



# Addressing comorbidity between mental disorders and major noncommunicable diseases

Background technical report to support implementation of the  
WHO European Mental Health Action Plan 2013–2020 and the  
WHO European Action Plan for the Prevention and Control of  
Noncommunicable Diseases 2016–2025



# **Addressing comorbidity between mental disorders and major noncommunicable diseases**

**Background technical report to support implementation of  
the WHO European Mental Health Action Plan 2013–2020  
and the WHO European Action Plan for the Prevention and  
Control of Noncommunicable Diseases 2016–2025**

**Alan Cohen**

# Abstract

Reduced healthy life expectancy due to the high burden of both mental ill health and noncommunicable diseases (NCDs) is a major public health concern in the European Region. The links between mental disorders and major NCDs are well established. In clinical practice, however, mental disorders in patients with NCDs as well as NCDs in patients with mental disorders are often overlooked. Premature mortality and disability could be reduced if there were a greater focus on comorbidity. This report addresses the needs of adults of working age with mental health problems – those with common mental disorders such as depression and anxiety and those with more severe conditions such as schizophrenia and bipolar affective disorder. It also addresses the needs of those with NCDs, specifically cardiovascular diseases, cancers, chronic respiratory diseases and diabetes mellitus. The report was prepared as a technical background paper to the WHO European Mental Health Action Plan 2013–2020 and the WHO European Action Plan for the Prevention and Control of Noncommunicable diseases 2016–2025. It is envisaged that the report will contribute to a better understanding of comorbidity by public health specialists and health care providers alike, which in turn will help to promote a more integrated approach for patients with comorbidity.

## Keywords

MENTAL HEALTH

CHRONIC DISEASE

HEALTH-CARE SYSTEMS

HEALTH

COMORBIDITY

NONCOMMUNICABLE DISEASES

ISBN: 9789289052535

Address requests for publications of the WHO Regional Office for Europe to:

Publications

WHO Regional Office for Europe

UN City, Marmorvej 51

DK-2100 Copenhagen Ø, Denmark

Alternatively, complete an online request form for documentation, health information or permission to quote or translate on the Regional Office web site (<http://www.euro.who.int/pubrequest>).

## © World Health Organization 2017

All rights reserved. The Regional Office for Europe of the World Health Organization welcomes requests for permission to reproduce or translate its publications, in part or in full.

The designations employed and the presentation of the material in this publication do not imply the expression of any opinion whatsoever on the part of the World Health Organization concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. Dotted lines on maps represent approximate border lines for which there may not yet be full agreement.

The mention of specific companies or of certain manufacturers' products does not imply that they are endorsed or recommended by the World Health Organization in preference to others of a similar nature that are not mentioned. Errors and omissions excepted, the names of proprietary products are distinguished by initial capital letters.

All reasonable precautions have been taken by the World Health Organization to verify the information contained in this publication. However, the published material is being distributed without warranty of any kind, either express or implied.

The responsibility for the interpretation and use of the material lies with the reader. In no event shall the World Health organization be liable for damages arising from its use. The views expressed by authors, editors, or expert groups do not necessarily represent the decisions or the stated policy of the World Health Organization.

# Contents

Acknowledgements	iv
Glossary	v
Abbreviations and acronyms	v
Executive summary	vi
1. Introduction	1
1.1 The burden of mental disorders and major noncommunicable diseases	1
1.2 Political commitment to addressing the burden of mental disorders and major noncommunicable diseases	1
1.3 Rationale and scope of the report	2
2. Relations between mental disorder and major noncommunicable diseases	3
2.1 Diabetes	3
2.2 Cardiovascular disease	8
2.3 Chronic respiratory diseases	14
2.4 Cancer	19
3. Implications for health services	23
3.1 Health service delivery	23
3.2 Strengthened knowledge and skills in the health workforce	24
4. Conclusions	25
5. References	26

# Acknowledgements

This report was written by Dr Alan Cohen, Director of Primary Care at the West London Mental Health Trust (rtd.).

Essential advice and support were provided to the main author by Dr Dan Chisholm, Dr Jill Farrington, Dr Matt Muijen and Dr Elena Shevkun, WHO Regional Office for Europe.

Dr Marilys Corbex and Dr Juan Tello, WHO Regional Office for Europe, provided valuable peer review comments.

The report was produced under the overall guidance of Dr Gauden Galea, Director of the Division of Noncommunicable Diseases and Promoting Health through the Life-course in the WHO Regional Office for Europe.

This publication was partially funded by the Government of the Russian Federation within the context of the WHO European Office for the Prevention and Control of Noncommunicable Diseases (NCD Office).

# Glossary

Integrated care	An approach to strengthen people centred health systems through the promotion of the comprehensive delivery of quality services across the life course designed according to the multidimensional needs of the population and the individual and delivered by a coordinated multidisciplinary team of providers working across settings and levels of care (1).
Multimorbidity	The presence of two or more chronic medical conditions in one individual.
Comorbidity	The presence of one or more additional diseases or disorders occurring concomitantly with a primary disease or disorder.
Noncommunicable diseases	Noncommunicable diseases (NCDs), also known as chronic diseases, are not passed from person to person. They are of long duration and generally slow progression. The four main types of noncommunicable diseases are cardiovascular diseases (CVD, like heart attacks and stroke), cancers, chronic respiratory diseases (such as chronic obstructed pulmonary disease and asthma) and diabetes.
Common mental disorders	Common mental disorders refer to two main diagnostic categories: depressive disorders and anxiety disorders. These are highly prevalent in the population, affecting mood or feelings, with symptoms ranging from mild to severe in terms of severity and from months to years in terms of duration. These disorders are diagnosable health conditions; they are distinct from the feelings of sadness, stress or fear that anyone may experience from time to time in their lives (2).
Severe mental disorders	Severe mental disorders refer to bipolar affective disorder, schizophrenia and other psychoses.

# Abbreviations and acronyms

COPD	chronic obstructive pulmonary disease
CVD	cardiovascular disease
DALY	disability-adjusted life-year
HbA1c	glycated haemoglobin
NCD	noncommunicable disease

# Executive summary

Reduced healthy life expectancy due to the high burden of mental disorders and major noncommunicable diseases (NCDs) is a significant public health concern in the European Region. Although attention is being given to scaling up the public health response to these conditions, far less attention is being paid to the well-established links that exist between them.

Mental disorders affect, and are in turn affected by, major NCDs: they can be a precursor or a consequence of chronic conditions such as cardiovascular disease (CVD), diabetes or cancer. Risk factors for these diseases, such as sedentary behaviour and harmful use of alcohol, are also risk factors for mental disorders and strongly link the two. In clinical practice, however, such interactions and comorbidities are routinely overlooked.

The aim of this report is to contribute to better understanding of comorbidity and to provide evidence that can be used by health care planners and providers to promote a more integrated approach to managing individuals with comorbid conditions. The primary focus is on the relations between common and severe mental disorders on the one hand and the four “major” NCDs that were the subject of the United Nations high-level meeting on NCDs: CVD, diabetes, cancer and chronic respiratory diseases. Common mental disorders comprise depressive and anxiety disorders, while severe mental disorders include psychosis and bipolar affective disorder.

## **Mental disorders and diabetes**

*Common mental disorders:* The relation between diabetes and depression is bidirectional: people with diabetes are more likely to develop depression, and depression is a risk factor for diabetes. Accordingly, people with diabetes should have regular checks to assess whether they are developing depression. It is therefore important that health care staff who provide diabetic care should be able to identify people who are depressed and know how to manage depression or to refer patients to appropriately trained and resourced health care professionals.

*Severe mental disorders:* Diabetes is more common among people with severe mental disorders. Therefore, health care staff who provide care to people with severe mental disorders should understand the clinical features of diabetes and be able to identify potential life-threatening episodes. Models of integrated care for people with severe mental disorders and diabetes should be further developed and evaluated.

## **Mental disorders and CVD**

*Common mental disorders:* Depression and anxiety predict the development of CVD and worsen its prognosis, but there is no evidence that screening for or treating depression and anxiety improves cardiovascular outcomes. For example, screening for and treating depression will not prevent a heart attack. The frequent coexistence of several NCDs, such as diabetes, hypertension and depression, indicates that a more integrated approach is required to health service planning, delivery and liaison between specialists in mental and physical health.

*Severe mental disorders:* The commonest cause of death among people with severe mental disorders such as schizophrenia and bipolar disorder is CVD. Identifying and managing modifiable risk factors for CVD in people with a severe mental disorder (such as alcohol and tobacco use) will reduce their risk for premature mortality. Discrimination against people with severe mental disorders prevents them from accessing services and increases their risks for premature death and disability from CVD. Addressing discrimination will therefore help to improve access to care for the physical health needs of people with severe mental disorders.

## **Mental disorders and chronic respiratory diseases**

*Common mental disorders:* Anxiety and depression are more common among people with respiratory diseases. As both chronic obstructive pulmonary disease (COPD) and asthma occur in unpredictable, life-threatening episodes, the concomitant presence of anxiety disorders is not surprising, and, in view of the increasing disability caused by COPD, it is also not surprising that depression is more common in such patients. The relation between common mental disorders and chronic respiratory conditions is bidirectional, complex and poorly understood. Pulmonary rehabilitation is a

multidisciplinary team approach to rehabilitating people with chronic respiratory disorders such as COPD and consists of physical training, occupational therapy, smoking cessation advice *and* psychological interventions.

*Severe mental disorders:* Smoking is much more common among people with severe mental disorder than the general population. Smoking is a major cause of COPD and exacerbates asthma. As COPD and asthma are more common among people with severe mental disorder, smoking is a significant factor in their increased rates of mortality and morbidity. The promotion and availability of appropriately tailored tobacco cessation programmes to people with a mental disorder will reduce the rate of smoking-related disease and related health outcomes.

### **Mental disorders and cancer**

*Common mental disorders:* A substantial proportion of people with cancer have a common mental disorder such as anxiety or depression. Evidenced-based approaches are available to identify people receiving palliative care who will benefit from treatment for depression and anxiety.

*Severe mental disorders:* Cancer may be more common among people with psychosis, but it is more likely to be due to lifestyle choices (e.g. smoking) than to the psychosis itself. People with a severe mental disorder are less likely to access health care services; therefore, if they have cancer, they are likely to present when the cancer is at a more advanced stage and have a poorer survival rate than people without a severe mental disorder. Improving access to health care and reducing discrimination for this group should therefore be priorities for health planners and managers.

### **Implications for health systems and services**

*Service delivery:* Addressing comorbidity due to mental disorders and major NCDs calls for an integrated, person-centred approach to the design, organization, management and improvement of health services. The principles and practice of such an approach are set out in a framework for action for integrated health services delivery published by the WHO Regional Office for Europe. Integrating services improves patient satisfaction, adherence to treatment and overall health outcomes. There is also good evidence that integration of services is cost-effective when done with a population-based approach. Several models have been proposed over the past 20 years or so for providing mental health care integrated into primary care and community care, including the collaborative care model, which has shown consistently good outcomes for patients. There is strong evidence for the effectiveness of collaborative care in the management of common mental health conditions. It should also be available for the management of these conditions when they occur with major NCDs.

*Human resource development:* Health workers often find it difficult to work in teams and in collaborative arrangements outside their specialties. An integrated, person-centred approach to the provision of services calls for a redefinition of health workforce competence. Primary care physicians and nurses should have the knowledge and skills to identify and manage common mental health conditions such as anxiety and depression, which occur frequently in people with CVD, cancer, diabetes and respiratory disorders. Equally, hospital health professionals should have the knowledge and skills to identify the presence of mental health conditions in people for whom they are managing a major NCD and to refer them for specialized care. Furthermore, mental health professionals should have the knowledge and skills to identify people who are at risk for an NCD such as diabetes, to ensure that they are referred to specialized care. Few current clinical guidelines explicitly include the identification and management of comorbid chronic health conditions, and this area also requires development and integration.



# 1. Introduction

The growing prevalence of comorbidity between mental disorders and major NCDs in the European Region is increasingly reflected in WHO policy documents endorsed by European Member States, such as the *European mental health action plan 2013–2020* (3) and the *Action plan for the prevention and control of noncommunicable diseases in the WHO European Region* (4). These plans include comorbidity and propose actions. The challenge now is to act.

The aim of this report is to contribute to better understanding of comorbidity and to provide evidence that can be used by policy-makers to promote a more integrated approach for managing individuals with comorbid conditions. The report proposes that clinical care packages be prepared and suggests some restructuring of the organization of care in order to deliver these packages. The report could also serve as a reference for training clinicians in managing patients with comorbidity, especially in primary care.

## 1.1 The burden of mental disorders and major noncommunicable diseases

Mental disorders are one of the greatest public health challenges in the European Region, from the point of view of prevalence, burden of disease and disability. Mental disorders, including depression, anxiety and schizophrenia, are the single largest cause of disability and early retirement in many countries and a major economic burden; policy action is therefore essential (4).

NCDs – mainly CVDs, cancers, chronic respiratory diseases and diabetes – are the most prevalent causes of death worldwide, and the European Region has the highest burden. Two disease groups, CVDs and cancer, cause almost three quarters of all deaths in the Region, and CVDs, cancer and mental disorders together are responsible for more than half the overall burden of disease (measured in terms of disability-adjusted life-years or DALYs) (4).

These already dramatic statistics do not take into account the importance of interactions between individual diseases or health conditions and their underlying risk factors. Mental disorders affect, and are in turn affected by, other NCDs: they can be a precursor or a consequence of an NCD such as CVD, diabetes or cancer. Risk factors for these diseases, such as sedentary behaviour and harmful use of alcohol, are also risk factors for mental disorders and strongly link the two. Despite these associations, such interactions and comorbidities are routinely overlooked (4). Premature mortality and disability could be reduced if there was a greater focus on comorbidity.

## 1.2 Political commitment to addressing the burden of mental disorders and major noncommunicable diseases

A number of WHO policy documents endorsed by WHO European Member States have recognized the burden of mental disorders and major noncommunicable diseases, the links that exist between physical and mental health and the importance of addressing them. These include:

- *Health 2020: the European policy framework for health and well-being* (5)
- *The European framework for action on integrated health services delivery: an overview* (1)
- *Priorities for health systems strengthening in the WHO European Region 2015–2020: walking the talk on people-centredness* (6)
- *Roadmap. Strengthening people-centred health systems in the WHO European Region: a framework for action towards coordinated/integrated health services delivery (CIHSD)* (7)
- *Global action plan for the prevention and control of noncommunicable diseases 2013–2020* (8)
- *Action plan for the prevention and control of noncommunicable diseases in the WHO European Region* (4)
- *Mental health action plan 2013–2020* (9)
- *The European mental health action plan 2013–2020* (3)

- *Making progress towards health workforce sustainability in the WHO European Region (10)*
- *Roadmap of actions to strengthen implementation of the WHO Framework Convention on Tobacco Control in the European Region 2015–2025: making tobacco a thing of the past (11)*
- *European action plan to reduce the harmful use of alcohol 2012–2020 (12)*

These policy documents state that health services should adapt to meet new needs. In the twenty-first century, this means putting NCDs, chronic conditions and multimorbidity at the top of the health policy agenda. Adapting and strengthening the competence of the health workforce is essential for moving forward, with new ways of working, training, planning, deploying and managing the health workforce. The policy documents also stress the importance of using effective, safe, evidence-based clinical interventions. The availability of relevant clinical guidelines will help health professionals to do so, and the best practices they describe are valuable to clinicians. Guidelines should take into account national differences in their approach to illness and disability and respond to the training needs of staff delivering both mental and physical health care.

### 1.3 Rationale and scope of the report

This report was written as a technical background document for two major WHO European regional action plans and as a technical briefing document for the European mental health action plan (3), specifically for its strategic objectives 4 – “People are entitled to respectful, safe and effective treatment” – and 5 – “Health systems provide good physical and mental health care for all”. It is also relevant for implementation of the WHO European action plan for the prevention and control of NCDs (4), which cross-references the mental health action plan throughout, particularly in its priority interventions on “Promoting active living and mobility”, “Cardio-metabolic risk assessment and management” and “Early detection and effective treatment of major NCDs”, as well as in its supporting interventions for “Promoting mental health” and “Promoting health within specific settings”.

The report addresses the relations between mental and physical health, specifically the needs of adults of working age with mental disorders, comprising both those with common mental disorders such as depression and anxiety and those with more severe conditions such as schizophrenia and bipolar affective disorder.<sup>1</sup> It also covers the needs of people with NCDs, specifically CVDs (like heart attacks and stroke), cancers, chronic respiratory diseases and diabetes. It does not include the mental health needs of children or young people or of older people with dementia.

The clinical evidence is reviewed and illustrated by clinical vignettes, which show the combined impact of mental and physical ill health on individuals. Several points are made. First, mental and physical health are closely bound and interrelated. This bond is frequently poorly understood; furthermore, the causality of the bond is bidirectional: people with mental disorders are more likely to have physical health disorders and vice versa. Secondly, people benefit from being managed as “whole individuals” and not separated into the medical and bureaucratic silos that have evolved to fit the structures of large health care providers.

The report targets public health specialists, clinicians and other health personnel – both those who deal with mental health and those who deal with physical health.

<sup>1</sup> In line with the global and also the regional mental health action plans, the term “mental disorder” is used throughout this report to denote a diagnosable disorder as determined by current disease classification systems. Other terms used regularly are “mental illness” and “mental health condition”.

## 2. Relations between mental disorder and major noncommunicable diseases

### 2.1 Diabetes

*Key facts:*

- 64 million people in the European Region live with diabetes, representing 5.2–13.3% of men and 3.3–14.2% of women in the Region (13).
- Tens of thousands of deaths are caused each year by diabetes, although 20% of cases of type 2 diabetes are preventable (13, 14).
- More than 80% of deaths from diabetes occur in low- and middle-income countries (14).
- WHO projects that diabetes will be the seventh leading cause of death in 2030 (15).
- A healthy diet, regular physical activity, maintaining a normal body weight and avoiding tobacco use can prevent or delay the onset of type 2 diabetes (16).

Diabetes is a chronic disease that occurs when the pancreas does not produce enough insulin or when the body cannot effectively use the insulin it produces (17). Hyperglycaemia is a common effect of uncontrolled diabetes and leads over time to serious damage to many of the body's systems, especially the nerves and blood vessels.

- Diabetes increases the risks for heart disease and stroke. In a multinational study, 50% of people with diabetes died of CVD (primarily heart disease and stroke) (18).
- Neuropathy in the feet combined with reduced blood flow increases the chance of foot ulcers, infection and eventually limb amputation.
- Diabetic retinopathy is an important cause of blindness due to long-term accumulated damage to the small blood vessels in the retina. Diabetes is responsible for 1% of global blindness (19).
- Diabetes is among the leading causes of kidney failure (16).
- The overall risk for death of people with diabetes is at least double that of people without diabetes (20).

#### **Diabetes and common mental disorders**

- Depression is two to three times more common in people with diabetes than in those without this disease (21) and more common among women (28%) than men (18%) (21, 22).
- The presence of depression was significantly associated with poor glycaemic control in people with either type 1 or type 2 diabetes (23).
- Over four years, depression was associated with persistently higher levels of glycated haemoglobin (HbA1c) (24).
- A systematic review of adherence to diabetic treatment showed a significant association between depression and non-adherence (25).
- A meta-analysis of studies of complications of diabetes found significantly more micro-vascular complications among patients who were also depressed (26).

WHO estimated in 2008 that, by 2030, diabetes would be the seventh most common cause of disability globally, responsible for 2.3% of all DALYs. Unipolar depression was estimated to be the most common cause of disability, representing 6.3% of all DALYs in 2030 (27).

Having diabetes may lead to depression, but depression may also be a risk factor for diabetes (28–30). Although hypotheses have been proposed to explain this bidirectional association, none has a solid foundation. Nevertheless, depression is

associated with a 60% increase in the risk for diabetes, and type 2 diabetes is associated with a 15% increase in the risk for depression (27).

A meta-analysis of 42 studies (21) indicated that having diabetes doubled the odds for comorbid depression. The prevalence of depression was significantly higher among women (28%) than men (11%) with diabetes and was much higher when estimated from self-administered questionnaires (31%) than from diagnostic interviews (11%).

When diabetes is well controlled, long-term complications are less likely. Control of diabetes is assessed by measuring blood glucose (most commonly in type 1 diabetes) or by measuring HbA1c, a lowering of which is often used to assess the effectiveness of medication for diabetes. Control of diabetes is poorer when comorbid depression is present. A meta-analysis of 24 studies (23) showed that the presence of depression was associated with poor glycaemic control. After four years, patients with both diabetes and depression had consistently higher HbA1c levels than those who were not depressed (24). People with both conditions had a 36–38% higher risk for death from any cause after two years (31).

It is less clear whether treating depression in patients with diabetes improves glycaemic control. None of three studies (32–34) of the effect of antidepressants on glycaemic control reported a significant improvement in HbA1c levels. A more recent meta-analysis of 14 randomized controlled trials (35) concluded that psychotherapeutic interventions with self-management of diabetes improved both depressive symptoms and glycaemic control, while antidepressant treatment alone (apart from sertraline) did not improve diabetes control. HbA1c was increased by 0.5%, indicating that the psychotherapeutic intervention was at least as effective as some diabetic medication.

Given the association between depression and diabetes, it is not surprising that a number of studies show increased use of health care facilities by patients with both conditions. In the United Kingdom in 2007, people considered to have the two conditions experienced more hospital admissions and more contacts with primary care physicians than people with only one of the conditions (36). In the USA, the risk of patients with the two conditions for admission to hospital was increased by 2.8 times over that of people with one of the conditions, and their stay was longer (37).

Le et al. (38) found that the cost of care was US\$ 1297 for people with only diabetes and US\$ 3264 for people who were also depressed; the overall health care costs were US\$ 4819 for people with only diabetes and US\$ 19 298 for those with both conditions. Other studies (39, 40) found that the costs for individuals with the two conditions were twice those of people who were not depressed and that they used more ambulatory care and had more prescriptions issued. Studies in the USA to assess the economic benefit of treating depression in people with diabetes (41, 42) showed both economic and clinical benefits. Caution should be exercised in assuming that similar savings could be made in countries with different systems of care.

### **Hannah's story**

*Presentation:* Hannah is a 48-year-old woman with type 2 diabetes. She presents to her primary care physician because she has had a cough and a cold and has been feeling tired for several months.

*Clinical background:* She has had type 2 diabetes for seven years, for which she takes metformin 500 mg twice daily. She has not seen her family doctor for about 15 months and has not had any of the checks for diabetes that her doctor recommends. She has no other illness and no drug sensitivity. Her doctor does not know her well. Her clinical record states that she is married with two children, that she doesn't smoke and that she works as an administrative assistant.

*The consultation:* The family doctor first assesses the presenting complaints – the cough and the cold – and learns that she has had the symptoms for five days and has no fever; her chest and throat are normal on examination. Before discussing her care, the doctor tells her that, in his opinion, she has a viral infection, that she will continue to improve and that she does not require a course of antibiotics. Hannah immediately looks crestfallen and insists that she must get better quickly as she must go to court the following week.

The doctor learns that Hannah's 18-year-old son is going to trial the following week and that she is very worried about what is going to happen to him. She was divorced some six months ago, and she is not receiving any financial support from her ex-husband. She is not sleeping, she cannot eat most of the time, and she is beginning to lose weight. Sometimes she binges on food and then feels guilty as she knows that this is problematic for her diabetes. Her employer is under financial pressure, and she fears that her job is at risk. She says that things are so difficult at present, that she has so many worries, so much pressure on her, that she feels that she just wants to "get away from it all".

*Clinical issues:* The family doctor is faced with a not-unusual problem: a simple presentation with a cough and cold has turned into something much more complex. The various issues are equally significant and must be addressed.

*Diabetes management:* Ideally, people with diabetes should be seen at least annually to check on their disorder, identify any complications and be offered advice and support. Hannah has not been to see a doctor or nurse for over 15 months and has not had any checks. Her diabetes control should be reviewed, damage to target organs checked by blood and urine tests and an examination undertaken, and this should be scheduled. The doctor expects the following:

- Hannah's diabetes is poorly controlled (23).
- She will require more hospital admissions and primary care contacts (36) and is at increased risk for early death (31) from any cause.
- She will require more medication for her diabetes (39, 40).

*Depression management:* Judging from Hannah's history so far, depression is a possible diagnosis, and the family doctor will have to decide whether to explore this possibility further at the present consultation or to schedule another appointment. The doctor has a number of issues to consider.

- What is the best way of making a diagnosis: history alone or administering a questionnaire to supplement the history?
- What would a diagnosis of depression mean to Hannah? Is there likely to be an issue of stigma? Would the diagnosis affect whether Hannah can access state funded benefits? Is the doctor allowed (by law) to make a mental health diagnosis?
- What treatment options are available? In some Member States, family doctors are not legally allowed to make a mental health diagnosis or to prescribe mental health drugs. In this case, antidepressants would not affect the control of diabetes, but cognitive behaviour therapy could improve both diabetic control and depression (35).

## Diabetes and severe mental disorders

- Diabetes is two to three times more common in people with a psychotic illness, schizophrenia or bipolar disorder (43).
- People with diabetes and a psychotic illness are more likely to die early than people with diabetes alone (43).
- Over 70% of people with severe mental disorder smoke, which significantly increases their risk for micro-vascular complications in diabetes. It has been estimated that smoking increases the risk for complications of diabetes by 14 times (44), including for CVD, kidney failure, blindness and erectile dysfunction.
- Over 21 million people worldwide suffer from schizophrenia (45) and a similar number from bipolar disorder. In Europe, schizophrenia and bipolar disorder together occur in about 2% of the total population (46).

Diabetes is more common among people with psychosis and schizophrenia, for three reasons: the effects of atypical antipsychotic medication, links between diabetes and schizophrenia and cultural and lifestyle factors. The relative importance of each cannot be distinguished; it is sufficient to acknowledge that they play a complicated, interrelated part in the increased prevalence of diabetes.

Second-generation and novel antipsychotic medication is well known to cause both obesity and diabetes (47, 48). A consensus statement in 2004 (49) presented considerable evidence of increased rates of obesity and diabetes in people on antipsychotic medication, although the authors recognized that not all second-generation drugs act in this way. Clozapine, olanzapine and risperidone were found to be particularly likely to cause significant weight gain, which may persist during the first year of treatment.

Although the possibility of a genetic link between some types of diabetes and schizophrenia remains an area of debate, there is some evidence of an association. Sir Henry Maudsley in 1897 wrote “The Pathology of the Mind”, in which he stated that “diabetes is a disease which often shows itself in families in which insanity prevails” (50). In 1919 (51) and 1952 (52), before the introduction of neuroleptic medication, it was reported that diabetes was more common among people with schizophrenia. A study in 2014 (53) found that a candidate gene for type 2 diabetes was a risk factor for schizophrenia, and there is some limited evidence that one type of maturity-onset diabetes in the young is associated with an increased risk for schizophrenia (54). With regard to cultural or lifestyle factors, people with schizophrenia are more likely to be unemployed and to be less well nourished; those who live in the community are more likely to eat cheap, high-calorie meals than a more balanced diet and are more likely to lead a sedentary life, thus disposing them to obesity and diabetes (55).

The provision of treatment for this group of patients presents considerable difficulties, as it can be complicated by their lack of insight and loss of initiative, sometimes associated with cognitive deficits. Glycaemic control may be poor and complications more common; complications are exacerbated by smoking, which is very common in this group of patients.

Few if any studies have addressed the quality of care for diabetes in this group; most have examined the increased prevalence. None has investigated the effectiveness of dedicated or specific interventions to improve glycaemic levels and reduce complications in people with schizophrenia. A recently introduced intervention for managing extreme obesity and poorly controlled diabetes is bariatric surgery. In 2012, Roux-en-Y gastric bypass surgery was shown to improve glycaemic control significantly, such that, two years after surgery, the diabetes of 75% of patients had resolved (56). While this intervention offers considerable benefits, there have been no published studies of use of bariatric surgery in people with schizophrenia or psychosis.

### **Amir’s story**

*Presentation:* Amir is a 38-year-old man with schizophrenia, who was asked to attend the family doctor by the practice nurse after Amir told her that he felt tired and thirsty all the time. She checked a urine sample and found that it was loaded with glucose.

*Clinical background:* Amir received a diagnosis of schizophrenia when he was 22 years old. Although his clinical records are not entirely clear, as he has moved quite frequently, he appears to be fit and healthy, apart from the schizophrenia. He went to the clinic relatively often for over 18 months to see the practice nurse for a number of self-limiting conditions and other physical health concerns, until five months previously, when he stopped attending. The few consultations before the gap in attendance were characterized by increasing confusion and generally chaotic behaviour, with shouting in the waiting room on several occasions.

The clinical record has no family history and does not state whether he smokes or works or whether his weight or blood pressure has been measured in the past 12 months.

*The consultation:* During the consultation, Amir is quiet, polite and apologetic for his previous behaviour. He explains that he had become increasingly unwell mentally and had been admitted to hospital five months previously. His psychiatrist recently changed his medication to clozapine, and he feels much more settled and comfortable on this new treatment. He has been home for two weeks and noticed that he was much more tired than previously and was drinking all the time. He mentioned this to his psychiatrist, who recommended that he see his family doctor.

The family doctor focuses on the combination of thirst and tiredness, which are cardinal symptoms of diabetes. Amir tells the doctor that both his father and his mother had type 2 diabetes and that his father died of a heart attack at the age of 55 years. Amir also tells the doctor that he has put on a lot of weight recently, from 91 kg (calculated body mass index, 33) to over 122 kg (calculated body mass index, 44). He believes the weight gain is due to his rehabilitation programme; before discharge, he was allowed out to buy meals from take-away restaurants, rather than eating on the ward. He admits that on trips off the ward he took the opportunity to buy cigarettes for his friends and started smoking himself. He currently smokes 20 cigarettes per day.

*Clinical issues:* This is a complicated picture, with several competing priorities. Confirming the diagnosis of diabetes is central to the consultation, but understanding how the diagnosis of schizophrenia can affect the diagnosis and management of diabetes is essential to treating Amir as “a whole person”.

*Management of diabetes:* The major clinical issue facing the family doctor is to confirm the diagnosis of diabetes.

- Diagnosing diabetes in people taking antipsychotic medication: WHO guidelines on the management of diabetes state that HbA1c can be used to diagnose most cases of diabetes but not in a small number of cases when the diabetes is of recent onset, especially if associated with antipsychotic medication, as in the case of Amir. Therefore, it would be inappropriate to use elevated HbA1c to diagnose diabetes (a normal value would be considered a “false negative”), and the fasting blood glucose level would be more accurate.
- Diabetes education: Amir should be given information on diabetes and how it is managed. A common misconception is that all patients with diabetes are treated by injections of insulin, while many people with schizophrenia who have been given injections of antipsychotic medication, sometimes against their will, are likely to refuse another injection. It is important to ensure that Amir understands that most patients can be treated by behaviour change and oral medication.
- Behaviour change: The importance of weight loss, diet and exercise cannot be overemphasized at this stage. Every effort should be made to support Amir in losing weight by adopting sensible eating habits and more exercise. Community programmes and access to a dietician and to exercise facilities are necessary to support him as he tries to change his behaviour. The likelihood that Amir is unemployed and depends on state benefits in view of his mental disorder increases the risk that he will find it difficult to adhere to a healthy diet and will resort to cheap, high-calorie meals. The consequence will be poorly controlled diabetes and the development of complications.
- Smoking cessation: Another important aim for Amir is to reduce and then stop smoking. Smoking significantly adversely affects diabetes and increases the risk for complications, such as kidney failure, blindness, impotence, nerve damage and high blood pressure. It is significant that Amir’s father died before the age of 60 years of a heart attack, as this is a further independent predictor of CVD. The combination of smoking, diabetes and a family history of CVD make Amir’s outlook poor, unless there are significant improvements in his lifestyle.

After the consultation, the family doctor will decide how best to inform the psychiatrist of the new diagnosis. Such communication will depend on local circumstances and local agreements.

## Conclusions

- The relation between diabetes and depression is bidirectional: people with diabetes are more likely to develop depression, and depression is a risk factor for diabetes.
- People with diabetes should have regular checks to assess whether they are developing depression.
- Health care staff who provide diabetic care should be able to identify people who are depressed and know how either to manage depression or to refer patients to appropriately trained and resourced health care professionals.
- Diabetes is more common among people with a severe mental disorder.

- Models of integrated care for people with a severe mental disorder and diabetes should be developed and evaluated.
- The role of antipsychotic medication in triggering diabetes should be further evaluated.
- Health care staff who provide care to people with a severe mental disorder should understand the clinical features of diabetes and be able to identify potential life-threatening episodes.
- Population-level interventions and health-promoting environments and settings can support healthy behaviour.

## 2.2 Cardiovascular disease

*Key facts (57):*

- CVD causes more than half of all deaths in the WHO European Region.
- CVD causes 46 times more deaths and 11 times more of the disease burden than AIDS, tuberculosis and malaria combined in Europe.
- Up to 80% of premature deaths from heart disease and stroke are preventable.
- Up to 20% of people with CVD suffer from depression.
- The presence of depression and/or anxiety at least doubles the risk for a poor outcome after a cardiac event.
- The cost of treating patients with depression and heart failure is double that of treating people with heart failure who are not depressed.
- People with severe mental disorder die 15–20 years earlier than the general population, most commonly from CVD.
- The risk of a person with a severe mental disorder for a heart attack or a stroke is at least double that of the general population, and the risk of a long stay as an inpatient is tripled.

CVDs are disorders of the heart and blood vessels that include:

- coronary heart disease: disease of the blood vessels that supply the heart muscle;
- cerebrovascular disease: disease of the blood vessels that supply the brain;
- peripheral arterial disease: disease of blood vessels that supply the arms and legs;
- rheumatic heart disease: damage to the heart muscle and heart valves by rheumatic fever, caused by streptococcal bacteria;
- congenital heart disease: malformations of the heart structure found at birth; and
- deep vein thrombosis and pulmonary embolism: blood clots in the leg veins, which can dislodge and move to the heart and lungs.

Heart attacks and strokes are usually acute events caused mainly by a blockage that prevents blood from flowing to the heart or brain. The most common cause is a build-up of fatty deposits on the inner walls of the blood vessels that supply the heart or brain. Strokes may also be due to bleeding from a blood vessel in the brain or from blood clots.

### **Risk factors for CVD**

The cause of a heart attack or a stroke is usually a combination of risk factors, such as tobacco use, an unhealthy diet and obesity, physical inactivity, harmful use of alcohol, hypertension, diabetes and hyperlipidaemia. These risk factors are described as “behavioural”, i.e. behaviour indirectly increases blood pressure and weight, which may increase the levels of glucose and lipids (fat) in the blood. The cumulative effect of these behavioural risk factors on individuals can be measured in primary care and estimated as the risk of the individual for a heart attack or stroke in the future. As well as individual behaviour, changes occur in society, associated with increasing age, urbanization and poverty, all of which increase the risk for CVDs. The changes associated with poverty and urbanization are particularly marked for people with a severe mental disorder, so that this group is at greatest risk for CVD.

All the risks can be reduced: through smoking cessation, increasing physical activity, eating healthily and drinking less alcohol, although to reduce the overall effects on CVD it may be necessary to supplement behavioural changes with medication. People with a mental disorder, however, may find addition of the pressure of behavioural change to the existing burden of mental disorder almost unbearable; their burden may be exacerbated by poverty and unemployment, which are more common among people with mental disorders.

Interventions to reduce the risk for CVD may be population-based or individual. Population-based changes to reduce the risk include comprehensive tobacco control policies; taxation to reduce the intake of foods that are high in fat, sugar and salt; building walking and cycle paths to increase physical activity; strategies to reduce harmful use of alcohol; and providing healthy meals to schoolchildren. Primary prevention of CVD in individuals can best be implemented by focusing on those at high risk, who can be identified by one of several “cardiovascular risk calculators”. Secondary prevention of CVD in people with established disease, including diabetes, includes treatment with aspirin, beta-blockers, angiotensin-converting enzyme inhibitors and statins. The benefits of primary and secondary interventions are largely independent, but, when they are accompanied by smoking cessation, nearly 75% of recurrent vascular events can be prevented. Currently, these interventions are not widely used, particularly in primary health care.

### **CVD and common mental disorders**

Guidelines have been published on the association between mental disorders and CVD (58). In a number of systematic reviews and meta-analyses (59–63), the authors concluded that depression predicts coronary heart disease and worsens its prognosis. Depression increases the risk for coronary heart disease by 1.6–1.9 times over that of the general population and increases the risk for a poor outcome by 2.4 times. In two meta-analyses (64, 65), anxiety disorders were found to be an independent risk factor for coronary heart disease and for adverse events after myocardial infarction. Similarly, depression increased the risk for coronary heart disease by 1.3 times and the risk of a poor outcome by 1.7 times.

The reasons for the associations between depression, anxiety and CVD have been examined in models. For example, two studies (66, 67) attempted to determine whether the thickness of the intima media layer in the wall of the carotid artery was linked to depression and the development of CVD. The thickness of this layer is used as a marker of atherosclerosis, which is the underlying pathological mechanism of CVD. Some data support the premise that depression is an inflammatory condition, which might be responsible for atherosclerosis in people with depression. A further study (68) provided some evidence for an immunological basis of the association between depression and CVD, which might explain the common inflammatory processes in the two conditions.

While a number of theories have been proposed, there is no consensus on the reason for the close association between depression and CVD. Other theories that have been proposed include the possible cardiotoxicity of antidepressants, excess smoking by people with a common mental disorder and the fact that people with depression are less likely to adhere to cardiac prevention and treatment regimens. Nevertheless, even when other confounding factors have been factored in, there still remains a clear association between common mental disorders and CVD (69).

A review of studies of the value of screening people with cardiac disorders for depression (70) indicated that, while people with depressive symptoms responded moderately well to either antidepressant medication or cognitive behaviour therapy (standard interventions for depression), cardiac outcomes were not improved. The standard treatment for depression is effective and safe in the management of depression co-existing with CVD (71–76). Lack of evidence that treating depression or anxiety improves cardiac outcomes should not obviate appropriate, evidence-based treatment for common mental disorders.

The economic impact of comorbidity with common mental disorders and CVD can be measured from either health service use or health service costs. Depression is associated with increased re-hospitalization rates of patients with CVD (77), and the rates of patients with depression and heart failure are two to three times higher than those without depression (78). Data on health service costs are available from a number of insurance companies in the USA. One study (79) showed that people with coronary artery disease or congestive cardiac failure have twice the costs of health care (excluding mental health treatment and medication) when they are also depressed. The extra costs are explained by poorer outcomes, more frequent attendance

at outpatient clinics, longer and more frequent hospitalization and more medication prescribed for the cardiovascular condition.

### **Gerald's story**

*Presentation:* Gerald is a 57-year-old man who goes to see the family doctor because he has central chest pain when walking up a flight of stairs.

*Clinical background:* Gerald is well known to the family doctor as has attended often over the past 10 years or so. He used to be a bank manager, but, after the global financial recession, he lost his job and became depressed. He has had three separate episodes of depression in the past 10 years; the first two responded to cognitive behaviour therapy, while the third required both behaviour therapy and antidepressant medication.

Gerald is unhappily married, smokes 10–15 cigarettes per day (he says he is trying to cut down) and is overweight (body mass index, 37; he says he is trying to eat healthily). He has been unemployed since he was made redundant 10 years ago, which contributes to his depressive episodes. Neither his blood pressure nor his cholesterol level has been recorded in the past 18 months but were previously at the upper end of normal.

*The consultation:* Gerald describes typical cardiac pain precipitated by exercise: central chest pain of a crushing quality radiating to his neck and left arm, brought on by exercise and relieved by rest. The pain started some three months previously but is getting worse and is now associated with shortness of breath. Gerald fears that he is having a heart attack and that he might die. He says that he wouldn't mind dying, as he has nothing to live for: he has no job, his marriage is poor, his children don't visit him, and he has no hobbies.

The family doctor examines Gerald, and finds that his blood pressure is elevated but there are no other significant findings apart from obesity. He discusses his findings with Gerald and arranges referral to a cardiologist for further investigation and referral to a psychiatrist for assessment of his depression.

*Clinical issues:* From a clinical perspective, the issues are fairly straightforward. This is a depressed man with significant CVD. Treatment can improve both conditions. The family doctor would, however, do well to expect difficulties: depression predicts coronary heart disease and a worse prognosis (59–63). Gerald is 2.4 times more likely to have a worse outcome than similar people without depression.

The clinical conundrum is what preventive measures the family doctor could have put in place to prevent the development of CVD. The evidence (70) suggests that screening people with cardiological disease for depression or anxiety does not influence cardiac outcomes; in Gerald's case, therefore, there would be little value in screening for depression after he developed angina, as it would be unlikely to improve his condition. Treating depression is, however, worthwhile, as it would improve Gerald's quality of life. Some European countries offer physical health checks and cardiovascular risk assessments to people over the age of 40 years. Whether this approach would have been successful in a case such as Gerald's is unclear, as uptake of these health checks is often poor. In countries where such checks are offered routinely, one preventive action could be to follow up Gerald's non-response to previous invitations to attend screening.

There is no evidence that early intervention for people with depression will prevent CVD. Nevertheless, it would be good practice to encourage people who are depressed not to smoke and to lose weight – because both are significant risk factors for cardiac disease and for mental health disorders. Gerald could be encouraged to stop smoking and referred to a smoking cessation service and advised to lose weight by taking more exercise; there is good evidence that exercise is effective in managing mild depression, although evidence that it prevents recurrence is limited. People with more severe depression may lack the motivation to start exercising, as they find behaviour change more complex and more difficult to initiate (80).

## **CVD and severe mental disorders**

The relation between CVD and severe mental disorder is particularly complex. People with severe mental disorders die 15–20 years earlier than those without (47, 81), and the commonest cause of death is CVD (82). Separating the elements that are responsible for these poor clinical outcomes is, however, difficult. The important elements include modifiable cardiovascular risk factors, antipsychotic medication and social determinants, although the relative contribution of each of these elements to increased mortality rates from cardiac disease cannot be quantified.

There are several well-recognized risk factors for CVD in people with a severe mental disorder. They are more likely to be overweight (see section 2.1), more likely to smoke (see section 2.3), more likely to have diabetes (see section 2.1) and more likely to have dyslipidaemia (see section 2.1). Other risk factors that should be considered in this group of patients are erectile dysfunction and hyper-prolactinaemia secondary to antipsychotic medication (83, 84) and chronic kidney disease secondary to lithium prophylaxis (85). These independent risk factors for CVD are a consequence of treatment prescribed for psychosis that significantly affects cardiovascular risk.

A study in the United Kingdom of the acceptability of screening for cardiovascular risk among people with psychosis in the community (86) showed that “interest in the risk assessment was greater than we had assumed”. Participation in the study was similar to that in other community studies. This study and another (87) indicate that contact with primary care services provides an opportunity to offer cardiovascular risk assessment and appropriate evidence-based interventions.

Cardiovascular risk can be calculated from algorithms for predicting the risk of an individual for a heart attack or stroke and/or dying from one (depending on which tool is used) in the subsequent 10 years. This is important, because many people have mild increases in several risk factors that, in combination, could result in an unexpectedly high total cardiovascular risk. The value of such predictions is to help communicate risk, so that patients can receive advice (and treatment if necessary) appropriate to their risk level.

Many cardiovascular risk prediction tools are used internationally, and some countries have produced their own. They differ in how they are derived, the risk factors they include and what they predict. For example, the WHO risk prediction charts (88) indicate the 10-year risk for a fatal or nonfatal major cardiovascular event (myocardial infarction or stroke) according to age, sex, blood pressure, smoking status, total blood cholesterol and presence or absence of diabetes mellitus, whereas the European Society of Cardiology (89) provides a risk assessment algorithm, SCORE, which predicts the risk for fatal events only according to age, sex, blood pressure, smoking status and total blood cholesterol. In the United Kingdom, a prediction tool called QRISK2 is used (90), which can also identify inequalities in the care of patients with coronary heart disease and severe mental disorder (91). The score was used in a study of patients in the three high-security forensic mental health hospitals in the United Kingdom (92), which showed that people with a severe mental disorder are less likely to have blood tests for lipids and that, if statins are clinically indicated, they are less likely to be prescribed for them than the general population. In these studies, a QRISK2 score > 20% (considered at the time of publication to be a high risk for a heart attack) was found for 1.7% of the general population, 4% of people with a severe mental disorder in the community and around 6% of people in the three high-security forensic hospitals.

### *Antipsychotic medication*

Second-generation antipsychotic medication is well known to be associated with a risk for induced metabolic syndrome (93). “Metabolic syndrome” is a term used to describe a number of clinical and biochemical abnormalities that frequently appear together and predict CVD (94). The abnormalities include insulin resistance, obesity (visceral adiposity), diabetes, hypertension and dyslipidaemia.

In order to distinguish whether the excess cardiovascular risk associated with severe mental disorder is due solely to antipsychotic medication or whether other factors are involved, a study was conducted to compare the development of metabolic syndrome in people with a first episode schizophrenia and people with chronic schizophrenia (95). The overall cardiovascular risk was lower in people with a first episode and similar to that of people with schizophrenia who had not yet taken any medication. The prevalence of diabetes and pre-diabetes was also similar in the two groups and much lower

than in the group that had been taking antipsychotic medication for some time. This medication therefore appears to play a significant role in the development of CVD.

Antipsychotic medication has two other important cardiovascular side-effects. It influences the electrical current that coordinates each contraction of the heart, placing the heart at greater risk for a fatal irregular rhythm (96). This so-called “torsades de pointes” can be recognized in the early stages by changes in the electrocardiogram characterized by an increase in the time between the QRS complex and the T wave, the QT interval. As it increases, it increases the risk for fatal cardiac arrhythmia.

The other complication of antipsychotic medication is an increase in the incidence of venous thromboembolism (blood clots in the veins) (97). Venous thromboembolism causes both deep vein thrombosis (blood clots in the deep veins of the calves) and pulmonary embolism (blood clots in the vessels of the lungs); the latter may be fatal. In a large primary care population, an association was found between the use of second-generation antipsychotics and the development of venous thromboembolism, and the effect was particularly marked in people who had recently started the medication. The effects are exacerbated by smoking. One study showed that people with a first episode of psychosis smoked frequently (95).

### *Social determinants*

People with a severe mental disorder less often access health care services or take up offers of cardiovascular prevention and screening programmes than other people (47, 81, 82, 98, 99). Contact with health care and access to services can, however, be improved by organizing specific clinics and a flexible primary care approach (86, 87).

A recent meta-analysis of studies of the causes of death of people with schizophrenia (100) showed that the standardized mortality rate from all causes increased from 1.84 in the 1970s to 2.98 in the 1980s and 3.20 in the 1990s, i.e the rate of death increased from 1.84 times higher than that of the general population to 3.20 times higher. The commonest cause of the increasing mortality rate is CVD. It is probable that the reduction in mortality in the general population as a result of healthier lifestyles is not reflected in groups of people with mental disorders.

### *Smoking*

Section 2.3 of this report describes the effect of smoking on the development of disorders such as chronic obstructive pulmonary disease and on overall mortality. Smoking also significantly contributes to the development of CVD (101, 102). The effect on CVD is separate from that on respiratory disease and is therefore additive.

Section 2.1 of this report discusses the consequences of smoking on diabetes management and the impact of poor diabetic control on cardiovascular disorders and vice versa. For example, chronic kidney disease can complicate the management of diabetes and is itself a risk factor for CVD. Chronic kidney disease and poor renal function can, separately, be a consequence of CVD, particularly hypertension.

The interplay among these various conditions is complex, posing particular difficulties for effective management of each condition; the addition of smoking exacerbates an already complicated clinical picture. It is the summative aspect of complex NCDs, smoking and social determinants that results in such poor outcomes and increases mortality rates among people with severe mental disorder.

### **Amir's story**

*Presentation:* Amir's story is outlined in section 2.1. During the first review after the diagnosis of diabetes some months previously, routine blood tests were conducted before an appointment to see the practice nurse to discuss aspects of his diabetes management.

*Clinical background:* Amir is well known to the family doctor, and his care has been quite complex. He was discharged from a mental health unit following a five-month admission, during which his medication was changed to clozapine. As a consequence, his weight increased, and, partly due to his family history (both his parents had type 2 diabetes), he developed fatigue and thirst two weeks after discharge, and type 2 diabetes was diagnosed.

*The consultation:* The doctor and Amir review his blood tests and find that HbA1c has continued to rise despite Amir's best efforts to lose weight; the level falls into the "poor" control category. The blood tests also show that his cholesterol is > 6.00 mmol/L, with a high level of low-density lipoprotein cholesterol, and that his renal function is less than optimum. His prolactin is elevated, secondary to the clozapine medication. His blood pressure is also elevated, at 150/95 mm Hg. Measurements taken by the practice nurse give similar results.

The doctor discusses these results with Amir and describes metabolic syndrome (93) to explain what is happening to him. The doctor and Amir discuss what should be done next to reduce the risks associated with metabolic syndrome.

*Clinical issues:* The family doctor is faced with a relatively young man with several chronic disorders that are acting together to significantly increase his risk for early death.

- Cardiovascular risk score: The probable risk for a heart attack or a stroke within the next 10 years can be estimated from the WHO risk score chart for patients with diabetes or national scores, if they exist. From Amir's data, the likelihood of a heart attack or stroke within the next 10 years is 27%, whereas the risk of a man of Amir's age (with the same family history and the same smoking history) without diabetes, obesity, dyslipidaemia or hypertension would be 4.5%. The same chart can be used to explain to Amir that his "heart age" is equivalent to that of a 65-year-old man. This approach is often more effective for explaining relative risk than "percentage risk" scores. Whichever method is used to calculate risk, the message is clear: Amir is at high risk for early death from CVD.
- The commonest cause of death among people with severe mental illness is CVD: they die 25–30 years earlier than people without a severe mental illness
- Balancing mental and physical health: The family doctor may consider what would happen if clozapine were stopped. The balance between supporting his mental health needs while ensuring that his diabetes and blood pressure are well controlled is a therapeutic dilemma. The potential interactions, side-effects and poor adherence of a person taking four, five or more different medications make this a very complicated clinical picture (103).

## Conclusions

- Depression and anxiety predict the development of CVD and worsen its prognosis.
- There is no evidence that screening for or treating depression and anxiety improves cardiovascular outcomes. For example, screening for and treating depression will not prevent a heart attack.
- The commonest cause of death among people with severe mental disorder such as schizophrenia and bipolar disorder is CVD.
- Identifying and managing modifiable risk factors for CVD in people with a severe mental disorder will reduce their risk for premature mortality.
- Discrimination against people with severe mental disorder prevents them from accessing services and increases their risk for premature death and disability from CVD. Addressing discrimination should therefore be a priority.
- The risk of every person with a severe mental disorder for a cardiovascular event should be measured annually with a recognized risk algorithm.
- The combination of several NCDs, such as diabetes, hypertension and CVD, and the presence of a severe mental disorder requires integrated by specialists in mental and physical health.
- Population-level interventions and health-promoting environments and settings can support healthy behaviour.

## 2.3 Chronic respiratory diseases

*Key facts (104):*

*Definition:* Chronic respiratory diseases are chronic diseases of the airways and other structures of the lung. Some of the most common are asthma, COPD, respiratory allergies, occupational lung diseases and pulmonary hypertension.

*Main risk factors:* tobacco smoking, indoor air pollution, outdoor pollution, allergens, occupational risks and vulnerability

*Other facts (105):*

- According to the WHO global status report on NCDs in 2010 (16), smoking is estimated to cause about 71% of all lung cancer deaths and 42% cases of chronic respiratory disease worldwide. Of the six WHO regions, the European Region had the highest overall prevalence of smoking in 2008, estimated to be nearly 29%.
- According to data for 1997–2006, over 12% of infant deaths in the Region were due to respiratory diseases. In general, the rates were considerably higher in eastern than in western Europe.
- Ozone pollution causes breathing difficulties, triggers asthma symptoms, causes lung and heart diseases and is associated with about 21 000 premature deaths per year in 25 countries in the WHO European Region.
- Most countries in the Region have introduced a wide range of comprehensive policies to reduce and eliminate tobacco smoking. For example, advertising of cigarettes and the sale of tobacco products to minors have been banned in more than 80% of the countries in the Region. Smoking in restaurants and bars continues to be regulated less strictly; Ireland, Turkey and the United Kingdom are the first countries to make public places 100% smoke free.

### Smoking and mental health

*Key facts (106):*

- One in three of all cigarettes smoked is smoked by a person with a mental disorder.
- While smoking in the general population has fallen by 25% in the past two decades, there has been no similar decrease in smoking among people with mental disorders.
- People with long-term mental health problems who wish to quit smoking are more likely to expect to fail than the general population.

Smoking is more prevalent among people with mental disorders than those without (107). In a survey of the general population of the United Kingdom by the Royal Colleges of Psychiatry and Physicians (106), 20% of the general population smoked, while 37% of the 4% of the total population who reported long-standing mental health problems smoked. The two Royal Colleges also analysed the computer records of primary care for over 2 million patients, which provided information on the relations between smoking and psychiatric diagnosis and between smoking and the use of psychotropic medication, which showed that the groups most likely to smoke are young (16–25 years), have a long-standing mental disorder such as schizophrenia or are in a lower socio-economic group.

The survey also addressed people in institutions, such as forensic mental health hospitals and prisons. In both these population groups, the prevalence of smoking was much higher, at about 80%. The survey also asked respondents about quitting smoking: 66% of the general population, 61% of those with a long-term mental disorder and 71% of those taking psychotropic medication wished to quit smoking; 55% of the general population and 79% of those with a long-term mental disorder expected to find it difficult to stop tobacco use for 24 h. Clinical experience of smoking cessation by people with long-term mental disorders indicates that the expectation of failure is very high, despite a desire to quit (106).

### Asthma

*Key facts:*

- Asthma is a major NCD. It is a chronic disease of the air passages of the lungs, which inflames and narrows them.

- Some 235 million people currently suffer from asthma. It is a common disease among children.
- Most asthma-related deaths occur in low- and lower–middle-income countries.
- The strongest risk factors for asthma are inhaled substances and particles that may provoke allergic reactions or irritate the airways.
- Medication can control asthma, and avoiding “triggers” can reduce the severity of asthma.
- Appropriate management of asthma can enable people to have a good quality of life.

## **COPD**

### *Key facts:*

- COPD is a life-threatening lung disease that interferes with normal breathing; it is more than a “smoker’s cough”.
- More than 3 million people died of COPD in 2012, equivalent to 6% of all deaths globally that year.
- More than 90% of COPD deaths occur in low- and middle-income countries.
- The primary cause of COPD is tobacco smoke (through tobacco use or second-hand smoke).
- The disease now affects men and women almost equally, due in part to increased tobacco use by women in high-income countries.
- COPD is not curable, but treatment can slow the progress of the disease and improve the quality of life.

## **Respiratory diseases and common mental disorders**

Although asthma and COPD are different disorders, numerous studies and reviews (107–111) demonstrate that anxiety and depression are more common in patients with these conditions: 10–40% also suffer from anxiety and/or depression.

The prevalence of depression increases with the severity of COPD (112) and has been estimated to be 2.5 times greater than that in controls (113), with a higher likelihood of exacerbation (114) and poorer survival outcomes (115). People with COPD are also more likely to have symptoms of anxiety: 10–19% of people with stable COPD and up to 58% of those recovering from acute exacerbation of COPD experience such symptoms (116).

The prevalence of a number of different forms of anxiety is higher in people with asthma than in those without asthma. Agoraphobia is found at the rate of 13%, as compared to 2.8% in the general population, and panic disorder occurs at rate of about 6.5% in people with asthma and in 2.3% of the general population (117). In a study in Germany, generalized anxiety disorder was four times more likely in people with current severe asthma than in controls (118).

One of the major symptoms of anxiety in people with COPD and asthma is hyperventilation, which can exacerbate the symptoms of these respiratory conditions. For example, inhaling cold air can significantly affect the highly sensitive airways of asthma patients, causing broncho-constriction, worsening the respiratory effects. Patients with respiratory conditions who are distressed by shortness of breath are advised to use an inhaler; however, many inhalers contain beta-adrenergic agonists such as salbutamol, one effect of which is to increase the pulse rate, which can exacerbate symptoms of stress or anxiety.

As both COPD and asthma occur in unpredictable, life-threatening episodes, the concomitant presence of anxiety disorders is not surprising. In view of the increasing disability caused by COPD in particular, it is also not surprising that depression is more common in such patients. A number of theories have been proposed to explain why anxiety and depression are more common in people with asthma or COPD. Some are psychological, e.g. the dyspnoea–fear theory attributed to the somatic effects of hyperventilation (119), while others are physical, e.g. the presence of abnormally sensitive carbon dioxide receptors in the central nervous system, which act as abnormal “suffocation detectors” (120). As is the case for diabetes and depression, most authors concur on two aspects: mental disorders are more common in people with chronic respiratory conditions, and the cause of this increased prevalence is complex, poorly understood and bidirectional.

## Management of respiratory diseases and comorbid mental disorders

### *Integrated treatment*

A cornerstone of treatment of COPD is pulmonary rehabilitation, which has been shown to have a significant effect on well-being and quality of life (121). Pulmonary rehabilitation is a multi-disciplinary team approach to rehabilitation for people with chronic respiratory disorders such as COPD and consists of physical training, occupational therapy, smoking cessation advice and psychological interventions (122). All these components must be present for a rehabilitation programme to be effective. A Cochrane review of studies of psychological interventions for people with asthma found that, although only a few studies were adequate, cognitive behaviour therapy improved the quality of life and reduced anxiety (123).

### *Medication*

While psychological treatment has been shown to be helpful in managing people with chronic respiratory disease, medication can increase the symptoms of anxiety. The beta-adrenergic agonist group of drugs are a mainstay of treatment in both COPD and asthma. They act on the airways to mimic the effect of adrenaline, expanding the airways and easing the symptoms of breathlessness. The side-effects of these medications, however, include exacerbation of the symptoms of anxiety, with sweating, palpitations and tachycardia. The effects on individuals can be confusing for both patients and doctors, as it may be difficult to distinguish between shortness of breath, hyperventilation and panic due to exacerbation of the respiratory disease, to anxiety and to the medication taken to relieve the symptoms.

Chronic respiratory disease is a frequent reason for admission to hospital and in some countries is the leading cause of emergency admissions (124). Significant costs are associated with hospital admission, and estimates have been made of the savings that could be made with psychological interventions in the management of chronic respiratory disease. In the United Kingdom, the hospital admissions and duration of stay of patients with end-stage COPD who were offered cognitive behaviour therapy were significantly reduced, with 1.2 fewer presentations to accident and emergency departments and 1.9 fewer days of hospitalization than a group that did not receive the therapy (125).

### **John's story**

*Presentation:* John is a 62-year-old man who visits his family doctor because he has been coughing frequently over the past two weeks, producing green sputum.

*Clinical background:* John is well known to the family doctor, as he suffers from COPD, and his condition is deteriorating. Three years ago, John was admitted only once to hospital for an acute chest infection, whereas this year he has been admitted three times. He continues to smoke 20 cigarettes per day. He is a widower, his wife having died 18 months previously from breast cancer. He has no children, and, since his wife died, he has become more reclusive. He has had numerous contacts with the practice during the past 18 months, mostly for conditions related to deteriorating lung function and COPD.

*The consultation:* John greets his doctor with a wry smile and says that he thinks he should go into hospital again, as he is producing green sputum. The family doctor takes a detailed history and examines John to assess whether he should be admitted. The history reveals that John has been producing green sputum for only a couple of days, has no fever but is coughing a bit more than usual. He has no other new symptoms. The examination is also relatively unremarkable; his chest is quiet when examined, there are no signs of infection, simple spirometry tests show no change from previous examinations, and the amount of oxygen in his blood (measured with a pulse oximeter) is normal.

When the family doctor tells John that he does not need hospital admission as he is physically quite well, John becomes very distressed. He says that the doctor doesn't understand, that he gets worse at night, has bouts of coughing that make him choke and becomes frightened that he will never catch his breath again. The inhalers that the doctor has prescribed just make his heart beat faster. The only place that he feels safe, he insists, is in hospital, and he must be admitted now.

*Clinical issues:* The issue for the family doctor is not a new one; clinical experience suggests that John is anxious rather than having a chest infection severe enough to warrant admission to hospital. Primary care clinicians act as gatekeepers to secondary care services. In this case, the family doctor must make the difficult decision of whether to refer this man to hospital. If John is admitted, even though this is not indicated clinically, scarce hospital resources will be used inappropriately (125). John will assume that, whenever he becomes anxious, the most effective treatment is admission to the respiratory unit in the local hospital. Admission to a respiratory unit is not a treatment for anxiety. The family doctor must offer an alternative to John for managing his anxiety while acknowledging his significant respiratory condition. That alternative might be the evidenced-based intervention of pulmonary rehabilitation, consisting of physical training, smoking cessation services, psychological services and occupational therapy (122).

### **Respiratory diseases and severe mental disorders**

In a study in the USA in 2004, the rate of COPD was 22.6% among people with a severe mental disorder and around 5% in the general population. The rate of smoking among the patients was 60%, partly explaining the increased prevalence of COPD (126).

A large study in Sweden in 2013 of comorbid conditions found that people with schizophrenia attending outpatient clinics or admitted as inpatients were twice as likely to suffer from COPD as people without schizophrenia. The most common causes of death were respiratory conditions such as pneumonia and COPD (127).

People with a severe mental disorder in the community smoke about 10% more than the general population, and those in institutions smoke 70–80% more. The combination of high levels of smoking and other health complications partly explains the disparity in life expectancy for this group of people, who die 25 years earlier than they would have done without a severe mental disorder. The combination of a mental disorder, smoking, diabetes or a CVD puts them at very high risk.

### **Smoking and antipsychotic medication**

Nicotine increases the rate at which some antipsychotic drugs are metabolized (106), so that smokers require higher doses of the medication to achieve the same response. Clozapine is used as a second-line drug for people whose psychosis has not responded to previous medication, and special reporting is required because of its side-effects. It has been estimated that the dosage of clozapine must be reduced by 25% when a patient stops smoking to avoid blood levels shooting up to toxic levels (128).

A study in the USA to address the concern that patients who stopped smoking would experience exacerbation of their psychotic symptoms showed that this was not the case (129). Another concern was that violence in forensic mental health services might increase when patients quit smoking; however, no increase in violent episodes and no deterioration in mental states was found when the three high-security forensic mental health hospitals in the United Kingdom became smoke-free in 2008 (130).

Studies specifically of the needs of people with severe mental disorder who stop smoking showed that programmes tailored to their needs are effective; the rates of uptake by patients are similar to those without a mental disorder, and, with appropriate support, similar outcomes are achievable (131).

A study to address the question of whether varenicline, a medication used to support smoking cessation, can be used in people with mental disorder found that it is both safe and effective for this group; suicide rates were not increased (132).

As COPD and asthma are more common among people with a severe mental disorder, smoking is a significant factor in their increased rates of mortality and morbidity. Appropriately tailored smoking cessation advice is effective and does not exacerbate mental disorder.

### **Amir's story**

*Presentation:* Amir's story is outlined in section 2.1. He is a 38-year-old man with schizophrenia, who comes to see his family doctor because he feels unwell, shaky, tired and confused.

*Clinical background:* Three months previously, Amir was discharged from hospital after his medication was changed to clozapine. Two weeks after discharge, he became tired and thirsty, and diabetes was diagnosed. Since then, he had been well, working hard to manage his diabetes by taking more exercise and eating a balanced diet. He also heeded the advice of the doctor and successfully gave up smoking. One week previously, he had gone from 30 cigarettes a day to none.

*The consultation:* Amir is unwell. He is unable to give a clear history, as he is dribbling excessively. He says that he has felt unwell for three or four days and that his thoughts are confused. He says that he feels quite different from when he is mentally unwell. The family doctor examines Amir and finds that he is disoriented in time and space, is unable to speak clearly, is dribbling excessively and has relatively low blood pressure and a rapid heart rate.

The doctor doesn't know the cause of this man's illness but is clear that he must be admitted to hospital as an emergency.

*Clinical issues:* The first question is what type of hospital is the most appropriate in these circumstances. Is the illness a mental or a physical one? The family doctor arranges admission to the local general hospital, where investigations and observation can be undertaken safely. Over the next four days, Amir recovers and is transferred to the mental health hospital for resumption and monitoring of his medication.

*Clozapine toxicity and smoking:* The clinical issue in this case is the consequences of smoking cessation: Amir was suffering from clozapine toxicity. When he was smoking, his blood nicotine level was high, and a high dose of clozapine was required to maintain an effective level because of its metabolism in the liver (106). When Amir stopped smoking on the advice of the family doctor, the liver metabolized clozapine more slowly, and the drug level rose, even though the dose was unchanged, resulting in the equivalent of an overdose.

### **Conclusions**

- One in three of all cigarettes smoked is smoked by a person with a mental disorder. Smoking is a major cause of COPD and exacerbates asthma.
- Anxiety and depression are more common among people with respiratory conditions; however, the relation between common mental disorders and respiratory conditions is bidirectional, complex and poorly understood.
- Pulmonary rehabilitation is an effective integrated care package for people with COPD. Cognitive behaviour therapy has also been shown to be effective in managing psychological problems in people with respiratory conditions and improving their quality of life.
- Smoking is much more common (70–80%) among people with a severe mental disorder than the general population (10–15%).

- Smoking worsens the outcomes of NCDs, particularly diabetes and CVD. It predicts the development of both lung cancer and COPD.
- Providers of mental health care should consider making their services smoke-free for both patients and staff.
- Population-level interventions and health-promoting environments and settings can support healthy behaviour.

## 2.4 Cancer

### *Key facts (133):*

- With more than 3.7 million new cases and 1.9 million deaths each year, cancer represents the second most important cause of death and morbidity in Europe.
- The number of new cases is expected to rise by about 25% over the next two decades in the European Region.
- Among men, the five most common sites of cancer diagnosed in 2012 in the Region were prostate, lung, colorectum, bladder and stomach.
- Among women, the five most common sites diagnosed were breast, colorectum, lung, corpus uteri and cervix.
- About one third of deaths from cancer are due to the five leading behavioural and dietary risks: tobacco use, alcohol use, high body mass index, low fruit and vegetable intake and lack of physical activity.
- Tobacco consumption and excessive alcohol consumption cause about 40% of the total cancer burden. The precise figures vary from country to country (134).

“Cancer” is a generic term for a large group of diseases that can affect any part of the body; other terms used are “malignant tumours” and “neoplasms”. A defining feature of cancer is rapid multiplication of abnormal cells that grow beyond their usual boundaries and which can then invade adjoining parts of the body and spread to other organs; the latter process is referred to as “metastasis”. Metastases are the main cause of death from cancer.

### **Cancer and common mental disorders**

#### *Key facts:*

- About 25% of people with cancer have anxiety and/or depression.
- Only 20% of people with cancer who also have anxiety and/or depression are recognized as having a mental health disorder and receive appropriate treatment.
- Anxiety and/or depression in people with cancer is associated with a poorer quality of life, poorer compliance with treatment, longer hospitalization and a higher risk for suicide.
- While severe mental disorder itself is not associated with an increased prevalence of cancer, the lifestyle often associated with severe mental disorder increases the risk for cancer. For example, the rate of smoking among people with schizophrenia is as high as 80%, which increases their risk for lung cancer or pneumonia, the commonest cause of death in this group of people. Furthermore, this group accesses screening programmes for cancer (e.g. breast, colorectal and cervix) less frequently than people without a severe mental disorder.

A meta-analysis of studies of the prevalence of emotional disorders in people with cancer showed a higher rate than in the general population (135). The prevalence of depression in palliative care settings was 25%, and rates of around 20% have been reported in oncological and haematological clinics. In many studies, diagnostic labels overlapped, and individuals often had more than one defined diagnosis. Few consistent correlates of depression were found, such as age, sex or clinical setting, that would predict the development, successful management or outcome of the mental health condition. The presence of common mental disorders such as anxiety and depression in people with cancer is associated with a poorer quality of life (136), poorer compliance with treatment (137), longer hospitalization (138) and a higher risk for suicide (139). The presence of depression varies during the illness. In a five-year observational study of women with breast cancer, 50% of women had depression and/or anxiety in the year after diagnosis, decreasing to 25% in years two, three and four and to 15% five years after diagnosis (140).

The authors of a recent review (141) found that mood disorders, like other long-term conditions, are two to three times more common among people with cancer, although the prevalence of depression depends on the site of the cancer and whether depression is identified by diagnostic interview or from a self-administered questionnaire. Similarly, the prevalence of depression can be influenced by the stage of cancer. A common conclusion of the papers reviewed was that more clinicians should be trained to assess, diagnose and treat depression in people with cancer. One explanation for the lack of treatment of depression is that the symptoms of cancer in palliative care overlap considerably with those of depression.

The criterion for a diagnosis of depression in the tenth revision of the International Classification of Diseases (142) is a depressed mood or loss of interest for the previous two weeks that is significant enough to affect social functioning and pleasure in life for most of each day. This is often accompanied by several of the following symptoms: depressed mood, diminished interest in most activities, significant weight gain or weight loss, insomnia or excess sleeping, agitation or psychomotor retardation, fatigue or loss of energy, feeling worthless, diminished ability to concentrate and recurrent thoughts of death. At least three of the items required for a diagnosis of depression – significant weight loss, fatigue and sleep disturbance – are also seen in terminally ill patients. Thus, diagnosis of depression is difficult, as weight loss, fatigue and insomnia may be somatic effects of cancer rather than depression. Under-treatment of people with depression and cancer has been ascribed to both confusion in diagnosis and the conclusion by clinicians that depression is “appropriate” for cancer patients (141).

In order to address this confusion, guidelines have been published in Australia on the screening, assessment and management of depression and anxiety in adult cancer patients (143). The guidelines recommend screening of all patients with cancer for anxiety and depression at key stages in their care pathway. Brief screening tools are recommended, with a more detailed questionnaire and a clinical interview to confirm the diagnosis if clinically indicated. The brief screening tools suggested are the Edmonton symptom assessment system (144) or the “distress thermometer” (145) with a checklist of problems; the more detailed questionnaire recommended is the “hospital anxiety and depression scale” (146).

Two Cochrane reviews have been conducted to identify interventions that might be appropriate for people with cancer who are emotionally disturbed, anxious or depressed. The first (147) specifically addressed psychosocial interventions in the 12 months after a diagnosis of cancer. The interventions reviewed were use of a “trained helper” and the provision of some form of talking therapy; alternative forms of therapy, such as CDs or DVDs, massage and acupuncture, were excluded. The authors found inconclusive evidence of an improvement in quality of life with the interventions, and no improvement in anxiety or depression, although there may have been a small improvement in mood. Nurse-led interventions by telephone or face to face showed some promise.

The second review (148) specifically addressed the benefits of antidepressants in patients with cancer. Few studies were found, and they were of poor quality, so it was difficult to draw firm conclusions. The authors recommended that a decision to prescribe antidepressants should be made case by case. They were unable to recommend specific antidepressants, as they found no direct comparisons of the efficacy of different agents.

The Australian guidelines (143) mentioned above recommend a stepped approach to care, broadly in line with other national guidelines on the management of depression and anxiety. Psychosocial interventions are recommended for mild or moderate disorders and antidepressants and/or cognitive behaviour therapy for moderate-to-severe disorders.

### **Jane’s story**

*Presentation:* Jane, a 52-year-old woman with advanced breast cancer, makes a regular planned visit to her family doctor.

*Clinical background:* Jane is well known to her family doctor, as she has had breast cancer for the past seven years. She has received several treatments, including surgery, chemotherapy and radiotherapy. At the latest consultation, her oncologist told her that the tumour was progressing, despite treatment.

Jane is married with a supportive husband and two adolescent children. She is off work while receiving treatment but wants to go back to work and resume a normal life. Apart from her two pregnancies, she had little contact with doctors before finding a lump in her breast.

*The consultation:* The consultation is difficult, as Jane and her husband, who has accompanied her to the consultation, are still coming to terms with the information given to her by the oncologist. The family doctor discusses the next steps with the couple and explores the current level of symptoms. He finds that she is losing weight and sleeping poorly and has lost interest in returning to work. She is tired all the time.

*Clinical issues:* The family doctor is faced with the difficult clinical problem of deciding whether the current set of symptoms are due to progression of the tumour or to depression. Jane's symptoms of weight loss, diminished interest, sleeping poorly and fatigue are all diagnostic features of depression (149), but they may equally be caused by spreading cancer. The doctor must decide what to offer to help the patient.

It has been reported (141) that some people with depression and terminal illness do not receive treatment. This may be because of diagnostic confusion (as in Jane's case) or because physicians consider it "appropriate" or "understandable" that the patient is depressed. The Australian guidelines (143) recommend initial use of a brief screening questionnaire and then, if appropriate, a more detailed questionnaire and a clinical interview. In Jane's case, it would be appropriate to discuss the possibility of depression with her and her husband and whether treatment should be given. The clinical evidence on the appropriate types of treatment is equivocal (147, 148), and the individual circumstances of each patient should be considered. The family doctor may find it helpful to discuss the best way to help and support this family with the oncologist or a palliative care specialist or with a psychiatrist with experience in this area.

## **Cancer and severe mental disorders**

The evidence on the prevalence of cancer in people with severe mental disorder is conflicting (150). Most studies cite increased rates of death from cancer in people with schizophrenia, but it is often difficult to distinguish whether this is due to the disorder itself or to lifestyle and other risk factors, such as a higher prevalence of smoking, delayed presentation, delayed access to health care or effects of antipsychotic medication. In two studies of screening for cancer (mainly cervical and breast cancer) among women with a severe mental disorder (151, 152), those with psychosis were less likely to attend.

In a recent review (153), cancer incidence was found to be similar among people with and without schizophrenia after control for other causes of mortality, decreased life expectancy and poorer health behaviour. A large study in Sweden found that people with schizophrenia were at no greater risk for cancer than the general population after correction for age and other sociodemographic variables (127). The same study showed, however, that the overall mortality rate was much higher for people with a severe mental disorder, the commonest causes of death being ischaemic heart disease and cancer. The cancer most commonly diagnosed was of the lung, which is not surprising in view of the increased prevalence of smoking.

A study in southeast London, United Kingdom, of electronically linked records of people with cancer and a mental disorder indicated that the increased mortality of people with a severe mental disorder was due not to the higher prevalence of cancer but to poorer survival rates. The survival rates of people with a severe mental disorder, depression, dementia or substance misuse after a diagnosis of cancer were significantly worse, independently of the stage of cancer at diagnosis (154).

A study in Australia found that the mortality rate from cancer of people with a mental disorder was 30% higher than that of the general population. Psychiatric patients were more likely to present with metastases than the general population and were less likely to have received surgery, radiotherapy or chemotherapy (155).

It can be concluded tentatively that people with a severe mental disorder are less likely to benefit from health care services to prevent and treat cancer than the general population. They are therefore more likely to die from cancer than people without a severe mental disorder.

### **Matt's story**

*Presentation:* Matt goes to visit his family doctor because he has been coughing up blood for three weeks.

*Clinical background:* Matt is a 62-year-old divorced man who has suffered from schizophrenia for 35 years or more. He lives alone and is unemployed but attends a day centre run by the local mental health services. He attends the family doctor irregularly and last attended some eight months previously. He is currently taking olanzapine for schizophrenia and enalapril to manage his relatively mildly elevated blood pressure. He is not known to be sensitive to any drug. His last recorded weight was 82 kg, and he smokes 40 cigarettes a day.

*The consultation:* Matt reports that he has been coughing for one or two months and has been bringing up blood mixed with green sputum for the past two to three weeks. He thinks he may have lost a little weight, as he needs to tighten his belt more often than before. Otherwise, he feels fine, and if it wasn't for the staff at the day centre badgering him to see the doctor, he wouldn't have bothered.

Clinical examination reveals an elderly man who looks wasted. He weighs 69 kg, and examination of the chest reveals a fixed monophonic wheeze that indicates an obstructive lesion on the right side. His liver is palpable and feels hard and lumpy, and lymph glands are palpable in the right armpit and the right shoulder (supraclavicular fossa). The family doctor fears that Matt has cancer of the lung and organizes an urgent chest X-ray.

*Clinical issues:* Matt's history and the examination raise many "red flags" for the doctor, who considers it likely that Matt has cancer of the lung. The initial management is relatively straightforward: a chest X-ray to confirm the diagnosis and then referral to an appropriate specialist to manage the cancer. The clinical findings indicate that the cancer is considerably more advanced than Matt's history would suggest. The finding is in line with the evidence that people with a severe mental disorder tend to present relatively late and are more likely to have distant metastases. The weight loss, enlarged liver and lymph node enlargement all indicate a cancer that has spread. The difficulty is in planning the longer-term care for this man, involving a psychiatrist and a team to provide support as he starts to deteriorate and is unable to attend the day centre.

Good communication between the family doctor, the oncologist and the psychiatrist is essential, and it is the role of the family doctor to coordinate (156) the care that Matt will need. The care plan should involve the psychiatric team, the oncology team, primary care and, inevitably, social care as well (as he lives alone and is unemployed), so that all Matt's needs are met. Coordinating such an approach to ensure that there is no duplication or gaps is complex and time consuming.

### **Conclusions**

- 25% of people with cancer have a common mental disorder such as anxiety or depression.
- All patients receiving palliative care should have a psychological assessment and, when appropriate, evidence-based psychological interventions as part of the treatment package.
- Evidenced-based approaches are available to identify people receiving palliative care who will benefit from treatment for depression and anxiety.
- Cancer may be more common among people with psychosis but is more likely to be due to lifestyle choices (e.g. smoking) than to the psychosis.

- People with a severe mental disorder are less likely to access health care services; therefore, if they have cancer, they are likely to present at a more advanced stage and have a poorer survival rate than people with no severe mental disorder. Access to health care and reducing discrimination for this group should therefore be priorities for health planners and managers.
- Providing palliative care for people with a severe mental disorder and cancer is challenging and requires excellent integration of care.
- Population-level interventions and health-promoting environments and settings can support healthy behaviour.

## 3. Implications for health services

### 3.1 Health service delivery

The European Framework for Action on Integrated Health Services Delivery was endorsed by WHO European Member States in 2016 (7). The framework defines “integrated health service delivery” as an approach for strengthening people-centred health systems by promoting comprehensive delivery of high-quality services designed to meet all the needs of the population and the individual throughout the life-course, delivered by a coordinated multidisciplinary team of providers in all settings and at all levels of care. The framework sets out four domains to be addressed for delivering integrated care: populations and individuals, service delivery, system enablers and change management.

Integrated care is not only important from the patient’s perspective. As described in the previous sections, integrated care is also desirable for:

- managing depression in people who have diabetes and reducing their hospital use.
- reducing the risk of people with severe mental disorder for premature death from CVD;
- providing integrated care for people with COPD by a pulmonary rehabilitation team to reduce emergency admissions for acute exacerbation; and
- providing psychological treatment to people with diabetes to improve management of the disease to the same extent as some medication.

Integrating care improves patient satisfaction, adherence to treatment and health outcomes, and there is good evidence that integrated care is cost-effective when applied in a population, all of which are good reasons for such structural reform. Several models have been proposed over the past 20 years or so for providing integrated mental and physical health care (157). A joint clinic, run by a consultation liaison between a family doctor and a specialist, is one model (158), and location of various services at one site is another. The most recent model and that best investigated is the collaborative care model (159), which has shown consistently good outcomes for patients. There is reasonable consensus on the characteristics of this type of care, and its effectiveness has been the subject of several systematic reviews (158–160).

The essential characteristics of collaborative care are (159): a multi-professional approach, structured management, scheduled patient follow-up and enhanced inter-professional communication. A systematic review of studies of collaborative care in depression (160) indicated that the overall outcomes and patient experiences were better than with treatment as usual. Collaborative care with psychological treatment (with or without antidepressant medication) was more effective than collaborative care with medication alone. A systematic review of collaborative care in people with severe mental disorder (159) was limited, as there was only one study of its use in bipolar disorder and none on patients with schizophrenia; thus, no conclusions can be drawn. In the consultation liaison model, the primary care physician retains responsibility for the patient, and a mental health specialist provides consultative support. One review (161) indicated that consultation liaison is less effective than collaborative care, but the studies were of poor quality, and it would be difficult to draw firm conclusions.

## 3.2 Strengthened knowledge and skills in the health workforce

### Primary care teams

The general practitioner is “the only clinician who operates at the nine levels of care: prevention, pre-symptomatic detection of disease, early diagnosis, diagnosis of established disease, management of disease, management of disease complications, rehabilitation, palliative care and counselling” (162). Ideally, most health conditions are expected to be dealt with in primary care. Therefore, the integration of mental and physical health care should be central to primary care services.

Primary care physicians should have the knowledge and skills to diagnose and manage common mental disorders such as anxiety and depression, which occur frequently in people with CVD, cancer, diabetes and respiratory disorders. Management should include access to specialists who deliver psychological therapy and who have the knowledge and skills to prescribe antidepressant medication when appropriate. If primary care physicians are expected to identify mental disorders in people with these major NCDs, they should have the competence to manage them and have access to effective evidence-based interventions.

Nurses who interact with and manage primary care attendees with one or more physical or mental health conditions are central to the pursuit and implementation of an integrated approach in primary care. They can improve day-to-day management of NCDs by working with primary care physicians (163).

### Hospital health workforce

In general hospitals, the provision of psychiatric care is essential. While medical and nursing professionals working in hospitals may have the knowledge and skills to identify people with mental health needs, treatment is usually provided by specialized mental health doctors and nurses. Each hospital should encourage the presence of liaison psychiatric staff to provide specialist advice on diagnosis and management.

Medical and nursing professionals working in hospitals should be aware of the association between severe mental disorders and major NCDs. Those specialized in the management of a particular NCD (e.g. diabetes or respiratory disease) should be able to identify the common mental disorders that are associated with that NCD and know how and when to refer such patients to a clinician who can manage the condition (e.g. a primary care team or mental health professional).

### Mental health workforce

While it is not the specific role of mental health care professionals to manage major NCDs, they can help to ensure that such services are available and that patients are oriented towards them. The mental health workforce (psychiatrists, psychologists, psychiatric nurses and other professionals) should have the knowledge and skills to screen for the presence of physical conditions such as diabetes and cardiovascular disorders in people with a severe mental disorder. Equally, they should be able to direct a person with a mental disorder to appropriate local services, such as a tobacco cessation programme or health promotion. The mental health workforce should also be able to identify patients who are deteriorating physically. NCDs such as diabetes, heart attacks or stroke can result in life-threatening emergencies, but emergencies may be more difficult to identify and require more intensive intervention in patients whose condition is already complex due to a mental disorder and the medication they are taking for that condition. All mental health care workers should therefore be able to identify patients whose physical health is suddenly deteriorating and know how to respond. Local circumstances will dictate how such liaison services and care are made available, for example by employing general practitioners, general physicians or physicians with a special interest in geriatrics to review and advise on the management of long-term mental disorders. Patients must have access to the most appropriate care. Thus, a patient in a mental health hospital should have access to physical health care services (liaison physicians), and a patient in a physical health care hospital should have access to mental health care (liaison psychiatrists) when clinical circumstances indicate the need. The form of access depends on local circumstances; there may be dedicated specialists on site, as recommended by the Royal College of Psychiatrists in the United Kingdom (164), or specialists may be available in a different location. Whatever model is used, the outcome must be the same: care for both physical and mental health is available for each individual.

## Guidelines

Many countries have evidenced-based guidelines for the management of a range of NCDs. Guidelines are effective tools for clinicians planning the most up-to date-treatment on the basis of the latest published evidence. They ensure consistency in the treatment of the same condition and ensure that patients know what treatment they can expect. The standards of care in guidelines enable the provision of services based on the best evidence.

This report shows, however, that there are few guidelines that include people with mental disorders (common or severe) who also have another NCD. These individuals have particular needs, which should be considered in designing, organizing and managing the provision of services that fill the gap left in most guidelines and facilitate access to high-quality care. Their care is complex, as managing one aspect may well worsen other aspects of care. For example, increasing the dose of antipsychotic medication to manage a worsening mental state may also worsen the same person's diabetes or CVD. Accordingly, guidelines for managing NCDs should also address the needs of people with a severe mental disorder and address the association between common mental disorders and major NCDs.

## 4. Conclusions

The aim of this report is to contribute to better understanding of comorbidity and to provide evidence that health planners and providers can use to promote a more integrated approach for managing individuals with comorbid conditions. Its focus has been a review of the clinical evidence for comorbidity between mental disorders and major NCDs. A number of conclusions arise from this review of the evidence.

### Common mental disorders

- People with diabetes should be checked regularly to determine whether they are developing depression.
- Depression and anxiety predict the development of CVD and worsen its prognosis. There is no evidence, however, that screening for or treating depression and anxiety improves cardiovascular outcomes. For example, screening for and treatment of depression will not prevent a heart attack.
- One in three of all cigarettes smoked is smoked by a person with a mental disorder. Smoking is a major cause of COPD and exacerbates asthma. Health care providers should encourage smoking cessation and provide appropriate interventions for both patients and staff.
- Pulmonary rehabilitation has been shown to be an effective integrated care package for people with COPD. Cognitive behaviour therapy is also effective for managing psychological problems in people with respiratory conditions and improving their quality of life.
- Only a fraction of people who are receiving palliative care and who also have anxiety or depression receive treatment for those conditions. There are evidence-based approaches to identifying people receiving palliative care who will benefit from treatment for depression and anxiety.
- Population-level interventions and health-promoting environments and settings can support healthy behaviour.

### Severe mental disorders

- Diabetes is more common and more complex to manage in people with a severe mental disorder. Managing such cases requires integration of care between metabolism specialists and psychiatrists.
- The role of antipsychotic medication in diabetes requires further research and evaluation.
- Identifying and managing modifiable risk factors for CVD in people with a severe mental disorder reduces their risk for premature mortality.

- Discrimination against people with a severe mental disorder discourages them from accessing services and increases their risks for premature death and disability from CVD. Addressing discrimination should therefore be a priority.
- The risk of every person with a severe mental disorder for a cardiovascular event should be measured annually in a recognized risk algorithm.
- Providers of mental health care should consider banning smoking in their services, for both patients and staff.
- People with a severe mental disorder are less likely to access health care services. Therefore, if they have cancer, they are likely to present when the disease is at a more advanced stage, and their survival rates are likely to be poorer. Access to health care for this group and elimination of discrimination should be priorities for health planners and managers.
- Population-level interventions and health-promoting environments and settings can support healthy behaviour.

The implications of these findings for health service design, organization, management and improvement are clear. Health systems should move towards a more person-centred, integrated model of care, which has been demonstrated to result in improved health outcomes. In implementing integrated health services delivery, health professionals have to look beyond specific diseases to address both the physical and the mental health needs of patients. Therefore, all health service settings should provide training in the detection, management and follow-up of comorbid chronic conditions.

The timing, resource requirements and key enablers of implementation or transformation will differ markedly between countries according to their cultural contexts and resources. Any sustained effort to bring about closer integration between mental and physical health services can be expected to result in a number of benefits, including greater satisfaction of people, who are treated as “whole people” rather than according to their condition; better clinical outcomes; and gains in efficiency due to better allocation of resources, less duplication of testing and services and timely interventions.

## 5. References<sup>2</sup>

1. The European framework for action on integrated health services delivery: an overview. Copenhagen: WHO Regional Office for Europe; 2016 ([http://www.euro.who.int/\\_\\_data/assets/pdf\\_file/0010/317377/FFA-IHS-service-delivery-overview.pdf](http://www.euro.who.int/__data/assets/pdf_file/0010/317377/FFA-IHS-service-delivery-overview.pdf)).
2. Depression and other common mental disorders. Global health estimates. Geneva: World Health Organization; 2017 (WHO/MSD/MER/2017.2).
3. The European mental health action plan 2013–2020. Copenhagen: WHO Regional Office for Europe; 2013 ([http://www.euro.who.int/\\_\\_data/assets/pdf\\_file/0004/194107/63wd11e\\_MentalHealth-3.pdf](http://www.euro.who.int/__data/assets/pdf_file/0004/194107/63wd11e_MentalHealth-3.pdf)).
4. Action plan for the prevention and control of noncommunicable diseases in the WHO European Region. Copenhagen: WHO Regional Office for Europe; 2016 ([http://www.euro.who.int/\\_\\_data/assets/pdf\\_file/0011/315398/66wd11e\\_NCDActionPlan\\_160522.pdf](http://www.euro.who.int/__data/assets/pdf_file/0011/315398/66wd11e_NCDActionPlan_160522.pdf)).
5. Health 2020: the European policy framework. Copenhagen: WHO Regional Office for Europe; 2013 (<http://www.euro.who.int/en/health-topics/health-policy/health-2020-the-european-policy-for-health-and-well-being>).
6. Priorities for health systems strengthening in the WHO European Region 2015–2020: walking the talk on people-centeredness. Copenhagen: WHO Regional Office for Europe; 2015 ([http://www.euro.who.int/\\_\\_data/assets/pdf\\_file/0003/282963/65wd13e\\_HealthSystemsStrengthening\\_150494.pdf](http://www.euro.who.int/__data/assets/pdf_file/0003/282963/65wd13e_HealthSystemsStrengthening_150494.pdf)).

<sup>2</sup> All websites accessed on 31 October 2016 unless otherwise indicated.

7. Roadmap. Strengthening people-centred health systems in the WHO European Region: a framework for action towards coordinated/integrated health services delivery (CIHSD). Copenhagen: WHO Regional Office for Europe; 2013 ([http://www.euro.who.int/\\_\\_data/assets/pdf\\_file/0004/315787/66wd15e\\_FFA\\_IHSD\\_160535.pdf](http://www.euro.who.int/__data/assets/pdf_file/0004/315787/66wd15e_FFA_IHSD_160535.pdf)).
8. Global action plan for the prevention and control of noncommunicable diseases 2013–2020. Geneva: World Health Organization; 2013 ([http://apps.who.int/iris/bitstream/10665/94384/1/9789241506236\\_eng.pdf?ua=1](http://apps.who.int/iris/bitstream/10665/94384/1/9789241506236_eng.pdf?ua=1)).
9. Mental health action plan 2013–2020. Geneva: World Health Organization; 2013 ([http://www.who.int/mental\\_health/action\\_plan\\_2013/en/](http://www.who.int/mental_health/action_plan_2013/en/)).
10. Buchan J, Perfilieva G. Making progress towards health workforce sustainability in the WHO European Region. Copenhagen: WHO Regional Office for Europe; 2015 ([http://www.euro.who.int/\\_\\_data/assets/pdf\\_file/0005/287456/Making-progress-towards-health-workforce-sustainability-in-the-WHO-European-Region-rev1.pdf?ua=1](http://www.euro.who.int/__data/assets/pdf_file/0005/287456/Making-progress-towards-health-workforce-sustainability-in-the-WHO-European-Region-rev1.pdf?ua=1)).
11. Roadmap of actions to strengthen implementation of the WHO Framework Convention on Tobacco Control in the European Region 2015–2025: making tobacco a thing of the past. Copenhagen: WHO Regional Office for Europe; 2015 ([http://www.euro.who.int/\\_\\_data/assets/pdf\\_file/0011/282962/65wd10e\\_Tobacco\\_150475.pdf?ua=1](http://www.euro.who.int/__data/assets/pdf_file/0011/282962/65wd10e_Tobacco_150475.pdf?ua=1)).
12. European action plan to reduce the harmful use of alcohol 2012–2020. Copenhagen: WHO Regional Office for Europe; 2015 ([http://www.euro.who.int/\\_\\_data/assets/pdf\\_file/0008/178163/E96726.pdf](http://www.euro.who.int/__data/assets/pdf_file/0008/178163/E96726.pdf)).
13. World Health Day 2016: Beat diabetes. Copenhagen: WHO Regional Office for Europe; 2016 (<http://www.euro.who.int/en/about-us/whd/world-health-day-2016-beat-diabetes>).
14. Global health estimates. Geneva: World Health Organization; 2014.
15. Mathers CD, Loncar D. Projections of global mortality and burden of disease from 2002 to 2030. *PLoS Med* 2006;3:e442.
16. Global status report on noncommunicable diseases 2010. Geneva: World Health Organization; 2011.
17. Definition, diagnosis and classification of diabetes mellitus and its complications: report of a WHO consultation. Part 1: Diagnosis and classification of diabetes mellitus. Geneva: World Health Organization; 1999 (WHO/NCD/NCS/99.2).
18. Morrish NJ, Wang SL, Stevens LK, Fuller JH, Keen H. Mortality and causes of death in the WHO multinational study of vascular disease in diabetes. *Diabetologia* 2001;44(Suppl 2):S14–S21.
19. Global data on visual impairments 2010. Geneva: World Health Organization; 2012.
20. Roglic G, Unwin N, Bennett PH, Mathers C, Tuomilehto J, Nag S, et al. The burden of mortality attributable to diabetes: realistic estimates for the year 2000. *Diabetes Care* 2005;28:2130–2135.
21. Anderson RJ, Freedland KE, Clouse RE, Lustman PJ. The prevalence of comorbid depression in adults with diabetes: a meta-analysis. *Diabetes Care* 2001;24:1069–1078.
22. Egede LE, Ellis C. Diabetes and depression: global perspectives. *Diabetes Res Clin Pract* 2010;87:302–312.
23. Lustman PJ, Anderson RJ, Freedland KE, de Groot M, Carney RM, Clouse RE. Depression and poor glycemic control: a meta-analytic review of the literature. *Diabetes Care* 2000;23:934–942.

24. Richardson LK, Egede LE, Mueller M, Echols CL, Gebregziabher M. Longitudinal effects of depression on glycemic control in veterans with type 2 diabetes. *Gen Hosp Psychiatry* 2008;30:509–514.
25. Gonzalez JS, Peyrot M, McCarl LA, Collins EM, Serpa L, Mimiaga MJ, et al. Depression and diabetes treatment nonadherence: a meta-analysis. *Diabetes Care* 2008;31:2398–2403.
26. de Groot M, Anderson R, Freedland KE, Clouse RE, Lustman PJ. Association of depression and diabetes complications: a meta-analysis. *Psychosom Med* 2001;63:619–630.
27. The global burden of disease: 2004 update. Geneva: World Health Organization; 2008.
28. Eaton W. Epidemiologic evidence on the comorbidity of depression and diabetes. *Psychosom Res* 2002;53:903–906.
29. Knol MJ, Twisk JW, Beekman AT, Heine RJ, Snoek FJ, Pouwer F. Depression as a risk factor for the onset of type 2 diabetes mellitus. A meta-analysis. *Diabetologia* 2006;49:837–845.
30. Mezuk B, Eaton WW, Albrecht S, Golden SH. Depression and type 2 diabetes over the lifespan: a meta-analysis. *Diabetes Care* 2008;31:2383–2390.
31. Katon JW, Von Korff M, Lin EHB, Simon G, Ludman E, Russo J, et al. The pathways study – a randomised trial of collaborative care in patients with diabetes and depression. *Arch Gen Psychiatry* 2004;61:1042–1049.
32. Lustman PJ, Griffith LS, Clouse RE, Freedland KE, Eisen SA, Rubin EH, et al. Effects of nortriptyline on depression and glycemic control in diabetes: results of a double-blind, placebo-controlled trial. *Psychosom Med* 1997;59:241–250.
33. Lustman PJ, Freedland KE, Griffith LS, Clouse RE. Fluoxetine for depression in diabetes: a randomized double-blind placebo-controlled trial. *Diabetes Care* 2000;23:618–623.
34. Williams JW Jr, Katon W, Lin EH, Noel PH, Worchel J, Cornell J, et al. The effectiveness of depression care management on diabetes-related outcomes in older patients. *Ann Intern Med* 2004;140:1015–1024.
35. van der Feltz-Cornelis CM, Nuyen J, Stoop C, Chan J, Jacobson AM, Katon W, et al. Effect of interventions for major depressive disorder and significant depressive symptoms in patients with diabetes mellitus: a systematic review and meta-analysis. *Gen Hosp Psychiatry* 2010;32:380–395.
36. Das-Munshi J, Stewart R, Ismail K, Bebbington PE, Jenkins R, Prince MJ. Diabetes, common mental disorders, and disability: findings from the UK National Psychiatric Morbidity Survey. *Psychosom Med* 2007;69:543–550.
37. Krein SL, Bingham CR, McCarthy JF, Mitchinson A, Payes J, Valenstein M. Diabetes treatment amongst VA patients with comorbid serious mental illness. *Psychiatr Serv* 2006;57:1016–1021.
38. Le TK, Able SL, Lage MJ. Resource use among patients with diabetes, diabetic neuropathy, or diabetes with depression. *Cost Effectiveness Resource Allocation* 2006;4:18.
39. Ciechanowski PS, Katon WJ, Russo JE. Depression and diabetes: impact of depressive symptoms on adherence, function, and costs. *Arch Intern Med* 2000;160:3278–3285.
40. Nichols L, Barton PL, Glazner J, McCollum M. Diabetes, minor depression and health care utilization and expenditures: a retrospective database study. *Cost Effectiveness Resource Allocation* 2007;5:4.

41. Simon GE, Katon WJ, Lin EHB, Rutter C, Manning WG, Von Korff M, et al. Cost-effectiveness of systematic depression treatment among people with diabetes mellitus. *Arch Gen Psychiatry* 2007;64:65–72.
42. Katon WJ, Russo JE, Von Korff M, Lin EHB, Ludman E, Ciechanowski PS. Long-term effects on medical costs of improving depression outcomes in patients with depression and diabetes. *Diabetes Care* 2008;31:1155–1159.
43. Vinogradova Y, Coupland C, Hippisley-Cox J, Whyte S, Penny C. Effects of severe mental illness on survival of people with diabetes. *Br J Psychiatry* 2010;197:272–277.
44. Haire-Joshu D, Thomas J. Gambling with addiction: dangerous beliefs about smoking and diabetes. *Diabetes Voice* 2005;50:15–18.
45. Schizophrenia. Geneva: World Health Organization; 2016 ([http://www.who.int/mental\\_health/management/schizophrenia/en/](http://www.who.int/mental_health/management/schizophrenia/en/)).
46. Psychosis and schizophrenia: management. Clinical guideline [CG82]. London: National Institute for Health and Care Excellence; 2009 (<https://www.nice.org.uk/guidance/CG82>).
47. Leucht S, Burkard T, Henderson J, Maj M, Sartorius N. Physical illness and schizophrenia: a review of the evidence. *Acta Psychiatr Scand* 2007;116:317–333.
48. Psychosis and schizophrenia in adults: prevention and management. Clinical guideline [CG178]. London: National Institute for Health and Care Excellence; 2014 (<https://www.nice.org.uk/guidance/CG178>).
49. American Diabetes Association, American Psychiatric Association, American Association of Clinical Endocrinologists, North American Association for the Study of Obesity. Consensus development conference on antipsychotic drugs and obesity and diabetes. *Diabetes Care* 2004;27:596–601.
50. Pendlebury J, Holt R. Managing diabetes in people with severe mental illness. *J Diabetes Nurs* 2010;14:328–338.
51. Kooy FH. Hyperglycaemia in mental disorders. *Brain* 1919;42:214–288.
52. Duc L. Contribution to the study of the disorders of carbohydrate metabolism in mental disorders: diabetes and psychoses. *Schweiz Arch Neurol Psychiatr* 1952;69:89–169.
53. Jurcczyk A, Nowesielska A, Przewozniak N, Aryee KE, Dilorio P, Blodgett D, et al. Beyond the brain: disrupted in schizophrenia 1 regulates pancreatic b-cell function via glycogen synthase kinase-3 b. *FASEB J* 2016;30:983–993.
54. Hasnain M. Genetic vulnerability in antipsychotic drug-induced diabetes. *Lancet Psychiatry* 2015;2:1049–1051.
55. Samele C, Patel M, Boydell J, Leese M, Wessely S, Murray R. Physical illness and lifestyle factors in people with their first presentation of psychosis. *Soc Psychiatry Psychiatr Epidemiol* 2007;42:117–124.
56. Mingrone G, Panunzi S, De Gaetano A, Guidone C, Iaconelli A, Leccesi L, et al. Bariatric surgery versus conventional medical therapy for type 2 diabetes. *N Engl J Med* 2012;366:1577–1585.
57. Cardiovascular diseases. Data and statistics. Copenhagen: WHO Regional Office for Europe; 2016 (<http://www.euro.who.int/en/health-topics/noncommunicable-diseases/cardiovascular-diseases/data-and-statistics>).
58. European guidelines on cardiovascular disease prevention in clinical practice (version 2012). *Eur Heart Journal* 2012;33:1635–1701.

59. Rugulies R. Depression as a predictor for coronary heart disease. a review and meta-analysis. *Am J Prev Med* 2002;23:51–61.
60. Wulsin LR, Singal BM. Do depressive symptoms increase the risk for the onset of coronary disease? A systematic quantitative review. *Psychosom Med* 2003;65:201–210.
61. Nicholson A, Kuper H, Hemingway H. Depression as an aetiologic and prognostic factor in coronary heart disease: a meta-analysis of 6362 events among 146 538 participants in 54 observational studies. *Eur Heart J* 2006;27:2763–2774.
62. Barth J, Schumacher M, Herrmann-Lingen C. Depression as a risk factor for mortality in patients with coronary heart disease: a meta-analysis. *Psychosom Med* 2004;66:802–813.
63. van Melle JP, de Jonge P, Spijkerman TA, Tijssen JG, Ormel J, van Veldhuisen DJ, et al. Prognostic association of depression following myocardial infarction with mortality and cardiovascular events: a meta-analysis. *Psychosom Med* 2004;66:814–822.
64. Roest AM, Martens EJ, de Jonge P, Denollet J. Anxiety and risk of incident coronary heart disease: a meta-analysis. *J Am Coll Cardiol* 2010;56:38–46.
65. Roest AM, Martens EJ, Denollet J, de Jonge P. Prognostic association of anxiety post myocardial infarction with mortality and new cardiac events: a meta-analysis. *Psychosom Med* 2010;72:563–569.
66. Violanti JM, Charles LE, Gu JK, Burchfiel CM, Andrew ME, Nedra JP, et al. Depressive symptoms and carotid artery intima-media thickness in police officers. *Int Arch Occup Environ Health* 2013;86:931–942.
67. Pizzi C, Costa GM, Santarella L, Flacco ME, Capasso L, Bert F, et al. Depression symptoms and the progression of carotid intima-media thickness: a 5-year follow-up study. *Atherosclerosis* 2014;233:530–536.
68. Wright L, Simpson W, Van Lieshout RJ, Steiner M. Depression and cardiovascular disease in women: is there a common immunological basis? A theoretical synthesis. *Ther Adv Cardiovasc Dis* 2014;8:56–69.
69. Maggi S. Review: Depression may increase mortality in coronary heart disease. *Evid Based Ment Health* 2005;8:66.
70. Thombs BD, de Jonge P, Coyne JC, Whooley MA, Frasure-Smith N, Mitchell AJ, et al. Depression screening and patient outcomes in cardiovascular care: a systematic review. *JAMA* 2008;300:2161–2171.
71. Berkman LF, Blumenthal J, Burg M, Carney RM, Catellier D, Cowan MJ, et al. Effects of treating depression and low perceived social support on clinical events after myocardial infarction: the Enhancing Recovery in Coronary Heart Disease Patients (ENRICH) randomized trial. *JAMA* 2003;289:3106–3116.
72. Lesperance F, Frasure-Smith N, Koszycki D, Laliberte MA, van Zyl LT, Baker B, et al. Effects of citalopram and interpersonal psychotherapy on depression in patients with coronary artery disease: the Canadian Cardiac Randomized Evaluation of Antidepressant and Psychotherapy Efficacy (CREATE) trial. *JAMA* 2007;297:367–379.
73. Freedland KE, Skala JA, Carney RM, Rubin EH, Lustman PJ, Davila-Roman VG, et al. Treatment of depression after coronary artery bypass surgery: a randomized controlled trial. *Arch Gen Psychiatry* 2009;66:387–396.
74. Glassman AH, O'Connor CM, Califf RM, Swedberg K, Schwartz P, Bigger JT Jr, et al. Sertraline treatment of major depression in patients with acute MI or unstable angina. *JAMA* 2002;288:701–709.

75. van Melle JP, de Jonge P, Honig A, Schene AH, Kuyper AM, Crijns HJ, et al. Effects of antidepressant treatment following myocardial infarction. *Br J Psychiatry* 2007;190:460–466.
76. Dowlati Y, Herrmann N, Swardfager WL, Reim EK, Lanctot KL. Efficacy and tolerability of antidepressants for treatment of depression in coronary artery disease: a meta-analysis. *Can J Psychiatry* 2010;55:91–99.
77. Fenton WS, Stover ES. Mood disorders: cardiovascular and diabetes comorbidity. *Curr Opin Psychiatry* 2006;19:421–427.
78. Jiang W, Alexander J, Christopher E, Kuchibhatla M, Gauden LH, Cuffe MS, et al. Relationship of depression to increased risk of mortality and rehospitalisation in patients with congestive heart failure. *Arch Intern Med* 2001;161:1849–1856.
79. Welch CA, Czerwinski D, Ghimire B, Bertsimas D. Depression and costs of health care. *Psychosomatics* 2009;50, no 4, pp 392–401.
80. Depression in adults: recognition and management. London: National Institute for Health and Care Excellence; 2009 ([www.nice.org.uk/guidance/cg90](http://www.nice.org.uk/guidance/cg90)).
81. Laursen TM, Munk-Olsen T, Agerbo E, Gasse C, Mortensen PB. Somatic hospital contacts, invasive cardiac procedures, and mortality from heart disease in patients with severe mental disorder. *Arch Gen Psychiatry* 2009;66:713–720.
82. Osborn DP, Levy G, Nazareth I, Petersen I, Islam A, King MB. Relative risk of cardiovascular and cancer mortality in people with severe mental illness from the United Kingdom's General Practice Research Database. *Arch Gen Psychiatry* 2007;64:242–249.
83. Novo S, Iacona R, Bonomo V, Evola V, Corrado E, Di Piazza M, et al. Erectile dysfunction is associated with low total serum testosterone levels and impaired flow-mediated vasodilation in intermediate risk men according to the Framingham risk score. *Atherosclerosis* 2015;238:415–419.
84. Meyer JM. Sexual dysfunction in patients treated with atypical antipsychotics. *J Clin Psychiatry* 2008;69:e26.
85. Rodrigo C, Lakshitha da Silva N, Gunaratne R, Rajapakse S, Asanka Da Silva V, Hanwella R. Lower estimated glomerular filtration rates in patients on long term lithium: a comparative study and a meta-analysis of literature. *BMC Psychiatry* 2014;14:4
86. Osborn DPJ, King MB, Nazareth I. Participation in screening for cardiovascular risk by people with schizophrenia or similar mental illnesses: cross sectional study in general practice. *BMJ* 2003;326:1122–1123.
87. Pirraglia PA, Rowland E, Wu WC, Friedmann PD, O'Toole TP, Cohen LB, et al. Benefits of a primary care clinic co-located and integrated in a mental health setting for veterans with serious mental illness. *Prev Chronic Dis* 2012;9:E51.
88. Cardiovascular risk prediction charts. Geneva: World Health Organization, 2016 ([http://www.who.int/cardiovascular\\_diseases/publications/Chart\\_predictions/en/](http://www.who.int/cardiovascular_diseases/publications/Chart_predictions/en/)).
89. SCORE risk charts. The European cardiovascular disease risk assessment model. Brussels: European Society of Cardiology; 2016 (<http://www.escardio.org/Education/Practice-Tools/CVD-prevention-toolbox/SCORE-Risk-Charts>).
90. Hippisley-Cox J, Coupland C, Vinogradova Y, Robson J, Minhas R, Sheikh A, et al. Predicting cardiovascular risk in England and Wales: prospective derivation and validation of QRISK2. *BMJ* 2008;336:1475–1482.

91. Hippisley-Cox J, Parker C, Coupland C, Vinogradova Y. Inequalities in the primary care of patients with coronary heart disease and serious mental health problems: a cross-sectional study. *Heart* 2007;93:1256–1262.
92. Hippisley-Cox J. Severe mental illness and cardiovascular risk. Report to West London Mental Health Trust (REC 11/EM/20345). Southall: West London Mental Health Trust; 2012.
93. Scigliano G, Ronchetti G. Antipsychotic-induced metabolic and cardiovascular side effects in schizophrenia: a novel mechanistic hypothesis. *CNS Drugs* 2013;27:249–257.
94. Alberti KG, Zimmet P, Shaw P. The metabolic syndrome, a new worldwide definition. A consensus statement from the International Diabetes Federation. *Diabetes Med* 2006;23:469–480.
95. Mottillo S, Filion KB, Genest J, Joseph L, Pilote L, Poirier P, et al. The metabolic syndrome and cardiovascular risk: a systematic review and meta-analysis. *J Am Coll Cardiol* 2010;56:1113–1132.
96. Querioz Claudio B, Nossar Costa MA, Penna F, Texeira Konder M, Celoria BMJ, Lopes de Souza L, et al. Impact of psychotropic drugs on QT interval dispersion in adult patients. *Arq Bras Cardiol* 2014;102:465–472.
97. Antipsychotic drugs and risk of venous thromboembolism: nested case-control study Parker et al. *BMJ* 2010;341:c4245
98. Druss BG. Improving medical care for persons with serious mental illness: challenges and solutions. *J Clin Psychiatry* 2007;68(Suppl 4):40–44.
99. Fleischhacker WW, Cetkovich-Bakmas M, De Hert M, Hennekens C, Lambert M, Leucht S, et al. Co-morbid somatic illnesses in patients with severe mental disorders: clinical, policy and research challenges. *J Clin Psychiatry* 2008;69:514–519.
100. De Hert M, Dekker JM, Wood D, Kohl KG, Möller HJ. Cardiovascular disease and diabetes in people with severe mental illness position statement from the European Psychiatric Association (EPA), supported by the European Association for the Study of Diabetes (EASD) and the European Society of Cardiology (ESC). *Eur Psychiatry* 2009;24:412–424.
101. Huffman MD. Cardiovascular health in low- and middle-income countries. *Curr Probl Cardiol* 2014;39:399–419.
102. Mendelsohn CP, Kirby DP, Castle DJ. Smoking and mental illness. An update for psychiatrists. *Australas Psychiatry* 2015;23:37–43.
103. Aronson JK, editor. *Meyler's side effects of psychiatric drugs*. 15th edition. Amsterdam: Elsevier; 2006:732.
104. *Chronic respiratory diseases*. Geneva: World Health Organization; 2015 (<http://www.who.int/respiratory/en/>).
105. *Chronic respiratory diseases. Quick facts and figures*. Copenhagen: WHO Regional Office for Europe; 2015 (<http://www.euro.who.int/en/health-topics/noncommunicable-diseases/chronic-respiratory-diseases/data-and-statistics>).
106. *Smoking and mental health (Royal College of Psychiatrists Council Report CR178)*. London: Royal College of Physicians and Royal College of Psychiatrists; 2013.
107. Lasser K, Boyd JW, Woolhandler S, Himmelstein DU, McCormick D, Bor DH. Smoking and mental illness. *JAMA* 2000;284:2606–2610.

108. Cooper CL, Parry GD, Saul C, Morice AH, Hutchcroft BJ, Moore J, et al. Anxiety and panic fear in adults with asthma: prevalence in primary care. *BMC Fam Pract* 2007;8:62.
109. Ten Thoren C, Petermann F. Reviewing asthma and anxiety. *Resp Med* 2000;94:409–415.
110. Carfella PA, Effing TW, Usmani ZA, Frith PA. Treatments for anxiety and depression in patients with chronic obstructive pulmonary disease: a literature review. *Respirology* 2012;17:627–638.
111. Yohannes AM, Alexopoulos GS. Depression and anxiety in patients with COPD. *Eur Respir Rev* 2014;23:345–349.
112. Omachi TA, Katz PP, Yelin EH, Gregorich SE, Iribarren C, Blanc PD, et al. Depression and health-related quality of life in chronic obstructive pulmonary disease. *Am J Med* 2009;122:778.
113. Van Manen JG, Bindels PJ, Dekker FW, Ijzermans CJ, van der Zee JS, Schadé E. Risk of depression in patients with chronic obstructive pulmonary disease and its determinants. *Thorax* 2002;57:412–416.
114. Jennings JH, Digiovine B, Obeid D, Frank C. The association between depressive symptoms and acute exacerbations of COPD. *Lung* 2009;187:128–135.
115. Ng TP, Niti M, Tan WC, Cao Z, Ong KC, Eng P. Depressive symptoms and chronic obstructive pulmonary disease: effect on mortality, hospital readmission, symptom burden, functional status, and quality of life. *Arch Intern Med* 2007;167:60–67.
116. Maurer J, Rebbapragada V, Borson S, Goldstein R, Kunik ME, Yohannes AM, et al. Anxiety and depression in COPD: current understanding, unanswered questions, and research needs. *Chest* 2008;134(4 Suppl.):43S–56S.
117. Shavitt RG, Gentil V, Mandetta R. The association of panic/agoraphobia and asthma. Contributing factors and clinical implications. *Gen Hosp Psychiatry* 1992;14:420–423.
118. Goodwin RD, Jacobi F, Thefeld W. Mental disorders and asthma in the community. *Arch Gen Psychiatry* 2003;60:1125–1130.
119. Ley R. Dyspneic-fear and catastrophic cognitions in hyperventilatory panic attacks. *Behav Res Ther* 1989;27:549–554.
120. Gorman JM, Askanazi J, Liebowitz MR, Fyer AJ, Stein J, Kinney JM, et al. Response to hyperventilation in a group of patients with panic disorder. *Am J Psychiatry* 1984;141:857–861.
121. Cochrane Database of Systematic Reviews. Pulmonary rehabilitation for chronic obstructive pulmonary disease (Plain language summary) (<http://www.ncbi.nlm.nih.gov/pubmedhealth/PMH0012318/>, accessed August 2015).
122. Informed Health Online. What is pulmonary rehabilitation? (<http://www.ncbi.nlm.nih.gov/pubmedhealth/PMH0072615/>, accessed August 2015).
123. Yorke J, Fleming SL, Shuldham CM. Psychological interventions for adults with asthma. *Cochrane Database Syst Rev* 2005;1:CD002982.
124. Clearing the air: a national study of chronic obstructive pulmonary disease. London: Commission for Healthcare Audit and Inspection; 2006.
125. Investing in emotional and psychological wellbeing. London: NHS Confederation; 2012.

126. Himelhoch S, Lehman A, Kreyenbuhl J, Dixon L. Prevalence of chronic obstructive pulmonary disease among those with serious mental illness. *Am J Psychiatry* 2004;161:2317–2319.
127. Crump S, Winkleby MA, Sundquist K, Sundquist J. Comorbidities and mortality in persons with schizophrenia: a Swedish national cohort study. *Am J Psychiatry* 2013;170:324–333.
128. Desai HD, Seabolt J, Jann MW. Smoking in patients receiving psychotropic medications: a pharmacokinetic perspective. *CNS Drugs* 2001;15:469–494.
129. Ziedonis D, Hitsman B, Beckham JC, Zvolensky M, Adler LE, Audrain-McGovern J, et al. Tobacco use and cessation in psychiatric disorders: National Institute of Mental Health report. *Nicotine Tob Res* 2008;10:1691–1715.
130. Cormac I. Impact of a total smoking ban in a high secure hospital. *Psychiatrist* 2010;34:413–417.
131. Gilbody S, Peckham E, Man MS, Mitchell N, Li J, Becque T, et al. Bespoke smoking cessation for people with severe mental ill health (SCIMITAR): a pilot randomised controlled trial. *Lancet Psychiatry* 2015;2:395–402.
132. Eden Evins A, Cather C, Pratt SA, Pachas GN, Hoepfner SS, Goff DC, et al. Maintenance treatment with varenicline for smoking cessation in patients with schizophrenia and bipolar disorder. *JAMA* 2014;311:145–154.
133. Ferlay J, Soerjomataram I, Ervik M, Dikshit R, Eser S, Mathers C, et al. Cancer incidence and mortality worldwide: GLOBOCAN 2012 v1.0 (IARC CancerBase No. 11). Lyon: International Agency for Research on Cancer; 2013 (<http://globocan.iarc.fr>, accessed 3 February 2017).
134. Cancer. Data and statistics. Copenhagen: WHO Regional Office for Europe; 2015 (<http://www.euro.who.int/en/health-topics/noncommunicable-diseases/cancer/data-and-statistics>, accessed August 2015).
135. Mitchell AJ, Chan M, Bhatti H, Halton M, Grassi L, Johansen C, et al. Prevalence of depression, anxiety, and adjustment disorder in oncological, haematological, and palliative-care settings: a meta-analysis of 94 interview-based studies. *Lancet Oncol* 2011;12:160–174.
136. Arrieta O, Angulo LP, Núñez-Valencia C, Dorantes- Gallareta Y, Macedo EO, Martínez-López D, et al. Association of depression and anxiety on quality of life, treatment adherence, and prognosis in patients with advanced non-small cell lung cancer. *Ann Surg Oncol* 2013;20:1941–1948.
137. Colleoni M, Mandala M, Peruzzotti G, Robertson C, Bredart A, Goldhirsch A. Depression and degree of acceptance of adjuvant cytotoxic drugs. *Lancet* 2000;356:1326–1327.
138. Prieto JM, Blanch J, Atala J, Carreras E, Rovira M, Cirera E, et al. Psychiatric morbidity and impact on hospital length of stay among hematologic cancer patients receiving stem-cell transplantation. *J Clin Oncol* 2002;20:1907–1917.
139. Shim EJ, Park JH. Suicidality and its associated factors in cancer patients: results of a multi-center study in Korea. *Int J Psychiatry Med* 2012;43:381–403.
140. Burgess C, Cornelius V, Love S, Graham J, Richards M, Ramirez A. Depression and anxiety in women with early breast cancer: five-year observational cohort study. *BMJ* 2005;330:702.
141. Lloyd-Williams M. Difficulties in diagnosing and treating depression in the terminally ill cancer patient. *Postgrad Med J* 2000;76:555–558.

142. International statistical classification of diseases and related health problems, 10th edition. Geneva: World Health Organization; 2016.
143. Butow P, Price MA, Shaw JM, Turner J, Clayton JM, Grimison P, et al. Clinical pathway for the screening, assessment and management of anxiety and depression in adult cancer patients: Australian guidelines. *Psycho-Oncology* 2015;24:987–1001.
144. Bruera E, Kuehn N, Miller MJ, Selmser P, Macmillan K. The Edmonton Symptom Assessment System (ESAS): a simple method for the assessment of palliative care patients. *J Palliat Care* 1991;7:6–9.
145. Holland JC, Andersen B, Breitbart WS, Buchmann LO, Compas B, Deshields TL, et al. Distress management. *J Natl Compr Cancer Netw* 2013;11:190–209.
146. Zigmond AS, Snaith RP. The hospital anxiety and depression scale. *Acta Psychiatry Scand* 1983;67:361–370.
147. Galway K, Black A, Cantwell M, Cardwell CR, Donnelly M. Psychosocial interventions to improve quality of life and emotional wellbeing for recently diagnosed cancer patients. *Cochrane Database Syst Rev* 2012;11:CD007064.
148. Ostuzzi G, Matcham F, Dauchy S, Barbui C, Hotopf M. Antidepressants for the treatment of depression in people with cancer. *Cochrane Database Syst rev* 2015;1:CD011006.
149. Diagnostic and statistical manual of mental disorders. 4th Edition. Washington DC: American Psychiatric Association; 1994.
150. Hodgson R, Wildgust HJ, Bushe CJ. Cancer and schizophrenia: is there a paradox? *J Psychopharmacol* 2010;24(Suppl 4):51–60.
151. Mitchell A, Pereira IE, Yadegarfar M, Pepereke S, Mugadza V, Stubbs B. Breast cancer screening in women with mental illness: comparative meta-analysis of mammography uptake. *Br J Psychiatry* 2014;205:428–435.
152. Tilbrook D, Polsky J, Lofters A. Are women with psychosis receiving adequate cervical cancer screening? *Can Fam Physician* 2010;56:358–363.
153. Irwin K, Henderson DC, Knight HP, Pirl WF. Cancer care for individuals with schizophrenia. *Cancer* 2014;120:323–334.
154. Chang CK, Hayes RD, Broadbent MTM, Hotopf M, Davies E, Møller H, et al. A cohort study on mental disorders, stage of cancer at diagnosis and subsequent survival. *BMJ Open* 2014;4:e004295.
155. Kisley S, Crowe E, Lawrence D. Cancer-related mortality in people with mental illness. *JAMA Psychiatry* 2013;70:209–217.
156. Hewlett E, Moran V. Making mental health count. The social and economic costs of neglecting mental health care (OECD Health Policy Studies). Paris: OECD Publishing; 2014.
157. World Health Organization and Calouste Gulbenkian Foundation. Integrating the response to mental disorders and other chronic diseases in health care systems. Geneva: World Health Organization; 2014.
158. Gillies D, Buykx P, Parker AG, Hetrick SE. Consultation liaison in primary care for people with mental disorders. *Cochrane Database Syst Rev* 2015;9: CD007193.

159. Reilly S, Planner C, Gask L, Hann M, Knowles S, Druss B, Lester H. Collaborative care approaches for people with severe mental illness. *Cochrane Database Syst Rev* 2013;11:CD009531.
160. Coventry PA, Hudson JL, Kontopantelis E, Archer J, Richards DA, Gilbody S, et al. Characteristics of effective collaborative care for treatment of depression: a systematic review and meta-regression of 74 randomized controlled trials. *PLoS One* 2014;9:e108114.
161. Sartorius N. Stigma and mental health. *Lancet* 2007;370:810–811.
162. Coleman R, Gill G, Wilkinson D. Noncommunicable disease management in resource poor settings; a primary care model from rural South Africa. *Bull World Health Organ* 1998;76:633–640.
163. Patel V, Simon G, Chowdhary N, Kaaya S, Araya R. Packages of care for depression in low- and middle-income countries. *PLoS Med* 2009;6:e1000159.
164. Whole-person care: from rhetoric to reality. Achieving parity between mental and physical health. Summary. London: Royal College of Psychiatrists; 2013 (<http://www.rcpch.ac.uk/system/files/protected/news/Achieving%20parity%20between%20mental%20and%20physical%20health.pdf>).

The WHO Regional  
Office for Europe

The World Health Organization (WHO) is a specialized agency of the United Nations created in 1948 with the primary responsibility for international health matters and public health. The WHO Regional Office for Europe is one of six regional offices throughout the world, each with its own programme geared to the particular health conditions of the countries it serves.

Member States

Albania  
Andorra  
Armenia  
Austria  
Azerbaijan  
Belarus  
Belgium  
Bosnia and Herzegovina  
Bulgaria  
Croatia  
Cyprus  
Czechia  
Denmark  
Estonia  
Finland  
France  
Georgia  
Germany  
Greece  
Hungary  
Iceland  
Ireland  
Israel  
Italy  
Kazakhstan  
Kyrgyzstan  
Latvia  
Lithuania  
Luxembourg  
Malta  
Monaco  
Montenegro  
Netherlands  
Norway  
Poland  
Portugal  
Republic of Moldova  
Romania  
Russian Federation  
San Marino  
Serbia  
Slovakia  
Slovenia  
Spain  
Sweden  
Switzerland  
Tajikistan  
The former Yugoslav  
Republic of Macedonia  
Turkey  
Turkmenistan  
Ukraine  
United Kingdom  
Uzbekistan



**World Health Organization Regional Office for Europe**  
UN City, Marmorvej 51, DK-2100 Copenhagen Ø, Denmark  
Tel.: +45 45 33 70 00 Fax: +45 45 33 70 01  
E-mail: [eucontact@who.int](mailto:eucontact@who.int)