportunities to be involved in healthy activities, which may contribute to poor lifestyle behaviours. They may be perceived as dangerous by others, which may drive the high rates of homicide victimization. When family members are involved, they may already be under a heavy caregiver burden, and additional physical health problems may overstretch family support.

It is important to emphasize that these factors are intertwined, and interrelationships at multiple levels likely contribute towards excess mortality.

TABLE 1. MULTILEVEL MODEL OF RISK FOR EXCESS MORTALITY IN PERSONS WITH SEVERE MENTAL DISORDERS (SMD)

INDIVIDUAL FACTORS	HEALTH SYSTEMS	SOCIAL DETERMINANTS OF HEALTH
<p>Disorder-specific</p> <ul style="list-style-type: none"> Severity of disorder Family history Symptoms/pathophysiology Early age of onset Recency of diagnosis Stigma <p>Behaviour-specific</p> <ul style="list-style-type: none"> Tobacco use Poor diet Inadequate physical activity Sexual and other risk behaviours Substance use (alcohol and drugs) Low motivation (e.g., treatment seeking, adherence) 	<p>Leadership</p> <ul style="list-style-type: none"> Absence of relevant policies and guidelines <p>Financing</p> <ul style="list-style-type: none"> Low investment in quality care <p>Information</p> <ul style="list-style-type: none"> Limited health information systems <p>Service delivery</p> <ul style="list-style-type: none"> Verticalization and fragmentation of health services Lack of care coordination and management Limited access to services <p>Human resources</p> <ul style="list-style-type: none"> Poor quality service provision Negative beliefs/attitudes of workforce Poor communication <p>Medications</p> <ul style="list-style-type: none"> Antipsychotic medications (no treatment, polypharmacy, higher than recommended dosages) 	<p>Public policies</p> <ul style="list-style-type: none"> Discriminating policies Low financial protection and limited coverage in health packages <p>Socio-economic position</p> <ul style="list-style-type: none"> Unemployment Homelessness Low health literacy <p>Culture and societal values</p> <ul style="list-style-type: none"> Stigma and discrimination in society Negative perceptions about persons with SMD <p>Environmental vulnerabilities</p> <ul style="list-style-type: none"> Infections, malnutrition Access to means of suicide Impoverished or unsafe neighbourhoods <p>Social support</p> <ul style="list-style-type: none"> Limited family, social and community resources

6. LANDSCAPE ANALYSIS: PROGRAMMES, GUIDELINES & INTERVENTIONS – SUMMARY

This session began with a presentation of a landscape analysis of existing interventions, programmes and guidelines developed to target excess mortality in SMD (see [Appendix 3](#)). Programs reviewed included those that targeted individual changes, such as lifestyle behaviours (including tobacco cessation and behavioural weight management) followed by those that focused on healthcare delivery systems, including antipsychotic medication guidelines, integrated care programmes, and stigma reduction, including packages of cardiometabolic screening tools and an algorithm of interventions and assessment protocols. A comparison of international and national guidelines was provided—those for the general population, followed by those specifically tailored or modified for persons with SMD, with a comparison of different types of recommendations. Some of the recommendations were the same for both persons with SMD and the general population (e.g., tobacco cessation), whereas for others, there was indication that persons with SMD might require more support (e.g., diet and physical activity guidelines).

After the session, two individual presentations focused on LAMICs. The first presentation focused on excess mortality in persons with SMD in Ethiopia and the unique characteristics that diverge from HICs: most persons with SMD die of infectious diseases; obesity and tobacco smoking are not very prevalent; and, the role of family members and caretakers may be especially important. The second presentation focused on innovations in primary care to target noncommunicable diseases (NCDs) in India, including the use of mobile health, collaborative care models and task-shifting.

The third panel presentation focused on identifying and reviewing existing guidelines, packages and programmes and highlighted the major components and gaps in existing approaches. Panellists presented on the role of diet and health promotion programmes during inpatient care, community-based behavioural weight management programmes designed specifically for this population and peer support and health and wellness programmes. In addition, several panellists from the WHO presented on the existing guidelines developed by the WHO, including those aimed at the prevention of NCDs, nutrition for health and development, violence and injury prevention, and the Mental Health Global Action Programme (mhGAP). The subsequent discussion focused on whether or not interventions aimed at NCDs, violence prevention and others, could be delivered and integrated as they are in persons with SMD or whether modifications would be necessary.

The final panel presentation focused on working towards developing an intervention framework ([Figure 1](#)) to reduce excess mortality and highlighted the feasibility and applicability of approaches that could be used in LAMICs. Panellists presented on the need for an integrated perspective, involvement of traditional healers, involvement of family members, focus on improving delivery systems and stigma reduction, especially among providers.

FIGURE 1. MULTILEVEL MODEL OF INTERVENTIONS TO REDUCE EXCESS MORTALITY IN PERSONS WITH SEVERE MENTAL DISORDERS (SMD)



7. INTERVENTION MODEL

Informed by the multilevel risk factor model, a comprehensive framework was developed that will be useful for designing, implementing and evaluating interventions and programmes to reduce excess mortality in persons with SMD (Figure 1). The first level of interventions is individual-focused, while the second focuses on health systems. Socio-environmental interventions are then incorporated, emphasizing broader social determinants of health, including social support and stigma reduction. Some programmes address components at multiple levels (e.g., simultaneously targeting individual behaviours and health systems through behavioural weight management plus care coordination); these are categorized based on the main emphasis of the programme. The assumption of the framework is that an effective approach must comprehensively target individual behaviours, health systems and social determinants of health.

Some interventions have proven to be effective but are not widely disseminated; others have not been rigorously tested; for some the evidence is mixed or inconclusive. For example, care programmes with an emphasis on monitoring and managing the adverse metabolic effects of antipsychotics are being implemented in several contexts, but many have not been well evaluated. Overall, the number and scope of truly tested interventions remain limited, and strategies for implementation and scaling up of programmes with a strong evidence base are scarce. Moreover, the majority of available interventions focus on a single or an otherwise limited number of risk factors.

Interventions at the *individual level* include strategies delivered to the individuals with SMD to target their mental health condition, physical health and lifestyle behaviours. Although individual-focused interventions are described separately, implementation of these interventions and their effectiveness are likely impacted by health care systems functioning and their capacity. The next level in the framework encompasses *interventions and programmes within health systems* targeting health care providers and service delivery components.

Strengthening of the six building blocks of the health systems – service delivery; health workforce; information; medical products, vaccines and technologies; financing; and leadership and governance (stewardship) would improve outcomes for persons with SMD. For example, care coordination, collaborative care or integrated care programmes include support to better equip health systems, usually through the provision of additional supportive members who can serve as a liaison between mental health and physical health care systems or through linking of delivery of physical and mental health services. This level of the intervention framework also includes health care leaders implementing national and international guidelines for care of persons with SMD in their organization, and aligning financing policy and information systems for the missions of improving and monitoring quality of care. The broadest level of the framework incorporates *socio-environmental factors and the social determinants of health*. This part of the model acknowledges the range of potential interventions originating from the community to address contributors to premature mortality. These can include peer support programs, stigma reduction interventions, and policy changes to healthy foods, and have less opportunities to be involved in healthy activities, which may contribute to poor lifestyle behaviours. They may be perceived as dangerous by others, which may drive the high rates of homicide victimization. When family members are involved, they may already be under a heavy caregiver burden, and additional physical health problems may overstretch family support.

8. POLICY & RESEARCH AGENDA

Incorporating lessons learned from the multilevel model of risk for excess mortality and the comprehensive intervention framework, key action points for policy and research agendas were proposed to decrease excess mortality in persons with SMD.

The policy agenda aims to develop WHO guidance to policy-makers on implementing the intervention framework and to identify actions to be taken by health systems, in clinical practice, and in the community (see [Appendix 4](#)).

In clinical practice, evidence from current literature combined with principles of health equity provide sufficient rationale to advance certain practice concepts. Individual practitioners can take steps now to provide guideline-consistent care. At minimum, the same guidelines for physical health care as the general population can be offered to persons with SMD. Practitioners should be especially attuned not to overlook somatic concerns and to pay attention to the lifestyle behaviours and physical health of persons with SMD. The evidence base and considerations for health equity support the following practices:

- Coordination of outpatient support efforts is recommended in the first year after discharge from hospital (e.g., following-up with health care providers, continuity of care) to help with reducing suicides (Organization for Economic Cooperation and Development, 2015). This may be especially needed among certain age groups of those with SMD who are at a high risk of suicide (Nordentoft et al., 2011).
- Patients with SMD should have providers responsible for their mental health and physical health. If these are different providers (e.g., psychiatrist and primary care physician), there should be communication and coordination between them, so that screening, preventive services, and monitoring for antipsychotic side effects (if applicable) are ensured (De Hert et al., 2011; University of Western Australia, 2010; Shiers & Curtis, 2014).
- Patients with SMD should be offered the same basic health screenings as the general population (e.g., cardiovascular risk and cancer).
- Providers should address tobacco cessation with every patient with SMD. Persons with SMD can quit and many want to quit smoking; however, practitioners often do not address tobacco cessation (Schroeder, 2016; Dixon, Dickerson, National Institute of Health and Care Excellence, 2015).

Lifestyle interventions with an evidence base in SMD to address health behaviours such as diet and physical activity should be considered. Behavioural interventions, if not already tailored, will likely need to be modified to account for motivational and cognitive challenges in this population. These may include social support strategies and environmental supports (i.e., resources or cues in the environment that facilitate functioning, such as smartphone reminders) (McGinty, Baller, Azrin, et al., 2016).

At the international policy level, reducing excess mortality in persons with SMD should be part of the broader health agenda. The WHO Mental Health Action Plan 2013-2020 established mental health as a fundamental component of WHO's definition of health, with objectives that include comprehensive and integrated mental health care services (World Health Organization, 2013). Mental health is now included as a priority in the United Nations Sustainable Development Goals. Reducing the life expectancy gap in those with SMD would also be a major step towards the goals of achieving universal health care coverage, effective treatment of non-communicable diseases, tobacco cessation, and suicide reduction (World Health Organization, 2014). These policies further promote the rights of persons with SMD to attain the highest level of health possible and full participation in society and at work.

Internationally, top-level integration in the plans and programmes among various efforts (e.g., mental health and substance abuse, non-communicable diseases, tobacco cessation, violence prevention, nutrition and physical exercise) would set a precedent for combining efforts and making strides in addressing complex, multifactorial health problems. This might lead to special considerations specifically for those with SMD across health domains that can help with closing the health equity gap in this vulnerable population. For example, the Package of Essential Noncommunicable (PEN) disease interventions for primary health care in low-resource settings recommends counseling for all health behaviours in the general population (World Health Organization, 2010). Persons with SMD may need more resources and more targeted approaches to implement any given guideline than the general population, and special considerations for this population (such as supportive assistance, longer duration and intensity of interventions, and cognitive tailoring) might be included in these documents. Such policies further converge with WHO Mental Health Action Plan's six cross-cutting principles of universal health care coverage, human rights,

evidence-based practice, a life course approach, a multisectoral approach, and the empowerment of persons with SMD.

At the national level, policies should be geared at strengthening existing health care platforms. These will facilitate the delivery and integration of effective interventions into the health system and the community to improve mental health (Shidhaye, Lund & Chhisholm, 2015). In addition to specific programmes targeting services for individuals and populations, national policies should enable and provide sufficient resources for routine data collection of key indicators of excess mortality in persons with SMD at local facilities, national and regional databases. Health information and surveillance systems will be needed to monitor mortality records and cite trends. Country-level data need to be specific to the needs of their populations, examining the impact of excess mortality in persons with SMD on disabilities and deaths, including prevalence of cardiovascular risks, infectious diseases and other relevant conditions. This will be especially important for LAMICs, where trends and needs may be different from high-income countries. Ultimately, this will allow for both intra-country and international comparisons and provide data to inform efforts to close the mortality gap.

The research agenda aims to develop WHO guidance to research organizations, including research funders, on generating additional knowledge in this area and to focus on how to make this research accessible and relevant to policy and practice (see [Appendix 5](#)).

Scientists working to understand causes of excess mortality and design and test interventions and programmes to decrease contributors to premature death in persons with SMD have made progress in recent years, and this is reflected in the evidence supporting the multilevel model of risk presented in this paper. At the same time, there is a need to delineate specific risk factors more clearly, identify which ones are modifiable, and how these may be different across settings, particularly in LAMICs.

While evidence for mental health treatments is strong, the evidence for effectiveness of interventions in ordinary settings to prevent and treat physical conditions in those with SMD is limited. Also missing in the literature is the role of resilience and other factors that may be protective, and a parsing out of the roles of factors that are intrinsic to SMD versus those related to socio-economic and health system variables. This includes the need for a better understanding of attributable risk for excess mortality in those with SMD.

Behavioural intervention trials are needed for other risk behaviours apart from unhealthy dietary habits, sedentary life style and tobacco smoking cessation, especially for comorbid substance abuse. For current evidence-based interventions, research is needed on optimal length and dose needed to positively affect health, which will also be important for resource allocation.

Interventions developed for the general population geared at NCDs, infectious diseases or other health problems are likely to be less effective for persons with SMD, given cognitive deficits and special needs of this population. Thus, interventions for SMD require tailoring. However, more work is needed on the degree of tailoring required. Multimodal approaches, which can include behavioural plus pharmacological interventions and include components such as peer support or technology are promising, but have yet to be studied systematically to clarify whether or which multi-component programs are effective, and which components of the intervention are most beneficial. Recent results suggest that some combined approaches may not be effective or may be dependent on existing health care systems (Speyer et al., 2016). We need to consider how structural interventions can facilitate these efforts. Many people with SMD have multiple cardiovascular and other risk behaviours which may be modifiable, and future research studies should test interventions addressing multiple risk factors, as well as those which are directly linked to mortality.

Research is needed to identify and manage barriers to and facilitators of implementing evidence-based guidance and policy recommendations at all levels (individual, health systems and social determinants) of the intervention framework. We need to understand how to deliver evidence-based interventions successfully in the real world, taking into account training and workforce issues and often-limited resources in local community settings. We need to understand to what extent interventions and programmes could or should be disseminated across countries.

Another important area of research will be to assess the effects of health system and policy interventions on excess mortality in SMD. We need to understand why those with SMD have not benefitted from trends in the general population towards reduced mortality in some diseases and smoking cessation. Researchers should take advantage of natural experiments and also design studies in health systems and at the population level to evaluate the impact of these programmes.

Although several guidelines for screening, monitoring and management of mental health and physical conditions have been developed from evidence-based best practices, the implementation of these guidelines has not been studied systematically to support their widespread implementation and impact on risk factors for excess mortality in persons with SMD. Similarly, integrated care programmes will need to be evaluated for their actual effectiveness on risk factors for excess mortality. Care coordination approaches are often elements of these integrated care programmes and have utilized providers, nurses, peers and others to play key roles in facilitating the adequate provision and connection of mental health and physical health care. Questions remain regarding the appropriate elements of care coordination, including tasks, roles and responsibilities of involved persons. Finally, as these are resource-intensive programmes, cost-effectiveness models of different approaches (Patel, 2011) in persons with SMD will be important, especially in low-resource settings. This will be particularly needed as we seek to prioritize understanding risk factors for premature mortality of persons with SMD in LAMICs.

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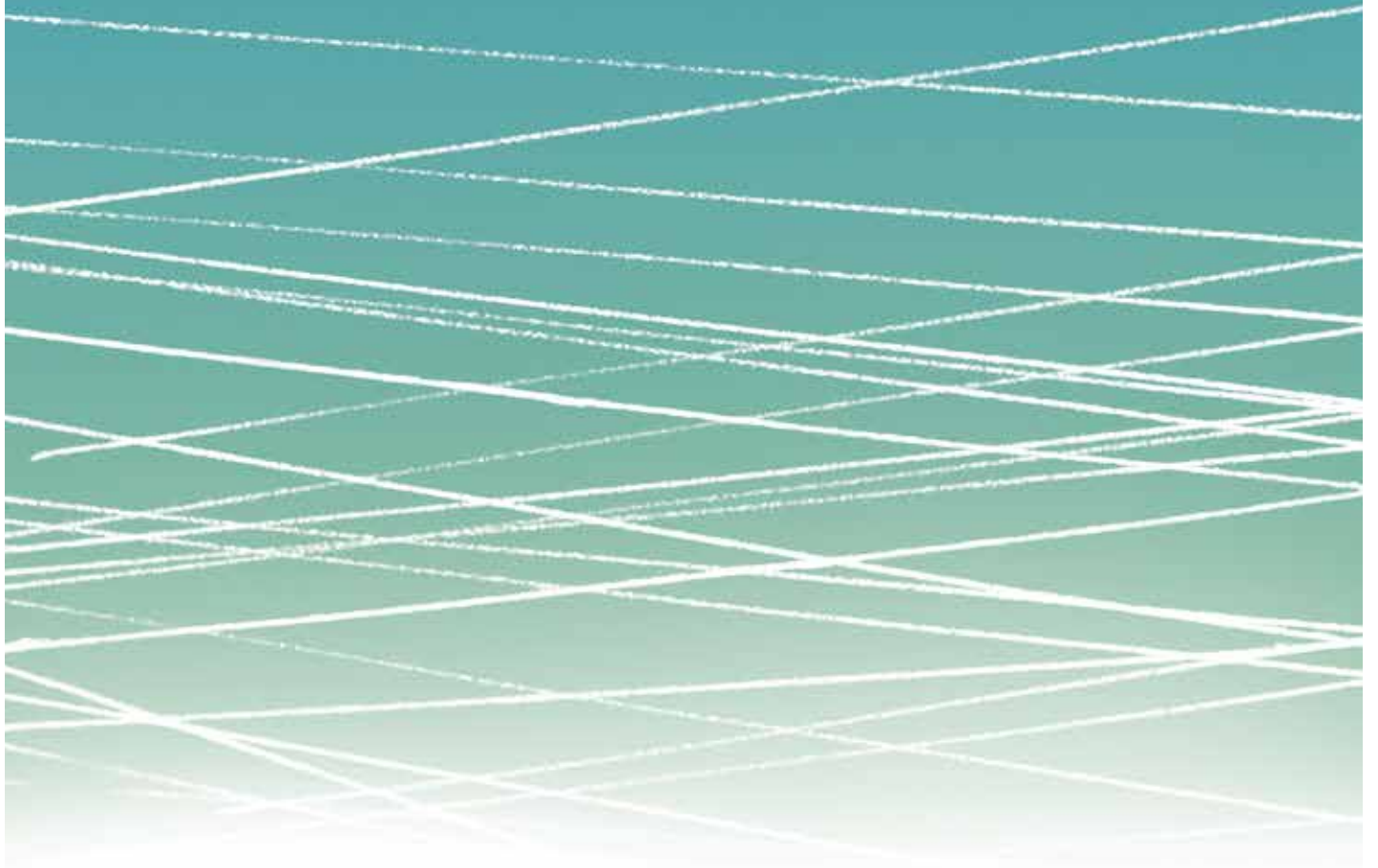
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APPENDIX 1

MEETING AGENDA



WHO Consultation
Excess Mortality among Persons with Severe Mental Disorders
18-20 November 2015

WHO/HQ Geneva, Switzerland
Meeting room M.105
AGENDA

Objectives

- To review the epidemiology and risk factors on excess mortality among persons with severe mental disorders with special attention to information from low- and middle-income countries.
- To review existing guidelines and best practices in this area and to develop an intervention framework.
- To advise WHO on the next steps for the development of a policy and research agenda to decrease excess mortality among persons with severe mental disorders.

Wednesday 18 November 2015 – Epidemiology & Risk Factors

10:30 – 11:00	Registration and coffee	
11:00 – 11:30	Welcome, Introduction & Objectives	<i>Shekhar Saxena</i>
11:30 – 12:00	Landscape analysis: <i>Epidemiology & Risk Factors</i>	<i>Nancy Liu & Tarun Dua</i>
12:00 – 12:20	<i>Low- and Middle-Income Countries Perspective</i>	<i>Abe Fekadu Wassie</i>
12:20 – 13:00	Discussion	
13:00 – 14:00	Lunch break	
14:00 – 15:30	Panel Discussion: <i>Methodological & Research Challenges</i>	<i>Benjamin Druss Merete Nordentoft Ezra Susser Somnath Chatterji Martin Prince Alexandra Fleischmann Moderator: Mario Maj</i>
15:30 – 16:00	Coffee break	

16:00 – 17:30	Panel Discussion: <i>Risk Factor Model</i>	<i>Thomas Munk Laursen Maria Elena Medina-Mora Hong Ma Alessandro De Maio Lubna Bhatti Guilherme Borges & Vladimir Poznyak Moderator: Maria Elena Medina-Mora</i>
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18:00 Reception

Thursday 19 November 2015 – Interventions, Guidelines & Packages

09:00 – 09:15	Summary of Day 1	
09:15 – 09:45	Landscape analysis: <i>Existing Guidelines, Packages & Programmes</i>	<i>Nancy Liu & Tarun Dua</i>
09:45 – 10:00	Country case study	<i>Dorairaj Prabhakaran</i>
10:00 – 11:15	Panel Discussion: <i>Existing Guidelines, Packages & Programmes</i>	<i>Chiyo Fujii Gail Daumit Gojka Roglic Tमितza Toroyan Ralph Aquila Dan Chisholm & Fahmy Hanna Moderator: Wolfgang Gaebel</i>

11:15 – 11:30 Coffee break

11:30 – 13:00	Panel Discussion: <i>Towards an Intervention Framework</i>	<i>Tarun Dua Kristian Wahlbeck Wolfgang Gaebel Thara Rangaswamy Graham Thornicroft Moderator: Graham Thornicroft</i>
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13:00 – 14:00 Lunch break

14:00 – 14:45	Group Work: <i>Leverage Points</i> <i>Working Group 1: Health Systems</i> <i>Working Group 2: Clinical</i> <i>Working Group 3: Community</i>	<i>Moderator: Thara Rangaswamy Moderator: David Shiers Moderator: Kenn Dudek</i>
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14:45 – 15:00 Coffee break

15:00 – 16:30	Group Presentations: <i>Leverage Points</i> <i>Working Group 1: Health Systems</i> <i>Working Group 2: Clinical</i> <i>Working Group 3: Community</i>	
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16:30 – 17:30	Discussion	
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Friday 20 November 2015 – The Way Forward: Policy & Research Agenda

09:00 – 09:15 Summary of Day 2

09:15 – 10:15 Policy Agenda

Moderator: Maria Elena Medina-Mora

10:15 – 10:45 **Coffee break**

10:45 – 11:45 Research Agenda

Moderator: Graham Thornicroft

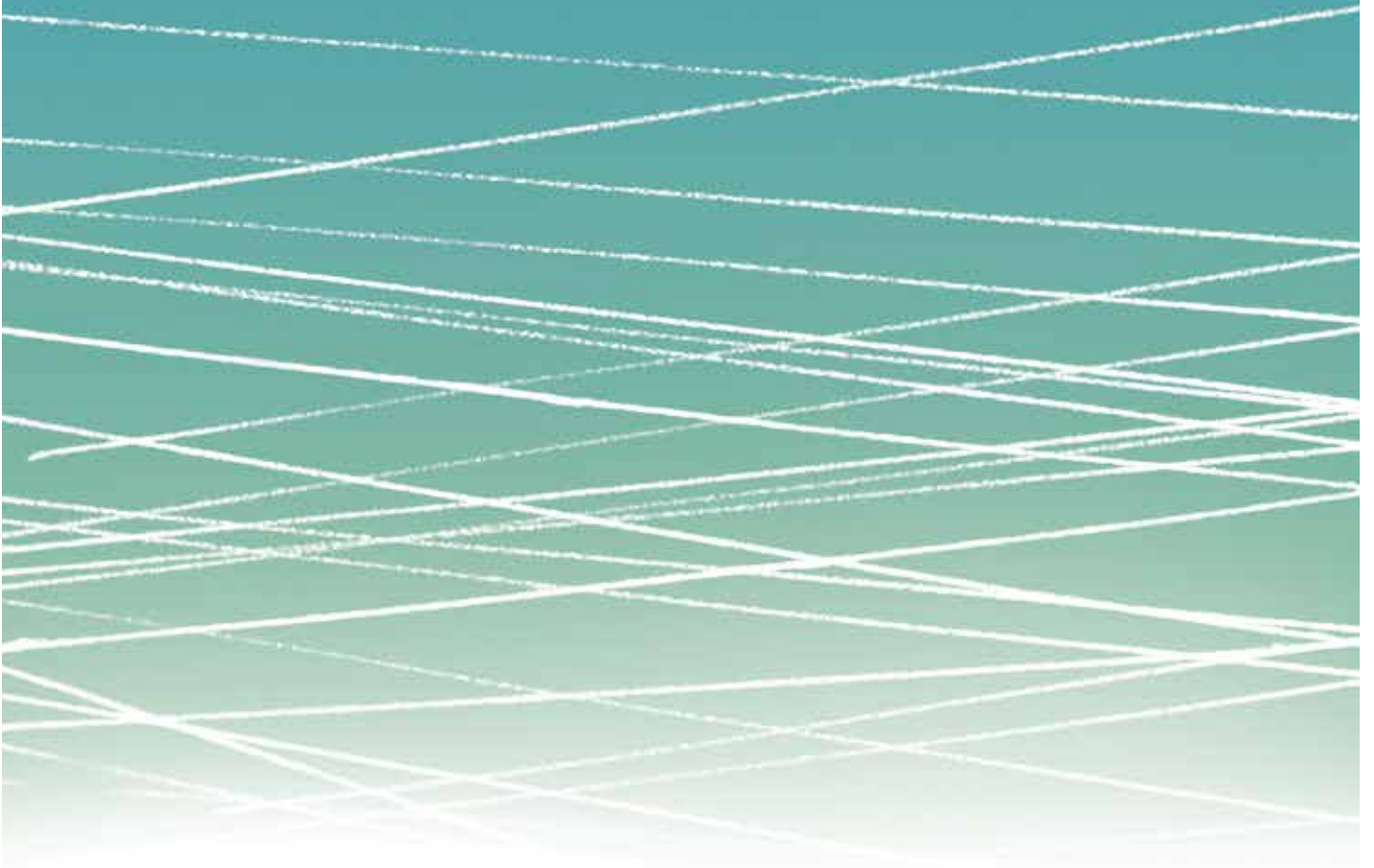
11:45 – 12:45 Open Discussion:
The Way Forward & Next Steps

Moderator: Shekhar Saxena

12:45 – 13:00 Closure

APPENDIX 2

LANDSCAPE ANALYSIS: EPIDEMIOLOGY AND CORRELATES



SUMMARY

OBJECTIVE

- We present an overview of the epidemiology and risk factors of excess mortality in persons with severe mental disorders (SMD), with special attention to information from low- and middle-income countries (LAMICs).

METHODS

- We reviewed and summarized systematic reviews and identified relevant studies through contact with a team of experts; requested data and additional analyses from senior authors; hand-searched reference lists of the peer reviewed and grey literature; and identified key informants who had access to primary or secondary unpublished information, especially from LAMICs.

FINDINGS

- Persons with SMD (i.e., schizophrenia and other psychotic disorders, bipolar affective disorder, moderate to severe depression) die about 10-20 years earlier than the general population.
- The vast majority of the literature comes from high-income countries (HICs); available data suggest that this may be worse in LAMICs.
- The majority of deaths are due to preventable diseases, especially cardiovascular disease, respiratory disease, and infections. Suicide continues to be an important cause of death, especially in the first year following discharge, and rates of homicide and accidents are significantly elevated.
- Excess mortality involves complex relationships among risk factors at the individual, health systems and socio-environmental levels.

IMPLICATIONS

- Despite decades of research and consistent documentation of this life expectancy gap, there has been little to no progress in narrowing this gap; in fact, most evidence suggests that this is increasing over time.
- More high quality studies from LAMICs are needed to more clearly understand the risk of excess mortality in persons with SMD in these settings.
- This review highlights the importance of a comprehensive framework for understanding the different contributions and mechanisms of risk factors in relation to excess mortality.
- Excess mortality in persons with SMD remains a major public health challenge that warrants action.

INTRODUCTION

The poor physical health and reduced life expectancy of persons with severe mental disorders (SMD) is well-documented in meta-analyses and systematic reviews (Brown, 1997; Harris & Barraclough, 1997; Brown et al., 2000; Saha et al., 2007; Cuijpers et al., 2014; Walker et al., 2015; Hayes et al., 2015), as well as reviews of reviews (e.g., Chesney et al., 2014). Additional studies, commentaries and editorials spanning the past decades have brought heightened awareness and attention to the topic, especially recently (Malzberg, 1932; Maj, 2008; Thornicroft, 2011; Charlson et al., 2015; Suetani et al., 2015). Despite this, at best, very little progress has been made (Wahlbeck et al., 2011)—in fact, most current evidence suggests that this excess mortality may be increasing significantly over time (Saha et al., 2007; Hoang et al., 2011; Osby et al., 2000; Laursen et al., 2010; Lawrence et al., 2013); recent studies show that standardized mortality ratios (SMRs) may be higher than those previously reported (e.g., Olfson et al., 2015).

In this paper, we reviewed the global extent of excess mortality in persons with SMD. Because most available information is from high-income countries (HICs), we focused additional attention on data available from low- and middle-income countries (LAMICs). Given that several reviews and meta-reviews have already been conducted, this landscape analysis is not meant to be exhaustive but seeks to present an overview of excess mortality in persons with SMD, along with its major correlates and risk factors, and present a comprehensive framework that can inform an intervention framework.

METHODS

We reviewed and summarized systematic reviews on excess mortality in persons with SMD; identified additional relevant studies through contact with a team of experts; requested data and additional analyses from senior authors; hand-searched reference lists of the peer reviewed and grey literature; and identified key informants who had access to primary or secondary unpublished information, especially from LAMICs. Where applicable, we requested additional analyses comparing HICs and LAMICs from authors of recent systematic reviews. Although it is clear that most mental disorders are associated with excess mortality, we limited the focus of this current review to persons with SMD: schizophrenia and other psychotic disorders (SCZ), bipolar affective disorder (BAD), and moderate-to-severe depression (DEP).

APPENDIX 2

FINDINGS

The following sections are organized accordingly: years of life lost, mortality risk compared with the general population and specific populations, causes of death (including natural causes, such as preventable physical illness and unnatural causes, like suicide and accidents) and finally, a comprehensive model that incorporates the the major correlates and risk factors that contribute to excess mortality.

MORTALITY RISKS COMPARED WITH THE GENERAL POPULATION & SPECIFIC POPULATIONS

YEARS OF LIFE LOST

Persons with SMD die about 10-20 years earlier than the general population. Though there is some variation in the range of years of life lost (YLL)—in the US, they die about 14 to 32 years earlier (Colton & Manderscheid, 2006) and in Nordic countries, they die about 11 to 20 years earlier (Laursen et al., 2013)—its extent appears pervasive and consistent, even in wealthy countries characterized by high social capital and income equality (Wahlbeck et al., 2011).

After additional requested analyses from senior authors (Walker et al., 2015; Cuijpers et al., 2014), data from systematic reviews show higher but not significantly different risk for all-cause mortality from LAMICs compared to HICs; however, the authors note that over 90% of studies included in reviews come from HICs, which are likely to affect these comparisons (Walker et al., 2015; Cuijpers et al., 2014).

Nevertheless, available data from LAMICs suggest that excess mortality is comparable, if not worse, in these areas. For example, in Ethiopia, persons with SMD died about 30 years earlier than the general population (Fekadu et al., 2015). Although life expectancy calculations among persons with SMD from LAMICs that also control for child mortality rates or similar biases are rare, they are, impressively, still available: in Ethiopia, the life expectancy for those with SCZ was 46.3 years (Fekadu et al., 2015), compared to 55.6 years, 60.1 years, and 58.3 years in Denmark, Finland, and Sweden, respectively (Nordentoft et al., 2013). A limited number of high-quality studies have examined the mean age at death among persons with SMD in LAMICs, using at least a 10-year follow-up period and an average age of 25 years at baseline. These studies reveal a similarly grim picture: the mean age at death among

persons with SCZ was 33.3 years in Bali, Indonesia (Kurihara, 2006); 34.2 years in Madras, India (Thara, 2004); 37.4 years in Butajira, Ethiopia (unpublished data, Fekadu et al., 2015); and before reaching age 40 in Nigeria (Abiodun, 1988). Life expectancy and age at death calculations are provided below in **Figures 1a and 1b**, respectively.

Data from HICs show that YLLs differ by disorder:

- Persons with SCZ died 10-20 years earlier (Chesney et al., 2014; Crump, Winkleby et al., 2013),
- Persons with BAD died 9-20 years earlier (Chesney et al., 2014; Crump et al., 2013) and
- Persons with DEP died 7-11 years earlier than those without these disorders (Chesney et al., 2014).

Limited data from one LAMIC suggest a different trend. In Ethiopia:

- Persons with DEP died 29.4 years earlier,
- Persons with BAD died 29.0 years earlier and
- Persons with SCZ died 27.7 years earlier than those without these disorders (Fekadu et al., 2015).

Most excess mortality data from LAMICs focus on SCZ; therefore, it is not clear whether the trend found by Fekadu and colleagues (2015) would extend to other LAMICs. It is possible that this comparable mortality among the different disorders may be partially explained by shared protective factors (e.g., greater family support and employment) and risk factors (e.g., less access to care, fewer mental health resources) in LAMICs, thereby leading different disorders to a similar mortality risk. Another possible explanation is that DEP may cause more disability in LAMICs than HICs, which can then lead to a poorer mortality outcome among the different disorders (Mogga et al., 2006). Because limited data are available, the heterogeneous outcomes characterizing LAMICs must be considered when generalizing these findings (Cohen et al., 2008).

In general, men tend to have greater YLLs and higher risk of all-cause mortality than women, a trend found in most studies from HICs (Wahlbeck et al., 2011) and LAMICs (Abiodun et al., 1988; Fekadu et al., 2015; Ran et al., 2007) and across the SMDs (Cuijpers et al., 2014b); however some variability remains (e.g., Menezes, 1996; Crump, Winkleby et al., 2015), with discrepancy among systematic reviews (e.g., no gender differences in mortality in SCZ in Saha et al., 2007). This discrepancy may be affected by the variability of prevalence of specific risk factors and causes of death among men versus women—for instance, rates of substance abuse, death by certain cancers, and suicide.

FIGURE 1A. LIFE EXPECTANCY IN PERSONS WITH SCHIZOPHRENIA

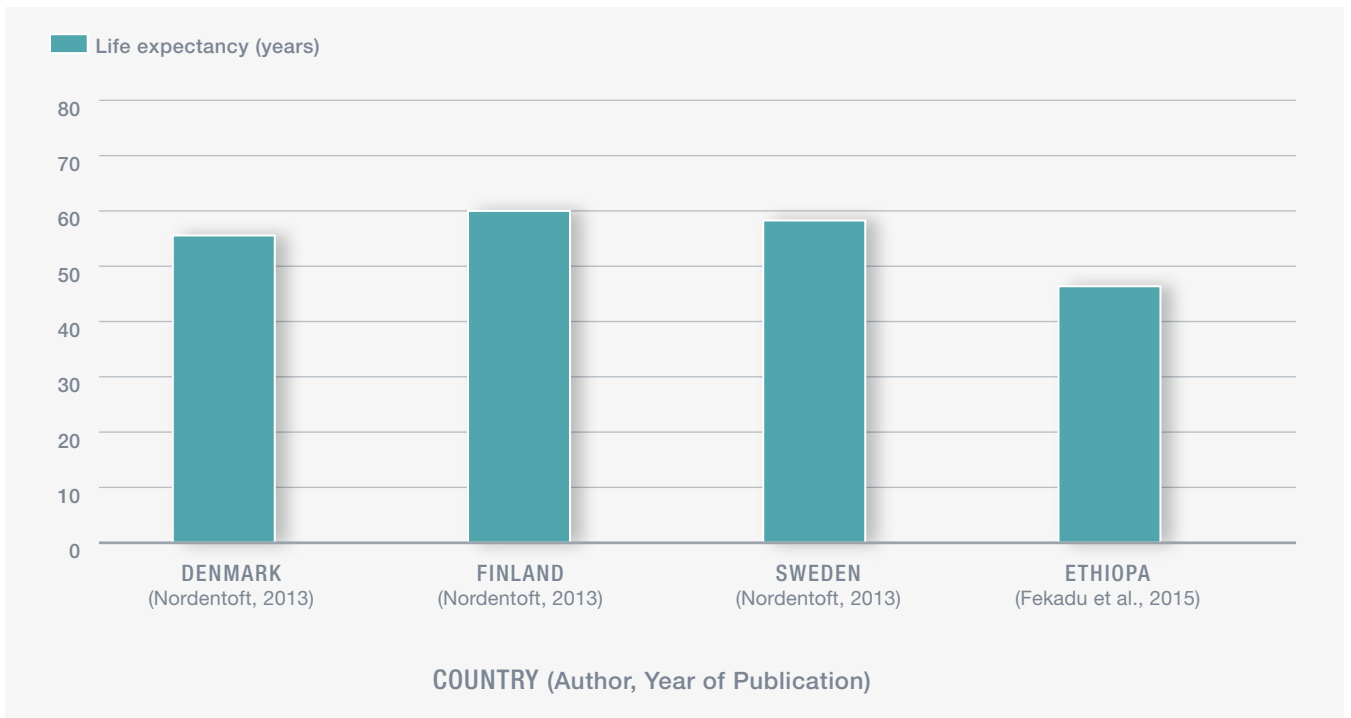
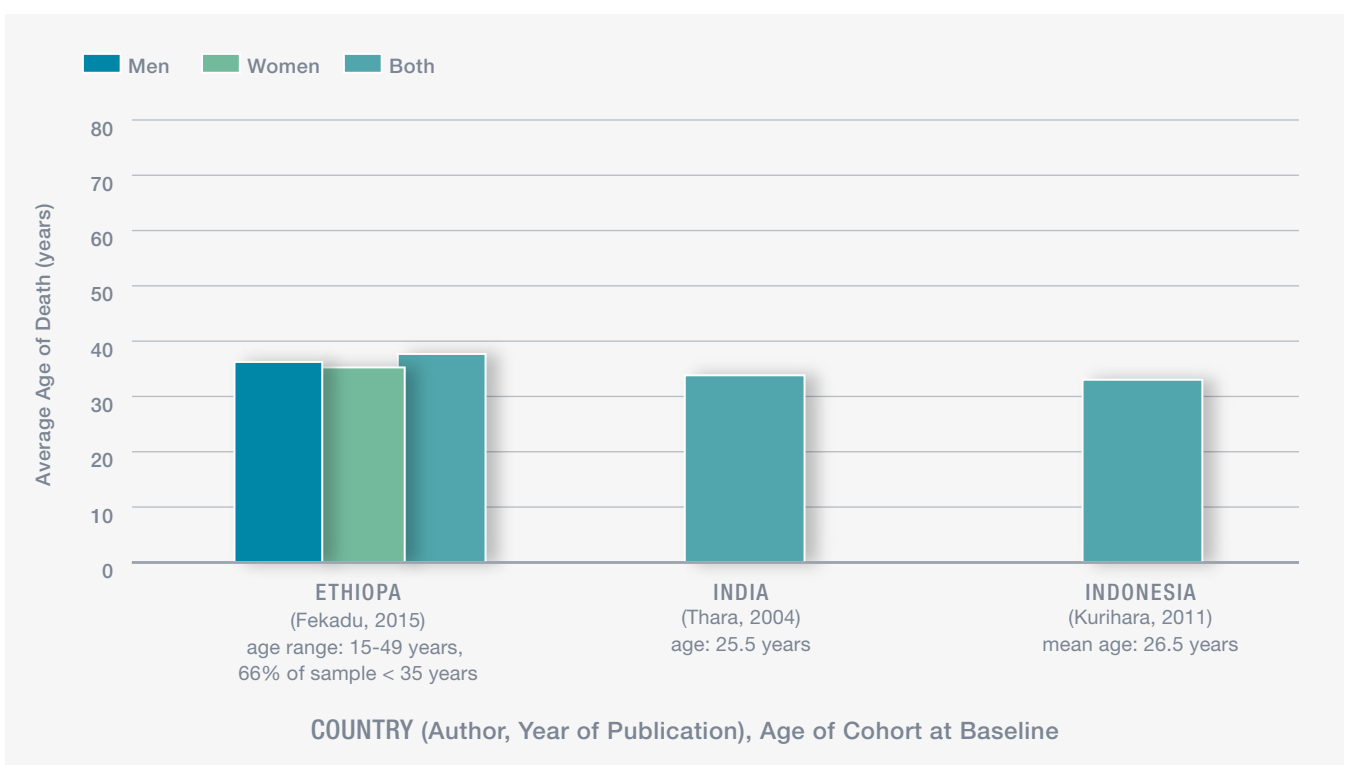


FIGURE 1B. AVERAGE AGE AT DEATH IN PERSONS WITH SCHIZOPHRENIA IN LOW- AND MIDDLE-INCOME COUNTRIES



APPENDIX 2

FINDINGS

STANDARDIZED MORTALITY RATIOS

Among most systematic reviews, persons with SMD die from all-causes about 2 to 3 times the rate of the general population, using standardized mortality ratios (SMRs).

- SCZ is associated with a well-documented 2.5- to 3-fold rate of all-cause mortality compared to the general population (Mortensen et al., 1993; Brown et al., 2000; Osby et al., 2000; Joukamaa et al., 2001; Heila et al., 2005; Saha et al., 2007; Crump, Winkleby et al., 2013; Walker et al., 2015). In a systematic review from 2007 pooling data from 27 different countries, the mean SMR for all-cause mortality in SCZ was 2.98 (SD=1.75) (Saha et al., 2007), similar to a meta-review published 7 years later (SMR=2.5; 95% CI, 2.2-2.4) (Chesney et al., 2014). Consistent with data suggesting an increasing trend over time (Saha et al., 2007), recent individual studies are reporting higher rates than past reviews: Medicaid recipients in the U.S., had an all-cause SMR=3.7 (95% CI, 3.7-3.7) (Olson et al., 2015).
- BAD is associated with a 2-fold rate for all-cause mortality compared with the general population (Westman et al., 2013). A meta-analysis of BAD summarizing 31 studies showed that the all-cause SMR was 2.05 (95% CI, 1.89-2.23) (Hayes et al., 2015), similar to a meta-review (SMR=2.2) (Chesney et al., 2014). The range in SMR from different studies was 1.24 (95% CI, 0.83-1.17) to 4.65 (95% CI, 1.89-2.23) (Hayes et al., 2015).
- In DEP, SMRs are not reported as commonly as the other disorders; instead relative risks (RR) for death as compared to the general population are typically reported and tend to be under 2 (Cuijpers et al., 2014). These numbers are provided in Figure 2. Of note, sub-threshold depression (sDEP) confers a similar risk for mortality that is not significantly different from the mortality risk in DEP (Cuijpers et al., 2013). In systematic reviews that have included it, the RRs for sDEP has been reported as 1.4 (95% CI, 0.9-2.0) (Chesney et al., 2014), 1.33 (95% CI, 1.11-1.61) (Cuijpers et al., 2013) and 1.65 (95% CI, 1.39-1.96) (Cuijpers et al., 2002) compared to those without sDEP. This finding has been documented in earlier studies (Harris & Barraclough, 1998; Wulsin, Vaillant, & Wells, 1999) and in older populations (Saz et al., 2001; Cole et al., 1997).

The SMRs in persons with SMD from LAMICs by disorder are below (see Figure 3):

- Persons with SCZ in Ethiopia had an over 3-fold rate of death compared to the general population in a 10-year follow-up study (SMR=3.03; 95% CI, 2.34-3.86) (Fekadu et al., 2015). Rural Chinese persons with SCZ had a 4-fold risk of death relative to the general population in a 10-year follow-up study (all-cause SMR=4.0; 95% CI, 2.4-5.8) (Ran et al., 2007). In Indonesia, the overall SMR for all-cause death in persons with SCZ was 4.85 (95% CI, 2.4-7.3), with a higher SMR for men (5.98, 95% CI, 2.4-9.5) compared to women (3.11, 95% CI, 0.1-6.2) in a 17-year follow-up study (Kurihara et al., 2011).
 - In general, studies with a shorter follow-up period tend to have higher SMRs, consistent with evidence from both HICs and LAMICs that the highest risks for mortality are in the earlier part of the follow-up period. Data from a 5-year follow-up of the Ethiopia cohort focusing on just those with SCZ revealed an SMR=5.98 (95% CI, 4.09-7.87) (Teferra et al., 2011).
 - In a 2-year follow-up study from Brazil, hospitalized persons with SCZ had an 8-fold risk of mortality compared to the general population (SMR=8.4, 95% CI, 4.0-15.9) (Menezes, 1996).
- In Ethiopia, persons with BAD had an SMR=1.50 (95% CI, 1.77-2.56) (Fekadu et al., 2015). There are limited data about excess mortality in BAD from LAMICs.
- In Ethiopia, persons with DEP had an SMR=1.70 (95% CI, 1.08-2.55) (Fekadu et al., 2015). The heightened risk of sub-threshold depressive symptoms appears important for this LAMIC: time spent in sDEP symptoms in persons with DEP was associated with risk of premature mortality, a finding that did not apply to SCZ or BAD (Fekadu et al., 2015). There are limited data about excess mortality in DEP and sDEP from LAMICs.

Length of follow-up likely contributes to the higher numbers reported in some studies, such as those found in the 5-year follow-up in Ethiopia (Teferra et al., 2011) and the 2-year follow-up in Brazil (Menezes, 1996). A number of authors and studies have highlighted that excess mortality appears to be highest in the initial stages of the disorder (Nordentoft, 2013; Fekadu 2015). Nevertheless, even in high quality studies with impressive follow-up periods (i.e., 10 years or more), such as those conducted by Fekadu (2015) in Ethiopia, Ran (2007) in China, and Kurihara (2007) in Indonesia, the all-cause SMRs appears greater compared with those from HICs.

FIGURE 2. ALL-CAUSE MORTALITY IN REVIEWS & META-REVIEWS

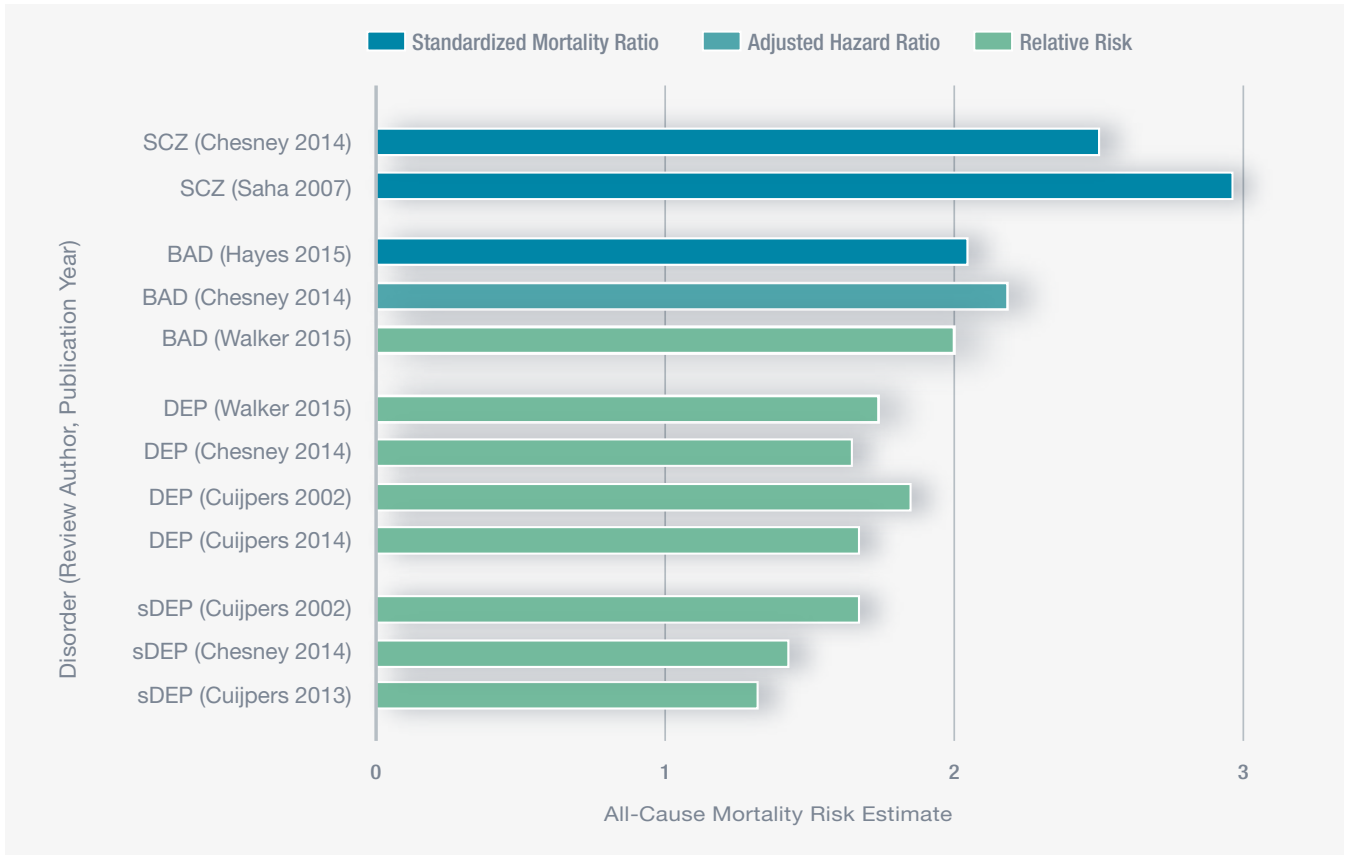
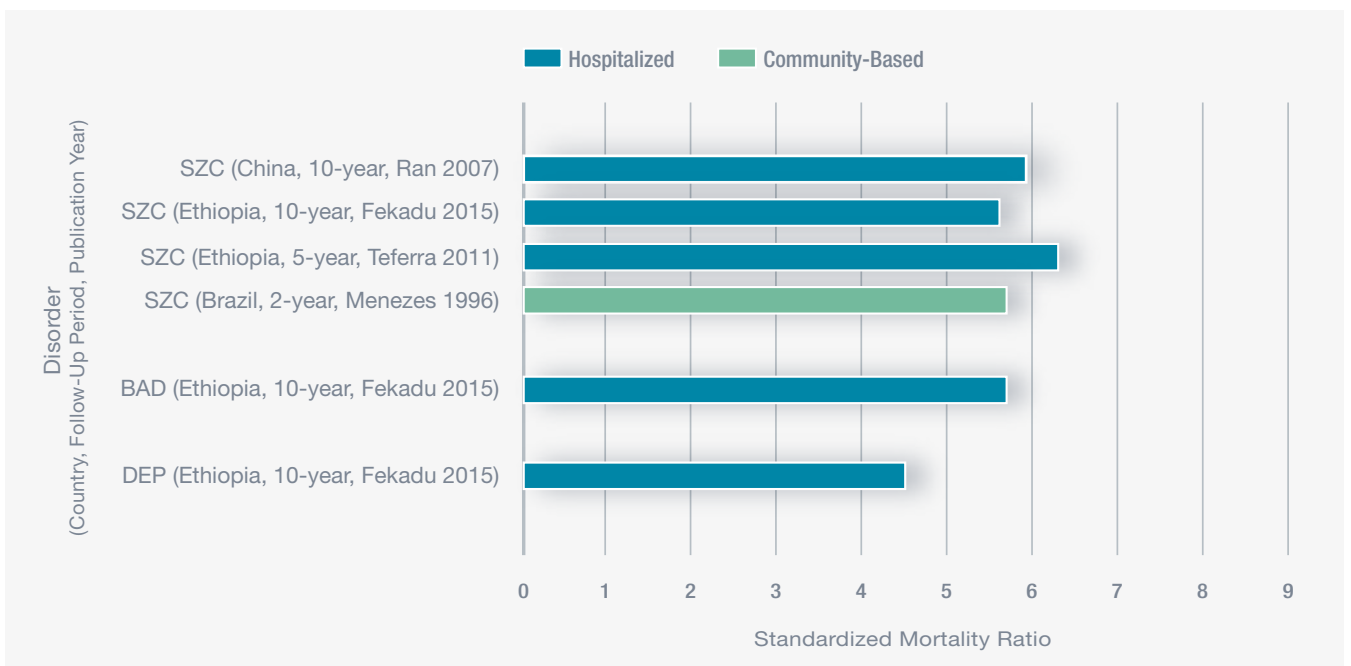


FIGURE 3. ALL-CAUSE MORTALITY IN LOW- AND MIDDLE-INCOME COUNTRIES



APPENDIX 2

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RELATIVE RISKS, HAZARD RATIOS AND ODDS RATIOS

Excess mortality is also quantified using RRs, hazard ratios (HR), adjusted hazard ratios (aHR), odds ratios (OR) and adjusted odds ratios (aOR) to compare mortality risks with the general population and specific populations. Studies using these comparisons provide further evidence that persons with SMD die at a higher rate than populations without these disorders and are quantitatively similar to the SMRs reported above. In a recent review, persons with any mental disorder (including common mental disorders) died about 2 to 3 times the rate of persons without a mental disorder (pooled RR=2.22; 95% CI, 2.12-2.33, from 148 studies; Walker et al., 2015).

- Similar to the SMRs reported above for SCZ, the RR for death in persons with psychoses was 2.54 (pooled RR from 65 studies, 95% CI, 2.35-2.75), compared to those without psychoses (Walker et al., 2015).
- Similar to the SMRs reported for BAD, the RR was 2.00 (pooled RR from 19 studies, 95% CI, 1.70-2.34), compared to those without BAD (Walker et al., 2015). In BAD, there was a slightly higher risk of mortality in women (aHR=2.34, 95% CI, 2.16-2.53) than in men (aHR=2.03, 95% CI, 1.85-2.23) (Crump, Sundquist et al., 2013).
- Persons with DEP have a just under two-fold risk of death compared with those without DEP (RR=1.81, 95% CI, 1.58-2.07 in Cuijpers & Smit, 2002; RR=1.64, 95% CI, 1.56-1.76 in Cuijpers et al., 2014a). The RR of mortality for DEP was 1.71 (pooled RR from 43 studies, 95% CI, 1.54-1.90) (Walker et al., 2015).

POPULATION ATTRIBUTABLE RISK

The population attributable risk (PAR) indicates the percentage of deaths that can be avoided if the risk factor were eliminated and also considers the prevalence of the diagnosis. Although this is not widely available in the literature on excess mortality in persons with SMD, one systematic review, by Walker et al. (2015) calculated that the PAR as 14.34% (i.e., 8 million deaths) for all mental disorders, 4.90% (i.e., 2.74 million deaths) for mood disorders, and 0.63% for psychoses (i.e., 350,000 deaths). The PAR was 7% for DEP (Cuijpers & Schoevers, 2004; Cuijpers et al., 2013). Of note, the PAR for sDEP is

similar, at 6.5% (Cuijpers et al., 2013), with a combined PAR of DEP and sDEP as 14.7% (Cuijpers et al., 2013). Several authors have noted that DEP contributes to more deaths overall due to its high prevalence (Walker et al., 2015; Cuijpers et al., 2004).

CAUSES OF DEATH

Nearly all of the major causes of death are elevated in persons with SMD (Saha et al., 2007). As shown in Figure 4, a large majority of these deaths (about two-thirds) are due to preventable physical illnesses. That is, most of the excess mortality is attributable to natural causes of death. The difference in life expectancy is not explained by unnatural deaths like suicide or accidents alone (Laursen, 2011; Crump, Winkleby et al., 2013). Laursen (2011) elegantly parsed out YLLs due to natural versus unnatural causes:

- Persons with SCZ lost 15.5 years of life due to cardiovascular diseases compared to 12.3 years due to external causes, like suicides, homicides, and accidents and
- Persons with BAD lost 11.3 years of life due to cardiovascular disease compared to 9.2 years due to external causes, like suicides, homicides, and accidents.

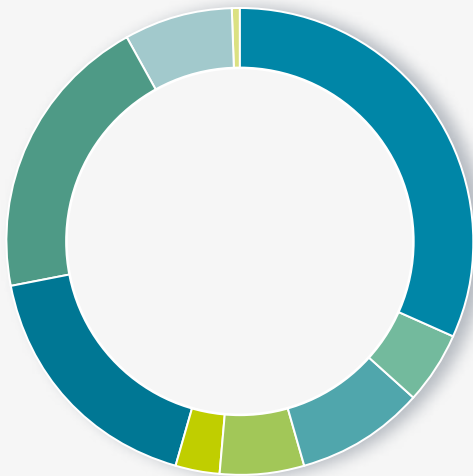
Although less detailed data are available from LAMICs, the majority of deaths are similarly due to physical conditions: in Ethiopia, 75% of deaths were due to natural causes, while about a quarter of deaths were due to unnatural causes (24.8%; Fekadu et al., 2015). In rural China, 65.3% of those with SCZ died due to natural causes, while 34.3% were due to unnatural causes (21.4% due to suicides and 13.2% due to accidents) (Ran et al., 2007). In a 17-year follow-up study for people with SCZ from Indonesia, 86.7% of deaths were due to physical diseases and 13.4% were due to suicide and accidents (Kurihara et al., 2011). Nevertheless, suicide continues to be an important cause of death, especially in the first year following discharge, and rates of homicide and accidents are significantly elevated.

FIGURES 4. MORTALITY BY CAUSE IN HIGH-INCOME AND LOW- AND MIDDLE-INCOME COUNTRIES (10+ YEARS FOLLOW-UP)

WESTERN AUSTRALIA

Lawrence 2013, Men with SCZ, 24-year follow-up,
Total N = 11,513, Deaths n = 1218

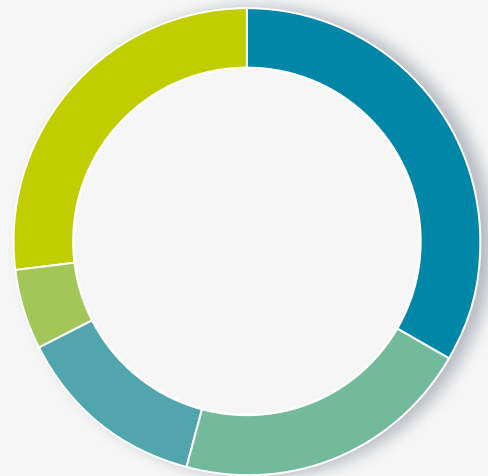
- Circulatory diseases, 31.8%
- Other natural, 17.5%
- Infectious diseases, 4.9%
- Suicide, 19.8%
- Neoplasms, 8.9%
- Accidents, 7.5%
- COPD, 5.8%
- Complications of medical care, 0.5%
- Diabetes mellitus, 3.3%



UNITED STATES

Druss 2011, SMD, 17-year follow-up
Total N = 1,725, Deaths n = 463

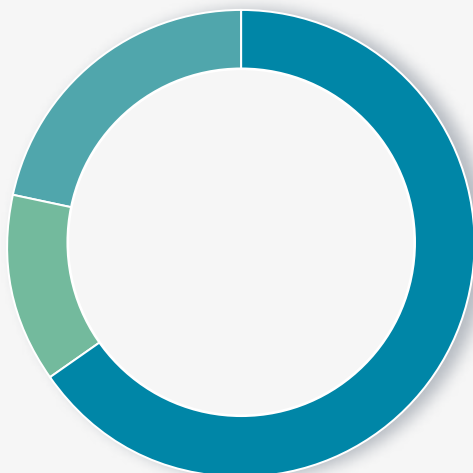
- Cardiovascular diseases, 33.9%
- Neoplasms, 21.0%
- Respiratory diseases, 13.5%
- Unnatural causes, like suicide, homicide and accidents, 5.4%
- Other, 26.2%



CHINA

Ran 2007, SCZ, 10-year follow-up, Total N = 500, Deaths n = 98

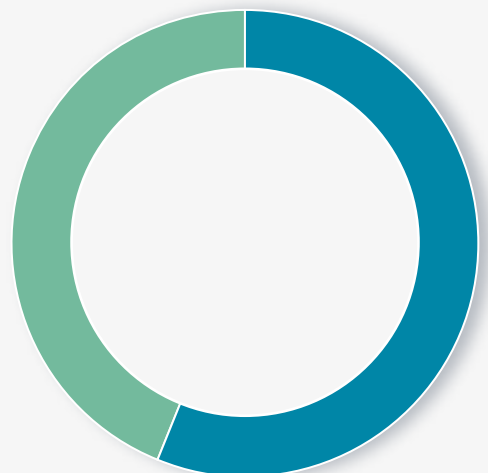
- Natural, 65.3%
- Suicide, 13.3%
- Accidents, 21.4%



INDIA

Thara 2004, SCZ, 20-year follow-up, Total N = 61, Deaths n = 16

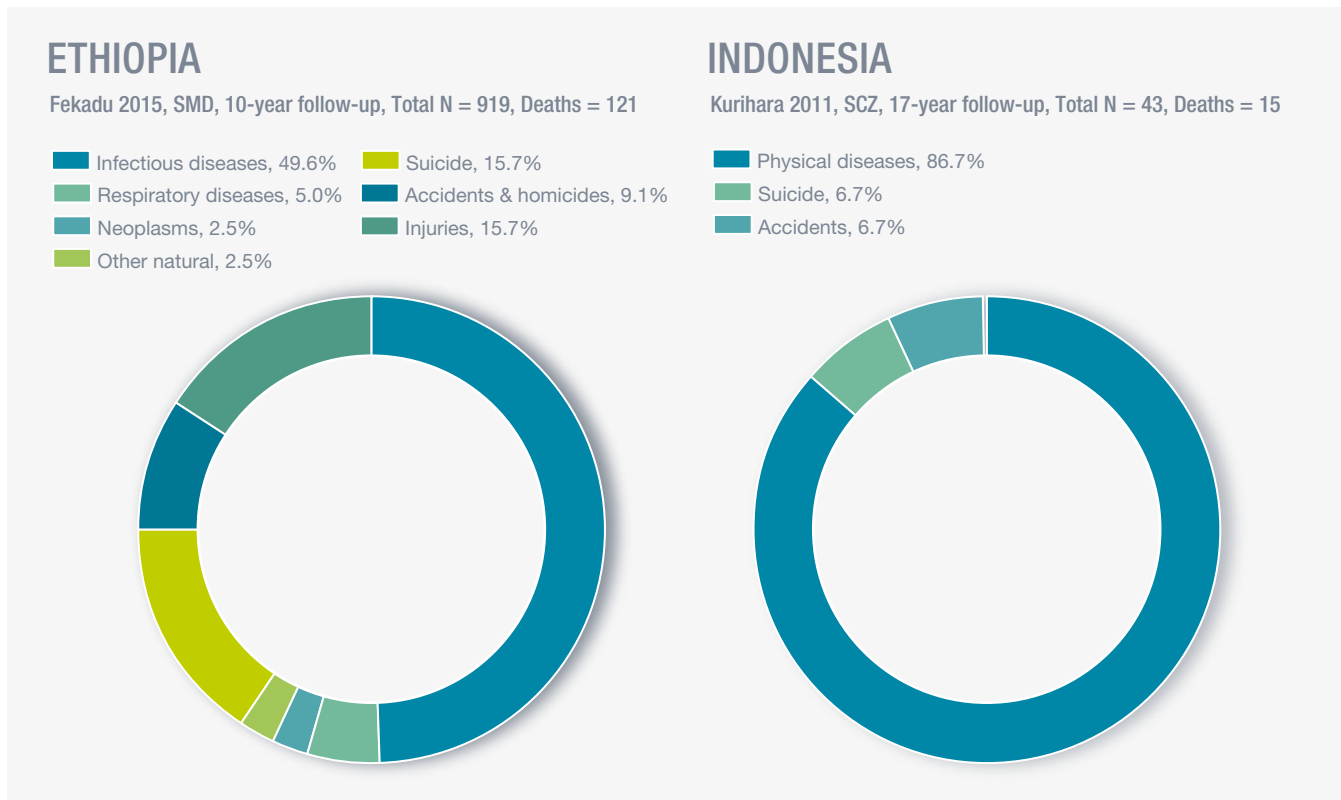
- Physical diseases, 56.3%
- Suicide, 43.8%



APPENDIX 2

FINDINGS

FIGURE 4. (CONT.) MORTALITY BY CAUSE IN HIGH-INCOME AND LOW- AND MIDDLE-INCOME COUNTRIES (10+ YEARS FOLLOW-UP)



NATURAL CAUSES OF DEATH

As seen in Figure 5, circulatory diseases are the major cause of death in persons with SMD in HICs. In LAMICs, infectious diseases are the major cause (e.g., Fekadu et al., 2015).

In HICs, the leading causes of death among persons with SMD are similar to those of the general population: heart disease, cancer, and respiratory and lung disease (Colton & Manderscheid, 2006). Despite the favourable trends in mortality in the general population, most persons with SMD die earlier and at a higher rate largely from preventable NCDs (Lawrence et al., 2003; Maj, 2008; Brown et al., 2000; Walker et al, 2015; Lawrence et al., 2013; Crump, Winkleby et al., 2013; Laursen et al., 2011; Nordentoft et al., 2013).

Persons with any mental disorder die about 2-3 times the rate from natural causes as those without a mental disorder, and there is some variation by disorder:

- Persons with SCZ die from natural causes about 2-3 times the rate as the general population (SMR=2.36, 95% CI,

2.16-2.58 in men and SMR=2.65, 95% CI, 2.42-2.90 in women; Crump, Winkleby et al., 2013). Similarly, among persons with recent-onset SCZ in Nordic countries (i.e., Denmark, Finland and Sweden), there was a 2.2-2.6 times higher mortality due to physical diseases and medical conditions (Nordentoft et al., 2013).

Of those who died of natural causes, women with SCZ died 10.5 years earlier than women without SCZ; men with SCZ died 13.1 years earlier than those without SCZ (Crump, Winkleby et al., 2013).

- In BAD, the SMR for death due to natural causes was 1.64 (95%CI 1.47 – 1.83) (Hayes et al., 2015). Similarly, among persons with recent-onset affective disorders in Nordic countries (i.e., Denmark, Finland and Sweden), there was a 1.7-1.9 times higher mortality due to diseases and medical conditions (Nordentoft et al., 2013).

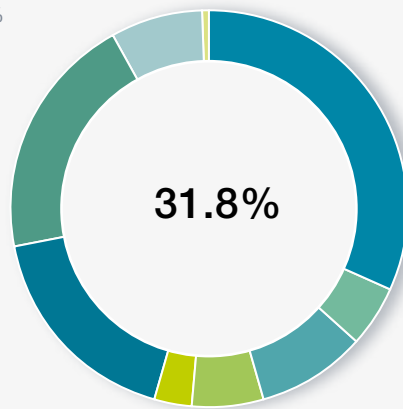
Similar to HICs, in rural China, the SMR for natural deaths for those with SCZ was 2.6 (95% CI, 1.7-4.1) (Ran et al., 2007).

FIGURE 5. MAJOR CAUSE OF MORTALITY IN HIGH-INCOME AND LOW- AND MIDDLE-INCOME COUNTRIES WITH 10+ YEARS FOLLOW-UP

WESTERN AUSTRALIA

Lawrence 2013, Men with SCZ, 24-year follow-up,
Total N = 11,513, Deaths n = 1218

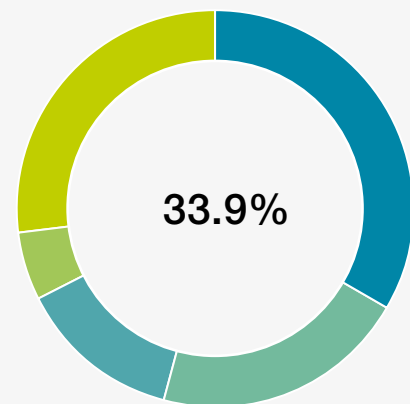
- **Circulatory diseases, 31.8%**
- Infectious diseases, 4.9%
- Neoplasms, 8.9%
- COPD, 5.8%
- Diabetes mellitus, 3.3%
- Other natural, 17.5%
- Suicide, 19.8%
- Accidents, 7.5%
- Complications of medical care, 0.5%



UNITED STATES

Druss 2011, SMD, 17-year follow-up
Total N = 1,725, Deaths n = 463

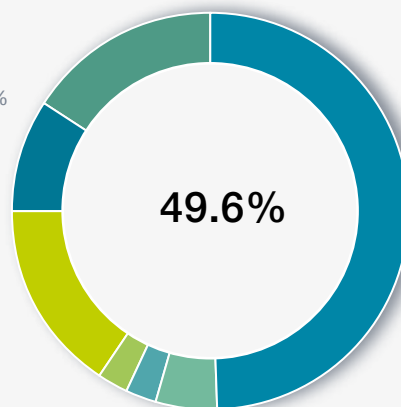
- **Cardiovascular diseases, 33.9%**
- Neoplasms, 21.0%
- Respiratory diseases, 13.5%
- Unnatural causes, like suicide, homicide and accidents, 5.4%
- Other, 26.2%



ETHIOPIA

Fekadu 2015, SMD, 10-year follow-up, Total N = 919, Deaths = 121

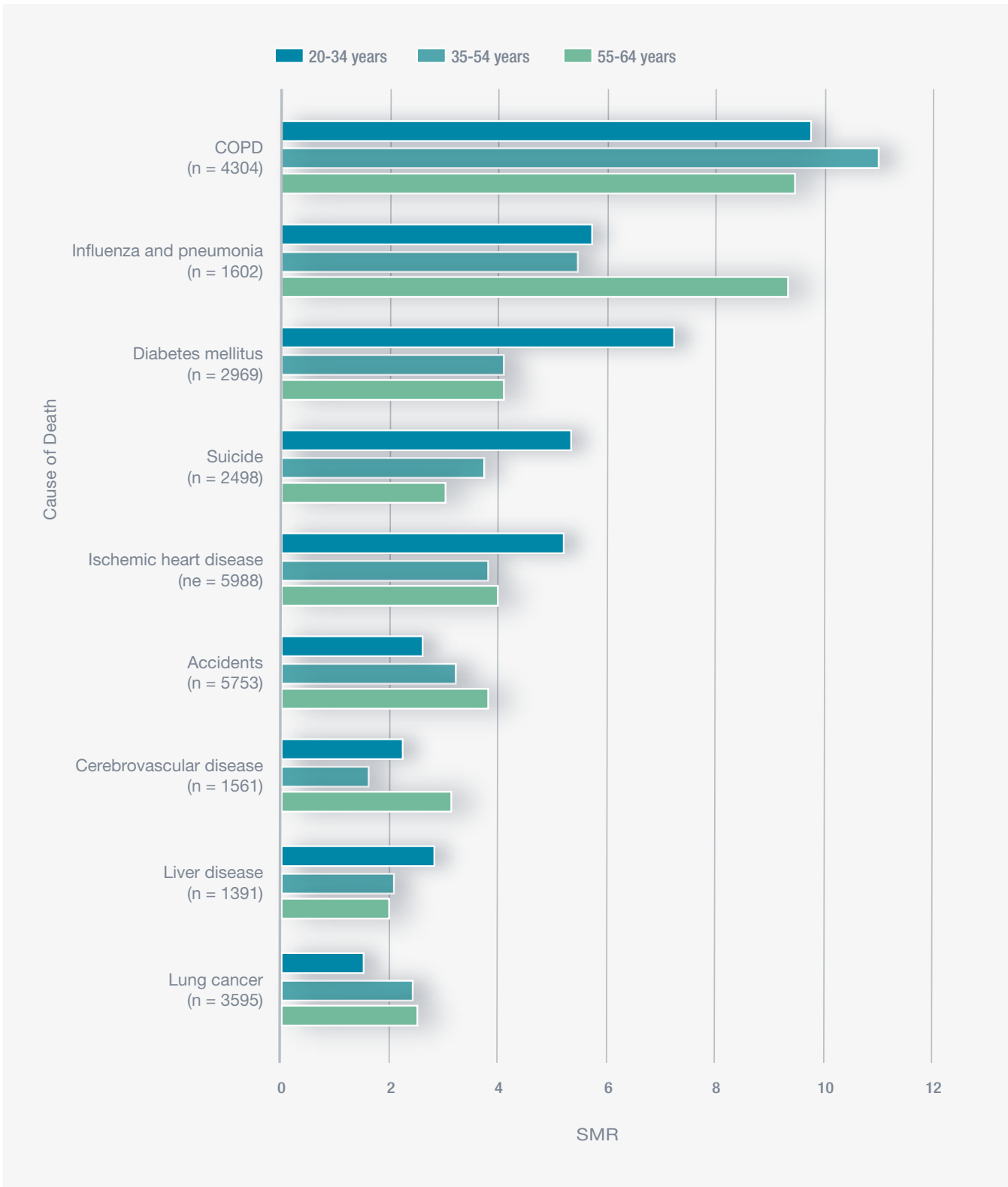
- **Infectious diseases, 49.6%**
- Respiratory diseases, 5.0%
- Neoplasms, 2.5%
- Other natural, 2.5%
- Suicide, 15.7%
- Accidents & homicides, 9.1%
- Injuries, 15.7%



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FIGURE 6. STANDARDIZED MORTALITY RATIOS BY CAUSE OF DEATH IN PERSONS WITH SCHIZOPHRENIA (FROM OLFSON ET AL., 2015)



A majority of persons with SMD die from circulatory diseases and die at about 2-3 times the rate from this as the general population; however when persons with SMD have respiratory diseases, influenza or pneumonia, they die at an even higher rate than circulatory diseases (e.g., see Figure 6 from Olfson et al., 2015). The heightened risk of mortality by natural causes is not due to age cohort effects alone (Olfson, 2015), nor can it be explained by smoking or substance use. Adjustment for smoking and other substance use disorders resulted in an attenuation of risk estimates by only 30% for lung cancer mortality and 10-20% for mortality from ischemic heart disease, stroke, influenza and pneumonia, or chronic obstructive pulmonary disease (Crump, Winkleby et al., 2013). Comorbidity of physical health problems appears to play a role: Laursen, Munk-Olsen and colleagues (2011) calculated that approximately 50% of the excess mortality due to natural causes of death in persons with SCZ or BAD is accounted for by chronic somatic comorbidity. Below are some of the most common causes of death in persons with SMD.

Circulatory diseases

This increased risk of death due to circulatory diseases is well documented, especially among persons with SCZ. Among those with any SMD, the HRs for coronary heart disease mortality was high across all age groups compared with controls: 3.22 (95% CI, 1.99-5.21) for those between the ages of 18-49 years, 1.86 (95%CI, 1.63-2.12) for those between the ages of 50-75 years, and 1.34 (95% CI, 1.17-1.54) for those older than 75 years (Osborn et al., 2007).

- In SCZ, cardiovascular disease is the single largest cause of death (Colton & Manderscheid, 2006) and major cause of excess premature mortality (Lawrence et al., 2013; Henekens et al., 2005; Laursen 2011). Up to 75% of patients with SCZ (compared to about 33% of the general population) die of coronary heart disease (Henekens et al., 2005).

In SCZ, most studies report an RR for death due to circulatory diseases around 2- to 3-fold compared to those without SCZ (Henekens et al., 2005; Laursen et al., 2013). In Sweden, there was a 2.42-fold (aHR, 95% CI, 2.12-2.77) risk for men and 2.94-fold (aHR, 95% CI, 2.56-3.37) risk for women of dying from cardiovascular disease compared to the general population (Crump, Winkleby et al., 2013). Comparing those with SCZ who died of heart conditions versus those in the general

population who also died of heart conditions from 3 Nordic countries, persons with SCZ had a two to three-fold risk of dying from cardiovascular disease (Laursen et al., 2013). In Israel, persons with SCZ with a diagnosis of cardiovascular disease had a 2.3-fold risk for death compared with those without SCZ (aHR=2.29, 95% CI, 2.10-2.50) (Gal et al., 2015). Among persons with SCZ who died from ischemic heart disease, women died 12.5 years earlier and men died 14.5 years earlier than other women and men without SCZ (Crump, Winkleby et al., 2013). This cannot be explained by lifestyle factors alone: after adjusting for smoking and other substance abuse disorder, death due to ischemic heart disease only decreased minimally: for women from 3.33 (95% CI, 2.73-4.05) to 3.28 (95% CI, 2.70-4.00) and for men from 2.20 (95% CI, 1.83-2.65) to 2.11 (95% CI, 1.75-2.54) (Crump, Winkleby et al., 2013).

- In BAD, the risk for death by circulatory disease is about twice as high compared to the general population (Westman et al., 2013). A systematic review of deaths from circulatory disease in persons with BAD found an SMR of 1.73 (95%CI 1.54 – 1.94) (Hayes et al., 2015). Similarly, data from the Nordic countries found a two-fold risk of death due to circulatory diseases in all countries for both sexes (Laursen et al., 2013). Persons with BAD died of cardiovascular disease approximately 10 years earlier than the general population (Westman et al., 2013).
- Persons with DEP have a 1.5-2.0 times higher risk of dying from circulatory diseases compared to the general population. Data from the Global Burden of Disease showed that the pooled RR risk of developing ischemic heart disease in those with DEP was 1.56 (95% CI, 1.30-1.87) (Charlson et al., 2013).

The relationship between DEP and circulatory disease appears to be bidirectional: persons with DEP are twice as likely to have a heart attack as the general population (Rugulies et al., 2002) and DEP further increases the risk of death in patients with cardiac disease (Whang et al., 2010). In a systematic review, compared with other heart disease patients, persons with comorbid DEP had a 1.72 (95% CI, 1.56-1.90) greater RR of dying compared to other heart disease patients (Cuijpers et al., 2014). In a 15-year population-based study of young people (mean age=28.1 years) that controlled for socioeconomic status, lifestyle factors and comorbid medical conditions, the PAR for ischemic heart disease in women with

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depression and a history of an attempted suicide was more than any traditional risk factor for ischemic heart disease (i.e., smoking, hypertension, diabetes mellitus, and obesity) (Shah et al., 2011). Further, the severity level of DEP appears associated with an incremental increased risk of circulatory problems among persons with DEP (Almas et al., 2015; Wei et al., 2014).

In LAMICs, circulatory disease deaths also appear common among persons with SMD: in rural China, 7 of 42 (16.7%) known death cases of those with SCZ in a 10-year cohort study were due to heart disease (Ran et al., 2007); however detailed data about deaths due to circulatory diseases are more limited from LAMICs and not reported in some settings, likely due to the few deaths attributed to this (e.g., Fekadu et al., 2015).

Respiratory diseases

Persons with SMD die due to respiratory diseases about 2 to 5 times the rate of the general population. The median prevalence of chronic obstructive pulmonary disease appears higher in this population, 8.9% (range: 2.0%-12.9%), compared to the general population (in the U.S.) is 6.3% (Janssen et al., 2015).

- In SCZ, death by chronic obstructive pulmonary diseases was 6.28 times higher for men (aHR; 95% CI, 4.66-8.46) and 3.31 times higher for women (aHR; 95% CI, 2.23-4.91) compared with the general population (Crump, Winkleby, et al., 2013). In the U.S., the SMRs for chronic obstructive pulmonary disease were 11.4 (95% CI, 10.9-11.7), 4.7 (95% CI, 4.3-2.1), 7.8 (95% CI, 5.0-10.6) and 11.6 (95% CI, 9.0-14.3) among White non-Hispanic, Black, non-Hispanic, other Non-Hispanic and Hispanic persons with SCZ, respectively (Olfson et al., 2015).
- In BAD, the SMR for deaths from respiratory disease were 2.92 (95%CI 2.00 - 4.23) (Hayes et al., 2015). Even after controlling for substance use disorders and age and sociodemographic variables, the risk for death by respiratory disease remained significantly elevated with a 2-fold risk of death for persons with BAD compared to the general population (Crump, Sundquist, et al., 2013).

- In DEP, there was a nearly 3-times higher mortality (RR=2.72; 95% CI, 1.96-3.77) in those who had DEP and chronic obstructive pulmonary disease compared with non-depressed patients with chronic obstructive pulmonary disease (Cuijpers et al., 2014). Among those with DEP, having a comorbid diagnosis chronic obstructive pulmonary disease was a significant predictor of death (Cuijpers et al., 2014).

Although limited data are available for specific causes of death, in rural China, 7 of 42 (16.7%) known death cases in persons with SCZ died due to respiratory disease (Ran et al., 2007). Only 5% of deaths were due to respiratory disease among persons with Ethiopia, where persons with SMD may exhibit few tobacco smoking behaviours (Fekadu et al., 2015).

Diabetes Mellitus

Persons with SMD have an about 2-4-fold risk of dying from diabetes mellitus.

- In SCZ, there is a 2.24 (1.42-3.53)-fold risk of death in men and 4.20 (2.73-6.46)-fold risk in women due to diabetes mellitus compared to the general population (Crump, Winkleby, et al., 2013), which are similar to studies by Laursen and colleagues (2011). A study from the UK found that after adjusting for age and gender, there was a greater risk of death in persons with comorbid diabetes and SCZ (HR=1.84, 95% CI, 1.42-2.40). A more recent study found higher SMRs for diabetes mellitus: 5.6 (95% CI, 5.3-5.9), 2.8 (95% CI, 2.6-3.0), 5.4 (95% CI, 4.1-6.6), and 4.0 (95% CI, 3.3-4.7) for White non-Hispanic, Black, non-Hispanic, Other Non-Hispanic and Hispanic persons with SCZ, respectively (Olfson et al., 2015).

This might be due to illness-related complications: Carney and colleagues (2006) found that persons with SCZ were about 2.11 times (OR; 95% CI, 1.36 to 3.28) more likely to have diabetes with complications than the general population.

- In BAD, men had an aHR of 2.63 (95% CI, 1.58-4.37) and women had an aHR of 3.39 (95% CI, 2.25-5.12) risk of dying from diabetes mellitus relative to those without BAD (Crump, Sundquist, et al., 2013).

- Persons with DEP and diabetes mellitus had a 1.61 (RR; 95% CI, 1.21-2.15) times risk of dying from diabetes mellitus compared with other patients with diabetes mellitus who did not have DEP (Cuijpers et al., 2014).

Cancer & Neoplasms

There are mixed results regarding the increased risks of death due to cancer in persons with SMD. Many studies have found null results, including large studies among persons with SMD (e.g., Lawrence, 2000), meta-analysis about the cancer incidence in persons with SCZ (Catts et al., 2008), and national linkage analysis studies in persons with SCZ (Levav et al., 2009); however there appears to be some variation among types of cancers:

- Among persons with any SMD, the aHR for deaths due to respiratory tumours was 1.32 (95% CI, 1.04-1.68) for those 50-75 years old; however this lost significance when controlling for smoking and social deprivation (Osborn et al., 2007).
- In SCZ, there is evidence of a higher risk of death due to breast cancer among women with SCZ (aHR=2.58, 95% CI 1.64-4.06) and colon cancer for men (aHR=2.34, 95%CI, 1.21-4.51) (Crump, Winkleby et al., 2013). A recent study from the US found significantly higher SMRs for cancer: 2.0 (95% CI, 2.0-2.1), 1.2 (95% CI, 1.2-1.3), 1.4 (95% CI, 1.2-1.7), and 1.6 (95% CI, 1.4-1.7) for White non-Hispanic, Black, non-Hispanic, Other Non-Hispanic and Hispanic persons with SCZ, respectively (Olfson et al., 2015). In this study, the highest SMRs were for lung cancer: 2.8 (95% CI, 2.7-2.9), 1.5 (95% CI, 1.4-1.6), 2.2 (95% CI, 1.6-2.8), and 2.4 (95% CI, 1.8-3.0) for White non-Hispanic, Black, non-Hispanic, Other Non-Hispanic and Hispanic persons with SCZ, respectively (Olfson et al., 2015).
- In BAD, a meta-analysis found that the SMR for cancer was 1.14 (95%CI, 1.10 – 1.21) (Hayes et al., 2015); however other single studies have shown mixed results about significant increased risks of cancer mortality in persons BAD (Crump, Sundquist, et al., 2013). Another linkage analysis from Israel showed standardized incidence ratios revealing an enhanced cancer risk for BAD in both genders (men=1.59, 95% CI, 1.01-2.17; women=1.75, 95% CI, 1.31-2.18) (BarChana, et al., 2008).

- In a systematic review among persons with DEP, the RR for cancer was 1.61 (95% CI, 1.37-1.88) compared with cancer patients without DEP (Cuijpers et al., 2014). Though beyond the scope of this paper, up to 50% of cancer patients suffer from a mental illness, especially depression and anxiety (Massie, 2004), and the presence or lack of treatment for depression can affect survival rates (Giese-Davis, et al., 2011).

In rural China, 9 of 42 (21.4%) known death cases died due to various cancers among in those with SCZ (Ran et al., 2007). Finally, and discussed in more detail in the correlates and risk factors section of this paper, a population-based study from Western Australia found a similar incidence rate of cancer in persons with SMD as in the general population but raised mortality (Lawrence et al., 2000). Similar findings by Crump, Winkleby, et al., 2013) suggest that persons with SMD may have similar rates of cancer but have a higher risk of dying of cancer due to under-diagnosis.

Infectious diseases

Infectious diseases appear to contribute to an increased risk of death in persons with SMD, with a 4- to 8-fold risk of death due to infection compared to the general population. The following sections are organized according to infectious diseases in general, followed by specific infections ranging from influenza or pneumonia to hepatitis B and C and human immunodeficiency virus (HIV).

- In a systematic review among persons with SCZ the SMR for deaths due to infectious diseases was 4.29 (10%-90% quintile, 1.6-7.8) (Saha et al., 2007).
- Among persons with BAD, the SMR for deaths due to infectious diseases was 2.25 (95%CI 1.70 - 3.00) (Hayes et al., 2015).

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There is a heightened risk of death for influenza or pneumonia:

- Among non-elderly persons with SCZ in the U.S., the SMR for influenza or pneumonia was 5.6 (95% CI, 4.1-7.1) for those aged 20-34 years and 5.2 (95% CI, 4.8-5.6) for those aged 35-54 years (Olfson et al., 2015). Poor pneumonia outcomes in Taiwan among persons with both SCZ and pneumonia has also been documented: there was a 1.37-fold greater risk of acute respiratory failure (aOR, 95% CI, 1.08-1.88), 1.81-fold greater risk of ICU admission (aOR, 95% CI, 1.37-2.40), and 1.34-fold greater risk of mechanical ventilation (aOR, 95% CI, 1.01-1.92) compared to those without SCZ, even after adjusting for characteristics of patients, physicians, hospitals, and potential clustering effects (Chen et al., 2011).
- Among persons with BAD, there was a 4-fold higher mortality risk due to influenza or pneumonia for both men (aHR=4.38, 95% CI, 2.76-6.96) and women (aHR=3.74, 95% CI, 2.39-5.88) (Crump, Sundquist et al., 2013).

There is also a high prevalence of hepatitis B and C:

- Among persons with SMD, about 20% of were infected with hepatitis C, approximately 11 times that of the population rate (Rosenberg et al., 2001). The prevalence of hepatitis B was 20.2 % (range: 12.5%-49.5%) among persons with SMD in the U.S., with a higher prevalence in inpatient populations, whereas in the overall US adult population the estimated prevalence is 0.3% (Janssen et al., 2015).
- Persons with SCZ were 7 times more likely to have hepatitis C than the general population (OR=7.54, 95% CI, 3.55 to 15.99) (Carney et al., 2006). The median prevalence of hepatitis C was 17.2 % (range: 1.9%-20.0%) with a higher prevalence in inpatient populations, whereas in the overall US adult population the estimated prevalence is 1.0% (Janssen et al., 2015).

High rates of HIV are also common in persons with SMD, as well as co-infection: over half (59%) of HIV-positive persons with SMD were co-infected with hepatitis C (Rosenberg et al., 2001).

- Among persons with SMD, the median prevalence of HIV was 1.8 % (range: 0.1%-5.0%) with a high rate among inpatient populations (3.8%), whereas the overall US adult population estimated prevalence of HIV is 0.5% (Janssen et al., 2015). HIV rates may be even higher in certain vulnerable populations, such as those who have SMD and are also homeless (Susser et al., 1993). Additionally, these numbers might also be underestimations, given low rates of medical care attention among those with SMDs and high rates of comorbid substance abuse.
- Persons with SCZ who are HIV-positive have an over 25-fold risk of dying compared to those who have neither of these (MRR=25.8, 95% CI, 18.8-34.3) (Helleberg et al., 2015).
- Although beyond the scope of this paper, there is a large literature on depression and HIV. Specifically, DEP symptoms are associated with less testing, worse HIV outcomes, accelerated disease progression, poor adherence and high-risk behaviours (Mayston et al., 2012). In a study from Tanzania among about 1,000 women who were HIV-positive, those with DEP symptoms had a higher mortality, HR=2.65 (95% CI, 1.89-3.71), even after controlling for psychosocial support, sociodemographic variables and clinical condition (Antelman et al., 2007).

In LAMICs, infectious diseases contribute to a significant amount of mortality in persons with SMD. In Ethiopia, nearly half (49%) of persons with all SMD in a 10-year follow-up died due to infectious disease (49%), mostly tuberculosis and malaria (Fekadu, 2015). In India, most deaths due to physical illnesses in persons with SCZ were infectious diseases, including tuberculosis, severe gastroenteritis and unknown fevers (Thara, 2004).

Malnutrition

Malnutrition was a cause of death in Ethiopia, where 13.2% died of malnutrition (Teferra et al., 2011). Although data on specific causes of natural death are limited in LAMICs, it is plausible that this finding might extend to other LAMICs.

Other diseases

Several other health problems remain either unknown or might be overshadowed by the other health comorbidities, as noted above. In this population, there is some evidence of musculoskeletal diseases, such as osteoporosis and lower bone mineral density, as well as very poor oral health, though it is not clear whether this is due to medication side effects, diet, smoking, or a number of other biological, behavioural and environmental risk factors (Correll et al., 2015). In rural China, among those with SCZ, nearly half of (42%) known death cases in a 10-year cohort study died due to “other diseases,” i.e., not cancer, heart disease, nor respiratory disease (Ran et al., 2007). More high quality data in LAMICs about specific causes of natural death are needed.

Unnatural Causes of Death

About 25% or less of deaths in persons with SMD are due to unnatural causes: suicide, accidents, and homicides.

Persons with SMD have a heightened risk by death due to all three categories. This appears similar in LAMICs: in Ethiopia, 24.8% (Fekadu et al., 2015) and in rural China, 34.3% (Ran et al., 2007) died of unnatural causes. Persons with SMD are at a heightened risk of dying from unnatural causes compared with the general population and this varies by disorder:

- Among persons with any mental disorder (including common mental disorders), a systematic review drawing from 106 studies, found the RR of mortality by unnatural causes was 7.22 (95% CI, 6.43-8.12) (Walker et al., 2015).
- Among persons with SCZ, the unnatural cause SMR was 3.12 (2.57-3.78) in men and 2.65 (95% CI, 4.57 (3.42-6.10) in women (Crump, Winkleby et al., 2015).
- Among persons with BAD, the unnatural death SMR = 7.42 (95% CI 6.43-8.55) (Hayes et al., 2015).

Although all SMD are associated with heightened risk of suicide, there is growing evidence of higher risks for accidental death, which appears more common than suicide (Crump et al., 2013c; Nordentoft et al., 2013), and homicides—persons with SMD appear to be especially overrepresented among homicide victims (Crump et al., 2013b). Furthermore, these deaths due to accidents and homicides also do not appear to be fully explained by comorbid substance use (Crump et al., 2013b). Risks for unnatural causes of death are presented below.

Suicide

It is well established that most mental disorders are associated with a higher prevalence of suicide; however, recent numbers of deaths due to suicide are much lower than previously reported, and range from about 4–8% of persons with SMD. This is likely due to the high quality and large population-based data that are currently available in some HICs. Past overestimates may also have been due to an historical focus on inpatient psychiatric populations (Crump, Ioannidis, et al., 2013), and small sample sizes and limited follow-up (Nordentoft, 2011). Higher burden of mortality is noted in the early phases of follow-up period and the disorder (Fekadu et al., 2015; Teferra et al., 2011). Moreover, suicide risk increases steeply during the first few years after first contact with psychiatric services (Nordentoft et al., 2011). In Israel, for example, 62% of suicides among persons hospitalized for psychiatric inpatient services occurred before discharge or within a year of discharge (Haklai, et al., 2011).

The current available data on lifetime rates of suicide and absolute risk for death show that:

- In SCZ, lifetime rates of suicide are 4.9-5.6% (Palmer et al., 2005). Another study found that the absolute risk for suicide in SCZ was 6.55% (95% CI, 5.85-7.34) for men and 4.91% (95% CI, 4.03-5.98) in women (Nordentoft, 2011). In SCZ, several have noted that the most frequent time suicide occurs is during illness onset (Palmer et al., 2005; Nordentoft, 2011). In national cohort data from Sweden, among men and women with SCZ, suicide accounted for 7.6% and 3.5% of all deaths, respectively (compared with 0.6% and 1.6% in the general population (Crump, Winkleby et al., 2013).
- Persons with BAD have the highest absolute risk of suicide among those with SMD. The absolute risk of suicide was 7.77% (95% CI, 6.01%-10.05%) for men and 4.78% (95% CI, 3.48%-6.56%) for women with BAD (Nordentoft, 2011).
- For persons with DEP, the absolute risk of suicide was 6.67% (5.72%-7.78%) for men and 3.77% for women (95% CI, 3.05%-4.66%) (Nordentoft, 2011).

In comparison, the absolute risk for suicide in a non-psychiatric population in Nordic countries was 0.72% (95% CI, 0.61%-0.86%) for men and 0.26% (95% CI, .020%-0.35%) for women (Nordentoft, 2011).

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In LAMICs, the available data reveal high rates of suicide:

- In Ethiopia, among those with SMD, 15.7% died by suicide (Fekadu et al., 2015).
- In Brazil, 5 of 7 deaths (71.4%) were suicides: however this was a 2-year follow-up study, likely highlighting the risk for suicide (as well as death from other physical conditions) in the year following discharge (Nordentoft et al., 2013).
- In persons with SCZ in the 20-year Madras Longitudinal Study, 7 of 16 deaths (43.8%) were suicides, all of whom were young, i.e., under 35 years of age (Thara, 2004). The most common suicide methods were hanging, self-immolation, and ingestion of poison (specifically pesticides) (Thara, 2004).
- In rural China, 21.4% died due to suicides (Ran et al., 2007). It is possible that this relatively higher risk may be related to access to means in the rural areas (Phillips et al., 2002).

Nevertheless, the risk for suicide among persons with SMD continues to be much higher than the general population:

- Among persons with recent-onset mental disorders in Nordic countries (i.e., Denmark, Finland and Sweden), there was a 12.5-23.0 times higher mortality due to suicide (Nordentoft et al., 2013). For persons hospitalized for psychiatric inpatient services in Israel, the RR for suicide was 16.34 (95% CI, 15.49-17.24) (Haklai et al., 2011).
- Persons with SCZ die by suicide about 13 times the rate of the general population (SMR=12.86; 10%-90% quantile, 0.7-174.3) (Saha et al., 2007), which is higher than previous systematic reviews (SMR=8.45; 95% CI, 7.98-8.95) (Harris & Barraclough, 1997).
- Persons with BAD die by suicide about 14 times the rate of the general population (SMR=14.44; 95% CI 12.43-16.78) (Hayes et al., 2015), similar to an older meta-analysis, SMR=12.12 (95% CI, 11.50-12.77) (Harris & Barraclough, 1997). Among persons with recent-onset affective disorders in Nordic countries (i.e., Denmark, Finland and Sweden), there was an 18.3-35.6 times higher mortality due to suicide (Nordentoft et al., 2013).

- Persons with DEP die from suicide about 20 times the rate of the general population (SMR=20.35; 95% CI, 18.27-22.59) (Harris & Barraclough, 1997). In person with sDEP, this rate is 12 times the general population (SMR=12.12; 95% CI, 11.50-12.77) (Harris & Barraclough, 1997).

The risk of death by suicide is also high in LAMICs:

- In rural China, the SMR for suicide among those with SCZ was 32.0 (95% CI, 18.5-52.5), with a higher rate among men (SMR=63.5, 95% CI, 6.2-32.8) than women (SMR=13.4, 95% CI, 6.2-3.8) (Ran et al., 2007).
- Other studies show even higher SMRs for suicide (e.g., Menezes et al., 2006); however these are limited to short follow-up.

Although not often reported in the literature, Walker and colleagues (2015) found that PAR estimates for death by suicides were 8.9% for SCZ, 4.8% for manic-depressive disorders, and 11.2% for DEP. In Hong Kong, the PAR for suicide was 27% among those with DEP and 22% among those with SCZ (22%) (Chan et al., 2009).

Homicide and Violent Deaths

Persons with any mental disorder are at a 5-fold risk of homicidal death compared to the general population (aHR=4.91, 95% CI, 3.99-6.03; Crump et al., 2013c). Compared with the general population, the mortality risk due to homicide (or violent deaths) was higher:

- In persons with SCZ (aHR=1.82, 95% CI, 0.85-3.86) (Crump et al., 2013c),
- In persons with BAD (aHR=2.38, 95% CI, 1.62-3.50 in Crump et al., 2013c; SMR for violent deaths= 3.68, 95% CI 2.77-4.90 in a systematic review by Hayes et al., 2015) and
- In persons with DEP (aHR=2.55, 95% CI 1.70-3.83) (Crump et al., 2013c).

This was not fully explained by comorbid substance abuse or other sociodemographic factors (Crump et al., 2013c). Crump and colleagues (2013c) posited several explanations: persons with SMD are more likely to live in poor neighbourhoods, which have higher homicide rates, and they may be less aware of their safety risks. Persons with any mental disorder (but especially SCZ and DEP) are commonly perceived by the general public as unpredictable or dangerous (Angermeyer, et al., 2006) which might result in aggressive acts against them. Additional sociodemographic risk factors associated with homicide among persons with any mental disorders included a two-fold rate among men versus women (HR=2.07, 95% CI 1.74-2.45), low education ($p < 0.001$), low income ($p < 0.001$), and living in a large city relative to a medium-sized (HR=0.80, 95% CI 0.65-0.98) or small/rural town (HR=0.78, 95% CI 0.63-0.98) (Crump et al., 2013c).

In LAMICs, violent deaths may be especially the case within institutionalized settings, where in some settings, providers or caretakers may have more stigmatized attitudes (Stefanovics et al., 2015) or human rights protections may not be fully developed in mental health policies for persons with SMD (Faydi et al., 2011). In a Nigerian cohort of persons with SCZ from Ilesa, 2 of 9 known deaths occurred when patients “had been beaten to death by night guards who had found them wandering” (Makanjuola et al., 1987).

Accidents

Persons with SMD are at an increased risk of accidental deaths, which include falls, transportation accidents and accidental poisonings (Crump et al., 2013c). Of note, accidental deaths appear to be more common than suicide in persons with SMD (Nordentoft et al., 2013; Crump et al., 2013c).

- Any mental disorder was associated with a 6.64-fold (aHR; 95% CI, 6.37-6.91) risk of death in men and 5.29-fold (aHR; 95% CI, 5.04-5.55) risk of death in women compared to those without the disorder (Crump et al., 2013c).
- In SCZ, the risk for death by accident was 2.61 (aHR, 95% CI, 2.20-3.11) times the rate in men and 3.15 (aHR, 95% CI, 2.38-4.16) times the rate in women compared to those without SCZ (Crump et al., 2013c). Among persons with recent-onset SCZ in Nordic countries (i.e., Denmark, Finland and Sweden), there was a 3.0-6.5 times higher mortality due to accidents compared with the general population (Nordentoft et al., 2013).

- For those with BAD, the risk for death by accident was 2.29 (aHR, 95% CI, 1.78-2.94) times the rate in men and 3.46 (aHR, 95% CI, 2.69-4.44) times the rate in women compared to those without BAD (Crump et al., 2013). Among persons with recent-onset BAD in Nordic countries (i.e., Denmark, Finland and Sweden), there was a 2.9-3.8 times higher mortality due to accidents compared with the general population (Nordentoft et al., 2013).
- For those with DEP, the risk for death by accident was 3.17 (aHR, 95% CI, 2.90-3.45) times the rate in men and the 2.92 (aHR, 95% CI, 2.66-3.20) times the rate in women without DEP (Crump et al., 2013).

In LAMICs, the risk of death by accidents among those with SMD appears important.

- Road traffic accidents and homicide together accounted for 9% of deaths in Ethiopia (Fekadu et al., 2015).
- In rural China, the SMR for accidents was 6.6 (95% CI, 4.3-10.2) in those with SCZ and 13.2% of deaths were due to accidents (Ran et al., 2007).
- In a Nigerian cohort, 5 of the 9 deaths that occurred took place in a traditional healer’s establishment (Makanjuola et al., 1987), though it remains unclear whether death was induced by practices or other reasons, such as lack of provision of required care.

Although alcohol and other substance use disorders were the strongest risk factors for accidental deaths, the heightened risk did not appear fully explained by comorbid substance use; moreover all mental disorders were strong risk factors for accidental deaths (Crump et al., 2013). Sociodemographic risk factors for accidental death included male gender, older age, unmarried status and low socioeconomic status (Crump et al., 2013c).

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RISK FACTORS & CORRELATES

The literature has identified several risk factors and correlates associated with excess mortality in persons with SMD. Most are shared by HICs and LAMICs alike; others appear context-specific. Although we understand much about the epidemiology of excess mortality in persons with SMD, our understanding about risk and protective factors remains

limited, especially those risk factors that can be effectively addressed, as well as protective factors that can be enhanced. Table 1 highlights several key risk factors and correlates have been identified according to a specific domain. A comprehensive framework can help inform an intervention framework that will help with conceptualizing how to effectively reduce the problem and burden of excess mortality in persons with SMD.

TABLE 1. MULTILEVEL MODEL OF RISK FOR EXCESS MORTALITY IN PERSONS WITH SEVERE MENTAL DISORDERS (SMD)

INDIVIDUAL FACTORS	HEALTH SYSTEMS	SOCIAL DETERMINANTS OF HEALTH
<p>Disorder-specific</p> <ul style="list-style-type: none"> Severity of disorder Family history Symptoms/pathophysiology Early age of onset Recency of diagnosis Stigma <p>Behaviour-specific</p> <ul style="list-style-type: none"> Tobacco use Poor diet Inadequate physical activity Sexual and other risk behaviours Substance use (alcohol and drugs) Low motivation (e.g., treatment seeking, adherence) 	<p>Leadership</p> <ul style="list-style-type: none"> Absence of relevant policies and guidelines <p>Financing</p> <ul style="list-style-type: none"> Low investment in quality care <p>Information</p> <ul style="list-style-type: none"> Limited health information systems <p>Service delivery</p> <ul style="list-style-type: none"> Verticalization and fragmentation of health services Lack of care coordination and management Limited access to services <p>Human resources</p> <ul style="list-style-type: none"> Poor quality service provision Negative beliefs/attitudes of workforce Poor communication <p>Medications</p> <ul style="list-style-type: none"> Antipsychotic medications (no treatment, polypharmacy, higher than recommended dosages) 	<p>Public policies</p> <ul style="list-style-type: none"> Discriminating policies Low financial protection and limited coverage in health packages <p>Socio-economic position</p> <ul style="list-style-type: none"> Unemployment Homelessness Low health literacy <p>Culture and societal values</p> <ul style="list-style-type: none"> Stigma and discrimination in society Negative perceptions about persons with SMD <p>Environmental vulnerabilities</p> <ul style="list-style-type: none"> Infections, malnutrition Access to means of suicide Impoverished or unsafe neighbourhoods <p>Social support</p> <ul style="list-style-type: none"> Limited family, social and community resources

INDIVIDUAL FACTORS

Risk factors and correlates at the individual level include characteristics inherent to the SMD or an individual's health-related behaviours. These include the severity of the SMD (e.g., symptoms, hospitalizations, impulsivity, and physiological and emotional dysregulation), affect the engagement or interaction of the person with the health care system (e.g., cognitive deficits, social skills deficits, low motivation or mistrust of providers), or consist of behaviours that lead to or exacerbate health problems. All of these factors may drive a reluctance to seek medical help, be unaware of physical health problems, and stay socially isolated.

Disorder-Specific Factors

Mortality rates are highest among inpatient populations (RR=2.42, 95% CI, 2.24-2.61) followed by outpatient populations (RR=2.08, 95% CI, 1.91-2.27) (Bjorkenstam et al., 2012). In a study from Ethiopia, for each of the SMD diagnostic groups, spending a higher percentage of follow-up time in an episode was associated with an increased risk of premature mortality (Fekadu et al., 2015).

Amotivation and similar motivational impairments, a key feature of SCZ (Foussias & Remington, 2010) and common in BAD and DEP, can lead to a cascade of poor treatment-seeking and self-care behaviours. In the same way, cognitive deficits are common across the SMD (van Os & Kapur, 2009) and are linked with a number of affective and behavioural patterns that impact the level of disability or impairment related to the disorder (Silverstein, 2008; Green et al., 2000). Social and communication skills deficits (Bellack et al., 2004) are related to impaired vocational functioning (Dickinson et al., 2007), contribute to social isolation, and may negatively affect interactions with healthcare providers. As a result, persons with SMD may be less able to communicate clearly about or understand their medical problems. For example, in the United States (US) only 23% of patients admitted to the acute medical care unit of a psychiatric hospital could adequately describe the nature or location of their pain or illness (Bunce et al., 1982). In addition, patients with SCZ diagnosed with a medical condition may not be able to describe it, or remember it, at a later date. Two years after a physical health diagnosis, only 14% of patients could name at least one of their physical problems (Bunce et al., 1982). Moreover, SCZ is also associated with a reduced responsiveness to pain (Kudoh, 2005; Dworkin et al., 1994;

Rosenthal et al., 1990), which may also be a side effect of anti-psychotic medications. Combined with altered perception of symptoms, symptom awareness and limited insight, symptoms of somatic diseases may go unrecognized.

Past negative experiences during involuntary psychiatric hospitalizations or similar treatment, paranoid symptoms, or biased beliefs, may lead persons with SMD to have negative attitudes and beliefs about their health care providers, which may reduce their likelihood of seeking care. Past interpersonal trauma may contribute to mistrust of others and contribute towards social isolation.

Behaviour-Specific Factors

Persons with SMD appear to have an elevated prevalence of every cardiovascular risk factor and risk behaviour. Less than 1% of persons with SMD met criteria 5 selected health indicators: non-smoker, exercise that meets recommended standards, good dentition, absence of obesity, absence of serious medical co-occurring illness (Dickerson, Brown, Daumit, et al., 2006).

The high rates of tobacco smoking among persons with SMD are well-known (Goldstein et al., 2009; Compton et al., 2006). However, whereas cigarette smoking in the general population has decreased from more than 50% to less than 25%, over 70% of persons with SCZ and 40-50% of those with DEP still smoke tobacco (Hughes et al., 1986; Zeidonis et al., 1994; Zeidonis et al., 1997). Tobacco smoking is one of the risk factors most likely to contribute substantially to reduced life expectancy in SCZ (Brown et al., 2000) and smoking-related illnesses account for a reduction in life expectancy of 3.5 years for men and 3.0 years for women (Juel & Sorensen, 2006).

Persons with SMD are 50% more likely to be obese (Compton et al., 2006). Among persons with SMD, 50% of women and 41% of men were obese compared with 27% and 20% respectively in the demographically matched comparison group (Dickerson et al., 2006); a higher BMI was associated with current hypertension and diabetes, a wish to weigh less and reduced health-related functioning (Dickerson et al., 2006). Similar results from the United Kingdom (UK) show rates of obesity to be about 50.6% among women and 28.7% of men between the ages of 18 to 44 years were obese compared with 16.6% and 13.6% in the general population (Filik et al., 2006). Another study found over a third (35.0%) of persons with SMD were obese (BMI>30) while 19.4% were

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morbidly obese (BMI>40) (Filik et al., 2006). Among 57 studies summarizing the prevalence of different conditions in those with SMD, the median overweight prevalence was 29.0% (range: 25.0-58.0%) and the median obesity prevalence was 40.6% (range: 26.0-55.0%) (Janssen et al., 2015) and this was somewhat higher for those dwelling in the community versus inpatients, whereas in the US adult population the prevalence rate ranges from 33.1%-35.4% for overweight and 29.4%-35.7% for obesity depending on the measurement method used (Janssen et al., 2015).

Persons with SMD commonly have poor diets (Henderson et al., 2006). They consume more sugar and saturated fats than the general population (Dipasquale, et al., 2013), are less likely to exercise (Daumit et al., 2005), and spend over 12 hours in sedentary activities on a daily basis (Janney et al., 2013). This is also true in non-Western countries, such as Korea, where there is a high prevalence of metabolic syndrome, including abdominal obesity and dyslipidemia, which might be related to a combination of adverse side effects of antipsychotic medication and physical inactivity (Kim, 2010). However, even those with SMD who are antipsychotic-naïve have a high prevalence of obesity, abdominal obesity, hypertension and elevated blood pressure, which were also frequent in those with antipsychotic exposure (Correll et al., 2014), suggesting that factors other than antipsychotic medication side effects may be driving this trend. Diet and lifestyle risk factors may be different in LAMICs, as malnutrition was a cause of death in one LAMIC (Fekadu et al., 2015).

Persons with SMD also frequently report poor sleep and sleep apnea, which can be related to physical health problems. Additionally, many have poor hygiene and dental care, including less dental visits and greater incidence of poor oral health, including periodontal disease, bleeding gums, ulcerations, and fractured teeth compared to the general population. Some medications can affect bone density and tobacco smoking can lead to poor oral health, which may exacerbate existing dental problems.

Persons with SMD are also less likely to attend medical screenings or when with a healthcare provider, make requests, likely due to communication or comprehension difficulties. For example, although cardiovascular and respiratory problems and conditions are elevated in persons with SMD, they attended primary care appointments less (2.3 times, 95% CI 2.0-2.7) than the general population (4.8 times, 95% CI 4.6-5.1) each year (Filik et al., 2006). They may be less

treatment compliant, less adherent to medications (both mental health related and non-mental health related), and attend follow-up appointments with providers less often. In Israel, 5.3% of persons with SCZ did not utilize any of their cardiovascular drug prescriptions compared with 2.9% among matched controls (Gal et al., 2015).

Over 50% of persons with SMD also use illicit drugs and/ alcohol at hazardous levels (Hunt et al., 2014). A substance abuse disorder on top of an SMD could double or trip their risk of death (Hjortoj et al., 2015). Alcohol and illicit drug use are major risk factors for mortality as well as a principal underlying cause of death (Revier et al., 2015). Substance use and abuse affects the physical functioning and progression of diseases and is a risk factor for many fatal diseases, as well as risk factors for infection. In particular, substance abuse also appears to increase the risk of persons with SCZ becoming infected with HIV (Helleberg, et al., 2015) and hepatitis C (Gimelfarb, et al., 2014), especially intravenous drug use, which is high among this population. It is also related to death due to injuries and violence and has repeatedly been associated with a high risk of unnatural death, particularly in first-episode patients with a lack of family involvement (Revier et al., 2015). It also increases the absolute risk of suicide (Nordentoft et al., 2011). Risky sexual activities are also over-represented in persons with SMD (Goldstein et al., 2009) and deliberate self-harm can increase the risk of death by suicide (Nordentoft et al., 2011).

HEALTH SYSTEMS

After taking individual factors into account the association between SMD and mortality is reduced but not altogether eliminated (Filik et al., 2006). For example, across many countries, there is a peak in excess mortality for both natural and unnatural causes during the first year after discharge from a psychiatric hospitalization (Nordentoft et al., 2013; OECD, 2015), suggesting a systematic failure of the health care system to prevent, identify, and treat physical diseases during hospitalization of persons with SMD.

Health system factors appear to play an important role and include treatments, delivery of services, and organizational characteristics such as the workforce or information systems infrastructure and will vary across different settings. There is a sparse literature on health systems leadership, financing and information system factors, though their role is important. For example, financial investment in mental health systems

continues to be critically low (Gilbert et al., 2015). The absence of relevant policies and guidelines, low investment in quality care and limited health information systems likely contribute towards an overall health care system that is ill-equipped to address the needs of persons with SMD.

Service Delivery

Fragmented health care systems (e.g., dichotomized physical and mental health care) present a challenge to meeting the complex health needs of persons with SMD (Laursen, Munk-Olsen, et al. 2011). Approximately 50% of the excess mortality due to natural causes of death in persons with SCZ or BAD included complex physical health comorbidities (Laursen, Munk-Olsen, et al., 2011). Health systems may not be equipped to deal with the complex somatic comorbidity in addition to mental health problems in this population and current approaches appear insufficient.

In primary care and other non-mental health settings, non-mental health providers may be uncomfortable or unfamiliar with providing care for persons with SMD. On the other hand, mental health providers may have limited expertise in recognizing and addressing physical health care needs (de Hert et al., 2011). They may have limited knowledge about physical conditions and may be less likely to prevent, manage, or intervene for physical health conditions. In one study, preventive services for physical health conditions were provided during only 11% of psychiatrist visits (Daumit et al., 2002). Psychiatrists might not be proficient at detecting physical symptoms and performing basic physical examinations for psychiatric patients (Maj, 2008). For example, the percentage of major physical illness that was not diagnosed by non-psychiatrist physicians in the US was about one third, whereas the percentages of cases not diagnosed by psychiatrist were nearly 50% (Koranyi, 1979). Psychiatrists may be unable or unwilling to perform physical and neurological examinations or may not be up-to-date on the management of common physical diseases (Maj, 2008). Furthermore, medication or screening guidelines may be perceived as a threat to the autonomy of mental health providers. As a result, there is currently limited consensus as to which health professionals should be responsible for the prevention and management of comorbid physical conditions in patients with SMD (Fleischhacker, et al., 2008).

Moreover, the information provided by health systems to providers may be inadequate. Screening and prevention guidelines for the general population may not take into

consideration the excess and premature mortality from non-communicable diseases (NCDs) in persons with SMD. Cardiovascular morbidity and mortality in persons with SCZ often occur before age 50 (Laursen, 2014); however the European guidelines for prevention of cardiovascular disease primarily target older persons because in the general population, individuals under the age of 50 have a very low risk of cardiovascular morbidity and mortality (Perk et al., 2012).

Human Resources

Yet, even among persons with SMD who are over 60 years old, there is evidence for less cardiovascular screening (Osborn et al., 2011). Although, the UK guidelines do make recommendations for CVD screening in persons with SMD, there is evidence that current practices do not meet these national guidelines: a study of patients in UK assertive outreach teams revealed that only 26% had received screening for blood pressure, 17% for BMI, 28% for glucose and 22% for lipids (Barnes et al., 2007).

This is consistent with a large and growing literature demonstrating that persons with SMD often receive poor quality of physical health care, spanning from health promotion and disease prevention to intervention. Persons with SMD, once connected to physical health services, receive less screening, management and intervention for their physical conditions. Although they have two times as many health care contacts* (Crump, Winkleby, et al., 2015), they receive less physical check-ups and screenings, less prescriptions and procedures, and less cardiovascular and cancer diagnoses (Lawrence et al., 2003; Kisley et al., 2009), even though they have a higher risk of dying from these conditions (Crump, Winkleby, et al., 2015; Lawrence et al., 2003; Laursen, Munk-Olsen, et al., 2009).

This may vary by context: patients with BAD in the US had worse physical health and greater comorbidity than those in Germany and the Netherlands (Post et al., 2014). In LAMICs, persons with SMD may not receive proper medical treatment. In Indonesia, Kurihara and colleagues (2011) note that of the 13 of 15 who died of physical diseases, only 3 (23.1%) had received medical treatment for the illness at the time of death. Additionally, the authors note that during index admission, no patients who suffered from physical disease were receiving any kind of treatment (Kurihara et al., 2011). In Bali, Indonesia, of the 11 subjects who died of natural causes, only 2 were receiving medical treatment at the time of their deaths (Kutihara et al., 2006). This might also be due to seeking non-traditional healers: in Nigeria 80% of patients

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with mental disorders sought religious guides or healers along with general practitioners (Toftegaard et al., 2015).

As mentioned above, persons with SCZ had twice as many outpatient clinic visits and hospital admissions* per year compared to those with SCZ (Crump et al., 2013); however they had no elevated rate of receiving a diagnosis across a number of diseases (such as ischemic heart disease, hypertension, lipid disorders, cancer) despite having a higher risk of dying for these diseases (Crump et al., 2013). Yet, they had an elevated mortality from ischemic heart disease (adjusted HR for women, 3.33, 95% CI, 2.73-4.05; for men, 2.2, 95% CI, 1.15-1.80) and cancer (adjusted HR for women, 1.71, 95% CI, 1.38-2.10; for men, 1.44, 95% CI 1.15-1.80) compared to those with SCZ (Crump, Winkleby, et al., 2013). Among all persons who died from ischemic heart disease or cancer, SCZ patients were less likely than others to have been diagnosed previously with these conditions (for ischemic heart disease, 26.3% compared with 43.7%; for cancer, 73.9% compared with 82.3%) (Crump, Winkleby, et al., 2013). The presence of these diagnoses appeared important for mortality: those with SCZ who were diagnosed had only a modestly greater mortality for ischemic heart disease and no increased cancer mortality risk compared to the general population. Men with SCZ who had been diagnosed with ischemic heart disease had only a slightly higher mortality risk than men without SCZ who had been diagnosed with ischemic heart disease (aHR=1.19, 95% CI, 1.01-1.41) and for women it was the same (Crump, Winkleby et al., 2013).

A review of invasive cardiac procedures and medication concluded that less of these may be a contribution to excess mortality in persons with SMD (Mitchell & Lord, 2010). Similarly, Laursen (2009) found that persons with SMD had a higher incidence rate ratio of heart disease contacts than non-psychiatric general population (1.11, 95% CI, 1.08-1.14); however in this same sample, excess mortality of persons with SMD was 2.90 (95% CI, 2.71-3.10). Five years after the first contact for somatic heart disease, risk of dying of heart disease was 8.26% for non-elderly (<70 years old) persons with SMD but only 2.86% in the non-psychiatric general population. Additionally, the fraction undergoing invasive procedures was also lower for those with SMD than the general population (7.04% vs. 12.27%, respectively) (Laursen et al., 2009). Similarly, Druss and colleagues (2002) found that persons with mental disorders were less likely to receive cardiovascular procedures after myocardial infarction. There is also reduced use of nearly all cardiac drugs in persons with SCZ compared with the general population (Laursen et al., 2013). In Australia, those with SMD were referred for less cardiac procedures, like coronary revascularization procedures (Lawrence et

al., 2010). Additionally, the ischemic heart disease mortality rate in persons with SMD did not diminish over the nearly 20 years of data (Lawrence et al., 2003), although these have decreased significantly in the general population.

For cancer, a study from Western Australia found that there was not an increased incidence rate of cancer among those with SCZ, but a higher cancer mortality in those with SCZ compared to the general community: 39% higher in men (95% CI, 32-46%) and 24% higher in women (95% CI, 17-32%) (Lawrence et al., 2000). In other words, although persons with SMD had the same cancer incidence as the general population, they were more likely to die from this (Lawrence et al., 2000).

When hospitalized for medical care, persons with SMD often have poor outcomes, including more adverse events, more days in an intensive care unit and more complications than those without SMD. Several studies have found poorer quality of medical care for health problems like cardiovascular disease (Mitchell, et al., 2009). In the US, compared to those without SCZ, persons with SCZ had at least twice the odds of several adverse events: infections due to medical care, (aHR=2.49, 95% CI, 1.28-4.88), postoperative sepsis (aOR=2.29; 95% CI, 1.49-3.51), postoperative deep venous thrombosis (aOR=1.96; 95%CI, 1.18-3.26), as well as a longer mean adjusted increase in length of stay by at least 10 days and elevated median hospital charges by at least \$20,000 for infections due to medical care, respiratory failure, deep vein thrombosis and sepsis (Daumit et al., 2006). Among these, respiratory failure or sepsis resulted in at least twice the adjusted odds for ICU admission and death (Daumit et al., 2006). Complication and death rates are also high among those with SCZ suffering from appendicitis who underwent appendectomy (Cooke et al., 2007) as well as preventable postoperative complications and injuries after coronary artery bypass surgery (Li et al., 2008). Similarly, national data from Taiwan showed that during inpatient hospitalizations for pneumonia, patients with SCZ have a 1.3-fold (aHR; 95% CI, 1.08-1.88) to 1.8-fold (aHR; 95% CI, 1.34-2.40) increased risk of adverse outcomes (i.e., ICU admission, acute respiratory failure, and mechanical ventilation) that were not necessarily due to the fault of the health-care providers or system during the inpatient admission. The differences in adverse clinical outcomes for medical hospitalizations disappeared after accounting for characteristics of hospitals, in particular those treated in medical centres fared better, suggesting that differences in adverse medical outcomes during somatic hospitalizations could be minimized by the quality of medical care (Chen et al., 2011). Daumit and colleagues (2006) speculate that sources of preventable adverse events could result from improper use of restraints, excessive dosing of

antipsychotics, and overlooking their interactions with other medications. Psychotropic medications may elevate the risk of respiratory and pulmonary irregularities (Copeland et al., 2007). Poor cooperation and compliance and patients may therefore be sicker and display later in the course of their disease, leading to more adverse outcomes after the time of diagnosis. When patients with SCZ are hospitalized on medical wards, health care professionals may be inexperienced at managing their special needs and may use antipsychotics inappropriately to control agitation. As a result, they may receive excessive dosing of antipsychotics or drug errors, which may cause over-sedation and lead to potential problems such as respiratory failure and sequelae from immobilization (e.g., venous thromboembolism) (Daumit et al., 2006).

Even under universal health care, persons with SMD are less likely to receive guideline-concordant treatment for cardiovascular problems, such as a coronary artery by-pass, prescriptions of beta-blockers and statins, admission for stroke, and revascularization procedures (Laursen, Munk-Olsen, et al., 2009; Kisley et al., 2009). The rate ratio for death of psychiatric patients was significantly increased (1.34), even after adjusting for potential confounders, including income and comorbidity (95% confidence interval [CI] 1.29-1.40), which was reflected in the adjusted rate ratio for first admissions (1.70, 95% CI 1.67-1.72) (Kisley, 2007). In some cases, psychiatric patients were significantly less likely to undergo specialized or revascularization procedures, especially those who had a history of being psychiatric inpatients (Kisley, 2007). In the latter case, adjusted rate ratios for cardiac catheterization, percutaneous transluminal coronary angioplasty and coronary artery bypass grafts were 0.41, 0.22 and 0.34, respectively, in spite of this populations increased risk of death (Kisley, 2007). In Israel, a country with national health insurance and a rehabilitation law specific for persons with mental disabilities, persons with SCZ received less cholesterol tests, stress tests, visits to specialists, drug utilization and a 30% decreased likelihood of surgical (e.g., cardiac) interventions than matched controls (aHR=0.70, 95% CI, 0.64-0.76) (Gal, Munitz, & Levav, 2015).

These poor health outcomes might be related to providers' negative beliefs and attitudes towards persons with SMD, including beliefs about the causes of illnesses, ability of persons with SMD to maintain an active and healthy lifestyle, or other beliefs about functioning (Jones et al., 2008). These may include beliefs about the causes of illnesses and treatment, as well as beliefs about the ability of persons with SMD to be able to maintain an active and healthy lifestyle or other beliefs about functioning. Diagnostic overshadowing is one example of negative attitudes and beliefs

and refers to the effect of a psychiatric diagnosis becoming the sole focus on a person with SMD and may affect the reduced screening, managing, and intervention of physical health conditions. Symptoms may not be recognized or may be regarded as psychosomatic. For example, when a patient had a psychiatric diagnosis, medical-surgical nurses estimated a decreased probability that the patient was having an MI and were less likely to respond to additional possible MI symptoms (McDonald et al., 2003). Poor treatment outcomes may reflect minimization or misinterpretation of somatic complaints as psychosomatic, delay in recognizing signs or symptoms that require timely attention, or a lack of adequate skills to deal with this population (Koranyi, 1979). Providers' attitudes towards patients with SMD appear related to treatment intentions, including their likelihood of referring patients to a specialist or refilling their prescription (Corrigan et al., 2014). Persons with SMD are often treated poorly by providers, including being ignored or made to wait longer for treatment, having their mental disorder diagnosis disclosed in front of other patients, not being listened to regarding the nature of the problem, and inflexibility in allowing patients to access to care (Henderson et al., 2014)

Medications

Medications for SMD may also affect the physical health of persons with SMD. Antipsychotic medications are associated with the greatest negative impact on physical health, followed by mood stabilizers, tricyclic antidepressants and newer antidepressants (Correll et al., 2015).

A mainstay of treatment for many persons with SMD, antipsychotic medications are associated with well-known side effects that can contribute to obesity, glucose intolerance and dyslipidemia (Correll et al., 2014; Torniaainen et al., 2015). Depending on the setting, both a lack of antipsychotic medication (e.g., Fekadu et al., 2015) and excess dosing of this medication (Cullen et al., 2013; Foley et al., 2011; Tornianinen et al., 2015) appear to be risk factors for elevated mortality, especially in LAMICs. For example, in Ethiopia, antipsychotic treatment for less than 50% of the (5-year) follow-up period was associated with a higher mortality (aHR=2.66, 95% CI, 1.054-6.72) (Fekadu et al., 2015).

No access to medications (especially antipsychotics and lithium) appears to be an important contributor to excess mortality. Clozapine, an older antipsychotic medication, appears to be associated with reduced mortality (Hayes et al., 2015) and can be protective, especially for unnatural causes of death, such as

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suicide. Similarly, a review found that lithium was associated with reduced mortality for suicide in persons with mood disorders (Cipriani et al., 2013). In rural China, there was no significant difference in the rates of suicide and all-cause mortality between never-treated and treated individuals with SCZ, though the SMRs were higher in never treated (SMR=10.4, 95% CI, 7.2-15.2) compared to treated individuals (SMR=6.5, 95% CI, 5.2-8.5) (Ran et al., 2009). Though a more distal indicator of medication use, duration of untreated psychosis is a predictor of excess mortality in LAMICs. In Indonesia, persons with greater than 1-year duration of untreated psychosis at baseline were 3.4 times (95% CI, 1.08-10.7) more likely to die than those with less than 1-year duration of untreated psychosis at baseline (Kurihara et al., 2011).

Sudden cardiac death has been associated with the use of antipsychotic medications (Strom et al., 2011). Users of both typical (IRR=2.00, 95% CI, 1.69-2.35) and atypical (IRR=2.27, 95% CI, 1.89-2.73) antipsychotic medications had higher rates of sudden cardiac death than did nonusers of antipsychotics (Ray et al., 2009). For both classes of drugs, the risk of sudden cardiac death among current users increased significantly with dose (Ray et al., 2009), similar to a finding by Osborn and colleagues (2007) showing that a higher dose of antipsychotics predicted greater risk of mortality from coronary heart disease and stroke (Osborn et al., 2007). Less is known about the long-term effects of exposure to atypical antipsychotics, though they may play a role in increasing mortality in SCZ, particularly cardiovascular mortality (Weinmann et al., 2009).

Newer antipsychotics, in particular, are well-known for side effects of weight gain, hypertension, hyperlipidemia, and altered glucose metabolism, which contribute to the risk for noncommunicable diseases (NCDs). A meta-analysis revealed that over a 10-week period, weight gain was on average was 4.45 kg with olanzapine, 2.92 kg with sertindole, 2.10 kg with risperidone, and 0.04 kg with ziprasidone (Allison et al., 2001). Correll and colleagues (2015) found that within one year of exposure to second-generation antipsychotics versus antidepressants, those exposed to the antipsychotics showed a higher risk of essential hypertension (aHR=1.16, 95% CI, 1.12-1.21, $p<0.0001$), diabetes mellitus (aHR=1.43, 95% CI, 1.33-1.53, $p<0.0001$), hypertensive heart disease (aHR=1.34, 95% CI, 1.10-1.63, $p<0.01$), stroke (aHR=1.46, 95% CI, 1.22-1.75, $p<0.0001$), coronary artery disease (aHR=1.17, 95% CI, 1.05-1.30, $p<0.01$) and hyperlipidemia (aHR=1.12, 95% CI, 1.07-1.17, $p<0.0001$).

Antipsychotic polypharmacy (i.e., using more than one antipsychotic agents concurrently) does not appear to be associated with increased mortality relative to antipsychotic monotherapy (Baandrup et al., 2010), nor did the concomitant use of antidepressants with an antipsychotic agent increase mortality (Tiihonen et al., 2012). However, polypharmacy using antipsychotic medication and benzodiazepines is associated with an increased risk for mortality (Baandrup et al., 2010; Tiihonen et al., 2012), both suicidal (HR=3.83, 95% CI, 1.45-10.12) and non-suicidal deaths (HR=1.60, 95% CI, 0.86-2.97) (Tiihonen et al., 2012). Polypharmacy also appears to be associated with an exacerbating effect on most physical diseases (Correll et al., 2015).

Medications other than antipsychotic medications are also associated with both significant physical health side effects; however they are also important for reducing mortality, especially by suicide. The risk of natural death did not increase with the number of concurrently used antipsychotic agents compared with antipsychotic monotherapy in a Danish registry study (Baandrup et al., 2010) or also have significant side effects (aside from the common side effects like nausea, diarrhea or agitation) that can impact physical health and functioning. Antidepressants can also lead to long-term weight gain, serotonin syndrome, and sexual dysfunction. Long-term use of benzodiazepines can cause cognitive impairments and paradoxical reactions (e.g., insomnia). Anticonvulsants and mood stabilizers are also associated with weight gain and hepatotoxicity.

In sum, those receiving continuous medication treatment (Cullen et al., 2013) at recommended dosages appear to have the lowest mortality (Tornianinen et al., 2015). Higher dosages, polypharmacy that includes benzodiazepines, and the age group of patients (e.g., young or old) appears to be associated with a greater effect of medications on physical health and mortality. Once medications like antipsychotics are prescribed, monitoring for potential side effects is important and requires knowledge and communication between providers (de Hert et al., 2011).

SOCIAL DETERMINANTS OF HEALTH

Social determinants of health include, but are not limited to public policies, an individual's socioeconomic position, cultural and societal values, environmental vulnerabilities and social support (Marmot et al, 2008).

Public policies

Persons with SMD often have limited access to health care either due to cost or denial of insurance coverage (Druss et al., 1998). In the US, they were about twice as likely as those without mental disorders to have been denied insurance because of a pre-existing condition (Druss et al., 1998). Having an SMD conferred a nearly 2-fold greater risk of delay in seeking care in the US because of cost and over twice the odds of being unable to obtain needed medical care (Druss et al., 1998). Persons with SMD may have reduced access to physical healthcare due to cost (Druss et al., 1998).

Socioeconomic position

Disability associated with the disorder may contribute towards unemployment, which is also a strong independent risk factor for increased mortality, whereas being employed appears to be protective (Kiviniemi, Suvisaari, Pirkola, et al., 2011; Crump, Winkleby, et al., 2011). Inability to work was also an independent predictor of mortality in a 10-year follow-up study in rural China (Ran et al., 2007). In LAMICs, unemployment appears less common among persons with SMD. For example, while only 7.1% of those with SCZ who died were employed in Sweden (Crump, Winkleby, et al., 2013), the rates of employment among those with SMD in LAMICs is much higher: 60.0% in India (Thara, 2004), 53.3% in Ethiopia (Fekadu et al., 2015) and 60.2% in China (Ran et al., 2007).

As a result, persons with SMD are more likely to be poor and at risk for homelessness. In HICs, homelessness and a low socioeconomic status confer additional mortality risk to those with SMD (Morrison, 2009; Nielsen, Hjorthoj, Erlangsen, et al., 2011; Barrow et al., 1999). Homelessness is linked to living up to 21.6 years less than those who are not homeless and the mean age of death among those who are homeless was less than 50 years (Nielsen et al., 2011). Those who are homeless, also experience more infectious disease (Raoult, 2012). Among those who are homeless, there is also excess mortality by suicide and unintentional injuries (Nielsen et al., 2011). In LAMICs, persons are likely

to become homeless for reasons other than SMDs, such as housing problem and unemployment. For example, in rural China, persons with SCZ who did not receive treatment were both more likely to become homeless and also have less social support (Ran et al., 2009).

Cultural and societal values and environmental vulnerabilities

Persons with SMD tend to live in less safe neighbourhoods, have less access to healthy foods, and have less opportunities to be involved in healthy activities, which may contribute to poor lifestyle behaviours. They may be perceived as dangerous by others, which may drive the high rates of homicide victimization.

Social support

Many persons with SMD in HICs have limited social support, including never being married or limited family involvement (e.g., 72.1% had never been married (Crump, Winkleby, et al., 2013). In particular, lack of family involvement in care appears to be associated with a high risk of substance abuse and unnatural death (Revier et al., 2015). In some LAMICs, such as India, family members may protect against malnutrition, dehydration and infections, which were more likely to occur in those who were living alone or "wandering" (Thara, 1994). They may also protect against being unemployed—for example, women with SCZ in India were usually cared for by a spouse or parents (Thara 1994). However, when family members are involved, they may already be under a heavy caregiver burden, and additional physical health problems may overstretch support (Fekadu et al, 2015).

CONCLUSIONS

Persons with SMD die approximately 10-20 years earlier than the general population. Despite several decades of research and well-documented evidence of this excess mortality, there has been little to no progress in reducing this gap; in fact, most evidence suggests that this discrepancy is increasing over time. Studies consistently demonstrate that they die from both natural and unnatural causes at least 2-3 times the rate of the population, with especially heightened risks of deaths due to cardiovascular disease, infectious disease, respiratory disease, suicide, homicides and accidents. Limited high quality data from LAMICs indicate that risks

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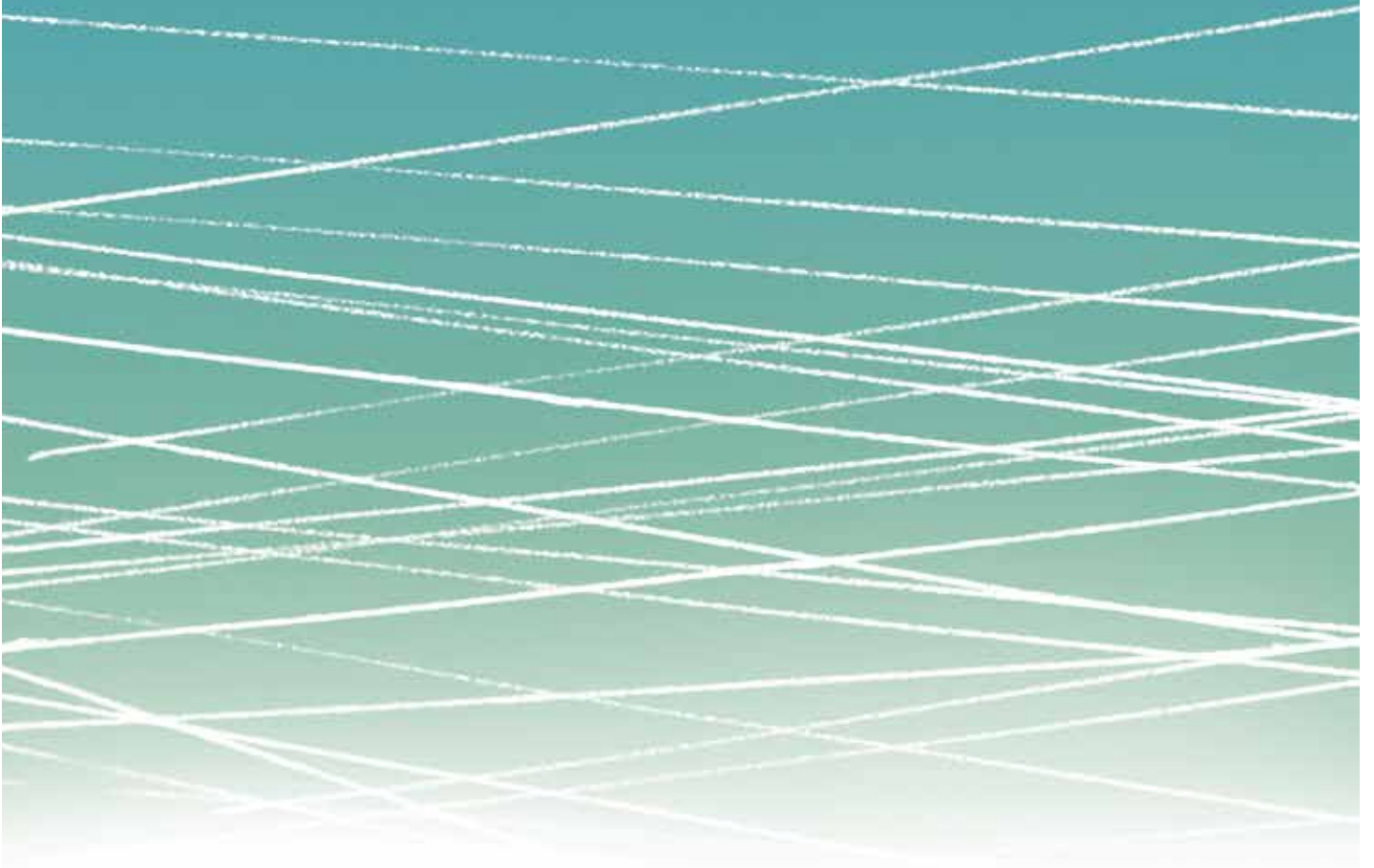
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APPENDIX 3

LANDSCAPE ANALYSIS: PROGRAMMES, GUIDELINES & INTERVENTIONS



SUMMARY

OBJECTIVE

- This is a broad overview of existing interventions, guidelines and packages to inform a comprehensive intervention framework to reduce excess mortality in persons with severe mental disorders (SMD).

METHODS

- We reviewed and summarized systematic reviews and identified relevant studies through contact with a team of experts; hand-searched reference lists of the peer reviewed and grey literature; and searched for WHO guidelines in relevant areas.

FINDINGS

- Although risk factors are well documented, our understanding about effective ways to intervene is very inadequate.
- Some interventions have proven to be effective but are not widely disseminated; others have not been rigorously tested; for some, the evidence is mixed or inconclusive.
- Several strategies developed for the general population appear relevant for those with SMD; however some may require additional modification and tailoring to be effective.
- Integrated care and case management or coordination approaches appear promising, as well as innovations in policy and systems-level change.
- Most current interventions have focused on single risk factors; efforts to apply innovations using a comprehensive intervention framework are only recently emerging.

IMPLICATIONS

- The number and scope of truly tested interventions in this area remain limited, and strategies for implementation and scaling up of programmes with a strong evidence base is scarce.
- More guidelines are needed at international and national levels, and research on the evaluation and implementation of these guidelines will be needed.

INTRODUCTION

Numerous interventions, guidelines and programmes have been developed to address the risk factors for excess mortality in persons with SMD. These primarily target individuals (e.g., mental health disorder management, physical health treatment, and lifestyle behavioural interventions), health systems (e.g., service delivery), and communities or policies (e.g., social support, stigma reduction, and health and social policies). Some interventions have proven to be effective but are not widely disseminated; others have not been rigorously tested; for several, the evidence is mixed or inconclusive. We sought a broad overview of existing interventions, guidelines, and packages to inform a comprehensive intervention framework to reduce excess mortality in persons with severe mental disorders (SMD).

METHODS

We reviewed and summarised systematic reviews and identified relevant studies through contact with a team of experts; requested data and additional analyses from senior authors; hand-searched reference lists of the peer reviewed and grey literature; and identified key informants who had access to primary or secondary unpublished information, especially from LAMICs. We also searched for WHO guidelines in relevant areas.

FINDINGS

Our first level of interventions is individual-focused, while the second focuses on health systems. We then incorporate socio-environmental interventions emphasizing broader social determinants of health, including social support, policies, and stigma reduction. Some programmes address components at multiple levels (e.g., simultaneously targeting individual behaviours and health systems through behavioural weight management plus care coordination); we have categorized them based on the main emphasis of the programme.

INDIVIDUAL-FOCUSED INTERVENTIONS

MENTAL HEALTH DISORDER MANAGEMENT

Early detection and appropriate treatment

Persons with SMD first of all require an early detection and appropriate treatment of their mental health condition. Especially in LMICs, no access to treatment or a long interval before mental health treatment is started can increase the risk for mortality (Fekadu et al., 2015; World Health Organization, 2008). A comprehensive tool to address most major mental health conditions, the Mental Health Gap Action Programme (mhGAP) intervention guide (World Health Organization, 2010a), incorporates evidence-based recommendations for psychosocial and pharmacological treatment for a range of disorders, including SMD. The guide's innovation is in facilitating the delivery of evidence-based mental interventions in LMICs through primary health care services, using specific assessments and decision points to reach a comprehensive management plan for each person. The WHO guidelines are based on the best quality evidence available and follow a systematic methodology for their development. The WHO mhGAP intervention guidelines (WHO, 2010a) provide an innovative approach to delivering evidence-based pharmacological and psychosocial care in non-specialized health settings for major mental, neurological and substance use disorders, especially in low-resource settings. It has been adopted worldwide and is being used to scale up services in areas where little to no mental health system exists or change current practice guidelines to be more in-line with the best available research from the literature. The mhGAP guidelines have been updated in 2015 and the guideline

implementation product – mhGAP Intervention Guide is currently being revised and Version 2.0 will be available in 2016. Although research on the implementation and impact of the guide is still ongoing, it offers a promising approach to effective and efficient delivery of mental health services.

The appropriate administration of medications can reduce excess mortality in persons with SMD. Recent studies and evidence summaries highlight the beneficial impact on mortality of continuous medication treatment (Sampson, Monsour, Maayan, et al., 2013; Janney, Ganguli, Richardson, et al., 2013), proper dosing ranges (Cullen, McGinty, Zhang, et al., 2013) and current and long-term use compared with no medication, particularly in schizophrenia (Tiihonen et al., 2009). Adherence to medication guidelines – such as the American Schizophrenia Patient Outcomes Research Team (PORT) Treatment Recommendations (Buchanan, Kreyenbuhl, Kelly, et al., 2010) – appear to have an effect on reducing mortality in schizophrenia.

Cullen and colleagues (2013) found that following the PORT guidelines was associated with reduced mortality among patients with SCZ. Among users of first-generation antipsychotics, doses greater than or equal to 1500 chlorpromazine dosing equivalents were associated with an increased risk of mortality (HR=1.88; 95% CI, 1.10-3.21). In addition to adequate dosing, continuity of antipsychotic treatment was also associated with mortality: HRs for mortality associated with annual continuity (>90%) and average antipsychotic continuity were 0.75 (95% CI, 0.58-0.98) and 0.84 (95% CI, 0.58-1.21), respectively (Cullen et al., 2013). These results are consistent with reviews of the evidence showing that continuous versus intermittent use of antipsychotic medications appears better at reducing relapse (Sampson et al., 2013). Outcomes monitoring systems and innovative service delivery programs will need to be developed in order to improve adherence to medication guidelines (Cullen et al., 2013; Barbui et al., 2014).

Interventions delivered at critical time points

The risk for suicide is highest within a year following discharge from a psychiatric hospitalization (Haklai, Goldberger, Stein, et al., 2011; Nordentoft et al., 2011). In a recent report by the Organization for Economic Cooperation and Development (2015), in several countries, suicide within 30 days of discharge amounted to at least one quarter of all suicides within the first year following discharge.

Thus, suicide prevention interventions (World Health Organization, 2014a) need to be an important component in mental health treatment plans for those with SMD. Suicide prevention, especially in the first few years following initial contact with mental health services, is recommended as a mandatory part of treatment programmes (Hawton & Saunderson, 2009). WHO guidelines recommend several evidence-based suicide interventions for non-specialist providers, including problem-solving strategies and ensuring limited access to means. Effective important and timely interventions include establishing closer communication with the patient and increased monitoring of symptoms and coordination with community-based services immediately after discharge. Good discharge planning and follow-up, enhanced levels of care immediately following discharge can help reduce suicide in the high-risk days immediately following discharge. Deliberate self-harm behaviours increase the risk for death by suicide (Laursen 2014; Runeson et al., 2010) and should also be carefully monitored. Multifaceted approaches could help with targeting both suicide and physical health, through the better integration of physical and mental health care, behavioural interventions, and changing professional attitudes, which may also help with suicide intervention and connection to providers. Providing suicide prevention during inpatient care, close coordination and follow-up with community care services upon and during the first year following discharge, close collaboration with primary care providers, and suicide intervention strategies in community-based primary or specialty care may help with reducing suicides among this high-risk population.

Injury and Violence Prevention

Few interventions have addressed victimization in persons with SMD, and more studies are needed in this area. A recent systematic review examining violence prevention strategies among persons with disabilities found that persons with SMD are at a heightened risk for violence victimisation; however few interventions have been developed to address this for persons with SMD (Hughes et al., 2012). Given the high incidence of a history of childhood maltreatment and interpersonal violence in this population, the prevention of revictimization might be an especially important focus. Other violence prevention strategies may include those aimed at law enforcement strategies, a finding also highlighted by Olfson and colleagues (2015).

For the general population, the WHO guidelines on violence prevention (2010c; available at: http://apps.who.int/iris/bitstream/10665/77936/1/9789241500845_eng.pdf?ua=1&ua=1) summarize the most effective interventions for violence, including intimate partner violence, sexual violence, elder abuse and suicide. These appear relevant for those with SMD but may require some modifications tailored to the needs of this group.

Recovery-oriented treatment

Recovery-oriented programmes with a focus on psychoeducation, increased awareness of symptoms, coping with stress, and problem-solving skills are also beneficial (McGuire, Kukla, Green, et al., 2014), along with strategies which support people with SMD and their families around treatment engagement (Dixon, Holoshitz, Nossel, et al., 2016). Though research is still unavailable, early intensive intervention initiatives may help with reducing suicides in this population. Early interventions, such as the Recovery After Initial Schizophrenia Episode (RAISE) initiative, have shown promising results on clinical and functional outcomes (Kane et al., 2015); however the impact of these programmes on suicide remains limited. Moreover, such high-resource comprehensive programs will be difficult to implement in low-resource settings.

PHYSICAL HEALTH TREATMENT

Early detection and appropriate treatment

Medical treatment for hypertension, diabetes mellitus and dyslipidemia should be similar for those with SMD as they are for the general population. However, self-management components (e.g., for diabetes) may require tailoring which accounts for cognitive, functional or motivational deficits. Available evidence suggests that interventions to improve screening for obesity, hyperlipidemia and hypertension have been effective at improving the detection of these conditions among persons with SMD (McGinty, Baller, Azrin, et al., 2016), although much more work is needed in this area.

APPENDIX 3

FINDINGS

LIFESTYLE BEHAVIOUR INTERVENTIONS

Tobacco cessation

Tobacco cessation interventions have proven beneficial in adults with schizophrenia and are recommended at the earliest possible phases of treatment (McGinty et al., 2016; Buchanan et al., 2010). Combination treatment with counselling and bupropion with or without nicotine replacement therapy or varenicline is efficacious and has benefits on both point abstinence and continuous abstinence from tobacco, though relapse is common (Evins, Cather, Pratt, et al., 2014).

Systematic reviews consistently show that bupropion (McGinty et al., 2015) and psychosocial interventions are effective for reducing smoking in persons with SMD, especially when these are combined (Stubbs et al., 2015); though recommendations differ slightly about nicotine replacement therapy (NRT) (Stubbs et al., 2015) and varenicline (NICE, 2014). Clinical recommendations include the following: for frontline pharmacological interventions, bupropion demonstrates particular promise with several reviews and meta-analyses demonstrating its effectiveness without any consistent reports of serious adverse events; patients should be offered behavioural and psychosocial support to help stop smoking and physical activity may also have a beneficial impact; and in practice, it is recommended that clinicians assess nicotine dependency, agree on the cessation goals, provide smoking cessation counselling, offer pharmacological support, monitor medication, weight, metabolic markers and offer exercise (Stubbs et al., 2015).

The UK National Institute for Health and Care Excellence (NICE) guidelines (2014) for persons with SCZ are similar and include offering help to stop smoking, even if previous attempts have been unsuccessful, and highlight the potential significant impact of reducing cigarette smoking on the metabolism of other drugs, particularly clozapine and olanzapine. NICE guidelines also recommend bupropion and nicotine replacement therapy (NRT) and varenicline, noting the importance of warning persons taking bupropion or varenicline that there is an increased risk of adverse neuropsychiatric symptoms and monitoring them regularly, particularly in the first 2-3 weeks. For individuals in inpatient settings, it is recommended that NRT be offered to help patients reduce or temporarily stop smoking (2011).

WHO guidelines on tobacco cessation for the general population are similar and include recommendations for psychosocial counselling and low-intensity pharmacology, like bupropion, if available (Figure 1). Of note, the WHO guidelines and health care provider training materials provide training on specific counselling techniques, including the 5A's (Ask, Advise, Assess, Assist, Arrange) and 5R's (Relevance, Risks, Rewards, Roadblocks, Repetition). Psychosocial counselling using the 5 A's has been implemented for tobacco cessation in persons with SMD in community mental health centres with modest cessation results at 12 months (Dixon et al., 2009) and some implementation barriers (Brown et al., 2015).

Although effective treatment and guidelines for smoking cessation in persons with SMD exist, Prochaska (2011) highlights several barriers—including beliefs or current practices about smoking and mental illness—that pervade both mental health and primary care practices. For example, providers might view smoking as therapeutic for the patient's symptoms or offer smoking as an incentive to comply with treatment. Only 4% of mental health patients reporting receiving assistance with quitting smoking from a mental health or general health care provider, even though persons with SMD are about as likely as the general population to want to quit smoking (Hall & Prochaska, 2011). Further, among smokers with mental illness, readiness to quit appears to be unrelated to the psychiatric diagnosis, severity of symptoms, or coexistence of substance abuse (Prochaska, 2011). Tobacco cessation should be started from the earliest phases of the SMD course (Correll et al., 2014) and be given utmost priority in clinical practice and all members of the multidisciplinary team should have a role, especially nursing staff in clinical practice (Stubbs et al., 2015).

Longer-term studies are needed to better understand optimal treatment duration, and importantly more work is needed to incorporate evidence-based tobacco cessation treatment into regular health care management for persons with SMD who smoke.

Behavioural weight management programmes

Behavioural weight loss programmes tailored for persons with SMD have been shown in randomized clinical trials to be successful in achieving clinically significant weight loss (Daumit, Dickerson, Wang, et al., 2013; Green, Yarborough, Leo, et al., 2015; Druss, von Esenwein, Compton, et al., 2010). Effective interventions are often built on those shown to be successful for improving diet and increasing exercise in the general population,

FIGURE 1. INTERNATIONAL AND NATIONAL GUIDELINES ABOUT TOBACCO CESSATION

World Health Organization (WHO) Building Capacity for Tobacco Control. Training for Primary Care Providers (2013)

<http://www.who.int/tobacco/quitting/en/>

and

National Institute for Health and Care Excellence (NICE) Guidelines for Smoking in Psychosis and Schizophrenia: Prevention and Management, 1.1.3 Physical Health (2014)

<http://www.nice.org.uk/guidance/cg178/chapter/1-recommendations>

WHO guidelines on treating tobacco dependence in primary care in the general population recommend psychosocial counselling first and then medication (if available). Counselling can include the 5 A's (Ask, Advise, Assess, Assist, Arrange) and the 5 R's (Relevance, Risks, Rewards, Roadblocks, Repetition). Article 14 (http://www.who.int/fctc/guidelines/adopted/article_14/en/) also recommends integrating brief advice and tobacco cessation counselling into existing healthcare systems. Details and training materials are provided in the primary care guides. External resources include a quit line to facilitate smoking cessation.

NICE guidelines recommend that persons with psychosis or schizophrenia should be offered help to stop smoking, even if previous attempts have been unsuccessful. Treatment options include nicotine replacement therapy or bupropion or varenicline. As of 2014, these were updated to warn people taking bupropion or varenicline that there is an increased risk of adverse neuropsychiatric symptoms and monitor them regularly, particularly in the first 2-3 weeks.

but with adaptations for cognitive needs of those with SMD, such as tailoring content and delivery to address memory and executive function deficits, and emphasizing environmental supports (Appel, Champagne, Harsha, et al., 2003; Whelton, Appel, Espeland, et al., 1998; World Health Organization, 2009).

Several meta-analytic and systematic reviews demonstrate the effectiveness of behavioural weight loss interventions in persons with SMD (Loh et al., 2006; Caemmerer, J., et al., 2012; Bonfioli, et al., 2012; McGinty et al., 2015). Most of these interventions focus on behavioural modification techniques, caloric restriction, and psychoeducation (Loh et al., 2006). Behavioural weight loss combined with metformin had a consistently good effect on BMI and weight loss in persons with SMD (McGinty et al., 2015). As noted by McGinty et al. (2015), although behavioural weight loss interventions for those with SMD versus the general population have many similar components, it is likely important to address memory and executive functioning deficits. These have been achieved in a number of ways, e.g., breaking large tasks or chunks of information into smaller components, repetition,

multimodal deliveries of information (Daumit et al., 2013). Moreover, behavioural interventions often require high frequency of contact and duration of interventions, which might need to be further enhanced for those with SMD (McGinty et al., 2015).

The American Schizophrenia Patient Outcomes Research Team (PORT) Psychosocial Guideline on non-pharmacological interventions for weight management in SCZ present a number of recommendations (Dixon, et al., 2010); key elements of weight-loss interventions should include psychoeducation and nutritional counselling in relation to caloric expenditure and portion control; behavioural self-management, including motivational enhancement; goal setting; weigh-ins; self-monitoring of food and activity levels; and modifications to diet and physical activity. In a review of physical health interventions for individuals with SMD, Richardson and colleagues (2005) noted that programmes that included social support, goal setting, self-monitoring, and behavioural shaping through small steps were more effective than straightforward health education alone.

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The Achieving Healthy Lifestyles in Psychiatric Rehabilitation (ACHIEVE) program is one behavioural weight management programme with tailoring specific to persons with SMD (Daumit et al., 2013). Conceptually, the intervention incorporated social cognitive and behavioural self-management strategies consistent with larger psychiatric rehabilitation principles of skill building and environmental supports. The intervention built on lifestyle interventions that studies have shown to be effective in the general population. In addition, it was tailored to address memory and executive functioning deficits (e.g., by dividing information into small components and targeting skills repeatedly). The intervention was composed of three contact types: group weight-management sessions, individual weight-management sessions, and group exercise sessions. Goals for the intervention group included reducing caloric intake by avoiding sugar-sweetened beverages and junk food (e.g., candy and high-fat snacks), eating five total servings of fruits and vegetables daily, choosing smaller portions and healthy snacks, and participating in moderate-intensity aerobic exercise. Group exercise started at a level appropriate for sedentary persons, with gradual increases in duration and intensity. Trained members of the study staff led all exercise classes for the first 6 months. Subsequently, a trained member of the rehabilitation-program staff offered some exercise sessions using a video. To reinforce intervention goals, participants monitored key behaviours with the use of a simplified tracking tool and met with intervention staff to monitor their weight. Session attention was incentivized with points that participants traded for small reward items (Daumit et al., 2013). The mean weight loss achieved in this trial was 3.2 kg (7.0 lb) at 18 months, similar to weight loss in lifestyle-intervention trials in the general population (Daumit et al., 2013).

Another weight loss and lifestyle intervention program to address antipsychotic medication side effects is the STRIDE program (Green et al., 2015). This program was based on another lifestyle intervention with the DASH (Dietary Approaches to Stop Hypertension) and guidelines for obesity treatment for individuals at risk for CVD. Participants kept records of food, beverages and calories consumed; servings of fruits, vegetables and low-fat dairy products; fibre and fat intake; daily minutes exercised; and nightly hours slept. The engaged in 6 months of weekly 2 hour group meetings with 20 minutes of physical activity. Goals included >25 minutes of moderate physical activity per day, primarily through walking: increased fruit, vegetable and low-fat dairy consumption; and improved sleep quality. Food and other monitoring records were used to assess progress and identify barriers to lifestyle change. Interventionists reviewed records to help participants evaluate and modify goals and plans.

Participants received a workbook to guide them on dietary content and a resistance band for strength training. SMD-specific adaptations included cognitive adaptations such as repetition, multimodal information, skill building exercise, practice assessments, psychoeducation, sleep hygiene, healthy diet on a budget, and stress management. Mental health counsellors and nutritional interventionists used engaging sessions and small group activities to facilitate acquisition and practice of behavioural self-management and problem-solving skills and to foster social support and program ownership. Core components included increasing awareness of health-related practices through monitoring, creating personalized plans, reducing energy intake by reducing portions, increasing consumption of low-calorie density foods, increasing physical activity, managing high-risk eating situations, graphing progress, and addressing effects of mental health on change efforts. In total, participants attended 14.5 of 24 sessions over 6 months and lost 4.4 kg (9.7 lb) more than control participants (95% CI, -6.96 kg to -1.78kg) and 2.6 kg (5.7 lb) more than the control group at 12 months. At 12 months, fasting glucose levels in the control group had increased from 106.0 mg/dL to 109.5 mg/dL and decreased in the intervention group from 106.3 mg/dL to 100.4 mg/dL. Medical hospitalizations were also reduced in the intervention group (6.7%) compared with the control group (18.8%) (Green et al., 2015).

The UK's NICE guidelines for persons with SCZ use a cross-referencing strategy and recommend offering interventions in line with NICE Obesity and Preventing Type 2 diabetes for the general population. For Preventing Type 2 diabetes among people at high risk, guidelines for the general population include lifestyle-change programmes, physical activity, tailored advice, awareness raising, weight management and dietary intake, as well as metformin.

For the general population, the WHO has produced behavioural guidelines on effective interventions for diet and physical activity that include counselling and group-based physical activity (WHO, 2010b). The Package of Essential Noncommunicable (PEN) disease interventions for primary health care in low-resource settings also recommends counselling for all health behaviours in the general population. The WHO guidelines on diet and physical activity appear relevant for persons with SMD, though programmes developed specifically for this population include much more supportive assistance (e.g., environmental supports, modifications for cognitive or motivational deficits) and integration into

existing programs (e.g., psychiatric rehabilitation programmes or community mental health centres) (McGinty et al., 2015).

In LAMICs, persons with SMD may die prematurely from malnutrition and infectious disease (e.g., Fekadu et al., 2015). Interventions may differ and the WHO (2013) guidelines on malnutrition and food insecurity and infectious disease appear relevant for persons with SMD in these settings

Interventions addressing substance abuse and risky sexual behaviour

There is a limited evidence base on effectiveness of interventions addressing substance abuse and risky sexual behaviour. The literature on interventions for reducing substance abuse in persons with SMD is large but inconsistent (Drake, O'Neal, Wallach, et al., 2008). Outcomes for these interventions remain limited, especially due to problems with engagement and retention in programmes (Mueser, Glynn, Cather, et al., 2012). Brief interventions can reduce mortality rates in those with problem drinking in non-psychiatric populations (Cuijpers et al., 2004) but the evidence appears less promising for populations with complex comorbidities (Roy-Byrne et al., 2014). Families may play an important role in treatment for substance abuse in this population (Reininghaus et al., 2015); however outcomes remain limited, especially due to problems with engagement and retention (Mueser et al., 2009).

For persons with substance use problems only, the WHO mhGAP guidelines (2010) recommend brief interventions for alcohol use assessment and management. Similarly, for persons with SMD and comorbid substance abuse, the Substance Abuse and Mental Health Administration (SAMHSA) recommends the Screening, Brief Intervention, Referral to Treatment (SBIRT) model. Overall, there is a need for more effective treatments to address substance abuse in persons with SMD.

The impact of interventions for reducing risky sexual behaviours is also limited, even though they might be able to increase other health promoting behaviours, such as immunizations. In a recent systematic review of risk reduction interventions aimed at high risk sexual behaviours in persons with SMD (e.g., unprotected intercourse, multiple partners, sex trade and illicit drug use), some interventions that have positive effects on condom use, condom protected intercourse, and of measures of HIV knowledge, attitudes to condom use and sexual behaviours and best practices (Pandor et al., 2015). One comprehensive intervention programme delivered in mental health care settings addressed

screening, testing, immunization, reducing risky behaviours and medical referrals for HIV and hepatitis, using a health promotion empowerment model; however, although participants had a higher prevalence of hepatitis B and C testing, higher immunization for hepatitis A and B, increased hepatitis knowledge and decreased substance use than the control group, risky sexual behaviour did not decrease (Rosenberg et al., 2010). This program, the STIRR (Screening, Testing for HIV and Hepatitis, Immunization for hepatitis B and C, Risk-reduction counselling and medical treatment Referral and support; Rosenberg et al., 2010) program was delivered in mental health care settings to high-risk patients with SMD. Components of STIRR include specialists who provide infectious disease services to their usual source of care, i.e., in mental health settings and includes 1 hour of contact over 3 sessions and employs health promotion and empowerment. Those randomized to STIRR went directly to the first session, which included: infectious disease education, screening for risk, pre-test counselling, blood draw for testing (HIV, HBV, HCV), first immunization and personalized risk-reduction education counselling and distribution of safety reminders (e.g., condoms), along with a blood test. Subsequent sessions focused on providing results, risk reduction counselling, medical referral and linkage if necessary and second immunization. Third and final sessions reinforced risk reduction and medical linkage (Rosenberg et al., 2010). Outcomes of the program were mixed: participants were more likely to be tested for HBV and HCV, be immunized for Hepatitis A and B, and reduce their substance abuse; however they showed no reduction in risk behaviour, were no more likely to be referred to care, and showed no increase in HIV knowledge (Rosenberg et al., 2010).

The PATH+ (Preventing AIDS through Health for HIV Positive persons; Blank, 2011; Blank, 2014) is integrated into programs of Assertive Community Treatment (PACT) community based mental health treatment. Advance practice nurses carried out the HIV regimens, covering a caseload of 3 to 5 patients. The treatment model included an individually tailored intervention to promote adherence in HIV positive persons with co-occurring mental disorders. Nurses provide in-home consultations and coordinated medical and mental health services for one year. Nurses served as the primary care coordinator among prescribing providers, pharmacists and case managers to organize medication regimens and help participants cope with barriers to medication adherence and promote the participant's ability for self-care. Basic interventions included meeting once a week at participant's home or place where they chose, and consisted of psychoeducation with pillboxes and beeping watches. Nurses were also available to attend appointments with patients and for purposes when there were issues with medication,

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communication or others needing physician attention (Blank et al., 2014). There were also good changes in CD4, viral load, and mental and physical functioning, all of which persisted at 12 months after the intervention (Blank et al., 2011; Blank et al., 2014).

These guidelines are similar to those developed by the WHO for HIV and HBV/HCV, including the use of task shifting, behavioural interventions, and risk reduction elements. WHO guidelines (WHO 2014b; WHO 2015) on HIV, HBV and HCV provide adaptations and special considerations for key populations, which may be relevant for those with SMD. In general, they focus attention on providing the same essential screening and management of these diseases, along with important additional interventions, including community empowerment, environmental supports, use of task shifting, violence prevention, and co-infections.

HEALTH SYSTEM-FOCUSED INTERVENTIONS

SERVICE DELIVERY

Screening for medical conditions

The next level in the framework encompasses interventions and programmes within health systems targeting health care providers and service delivery components. These will vary across different settings depending upon many parameters, such as the number of specialists versus primary care providers, the different distribution of health risk factors, the presence or absence of universal health care, and the availability of health technologies and medications. Strengthening of the six building blocks of the health systems - service delivery; health workforce; information; medical products, vaccines and technologies; financing; and leadership and governance (stewardship) would improve outcomes for persons with SMD (World Health Organization, 2007).

Screening programs developed for the general population may be different or require further modification when used for persons with SMD. For example, although guidelines like the UK National Institute for Health and Clinical Excellence on SCZ recommend more intensive screening for cardiovascular risk in persons with SMD, models like the Cox Framingham risk prediction may not accurately determine the risk in persons with SMD, especially considering the SMD-specific

exposures, like antipsychotic medication. In the development of this risk model, the Prediction and Management of Cardiovascular Risk in People with Severe Mental Illness (PRIMROSE) risk model was compared against the Cox Framingham model in predicting fatal and nonfatal cardiovascular events (i.e., myocardial infarction, angina pectoris, coronary heart disease, major coronary surgery and revascularization, cerebrovascular accident, and transient ischemic attack) in both North America and UK populations. Although still relatively new in its investigation process, the PRIMROSE models were more effective at predicting cardiovascular disease risk than the Cox Framingham models, suggesting the value of including risk factors beyond standard variables in the Cox Framingham, including systolic blood pressure, smoking, BMI and diabetes. They include additional variables: psychiatric diagnosis, psychotropic medication at baseline, harmful use of alcohol, use of antidepressants at baseline, and a social deprivation score (Osborn et al., 2015).

Care coordination or collaborative care strategies

Care coordination, collaborative care or integrated care programmes include support to better equip health systems, usually through the provision of additional supportive members who can serve as a liaison between mental health and physical health care systems or through linking of delivery of physical and mental health services. Few randomized trials have tested care coordination programmes for physical health conditions and cardiovascular risk factors in adults with SMD. In general, care programmes with an emphasis on monitoring and managing the adverse metabolic effects of antipsychotics are being implemented in several contexts, but many have not been well evaluated.

Collaborative care programs seek to increase the overlap between mental health and primary care provision. These can be coordinated, co-located or integrated (SAMHSA, 2015). Coordinated care has separate facilities and its key element is communication between providers. Co-located care is in the same facility but with separate systems with regular communication and its key element is physical proximity. Integrated care involves close to full collaboration and its key element is practice change with regular meetings for integrated care provision (SAMHSA, 2015). These can be delivered in mental health care settings, primary care settings, or community-based settings. A number of programs have examined these models in persons with SMD; however there is limited systematic evaluation of these programs.

An emerging area focuses on a case manager or care coordinator who serves as the liaison between multiple healthcare providers, as well as those involved in other domains of functioning, including employment, socialization and peer support. Although a consistent definition or taxonomy of the key activities of case management or care coordination is only recently being developed (Lukersmith et al., 2015), this work began in the mental health field and has been applied to various other fields, include ageing populations, among those with traumatic brain injuries, as well as social situations (e.g., community re-entry among prisoners). These are generally for complex interventions comprised of multiple components of care that are dependent and interdependent on one another. In health care, they are generally used to target those with chronic conditions. Patel and Chatterji (2015) state that the best-established model in collaborative care is a team approach that features a non-specialist case manager who coordinates care with primary care physicians and specialists. These may additionally span beyond physical and mental care management and might include social aspects of care, such as supported employment, particularly the Individual Placement and Support (IPS) model (Burns et al., 2007).

One intervention utilized a nurse care manager at a community mental health center to help participants become more involved in their own health care, communicate with physical and mental health providers, and assist in minimizing system-level barriers for health care (Osborn, Nazareth, Wright, et al., 2010). At 12 months, nearly 60% of those in the intervention group received recommended preventive services compared to just over 20% in the control group. In addition, the former were more likely to have a primary care provider (71.2% vs. 51.9%) and, among the subset with laboratory data, they had lower (better) Framingham cardiovascular risk scores (Osborn et al., 2010). These screening programs use nurse-led screening in a community mental health team to increase the identification of CVD risk factors. These appear effective for increasing screening among persons with SMD (Osborn et al., 2010). In the study by Osborn and colleagues (2010), more persons with SMD received screening for blood pressure, cholesterol, glucose, BMI, smoking status and their Framingham score in the nurse-led screening intervention arm than the control group.

The Primary Care Access Referral and Evaluation (PCARE; Druss, von Esenwein, et al., 2010) is a coordinated care model where care managers in community mental health settings provided communication and advocacy with medical providers, health education for patients, and support in overcoming system-level fragmentation and barriers to primary medical care. At 12

months, those in PCARE received an average of 58.7% of recommended preventive services compared to 21.8% in the usual care group ($p < 0.001$). They received a significantly higher proportion of evidence-based services for cardiometabolic conditions (34.9% vs. 27.7%, $p = 0.03$), and were more likely to have a primary care provider (71.2% vs. 51.9%, $p = 0.008$). On the SF-36, a composite measure of health functioning, those in the intervention group showed significant improvement on the mental component summary score and a non-significant improvement on the physical component summary score. Among subjects with available laboratory data, Framingham Cardiovascular Risk Scores were significantly lower (better) for intervention (6.9%) than control (9.8%) subjects ($p = 0.02$).

A recent trial examined a one-year intervention of care coordination alone, lifestyle coaching plus care coordination, or treatment as usual in adults with schizophrenia-spectrum disorders and increased waist circumference, with a primary outcome of cardiovascular risk reduction (Speyer, Norgaard, Birk, et al., 2016). A nurse delivered care coordination, including contacting primary care providers and communicating test results and need for physical health care to participants. Lifestyle coaching provided weekly home visits with cardiovascular risk factor counseling based on individual participant preferences. The study did not find differences in outcomes, which may be due in part to the preexisting high quality of health care delivery. Also, while incorporating participant preferences is an important component of behaviour change, the resultant lifestyle coaching may not have been efficacious enough for change in risk behaviours. As suggested by the authors, environmental change may be a next step to investigate for lifestyle modification in that setting (Speyer et al., 2016).

Guidelines for integrated delivery of mental and physical health care

Guidelines that incorporate combinations of screening for physical health conditions, care coordination among mental health and primary care providers, metabolic monitoring, and delivery of medical services in mental health settings have been implemented in several countries, including the US, the UK and Australia (Barnes, Paton, Cavanagh, et al., 2007; National Institute for Health and Care Excellence, 2014; Substance Abuse and Mental Health Services Administration, 2013; University of Western Australia, 2010a; University of Western Australia, 2010b; Shiers & Curtis, 2014). These are described briefly below.

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In the US, the Substance Abuse and Mental Health Services Administration has funded nearly 200 grants since 2009 for community-based agencies to create or increase the capacity to provide primary care services to persons with SMD at settings where they already receive mental health care (Substance Abuse and Mental Health Services Administration, 2014). An evaluation of the first years of the program reported that sites provided a range of integrated behavioural health and primary care services to persons with need for care (Scharf, Eberhart, Schmidt Hackbarth, et al., 2014). Challenges included lower than estimated consumer engagement, financial sustainment, and organizational culture issues. In addition, implementation of lifestyle behavioural interventions for weight management and tobacco smoking was challenging. Several suggestions were put forth for current and future agencies receiving funding, such as incorporating strategies to improve consumer access to services and addressing fidelity to evidence-based wellness interventions. The US-based Substance Abuse and Mental Health Administration (SAMHSA) has several resources on integrating behavioural health into primary care or primary care into behavioural health. SAMHSA also places an emphasis on substance abuse, in addition to mental health care and physical health care. In general, the care management endorsed by SAMHSA is consistent with the shift away from a focus on episodic acute care to health management of defined populations, especially those living with chronic health conditions. This shift necessitates integrating primary and behavioural health care, explicitly building care manager or behavioural health consultant and a consulting psychiatrist functions into the medical home model. The health home model is a team-based clinical approach that includes the consumer, his or her providers, and family members, when appropriate. It builds linkages to community supports and resources as well as enhances coordination and integration of primary and behavioural health care to better meet the needs of people with multiple chronic diseases, like persons with SMD. A report from February 2014 identifies the growing use of health homes, largely due to recent federal changes to health care reimbursement but also notes the limited research that evaluates its effectiveness for improving the lives of persons with SMD.

In Western Australia, the Western Australia Department of Health Mental Health Division developed a package of Clinical Guidelines for the Physical Health Screening of Mental Health Consumers and a set of Health Nurse Practitioner protocols (Stanley & Laugharne, 2011). The package was built up as a preventive, evidence-based framework for mental health

services, to facilitate coordination of care between health providers and with mental health consumers, relevant for hospital, clinic or community care settings. The set of protocols focuses on nurse practitioners in mental health, and highlights their role as both coordinators and providers, including for: comprehensive physical health evaluation; management and referral; education and support to consumers; enhancing continuity of care for patients; facilitating communication, appropriate access and utilization of hospital services for persons with SMD; collaboration between mental health professionals and primary care, including dietitians and other lifestyle consultants; provision of health promotion; assisting the patient in making appointments or involving the case manager in ensuring the patient is able to attend appointments. It can be used or adapted for inpatient, outpatient, or community care situations. It is recommended to be conducted within 48 hours of a person's first presentation to a mental health service and includes medication monitoring physical examinations and lifestyle and psychosocial assessment with time and role delineations for tasks by various providers (e.g., primary care provider, mental health care provider, nurses, and case workers) as well as monitoring and assessment tools. From this, a clinical guidelines for physical care of mental health consumers assessment and monitoring package was developed. It includes a metabolic syndrome algorithm wall chart, a clinician handbook, a psychosocial assessment booklet, and a set of three screening forms. It focuses on the key dimensions of medication effects, lifestyle, existing or developing physical disorders, alcohol and illicit drug use, and psychosocial factors (Stanley & Laugharne, 2011). The second protocol specifically focuses on nurse practitioners in mental health (NPMH), and highlights their role as both a coordinator and provider of a several services: comprehensive physical assessment, planning of therapeutic interventions, treatment, evaluation, consultation, education and support to mental health service patients, ordering of diagnostic tests, reviews, interpreting and referring onto GP or mental health medical officers if abnormalities are detected, enhance continuity of care for patients across the primary and tertiary sector, facilitate the improve communication, access and utilization of hospital services for persons with SMD, promote collaboration between mental health professionals and primary care, specifically dietitians and other lifestyle consultants, the provision of preventative health education and health promotion, including advice for patients to have reproductive health checks, eye and dentist checks, assisting the patient in making appointments or involving the case manager in ensuring the patient is able to attend

appointments, obtaining comprehensive patient and family health histories, and provision of staff education on physical health issues. Detail about the NPMH in the larger system and coordination of care are delineated, including referring the patients who is starting on antipsychotic medications or mood stabilizers to the NPMH for initial assessment and screening of physical health needs, referring them to a GP or mental health provider and as indicated, other providers, as necessary, including diabetes educator, dietician, pathology services, imaging services: echocardiograms and ECGs, occupational therapists for programmes on healthy lifestyles, cardiologists, and psychiatrists. In addition, monitoring tools and tables are provided with parameters for measurements and test results. This program also has major indicators (e.g., number of reportable clinical incidents or near misses relating to inappropriate care provided by NPMH), as well as programmatic review (i.e., every two years by the MH program manager every two years, or sooner if required). A 2010 report (University of Western Australia, 2010a) showed three key areas of concern: standardization across services, fidelity and frequency of use, and sustainability of the guidelines. Recommendations included management plans specific to each setting, and coordination between health professionals to prevent repetition of screening or failure to screen.

In New South Wales, Australia, a metabolic monitoring programme (New South Wales Government, 2012) is used to guide public mental health workers to monitor and manage metabolic syndrome and provide education to clinicians and patients. A study showed that this was implemented with about 60% coverage of monitoring of blood glucose and lipids and 54% of weight measurement. The compliance with measurement of waist circumference was lower (7%) (Organ, Nicholson, & Castle, 2010). This clinical documentation module on Metabolic Monitoring is used to inform public mental health services (inpatient and community mental health services) to monitor and manage metabolic syndrome and the provision of education for clinicians and patients. It provides monitoring forms to be used for target populations at risk for metabolic syndrome, including those on antipsychotic medication, with familiar physical risk factors, and with personal physical risk factors. Recommendations are to use it at baseline (when the patient is drug naive) and every 3 months, with increased frequency when abnormalities are identified. A study showed that this was able to be implemented with about 60% coverage of monitoring of blood glucose and lipids and 54% on weight measurement; less compliance with measurement of waist circumference (7%) (Organ, et al., 2010).

In the UK, the National Institute for Health and Care Excellence (NICE) guidelines on psychosis and schizophrenia (NICE, 2014) include direction about providers' assessment and treatment of physical health conditions, and routine monitoring of the physical health side effects of medication, offering behavioural counseling and linking to other guidelines (e.g., obesity or diabetes) when appropriate. Since 2009, NICE has recommended that mental health care providers routinely monitor weight and cardiovascular and metabolic indicators of morbidity in people with SMD and offer interventions for obesity, lipid modification or preventing type II diabetes, as appropriate. In 2014, NICE provided updated guidelines about physical health in persons with SMD, specifically new tobacco cessation recommendations. In addition, the guidelines specifically called for data collection on the prevalence of those with schizophrenia who received combined healthy eating and physical activity interventions and tobacco cessation interventions.

The UK NICE clinical guidelines for persons with SMD include direction about providers' assessment and treatment of physical health conditions, routine monitoring of the physical health side effects of medication, offering behavioural counselling and linking to other guidelines (e.g., obesity or diabetes) when appropriate. In assessment and care planning, it is recommended that teams carry out a comprehensive multidisciplinary assessment of people with psychotic symptoms in secondary care. This should include assessment by a psychiatrist, a psychologist or a professional with expertise in the psychological treatment of people with psychosis or SCZ. This assessment should address the following domains:

- Psychiatric (mental health problems, risk of harm to self or others, alcohol consumption and prescribed and non-prescribed drug history)
- Medical, including medical history and full physical examination to identify physical illness (including organic brain disorders) and prescribed drug treatments that may result in psychosis
- Physical health and wellbeing (including weight, smoking, nutrition, physical activity and sexual health)
- Psychological and psychosocial, including social networks, relationships and history of trauma
- Developmental (social, cognitive and motor development and skills, including coexisting neurodevelopmental conditions)
- Social (accommodation, culture and ethnicity, leisure activities and recreation, and responsibilities for children or as a career)

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- Occupational and educational (attendance at college, educational attainment, employment and activities of daily living)
- Economic status

Medication guidelines supported by NICE recommend understanding physical comorbidity and key guidelines, especially for antipsychotic medication. In addition to choices of antipsychotic medication being made jointly between the provider and patient, when starting an antipsychotic medication, providers are recommended to measure and record the person's weight or BMI, pulse, blood pressure, fasting blood glucose or HbA1c, and blood lipid profile. Before starting antipsychotic medication, it is recommended to offer the person an electrocardiogram (ECG) if:

- It is specified in the drug's summary of product characteristics (SPC) or
- A physical examination has identified a specific cardiovascular risk (such as hypertension) or
- There is a family history of cardiovascular disease, a history of sudden collapse, or other cardiovascular risk factors such as cardiac arrhythmia or
- The person is being admitted as an inpatient.

Additional guidelines include treatment with an explicit individual therapeutic trial, not routinely prescribing a dose above the maximum recommended. NICE guidelines also state that for persons with psychosis and SCZ, there should be routine monitoring of weight, cardiovascular and metabolic indicators of morbidity in people with psychosis and SCZ. These should be audited in the annual team report. Trusts should ensure compliance with quality standards on the monitoring and treatment of cardiovascular and metabolic disease in people with psychosis or SCZ through board-level performance indicators.

Monitoring and recording the following with antipsychotic medication is recommended regularly and systematically throughout treatment:

- Pulse and blood pressure after each dose change
- Weight or BMI weekly for the first 6 weeks, then at 12 weeks
- Blood glucose or HbA1c and blood lipid profile at 12 weeks
- Response to treatment, including changes in symptoms and behaviour
- Side effects and their impact on physical health and functioning
- Emergence of movement disorders
- Adherence

On the delineations of roles, there is a time-specific role of mental health providers followed by either transferring to

primary care providers or shared care. It is recommended that the mental health providing team should maintain responsibility for monitoring the efficacy and tolerability of antipsychotic medication for at least the first 12 months or until the person's condition has stabilized, whichever is longer. Thereafter, the responsibility for this monitoring may be transferred to primary care under shared-care arrangements. Guidelines also state that when using these medications, monitoring of side effects should be in place. It is also recommended that mental health care providers routinely monitor weight and cardiovascular and metabolic indicators of morbidity in people with SMD.

The NICE guidelines also focus on sharing care, which is described in the following manner:

- Routinely monitor for other coexisting conditions, including depression, anxiety and substance misuse particularly in the early phases of treatment
- Write a care plan in collaboration with the service user as soon as possible following assessment, based on a psychiatric and psychological formulation, and a full assessment of their physical health. Send a copy of the care plan to the primary healthcare professional who made the referral and the service user.
- For people who are unable to attend mainstream education, training or work, facilitate alternative educational or occupational activities according to their individual needs and capacity to engage with such activities, with an ultimate goal of returning to mainstream education, training or employment.

Since 2009, NICE has recommended that all teams providing services for people with psychosis or SCZ should offer a comprehensive range of interventions consistent with the guidelines. It is recommended that individuals are asked about use of alcohol and tobacco, prescription and non-prescription medication and illicit drugs with the person and their carer if appropriate. Guidelines for secondary care include that for those their mental health care provider should offer taking antipsychotic medications and long-term medications, persons with SMD. If a person has rapid or excessive weight gain, abnormal lipid levels or problems with blood glucose management, providers must take into account the effects of medication, mental state, other physical health and lifestyle factors in the development of these problems and offer interventions in line with the NICE guidelines on obesity, lipid modification or preventing type II diabetes.

As noted earlier, as of 2014, NICE guidelines have included many new guidelines about physical health in persons with

SMDs, and as noted above, new recommendations to include in care help for tobacco cessation. The new 2014 guidelines about physical health include the following:

- People with psychosis or SCZ, especially those taking antipsychotics, should be offered a combined healthy eating and physical activity programme by their mental healthcare provider.
- If a person has rapid or excessive weight gain, abnormal lipid levels or problems with blood glucose management, offer interventions in line with relevant NICE guidelines, especially obesity, lipid modification and preventing type 2 diabetes.
- Offer people with psychosis or SCZ who smoke help to stop smoking, even if previous attempts have been unsuccessful. Be aware of the potential significant impact of reducing cigarette smoking on the metabolism of other drugs, particularly clozapine and olanzapine.

Regarding how to implement and monitor these guidelines, NICE provides the following quality statement:

- The structure is evidence of local arrangements to ensure that adults with SCZ are offered combined healthy eating and physical activity programmes and help to stop smoking.
- Data collection process will be the number of those who received combined healthy eating and physical activity divided by the number of adults with SCZ in the past 12 months. The same process will be in place for receiving help to stop smoking.
- The outcome will be type 2 diabetes, obesity rates, and smoking rates in adults with SCZ.

Most recently, a multi-country effort has encouraged the use of the Lester UK Adaptation of the Australian Positive Cardiometabolic Health Resource, which summarizes safe interventions to help frontline staff make assessments of cardiac and metabolic health in persons with SMD (Shiers & Curtis, 2014). Dissemination efforts include a downloadable poster and forms for clinicians and clinics, service user cards for persons with SMD to approach their general practitioner or mental health provider in order to get additional help, and an action planning toolkit to help with the health care delivery system implementation of the resource. The National Health Service (NHS) of the UK has promoted the use of the Lester UK adaptation of the Australian Positive Cardiometabolic Health Resource. As of November 2015, it was endorsed by the NICE guidelines on psychosis and SCZ in adults. This is a clinical tool that summarizes safe interventions to help frontline staff make assessments of cardiac and metabolic health in

persons with SMD. Its slogan, “Don’t just screen, intervene,” highlights both screening and management of the major NCDs in persons with SMD. The National Audit of Schizophrenia has targeted multiple key groups in the dissemination and use of this resource and provided resources for each group. These include a downloadable poster and forms for clinicians and clinics, service user cards for persons with SMD to approach their general practitioner or mental health provider in order to get additional help, and an action planning toolkit to help with the healthcare delivery system implementation of this resource.

Finally, for LAMICs that may be implementing mental health in primary care settings, the World Health Organization’s PEN (2010b) guidelines for primary care in low-resource settings focus on screening, prevention and management of the major contributors of excess mortality in persons with SMD, including heart attacks, strokes, diabetes and hypertension. The WHO PEN is a conceptual framework for strengthening equity and efficiency of primary health care in low-resource settings and identifies core technologies, medicines and risk prediction tools. These guidelines are user-friendly and directed at key assessment and screening for target populations.

Overall, this level of the intervention framework also includes health care leaders implementing national and international guidelines for care of persons with SMD in their organization, and aligning financing policy and information systems for the missions of improving and monitoring quality of care (Druss & Bornemann, 2010). An important question for organizational leaders is who will deliver an evidence-based preventive health or care coordination intervention to decrease premature mortality in SMD. For example, dieticians and exercise leaders may be cost prohibitive, and sustainability may be more likely if mental health employees could deliver a physical health intervention. However, if mental health providers are to implement the intervention, they will likely need specific training and supervision. This is an important area for future research.

While many components of these health system-focused interventions are evidence based, implementation of these programmes and guidelines on the whole have not been formally evaluated for their success in achieving their intended outcomes. Furthermore, these programmes are largely based on high-income countries; the degree to which they are feasible in LAMICs will be an important area of further study. Meanwhile, as the provision of mental health care grows in LAMICs in primary care settings (World Health Organization, 2008), these settings may provide opportunities to further test and refine effective models of mental health care that can reduce excess mortality.

APPENDIX 3

FINDINGS

COMMUNITY-LEVEL AND POLICY-FOCUSED INTERVENTIONS

The broadest level of the framework incorporates socio-environmental factors and the social determinants of health. This part of the model acknowledges the range of potential interventions originating from the community to address contributors to premature mortality.

SOCIAL SUPPORT

Peer support programmes, family support programmes, and mental health and consumer advocacy groups

Peer support programmes, family support programmes, and mental health consumer groups (Semrau, Lempp, Keynejad, et al., 2016) are important potential resources that can implement or assist with health interventions, whether focused on health behaviours, chronic disease self-management, or recovery-based programmes.

Evidence for peer-led interventions for chronic disease self-management appears promising: a 6-week programme tailors chronic disease self-management interventions for those in the general population to those with SMD, delivered by peers with SMD (Lorig, Sobel, Stewart, et al., 1999), and addresses tasks common across chronic health conditions such as action planning and feedback, modeling of behaviours and problem-solving, reinterpretation of symptoms and training in specific disease management techniques. The programme has been shown to improve health status and efficiency of health care utilization. The available evidence shows improvements in quality of life, medication adherence, and a primary care visit (Druss, Zhao, von Esenwein et al., 2010). The Health and Recovery Peer (HARP) Program (Druss, Zhao, et al., 2010) is an adaptation of the Chronic Disease Self-Management Program for mental health consumers and is comprised of a manualised, six-session intervention, delivered by mental health peer leaders, which helps participants become more effective managers of their chronic illnesses. A pilot study found that at 6 months follow-up, participants in the intervention trial had significantly greater improvement in patient activation and in having one or more primary care visit (68.4% vs. 51.9% with one or more visit). Intervention participants also had greater physical health-related quality of life, physical activity, and medication adherence (Druss, Zhao, et al., 2010). In a small

randomized trial of a different adaptation of the same programme, also using peers with SMD and consisting of 13 weekly group sessions, participants showed improvement in self-management and better use of health care compared to controls (Lorig et al., 1999). Both of these studies had relatively short follow-up and used self-report measures for outcomes; however, they support recovery-oriented illness self-management interventions for persons with SMD and a chronic medical condition as well as roles for peers with SMD to deliver these interventions. More work is needed to develop the evidence base for peer-led and peer-supported interventions to improve physical health in persons with SMD.

STIGMA REDUCTION INTERVENTIONS

Directed toward communities with SMD and general public

Stigma reduction programmes (Semrau, Evans-Lacko, Koschorke, et al., 2015; Thornicroft, Metha, Clement, et al., 2016) appear important for improving the lives of persons with SMD, within and beyond the health care community. A recent review of effective interventions to reduce mental health related stigma and discrimination reported that, for the general population, interventions can improve short-term attitudes, and of these, social-contact based interventions seem to be the most effective. Two reviews were recently published on effective interventions to reduce mental health related stigma and discrimination and have highlighted that social contact appears to be the most effective way to reduce stigma (Thornicroft et al., 2015). There is also limited research on the effect of stigma reduction efforts in LMICs (Semrau et al., 2015). For those with mental disorders, group-level interventions appear helpful. However, across studies for those with and without SMD, further research is needed with strong designs, longer-term follow-up and a focus on mental health consumers' perceptions of stigma. In addition, studies should examine behavioural and not only attitudinal change as a result of interventions to decrease stigma and discrimination (Thornicroft et al., 2016), as well as effective stigma reduction strategies in LMICs (Semrau et al., 2015).

POLICY LEVEL INTERVENTIONS

The factors in this part of the model link across to both health system and individual-focused interventions. Public health

policies affect health systems, and specific environmental or social support programmes are often implemented through health systems (e.g., peer support programmes). Public health policies such as mental health parity or insurance coverage affect the services that the individual mental health consumer can access and will be critical to their sustainability. However, an evidence base for policies that effectively reduce excess mortality in persons with SMD is still needed.

Comprehensive health care packages, insurance parity and quality

On a wider scale, policies that have a beneficial effect on all individuals may also be beneficial for those with SMD, or policies may need to be shaped specifically to influence health for persons with SMD. In the UK, the Health and Social Care Act 2012 and “Parity of Esteem” (<https://www.england.nhs.uk/mentalhealth/parity/>) established new legal responsibility for the National Health System (NHS) to deliver parity between mental and physical health, i.e., ensuring that there is as much focus on improving mental health as physical health and that persons with mental health problems receive an equal standard of care. Active components and indicators of this parity include: waiting time standards for some mental health services, improving acute crisis services and how police forces respond to emergencies among persons with SMD, increasing funding for mental health services, and continuing access to psychological therapies to address common mental disorders in primary care. Furthermore, the Commissioning for Quality and Innovation Scheme provided additional income for national health system trusts that meet specific indicators for people with mental health problems under that care, including recording relevant data on patient health, completing yearly physical health checks, and encouraging smoking cessation. Critically, the scheme mandated communication with the patient’s general practitioner on discharge from hospital or after review by a community team. Sustainability of such policies will prove important in the future.

Additionally, the US system has included legislation to address parity between mental health and medical services and later the patient protection legislation required that mental health and substance use disorder coverage be included in essential benefits packages offered in insurance plans (Cummings et al., 2013). Legislation can also lead to protections from discrimination in school and employment; however knowing how policy-level interventions need modifications to best improve and lengthen the lives of persons with SMD will be important for future impact. For example, protection legislation may be in

force, but individuals may not seek this protection due to not wanting to be identified as having a mental disorder (Cummings et al., 2013). In the US, a proposed option is the designation of persons with SMD as a health disparity group by the federal government, which would also require the tracking of vital health statistics separately for this population and make them eligible for more technical assistance opportunities (Druss & Bornemann, 2010).

Public health programmes (tobacco cessation, HIV prevention, suicide prevention)

Public health policies providing mental health parity could greatly improve lives of those with SMD. Policy-level interventions that affect screening or management of suicide, HIV or tobacco smoking are especially relevant to those with SMD and may have even greater effects on the health and well-being of this high-risk population. These have been described above as individual treatments, but are relevant for larger public health systems in order to have a wide and sustained impact on prolonging the lives of those with SMD.

Employment, housing, and social welfare sector involvement

Employment programs such as supported employment (e.g., Burns, Catty, Becker, et al., 2007) and policies to provide stable housing may impact the ability of persons with SMD to fully integrate into society, which should lead to improved physical health.

CONCLUSIONS

The increasing awareness of poor physical health, high mortality rates and poor provision of physical health care among persons with SMD has led to the development of several interventions and programmes. Overall, the number and scope of truly tested interventions remain limited, and strategies implementation and scaling up of programmes with a strong evidence base are scarce. Moreover, the majority of available interventions focus on a single or an otherwise limited number of risk factors. The assumption of our framework is that an effective approach must comprehensively target individual behaviours, health systems and social determinants of health. However, the effective and scalable combinations of these different interventions have yet to be fully evaluated.

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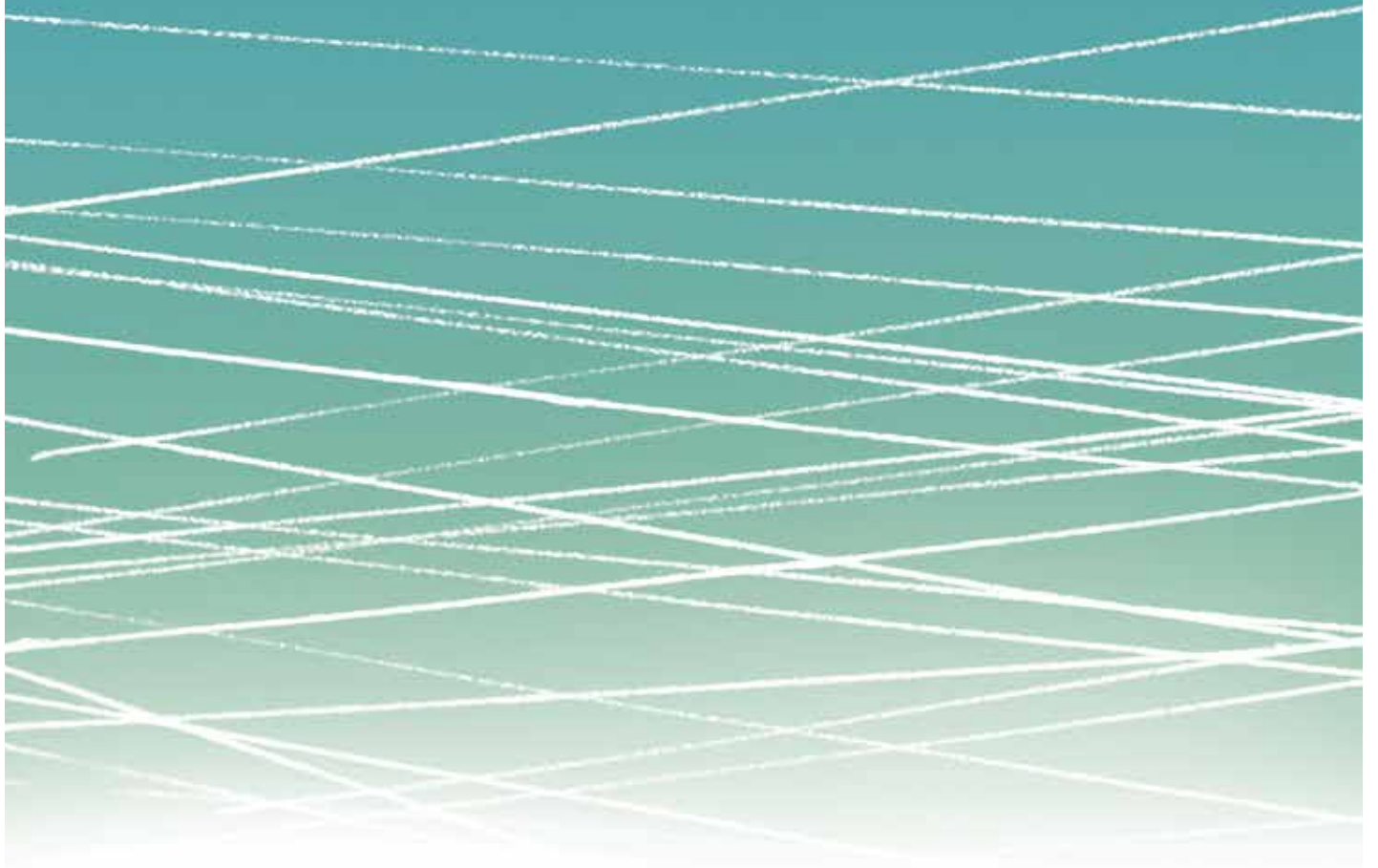
TABLE 1. MULTILEVEL MODEL OF RISK FOR EXCESS MORTALITY IN PERSONS WITH SEVERE MENTAL DISORDERS (SMD)

GUIDE-LINES	HEALTH TOPIC	GENERAL POPULATION	SMD MORTALITY-RELEVANT
WHO	Mental health (mhGAP)		<ul style="list-style-type: none"> Chronic obstructive pulmonary disease Referral of suspected breast and cervical cancer through an integrated approach Health education and counselling healthy behaviors
	Noncommunicable diseases (NCDs)	Management guidelines and algorithms for major NCDs: <ul style="list-style-type: none"> Hypertension Diabetes Raised cardiovascular risk Asthma Chronic obstructive pulmonary disease Referral of suspected breast and cervical cancer through an integrated approach Health education and counselling healthy behaviors 	All are relevant; no specific guidelines developed for persons with SMD; some evidence to indicate SMD-specific modifications for cardiovascular disease risk prediction models (Osborn et al., 2015) and need for modification and tailoring for weight and diet programmes to account for cognitive deficits (McGinty et al., 2015).
	Tobacco cessation	Brief advice (5 A's, 5 R's) + low-cost pharmacological therapy	Demential; Similar guidelines
	HIV Prevention	Essential health sector interventions <ul style="list-style-type: none"> Comprehensive condom and lubricant planning Harm reduction Behavioural interventions HIV testing and counselling HIV treatment & care Prevention & management of co-infections Sexual and reproductive health interventions Essential strategies for an enabling environment <ul style="list-style-type: none"> Legislation Stigma and discrimination Community empowerment Addressing violence against people from key populations 	Key populations; same as general population <ul style="list-style-type: none"> Task shifting Community empowerment Practice recommendations for reducing violence Law enforcement training
	Oral Health	No official guidelines developed yet, but the WHA 60.17 focuses on an action plan for integrated disease prevention in oral health	WHA 60.17: (3) to promote the availability of oral-health services that should be directed towards disease prevention and health promotion for poor and disadvantaged populations, in collaboration with integrated programmes for the prevention of chronic noncommunicable diseases

GUIDE-LINES	HEALTH TOPIC	GENERAL POPULATION	SMD MORTALITY-RELEVANT
WHO	Hepatitis B Infection	Treatment & care	Key populations; Similar guidelines as HIV key populations <ul style="list-style-type: none"> Incentives to complete vaccination schedule Offer peer interventions Promote alcohol reduction
	Hepatitis C Infection	Similar as above	Key populations; Similar to HBV
	Violence & Injuries	<ul style="list-style-type: none"> Developing safe, stable and nurturing relationships between children and their parents and caregivers Developing life skills in children and adolescents Reducing the availability and harmful use of alcohol Reducing access to guns, knives and pesticides Promote gender equality to prevent violence against women Changing cultural and social norms that support violence Victim identification, care and support programmes 	None; systematic review
	Nutrition for Health Development	<ul style="list-style-type: none"> Vitamin and mineral requirements in human nutrition Food-based dietary guidelines and health promotion Recommended iodine levels in salt Sugar intake for adults and children Nutritional care and support for patients with TB 	None
NICE	Antipsychotic medication	–	<ul style="list-style-type: none"> Physical health and side effect monitoring Delineation of monitoring timeframe and collaboration among primary and mental health care
	Shared care	–	<ul style="list-style-type: none"> Delineation of roles and description of collaboration among different providers
	Cardiometabolic screening	–	<ul style="list-style-type: none"> Assessment and management of cardiac and metabolic health using the Lester tool
	Tobacco cessation	–	<ul style="list-style-type: none"> Pharmacological therapy in mental health care
	Healthy eating and physical activity	–	<ul style="list-style-type: none"> Offer combined physical activity and healthy eating programmes
	Obesity & diabetes management	–	<ul style="list-style-type: none"> Cross-referencing to Obesity, Lipid Modification & Preventing Type 2 Diabetes guidelines

APPENDIX 4

POLICY AGENDA: KEY MESSAGES



Develop a policy brief

- To increase awareness and disseminate information to relevant structures
- Contextualize as part of the broader international health agenda
 - Focus on direct relationships with the following:
 - UN Sustainable Development Goals
 - Six cross-cutting principles of the WHO Mental Health Action Plan
 - Universal health coverage
- Highlight how mental disorders cause not only disability but death
- Develop a set of key messages to deliver to key stakeholders: e.g., “Why are people dying prematurely?”
 - Make country-specific with numbers
 - Dying x years earlier than the general population, x will die in your country this year, x years of productivity lost
 - In low and middle income countries (LAMICs), infectious diseases are more relevant than smoking or obesity; however non-communicable disease (NCD) risk factors are also becoming increasingly relevant and prevalent in LAMICs
- Highlight problems but demonstrate available solutions
 - Include what can be done and who can do what
 - Identify possible barriers followed by solutions
 - Emphasize early identification and prevention of risk factors
- Develop a media package

Frame this as a rights-based/equality issue

- This is a vulnerable group who is not getting the coverage it needs
- The promotion of this issue advances universal health coverage
 - Window of opportunity to work within health systems to strengthen them

Involve users, families and advocacy groups

- Advocacy has to go hand-in-hand with solution-based policies
- Advocacy & engagement of various stakeholders (e.g., government, ministries of health, NGOs, health services and workforce, academics, private industry, consumers, caregivers, community)
- Create a movement
 - Catchy slogan that focuses on reducing preventable disease and improving quality of life

Incorporate into current clinical practice

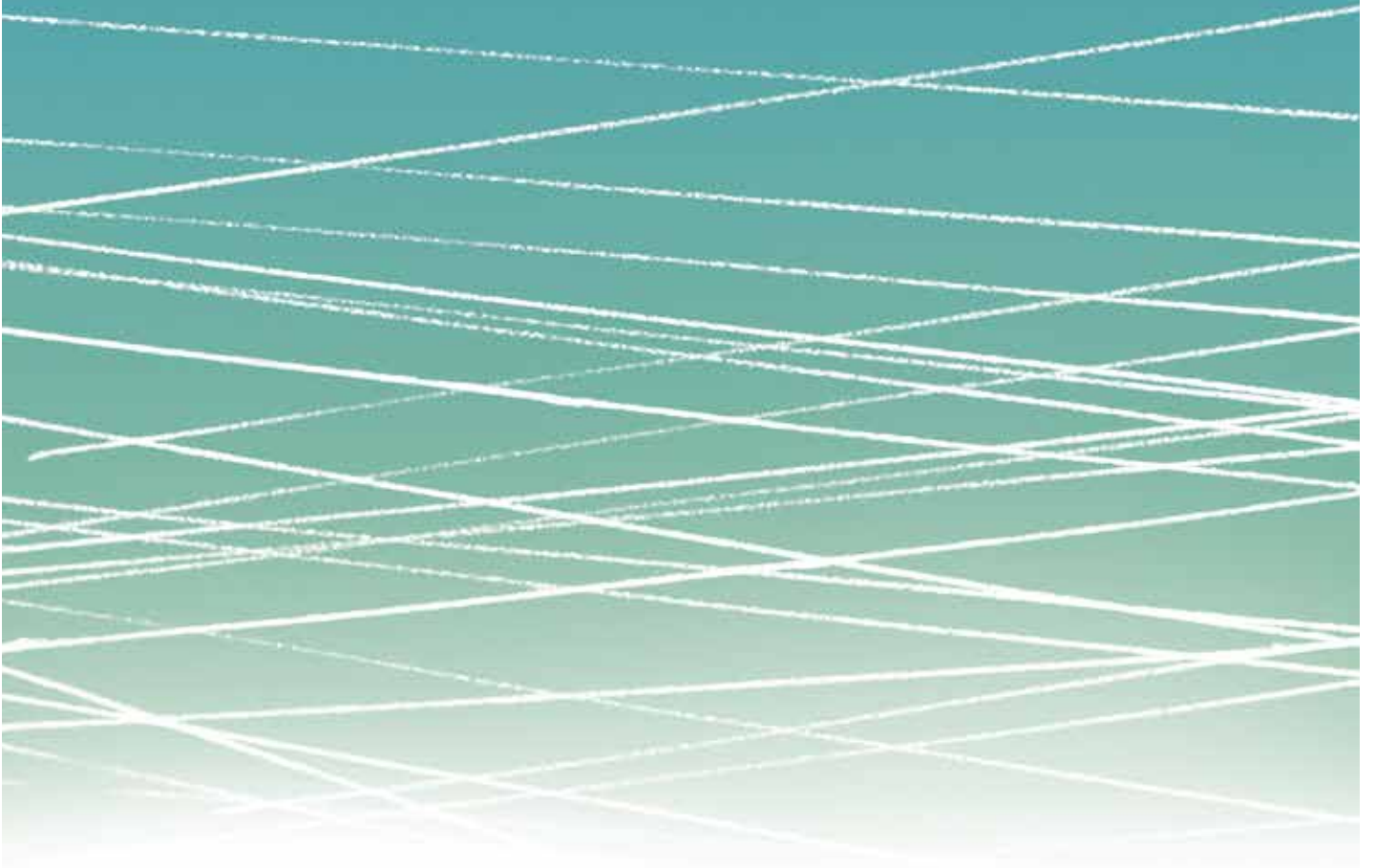
- Produce brief guidance to change practice and circulate to key audience
- Highlight that what we know is enough to advance promoting practice change
- Emphasize how:
 - Much of excess mortality is preventable
 - Quality of life of persons with severe mental disorders (SMD) and their families can be improved
- Integrate the concept into plans and programs of other WHO departments e.g., accidents, suicide, violence, tobacco cessation, substance abuse, nutrition, physical exercise

Improve health systems or delivery and information systems

- Use routine data collection at local facilities, national and regional levels databases, health information and surveillance systems to monitor mortality records and cite trends
- Build up information systems
 - Identify and require minimum indicators necessary for all countries (e.g., age at death and cause of death)
 - Set-up sentinel surveillance sites to monitor population health over time
- Pilot project with other stakeholders, MoH/NGOs to monitor and evaluate

APPENDIX 5

RESEARCH AGENDA: KEY MESSAGES & POINTS OF ACTION



Expand our understanding of excess mortality in low and middle income countries (LAMICs) and how this differs from high income countries (HICs), especially:

- To Epidemiology and correlates: focus on identifying characteristics specific to excess mortality in LAMICs. Malnourishment, infectious disease, limited activity and responsibilities of the family are important in LAMICs, whereas smoking, obesity and chronic conditions may not be as prevalent—however, NCD risk factors are also growing in relevance and prevalence in LAMICs
- Interventions, packages and programs: develop interventions to target risk factors specific to LAMICs

Disentangle risk factors to guide development of interventions and intervention studies

- To Parse out factors at the different individual, health systems and socio-environmental levels
- Clarify the trajectory of individuals through a system, with their families, and the contextual circumstances leading up to death
- Better understand the role of psychopharmacological agents in excess mortality

Conduct intervention studies

- To Determine which guidelines and interventions work as they are and which require modifications
- If modifications are necessary, specify what modifications for which interventions
- Explore innovative delivery platforms and implementation strategies (e.g., with peers, at a structural level such as treatment facilities, and in different settings such as places of employment)
- Use pragmatic trials for real-world effects
- Explore how mhGAP can be integrated for the management of physical conditions and from this, pilot and test new packages of care

Implementation science for the uptake and use of guidelines

- To Explore the impact of integrated care and coordinated care/case management on excess mortality and associated risk factors, especially in LAMICs
- Identify leverage points that lead to changes in provider practice and patient outcomes

- Identify barriers, demonstrate health gains and model the reduction in mortality
- Use community health workers, nurses, family members, peers and others
- Determine the intensity and duration of support/training of key workforce required to take care of the top 3-5 causes of mortality
- Determine whether this can be done at a cost affordable to a low-resource setting

Gain a better understanding of the different perspectives involved

- To Use qualitative methods to understand the experiences of users, providers, family members, and others
- Understand professionals' receptivity to education, interventions and accountabilities

Identify how to overcome attitudinal and practice barriers of the health workforce

- To Test and apply strategies to effectively shift attitudes (e.g., exposure to service users during training)
- Review to what extent strategies are already known and barriers to their implementation

Use big data

- To understand current practice: e.g., trajectories through a system, utilization, costs
- To clarify the role of risk factors: e.g., systems characteristics, quality of care, types of settings, social determinants, comorbidities, differential exposures and complex interactions
- To understand temporality: identify when results and changes occur
- To link systems of care: primary care, specialty mental health care, inpatient to community-based care
- To innovate: design natural experiments (e.g., impact of incentives on health practitioner behavior change) and intervene at a structural level

Use consortia or partnerships to share information and learn from each other

- Pooled resources can help advance our understanding

