Violence in severe mental illness: risk factors, risk assessment, and prevention

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Abstract

Individuals with severe mental illness are at increased risk of violence compared with the general population. Risk factors for violence need clarification as a basis for risk assessment, and to inform evidence-based risk management. The aim of this thesis is to examine the risk factors for violence in schizophrenia-spectrum disorders, create a simple, scalable risk assessment tool to predict violence in forensic psychiatric populations, and review the evidence for violence prevention interventions in psychiatry.

The first study reports risk factors for violence in a Swedish total population cohort of patients with schizophrenia-spectrum disorders (n=24,297), using register data. Substance use disorders, previous criminality, and self-harm were strong predictors of violence in patients, but also in unaffected sibling and general population controls.

The second study used pre-specified criminal, sociodemographic, and clinical risk factors to derive a clinical prediction rule for violent crime within 12 and 24 months of discharge from forensic psychiatric hospitals in Sweden (n=2,248). The model was used to develop a 12-item online tool (FoVOx) with good measures of calibration and discrimination (area under the curve = 0.77 at 12 and 24 months).

The third study reports an umbrella review of violence prevention interventions in psychiatry, through searches in ten bibliographic databases, and assesses the strength of evidence for each review using the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) approach. Out of five included reviews, only one received a GRADE rating of 'moderate', and reported that therapeutic community interventions may reduce reincarceration in drug-using offenders with mental illness.

Given the lack of intervention research in violence prevention in psychiatry, and considering the shared risk factors between populations, interventions from non-psychiatric populations may need to be relied upon. Research recommendations include the validation of FoVOx, and routine inclusion of violence outcomes in primary research.

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Publications arising from thesis

Wolf A, Whiting D, Fazel S
Violence prevention in psychiatry: an umbrella review of interventions in general and forensic psychiatry
Journal of Forensic Psychiatry & Psychology (2017)

Wolf A, Fanshawe TR, Sariaslan A, Cornish R, Larsson H, Fazel S
Prediction of violent crime on discharge from secure psychiatric hospitals: a clinical prediction rule (FoVOx)
European Psychiatry (2017)

Fazel S, Wolf A, Palm C, Lichtenstein P
Violent crime, suicide, and premature mortality in patients with schizophrenia and related disorders
Lancet Psychiatry (2014)

Related publications

Fazel S, Wolf A, Larsson H, Lichtenstein P, Mallett S, Fanshawe TR
Identification of low risk of violent crime in severe mental illness with a clinical prediction tool (OxMIV)
Lancet Psychiatry (2017)

Fazel S, Wolf A, Fiminska Z, Larsson H
Mortality, Rehospitalisation and Violent Crime in Forensic Psychiatric Patients Discharged from Hospital: Rates and Risk Factors
PLOS ONE (2016)

Fazel S, Wolf A, Chang Z, Larsson H, Goodwin GM, Lichtenstein P
Depression and violence: a Swedish population study
Lancet Psychiatry (2015)

Wolf A, Gray R, Fazel S
Violence as a public health problem: an ecological study of 169 countries
Social Science & Medicine (2013)

Lv Y, Wolf A, Wang X
Experienced stigma and self-stigma in Chinese patients with schizophrenia
General Hospital Psychiatry (2012)

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Introduction

Violence

Impact of violence

Violence is currently among the top twenty causes of years of life lost[1] and in the top thirty for loss of disability adjusted life-years.[2] On both measures, the 2015 Global Burden of Disease Study found a relative increase in the contribution of violence to morbidity and mortality worldwide. Though the financial impact of violence is large – costing $64.4 billion a year in lost productivity in the US alone, and $5.6 billion in additional health service costs[3] – much of the human cost in grief and pain is invisible. There is increasing recognition of the public health importance of violence,[4] and evidence-based interventions are needed to reduce the worldwide burden of violence.[5]

Definition

The World Health Organization defines violence as "The intentional use of physical force or power, threatened or actual, against oneself, another person, or against a group or community, that either results in or has a high likelihood of resulting in injury, death, psychological harm, maldevelopment or deprivation."[6] This thesis will look at interpersonal violence, and exclude both self-directed violence, and warfare. In particular, this thesis will examine what has been defined as 'hard' violence outcomes, such as police and hospital recorded violent incidents (as opposed to 'soft' outcomes, which include arrests without convictions, self-reported violence perpetration and victimisation, and measures of aggression). While this definition will not capture certain forms of violence (for example less severe offences directed at family members, care professionals, or other vulnerable people), it does have several advantages. First, as a more specific measure, it does include severer forms of violence, representing the highest public health burden.

Second, using 'hard' outcomes provides more generalisability, as the definitions and recording of alternative measures such as arrests or self-reported violence are more heterogeneous across countries and jurisdictions.[4,7] Third, the data source used in this thesis, Swedish national registers, has total population coverage for psychiatric diagnoses and criminal convictions and has previously been used in epidemiological investigations into the link between severe mental illness and violent crime.[8]

Severe mental illness

Though the definition of the phrase 'severe mental illness' varies, it is generally accepted to include diagnoses of schizophrenia, bipolar disorder, and other psychotic disorders.[9]

Schizophrenia

Schizophrenia is a group of psychiatric disorders in which a person's perceptions, thoughts, mood and behaviour are significantly altered. Symptoms are generally divided into 'positive' and 'negative' symptoms.[10] Positive symptoms include delusions (unusual beliefs held despite superior evidence to the contrary), hallucinations (sensory perceptions in the absence of external stimuli, most commonly hearing voices), and disordered thinking (as evidenced by speech that becomes muddled and hard to understand). Negative symptoms include deficits in motivation, attention, memory, and social functioning, and affective blunting.

An often-cited lifetime prevalence of schizophrenia is 0.7%, though substantial variations within and between countries have been reported,[11] only in part explained by differences in study methodology.[12] Nevertheless, evidence on reasons for country-level differences in prevalence remains limited.[13] Despite a prevalence lower than many other chronic illnesses, schizophrenia is among the highest contributors to the global burden of disease and disability,[14] due to its lifelong and profound effects on patients and their families, its early onset (usually between ages 15-30), and associated health risks

(including substance misuse, obesity, lack of exercise, and poverty).[9] Schizophrenia is associated with an increased risk of all-cause and suicide mortality,[15,16] with a systematic review finding pooled standardized mortality ratios (SMRs) of 2.5 and 12.9, respectively.[17]

Bipolar disorder

Bipolar disorder is a cyclical psychiatric disorder associated with episodes of mood swings ranging from periods of depression, to manic or hypomanic highs, or mixed affective episodes.[18] Though episodes of mania or hypomania are a necessary characteristic in the diagnosis of bipolar disorder, depressive symptoms often predominate in terms of symptom frequency.[19] Depressive episodes are similar to those experienced in unipolar major depression and, in those with a first episode of depression, it may not be possible to distinguish between the two diagnoses.[20] Episodes of mania and hypomania may include inflated self-esteem, disinhibition, and decreased need for sleep.[20] Psychotic symptoms can occur in the more severe states of both mania and depression.[21]

The mean pooled point prevalence of bipolar spectrum disorders used in the global burden of disease studies was 0.7%, with some differences found across sex, economic status, and bipolar subtype.[22] Bipolar disorders are also among the highest contributors to the global burden of disease and disability,[14] with onset usually before age 30 (with a second small peak around age 45).[20] Individuals with bipolar disorder are at increased risk of all-cause and suicide mortality with standardized mortality ratios (SMRs) of 2.0 and 17.1, respectively.[17]

Forensic psychiatry

Forensic psychiatry is the psychiatric sub-speciality that helps and works with mentally disordered people who are at risk to the public, whether is in prisons, secure hospitals, or

the community. Patients in secure hospitals are generally held under the Mental Health Act and include individuals who have committed offences while mentally ill, have been diagnosed or require specialist treatment while in prison, as well as non-offending patients who cannot be adequately managed in a general psychiatric inpatient hospital setting. While psychiatric inpatient numbers have continued to be reduced in Western countries in the last two decades,[23] forensic psychiatry has seen the opposite trend; a recent overview found forensic psychiatric inpatient beds have increased steadily from 1990 to 2012.[24] There are now over 7000 beds in England and Wales[25] and about a fifth of the mental health budget in England and Wales goes to forensic psychiatric services.[26] Annual costs per patient are estimated (in 2011 prices) at between €190,000 (around £160,000) in low secure and €340,000 (£290,000) in high secure hospital.[25] One of the key justifications for such high costs has been that forensic psychiatric patients are at increased risk of repeat violence on release from hospital compared to general psychiatric patients (discussed in Chapter III), and therefore their treatment should address a wide range of needs.

Violence in severe mental illness

Compared to the general population, individuals with severe mental illness (schizophrenia-spectrum and bipolar disorders) have increased risks for violence. The first large population based study to examine the link between mental illness and violence was published in 1990, using data on 10,059 individuals from the NIMH Epidemiologic Catchment Area project.[27] Compared to a rate of 2% in those with no mental health disorder, 13% of individuals with schizophrenia-spectrum disorder and 11% of individuals with bipolar disorder reported violent behaviour in the previous 12 months. The rate increased further in those with multiple psychiatric comorbidities. However, these

findings were based on a small number of individuals with mental illness (114 with schizophrenia-spectrum and 30 with bipolar disorders) and used self-report data.

A 2000 study, based on the Dunedin birth cohort of 1,037 individuals in New Zealand,[28] is one of the most highly cited in the field, and reports a 5-fold increase in court convictions for violence in individuals with schizophrenia-spectrum or bipolar disorders compared to those with no psychiatric disorder. This corresponds to an absolute risk of 15% in a 12-month period when individuals were 20 years old. While this study's findings benefit from more reliable data sources by using court convictions, and enrolling consecutive births (with 91% consenting), the odds ratio analyses were based on even smaller numbers of individuals (39 with schizophrenia-spectrum disorders, and 19 with bipolar disorders). Similarly, in the UK, a 2006 study[29] of 8,367 individuals found no significant association between psychosis (n=51) and self-reported violent behaviour over the previous 5 years (adjusted Odds Ratio: 3.2, 95% CI: 0.35-29.6). This is likely due to low statistical power, as the study reported an absolute risk of self-reported violence of 17% in those 5 years. Additionally, their analyses adjusted for "sex, age, social classes III–V, marital status, employment, any personality disorder, any affective/anxiety disorder, alcohol dependence, and drug dependence", a number of which are thought to be on the causal pathway between psychosis and violence and should therefore not be considered confounders.

More recently, larger samples and more precise estimates were derived using both meta-analysis and national register studies. A 2009 systematic review of 20 individual studies reporting data from 18,423 patients with schizophrenia-spectrum disorders reported the odds of violence to be increased up to 7-fold compared with general population controls.[30] However, the review found that most of this excess risk was mediated by substance abuse comorbidity – another key risk factor for violence – and

highlighted the need for public health strategies to focus on substance abuse. In bipolar disorder, a 2014 Swedish total population study of 15,337 individuals followed-up over 26 years found the risk of violent crime to be increased 5-fold in patients with bipolar disorder compared with the general population,[31] and again highlights substance misuse as a contributing factor.

Though most individuals with mental disorders are not violent in their lifetimes, increased relative risks, and the public's perception of this risk, contribute to stigma and self-stigma.[32] Media coverage of events associated with severe mental illness have been shown to increase stigma and perceived dangerousness in both observational settings (following two highly publicised attacks),[33] and in experimental settings (where some participants were exposed to a news story on mass shooting reportedly committed by a man with mental illness).[34] Even in fiction, the majority of English-language movie characters portrayed as having psychosis displayed violent behaviour toward themselves or others.[35] It is therefore unsurprising that almost half of Americans believe that persons with serious mental illness are "far more dangerous than the general population".[36] Robust data on absolute risks, risk factors, and interventions to reduce the risk of violence, combined with public awareness campaign, have the potential to reduce stigma and self-stigma and improve care for patients.[37]

Risk assessment and management

After several studies in the 1980s finding little evidence to support the use of unstructured clinical judgment in violence prediction,[38] risk assessment has generally been conducted using structured instruments. These range from checklists to more complex decision trees, and generally categorise individuals into high and low risk groups. They are often used in clinical settings, especially forensic psychiatry, to inform treatment,[39] and in criminal justice systems to estimate an individual's risk of recidivism

and influence sentencing.[40,41] Hundreds such tools exist, with more appearing every month,[42] and the majority are locally adapted and unvalidated.[43]

The two most commonly used tools in forensic psychiatry are the Historical Clinical Risk Management-20 (HCR-20) and the Violence Risk Appraisal Guide (VRAG).[42] The HCR-20 was designed to predict the risk of violence in psychiatric patients and is comprised of 20 items organised into three scales: historical factors (10 items, including substance misuse, previous violence, psychopathy, and relationship instability), clinical factors (5 items, including lack of insight, impulsivity, and treatment non-response), and risk management factors (5 items, including lack of personal support, exposure to destabilizers, and stress). Items were included based on expert input in 1997 rather than a systematic review of the evidence (an approach the authors described as "What variables might clinicians and administrators consider as they attempt evaluations of risk of violence in cases where psychiatric disorders are thought to be involved?")[44] and the derivation did not include any statistical performance measures. Each item is to be scored as '0' (item not present), '1' (item possibly present), or '2' (item definitely present).[45] Age and sex, two of the strongest predictors of violence and considered important for face validity, were not included. As a structured clinical judgment tool, the total score is not directly used to derive a risk score. Instead, the tool is used as a checklist to guide the clinician's judgment in assigning a risk category of low, moderate, or high.

The VRAG was designed to assess the risk of violence among individuals who have already committed criminal violence.[46] It contains 12 items, including on substance misuse, previous offence, age at index offence, family background, and clinical factors. Items were selected from 42 candidate variables collected from a single sample of 618 mentally disordered Canadian offenders (of whom 191 reoffended). Of those, 332 individuals had been admitted to a maximum-security prison, the remaining 286 had

been admitted only for a brief pretrial psychiatric assessment. This was therefore a heterogenous sample, and did not include patients from low and medium secure institutions (which make up the majority of forensic patients) with questionable generalizability to these groups. As will be discussed in Chapter II, 191 events do not provide sufficient statistical power to select from 42 candidate variables. Each item was given its own scoring system based on weighting from multivariable models, with a total score ranging from -24 to +32. As an actuarial tool, the score is then converted directly into one of three risk categories. The derivation study reports performance measures at five different cut-offs (which were not pre-specified), and does not provide an overall performance measure. As with the HCR-20, the offender's sex was not one of the variables considered and was therefore not included in the final model, though it did include age.

A systematic review of 30 studies assessing commonly used risk assessment tools reported an average overall discrimination performance – as measured by the Area Under the Curve – of 0.72 for the prediction of violent offending. However, as will be discussed in Chapter II, this number should not be interpreted in isolation, and should be interpreted with caution due to a number of important limitations in the methods and reporting of results.

Crucially, current clinical guidelines in the UK provide little guidance on the management of risk to others. The Royal College of Psychiatry good practice guide[47] does not identify or recommend specific evidence-based interventions to reduce the risk of violence. Rather, it advises clinicians to draw up a risk management plan based on dynamic risk factors (in particular substance misuse), supervision, and the use of the Mental Health Act when required. Continued risk assessment is recommended, though it is acknowledged that there is "evidence that many risk-assessment tools do not generate

statistically reliable data".[47] A synthesis of the current evidence in violence prevention research in psychiatry is therefore required for public policy and planning and the development of preventive interventions and research.

Aims

This D.Phil. focuses on violence risk assessment and prevention in severe mental illness, and consists of three parts, answering three questions:

(1) What are the risk factors for violence in schizophrenia-spectrum disorders, and are they shared across other populations?

(2) Can these risk factors be used to create a simple, scalable risk assessment tool to predict violence in forensic psychiatric populations?

(3) What evidence-based interventions exist to reduce the risk of violence in psychiatry?

In both schizophrenia and bipolar disorder, the age-standardized rates of disability-adjusted life years attributable to those conditions did not significantly change between 1990 and 2010,[14] underscoring the need for better prevention and treatment options, as well as implementation of existing cost-effective interventions. Therefore, this thesis examines the existing evidence in violence prevention in severe mental illness, and presents the development of a free, simple, and scalable violence prediction tool, to free up clinical time and resources for treatment and management.

Chapter I - Schizophrenia and violence risk factors: a Swedish population study

Introduction

Little is known about risk factors that are linked to violence in those with schizophrenia-spectrum disorders, whether they are modifiable, and to what extent these factors are specific to schizophrenia-spectrum disorders or shared with the general population. Additionally, there is uncertainty as to whether these risks factors are unique to violence, or shared across other adverse outcomes, including suicide and all-cause mortality. Research has focused on these outcomes and risk factors separately, and rates and risk factors for any adverse outcome are rarely reported.[48] Such information is necessary to trial therapies and preventative strategies to mitigate risks. In addition, risk factor information is necessary to develop clinical prediction rules that would assist in risk assessment,[49] including the development of a novel tool presented in Chapter II.

A related area of uncertainty and considerable debate is trends over time, with some studies reporting increased relative risks over time for convictions of a violent offence[50] as well as suicide and death,[51] but secular trends have made these data difficult to interpret. The emerging reinstitutionalization of patients in some parts of the world[52] may have been partly driven by concerns about deinstitutionalization,[23] although wider socio-political factors are likely to be important.[53]

The previous largest study was published in 2009 using Swedish registers[30] and suffered from a number of weaknesses that this chapter addresses. First, it focused on patients with schizophrenia rather than all schizophrenia-spectrum disorders, meaning results may have been affected by reclassification bias due to changes in diagnostic criteria and trends over time. Second, though general population controls were matched by age and

sex, the beginning of the follow-up periods differed between cases and controls. General population controls were followed up from age 15 and not the age of diagnosis of their matched case. This complicates the interpretation of the findings as controls had longer periods of time-at-risk, and included young adulthood which is linked to higher rates of violence. Furthermore, the current study benefits from updated registers with longer follow-up and a larger sample size, for higher statistical precision, and power to conduct additional analyses, including time trends and interaction effects.

Therefore, to address the uncertainties above, this chapter examines all patients with diagnoses of schizophrenia-spectrum disorders in secondary care in Sweden over 38 years, rates of violence, and three major risk factors and their interactions: self-harm, substance abuse, and previous self-harm. Risk factor analyses are repeated across populations and other adverse outcomes. Finally, I examine trends over time for the relative odds of each adverse outcome, and how these varied in subgroups (sex, immigration status, comorbid substance abuse), and with changes in inpatient bed numbers.

Methods

The study was conducted using Swedish national registers, an approach chosen for five key advantages. First, Nordic countries are in a unique position of having high-quality nationwide registers[54] which, unlike for example the clinical register in England and Wales (Clinical Practice Research Datalink; CPRD),[55] do not give citizens the option of 'opting-out', and are not affected by the 2018 EU General Data Protection Regulation.[54] Cohort datasets such as the Avon Longitudinal Study of Parents and Children (ALSPAC) require individual and continued participant consent and questionnaire completion, which may lead to selection and attrition biases as those consenting may be different to those not consenting. For instance, while 82% of mothers (11,264 of 13,761 in the original sample) had completed some questionnaires and could be included in certain 18-year follow-up analyses, only half had completed all questionnaires.[56] Of the 11,264, less than half attended when invited to a follow-up clinic; those who did not attend were younger, from lower social class backgrounds, and less likely to have a university degree.[56] The use of Swedish registers ensures full nationwide coverage and therefore maximises sample size while maintaining external validity. In contrast, the CPRD has a coverage of less than 10% of the population, again with possible important differences between those covered and those not covered by the dataset.[55] Second, the validity of diagnoses in the Swedish patient registers has been researched extensively, with a 2011 paper reviewing 132 relevant papers.[57] The review found good diagnostic validity, with positive predictive values generally around 85-95%. Though a 2010 review of 212 CPRD validation studies found estimates of validity to be generally high, the quality of reporting was considered too low to permit a clear interpretation.[58] Third, the linkage potential of Swedish registers was essential to this project, in particular linkage with crime and family data. CPRD data cannot currently be linked to official crime records, or to family information to create

genetically-informed designs, making this type of study unfeasible. Fourth, findings from Swedish registers in this study are likely to be generalizable to other high-income countries, as Sweden reports similar prevalence rates of schizophrenia,[11] violent assault,[59] and suicide incidence[60] to those in other high-income countries. Generalizability to other Western countries is also suggested by an internationally recognized measure of psychiatric morbidity – that of age-adjusted disability-adjusted life years, which is similar in Sweden and other Western countries.[61] Finally, of the Nordic countries, Sweden has the largest population, and therefore the largest sample size and highest precision for statistical analyses. As a result, the current study is the largest study of patients with schizophrenia-spectrum disorders to date, and includes over 24,000 individual cases, and 480,000 general population controls.

The Regional Ethics Committee at the Karolinska Institutet approved the study (2009/939-31/5). Data were merged and anonymized by an independent government agency (Statistics Sweden), and the code linking the personal identification numbers to the new case numbers was destroyed immediately after merging. Therefore, informed consent was not required.

Study setting

Nationwide, longitudinal, Swedish population registers were linked: the Patient Register, the Medical Birth and the Cause-of-Death Registers (held at the National Board of Health and Welfare), the Longitudinal Integration Database for Health Insurance and Labour Market Studies and Multi-Generation Register (Statistics Sweden), and the Conscription Register (Defence Recruitment Agency). The Multi-Generation Register connects each person born in Sweden in or after 1933 and ever registered as living in Sweden after 1960 to their parents. Similar information exists for immigrants who became citizens of Sweden before age 18, together with one or both parents. All residents including

immigrants have a unique ten-digit personal identification number that is used in all national registers, thus making the linking of data in these registers possible.[62] I selected the cohort of those born between 1958 and 1994, which were followed from 1972 to the end of follow-up in 2009 (n=7,238,800).

All 24,297 individuals who had been discharged from hospitals from 1972 to 2009, and who had been diagnosed with a schizophrenia-spectrum disorder on at least two separate occasions were identified. Using the Multi-Generation Register, I also identified unaffected siblings (n=26,357) of patients with schizophrenia-spectrum disorders. Each patient was linked to 20 age- and sex-matched controls. Their unaffected siblings were also independently linked to 20 age- and sex-matched controls. Both controls and siblings had no diagnoses of schizophrenia-spectrum disorders, but may have had other psychiatric diagnoses.

Schizophrenia-spectrum disorders

The Patient Register includes data on all individuals admitted to any hospital for assessment and/or treatment in Sweden (including secure hospitals and the few private providers of inpatient healthcare) from 1972, or individuals having outpatient appointments with psychiatrists from 2001 onwards. Diagnoses are based on the International Classification of Diseases, Eighth Revision (ICD-8) (1972–1986, code 295), ICD-9 (1987–1996, codes 295; 297A, B, C, W, X; 298W, X) and ICD-10 (1997–2004, codes F20-F22; F25-F29). Two or more patient episodes were used as part of the inclusion criteria to increase diagnostic precision by minimizing false-positive diagnoses.[63] Including those with only one patient episode would include a proportion of individuals who do not have schizophrenia-spectrum disorders but have been misclassified where a later diagnosis of bipolar disorder, personality disorders, substance-induced psychosis, and other disorders is made. Though this decision was made on

theoretical grounds there is empirical evidence that suggests that using one episode would make little difference to risk estimates. A previous study on violence in schizophrenia examined the effects of including those with only one episode,[8] and the adjusted odds ratios in this sample were overlapping with the main sample using two patient episodes.

Diagnostic validity

Schizophrenia diagnoses in the Patient Register concord well with diagnoses obtained by clinical record reviews and interviews, reflected in κ (Cohen's kappa, a measure of inter-rater agreement) values of 0.74–0.76.[64] In another study, 86% of hospital register schizophrenia diagnoses corresponded with diagnoses of DSM-IV schizophrenia syndrome made from file-based reviews by psychiatrists.[65] However, the specificity (true negative rate) is at best fair.[64] Hence, some individuals with a schizophrenia diagnosis in the Patient Register will be diagnosed with other mental disorders for any one inpatient episode, which led to the decision to use diagnoses on two different occasions to define cases.[57] Less is known about comorbid psychiatric disorders, although there is one study that found fair to moderate agreement for comorbid substance use disorders in schizophrenia (κ of 0.37, standard error=0.23, $p<0.001$, corresponding to 68% full agreement).[8] Since only around 1% of hospital admissions have missing personal identification numbers,[66] the Patient Register has been used in a variety of epidemiological investigations.[8]

Outcome measures

Conviction of a violent offence was defined as homicide and attempted homicide, aggravated assault (an assault that is life-threatening in nature or causes severe bodily harm), common assault, robbery, arson, any sexual offense (rape, sexual coercion, child

molestation, and sexual harassment [including indecent exposure]), and illegal threats or intimidation.[67] Conviction data were used because the Criminal Code in Sweden determines that individuals are convicted as guilty regardless of mental illness (i.e., being judged as not guilty by reason of insanity is not possible). Thus, conviction data included persons who received custodial or noncustodial sentences and individuals transferred to forensic hospital (e.g., individuals who were psychiatrically assessed and thought to have suffered from psychosis or other severe mental disorder at the time of the offense). Furthermore, conviction data included those cases in which the prosecutor decided to caution or fine (e.g., less serious sexual crimes and some juvenile cases). In addition, though certain factors may affect sentencing, plea-bargaining at the conviction stage is not part of the Swedish legal system.[68] Therefore, conviction data more accurately reflect the extent of officially resolved criminality in the population. The Crime Register has total national coverage—only 0.05% of all registered convictions had incomplete personal identification numbers during the years 1988–2000.[66]

Causes of death data were retrieved for all individuals who died between 1972 and 2009, to investigate rates of premature mortality, which was defined as death before age 56. Suicides were defined as including undetermined deaths (ICD codes Y10-Y34) as their exclusion would underestimate actual rates.[69] As the Cause-of-Death register covers more than 99% of deaths in Swedish residents, including those occurring outside Sweden, the loss of information on death by suicide was minimal.[70] Data on all convictions of a violent offence during the years 1972–2009 were retrieved for all individuals in the cohort from the National Crime Register, which includes conviction data on all persons aged 15 (the age of criminal responsibility) and older.

Risk factors

Risk factors were included based on three criteria. First, existing risk factor evidence was examined for candidate variables. In particular, a 2012 systematic review of risk factors for violence was used to determine inclusion of sociodemographic, criminal, clinical, and family variables.[71] The strongest associations identified in the review included male sex, homelessness, low socio-economic status, previous violence, substance misuse, treatment non-adherence, and low impulse control. Second, an emphasis was placed on modifiable risk factors (e.g., substance misuse) that could be used to help identify treatment targets. Third, variables which would be routinely collected in clinical practice or risk assessment were included to inform the derivation of the risk assessment tool in Chapter II.

A number of variables were considered but were not included either because of unavailability in Swedish registers, or concerns around generalisability, or low diagnostic validity. For instance, patient registers do not currently record information on psychological treatments; other treatment variables, such as medication, only became available after the completion of this study. Homelessness was not included as a variable due to incomplete reporting, and in view of likely problems with generalisability as definitions and services vary across countries. Though a primary diagnosis of personality disorder has been found to have good validity in Swedish registers, this is not the case when used as a secondary (comorbid) diagnosis (with positive predictive values as low as 55% in forensic samples),[57] and was therefore excluded. Finally, the 2012 review reported a number of psychosis-specific symptoms and symptom scores (e.g., low impulse control) as risk factors for violence, though these could not be included as they are not routinely recorded in Swedish registers. Symptoms are not collected in the Patient Register, rather these registers are limited to ICD diagnostic codes.

Socio-demographic factors

Family disposable income at age 15 was used as a proxy for income, and used as a dichotomous variable (lowest tertile vs. top two tertiles). If this was unavailable, family disposable income, at age 16 was used or at the age when it first became available. Single marital status was defined as being unmarried at first diagnosis. Immigrant status was defined as being born outside of Sweden. Missing data were not replaced by imputation or other methods.

Parental factors

Data were extracted on parental immigration status (born abroad), and suicide, convictions of a violent offence, psychiatric diagnoses, and alcohol or drug diagnoses, occurring before their child's first diagnosis of schizophrenia-spectrum disorder to avoid issues of reverse causality.

Drug and alcohol

Drug and alcohol use disorders were defined using inpatient (1972–2008) and outpatient (2001–2008) primary or secondary diagnoses (ICD-8: 303, 304; ICD-9: 303, 304, 305.1, 305.9; ICD-10: F10-F19, except x.5) in patients and controls.

Number of inpatient beds

As a proxy for number of psychiatric inpatient beds, I extracted the total number of nights in inpatient episodes in the entire psychiatric patient population, for each year from 1972 to 2009.

Risk factor analyses

Individuals with schizophrenia-spectrum disorders were followed longitudinally after diagnosis until their first conviction for a violent offense, emigration, death, or end of follow-up (Dec 31, 2009). I used Cox regression modelling that provided hazard ratios

(HRs) with 95% confidence intervals (CIs), to account for time-at-risk. All analyses were stratified by sex. To examine the mechanisms behind risk factors, I estimated hazard ratios, for the same outcome and exposures, in unaffected siblings and general population controls. To assess interactions between the three strongest risk factors (self-harm, substance abuse, violent criminality), I report (i) two- and three-way interaction terms and significance, (ii) Harrell's concordance-index statistics for models with and without interaction terms,[72] and (iii) absolute rates of adverse outcomes in those with none, one, or more risk factors.

Time trends

As per related work using matched controls,[8] I estimated the association between having been diagnosed with schizophrenia and causes of death, using the clogit command in Stata, version 12 (StataCorp). The clogit command fits conditional (fixed effects) logistic regression models to matched case–control groups. I included two confounders (low family income, and born abroad) on theoretical grounds, and also tested whether they were each independently associated with either case or control and outcome measures, respectively, in univariate analyses at the 5% level of significance.[73]

For each outcome, I calculated odds ratios (adjusted for low income and being born abroad) by year of diagnosis in patients with schizophrenia-spectrum disorders compared to age- and sex-matched controls, using conditional logistic regression. Age at first diagnosis (i.e., age at beginning of follow-up) was included as an interaction term to account for period effects. Next, I similarly calculated odds ratios in unaffected siblings compared to general population controls. Finally, I produced graphs showing annual ratios of these two odds ratios to compare relative trends in patients and unaffected siblings. Graphs show data points from 1979 onwards (as there was low incidence of sibling outcomes before this date) using three year rolling averages.

To statistically test for trends over time, I included the interaction term between casenesss and year of first diagnosis.[74] The coefficient of this term shows the change in the odds ratio of an adverse outcome for each additional calendar year.

Then, I compared patient analyses to sibling analyses using ratios of odds ratios (ROR).[75] This ROR takes into account temporal changes in unaffected siblings (Figure I.1, page 22). An ROR of 1.0 would mean that the time trend in e.g., violence in patients with schizophrenia (compared to the general population) is the same as the time trend in unaffected siblings (compared to the general population), i.e., the time trend in violence in patients with schizophrenia is fully confounded by environmental and genetic factors shared by siblings.

In a separate trend analysis, the number of annual inpatient nights (in millions) was included as an interaction term (instead of year of diagnosis) to ecologically examine the association between inpatient bed use and odds ratios of adverse outcomes.

All analyses were conducted using SPSS, version 20 (SPSS Inc., Chicago, Ill.) and STATA, version 12 (Stata Corp., College Station, Tex.).

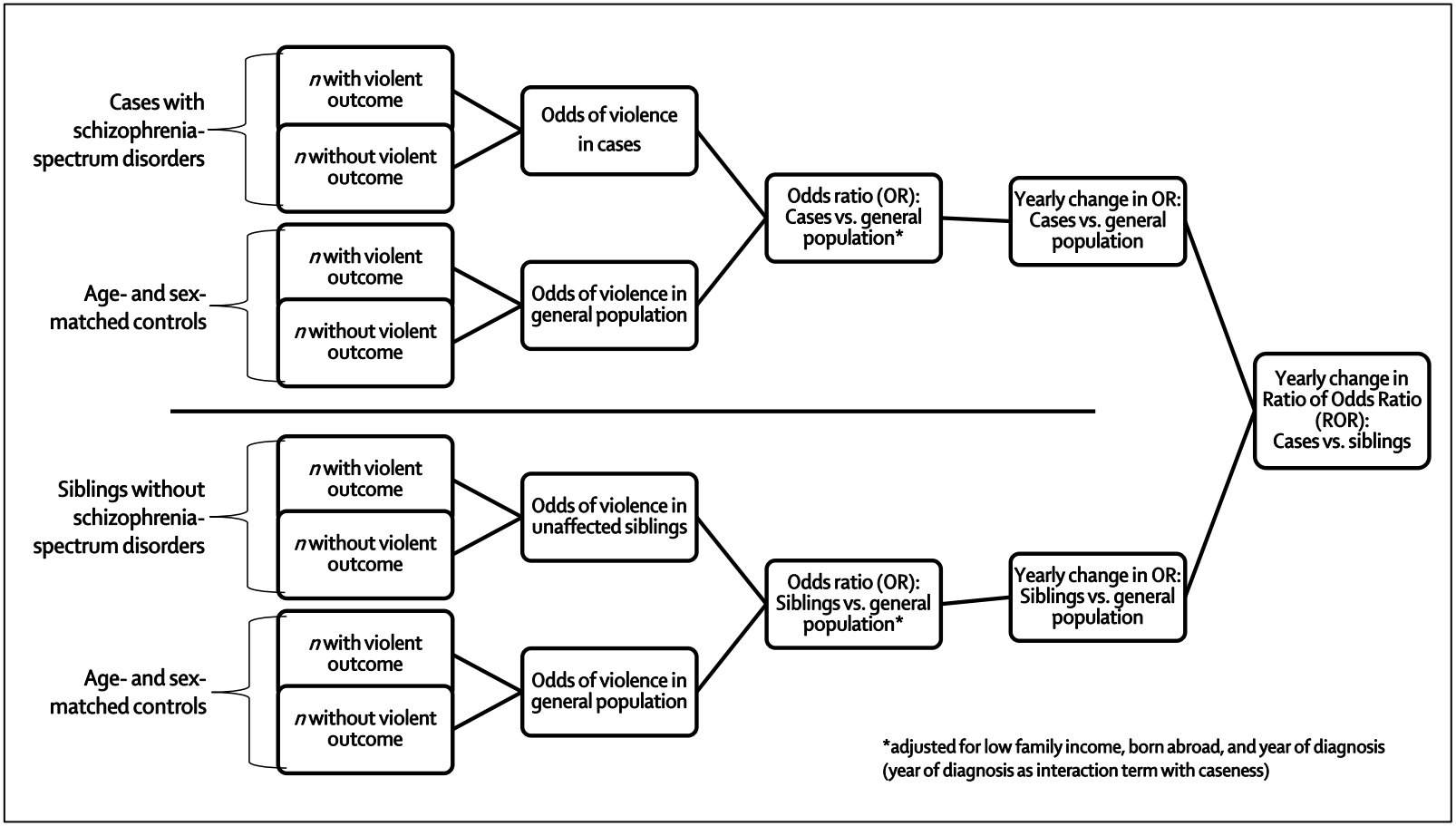

Figure I.1. Ratio of Odds Ratios. This figure illustrates the analyses used to compare relative changes in adverse outcomes in patients, to the relative changes in their unaffected siblings.

Findings

Descriptive statistics of 24,297 individuals (14,261 men, and 9,676 women) with diagnoses of schizophrenia-spectrum disorders between 1972 and 2009 are presented in Table I.1 (page 23). Men had a mean age at first diagnosis of 28.8 (SD=7.8) and women 29.8 (SD=8.3). The mean (SD) follow-up time was 9.5 years (SD=7.6) for convictions of a violent offence, and 10.6 years (SD=7.8) for mortality. In patients, 13.9% of men and 4.7% of women experienced a major adverse outcome within 5 years of first diagnosis (Figure I.2, page 24).

	Men (n=14,621)	Women (n=9,676)
Schizophrenia	5,704 (39.0%)	2,846 (29.4%)
Socioeconomic factors		
Age at 1st diagnosis (SD)	28.8 (7.8)	29.8 (8.3)
Income in lowest tertile	5,723 (39.1%)	4,026 (41.8%)
Born abroad	3,639 (24.9%)	2,400 (24.8%)
Single	11,592 (79.3%)	6,588 (68.1%)
Parental factors before diagnosis		
Alcohol or drug use disorders	809 (5.5%)	463 (4.8%)
Any offence	911 (6.2%)	594 (6.1%)
Violent offence	423 (2.9%)	266 (2.7%)
Suicide	268 (1.8%)	202 (2.1%)
Psychiatric diagnosis	1,369 (9.4%)	872 (9.0%)
Born abroad	1,930 (13.2%)	1,108 (11.5%)
Individual factors before diagnosis		
Alcohol use disorders	1,047 (7.2%)	410 (4.2%)
Drug use disorders	1,501 (10.3%)	600 (6.2%)
Any offence	6,507 (44.5%)	1,639 (16.9%)
Violent offence	3,409 (23.3%)	497 (5.1%)
Non-violent offence	5,966 (40.8%)	1,501 (15.5%)
Self-harm	1,419 (9.7%)	1,440 (14.9%)

Table I.1. Descriptive data for risk factors in patients with schizophrenia-spectrum disorders

The prevalence of individual risk factors before diagnosis was higher in individuals with schizophrenia-spectrum disorders compared to their unaffected siblings (Table I.2, page 24) or age and sex-matched general population controls (Table I.3, page 25).

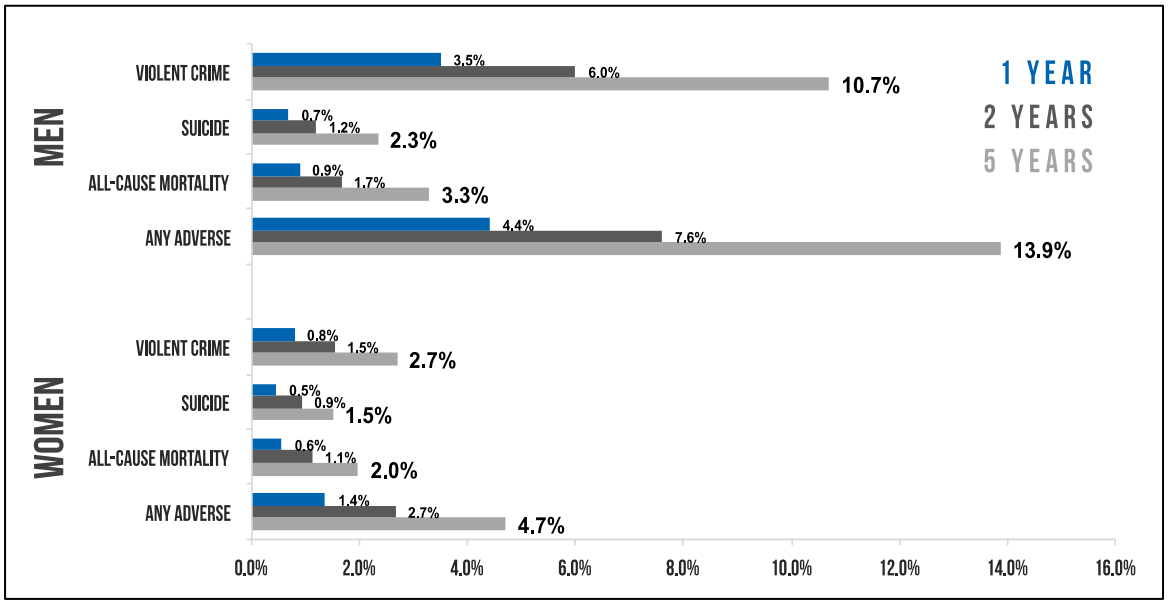

Figure I.2. Incidence of conviction of a violent offence, suicide, premature mortality, and any adverse outcome within 1, 2, and 5 years of first diagnosis in patients with schizophrenia-spectrum disorders

	Men (n=13,577)	Women (n=12,780)
Socioeconomic factors		
Income in lowest tertile	3,109 (22.9%)	3,262 (25.5%)
Born abroad	1,599 (11.8%)	1,581 (12.4%)
Parental factors before matching		
Alcohol or drug use disorders	300 (2.2%)	295 (2.3%)
Any offence	663 (4.9%)	672 (5.3%)
Violent offence	246 (1.8%)	243 (1.9%)
Suicide	255 (1.9%)	225 (1.8%)
Psychiatric diagnosis	801 (5.9%)	810 (6.3%)
Born abroad	2,521 (18.6%)	2,458 (19.2%)
Individual factors before matching		
Alcohol use disorders	345 (2.5%)	144 (1.1%)
Drug use disorders	214 (1.6%)	106 (0.8%)
Any offence	3,949 (29.1%)	1,059 (8.3%)
Violent offence	1,344 (9.9%)	167 (1.3%)
Non-violent offence	3,703 (27.3%)	998 (7.8%)
Self-harm	266 (2.0%)	422 (3.3%)

Table I.2. Descriptive data for risk factors in unaffected siblings

	Men (n=292,420)	Women (n=193,520)
Socioeconomic factors		
Income in lowest tertile	82,900 (28.3%)	58,471 (30.2%)
Born abroad	53,806 (18.4%)	35,626 (18.4%)
Parental factors before matching		
Alcohol or drug use disorders	9,744 (3.3%)	6,579 (3.4%)
Any offence	13,536 (4.6%)	8,931 (4.6%)
Violent offence	3,975 (1.4%)	2,574 (1.3%)
Suicide	3,138 (1.1%)	2,180 (1.1%)
Psychiatric diagnosis	12,996 (4.4%)	8,871 (4.6%)
Born abroad	21,104 (7.2%)	13,797 (7.1%)
Individual factors before matching		
Alcohol use disorders	2,834 (1.0%)	1,156 (0.6%)
Drug use disorders	1,570 (0.5%)	755 (0.4%)
Any offence	54,633 (18.7%)	9,644 (5.0%)
Violent offence	14,452 (4.9%)	1,090 (0.6%)
Non-violent offence	50,775 (17.4%)	9,159 (4.7%)
Self-harm	3,133 (1.1%)	3,071 (1.6%)

Table I.3. Descriptive data for risk factors in general population controls

Violence risk factors

Among individuals with schizophrenia-spectrum disorders, 10.7% of men and 2.7% of women were convicted of a violent offence within 5 years of first diagnosis (Figure I.2, page 24). A number of socio-demographic factors (low income and being born abroad), and individual factors before first diagnosis (previous conviction, and drug and alcohol use) were associated with violent convictions in patients and unaffected siblings.

Risk factors in the comparison groups were in the same direction as in the cases, but hazard ratios were mostly higher in unaffected siblings and general population controls (Table I.4, page 26). For instance, drug use disorders increased the risk of violent crime 3.1 times in male patients, 10.4 times in male unaffected siblings, and 16.2 times in male general population controls (all compared to individuals in the same sample but without drug use disorders). This observed gradient in hazard ratios from cases, to unaffected siblings, to general population controls is consistent with previous research reporting shared aetiology between schizophrenia-spectrum disorders, substance misuse, and adverse outcomes.[76]

	Schizophrenia	Unaffected siblings	General population
Socioeconomic factors			
Sex			
Male	3.3 (3.0-3.6)	6.3 (5.3-7.6)	7.8 (7.2-8.5)
Low income			
Male	1.4 (1.3-1.5)	1.6 (1.4-1.9)	1.7 (1.7-1.8)
Female	1.4 (1.2-1.7)	2.1 (1.5-3.0)	2.1 (1.8-2.5)
Born abroad			
Male	1.7 (1.5-1.8)	2.4 (2.0-2.8)	2.1 (2.0-2.2)
Female	1.4 (1.2-1.7)	1.8 (1.1-2.7)	2.0 (1.7-2.4)
Single			
Male	1.0 (0.9-1.1)	n/a	1.0 (0.9-1.0)
Female	1.0 (0.8-1.2)	n/a	0.9 (0.8-1.1)
Parental factors before diagnosis			
Alcohol or drug use disorders			
Male	1.8 (1.5-2.1)	1.6 (1.1-2.4)	2.5 (2.3-2.7)
Female	1.9 (1.4-2.7)	3.1 (1.5-6.2)	3.1 (2.4-4.0)
Any offence			
Male	1.3 (1.1-1.6)	1.4 (1.1-1.9)	1.7 (1.6-1.9)
Female	1.5 (1.1-2.0)	1.7 (0.9-3.3)	2.2 (1.7-2.9)
Violent offence			
Male	2.1 (1.8-2.6)	2.7 (1.9-3.8)	3.5 (3.1-3.9)
Female	2.0 (1.3-3.1)	3.9 (1.9-8.1)	4.7 (3.4-6.5)
Suicide			
Male	1.3 (1.0-1.7)	1.9 (1.3-2.8)	1.7 (1.4-2.0)
Female	1.6 (1.0-2.6)	2.0 (0.7-5.3)	1.8 (1.1-3.1)
Psychiatric diagnosis			
Male	1.1 (1.0-1.3)	1.2 (0.9-1.6)	1.6 (1.5-1.8)
Female	1.4 (1.1-1.9)	2.0 (1.2-3.5)	2.0 (1.5-2.6)
Born abroad			
Male	1.4 (1.3-1.6)	2.3 (2.0-2.6)	2.2 (2.0-2.3)
Female	1.3 (1.0-1.7)	2.0 (1.4-2.9)	1.8 (1.4-2.3)
Individual factors before diagnosis			
Alcohol use disorders			
Male	2.6 (2.3-2.9)	7.4 (5.9-9.3)	9.0 (8.2-9.9)
Female	4.5 (3.4-6.0)	21.3 (12.7-35.6)	19.8 (14.6-26.7)
Drug use disorders			
Male	3.1 (2.8-3.5)	10.4 (8.1-13.4)	16.2 (14.6-17.9)
Female	5.1 (4.1-6.5)	23.4 (13.4-41.1)	36.0 (27.0-48.0)
Any offence			
Male	3.8 (3.5-4.1)	6.7 (5.8-7.7)	7.0 (6.7-7.3)
Female	5.0 (4.2-6.0)	12.7 (9.0-17.8)	13.9 (11.9-16.2)
Violent offence			
Male	4.3 (4.0-4.7)	9.9 (8.6-11.4)	11.6 (11.1-12.2)
Female	7.7 (6.2-9.6)	24.5 (15.5-38.6)	33.8 (27.0-42.2)
Non-violent offence			
Male	3.5 (3.2-3.8)	6.1 (5.3-7.0)	6.5 (6.3-6.8)
Female	4.9 (4.1-5.8)	12.2 (8.7-17.2)	12.8 (11.0-15.0)
Self-harm			
Male	1.8 (1.6-2.1)	5.8 (4.3-7.6)	5.7 (5.2-6.4)
Female	1.5 (1.2-1.9)	10.2 (6.8-15.5)	8.5 (6.6-10.9)

All values are hazard ratio (95% confidence interval); all analyses adjusted by age at diagnosis

Table I.4. Risk factors for conviction of a violent offence in patients with schizophrenia, unaffected siblings, and general population controls

In fact, the 2016 paper using Swedish total population family-based genetic models found that between half and two-thirds of the correlations between severe mental illness, substance misuse and violence were explained by shared genetic factors. An additional explanation for this finding is a so-called statistical 'ceiling effect'. (1) As patients have on average a higher number of risk factors (including the risk factor of having a diagnosis of schizophrenia-spectrum disorder), individual risk factors do not have an additive effect on adverse outcomes but have diminishing marginal effects. (2) In groups with lower base rates of violence (e.g., general population controls), small changes in absolute risk translate into larger changes in relative risks (e.g., an increase from 0.1% to 0.6% is equivalent to an absolute increase from 0.5% to 1.0%, but is a six-fold relative increase compared to a two-fold relative increase), which is also observed in the case of higher hazard ratios in female samples (who have lower base rates).

Risk factor interactions

For violence, the substance use and violence interaction term was significant (HR=0.7, 95% CI: 0.5-0.8), meaning that the increased risk of violence due to both previous violence and substance abuse is smaller than that of the two individual risk factors combined (Table I.5, page 27). The same was true for all pair-wise interaction for all-cause mortality (Table I.5). However, the three-way interaction (self-harm, previous violent crime, substance abuse disorders) was significantly raised (HR=2.2, 95% CI: 1.1-4.1). No significant risk factor interactions were found in suicide mortality.

Interaction	Violence	Suicide	All-cause
Substance use x Violence	0.7 (0.5-0.8), p<0.001	p=0.949	0.6 (0.4-0.8), p=0.003
Substance use x Self-harm	p=0.332	p=0.388	0.6 (0.4-0.9), p=0.026
Violence x Self-harm	p=0.697	p=0.375	0.6 (0.4-0.9), p=0.028
Three-way Interaction	p=0.687	p=0.963	2.2 (1.1-4.1), p=0.019

Table I.5. Interactions between three key risk factor and adverse outcomes in patients with schizophrenia-spectrum disorders

			Violence				Suicide				All-cause			
			Male		Female		Male		Female		Male		Female	
			HR	Obs5yr	HR	Obs5yr	HR	Obs5yr	HR	Obs5yr	HR	Obs5yr	HR	Obs5yr
O	O	O	1.0 (ref)	6.8%	0.4 (0.3-0.5)	1.8%	1.0 (ref)	2.3%	0.6 (0.5-0.8)	1.4%	1.0 (ref)	3.0%	0.7 (0.6-0.8)	1.8%
X	O	O	2.5 (2.3-2.7)	15.1%	1.1 (0.9-1.3)	6.5%	1.3 (1.0-1.7)	2.1%	0.8 (0.5-1.3)	2.4%	2.1 (1.9-2.3)	5.0%	1.4 (1.2-1.7)	2.9%
O	X	O	1.2 (1.0-1.4)	9.5%	0.5 (0.3-0.8)	3.0%	2.3 (2.1-2.5)	6.3%	1.5 (1.2-1.7)	3.1%	2 (1.8-2.2)	7.3%	1.3 (1.2-1.5)	3.5%
O	O	X	3.9 (3.8-4.0)	24.1%	1.6 (1.5-1.8)	12.0%	1.3 (1.1-1.5)	2.9%	0.8 (0.6-1.2)	0.5%	1.6 (1.5-1.8)	4.5%	1.1 (0.9-1.3)	0.5%
X	X	O	2.5 (2.3-2.8)	13.4%	1.1 (0.8-1.4)	7.1%	2.4 (2.0-2.8)	4.2%	1.5 (1.2-2.0)	2.9%	2.7 (2.4-3.0)	5.7%	1.8 (1.5-2.2)	4.6%
X	O	X	6.5 (6.4-6.7)	35.7%	2.8 (2.6-3.0)	32.8%	1.7 (1.5-2.1)	3.4%	1.1 (0.8-1.5)	1.1%	2.1 (1.9-2.3)	5.2%	1.4 (1.2-1.7)	3.6%
O	X	X	4.8 (4.6-5.1)	30.2%	2.1 (1.8-2.3)	16.8%	2.3 (1.9-2.8)	4.8%	1.5 (1.1-2.0)	2.1%	2.0 (1.7-2.4)	5.7%	1.3 (1.0-1.8)	3.7%
X	X	X	7.6 (7.4-7.8)	39.3%	3.2 (3.0-3.5)	28.4%	2.4 (2.0-2.8)	3.9%	1.5 (1.2-2.0)	8.4%	3.5 (3.3-3.8)	6.4%	2.4 (2.1-2.7)	17.4%

HR=Hazard ratio and 95% Confidence Interval. Obs5yr=adverse events observed within 5 years of diagnosis

Table I.6. Hazard ratios and 5-year rates of adverse outcomes for men and women with schizophrenia-spectrum disorders with or without risk factors

Hazard ratios in those with one or more risk factors are presented in Table I.6 (page 28), using a model with pair-wise and three-way interactions. For violence, observed 5-year rates ranged from 1.8% in women with no risk factors, to 39.3% in men with all three risk factors. Five-year suicide rates ranged from 0.5% to 8.4%, and all-cause mortality rates from 0.5% to 17.4%.

To evaluate improvements in model discrimination, concordance statistics were compared in models with and without interactions. However, including interaction terms had negligible effects on discrimination for violence (C-index of 0.691 with or without interactions), suicide (0.571 with or without interactions), and all-cause mortality (0.585 with or without interactions).

Time trends

There was evidence of an increase, between 1972 and 2009, in the adjusted odds ratios of violence, suicide, and all-cause mortality in schizophrenia-spectrum patients compared to general population controls. To test for residual confounding in this association, I also investigated trends for risks of adverse outcomes in unaffected siblings compared to general population controls and found an increase in the odds ratio of all-cause mortality, but not violence or suicide. Finally, comparing these two analyses (and therefore comparing schizophrenia-spectrum patients to their unaffected siblings), I found an average yearly increase in the ratio of odds ratios of violence of 1.1% (95% CI: 0.1% to 2.2%; Figure I.3, page 33). A non-significant increase in this ratio of odds ratios was found for suicide (1.7% increase per year; 95% CI: -0.9% to 4.3%), and no significant changes for all-cause mortality (0.2% increase by year; 95% CI: -1.3% to 1.6%). No differences were found when stratifying by sex, immigration status, or previous substance use disorders (Table I.7 to Table I.9, pages 30-32).

	Increases in odds ratios of violence, by calendar year		
	(1) Patients vs. General population analysis aOR (95% CI)	(2) Unaffected siblings vs. General population analysis aOR (95% CI)	Ratio of Odds Ratios ROR (95% CI)
All (n=24,297)	1.3% (0.6% to 2.0%)	0.1% (-0.7% to 1.0%)	1.1% (0.1% to 2.2%)
Sex			
Male (n=14,621)	1.6% (0.9% to 2.4%)	0.1% (-0.8% to 0.9%)	1.6% (0.4% to 2.7%)
Female (n=9,976)	0.1% (-1.8% to 1.9%)	0.7% (-1.5% to 3.0%)	-0.6% (-3.5% to 2.3%)
Substance use			
With (n=5,056)	0.4% (-1.7% to 2.5%)	0.7% (-2.1% to 3.5%)	-0.3% (-3.7% to 3.2%)
Without (n=19,241)	0.6% (-0.3% to 1.5%)	0.0% (-1.0% to 1.1%)	0.5% (-0.8% to 1.9%)
Born abroad			
Yes (n=6,039)	0.7% (-1.4% to 2.8%)	-0.2% (-3.2% to 2.9%)	0.9% (-2.7% to 4.7%)
No (n=18,258)	1.3% (0.5% to 2.1%)	0.4% (-0.5% to 1.4%)	0.9% (-0.4% to 2.1%)

Table I.7. Effects of year of diagnosis on adjusted odds ratios of violence, stratified by sex, born abroad, and substance use disorder

	Increases in odds ratios of suicide, by calendar year		
	(1) Patients vs. General population analysis aOR (95% CI)	(2) Unaffected siblings vs. General population analysis aOR (95% CI)	Ratio of Odds Ratios ROR (95% CI)
All (n=24,297)	2.6% (1.0% to 4.3%)	1.0% (-1.0% to 3.0%)	1.7% (-0.9% to 4.3%)
Sex			
Male (n=14,621)	3.1% (1.2% to 5.0%)	1.5% (-0.8% to 3.9%)	1.5% (-1.5% to 4.6%)
Female (n=9,976)	1.0% (-2.4% to 4.5%)	-0.4% (-3.9% to 3.2%)	1.4% (-3.4% to 6.5%)
Substance use			
With (n=5,056)	5% (-0.7% to 11.1%)	4.2% (-3.4% to 12.3%)	0.8% (-8.2% to 10.8%)
Without (n=19,241)	2% (-0.1% to 4.1%)	1.1% (-1.3% to 3.5%)	0.9% (-2.2% to 4.1%)
Born abroad			
Yes (n=6,039)	4.2% (-6.7% to 16.4%)	-18.2% (-45.4% to 22.6%)	27.4% (-16.3% to 94%)
No (n=18,258)	2.2% (0.4% to 4.1%)	1.6% (-0.4% to 3.7%)	0.6% (-2.1% to 3.4%)

Table I.8. Effects of year of diagnosis on adjusted odds ratios of suicide, stratified by sex, born abroad, and substance use disorder

	Increases in odds ratios of all-cause mortality, by calendar year		
	(1) Patients vs. General population analysis aOR (95% CI)	(2) Unaffected siblings vs. General population analysis aOR (95% CI)	Ratio of Odds Ratios ROR (95% CI)
All (n=24,297)	1.6% (0.5% to 2.7%)	1.4% (0.4% to 2.5%)	0.2% (-1.3% to 1.6%)
Sex			
Male (n=14,621)	1.6% (0.4% to 2.9%)	1.4% (0.2% to 2.6%)	0.2% (-1.5% to 2.0%)
Female (n=9,976)	1.4% (-0.6% to 3.5%)	1.4% (-0.4% to 3.2%)	0.1% (-2.6% to 2.8%)
Substance use			
With (n=5,056)	3.3% (-0.4% to 7.2%)	0.9% (-3.1% to 5.2%)	2.4% (-3.1% to 8.2%)
Without (n=19,241)	0.8% (-0.5% to 2.2%)	1.4% (0.2% to 2.6%)	-0.5% (-2.3% to 1.2%)
Born abroad			
Yes (n=6,039)	-1.6% (-5.6% to 2.6%)	-4.7% (-10.7% to 1.6%)	3.3% (-4.3% to 11.6%)
No (n=18,258)	1.7% (0.5% to 2.9%)	1.9% (0.8% to 3.0%)	-0.2% (-1.8% to 1.4%)

Table I.9. Effects of year of diagnosis on adjusted odds ratios of all-cause mortality, stratified by sex, born abroad, and substance use disorder

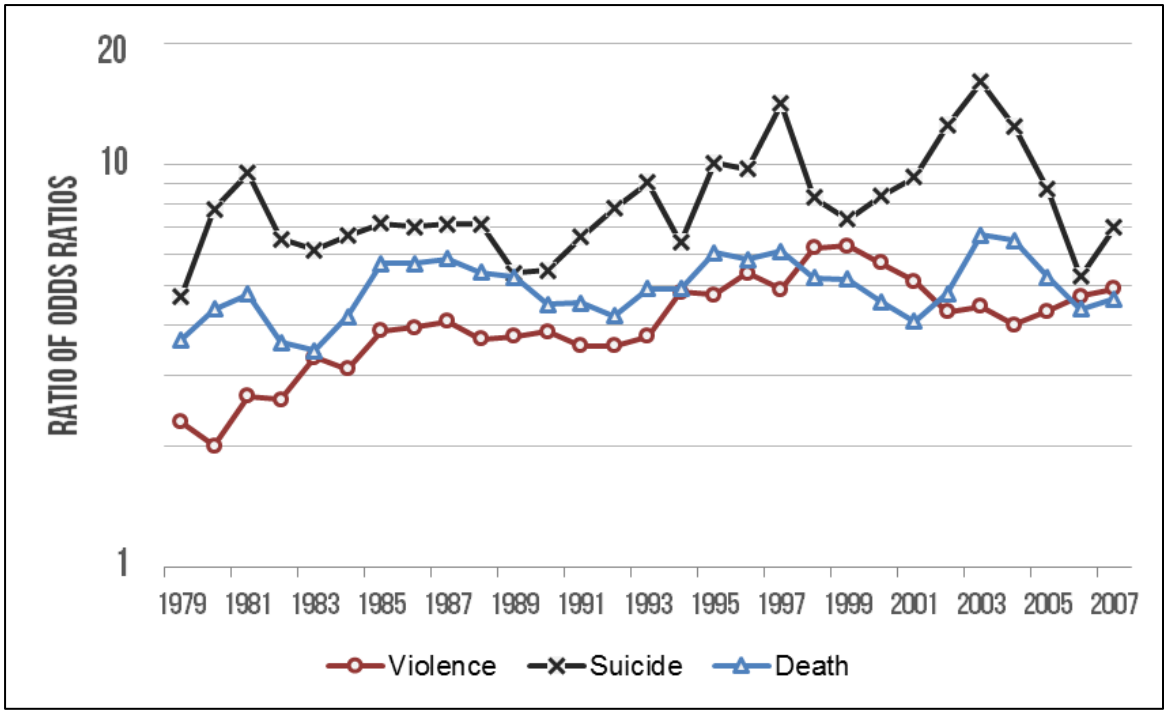

Figure I.3. Ratio of odds ratios of adverse outcomes, by year of diagnosis. The ratio of odds ratios compares the relative change in adverse outcomes in patients with schizophrenia-spectrum disorders to the relative change in their unaffected siblings, over time.

Yearly inpatient nights decreased steadily by an average of 0.3 million nights annually between 1973 and 2009. Examining the relationship between yearly inpatient nights and adverse outcomes, I found that the number of inpatient nights was negatively associated with violence but not significantly for suicide or all-cause mortality (Table I.10), i.e., a lower number of annual inpatient nights was associated with more violence perpetrated by those with schizophrenia-spectrum compared to unaffected siblings.

	Patients vs. General population aOR (95% CI)	Unaffected siblings vs. General population aOR (95% CI)	Ratio of Odds Ratios ROR (95% CI)
Violence	5.6% (3.5% to 7.6%)	-0.4% (-2.3% to 2.1%)	5.9% (2.6% to 8.4%)
Suicide	7.7% (3.3% to 11.8%)	2.3% (-2.9% to 7.2%)	5.5% (-1.3% to 11.8%)
All-cause mortality	5.1% (2.3% to 7.8%)	1.7% (-1.0% to 4.4%)	3.4% (-0.6% to 7.2%)

aOR = adjusted odds ratios; adjusted for low family income and being born abroad, and controls are age- and sex-matched. 95% CI = 95% Confidence Interval. The Ratio of Odds Ratios measures changes in rates of adverse outcomes in patients compared to unaffected siblings and is the ratio of the values in the first two columns.

Table I.10. Relationship between the number of yearly inpatient nights on adjusted odds ratios of adverse outcomes. For example, every year the odds ratio of violence in patients with schizophrenia-spectrum disorders compared to general population controls increased on average by 5.6%

Interpretation

In this study of 24,297 individuals with schizophrenia-spectrum disorders that were followed up for 38 years, I examined rates and risk factors for violence, as well as suicide and all-cause mortality. Within 5 years of first diagnosis, 10.7% of men with schizophrenia-spectrum disorders were convicted of a violent offence, 2.3% died from suicide and 3.3% died from all causes. In women, within 5 years of diagnosis, 2.7% were violently convicted, 1.5% died from suicide and 2.0% died from all causes. In total, 13.9% of the men and 4.7% of the women suffered one of these outcomes within 5 years of diagnosis. Although considerable research has focused on primary prevention in schizophrenia, the data suggest that secondary prevention of adverse outcomes remains a substantial challenge.

Investigating risk factors for these outcomes should assist in providing targets for intervention. Three risk factors typically increased risks for all three outcomes: drug use disorders, a history of violent criminality, and self-harm, all present before diagnosis. This may allow for identification of high-risk patients, but also suggests that those individuals at high risk of developing psychosis could benefit from interventions that reduce drug use, self-harm, and criminality. Early interventions services, increasingly being trialled in many countries,[77] could prioritise such interventions in addition to those that reduce the likelihood of progression to schizophrenia.

Trends in adverse outcomes over the last few decades have been the cause of considerable controversy in psychiatry.[23] Like many European countries, Sweden experienced deinstitutionalization from the 1970s in a gradual way. I used a novel approach to examine trends, and by comparing odds of adverse outcomes in patients compared with their unaffected siblings, I have tried to adjust for residual confounding; in other words, I have attempted to take account of secular changes that would

differentially affect the families of patients with severe mental illness compared with the general population (such as income or parental drug and alcohol use that does not come to medical attention). In addition, investigating the broad diagnostic category of schizophrenia-spectrum disorders limited the effects of changes over time in classification between individual psychoses. For conviction of a violent offence, there was an increase in risk compared with both general population controls and unaffected siblings over time. This was stronger when adjusted by changes in inpatient bed numbers. For suicide and all-cause mortality, there were increases in risk compared with general population controls, which remained increased in sibling comparisons, though non-significantly. Previous studies have used general population comparisons and found significant increases in all-cause mortality,[11,51] and suicide[78] over time, and my study confirms these findings using a more robust methodology. None of the trends I investigated were downward suggesting that new treatments have not translated in reducing adverse outcomes for these patients in Sweden. I did not find different trends when stratifying by sex, immigration background, or substance use.

Strengths & Limitations

This study benefits from a number of strengths, including the use of population registers and at least two patient episodes allowing me to obtain good diagnostic specificity with a large sample size. Furthermore, through register linkages, I examined risk factors occurring before diagnosis, and risk factors in general population and unaffected sibling controls. Weaknesses include a restricted set of risk factor information, and the study being conducted in a single country. However, as discussed above the prevalence of schizophrenia,[11] violent assault,[59] and suicide incidence[60] in Sweden are similar to that in other high-income countries, and the psychiatric morbidity of schizophrenia which is similar in Sweden and other Western countries.[61] Prevalences of psychotic disorders differ

minimally across European countries with a median prevalence of 1% for psychotic illness.[79] Another limitation is that I used patient registers, so prevalence rates of drug and alcohol use disorders will have been underestimated, particularly in population controls who may not come into contact with health services. However, this sample represents individuals who access services and, therefore, those for whom interventions could potentially be provided. I could not investigate modification of risk factors through treatment as these data are only available recently and solely for medication. Finally, controls in the sample may include those with other mental health issues, but no diagnoses of schizophrenia-spectrum disorders. Therefore findings may be conservative estimates, as other mental disorders are associated with adverse outcomes.

Conclusions

In conclusion, schizophrenia-spectrum disorders are associated with substantially increased rates of convictions of a violent offence, as well as suicide, and all-cause mortality. I have demonstrated that three factors are associated with these risks, namely self-harm, substance use disorders, and violent crime, which were also reported in the general population. A combination of population-based and targeted strategies may be necessary to reduce the risks of violence, suicide, and all-cause mortality. For instance, more restrictive or resource-intensive interventions may need to be limited to those with the highest risk of adverse outcomes to limit unnecessary treatment (and therefore side-effects) and overall costs. However, we can only adequately allocate targeted strategies if we are able to identify those who are at higher risk of offending and match them to interventions according to treatment needs. Therefore, the next chapter derives a risk prediction model in one such high-risk group, namely individuals discharged from secure mental health services, using findings on risk factor effects and interactions of this chapter.

Chapter II - Prediction of violent crime on discharge from secure psychiatric hospitals

Introduction

Over 90% of medium secure forensic units in England use one or more violence risk prediction tools,[43] and their use is recorded as a key NHS service outcome.[80] Current approaches are resource intensive and time consuming, taking up to 16 person-hours for the first assessment[81] and many hours for subsequent ones. Though simple scalable tools have been developed in general psychiatry, they have not been widely adopted.[82,83] Additionally, there is uncertainty around the extent to which the use of risk assessment tools have impacted outcomes, with only one randomised controlled trial to date reporting no improvements when adding a structured clinical judgment tool to existing routine violence risk assessment in mental health outpatients.[84]

Reviews of existing tools have reported three important limitations. First, a review of instruments used to predict violence and antisocial behaviour in 73 samples generally reported limited accuracy, and a mean sample size of less than two hundred individuals per study. [49] Second, a separate review found authorship bias in the publication of risk prediction tools, showing significantly higher predictive validity findings in studies conducted by the tool designers (compared to independently conducted validations) and no conflict of interest disclosures where appropriate.[85] A third review reported considerable variation in what constitutes 'high-risk' both across and within instruments,[42] so that using such categorizations in current tools has questionable usefulness.[86]

Furthermore, risk tools are typically developed in non-psychiatric samples and their external validity is worse in forensic psychiatric populations. For example, two recent

studies of the HCR-20's performance in predicting violence in forensic psychiatric populations in Belgium[87] and Scotland[88] both reported reduced AUCs of 0.60. Finally, the most commonly used tools were developed using methods that are now considered obsolete, and provide insufficient detail when reporting predictive validity studies.

Current tools require regular training that is typically a few days in duration and that usually costs hundreds of pounds,[89] with no indication that associated costs reflect predictive performance or clinical relevance. A number of tools are used to assess criminogenic needs as well as risk, therefore conflating both concepts and potentially detracting from their predictive accuracy. Due to these problems, simple scalable tools have been developed, including two for inpatient violence in psychiatry (Broset[90] and DASA[91]), one in severe mental illness for violent crime (OxMIV),[92] and another for use in released prisoners to predict violent reoffending (OxRec).[93] These types of tools have several advantages, including transparency in decision-making, the potential to help with the allocation of scarce resources and interventions based on risk, and may aid communication across services, in particular at transition points (e.g., from medium to low secure, or high to medium secure environments).

Based on the existing clinical and methodological literature, including the findings reported in Chapter I, this chapter describes the development of a simple, free, scalable tool to assess the risk of violence in patients discharged from secure and forensic psychiatric hospitals, using Swedish routinely collected data.

Methods

As discussed in Chapter I, the use of Swedish registers has a number of advantages, including longitudinal linkage between health and crime data, a relatively large total population, and nationwide coverage. The last of these characteristics is of particular importance here: a risk prediction tools created in a selected sample or non-nationwide cohort study may perform well in validation, but generalizability and performance in practice will be uncertain and likely reduced.

In particular, the methods in this chapter were designed to address common errors in the design and analysis of risk prediction tools. In a commentary piece on selecting risk assessment tools,[94] I propose a ten-point methodological guide to support decision makers; five of them are directly relevant to this derivation study. Two of the points focus on the need for a protocol, finalised before any statistical analyses are performed, to minimise the risk of multiple testing and outcome switching. The protocol should be written in a systematic and reproducible way, and the final paper should discuss and justify any methodological deviations.[95] Next, the number of variables considered for inclusion should be appropriate for the sample size. The general rule of thumb is that there should be no more than one variable tested for each 10 events in the sample (i.e., for each 10 violent crimes in this study).[96] Additionally, included variables should be weighted according to their statistical association with the outcome in multivariate models, rather than using simplistic equal weighting for all variables.[97] Finally, when external validation is not feasible, internal validation should be performed to provide an estimate of the accuracy of the reported performance measures. These considerations have all informed the methodology below.

With this in mind, I conducted a longitudinal cohort study of all individuals aged 15-65 discharged from secure and forensic psychiatric hospitals into the community between

1992 and 2013 through linkage of population-based registers in Sweden. The final study cohort consisted of all discharged individuals, with a single discharge for each patient, selected at random, with equal probability. This means that all individuals were included and, for each individual, all but one discharge was discarded. Repeat discharges complicate model fitting and interpretation, and were excluded. Each individual was followed from the day of discharge until first violent offending, death, emigration or end of follow-up (12 or 24 months post-discharge). If an individual was rehospitalised without a reoffence, this did not end follow-up as crimes committed during rehospitalisation were included. The study was approved by the Regional Ethics Committee at Karolinska Institutet.

Measurement of risk factors

Using similar methodology to the study in Chapter I, data from several national registers were linked to obtain information on risk factors, with unique personal identification numbers enabling accurate linkage.[62] Socio-demographic factors were obtained from the Total Population Register[98] and the Longitudinal Integration Database for Health Insurance and Social Studies. Civil status (ever married versus never married) was classified as a binary variable. Number of years in education was recoded as a categorical variable (9 years, 9-12 years, >12 years). From the National Crime Register, I obtained information on any previous violent crime conviction. In line with previous work[67] and the study in Chapter I, violent crime was defined as homicide, assault, robbery, arson, any sexual offence, or threats and harassment. Serious violent crime was defined as homicide or attempted homicide, aggravated assault, aggravated robbery, rape, sexual coercion, or sexual exploitation.

Psychiatric disorders were extracted from the National Patient Register, which provides diagnoses for all inpatient psychiatric hospital admissions in Sweden since 1973 and

outpatient care since 2001, according to the International Classification of Diseases (Eighth Revision [ICD-8], 1973-1986; Ninth Revision [ICD-9], 1987-1996; or Tenth Revision [ICD-10], 1997-2009).

The following specific/groups of psychiatric disorders were investigated: (1) primary diagnosis at discharge - as schizophrenia-spectrum disorders (ICD-9: 295, 297, 298 ; ICD-10: F20-F29), bipolar disorders (296 excl. 296D; F30-F31), unipolar depression (296B, 300E, 311; F32-F34.1), Anxiety disorder (300 excl. 300E, 309 ; ICD-10: F41, F43, F44, F45, F48), and other primary diagnoses (2) drug use disorder at hospitalization or discharge (292, 304, 305X; F11-F19), (3) alcohol use disorder at hospitalization or discharge (291, 303, 305A; F10), (4) diagnosis of personality disorder at discharge (301; F60-F62) (5) number of previous inpatient episodes (≥ 5 episodes, or < 5), (6) one or more previous forensic inpatient episodes, (7) any drug use disorder (lifetime), (8) any alcohol use disorder (lifetime), and (9) length of stay of current forensic hospital episode (≥1 year vs. <1 year).

Measurement of outcomes

The primary outcome was the occurrence of violent offending within 24 months of discharge from hospital, with 12 months post-discharge a secondary outcome. Repeat offences by an individual within these two years were not considered. Violent crime was defined as above.

Statistical methods

Statistical analysis was based on Cox regression, adjusting for risk factors as described below. The statistical protocol for FoVOx can be found in Appendix A (page 135)

Adjustment for risk factors

Based on existing evidence into criminal history, socio-demographic and clinical factors,[71,99] the results presented in Chapter I, and discussions with clinical colleagues, variables were grouped on the anticipated strength of association with the outcome in two levels of priority.[96,100] All variables were categorised in this way, a priori before any statistical analysis was carried out (see below for description of variable groups). Table II.3 (page 50) specifies the group to which each variable was assigned. This approach was followed for three reasons. First, the maximum number of candidate variables was based on statistical power considerations, with no more than one variable to be considered per 10 events. This reduces the chance of identifying spurious associations. Second, to limit the number of candidate variables, those thought essential for face validity were included regardless of significance. For instance, age and sex are known to be two of the strongest predictors for violence, and a model without their inclusion may be less acceptable to clinicians.[94] Third, a risk tool based on a more parsimonious model requires less workload and is easier to complete by clinicians, and external validation more likely to be feasible (as not all variables may be available in new samples).

Risk factor groups

Group 1 consists of variables thought necessary to include in the statistical model regardless of statistical significance, in order to ensure face validity and to reduce the number of candidate predictors used in the variable selection procedure described below.

Group 2 consists of variables thought likely to show an association with the outcome, but which are not required to be included to achieve face validity. These variables were included in a backwards stepwise selection procedure, with Group 1 variables always retained in the model, such that they were sequentially rejected in order of p-value until no Group 2 variables remained with p-values greater than 0.1.

Interaction effects were not considered. Testing for interaction effects would have required a substantially increased sample size to prevent multiple testing leading to false positives, and was therefore not included in our protocol. Additionally, interaction effects complicate interpretation of results, and analyses in Chapter I suggest that inclusion of interaction terms have no significant effect on predictive performance.

Missing data

Missing data was imputed via multiple imputation using chained equations (with twenty imputations) using a regression model that used as explanatory variables all other risk factors that were candidates for inclusion in the model, and the outcome variable.[101] Estimates of coefficients in the final prediction rule were obtained by pooling across imputations, and presenting 95% confidence intervals.[102]

Internal validation and goodness of fit

As discussed above, both derivation and external validation studies require a minimum number of events for statistical power. It was therefore not possible, given the relatively small number of forensic psychiatric inpatients in Sweden, to perform both a derivation and external validation study. The validity of the model was therefore assessed internally only.

A common form of internal validation consists of splitting the original sample into two random groups and calculating performance measures in both subsamples. This form of splitting is occasionally presented as an external validation, but it is not due to the randomization and equal distribution of predictor variables. It is also a statistically inefficient form of internal validation, unlike bootstrapping methods. Bootstrapping is a statistical tool relying on random sampling with replacement to measure the accuracy of sample estimates,[103] in this case sensitivity, specificity, and positive and negative

predictive values. Bootstrapping was used to create 100 samples drawn with replacement from the dataset, with averages and confidence intervals presented, essentially showing the certainty around estimates after random resampling.

Predictive accuracy was summarised using the following measures: 1) the concordance index[72] to assess discrimination (ability of the model to distinguish between those who do and do not commit a violent crime, with a value of one meaning perfect discrimination); 2) the Brier score[104] for calibration (model goodness of fit – whether the predicted risk is systematically off target, with zero meaning perfect calibration); the Brier score measures the mean squared difference between the predicted probability and the actual outcome (violent crime or no violent crime) 3) sensitivity (true positive rate), specificity (true negative rate), positive predictive value, and negative predictive value based on the 5% and 20% thresholds of predicted probability at 12 and 24 months post-discharge.[105] These measures were calculated using the predicted probabilities obtained by averaging the predictions from each of the multiply-imputed datasets, each applied to the final model. Pre-specified cut-offs were informed by a systematic review of 15 studies on violent offending following discharge from forensic psychiatric hospitals,[106] that reported a pooled rate of 3,900 per 100,000 person-years, or around 4% per year. The proportional hazards assumption was tested using the Grambsch and Therneau test.[107] The proportions of predicted and observed events at different levels of predicted probability were compared using a calibration plot.

Sensitivity analyses

Two sensitivity analyses were performed, which were not pre-specified. First, I re-fitted the final model using only discharges in 2001 or later (introduction of ICD-10) to examine differences in the effects of risk factors due to secular trends or reporting differences.

Second, I re-fitted the model in those under 40 only, as some sociodemographic variables may be have been recorded differently in older patients.

Stata (version 12) and R version 3.2.1 were used for all analyses. The TRIPOD statement was followed (Table II.1, page 47).[95]

Web calculator

The model coefficients were used to develop a web calculator called FoVOx (Forensic psychiatry and Violence tool Oxford), which is free to use, and available through the OxRisk.com platform. This calculator provides both a risk classification (low [<5%], medium [5-20%], high [≥20%]; based on 24 month violent offending risk) and a probability of violent offending within the next 12 or 24 months.

I created the OxRisk.com platform to enable intuitive and easy access to FoVOx (as well as several other risk calculators) from any device with a connection to the internet. The platform is based on WordPress, a free and open-source content management system used by over a quarter of all websites worldwide.[108] WordPress technology was chosen due to its strong security features (including end to end encryption and regular security updates)[109] and a broad range of available plugins to expand its functionality.

I used the 'Calculated Fields Form' plugin[110] which was adapted to create a form with dynamically calculated fields, based on the coefficients from the FoVOx model (see Figure I.1, page 48, for a screenshot of the OxRisk.com editing platform). This setup provides a straightforward way to add additional risk tools, and create versions in multiple languages. The OxRisk.com platform now hosts four different calculators in up to four languages, with an adaptive design for mobile devices.

Section/Topic			Checklist Item	Page
Title and abstract				
Title	1	D;V	Identify the study as developing and/or validating a multivariable prediction model, the target population, and the outcome to be predicted.	37
Abstract	2	D;V	Provide a summary of objectives, study design, setting, participants, sample size, predictors, outcome, statistical analysis, results, and conclusions.	-
Introduction				
Background and objectives	3a	D;V	Explain the medical context (including whether diagnostic or prognostic) and rationale for developing or validating the multivariable prediction model, including references to existing models.	37-38
	3b	D;V	Specify the objectives, including whether the study describes the development or validation of the model or both.	
Methods				
Source of data	4a	D;V	Describe the study design or source of data (e.g., randomized trial, cohort, or registry data), separately for the development and validation data sets, if applicable.	39-40
	4b	D;V	Specify the key study dates, including start of accrual; end of accrual; and, if applicable, end of follow-up.	
Participants	5a	D;V	Specify key elements of the study setting (e.g., primary care, secondary care, general population) including number and location of centres.	39-40
	5b	D;V	Describe eligibility criteria for participants.	
	5c	D;V	Give details of treatments received, if relevant.	
Outcome	6a	D;V	Clearly define the outcome that is predicted by the prediction model, including how and when assessed.	41
	6b	D;V	Report any actions to blind assessment of the outcome to be predicted.	-
Predictors	7a	D;V	Clearly define all predictors used in developing or validating the multivariable prediction model, including how and when they were measured.	42, T
	7b	D;V	Report any actions to blind assessment of predictors for the outcome and other predictors.	-
Sample size	8	D;V	Explain how the study size was arrived at.	40
Missing data	9	D;V	Describe how missing data were handled (e.g., complete-case analysis, single imputation, multiple imputation) with details of any imputation method.	43
Statistical analysis methods	10a	D	Describe how predictors were handled in the analyses.	42
	10b	D	Specify type of model, all model-building procedures (including any predictor selection), and method for internal validation.	42-43, T
	10c	V	For validation, describe how the predictions were calculated.	
	10d	D;V	Specify all measures used to assess model performance and, if relevant, to compare multiple models.	
	10e	V	Describe any model updating (e.g., recalibration) arising from the validation, if done.	-
Risk groups	11	D;V	Provide details on how risk groups were created, if done.	45
Development vs. validation	12	V	For validation, identify any differences from the development data in setting, eligibility criteria, outcome, and predictors.	-

Table II.1. TRIPOD Checklist

Results				
Participants	13a	D;V	Describe the flow of participants through the study, including the number of participants with and without the outcome and, if applicable, a summary of the follow-up time. A diagram may be helpful.	49, T
	13b	D;V	Describe the characteristics of the participants (basic demographics, clinical features, available predictors), including the number of participants with missing data for predictors and outcome.	
	13c	V	For validation, show a comparison with the development data of the distribution of important variables (demographics, predictors and outcome).	-
Model development	14a	D	Specify the number of participants and outcome events in each analysis.	49, T
	14b	D	If done, report the unadjusted association between each candidate predictor and outcome.	-
Model specification	15a	D	Present the full prediction model to allow predictions for individuals (i.e., all regression coefficients, and model intercept or baseline survival at a given time point).	T
	15b	D	Explain how to the use the prediction model.	55,T
Model performance	16	D;V	Report performance measures (with CIs) for the prediction model.	52-54, T
Model-updating	17	V	If done, report the results from any model updating (i.e., model specification, model performance).	-
Discussion				
Limitations	18	D;V	Discuss any limitations of the study (such as nonrepresentative sample, few events per predictor, missing data).	59-61
Interpretation	19a	V	For validation, discuss the results with reference to performance in the development data, and any other validation data.	-
	19b	D;V	Give an overall interpretation of the results, considering objectives, limitations, results from similar studies, and other relevant evidence.	58-59
Implications	20	D;V	Discuss the potential clinical use of the model and implications for future research.	58-63
Other information				
Supplementary information	21	D;V	Provide information about the availability of supplementary resources, such as study protocol, Web calculator, and data sets.	A
Funding	22	D;V	Give the source of funding and the role of the funders for the present study.	A

Items relevant only to the development of a prediction model are denoted by D, items relating solely to a validation of a prediction model are denoted by V, and items relating to both are denoted D;V.
We recommend using the TRIPOD Checklist in conjunction with the TRIPOD Explanation and Elaboration document. A: Appendix; T: Tables

Table II.1. TRIPOD Checklist (continued)

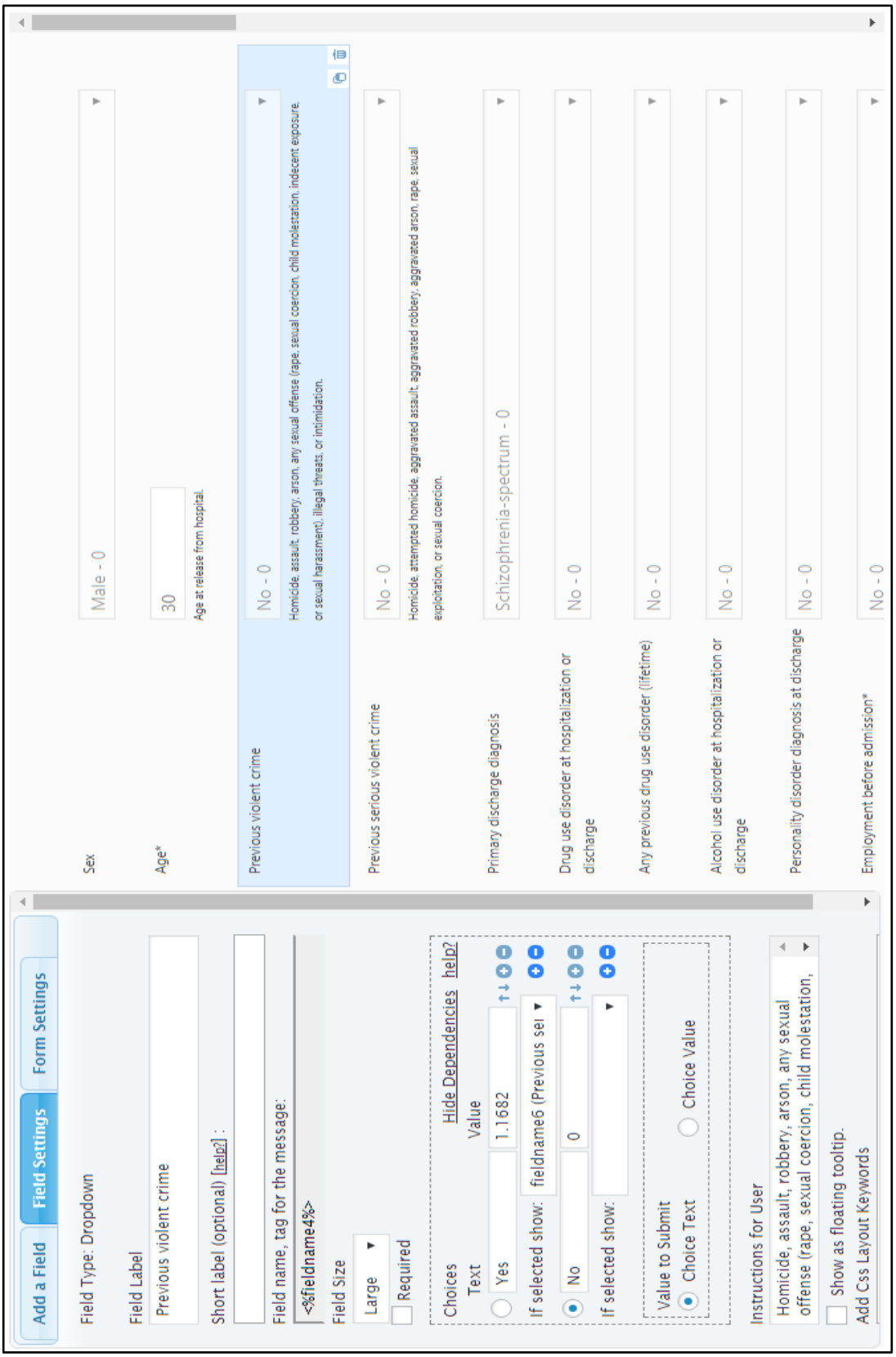

Figure II.1. OxRisk.com editing platform

Findings

In a cohort of 2,248 forensic psychiatric patients with 2,933 discharges into community settings between 1 January 1992 and 31 December 2013, 155 (6.9%) committed violent offences within 12 months, and 244 (10.9%) within 24 months; 34 (1.5%) committed a serious violent crime within 24 months (see Table II.2 for types of crime pre- and post-discharge). The median age at discharge was 36 years, and 86% of the cohort were male (Table II.2 for baseline characteristics).

Type of offence	Pre-discharge	Post-discharge*
Any violent crime	1,836 (81.7%)	244 (10.9%)
Serious violent crime	590 (26.2%)	34 (1.5%)
Homicide and attempted homicide	253 (11.3%)	8 (0.4%)
Aggravated assault	207 (9.2%)	20 (0.9%)
Aggravated robbery	24 (1.1%)	0 (0%)
Rape, sexual coercion, sexual exploitation	130 (5.8%)	6 (0.3%)
Other violent crime	1,470 (65.4%)	211 (9.4%)
Common assault	678 (30.2%)	98 (4.4%)
Assaulting an officer	390 (17.3%)	66 (2.9%)
Other sexual offences	79 (3.5%)	7 (0.3%)
Robbery	125 (5.6%)	14 (0.6%)
Arson	21 (0.9%)	0 (0%)
Threats and harassment	771 (34.3%)	111 (4.9%)
None	412 (18.3%)	2,004 (89.1%)

Some cases committed more than one type of crime. *First crime within 2 years of discharge

Table II.2. Number of individuals with violent crime pre- and post-discharge, by type of offence

Risk factors

Risk factors included in the final model were age at discharge, male sex, previous violent crime, previous serious violent crime, primary diagnosis at discharge, drug use disorder at hospitalization or discharge, alcohol use disorder at hospitalization or discharge, personality disorder diagnosis at discharge, employment before admission, five or more previous inpatient episodes, lifetime drug use disorder, and twelve or more months length of stay. The strongest predictors were previous violent crime (hazard ratio [HR]: 3.2; 95% CI 2.3 to 4.5) and sex (female vs. male HR: 0.4, 95% CI 0.3 to 0.6 (Table II.4).

Previous serious violent crime was associated with a lower risk than non-serious violent crime, but a doubling compared to no violent crime (as serious violent crime is a subset of all violent crime). The model showed good overall discrimination over the total follow-up (concordance index: 0.73). I found no significant differences in risk factors after conducting sensitivity analyses restricted to discharges post-2001 (Table II.5, page 51), or those under 40 (Table II.6, page 52).

Risk factors	n=2,248
Group 1 variables	
Sex (male)	1,938 (86%)
Age at discharge (IQR)	36 (29-45)
Previous violent crime	1,836 (81.7%)
Previous serious violent crime	590 (26.2%)
Primary diagnosis at discharge	
Schizophrenia-spectrum	944 (45.7%)
Bipolar disorder	130 (6.3%)
Unipolar depression	97 (4.7%)
Anxiety disorders	139 (6.7%)
Other*	754 (36.5%)
Drug use disorder at hospitalisation or discharge	540 (26.2%)
Alcohol use disorder at hospitalisation or discharge	219 (10.6%)
Personality disorder at discharge	563 (27.3%)
Group 2 variables	
Marital status (single)	1,648 (74.4%)
Employment before admission	171 (7.6%)
Educational level	
Lower secondary	1,084 (54.1%)
Upper secondary	819 (40.8%)
Post-secondary	102 (5.1%)
Number of previous inpatient episodes (five or more)	1,110 (52.6%)
Previous forensic inpatient episode (one or more)	755 (33.6%)
Lifetime drug use disorder	1,050 (49.0%)
Lifetime alcohol use disorder	780 (34.7%)
Length of stay in forensic hospital (12 months or more)	986 (43.9%)

Primary diagnosis, drug use and alcohol use disorders at hospitalization or discharge, and personality disorder had 8.2% of missing data. Educational level had 10.8% missing, marital status 1.4%, number of previous inpatient episodes 6.2%, lifetime drug use disorder 4.6%, and lifetime alcohol use disorder 5.7%.

*In the 'Other' group, 356 (47.2%) had a primary diagnosis of personality disorder, 152 (20.2%) alcohol or drug use disorder, 49 (6.5%) autism spectrum disorder.

Table II.3. Baseline characteristics and variable grouping for a cohort of secure psychiatric patients. Group 1 variables were included regardless of significance; Group 2 were tested for inclusion.

Variable	Hazard ratio (95% CI)	p-value
Sex (female)	0.43 (0.29-0.64)	<0.001
Age at discharge	0.97 (0.96-0.98)	<0.001
Previous violent crime	3.22 (2.28-4.53)	<0.001
Previous serious violent crime	0.64 (0.51-0.80)	<0.001
Primary diagnosis at discharge		
Schizophrenia spectrum	1.00 (ref)	n/a
Bipolar disorder	1.82 (1.24-2.66)	0.002
Unipolar depression	1.33 (0.83-2.14)	0.234
Anxiety disorders	1.12 (0.72-1.74)	0.610
Other	1.36 (1.06-1.73)	0.014
Drug use disorder at hospitalisation or discharge	0.89 (0.69-1.15)	0.366
Alcohol use disorder at hospitalisation or discharge	1.26 (0.94-1.67)	0.116
Personality disorder at discharge	1.36 (1.09-1.69)	0.006
Employment before admission	0.56 (0.37-0.86)	0.007
Number of previous inpatient episodes (five or more)	0.63 (0.51-0.77)	<0.001
Lifetime drug use disorder	2.22 (1.71-2.87)	<0.001
Length of stay in forensic hospital (12 months or more)	0.63 (0.52-0.77)	<0.001

Table II.4. Associations between risk factors and violent crime in multivariate regression model (after multiple imputation)

Variable	Hazard ratio (95% CI)	p-value
Sex (female)	0.38 (0.21-0.69)	0.001
Age at discharge	0.97 (0.95-0.98)	<0.001
Previous violent crime	2.80 (1.60-4.89)	<0.001
Previous serious violent crime	0.69 (0.50-0.96)	0.026
Primary diagnosis at discharge		
Schizophrenia spectrum	1.00 (ref)	n/a
Bipolar disorder	2.11 (1.14-3.89)	0.017
Unipolar depression	0.95 (0.34-2.67)	0.925
Anxiety disorders	1.27 (0.69-2.33)	0.444
Other	1.59 (1.15-2.18)	0.005
Drug use disorder at hospitalisation or discharge	1.07 (0.75-1.53)	0.716
Alcohol use disorder at hospitalisation or discharge	1.32 (0.84-2.07)	0.233
Personality disorder at discharge	1.43 (1.04-1.97)	0.027
Employment before admission	0.63 (0.31-1.25)	0.184
Number of previous inpatient episodes (five or more)	0.68 (0.50-0.91)	0.009
Lifetime drug use disorder	2.45 (1.66-3.62)	<0.001
Length of stay in forensic hospital (12 months or more)	0.70 (0.52-0.93)	0.013

Table II.5. Sensitivity analysis: Associations between risk factors and violent crime in the derivation sample from the multiple regression model (after multiple imputation), discharges from 2001 only

Variable	Hazard ratio (95% CI)	p-value
Sex (female)	0.39 (0.24-0.63)	<0.001
Age at discharge	0.98 (0.96-1.00)	0.042
Previous violent crime	2.99 (2.01-4.44)	<0.001
Previous serious violent crime	0.55 (0.42-0.72)	<0.001
Primary diagnosis at discharge		
Schizophrenia spectrum	1.00 (ref)	n/a
Bipolar disorder	0.98 (0.54-1.79)	0.957
Unipolar depression	0.91 (0.48-1.74)	0.781
Anxiety disorders	1.07 (0.65-1.76)	0.780
Other	1.19 (0.90-1.58)	0.219
Drug use disorder at hospitalisation or discharge	0.89 (0.65-1.22)	0.461
Alcohol use disorder at hospitalisation or discharge	1.17 (0.81-1.69)	0.392
Personality disorder at discharge	1.55 (1.20-1.99)	0.001
Employment before admission	0.48 (0.27-0.84)	0.011
Number of previous inpatient episodes (five or more)	0.61 (0.48-0.78)	<0.001
Lifetime drug use disorder	2.10 (1.52-2.89)	<0.001
Length of stay in forensic hospital (12 months or more)	0.67 (0.54-0.85)	0.001

Table II.6. Sensitivity analysis: Associations between risk factors and violent crime in the derivation sample from the multiple regression model (after multiple imputation), age <40 at discharge only

Statistical performance

For risk of violent offending at 24 months after discharge, using the 5% cut-off (low to medium), sensitivity was 96% and specificity 21%. Positive and negative predictive values were 19% and 97%, respectively. Using the 20% cut-off (medium to high), sensitivity was 55%, specificity 83%, and the positive and negative predictive values were 37% and 91%, respectively. The concordance index (AUC) was 0.77 (Figure II.2, page 53), and the Brier score (Br: 0.0876) was lower than that using the mean predicted probability (Br: 0.0985) or using a predicted probability of zero, i.e., classifying all individuals as low risk (Br: 0.1108). In the low, medium, and high-risk groups, 3.4%, 11%, and 37% had a violent offence within 24 months (Figure II.3, page 53).

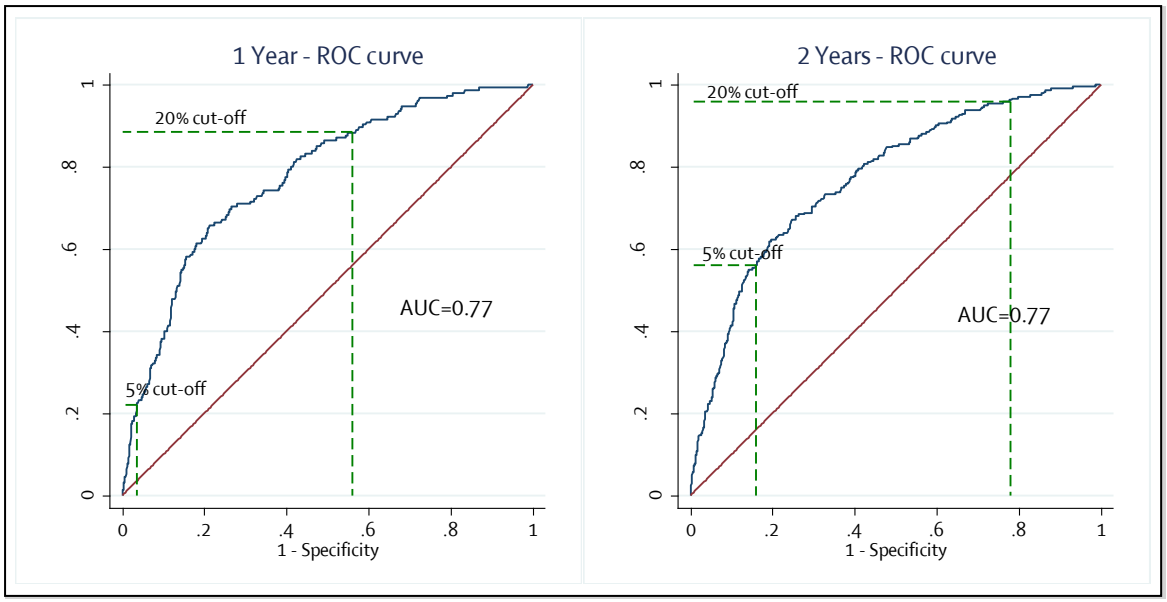

Figure II.2. Model discrimination shown by receiver operating characteristics (ROC) curves.

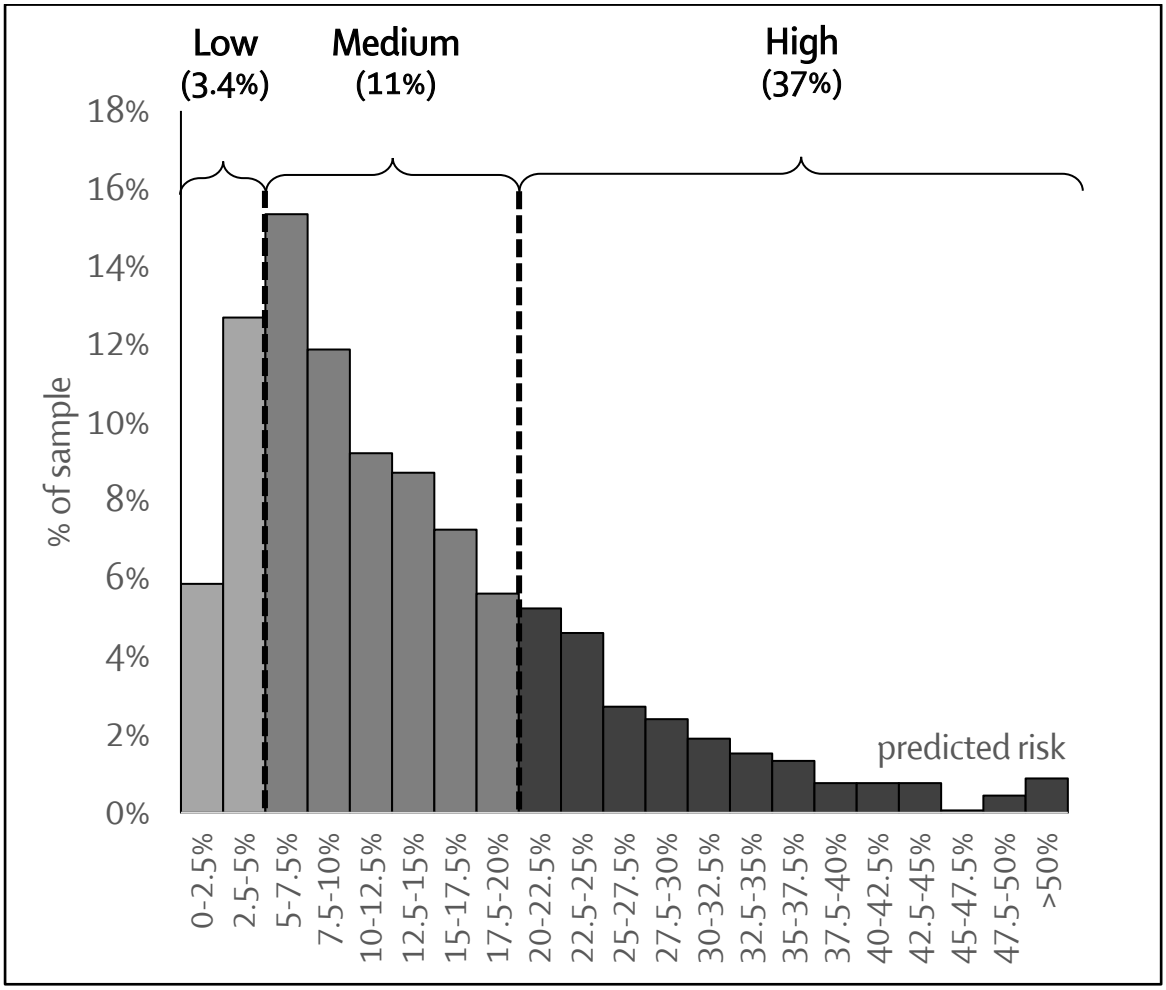

Figure II.3. Observed and predicted risk of violent crime at 24 months, by risk categorisation

For risk of violent offending at 12 months after discharge, using the 5% cut-off, sensitivity was 88% and specificity 44%. Positive and negative predictive values were 13% and 97%, respectively. Using the 20% cut-off, sensitivity was 22%, specificity 96%, and the positive and negative predictive values were 34% and 93%, respectively. The concordance index (AUC) was 0.77 (Figure II.2, page 53), and the Brier score (Br: 0.0607) was lower than that using the mean predicted probability (Br: 0.0657) or using zero (Br: 0.0707).

Calibration and internal validation

Calibration plots indicate adequate calibration of the predicted probabilities against observed proportions of violent offending at 12 and 24 months (Figure II.4, page 54). Bootstrapping showed good predictive accuracy at both 12 and 24 months (Table II.7, page 55), though sensitivity dropped slightly. Two by two tables comparing predicted and observed outcomes are presented in Table II.8 (page 55).

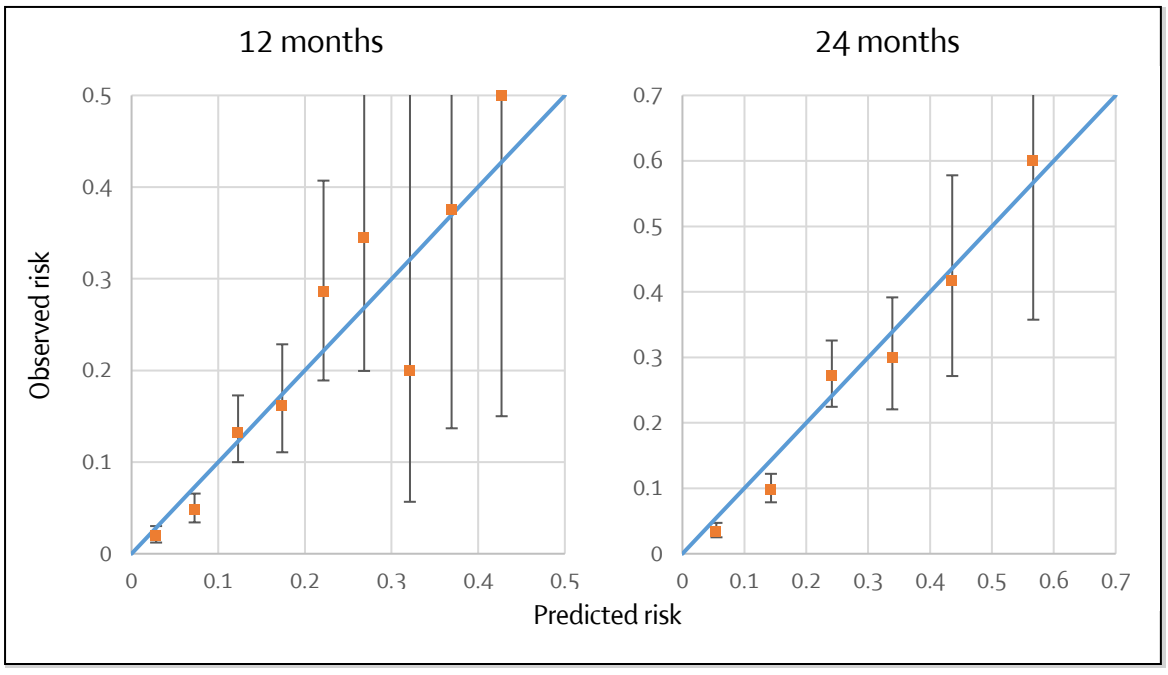

Figure II.4. Calibration plots comparing predicted and observed risks of violent crime in those discharged from secure hospitals, at 12 and 24 months post-discharge

Cut-off	Measure	12 months Model	12 months Bootstrapped mean (95% CI)	24 months Model	24 months Bootstrapped mean (95% CI)
5%	Sensitivity	88%	86% (85-87)	96%	95% (94-95)
	Specificity	44%	46% (44-47)	21%	24% (23-25)
20%	Sensitivity	22%	22% (20-24)	55%	51% (49-53)
	Specificity	96%	95% (94-95)	83%	82% (81-83)

Table II.7. Internal validation, comparing model performance with 100 samples drawn with replacement (bootstrapping)

Cut-off		12 months Outcome +	12 months Outcome -	12 months Total	24 months Outcome +	24 months Outcome -	24 months Total
5%	Prediction +	140	931	1071	239	1050	1289
	Prediction -	19	727	746	10	284	294
	Total	159	1658	1817	249	1334	1583
20%	Prediction +	35	69	104	138	232	370
	Prediction -	124	1589	1713	111	1102	1213
	Total	159	1658	1817	249	1334	1583

Tables are based on those with full 12 months follow-up or event (n=1817) or with full 24 months of follow-up or event (n=1583)

Table II.8. Two by two tables used to derive sensitivity, specificity, and positive and negative predictive values (after multiple imputation)

Web calculator

A beta version of the online risk calculator for violent offending (based on the coefficients in Table II.9) can be found at https://oxrisk.com/fovox (see screenshot Figure II.5, page 57). If missing values are present, the calculator reports the upper and lower range of estimates of risk, allowing for these missing variables.

Variable	Coefficient
Sex (female)	-0.0299
Age at discharge	-0.8407
Previous violent crime	1.1682
Previous serious violent crime	-0.4480
Primary diagnosis at discharge	
Schizophrenia spectrum	0
Bipolar disorder	0.5994
Unipolar depression	0.2867
Anxiety disorders	0.1142
Other	0.3040
Drug use disorder at hospitalisation or discharge	-0.1188
Alcohol use disorder at hospitalisation or discharge	0.2288
Personality disorder at discharge	0.3052
Employment before admission	-0.5780
Number of previous inpatient episodes (five or more)	-0.4676
Lifetime drug use disorder	0.7964
Length of stay in forensic hospital (12 months or more)	-0.4576

LC (linear combination) = ∑ beta*value of risk factor
Risk of violent offending within 12 months = 1 – 0.9280^exp(LC)
Risk of violent offending within 24 months = 1 – 0.8762^exp(LC)

Table II.9. FoVOx model coefficients, used for internal validation and on the OxRisk.com website

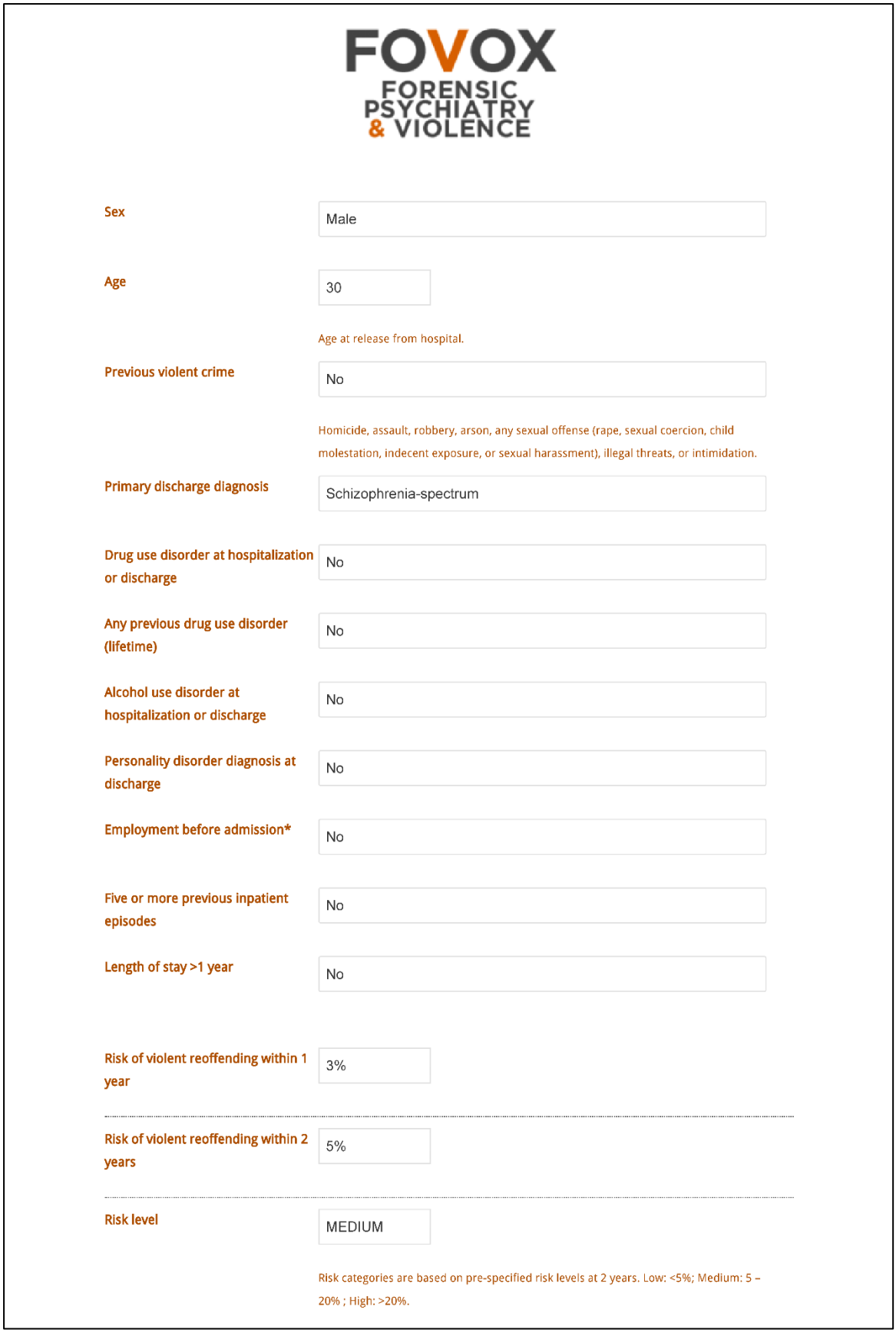

Figure II.5. FoVOx calculator on the OxRisk.com website

Interpretation

I have developed a prediction model for the risk of violent offending after discharge from forensic psychiatric hospitals. The model demonstrated good measures of discrimination and calibration, and was used to develop an online tool (FoVOx) that is free, scalable, and easy to use.

The model identifies around a fifth of patients as low risk (defined as individuals with <5% of violent crime within two years of discharge), of which only 3% offended within 24 months of discharge. The 'prevention paradox' (where a majority of adverse outcomes occur in those considered low risk, in part because most people find themselves in that category) has also been cited as a criticism against violence risk assessment.[86] However, at 24 months post-discharge, the model correctly identified 55% of offenders as high risk and, of all those classified as high risk, 37% did subsequently offend. Furthermore, the use of the actuarial score allows for good discrimination between individual patients, and could be used for treatment matching. At both 12 months and 24 months, the model showed a concordance index of 0.77. This means that in 77% of discordant pairs (i.e., where one offends and the other one does not), FoVOx correctly assigned a higher risk to the offending individual.

In this model, previous serious violent crime was associated with a smaller increase in risk (doubling) than any violent crime (tripling) compared to no violent crime, which is consistent with some earlier work that finds that very serious offences, such as homicide, are weaker correlates of recidivism.[111] A length of stay of 12 months or more was found to be protective (adjusting for all other factors in the model, including age), and likely to be subject to post-discharge statutory supervision. The finding that five or more previous inpatient episodes was associated with a lower risk of violence suggests that these

patients are known to services and therefore interventions may already have been put in place before severe relapses.

Using a simple tool can potentially free up clinical time to treat and manage violence risk in this patient group.[112] Promising interventions to reduce the risk of violence include treatment of comorbidities and other modifiable risk factors. For example, treating substance use disorders through therapeutic community interventions after discharge may reduce reoffending (Chapter III).

Strengths & Limitations

Risk assessment will need to be linked to risk management to improve patient outcomes and future work will need to examine how this can be most effectively done. However, compared to current risk assessment approaches, FoVOx has some advantages. First, it uses robust methodology, and used a design, cut-offs, risk factors, and internal validation that were pre-specified before any analyses were performed, to minimise the risk of multiple testing and false positive associations. In contrast, the derivations of the two most commonly used risk assessment tools (HCR-20 and VRAG) were not based on any prespecified protocol or analysis plan.

Second, it had a large sample size of over 2,200 individuals, the total cohort of those discharged from secure hospitals in Sweden between 1992 and 2013. The use of Swedish registers improves generalisability to future Swedish individuals in the forensic mental health system, and to other countries and jurisdictions by including all discharged individuals without selection or attrition bias. This study is therefore the largest derivation study for a risk assessment tool in forensic psychiatry. In contrast, the HCR-20 derivation study was not based on statistical analyses, and the VRAG was based on a heterogeneous and selected sample of under 700 individuals and tested more variables than statistically appropriate.

Third, FoVOx has been developed specifically in forensic psychiatric patients, whereas other common approaches have been developed using heterogeneous samples from criminal justice and forensic psychiatry, and risk factors and baseline risks differ from general psychiatry or prison populations.[93] Hence, it is not surprising that field studies show considerable shrinkage in the predictive accuracy of tools such as the HCR-20 in forensic samples,[87] as it was originally designed to be used in general psychiatric samples.

Fourth, by basing the analysis plan on previous systematic reviews, the findings in Chapter I, and discussions with clinicians, FoVOx is a parsimonious model with appropriately weighted items, including ones considered important for face validity. In particular, the model includes the individual's age and sex, which had not been included in the HCR-20 or VRAG (the latter only includes age).

Fifth, there may be clinical benefits in freely available and quicker risk assessment in that resources can be redirected towards clinical care and risk management, and more resource intensive forms of risk assessment could be limited to those scoring higher in FoVOx. Additionally, risk scores may be used for treatment matching by prioritising interventions in those groups who are found to be at highest risk of reoffending, or have specific modifiable risk factors (e.g., substance misuse treatment). Further, psychiatric services in countries without the resources required for training and other costs of current approaches will likely benefit from a simple risk score to support clinical judgement. In particular, the tool and its methodology have been published in an open-access journal, and FoVOx is freely available on the OxRisk webpage and can be used on any web-connected device.

Finally, all included risk factors were from routinely collected register data and are likely to be known for most patients without additional interviewing; equally, some items can be marked as unknown in the FoVOx calculator if they are unavailable. If one or more

items are marked as unknown, FoVOx provides a risk range, based on the lower and upper bound of possible answers to provide further information around the estimates' uncertainty.

The performance of FoVOx is typically better than other tools used in forensic psychiatry, which show AUCs for any violence within 12 months of discharge of 0.70 or less,[113] compared to 0.77 for FoVOx. Similarly, FoVOx performs no worse when compared to a wide-ranging review of such instruments used in criminal justice and forensic psychiatry, with A 2012 review of studies from 73 samples reporting a median AUC value of 0.72.[49] including the Medium Security Recidivism Assessment Guide which reported an AUC of 0.76 for the prediction of serious offending in an internal validation sample.[114]

The FoVOx risk prediction tool does however have several limitations. Detailed genetic or psychological scales are not routinely recorded in registers and could therefore not be included, though these risk factors showed weaker evidence of association with violence when examined in a previous review.[71] Additionally, as discussed in Chapter I, it was not possible to include a number of dynamic risk factors, including treatment variables medication, psychological therapies, or adherence. Therefore, one limitation is the use of mostly static risk factors, and FoVOx should thus not be used to monitor within-individual changes in risk, for which other tools may be more appropriate.[106,115] This may also affect the acceptability of the tool, as successful risk management interventions do not translate into changes in FoVOx scores. It is therefore important for FoVOx to be considered as an adjunct to clinical decision-making. As with other risk prediction tools, the potential labelling of individuals as 'high-risk' should be considered within the context of the stigma already experienced by individuals with severe mental illness, as discussed in the Introduction. However, the use of an absolute risk score (which clearly indicates

that, even in the high-risk group, the vast majority of individuals do not offend) can help provide nuance to a complex conversation with patients, their carers, and wider society.

Another limitation is that, due to the small number of individuals in secure psychiatric hospitals in Sweden, it was not possible to perform an external validation of the model, despite using the largest development sample of any forensic psychiatry risk assessment tool to date. Though bootstrapping showed good predictive accuracy in internal validation, FoVOx will need to be externally validated in different samples, in particular as other jurisdictions will have different legal frameworks with which to detain mentally disordered offenders. However, Sweden and England for instance have similar provisions for individuals at higher risk. In Sweden, about two thirds of forensic psychiatric patients are under 'special court supervision' which means that they cannot be discharged without court approval.[116] In England and Wales, restriction orders (under Sections 41 or 49 of the Mental Health Act) can be used to supplement hospital detention, and in 2015, there were around 4600 of these (which amounts to around 60% of the total forensic psychiatric population).[117] Additionally, due to the low number of post-discharge serious violent crimes, it was not possible to assess the performance of the model in predicting serious violence. Another issue is the generalizability of the effects of risk factors, but univariate analyses from two large UK-based studies find similar associations, including for age, sex, length of stay, substance use disorders, and psychiatric diagnoses.[118,119]

The 'ceiling effect' – the idea that we have reached a plateau in the performance of risk assessment – suggests that further optimizing such tools may have limited potential. Future research into psychological, genetic or epigenetic risk factors, or dynamic monitoring, may raise this ceiling. However, until such a time, the emphasis should be on reaching the ceiling in the most cost-effective way. Tools like FoVOx show similar performance to other tools, but are easier, quicker, and free to use whilst at the same time

being scalable, fully transparent, and less subjective. Indeed, while measures of interrater reliability of non-actuarial clinical judgement tools are generally high in research settings,[120] this may not be the case when used in adversarial settings, for example in criminal proceedings.[121] Future research should therefore compare risk assessment tools not only in their overall statistical performance, but also in other domains including acceptability to patients and clinicians, resource use (for training and licensing), and implementation research.

Conclusions

How FoVOx can be incorporated into clinical practice will require feasibility and acceptability studies, in discussion with clinicians. It is possible that the probability scores provided can be used as evidence to external bodies that require this information, such as mental health tribunals, and also in the transition from forensic to general psychiatric services where evidence of low risk may need demonstrating in different ways, including risk scores. Assuming that these tools are unlikely to reach beyond AUCs of 0.80, the research focus should move to risk management. Randomized controlled trial evidence of the effectiveness of risk assessment in reducing violence is currently limited to one study.[84] Therefore, research should move beyond optimizing tools for risk assessment, and implement free and simple risk tools. New work should focus on risk management that is linked to interventions to reduce risks, such as treating comorbid substance use disorders,[122] and improving treatment adherence.[123] To help inform future risk management practice and research, the following chapter reviews the literature on violence prevention strategies in psychiatry.

Chapter III - Violence prevention strategies in psychiatry: an umbrella review

Introduction

The utility of violence risk assessment is dependent not only on its accuracy, but on its ability to help reduce this risk, through connecting it to risk management and a targeted use of evidence-based violence prevention interventions. Previous work on violence prevention in psychiatry has mostly focused on either modifiable risk factors,[99] or used subjective or intermediate outcomes such as aggression scales.[124] Modifiable risk factors, however, may be genetically confounded,[76] and thus interventions to alter them may not necessarily decrease violence risk. Similarly, a reduction in aggression scores may not necessarily lead to a reduction in violence.

As reported in the time trend analyses in Chapter I, the relative risk of violence in psychiatric patients has increased over time compared to general population controls. Forensic psychiatric patients in particular are at increased risk of repeat violence on release from hospital compared to general psychiatric patients. Although rates of reoffending following discharge from secure hospitals may compare favourably to certain comparative groups including prisoners of similar age and sex, they remain high and a recent systematic review reported rates ranging from 273 to 8,403 per 100 000 person-years.[105] This included studies from three European countries, showing high rates of violent offending following discharge from secure hospitals in England & Wales (7 studies; 1589 to 8403 per 100 000 person-years, Sweden (3 studies; 1041 to 3019 per 100 000 person-years), and Norway (one study; 486 per 100 000 person-years). Absolute risks of reconviction for grave offences (that could potentially attract life sentences) following

discharge are around 7% within two years of discharge, as found in two recent representative studies from the UK.[118,125]

In order to assess existing evidence on violence prevention, this chapter presents an umbrella review of intervention research in the patient population from Chapter II, forensic psychiatry, as well as two related groups: mentally disordered offenders, and all psychiatric patients. Umbrella reviews can combine different designs, samples, and interventions which do not lend easily themselves to a systematic review, and allow for the identification of areas where research is lacking primary and secondary studies. Umbrella reviews can assess multiple interventions by including all relevant systematic reviews and meta-analyses,[126] and therefore identify interventions with sufficient evidence for implementation in clinical practice. Validated risk tools such as FoVOx can then help identify those at high risk that could benefit from evidence-based interventions to reduce rates of violence.[93]

Methods

Umbrella reviews are a type of systematic review that examine multiple treatment comparisons for a particular population or outcome, by including previous systematic reviews and meta-analyses, rather than primary studies. This approach was deemed most appropriate for five reasons. First, compared to single treatment systematic reviews, umbrella reviews include multiple treatments, and are therefore considered more useful for informing guidelines and clinical practice.[127] This level of evidence is required to link risk assessment from Chapter II to successful risk management. Second, unlike single treatment systematic reviews, this approach provides a broad summary of the evidence and highlights gaps in both the secondary and primary literature, by summarising existing reviews and additionally including so-called 'empty reviews' (systematic reviews that considered but did not identify studies eligible for inclusion for violence prevention). Third, as a type of systematic review, umbrella reviews avoid the subjective selection bias found in narrative reviews.[128] This type of bias was further minimized by following a fully prespecified protocol. Fourth, a multi-treatment systematic review would have complicated the interpretation and comparison of large number of individual studies using different designs, interventions, populations, and outcomes. Initial scoping searches without restriction to systematic reviews found over 27,000 results in MEDLINE alone (Table III.1, line 5, page 69) with hundreds of (often low-quality) eligible studies. Similarly, due to significant clinical heterogeneity, network meta-analysis was considered but rejected as the transitivity assumption would not be met (e.g., a study on antipsychotics in schizophrenia patients with a history of aggression[129] could not be included in the same network as a study on therapeutic community programs in female drug-using offenders with co-occurring mental illness[130]). Fifth, by focusing on previous systematic reviews, other inclusion criteria could be broadened, for example by including

non-randomized designs. This provides a more complete picture of the evidence, in particular in the field of forensic psychiatric research where randomization sometimes raises ethical concerns around consent and withholding treatment, and can be impractical or lacking ecological validity.[131] In particular, forensic patients can be excluded from randomized studies if deemed too dangerous (risk to themselves or others) and they are therefore also often harder to follow-up. Nevertheless, umbrella reviews are limited by the quantity and quality of the included studies and, much like other types of reviews discussed, may be affected by reporting or selection bias.[132]

Inclusion criteria

For inclusion, reviews had to evaluate the effectiveness of violence prevention interventions in (1) all psychiatric patients, (2) mentally disordered offenders, or (3) forensic psychiatric inpatients. Reviews focusing on interventions for patients with only diagnoses of intellectual disabilities or substance use disorders were excluded.

Interventions

All types of interventions were included if they examined effects on violence, as defined below.

Outcomes

The outcome to be examined in this umbrella review was violence using a 'hard' or objective outcome measure, such as police or hospital recorded violence, criminal violence, or reincarceration. Aggression or violence scales, or non-violent recidivism were not included. Whilst non-violent offences may lead to reincarceration, the severity threshold is higher than for rearrests or reoffending[7] and it is therefore likely that the majority of events would be relevant.

Types of studies

Systematic reviews and meta-analyses of intervention studies were included. Intervention studies include both randomized and non-randomized controlled designs. Studies without control groups, observational studies, theoretical studies, opinion, and non-systematic reviews were excluded. Meta-analyses were only included if conducted within the context of a systematic review.

Search strategy

The search strategy used is reported in Table III.1 below. The following databases were searched from inception to August 5, 2015: MEDLINE, EMBASE, CINAHL, Web of Science, Scopus, the JBI Database of Systematic Reviews and Implementation Reports, the Cochrane Database of Systematic Reviews, DARE, the PROSPERO register, and Epistemonikos. Titles and abstracts were scanned for potentially eligible reviews, before retrieving full articles. No language restrictions were applied.

	Search term
1	prevent* OR risk management OR risk reduction OR deter*
2	violen* OR homicid* OR assault* OR rape OR robber* OR bully*
3	1 AND 2
4	recidiv* OR reoffend* OR repeat offend*
5	3 OR 4
6	systematic review OR meta-analysis
7	5 AND 6

Table III.1. Search strategy for umbrella review

Assessment of evidence

The strength of evidence for each systematic review was assessed using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) scale[133] and given a rating of 'high', 'moderate', 'low', or 'very low' quality, using GRADEpro 3.6.1. Ratings were based on the review articles and not individual constituent studies. The GRADE rating is not an assessment of the methodological quality of a review, but of the overall quality of evidence presented in that review, in this case the quality of evidence

supporting the use of a particular intervention to prevent violence. Reviews were not excluded based on methodological quality.

GRADE assigns initial scores based on the type of study design (+4 for randomized, and +2 for non-randomized studies) and then adjusts this score according to four domains: risk of bias, inconsistency, indirectness, and imprecision. In each domain, the overall score can be downgraded by one (serious threat) or two points (very serious threat).

The four domains can be described as follows: (1) Risk of bias evaluation includes an assessment of the study design, including treatment allocation, follow-up, and blinding where applicable. For instance, a review may be marked down for unclear or suboptimal randomization methods (e.g., tossing a coin). (2) Inconsistency examines heterogeneity that reduces the confidence in the overall findings. For example, a review should be downgraded if included studies report inconsistent findings, such as different effect estimates with non-overlapping confidence intervals, or if it reports high statistical heterogeneity (e.g., Q or I-square). (3) Indirectness considers whether the studied population or interventions correspond to what the assessor believes to be important. Combining multiple different interventions reduces the confidence of the applicability of a review's findings to individual constituent interventions. (4) Imprecision refers to the overall statistical certainty of the findings, with downgrading appropriate for small sample sizes or large confidence intervals for effect estimates.

Data collection

Two independent reviewers (myself and Daniel Whiting, University of Oxford) scanned titles and abstracts and used a data extraction sheet to collect information on the citation, type of review, participants, intervention, setting, relevant outcomes, databases searched, date range, number of relevant studies included, instrument (if any) used to assess the quality of those studies, results, and any additional comments. We planned for

discrepancies in data extraction to be resolved by consensus, but no discrepancies occurred.

Data presentation

Systematic reviews were grouped by population: (1) general psychiatric patients, (2) mentally disordered offenders, or (3) forensic psychiatric inpatients. Descriptive data were presented for each review. As included reviews used different study designs (randomized and non-randomized studies), populations (general psychiatry, mentally disordered offenders, forensic psychiatry), and interventions, effect sizes were not calculated as direct comparisons would likely be misleading. Reviews that included violence outcomes but found no relevant studies were reported separately.

The protocol for Chapter III can be found in Appendix B (page 139).

Findings

Three systematic reviews and two meta-analyses met the inclusion criteria for this umbrella review (see Figure III.1 for PRISMA diagram, page 73). These included a total of fifteen studies (n=8,876 patients in total), of which seven were randomized (n=1,157). Two reviews were found on general psychiatric patients, three on mentally disordered offenders, and none on forensic psychiatric inpatients.

General psychiatric patients

One meta-analysis and one systematic review included any psychiatric patients and objective violence outcomes (Table III.2, page 74).

A meta-analysis of adults with severe mental disorders found two randomized studies on compulsory community treatment and found a pooled rate ratio of 0.8 (95% CI 0.6 to 1.2) of being 'arrested or picked up by police for violence against a person' when compared to standard care.[134]

In adults with schizophrenia spectrum disorders, a review found two non-randomized studies of pharmacological interventions.[135] One found a decrease in assaults, the other no difference.

Mentally disordered offenders

Two systematic reviews and one meta-analysis included interventions targeted at mentally disordered offenders (Table III.3, page 74). One was a meta-analysis of interventions in adults with mental disorders formally dealt with by the criminal justice system. This included six non-randomized studies that were categorised into two cognitive/social, two medical, and two service linkage interventions. The combined effect size on violent crime of all six interventions was 0.2 (95% CI 0.03 to 0.5).[136] Effect sizes were not reported by intervention type.

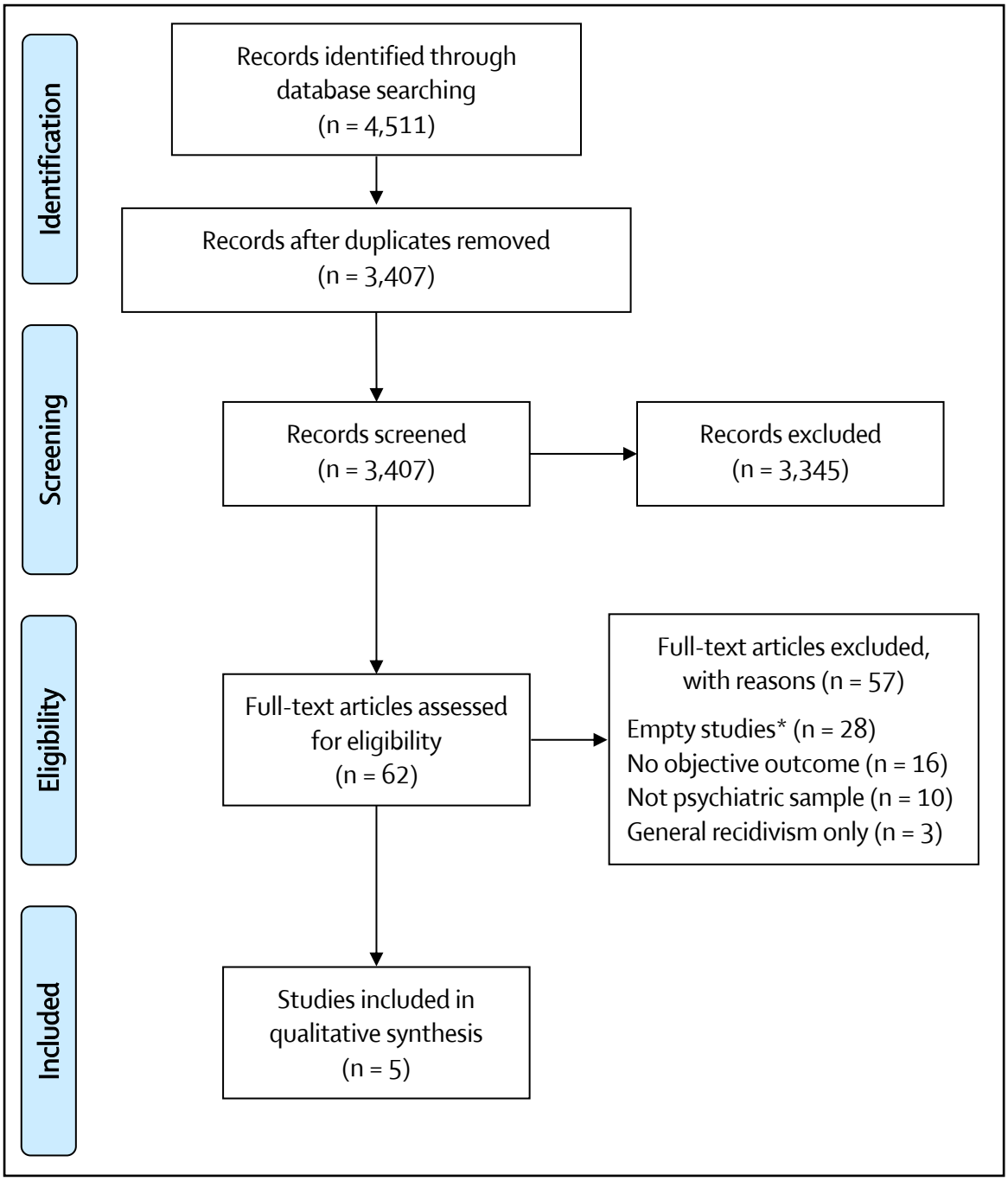

Figure III.1. PRISMA Flow Diagram

*See Table III.5 (page 78) for systematic reviews with no results

In adults with antisocial personality disorder and a previous offence, another review found two randomized studies.[137] This review reported that Modified Therapeutic Community interventions significantly decreased reincarceration (Odds Ratio [OR] = 0.04, $p<0.05$); Assertive Community Treatment saw a non-significant decrease (OR=0.6). Confidence intervals were not reported.

	Studies	Population	Intervention	Outcome	Findings	GRADE
Kisely (2014)	2 randomized studies, n=416	Adults with severe mental disorders	Compulsory community treatment vs standard care	Arrested/picked up by police for violence against a person	Pooled Rate Ratio of 0.8 (95% CI 0.6 to 1.2)	Low
Victoroff (2015)	2 non-randomized studies, n=42	Adults with schizophrenia spectrum disorders	Pharmacological interventions	Assaults	One study found a decrease in assaults following treatment, the other found no difference.	Very low

Table III.2. Systematic reviews on general psychiatric patients. See main text for full description of studies.

	Studies	Population	Intervention	Outcome	Findings	GRADE
Martin (2012)	6 non-randomized studies with 7 effect sizes, n=7,677	Adults with mental disorders formally processed by the criminal justice system	2 cognitive/social, 2 medical, and 2 service linkage interventions*	Violent crime	Overall pooled Effect Size of 0.2 (95% CI 0.03 to 0.5)	Very low
Wilson (2014)	2 randomized studies, n=105	Adults with antisocial personality disorder and a previous offence	1 Assertive Community Treatment (ACT), 1 Modified Therapeutic Community (MCT)	Reincarceration	Non-significant decrease in reincarceration for ACT (OR=0.6), significant decrease for MCT (OR=0.04, p<0.05)	Very low
Perry (2015)	3 randomized studies, n=636	Adult drug-using offenders with co-occurring mental illness	Therapeutic community and aftercare	Reincarceration	Versus mental health programme: (Rate Ratio 0.3, 95% CI 0.1 to 0.6). Versus parole supervision case management (RR 0.5, 0.3 to 0.9). Versus cognitive behavioural intervention (RR 0.7, 0.4 to 1.2).	Moderate

Table III.3. Systematic reviews on mentally disordered offenders. See main text for full description of studies.

The third review was in adult drug-using offenders with co-occurring mental illness. This found three randomized studies on the effects of therapeutic community and aftercare on reincarceration.[138] Therapeutic community and voluntary residential aftercare (RR 0.3, 95% CI 0.1 to 0.6) and re-entry modified therapeutic community treatment (RR 0.5, 95% CI 0.3 to 0.9) both significantly decreased reincarceration. Another therapeutic community program found a non-significant decrease (RR 0.7, 95% CI 0.4 to 1.2).

Forensic psychiatric inpatients

I did not identify any systematic reviews examining interventions to reduce violence in forensic psychiatric inpatients.

Quality of evidence

Four of the reviews received a GRADE rating of 'low'[134] or 'very low'[135-137] (page 74). Only the review on therapeutic community and aftercare interventions in adult drug-using offenders with co-occurring mental illness received a rating of 'moderate'.[138] For the summary GRADEpro score derivation table, see Table III.4 (page 76).

As per GRADE guidelines, reviews including randomized studies (Kisely 2014, Wilson 2014, and Perry 2015) were assigned an initial score of 4; reviews of non-randomized studies (Victoroff 2015, and Martin 2012) were assigned score of 2. Each study was then evaluated on risk of bias, inconsistency, indirectness, and imprecision.

The review by Kisely (+4) was downgraded for risk of bias (-1), as it provided no information on the randomization and allocation concealment used. It was also downgraded for imprecision (-1): though it included 416 individuals, findings were based on only two studies. It therefore received an overall score of '2' or 'low'.

	Kisely (2014)	Victoroff (2015)	Martin (2012)	Wilson (2014)	Perry (2015)
Initial score	+4 randomized studies	+2 non-randomized	+2 non-randomized	+4 randomized studies	+4 randomized studies
Risk of bias	-1 allocation unclear	0	0	-1 allocation unclear	-1 allocation unclear
Inconsistency	0	-1 heterogeneity	-1 heterogeneity	-1 heterogeneity	0
Indirectness	0	0	-1 mixed interventions	0	0
Imprecision	-1 only two studies	-2 two studies, (n=42)	0	-2 two studies, (n=105)	0
Total score	= 2 Low	≤ 1 Very low	≤ 1 Very low	≤ 1 Very low	= 3 Moderate

Table III.4. Summary of GRADE scoring. See main text for justification of scores

The review by Victoroff (+2) was downgraded for inconsistency (-1) as one study found a decrease in assaults following pharmacological intervention, and the other found no effect. The review was also downgraded by two points for imprecision (-2) due to an overall sample size of 42 from two studies. The review received an overall score below one, or 'very low'.

Martin's review (+2) was similarly downgraded on inconsistency (-1) due to statistical heterogeneity in effect sizes in the six included studies. It was also downgraded on indirectness (-1) or clinical heterogeneity as it combined vastly different types of interventions (cognitive/social, medical, and service linkage interventions). It received an overall score below one, or 'very low'.

Wilson's review (+4) was downgraded due to risk of bias (-1; unclear randomization and allocation concealment methods) and inconsistency (-1; one study with a positive and one with negative finding for the effect of the intervention on violence). It was also

downgraded by two points for imprecision (-2) due to sample size (two studies and 105 individuals), receiving an overall rating below one, or 'very low'.

Finally, the review by Perry (+4) was downgraded for risk of bias only (-1) due to unclear randomization and allocation concealment. It was not downgraded on inconsistency, indirectness, or imprecision, receiving a final score of three, or 'moderate'.

Reviews with no studies

I found a further 28 reviews that included violence as an outcome in their protocols but identified no relevant studies: 24 on general psychiatric patients, 4 on mentally disordered offenders, and none on forensic psychiatric inpatients. Some of these reviews only identified studies on aggression scales or other subjective outcomes, or non-controlled studies, and were therefore not eligible for inclusion. The 28 reviews are presented in Table III.5 (page 78).

Reference number and population		Intervention
Forensic inpatients		
-	None	
Mentally disordered offenders		
#1	Psychopathic Sexual Offenders	Any
#2	Antisocial personality disorder	Psychological interventions
#3	Offenders with mental illness	Any
#4	Clinical and forensic settings	Psychological therapies
Mental health patients		
#5	Violent and aggressive behaviour	Sodium valproate
#6	Schizophrenia	Beta-blocker supplementation
#7	Acute psychotic illnesses	Clotiapine
#8	Acutely disturbed/agitated	Olanzapine IM or velotab
#9	Schizophrenia	Antidepressants
#10	Schizophrenia, stable on chlorpromazine	Chlorpromazine cessation
#11	Schizophrenia	Lithium
#12	Schizophrenia	Valproate
#13	Schizophrenia	Monetary incentives
#14	Schizophrenia	Chlorpromazine
#15	Antisocial personality disorder	Pharmacological interventions
#16	Psychosis	Early intervention services
#17	Schizophrenia	Pharmacological interventions
#18	Borderline personality disorder	Crisis intervention
#19	Acute schizophrenia and similar	Zuclopenthixol acetate
#20	Schizophrenia	Maintenance antipsychotics
#21	Schizophrenia and special populations	Oral versus depot antipsychotics
#22	Schizophrenia	Fluphenazine (oral)
#23	Schizophrenia or related psychoses	Pimozide
#24	Schizophrenia	Chlorpromazine
#25	Schizophrenia	Pericyazine
#26	Schizophrenia	Carbamazepine
#27	Sexual offenders or at risk of offending	Pharmacological interventions
#28	Delusional disorder	Any

References are provided on the next page.

Table III.5. Systematic reviews with no results

#1	Doren DM, Yates PM. Effectiveness of sex offender treatment for psychopathic sexual offenders. International Journal of Offender Therapy and Comparative Criminology. 2008;52(2):234-45. doi: 10.1177/0306624x07303914.
#2	Gibbon S, Duggan C, Stoffers J, Huband N, Völlm BA, Ferriter M, et al. Psychological interventions for antisocial personality disorder. Cochrane database of systematic reviews (Online). 2010;(6):CD007668. doi: 10.1002/14651858.CD007668.pub2.
#3	Morgan RD, Flora DB, Kroner DG, Mills JF, Varghese F, Steffan JS. Treating Offenders With Mental Illness: A Research Synthesis. Law and Human Behavior. 2012;36(1):37-50. doi: 10.1037/h0093964.
#4	Ross J, Quayle E, Newman E, Tansey L. The impact of psychological therapies on violent behaviour in clinical and forensic settings: A systematic review. Aggression and Violent Behavior. 2013;18(6):761-73. doi: 10.1016/j.avb.2013.09.001.
#5	Lindenmayer JP, Kotsaftis A. Use of sodium valproate in violent and aggressive behaviors: a critical review. The Journal of clinical psychiatry. 2000;61(2):123-8.
#6	Shek E, Bardhan S, Cheine Maxim V, Ahonen J, Wahlbeck K. Beta-blocker supplementation of standard drug treatment for schizophrenia. Cochrane Database of Systematic Reviews 2001, Issue 3. Art. No.: CD000234. DOI: 10.1002/14651858.CD000234.
#7	Berk M, Rathbone J, Mandriota-Carpenter Simone L. Clotiapine for acute psychotic illnesses. Cochrane Database of Systematic Reviews 2004, Issue 4. Art. No.: CD002304. DOI: 10.1002/14651858.CD002304.pub2.
#8	Belgamwar Ravindra B, Fenton M. Olanzapine IM or velotab for acutely disturbed/agitated people with suspected serious mental illnesses. Cochrane Database of Systematic Reviews 2005, Issue 2. Art. No.: CD003729. DOI: 10.1002/14651858.CD003729.pub2.
#9	Rummel-Kluge C, Kissling W, Leucht S. Antidepressants for the negative symptoms of schizophrenia. Cochrane Database of Systematic Reviews 2006, Issue 3. Art. No.: CD005581. DOI: 10.1002/14651858.CD005581.pub2.
#10	Almerie Muhammad Q, Alkhateeb H, Essali A, Matar Hosam E, Rezk E. Cessation of medication for people with schizophrenia already stable on chlorpromazine. Cochrane Database of Systematic Reviews 2007, Issue 1. Art. No.: CD006329. DOI: 10.1002/14651858.CD006329.
#11	Leucht S, Kissling W, McGrath J. Lithium for schizophrenia. Cochrane Database of Systematic Reviews 2015, Issue 10. Art. No.: CD003834. DOI: 10.1002/14651858.CD003834.pub3.
#12	Schwarz C, Volz A, Li C, Leucht S. Valproate for schizophrenia. Cochrane Database of Systematic Reviews 2008, Issue 3. Art. No.: CD004028. DOI: 10.1002/14651858.CD004028.pub3.
#13	Michalczuk R, Mitchell A. Monetary incentives for schizophrenia. Cochrane Database of Systematic Reviews 2009, Issue 4. Art. No.: CD007626. DOI: 10.1002/14651858.CD007626.pub2.
#14	Ahmed U, Jones H, Adams CE. Chlorpromazine for psychosis induced aggression or agitation. Cochrane database of systematic reviews (Online). 2010;(4):CD007445. doi: 10.1002/14651858.CD007445.pub2.

#15	Khalifa N, Duggan C, Stoffers J, Huband N, Völlm Birgit A, Ferriter M, et al. Pharmacological interventions for antisocial personality disorder. Cochrane Database of Systematic Reviews 2010, Issue 8. Art. No.: CD007667. DOI: 10.1002/14651858.CD007667.pub2.
#16	Marshall M, Rathbone J. Early intervention for psychosis. Cochrane Database of Systematic Reviews 2011, Issue 6. Art. No.: CD004718. DOI: 10.1002/14651858.CD004718.pub3.
#17	Topiwala A, Fazel S. The pharmacological management of violence in schizophrenia: a structured review. Expert Review of Neurotherapeutics. 2011;11(1):53-63. doi: 10.1586/ern.10.180.
#18	Borschmann R, Henderson C, Hogg J, Phillips R, Moran P. Crisis interventions for people with borderline personality disorder. Cochrane Database of Systematic Reviews 2012, Issue 6. Art. No.: CD009353. DOI: 10.1002/14651858.CD009353.pub2.
#19	Jayakody K, Gibson RC, Kumar A, Gunadasa S. Zuclopenthixol acetate for acute schizophrenia and similar serious mental illnesses. Cochrane Database of Systematic Reviews 2012, Issue 4. Art. No.: CD000525. DOI: 10.1002/14651858.CD000525.pub3.
#20	Leucht S, Tardy M, Komossa K, Heres S, Kissling W, Davis John M. Maintenance treatment with antipsychotic drugs for schizophrenia. Cochrane Database of Systematic Reviews 2012, Issue 5. Art. No.: CD008016. DOI: 10.1002/14651858.CD008016.pub2.
#21	Zhornitsky S, Stip E. Oral versus long-acting injectable antipsychotics in the treatment of schizophrenia and special populations at risk for treatment nonadherence: A systematic review. Schizophrenia Research and Treatment. 2012. DOI: 10.1155/2012/407171.
#22	Matar Hosam E, Almerie Muhammad Q, Sampson S. Fluphenazine (oral) versus placebo for schizophrenia. Cochrane Database of Systematic Reviews 2013, Issue 7. Art. No.: CD006352. DOI: 10.1002/14651858.CD006352.pub2.
#23	Mothi M, Sampson S. Pimozide for schizophrenia or related psychoses. Cochrane Database of Systematic Reviews 2013, Issue 11. Art. No.: CD001949. DOI: 10.1002/14651858.CD001949.pub3.
#24	Adams CE, Awad GA, Rathbone J, Thornley B, Soares-Weiser K. Chlorpromazine versus placebo for schizophrenia. Cochrane Database of Systematic Reviews 2014, Issue 1. Art. No.: CD000284. DOI: 10.1002/14651858.CD000284.pub3.
#25	Matar Hosam E, Almerie Muhammad Q, Makhoul S, Xia J, Humphreys P. Pericyazine for schizophrenia. Cochrane Database of Systematic Reviews 2014, Issue 5. Art. No.: CD007479. DOI: 10.1002/14651858.CD007479.pub2.
#26	Leucht S, Helfer B, Dold M, Kissling W, McGrath J. Carbamazepine for schizophrenia. Cochrane Database of Systematic Reviews 2014, Issue 5. Art. No.: CD001258. DOI: 10.1002/14651858.CD001258.pub3.
#27	Khan O, Ferriter M, et al. Pharmacological interventions for those who have sexually offended or are at risk of offending. Cochrane Database of Systematic Reviews 2015, Issue 2. Art. No.: CD007989. DOI: 10.1002/14651858.CD007989.pub2.
#28	Skelton M, Khokhar Waqqas A, Thacker Simon P. Treatments for delusional disorder. Cochrane Database of Systematic Reviews 2015, Issue 5. Art. No.: CD009785. DOI: 10.1002/14651858.CD009785.pub2.

Table III.6. Systematic reviews with no results; references.

Interpretation

This umbrella review summarised the literature on violence prevention in general psychiatric patients, mentally disordered offenders, and forensic psychiatric inpatients. Three systematic reviews and two meta-analyses with a total of 8,876 patients met the inclusion criteria. However, no reviews were found specifically in forensic psychiatric patient groups.

Four of the reviews received a GRADE rating of 'low' or 'very low' largely due to lack of randomization[135,136] or limited sample size.[134,137] GRADE ratings are not a rating of the methodological quality of the reviews, but of the quality of the evidence in those reviews.[133] Therefore, it is also a measure of the 'completeness' in evidence, or whether future additional research is likely to affect current conclusions. For instance, a GRADE rating of 'high' for a review finding that a certain intervention is ineffective, would suggest that completing additional studies is unlikely to alter that conclusion. The meta-analysis on therapeutic community and aftercare was rated 'moderate', and suggests that it may have some effect in reducing reincarceration rates.[138] For the remaining interventions, there is currently insufficient quality evidence to reach any firm conclusion. In other words, this is not a finding of an evidence of absence (of a violence prevention effect), but an absence of evidence. Further studies are therefore warranted to examine the effects of different types of community treatment or pharmacological interventions on violence in individuals with mental illness. These should employ rigorous methods, including randomisation, adequate allocation concealment, sample size calculations, and prospective clinical trial registration.

Due to the limited systematic review evidence, violence prevention in psychiatric populations may need to rely on strategies in general populations and assume that risk factors are shared between target populations. As the results of Chapter I show, drug use

disorders, previous criminality, and self-harm are risk factors for violence in both clinical and non-clinical populations, suggesting shared mechanisms. According to the National Crime Survey, violent victimization may be another shared risk factor.[139] Interventions to reduce paranoia may reduce violence risk in clinical and non-clinical populations as symptoms appear to exist on a continuum.[140] However, other specific risk factors like psychotic symptoms or treatment non-adherence,[71] are unlikely to be shared suggesting some prevention strategies may need to be tailored to specific populations.

Strengths & Limitations

Umbrella reviews are limited by the quantity and quality of available systematic reviews, and current reviews may not cover all existing research on interventions. However, I found an additional 28 reviews on interventions including pharmacological management, early intervention services, and monetary incentives, which reported no studies with violence outcomes. Nevertheless, some interventions may have randomized trial evidence without any relevant systematic reviews. For example, there are two RCTs on risk assessment and violence prevention,[84,141] (one discussed in Chapter II above on outpatient violence, and a second trial on risk assessment to reduce violence in acute psychiatric inpatient wards) but I found no reviews on risk assessment as an intervention. As this umbrella review focused only on violence as an outcome, reviews that addressed 'softer' related outcomes such as aggression (which typically includes verbal abuse), and broader clinical, rehabilitation, and social outcomes, were not included.[124] For instance, the review of pharmacological interventions found little evidence to support their use.[135] However, a highly cited review of randomized trials of antipsychotic medication in schizophrenia (excluded as it combined measures of both aggression and violence)[142] found an overall decrease in violent or aggressive behaviour with a pooled risk ratio of 0.3

(0.2-0.5), suggesting that the pharmacological treatment of psychiatric symptoms may reduce the risk of violence.

This umbrella review found one promising intervention, namely therapeutic community treatments. Therapeutic communities attempt to address drug and alcohol use disorders and related issues through structured daily regimens and a focus on self-help and self-reliance.[143] The reduction in reincarceration may therefore be mediated by substance use treatment as over a quarter of prisoners are estimated to have been under the influence of drugs at the time of their offence.[144] However, as the review did not provide data on the types of offences leading to reincarceration, a number of these could be due to non-violent drug related offences.

Proponents of compulsory community treatment argue that this form of intervention is less restrictive than subjecting people with severe mental illness to repeated hospital admissions, and may bring more stability to their lives.[134] However, the evidence is currently limited and no firm conclusions can be drawn, including on the effect of this type of intervention on violence.

The lack of research in violence prevention is likely due in part to the associated costs and difficulties in recruiting patients and conducting randomized controlled trials in forensic psychiatry.[145] Research in general psychiatric populations requires larger sample sizes and longer follow-ups to detect differences in police or hospital recorded violence compared to aggression scales as it is a rarer outcome. To overcome this, future research should consider novel designs involving linkage of randomized intervention data and register-based data,[146] and improve identification of high-risk groups through validated risk tools (such as the one presented in Chapter II) and monitoring of dynamic risk.[106] Furthermore, risk tools can be used to create enriched samples for intervention research by including only high risk groups. Finally, RCTs with primary outcomes on relapse,

symptomatic improvement, and rehospitalisation should consider including secondary outcomes specific to violence, in particular as risk often guides treatment decisions. Even if statistical power may be low for individual RCTs, having such information available could be the basis of collaborative meta-analyses.

Conclusions

In conclusion, this umbrella review found an overall lack of evidence for interventions to prevent violence in psychiatric patients, and interventions from non-psychiatric populations, or those with evidence on proxy outcomes (such as aggression), may need to be relied upon until higher quality and more research becomes available. The interventions identified in this review, in particular therapeutic community treatments, warrant further research to establish their effectiveness in reducing violence risk. The following chapter provides some reflections on this thesis, the three findings chapters, and how they have evolved from the original DPhil proposal.

Chapter IV - Reflections

On writing this chapter, I drew upon reflections both on how my work had developed through the process of undertaking this DPhil but also on my development as an academic through the process. As someone without a clinical background, nor a background in psychiatry, let alone forensic psychiatry, I entered this DPhil from the perspective of a research methodologist. Two things motivated me: first, the intellectual challenge of using the critical reasoning and research skills I had obtained in my undergraduate and Masters years; second, the ethical pursuit of contributing to an area of research that benefits some of the most disadvantaged groups in society. In 2012, I began my journey in the field of forensic psychiatry as a research assistant in the group where I would start my doctorate a year later. This chapter details this journey and my reflections on the field, my contributions to it, as well as my thoughts on psychiatry and medical research.

Research journey

Though my background was originally in the study of Philosophy, Politics, and Economics, which contained elements of research methodology, it was extracurricular work within my university's Social Policy department which eventually led me to medical research. In one of these projects, I researched ecological risk factors for repeat abortions in England; another was a critical appraisal of the Child Development Index, which was later cited by a United Nations Development Programme (UNDP) report on composite measures used in development.[147] The methods I used were fascinating to me. I realised that, even with the type of critical reasoning skills my first degree had offered me, it was still surprisingly easy to be wrong, easy to jump to wrong conclusions. In particular, extrapolating from the individual to the population, or from association to presumed

causation, seemed like common and facile *non sequiturs*. Incorrect reasoning, and inadequate research methodology or interpretation contribute to anything from innocuous health fads to medical disasters (one of which, the use of flecanaide for arrythmias, I discuss later in this chapter). Arguably some of the most advanced methods, and the area where being wrong matters most, can be found in health research. I enrolled in the MSc in Applied Health Research to further develop my interests in research methods, and start acquiring the skills that would allow me to contribute to medical research myself. A year later, I was seeking a new research opportunity, and I chose to apply to a research assistant position in forensic psychiatric epidemiology as I felt that this was a relatively under-researched area which also satisfied both the intellectual and ethical ambitions I wanted to pursue.

Research areas and methods

When I started my research in the Forensic Psychiatry group at Oxford, some of the methods were very familiar to me, such as those involved in my contribution to a systematic review on risk of suicide in prisoners with bipolar disorder.[148] When I worked on another systematic review on the prevalence of infectious diseases in homeless people,[149] I was also familiar with the disease areas. From the very beginning however, the bulk of my work involved new methods and a new area of medicine – psychiatry, and in particular forensic psychiatry, the overlap between psychiatry and criminology. Later in this chapter, I will discuss my personal views on psychiatry and the methods I discovered during my DPhil.

My previous encounter with the forensic world was in a module on the philosophy of criminology, where I concluded that the objective of the criminal justice system should be restorative, through deterrence, incapacitation, and rehabilitation, not retribution. How this is to be achieved however is primarily an empirical, not just a philosophical question.

My first piece of research examined associations between ecological, country-level, factors (including income inequality, education, and health spending) and rates of violence in 169 countries.[4] This prompted me to consider violence as a public health problem, and how this field could benefit from methods successfully applied to other areas of public health. By cowriting a paper on the stigma and self-stigma in Chinese patients with schizophrenia, I began to reflect on additional complexities when focussing not just on the criminological, but on overlap of the criminological with the psychiatric.[150] For example, I was particularly struck by unique ethical dilemmas relating to sectioning prior to conviction for, or even suspicion of, criminality.

Thanks to existing links and collaborations between my research group and the Karolinska Institutet in Sweden, I learned about Swedish registers. They are an exceptional research resource as Sweden and other Nordic countries are unique in the world for having national coverage of health, sociodemographic, criminological, and family data, which are made available to researchers. Cultural differences between Nordic countries and most other developed countries in part explain for why these registers exist in those but not other parts of the world, including a "high degree of public trust in research, plus the belief in social equality and mutual responsibility".[54] In contrast, I found it interesting that care.data, an attempt in England to create an arguably more modest national health database, was scrapped by the government after it "failed to win the public's trust and lost the battle for doctors' support".[151] These examples also began to shift my views towards supporting more open collection of medical data for public health research, subject to appropriate anonymisation, data governance and access.

Aside from the depth and breadth of Swedish registers, the aspect of this resource I found most interesting was the Multi-Generation register.[152] In traditional observational studies, matching of exposed to non-exposed individuals is often performed to reduce

bias due to confounding, typically by matching individuals by sex and age. Bias is then further reduced by adjusting for measured confounders. However, significant differences between the exposed and non-exposed individuals will remain due unmeasured (or unmeasurable) confounding, including individuals' genetic makeup and upbringing – or 'residual genetic and familial confounding' as it has been referred to in this thesis. Instead of comparing exposed individuals to e.g. ten age- and sex-matched controls, Swedish registers make it possible to compare exposed individuals to their unexposed siblings, taking into account some of the genetic and familial confounding (on top of adjusting for age, sex, and other confounders as appropriate).

I first used data from Swedish registers, including the Multi-Generation register, in two studies on premature mortality in epilepsy,[153] and on traumatic brain injury,[154] looking specifically at the role of psychiatric comorbidity. In both diagnostic groups we observed an increased risk of premature mortality. However, in individuals with epilepsy the increased risk compared to general population controls was similar to the increased risk compared to unaffected siblings; in individuals with traumatic brain injury, the latter was attenuated. This suggested that the link with premature mortality was partly confounded by genetic or familial factors in individuals with traumatic brain injury, but not epilepsy. This approach had also previously been used by our group to examine the association between epilepsy and violence, as medical textbooks had suggested that a positive association between the two existed. In line with the textbooks, the study found that, compared to age and sex-matched controls, individuals with epilepsy had an increased risk of violence.[155] However, when compared to their unaffected siblings, this association disappeared, suggesting that genetic and familial factors had confounded the relationship between epilepsy and violence.

Variations on this method have been developed, including the use of half-sibling comparison, and twin comparisons, as Sweden has the largest twin register in the world, including the ability to distinguish between monozygotic and dizygotic twins. We used both of these approaches in a study on depression and violence.[156] By comparing the effects of depression in monozygotic and dizygotic twins, we were able to unpick genetic factors from environmental factors. If risks are attenuated in monozygotic twins compared to dizygotic twins, this suggests genetic confounding, as the former group share all of their genes, whereas the latter share half. Similarly, comparing maternal half-siblings to paternal half-siblings gives an indication of environmental vs. genetic confounding. As children of separated parents are more likely to live with their mothers than with their fathers, maternal half-siblings are more likely to live with their mothers and therefore share their environment, whereas both groups share the same proportion of their genes. Whilst obviously none of these methods replace experimental research and randomisation (as discussed in the next chapter), they represent a small but significant step closer towards measuring causation. In particular, they provide a tool for disproving previously observed associations, as in the epilepsy and violence example above.

Thesis proposal

I decided to undertake a DPhil to give myself the time to explore specific research questions in more depth and develop necessary skills to allow me to better contribute to the field. As is often the case, the original thesis proposal did not remain static, but it evolved and transformed over the DPhil years. This section details how and why each chapter changed from the original proposal, to the research presented in this thesis.

Chapter I

For the first chapter, I proposed to use Swedish registers, and methods broadly similar to those discussed in Chapter I, to focus on distal risk factors for violent crime in schizophrenia, including IQ and low birth weight. However, three things quickly became clear. First, in order for this study to provide the background research for the risk assessment tool in Chapter II, a much broader range of risk factors would need to be examined, including the most researched ones such as previous violence, and substance misuse. IQ and low birth weight data on the other hand were only available for a subset of patients, with IQ in particular being only available for Swedish (male) conscripts. Second, due to changes in diagnostic terminology and coding practices over the period considered, restricting the cohort to individuals with schizophrenia diagnoses (and not schizophrenia-spectrum diagnoses) would have complicated interpretation due to potential reclassification bias. Third, the Swedish data resource I had available could answer an additional important and related research question – on time trends of adverse outcomes in schizophrenia-spectrum disorders – in a unique and novel way.

Our group's previous research using Swedish registers had generally presented the relative likelihood of adverse outcomes as odds ratios comparing cases to general population controls, and presented separate odds ratios for unaffected siblings compared to general population controls. However, without additional statistical work, it wasn't always clear whether any difference between these two measures were statistically significant. I proposed additionally presenting ratios of odds ratios and associated 95% confidence intervals, which present a statistical comparison of the two odds ratios (as shown in Figure I.1, page 22). This method lent itself well to examining time trends and, by comparing relative time trends in individuals with schizophrenia-spectrum disorders to those time trends in unaffected sibling, I presented the first time trend analysis for

adverse outcomes in schizophrenia-spectrum disorders adjusting for genetic and familial confounding, which formed part of a paper published in the inaugural issue of the Lancet Psychiatry in June 2014.[157]

Chapter II

The risk assessment tool in Chapter II was presented in the thesis proposal as a scalable violence risk assessment tool, proposing to use a similar methodological approach to current cardiovascular risk assessments such as QRisk.[158] However, with little additional methodological detail at this stage, this would become a key learning experience of this thesis. As discussed in the introductory chapter, hundreds of risk assessment tools exist and more are created every year, so creating a new one should not have presented a big hurdle. Creating one based on robust methods however would require a much deeper understanding of risk assessment.

Around the same time as a I began working on Chapter II, colleagues and I started to collaborate with members of the Nuffield Department of Primary Care Health Sciences on the Oxford Mental Illness and Violence tool (OxMIV).[92] FoVOx was conceived alongside OxMIV, and benefitted from the methods and approaches I studied whilst working on OxMIV. Instead of a 'quick and dirty' analysis of the data to find a statistical model that looked adequate, no analyses were performed in the first twelve months of the project. Instead, our team went through many iterations of an analysis protocol, to ensure four things. First, that our risk tool would be based on robust statistical methods with appropriate measures of calibration and discrimination. Second, that it would be useable by and acceptable to clinicians by involving them from the very beginning. Third, that it would be as generalizable as possible to other settings by considering which variables may or may not be available outside Sweden. And finally, to ensure that our final model would be devoid of multiple testing bias by pre-specifying analysis parameters. To my

knowledge, before OxMIV and FoVOx, no violence risk assessment tools had been derived using a pre-specified protocol. This is a vital distinction, which I discuss in more detail later in this chapter.

Chapter III

The chapter that changed most from its original proposed form in the thesis proposal is unquestionably Chapter III. The proposal planned a systematic review and meta-analyses of primary and secondary violence prevention interventions worldwide, to include previous reviews, meta-analyses, randomized-controlled trials, and even ecological and population-bases studies, through searching multiple databases and scanning bibliographies of relevant articles, without time or language restrictions. Subsequently, I planned to present the findings of the review to an expert panel at a forensic conference for an evaluation of interventions using multi-criteria decision analysis.[159] Scoping searches at the time had indicated that there was a vast body of existing research, including on "domestic violence, alcohol pricing, school-based violence, and interventions in psychiatric inpatients". The question I had wanted to answer was: If your aim is to reduce violence, which interventions should you consider first?

My very first conference trip was to the International Association of Forensic Mental Health Service (IAFMHS) in Maastricht in 2013, where I gave three oral presentations. In the first, I shared some initial findings from Chapter I; in the second, I presented the results of the previously mentioned systematic review on suicide rates in prisoners with bipolar disorder. In my third and last presentation, I introduced the systematic review protocol from my thesis proposal and asked attendees for feedback. My first slide had already suggested that I would be presenting the findings of the review a year later, at the subsequent IAFMHS conference, for the anticipated expert panel discussions. In the end, I did not attend the IAFMHS conference in 2014, but I did attend the next one in

Manchester in 2015. Though I presented the final findings of Chapter I, my other oral presentation did not share the findings of the systematic review. Instead, it provided an updated review protocol for discussion.

What had happened? Partly, other projects and elements of this thesis had taken priority in that time, somewhat delaying the systematic review. The main change however had been to the planned project itself, not the timeline. As I began drafting a more detailed analysis plan, a number of things became clear. First, attempting to essentially summarise the existing body of research on violence prevention was a huge endeavour, which would not be feasible within the scope of a DPhil thesis. For comparison, a systematic review on violence prevention published in 2012[160] represented an entire NIHR Health Technology Assessment. Additionally, it was a six-year update to an existing review, and included solely secondary prevention interventions, and no multi-criteria decision analysis. Second, this review would have included hundreds of studies with vastly different populations, settings, interventions, comparisons, study designs, and reporting quality. This heterogeneity would not only have made it difficult to summarise findings and present them in a clear and consistent manner; but including these studies in the same review would have complicated interpretation as direct comparisons between study designs or interventions would have been largely inappropriate. Finally, it went beyond the clinical focus of the thesis, seeking to include all violence prevention interventions, not just those relevant to psychiatry. It was therefore not clear how this chapter would link to others in the thesis. Though – with the benefit of hindsight – it now seems somewhat obvious, the initial project was not appropriate for a thesis chapter. Given the overall focus of this DPhil, I proposed to review interventions that may benefit individuals identified as high-risk by FoVOx, the risk assessment tool presented in Chapter II. To provide a clear summary of the existing research on interventions backed by evidence of

sufficient quality to use in practice, and to avoid the problems discussed above, I chose to conduct an umbrella review, (with further justification for this choice presented in Chapter III). This experience has been useful by teaching me how to work within given constraints, better plan large research projects, and re-evaluate as the scale of work involved becomes clearer.

Beyond the statistics

The above section has primarily focused on the individual chapters and their methodologies. However, my time as a DPhil student has also included equally important dissemination and public engagement work, and work to translate research findings into practice.

Peer-review & media

In my time at the Department of Psychiatry, I published over a dozen peer-reviewed articles on a range of different topics, using different methodologies. Finding myself on either side of the peer-review process, the imperfect cornerstone of science, has been as interesting as it has been rewarding, even if at times frustrating. Despite its questionable business model, academic publishing is currently essential in the dissemination of research findings. My first paper, on infectious diseases in homeless people, went through two rounds of peer-review, which substantially improved the final manuscript. By the time I submitted the individual chapters of this thesis to journals, the process had become much more familiar, and I had acquired the persistence necessary to get one's scientific voice heard in the face of rejections or revisions. Some of the papers I had worked on gathered attention from the media, and the manuscript based on Chapter I was covered by news outlets including Newsweek,[161] Vox,[162] and Deutschlandfunk.[163] Perhaps unsurprisingly, the abovementioned paper on depression and violence gathered the most

interest – and was also probably at highest risk of being misreported. Colleagues and I therefore collaborated with the Science Media Centre (a non-profit organisation whose aim is to improve access to accurate, evidence-based scientific reporting) to organise an advance briefing and question and answer session with journalists from the national and international media. I relished the challenge of presenting on the methodology and results of the research (including the use of Swedish registers, and the interpretation of the ratio of odds ratios for sibling analyses), and responding to requests for clarification from journalists, whilst colleagues presented the clinical context and interpretation of our findings. Except for one British newspaper who began their article with a sensationalist headline (though even this was amended after we contacted them), reporting of the findings was generally accurate and sensible, which was a welcome outcome to which I had contributed and learned from.

Correspondence & perspective

As I learned more about the forensic psychiatry, attended more conferences, and received invitations to peer-review other researchers' work, it became clear that the potential for misinterpretation and misrepresentation was is no way limited to the media or the lay person. Risk and risk assessment in particular appear to be poorly understood not only by society, but also by too many clinicians and researchers (as evidenced by ongoing debates regarding different screening programmes). In forensic psychiatry, I believe this lack of understanding of the complexities or risk assessment to be the primary reason behind the current state of affairs where hundreds of unvalidated risk prediction tools are used daily throughout the world, and why great faith is placed in (often very expensive) tools despite insufficient evidence to support their use (I discuss the methodological aspects of this in more detail later in this chapter).

Fortunately, the peer-review process does not end at publication, as many journals encourage correspondence from readers, and I was eager to contribute to these discussions. My first published correspondence was on the appropriateness of pooling prevalence rates (in a paper on infectious diseases in people with severe mental illness) given substantial unexplored clinical and statistical heterogeneity.[164] Subsequently however, the focus of my work here too shifted to risk assessment. My next correspondence piece, to the British Journal of Psychiatry, was entitled "Overstating the lack of evidence on suicide risk assessment"[165] and written in response to a systematic review of risk scales for suicide prediction following self-harm. I argued that, though some criticisms of existing risk scales were valid, these were insufficient to dismiss the entire field of suicide risk prediction. I believe that this dismissal is premature as the alternative approach (preventing suicide without the use of risk scales) has not been assessed with the same rigour and objectivity. This is explored in the final section of this chapter, and in more depth in the concluding chapter.

In a separate correspondence piece to the same journal,[166] I responded to a manuscript comparing the predictive performance of actuarial risk scales to that of clinicians when estimating risk of repeat self-harm. The original manuscript found that the examined risk scales performed *no better* than clinician ratings, and the authors saw this as a strong argument against risk scales. My response however was that, equally, they found that certain risk scales perform *no worse* than clinician ratings. This seemed to me a favourable finding for risk scales, in particular as those clinicians had just used those very same scales to inform their ratings, and also worked at arguably some of the best teaching hospitals in the UK. I therefore suggested that future research should examine whether additional clinician input after actuarial risk assessment (i.e. clinicians deviating from or disagreeing

with the score provided by the risk scale) would improve or worsen predictive performance.

These correspondence pieces and my other work on risk assessment developed these skills further and also informed a Perspective article in the form of a 10-point guide,[94] published in the Evidence-Based Mental Health journal, and discussed in the Methods section of Chapter II.

OxRec in the Netherlands

Perhaps the most exciting part of my research journey was our collaboration with Dutch Probation to validate OxRec (the Oxford Risk of Recidivism tool)[93] in the Netherlands for use in the Dutch judicial system. OxRec, a risk prediction tool for offenders released from prison, was first derived and validated in Sweden using methods similar to FoVOx, and was the first risk calculator to be added to OxRisk.com platform. In September 2016, my supervisor was contacted by the Dutch Probation Organisations to start a dialogue on risk assessment as they were in the process of updating their risk assessment platform. With the help of a Dutch colleague within the department, I created a Dutch version of OxRec to share with our collaborators through the OxRisk website. This led to further discussions and a trip to the Netherlands to begin working on a protocol for a validation study of OxRec using Dutch data. Whilst learning more about the public policy side of risk assessment, presenting the methods behind OxRec to colleagues from Dutch Probation also heightened my communication skills by my having to adapt to expert but non-statistical audiences.

Validation of OxRec in a new country added a number of complexities to the project. In particular, we had to establish *a priori* (for reasons discussed in this chapter, including avoiding multiple testing) how best to capture the definitions used in the original OxRec using variables collected in the Netherlands. Resolving these uncertainties was a

collaborative effort including our research group, colleagues from Nuffield Department of Primary Care Health Sciences, and colleagues from Dutch Probation. Additionally, we knew that recidivism rates in the Netherlands were lower than in Sweden, and would therefore have to establish whether similar risk factors applied to both countries' prison populations. As a result, our protocol had to include steps for recalibration for both baseline risks and individual variable coefficients without compromising the external validity of the model. Working through these steps within a multidisciplinary team deepened my understanding of the complexities and nuances of risk assessment and strengthened the field by setting a precedent on the use of robust validation methodology. After a successful pilot at the end of 2017, OxRec is now routinely used by Dutch Probation throughout the Netherlands as part of their risk assessment and probation reports.

OxRisk.com

It was of great importance to me that the science and code behind FoVOx would be made available in an open-access format, to be easily reviewed by and accessible to the scientific community. I believe that, by adopting a free and easily accessible website (OxRisk, which hosts multiple risk tools created by our group), this approach has also contributed to the tools' success. As work began on the first OxRisk calculator, I started to design the OxRisk.com platform with these ambitions in mind. The original thesis proposal mentioned QRisk, a cardiovascular risk tool with an online version available. The design of the QRisk website however had seen no substantial changes in recent years and lacked features which had become part and parcel of modern web pages, including responsive web design (the ability for the website to adapt its design to any device, including mobile phones and tablets). Though I had some rudimentary self-taught web design skills from my teenage years, creating a well-designed online tool was beyond my abilities at the

time. I attended beginners' coding classes organised by the IT Learning Centre, to learn more about both Javascript and PHP (recursive acronym for PHP: Hypertext Preprocessor), two scripting languages designed for web development. This provided me with some basic understanding, but nowhere near enough to build this type of website from scratch. However, I discovered that there are vast libraries of free and open-source software and code available online, which I was hoping to adapt and repurpose for OxRisk.com. As discussed in Chapter II, I combined blogging software (WordPress) with additional code typically used for online shopping websites. The code previously used for enabling customization of e.g. t-shirt colour and size to calculate a price, was now being used to calculate a predicted risk of reoffending. I also attended a beginners' Photoshop course, to enable me to create the OxRisk.com logo, as well as individual logos and colour schemes for each risk tool. I have since used those newly acquired skills to create Oxford-FB.com, a platform for a study[167] on social media and mental wellbeing I conducted alongside my DPhil, and FPRS.org, the website of the Forensic Psychiatry Research Society. As there is much common ground between coding languages and structures, learning about Javascript and PHP has also helped with acquiring new research skills, such as using the Stata and R statistical software packages and learning basic SQL and Python coding for data management.

Research perspectives

In this section I begin with a broad comparison between research in psychiatry and research in other medical specialities, as these considerations weighed on me as I chose to begin, and ultimately continue, pursuing research in psychiatry. I then discuss specific concepts which I believe to be key in understanding and improving the future of medical and psychiatry research, including the (mis)use of proxy outcomes, the importance of protocols, and the ethics of risk assessment.

Psychiatry

Psychiatry, for better or worse, is generally considered unique within the medical specialities. In particular, a version of the stigma experienced by psychiatric patients (as discussed in the introduction) seems to also be experienced by mental health professionals, and by the discipline as a whole. As someone new to mental health, it was important for me to better understand this stigma, why it exists and persists, and my potential role in seeking to reduce this stigma through my research. Particularly surprising was the fact that misconceptions about psychiatry were common not just among the general public but also medical students, with a quarter of them reporting that they would be uncomfortable sitting next to a psychiatrist at a party, and half thinking that psychiatrists "know what you are thinking"[168] (which also suggests that up to a quarter thought psychiatrists knew what they were thinking but still didn't mind sitting next to them at a party!).

However, these concerns did not really seem material to the importance and relevance of psychiatry and, the more I discovered about the practice of and research in psychiatry, the more I disagreed with suggestions that psychiatry as a medical speciality was in any way inferior. A primary aim of medicine is to reduce human suffering. While treating physical symptoms is one way to achieve this, the symptom itself is used as a proxy for

suffering. Proxies may not always be appropriate (more on proxy measures below) and research in psychology suggests that the life satisfaction of individuals with certain permanent physical disabilities returns to, and is predicted by, levels of life satisfaction pre-disability.[169] Similarly, to use an example discussed in the umbrella review above, high blood pressure in and of itself does not cause suffering, but is instead used as a proxy for the risk of long-term adverse outcomes. In contrast, psychiatry often deals with suffering and happiness in a more direct way, by seeking to treat ill mental health, which almost by its very definition causes harm to either the person or to others.

As a more substantive criticism, some medical students believed that, unlike other medical specialities, psychiatry lacked effective treatment options. Similarly, a review by Leucht et al. began by noting a "deep mistrust of psychiatry fostered by reports suggesting that psychotropic drug efficacy is very small".[170] However the review, which examined the efficacy of psychiatric medication in relation to the efficacy of general medicine medication, concluded that the effect sizes of medications in both groups were in fact largely comparable.

I would therefore conclude that the interventions in psychiatry are likely as effective as those in other medical disciplines, and that its aims are as if not more important. Given however that it is estimated that 85% of research is 'wasted' (largely due to non-publication of results, inappropriate methods, or unnecessary duplication),[171] this favourable comparison is as concerning as it is reassuring. The following sections therefore consider two key sources of research waste in psychiatry and other medical research.

Proxy outcomes

During my Masters degree, a case study that really stuck with me was on the history of a drug called flecainide. In patients who had suffered from myocardial infarctions (MI),

those with comorbid arrythmia were found to be at increased risk of sudden death compared to patients without comorbid arrythmia. As an antiarrhythmic agent, flecainide was adopted widely in the treatment of MI patients with arrythmia, and its effects on arrythmia was considered an adequate surrogate for drug approval by the FDA. However, this was based on the untested assumption that, because arrythmia is associated with early death, the treatment of arrythmia would result in a decrease in the risk of early death. Five years after the drug was first approved, a placebo-controlled randomized controlled trial funded by the US National Institute for Health was finally initiated, despite outcries from some doctors and patient groups. Critics questioned the ethics of patients receiving a placebo for their condition when flecainide was assumed to be effective. However, the trial showed a significantly greater number of deaths and cardiac arrests in the active group (Risk Ratio: 2.6 (95% CI: 1.6 to 4.4)[172] and subsequent analyses estimated that the prescription on flecainide in the 1980s led to over 50,000 premature deaths.[173] Interestingly, research has since indicated that flecainide may actually benefit a subgroup of those originally treated in the CAST trial,[174] further highlighting the need for high-quality randomized evidence.

For me, this was a prime example of how easy it is to jump to erroneous conclusions which can only be corrected through the use of appropriate research methods. It has also shaped my views of risk assessment, and modifiable risk factors in particular. For instance, substance misuse is the archetypal example of a modifiable risk factor for violence. There is a large body of evidence showing that individuals with substance misuse problems are at increased risk of being violent, and this includes the findings in Chapter I and II of this thesis. It is also entirely plausible that treating a person's substance use disorder will reduce their risk of violence, for example by reducing the impulsivity in acute use or irritability in periods of withdrawal. However, substance misuse could also just be a

marker of something else which is itself related to violence, rather than substance misuse being a causal factor for violence. The findings in Chapter II lend some support to this idea (see Table II.6). Lifetime drug use disorder doubled the risk of violence in this patient sample, while current drug use disorder had no significant association with violence in the multivariable model. In other words, stopping substance misuse did not appear to reduce the risk of violence. A 2016 paper on the genetic and environmental determinants of violence risk in psychotic disorders,[76] conducted by colleagues in Oxford and the Karolinska Institutet, showed that two thirds of the correlation between schizophrenia and violence could be attributed to genetic influences shared between schizophrenia, substance misuse, and violent crime. Their findings also support the hypothesis that substance misuse may, at least in part, be a marker for genetic influences which increase the risk of violence, rather than a modifiable causal risk factor. However, it is important to note that, unlike arrythmia, substance misuse is a serious condition in and of itself, and should be treated even if there is little or no proven effect on violence (see Chapter III). However, if substance misuse interventions are used to reduce the risk of violence, using substance misuse as a proxy outcome may be inappropriate, albeit plausible. It is insufficient to base clinical practice on plausibility and theory. This plausibility should be used to inform research, not practice.

Protocols

Double-blind placebo-controlled trials are often considered the gold standard of medical research. Though the methods are well-established and perhaps more straightforward than those used in observational research, recent lobbying efforts (including the AllTrials campaign) have highlighted the issues of non-publication of trials and outcome switching. I would argue that these same issues apply to observational research, and mandatory study protocol registration should be considered.

I have attended many conferences covering research methods for observational research. New and complex statistical methods for e.g. multiple imputation or propensity scores were presented and discussed, which may well provide incremental improvements to the output of the research community. However, if I were asked to name the biggest obstacle to improving medical research, it would not be a lack of appropriate statistical methods. Researchers continue to argue over what the best methodology may be, even though answering this question may have little overall impact on public health. Attempting to answer this question through consensus may also be fruitless, as differences of opinion (e.g. frequentists vs. Bayesians) are unlikely to be easily resolved. So, whilst we may not know what the best methods are for a given research question, most researchers can easily distinguish between good methods and bad methods, and that may well be good enough. I do not believe that what we need is better methods. Researchers trying multiple good methodological approaches until they find the one that gives a satisfactory result is in my view far more worrisome than the same researchers failing to use the "best" approach. Instead, we need to start using existing methods properly, and the only way to achieve this is through pre-specified protocols. This is as true in observational research as it is in randomized trials.

Without a protocol, researchers may be tempted to alter some analysis parameters until they get the result they were hoping for, expecting, or believe is publishable. Using the best statistical methods may be meaningless if they are the nth attempt at answering the very same question using a series of equally valid statistical methods and assumptions. In particular, the lack of protocol will bias research findings towards the researcher's preconceptions, or the existing literature. If a researcher finds results consistent with their expectations, they will assume their methods are correct. If a researcher finds unexpected results, methods will be double and triple checked, and they may be tempted to adjust

parameters and analyses to support the original hypothesis. This is particularly troublesome for the peer-review process. Without a protocol, a reviewer can only judge what is in front of them, and will not know what other analyses have been attempted but not reported. The methods may be appropriate, but the outcome and interpretation will be misleading if multiple testing, outcome switching, or other changes in analyses have occurred and not been reported as protocol deviations.

Ethics of risk assessment

Risk assessment, and in particular risk assessment in psychiatry, brings up critical ethical questions. Though all valid, the questions I have been asked over the last few years varied depending on the background and profession of the person I was discussing my research with. For instance, lay people questioned whether it was right to conduct risk assessment at all, whether it was right to curtail an individual's freedom based on such assessments. Clinical colleagues sometimes argued that statistical risk prediction could not be applied to the individual and that clinical observation should be relied upon. Fellow methodologists questioned the ethics of using risk assessment tools without knowing whether their use benefits patients or society. Though it would be wrong to assume that this section could do justice to the complexities and nuances behind each of these questions, it would be equally wrong to fully uncouple the science from the ethics, and leave others to answer these questions. I therefore provide my personal thoughts below.

To answer the first question, it seems that some form of risk assessment is almost inevitable. If we accept that one of the aims of psychiatry and the judicial system is to reduce the risk of harm to self or others, then risk assessment (statistical or otherwise) becomes necessary – and has always existed. But what form should this risk assessment take? In some ways, risk assessment in psychiatry is no different to risk assessment in other fields, including for example cardiovascular disease. A measurement of high blood

lipids in and of itself is uninteresting. Aside of course from its link to concurrent symptoms, the reason a doctor will be interested in high blood lipids (or high blood pressure, or heart arrythmia as discussed above) is their association with future adverse events. Though high cholesterol increases the risk of cardiac events, the absolute risk remains low. Even after inclusion of multiple risk factors into a complex risk prediction tools (QRisk), the vast majority of those considered at high risk of cardiac events will not experience one.[158] Similarly, the risk assessment area of psychiatry is less interested in the risk factors in and of themselves, than in their ability to predict adverse events such as suicide or violence. The question then becomes one of cost-benefit, and whether this prediction can be linked to interventions to reduce the risk – or the question asked by the methodologist.

To expand on the questions from the clinicians, I believe there are similarities between the aversion some doctors have to statistical risk assessment, to their aversion to clinical checklists. This is perhaps unsurprising as risk assessment could be considered a complex checklist, removing some decision-making independence from the clinician and shifting it to a standardised and automated system. Their sentiment is understandable, particularly as clinicians have sometimes decades of training behind them, as well as front-line clinical experience which could never be summarised in a checklist or statistical model. Indeed, it could obviously be true that some clinicians perform better without some checklists or actuarial risk assessment. However, without the research we do not know whether that is the case, or which clinicians this may apply to (or whether individual clinical performance is related to the level of aversion to checklists or risk assessment). It is also clear from the evidence that many checklists do improve clinical outcomes for the 'average' doctor, in part by raising the 'floor' of clinical effectiveness. To quote the headline of a 2017 Harvard Gazette article, "Checklists are boring, but death is worse".[175]

Most checklists and risk assessments are designed to guide clinical decisions (with varying levels of final clinical autonomy), and allow for deviation from recommendations if deemed clinically appropriate. As discussed above, a fascinating empirical question which I believe needs to be explored is whether those deviations improve outcomes or prediction. For instance, when clinicians adjust a risk score produced by FoVOx (based on additional clinical observation not captured by FoVOx), does the overall predictive performance increase, or decrease?

The last question relating to the ethics of risk assessment, coming from the methodologist, is perhaps the most difficult to answer. Why risk assess if there is little evidence that doing so improves patient outcomes? Part of the answer is that unlike for example screening for prostate cancer – where the medical community will argue primarily about the cost-benefit analyses of such screening programmes – risk assessment research in psychiatry often sidesteps this issue. Risk assessment for violence and suicide is legally mandated in a number of settings, and the question could be rephrased as "Given risk assessment has to be done, how can we maximise its benefits and minimize its harms?". Nevertheless, this obviously begs the question of how and whether this legal mandate is ethically justified. In some ways, that legal question is then no different to the cost-benefit question, albeit with the added complexities of quantifying the costs and benefits of potential imprisonment, sectioning, and the risks of loss of life. Sadly, this continues to be an under-researched area, and without legal mandate, there is currently little evidence to support the use of risk assessment.

In summary, I set out to use this DPhil to help advance the research in forensic psychiatry and improve the discourse around the complexities of risk assessment and management,

through active collaboration, public engagement, and research dissemination. The next and final chapter summarises the findings of Chapters I, II, and III, discusses their implications and provides practical recommendations for clinical practice and research.

Conclusions

The aims of this thesis were to examine the risk factors for violence in schizophrenia-spectrum disorders, to create a simple, scalable risk assessment tool to predict violence in forensic psychiatric populations, and to review the evidence for violence prevention interventions in psychiatry. Chapter I reported a study of 24,297 individuals with schizophrenia-spectrum disorders that were followed up for 38 years, and examined rates and risk factors for violence, suicide, and all-cause mortality. Within 5 years of first diagnosis, 10.7% of men and 2.7% of women with schizophrenia-spectrum disorders were convicted of a violent offence. Three risk factors increased risks in patients, but also in controls: drug use disorders, a history of violent criminality and self-harm. Chapter II reported the derivation of FoVOx, a 12-item online tool for the prediction of violent crime within 12 and 24 months of discharge from forensic psychiatric hospitals. The model uses pre-specified criminal, sociodemographic, and clinical risk factors from 2,248 discharged patients, and showed good measures of calibration and discrimination (area under the curve = 0.77 at 12 and 24 months). In Chapter III, I summarised the existing evidence for violence prevention interventions in psychiatry. Out of five included reviews, four received GRADE quality of evidence ratings of 'low' or 'very low'. One review received a GRADE rating of 'moderate', and reported that therapeutic community and aftercare interventions may be effective in reducing reincarceration in adult drug-using offenders with co-occurring mental illness.

Investigating risk factors for adverse outcomes should assist in providing targets for intervention, and my findings suggest that those individuals at high risk of developing psychosis could benefit from primary prevention interventions, delivered through early

intervention services, that seek to prevent modifiable risk factors, in particular drug use, self-harm, and criminality.

By using a novel approach to examine trends in adverse outcomes, my study confirms previous findings of relative increases in the rates of suicide[78] and premature mortality[11,51] in patients with severe mental illness, and finds similar increases in violence. This is the largest study of its kind, and the first to adjust for residual genetic and familial confounding. These findings are also consistent with a lack of decrease in the burden of disease attributable to severe mental illness,[14] and new treatments having not translated to a reduction in adverse outcomes for these patients.

Treatment plans are often informed by risk assessment tools, both to identify needs, and direct interventions towards those at the highest risk, or most likely to benefit.[39] Almost all forensic units in England use such tools, though the majority are locally adapted, unvalidated instruments.[43] FoVOx has been developed specifically in forensic psychiatric patients using routinely collected register data from a total population cohort of over 220 patients. It is the first tool in forensic psychiatry to use a protocol with pre-specified cut-offs, design, risk factors, and internal validation. The risk tool and model coefficients are freely available, simplifying future external validation in other countries, and use in resource-poor settings. Free and quick risk assessment can also enable resources to be redirected towards clinical care and risk management, and interventions to be targeted appropriately. As risk assessment is already routinely done in forensic psychiatry, there are obvious benefits to improving their predictive accuracy, while reducing their complexity and resource implications. FoVOx can provide a clearly defined risk score for an individual to external bodies, such as mental health tribunals, who often request information on risk of violence. Further, in the transition of some patients from forensic to general psychiatry, information on risk is important in the liaison between

these services, and probability scores and clearly defined thresholds, as provided by FoVOx, can be used as part of a transition to general psychiatric services.

However, my study finds that there is currently a lack of research and evidence to support the use of interventions in psychiatry to reduce the risk of violence. My study is the first umbrella review on violence prevention in psychiatry, which is a type of systematic review that can assess multiple interventions by including all relevant existing systematic reviews. Though 33 systematic reviews were identified which included violent outcomes in their inclusion criteria, 28 of those included no relevant studies, and the remaining five were generally scored as low on quality of evidence. This highlights the need for high quality primary research in violence prevention, and the routine addition of secondary outcomes specific to violence in intervention trials in psychiatry.

Strengths and limitations

The primary strength of this thesis is its emphasis on robust and transparent methods, by identifying the most appropriate data sources and best available statistical approach for each research questions. For instance, by using Swedish national registers, Chapters I and II are the largest studies to date examining risk factors in schizophrenia-spectrum disorders, and deriving a violence risk prediction tool in forensic psychiatry, respectively. In addition, Chapter I benefits from an entirely novel approach to account for genetic and shared environmental confounding, by comparing individuals with schizophrenia-spectrum disorders to their unaffected siblings. Chapter II introduces methodology previously established in other areas of medicine (in particular cardiovascular disease) to forensic psychiatric risk prediction for the first time, including the use of prespecified protocols, sample size calculations, and internal validation. A prespecified protocol was also used for the study in Chapter III to provide a first summary of the violence prevention evidence in psychiatry through the use of an umbrella review.

However, the methods used also have some important limitations. For instance, the nature of the designs and data used for Chapters I and II do not allow for causal interpretations between identified risk factors and violence. In other words, as these studies were based on routinely collected observational data, no causal inferences can be made. For instance, a parental criminal conviction may not directly cause an increased risk of violence in the child. Instead, both the risk factor and the outcome may be due to one or more third factors (e.g., shared environment or genetic predisposition).[76] Observational studies cannot by design support unequivocal causal inferences, due to various types of confounding. Though methods exist to adjust for confounders (e.g., statistical adjusting for risk factors, family-based designs, or propensity score matching), these are imperfect due to residual confounding (including unmeasured and imperfectly-measured confounding), and they run the risk of over-adjusting if a specific risk factor is in fact on the causal pathway. For example, if a diagnosis of schizophrenia increases the risk of substance misuse, and substance misuse increases the risk of violence, then adjusting for substance misuse would mask some of the relationship between schizophrenia and violence. Experimental (e.g., randomized controlled trials) or certain quasi-experimental designs (e.g., regression discontinuity designs) are necessary to establish causality. However, these are often costly and generally have shorter follow-up times. Therefore, new designs have been established as a cross between RCTs and register-based designs, by combining randomization with the long-term routine follow-up through registers at minimal cost. Finally, it should be pointed out that the aims and findings of Chapters I and II are not based on an assumption of causality. Chapter I identifies risk factors and trends; Chapter II uses risk factors to create a risk prediction model. Identifying A as a risk factor for B does not imply that removing A will reduce the

risk of B, and both studies seek to find associations and make predictions, not establish causality.

One of the strengths of actuarial tools with objective variables such as FoVOx, over structured clinical judgment or more subjective tools is their ability to raise the 'floor of expertise'. Validation studies are often conducted in teaching hospitals and with more experienced clinical staff and the performance of structured clinical judgment tools is likely to be lower in other settings, and outside the context of research. In contrast, the objective measurement of actuarial tools will provide a performance 'floor' to more junior clinicians or less research-focused settings. Similarly, they can provide consistency in resource poor settings such as low- and middle-income countries.

As previously discussed, Swedish data was chosen for its completeness, established diagnostic validity, and overall sample size. However, this choice also has an significant limitation, as this meant that data came from one specific country. This is important as, particularly in an area such as forensic psychiatry, there will be jurisdictional differences between Sweden and other countries, as well as differences in diagnostic definitions and practices, base rates, recording of crime etc. These kinds of differences may affect validity in two different ways. The first primarily has an impact on discrimination: if risk factors do not have the same or similar effects on the outcome, then the tool will not be able to discriminate between someone who offends and someone who doesn't, as the overall relative ranking of individual patients risks will be affected. The second effect on validity primarily affects calibration: if risk factors have similar effects but the baseline risk is different, the accuracy of FoVOx's absolute score will be reduced. This could happen for a variety of reasons, including more effective overall treatment in a different country or jurisdiction, but also differences in thresholds for admission or conviction of individuals. In this case, though the model would be similarly effective at discriminating between

offenders and non-offenders, it would not perform as well at predicting absolute risk, as all individuals would on average have a disproportionately lower (or higher) predicted risk of violence than their actual observed risk. Differences in the prevalence of risk factors would not affect model performance if risk factor effects and baseline risk are comparable as individual risk would still be calculated appropriately. Risk assessment tools can be recalibrated for improved performance, as discussed below.

Some have argued that risk assessment is inherently impossible or not worth pursuing. The argument usually goes as follows: due to low base rates, the majority of those identified as high-risk will not have the event and, as most individuals will be identified as low-risk, most of the events will occur in the low-risk group.[176] Therefore, false-positive cases will receive unnecessary treatment, and false-negatives will have resources diverted away from them. Instead, it is argued, all patients should receive appropriate treatment and the emphasis should be on need rather than risk. This argument is however simplistic and lacking normativity, for four reasons. First, while decades of research have informed our knowledge of the statistical performance of existing risk assessment tools, little is currently known of the associations or effects of needs-based approaches. In other words, while we know what the strengths and limitations are of risk assessment, we do not yet have the same level of information on purely needs-based approaches. Further research is needed to evaluate the effects of such approaches on patient needs and risk to others. Second, though it is correct that risk assessment tools are far from perfect, this is not in itself an argument for switching to alternative but untested (and potentially inferior) approaches. For instance, the performance of risk assessment tools in psychiatry is comparable to cardiovascular risk tools[49] which are recommended for linking to appropriate interventions (e.g., statins), even though most of those identified as high cardiovascular risk individuals will not suffer from cardiovascular events.[177] Nevertheless,

statins have a very strong evidence base for their effectiveness, and low rates of harm, and such interventions are currently not available for mentally ill offenders. Third, whilst the idea of ensuring all patients receive appropriate treatment has obvious theoretical and intuitive appeal, it provides little guidance on what ought to happen in practice. Resource-limited settings require difficult decisions on treatment allocation, ensuring they go to those most likely to benefit. For instance, interventions designed primarily to reduce the risk of violence may be less cost-effective in individuals identified as low-risk. Additionally, most interventions are not side-effect free, and some are indicated only if risk to self or others has been established. Fourth, risk assessment can provide important transparency to clinical decision-making and a 'common language' for clinicians to discuss risk with patients, carers, and colleagues. Nevertheless, a purely needs-based approach may prove to be superior to current recommendations, but this needs to be thoroughly investigated, and any change in practice should be based on sufficient high-quality experimental evidence.

Another limitation, relevant to all three chapters, is the choice of outcome measures. This thesis focuses on the more severe outcome measures by including only 'hard' measures of violence. First, this may underestimate rates of actual violence as the threshold for recording is higher than for example for less severe forms of aggression. Second, this excludes other outcomes which may be more common and relevant to patients and clinicians, from aggression scales, to measures of quality of life or symptomatology. However, these types of outcome measures generally require additional data collection, with added limitations in terms of generalizability (e.g., non-consenting individuals), and sample size is therefore unlikely to reach the thousands of individuals needed for the statistical power for clinical risk prediction (at least without considerable resource and time implications).

Aside from the limitations discussed above and in the three chapters, this thesis has a number of conceptual limitations, some of which I have tried to address through research not directly linked to this thesis. First, severe mental illness only includes a relatively small proportion of the population with mental health disorders. For instance, major depressive disorders are around four times as prevalent as bipolar and schizophrenia disorders combined, and are responsible for a quarter of the disability-adjusted life years lost to mental, neurological, and substance use disorders.[14] Examining the link between depression and violence, colleagues and I found a small increase in risk in a Swedish total population study of outpatients (n=47,158), a finding that was confirmed in sibling and twin analyses.[156] Second, FoVOx is a violence risk prediction tool designed for forensic psychiatry, a specific subset of patients with severe mental illness. However, colleagues and I have also created risk calculators for all patients with schizophrenia-spectrum or bipolar disorders (OxMIV and OxMIS, for violence and suicide; n=75,158). OxMIV has been externally validated and shows good measures of calibration and discrimination;[92] OxMIS is currently being written up for publication. Both calculators are also freely available online at https://oxrisk.com.

Implications for clinical practice

Until the current ceiling in predictive performance is lifted, similarly effective tools with lower resource implications should be considered, to improve overall cost-effectiveness. Tools like FoVOx show similar performance to other tools, but are easier, quicker, and free to use whilst at the same time being scalable, fully transparent, and less subjective. While the tool uses mostly static risk factors, it could nevertheless be used to target dynamic or more resource intensive forms of risk assessment to those scoring higher in FoVOx. How FoVOx can be incorporated into clinical practice will require feasibility and acceptability studies, in discussion with clinicians. Given the current lack of experimental evidence

supporting the use of risk assessment in psychiatry, changes to practices should be piloted and assessed before considering wider adoption.

Similarly, to be effective, risk assessment needs to be linked to risk management, but I found limited evidence for effective interventions in psychiatry. In drug-using offenders with co-occurring mental illness, therapeutic community and aftercare interventions may reduce the risk of reincarceration. For other mental health populations, more theoretical approaches may need to be used until more evidence becomes available. First, as I found substantial overlap in risk factors for violence between patients and general population controls, interventions shown to be effective in other populations may be effective in individuals with severe mental illness. Second, this suggests that population-based primary prevention programs to address modifiable risk factors, such as substance use disorders, may reduce the risk of violence. Finally, interventions which affect proxy outcomes such as aggression scales, may translate into overall reductions in violence.

Implications for research

As it was not possible to perform an external validation of FoVOx, the model should be statistically validated in other countries. As discussed above, given that the model was developed in Sweden, validation in other jurisdictions may show differences in statistical performance in either discrimination or calibration. Future research needs to establish the optimal way of addressing and reporting such differences, for instance through prespecified recalibration methods. We have recently validated another OxRisk calculator (OxRec, for predicting the risk of recidivism in released prisoners)[93] in a new sample. Much like FoVOx, OxRec was developed using Swedish data; an external validation was subsequently done using Dutch probation and prison data. Due to differences in baseline risk (with a lower risk in the Netherlands), the model was recalibrated to more accurately predict the range of risks in the Netherlands. The paper is pending publication, and sets a

precedent for appropriate validation methodology, in a new and evolving field of research.

Two clinical validation studies of FoVOx (one in Finland, one in Oxford) are currently being conducted. This type of study examines clinical feasibility and acceptability, and the effects (if any) of using FoVOx on risk management. An EU-funded project (EU-VIORMED) is planning a comparison of the predictive performance of FoVOx and the HCR-20 in forensic psychiatric inpatient violence across a number of European countries. Long-term RCTs and economic modelling comparing FoVOx to existing risk assessment protocols will be needed to understand its full impact on clinical practice, treatment allocation, rates of violence, stigma, and overall resource use. At the same time, violence risk assessment is an evolving field, and future research may further increase predictive performance, by including biological, psychological, genetic, or epigenetic risk factors, and elements of dynamic monitoring.

Considering the current lack of high-quality research in the field of violence prevention, and the large social and economic burden associated with interpersonal violence, this area of research should be prioritised. However, this prioritisation needs to be done appropriately, and learning from the wider medical literature. As discussed in the previous chapter, an estimated 85% of health research is 'wasted', due to non-publication of results, inappropriate methods, or unnecessary duplication.[171] Based on this thesis and the wider literature, five recommendations for forensic psychiatric intervention research can be made. First, as violence is a relatively rare outcome, individual prevention RCTs will be not have sufficient statistical power to detect significant effects. RCTs with primary outcomes on relapse, symptomatic improvement, and rehospitalisation should consider routinely including secondary outcomes specific to violence, which could be the basis of collaborative meta-analyses. Second, statistical power could be improved by including

only high-risk groups by identifying them using validated risk assessment tools, or increasing follow-up duration through linkage to register-based data. Third, the types of interventions identified in the clinical practice recommendations above should be considered as candidates for further trials. This includes evidence-based interventions from non-psychiatric samples or settings, interventions designed to address modifiable risk factors, or those identified as having a low GRADE rating as future research may provide support for such approaches. Fourth, implementation research should consider effectiveness, cost-effectiveness, as well as possible effects of over- or undertreatment, and stigma. Fifth, as with all health research, research in forensic psychiatry should be based on prespecified protocols, the best available methods, and build on existing evidence to avoid research waste.

Conclusions

Through focusing on the best methods and data sources currently available, I have reported on risk factors for adverse outcomes in schizophrenia-spectrum disorders, derived and internally validated a novel, simple, and scalable violence risk assessment tool for use in forensic psychiatry, and reviewed the state of evidence on violence prevention in psychiatry. Drops in the rates violent crime over the last few decades have not translated into similar improvements in populations with severe mental illness, despite continuing efforts to improve risk assessment and management. By providing a critical overview of the relationship between mental illness and violence, this thesis hopes to encourage readers to take a step back and encourage a better way forward for violence prevention research. Future research in forensic psychiatry should therefore focus on the best available methods, data sources, reporting standards, and build on existing evidence, to improve the field's evidence-base and treatment guidelines, and minimize research waste.

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Appendix A: Protocol for Chapter II

Clinical prediction rules for persons discharged from secure and forensic psychiatric hospitals for risk of violent crime – protocol

SUMMARY:

Design: Register-based cohort study.

Data: Swedish databases linking hospital, crime, prescriptions, and socioeconomic data.

Participants: The study cohort is defined as individuals aged 15-65 discharged from secure and forensic psychiatric hospitals into the community during the study period.

Study period: Discharges from secure and forensic psychiatric hospitals that occurred between 1st January 1992 and 31st December 2013 will be used to develop the model: one discharge per person, chosen at random. Data on most risk factors are available from 1973 and are therefore not subject to the same 1992 start date for discharge.

Risk factors: Sociodemographic, criminological, clinical, and treatment factors. See Appendix for full list.

Primary outcomes: (i) Any violent crime within 12 months of discharge, (ii) any violent crime within 24 months of discharge.

Outputs: The main objective is to produce models that estimate the probability of events for the primary outcomes, with appropriate measures of predictive accuracy. These models will be used to obtain a scoring system for the calculation of risk to be used prospectively at time of discharge. A risk category will be reported: 'Low' (<5%), 'Medium' (5-20%), and 'High' (>20%) according to individual's predicted risk of any violent offending within 24 months.

Statistical Analysis

Statistical analysis will be based on Cox proportional hazard regression, adjusting for risk factors for violent offending within (i) 12 months, and (ii) 24 months. The method of analysis will be the same in both of these scenarios.

Random selection of discharge

Given a starting data-set of all patients and all patient discharges between Jan 1, 1992 and Dec 31, 2013, a discharge will be selected at random, with equal probability. The randomly selected discharge defines the final data-set for analysis, i.e., there will be no subsequent resampling of discharges.

Adjustment for risk factors

Risk factors will be considered in two groups of decreasing levels of priority.

Group 1 consists of variables that will be included in the statistical model regardless of statistical significance. These include demographic, criminological, and clinical variables.

Group 2 consists of variables likely to show an association with outcomes but which are not required to be included to achieve face validity. The model will use a backwards stepwise selection procedure to determine whether to retain these variables in the model, with Group 1 variables always retained and Group 2 variables sequentially rejected in order of p-value until no group 2 variables remain that have p-values greater than 0.1.

This strategy of risk factor adjustment recognises that the final model must demonstrate face validity, whilst simultaneously allowing the inclusion of additional risk factors if they show an association with outcome variables. The variables are considered in two groups in this way to recognise that a parsimonious model is preferable (i.e., easier to use in practice), provided that it has acceptable predictive ability.

Missing data

Covariates that have more than 30% missing data will be excluded. Missing data on covariates with at most 30% missing data will be imputed via multiple imputation (with twenty imputations) using a regression model that uses other risk factors, the outcome variables and the Nelson–Aalen cumulative hazard function as explanatory variables. Estimates of coefficients in the final prediction rule will be combined across imputations at each stage of the variable selection process, as well as in the final model.

Validation and goodness of fit

Once a 'final' model has been found using the steps outlined above, its internal validation will be assessed using bootstrapping to assess its predictive accuracy. Predictive accuracy will be summarised using several summary measures, including the concordance index, and Brier score. The proportions of predicted and observed events at different levels of predicted probability will be compared using a calibration plot. Sensitivity, specificity, positive and negative predictive values will be calculated using risk thresholds on predicted probability at both the low vs. medium/high (5%) and low/medium vs. high (20%) cut-offs. Miscalibration over time (year of discharge) will be examined.

Presentation of findings

The main output of the model will be a predictive probability, indicating the probability of occurrence of the outcomes of interest within 24 months. The estimated coefficients of individual risk factors will be examined with a view to: (i) simplifying the prediction rule in order to make it easier to use in practice, for example by using integer-valued coefficients or even by dichotomising numerical variables, provided this does not compromise its predictive accuracy; and (ii) justifying a categorisation of the predicted probability into risk categories (for example 'Low risk' [<5%], 'Medium risk' [5-20%] and

'High risk' [>20%]). The latter would also benefit from an assessment of the number and characteristics of individuals that fall into the proposed categories.

Generalisability

Variables are defined in such a way as to help the generalisability of the model to other settings. When the final model is used for prediction, it is possible that some variables that are included as covariates may be missing. We will provide guidelines for using the model for prediction in this scenario, for example by presenting a range of lower and upper values.

Appendix B: Protocol for Chapter III

Violence prevention strategies in psychiatry: an umbrella review

Inclusion criteria

Violence prevention interventions in (1) all psychiatric patients, (2) mentally disordered offenders, or (3) forensic psychiatric inpatients. Reviews focusing on interventions for patients with only diagnoses of intellectual disabilities or substance use disorders will be excluded.

Interventions

All types of interventions examining effects on violence, as defined below.

Outcomes

'Hard' or objective violence outcome measure, such as police or hospital recorded violence, criminal violence, or reincarceration. Aggression or violence scales, or non-violent recidivism will be excluded.

Types of studies

Systematic reviews and meta-analyses of intervention studies. Intervention studies including both randomized and non-randomized controlled designs. Studies without control groups, observational studies, theoretical studies, opinion, and non-systematic reviews will be excluded.

Search strategy

The search strategy used will be:

1 – *prevent** OR *risk management* OR *risk reduction* OR *deter**

2 – *violen** OR *homicid** OR *assault** OR *rape* OR *robber** OR *bully**

3 – 1 AND 2

4 – *recidiv** OR *reoffend** OR *repeat offend**

5 – 3 OR 4

6 – *systematic review* OR *meta-analysis*

7 – 5 AND 6

The following databases will be searched from inception to the present: Medline, EMBASE, CINAHL, Web of Science, Scopus, the JBI Database of Systematic Reviews and Implementation Reports, the Cochrane Database of Systematic Reviews, DARE, the PROSPERO register, and Epistemonikos. Titles and abstracts will be scanned for potentially eligible reviews, before retrieving full articles. No language restrictions will be applied.

Assessment of evidence

The strength of evidence for each systematic review will be assessed using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) scale[133] and given a rating of 'high', 'moderate', 'low', or 'very low' quality, using GRADEpro 3.6.1. Reviews will not be excluded based on methodological quality. Quality assessment of individual intervention studies is beyond the scope of this umbrella review.

Data collection

A data extraction sheet will be used by two independent reviewers to extract information on the citation, type of review, participants, intervention, setting, relevant outcomes, databases searched, date range, number of studies included, instrument (if any) used to assess the quality of those studies, results, and any additional comments. Discrepancies in extraction will be resolved by consensus.

Data presentation

Only descriptive data will be presented for each review.