EPIDEMIOLOGY AND GENETIC RISK FACTORS OF SUICIDAL BEHAVIOUR IN SOUTH AFRICA

by

Tahira Kootbodien

MBChB MPH

Thesis presented for the degree of

Doctor of Philosophy

in the Division of Human Genetics, Department of Pathology,

Faculty of Health Sciences, University of Cape Town

Supervisors

Professor Raj Ramesar,

Professor Leslie London and

Professor Lorna J Martin

1 June 2023

Abstract

Background: Suicide is an urgent public health problem. Fatal suicidal behaviour (individuals who died by suicide) and non-fatal suicidal behaviour (attempted suicide, self-harm, and suicidal ideation) comprise a complex interplay of individual, social, environmental, and biological factors, that are not fully understood. Given the considerable societal cost associated with suicide and health inequality in South Africa, there is a critical need to determine the burden of suicide and risk factors associated with suicide, to understand who is most at risk to inform effective prevention efforts. Despite clear evidence of multiple risk factors, suicidal behaviour remains difficult to predict and prevent. Prevention efforts in South Africa may be limited by the lack of a national suicide prevention plan and the low base rate of individuals who died by suicide may impede research comparing fatal and non-fatal suicidal behaviour in settings such as ours. In addition, existing suicide data are derived primarily from high-income countries rather than low- and middle-income countries (LMICs) where suicide and poverty levels are high, and the mental health treatment gap is large. The purpose of this study was to broaden our understanding of suicidal behaviour in South Africa by combining various data sources, each representing a unique perspective of the problem, to build on existing knowledge that may inform suicide prevention strategies in South Africa.

This thesis is organised into four studies and aimed to investigate risk factors associated with suicidal behaviour and to identify opportunities for targeted suicide prevention. The specific objectives of each study component were as follows:

- To describe trends and demographic risk factors in deaths from suicide as well as other conditions that may include suicide to identify populations at risk in South Africa (Study 1).

- To investigate the association between environmental and occupational organophosphate pesticide (OP) exposure and attempted suicide in adults admitted to hospital in Cape Town, South Africa (Study 2).
- To explore the genetic architecture underlying suicidal behaviour and psychiatric disorders to understand the genetic factors that increase the risk of suicidal behaviour (Study 3).
- To describe healthcare utilisation 12 months before suicidal behaviour among individuals who attempted suicide and who died by suicide, to identify opportunities for prevention in Cape Town, South Africa (Study 4).

Methods: This thesis included an ecological time-series study of national suicide mortality data from Statistics South Africa using joinpoint regression analysis (Study 1, N=10.3 million recorded deaths from 1997 to 2016; 8,573 deaths from suicide); a conditional logistic regression analysis of an attempted suicide hospital-based case-control study (Study 2, N=400; 200 cases and controls); a genome-wide genetic correlation study of suicidal ideation, self-harm, attempted and fatal suicide (samples [n] ranged from 62,648 to 125,844), and selected psychiatric disorders (n ranged from 9,954 to 386,533) using a genomic structural equation modelling approach (Study 3); and a retrospective cohort of linked electronic health records of individuals who attempted suicide and were admitted to hospital and a case series of fatal suicides on whom forensic autopsies were performed at a mortuary in Cape Town (Study 4, N=484).

Results: The key findings in this study show that (i) suicide mortality rates were consistently higher in men than women between 1997 and 2016 (Study 1). Suicide rates increased by 7.7% among young people aged 15 to 29 years. Hanging, poisoning and firearms were the most frequent methods of suicide used. Subgroup analysis showed suicide by hanging and

poisoning mortality rates increased by 2.9% and 3.7% across 20 years. Suicide deaths were underreported and may be included among deaths by accidental injuries and undetermined intent. However, these patterns varied by method of death (hanging, poisoning and firearm injury) over the study period. The largest proportion of suicide deaths may be potentially misclassified as accidental hanging and hanging by undetermined intent, and to a lesser extent, accidental poisoning and poisoning by undetermined intent. In contrast, firearm-related deaths were more likely to indicate a homicide than a suicide death. Missing data on select sociodemographic variables limited the accuracy and generalisability of our findings.

(ii) Pesticide use in homes and gardens was common (85%); however, there was no association between attempted suicide and environmental (household, garden, and occupational) OP exposure (Study 2). Hazardous drinking and unemployment with no household income were significantly associated with an increased risk of attempted suicide while sharing the house with more than three persons was protective.

(iii) We observed strong significant genetic correlations (rg) between suicidal ideation, attempted suicide, and self-harm (rg range, 0.71 to 1.09) and moderate-to-strong genetic correlations between suicidal behaviour traits and a range of psychiatric disorders (Study 3). The strongest genetic correlation was noted for major depressive disorder and suicidal ideation (Ever contemplated self-harm, rg=0.86±0.07, $p=1.62x10^{-36}$). Multivariate genomic analysis revealed a single (common) factor structure for suicidal behaviour traits, major depressive disorder, attention-deficit hyperactivity disorder (ADHD), and alcohol use disorder. Approximately 2,951 genes and 98 sub-network hub genes were associated with the common factor, and shared biological pathways include involvement in developmental biology, signal transduction and RNA degradation.

(iv) Approximately two-thirds of cases had at least one prior visit to a health care facility in the 12 months leading to suicidal behaviour (Study 4). The prevalence of psychiatric disorders was lower for individuals who died by suicide than attempted suicides but both groups interacted equally (approximately 65%) with the healthcare system during the 12 months leading to suicidal behaviour. Patients who used primary care services in the year before dying by suicide attended for the management of their chronic conditions (such as cardiovascular disease and diabetes) and emergency medical care for assault-related injuries. For attempted suicides, common reasons for a healthcare visit were for management of their chronic condition, HIV care, and a psychiatric diagnosis of depression, bipolar, or substance use disorders.

Conclusions: This study expands on previous research and shows that while common risk factors are shared by individuals with fatal and non-fatal suicidal behaviour, the degree of risk varies across suicide groups, age, and sex. Findings of increased genetic risk of suicidal behaviour among individuals with psychiatric disorders suggest that identification and early treatment of co-morbid psychiatric disorders (major depression, alcohol use disorder, ADHD, and schizophrenia) should be included in suicide prevention strategies. Evidence of potential misclassification of suicide death within accidental injuries and undetermined intent categories may explain the underestimation of suicide mortality reported in this study. Combined with the high proportion of missing data in the national vital statistics and poor data quality of external causes of death, these findings suggest a critical need for ongoing training on the cause of death certification and further interventions to improve suicide data quality. Further, continued monitoring of suicide mortality data and linking electronic health records may provide opportunities for suicide surveillance that can help identify where prevention strategies should be allocated for maximum benefit, such as primary healthcare outpatient facilities, emergency treatment centres, and antiretroviral clinics.

Declaration

This thesis is presented in fulfilment of the requirements for the degree of Doctor of Philosophy in the Department of Pathology, Faculty of Health Science, University of Cape Town. I declare that this thesis is my original work or, in the case of multi-authored papers, constitutes work for which I was the lead author. My contribution to multi-authored papers is outlined at the beginning of each results chapter.

I confirm that I have been granted permission by the University of Cape Town's Doctoral Degrees Board to include the following publications in my thesis, and where co-authorships are involved, my co-authors have agreed that I may include the publications. Four published manuscripts are included in the thesis and are presented as self-contained chapters in the following order:

1. Kootbodien T, Naicker N, Wilson KS, Ramesar R and London L. Trends in suicide mortality in South Africa, 1997 to 2016. *International Journal of Environmental Research and Public Health.* 2020. 17(6):1850.

   This paper was substantially revised for this dissertation based on examiner feedback. The original paper is available at the URL:

   https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7142470/

2. Kootbodien T, Holtman Z, Asmal L, Joska J, Chiliza B, Smith P, Stallones L, Ramesar RS, London L. Organophosphate pesticide exposure as a risk factor for attempted suicide in Cape Town, South Africa: a case-control study. *Archives of Environmental & Occupational Health*. 2021 Dec 15:1-1.

3. Kootbodien T, London L, Martin LJ, Ramesar RS. The shared genetic architecture across suicidal behaviour and psychiatric disorders: a genomic structural equation modelling study. *Frontiers in Genetics*. 2023 March 7:14.

4. Kootbodien T, Bantjes J, Joska J, Asmal L, Chiliza B, Stallones L, Holtman Z, Martin LJ, Ramesar RS, London L. Healthcare utilisation 12-months prior to fatal and non-fatal suicidal behaviour in Cape Town, South Africa. *Archives of Suicide Research.* 2022 Nov 30:1-15.

Consistent with the University of Cape Town guidelines, the text of each paper is presented verbatim within this thesis unless otherwise indicated (Paper 1). There are minor discrepancies in terminology between the papers. Minor changes have been made to spelling, style and figure and table numbers to ensure consistency throughout this thesis.

My contribution to each manuscript is outlined at the start of each chapter. I was the lead and corresponding author on all manuscripts, prepared the datasets for analysis, conducted all analyses and drafted all versions of the manuscripts. All co-authors reviewed and approved the submitted manuscripts.

Signature:

Date: 1 June 2023
Student name: Tahira Kootbodien
Student number: KTBTAH001

Table of contents

List of Tables

List of Figures

List of Supplementary materials

Supplemental Tables

Supplemental Figures

Acknowledgements

I would like to thank the participants in the data cohorts included in this study and the researchers who conducted the original epidemiological and genetic studies for making their data accessible, thereby making this work possible.

My gratitude extends to my supervisors for their invaluable advice, patience and continuous support and for providing the opportunity to be part of this collaborative project. To Professor Raj Ramesar, thank you for your generous support and encouragement, and for providing me with opportunities that have strengthened my capacity as a researcher. To Professor Leslie London, who has walked beside me on my public health journey for more than a decade, thank you for your constructive and meticulous supervision which has enabled my growth throughout both my postgraduate experiences thus far. I am deeply grateful for your invaluable mentorship throughout my career. To Professor Lorna Martin, thank you for your guidance, insightful comments and mentorship throughout the study.

I am also grateful to the funders who made this research possible: the American Foundation for Suicide Prevention, the National Research Foundation and the South African Medical Research Council through its Division of Research Capacity Development under the SAMRC Clinician Researcher Programme. Computations were performed using facilities provided by the University of Cape Town's ICTS High Performance Computing team: hpc.uct.ac.za

Lastly, to my family. For everything.

"Do not lose hope, nor be sad."
Quran 3:139

"As you start to walk on the way, the way appears."
Rumi

Abbreviations

ADHD	Attention deficit and hyperactivity disorder
AAPC	Average annual percentage change
APC	Annual percentage change
AIC	Akaike's information criterion
ASMR	Age-standardised mortality rates
AUD	Alcohol use disorder
AUDIT	10-item Alcohol Use Disorders Identification Test
BIP	Bipolar disorder
BIS-II	Barratt's Impulsivity Scale
BMI	Body mass index
BPAQ-SF	Buss-Perry Aggression Questionnaire – short form
CES-D	Centre for Epidemiologic Studies Depression Scale
CFA	Confirmatory factor analysis
CFI	Comparative fit index
CI	Confidence interval
DAPs	Dialkyl phosphate metabolites
DEP	Dimethyl phosphate
df	Degrees of freedom
DMP	Dimethyl phosphate
DMTP	Dimethyl thiophosphate
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition
EAS	East Asian ancestry
EUR	European ancestry
GWAS	Genome-wide association studies

ICD-10	International Classification of Disease
LD	Linkage disequilibrium
LDSC	Linkage Disequilibrium Regression Score
LMIC	Low- and middle-income countries
LOD	Logarithm of odds
MDD	Major depressive disorder
OP	Organophosphate pesticides
OR	Odds ratio
PHDC	Provincial Health Data Centre
PGC	Psychiatric Genomics Consortium
SASH	South African Stress and Health
rg	Genetic correlation
SB	Suicidal Behaviour
SCZ	Schizophrenia
SD	Standard deviation
SDG	Sustainable Development Goals
SE	Standard error
SEM	Structural equation modelling
SNP	Single nucleotide polymorphism
SRMR	Standardised root mean squared residual
SSI	Beck's Scale for Suicidal Ideation
UCT	University of Cape Town
WHO	World Health Organisation

Chapter 1 Introduction

In this introductory chapter, the definitions of suicidal behaviour are discussed, followed by an overview of the magnitude of the problem globally, and in South Africa. This chapter explores the factors associated with suicidal behaviour, summarising existing literature and highlighting potential research gaps. The chapter concludes by stating the research questions that shaped the study design, study aims and objectives and outlines the structure of the thesis.

1.1 Defining suicidal behaviour

Suicidal behaviour is a broad term used to describe a range of behaviours. The definition of suicide has varied over many years (Silverman et al., 2007). This variation has had implications in clinical and research settings on how suicide is measured and compared across populations. The need for standardised nomenclature has been noted for some time (Posner et al., 2007, Silverman et al., 2007, O'Carroll et al., 1996, Silverman and Leo, 2016). In 1996, O'Carroll and colleagues proposed terminology to standardise reporting guidelines and improve communication on suicide research (O'Carroll et al., 1996). The terminology was subsequently revised to improve suicide surveillance, for early detection and prevention of suicidal behaviour in clinical settings (Silverman et al., 2007). More than two decades later, there remain several nomenclatures and classification systems of suicide available, with many inconsistencies (Silverman and Leo, 2016), that may hinder how suicidal behaviour is defined, measured and classified, contributing to the lack of comparability across the globe.

In this thesis, we use the definitions and terminology outlined by the World Health Organisation (WHO, 2014b) and the Columbia Classification Algorithm of Suicide Assessment (Posner et al., 2007). Suicidal behaviour consists of a spectrum of behaviours that includes suicidal ideation, planning, self-harm, suicide attempt, and suicide death (WHO,

2014b). Suicidal ideation involves thoughts related to ending one's life, while a suicide attempt is defined as potentially self-injurious behaviour associated with at least some intent to die, and deliberate self-harm is any type of self-injurious behaviour, including suicide attempts and non-suicidal self-injury or unintentional suicide (Turecki and Brent, 2016). Deliberate self-harm is an outdated term and the equivalent term "self-harm" will be used throughout the thesis. Collectively, we refer to suicidal ideation, attempt and self-harm as non-fatal suicidal behaviour. Individuals who died by suicide or fatal suicidal behaviour, are self-injurious behaviour associated with at least some intent to die, which results in a fatality (Posner et al., 2007, Turecki and Brent, 2016) (Figure 1.1).

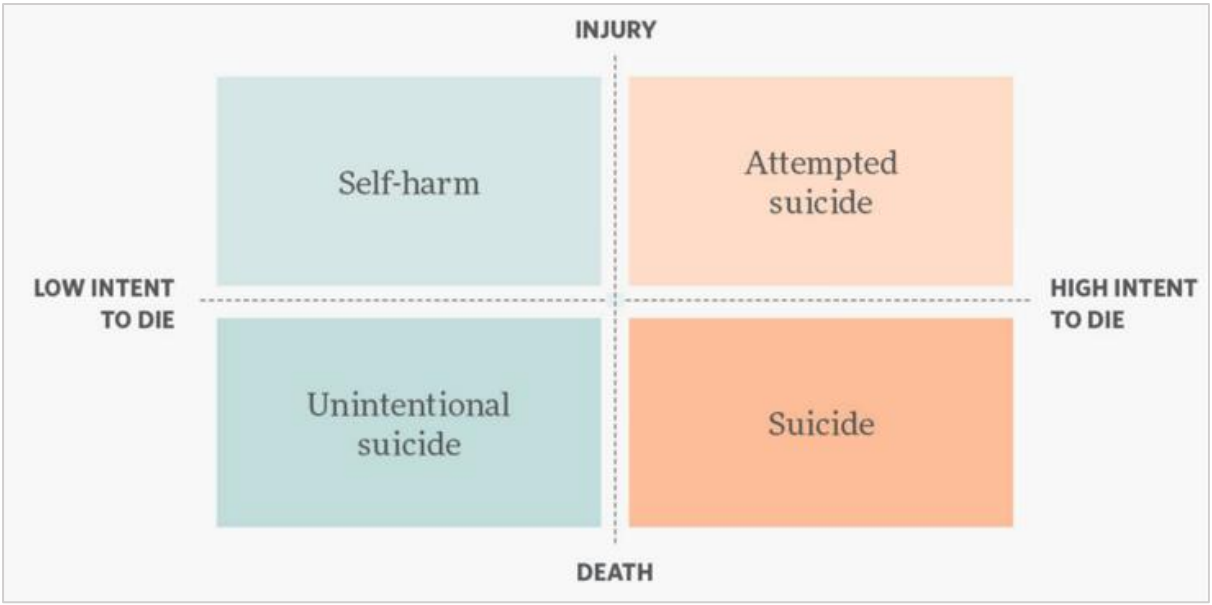


Figure 1.1 Nomenclature for suicidal behaviour (Centre for Suicide Prevention, 2016)

1.2 Global perspective on suicidal behaviour

Suicide is a serious public health concern. Listed among the top 20 causes of death worldwide, approximately 700,000 people died by suicide in 2019, accounting for approximately 1.3% of all deaths (WHO, 2021). Suicide is especially prevalent in low- and middle-income countries (LMICs), accounting for approximately 77% of global suicides,

with LMIC countries reporting suicide rates higher than the reported global average of 9.0 per 100,000 (WHO, 2021) (Figure 1.2).

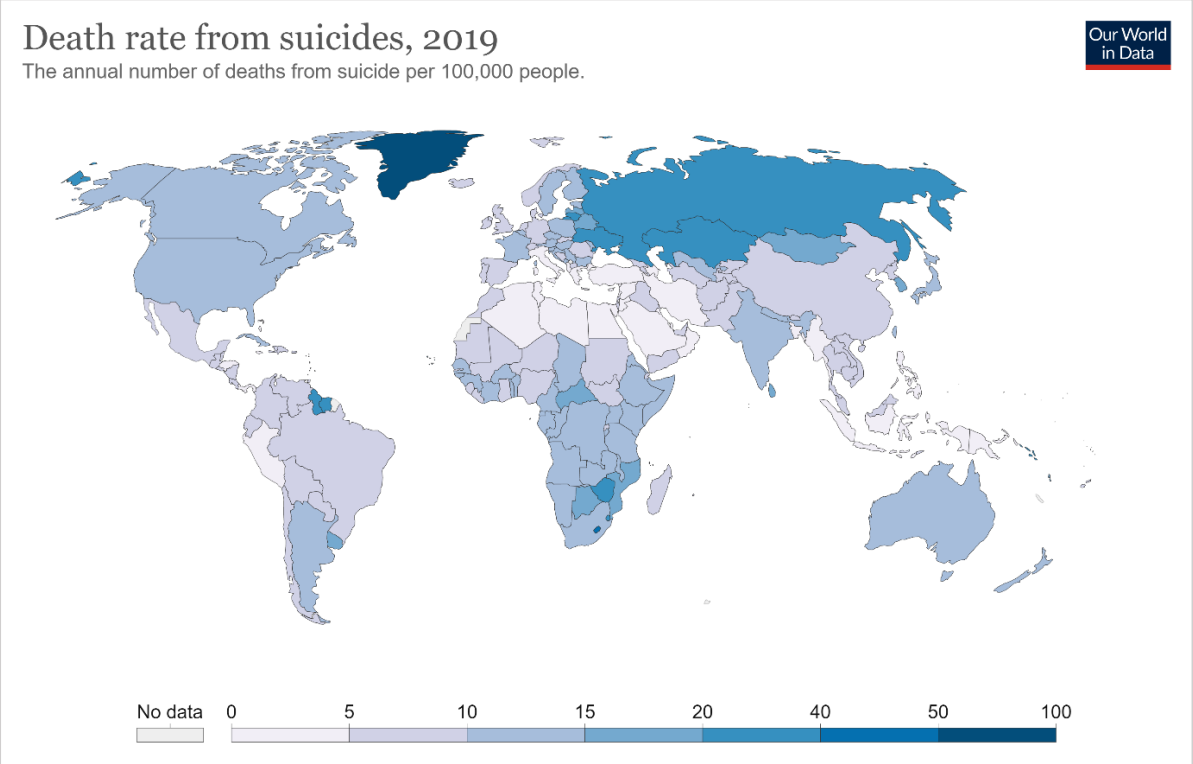


Figure 1.2 Global age-standardised suicide mortality rates (per 100 000 population), for men and women, 2019 (Source: IHME, Global Burden of Disease)

Globally, suicide rates have decreased by 33% from 1990 to 2016 (Naghavi, 2019). However, this decline was not uniform across countries. Suicide mortality rates vary by age, sex, region and country, suggesting that cultural and socioeconomic factors may contribute to the variation in suicide mortality (Naghavi, 2019). Suicide mortality rates are 2.3 times higher in men than women (WHO, 2021). According to the Global Burden of Diseases, Injury and Risk Factors Study (GBD 2019), suicidal behaviour was estimated to be responsible for nearly 34.1 million disability-adjusted life years (DALYs) globally in 2019, of which the majority occurred in those aged 10–49 years (Vos et al., 2020, IHME).

The choice of suicide method may vary by socioeconomic levels of countries (Ajdacic-Gross et al., 2008); social, religious and cultural beliefs, and availability and access to means

(Meltzer et al., 2008). Among individuals who die by suicide, the most common methods of suicide are hanging, pesticide poisoning and firearm use (Ajdacic-Gross et al., 2008), while pesticide poisoning was the most common method used in LMICs (Gunnell et al., 2007).

Suicide attempts are more common than fatal suicide (Bertolote and Fleischmann, 2002). Based on data from the WHO World Mental Health community surveys across 21 countries, the 12-month prevalence of suicide attempts was approximately 0.3% to 0.4% (Borges et al., 2010), while among individuals with suicidal ideation, the 12-month prevalence of an attempt was much higher, approximately 15.1% to 20.2% (Borges et al., 2010).

A growing body of research has documented several similarities and differences between individuals who engaged in non-fatal suicidal behaviour from those with fatal suicidal behaviour (Beautrais, 2001, DeJong et al., 2010, Fushimi et al., 2006, Paris, 2006). While some characteristics may be shared between individuals with fatal and non-fatal suicidal behaviour, previous studies have shown that individuals with fatal suicidal behaviour are mainly men and were more likely to use lethal and violent methods of suicide, such as hanging, jumping from a height and firearm-related deaths and this risk increases with age (DeJong et al., 2010, Beautrais, 2001). Individuals who engaged in non-fatal suicidal behaviour are more likely to be women, diagnosed with a psychiatric disorder, have previously attempted suicide (Fushimi et al., 2006) and were more likely to use non-violent methods of suicide, such as poisoning and gassing (Paris, 2006, Beautrais, 2001).

1.3 Suicide in South Africa

In 2019, suicide rates in Africa were higher than the reported global average (11.2 vs. 9.0 per 100 000 deaths, respectively) and remain alarmingly high in South Africa (23.5 per 100,000 population) (WHO, 2021). In 2016, sub-Saharan Africa had the third highest regional suicide

mortality rate (ASMR 16.3 per 100,000) in the world, with approximately 11,000 suicide deaths contributing to the burden of disease (Naghavi, 2019). Suicide rates in Africa are at least three times higher in men than women (Mars et al., 2014) and, in South Africa, approximately five times higher in men compared to women (Matzopoulos et al., 2015); although the distribution varies across population groups and cities (Burrows and Laflamme, 2006). Hanging and poisoning were the most common methods of suicide used in South Africa (Scribante et al., 2004, Stark et al., 2010). The estimated South African lifetime prevalence of suicidal ideation and an attempt is 9.1% and 2.9%, respectively, with women reporting twice as many attempts as men (Joe et al., 2008).

Several steps have been taken toward addressing the burden of suicide globally and in South Africa. In 2013, the World Health Assembly adopted the WHO Comprehensive Mental Health Action Plan 2013–2020, which aimed to achieve the global target of increasing service coverage for mental disorders by 20% and reducing the rate of suicide in countries by 10% by 2020 (WHO, 2013). The plan was subsequently extended until 2030 and the targets were further set to reduce the rate of suicide by one-third, which aligned with the UN Sustainable Development Goals (SDG) to reduce premature mortality from non-communicable diseases by one-third (WHO, 2016). These targets were embraced by the South African government which led to the adoption of a new National Mental Health Policy Framework and Strategic Plan (2013-2020) in July 2013 (Department of Health, 2014). The policy made provision for the integration of mental health services, including suicide prevention and treatment, at the primary care level. However, plagued with a lack of funding, poor infrastructure and limited healthcare workers to adequately implement the Plan (Docrat et al., 2019a), the National Mental Health Policy Framework and Strategic Plan have since lapsed and urgently need to be updated. Despite estimates that suicide from LMICs

contributes 77% of the global suicide rate (WHO, 2021), South Africa, like most LMICs, does not yet have a national suicide prevention program.

South Africa has a high burden of morbidity and mortality from violence and injury. Combined, violence and injuries were the second leading cause of death and lost disability-adjusted life years in South Africa in 2000 (Norman et al., 2007). In addition, South Africa's rates of firearm deaths were amongst the highest in the world (Groenewald et al., 2003), exacerbated by widespread access to illegal firearms and an increased number of newly licenced firearm owners (Matzopoulos et al., 2018). Since 2001, there has been a decline in firearm deaths. Data from the National Injury Mortality Surveillance System (NIMSS) reported a decrease in firearm homicide deaths from 2001 to 2005 (37.5 to 22.5 per 100,000) (Matzopoulos et al., 2014) and 2009 (11.2 per 100,000) (Matzopoulos et al., 2015). The decrease has been attributed to the introduction of the South African Firearm Control Act of 2000 (South Africa, 2000), which regulates the number of circulating firearms and the people who own them.

1.4 Challenges in estimating suicide mortality

While there is a wealth of mental health data available in the public domain, measuring the burden of suicidal behaviour remains a challenge. In this thesis, I propose to analyse suicide data from a diverse set of data sources and apply various methodological approaches to determine risk factors associated with suicidal behaviour that are generalisable to a South African population to inform appropriate interventions. The data presented in this thesis include South African vital statistics, electronic health records and data from hospital-based studies and international suicide genetics data. Data from multiple sources, especially the use of routine surveillance data such as vital statistics may have varying degrees of data quality.

In addition, there may be variations in how individual suicidal behaviours are defined and how data are aggregated.

The quality of mortality data is limited by the information obtained from the death certificate and how data is processed. Suicide deaths may be underreported because of religious beliefs (Pritchard et al., 2020), stigma and legal considerations (Tøllefsen et al., 2012). Suicide deaths may also be underreported because of uncertainty in determining the manner of death or intention i.e., suicide, accidental, homicide, undetermined intent or natural cause of death, variation or inconsistencies in how the underlying cause of death is ascertained (Mathers et al., 2005, Kapusta et al., 2011) and if there is insufficient evidence to determine the suicide verdict (Tøllefsen et al., 2012). The quality of suicide data, which includes completeness and timeliness, varies by country (Figure 1.3) (Kapusta et al., 2011). Because of potential misclassification, many countries have reported and compared suicide mortality with injury deaths of undetermined intent (Y10-Y34) and accidental death (Bhalla et al., 2010, Ohberg and Lonnqvist, 1998, Värnik et al., 2012, Tøllefsen et al., 2015). In the United Kingdom, it is conventional to combine suicide deaths with deaths where the intent was undetermined, as most 'open verdicts' or undetermined deaths are considered to be 'probable suicides' (Linsley et al., 2001). In general, a person who died by hanging or by firearm injury is more likely to be categorised as a suicide, whereas the intent of death by drowning and poisoning is more difficult to determine without a suicide note or an interview with family members. Where data quality is poor, additional data are obtained from verbal autopsies and statistical methods are applied to redistribute or reassign cause of death categories that may include suicide deaths, such as undetermined intent (Y10-Y34), unknown causes of death (R99) and exposure to unspecified factors (X59), to account for possible misclassification of suicide (Naghavi, 2019).

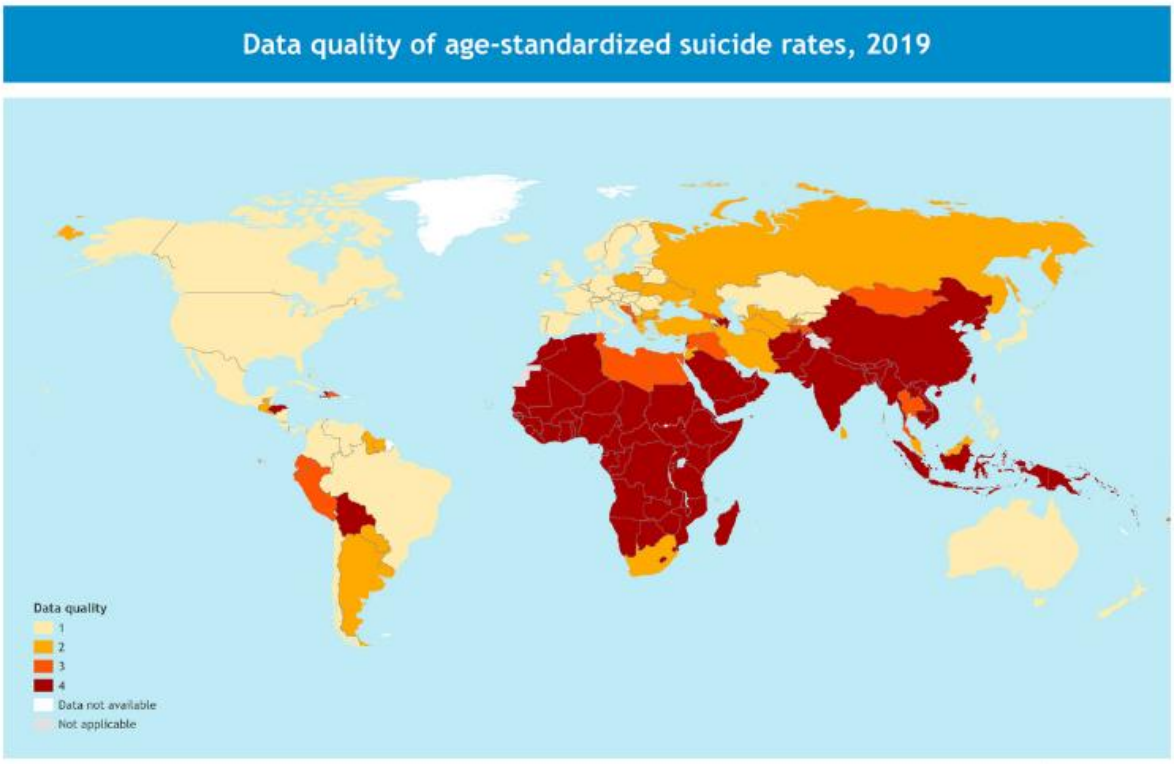


Figure 1.3 Global suicide data quality, 2019 (WHO, 2019)

According to the World Health Organisation, the quality of South African suicide mortality data is classified as medium, with 90% completeness (WHO mortality database, 2023), meaning that statistical modelling approaches are used to estimate South African suicide rates. The South African Births and Deaths Registration Act of 1992 (South Africa, 1992) mandates that every death record is registered with the Department of Home Affairs. In the event of an unnatural death, the Inquests Act of 1959 (South Africa, 1959) states that a medical or post-mortem inquiry should be performed to determine the underlying cause of death before a death certificate can be issued. Therefore, reliable mortality data in South Africa is dependent on completing these steps as accurately and timely as possible. However, the quality of the South African mortality data can be limited by delays in death registration, the accuracy of the underlying cause of death information and the large proportion of undetermined, unspecified and unknown causes of death (Statistics South Africa, 2018). In this thesis, I examined South African vital statistics to investigate trends in suicide and other

causes of death that may include suicide (death by accidental injuries, undetermined intent and homicide) to assess their potential for the misclassification of suicide and to identify populations at risk in South Africa *(Chapter 2 - Study 1, Publication 1).*

1.5 Risk factors associated with suicidal behaviour

Many factors contribute to an increased risk of suicidal behaviour. Due to its complexity, suicidal behaviour can be difficult to predict, which can be challenging when implementing appropriate prevention strategies (Turecki and Brent, 2016). Understanding the events leading to suicidal behaviour is important for risk assessment and the development of appropriate interventions to improve prevention efforts. Many theoretical models explain the psychological mechanisms of suicidal behaviour. One of the most influential models is the stress-diathesis theory, which assumes that an individual is at increased risk of suicidal behaviour when there are both a predisposing vulnerability and a triggering stress factor (van Heeringen, 2012). While there are many interpretations as to what constitutes vulnerability and stressors, Mann and colleagues proposed a clinical model that linked abnormalities in serotonergic function (Mann et al., 1999). The authors hypothesise that an individual with a predisposing vulnerability (impulsive aggression that is increased by low serotonin activity) and a stressor (psychiatric illness) is more likely to experience suicidal ideation and impulsivity and is, therefore, more likely to act on those thoughts (Mann et al., 1999). Building on this theory, McGirr and Turecki proposed a model to incorporate predisposing factors (such as family history), mediating factors (such as impulsive aggression or chronic substance abuse) and precipitating factors (such as psychiatric illness) associated with increased suicide risk at the population and individual level (McGirr and Turecki, 2007, Turecki and Brent, 2016) (Figure 1.4). The model illustrated additional factors such as

improved access to medical and mental health services and restriction of means, can reduce the incidence of suicide (Turecki and Brent, 2016).

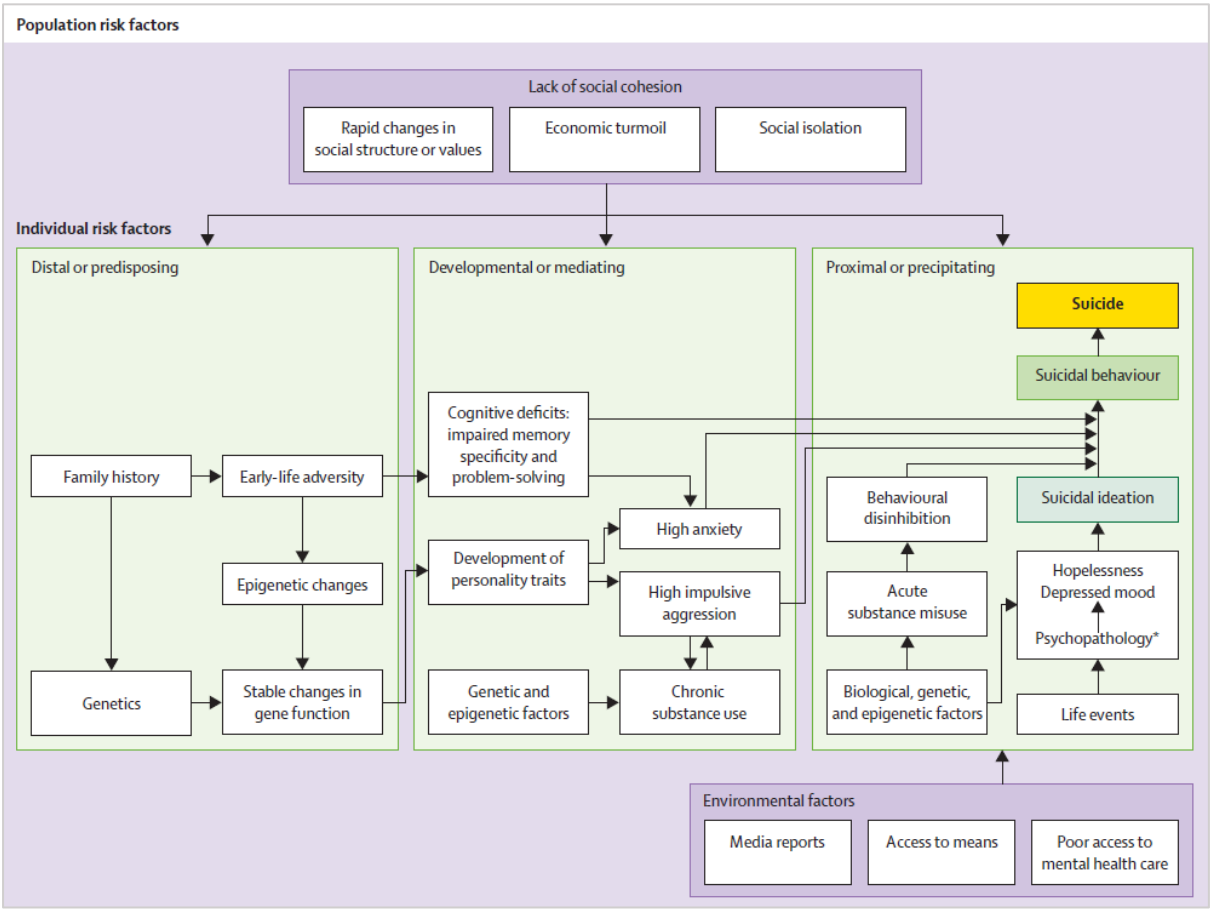


Figure 1.4 Model of suicide risk at the population and individual level (Turecki and Brent, 2016)

Previous research has explored the progression of suicidal thoughts to suicidal behaviour by applying various theories of suicide (May and Klonsky, 2016, Nock et al., 2013). One of the contemporary theoretical models proposes an ideation-to-action framework (Klonsky and May, 2015) that suggests the development of suicidal ideation and the progression from ideation to attempts are distinct processes with distinct predictors because most individuals with suicidal ideation do not attempt suicide. Several studies have highlighted that the risk factors involved in the development of suicidal ideation are different from those who transition to suicide attempts (Nock et al., 2008, Klonsky et al., 2017). Within this

framework, the Interpersonal Psychological Theory of Suicidal Behavior theory proposed that for fatal suicide to occur an individual needs to have a desire to die by suicide and the capability for suicide (Joiner, 2007). Understanding the theoretical models underlying suicidal behaviour will help us to understand how risk factors interact with one another and lead to suicide.

Attempted suicide is considered an important predictor of subsequent suicide (Hawton et al., 2015, Harris and Barraclough, 1997). A meta-analysis of 17 studies showed that the risk of death after re-attempting suicide is higher in the first year after an attempted suicide, with 2.3% of subsequent re-attempts resulting in death (Bostwick et al., 2016). Research findings also showed that individuals with suicidal thoughts are at increased risk for later or subsequent suicidal ideation, attempts and death (Ribeiro et al., 2016); however, most individuals may never act on their thoughts (Nock et al., 2009).

It is well established that psychiatric comorbidities play an important role in the development of suicidal behaviour (Cavanagh et al., 2003, Nock et al., 2008), as approximately 90% of individuals in high-income countries who die by suicide have a diagnosed psychiatric disorder (Arsenault-Lapierre et al., 2004). Lower prevalence estimates were reported in a recent meta-analysis of studies from LMICs (Knipe et al., 2019). The authors found that the prevalence of a psychiatric disorder in LMICs was 58% in individuals who died by suicide and 45% in attempted suicides (Knipe et al., 2019), however, the authors noted the high degree of heterogeneity between studies. Specifically, suicidal behaviour has been associated with depression, bipolar mood disorders, schizophrenia, post-traumatic stress disorder (PTSD), substance use and eating disorders (Nock et al., 2010, Arsenault-Lapierre et al., 2004, Mann et al., 1999, Pompili et al., 2010), and has also been linked to attention deficit hyperactivity disorder (ADHD) (Giupponi et al., 2018) and sleep disorders (Bernert et al.,

2015). Among patients diagnosed with a mental illness, mental healthcare services are reported to be underutilised, with only 15.9% of individuals with psychological disorders receiving treatment in South Africa (Herman et al., 2009, Williams et al., 2008). Understanding the burden of mental disorders is relevant in LMIC settings such as ours, given the high prevalence of mental disorders (30% lifetime prevalence of common mental disorders) (Herman et al., 2009), poor mental health service use (Seedat et al., 2009, Williams et al., 2008) and large mental health treatment gap (Seedat et al., 2009) in South Africa.

Pesticides, generally known for their neurotoxicity, are used extensively throughout the world. Organophosphate pesticides (OP) are extensively used for agricultural production and use in and around the home. South Africa is considered one of the largest consumers of pesticides in sub-Saharan Africa (Zhang et al., 2011), with the agricultural sector accounting for a large percentage of pesticide sales (Naidoo and Buckley, 2003). It is also common practice in South Africa to use pesticides for the control of insects and rodents in households (Tolosana et al., 2009), resulting in a large proportion of individuals potentially exposed to low pesticide concentrations. Epidemiological studies have demonstrated long-term neurological effects in rural and agricultural populations. Long-term exposure to low doses of OP is a risk factor for neurobehavioural changes such as depression and increased impulsivity and may contribute to an increased risk of suicide (London et al., 2005). There is strong evidence suggesting that OP exposure predisposes to depression among farmworkers and their spouses (Beseler et al., 2008, Beseler et al., 2006). Freire and Koifman (2013) also reported an elevated risk of depression with a history of previous pesticide poisoning. Further, the authors reported an increased risk of suicide in areas with intensive pesticide use (Freire and Koifman, 2013). However, the contribution of chronic low-dose pesticide exposure to depression and suicide in the absence of pesticide poisoning remains uncertain (London et al., 2012). This thesis will attempt to address this gap in the literature by

investigating the association between pesticide exposure in the general population and attempted suicide in a hospital-based case-control study in Cape Town, South Africa *(Chapter 3 – Study 2, Publication 2).*

Social, cultural and other risk factors can interact to increase the risk of suicidal behaviour. Injuries due to interpersonal violence contribute substantially to the national burden of disease in South Africa (Matzopoulos et al., 2004, Norman et al., 2010). In South Africa, the lifetime prevalence of having experienced a traumatic event is nearly 75% (Williams et al., 2007). Moreover, South Africans are more likely to experience multiple traumatic events and are at increased risk of psychological distress (Williams et al., 2007). Further reports have shown that men who have experienced criminal assault and childhood abuse were more likely to have PTSD, while the risk of this disorder in South African women was increased for those with a history of intimate partner violence (Kaminer et al., 2008). Survivors of violence are at increased risk of developing depression, PTSD, substance use disorder (Hedtke et al., 2008) as well as suicidal behaviour (Wiederman et al., 1998).

While factors such as family connections, employment and access to treatment may protect individuals from suicidal behaviour (McLean et al., 2008), certain life events may serve as precipitating factors for suicide. Early life adversity, comprising of physical and sexual abuse, parental death and parental divorce is a well-established distal risk factor for suicide (Bruwer et al., 2014). Social isolation also increases the risk of suicide. Early studies have shown that individuals who are socially isolated are more vulnerable to suicide than those who have strong relationships with others (Trout, 1980). Sexual orientation may also be related to an increased risk of suicide. A meta-analysis by King et al. (2008) reported that the risk for lifetime mood, anxiety and substance use disorders was at least 1.5 times higher in

gay men, lesbians, and bisexual men and women. In addition, sexual orientation minorities were 2.5 times more likely to have attempted suicide in their lifetime (King et al., 2008).

Previous studies report that socioeconomic factors, such as measures of poverty increase the risk of suicide (Iemmi et al., 2016). Food insecurity, housing conditions, unemployment and economic inequalities are associated with an increased risk of common mental disorders (Lund et al., 2010) and suicide (Iemmi et al., 2016) in LMICs where over 75% of suicides occur (WHO, 2014b). Poverty has also been associated with higher rates of injury and violence (WHO, 2014a). In addition, poverty intersects with the social determinants of mental health such as education, adverse childhood experiences and access to health care (Peters et al., 2008). In South Africa, more than half (55.5%) of the population (30.3 million) live below the national poverty line, while a quarter (13.8 million) live in extreme poverty, unable to afford enough food to meet physical needs (World Bank, 2020). In this thesis, measures of poverty are examined to understand the relationship between poverty and suicide which is essential for developing effective suicide prevention interventions. These measures include education and occupation data from vital statistics dataset (*Chapter 2 - Study 1, Publication 1)*, education, employment and source of income data *(Chapter 3 - Study 2, Publication 2)* from South African populations and education levels and monthly income data from international studies *(Chapter 4 - Study 3, Publication 3).*

1.6 Genetic factors and suicidal behaviour

Psychiatric genomics is a growing field that holds much promise for the prevention, diagnosis and treatment of psychiatric disorders, including suicidal behaviour. It is well-established that suicidal behaviour runs in families (Hawton and van Heeringen, 2009, Brent and Mann, 2005, Brent and Melhem, 2008). A family history of suicidal behaviour can increase the risk of suicide two-fold (Runeson and Åsberg, 2003, Qin et al., 2002) and increase the risk of

attempted suicide three- (Mitterauer, 1990) to six-fold (Sorenson and Rutter, 1991). Adoption, twin and family studies have found that genetic factors account for 30-55% of suicide in families, independent of psychiatric illness (reviewed by Brent and Mann, 2005, Brent and Melhem, 2008, Voracek and Loibl, 2007).

The approach to genetic studies has changed considerably over the past decade, from small candidate gene association studies to a wave of genome-wide association (GWAS), generating rich resources of publicly available genetic data from large cohorts. The use of GWAS technology has revolutionised the understanding of complex diseases. However, even with the advance in technology, discoveries in suicide research have been modest because of small sample sizes and inconsistencies in the genetic findings reported by earlier studies (Galfalvy et al., 2015, Mullins et al., 2014, Perlis et al., 2010, Zai et al., 2015). Larger sample sizes are made possible by meta-analysis of GWAS data by consortia such as the Psychiatric Genetics Consortium Suicide Working Group (PGC SUI) and have substantially increased the statistical power of suicide attempt studies (Mullins et al., 2022, Mullins et al., 2019).

The rapid increase in the availability of genomic data has provided opportunities for the advancement of post-genome-wide methodologies to understand the underlying mechanisms of complex diseases (Cirillo et al., 2017). In keeping with the findings of our literature review presented in *Chapter 4 (Section 4.1)*, our current understanding is that suicidal behaviour is complex and polygenic. Suicidal behaviour shares genetic influences with a range of behavioural and psychiatric disorders, suggesting a shared genetic aetiology (Erlangsen et al., 2018, Levey et al., 2019, Mullins et al., 2019). Further examination of genomic data using post-GWAS analytical techniques can therefore provide insight into neurobiological mechanisms and pathogenesis of suicide and may be used to imply suicide risk. This provides the third research focus of the thesis exploring the genetic architecture underlying suicidal

behaviour and psychiatric disorders to understand the biological pathways leading to suicidal behaviour, which is addressed in *Chapter 4 (Study 3, Publication 3).*

Psychiatric genetic association findings reported from predominantly populations of European ancestry are generalisable to other European populations (Lee et al., 2019). However, it is not clear how these findings translate to populations of other ancestries. The increasing numbers of large-scale studies in European populations and low participation rate among under-represented populations, such as African populations, implies that the prediction accuracy of disorders taken from studies of European populations may be inadequate for African ancestry populations (Majara et al., 2023). Further, Sub-Saharan African populations represent the most genetically diverse populations globally (Sengupta et al., 2021). To date, multi-ancestral psychiatric studies have been slow to emerge (Duncan et al., 2018, Hettema et al., 2020).

While understanding the advantages of conducting original psychiatric genetic research in South African populations (Hettema et al., 2020), there were no South African genetic datasets publicly available for suicidal behaviour. For this reason, the exploratory genetic study presented in *Chapter 4* of this thesis analysed genetic datasets of suicidal behaviour and psychiatric disorders in populations of European and East Asian ancestry that were accessible and available in the public domain, which will limit the generalisability of the study findings to our study population. Extensive efforts and investment have been undertaken to increase the representation of individuals with African ancestry in genomic research (Bentley et al., 2020, Mulder et al., 2018, Rotimi et al., 2014). However, achieving the desired large-scale sample sizes will require more time and continued efforts. Meanwhile, it is also understood that precision medicine will likely integrate many biological mechanisms and disease pathways into possible treatments for diverse populations (Bourdon et al., 2020, Niculescu et

al., 2017). Thus, this exploratory study lays the groundwork for future genetic suicidal behaviour studies in South African populations.

1.7 Rationale for the thesis

Suicide is a serious public health problem and is a leading cause of death in the world. According to the Global Burden of Disease 2019 Study, the suicide rate is decreasing worldwide (Naghavi, 2019). However, these patterns vary considerably between countries. Suicide is especially prevalent in LMICs, with the African region reporting suicide rates higher than the global average (WHO, 2021), and seemingly increasing year on year. The economic impact of suicide is staggering, due to the high proportion of suicide observed in young adulthood and the associated loss in productivity (Iemmi et al., 2016). In South Africa, the loss of income due to mental illness such as depression and anxiety disorders alone is high and is estimated at approximately $3.6 billion (Lund et al., 2013), with an estimated overall cost of suicide of $1.2 billion in 2017 (Kirigia et al., 2020). Given the considerable economic cost associated with suicide (Lund et al., 2013) and health inequality in South Africa (Coovadia et al., 2009), there is an urgent need to determine the burden of suicide and associated risk factors to understand who is most at risk and what opportunities exist for suicide prevention efforts.

According to the World Health Organisation, suicide can be prevented, if timely measures are taken (WHO, 2018b). Despite clear evidence of the multiple risk factors associated with suicidal behaviour (reviewed by Cavanagh et al., 2003, Freire and Koifman, 2013, Lund et al., 2010, Mars et al., 2014, McLean et al., 2008), there are limitations to our knowledge that make suicide difficult to predict and prevent. First, South Africa does not have a national suicide prevention plan (WHO, 2018b) and therefore lacks a cohesive national public health response. Second, much of the existing suicide data are derived primarily from high-income

countries, rather than from LMIC settings, where suicide is concentrated (Naghavi, 2019) and poverty levels (Bantjes et al., 2018, Iemmi et al., 2016, Lund et al., 2010) and harmful alcohol use are high (WHO, 2018a). In particular, there is extensive literature on the disparities in access to healthcare services in LMICs, which could be explained by underperforming health systems due to a lack of resources, and geographic and financial barriers that are not experienced in high-income countries (Peters et al., 2008, Bitton et al., 2019).

Third, there is a large mental health treatment gap in South Africa (Docrat et al., 2019a), meaning a large proportion of individuals with mental illness are untreated. The burden of mental illness in South Africa is substantial and is steadily rising with other non-communicable diseases (Mayosi et al., 2009). This could be partly explained by the shared risk factors between non-communicable diseases and mental disorders, such as harmful alcohol use, tobacco use, and environmental and socioeconomic factors (Stein et al., 2019). Severe mental disorders are associated with an increased risk of suicide and suicide attempts compared to the general population (Harris and Barraclough, 1997, Nock et al., 2009, Nock et al., 2010). Further, existing evidence supports the early identification and treatment of mental disorders as an important suicide prevention strategy (Wasserman et al., 2021, Wasserman et al., 2012).

Fourth, primary care services are often the first point of contact within the health care system and are therefore uniquely placed to promote mental wellness and screen, diagnose and treat mental health conditions and provide appropriate referral into psychiatric care. In high-income countries, reports of up to 80% of suicides attended primary care services in the year before death (Luoma et al., 2002, Stene-Larsen and Reneflot, 2017), suggest that there are opportunities to integrate suicide prevention strategies into primary healthcare. For example,

as the management of patients with chronic conditions mostly occurs in primary care, there may be opportunities to screen, diagnose and treat patients with common mental disorders (depression and anxiety) and appropriately refer them if needed. While this pattern of contact with the healthcare system before suicidal behaviour is well established in high-income countries, it is not clear if the same is true in low-resource settings where mental healthcare workers are comparatively scarce. Establishing if the same pattern of contact with the healthcare system exists among suicidal individuals in LMICs, could have important implications for the allocation of suicide prevention resources and suicide prevention programmes in resource-constrained environments.

Fifth, there is an absence of studies on the relationship between environmental factors, particularly OP exposure, and attempted suicide in the general population. Much of the existing literature focuses on farm workers and/or agricultural communities. Pesticides are well-recognised as agents for suicide. Pesticide self-poisoning accounts for about one-third of the world's suicides (Gunnell et al., 2007), and is the most common method of suicide in LMICs (Mew et al., 2017). However, exposure to OPs may also increase the risk of suicide. Further, evidence of increased suicidal behaviour and mortality among agricultural and occupational populations exposed to OP (Freire and Koifman, 2013, London et al., 2012, MacFarlane et al., 2011, Mew et al., 2017, Beseler et al., 2006, Beseler and Stallones, 2008) suggests that continuous pesticide exposure plays a critical role in suicide risk. In addition, there is compelling evidence that pesticide-related suicide mortality can be reduced by restricting access to highly lethal methods of suicide, such as OP (Knipe et al., 2017, Gunnell et al., 2007), indicating that pesticide self-poisoning is amenable to prevention efforts. To the best of our knowledge, this is the first study to investigate the relationship between household and garden OP exposure and attempted suicide in the general population.

Lastly, while progress has been made, the underlying biology of suicidal behaviour is still poorly understood. Previous studies have emphasised strong genetic relationships between suicidal behaviour and psychiatric disorders (Bondy et al., 2006, Brent and Mann, 2005, DiBlasi et al., 2021, Turecki, 2001, Turecki and Brent, 2016), however, a recent study has found evidence suggesting that the genetic architecture of attempted suicide may also be partly distinct from psychiatric disorders (Mullins et al., 2022). Understanding the underlying biological pathways involved in suicidal behaviour could lead to better prediction of suicide risk and provide potential avenues for treatment and prevention strategies. Taken together, the purpose of this study was to broaden our understanding of suicidal behaviour in South Africa by combining various data sources to strengthen the evidence base and build a more coherent picture of suicidal behaviour. By improving our understanding, we aimed to identify key areas to improve the effectiveness of suicide prevention in South Africa.

1.8 Research questions and study objectives

The overarching research question that guided the design of this thesis was: *Why do people become suicidal and do opportunities exist for suicide prevention in South Africa?*

In my effort to answer this question, two primary research questions were explored through four studies. The first question, *what risk factors (sociodemographic, environmental and biological factors) are associated with suicidal behaviour?*, aimed to provide insight into the patterns and predictors of suicidal behaviour in South Africa. The second question, *what opportunities for suicide prevention can be identified for individuals at risk of suicidal behaviour?*, aimed to identify opportunities for targeted suicide prevention strategies. The study objectives are listed below.

Study objectives

1. To determine trends in suicide mortality and patterns in suicide methods as well as other conditions that may include suicide to identify populations at risk in South Africa (Study 1).
2. To investigate the association between environmental (household and garden use) and occupational OP exposure in the general population and attempted suicide in adults admitted to hospital in Cape Town, South Africa (Study 2).
3. To explore the genetic architecture underlying suicidal behaviour and psychiatric disorders to understand the biological pathways leading to suicidal behaviour (Study 3).
4. To describe healthcare utilisation 12 months before suicidal behaviour among individuals who attempted suicide and who died by suicide, to identify opportunities for prevention and to compare the prevalence and timing of healthcare service utilisation by suicidal behaviour, in Cape Town, South Africa (Study 4).

1.9 Thesis overview

This body of work includes four publications, each reporting data from distinct but related suicide studies. Four studies were conducted to broaden our understanding of suicidal behaviour in South Africa, combining various data sources, each representing a unique perspective of the problem, to build on existing knowledge that may inform suicide prevention strategies in South Africa (Figure 1.5). The first three studies investigated risk factors associated with suicidal behaviour and the fourth study aimed to identify opportunities for prevention.

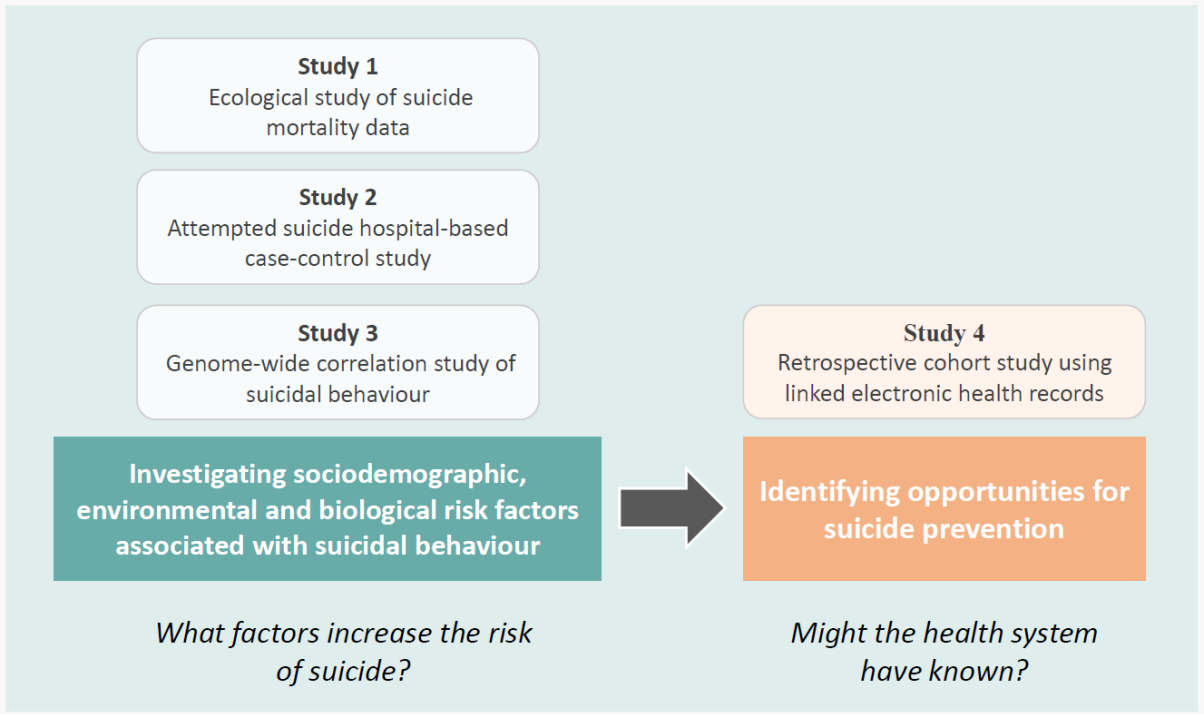


Figure 1.5 Study overview

The doctoral study began with an ecological time-series study of existing national vital statistics data from Statistics South Africa, to determine trends in death from suicide as well as demographic risk factors that increase the risk of suicide and inform our understanding of patterns of suicide mortality in South Africa. Because of the problems of missing or misclassified data, the study also examined trends and demographic risk factors related to other conditions that may include suicide, viz accidental deaths, deaths for which the intent cannot be determined (undetermined deaths) and homicide (Study 1).

Next, I conducted a secondary analysis of an attempted suicide hospital-based case-control study that served to increase our understanding of the relationship between sociodemographic and environmental factors, focusing on one particular understudied risk factor, OP exposure and attempted suicide (Study 2).

Thereafter, I performed an exploratory study of large genome-wide association (GWA) summary data to understand the underlying biology of suicidal behaviour (Study 3).

However, due to the absence of large genetic suicide data (n > 1,000) in South Africa and Africa, I obtained publicly available GWAS summary statistics of populations in high-income countries (United Kingdom, Europe, North America and Japan).

Although based on three different data sets, these three studies provide some insight into the antecedent risk factors for suicide, including environmental (OP) and personal (demographic and genetic) factors. The next logical step was to consider whether the healthcare utilisation behaviour of persons attempting or completing suicide could have provided an opportunity for early intervention by the health services.

Therefore, the final study was a retrospective analysis of linked electronic health records of individuals who attempted suicide and those who died by suicide (Study 4). Patients who attempted suicide were cases from the hospital-based case-control study and a hospital-based case-series study, and individuals who died by suicide were obtained from a mortuary case series in Cape Town. Data about health care utilisation in the five years preceding suicidal behaviour were sought from the Provincial Health Data Centre (PDHC) of the Western Cape and were linked to each participant. Findings from this study provided information about how frequently healthcare services were accessed and the services most commonly accessed and sought to identify potential opportunities for targeted intervention.

1.10 Thesis outline

This thesis consists of six chapters, including four publications, each reporting data from studies of individuals with suicidal behaviour. In this exploratory study, both fatal and non-fatal suicidal behaviours are investigated, using a range of methodologies, to build on existing knowledge that may inform suicide prevention strategies in South Africa. Three results chapters (Chapters 2, 3 and 5) map the epidemiology of suicidal behaviour through three distinct but related studies and Chapter 4 explores the genetics of suicide.

Chapter 1 introduced the topic of suicidal behaviour, which includes the definitions and epidemiology of suicidal behaviour. Chapters 2, 3 and 4 examined the sociodemographic, environmental and genetic risk factors associated with suicidal behaviour. Chapter 2, the first of three studies mapping the epidemiology of suicide (Study 1), investigated trends in suicide mortality rates, the methods of fatal suicide and years of potential life lost in South Africa over 20 years, from 1997 to 2016. The importance of national-level suicide mortality data and its limitations are discussed, particularly in light of large quantities of missing data in Statistics South Africa data sets and the uncertain quality of the data. Chapter 3, the second of three epidemiological studies, examines an understudied environmental risk factor (Study 2) and investigated the association between long-term household, garden and occupational OP exposure and attempted suicide in a hospital-based case-control study, in Cape Town, South Africa. The prevalence and risk factors associated with attempted suicide are presented, and the feasibility of long-term pesticide exposure assessments in our study population is discussed. Chapter 4 explored the underlying biological architecture of suicidal behaviour and its relationship with psychiatric disorders using publicly available GWA studies summary data (Study 3), to provide insight into pathways leading to fatal suicidal behaviour. Chapter 5, the third study mapping the epidemiology of suicide, describes the use of healthcare services and mental healthcare services one year before suicidal behaviour in Cape Town, South Africa, using linked electronic health records of individuals who engaged in fatal and non-fatal suicidal behaviour, to identify opportunities for targeted suicide prevention efforts (Study 4). Chapter 6 is the concluding chapter of the thesis and contains a general discussion of the findings presented, the implications for suicide prevention and recommendations for future work in the field.

Chapter 2 Trends in suicide mortality in South Africa, 1997 to 2016

Kootbodien T, Naicker N, Wilson KS, Ramesar R and London L. Trends in suicide mortality in South Africa, 1997 to 2016. *International Journal of Environmental Research and Public Health.* 17, no. 6 (2020): 1850.

Contributions of co-authors and candidate:

TK, RR and LL conceptualized the study. TK conducted the analysis, led the data interpretation and drafted the manuscript. Co-authors NN, KW, RR and LL reviewed the draft and made conceptual and intellectual contributions in specific areas of their expertise. All authors read and approved the final manuscript.

This is the first of three publications mapping the epidemiology of suicide. This ecological time-series study addresses the first objective of the thesis by describing the patterns (utilising joinpoint regression analysis) in suicide as well as other conditions that may include suicide such as accidental death and death by undetermined intent by age and sex and selected sociodemographic factors, over 20 years, to identify populations at risk in South Africa.

This paper was substantially revised for this dissertation based on examiner feedback. The original paper is available at https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7142470/.

2.1 Abstract

Background: Mortality data are essential to monitor and raise awareness of the risk of suicide in South Africa. However, vital registration suicide mortality data are often misclassified as accidental death or death of undetermined intent leading to underreporting. This study evaluated trends in suicide rates to identify populations at risk in South Africa from 1997 to 2016 and deaths classified as accidental, homicide and undetermined intent to assess their potential for analysis as a category that may include underlying suicide.

Methods: Underlying cause of death information was retrieved from vital registration data from Statistics South Africa. Cause of death was categorised as due to suicide (X60-X84 and Y87), injury of undetermined intent (Y10-Y34), death from external causes (R99) and subcategories of death by accidental injury and assault. We estimated the age-standardised mortality rate (ASMR) and compared annual percentage changes (APC) in ASMR of adults (15 years and older at age of death) from 1997 to 2016 using joinpoint regression analysis.

Results: From 1997 to 2016, there were 8,753 suicide deaths (0.1% of all deaths) and 462,377 deaths by undetermined intent (4.5%). The ASMR for suicide was 0.9 and 1.0 per 100,000 in 1997 and 2016, respectively; the equivalent ASMR for death by undetermined intent was 116.6 and 2.7 per 100,000 in 1996 and 2017. Suicide mortality rates were consistently higher for men than women across 20 years and increased significantly by 7.7% per year (average APC 95% CI 0.8% to 15.0%) among young people aged 15-29 years. Suicide mortality rates for hanging and poisoning increased by 2.9% and 3.7% across 20 years. The largest proportion of suicide deaths were potentially misclassified as accidental hanging and hanging by undetermined intent, and to a lesser extent, accidental poisoning and poisoning by undetermined intent. In contrast, firearm-related deaths were more likely to indicate a homicide than a suicide death.

Conclusion: The results show that suicide contributes substantially to premature death and

demonstrates the need for targeted interventions, especially among young men in South Africa. Caution is advised when interpreting patterns in suicide mortality from national registration data due to undercounting of suicide deaths and high ill-defined, accidental injury and undetermined intent mortality rates. These categories should therefore be examined when assessing suicide trends.

2.2 Introduction

Suicide is a serious public health concern. Suicide contributed approximately 817,000 deaths to global mortality in 2016, accounting for 1.5% of the total deaths in the world (Naghavi, 2019). Findings from the Global Burden of Disease Study 2016 showed that while an increase in the absolute number of suicide deaths worldwide was observed from 1990 to 2016, there was a significant decrease in the global age-standardised suicide mortality rate (ASMR) by a third, from 16.6 deaths per 100,000 to 11.2 deaths per 100,000 population (Naghavi, 2019). It is estimated that approximately 80% of all suicides occur in low- and middle-income countries (WHO, 2014b). In 2016, Southern sub-Saharan Africa had the third-highest regional suicide mortality rate (ASMR 16.3 per 100,000) in the world, with approximately 11,000 suicide deaths contributing to the burden of disease (Naghavi, 2019).

Suicide is a complex behaviour consisting of an interplay between many risks and protective factors impacting the individual, family, community and societal levels (Joiner, 2007, van Heeringen, 2012). Suicide varies with sex and age groups across different countries and regions. Suicide mortality is higher among men than women in general, with women reporting more suicidal thoughts and men more likely to die by suicide (Bertolote, 2001). Suicide rates in Africa are reported to be at least three times higher in men than women (Mars et al., 2014) and approximately five times higher in South African men compared to women (Matzopoulos et al., 2015), although the distribution varies across population groups and

cities (Burrows and Laflamme, 2006). Globally, suicide mortality is higher among younger adults and adults later in life, whereas in Sub-Saharan Africa, the suicide mortality rate increases with age (Bertolote and Fleischmann, 2002). The choice of suicide method varies by socioeconomic levels of countries (Ajdacic-Gross et al., 2008); social, religious and cultural beliefs; and availability and access to means (Meltzer et al., 2008). Variability in the common methods of suicide (hanging, use of firearms or poisoning) has been reported across African countries (Mars et al., 2014), with hanging, poisoning and firearm suicide reported as the most common methods used in South Africa (Scribante et al., 2004, Stark et al., 2010).

Reliable suicide mortality data are important for suicide monitoring and identifying the mental health needs of a population (Mathers et al., 2005). Moreover, it can inform prevention efforts by monitoring progress in the implementation of programmes (Lopez et al., 2007), to reduce the morbidity and mortality associated with mental illness. According to the World Health Organisation, the quality of death registry data varies by country. The quality of the South African 1996 mortality data was evaluated as low (Mathers et al., 2005). The evaluation of the South African 1997 to 2007 mortality data showed substantial improvements in data completeness and coverage; however, the persistently high proportion of ill-defined or non-specific codes (>10%) used in mortality data suggested that the data was still unsatisfactory (Joubert et al., 2013).

The accuracy and validity of suicide data have been questioned repeatedly in many countries (O'Donnell and Farmer, 1995, Ohberg and Lonnqvist, 1998). A systematic review of 31 studies mostly from Europe and North America found varying degrees of reliability, ranging from poor (underreporting of more than 30%) to fairly reliable (underreporting of less than 10%) (Tøllefsen et al., 2012). Misclassification through non-random bias can occur when factors such as religious beliefs, stigma and legal implications affect the recording of the final

cause of death resulting in the miscoding of suicide deaths and subsequent underreporting of suicide. Suicide may also be misclassified non-randomly by manner or method of death. For example, it is harder to determine the intent of a fatal poisoning than compared to hanging which is more likely to be a suicide. Similarly, a firearm injury could be a suicide but is more likely to be a homicide or accidental firearm injury in South Africa, based on postmortem findings of a nationally representative sample (Matzopoulos et al., 2015). In this study, we aimed to investigate trends in suicide and deaths classified as accidental, homicide and undetermined intent to assess their potential for analysis as a category that may include underlying suicide and to identify populations at risk in South Africa.

2.3 Methods

2.3.1 Data sources and data management

We obtained the underlying cause of death data based on death certificate information reported to Statistics South Africa from the national (governmental) Department of Home Affairs for each year for twenty years from 1997 to 2016. Data from the observation period were derived from statistics published on the Statistics South Africa website and are available online (Statistics South Africa). Suicide was defined as a death resulting from intentional self-harm according to the World Health Organisation (WHO) International Statistical Classification of Diseases and Related Health Problems 10th revision (ICD-10), which uses codes X60 to X84 and Y87 to identify all suicide methods. Suicide methods were classified into hanging (X70), drowning (X71), self-poisoning (X60-X69), firearm discharge (X72-X75), blunt or sharp objects (X78-X79), fire, heat and hot substances (X76-X77), jumping from a high place or moving object (X80-X81), crashing of motor vehicle (X82) and unspecified means (X83-X84). In the absence of definitive evidence of suicide, such as a suicide note, the manner of death can provide further indication of possible suicide intent.

The presumption is that death by hanging for which no intent was established would likely be categorised as suicide; a firearm death may be categorised as suicide but is more likely to be assigned as a homicide or accidental death and death by poisoning may be categorised as either a suicide or accidental death. We explore this presumption by analysing deaths due to accidental causes (W00-X59), deaths for which intention could not be established (Y10-Y34) and homicide-related deaths (X85-Y09) by method of death (hanging, poisoning and firearm) alongside analysis of suicide deaths to identify if misclassification of suicide deaths could explain different patterns.

Deaths classified as undetermined intent (Y10-Y34) were further classified into hanging (Y20), poisoning (Y10-Y19) and firearm injury (Y22-Y24). Accidental injury deaths included accidental death by hanging (W75-W76), poisoning (X40-X49) and firearm injury (W32-W34). To assess possible misclassification of suicide deaths as homicides, we examined assault-related deaths by hanging and threats to breathing (X91), poisoning (X85) and firearm injury (X93-X95). The dataset also included ill-defined or unknown causes of death (R99) and accidental exposure to unspecified factors (X59). The proportion of missing information is indicated by the percentage unspecified for each sociodemographic characteristic.

2.3.2 Statistical analysis

We used mid-year population estimates to calculate age-standardised mortality rates (ASMR) by sex for all years, except for 1997 to 2001, where mid-year population by age group was not available. For that period, we used the 1996 South African census data to calculate ASMRs for 1997 to 2000 and presumed that the relative proportion of age and sex remained constant and, for 2001, we used the 2001 census data for that year. The rates were

standardised to the WHO standard population (Ahmad et al., 2001). Individuals for whom sex or age was unspecified or unknown were not included in the analyses.

Multiple logistic regression analyses were performed to identify sociodemographic factors associated with suicide. Variables with less than 25% missing data and associated univariate analysis p-values of <0.10 were included in the multivariate analysis. The comparison group were non-suicide deaths (n=10,292,051). The final model is presented using odds ratios (ORs) and 95% confidence intervals (CI). Level of significance was set at 0.05. Data were cleaned and analysed using Microsoft Excel 2013 and STATA version 15.

We used joinpoint regression analysis to identify changes in age-standardised mortality trends in men and women and age-specific mortality rate by cause of death using the Joinpoint Regression Program, Version 4.5.0.1 (Statistical Research and Applications Branch, National Cancer Institute (JoinPoint Regression Program Version 4.0.4, 2013). The Joinpoint Regression Program determines the minimum number of "join" points that adequately fit the data and composes continuous linear phases or line segments by selecting the best-fitting log-linear model (Kim et al., 2000). A significance level of 0.05 was used for the permutation test with 4,499 randomly permuted datasets. We analysed trends in cause of death data by age and sex and summarised the changes (increased, decreased or remained stable) in mortality rates as the annual percentage change (APC) and average APC across 20 years and 95% confidence intervals.

As ASMRs are influenced by deaths in older populations and the distribution of suicide mortality rates are high among younger adults as well as older populations (Bertolote and Fleischmann, 2002), we calculated years of potential life lost (YPLL) as a measure of premature mortality that estimates the average time a person would have lived if death had not occurred prematurely (Gardner and Sanborn, 1990). The YPLL method assumes that if

the person had not died from suicide, they would have lived until 65 years of age. YPLL was standardised to the WHO standard population to account for the changes in the population age structure over time.

Because of the low number of reported suicide deaths, we analysed categories of death other than suicide as a way to infer if the findings could be generalised. We hypothesised (a priori) that a large proportion of all hanging-related deaths are suicide deaths. We examined trends in mortality rates for accidental hanging and hanging by undetermined intent by year, age and sex to assess if these distributions were similar to hanging deaths confirmed as suicide (X70). Next, we hypothesised that a much smaller proportion of all firearm-related deaths are suicide deaths (X72-X75), as firearm-related deaths are more likely to be accidental or firearm homicides. Finally, we hypothesised that an equal proportion of poisoning-related deaths may be either accidental poisoning (X40-X49) or suicide by poisoning (X60-X69).

2.4 Results

2.4.1 Description of the study population

Table 2.1 describes the characteristics of all deaths, deaths by suicide (intentional self-harm, X60-X84, Y87) and undetermined intent (Y10-Y34) in South Africa between 1997 and 2016. During the 20-year observation period, there were approximately 10.3 million recorded deaths in people 15 years and older in South Africa, of which 8,573 deaths (0.1% of all deaths) were due to suicide and 462,337 (4.5%) deaths were classified as undetermined intent.

Men accounted for 78.2% (6,699) of all suicide deaths. The mean age of suicide was similar between men (35 ± 14.9 years) and women (35 ± 18.2 years, p = 0.535). Approximately 73% (6237) of all suicides occurred in men and women aged 15 to 44 years. The number of

suicide deaths increased between 1997 and 2016, with nearly a third (30.1%) of suicide deaths occurring in the last 5 years of the study period between 2012 and 2016. KwaZulu Natal province reported the highest number of suicides (31.4%), followed by the Western Cape province (12.8%). Black African population group had the highest proportion of suicide deaths (62.3%) and accounted for 62% of all deaths. The majority of individuals who died by suicide were single (67.2%), had less than grade 12 (53.4%) school education and 89.1% were in the category that combined unemployed individuals with those who had insufficient information on the death certificate to classify an occupation.

Among injury-related deaths where the intent could not be determined (Y10-Y34), the number of undetermined deaths decreased over time, and the lowest proportion of undetermined deaths (6.2%) was recorded between 2012 and 2016. Similar to individuals who died by suicide, the majority of undetermined deaths were men (76.9%), between the ages of 15 and 44 years (67.6%), Black African (56.6%), single (66.2%) and 95.4% were either unemployed or did not have a specified occupation. Approximately 41% had less than grade 12 school education. The largest proportion of all undetermined deaths was reported in Gauteng province (27.3%), followed by KwaZulu Natal (21.5%), Eastern Cape (13.4%) and Western Cape province (13.2%). The percentage of missing (unspecified) data for all deaths was highest for the variables occupation (92.6%), educational attainment (61.9%), population group (25.3%) and marital status (14.7%). Findings related to these categories, particularly occupation (that combined unemployment together with missing data) and educational attainment, should therefore be interpreted with caution.

Approximately 80% of all suicide deaths were determined by autopsy or post-mortem examination, followed by 5.2% of deaths ascertained by the opinion of a medical practitioner or professional nurse. In comparison, 65% of all undetermined deaths were ascertained by

autopsy or post-mortem examination. Approximately 31% of all undetermined deaths did not have an autopsy compared to 8% of all suicide deaths. When we examined the frequency of autopsies by method of death, irrespective of intent of death, 81% (54,303) of all hanging-related deaths, 81% (99,141) of all firearm-related deaths and 55% (23,856) of all fatal poisonings underwent a forensic autopsy to determine the cause of death. Approximately 44% of suicide deaths and nearly 60% of undetermined deaths did not have a place of death specified.

Table 2.1 Description of suicide (intentional self-harm, X60-X84, Y87) deaths and deaths of undetermined intent (Y10-Y34) in adults (ages 15+ years) that occurred in South Africa, between 1997 and 2016.

Characteristic	**All deaths**	**Suicide**	**Undetermined intent**	**p-value**
By 5-year interval	N (column percent)	N (row percent)	N (row percent)	
Years				
1997-2001	1,993,188 (19.3)	1,405 (0.07)	201,508 (10.1)	
2002-2006	2,926,276 (28.4)	2,318 (0.08)	185,197 (6.3)	
2007-2011	2,930,677 (28.5)	2,142 (0.07)	46,929 (1.6)	
2012-2016	2,450,483 (23.8)	2,708 (0.11)	28,703 (1.1)	<0.001
Total N	10,300,624 (100)	8,573 (0.1)	462,377 (4.5)	
By demographic attribute	N (column percent)	n (column percent)	n (column percent)	
Sex				
Female	4,916,845 (47.7)	1,855 (21.6)	105,060 (22.7)	
Male	5,341,112 (51.8)	6,699 (78.2)	355,341 (76.9)	
Unspecified	42,667 (0.5)	19 (0.2)	1,936 (0.4)	0.001
Broad age-group				
15-29	1,239,064 (12.0)	3,656 (42.6)	167,934 (36.3)	
30-44	2,358,765 (22.9)	2,581 (30.1)	144,765 (31.3)	
45-59	1,922,483 (18.7)	1,301 (15.2)	68,790 (14.9)	
60 and older	4,780,312 (46.4)	990 (11.6)	75,803 (16.4)	
Unspecified	47,196 (0.5)	45 (0.5)	5,045 (1.1)	<0.001
Population group				
Black African	6,345,638 (61.6)	5,594 (62.3)	261,809 (56.6)	
Indian or Asian	692,739 (6.7)	763 (8.9)	28,779 (6.2)	
White	141,167 (1.4)	156 (1.8)	7,497 (1.6)	
Coloured	511,225 (5.0)	958 (11.1)	28,256 (6.1)	
Unspecified	2,609,855 (25.3)	1,102 (12.9)	135,996 (29.4)	<0.001
Province of death				
Western Cape	908,807 (8.8)	1,094 (12.8)	61,183 (13.2)	
Eastern Cape	1,494,194 (14.5)	972 (11.3)	61,747 (13.4)	
Northern Cape	275,700 (2.7)	932 (10.9)	8,750 (1.9)	
Free State	822,720 (8.0)	489 (5.7)	26,527 (5.7)	
KwaZulu-Natal	2,268,790 (22.0)	2,690 (31.4)	98,254 (21.5)	
North West	757,850 (7.4)	612 (7.1)	27,276 (5.9)	
Gauteng	2,077,960 (20.2)	482 (5.6)	126,166 (27.3)	
Mpumalanga	761,841 (7.4)	683 (8.0)	28,040 (6.1)	

Limpopo	895,349 (8.7)	571 (6.7)	23,551 (5.1)	
Outside of SA	23,247 (0.2)	37 (0.4)	646 (0.1)	
Unspecified	14,166 (0.1)	11 (0.1)	197 (<0.1)	<0.001
Marital status				
Never married	4,938,919 (49.5)	5,739 (67.2)	303,909 (66.2)	
Married	2,258,185 (22.6)	1,610 (18.8)	94,431 (20.6)	
Widowed/divorced	1,319,550 (13.2)	531 (6.2)	30,729 (6.7)	
Unspecified	1,467,335 (14.7)	666 (7.8)	30,065 (6.5)	<0.001
Educational attainment				
Less than Grade 12	3,760,504 (36.5)	4,582 (53.4)	191,557 (41.4)	
Tertiary	168,719 (1.6)	313 (3.7)	9,023 (2.0)	
Unspecified	6,371,401 (61.9)	3,678 (42.9)	261,757 (56.6)	<0.001
Occupation groups				
Managers	29,474 (0.3)	36 (0.4)	1,275 (0.3)	
Professionals	75,903 (0.7)	70 (0.8)	1,651 (0.4)	
Technicians	28,035 (0.3)	25 (0.3)	1,089 (0.2)	
Clerks	37,000 (0.4)	36 (0.4)	835 (0.2)	
Service workers	84,134 (0.8)	139 (1.6)	3,136 (0.7)	
Agricultural workers	39,352 (0.4)	92 (1.1)	937 (0.2)	
Trade workers	91,354 (0.9)	101 (1.2)	2,910 (0.6)	
Plant operators	85,309 (0.8)	107 (1.3)	3,060 (0.7)	
Elementary	297,218 (2.9)	332 (3.9)	6,292 (1.3)	
Unspecified/unemployed	9,532,845 (92.6)	7,635 (89.1)	441,152 (95.4)	<0.001
Place of death				
Hospital	4,617,345 (44.8)	1,628 (19.0)	97,091 (21.0)	
Home	2,833,498 (27.5)	2,301 (26.8)	61,074 (13.2)	
Dead on arrival	235,404 ((2.3)	597 (7.0)	30,983 (6.7)	
Nursing home	217,724 (2.1)	77 (0.9)	1,744 (0.4)	
Unspecified	2,396,653 (23.3)	3805 (44.4)	271,526 (58.7)	<0.001
Ascertainment of death				
Autopsy/post mortem	3,534,420 (34.3)	6,819 (79.5)	301,551 (65.2)	
Opinion of medical practitioner	3,210,953 (31.2)	449 (5.2)	5,836 (1.3)	
Interview with family member	291,311 (2.8)	37 (0.4)	649 (0.1)	
Autopsy results may be available	195,432 (1.9)	63 (0.7)	5,400 (1.2)	
Autopsy not performed	1,956,076 (19.0)	668 (7.8)	141,382 (30.6)	
Unspecified	1,112,432 9 (10.8)	537 (6.3)	7,519 (1.6)	<0.001

Suicide mortality risk was higher for men (ORadj=3.16, 95% CI 2.99-3.35) than women and higher across all age groups compared to individuals aged 60 and older (Table 2.2). The risk was notably higher for those aged 15-29 years (ORadj = 16.69, 95% CI 15.39-18.11). Suicide risk was also increased for individuals aged 30-44 years (ORadj=5.84, 95% CI 5.38-6.33) and 45-59 years (ORadj=2.97, 95% CI 2.72-3.25). All population groups were at higher risk of suicide compared to Black African individuals. Although the odds of suicide were greater among individuals who had never married, the association did not persist after adjustment (ORadj=0.91, 95% CI 0.87-1.01).

Table 2.2 Summary of crude and adjusted odds ratio (OR) for suicide in relation to sociodemographic factors (n=8,490,562)

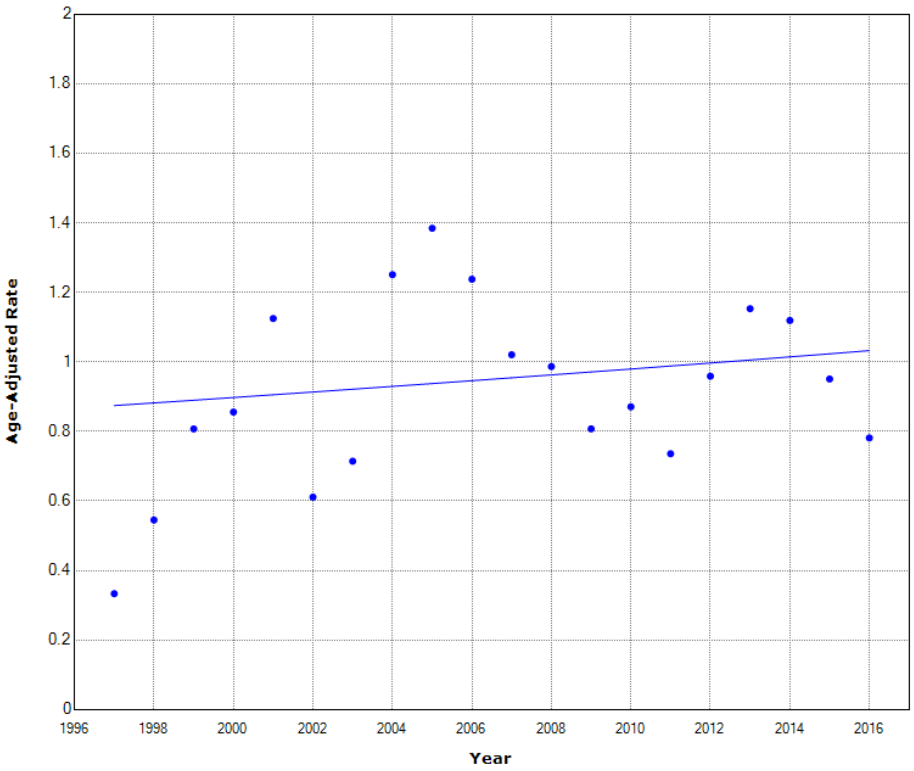
Characteristic	Suicide deaths (n,%)	Non-suicide deaths (n,%)	Crude OR	95% CI	Adj OR	95% CI	*p*-value
Years							
1997-2001	1,405 (16.4)	1,991,783 (19.4)	Ref		Ref		
2002-2006	2,318 (27.0)	2,923,958 (28.4)	1.12	1.05-1.20	1.08	1.00-1.16	0.029
2007-2011	2,142 (25.0)	2,928,535 (28.5)	1.04	0.97-1.11	1.05	0.97-1.12	0.216
2012-2016	2,708 (31.6)	2,447,775 (31.6)	1.57	1.47-1.67	1.61	1.51-1.73	<0.001
Sex							
Female	1,855 (21.6)	4,914,990 (47.8)	Ref		Ref		
Male	6,699 (78.2)	5,334,413 (51.8)	3.32	3.16-3.50	3.16	2.99-3.35	<0.001
Unspecified	19 (0.2)	42,628 (0.4)	1.18	0.75-1.86	1.38	0.81-2.34	0.227
Broad age-group							
15-29	3,656 (42.6)	1,235,408 (12.0)	17.62	16.07-19.31	16.69	15.39-18.11	<0.001
30-44	2,581 (30.1)	2,356,184 (22.9)	6.52	5.93-7.17	5.84	5.38-6.33	<0.001
45-59	1,301 (15.2)	1,921,182 (18.7)	4.03	3.64-4.46	2.97	2.72-3.25	<0.001
60 and older	990 (11.6)	4,732,126 (16.5)	Ref		Ref		
Unspecified	45 (0.5)	47,151 (0.5)	4.56	3.38-6.15	4.73	3.24-6.92	<0.001
Population group							
Black African	5,594 (62.3)	6,340,044 (61.6)	Ref		Ref		
Indian/Asian	763 (8.9)	691,976 (6.7)	1.01	0.98-1.00	1.76	1.49-2.07	<0.001
White	156 (1.8)	141,011 (1.3)	1.30	1.25-1.32	2.53	2.33-2.74	<0.001
Coloured	958 (11.1)	510,267 (5.0	1.38	1.34-1.38	2.57	2.39-2.76	<0.001
Unspecified	1,102 (12.9)	2,608,753 (25.4)	0.47	0.45-0.51	0.58	0.53-0.61	<0.001
Marital status							
Never married	5,739 (67.2)	4,933,180 (49.5)	1.63	1.49-1.52	0.91	0.87-1.01	0.089
Married	1,610 (18.8)	2,256,575 (22.6)	Ref		Ref		
Widow/divorced	531 (6.2)	1,319,019 (13.2)	0.55	0.54-0.55	0.87	0.79-0.99	0.010
Unspecified	666 (7.8)	1,466,669 (14.7)	0.64	0.58-0.70	0.53	0.48-0.57	<0.001

2.4.2 Trends in suicide mortality

Table 2.3 summarises the number of deaths and age-standardised mortality rate of suicide (X60-X84, Y87), injury of undetermined intent (Y10-Y34), subcategories of death by accidental injury and death from external causes (R99). These groups are often described alongside suicide deaths as it may explain the reason for possible undercounting of deaths due to suicide. Annual suicide deaths increased from 111 in 1997 to 445 in 2016. However, annual changes in suicide deaths were highly variable and although there was an overall increase, the trend line did not indicate a significant increase in suicide mortality rates (average annual percentage change [average APC], 0.9% per year, 95% CI -1.4% to 3.3%, p=0.440) (Figure 2.1A). However, suicide rates were consistently higher in men than women across 20 years and no significant increase was observed in mortality rates for both men and

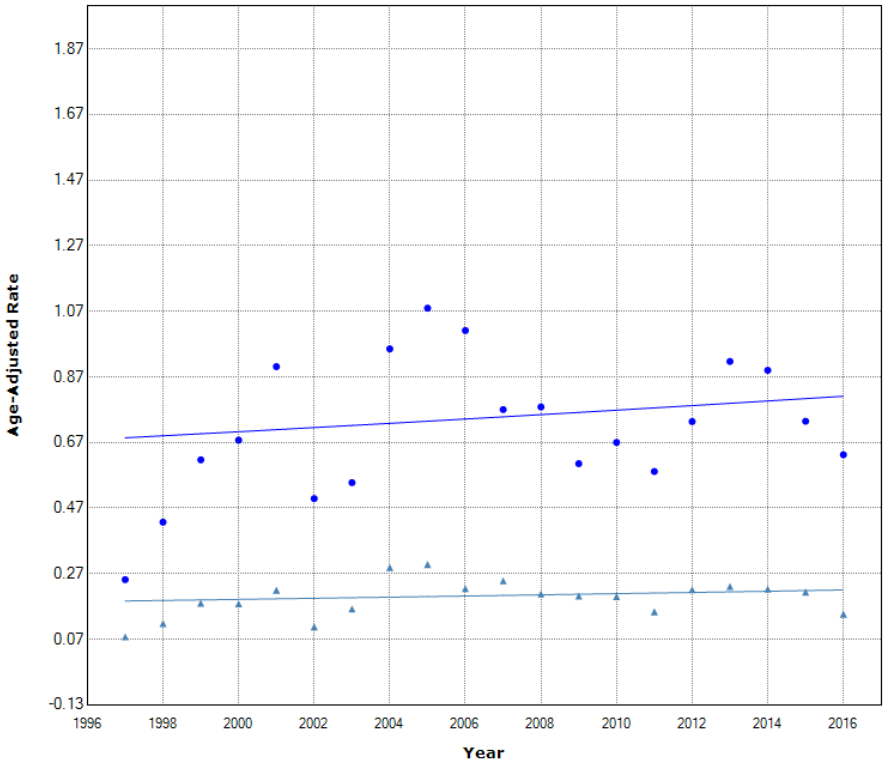
women (Figure 2.1 B). Suicide mortality rates significantly increased by 7.7% per year (average APC, 95% CI 0.8% to 15.0%) among young people aged 15 to 29 years (Figure 2.1 C).

A. Suicide mortality rate



X60-X84, Y87 Suicide
1997-2016 AAPC 0.90 (-1.4, 3.3)

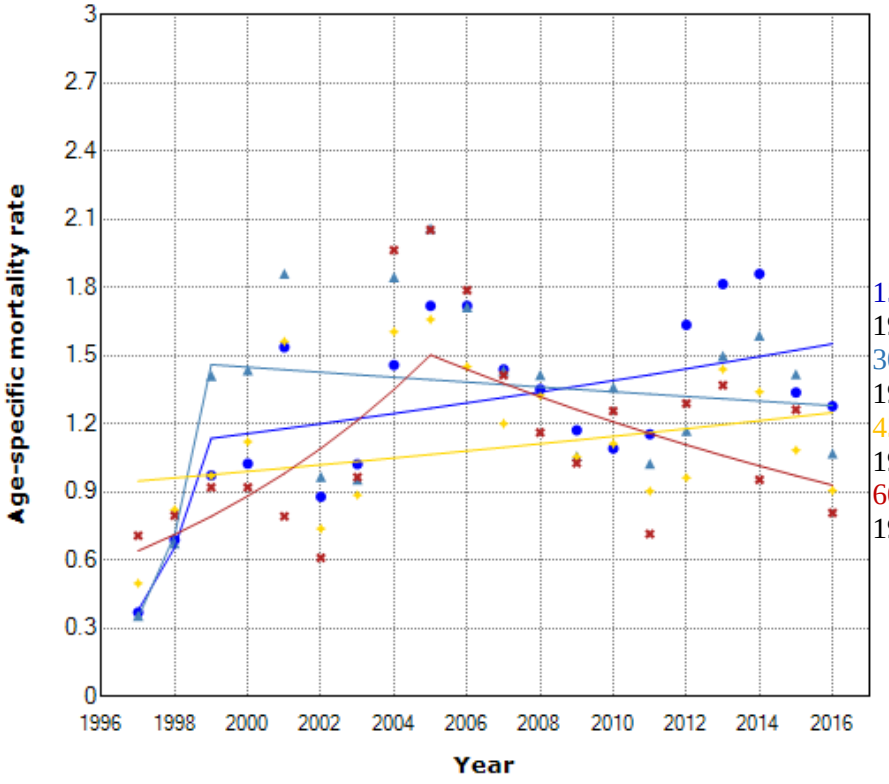
B. Suicide mortality rate by sex



Men
1997-2016 AAPC 0.90 (-2.6, 11.8)

Women
1997-2016 AAPC 0.80 (-1.8, 7.4)

C. Suicide mortality rate by age group



15-29 years
1997-2016 AAPC 7.7 (0.8, 15.0) *
30-44 years
1997-2016 AAPC 7.1 (-0.5, 15.4)
45-59 years
1997-2016 AAPC 1.5 (-0.9, 3.9)
60+ years
1997-2016 AAPC 2.0 (-2.5, 6.7)

Figure 2.1 Age-standardised mortality rates for (A) suicide, (B) suicide by sex and (C) age-specific mortality rates by age group.

* *- indicates that the average APC (AAPC) over 20 years is significantly different from zero at the alpha = 0.05 level.*

Table 2.3 Definition of causes of death, number of deaths, age-standardised mortality rate (ASMR) per 100,000 population in 1997 and 2016, and the average annual percentage change (APC) in ASMR from deaths by suicide (intentional self-harm), undetermined intent, accidental injury and homicide-related injury – both sexes

Cause of death by ICD-10 codes	Definition of death codes	Total No of Deaths	% Deaths	1997		2016		Average annual percentage change (95% CI)
				No of deaths	ASMR per 100,000	No of deaths	ASMR per 100,000	
X60-X84, Y87	**Intentional self-harm/suicide**	8,573	**0.1**	111	0.87	445	1.03	+ 0.9% (-1.4 to 3.3)
X70	Hanging	4,739	55.3	61	0.24	295	0.49	+ 2.9% 0.6 to 5.2) *
X60-X69	Poisoning	1,704	19.5	21	0.12	81	0.14	+ 3.7% (1.3 to 6.1) *
X72-X74	Firearm	638	7.3	5	0.10	32	0.07	- 2.0% (-5.2 to 1.2)
Y10-Y34	**Undetermined intent**	462,337	**4.5**	46,938	116.56	1,640	2.69	- 18.0% (-14.3 to -21.5) *
Y20	Hanging	24,836	5.4	715	2.06	0	0	- 33.3% (-47.3 to -15.7) *
Y10-Y19	Poisoning	22,889	5.0	488	1.21	1,621	2.89	+ 4.7% (1.9 to 7.5) *
Y22-Y24	Firearm	62,306	13.5	2,044	7.01	0	0	-27.6 (-67.2 to 59.8)
W00-X59	**Accidental injury** ¥	355,546	**3.5**	2,762	14.37	30,591	52.55	+ 8.8 (4.6 to 13.1) *
W75-W76	Hanging	37,148	10.4	29	0.09	4,066	7.19	+ 26.0% (9.1 to 45.4) *
X40-X49	Poisoning	18,726	5.3	663	1.69	905	0.84	- 3.6% (-5.5 to -1.7) *
W32-W34	Firearm	58,841	16.5	617	1.43	6,157	9.66	+ 10.6 (-18.0 to 49.0)
X59	Unspecified factors	168,181	47.3	1,142	6.37	17,115	32.30	+ 8.9% (1.9 to 16.4) *
X85-Y09	**Assault/homicide**	89,183	**0.87**	1,360	6.28	7,568	12.59	+ 3.7 (1.9 to 5.6) *
X91	Assault by strangulation	375	**<0.1**	3	0.01	19	0.03	+ 4.7 (-6.3 to 16.9)
X85	Assault by poisoning	3	**<0.1**	-		-		-
X93-X95	Assault by firearm	2,047	**<0.1**	8	0.01	60	0.10	+ 10.6 (-11.4 to 38.1)
R99	Ill-defined causes of death	1,196,031	**11.6**	34,704	133.99	51,993	116.94	- 0.8% (-1.4 to 0.5)
	Combined (excludes homicide/assault)							
X70, W75-W76, Y20	Hanging-related death	66,723	**0.6**	850	2.29	4,361	8.23	+ 7.0% (3.8 to 10.2) *
X60-X69, Y10-Y19, X40-X49	Poisoning-related death	43,319	**0.4**	1,172	2.39	2,607	3.93	+ 2.7% (-0.7 to 6.1)
W32-W34, X72-X74, Y22-Y24	Firearm-related death	121,785	**1.2**	2,603	7.26	6,122	10.97	+ 2.2% (-0.7 to 5.2)

Total number of deaths (1997 to 2016) = 10,300,624; numbers in bold indicate percentage of total number of deaths. Mortality rates for assault by poisoning not calculated due to low numbers (X85, n=3); ¥ excludes transports accidents; * - indicates that the average APC over 20 years is significantly different from zero at the alpha = 0.05 level.

2.4.3 Years of potential life lost due to suicide

In South Africa, the burden of premature mortality was estimated as a total of 37 million (37,310,985) YPLL for all causes of death from 1997 to 2016; and less than 1% (0.65%, 243,429 YPLL) were due to suicide (Table 2.4). The average annual lives lost due to suicide was 9,559 YPLL (rate, 5.73 per 10000 population) among men and 2,612 YPLL (rate, 1.49 per 10,000 population) among women. YPLL rates were highest in 2004 and 2005 for men and in 2004 and 2014 for women.

Table 2.4 Years of potential life lost (YPLL) estimates by all causes of death and suicide-specific causes of death by year and sex

Year	Male				Female			
	All causes (YPLL)		Suicide-specific (YPLL)		All causes (YPLL)		Suicide-specific (YPLL)	
	Total YPLL	Rate per 1000	Total PYLL	Rate per 1000 †	Total PYLL	Rate per 1000 †	Total PYLL	Rate per 1000 †
1997	2 398 233	209.88	2325	0.20	1 471 662	116.12	595	0.04
1998	2 792 467	244.48	3912	0.29	1 862 922	145.78	1237	0.09
1999	2 997 012	262.39	6595	0.51	2 223 997	172.00	1805	0.13
2000	3 263 040	286.10	6625	0.52	2 694 757	207.61	2035	0.14
2001	3 598 960	274.09	11 635	0.78	3 135 470	207.78	2712	0.17
2002	3 988 685	296.95	6297	0.42	3 737 317	248.45	1667	0.09
2003	4 421 255	323.76	6967	0.45	4 295 517	281.71	2007	0.12
2004	4 555 435	328.59	11 152	0.72	4 638 935	300.71	3330	0.20
2005	4 653 162	330.58	13 457	0.85	4 725 847	302.97	3322	0.19
2006	4 717 585	328.82	13 370	0.81	4 707 187	297.83	2712	0.16
2007	4 671 250	319.02	10 507	0.62	4 483 875	279.87	3237	0.18
2008	4 580 495	306.39	10 565	0.62	4 307 242	264.37	2920	0.16
2009	4 386 215	276.70	8 305	0.47	4 725 847	282.27	2885	0.16
2010	4 058 652	260.99	8 822	0.50	3 661 447	216.78	2852	0.15
2011	3 705 815	233.27	8 767	0.48	3 164 912	184.45	2422	0.13
2012	3 505 240	214.99	11 500	0.60	2 860 962	163.65	3532	0.18
2013	3 356 222	201.23	14 272	0.75	2 605 087	146.71	3265	0.17
2014	3 284 210	192.78	14 370	0.75	2 457 035	136.29	4065	0.21
2015	3 249 292	186.68	11 252	0.58	2 331 967	127.35	3227	0.17
2016	3 133 707	175.98	10 485	0.53	2 187 140	117.53	2422	0.13

† Rate per 1000 - age-standardised rate per 1000 population

2.4.4 Trends in suicide methods

Suicide by hanging (X70) was the most common method of suicide and accounted for 55.3% (4,739) of all suicides (Table 2.3, Figure 2.2). Poisoning was the second most common

method of suicide used, accounting for approximately 20% (1,704) of all suicides, followed by firearm-related suicide (638, 7.3%). Hanging was the leading method of suicide in men (4,057, 60.6%), followed by poisoning (drug poisoning, 5.3%; pesticide poisoning, 1.7%, poisoning by other means, 7.4%) and firearm use (578, 8.6%). Poisoning (738, 39.8%) was the leading method of suicide in women (drug poisoning, 21.9%; pesticide poisoning, 5.0% and poisoning by other means, 12.9%), followed closely by hanging (670, 36.1%). Deaths due to pesticide poisoning and drugs in the total population were 2.4% (208) and 8.7% (766), respectively. Approximately 6% of all suicides did not have a method of death specified (X83-X84).

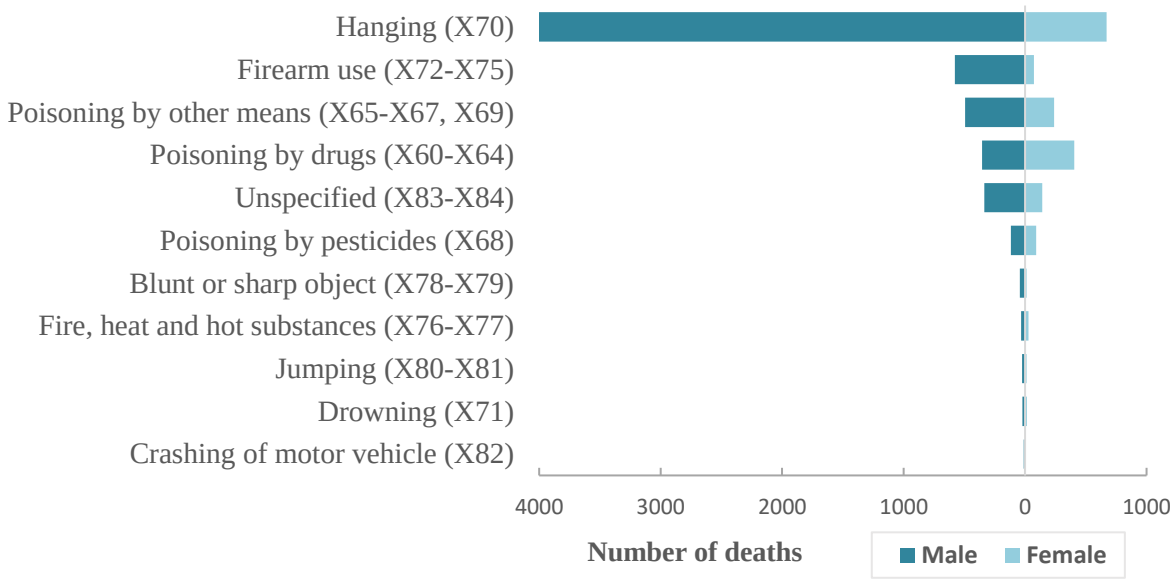


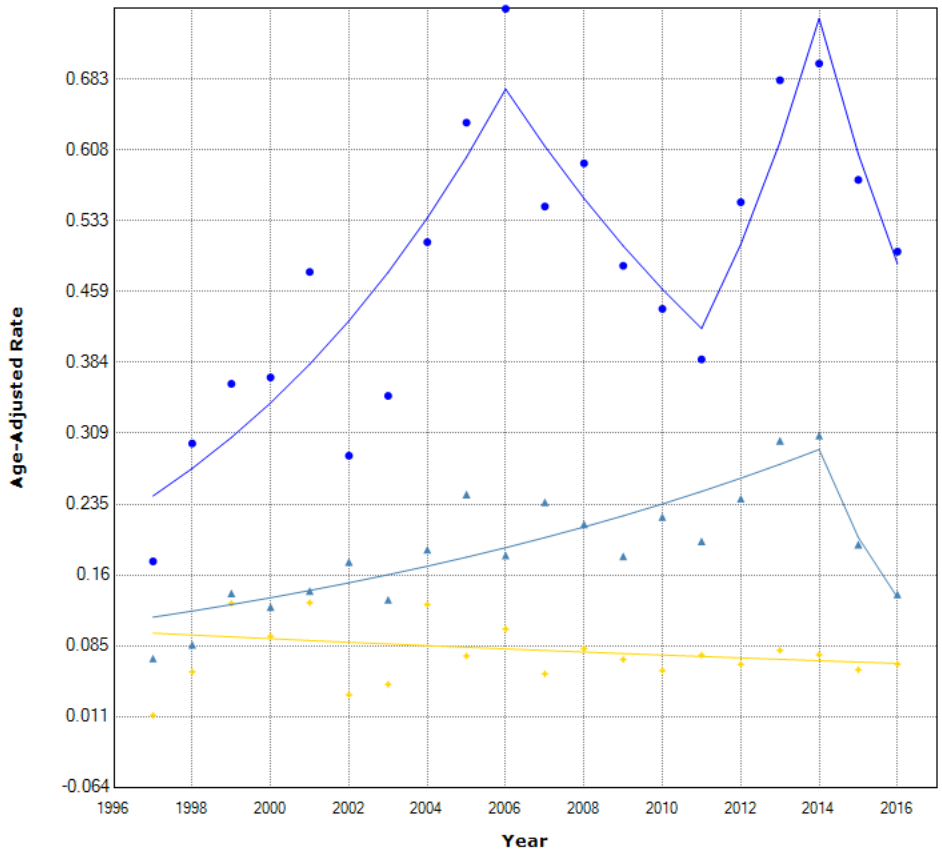
Figure 2.2 Number of deaths by method of suicide in men and women

Suicide rates involving hanging and poisoning increased by 2.9% per year (average APC 95% CI 0.6% to 5.2%) and 3.7% per year (average APC 95% CI 1.3% to 6.1%), respectively over the full study period (Figure 2.3A). Disaggregated by gender, suicide rates by hanging and poisoning increased for men and women across 20 years (Figures 2.3 B and C). Suicide deaths involving hanging in men and women increased significantly by 3.5% (95% CI 1.1%

to 6.0%) and 3.0% (95% CI 0.6% to 5.4%), respectively. Similarly, suicide deaths by poisoning increased by 3.9% (average APC 95% CI 1.8% to 6.0%) in men and 6.7% (95% CI 2.3% to 11.3%) in women over 20 years. The increase in suicide by poisoning trends was more pronounced in women than men.

Firearm-related suicide mortality rates decreased by 2.0% per year but the percentage change overall was not significant (average APC 95% CI -5.2% to 1.2%). Suicide-related firearm use in men decreased by 1.2% per year from 1997 to 2016 but was not significant (95% CI -4.0% to 1.6%). Trends for firearm use in women could not be assessed as there were no reported deaths by firearm use in 2008. An interrupted time series analysis of suicide by firearm mortality before and after enactment of the South African Firearm Control Act of 2000, i.e. 1997-2003 and 2004-2016 shows a 31.0% increase in suicide deaths by firearm (1997-2003, average APC 95% CI -25.9 to 131.5) and a significant 3.3% decrease after the legislation came into effect (2004-2016, average APC -6.4 to -0.1), suggesting that the decrease in suicide by firearms may have been due to the enactment of Firearm Control Act of 2000.

A. Suicide mortality rate by method of suicide

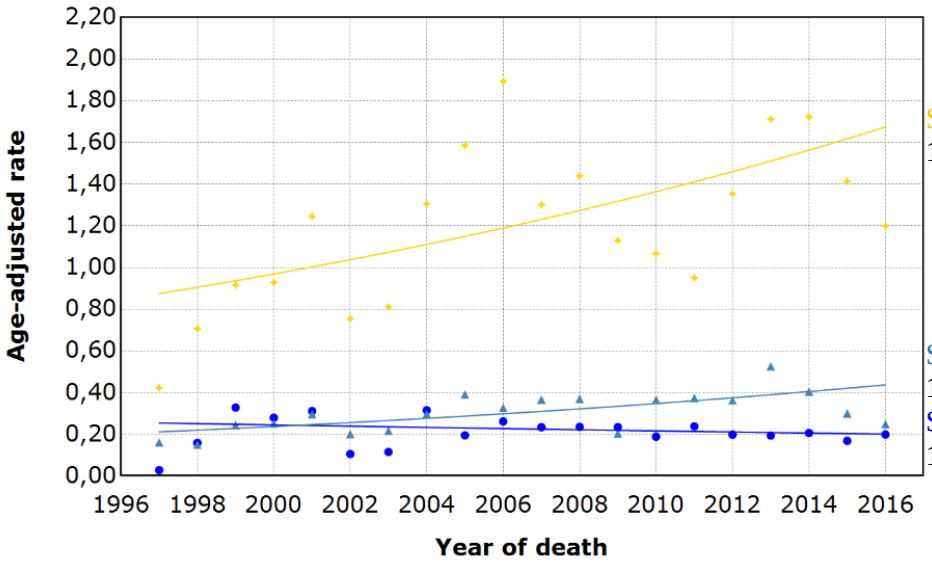


Suicide by hanging
1997-2016 AAPC 2.9 (0.6, 5.2) *

Suicide by poisoning
1997-2016 AAPC 3.7 (1.3, 6.1) *

Suicide by firearm injury
1997-2016 AAPC -2.0 (-5.2, 1.2)

B. Suicide mortality rate by method of suicide in men



Suicide by hanging
1997-2016 AAPC 3.5 (1.1, 6.0) *

Suicide by poisoning
1997-2016 AAPC 3.9 (1.8, 6.0) *

Suicide by firearm injury
1997-2016 AAPC -1.2 (-4.0, 1.6)

C. Suicide mortality rate by method of suicide in women

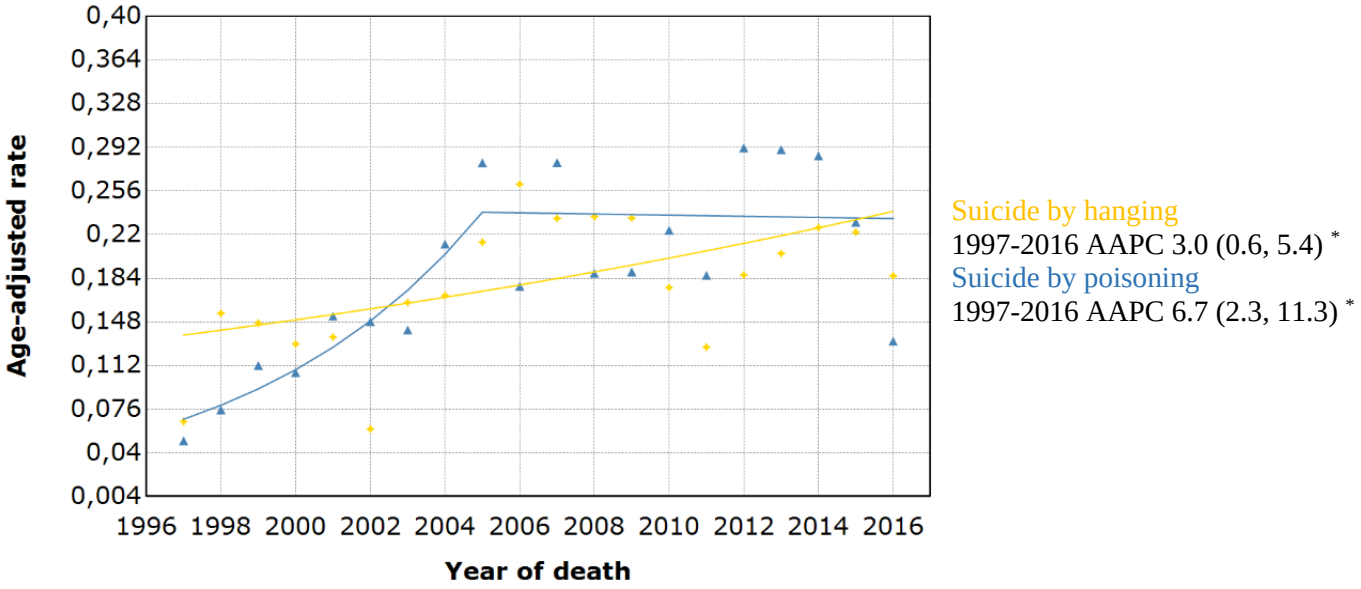
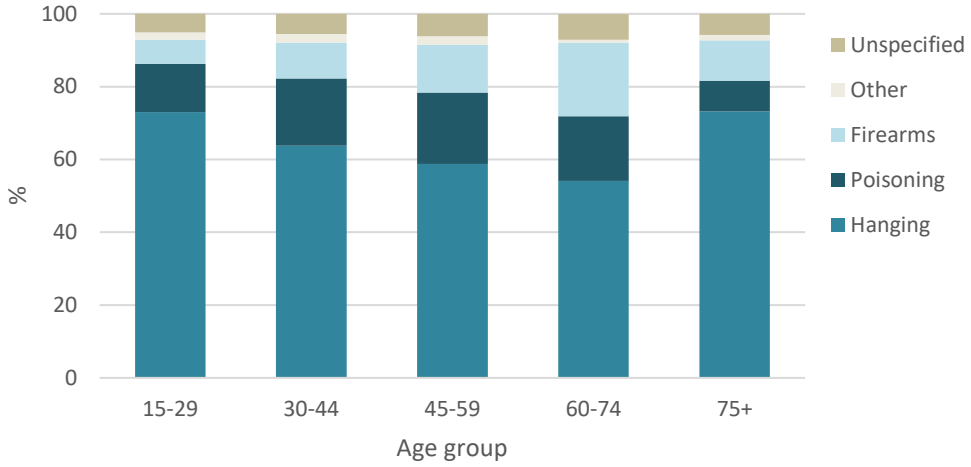


Figure 2.3 (A) Age-standardised suicide mortality rates by method of suicide and in (B) men and (C) women

The distribution of the methods of suicide by broad age groups is shown in Figure 2.4. Hanging was the most common method of suicide in men across all age groups over the entire observation period and was more evident in young men aged 15 to 29 years and older men, 75 years and older. The use of firearms was most prevalent among men aged 60 to 74 years and in women aged 45 to 49 years. Poisoning was the most common method of suicide among younger women aged 15 to 59 years, whereas hanging was more common among women older than 60 years.

A. Men



B. Women

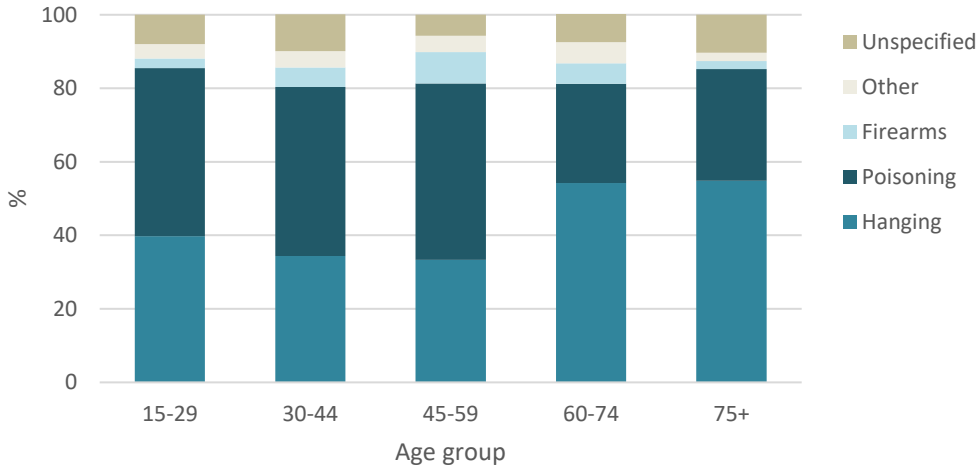


Figure 2.4 Distribution of suicide deaths by method of death for broad age groups for men and women, 1997-2016

2.4.5 Accidental, undetermined and homicide-related deaths as possible sources of underreported suicides

Is it possible that categories where the cause of death was unspecified or unknown (R99), the method of accidental death was not specified (X59) and injury-related deaths where the intent could not be determined (Y10-Y34) hide deaths due to suicide?

We examined patterns in mortality rates for these categories and suicide mortality rates to assess if these deaths may be misclassified suicides (Table 2.3, Figure 2.5). The age-standardised mortality rate for events of undetermined intent (Y10-Y34) decreased significantly by 18% per year (average APC 95% CI -14% to -21.5%) over 20 years. Approximately half (50.8%, 235,027) of the deaths by undetermined intent also reported no method of death (Y34). Ill-defined or unknown causes of death (R99) accounted for 11.6% (1,196,031) of all causes of death over the full study period. While we observed a decrease in ill-defined mortality rate from 2008 to 2016, the overall change was not significant (1997-2016 -0.8% (95% CI -1.4% to 0.5%). Accidental death by exposure to unspecified factors (X59) accounted for 1.6% (168,181) of all deaths. In contrast to the decrease in rates observed for deaths by undetermined intent, the unspecified cause of death mortality rate increased by approximately 9% per year (average APC 95% CI 1.9% to 16.4%) over 20 years (Figure 2.5).

The use of cause-of-death codes where data is insufficient or incomplete (R99) directly relates to the quality of the mortality data. The high percentage of overall deaths reported as ill-defined (>10%) affects the validity of the data and signifies shortcomings with how cause of death is coded. In addition, it is difficult to account for suicide deaths when the method of accidental injury is not specified (X59). Therefore, suicide deaths may have been included in these categories, but we cannot speculate on the extent of the possible misclassification.

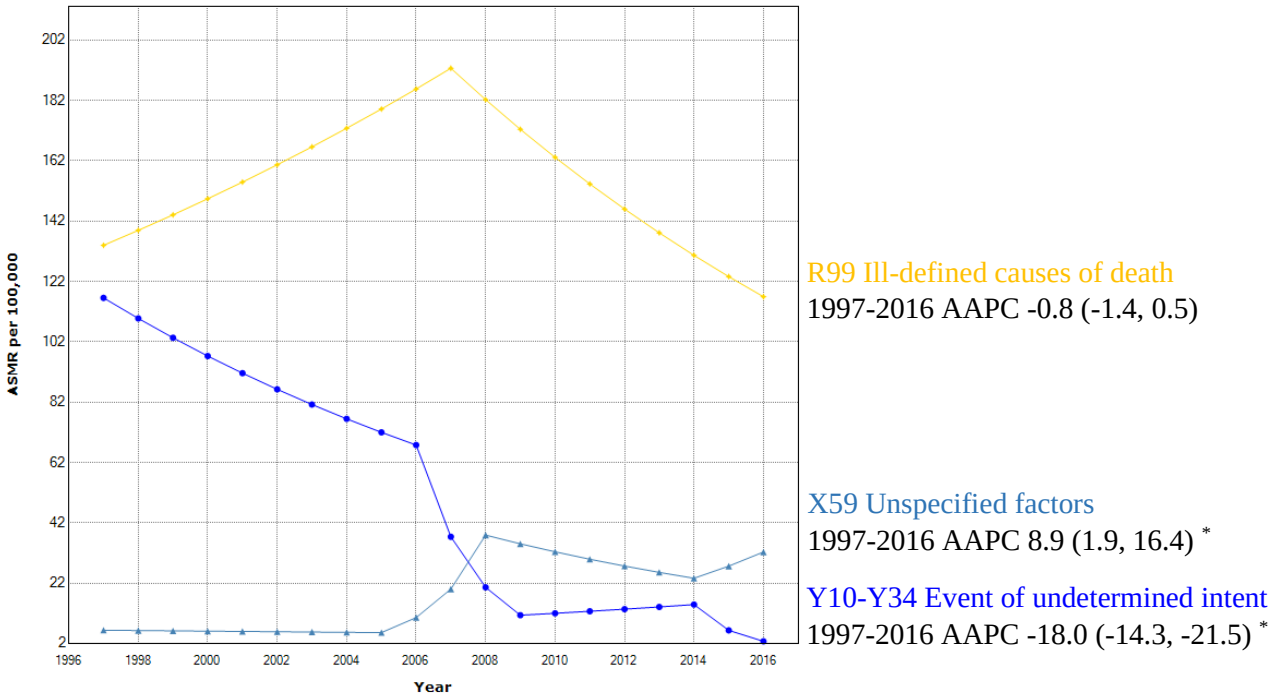


Figure 2.5 Age-standardised mortality rate for ill-defined causes of death (R99), events of undetermined intention (Y10-Y34) and accidental injury by unspecified factors (X59)

Is it possible that injury-related deaths of undetermined intent (Y10-Y34) and subcategories of death from external causes i.e., accidents and homicides hide deaths due to suicide?

To answer this question, we examined cause of death by method (hanging, poisoning and firearm injury) and by intent of death (accidental, suicide, homicide and undetermined intent). Overall, we observed an 18% decrease in undetermined deaths (Y10-Y34), while accidental injury (W00-X59) increased by 8.8% per year (average APC 95% CI 4.6% to 13.1%) and homicides increased by 3.7% per year (average APC 95% CI 1.9% to 5.6%) over 20 years (Table 2.2).

Hanging-related deaths: Mortality patterns of accidental hanging (W75-W76) and hanging of undetermined intent (Y20) were different to suicide-related hanging (X70) (Figure 2.6, Table 2.2). However, on average, mortality rates for accidental hanging (average APC 26.0%, 95% CI 9.1% to 45.4%) and suicide involving hanging (average APC 2.9%, 95% CI 0.6% to 5.2%) increased over 20 years, while hanging by undetermined intent (Y20) decreased by

33.3% (average APC 95% CI -47.3% to -15.7%) per year over 20 years. The sharp 59% annual decline (APC 95% CI -75% to -33%) observed between 2006 and 2016 coincided with the rapid annual increase (171%) in accidental hanging across the same period (2006-2008, APC 95% CI 60% to 357%). There were no deaths reported for hanging by undetermined intent in 2015 and 2016. By 2015, all deaths by hanging of undetermined intent were reallocated to accidental hanging. These findings suggest that suicide deaths involving hanging may be included among deaths classified as hanging by undetermined intent in the first half of the 20-year study period and among deaths classified as accidental hanging from 2004 onward. Homicide-related strangulation/hanging remained stable over the study period (average APC 4.7%, 95% CI -1.4% to 10.2%).

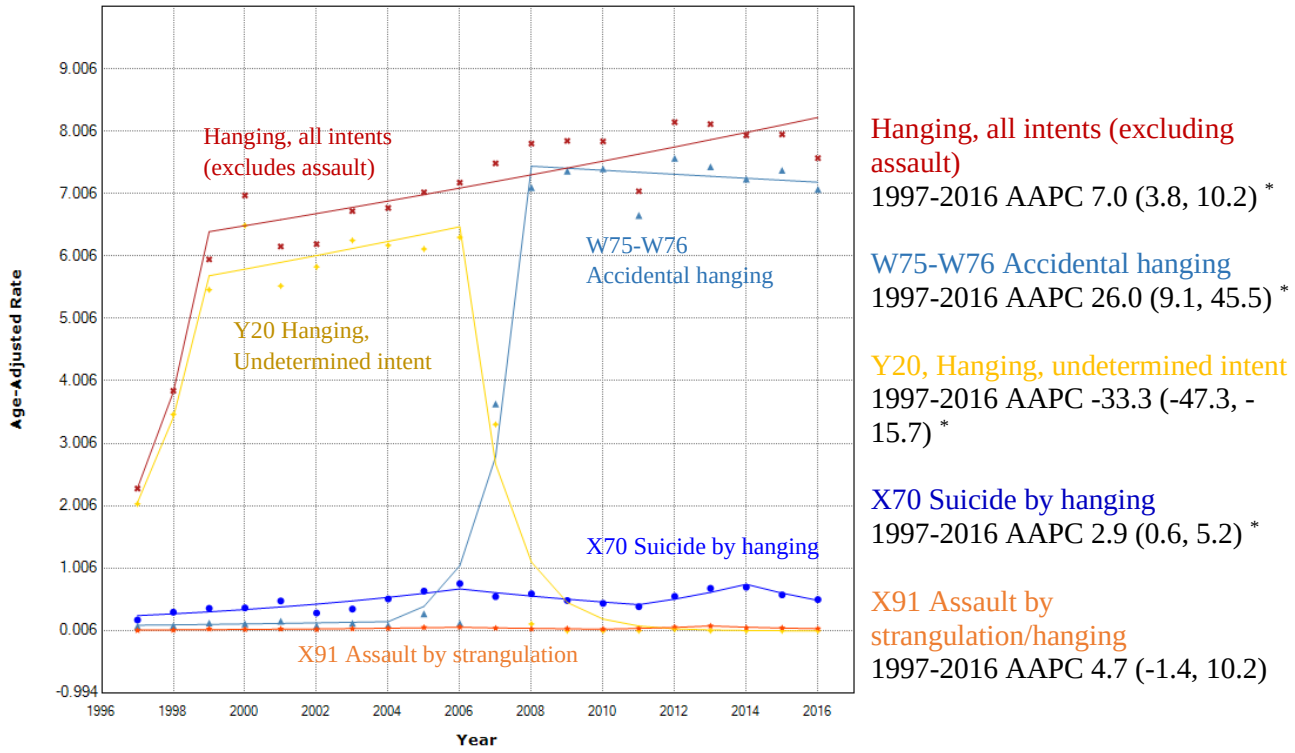


Figure 2.6 Trends in age-standardised hanging-related mortality rates per 100,000 in South Africa, 1997 to 2016

Data markers represent observed rates; lines represent joinpoint regression using one joinpoint; AAPC = average annual percentage change; * - indicates that the AAPC is significantly different from zero at the alpha = 0.05 level.

Poisoning-related deaths: Similar to the increase observed in suicide-related poisoning mortality rate over 20 years, poisoning by undetermined intent increased by 4.7% (average APC 95% CI 1.9% to 7.5%), while accidental poisoning decreased by 3.6% per year (average APC 95% CI -5.5% to -1.7%) (Figure 2.7). There were only 3 homicide-related poisoning deaths reported in 20 years. While it is possible that the change in accidental poisoning accurately represents a true decrease in mortality rate, it is also likely that deaths categorised as poisoning by undetermined intent may include wrongly assigned accidental poisoning deaths as well as suicide deaths involving poisoning throughout the study period.

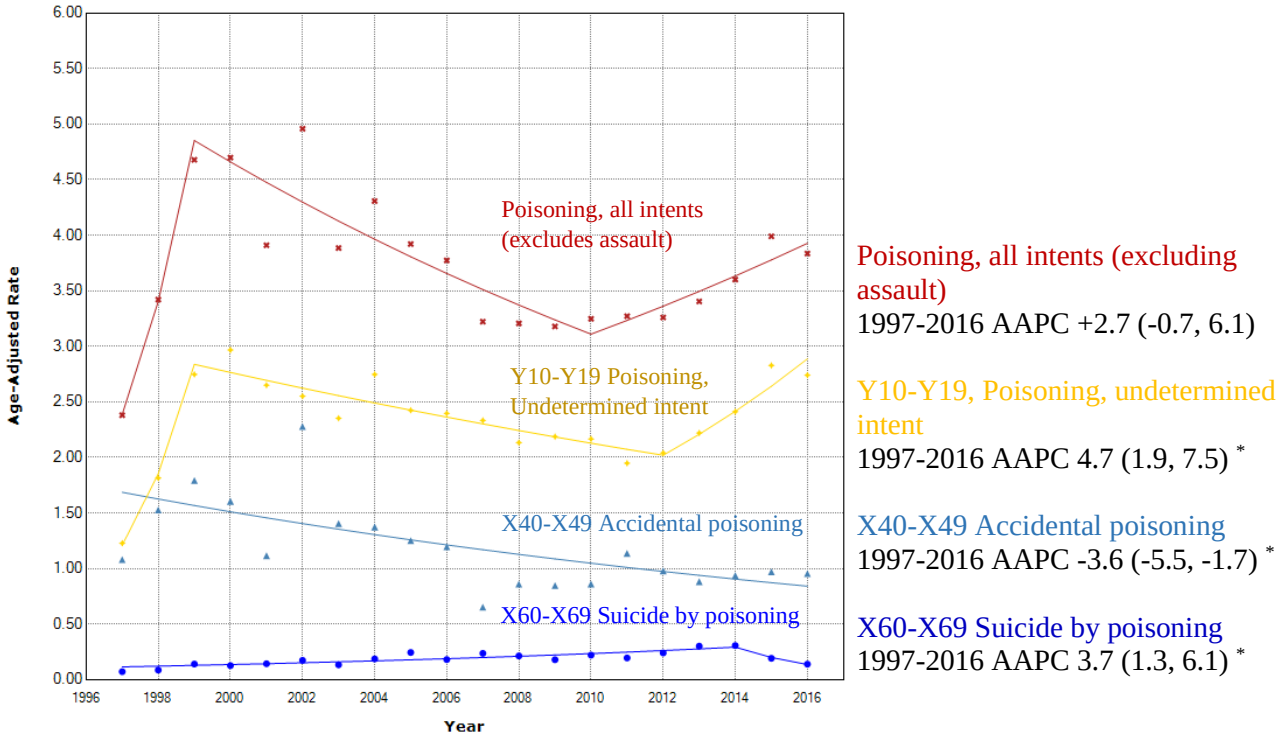


Figure 2.7 Trends in age-standardised poisoning-related mortality rates per 100,000 in South Africa, 1997 to 2016

Data markers represent observed rates; lines represent joinpoint regression using one joinpoint; AAPC = average annual percentage change; * - indicates that the AAPC is significantly different from zero at the alpha = 0.05 level.

Firearm-related deaths: Suicide (X72-X74) and homicide-related firearm mortality rates (X93-X95) were very low compared to accidental firearm deaths (W32-W34) and firearm

deaths of undetermined intent (Y22-Y24) (Figure 2.8). Similar to the patterns observed for hanging-related deaths, firearm deaths by undetermined intent decreased from 2000 to 2006 (APC -11.5%, average APC 95% CI -18.7 to -3.6%) and accidental firearm mortality rates increased sharply between 2004 and 2007 (APC 113%, average APC 95% CI -58.8% to 302.0%). By 2016, there were no deaths reported for firearm injury by undetermined intent (Table 2.2). Taken together, these findings suggest that firearm-related suicides and homicides may have been included among deaths coded as due to firearm injury of undetermined intent before 2008 and among accidental firearm deaths over the study period. Despite the erratic fluctuations in trends observed for firearm-related deaths, on average the changes in firearm mortality rates over the study period were not significant.

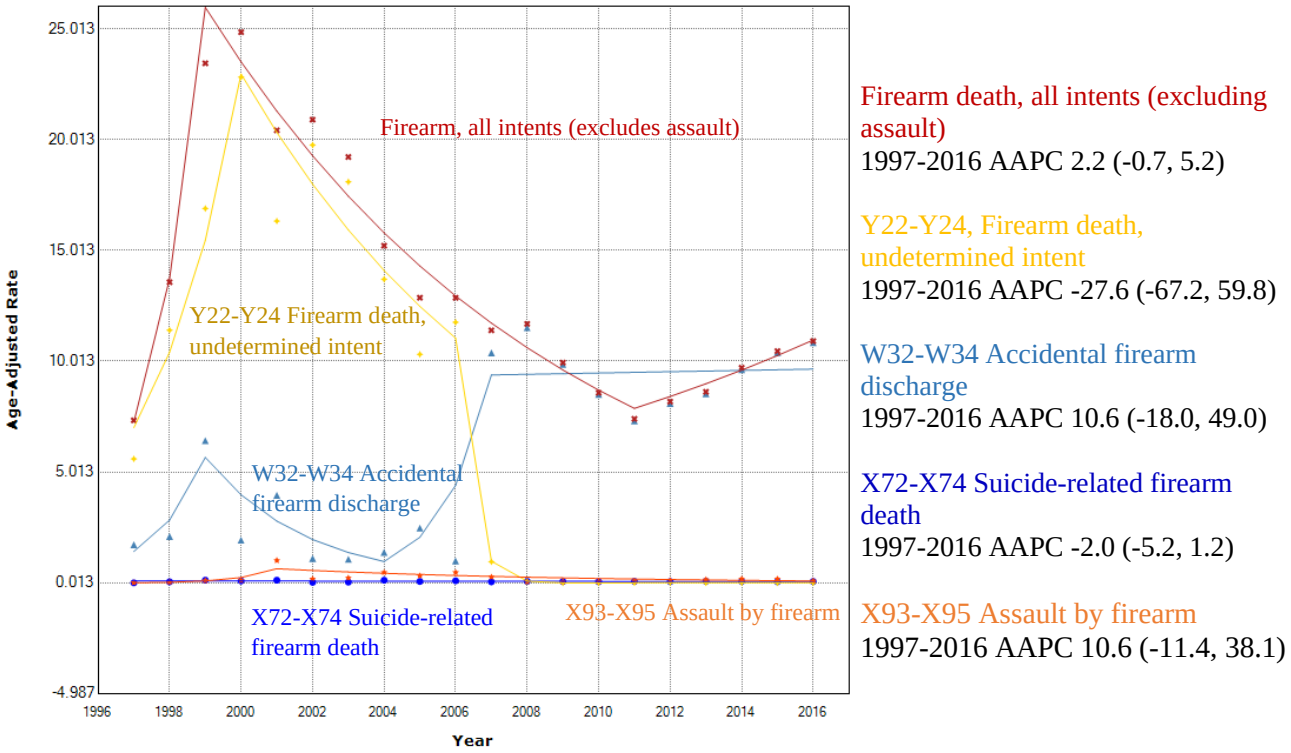


Figure 2.8 Trends in age-standardised hanging, poisoning and firearm-related mortality rates per 100,000 in South Africa, 1997 to 2016.

2.4.6 Suicide, hanging, poisoning and firearm-related deaths by age and sex

Next, we examined all deaths (excluding homicide) due to hanging, poisoning and firearm injury and compared trends in mortality rates by age and sex with suicide rates to assess if patterns were similar. From 1997 to 2016, mortality rates were consistently higher for men than women for all methods of death (Table 2.5, Figure 2.9 and Figure 2.10). The increase in suicide rates for 15-29 years (7.7%) and 30-44 years (7.1%) was similar to the increase observed for hanging rates for the same age groups (7.4% and 7.1%, respectively). The three-fold increase in mortality rates for hanging, irrespective of age or sex, suggests that the largest proportion of underreporting of suicide can be explained by suicide deaths wrongly assigned to undetermined intent (before 2006) and accidental hanging (after 2006). The almost twofold increase in poisoning deaths was similar to the twofold increase observed in suicide rates in men and women over the same period. The highest increase (2.7-fold) was observed for young people aged 15-29 years. Patterns in firearm deaths differed from suicide rates; there was a two-fold increase in mortality for men from 1997 to 2016, while mortality rates for women remained constant. The increase in firearms deaths over this period by the different demographic variables was modest - either stayed more or less the same or increased modestly, never more than double. The biggest increase was 1.7-fold for ages 15 to 44.

In summary, patterns of fatal hanging mortality rates by age and sex were similar to suicide mortality rates. The patterns for fatal poisoning by age and sex matched the patterns for suicide rates to a lesser degree, while the patterns in firearm-related rates were different to suicide. In line with our a priori hypotheses, these findings suggest that hanging and poisoning-related deaths are more likely to mask suicide while firearm-related deaths are more likely to represent misclassified homicides than suicide deaths, given the high rate of violent crime in South Africa (Matzopoulos et al., 2014).

Table 2.5 Average annual percentage changes in suicide, hanging, poisoning and firearm-related mortality rates by sex and age group from 1997 to 2016

Cause of death	N (%)	1997		2016		Average APC from 1997-2016 *	Ratio 2016 to 1997
		No of deaths	ASMR per 100,000	No of deaths	ASMR per 100,000		
Sex							
Men							
Suicide	6,699 (78.3)	86	0.33	351	0.74	+ 0.9 (-2.6 to 11.8)	2.2
Hanging	54,892 (82.6)	646	1.80	3,536	6.82	+ 7.3 (4.1 to 10.6) *	3.8
Poisoning	25,602 (59.4)	682	1.42	1,541	2.47	+ 3.0 (0.1 to 5.9) *	1.7
Firearm	104,931 (86.5)	2,226	5.99	5,483	9.75	+ 2.6 (-0.6 to 5.9)	1.6
Women							
Suicide	1,855 (21.7)	24	0.11	78	0.19	+ 0.8 (-1.8 to 7.4)	1.7
Hanging	11,586 (17.4)	154	0.48	658	1.36	+ 5.6 (1.6 to 9.8) *	2.8
Poisoning	17,475 (40.6)	306	0.95	1,050	1.42	+ 2.1 (-2.4 to 6.9)	1.5
Firearm	16,365 (13.5)	431	1.23	669	1.22	- 0.1 (-3.1 to 3.0)	1.0
Age group							
Age 15-29 years							
Suicide	3,656 (42.7)	43	0.38	197	1.55	+ 7.7 (0.8 to 15.0) *	4.1
Hanging	28,907 (43.3)	343	3.13	1,859	12.15	+ 7.4 (5.3 to 9.5) *	3.9
Poisoning	10,210 (23.6)	223	1.85	724	4.91	+ 5.3 (2.5 to 8.2) *	2.7
Firearm	52,848 (43.4)	1,092	9.3	2,404	16.0	+ 2.9 (0.0 to 5.8) *	1.7
Age 30-44 years							
Suicide	2,581 (30.1)	28	0.35	132	1.28	+ 7.1 (-0.5 to 15.4)	3.7
Hanging	20,279 (30.4)	246	3.24	1,420	11.95	+ 7.1 (5.2 to 9.1) *	3.7
Poisoning	10,610 (23.5)	244	3.00	628	5.21	+ 3.0 (0.7 to 5.3) *	1.7
Firearm	42,599 (35.0)	878	11.36	2,365	19.41	+ 2.9 (0.6 to 5.2) *	1.7
Age 45-59 years							
Suicide	1,301 (15.2)	20	0.95	64	1.25	+ 1.5 (-0.9 to 3.9)	1.3
Hanging	9,082 (13.6)	109	2.86	559	8.43	+ 5.9 (2.9 to 8.9) *	2.9
Poisoning	6,338 (14.6)	140	3.51	400	5.92	+ 2.8 (-0.4 to 6.1)	1.7
Firearm	16,737 (13.7)	354	8.70	919	12.72	+ 2.0 (-0.4 to 4.5)	1.5
Age 60 + years							
Suicide	1,035 (12.0)	20	0.64	52	0.93	+ 2.0 (-2.5 to 6.7)	1.5
Hanging	8,455 (12.7)	152	3.71	523	8.81	+ 4.7 (1.8 to 7.6) *	2.4
Poisoning	16,611 (38.7)	565	6.16	855	6.28	+ 0.1 (-3.0 to 3.3)	1.0
Firearm	9,601 (7.9)	342	9.63	501	9.17	- 0.3 (-2.8 to 2.4)	1.0

Causes of death (excluding assault) were identified by the following ICD-10 codes: suicide (X60-X84, Y87), hanging-related death, all intents (W75-W76, X70 and Y20), poisoning-related death, all intents (X40-X49, X60-X69, Y10-Y19) and firearm-related death, all intents (W32-W34, X72-X74 and Y22-Y24). * - indicates that the average APC is significantly different from zero at the alpha = 0.05 level. Age-standardised mortality rates were calculated for sex and age-specific mortality rates were calculated for each age group.

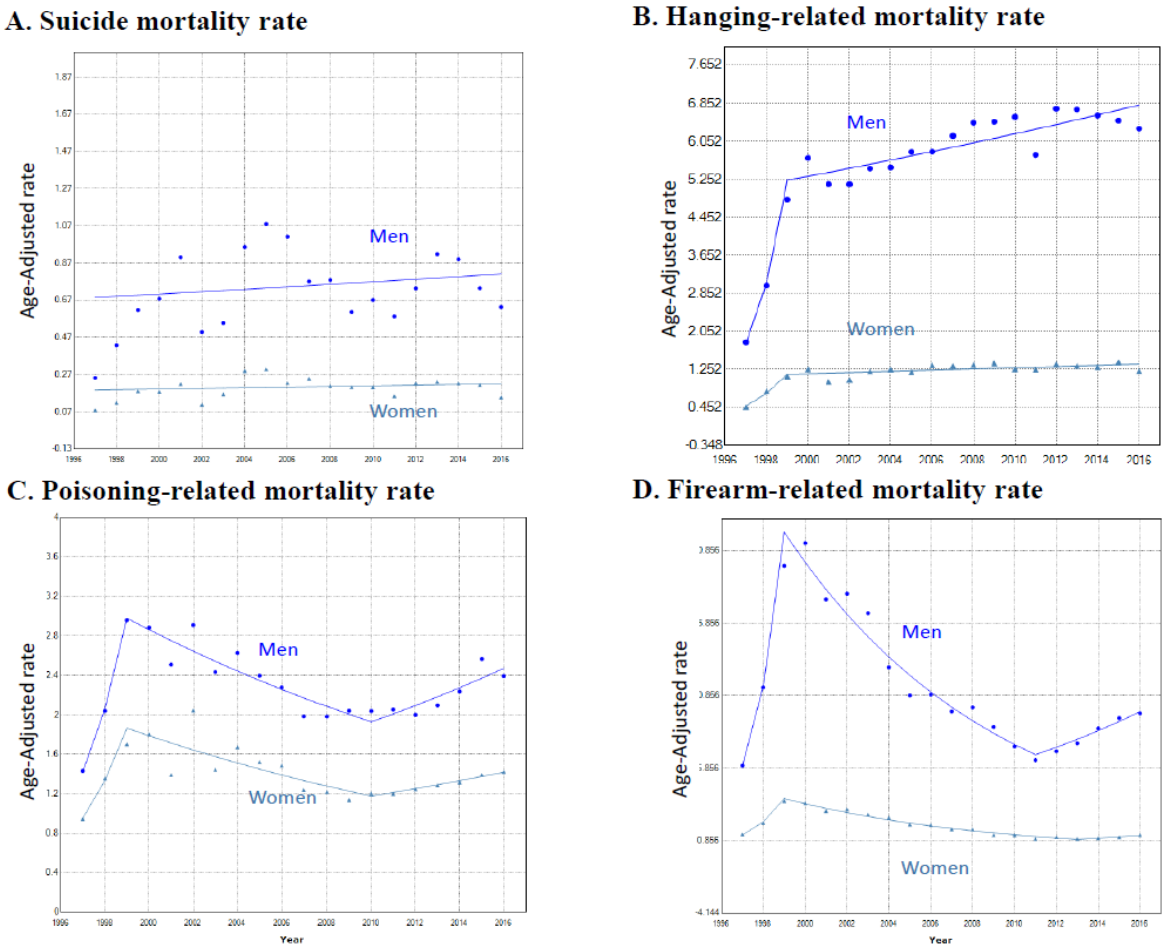


Figure 2.9 Trends in suicide, hanging, poisoning and firearm-related mortality rate by sex (excludes homicide/assault)

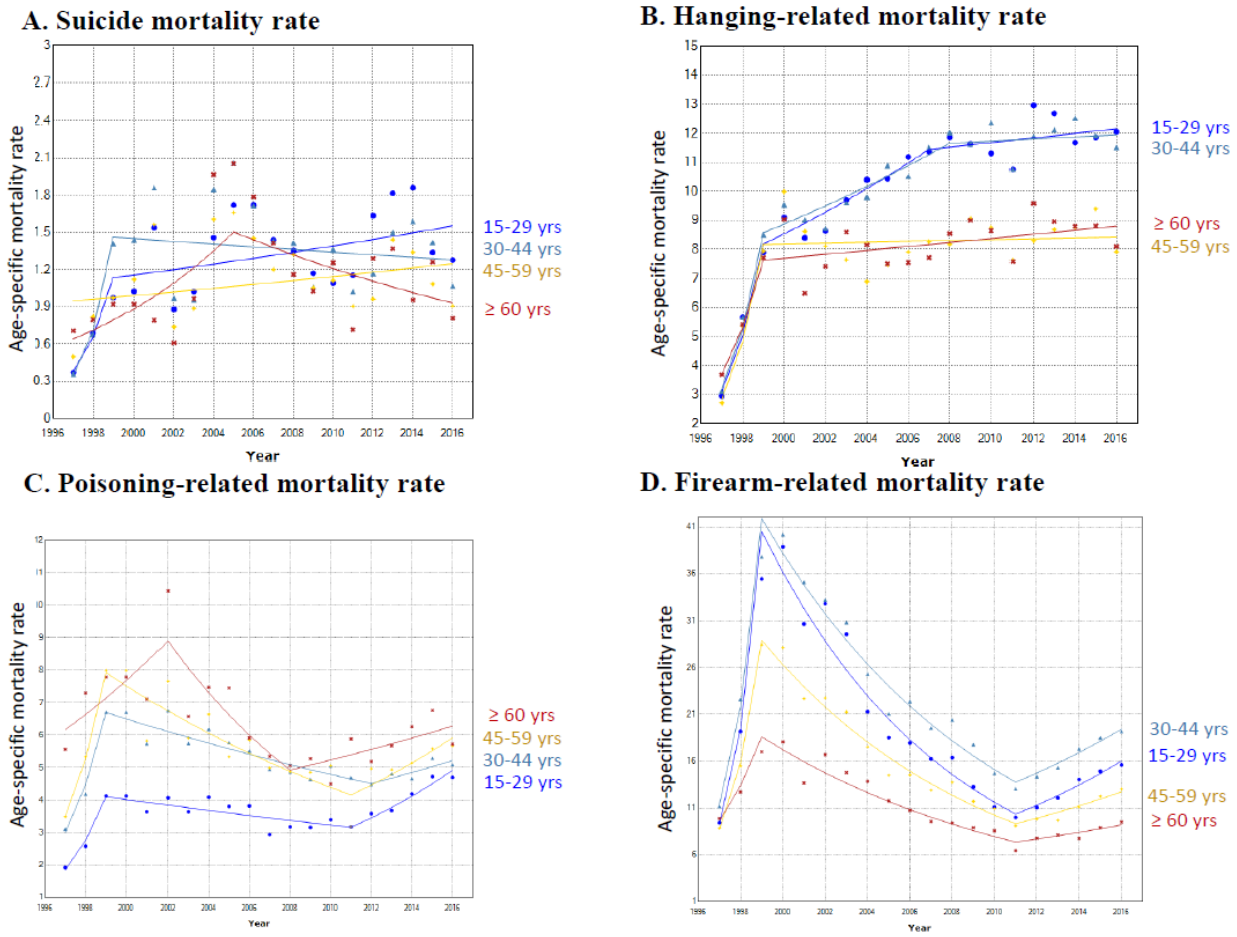


Figure 2.10 Trends in age-specific suicide, hanging, poisoning and firearm-related mortality rates by age group (excludes homicide/assault)

2.5 Discussion

This study describes profiles of suicide mortality, alongside mortality due to accidental injury, homicide and death by undetermined intent in South Africa over 20 years. This approach allowed us to explore issues in mortality data quality, such as potential misclassification and uncertainty regarding the intention of injury-related death that can result in underreporting (Bhalla et al., 2010) and affect the interpretation of suicide trends. Our results suggest that suicide deaths in South Africa are underreported. Despite this limitation, we found that suicide rates increased by 8% among young people aged 15 to 29 years and suicide rates by hanging and poisoning increased by 2.9% and 3.7%, respectively over the study period.

We reported a far lower number of suicide deaths (8,573) and accompanying suicide rates (1997 to 2016, ASMR range 0.9 to 1.0 deaths per 100,000 people) than expected given the suicide rates reported for South Africa by the World Health Organisation (2000 to 2019, 26.6 to 23.5 deaths per 100,000 people) (WHO, 2021). Similar to many African countries, quality suicide mortality data in South Africa is hampered by many factors, including the lack of a national suicide surveillance program, stigma (Frey et al., 2016), religious and cultural beliefs (Mars et al., 2014), doctors that are not adequately trained to complete the cause of death medical certificate (Bradshaw et al., 2010) and an absence or inadequate evidence to determine that a person died by suicide. We reported a male predominance in suicide rates that are consistent with previous findings in South Africa (Scribante et al., 2004, Burrows and Laflamme, 2006, Flisher et al., 2004). Suicide mortality rates were highest for those aged 15 to 29 years. We observed an 8% increase in suicide rates from 1997 to 2016 in this age group, consistent with findings from the Global Burden of Disease Study (GBD 2019 Adolescent Mortality Collaborators, 2021). Explanations for differing mortality trends by sex among young adults may reflect differing risk profiles and requires further investigation.

We did not observe an overall decline in suicide mortality as reported by the 2016 Global Burden of Disease Study (Naghavi, 2019). Instead, we have shown a 2.9% increase in suicide by hanging and a 3.7% increase in suicide by poisoning, while firearm suicide rates remained stable over the study period. Hanging was the most frequently used suicide method in South Africa, accounting for 55% of all suicide deaths, consistent with previous South African studies (Burrows and Laflamme, 2006, Scribante et al., 2004). In contrast to our findings, where traditionally, women have chosen less lethal suicide methods such as poisoning while men chose highly lethal methods such as hanging and firearm use (Denning et al., 2000), we reported an increase in hanging for both sexes. This is of particular concern, as hanging has a high fatality rate of more than 70% (Gunnell et al., 2005). Furthermore, it presents a

challenge for prevention efforts, as hanging is often chosen for its easy access to everyday household items such as ropes and belts that can be used as ligatures (Biddle et al., 2010).

Notable increases in poisoning-related suicide rates were shown for men and women over 20 years. Similar to findings from the United Kingdom (Office for National Statistics, 2022), poisoning accounted for approximately 20% of all suicides in South Africa. According to the World Health Organisation (WHO), pesticide poisoning accounts for 30% of all suicides in the world (Bertolote et al., 2006) and is a prominent method of suicide used in Sub-Saharan Africa (Mars et al., 2014). However, we reported a low prevalence of suicide by pesticide poisoning (2.4%) that is consistent with forensic mortality reports from Bloemfontein (7%, n=469) (Stark et al., 2010) and the Salt River Mortuary in Cape Town (0.65%, n=104) (Patience, 2018). In general, it is difficult to ascertain intent for poisoning deaths, especially drug poisoning, as there is no toxicological difference between accidental and intentional poisoning. Without clear evidence of suicide intent, poisoning deaths are classified as accidental. In addition, where toxicology samples are not analysed due to the backlog that delays testing at forensic chemistry laboratories (Engelbrecht et al., 2017), these deaths are not labelled as due to poisoning irrespective of intent and may be categorised as an accidental injury of unspecified factors (X59), an unspecified event of undetermined intent (Y34) or ill-defined cause of death (R99) at the time of death certification.

Firearm-related suicide rates were very low and while not significant showed a 2% annual decrease over 20 years. In addition, firearm-related trends did not match temporal and gender trends and to some extent age patterns for suicide mortality rates. This could be explained by the introduction of the South African Firearm Control Act of 2000 (South Africa, 2000), which regulates the number of circulating firearms and the people who own them. However, this does not explain the 10.6% increase on average per year in accidental firearm deaths

(also not significant) over 20 years and the substantial underreporting of firearm-related homicide in South Africa (Matzopoulos et al., 2015, Matzopoulos et al., 2014). A retrospective analysis of 2009 post-mortem data reported three times as many deaths from homicide than deaths recorded by mortality registration data from Statistics South Africa (Matzopoulos et al., 2015). In contrast to our findings, data from the National Injury Mortality Surveillance System (NIMSS) showed that South Africa had one of the highest homicide rates in the world in 2000 (Norman et al., 2007), of which more than half (54%) were firearm-related (Groenewald et al., 2003). In contrast to patterns observed for hanging and poisoning deaths, our findings suggest that accidental firearm deaths and firearm-related deaths of undetermined intent are more likely to represent misclassified homicides rather than suicides by firearm injury. Taken together, our study findings suggest that the vital statistics data may not be suitable for surveillance of firearm-related deaths (Prinsloo et al., 2017). Further, the low number of homicide-related firearm deaths indicates that initiatives to improve mortality data quality are critically needed.

In light of the high proportion of undetermined and accidental deaths, it is plausible that suicide deaths may have been misclassified as accidental, homicide or undetermined intent. Misclassification of injury-related deaths is more likely in the absence of an autopsy. It also follows that a lower proportion of undetermined deaths (63%) had a forensic autopsy examination compared to suicide, hanging and firearm-related deaths (approximately 80% for each group, respectively). In addition, the Inquests Act 58 of 1959 (South Africa, 1959) that prohibits forensic pathologists from reporting the manner of death on the basis that it may prejudice the findings of an inquest (Prinsloo et al., 2017) may have also contributed to the underreporting of suicide deaths. This means that the cause of death captured in the official vital statistics may not reflect the final diagnosis once the investigation is complete. The high proportion of suicide and undetermined deaths occurring outside of a hospital (including the

high proportion of unspecified data for place of death, 44% and 59% respectively) may also have contributed to wrongly assigned suicide deaths, when death notification forms are completed by non-medical personnel.

Hanging-related deaths represented the largest proportion of potential misclassified suicide deaths. Accidental and undetermined deaths by hanging outnumbered suicide deaths by 5-8:1. The large number of accidental and undetermined deaths by hanging are likely suicides as deaths by accidental hanging are very rare, mostly occurring in the context of auto-erotic asphyxia." Could changes to the ICD-10 coding convention have reclassified suicide deaths as accidental deaths from undetermined intent from 2006? Our findings suggest that these changes may explain the sharp decrease in hanging and firearm injury by undetermined intent that coincided with the astronomical rise in accidental hanging (171%) and accidental firearm mortality rates (113%) in the same period. However, this only explains that deaths that were previously misclassified as undetermined intent were reclassified and further wrongly assigned as accidental deaths.

Strengths and limitations

The main strength of this study is the use of 20 years of national vital statistics data to assess changes in suicide, accidental, homicide and undetermined intent mortality rates using joinpoint regression analyses.

The comparisons highlight the underreporting and possible misclassifications of suicide deaths previously described in the vital registration data (Burrows and Laflamme, 2007, Matzopoulos et al., 2015) and support an urgent need for intervention. Completeness of death registration data is necessary for the accurate calculation of mortality rates. The redistribution of undetermined deaths to accidental and the recent decrease in ill-defined causes of death suggests there has been some improvement in the quality of death registration data after 2006

(Burrows and Laflamme, 2007, Mathers et al., 2005). However, an important limitation was that half of the undetermined deaths (n=235,037) did not have a reported manner or method of death (Y34, unspecified event of undetermined intent) and were therefore not included when analysing mortality rates by method of death. In addition, while there was a decrease in unknown causes of death (R99) and exposure to unspecified factors (X59), these groups represent a combined 12.2% (n=1,364,212) of all deaths which may also include suicide deaths that could not be examined further by method of death. In the absence of general population data, the use of non-suicide deaths as the control population in the logistic regression models may only infer differences between suicide and non-suicide deaths rather than risk factors of suicide deaths in the general population. In addition, the high proportion of missing data (ranging from 15% for education to 93% for occupation) for most sociodemographic characteristics limits the interpretation of differences between suicide deaths and deaths by undetermined intent. While these findings should be considered with caution, individuals who died by suicide and undetermined intent shared similar characteristics (the majority were men, aged 15 to 29 years, Black African and had never been married) providing further evidence that some suicide deaths may be misclassified as deaths of undetermined intent. In addition, the high proportion of missing sociodemographic data meant that mortality rates could only be examined by age and sex. Given the large proportion of missing data, ongoing training is desperately needed on the cause of death certification skills. Without further efforts to improve the sociodemographic data alongside the cause of death data, we miss an important opportunity to examine the relationships between suicide and education and occupation at a national level.

2.6 Conclusion

This study found that mortality due to suicide varies by sex, age group and method of suicide in the South African population across 20 years. The increase in young adult suicide mortality and suicide by hanging and poisoning in men and women highlights an urgent need for intervention.

However, the study also provides evidence of likely underreporting and misclassification of suicide deaths into accidental deaths and death by undetermined intent. Closer inspection of method of injury-related death (hanging, poisoning and firearm injury) by intent (intentional, accidental, homicide and undetermined intent) revealed potential misclassification of suicide, especially for hanging and to a lesser extent poisoning deaths. Joint examination of firearm injury alongside suicide deaths suggests caution when interpreting firearm-related mortality rates. It is therefore important to examine injury-related death such as suicide by method or manner of death and intent, as excluding these categories may include misclassified suicide deaths and may lead to misinformed prioritisation strategies. This study highlights the urgent need to improve the completeness and data quality of the national suicide data in South Africa. Efforts to improve our understanding of the epidemiology of suicide should continue to reduce the morbidity and mortality associated with suicide. Thus, surveillance of vital statistics data remains a critical epidemiological tool for evaluating the effectiveness of health services and current mental health policies and can inform targeted prevention strategies for those at increased risk of suicide in South Africa.

Chapter 3 Organophosphate pesticide exposure as a risk factor for attempted suicide in Cape Town, South Africa: a case-control study

Kootbodien T, Holtman Z, Asmal L, Joska J, Chiliza B, Smith P, Stallones L, Ramesar RS, London L. Organophosphate pesticide exposure as a risk factor for attempted suicide in Cape Town, South Africa: a case-control study. *Archives of Environmental & Occupational Health*. 2021 Dec 15:1-1. doi 10.1080/19338244.2021.2018983.

Contributions of co-authors and candidate:

LL, JJ, LA, LS, RSR and CB designed the study. LL is the study lead, wrote the study protocol and obtained study funding. TK conceptualised and conducted the analyses, lead the data interpretation and drafted the manuscript. ZH was involved in the data collection, data management and quality control of the data. PS contributed to the laboratory analysis of hair samples. All co-authors reviewed and contributed to the final draft of the paper.

This is the second of three publications mapping the epidemiology of suicide. The previous paper examined mortality rates and patterns of suicide in South Africa. This hospital-based case-control study of attempted suicide addresses the second objective of the thesis and focuses on one potential environmental risk factor that is understudied in the literature, organophosphate pesticide (OP) exposure. OPs are used extensively for agricultural production and in and around the home for the control of insects and rodents in South Africa, resulting in a large proportion of individuals potentially exposed to low pesticide concentrations. Studies have shown that OP exposure predisposes to depression among farmworkers and increases the risk of suicide in agricultural communities with intensive pesticide use. Further, no studies have investigated the association between OP exposure and attempted suicide in the general population in South Africa.

3.1 Abstract

Pesticides are a commonly used agent for suicide in many low- and middle-income countries (LMICs). However, accumulating evidence suggests that organophosphate pesticide (OP) exposure may also increase the risk of suicide. We conducted a hospital-based case-control study to investigate whether prior household, garden or occupational OP exposure was associated with attempted suicide using conditional logistic regression modelling. Participants who attempted suicide by any means and were admitted to two Western Cape Province hospitals in South Africa were compared to a sample of controls matched by age, sex and time of admission with unrelated conditions, between August 2015 and August 2017. The means of attempted suicide were not recorded. OP exposure was determined by dialkyl phosphate (DAP) metabolites detected in hair and by environmental and occupational history. Approximately 85% of participants reported using pesticides in the home or garden and 15% of participants reported current or past occupational exposure while working on a farm. Attempted suicide was not associated with reported home or garden OP use (Odds ratio [OR]=0.59, 95% CI 0.33-1.04), hair DAP metabolites (OR=1.00, 95% CI 0.98-1.02) or current or past agricultural work (OR=1.08, 95% CI 0.62-1.87), but was associated with hazardous drinking and unemployment with no household income. We found no evidence that attempted suicide was associated with environmental or occupational pesticide use in an urban South African population attending an emergency centre.

Keywords: organophosphate pesticide exposure, attempted suicide, case-control study

3.2 Introduction

Suicide is a serious public health challenge globally and is an important cause of premature death in low- and middle-income countries (LMIC) (WHO, 2014b). Information on suicide from LMICs is limited, and where data are available, suicide rates are considered to be

underestimated (Vijayakumar et al., 2005). The quality of suicide data is poor in countries such as India, China and Sri Lanka (Chen et al., 2012) and is likely due to underreporting (Hendin et al., 2008). Similarly, in Africa, the estimated overall suicide rate across 16 countries is 3.2 per 100,000 population (Mars et al., 2014), which is much lower than the global suicide rate of 16 per 100,000 population. Suicide carries negative religious and cultural beliefs that may contribute to the underreporting or deliberate concealment of suicide in Africa (Mars et al., 2014). In South Africa, estimates for the suicide rate range from 11.5 to 25 per 100,000 (Matzopoulos et al., 2015, Mars et al., 2014), with a male-to-female ratio of 4.6:1 (Burrows and Schlebusch, 2008). Suicide attempts are 10 to 40 times more common than fatal suicidal behaviour (Bertolote and Fleischmann, 2002) and are considered a risk for subsequent suicidal behaviours (Bertolote et al., 2010). The estimated South African lifetime prevalence of suicidal ideation and an attempt is 9.1% and 2.9%, respectively, with women reporting twice as many attempts as men (Joe et al., 2008).

Pesticides are a common agent used for suicide (Gunnell et al., 2007, dos Santos et al., 2020). Agricultural pesticide poisoning, especially prevalent in Asia, contributes significantly to the global burden of suicide (WHO, 2014b). According to the World Health Organisation, pesticide poisoning accounts for only 3.5% of deaths by suicide in the African region, compared to the South East Asia Region where it accounts for 11.3% of all suicides (Mew et al., 2017). However, a review by Mars et al. (2014) found that pesticide poisoning, along with hanging, were among the most frequently used suicide method in Africa. Dying from pesticide self-poisoning can be considered an occupational condition (Eddleston, 2018), as the means of suicide is readily accessible and less regulated in agricultural settings in LMICs (WHO, 2014b). Epidemiological studies have reported an association between a history of organophosphate (OP) pesticide poisoning and neurobehavioural changes, such as depression, aggression and increased impulsivity in farming populations (Beseler et al., 2006,

Beseler and Stallones, 2008, Freire and Koifman, 2013, London et al., 2012). OP exposure may also increase the risk of suicide by increasing impulsivity and depression (London et al., 2005). A review by Freire and Koifman (2013) reported four studies that showed an increased risk of suicide (odds ratio [OR] ranging from 1.60 to 2.61) in areas of intensive pesticide use. However, less is known about the association between long-term pesticide exposure and suicide, in the absence of pesticide poisoning (Freire and Koifman, 2013).

With the growing use of pesticides to increase agricultural production and for applications in and around the home, the cumulative effect of pesticides on mental health is a mounting concern. South Africa is considered one of the largest consumers of pesticides in sub-Saharan Africa (Zhang et al., 2011). Household pesticides are commonly used for the control of insects and rodents in South African homes (Tolosana et al., 2009), including the illegal sale of agricultural pesticides such as chlorpyrifos and aldicarb in informal settlements for vermin control (Roomaney et al., 2012). Pesticide use increases the risk of acute poisoning, particularly among children (Balme et al., 2010), but also potentially exposes individuals to low pesticide concentrations over extended periods. While extensive research has been conducted on the effects of OP pesticides on the mental health of agricultural workers and rural communities exposed to high levels of pesticides (Freire and Koifman, 2013, London et al., 2005), less information is available on the general population who are exposed to low levels of pesticides in the household. This study aimed to investigate the association between environmental and occupational OP pesticide exposure in the general population and attempted suicide in adults living in Cape Town, South Africa.

3.3 Methods

3.3.1 Study population and case definition

This case-control study was conducted between August 2015 and August 2017 at one regional and one tertiary-level hospital providing psychiatric emergency services in Cape Town, South Africa. Patients who attempted suicide and were admitted to hospital were approached by the study team once the attending clinician assessed the patient's condition as clinically stable. Informed consent was obtained from those willing to participate. Cases were patients, 18 years and older, of any sex who were admitted for attempted suicide by any means. Participants were recruited from the medical casualty (emergency units) at the respective hospitals on the basis that this was the route of admission for almost all patients presenting with attempted suicide. Patients meeting inclusion criteria were identified and once the patient was stabilised and the clinician confirmed they were not too ill to approach for an interview, the patients then underwent a process of recruitment involving informed consent. In some patients, this would have meant following them to the ward where they had been admitted to interview them. Patients with cancer were generally not admitted to the Emergency Unit unless very ill and for reasons of avoiding intrusive recruitment, we did not include patients with a known diagnosis of cancer. Given that both neurological and cardiovascular conditions have been associated with both pesticide exposure and with suicide risk, we avoided these diagnoses to minimise confounding.

The means of attempted suicide were not recorded. Patients who died by suicide were excluded. For each index case, a control was recruited, who was matched for age and sex and admitted to the hospital within 24 hours of the index patient with a diagnosis other than suicide (orthopaedic, surgical or medical condition, other than cardiovascular disease, neurological illness or cancer). For both cases and controls, we excluded individuals not fluent in either of the local languages (English, Afrikaans or Xhosa) or who were diagnosed

with severe psychological or other medical states (such as delirium) that could compromise the participant's ability to give informed consent. Refusals were replaced by cases or controls who met with inclusion criteria, and, in the case of the controls, met the matching criteria.

3.3.2 Measures

Sociodemographic information and occupational and environmental history were collected using a structured questionnaire administered by trained fieldworkers. Socioeconomic status variables included education, income, employment status in the last 12 months and current occupation. None of the participants was retired. Occupation groups were adapted from the International Standard Classification of Occupations (ISCO, version 2012) and combined into four groups: unemployed; managers, craft, service and sales workers; clerks, skilled agriculture and elementary workers; and plant operators, technicians and professionals. Occupations based on pesticide exposure included current and past agriculture work, including those who worked as a sprayer or spray operator. Behavioural risk factors measures included current smoking habits (cigarette, pipe, cannabis and methamphetamine) and hazardous drinking. The Alcohol Use Disorders Identification Test (AUDIT), a 10-item self-rating questionnaire, developed by the World Health Organisation (Saunders et al., 1993), was used to screen for hazardous drinking. We used the recommended AUDIT cut-offs of 5 for men and 3 for women to detect risky alcohol use (Johnson et al., 2013).

As HIV infection is common in South Africa (UNAIDS, 2018) and is a risk factor for suicidal behaviour, we identified positive HIV status based on self-report and/or consented review of medical records. An HIV rapid screening test was offered to participants who were unaware of their status or who self-reported an HIV-negative status. Testing was not offered if there was evidence of a positive HIV test result in the medical records. HIV status was categorised as HIV positive (a positive result documented in the medical records or a self-

reported positive result or a positive result on a rapid test); HIV negative (a negative result on a rapid screen or a negative result documented in the medical records) and declined to test.

Mental health variables included depressive symptoms, aggression and impulsivity. Depression was assessed using the Center for Epidemiologic Studies Depression Scale (CES-D). The CES-D consists of 20 questions and measures four factors: depressed affect, positive affect, somatic and retarded activity and interpersonal relations. The total score ranges from 0 to 60, and CES-D≥16 indicates an increased risk of clinical depression (Weissman et al., 1977).

Impulsivity levels were assessed with the 30-item Barratt's Impulsivity Scale (BIS-II). The BIS-II is a self-report questionnaire that measures three dimensions of impulsivity: attentional, motor and non-planning impulsiveness (Patton et al., 1995). Attentional impulsivity assesses the ability to focus or concentrate; motor impulsivity assesses the tendency to act without thinking and non-planning impulsivity measures the lack of future orientation or forethought. A total score of 72 or more indicates high impulsivity (Stanford et al., 2009).

Participants completed the short form of the Buss-Perry Aggression Questionnaire (BPAQ-SF) to assess their level of aggression (Bryant and Smith, 2001). The BPAQ-SF is a 12-item self-report scale, shortened from the original 29-item BPAQ, that assesses four dimensions of aggression: physical aggression, verbal aggression, anger and hostility (Bryant and Smith, 2001). Higher scores indicate higher levels of aggressive behaviour. As no formal cut-off score has been established for the short form of the BPAQ, we applied a cut-off of 33 (median of the total sample) to categorise respondents as having higher versus lower levels of aggression.

Sexual minorities are at increased risk of suicidal behaviour (Hottes et al., 2016). We used the Sexual Orientation Identity scale, a 14-item self-report questionnaire, to measure the sexual orientation identity of participants by the following four factors: orientation to females, orientation to males, heterosexual identity, and LGB identity (Worthington and Moreno, 2005). Each item has a Likert scale ranging from 1 (never) to 6 (always), and participants rated themselves on questions relating to sexual arousal, sexual attraction, sexual fantasies, sexual behaviour, and romantic relationships.

Controls were screened for suicidal ideation with Beck's Scale for Suicidal Ideation (SSI) to identify potential misclassification. The SSI is a 19-item self-report questionnaire designed to assess suicidal intention (Beck et al., 1979). Each item consists of three alternative statements graded in intensity from 0 to 2. The higher the total score, the greater the severity of suicide ideation. During the pilot study, controls experienced distress when answering questions about suicide. The SSI was shortened, and participants were asked to complete only the first four questions: "How strong is your wish to live?" (0=moderate to strong, 1=weak, 2=none); "How strong is your wish to die?" (0=none, 1=weak, 2=moderate to strong); "What is stronger your wish to live or die?" (0=for living outweighing dying, 1=about equal, 2=for dying outweighing living) and "How strong is your desire to make an active suicide attempt?" (0=none, 1=weak, 2=moderate to strong). SSI≥6 was used to indicate clinically significant suicidal ideation (Sokero et al., 2003). We characterised two groups of controls as being at risk of attempting suicide: those who reported a *weak or moderate to strong desire* to make an active suicide attempt and those with a total score of more than 6 (SSI≥6).

All instruments demonstrated adequate internal consistency. The Cronbach's alpha of the CES-D, BIS-II, BPAQ-SF, AUDIT and Sexual Orientation Identity Scale was 0.92, 0.80, 0.82, 0.91 and 0.90, respectively.

3.3.3 OP pesticide exposure assessment

OP exposure was measured using self-reported environmental and occupational history and measurement of non-selective OP metabolites in hair samples. Participants provided information on the lifetime use of pesticides, including the name of the pesticides, what it was intended for, and the frequency (intermittent, such as seasonal or continuous) and duration (none, less than a year and one year or more) of use. Where participants were unsure of the commercial name of the pesticide, participants provided descriptions of the products used. Based on the pesticide product name, description and active ingredient, we categorised the pesticides as likely OP, unlikely and unsure. Participants were asked if they lived near a farm or worked on a farm where pesticides were sprayed and if they were ever poisoned by pesticides.

OP metabolites were measured in hair samples from a sub-sample of 56 cases and 44 controls (25% of the study sample). Approximately 100g of hair, cut close to the scalp from the nape of the neck, was analysed for three dialkyl phosphate (DAPs) metabolites: dimethyl phosphate (DMP), dimethyl thiophosphate (DMTP) and diethyl phosphate (DEP). The quantification of the three DAP metabolites followed a decontamination step, solid-liquid extraction, followed by liquid-liquid extraction, and analysis by liquid chromatography-mass spectrometry. DAPs are non-specific biomarkers of OP exposure (because they are potential metabolites of most OPs) and are used for the assessment of cumulative OP exposure (Kavvalakis and Tsatsakis, 2012). Levels of detection limits were 20 pg/mg for DMP, DEP and DMTP.

A sample size calculation was performed assuming a measure of effect of 1.8 (Stallones, 2006) and a DAP metabolite exposure prevalence of 25% (based on reports of the USA population where the detection of DAP metabolites ranged from 25% to 50%) (Barr et al., 2004), generating a sample size of 199 cases and 199 controls.

3.3.4 Data analysis

Data were analysed using Stata statistical software, release 15 (College Station, TX). All measures were tested for normality using the Shapiro-Wilk test. Total AUDIT, BPAQ-SF and CES-D scores were not normally distributed and were summarised using median and interquartile range (IQR) and compared using Mann-Whitney tests. The total BIS-II (impulsivity) score was normally distributed and was summarised using mean and standard deviation (SD) and tested using the Student's t-test. Associations between behavioural measures were measured using Spearman's correlation coefficient.

Total DAP metabolites are the sum of DEP and DMP levels. Hair DEP, DMP and DAP concentrations were not normally distributed and summarised using median and IQR (expressed in pg/mg) and compared using the Mann-Whitney test. Because many hair DAP levels fell below the level of detection (LOD), it was transformed into a dichotomous variable to assess the presence (1; above the LOD) and absence (0; below the LOD) of metabolites.

We investigated suicide risk with OP exposure in two separate models, using self-reported OP exposure history (n=400) and the presence or absence of hair DAP metabolite levels (n=100), using multivariable conditional logistic regression analysis by estimating the odds ratios (OR) and 95% confidence intervals (CI). Age and sex were not included in the model as this was accounted for by matching cases and controls. Possible confounding variables (described in Table 3.1) included education level, home language, income, occupation group, number of people living in the household (as a measure of social connection), HIV status, alcohol use and smoking history. We did not consider depression, aggression and impulsivity as potential confounders as they may be in the causal pathway. We evaluated all covariates associated with suicide as potential confounders ($p<0.10$). We conducted manual forward selection model building to identify variables to include in the multivariate analyses using likelihood ratio tests ($\alpha=0.05$) and the lowest Akaike's information criterion (AIC) (Model

A). Model-checking and diagnostics confirmed the best choice of model. The Hosmer-Lemeshow test was used to assess the fit of the model (Hosmer Jr et al., 2013). The level of significance was set at 0.05. In the sensitivity analysis, we removed controls who reported at least a weak desire to make an active suicide attempt (Model B) and controls with a total SSI score ≥ 6 (Model C).

Ethical approval was obtained from the University of Cape Town's Health Science Faculty Human Research Ethics Committee (Ref: 393/2014). All participants gave informed written consent. Participants who were found to be HIV positive on the rapid screening test were referred for further management.

3.4 Results

Characteristics of the cases (n=200) and controls (n=200) are summarised in Table 3.1. On average, participants were 29 years old, ranging from 18 to 59 years, and 68% were women. Among the cases, the majority (73%) had reached secondary level education, 4% were unemployed with no household income, and 47% were current cigarette smokers. Among the controls, 82% reached secondary level education, 1% were unemployed with no household income, and 33% were current cigarette smokers. There were only two current farmworkers in the study population and both were (attempted suicide) cases. There were no significant differences in education levels, home language, presence of any income, occupation groups, current or past agriculture work or HIV status between cases and controls.

Table 3.1 Description of the study sample overall and by attempted suicide cases and matched hospital controls

Characteristic	***Total (n=400)***	***Cases (n=200)***	***Controls (n=200)***	***p-value***
Sociodemographics				
Median age in years (IQR)	29 (18-59)	28 (18-58)	29 (18-58)	0.736
n (%) Age group				
18-29	209 (52.3)	106 (53.0)	103 (51.5)	
30-39	90 (22.5)	42 (21.0)	48 (24.0)	
40-49	68 (17.0)	36 (18.0)	32 (16.0)	
50 years and older	33 (8.2)	16 (8.0)	17 (8.5)	0.871
n (%) Female	270 (67.6)	135 (67.5)	135 (67.5)	0.972
Education level reached				
Primary level or no formal education	28 (7.0)	19 (9.5)	9 (4.5)	
Secondary level education	308 (77.0)	145 (72.5)	163 (81.5)	
Tertiary level education	64 (16.0)	19 (9.5)	28 (14.0)	0.064
n (%) Home language				
Afrikaans	187 (46.8)	102 (51.0)	85 (42.5)	
IsiXhosa	131 (32.8)	64 (32.0)	67 (33.5)	
English	46 (11.5)	20 (10.0)	26 (13.0)	
Shona	9 (2.3)	3 (1.5)	6 (3.0)	
Other, e.g., Zulu, French	27 (6.8)	11 (5.5)	16 (8.0)	0.343
Median number of people in household (IQR)	4.0 (1-11)	3.5 (1-10)	4.0 (1-10)	0.034
n (%) Lives alone	40 (10.0)	25 (12.5)	15 (7.50)	0.096
n (%) Employed in the past 12 months	254 (63.5)	124 (62.0)	130 (65.0)	0.584
n (%) Presence of any income				
Any employment	251 (62.7)	122 (61.0)	129 (64.5)	
Unemployed and other sources of income	140 (35.0)	70 (35.0)	70 (35.0)	
Unemployed with no income	9 (2.3)	8 (4.0)	1 (0.5)	0.060
Occupation group				
Unemployed	149 (37.3)	78 (39.0)	71 (35.5)	
Managers, craft, service and sales workers	94 (23.5)	38 (19.0)	56 (28.0)	
Clerks, skilled agriculture and elementary workers	94 (23.5)	48 (24.0)	46 (23.0)	
Plant operators, technicians and professionals	63 (15.7)	36 (18.0)	46 (13.5)	0.164
Current or past agriculture work	60 (15.0)	31 (15.5)	27 (15.5)	0.779
Smoking habits				
Current cigarette smoker (%)	160 (40.0)	94 (47.0)	66 (33.0)	0.004
Cannabis (%)	30 (7.5)	18 (9.0)	12 (6.0)	0.261

Methamphetamine (%)	9 (2.2)	5 (2.5)	4 (2.0)	0.724
Pipe tobacco (%)	3 (0.8)	1 (0.5)	2 (1.0)	0.559
HIV status				
HIV positive (%)	48 (12.0)	20 (10.0)	28 (14.0)	
HIV negative (%)	273 (68.2)	141 (70.5)	132 (66.0)	
Declined (%)	79 (19.8)	39 (19.5)	40 (20.0)	0.440

The prevalence of depression, impulsivity, aggression and hazardous drinking by cases and controls are summarised in Table 3.2. Participants who attempted suicide had a higher prevalence of depression (87.0% vs 46.5%, $p < 0.001$), aggression (62.5% vs 40.0%) and hazardous drinking (53.0% vs 39.0%, $p=0.005$) than hospital controls. While the prevalence of impulsivity was high among cases (71.5%) and controls (73.0%), there was no significant difference between the groups. Similarly, there was no difference in sexual orientation identity scores between groups.

Table 3.2 Prevalence of depression (CES-D), impulsivity (BIS-II), aggression (BPAQ-SF) and hazardous drinking (AUDIT) by cases and controls

Characteristic	***Total*** ***n = 400***	***Cases*** ***n = 200***	***Controls*** ***n = 200***	***p-value***
Median total depression (CESD) score (IQR)	24.5 (0-56)	34.0 (3-55)	14 (0-51)	< 0.001
n % Depression (CESD ≥ 16)	267 (66.8)	174 (87.0)	93 (46.5)	< 0.001
Mean total impulsivity score ± SD	74.6 ± 5.4	74.7 ± 5.8	74.7 ± 5.1	0.859
n % Impulsivity (BIS-II ≥ 72)	289 (72.3)	143 (71.5)	146 (73.0)	0.761
Median total aggression (BPAQ-SF) score (IQR)	33.0 (12-64)	36.0 (14-64)	30.0 (12-56)	< 0.001
n % Aggression (BPAQ-SF ≥ 33)	205 (51.3)	125 (62.5)	80 (40.0)	< 0.001
Median AUDIT sum score (IQR)	2 (0-34)	5 (0-32)	1 (0-27)	< 0.001
n % Hazardous drinking	184 (46.0)	106 (53.0)	78 (39.0)	0.005
Median Sexual Orientation Identity Scale score (IQR)				
Orientation towards females	5 (0-30)	5 (4-30)	5 (0-30)	0.988
Orientation towards males	19 (0-30)	19.5 (5-30)	19 (0-30)	0.897
LGB identity	2 (0-12)	2 (2-12)	2 (0-12)	0.984
Heterosexual identity	12 (0-12)	12 (2-12)	12 (0-12)	0.234

We identified two groups of controls who may have been misclassified: 20 participants (10%) who reported a weak or moderate to strong desire to make an active suicide attempt and 13 participants (6.5%) who had a total SSI score ≥ 6. All participants in the latter group also expressed at least a weak desire to make an active suicide attempt.

Approximately 5% (17/341) of participants who applied pesticides in the garden and home likely used OP pesticides. We examined the relationship between attempted suicide and the type of pesticide reported as likely OP, unlikely and unsure, and found no difference between cases and controls (p=0.558). Table 3.3 compares the reported environmental and occupational pesticide exposure by cases and controls. Reported household and garden pesticide use was higher among controls than cases (p=0.067), and more pesticides were used in homes than in gardens. There were no significant differences in reported environmental and occupational pesticide exposure and attempted suicide. A history of occupational exposure was infrequent. Nine participants reported working as a pesticide applicator previously, and 15% (59) of participants reported previous work on a farm where pesticides were applied. Cases were twice as likely to report previous pesticide poisoning but the difference was not statistically significant.

Table 3.3 Summary of reported environmental and occupational pesticide exposure by cases and controls

General pesticide exposure	**Total**		**Cases**		**Controls**		**p-value**
	n = 400		**n = 200**		**n = 200**		
Pesticide use in home/garden							
No (%)	59	(14.8)	36	(17.9)	23	(11.5)	
Yes (%)	341	(85.2)	164	(82.1)	177	(88.5)	0.067
Pesticide use in the home							
No (%)	68	(17.0)	41	(20.4)	27	(13.5)	
Yes (%)	332	(83.0)	159	(79.6)	173	(86.5)	0.066
Pesticide use in the garden							
No (%)	356	(87.3)	178	(89.1)	178	(89.0)	
Yes (%)	44	(12.7)	22	(10.9)	22	(10.0)	0.986

Duration of pesticide use							
None (%)	59	(14.9)	38	(18.9)	26	(13.0)	
Months (%)	82	(20.8)	33	(16.4)	49	(24.5)	
≥ 1 year (%)	254	(64.3)	130	(64.7)	125	(62.5)	0.065
Frequency of pesticide use							
Intermittent e.g., seasonal (%)	256	(64.0)	128	(64.0)	128	(64.0)	
Continuous e.g., daily, weekly (%)	144	(36.0)	72	(36.0)	72	(36.0)	0.970
Lives near or next to a farm where pesticides were sprayed							
No (%)	364	(91.0)	186	(92.5)	179	(89.5)	
Yes (%)	36	(9.0)	15	(7.5)	21	(10.5)	0.287
Worked on a farm where pesticides were sprayed							
No (%)	341	(85.0)	170	(84.6)	171	(85.5)	
Yes (%)	59	(15.0)	31	(15.4)	29	(14.5)	0.796
Worked as a sprayer or spray operator							
No (%)	391	(97.8)	195	(97.5)	196	(98.0)	
Yes (%)	9	(2.2)	5	(2.5)	4	(2.0)	0.742[#]
Ever poisoned by pesticides							
No (%)	376	(94.0)	184	(92.0)	192	(96.0)	
Yes (%)	24	(6.0)	16	(8.0)	8	(4.0)	0.095
Medical visits related to pesticide poisoning							
No (%)	400	(96.7)	191	(95.5)	196	(98.0)	
Yes (%)	13	(3.3)	9	(4.5)	4	(2.0)	0.159[#]
# Fisher exact test							

Overall, the detection of non-selective metabolites of OPs (DAPs) was low (14%), and diethyl phosphate (DEP), and dimethyl phosphate (DMP) levels were recovered in only 9% and 7% of samples, respectively. Median hair DEP and DMP metabolite concentrations were 33.59 pg/mg (IQR, 33.59-34.43) and 28.62 pg/mg (IQR, 26.57-31.75), respectively. All hair samples were below the level of detection (LOD) for DMTP. The total DAP (the sum of DEP and DMP levels) median concentration was 0 pg/mg. Fig. 3-1 shows the distribution of these estimates. There were no differences in the hair DEP, DMP and total DAP metabolite

concentrations among cases and controls (Supplemental Table 3.1).

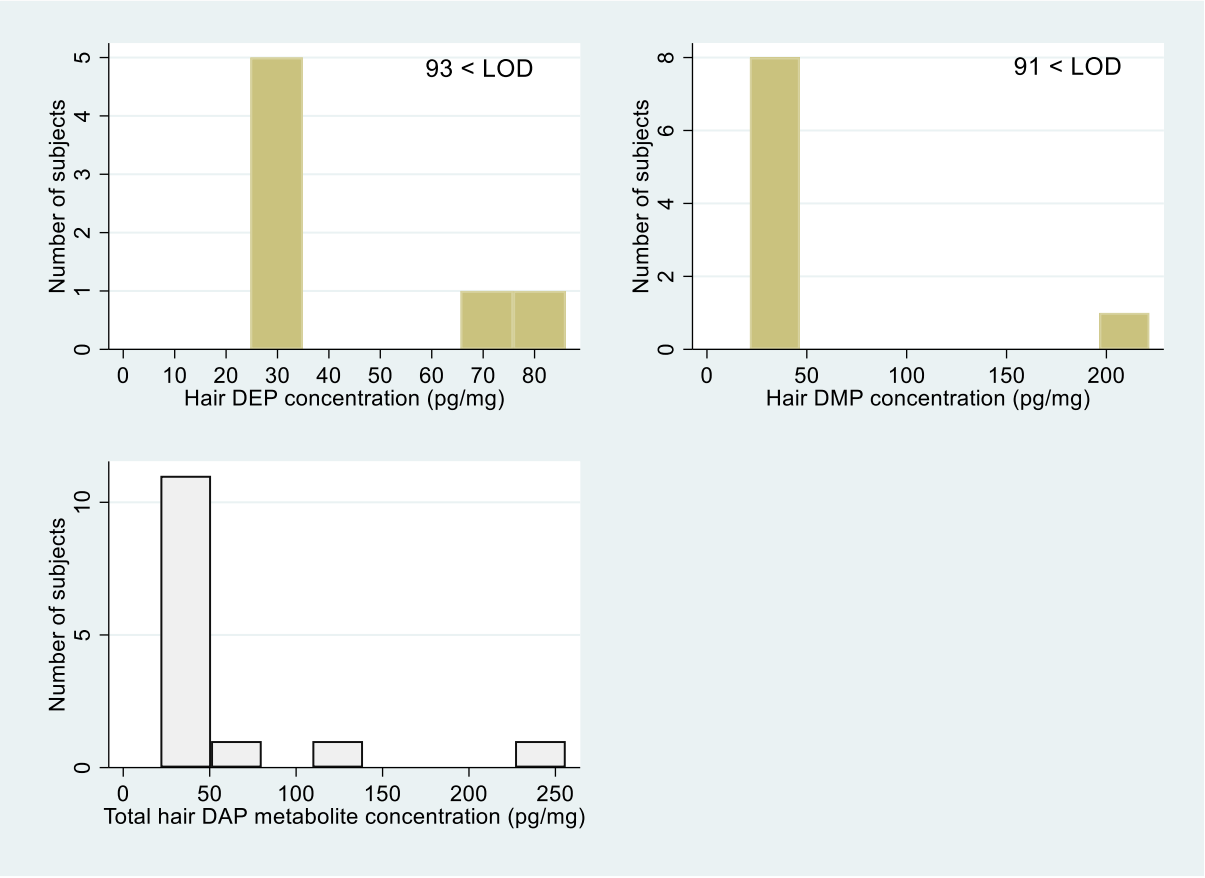


Figure 3.1 Frequency and distribution of log10-transformed DAP concentration

We found no association between attempted suicide and household and garden pesticide use (OR=0.59, 95% CI 0.33-1.04), or current or past agriculture work (OR=1.08, 95% CI 0.62-1.87) (Model A, Table 3.4). Although the crude Odds Ratio for the association between attempted suicide and a history of pesticide poisoning was 2.1, this was not statistically significant. Unemployment with no income (OR=8.39, 95% CI 1.00-70.03), and hazardous drinking (OR=1.82, 95% CI 1.20-2.76) were associated with an increased risk of attempted suicide. Sharing a house with more than three persons was associated with 50% lower odds of attempting suicide (OR=0.50, 95% CI 0.32-0.80).

In the sensitivity analysis, we excluded 20 (10%) controls who expressed a weak or moderate to strong desire to make a suicide attempt (Model B). The associations found appeared

similar to those for the whole sample, confirming no association between OP pesticide exposure and attempted suicide. A further sensitivity analysis, excluding 13 controls who reported suicidal ideation (SSI ≥ 6) (Model C), did not substantially change the risk factors associated with suicide attempts for the whole sample. This suggests that if misclassification of the disease outcome were present, it is unlikely to affect the ability to detect associations between the risk factors and suicide.

In a separate analysis of 100 participants who provided hair samples (22% of cases and 28% of controls), we also found no association between attempted suicide and a qualitative measure of DAP metabolites (presence/absence) (OR=1.00, 95% CI 0.98-1.02).

Further analyses of behavioural variables among the controls, found a moderate correlation between suicidal ideation and aggression levels (Spearman rho=0.32, p<0.001, n=200). The strength of the relationship weakened but remained significant when 20 controls expressed at least a weak desire to make a suicide attempt (Spearman rho=0.20, p=0.008, n=180) and when 13 controls who reported suicidal ideation i.e., SSI≥6 (Spearman rho=0.25, p<0.001, n=187) were excluded from the analysis.

There was no association between attempted suicide and current or past agriculture work. In a separate multivariate analysis examining the association between occupation groups and attempted suicide (Supplemental Table 3.2), unemployed participants (OR=1.87, 95% CI 1.08-3.15) were at increased risk of attempted suicide compared to managers, craft and service and sales workers. Plant operators, technicians and professionals (OR=1.75, 95% CI 0.96-3.18) and clerks, agriculture and elementary workers (OR=1.87, 95% CI 0.96-3.63) were associated with an increased risk of attempted suicide, at 10% level of significance. Further analyses showed no significant association between sexual orientation identity and attempted suicide (Supplemental Table 3.3).

We tested for a moderation/mediation effect between hazardous drinking and unemployment status. We found no evidence of an interaction between hazardous drinking and unemployment/presence of income (Supplementary Table 3.4).

- Model A, n=400, unemployed_with_other_income*hazard.drink: adjOR=1.27, 95% CI 0.62-2.56, p=0.531).
- Model B, n=380, unemployed_with_other_income*hazard.drink: adjOR=1.61, 95% CI 0.75-3.44, p=0.222).
- Model C, n=387, unemployed_with_other_income*hazard.drink: adjOR=1.56, 95% CI 0.74-3.30, p=0.243).

Table 3.4 Factors associated with attempted suicide in the total sample (Model A) and sensitivity analyses (Model B, Model C)

Characteristic	n	%	Model A (n= 400)				Model B (n = 380)		Model C (n = 387)	
			Crude OR (95% CI)	p-value	Adjusted OR (95% CI)	p-value	Adjusted OR (95% CI)	p-value	Adjusted OR (95% CI)	p-value
Number of people living in a household										
< 3	106	(26.5)	Reference		Reference		Reference		Reference	
≥ 3	394	(73.5)	0.51 (0.32-0.80)	0.003	0.50 (0.32-0.80)	0.004	0.45 (0.27-0.73)	0.001	0.46 (0.29-0.76)	0.002
Presence of any income										
Any employment	251	(62.8)	Reference		Reference		Reference		Reference	
Unemployed and other sources of income	140	(35.0)	1.06 (0.70-1.59)	0.791	1.18 (0.77-1.82)	0.452	1.37 (0.87-2.15)	0.174	1.32 (0.84-2.06)	0.222
Unemployed with no income	9	(2.3)	8.46 (1.04-68.64)	0.046	8.39 (1.00-70.03)	0.049	7.96 (0.94-67.27)	0.057	8.16 (0.97-68.88)	0.053
Hazardous drinker										
No	216	(54.0)	Reference		Reference		Reference		Reference	
Yes	184	(46.0)	1.76 (1.18-2.62)	0.005	1.82 (1.20-2.76)	0.005	2.15 (1.39-3.31)	0.001	2.09 (1.37-3.22)	0.001
Pesticide use in home/garden										
No	59	(14.7)	Reference							
Yes	341	(85.3)	0.59 (0.33-1.04)	0.069						
Ever poisoned by pesticides										
No	376	(94.0)	Reference		Reference		Reference		Reference	
Yes	24	(6.0)	2.09 (0.87-4.99)	0.098	1.61 (0.66-3.96)	0.304	1.86 (0.74-1.94)	0.450	1.96 (0.72-5.29)	0.184

Model fit: (A) Hosmer-Lemeshow X^2 (7,9) = 7.87, p = 0.446; (B) Hosmer-Lemeshow X^2 (8,10) = 4.19, p = 0.839; (C) Hosmer-Lemeshow X^2 (8,10) = 2.43, p = 0.838

3.5 Discussion

We aimed to investigate the association between OP exposure and attempted suicide in adults. We found no evidence that attempted suicide was associated with environmental or occupational pesticide use in an urban South African population attending an emergency centre. The absence of an association was found when OP exposure was measured by self-reported exposure history as well as hair DAP metabolite levels. Findings from the sensitivity analysis that accounted for potential misclassification of the suicidal behaviour among the controls gave similar patterns of association between OP pesticide exposure and attempted suicide. Attempted suicide was associated with hazardous drinking and unemployment with the absence of an income. Current or past agriculture work was not associated with attempted suicide. In this sample, only two participants were current skilled agricultural workers and both were cases. However, these differences were not statistically significant because of low numbers; similarly, the crude Odds Ratio suggesting an increased risk of suicide for those with a history of pesticide poisoning (OR=2.1) was not statistically significant because of low study power, due to very low numbers reporting previous pesticide poisoning (24/400, 6%). In addition, these pesticides may not have been OP-based.

Nonetheless, several epidemiological studies investigating the association between OP pesticide exposure and suicidal behaviour have targeted agricultural or rural communities where exposure to pesticides was occupational rather than the general population (London et al., 2005, MacFarlane et al., 2011, Freire and Koifman, 2013). With the high prevalence of reported household and garden pesticide use, many exposures, which are traditionally associated with farming, are becoming more commonplace in the urban environment (Roomaney et al., 2012, Tolosana et al., 2009). Despite this, we reported low detection levels of OP pesticide metabolites. Hair DAP levels reported in this study were similar to the

median DAP concentrations reported in a rural Sri Lankan population (Knipe et al., 2016) and lower than those reported in a study of the general population in Greece which ranged from 40 to 165 pg/mg (Tsatsakis et al., 2010). Exposure misclassification may have been introduced if participants could not name the pesticides used in the home, which may not have been organophosphate-based.

We discussed the associations found between suicide and the following variables: hazardous drinking, lack of income and income, and proposed possible explanations for these associations. Hazardous alcohol consumption is a significant risk factor for suicide attempts and death, as suicide attempts are often unplanned or impulsive (Pompili et al., 2010). South Africa has the highest hazardous drinking prevalence (37%) compared to six other countries; South Africans drink less frequently but consume the highest quantity of alcohol (Chaiyasong et al., 2018). Both hazardous alcohol consumption and aggression are recognised risk factors for suicide (Pompili et al., 2010), and the consistency with the literature found in this study suggests the outcome measures were consistently and validly applied. Though we found no direct association between impulsivity and suicide, aggression is often comorbid with alcohol dependence (Pompili et al., 2010) and other personality traits such as anger and impulsivity (Critchfield et al., 2004).

The strongest OR in our study was the association between suicide risk and unemployment with no income as a marker of extreme poverty (OR approximately 8.39), a finding supported in previous studies (Iemmi et al., 2016). Among those employed, we found that plant operators, technicians and professionals were at higher risk of attempting suicide compared to managers, craft and service and sales workers. The variation in suicide risk may partly be explained by debt, poor physical health, and risk of injury (Agerbo et al., 2007, Windsor-Shellard and Gunnell, 2019). Workplace programs that promote mental and physical wellness

may be key to suicide prevention efforts. Our results may be confounded by public-private hospital bias, where professionals and technicians who are more likely to attend private healthcare are sent to public hospitals for life-threatening psychiatric emergencies, such as attempted suicide. Further investigation is needed to determine the role of occupation in suicide as well as the effect of hospital bias.

Limitations

There are limitations to this study. As the data were collected from patients attending two public health sector hospitals in the Western Cape Province in South Africa, the results might not be readily generalisable to other patient populations across the country, including those not presenting to healthcare services. In particular, the low representation of agricultural workers in the sample may undercount those occupations most exposed. The measurement of OP pesticide exposure in hair was meant to account for all routes of exposure but the utility of this measure was limited by the low proportion of participants willing to donate hair (25%) which likely reduced the power of the analysis and forced us to rely on self-report measures vulnerable to potential biases. While collecting hair samples for the measurement of OP metabolites was reportedly easily achievable in other populations (Knipe et al., 2016, Tsatsakis et al., 2010), this was not seen in our study population. Cultural preferences and concerns regarding the potential for hair to be used for "witchcraft" practices may have influenced low hair sample donation (Salmen, 2009). Additional challenges in obtaining hair samples included very short or shaven hairstyles and the use of "weaves" added to natural hair. The use of alternative biomarkers such as urine DAPs metabolites may have increased the power of the analysis but would have reflected a shorter OP exposure time. We did not collect information on the means of a suicide attempt. Thus, we were unable to identify individuals with chronic exposure to OP from the subgroup with acute pesticide poisoning

i.e., those who used pesticides as a means of attempting suicide. Therefore, future studies should include the means of a suicide attempt and possibly alternative biomarkers such as urine DAPs metabolites to identify individuals with chronic OP exposure from those with acute pesticide poisoning. While we found no association between OP pesticide exposure and suicide, this study highlights the need to develop feasible approaches, other than hair samples, to assess long-term pesticide exposure in our population.

Potential exposure misclassification may have been introduced if the pesticide exposure reported included agents that are not neurotoxic or related to affective changes. Misclassification of suicidal behaviour in the controls may also have impacted the results. We initially experienced difficulty when screening for potential suicidal ideation among the controls who reported distress when answering the full SSI. We responded to the ethical dilemma by allowing controls to complete a shortened questionnaire. The sensitivity analyses, however, revealed no substantial change in patterns of associations between risk factors and attempted suicide. Therefore, it seems unlikely that potential suicidal ideation among the controls would explain the lack of a significant association between OP exposure and attempted suicide. Lastly, the study did not take into account past suicide attempts and the method used to attempt suicide which should be considered for future research.

3.6 Conclusion

To the best of our knowledge, this is the first study to investigate the association of occupational and domestic OP exposure with suicidal behaviour in an urban setting. We did not show any positive associations between OP exposure and suicide risk, though the analyses were limited by low study power. This study highlights the need to develop feasible alternatives to hair samples, to assess long-term pesticide exposure in our study population.

Clinical assessments of suicide risk to address current and repeat events could include items of hazardous drinking to identify groups at increased risk of suicide.

Supplemental Table 3.1 Summary of hair DAP concentrations (pg/mg) above the level of detection (n=100)

Metabolite	**Group**	**n**	**% Detection frequency**	**p-value***	**Mean (SD)**	**Median**	**IQR**	**p-value****
DEP	Case	56	5.5		0	0	0	
	Control	44	9.1	0.486	0.57 (3.79)	0	0	0.889
DMP	Case	56	10.7		2.32 (8.84)	0	0	
	Control	44	6.8	0.498	6.44 (30.42)	0	0	0.657
DMTP	Case	56	0		< LOD	< LOD		
	Control	44	0	0	< LOD	< LOD		
DAP	Case	56	-		7.07 (21.68)	0	0-31.75	
	Control	44	-		8.09 (35.03)	0	0-28.84	0.908

dialkyl phosphate (DAP), dimethyl phosphate (DMP), dimethyl thiophosphate (DMTP) and diethyl phosphate (DEP) metabolites; level of detection limits (LOD); DAP = DEP + DMP

* Two-sample test of proportions

**Mann-Whitney test

Supplemental Table 3.2 Factors (including occupation group) associated with attempted suicide

Characteristic	n	%	Crude OR (95% CI)	p-value	Adjusted (95% CI)	p-value
Number of people living in a household						
< 3	106	(26.5)	Reference		Reference	
≥ 3	394	(73.5)	0.51 (0.32-0.80)	0.003	0.48 (0.30-0.77)	0.002
Occupation						
Managers, craft and service and sales workers	94	(23.5)	Reference		Reference	
Unemployed	149	(37.3)	1.62 (0.96-2.73)	0.071	1.87 (1.08-3.15)	0.025
Clerks, agriculture and elementary workers	94	(23.5)	1.53 (0.86-2.74)	0.144	1.75 (0.96-3.18)	0.066
Plant operators, technicians and professionals	63	(15.7)	1.97 (1.02-3.75)	0.041	1.87 (0.96-3.63)	0.064
Hazardous drinker						
No	216	(54.0)	Reference		Reference	
Yes	184	(46.0)	1.76 (1.18-2.62)	0.005	1.85 (1.21-2.82)	0.004
Pesticide use in home/garden						
No	59	(14.7)	Reference			
Yes	341	(85.3)	0.59 (0.33-1.04)	0.069		
Ever poisoned by pesticides						
No	376	(94.0)	Reference		Reference	
Yes	24	(6.0)	2.09 (0.87-4.99)	0.098	1.56 (0.63-3.85)	0.427

Supplemental Table 3.3 Association between attempted suicide and sexual orientation identity scale

Characteristic	**Median (IQR)**	**SD**	**Adjusted OR* (95% CI)**	**p-value**
Sexual orientation identity scale				
Orientation towards females (IQR)	11.41	9.49	0.97 (0.92-1.01)	0.128
Orientation towards males (IQR)	17.11	9.89	0.99 (0.96-1.03)	0.791
LGB identity (IQR)	10.41	2.76	1.01 (0.96-1.12)	0.833
Heterosexual identity (IQR)	2.37	1.56	0.96 (0.82-1.13)	0.606

* Adjusted for hazardous drinking, presence of any income, number of people living in a household and occupation group

Supplemental Table 3.4 Factors associated with attempted suicide in the total sample (Model A) and sensitivity analyses (Model B, Model C) with interaction terms

Characteristic	Model A (n= 400)		Model B (n = 380)		Model C (n = 387)	
	Adjusted OR (95% CI)	**p-value**	**Adjusted OR (95% CI)**	**p-value**	**Adjusted OR (95% CI)**	**p-value**
Number of people living in a household						
< 3	Reference		Reference		Reference	
≥ 3	0.51 (0.32-0.81)	0.004	0.47 (0.27-0.73)	0.005	0.48 (0.29-0.79)	0.004
Presence of any income						
Any employment	Reference		Reference		Reference	
Unemployed and other sources of income	1.46 (0.77-1.82)	0.186	1.57 (0.87-2.15)	0.174	1.62 (0.91-2.88)	0.174
Unemployed with no income	6.11 (1.00-57.33)	0.113	6.02 (0.94-67.27)	0.057	5.88 (0.62-55.35)	0.057
Hazardous drinker						
No	Reference		Reference		Reference	
Yes	1.11 (1.20-2.76)	0.486	1.58 (0.89-3.31)	0.226	1.64 (0.76-3.50)	0.207
Interaction term (base: any employment)*						
Unemployment and other sources of income x hazardous drinking	1.27 (0.62-2.56)	0.531	1.61 (0.75-3.44)	0.222	1.56 (0.74-3.30)	0.243
Ever poisoned by pesticides						
No	Reference		Reference		Reference	
Yes	1.63 (0.66-4.03)	0.290	2.05 (0.76-5.55)	0.156	1.94 (0.38-3.01)	0.193

* Interaction term unemployment with no income x hazardous drinking only had 4 observations and was dropped from the analysis.

Chapter 4 The shared genetic architecture of suicidal behaviour and psychiatric disorders: a genomic structural equation modelling study

Kootbodien T, London L, Martin LJ, Ramesar RS. Exploring the shared genetic architecture of suicidal behaviour and psychiatric disorders: a genomic structural equation modelling study. *Frontiers in Genetics*, 2023 March 7:14.

Contributions of co-authors and candidate:

TK, RR and LL conceptualized the study. TK conducted the analyses, lead the data interpretation and drafted the manuscript. Co-authors RR, LJM and LL reviewed the draft and made conceptual and intellectual contributions in specific areas of their expertise. All authors read and approved the final manuscript.

This paper addresses the third study objective of this thesis and expands the investigation of risk factors of suicidal behaviour to include an exploratory analysis of the genetic architecture of suicidal behaviour. This chapter is presented in two parts: the first part reviews the literature of genome-wide association studies (GWAS) of suicidal behaviour and the second part is the published paper that demonstrates significant genetic relationships between suicidal behaviours (ideation, attempt and self-harm and suicide death) and previously implicated psychiatric disorders.

4.1 Literature review

Fourteen studies describing associated genes and single nucleotide polymorphisms (SNPs) were summarised in Table 4.1. Only three out of the 14 GWA studies included participants who died by suicide. A search was performed in PubMed for original research articles published before the end of May 2022. We combined the search strategy of free-text terms and Medical Subject Headings (MeSH) controlled vocabulary for suicidal behaviour: "suicidal ideation", "suicide, attempted", "suicide, completed", "suicide" (separated by OR) with the terms "genetics" and "genome-wide association studies". Articles published in English were selected and included groups with fatal and non-fatal suicidal behaviour.

Early genome-wide assessments of suicidal behaviour (six GWA studies before 2018) in patients with psychiatric disorders either found no association, reported suggestive findings ($p<5x10^{-6}$) or significant associations that could not be replicated. This was most likely due to small sample sizes as studies were underpowered to detect small effect sizes. An investigation of 1,295 bipolar patients and 176 depression patients with a history of attempted suicide showed an association between a variant (rs2576377) in the *ABI3BP* gene and attempted suicide in individuals with depression but these findings could not be replicated (Perlis et al., 2010). Schosser and colleagues (2011) found no association with either attempted suicide or suicidal ideation in a genome-wide study of 2023 participants with major depressive disorder. Suggestive evidence of an association was reported for the *GFRA1* (rs4751955) gene in individuals with an increased suicidal score, and the *KIAA1244* (rs203136) gene in individuals with a history of attempted suicide; however these findings could not be replicated (Schosser et al., 2011). Willour and colleagues (2012) subsequently compared 1,201 bipolar patients with a history of attempted suicide with 1,497 bipolar

Table 4.1 Summary of genome-wide association studies on suicidal behaviour

Reference	**Main outcome**	**Ancestry**	**Psychiatric diagnoses N (cases)**	**Findings (significant / suggestive)**
Perlis et al., 2010	SA	EUR	BPD: 3117 (1295) MDD: 1273 (176)	Significant; MDD: *ABI3BP* (rs2576377); Could not replicate
Schosser et al., 2011	SS, SA	EUR	MDD: 2023 (251)	Suggestive; SS: *GFRA1* (rs4751955); SA: *KIAA1244* (rs203136n); Could not replicate
Willour et al., 2012	SA	EUR	BPD: 2698 (1201)	Significant; 2p25, *ACP1*, *SH3YL1*, *FAM150B* (rs300774)
Mullins et al., 2014	SA, SI	EUR	MDD: 3304 (827) BPD: 440 (69)	no SNPs of genome-wide significance; Suggestive; *HK2* (rs17010519), *NYAP2* (rs2030199)
Galfalvy et al., 2015	SA, SD	EUR	MDD/BPD: 1810 (577) SA: 260; CS: 317	Suggestive; SA: *DPP10* (rs4308128, rs1374268), *STK32B* (rs1530609), *CTNNA3* (rs10997260) Suggestive: CS: *TBX20* (rs336284, rs2240994, rs17675131, rs4723402, rs2109090, rs320461, rs990633, rs12538684)
Zai et al., 2015	SS, SA	EUR	BPD: 1123 (959)	Suggestive; *IL7* (rs10448042, rs10448044), *TMX3* (rs3851150, rs7244261)
Erlangsen et al., 2018	SA	EUR	MDD: 6024; Controls: 44240	Significant; *PDE4B* (rs4554696)
Mullins et al., 2019	SA	EUR	MDD: 10408 (1622); BPD: 8764 (3264); SCZ: 4629 (2946)	Significant; MDD: *ARL5B* (rs45593736); BPD: chr4_23273116_D; Could not replicate
Levey et al., 2019	SA	EUR, AFR	SA: 1131; Controls: 5189	Significant; *ARNTL2-AS1* (rs683813), *LDHB* (rs1677091), Chr 18 (rs72740082), *FAH* (rs72740082)
Strawbridge et al., 2019	SA	EUR	122 935	Significant; *ZCCHC7* (rs62535711), *CNTN5* (rs598046), rs7989250 locus on chr 13
Otsuka et al., 2019	SD	EA	CS: 746; Controls: 14049	Suggestive; Age: *GTF2IRD1* (rs73135307)
Docherty et al., 2020	SD	EUR	CS: 3413; Controls: 14810	Significant: Chr 13 (rs34399104, rs35518298, rs34053895, rs66828456, rs35502061), Chr 15 (rs35256367)
Coon et al., 2020	SA	EUR	43 high-risk families	Significant: *SP110* (rs181058279), *AGBL2* (rs76215382), *SUCLA2* (rs121908538), *APH1B* (rs745918508); 207 genes implicated
Mullins et al., 2022	SA	EUR	SA: 29782, Controls:519961	Significant: intergenic region on chr 7 (rs62474683), *MHC* (rs71557378)

SA: suicide attempt; SI: suicidal ideation; SS: suicidal score; SD: suicide death; MDD: Major depressive disorder; BPD: Bipolar disorder; SCZ: Schizophrenia; Significant: a p-value lower than 1e-08; Suggestive: a p-value between 1e-07 and 1e-04; EUR: European, EA: East Asian, AFR: African American

patients with no history of suicidal behaviour. The authors reported a significant signal on chromosome 2p25 (rs300774), in an intergenic region between the genes, *SH3YL1, ACP1* and *FAM150B* (Willour et al., 2012). Two studies reported suggestive associations with suicidal behaviour (Mullins et al., 2014, Galfalvy et al., 2015). Mullins and colleagues (2014) found suggestive loci in individuals with mood disorders who attempted suicide, but none reached genome-wide significance. Galfalvy and colleagues (2015) also reported suggestive associations for the genes, *DPP10, STK32B* and *CTNNA3* in depressed individuals who attempted suicide (257 attempted suicides and 300 non-attempter controls) and seven SNPs of the *TBX20* gene (associated with brainstem motor neuron development) among 317 individuals who died by suicide. A subsequent study analysed the severity of suicidal behaviour in 959 bipolar patients and identified suggestive markers in two chromosomal regions, namely on chromosomes 8 and 10 (Zai et al., 2015).

Subsequently, larger study populations were made possible by sharing data and meta-analyses of GWA studies through networks, such as the Psychiatric Genomics Consortium, providing the advantage of greater precision and power. A Danish study found three significant SNPs (rs4809706, rs4810824 and rs6019297) on chromosome 20 associated with attempted suicide among 6,024 individuals diagnosed with a mental illness (and 44,240 healthy controls) and a significant association between *PDE4B* (rs4554696) on chromosome 1 and attempted suicide in a sub-group with depression (Erlangsen et al., 2018). Using a cohort of 6,569 individuals diagnosed with either major depression, bipolar disorder or schizophrenia from the Psychiatric Genomics Consortium (Mullins et al., 2019), the authors reported an insertion-deletion polymorphism on chromosome 4 in bipolar individuals who attempted suicide (and 17,232 control individuals with no history of suicidal behaviour). In another large GWA study of 122,935 individuals from the UK Biobank cohort, three novel genome-wide significant loci were reported for suicidality, based on self-reported measures:

ZCCHC7 (rs62535711) locus on chromosome 9, *CNTN5* (rs598046) locus on chromosome 11 and SNP rs7989250 on chromosome 13 (Strawbridge et al., 2019). In the same year, Levey and colleagues (2019) reported a significant association with suicidal behaviour among 2,439 European Americans (*LDHB*, rs1677091) and three significant markers associated with suicidal behaviour among 3,881 African-Americans with depression: *ARNTL2* on chromosome 12 (rs683813), *FAH* on chromosome 15 (rs72740082), and SNP rs11876255 on chromosome 18. In another large study of 29,782 suicide attempt cases, two significant loci were reported, the major histocompatibility complex and an intergenic region on chromosome 7, associated with a suicide attempt that was not mediated through psychiatric disorders (Mullins et al., 2022).

Three recent studies were undertaken on cohorts of fatal suicidal behaviour (Coon et al., 2020, Docherty et al., 2020, Otsuka et al., 2019). A study among 746 individuals who died by suicide and 14,049 controls in an East Asian population reported no genome-wide significant SNPs but found a suggestive association between age at suicide and *GTF2IRD1* (rs73135307) (Otsuka et al., 2019). In the largest study of 3,413 individuals with fatal suicidal behaviour in Utah, USA, Docherty and colleagues (2020) identified two genome-wide significant loci on chromosomes 13 and 15. Coon and colleagues (2020) identified 207 target genes in regions of significant familial segregation among 43 families at high risk of completing suicide from the Utah population-based study and reported four significant loci associated with increased risk of suicide (*SP110,* rs181058279; *AGBL2,* rs76215382; *SUCLA2,* rs121908538; *APH1B,* rs745918508).

Where GWAS are underpowered to detect significance, polygenic risk scores (PRS) can be applied to summarise the genetic effects of alleles with small individual effects that collectively account for a substantial proportion of variation in risk (Dudbridge, 2013).

However, studies have reported low PRS for attempted suicide of 0.4% (Mullins et al., 2019) to 0.7% (Levey et al., 2019), suggesting that these scores should not be used to predict suicide risk in clinical settings. More work is therefore needed before PRS can be used to inform personalised interventions in clinical practice related to suicidality (Lewis and Vassos, 2020).

In summary, GWA studies are powerful tools that have advanced our understanding of suicidal behaviour. Genomic data can provide insight into neurobiological mechanisms and pathogenesis of suicide and can be used to imply suicide risk. Our current understanding from the reviewed literature is that suicidal behaviour is complex and polygenic. From the review of the literature, 22 genes/SNPs were associated with suicidal behaviour (*ABI3BP* rs2576377, 2p25, *ACP1*, *SH3YL1*, *FAM150B* rs300774, *PDE4B* rs4554696, *ARL5B* rs45593736, chr4_23273116_D, *ARNTL2-AS1* rs683813, *LDHB* rs1677091, Chr 18 rs72740082, *FAH* rs72740082, *ZCCHC7* rs62535711, *CNTN5* rs598046, 6 loci on Chr 13 (rs7989250, rs34399104, rs35518298, rs34053895, rs66828456, rs35502061), Chr 15 rs35256367, *SP110* rs181058279, *AGBL2* rs76215382, *SUCLA2* rs121908538, *APH1B* rs745918508, Chr 7 rs62474683 and MHC rs71557378. The majority of genetic investigations in suicidal behaviour have been performed in populations of European ancestry and include individuals with fatal suicidal behaviour compared to non-fatal suicidal behaviour (ideation, self-harm and attempt). Therefore, replication and validation of these variants need to be undertaken in diverse populations across the spectrum of suicidal behaviour to improve precision in medical care. Thus far, genetic studies have shown promising results regarding suicide risk variants and pathways. Importantly, genomic studies are likely to reveal shared biological pathways and risk factors for a range of neuropsychiatric conditions. It seems probable, that as GWA studies become larger and more diversity is introduced in study populations, novel pathways will be discovered to provide possible

intervention targets or offer new prevention strategies. Identifying biomarkers of risk is important to develop more targeted and efficient strategies. The improved understanding that will emerge from the molecular studies can lead to improved diagnosis and prevention of those at risk of suicide.

4.2 Non-expert summary

Suicidal behaviour (SB) is a broad term used to describe a range of behaviours that include ideation, attempt, self-harm and death. Contemporary theoretical models propose an ideation-to-action framework (Klonsky and May, 2015) that suggests the development of suicidal ideation and the progression from ideation to attempts are distinct processes with distinct predictors because most individuals with suicidal ideation do not attempt suicide. In addition, these psychological models highlight the complex interaction between biological, environmental and social factors with SB. The co-occurrence of SB and psychiatric disorders is well studied in epidemiological and family studies, and previous research has shown that individuals with severe mental illness are at increased risk of SB.

The heritability of suicidal behaviour is a proportion that ranges from 0 (where genetics explains nothing about the disease/condition of interest) to 1.0 (where genetics are the only reason explaining the difference in the disease/condition) which measures the relative importance of genetic and environmental influences on the development of SB. Heritability is a population estimate that does not indicate the degree to which SB is genetic but rather is an indication of SB differences that is the result of genetic factors. The heritability of SB ranges from 38%-55% (Brent and Mann, 2005, Brent and Melhem, 2008, Voracek and Loibl, 2007), which informs us that on average, 38% to 55% of differences that we observe in SB can be attributed to genetic individual differences and corresponds to h^2 of 0.38-0.55, while the remaining 45% to 62% is explained by unique environmental factors.

Behavioural genetic studies have increasingly allowed scientists to control for confounding factors and investigate previously unobserved measures. Environmental factors are also an important determinant of suicidal behaviour. For example, a set of genes indicative of low household income can be applied in a genetics association study as a proxy for lower socioeconomic status. In this study, the identification of genetic factors associated with educational attainment and household income represents proxies for socioeconomic status.

A genome-wide association study (GWAS) is a hypothesis-free approach that involves rapidly scanning DNA sequence variations across the genome to identify genetic risk factors associated with common, complex diseases or conditions such as suicidal behaviour. In this secondary analysis of GWAS summary data, we examined the covariances among suicidal behaviours and psychiatric disorders and determined the genetic correlation between traits. Genetic correlation (rg) measures genetic similarity between two traits. It measures the extent to which the genetic effects of one trait, in this study, suicidal behaviour, overlap with the genetic effects that influence another trait, a psychiatric disorder. Genetic correlation is calculated by dividing the genetic covariance (ρ_g) by the product of the square root of the heritability of the two traits $\sqrt{(h_1^2 h_2^2)}$: rg = $\rho_g/\sqrt{(h_1^2 h_2^2)}$. Genetic correlations may be negative or positive and can range from -1.0 to 0, indicating no correlation or the traits are completely independent to +1.0, implying that the same genes influence a range of suicidal behaviours and psychiatric traits, thus indicating shared genetic aetiology. In other words, highly correlated traits (closer to 1.0) such as attempted suicide and major depressive disorder (rg=0.86), indicate that approximately 86% of the genetic factors that influence major depressive disorder, also influence suicidal behaviour. A positive genetic correlation between two traits means that shared genetic variants have an allelic effect in the same direction. For instance, the genetic factors that increase major depressive symptoms may also increase suicidal behaviour. Similarly, a negative genetic correlation implies a genetic effect in

opposite directions. We reported a negative genetic correlation between household monthly income and attempted suicide (rg=0.325). This implies the genetic factors that increase household monthly income, also decrease suicide attempts. In other words, higher household monthly income, a proxy for higher socioeconomic status, is protective against suicide attempts.

The current study aimed to offer insight into the genetic architecture of SB (suicidal ideation, attempt and self-harm), as well as the shared genetic basis between psychiatric disorders and SB. I identified genome-wide association studies (GWAS) for SB, psychiatric disorders and behavioural and socioeconomic environmental variables, and obtained summary statistics from 28 studies in total. I then performed a genomic exploratory factor analysis (EFA) to uncover the underlying genetic structure of a set of variables relating to suicidal ideation (Thought life was not worth living, TLWNL), self-harm (Ever self-harmed, ESH) and attempted suicide (SA) and seven psychiatric disorders (major depressive disorder, schizophrenia, bipolar disorder, ADHD, PTSD, anorexia, alcohol use disorder and insomnia) using genomic structural equation modelling (Genomic SEM). Applying a genomic SEM modelling approach allowed us to examine SB as a single trait that could not otherwise be measured in the sample. I explored several genomic SEM models, including one latent factor underlying SB and psychiatric disorders, a two-factor model with separate latent factors for SB and psychiatric disorders and a three-factor model that did not converge. As the model fit of the two-factor model did not improve on the single latent factor, the one-factor model that included both suicidal behaviour (suicide ideation, attempt and self-harm) and psychiatric disorders was revised and was chosen as the best fit for the data.

Findings from this analysis indicate that ideation, attempt and self-harm were strongly genetically correlated with each other and provide support for the possibility that suicidal behaviour may exist on a spectrum of behaviours from thinking of suicide to acting on these

thoughts. When examining the relationship between SB and psychiatric disorders, these constructs were not genetically distinct but rather our findings suggest a common genetic pathway to suicidal behaviour across major depression, alcohol use disorder and ADHD. However, this analysis was limited to only non-fatal SB because of the low base rate of suicide.

4.3 Abstract

Background: Suicidal behaviour (SB) refers to behaviours, ranging from non-fatal suicidal behaviour, such as suicidal ideation and attempt, to individuals who die by suicide. Despite recent advancements in genomic technology and statistical methods, it is unclear to what extent the spectrum of suicidal behaviour is explained by shared genetic aetiology.

Objectives: We explored the genetic correlation between suicidal ideation, attempt, self-harm and fatal suicidal behaviour using publicly available genome-wide association studies (GWAS) summary data and examined the relationship between SB and psychiatric disorders, anthropometric, behavioural and socioeconomic-related traits, to provide insight into pathways leading to fatal SB.

Methods: We identified nine genome-wide association statistics of suicidal behaviour (sample sizes, n, ranging from 62,648 to 125,844), ten psychiatric traits [n up to 386,533] and collectively, nine summary datasets of anthropometric, behavioural and socioeconomic-related traits [n ranging from 58,610 to 941,280]. We calculated the genetic correlation among these traits and modelled this using genomic structural equation modelling, identified shared biological processes and pathways between suicidal behaviour and psychiatric disorders and evaluated potential causal associations using Mendelian randomisation.

Results: Among populations of European ancestry, we observed strong positive genetic correlations between suicide ideation, attempt and self-harm (rg range, 0.71–1.09) and

moderate to strong genetic correlations between suicidal behaviour traits and a range of psychiatric disorders, most notably, major depression disorder (rg = 0.86, p = 1.62×10^{-36}). Multivariate analysis revealed a common factor structure for suicidal behaviour traits, major depression, attention deficit hyperactivity disorder (ADHD) and alcohol use disorder. The derived common factor explained 38.7% of the shared variance across the traits. We identified 2,951 genes and 98 sub-network hub genes associated with the common factor, including pathways associated with developmental biology, signal transduction and RNA degradation. We found suggestive evidence for the protective effects of higher household income levels on suicide attempt [OR = 0.55 (0.44–0.70), p = 1.29×10^{-5}] and while further investigation is needed, a nominal significant effect of smoking on suicide attempt [OR = 1.24 (1.04–1.44), p = 0.026].

Conclusion: Our findings provide evidence of shared aetiology between suicidal behaviour and psychiatric disorders and indicate potential common molecular mechanisms contributing to the overlapping pathophysiology. These findings provide a better understanding of the complex genetic architecture of suicidal behaviour and have implications for the prevention and treatment of suicidal behaviour.

Keywords: genetic correlation, genome-wide association study, suicidal behaviour

4.4 Introduction

Suicidal behaviour is a major public health concern. It is estimated that approximately 700,000 individuals die by suicide every year; with a global suicide rate of 9.0 per 100,000 population (WHO, 2021). According to the Global Burden of Diseases, Injury and Risk Factors Study (GBD 2019), suicidal behaviour was estimated to be responsible for nearly 34.1 million disability-adjusted life years (DALYs) globally in 2019, of which the majority

occurred in those aged 10–49 years (Vos et al., 2020, IHME). Worldwide, suicide is the fourth leading cause of death in 15-29-year-olds (WHO, 2021).

Suicidal behaviour is a broad and complex term used to describe suicidal thoughts and a range of self-injurious behaviour involving intent to die (suicide attempt, self-harm and death) (Posner et al., 2007). Attempted suicide is considered an important risk factor for subsequent suicide (Hawton et al., 2015) and is 25 to 30 times more common than fatal suicide (Schmidtke et al., 1996). The risk of death after re-attempting suicide is higher in the first year after an attempted suicide, with 2.3% of subsequent re-attempts resulting in death (Bostwick et al., 2016). While there has been substantial evidence that individuals with suicidal thoughts are at increased risk for later or subsequent suicidal ideation, attempts and death (Ribeiro et al., 2016), most individuals may never act on their thoughts (Nock et al., 2009). Previous research has explored the progression of suicidal thoughts to suicidal behaviour by applying various theories of suicide (May and Klonsky, 2016, Nock et al., 2013). Several studies have highlighted that the risk factors involved in the development of suicidal ideation are different from those who transition to suicide attempts (Nock et al., 2008, Klonsky et al., 2017). Given that suicidal behaviour is an outcome that results from many factors, and the spectrum of behaviour may reflect a continuum of suicide risk (Sveticic and De Leo, 2012), it is important to understand the pathways leading to fatal suicide. Understanding the pathways from less to severe suicidal behaviour is relevant as it provides additional opportunities for suicide prevention at different stages of risk.

Suicidal behaviour is partly genetic, with moderate heritability estimates ranging from 38-55% in adoption, twin and family studies (reviewed by Brent and Mann, 2005, Brent and Melhem, 2008, Voracek and Loibl, 2007) and 17% and 36% for suicide attempt and ideation respectively when controlling for psychiatric illness (Fu et al., 2002). It is well established that psychiatric comorbidities play an important role in the development of suicide, as

approximately 90% of individuals who die by suicide have been reported to have a diagnosed psychiatric disorder (Arsenault-Lapierre et al., 2004). Psychiatric disorders such as depression, bipolar mood disorders, schizophrenia, post-traumatic stress disorder, substance use and eating disorders have been associated with suicide (Nock et al., 2010). Suicide has also been linked to attention deficit hyperactivity disorder (ADHD) (Giupponi et al., 2018) and sleep disorders (Bernert et al., 2015). Other risk factors include smoking (Poorolajal and Darvishi, 2016), poverty (Iemmi et al., 2016) and educational disparities (Lorant et al., 2021). Moreover, SB is also included as part of the diagnostic criteria for major depression and bipolar disorders (Fehling and Selby, 2021), meaning that suicide or suicidal behaviour is considered to be a symptom of these disorders. Studies have shown that many psychiatric disorders share a common set of genetic factors (Caspi et al., 2014, Allegrini et al., 2020, Cross-Disorder Group of the Psychiatric Genomics Consortium, 2019). The shared genetic liability captured onto a single dimension called the *p* factor, may explain why so many psychiatric disorders are comorbid (Plomin et al., 2016). The theoretical concept, the *p* factor, suggests that components of the underlying pathology of psychiatric disorders may be shared across several (if not all) psychiatric disorders. This framework was further supported by Allegrini and colleagues who reported that the *p* factor remained stable across childhood and adolescence over a life course, suggesting that the shared genetic influences of psychiatric disorders in childhood is also linked to the development of adult psychiatric disorders (Allegrini et al., 2020). While still in its infancy, research findings from investigations on the *p* factor suggest that the comorbidity of several psychiatric disorders may be explained by a common or shared genetic pathway/s.

While genome-wide association studies (GWAS) have continued to explain only a small proportion of the heritability of suicidal behaviour, the increase in the availability of data from studies with larger sample sizes over the last few years has expanded the scope of

available statistical methods to improve the understanding of suicide burden (Wang et al., 2011, Loos, 2020). One such method, the analyses of single nucleotide polymorphism (SNP)-based genetic correlations using genomic structural equation modelling (GenomicSEM), have identified patterns of shared genetic architecture across many psychiatric disorders (Grotzinger et al., 2019, Lee et al., 2019). In this study, we proposed a common factor model that represents an extension of the general psychopathology or genomic "p factor" that includes suicidal behaviour using Genomic SEM. We performed a gene/pathway-specific meta-analysis and functional enrichment to identify a set of genes at the subnetwork level significantly associated with the common factor. We applied Mendelian randomisation to identify potentially pleiotropic and causal relationships between modifiable risk factors and suicidal behaviour and further highlighted potential drugs interacting with the subnetwork genes that may be targeted for future drug development.

4.5 Methods

4.5.1 Description of GWAS summary data

This study was conducted using 28 publicly available genome-wide association studies (GWAS) summary data generated by previous studies. Search strategies for identifying GWAS datasets are outlined in Appendix F. We identified nine SB traits, ten psychiatric traits, and five behavioural and two anthropometric and socioeconomic-related variables (Table 4.1, web links for downloading data provided). Population ancestry was grouped as European if the study population was described as "Caucasian" or "White" by the author and as East Asian if the study population was described as "Japanese" or "Han Chinese". Suicidal behaviour datasets were derived from GWAS samples of both sexes of European ancestry for suicidal ideation (n=4), suicide attempt (n=2), and self-harm (n=2), and one dataset of East Asian ancestry was obtained for individuals who died by suicide.

Briefly, the self-report measures of suicide ideation and self-harm were derived from GWAS studies of the UK Biobank (UKB) population (sample sizes ranged from 62,648 to 125,844) and accessed from the Neale lab (see weblinks/URLs, Table 4.2). Data within the UKB are structured in datasets and identified using field codes. Suicide ideation measures included recent (i.e., over the last two weeks) thoughts of suicide or self-harm (UKB field 20513); thoughts that life was not worth living (UKB field 20479); ever contemplated self-harm (UKB field 20485), and having thoughts of death during worst of depression (UKB field 20437). Two datasets of self-reported self-harm include ever self-harmed (field 20480, n=117,610) and attempted self-harm and needed hospital treatment (UKB field 20554, n=117,733). Attempted suicide datasets were obtained from the UK Biobank study, a self-report measure indicating having ever attempted suicide (UKB field 20483; n=4,933) and attempted suicide cases (n=6,024) and controls (n=44,240) from a GWAS study from the Lundbeck Foundation Initiative for Integrative Psychiatric Research (iPSYCH) (n=50,254).

GWAS summary statistics were identified (Table 4.2) for psychiatric traits in individuals of European ancestry (n=7; schizophrenia, bipolar disorder, major depression disorder, anorexia nervosa, PTSD, ADHD and insomnia) and East Asian ancestry (n=2, schizophrenia and major depressive disorder). Behavioural traits included the average number of drinks per week and smoking habits among individuals of European and East Asian ancestry. Drinks per week (DPW), defined as the average number of drinks a participant reported drinking each week, aggregated across all types of alcohol, was examined in a combined approach with GSCAN consortium and UK Biobank (UKB) (Liu et al., 2019) (N=941,280), while cigarettes per day were defined as the average number of cigarettes smoked per day, either as a current or former smoker (Liu et al., 2019) (n=337,334). Summary-level data was obtained for socioeconomic-related traits i.e., household monthly income from UK Biobank (Hill et al., 2016) and education years (Okbay et al., 2016).

Table 4.2 Data sources and description of suicidal behaviour, psychiatric, behavioural and socioeconomic datasets

Phenotype/Reference	Ancestry	Consortium/Source	Sample size	Variable	#Cases	#Controls	Web links/URLs
Suicidal behaviour							
Suicidal ideation							
Recent thoughts of suicide or self-harm	EUR	UK Biobank/Neale lab	125,844	Ordinal	NA	NA	https://www.nealelab.is/uk-biobank
Thought life not worth living	EUR	UK Biobank/Neale lab	117,291	Ordinal	NA	NA	https://www.nealelab.is/uk-biobank
Thoughts of death during worst depression	EUR	UK Biobank/Neale lab	62,648	Binary	32,630	30,018	https://www.nealelab.is/uk-biobank
Ever contemplated self-harm	EUR	UK Biobank/Neale lab	117,610	Ordinal	NA	NA	https://www.nealelab.is/uk-biobank
Suicide attempt							
Attempted suicide (Erlangsen et al. 2018)	EUR	iPSYCH	50,264	Binary	6,024	44,240	https://ipsych.dk/en/research/downloads/
Ever attempted suicide	EUR	UK Biobank/Neale lab	4,933	Binary	2.658	2.275	https://www.nealelab.is/uk-biobank
Self-harm							
Ever self-harmed	EUR	UK Biobank/Neale lab	117,733	Binary	5,099	112,634	https://www.nealelab.is/uk-biobank
Seeking mental health services	EUR	UK Biobank/Neale lab	117,733	Binary	1,693	116,040	https://www.nealelab.is/uk-biobank
Fatal suicide							
Suicide death (Otsuka et al. 2019)	EAS		14,795	Binary	746	14,049	
Psychiatric traits							
Schizophrenia (Pardinas et al. 2018)	EUR	Clozuk + PGC2	105,318	Binary	40,675	64,643	https://walters.psycm.cf.ac.uk/
Schizophrenia (Lam et al. 2019)	EAS	PGC	58,140	Binary	22,778	35,362	https://www.med.unc.edu/pgc/download-results/
Bipolar Disorder (Stahl et al. 2019)	EUR	PGC2 BD	51,710	Binary	20,352	31,358	https://www.med.unc.edu/pgc/download-results/
MDD (Giankopolou et al. 2021)	EAS	PGC	194,548	Binary	15,771	178,777	https://www.med.unc.edu/pgc/download-results/
MDD (Wray et al. 2018)	EUR	PGC	480,359	Binary	135,458	344,901	https://www.med.unc.edu/pgc/download-results/
Anorexia Nervosa (Duncan et al. 2017)	EUR	PGC	14,477	Binary	3,495	10,982	https://www.med.unc.edu/pgc/download-results/
PTSD (Duncan et al. 2018)	EUR	PGC	9,954	Binary	2,489	7,465	https://www.med.unc.edu/pgc/download-results/

ADHD (Demontis et al. 2018)	EUR	PGC	53,293	Binary	19,099	34,194	https://www.med.unc.edu/pgc/download-results/
Alcohol use disorder (Walters et al. 2018)	EUR	PGC	38,686	Binary	10,206	28,480	https://www.med.unc.edu/pgc/download-results/
Insomnia (Jansen et al. 2019)	EUR	UK Biobank	386,533	Binary	109,402	277,131	https://ctg.cncr.nl/software/summary_statistics
Behavioural traits							
Drinks per week (Liu et al. 2019)	EUR	GSCAN	941,280	Ordinal	NA	NA	https://conservancy.umn.edu/handle/11299/201564
Drinks per week (Matoba et al. 2020)	EA	GWAS catalogue	58,610	Ordinal	NA	NA	https://www.ebi.ac.uk/gwas/downloads/summary-statistics/
Cigarettes per day (Liu et al. 2019)	EUR	GSCAN	337,334	Ordinal	NA	NA	https://conservancy.umn.edu/handle/11299/201564
Cigarettes per day (Matoba et a. 2019)	EA	BBJ	72,655	Ordinal	NA	NA	http://jenger.riken.jp/en/result
Smoking (ever vs. never) Kanai et al. 2021	EA	BBJ	176,166	Binary	88,277	87,889	https://pheweb.jp/pheno/Smoking_Ever_Never
Anthropometric traits							
Body mass index (Locke et al. 2015)	EUR	GIANT consortium	322,154	Ordinal	NA	NA	https://www.nealelab.is/uk-biobank
Body mass index (Sakau & Kanai et al. 2021)	EA	BBJ	163,835	Ordinal	NA	NA	https://pheweb.jp/pheno/BMI
Socioeconomic traits							
Household Income (Hill et al. 2016)	EUR	UK Biobank	112,151	Ordinal	NA	NA	http://www.ccace.ed.ac.uk/node/335
Education in years (Okbay et al. 2016)	EUR	SSGAC	293,723	Ordinal	NA	NA	https://thessgac.com/papers/

-NA not applicable; EUR European ancestry; EAS East Asian ancestry; BBJ Biobank Japan; PGC Psychiatric Genomics Consortium.

4.5.2 Data formatting, SNP-based heritability and genetic correlation estimation

Data formatting: Datasets were formatted according to requirements for linkage disequilibrium score regression (LDSC) and genomic structural equation modelling (SEM) (Bulik-Sullivan et al., 2015, Grotzinger et al., 2019). We obtained publicly available pre-computed linkage disequilibrium (LD) scores and weights of the 1000 Genomes European and East Asian reference (https://data.broadinstitute.org/alkesgroup/LDSCORE/). GWAS summary statistics were filtered for SNPs included in HapMap3 to reduce the likelihood of bias induced by poor imputation quality. SNPs were excluded if minor allele frequency (MAF) < 1% and information (INFO) scores < 0.9 or if they were located in the human major histocompatibility complex (MHC) region. Datasets without a marker name (rsID) were annotated using ANNOVAR software, with avsnp142, an abbreviated version of dbSNP 142 with left-normalization, on human genome build hg19 (Wang et al., 2010).

SNP-based heritability: SNP-based heritability estimates and pairwise genetic correlation were calculated for each dataset using LDSC software (https://github.com/bulik/ldsc) (Bulik-Sullivan et al., 2015). SNP-based heritability quantifies the proportion of variance in a trait that is explained by all measured SNPs / common variants used in a GWAS of unrelated individuals. Heritability estimates are presented in Table 4.3 and expressed on the observed scale. Lower heritability estimates with larger standard errors relative to the estimate indicated that there was not enough power to detect the SNP-based heritability estimate based on available datasets. Lower heritability estimates with larger standard errors relative to the estimate indicated larger uncertainty in the SNP-based heritability estimate. The genomic inflation factor (or lambda genomic control factor, λGC) compares the median of the resulting chi-squared statistics (χ^2) divided by the expected median of the chi-squared distribution and was used to assess systematic bias or genomic inflation present in the GWAS summary data due to population stratification. A λGC estimate of around 1, indicates no

systematic bias. An LDSC intercept near 1 indicates little or no confounding and larger than 1.3 indicates that the results might be affected by confounding bias (Bulik-Sullivan et al., 2015b). SNP intercepts indicated no confounding bias in this study. The results were visualised using the corrplot package in R (R Core Team, 2017). We retained four (Thought life is not worth living [TLNWL], Ever contemplated self-harm [ECSH], Attempted suicide [SA], Ever self-harmed [ESH]) of the nine SB GWAS summary data with genetic correlation estimates with heritability z-scores above 4, as scores below 4 do not produce reliable estimates (Bulik-Sullivan et al., 2015, Grotzinger et al., 2019).

Genetic correlation: We calculated pairwise genetic correlation i.e., the standardised proportion of the variance shared by the phenotypes that can be attributed to genetic factors, using LDSC. Correlations are reported as the coefficient ± standard error. To note, the LDSC estimator is unbounded and can produce genetic correlation estimates outside of −1 to 1 due to sampling variation. (See https://groups.google.com/g/ldsc_users/c/3jtyM4mmTGs). Genetic correlations were corrected for multiple testing based on the total number of correlations by applying a Bonferroni corrected threshold of $p<0.05/17 = 3.125x10^{-3}$ for 17 previous GWAS studies of European ancestry and seven GWAS studies of East Asian ancestry ($p<0.05/7=0.007$).

4.5.3 Genomic structural equation modelling

We performed exploratory and confirmatory factor analysis using the R-package Genomic Structural Equation Modelling (GenomicSEM) (Grotzinger et al., 2019). This method performs structural equation modelling using GWAS summary statistics, allowing us to explore the genetic factor structure of the suicidal behaviour traits and psychiatric traits. We used the Genomic SEM's multivariable LD score regression method to estimate the genetic covariance matrix (S) and sampling covariance matrix (V) for all traits. All SNPs were standardized using the sumstats function in Genomic SEM (Grotzinger et al., 2019). We fit

models using genetic covariance and sampling covariance matrices to examine the genome-wide factor structure of the data. We derived a single genomic factor or common factor containing genome-wide factor loadings representing each SNP contribution to the shared liability of suicidal behaviour and psychiatric disorders. Because 'Ever contemplated self-harm' (ECSH) was highly correlated with 'Thought life not worth living' (TLNWL), we retained the suicidal ideation trait with the highest SNP heritability z-score i.e., TLNWL (z-score=13.61). Next, we performed an exploratory **fac**tor **anal**ysis of the S matrix with one, two and three factors using promax rotation in the R package **factanal** to guide the construction of a follow-up model. Standardised loadings of more than 0.4 were retained. We assessed model fit by comparing recommended test results and cut-offs; a good fit is indicated by a Comparative Fit Index (CFI) ≥ 0.95, Standardized Room Mean Square Residual (SRMR) ≤ 0.05 and lower AIC values indicate a better fit (Grotzinger et al., 2019). We extended genomicSEM to examine the relationship between the common factor and socioeconomic-related (education years and household income) and behavioural risk factors (smoking and average drinks per week). Because of the low SNP-based heritability z-scores (z-scores < 4) observed among populations of East Asian ancestry, genomic SEM analyses were conducted on datasets of European ancestry populations only.

4.5.4 Gene and pathway-specific meta-analysis

We performed gene/pathway-specific meta-analysis by combining the effect size of multiple SNPs within genes and genes within subnetwork/pathways using ancMETA, a Bayesian graph-based framework (Chimusa and Defo, 2022), for the derived common factor (TLNWL, ESH, SA, MDD, ADHD and AUD). AncMETA uses a Bayesian posterior probability approach that extracts common SNPs, combines the results into known biological protein-protein network datasets, performs the meta-analysis at gene and sub-network level and identifies the most significant subnetwork hubs to understand the biological pathways

(Chimusa and Defo, 2022). Common SNPs (n=6,870,289) were extracted from all studies and mapped to genes located within or less than 20 kb distance up/downstream of the protein-coding gene using FUMA (Watanabe et al., 2017), and were included as potential candidate genes for ancMETA analysis. Input SNPs were mapped to 16,530 protein-coding genes at the gene level, of which 2,951 genes were considered to have a fixed effect, meaning the effect of each gene is assumed to be shared equally across all six traits. The genome-wide significant threshold for the gene-based test was determined to be $p=0.05/16,530=3.02 \times 10^{-6}$. At the sub-network level, ancMETA identified 693 significant hub genes, of which 98 genes had a fixed effect. The genome-wide significant threshold was determined to be $p=0.05/693=7.22 \times 10^{-5}$. We applied the most recent version of the human protein to protein interactions (PPI) network from the IntAct database (IntAct release 239) (Kerrien et al., 2012). We performed pathway enrichment analysis on the subnetwork genes based on gene ontology (GO) and KEGG and Reactome pathways and visualised the PPI network using the Cytoscape version 3.7.2, (Shannon et al., 2003), plug-in StringApp (Doncheva et al., 2019). GO included the enrichment of subnetwork hub genes in terms of molecular function, biological process and cellular component. A p-value of <0.05 statistical significance was set as an enrichment standard to determine the biological importance of hub genes. We identified drug-gene interactions through the Drug-Gene Interaction Database v4.0 (DGIdb 4.0) (Freshour et al., 2020), an open-access database and a web interface (www.dgidb.org). DGIdb collects data on drug-gene interaction and druggable genes from 30 different sources and 22 databases (Freshour et al., 2020). We determined the second level classification (therapeutic subgroup) of each drug using the anatomical therapeutic chemical (ATC) classification from the World Health Organisation Collaborating Centre for Drug Statistics Methodology (https://www.whocc.no/atc_ddd_index/). We visualised the interaction between

the genes significantly associated with the common factor and each therapeutic subgroup using the R package circlize v0.4.15 (Gu et al., 2014).

4.5.5 Mendelian randomisation

We performed Mendelian randomisation to determine if the genetic correlations between the modifiable risk factors and suicidal behaviour arise from genes with pleiotropic effects and biological influences across the traits, or if the effects are causal. Mendelian randomisation uses genetic variants as a proxy for modifiable risk factors (an exposure) to estimate the causal effect on the outcome (Smith and Ebrahim, 2004). The principles of Mendelian randomisation can be applied to overcome bias by estimating the effect between the risk factor and outcome, in the absence of unmeasured confounders. However, the validity of Mendelian randomisation analysis is dependent on three assumptions: (i) the instrument variable (genetic variant) should be associated with the exposure, (ii) the instrument variable is independent of the outcome, conditional on the exposure and (iii) the instrument variable is not associated with the unmeasured confounder (Burgess and Small, 2016). We used the twoSampleMR (Hemani et al., 2018), MRcML (Xue et al., 2021) and MR-APSS (Hu et al., 2022) packages in R to assess the potential causal effect of cigarettes smoked per day, alcoholic drinks per week, household income and educational achievement (school years) on suicidal behaviour risk where the cross-trait genetic correlation Bonferroni p-value > the corrected threshold of 9.615×10^{-4}. For instrument variables (IV), we used the GWAS for the behavioural and socioeconomic-related traits listed in Table 4.2. We used the inverse-variance weighted (IVW) method with a multiplicative random effects model as the primary method and the weighted median, MR-Egger and RadialMR methods as sensitivity analyses and to detect pleiotropy. An MR-Egger intercept test of $p > 0.05$, indicates no evidence of directional pleiotropy. We used heterogeneity markers (Cochran Q-derived $p < 0.05$) from the IVW approach to represent potential horizontal pleiotropy. We applied RadialMR to detect

potential outliers and removed the outliers to re-estimate the exposure-SB relationship. Genome-wide significant SNPs were selected at $p<5x10^{-8}$ significance and were clumped to ensure independence at linkage disequilibrium (LD) $r^2 = 0.001$ and distance of 10 000 kb. If an SNP from the instrument was unavailable in the outcome, an attempt to find proxies was made with a minimum LD $r^2 = 0.8$ and palindromic SNPs were aligned with minor allele frequency < 0.3. Additional sensitivity analyses were performed using the constrained maximum likelihood and model averaging and Bayesian Information Criterion (cML-MA-BIC) method (Xue et al., 2021) and the Mendelian Randomisation Accounting for Pleiotropy and Sample Structure simultaneously (MR-APSS) approach (Hu et al., 2022). The cML-MA-BIC method accounts for correlated and uncorrelated horizontal pleiotropy and addresses the potential violation of instrument variable assumptions identifying invalid instruments. If the goodness of fit p value was > 0.05, we applied the cML-MA-BIC method, otherwise the cML-MA-BIC-DP (data perturbation) method was applied. In addition to assessing horizontal pleiotropy, the MR-APSS approach accounts for sample structure simultaneously and allows the inclusion of more genetic variants with moderate effects as instrument variables to improve statistical power without inflating type I errors (Hu et al., 2022). For MR-APSS, we applied its default instrument variable threshold of $5x10^{-5}$, while a threshold of $5x10^{-8}$ was applied for IVW, weighted median, MR Egger and cML-MA-BIC. The relationship between household income and TLNWL and ESH was not tested due to sample overlap as the three datasets were obtained from the UKBiobank cohort, and may introduce biased estimates. Reported estimates were converted to odds ratios where the outcome was binary, and interpreted using a conservative p-value threshold (0.05/number of factors with available summary statistics=0.0083).

4.6 Results

4.6.1 SNP-based heritability

We found significant SNP-based heritability estimates of SB traits of European ancestry ranged from 0.0129±0.0038 (1.3%) for Self-harm needing hospital treatment to 0.1461±0.0892 (14.6%) for Ever attempted suicide (ESH), and 0.078±0.0303 (7.8%) for individuals who died by suicide in populations of East Asian ancestry (Table 4.4).

4.6.2 Genetic correlation between suicidal behaviour (SB) and psychiatric, behavioural, anthropometric and socioeconomic-related traits

We used cross-trait LD Score regression (LDSC) to estimate genetic correlations among SB, psychiatric disorders and socioeconomic-related traits among populations of European ancestry. We observed strong positive and significant correlations within the SB traits (average genetic correlation (rg) = 0.92, range, 0.71 to 1.09), (Figure 4.1A). This means that the genetic factors that increase the risk of suicidal ideation, also increase the risk of attempt and self-harm. The genetic correlations were strongest between SA and ECSH (rg=1.09 ± standard error (SE) 0.14, p=1.049 x 10^{-15}) and between SA and ESH (rg=0.99±0.16, p=1.027 x 10^{-9}) and slightly lower between SA and TLNWL (rg=0.71±0.09, p=2.382x10^{-26}). As expected, suicidal ideation phenotypes (TLNWL and ECSH) were highly correlated (rg=0.97±0.03, p=2.52x10-^{127}).

After multiple testing corrections (p=0.05/17 traits=0.003125), five psychiatric disorders, smoking and drinking habits, and education and monthly income were significantly genetically correlated with four SB traits among populations of European ancestry (Table 4.4, Figure 4.1A and B). The strongest correlation with the SB traits was MDD and ECSH (rg=0.86±0.07, p=1.62x10^{-36}). Moderate positive and significant genetic correlations were observed between schizophrenia and ECSH (rg=0.30±0.04, p=1.39x10^{-12}). Similarly,

moderate positive genetic correlations were observed for bipolar disorder and ESH ($rg=0.34\pm0.07$, $p=1.11x10^{-5}$), ADHD and attempted suicide (SA) ($rg=0.59\pm0.07$, $p=1.41x10^{-19}$), and AUD and SA ($rg=0.54\pm0.14$, $p=0.0002$).

Among the behavioural traits, the strongest genetic correlations were observed for smoking habits and SA ($rg=0.35\pm0.07$, $p=8.27x10^{-7}$), and drinking habits and SA ($rg=0.17\pm0.05$, $p=0.0014$). In contrast, education ($rg=-0.34\pm0.05$, $p=1.41x10^{-10}$) and monthly income were negatively associated ($rg=-0.33\pm0.09$, $p=0.0004$) with attempted suicide, meaning that education years and household monthly income was protective against suicide attempt.

Among populations of East Asian ancestry (Figure 4.1C), individuals who died by suicide were moderately correlated with schizophrenia ($rg=0.35\pm0.13$, $p=0.0067$). We observed no associations between fatal suicide and MDD, drinking and smoking habits and BMI.

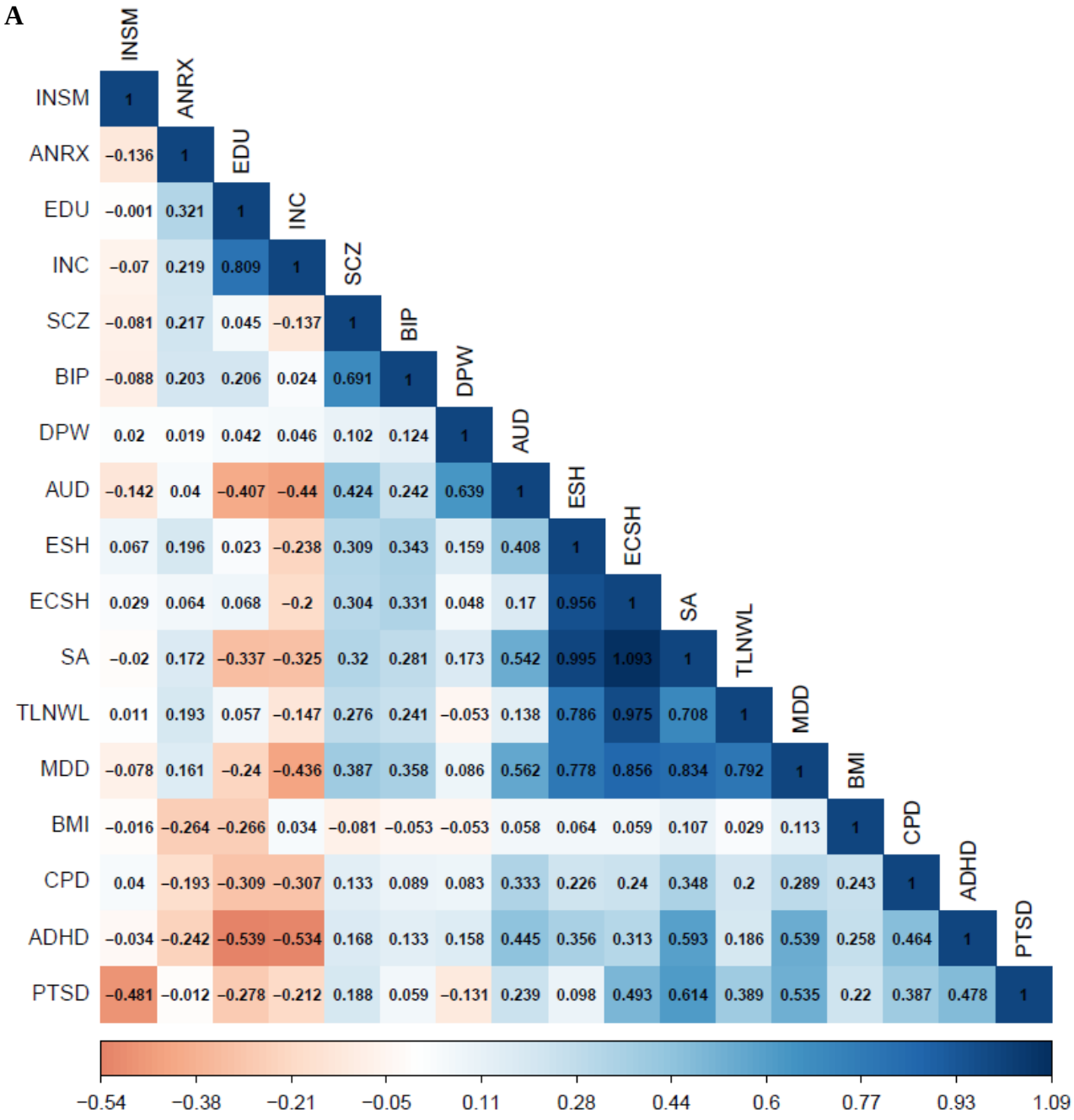
Table 4.3 Results of univariate SNP-based heritability estimates using LD-score regression of predicted probability of suicidal behaviour (SB), psychiatric disorders and education in years and income.

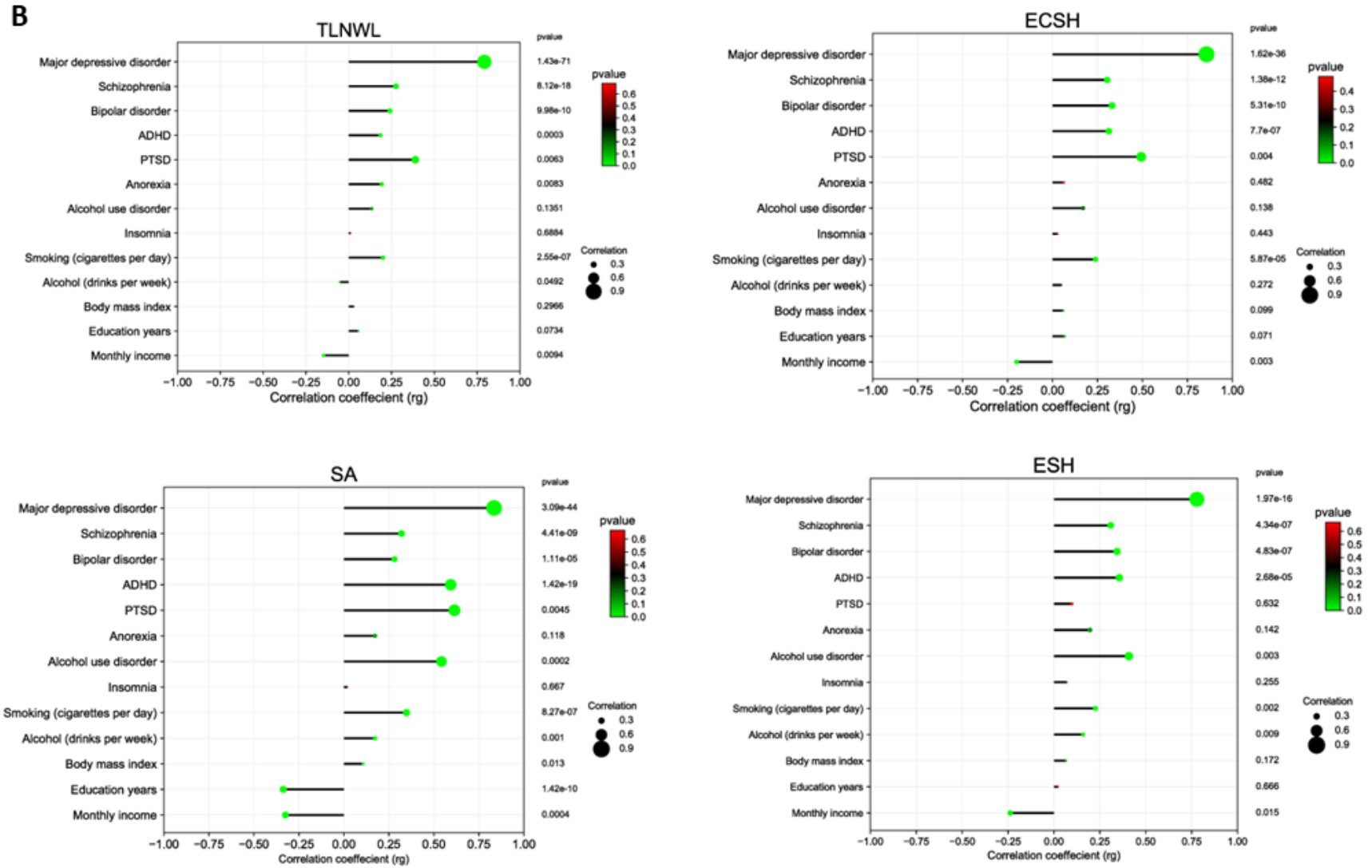
Phenotype/Reference	Ancestry	# of SNPs	SNP-based heritability (SE)[a]	z-score	Mean χ^2	λ GC	Intercept (SE) [a]
Suicidal Behaviour (SB)							
Suicidal ideation							
Recent thoughts of suicide or self-harm	EUR	9,561,902	0.0143 (0.0038)	3.76	1.0402	1.0426	1.0067 (0.0064)
Thought life not worth living	EUR	1,096,648	0.0735 (0.0054)	13.61	1.1788	1.1578	1.0087 (0.0072)
Thoughts of death	EUR	13,559,508	0.0246 (0.0071)	3.46	1.0314	1.0309	1.0012 (0.0065)
Ever contemplated self-harm	EUR	11,386,518	0.0427 (0.0051)	8.38	1.1190	1.1093	1.0206 (0.0068)
Suicidal attempt							
Attempted suicide (Erlangsen et al. 2018)	EUR	11,601,089	0.0799 (0.0123)	6.49	1.1107	1.0988	1.0225 (0.0092)
Ever attempted suicide	EUR	10,941,854	0.1461 (0.0892)	1.64	1.0085	1.0061	0.9946 (0.0062)
Fatal suicide							
Fatal suicide (Otsuka et al. 2019)	EA	8,381,404	0.0776 (0.0303)	2.56	1.0756	1.0741	1.0514 (0.0075)
Self-harm							
Ever self-harmed	EUR	12,075,154	0.0217 (0.0044)	4.93	1.0613	1.0536	1.0107 (0.0066)
SH needing hospital treatment	EUR	10,169,094	0.0129 (0.0038)	3.39	1.0364	1.0410	1.0065 (0.0062)
Psychiatric disorders							
Schizophrenia (Pardinas et al. 2018)	EUR	1,153,380	0.4100 (0.0138)	29.71	1.9325	1.6822	1.0702 (0.0113)
Schizophrenia (Lam et al. 2019)	EA	10,694,924	0.3784 (0.0222)	17.05	1.3100	1.2464	1.0002 (0.0096)
Bipolar Disorder (Stahl et al. 2019)	EUR	1,184,385	0.3872 (0.0190)	20.39	1.3670	1.3061	1.0189 (0.0081)
MDD (Wray et al. 2018)	EUR	1,081,131	0.0774 (0.0047)	15.74	1.2659	1.2365	0.9954 (0.0092)
MDD (Giankopolou et al. 2021)	EA	7,440,942	0.0080 (0.0022)	3.64	1.0419	1.0345	1.0093 (0.0065)
Anorexia nervosa (Duncan et al. 2017)	EUR	10,120,601	0.2403 (0.0382)	6.29	1.0793	1.0772	1.0089 (0.0095)

PTSD (Duncan et al. 2018)	EUR	13,206,098	0.0464 (0.0205)	2.26	1.0127	1.0165	0.9939 (0.0059)
ADHD (Demontis et al. 2018)	EUR	8,047,421	0.2268 (0.0145)	15.64	1.2966	1.2531	1.0336 (0.0102)
Alcohol use disorder (Walters et al. 2018)	EUR	9,271,144	0.0952 (0.0199)	4.78	1.0601	1.0588	1.0182 (0.0063)
Insomnia (Jansen et al. 2019)	EUR	1,117,678	0.0456 (0.0019)	24.00	1.3617	1.3061	1.0140 (0.0078)
Behavioural traits							
Drinks per week (Liu et al. 2019)	EUR	11,916,706	0.0485 (0.0021)	23.09	1.4472	1.3169	0.9267 (0.0084)
Drinks per week (Matoba et al. 2020)	EA	5,961,480	0.0731 (0.0420)	1.740	1.0892	1.0225	1.0009 (0.0080)
Cigarettes per day (Liu et al. 2019)	EUR	12,003,613	0.0724 (0.0068)	10.65	1.3301	1.2201	0.9595 (0.0095)
Cigarettes per day (Matoba et al. 2019)	EA	5,925,778	0.0669 (0.0116)	5.76	1.1059	1.0957	1.0096 (0.0088)
Smoking (ever vs. never) Kanai et al. 2019	EA	13,531,752	0.0290 (0.0042)	6.90	1.1092	1.0975	1.0024 (0.0081)
Anthropometric traits							
Body mass index (Locke et al. 2015)	EUR	2,554,637	0.1297 (0.0056)	23.16	1.2603	1.0772	0.6729 (0.0079)
Body mass index (Sakau & Kanai et al. 2021)	EA	13,236,464	0.1772 (0.0078)	22.72	1.6636	1.4926	1.0740 (0.0188)
Socioeconomic-related traits							
Household monthly income (Hill et al. 2016)	EUR	1,217,311	0.0599 (0.0056)	10.70	1.1613	1.1428	1.0290 (0.0071)
Education years (Okbay et al. 2016)	EUR	8,146,840	0.1108 (0.0037)	29.95	1.6445	1.4745	0.9377 (0.0092)

[a] SE – Standard error, MDD – major depressive disorder, PTSD – post-traumatic stress disorder, ADHD – attention deficit hyperactivity disorder

A


INSM ANRX EDU INC SCZ BIP DPW AUD ESH ECSH SA TLNWL MDD BMI CPD ADHD PTSD
INSM 1
ANRX −0.136 1
EDU −0.001 0.321 1
INC −0.07 0.219 0.809 1
SCZ −0.081 0.217 0.045 −0.137 1
BIP −0.088 0.203 0.206 0.024 0.691 1
DPW 0.02 0.019 0.042 0.046 0.102 0.124 1
AUD −0.142 0.04 −0.407 −0.44 0.424 0.242 0.639 1
ESH 0.067 0.196 0.023 −0.238 0.309 0.343 0.159 0.408 1
ECSH 0.029 0.064 0.068 −0.2 0.304 0.331 0.048 0.17 0.956 1
SA −0.02 0.172 −0.337 −0.325 0.32 0.281 0.173 0.542 0.995 1.093 1
TLNWL 0.011 0.193 0.057 −0.147 0.276 0.241 −0.053 0.138 0.786 0.975 0.708 1
MDD −0.078 0.161 −0.24 −0.436 0.387 0.358 0.086 0.562 0.778 0.856 0.834 0.792 1
BMI −0.016 −0.264 −0.266 0.034 −0.081 −0.053 −0.053 0.058 0.064 0.059 0.107 0.029 0.113 1
CPD 0.04 −0.193 −0.309 −0.307 0.133 0.089 0.083 0.333 0.226 0.24 0.348 0.2 0.289 0.243 1
ADHD −0.034 −0.242 −0.539 −0.534 0.168 0.133 0.158 0.445 0.356 0.313 0.593 0.186 0.539 0.258 0.464 1
PTSD −0.481 −0.012 −0.278 −0.212 0.188 0.059 −0.131 0.239 0.098 0.493 0.614 0.389 0.535 0.22 0.387 0.478 1
−0.54 −0.38 −0.21 −0.05 0.11 0.28 0.44 0.6 0.77 0.93 1.09


B
TLNWL
Major depressive disorder
Schizophrenia
Bipolar disorder
ADHD
PTSD
Anorexia
Alcohol use disorder
Insomnia
Smoking (cigarettes per day)
Alcohol (drinks per week)
Body mass index
Education years
Monthly income
pvalue
1.43e-71
8.12e-18
9.96e-10
0.0003
0.0063
0.0083
0.1351
0.6884
2.55e-07
0.0492
0.2966
0.0734
0.0094
pvalue
0.6
0.5
0.4
0.3
0.2
0.1
0.0
Correlation
0.3
0.6
0.9
−1.00 −0.75 −0.50 −0.25 0.00 0.25 0.50 0.75 1.00
Correlation coeffecient (rg)
ECSH
Major depressive disorder
Schizophrenia
Bipolar disorder
ADHD
PTSD
Anorexia
Alcohol use disorder
Insomnia
Smoking (cigarettes per day)
Alcohol (drinks per week)
Body mass index
Education years
Monthly income
pvalue
1.62e-36
1.38e-12
5.31e-10
7.7e-07
0.004
0.482
0.138
0.443
5.87e-05
0.272
0.099
0.071
0.003
pvalue
0.4
0.3
0.2
0.1
0.0
Correlation
0.3
0.6
0.9
−1.00 −0.75 −0.50 −0.25 0.00 0.25 0.50 0.75 1.00
Correlation coeffecient (rg)
SA
Major depressive disorder
Schizophrenia
Bipolar disorder
ADHD
PTSD
Anorexia
Alcohol use disorder
Insomnia
Smoking (cigarettes per day)
Alcohol (drinks per week)
Body mass index
Education years
Monthly income
pvalue
3.09e-44
4.41e-09
1.11e-05
1.42e-19
0.0045
0.118
0.0002
0.667
8.27e-07
0.001
0.013
1.42e-10
0.0004
pvalue
0.6
0.5
0.4
0.3
0.2
0.1
0.0
Correlation
0.3
0.6
0.9
−1.00 −0.75 −0.50 −0.25 0.00 0.25 0.50 0.75 1.00
Correlation coeffecient (rg)
ESH
Major depressive disorder
Schizophrenia
Bipolar disorder
ADHD
PTSD
Anorexia
Alcohol use disorder
Insomnia
Smoking (cigarettes per day)
Alcohol (drinks per week)
Body mass index
Education years
Monthly income
pvalue
1.97e-16
4.34e-07
4.83e-07
2.68e-05
0.632
0.142
0.003
0.255
0.002
0.009
0.172
0.666
0.015
pvalue
0.6
0.5
0.4
0.3
0.2
0.1
0.0
Correlation
0.3
0.6
0.9
−1.00 −0.75 −0.50 −0.25 0.00 0.25 0.50 0.75 1.00
Correlation coeffecient (rg)

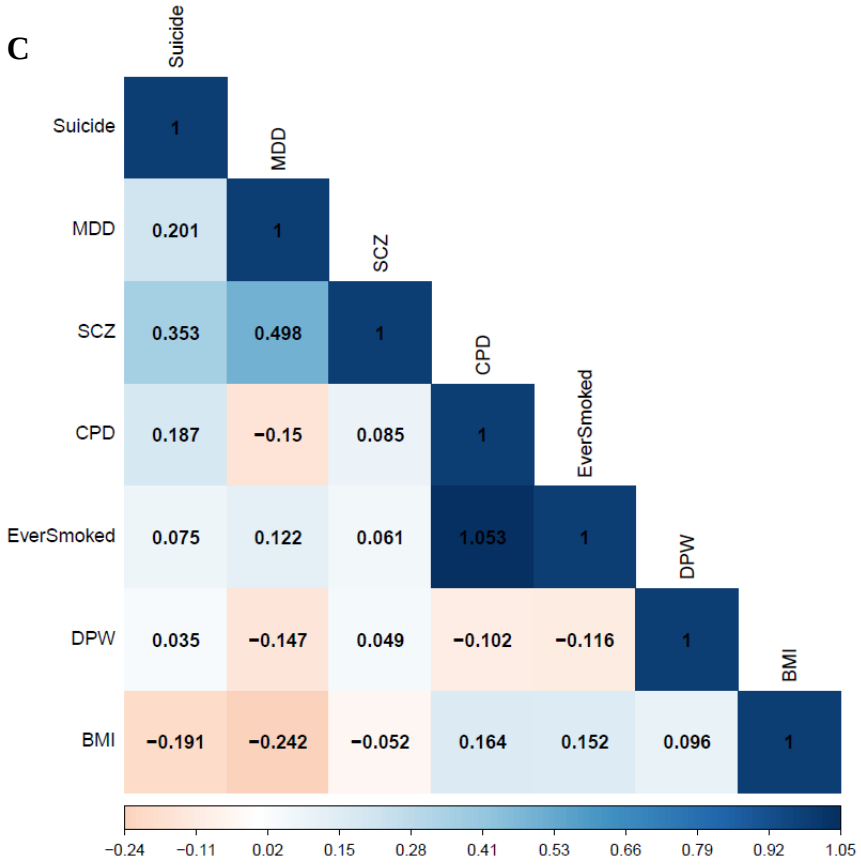


Figure 4.1 Pairwise LDSC-estimated genetic correlation between SB and psychiatric disorders, behavioural and SES traits

(A) Heatmap showing the correlation between 17 traits among European populations, (B) a correlation dot plot showing the association between four suicidal behaviour traits (TLNWL, ECSH, SA and ESH) and psychiatric disorders, behavioural and socioeconomic (SES)-related traits among European populations. The size of the dot represents the strength of the correlation, and (C) a heatmap of seven traits including fatal suicide among East Asian populations. The strength of the genetic correlation is presented as a heat scale on the x-axis with blue colour indicating positive and red colour representing negative correlations. Light colours represent lower correlation estimates, whereas darker colours indicate stronger correlations.

Asterisk (*) indicates a value above Bonferroni-corrected p-value threshold: α=0.05/17 traits=0.003125. The strength of the genetic correlation is presented as a heat scale on the x-axis with blue colour indicating positive and red colour representing negative correlations. Light colours represent lower correlation estimates, whereas darker colours indicate stronger correlations.

Abbreviations: (SB traits) TLNWL = Thought life is not worth living, ECSH = Ever contemplated Self-harm, ESH = Ever self-harmed, SA = Suicide attempt; (Psychiatric, behavioural and socioeconomic-related traits) MDD = major depression disorder, SCZ = schizophrenia, BIP = bipolar disorder, AUD = alcohol use disorder, ADHD= attention deficit hyperactivity disorder, PTSD = post-traumatic stress disorder, ANRX = anorexia nervosa, INSM = insomnia, BMI = body mass index, DPW = drinks per week, CPD = cigarettes per day, INC = monthly income and EDU = education in years.

Table 4.4 Genetic correlations between SB traits, psychiatric disorders, behavioural traits and socioeconomic-related traits among populations of European ancestry

Suicidal behaviour traits	Psychiatric, behavioural and socioeconomic-related traits	Genetic correlation (rg)	Standard error	p-value *
Thought life was not worth living (TLNWL)	Major depressive disorder	0.792	0.044	1.4332×10^{-71} *
	Schizophrenia	0.276	0.032	8.1157×10^{-18} *
	Bipolar disorder	0.241	0.039	9.9756×10^{-10} *
	ADHD	0.186	0.052	0.0003 *
	PTSD	0.389	0.142	0.0063
	Anorexia	0.193	0.073	0.0083
	Alcohol use disorder	0.134	0.093	0.1351
	Insomnia	0.011	0.027	0.6884
	Smoking (cigarettes per day)	0.200	0.038	2.5530×10^{-7} *
	Alcohol (drinks per week)	-0.053	0.037	0.0492
	Body mass index	0.029	0.028	0.2966
	Education years	0.057	0.032	0.0734
	Monthly income	-0.147	0.057	0.0094
Ever contemplated self-harm (ECSH)	Major depressive disorder	0.856	0.068	1.6172×10^{-36} *
	Schizophrenia	0.304	0.043	1.3846×10^{-12} *
	Bipolar disorder	0.331	0.053	5.3113×10^{-10} *
	ADHD	0.313	0.064	7.6955×10^{-7} *
	PTSD	0.493	0.171	0.0040
	Anorexia	0.064	0.091	0.4824
	Alcohol use disorder	0.170	0.114	0.1379
	Insomnia	0.029	0.038	0.4426
	Smoking (cigarettes per day)	0.239	0.060	5.8733×10^{-5} *
	Alcohol (drinks per week)	0.048	0.044	0.2723
	Body mass index	0.059	0.035	0.0992
	Education years	0.068	0.038	0.0700
	Monthly income	-0.200	0.068	0.0033
Attempted suicide (SA)	Major depressive disorder	0.834	0.059	3.0921×10^{-44} *
	Schizophrenia	0.320	0.055	4.4136×10^{-9} *
	Bipolar disorder	0.281	0.064	1.1109×10^{-5} *
	ADHD	0.593	0.065	1.4159×10^{-19} *
	PTSD	0.614	0.216	0.0045
	Anorexia	0.173	0.111	0.1184
	Alcohol use disorder	0.542	0.145	0.0002 *
	Insomnia	0.020	0.047	0.6673
	Smoking (cigarettes per day)	0.348	0.070	8.2685×10^{-7} *
	Alcohol (drinks per week)	0.173	0.050	0.0014 *
	Body mass index	0.107	0.043	0.0132
	Education years	-0.337	0.053	1.4160×10^{-10} *
	Monthly income	-0.325	0.091	0.0004 *
Ever self-harmed (ESH)	Major depressive disorder	0.778	0.095	1.9721×10^{-16} *
	Schizophrenia	0.309	0.061	4.3483×10^{-7} *
	Bipolar disorder	0.343	0.068	4.8327×10^{-7} *
	ADHD	0.356	0.085	2.6826×10^{-5} *
	PTSD	0.098	0.204	0.6324
	Anorexia	0.196	0.134	0.1424
	Alcohol use disorder	0.408	0.136	0.0027 *
	Insomnia	0.067	0.059	0.2551
	Smoking (cigarettes per day)	0.226	0.073	0.0015 *
	Alcohol (drinks per week)	0.159	0.062	0.0096
	Body mass index	0.064	0.047	0.1716
	Education years	0.023	0.053	0.6656
	Monthly income	-0.238	0.098	0.0149

ADHD-attention deficit hyperactivity disorder, PTSD-post-traumatic stress disorder. Note: genetic correlations were calculated using LDSC (linkage disequilibrium score regression). * - indicates value above Bonferroni-corrected p-value threshold: α=0.05/17 traits=0.003125.

4.6.3 Genomic structural equation modelling

First, we tested a model in which three SB traits (TLNWL, ESH and SA) and seven psychiatric traits (MDD, SCZ, BIP, AUD, ADHD, ANRX and INSM) loaded onto a single common latent factor (Table 4.5, Figure 4.2A). Model fit was fair for the common factor model in which the loadings were freely estimated (chi-square, $X^2(35)=794.66$, AIC=834.66, CFI=0.753, SRMR=0.127). Standardised loadings indicated that MDD and SA loaded most strongly onto the common factor, while anorexia nervosa and insomnia loaded the weakest. We then assessed the fit of a correlated two-factor model where three suicidal behaviour traits were loaded onto the latent suicidal behaviour factor and seven psychiatric traits were loaded onto a psychiatric latent factor (Figure 4.2B). We observed a strong correlation between the two latent factors (rg=0.77±0.04), however, the model fit remained suboptimal ($X^2(34)=747.07$, AIC=789.07, CFI=0.768, SRMR=0.125).

Table 4.5 Model fit statistics for each of the SEM models performed

Model	**χ^2 statistic**	**df**	**p-value**	**AIC**	**CFI**	**SRMR**
Common factor model (10 indicators)	794.66	35	$2.59x10^{-144}$	834.66	0.753	0.127
Correlated two-factor model (10 indicators)	742.48	34	$3.84x10^{-134}$	784.48	0.770	0.119
Confirmatory factor analysis (CFA)						
One-factor solution (6 indicators)	51.31	8	$2.28x10^{-8}$	77.31	0.964	0.086
Two-factor solution (5 indicators)	32.97	5	$3.82x10^{-6}$	52.97	0.965	0.086
Three-factor solution (7 indicators)	The model did not converge.					
Revised common factor model (6 indicators)	47.19	7	$5.11x10^{-8}$	75.19	0.954	0.083

χ^2 - chi-squared statistic, df - degrees of freedom, AIC - Akaike's Information Criterion, CFI - Comparative Fit Index, SRMR - standardised root mean squared residual. Good fit is indicated by CFI > 0.90 and SRMR < 0.85.

Next, we conducted an exploratory factor analysis and examined different factor structures that would fit the data best (Table 4.6). While both the one- (Figure 4.2A) and two-factor (Figure 4.2B) CFA solutions of the 10 items fit the data adequately, the second latent factor of the two-factor solution was underspecified and explained only 11.2% of the variance. We then specified factor loadings to ≥ 0.4, decreasing the 10 items to six. The modified one-

factor model now had strong loadings for all six indicators (traits) and explained 61.3% of the variance. To further improve model fit, we evaluated a revised common factor solution of six indicators that allowed for correlated indicator residuals between ADHD and AUD and between ESH and SA (Figure 4.2C). This model fit the data best across all model specifications (X2(7)=51.31, AIC=75.15, CFI=0.954 and SRMR=0.083), suggesting that this model may represent a common or shared genetic pathway/s to suicidal behaviour across MDD, ADHD and AUD.

Table 4.6 EFA of suicidal behaviour and psychiatric traits

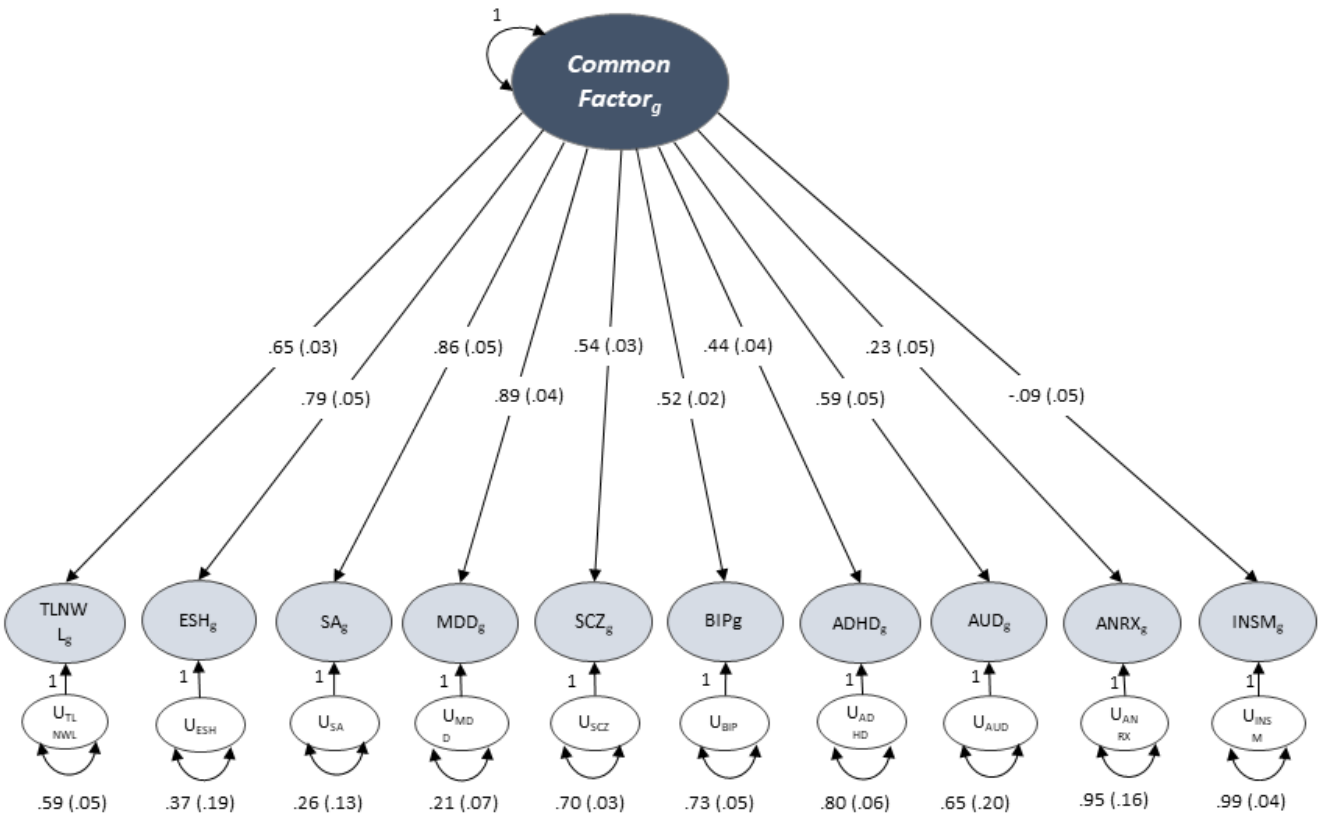
	One Factor Model		**Two Factor model**		
	Factor 1	**Uniqueness**	**Factor 1**	**Factor 2**	**Uniqueness**
TLNWL	**0.695**	0.517	**0.807**	-0.209	0.407
ESH	**0.954**	0.089	**1.026**	-0.113	0.005
SA	**0.997**	0.005	**0.922**	0.194	0.005
MDD	**0.838**	0.298	**0.748**	0.216	0.295
SCZ	0.318	0.899	0.292		0.901
BIP	0.277	0.923	0.346	-0.116	0.891
ADHD	**0.578**	0.666	0.177	**0.876**	0.106
ANRX	0.171	0.971	0.257	-0.219	0.920
INSM		1.000		-0.182	0.969
AUD	**0.492**	0.758	0.337	0.339	0.702
Proportion of variance	0.387	0.613	0.354	0.112	0.534
Cumulative variance	0.387	0.613	0.354	0.466	0.534
Correlation of factors					
Factor 1	1	-	1	0.303	-
Factor 2	-	-	0.303	1	-

Note: Results derived from an exploratory factor analysis with promax rotation; TLNWL=Thought life was not worth living, ESH=Ever self-harmed, SA=Attempted suicide, MDD=major depression disorder, SCZ=schizophrenia, BIP=bipolar disorder, ADHD=attention deficit hyperactivity disorder, ANRX=anorexia nervosa, INSM=insomnia, AUD=alcohol use disorder. Numbers in bold indicates factor loadings ≥ 0.40

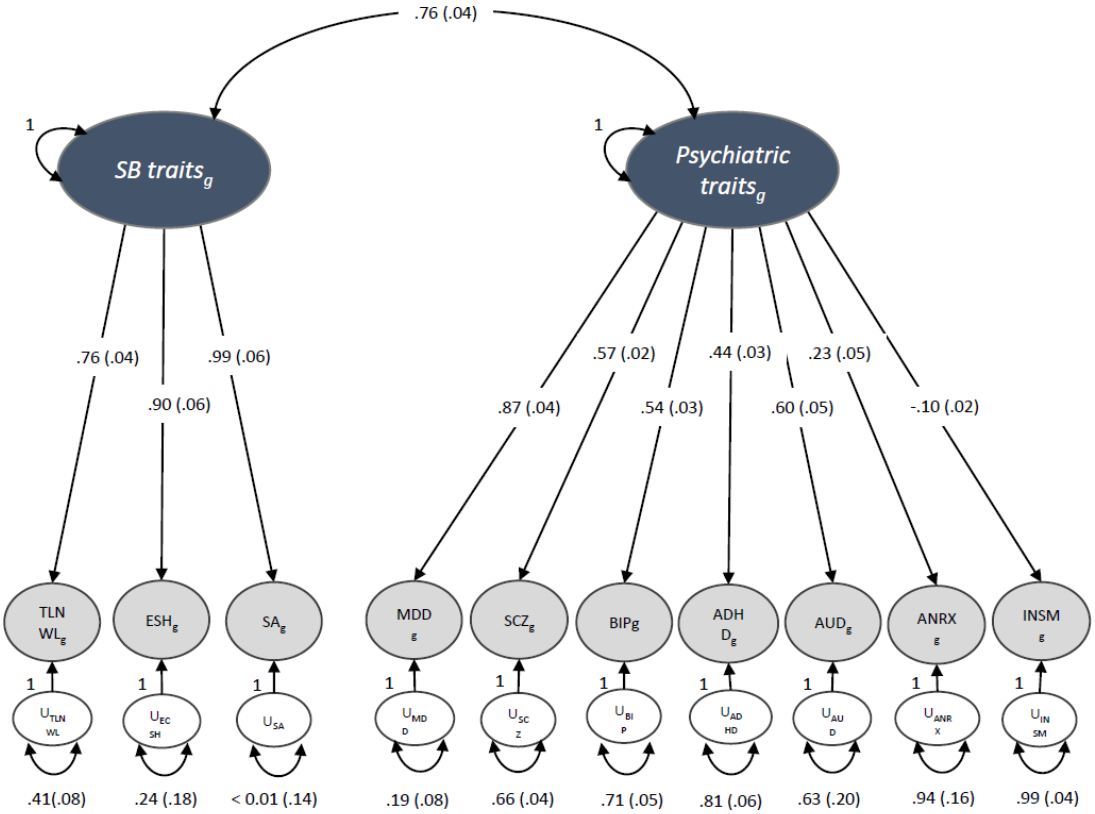
We extended genomic SEM to determine the genetic correlations between the revised common factor model (that represents SB [suicidal ideation, attempt and self-harm] and psychiatric disorders [MDD, ADHD and AUD]) and selected socioeconomic and behavioural traits. The revised common factor had a moderate positive correlation with smoking (rg=0.47±0.03) and inverse correlations with monthly income (rg=-0.52±0.04) and education

years (rg=-0.37±0.02). Weak positive correlations were observed between the common factor and drinks per week (rg=0.18±0.02) and BMI (rg=0.19±0.02). In other words, the genetic factors that increase smoking and drinking habits i.e., the number of cigarettes per day and drinks per week also increase SB/psychiatric disorders. In contrast, the genetic factors that influence an increase in education years and monthly income also decrease SB/psychiatric disorders; meaning higher education and household monthly income, a proxy for socioeconomic status is protective for SB, MDD, ADHD and AUD.

A



B


.76 (.04)
SB traits g
Psychiatric traits g
.76 (.04)
.90 (.06)
.99 (.06)
.87 (.04)
.57 (.02)
.54 (.03)
.44 (.03)
.60 (.05)
.23 (.05)
-.10 (.02)
TLN WL g
ESH g
SA g
MDD g
SCZ g
BIPg
ADH D g
AUD g
ANRX g
INSM g
U TLN WL
U EC SH
U SA
U MD D
U SC Z
U BI P
U AD HD
U AU D
U ANR X
U IN SM
.41(.08)
.24 (.18)
< 0.01 (.14)
.19 (.08)
.66 (.04)
.71 (.05)
.81 (.06)
.63 (.20)
.94 (.16)
.99 (.04)

C

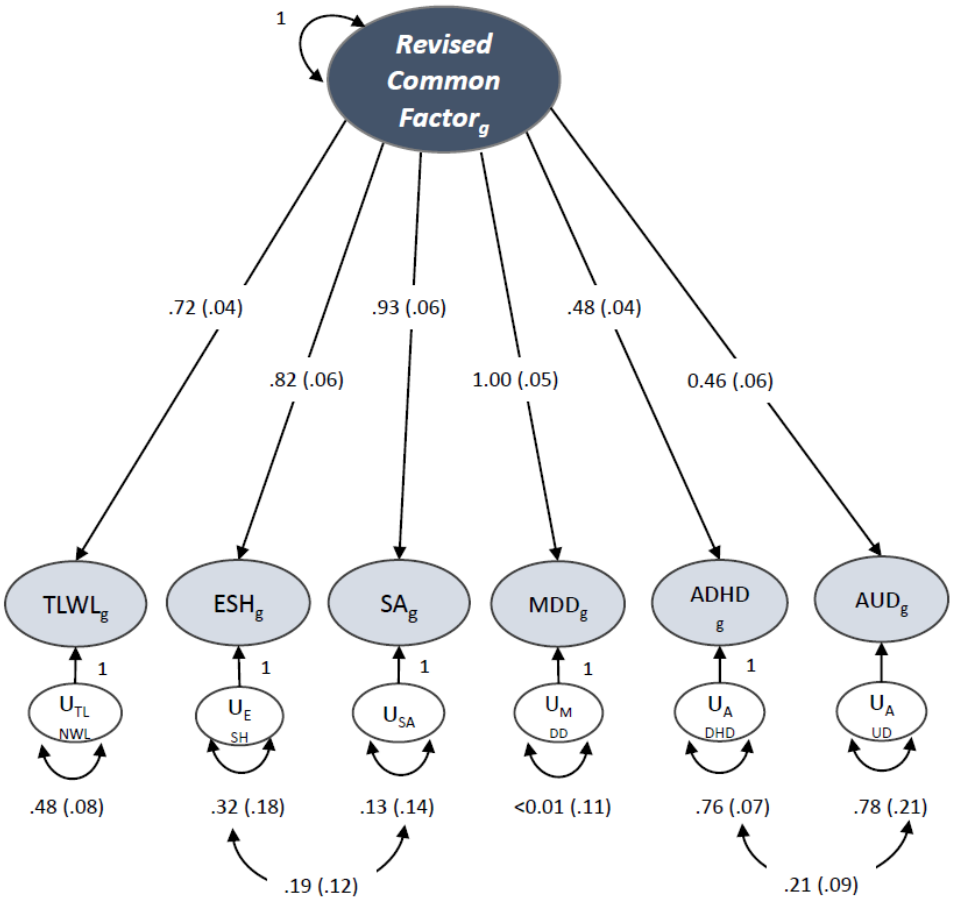

Revised Common Factor g
.72 (.04)
.82 (.06)
.93 (.06)
1.00 (.05)
.48 (.04)
0.46 (.06)
TLWL g
ESH g
SA g
MDD g
ADHD g
AUD g
U TL NWL
U E SH
U SA
U M DD
U A DHD
U A UD
.48 (.08)
.32 (.18)
.13 (.14)
<0.01 (.11)
.76 (.07)
.78 (.21)
.19 (.12)
.21 (.09)

Figure 4.2 Genomic structural equation models of the standardised solutions of the SB and psychiatric traits

Figure A displays the path diagram (with standard errors in parenthesis) for the common factor model where there is only one factor that depicts the overarching common variance between all included traits.

Figure B displays a two-factor model with three SB traits loaded onto the latent suicidal behaviour factor and seven psychiatric traits loaded onto a psychiatric latent factor.

Figure C displays the path diagram for the revised common factor model which shows the factor loadings for traits that displayed a loading ≥ 0.40 at EFA. SCZ, BIP, ANRX and INSM did not meet the factor loading threshold.

4.6.4 Genes and pathways associated with the derived common factor

ancMETA was used to perform gene and pathway-specific meta-analysis and estimate the aggregated genetic effects and the level of significance of the derived common factor (TLNWL, ESH, MDD, ADHD and AUD) on 16,530 genes. This technique identified 2,951 genes that were associated ($p<3.02 \times 10^{-6}$) with the common factor at the gene level (Table 4.7) and 98 genes at the sub-network level ($p< 7.22 \times 10^{-5}$, Figure 4.3). At gene level, the most significant gene ($p=2.43 \times 10^{-43}$) associated with the common factor was GDNF Family Receptor Alpha 3 (*GFRA3*), located on chromosome 5 and is involved in RAF/MAP kinase cascade pathway and nervous system development (Gaudet et al., 2011). Genes with significant but small effects across the six traits include the developmental pluripotency associated factor 4 (*DPPA4)* located on chromosome 3, ankyrin repeat domain 46 (*ANKRD46)* located on chromosome 8, KH domain containing 3 Like (*KHDC3L)* located on chromosome 6 and neuronal olfactomedin related ER localized protein 2 (*OLFM2)*, located on chromosome 19.

Table 4.7 Top genes identified by gene and sub-network meta-analysis of the derived common factor

Gene	#Study	Overall p-value	Beta	SD	Tau Square	P_TLNWL	P_ESH	P_SA	P_MDD	P_AUD	P_ADHD
Gene level											
GFRA3	6	2.429E-43	3.876E-05	0.0002	0	0.0041	0.4680	0.0044	0.0024	0.0090	0.0049
DPPA4	6	3.631E-42	0.0004	0.0003	0	0.0010	0.4054	0.0035	0.0022	0.0756	0.0035
ANKRD46	6	2.188E-40	-2.828E-05	9.859E-05	0	0.0042	0.3267	0.0029	0.0054	0.1199	0.0030
KHDC3L	6	3.769E-40	-6.219E-05	0.0002	0	0.0025	0.3985	0.0035	0.1436	0.0078	0.0056
OLFM2	6	6.614E-40	2.269E-05	0.0001	0	0.0091	0.3470	0.0036	0.0084	0.0172	0.0039
Subnetwork level											
TOB1	6	3.154E-27	-0.00149	0.00089	0	0.0583	0.4959	0.3519	0.0888	0.3263	0.3633
RANBP9	6	1.395E-25	0.00013	0.00019	0	0.1193	0.4667	0.3098	0.4951	0.1708	0.4679
SRSF3	6	1.428E-24	0.00044	0.00017	0	0.4988	0.1240	0.2755	0.2245	0.1954	0.2748
HSPB3	6	1.862E-23	-0.00025	0.00025	0	0.1640	0.4588	0.4746	0.1832	0.2255	0.3668
STK24	6	4.081E-23	-0.00019	0.00031	0	0.1239	0.1228	0.3988	0.4963	0.1554	0.3134

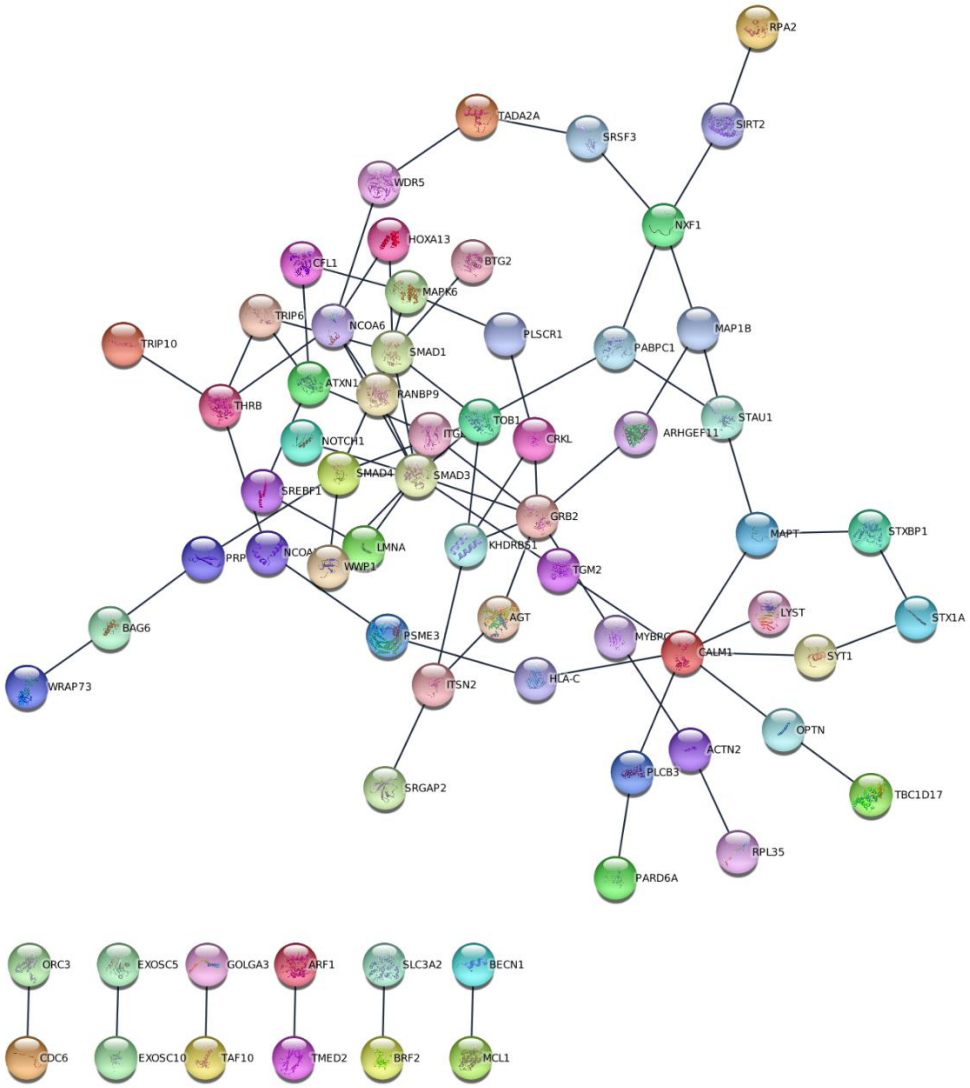
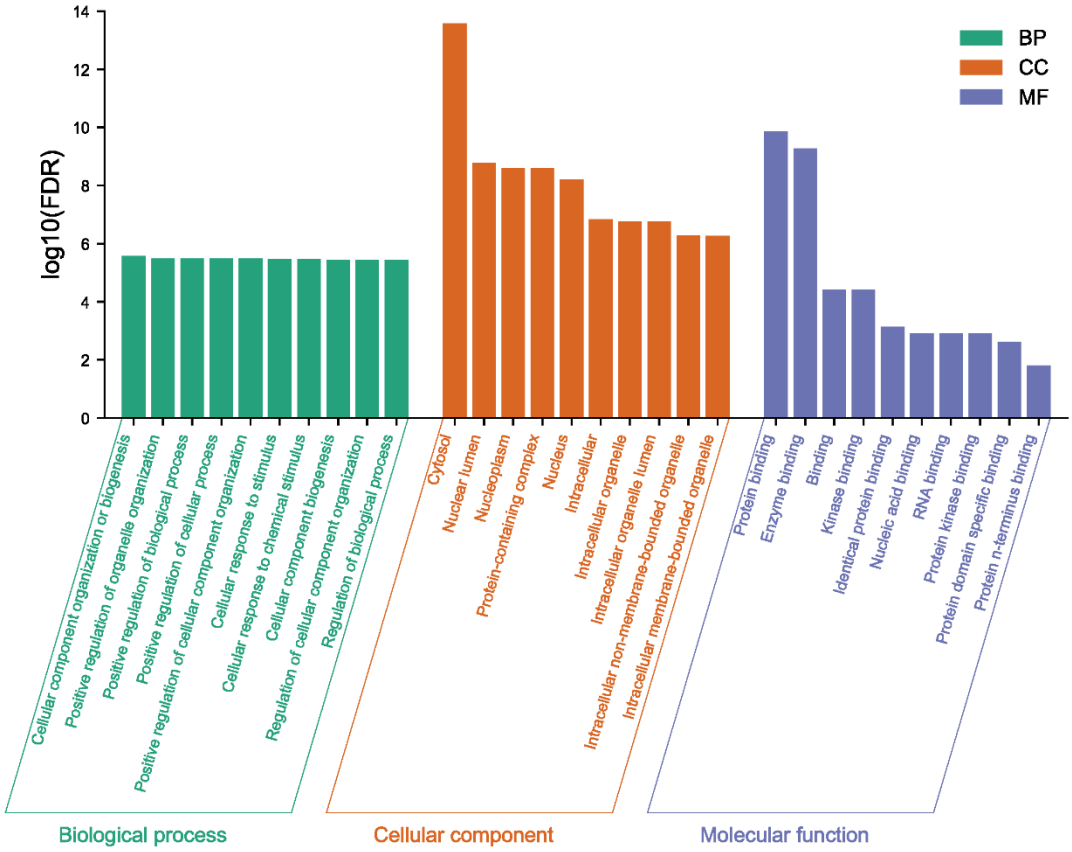


Figure 4.3 Visualisation of the 98 sub-network genes associated with the derived common factor.

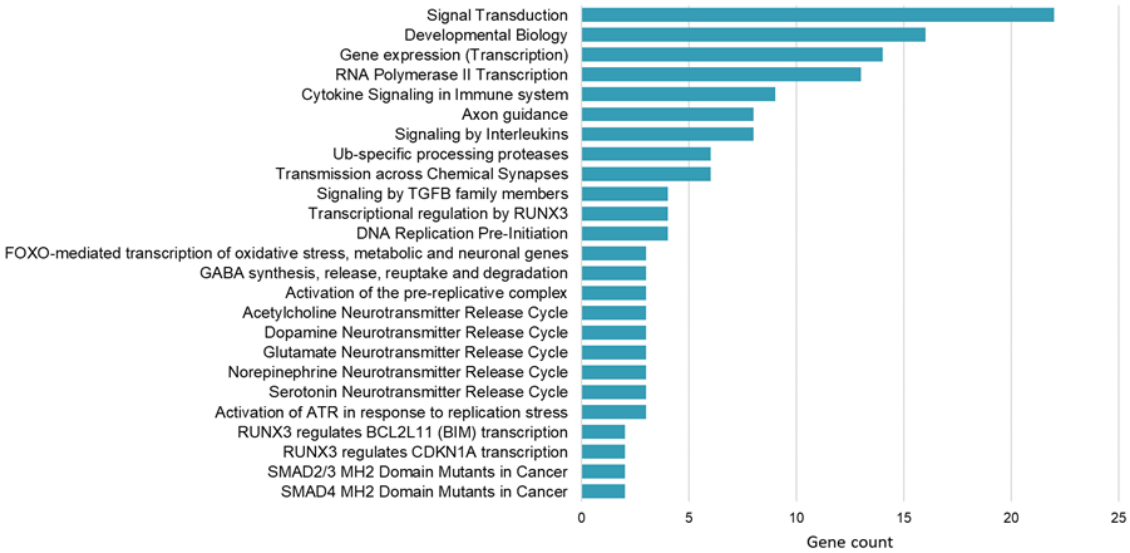
The most significant ($p=3.15x10^{-27}$) gene at the sub-network level was the transducer of ERBB2, 1 (*TOB1)*, located on chromosome 17. In addition, the top sub-network genes were RAN binding protein 9 (*RANBP9),* located on chromosome 6, involved in developmental biology, signaling pathways and nervous system development; Serine and Arginine Rich Splicing Factor 3 *(SRSF3)*, located on chromosome 6, Heat shock protein Family B (small) member *3 (HSPB3)* located on chromosome 5, and Serine/Threonine Kinase 24 *(STK24)* on chromosome 13.

We identified 25 Reactome pathways and four KEGG pathways linking the six traits (FDR<0.05, Figure 4.4). KEGG pathways were related primarily to genetic information processing (RNA degradation), while Reactome pathways were related to developmental biology, particularly, nervous system development, signal transduction and gene expression (transcription). Together with two Reactome pathways (SMAD4 MH2 Domain Mutants in Cancer and SMAD2/3 MH2 Domain Mutants in Cancer), two KEGG pathways were related to pathways in cancer. Sub-network (hub) genes were mostly involved in developmental biology (Reactome pathway, FDR=0.018), signal transduction (Reactome pathway, FDR=0.047) and RNA degradation (KEGG pathway, FDR=0.0028). We observed that *SMAD3* and *SMAD4* (SMAD family members 3 and 4) appeared in most enrichment pathways (Figure 4.3). In Gene Ontology (GO), we identified 373 categories jointly associated with the common factor: 322 biological processes, 32 cellular components and 19 molecular functions. GO enrichment analysis showed that the sub-network genes were mainly located in the cytosol (FDR=2.6×10^{-14}) and nuclear lumen (FDR=1.69×10^{-9}). Moreover, sub-network genes were enriched in molecular functions relating to protein binding (FDR=1.37×10^{-10}) and enzyme binding (FDR=5.23×10^{-10}). Likewise, cellular component organisation or biogenesis (FDR=2.63×10^{-6}) was identified as the most significant biological process. Most of the subnetwork genes were highly expressed in the central nervous system (FDR=1.27×10^{-7}), nervous system (FDR=1.27×10^{-7}), and the brain (FDR=1.79×10^{-7}, Figure 4.4D).

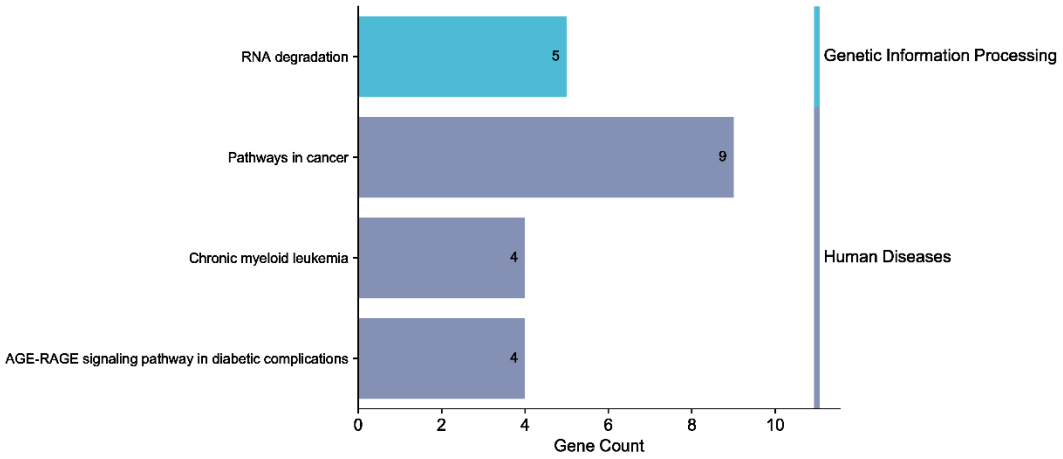
A


log10(FDR)
14
12
10
8
6
4
2
0
BP
CC
MF
Cellular component organization or biogenesis
Positive regulation of organelle organization
Positive regulation of biological process
Positive regulation of cellular process
Positive regulation of cellular component organization
Cellular response to stimulus
Cellular response to chemical stimulus
Cellular component biogenesis
Regulation of cellular component organization
Regulation of biological process
Cytosol
Nuclear lumen
Nucleoplasm
Protein-containing complex
Nucleus
Intracellular
Intracellular organelle
Intracellular organelle lumen
Intracellular non-membrane-bounded organelle
Intracellular membrane-bounded organelle
Protein binding
Enzyme binding
Binding
Kinase binding
Identical protein binding
Nucleic acid binding
RNA binding
Protein kinase binding
Protein domain specific binding
Protein n-terminus binding
Biological process
Cellular component
Molecular function

B


Signal Transduction
Developmental Biology
Gene expression (Transcription)
RNA Polymerase II Transcription
Cytokine Signaling in Immune system
Axon guidance
Signaling by Interleukins
Ub-specific processing proteases
Transmission across Chemical Synapses
Signaling by TGFB family members
Transcriptional regulation by RUNX3
DNA Replication Pre-Initiation
FOXO-mediated transcription of oxidative stress, metabolic and neuronal genes
GABA synthesis, release, reuptake and degradation
Activation of the pre-replicative complex
Acetylcholine Neurotransmitter Release Cycle
Dopamine Neurotransmitter Release Cycle
Glutamate Neurotransmitter Release Cycle
Norepinephrine Neurotransmitter Release Cycle
Serotonin Neurotransmitter Release Cycle
Activation of ATR in response to replication stress
RUNX3 regulates BCL2L11 (BIM) transcription
RUNX3 regulates CDKN1A transcription
SMAD2/3 MH2 Domain Mutants in Cancer
SMAD4 MH2 Domain Mutants in Cancer
0
5
10
15
20
25
Gene count

C



D

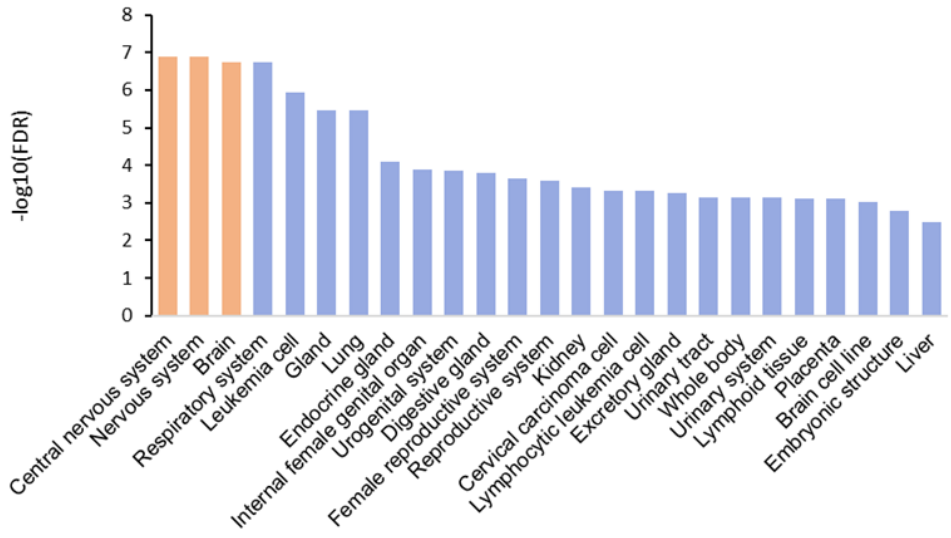


Figure 4.4 Gene ontology (GO) functional analysis histogram (A), bar plot of Reactome (B) and KEGG pathway enrichment analysis (C) and enriched tissues (D).

Drug-gene interactions: We explored potential drug-target genes among the 98 sub-network genes significantly associated ($p=7.22x10^{-5}$) with the common factor, for known drug interactions in the Drug Gene Interaction Database v4.0 (DGIdb 4.0) (Freshour et al., 2020). A total of 246 interactions were identified for 26 genes and 190 drugs. Anatomical therapeutic chemical (ATC) classifications were available for 185 drugs that were assigned to

47 therapeutic subgroups (Figure 4.5). The greatest number of drug-gene interactions were observed between antineoplastic agents (L01 drug classification) and *SMAD4* (SMAD Family Member 4, n=11), *NOTCH1* (Notch Receptor 1, n=9) and *APEX1* (Apurinic/Apyrimidinic Endodeoxyribonuclease 1, n=7). Additional interactions were observed between *APEX1* and N04, anti-Parkinson drugs and between *AGT* (Angiotensinogen) and C09, drugs acting on the renin-angiotensin system.

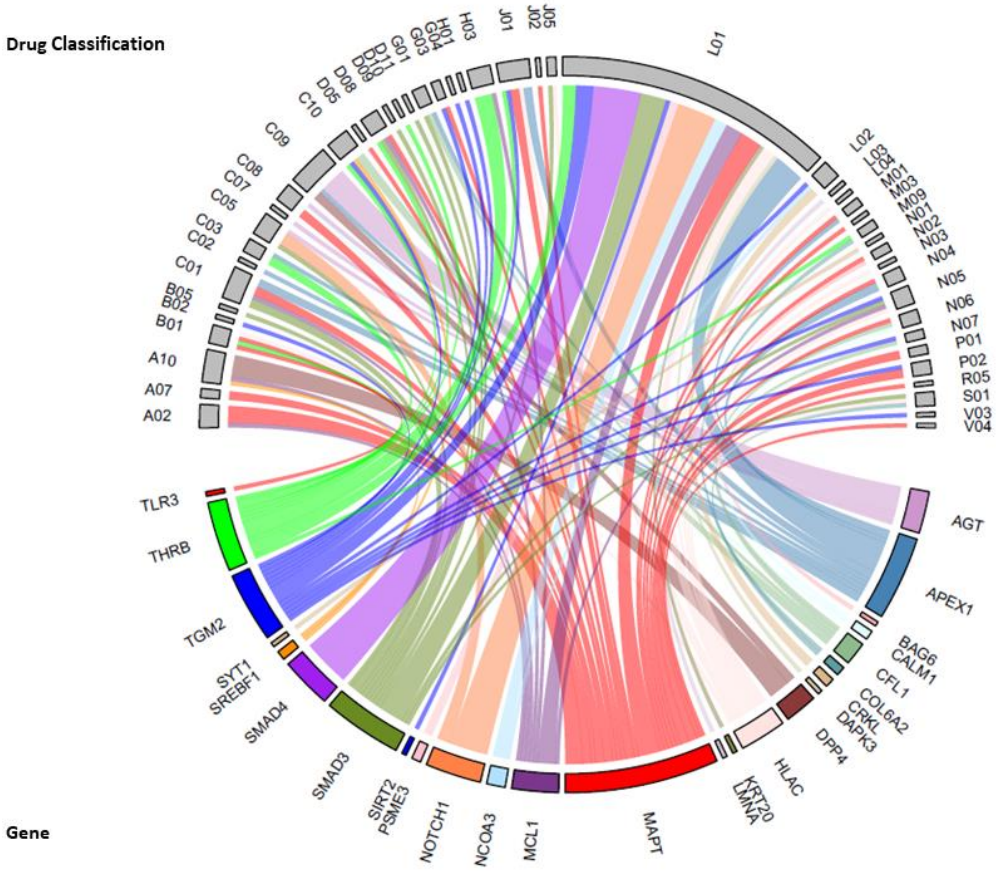


Figure 4.5 Chord diagram of sub-network genes associated with the common factor and the drug-gene interactions with the second level Anatomical Therapeutic Chemical (ATC) classification (therapeutic subgroup) of drugs. The width of each line represents the number of drugs known to interact with each gene.

Therapeutic subgroup ATC Drug classifications: A02=Drugs for acid-related disorders, A07=antidiarrheals, intestinal anti-inflammatory/anti-infective agents, A10=drugs used in diabetes, B01=antithrombotic agents, B02=antihemorrhagics, B05=blood substitutes and perfusion solutions, C01=cardiac therapy, C02=antihypertensives, C03=diuretics, C05=vasoprotectives, C07=beta blocker agents, C08=calcium channel blockers, C09=agents acting on renin-angiotensin system, C10=lipid modifying agents, D05=antipsoriatics, D08=antiseptics and disinfectants, D09=medicated dressing, D10=anti-acne preparations, D11=other dermatological preparations, G01=gynecological anti-

infective and antiseptics, G03=sex-hormones and modulators of the genital system, G04=urological, H01=pituitary and hypothalamic hormones and analogues, H03=thyroid therapy, J01=antibacterial for systemic use, J02=antimycotics for systemic use, J05=antivirals for systemic use, L01=antineoplastic agent, L02=endocrine therapy, L03=immunostimulants, L04=immunosuppressants, M01=anti-inflammatory and antirheumatic products, M03=muscle relaxants, M09=other drugs for disorders of the Musculo-skeletal system, N01=anesthetics, N02=analgesics, N03=antiepileptics, N04=anti-Parkinson drugs, N05=psycholeptics, N06=psychoanaleptics, N07=other nervous system drugs, P01=antiprotozoals, P02=anthelmintics, R05=cough and cold preparations, S01=opthalmologicals, V03=all other therapeutic products, V04=therapeutics radiopharmaceuticals.

4.6.5 Causal effect of modifiable risk factors on suicidal behaviour

We used the genetic variants associated with suicidal behaviour and genetic variants associated with smoking, alcohol drinking, education achievement and household income to determine the unique effects of each modifiable risk factor on suicidal behaviour. Mendelian randomisation analyses showed a nominal association at the $p<0.05$ threshold of the potential effect of smoking on the risk of a suicide attempt (OR_{IVW} 1.24, 95% CI 1.03-1.49, p=0.026), and suggested no causative relationship between smoking and suicidal ideation (TLNWL, $ß_{IVW}$ 0.017, SE 0.015, p=0.263) or self-harm (ESH OR_{IVW} 1.00, 95% CI 0.99-1.01, p=0.437) (Table 4.8, Supplementary Figure 4.1). The intercept from the MR Egger method for suicide attempts showed minimal indication of directional pleiotropy (p=0.053), and there was evidence of substantial heterogeneity (Cochran's Q statistic $p=3.53x10^{-3}$). High levels of heterogeneity in the estimated effects from each SNP are an indication of the potential pleiotropic effects of some of the SNPs associated with smoking and suicide attempt. We conducted a sensitivity analysis, using a radial regression framework, and identified a variant (rs34406232) on the *EGLN2* gene, as an outlier potentially introducing bias to IVW and MR Egger estimates (Supplemental Figure 4.1). After removing the outlier, the estimate of cigarettes smoked per day on suicide attempt remained significant (random effects model: β_{IVW} 0.27, SE=0.08, $p=7.05x10^{-3}$) and the Cochran's Q statistic for heterogeneity was 32.61 (p=0.001), indicating that removing the SNP made no substantive difference to the results.

Table 4.8 Two-sample Mendelian Randomisation analysis of the effect of behavioural and socioeconomic-related traits on suicidal behaviour

Exposure	**Outcome**	**Method**	**N SNPs**	**OR [95% CI] / β (SE)**	**p**	**Directional pleiotropy**		**Heterogeneity**	
						Intercept	**p**	**Q**	**p**
Cigarettes smoked per day	TLNWL[a]	MR Egger	22	-0.043 (0.020)	0.053	0.005	0.002	20.03	0.456
		IVW	22	0.017 (0.015)	0.263			32.07	0.058
		Weighted median	22	0.001 (0.016)	0.957				
		cML-MA-BIC	22	0.075 (0.026)	0.004				
		MR-APSS	165	0.289 (0.089)	$1.23x10^{-3}$				
	ESH	MR Egger	22	0.989 [0.978-1.002]	0.108	0.001	0.019	24.03	0.241
		IVW	22	1.002 [0.994-1.010]	0.519			31.85	0.060
		Weighted median	22	0.997 [0.987-1.005]	0.437				
		cML-MA-BIC	22	1.002 [0.939-1.069]	0.574				
		MR-APSS	165	1.352 [1.127-1.622]	$1.15x10^{-3}$				
	SA	MR Egger	14	0.711 [0.418-1.209]	0.232	0.025	0.053	32.26	$1.26x10^{-3}$
		IVW	14	1.237 [1.026-1.492]	0.026			44.69	$3.53x10^{-5}$
		Weighted median	14	1.224 [1.038-1.443]	0.016				
		cML-MA-BIC-DP	14	1.297 [1.145-1.468]	$4.16x10^{-5}$				
		MR-APSS	165	2.596 [1.428-4.717]	$1.75x10^{-3}$				
Alcoholic drinks per week	SA	MR Egger	21	1.075 [0.731-1.579]	0.718	0.004	0.349	49.57	0.0001
		IVW	21	1.233 [0.948-1.602]	0.117			51.97	0.0001
		Weighted median	21	1.097 [0.834-1.362]	0.400				
		cML-MA-BIC-DP	21	1.191 [1.005-1.414]	0.044				
		MR-APSS	231	1.359 [0.942-1.961]	0.010				
Education (school years)	SA	MR Egger	53	1.051 [0.307-3.591]	0.936	-0.003	0.738	176.32	$1.03x10^{-31}$
		IVW	53	0.854 [0.685-1.065]	0.162			176.77	$1.69x10^{-15}$
		Weighted median	53	0.884 [0.714-1.094]	0.259				
		cML-MA-BIC	53	0.882 [0.769-1.012]	0.073				
		MR-APSS	392	0.526 [0.381-0.727]	$9.61x10^{-5}$				
Household income	SA	MR Egger	37	1.294 [0.463-3.615]	0.625	-0.016	0.106	104.24	$8.35x10^{-9}$
		IVW	37	0.554 [0.437-0.704]	$1.29x10^{-5}$			112.43	$8.58x10^{-10}$
		Weighted median	37	0.606 [0.479-0.766]	$2.85x10^{-5}$				
		cML-MA-BIC-DP	37	0.603 [0.525-0.691]	$3.85x10^{-11}$				
		MR-APSS	296	0.202 [0.051-0.920]	0.038				

[a] Associations are expressed as beta coefficients, Intercept = MR Egger intercept, Q = Cochran's Q statistic, cML-MA-BIC = constrained maximum likelihood and model averaging and Bayesian Information Criterion method, cML-MA-BIC-DP = constrained maximum likelihood and model averaging and Bayesian Information Criterion (data perturbation) method, MR-APSS = Mendelian Randomisation Accounting for Pleiotropy and Sample Structure simultaneously.

In addition, the cML-MA-BIC-DP results (OR=1.30, 95% CI 1.14-1.47%, p=4.16x10^{-5}) and the MR-APSS method (OR=2.60, 95% CI 1.428-4.717, p=1.75x10^{-3}) were consistent with IVW method, with significant associations observed at the p-value threshold of 0.0083 (Supplemental Figure 4.2), suggesting a potential causative relationship between cigarettes smoked per day and suicide attempt.

We also observed a potential beneficial effect of household income level on suicide attempt, with genetically predicted higher household income (odds ratio per one standard deviation increase in household income) potentially leading to a 45% decrease in the probability of attempting suicide (OR_{IVW} 0.55, 95% CI 0.44-0.70, p=1.29x10^{-5}) (Table 4.8 and Supplementary Figure 4.3). Similarly, the MR Egger intercept (p=0.106) suggests directional pleiotropy was not biasing the estimate, while the Cochran's Q statistic (p=8.35x10^{-3}) showed high levels of heterogeneity, indicating that some SNPs are pleiotropic but the average pleiotropic effect is close to zero and therefore balanced. We conducted a sensitivity analysis removing two variants (rs11665242 on the *DCC* gene and rs589914 on the *RP11-734C14.2* gene) and the effects remained constant (random effects model β_{IVW} = -0.502, SE=0.111, p=7.398x10^{-5}). Additional sensitivity analyses showed that the cML-MA-BIC-DP method (OR 0.60, 95% CI 0.53-0.69, p=3.85x10^{-11}) yielded a similar result to IVW and weighted median methods (Table 4.8), while the association from MR-APSS method was nominally significant (OR 0.20, 95% CI 0.05-0.92, p=0.038) (Table 4.8, Supplemental Figure 4.2). These findings show a potential inverse relationship between higher household income and suicide attempt.

Our findings did not suggest a causal relationship association between suicide attempt and alcohol drinks per week or educational achievement (school years). There was no indication of directional pleiotropy (MR Egger intercept p=0.349), however, Cochran's Q statistic

(p=0.0001) showed heterogeneity between individual SNP estimates at the global level (p=0.0001), suggesting that some SNPs are pleiotropic but the average pleiotropic effect is close to zero (Supplemental Figure 4.3). We identified SNP rs4309187 in the DRD2 gene as a potential outlier and re-estimated the model after removing the outlier and the p-value for Cochran's Q statistic remained significant (p=0.006).

4.7 Discussion

In the present study, we analysed summary-level data from large-scale GWAS to examine the genetic correlation between suicidal behaviours and psychiatric disorders using genomic structural equation modelling. We observed strong genetic correlations between suicidal behaviour traits and moderate to strong genetic correlations between suicidal behaviour and psychiatric disorders, particularly major depression disorder. Exploratory factor analysis of individuals of European ancestry revealed a single factor that represents a common genetic pathway to suicidal behaviour across major depression, alcohol use disorder and ADHD. We identified 98 sub-network hub genes associated with the common factor and observed pathways enriched in developmental biology, signal transduction, gene transcription and RNA degradation. Most of the subnetwork hub genes were highly expressed in the central nervous system. We identified several drug-gene interactions, involving genes in the common or shared genetic pathways that may be worth investigating as potential targets for the prevention and treatment of MDD, alcohol use disorder, ADHD and suicidal behaviour (common factor).

The observed strong genetic correlations within the non-fatal suicidal behaviour traits suggest that suicidal ideation, self-harm and attempted suicide have a shared genetic component and provide support for the possibility that suicidal behaviour may exist on a spectrum of behaviours from thinking of suicide to acting on these thoughts (Caspi et al., 2014). This

finding counters the ideation-to-action model that suggests that the development of suicidal ideation and the progression from suicide ideation to attempts are distinct processes with distinct explanations (Klonsky and May, 2015). As a separate construct, non-fatal suicidal behaviour was not genetically distinct, but rather our findings suggest an interconnected network of suicidal behaviour and major depression, ADHD and alcohol use disorder that supports established epidemiological (Turecki and Brent, 2016, Fazel and Runeson, 2020) and genomic associations (DiBlasi et al., 2021, Mirkovic et al., 2016).

We identified significant positive correlations between non-fatal suicidal behaviour and psychiatric disorders, with the strongest correlation observed for major depressive disorders in individuals of European ancestry. Genetic factors play an important role in the aetiology of psychiatric disorders, with heritability estimates from twin and family studies ranging from 32%-79% for major depression (Sullivan et al., 2000, Smoller et al., 2019), 77%-88% for ADHD (Faraone and Larsson, 2019), 81% for schizophrenia, and 57% for substance use disorders (Sullivan et al., 2012). There is well-supported evidence that psychiatric disorders are polygenic, that many common variants with small effects contribute to an increased risk (Sullivan et al., 2018) and GWAS studies have shown significant genetic overlap between psychiatric traits (Cross-Disorder Group of the Psychiatric Genomics Consortium, 2019, Lee et al., 2019). Depression is a well-known risk factor for suicidal behaviour (Malone et al., 1995) and several recent large GWAS have shown an overlap between suicide attempt and depression using genetic correlation analyses or polygenic risk scoring (PRS) (Mullins et al., 2019, Strawbridge et al., 2019, Ruderfer et al., 2019, Levey et al., 2019). Further, Mullins et al. (2019) reported polygenic risk scores for major depression were associated with an increased risk of attempted suicide for individuals with major depression and schizophrenia (Mullins et al., 2019). ADHD, a neurodevelopmental disorder, has been associated with depression, schizophrenia and substance use disorder in later life (Tistarelli et al., 2020), as

well as an increased risk of attempted and fatal suicide (Ljung et al., 2014), suggesting common underlying risk variants contribute to these disorders. A recent meta-analysis showed alcohol use disorder increases the risk of suicidal ideation, attempt and suicide completion (Darvishi et al., 2015). Further, findings from recent GWAS studies showed that PRS of fatal suicide was associated with greater alcohol use and schizophrenia (Docherty et al., 2020), while attempted suicide was genetically correlated with alcohol dependence (Mullins et al., 2022). These findings suggest that there is a component of common genetic variation that is shared between suicidal behaviours and MDD, ADHD, schizophrenia and alcohol use disorder. It is possible that cross-trait assortive mating, which is explained by individuals choosing partners with specific characteristics that have no genetic relationship, may have substantially inflated the genetic correlation estimates and biased the Mendelian randomisation results (Border et al., 2022). Assortive mating across psychiatric disorders can increase the correlation between the traits of the parents, which in turn increases the correlation between the psychiatric traits of their offspring (Nordsletten et al., 2016), and may explain the genetic comorbidity across psychiatric disorders.

We identified 98 potential sub-network (hub) genes and key pathways associated with the common factor. Among the hub genes, *TOB1, RANBP9*, *SRSF3, HSPB3* and *STK24* were among the most significant. Findings from enrichment analysis suggest that the hub genes were mainly involved in developmental biology, signal transduction, gene transcription and RNA degradation pathways. *SMAD3* and *SMAD4* genes, observed in most enrichment pathways are members of the SMAD family and code for intracellular signal transducer proteins involved in transforming growth factor-beta (TGF-ß) signaling. The TGF-beta/SMAD signaling pathway plays an important role in neurogenesis in the hippocampus and has been implicated in the development of mood disorders and the manifestation of

depression and anxiety disorders (Hiew et al., 2021). Interestingly, variants in *SMAD3* have also been linked to smoking behaviour (Justice et al., 2017).

Among the top hub genes associated with the common factor, *TOB1, RANBP9, HSPB3* and *SRSF3* were also linked to neurodegenerative disorders, such as Alzheimer's disease, Parkinson's, and amyotrophic lateral sclerosis, through various pathways. The RNA degradation pathway, linked to *TOB1* as indicated by the KEGG enrichment analysis, is a critical step in the control of various biological pathways. In neurons, the nonsense-mediated RNA decay (NMD) pathway serves as a regulatory mechanism to control mRNA, and mutations in the NMD genes have been associated with neurodevelopmental disorders, such as schizophrenia and neurodegenerative disorders, such as amyotrophic lateral sclerosis (Jaffrey and Wilkinson, 2018). *TOB1,* which codes for an antiproliferative protein that targets mRNA deadenylation and decay (Hosoda et al., 2011), has previously been associated with neurodegenerative disorders (Weskamp and Barmada, 2018), such as multiple sclerosis (Gironi et al., 2016) and a *TOB1* deletion has been associated with hippocampus-mediated acute stress response in animal models (Youssef et al., 2022). The primary role of the signal transduction pathway is to regulate overall growth and behaviour. *RANBP9* has been implicated in the nervous system development pathway and the regulation of a number of signaling pathways, including the signal transduction pathway. *RANBP9* interacts with proteins involved in Alzheimer's disease and has been associated with schizophrenia (Das et al., 2017). *HSPB3* [heat shock protein family B (small) member 3], is involved in the inhibition of the apoptosis pathway and regulates cell death by inhibiting actin polymerization. *HSPB3* has previously been linked to alcohol dependence (Kapoor et al., 2014) and neurodegenerative disorders such as Alzheimer's and Parkinson's disease (Vendredy et al., 2020). *SRSF3* (serine and arginine-rich splicing factor 3) plays a key role in the metabolism of RNA/ gene transcription (Watanuki et al., 2008). Abnormal expression of

SRSF3 can lead to aberrant gene splicing and the development of neurodegenerative disorders (Xiong et al., 2022). *STK24* (sterine/threonine kinase 24), promotes apoptosis in response to stress stimuli and caspase activation and can act as a regulator of axon regeneration in optic and radial nerves and is involved in programmed cell death (Mardakheh et al., 2016). *STK24* has been implicated in unipolar depression (Levey et al., 2019, Howard et al., 2019) and schizophrenia (Lam et al., 2019). It is worth noting that processes related to neurodegeneration may be due to the older age of study participants in UK Biobank from whom suicidal behaviour traits were obtained. Taken together, psychiatric and neurodegenerative disorders represent a heterogeneous group of neurological conditions and future studies investigating the shared molecular characteristics between suicidal behaviour, MDD, ADHD and alcohol use disorder should be explored in a younger target population to better understand the pathophysiological mechanisms that underlie psychiatric and neurodegenerative disorders.

We found positive genetic correlations between suicidal behaviour and modifiable risk behaviours such as smoking and average alcohol drinking per week, that are consistent with the observed increase in these behaviours among individuals with suicidal behaviour (Polimanti et al., 2021, Poorolajal and Darvishi, 2016) and are indicative of a shared genetic basis for these traits. The prevalence of tobacco smoking is known to be higher among individuals with mental health conditions compared to the general population (Prochaska et al., 2017). Further, tobacco smoking is considered an independent risk factor for suicidal behaviour; a meta-analysis showed that smokers are at higher risk of suicidal ideation (OR=2.05, 95% CI 1.53-2.28), suicide attempt (OR=2.84, 95% CI 1.49-4.19) and fatal suicide (RR=1.83, 95% CI 1.64-2.02) (Poorolajal and Darvishi, 2016). A causal association was found between earlier smoking initiation, lifetime smoking, depression and schizophrenia (Wootton et al., 2020). We used genetic variants associated with smoking and

found nominally significant MR results, pointing to the potentially harmful effect of smoking intensity (increased cigarettes smoked per day) on suicide attempts, although findings were not consistent across all sensitivity analyses. Nevertheless, our results align with the literature on the relationship between smoking and suicidal behaviour (Poorolajal and Darvishi, 2016) and merit further investigation for including smoking cessation and prevention in suicide prevention programs. The negative genetic correlations between suicidal behaviour and socioeconomic-related variables i.e., education achievement and monthly income support previously reported associations between indicators of poverty and suicidal behaviour (Iemmi et al., 2016, Lorant et al., 2021). In addition, we found suggestive evidence for the protective effect of genetically predicted higher household income levels on the risk of suicide attempt. Earlier work by Dohrenwend et al. has suggested that the high rate of mental disorders in disadvantaged populations can be explained by the social selection theory, that individuals with mental illness have a predisposition to declining socioeconomic status due to possible genetic factors, hospitalisations related to mental illness, and/or loss of work (Dohrenwend et al., 1992).

Our study findings suggest that individuals with major depression, ADHD or alcohol use disorder are at increased risk of suicidal behaviour. Understanding the shared biological mechanisms and pathways that may account for the similarities between suicidal behaviour and psychiatric disorders at the epidemiological, neuropathological, and molecular levels could provide potential avenues to treatment and prevention strategies. We found a number of interactions between the hub genes and the ATC therapeutic sub-groups. These exploratory findings, to be interpreted with caution, suggest that pharmaceutical treatments that are currently available may target the genetic component of the common factor. The most notable drug-gene interactions were observed between drugs grouped in the L01 drug classification, which comprises antineoplastic and immune-modulating agents, and *SMAD4* and *NOTCH1*

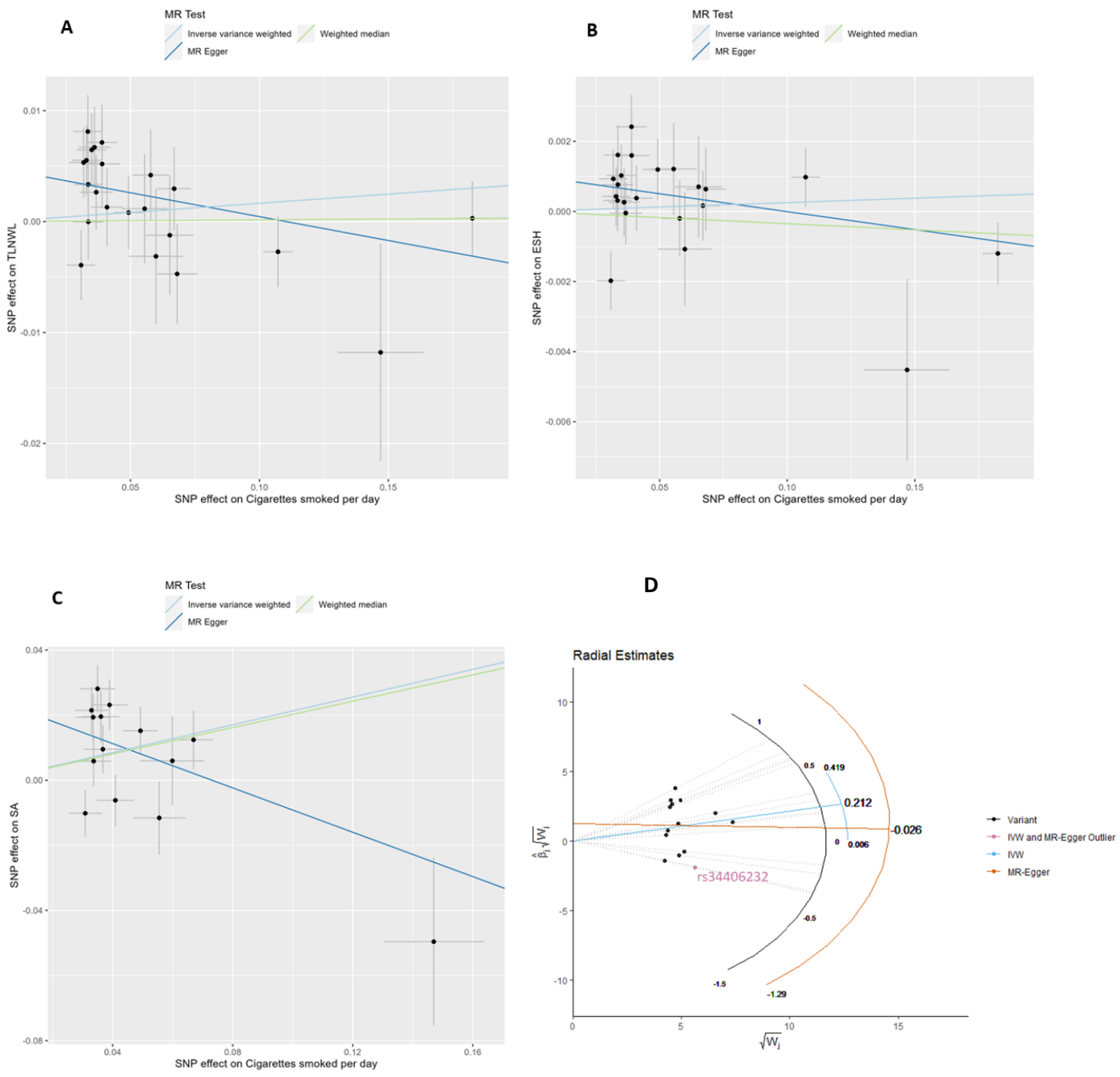
genes. Additional drug-gene interactions were observed for *APEX1* (Apurinic/Apyrimidinic Endodeoxyribonuclease 1) and N04 drug classification, which comprises of anti-Parkinson drugs, and includes anticholinergic and dopaminergic agents.

Our study has limitations. First, while we planned to analyse the full spectrum of fatal and non-fatal suicidal behaviour in the exploratory factor analysis, only one of the nine publicly available genome-wide summary datasets consisted of individuals who died by suicide and the population was of East Asian ancestry. Owing to the confounding effects of ancestral variation in LD score regression, our factor analysis included only non-fatal suicidal behaviour data of individuals of European ancestry. Therefore, the findings from the genetic factor analyses relate only to non-fatal suicidal behaviour and do not include fatal suicide. Second, our factor analysis findings are generalisable only to populations of European ancestry. The modest SNP-based heritability (z-scores < 4) of fatal suicides and psychiatric traits of East Asian populations meant that we could not explore the factor structure of these traits independently for individuals of East Asian ancestry. As most suicides in the world occur in low- and middle-income countries (WHO, 2021), the current analysis should be extended to include diverse populations, e.g., African and ad-mixed populations as sufficient data becomes available. This is crucial to understanding the link between suicidal behaviour and psychiatric traits to advance precision medicine efforts in countries and populations with mixed genetic ancestry patterns, where it is needed most. In this study, we used suicidal behaviour datasets (self-harm and suicidal ideation) from a population-based cohort, i.e., UK Biobank, who are predominantly healthy, middle-aged individuals who lived in less socioeconomically deprived areas and were less likely to drink and smoke than the general population (Fry et al., 2017). Suicide attempt data were obtained from a large population-based sample in Denmark. However, these individuals were diagnosed with severe mental disorders. This may explain the strength of the association observed between attempted

suicide and psychiatric disorders compared to weaker associations observed for suicidal ideation and self-harm. Further, the difference in socioeconomic levels may also have explained the lack of genetic association observed between suicidal ideation/self-harm and education attainment and household monthly income compared to individuals who attempted suicide. Fourth, four of the ten suicidal behaviour traits had low SNP-based heritability estimates and were therefore underpowered and not included in the genetic factor analyses. This reduced the number of datasets available for analysis; however, we were able to include at least one dataset that represented each of the SB phenotypes: suicidal ideation, suicide attempt, self-harm or fatal suicide. Fifth, while Mendelian randomisation is less likely to be affected by confounding compared to observational studies, this method is limited by the number of instrumental variables available. In our study, the instrumental variables were adequate for the exposures but we were unable to test reverse causality due to the low number of instruments or lack of suitable variants for suicidal behaviour. Sixth, suicidal behaviour was defined either by self-reported items or cases identified by ICD-10 coding of hospital inpatient and death registries. Therefore, some misclassifications are expected in individuals who may have underreported their symptoms, which may underestimate suicidal behaviour. In addition, there are known sex differences in the genetic influences of psychiatric disorders (Merikangas and Almasy, 2020) and sex-specific effects have also been identified in individuals with suicidal behaviour (Kia-Keating et al., 2007, Powers et al., 2020). We could not analyse our data stratified by sex, as sex-specific summary datasets for all datasets were not available. However, as larger, well-powered summary statistics become available, this could be addressed in the future. Lastly, this study is limited by the suicidal behaviour data that was publicly available. Because fatal suicidal behaviour is less common than non-fatal suicidal behaviour, there is less of data available for fatal suicides as GWAS studies of rare outcomes require more time and resources to obtain large sample sizes.

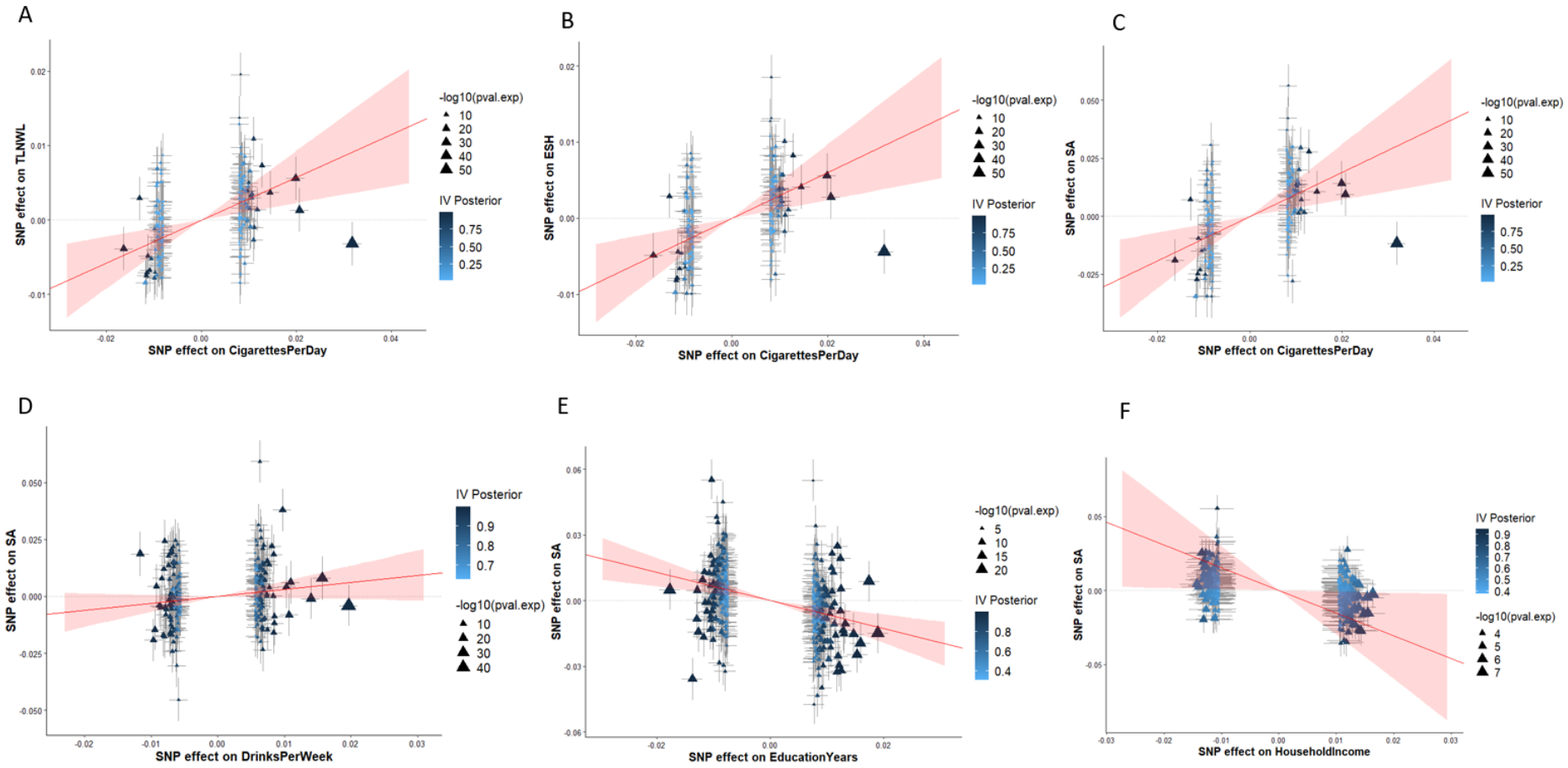
4.8 Conclusions

In conclusion, our study results support previous findings of genetic overlap between suicidal behaviour and psychiatric disorders. This highlights the importance of further investigation into the overlapping influences of these phenotypes with larger sample sizes and diverse ancestry. Understanding the biology reflected by this commonality may provide novel mechanistic insights that could help prioritise targets for suicidal behaviour for early intervention.

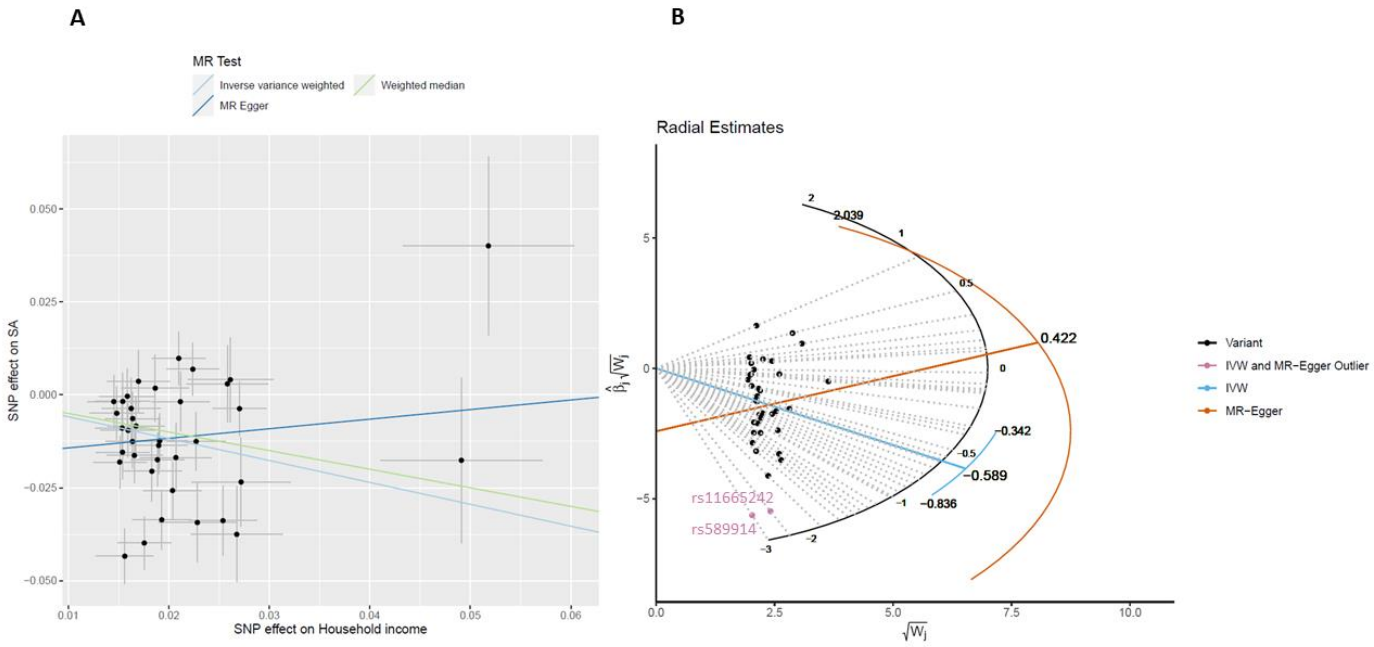


*Supplemental Figure 4.1 Scatter plots to visualize the causal effect of cigarettes smoked per day on suicidal behaviour risk. (A) TLNWL, (B) ESH and (C) SA. The Radial plot (D) of SNP-suicide attempt associations (beta*sqrt(Wj)) versus SNP-cigarette smoked per day level associations (sqrt(Wj)), with the outlier in purple.*

SNP = single nucleotide polymorphism; TLNWL = Thought life is not worth living; ESH = Ever self-harmed; SA = Suicide attempt; MR = Mendelian randomization; IVW = inverse variance weighting.



Supplemental Figure 4.2 Visualisation of MR-APSS results using the default instrument variable (IV) threshold of $5x10^{-5}$. The estimated causal effect is indicated by a red line with 95% confidence interval indicated by a shaded area. Triangles indicate observed SNP effects with error bars. A valid instrument variable is indicated by dark blue triangle and invalid instrument by light blue triangle. SNP effects on (A) cigarettes per day and TLNWL, (B) cigarettes per day and ESH, (C) Cigarettes per day and SA, (D) Drinks per week and SA, (E) Education years and SA and (F) Household income and SA are shown.



Supplemental Figure 4.3 Scatter plot (A) and radial plot (B) of the effect of household income on the risk of a suicide attempt

Chapter 5 Healthcare utilisation 12 months prior to fatal and non-fatal suicidal behaviour in Cape Town, South Africa

Kootbodien T, Bantjes J, Joska J, Asmal L, Chiliza B, Stallones L, Holtman Z, Martin LJ, Ramesar RS, London L. Healthcare utilisation 12-months prior to fatal and non-fatal suicidal behaviour in Cape Town, South Africa. *Archives of Suicide Research*, accepted.

Contributions of co-authors and candidate:

I contributed to the design of the study, performed the analysis and wrote the full draft and final version of this paper. My co-authors, JB, JJ, LA, CB, LS, ZH, LJM, RSR and LL, reviewed the draft and contributed to the final draft of the paper.

The previous three papers examined the sociodemographic, environmental and genetic risk factors associated with suicidal behaviour, to identify populations at risk. This study is the third publication mapping the epidemiology of suicide and aims to answer the research question, *what opportunities for suicide prevention can be identified for individuals at risk of suicidal behaviour?* This study is a retrospective cohort analysis using linked electronic health records of patients who attempted suicide and those who died by suicide.

5.1 Abstract

The purpose of this study was to characterise healthcare use for medical and mental health one year before suicidal behaviour among individuals with fatal and non-fatal suicidal behaviour (NFSB) in Cape Town, South Africa. We linked electronic health records of 484 participants from a case series of 93 fatal suicides on whom forensic autopsies were performed at a mortuary in Cape Town, between August 2014 and January 2016; and 391 patients admitted to hospital following NFSB between June 2014 and March 2015, and between August 2015 and August 2017. Time from the last healthcare visit to the date of suicidal behaviour (fatal or non-fatal) was calculated, and Kaplan Meier curves were used to compare the differences by psychiatric diagnoses and study group. Overall, 64.5% of fatal suicides and 65.9% of NFSB patients sought general healthcare in the year before exhibiting suicidal behaviour. Most of these visits occurred at hospital outpatient clinics (40.8%) and primary healthcare facilities (31.3%). The prevalence of pre-existing psychiatric diagnoses and the use of mental healthcare services was lower for individuals who died by suicide compared to NFSB patients. Common reasons for a healthcare visit among individuals with fatal suicidal behaviour were chronic disease and assault; and among NFSB patients, reasons were psychiatric illness (depression, bipolar and/or substance use disorders), chronic disease and HIV. A large proportion of individuals with fatal and NFSB interacted with the healthcare system before suicidal behaviour. These findings suggest opportunities for suicide prevention at primary healthcare facilities, antiretroviral treatment centres and emergency departments.

Keywords: healthcare utilisation; non-fatal suicidal behaviour; fatal suicide; access

5.2 Introduction

Suicide prevention is a public health priority, with the global suicide rate estimated at 11.2 per 100 000 population (Naghavi, 2019), and the lifetime prevalence of non-fatal suicidal behaviour (NFSB) estimated to be between 0.4% and 4.2% (Bertolote et al., 2005). Suicide prevention is challenging particularly because the risk of suicidal behaviour is difficult to predict accurately (Franklin et al., 2017), the causes of suicidal behaviour are multifactorial (Turecki and Brent, 2016), and the low base rate of fatal suicide impedes research in this area (Bunney et al., 2002). Furthermore, suicide prevention efforts in low- and middle-income countries (LMICs) are hampered by the scarcity of medical resources, competing for public health demands, and limited reliable data on suicidal behaviour in these regions of the world (WHO, 2012). Consequently, much of what we know about the epidemiology of suicide and the science of suicide prevention comes from high-income industrialised countries in Europe and North America.

Psychiatric disorders, particularly mood, psychotic-spectrum, and substance use disorders, are well-established risk factors for suicidal behaviour (Cavanagh et al., 2003, Nock et al., 2010, Vijayakumar et al., 2011), suggesting that suicide prevention efforts should focus on increasing access to mental healthcare and improving health professionals' ability to identify and manage common mental disorders (Zalsman et al., 2016). Data from high-income countries (HICs) suggests that primary healthcare settings may be particularly appropriate sites for targeted suicide prevention, since rates of suicidal behaviour are typically marked among patients with medical conditions, including HIV (Ahmedani et al., 2014), and contact with primary healthcare providers in the time leading up to suicide is common (Stene-Larsen and Reneflot, 2017). Earlier, a systematic review reported that 45% of suicide decedents had contact with primary healthcare services in the preceding month (Luoma et al., 2002), and a recent meta-analysis found that 80% of suicide decedents had contact with primary healthcare

services in the year before completing suicide, and 31% had contact with mental healthcare services (Stene-Larsen and Reneflot, 2017).

Contact with mental health services before suicide seems to be less common than contact with primary healthcare services in general. For example, one systematic review found only 32% of suicide decedents had contact with mental healthcare services in the year before suicide, and 19% within one month before suicide (Luoma et al., 2002); and another meta-analysis found that in the year before death, only 18.3% of suicide decedents had contact with inpatient mental health services and 26.1% had contact with outpatient mental health services (Walby et al., 2018). Approximately 64% of individuals who died by suicide accessed primary care services in the year before death (Ahmedani et al., 2014). While this pattern of contact with the healthcare system before engaging in suicidal behaviour is well established in high-income countries, it is not clear if the same is true in low-resource settings where mental healthcare workers are comparatively scarce. Establishing if the same pattern of contact with the healthcare system exists among suicidal individuals in LMICs could have important implications for the allocation of suicide prevention resources and suicide prevention programmes in resource-constrained environments.

There are several reasons why patterns of healthcare utilisation among suicidal individuals in LMICs may differ from those observed in HICs. For one thing, healthcare in LMICs is inaccessible and unaffordable compared to many HICs (Kruk et al., 2009, Petersen et al., 2019). Furthermore, several studies from LMICs report that individuals with psychiatric disorders have considerably less contact with healthcare services than those from HICs. The World Health Organisation World Mental Health Survey found that approximately 2% of Nigerian respondents had contact with mental healthcare services in the last year, compared to 18% of individuals from the USA (Wang et al., 2007). Similar patterns of low mental

healthcare utilisation have been reported among individuals with psychiatric conditions in Rwanda (Umubyeyi et al., 2016) and Tunisia (Khiari et al., 2019). It is within this context, that we investigated the prevalence and timing of healthcare utilisation 12 months before suicidal behaviour among individuals who died by suicide or engaged in medically serious NFSB, in Cape Town, South Africa.

South Africa, an Upper-Middle Income Country (UMIC), has a reported suicide rate of 12.8 per 100 000 with the lifetime prevalence of NFSB estimated at 2.9% (Joe et al., 2008). The country's health system has been characterised as a resource-constrained environment and has been described as 'weak' compared to even LMICs (Chopra et al., 2009). Furthermore, the country's healthcare system is under considerable strain due to four "colliding epidemics" (i.e., HIV and tuberculosis; chronic illness and mental health; injury and violence; and maternal, neonatal and child health) (Chopra et al., 2009, Mayosi et al., 2012). Access to mental healthcare is restricted in South Africa (Marais and Petersen, 2015), and the treatment gap for mental disorders is large in South Africa (Docrat et al., 2019a), especially for individuals living with HIV (Ruffieux et al., 2021). In addition, there is no national suicide prevention strategy as yet (WHO, 2018b), and to date, no studies have explored the pattern of healthcare utilisation among individuals in the period before engaging in fatal or non-fatal suicidal behaviour.

5.3 Methods

This retrospective descriptive study aimed to describe health care utilisation in 12 months leading to suicidal behaviour and to compare patterns of health service contact by individuals with suicidal behaviour and psychiatric diagnoses.

5.3.1 Source of participants

Data were collected from two sources (n=552); patients admitted to hospital for medically serious NFSB (i.e., self-directed violence with non-zero intent to die which resulted in admission to hospital but did not result in death), and individuals who died by suicide. The sample of NFSB patients (n=413) was recruited from three hospitals (two tertiary and one secondary level hospital) in Cape Town, between June 2014 and March 2015, and between August 2015 and August 2017. The sample of individuals who died by suicide (n=139) was recruited over two years from all cases at the Salt River mortuary in Cape Town between August 2014 and January 2016. Forensic autopsies were performed by a forensic pathologist to confirm suicide as the cause of death. No individuals were included in both the NFSB and the fatal suicidal behaviour groups and were confirmed by comparing full name, sex and date of birth for duplicates in the two groups.

5.3.2 Data collection

Trained healthcare professionals collected data for NFSB patients from medical records and interviews with hospitalised patients once they were medically stable and able to provide consent. Data for suicide decedents were collected from mortuary records and family members who were interviewed by a forensic officer using a structured questionnaire. The data collected from participants included: identifying information (i.e., name, date of birth, identity number, hospital number, and admission date); demographic information (i.e., age and sex); method of self-injury (i.e., hanging, gunshot, drug poisoning, pesticide poisoning, chemical poisoning, gas poisoning and other) and medical history in the preceding five years (i.e., previous NFSB, past medical and psychiatric history, medications prescribed, and exposure to violence).

Data about healthcare utilisation in the preceding 5 years were sought for all participants from the Provincial Health Data Centre (PHDC) of the Western Cape. The PHDC links all

person-level health data collected by public hospitals, community health centres and primary healthcare clinics in the province (Boulle et al., 2019). Primary healthcare clinics provide basic essential health services based on the need of the community while community health centres provide, in addition, maternity and emergency services.

Participant information was matched with electronic PHDC records to obtain information about healthcare utilisation including the site (i.e., primary healthcare facility, community health centre, or hospital admissions), the reason for accessing care (e.g., treatment for HIV, TB, and chronic diseases), laboratory data, prescription and dispensing data, and the number of appointments. Electronic health data were retrieved, using reliable algorithms consisting of various combinations of demographic data and utilisation linkups to match patients with reasonable certainty if the hospital number or ID number was not available. In this way, healthcare utilisation data were obtained for approximately 88.0% (n=484) of participants: 66.9% (93/139) of suicide decedents and 95.1% (391/411) of NFSB patients. Approximately 33% of decedents and 5% of NFSB patients could not be traced and were therefore not included in the analysis.

Diagnosis of a psychiatric or substance use disorder was recorded using ICD-10 codes, including bipolar affective disorder (F31), schizophrenia (F20-F29), depressive disorders (F32) and mental and behavioural disorder due to a psychoactive substance (F10 to F19). Information for psychiatric and substance use disorders was also obtained from medical records where these had been recorded or were inferred by the prescription of psychotropic medications.

A broad range of ICD-10 codes (X85-Y09, indicative of assault) was used to identify a history of injury and violence. HIV diagnoses were determined by positive laboratory results and/or evidence of being on antiretroviral treatment and attending an HIV treatment centre. A

history of NFSB was indicated by ICD-10 code Z91.5 (personal history of self-harm) and a previous admission for self-harm (X60-X84). Head injury was indicated by ICD-10 codes S00-S09 and T90. A diagnosis of diabetes (E10-E14), cardiovascular disease (I00-I52), cancer (C00-D48), and/or neurological conditions (G00-G99) indicated a chronic disease other than HIV.

Healthcare utilisation was defined as any medical-related visit to a primary care or hospital-based facility. Mental healthcare utilisation was defined as a mental health-related visit to a mental health inpatient care facility, mental health outpatient clinic at a hospital or primary mental healthcare service.

5.3.3 Data analysis

Data were checked, cleaned, and analysed in Stata version 15. Descriptive statistics were used to describe sample characteristics. Means and standard deviations were used to summarise normally distributed continuous variables, and a t-test was used to compare means across the fatal and NFSB groups. Categorical variables were summarised using frequencies and percentages and compared using Pearson's chi-square or Fisher's exact test, as appropriate.

Time to event was defined as the number of days between the last health facility visit and suicidal behaviour (fatal or non-fatal). Kaplan Meier curves were used to compare differences in patterns of healthcare utilisation by psychiatric diagnoses and study groups. Tests for equality of nonparametric comparisons were performed using log-rank tests. The relationship between covariates and time from the last facility visit to suicidal behaviour was modelled using Cox proportional hazards model. Covariates included age, sex, chronic disease, psychiatric or substance use disorder diagnoses, previous NFSB, HIV, head injury and a history of assault. Variables with a p-value lower than 0.2 were included in a multivariate

Cox regression model. Both adjusted and unadjusted hazard ratios (HR) and 95% confidence intervals (CI) were calculated. The significance level was set to 0.05.

5.3.4 Ethical considerations

Ethical approval for this study was obtained from the Stellenbosch University Health Research Ethics Committee (reference number: N13/05/074) and the University of Cape Town Health Science Faculty Human Research Ethics Committee (reference numbers: 645/2013, 393/2014, 073/2014, 219/2015 and 461/2019). Institutional permission was also secured from the relevant authorities in the Department of Health. Written informed consent was obtained from NFSB patients before data collection, and all data were collected by trained mental health professionals. For suicide decedents, informed consent was obtained from a family member of the deceased before data collection. All de-identified data were securely stored on password-protected computers.

5.4 Results

5.4.1 Sample characteristics

The final sample consisted of 484 individuals with linked electronic health records: 93 individuals who died by suicide and 391 patients with NFSB. Compared to NFSB patients, fatal suicides were significantly older (mean age:35.6 years vs. 32.4 years, p=0.030), and two-thirds were men (66.7% vs. 37.3%, p<0.001). Approximately 76.2% (298/391) of NFSB patients were admitted to a tertiary hospital and 23.8% (93/391) were admitted to a secondary hospital at the time of attempted suicide. There was no significant difference in age (30.4 years vs. 33.1 years, p=0.231) or sex distribution (32.3% vs. 38.9%, p=0.246) between NFSB patients receiving secondary and tertiary levels of care.

The prevalence of a known psychiatric disorder and/or chronic disease, including HIV, diagnosed at the time of suicidal behaviour or in the preceding 5 years is provided in Table 5.1. NFSB patients were more likely than those who died by suicide to have a known psychiatric condition before suicidal behaviour (47.3% vs 19.4%, $p<0.001$). Hanging (48.9%) was the most common method of fatal suicide, followed by drug poisoning (29.6%) and pesticide poisoning (10.3%). Drug poisoning, defined as intentional self-poisoning by non-opioid analgesics, anti-epileptics, psychotropic drugs, narcotics, other drugs acting on the nervous system and/or unspecified drugs and biological substances, was the most common method of NFSB (30.9%); however, approximately 62% (n=242) of NFSB patients had no information on the method of self-harm. Compared to NFSB patients, suicide decedents had a significantly higher prevalence of chronic disease (18.2% vs. 10.0%, $p=0.030$); and a non-significant higher prevalence of history of assault (5.4% vs 3.1%). Of the 17 individuals with a history of assault, 13 (76%) were men. There was no significant difference in the prevalence of HIV between suicide decedents (4.5%) and NFSB patients (5.7%).

Table 5.1 Comparison of psychiatric diagnoses, method of self-injury and medical history by suicidal behaviour

Characteristic	**Fatal SB (n=93)**	**NFSB (n=391)**	**p-value**
Psychiatric history before outcome diagnosis			
Any mental health diagnosis (n, %)	18 (19.4)	183 (47.3)	<0.001
Depression (n, %)	11 (12.0)	95 (24.3)	<0.001
Bipolar disorder (n, %)	4 (4.5)	14 (3.6)	0.683†
Schizophrenia (n, %)	0	16 (4.1)	0.052†
History of NFSB (n, %)	2 (2.3)	28 (7.2)	0.093†
Substance use disorder (n, %)	2 (2.3)	36 (9.3)	0.028†
Method of self-injury			
Hanging (X70)	43 (48.9)	2 (0.5)	
Drug poisoning (X60-X64)	26 (29.6)	121 (30.9)	
Pesticide poisoning (X68)	9 (10.3)	7 (1.8)	
Gunshot (X72-X74)	2 (2.3)	0 (0)	
Chemical poisoning (X66)	2 (2.3)	3 (0.8)	
Gas poisoning (X67)	1 (1.1)	1 (0.3)	
Intentional self-harm with a blunt or sharp object (X78-X79)	1 (1.1)	12 (3.0)	
Other‡	4 (4.6)	3 (0.8)	
Unknown	0 (0)	242 (61.9)	§
Medical history			
Chronic disease (n, %)	16 (18.2)	39 (10.0)	0.030
History of assault (n, %)	5 (5.4)	12 (3.1)	0.223
HIV diagnosis (n, %)	4 (4.5)	22 (5.7)	0.800†
Head injury (n, %)	2 (2.3)	12 (3.1)	0.686†

† Fisher's exact test, ‡ Other includes jumping in front of moving object (X81), burning (X76) and intentional self-harm by unspecified means (X84), § analysis could not be done due to many missing values.

5.4.2 Healthcare utilisation

Approximately 65.5% (317) of individuals visited a healthcare facility at least once in the 12 months before engaging in any form of suicidal behaviour, over half (53.4%, 261) within the previous six months, one-quarter (25.4%, 123) within four weeks and 12.2% (59) within two weeks. There were no significant differences between individuals who visited a healthcare facility at least once (64.5% vs. 65.9%, p=0.899) or accessed mental health services at least once (20.0% vs. 27.6%, p=0.226) by fatal and non-fatal suicidal behaviour in the preceding 12-months (Table 5.2). However, on average, NFSB patients had more visits to a healthcare facility for any general medical condition (15.8 vs. 12.3, p=0.013) and had longer hospital stays (1.3 days vs. 0.5 days, p=0.001) than fatal suicides. Of the general medical visits before suicidal behaviour, hospital outpatient clinic visits (40.8%) and primary care visits (31.3%) were the most common for both groups combined. Before suicidal behaviour, primary healthcare outpatient visits were more common among NFSB patients than fatal suicides (78.6% vs. 56.5%, p=0.017). There were no significant differences in the utilisation of any healthcare or mental healthcare service at six months, four weeks, and two weeks before suicidal behaviour by group (Figure 5.1).

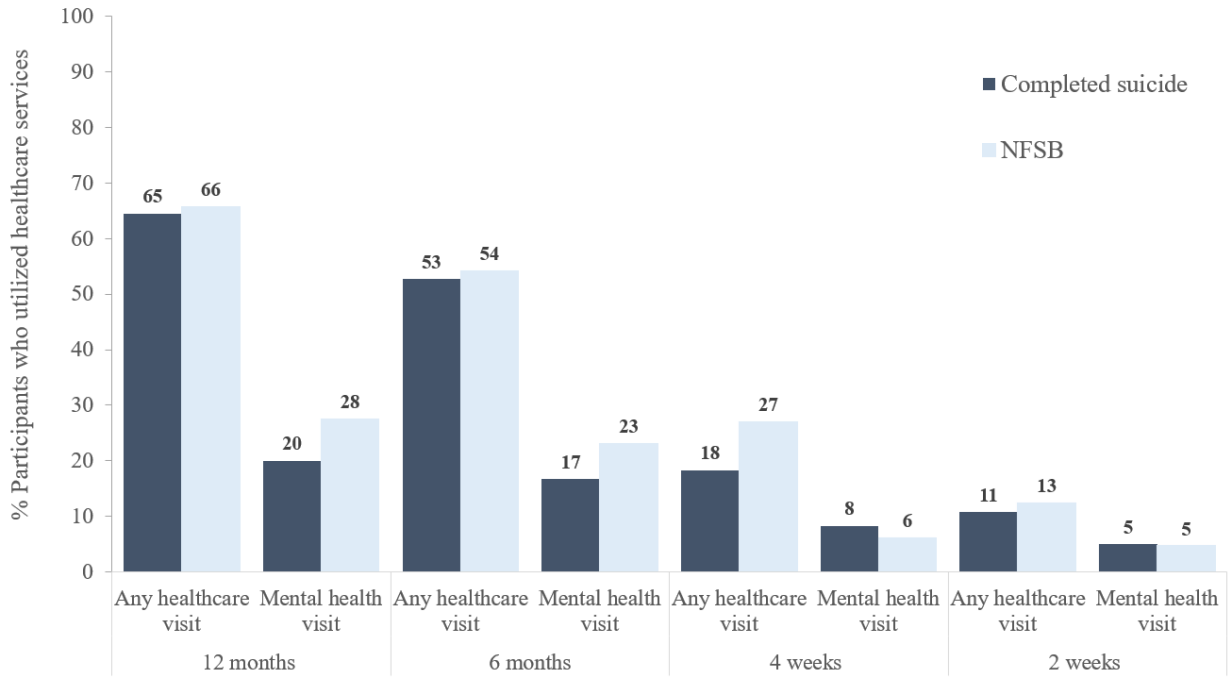


Figure 5.1 Percentage of any healthcare and mental health visits by participants who died by suicide and NFSB patients at 12 months, six months, four weeks and two weeks

When stratifying NFSB patients by level of care, there was no difference in the utilisation of any healthcare service 12 months before suicidal behaviour across three groups (fatal suicidal behaviour, 64.5%; NFSB patients receiving secondary level care, 72.0% and NFSB patients receiving tertiary level care 63.1%, p=0.284). However, the utilisation of mental health services 12 months before suicidal behaviour differed significantly across the three groups (fatal suicidal behaviour, [12/60] 20.0%; NFSB patients receiving secondary level care, [73/188] 38.8% and NFSB patients receiving tertiary level care [9/67] 8.9%, p<0.001).

Table 5.2 Participants who visited healthcare facilities at 12 months, 6 months, 4 weeks, and 2 weeks before suicidal behaviour

Variable	**Fatal SB (n=93)**	**NFSB (n=391)**	**p-value**
12 months before suicidal behaviour			
Any healthcare visit (n,%)	60 (64.5)	257 (65.7)	0.899
Mental health visit (n,%)	12 (20.0)	71 (27.6)	0.226
Average number of visits	12.3	15.8	0.013
Average length of stay (in days)	0.5	1.3	0.001
Total visits (n,%)	127	913	
Type of any healthcare visit in the past year			
Hospital admissions (n,%)	32 (25.2)	258 (28.3)	0.717
Hospital outpatient visits (n,%)	49 (38.6)	375 (41.1)	0.738
Primary healthcare (PHC) visits (n,%)	46 (36.2)	280 (30.6)	0.448
PHC outpatient visits	26/46 (56.5)	138/280 (78.6)	0.017
Pharmacy visits	7/46 (15.2)	36/280 (12.9)	0.869
ART clinic visits	2/46 (3.6)	15/280 (5.4)	0.914
Laboratory tests	11/46 (23.9)	45/280 (16.1)	0.543
6 months before suicidal behaviour			
Any healthcare visit (n,%)	49 (52.7)	212 (54.2)	0.790
Mental health visit (n,%)	10/60 (16.7)	59/257 (23.1)	0.344
Average number of visits	7.9	11.0	0.010
Average length of stay (in days)	0.7	1.5	<0.001
4 weeks before suicidal behaviour			
Any healthcare visit (n,%)	17 (18.3)	106 (27.1)	0.199
Mental health visit (n,%)	5/60 (8.3)	16/257 (6.2)	0.869
Average number of visits	4.0	6.5	0.025
Average length of stay (in days)	0.2	1.1	0.003
2 weeks before suicidal behaviour			
Any visit (n,%)	10 (10.8)	49 (12.5)	0.369
Mental health visit (n,%)	3/60 (5.0)	12/257 (4.7)	0.616
Average number of visits	4.0	4.5	0.683
Average length of stay (in days)	0.6	0.4	0.563

Kaplan-Meier curves for the length of time between the last contact or visit with any healthcare service and suicidal behaviour were represented by known psychiatric diagnoses and suicidal behaviour groups (Figure 5.2). There was a significant difference in the median length of time from the last contact with healthcare services to suicidal behaviour between participants with a previously diagnosed psychiatric disorder (58 days) and those with no psychiatric diagnosis (146 days; log-rank test, $p<0.001$) (Figure 5.2a). The probability of any healthcare visit 12 months before suicidal behaviour was approximately 0.84 for those with a known psychiatric disorder compared to 0.67 for those with no known psychiatric diagnosis. In addition, there was a significant difference in the median length of time from the last contact with a healthcare facility to suicidal behaviour for NFSB patients (94 days) compared to fatal suicide (156 days) (log-rank test $p=0.029$, Figure 5.2b). The probability of any healthcare visit before 12 months of suicidal behaviour was approximately 0.76 for NFSB patients and 0.66 for those who died by suicide.

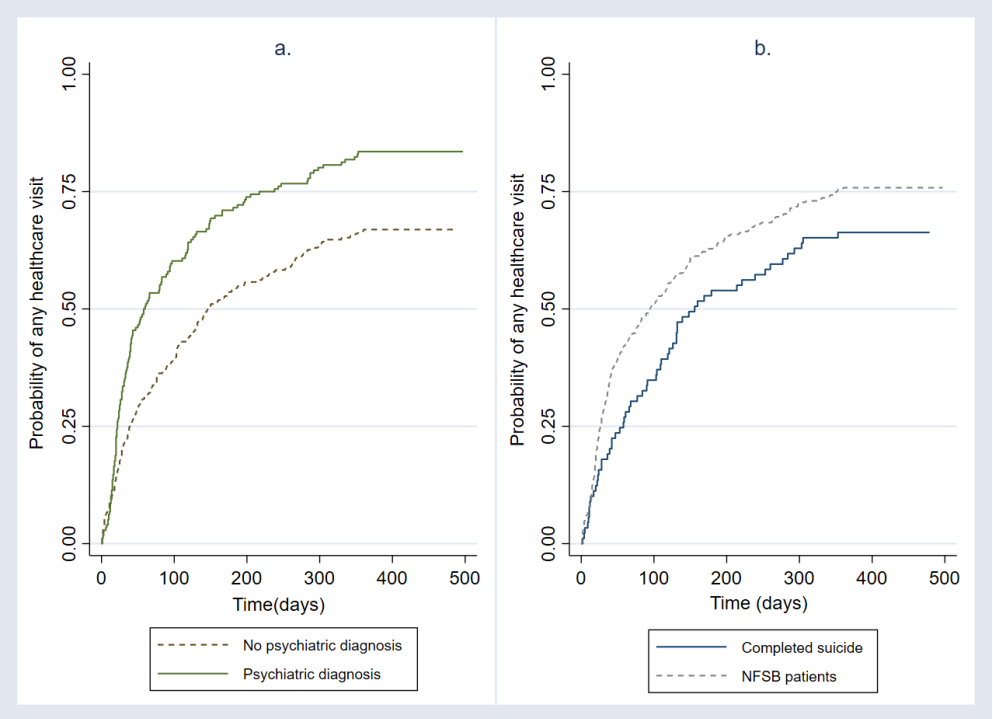


Figure 5.2 Kaplan-Meier estimates of time from the last health facility visit to suicidal behaviour in Cape Town, South Africa, by (a) psychiatric diagnosis and (b) suicidal behaviour

Table 5.3 displays the Cox-proportional hazards regression models of covariates that contributed independently to utilising healthcare services within a year of suicidal behaviour, for those who died by suicide (Model A), NFSB patients (Model B), and both groups combined (Model C). In Model A (fatal suicidal behaviour), the time from the last healthcare visit to death by suicide in the year before suicide was shorter for participants with chronic disease (adjusted HR=3.80, 95% CI 1.77-8.16) and history of assault (adjusted HR=3.85, 95% CI 1.36-10.92). In other words, individuals who died by suicide used healthcare services for the treatment of chronic diseases and injuries from assault in the year before dying. NFSB patients (Model B) used healthcare services in the year before attempting suicide, for the treatment of mental illness (depression [adjusted HR=1.88, 95% CI 1.36-2.61], bipolar disorder [adjusted HR=2.83, 95% CI 1.39-5.98], substance use disorder [adjusted HR=2.19, 95% CI 1.47-3.31]), chronic disease (adjusted HR=1.48, 95% CI 1.02-2.18), and HIV infection (adjusted HR=1.97, 95% CI 1.21-3.21). In the total population (n=484, Model C), fatal and NFSB patients used healthcare services in the year before suicidal behaviour for treatment of depression (adjusted HR=1.91, 95% CI 1.42-2.57), bipolar disorder (adjusted HR=2.37, 95% CI 1.30-4.29), substance use disorder (adjusted HR=2.24, 95% CI 1.52-3.30), chronic illness (adjusted HR=1.72, 95% CI 1.24-2.40) and HIV infection (adjusted HR=1.88, 95% CI 1.21-2.93).

Table 5.3 Cox proportional hazards regression analysis of factors associated with healthcare contact 12 months before suicidal behaviour in the study population

Variables	**Model A** (n=93) **Fatal suicidal behaviour**			**Model B** (n=391) **Non-fatal suicidal behaviour**			**Model C** (n=484) **All**		
	HR	**95% CI**	**p-value**	**HR**	**95% CI**	**p-value**	**HR**	**95% CI**	**p-value**
Age	1.00	0.98-1.02	0.673	1.01	0.99-1.02	0.400	1.00	0.99-1.01	0.447
Depressive disorder	1.38	0.60-3.14	0.447	1.88	1.36-2.61	<0.001	1.91	1.42-2.57	<0.001
Bipolar disorder	1.61	0.52-4.91	0.403	2.83	1.39-5.98	0.005	2.37	1.30-4.29	0.004
Substance use disorder	2.11	0.49-8.89	0.310	2.19	1.47-3.31	<0.001	2.24	1.52-3.30	<0.001
Chronic disease	3.80	1.77-8.16	0.001	1.48	1.02-2.18	0.043	1.72	1.24-2.40	0.001
HIV diagnosis	1.19	0.19-7.49	0.847	1.97	1.21-3.21	0.007	1.88	1.21-2.93	0.005
History of assault	3.85	1.36-10.92	0.011	1.13	0.58-2.17	0.713	1.72	0.75-2.19	0.367

5.4.3 Characteristics of participants not in contact with health services

Approximately 12% (66) of participants had not utilised healthcare services in the preceding five years, and 31% (169) of participants had not utilised healthcare services in the 12 months before suicidal behaviour but had done so more than one year ago. Among NFSB participants who had not utilised healthcare services in the past year, 26/136 (19.1%) NFSB patients received secondary-level care and 110/136 (80.1%) NFSB patients received tertiary-level care at the time of their suicidal behaviour. Approximately 61% of fatal suicidal behaviour patients who had not utilised healthcare services were men, with a mean age of 32.6 years (Supplementary Table 5.1), while 42% of NFSB patients were men, with a mean age of 30.8 years; 38% of patients had a known psychiatric diagnosis, of which depression was the most common (10.3%).

5.5 Discussion

Understanding the patterns of healthcare utilisation among individuals who engage in non-fatal and fatal suicidal behaviour has implications for planning suicide prevention programmes and resource allocation. This study sought to investigate patterns of healthcare utilisation in the 12 months preceding fatal and non-fatal suicidal behaviour in South Africa. Approximately two-thirds of individuals who engaged in non-fatal or fatal suicidal behaviour had visited a healthcare facility at least once in the 12 months preceding their suicidal behaviour. This pattern of healthcare utilisation before suicidal behaviour is in keeping with those reported in HICs, where primary healthcare contact in the past year typically ranges between 45% and 80% (Luoma et al., 2002, Stene-Larsen and Reneflot, 2017).

Nearly half of NFSB patients had a psychiatric disorder diagnosed previously before a suicide attempt, compared to one-fifth of those who died by suicide. However, we found no

difference in the frequency of mental health visits in the past year between suicide decedents and NFSB patients. Among those with psychiatric disorders, healthcare visits in the year before suicidal behaviour were associated with depression and HIV infection, while healthcare visits among those without a diagnosed psychiatric disorder were associated with chronic disease and HIV infection. These findings are in line with previous studies reporting high rates of suicidal behaviour among individuals receiving HIV treatment in South Africa (Bantjes and Kagee, 2021) and highlight the potential for suicide prevention to be integrated into primary healthcare settings.

The prevalence of at least one mental health visit in the last 12 months (20.0%) among those who died by suicide was lower in this study than previously reported in high-income countries (26% to 67%) (Schaffer et al., 2016, Walby et al., 2018). We found that 27.6% of NFSB patients utilised mental health services in the preceding 12 months, which is in keeping with the findings of a systematic review reporting that, on average, 30% of individuals reporting suicidal ideation or NFSB had contact with mental healthcare services in the preceding year (Hom et al., 2015).

We found no record of a mental health diagnosis among 80% of suicide decedents, which is significantly lower than the findings reported in a meta-analysis of 27 studies from HICs, where 87% of suicide decedents had a record of a mental disorder (Arsenault-Lapierre et al., 2004). It is not known in our study whether suicide decedents who used any healthcare service in the year before death (65%) had recognisable mental disorder symptoms. Individuals may choose not to disclose their suicidal thoughts to a healthcare provider for fear of stigmatisation, shame or embarrassment (Frey et al., 2016), or involuntary hospitalisation (Blanchard and Farber, 2020). It is possible that among our sample of fatal suicides, there were individuals who had undiagnosed mental health conditions, even though they were in

contact with healthcare providers in the 12 months before completing suicide. Treatment rates among people with mental disorders are low in South Africa (Jack et al., 2014, Bantjes et al., 2020), and it seems plausible that among our sample of those who died by suicide, a large number had undiagnosed and hence unmanaged psychiatric conditions, which would have significantly increased their risk of suicide (Cavanagh et al., 2003, Nock et al., 2010, Vijayakumar et al., 2011). Depression was the most common mental disorder diagnosed in our study population, and among NFSB patients, healthcare visits in the past year were significantly associated with diagnosis of depressive, bipolar affective, and substance use disorders. Future psychological autopsy studies may help to shed light on the prevalence of mental disorders among South African with fatal suicide behaviour and the implications of this for suicide prevention.

Our finding of relatively high healthcare utilisation in the year preceding suicidal behaviour strongly suggests that it may be helpful to integrate suicide prevention strategies into primary healthcare settings in South Africa, as has been suggested in HICs (Ahmedani et al., 2014, Luoma et al., 2002, Stene-Larsen and Reneflot, 2017). Training primary healthcare physicians to identify and manage mental health problems is an empirically supported suicide prevention strategy (Mann et al., 2021), which may be effective in South Africa. This recommendation is supported by a population-attributable risk analysis showing that identifying and treating common mental disorders in HIV treatment centres in South Africa could result in as much as a 63.4% proportional decrease in the prevalence of suicide risk among patients receiving antiretroviral therapy (Bantjes and Kagee, 2021). However, implementing suicide screening procedures in primary healthcare settings is far from simple. This may be due to the shortage of healthcare professionals in South Africa (Docrat et al., 2019a), and the low sensitivity and high false positive rate of the available suicide screening instruments to reliably and accurately identify individuals at risk of engaging in suicidal

behaviour (Rudd, 2021) and the absence of adequate referral pathways for patients identified as high risk. Healthcare settings can play a role in suicide prevention by implementing risk screening with an appropriate follow-up of at-risk individuals. Thus, suicide risk screening should be part of a program and in the absence of a national prevention policy in South Africa, the integration of suicide screening and interventions in the healthcare system should be clearly outlined. It has been suggested that machine learning-based suicide risk algorithms targeting electronic health records could be a more reliable approach to identifying at-risk patients (Simpson et al., 2021), but it seems unlikely that this will be viable in most LMICs.

Strength and limitations

Our study is one of only a few in an LMIC that has retrospectively tracked healthcare utilisation among individuals who have died by suicide or engaged in medically serious NFSB and lends support to the idea that suicide prevention strategies should be integrated into primary healthcare settings in South Africa. However, the study has limitations. We obtained electronic clinic data on suicidal behaviour patients utilising public health services. Since all fatal suicides, irrespective of whether they have utilised public or private healthcare services, are confirmed by a forensic pathologist at a state mortuary, we had access to the full population of suicide decedents. However, in one-third of the suicide decedents, there was insufficient identifier information to enable a trace to be made in the provincial data centre dataset leaving us with a 33% non-response rate in this sub-group.

Additionally, according to a recent South African household survey, approximately 15% of individuals had private health insurance and predominantly accessed private care, while an estimated 27% of households reported using private healthcare services as their primary access point to healthcare (Statistics South Africa, 2020). Therefore, it is likely that utilization data may not have been available for NFSB patients and those who died by suicide

who accessed private healthcare services. The missing data could also be explained by the movement into the province by internal migrants for individuals seeking employment opportunities. Therefore, participants could have visited healthcare facilities in other provinces in the year preceding suicidal behaviour, and it would not have been recorded in the database.

The missing data on suicide decedents may have introduced bias. We used a complete-case approach when analysing the time-to-event data, which, while it resulted in reduced sample size and power of the analysis. Missing data on individuals with fatal suicide were more likely to occur where no contact occurred, potentially leading to over-estimation of contact rates. Our study compared how individuals at high risk of suicidal behaviour (fatal suicide or medically serious non-fatal suicidal behaviour) accessed healthcare services. This study does not include a control group from the general population, which limits our understanding of how suicide decedents or individuals with NFSB utilised healthcare services compared to the general population. Nonetheless, even in the absence of such contextual information, it is still possible from these data to identify opportunities for potential intervention to reduce harmful outcomes amongst this high-risk population. Sociodemographic information on fatal suicides was based on medical records and an autopsy database, whereas NFSB patients completed questionnaires. Therefore, we could not determine additional sociodemographic factors associated with healthcare contacts such as education levels and socioeconomic characteristics, as this information was not available on the deceased participants. We could not assess the severity of the mental illness as this could not be determined from ICD-10 codes. In addition, the study findings were based on the accuracy and completeness of clinicians/administrators providing appropriate ICD-10 codes for each encounter at health facilities. A large proportion of ICD-10 codes (62%) was missing on the method of suicide,

among the NFSB patients. The omission of ICD-10 codes meant that we could not analyse suicide methods by suicidal behaviour and by healthcare contact.

5.6 Conclusion

In conclusion, understanding patterns of healthcare utilisation by suicidal individuals in low-resource settings could help to inform where prevention strategies should be allocated for maximum benefit. Our data show that there may be considerable potential for targeted suicide prevention in primary healthcare settings and HIV treatment centres in SA. This study highlights the scope and opportunity of linking electronic health records with person-level data for retrospective surveillance of individuals who attempt suicide and who die by suicide. More research is needed to identify cost-effective and sustainable interventions that could be effectively employed in these settings and may include improving the capacity of primary healthcare workers to identify and manage individuals at risk of suicidal behaviour. Further research is also needed to identify those who do not access healthcare services before suicide.

Supplemental Table 5.1 Characteristics of participants who had not utilised healthcare services in the 12 months before suicidal behaviour (n=169)

Characteristic	**Fatal SB**	**NFSB**
n	33	136
Age (mean ± SD)	32.6 ± 13.5	30.8 ± 12.6
Age group		
18-34 years	23 (69.7)	101 (74.3)
35-50 years	7 (21.2)	23 (16.9)
51-64 years	2 (6.1)	10 (7.4)
65+ years	1 (3.0)	2 (1.4)
Sex (% male)	20 (60.6)	57 (41.9)
Psychiatric history		
Any mental health diagnosis (n,%)	1 (3.0)	51 (37.5)
Depression (n,%)	1 (3.0)	14 (10.3)
Bipolar disorder (n,%)	0 (0)	0 (0)
Schizophrenia (n,%)	0 (0)	3 (2.2)
Substance use disorder (n,%)	0 (0)	2 (1.5)
History of NFSB (n,%)	0 (0)	7 (5.2)
Medical history		
Chronic medical condition (n,%)	0 (0)	3 (2.2)
History of assault (n,%)	0 (0)	2 (1.5)
HIV diagnosis (n,%)	0 (0)	2 (1.5)
Head injury (n,%)	1 (3.0)	3 (3.4)

Chapter 6 Discussion and Conclusions

Suicide is a leading cause of death throughout the world and remains one of the greatest challenges facing health services, researchers and clinicians to date. It should be clear by this point that suicidal behaviour is a result of the complex interaction between many factors including biological, psychological, environmental, occupational, social and cultural factors that contribute to increased risk, necessitating a multisectoral approach for comprehensive suicide prevention strategies (WHO, 2018b). This chapter draws on the accumulated evidence from multiple data sources, both local to South Africa, and internationally, using methodologies presented in Chapters 2 to 5 and aims to synthesise findings to improve our understanding of the burden of suicidal behaviour. This concluding chapter reflects on the overall findings in terms of their implications for suicide prevention and future research and describes the overall limitations of this study.

6.1 Synopsis of findings

The overall aim of this thesis was to provide insights into patterns and predictors of suicide behaviour in South Africa and to identify opportunities for targeted suicide prevention strategies. The specific objectives included: (i) describing the changes in suicide mortality rate in South Africa over 20 years from 1997 to 2016 to enhance our understanding of long-term trends in suicide to identify populations at risk and examine other cause of death categories that may include suicide, (ii) investigating the association between environmental and occupational organophosphate pesticide (OP) exposure in the general population and attempted suicide in adults living in Cape Town, South Africa, in a hospital-based case-control study, (iii) exploring the genetic architecture underlying suicidal behaviour and psychiatric disorders to understand the contribution of genetic factors to the risk of suicidal behaviour using genome-wide summary data, and (iv) linking electronic health records to

compare the patterns in the use and timing of healthcare services 12 months before suicidal behaviour for individuals who died by suicide or attempted suicide in Cape Town, South Africa.

The present study aimed to define the problem of suicide in South Africa by analysing mortality data over time and identifying risk and protective factors through a series of epidemiological investigations to highlight opportunities for suicide prevention strategies for maximum reach and impact. A summary of chapters, analytic approaches and key findings are presented in Table 6.1. The overall thesis findings are summarised within the framework of the conceptual suicide model (Figure 6.1).

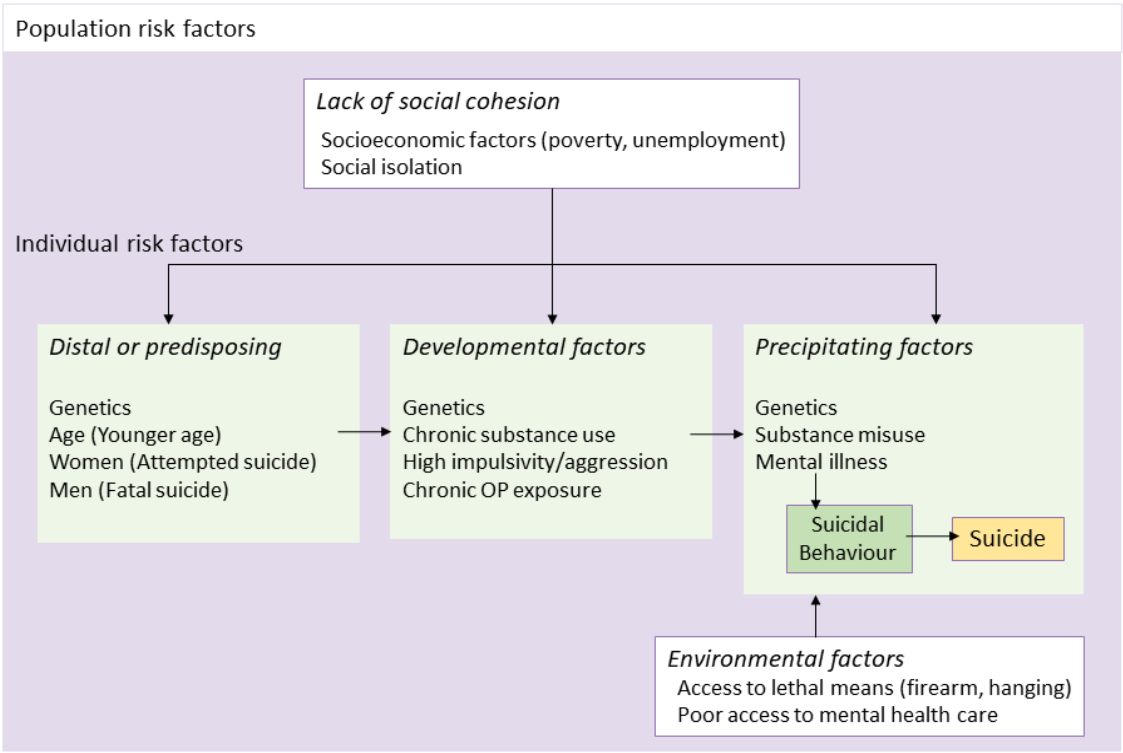


Figure 6.1 Model of suicide risk at the population and individual level (adapted from Turecki and Brent, 2016): graphical summary of thesis findings

In Chapter 2 (Study 1), we reported substantial underreporting of suicide deaths. We observed an increase in suicide rates among young people ages 15 to 29 years. Hanging, poisoning and firearm deaths were the most frequent methods used. There was an increase in

suicide by hanging and poisoning over 20 years from 1997 to 2016, highlighting the burden of suicide in South Africa. The largest proportion of suicide deaths were potentially misclassified as accidental hanging and hanging by undetermined intent, and to a lesser extent, accidental poisoning and poisoning by undetermined intent. In contrast, firearm-related deaths were more likely to indicate a homicide than a suicide death.

In Chapter 3 (Study 2), we explored the association between an understudied environmental risk factor, OP exposure and attempted suicide and found that household and occupational exposure to OP was unrelated to attempted suicide. In Chapter 4 (Study 3), the study demonstrated strong genetic correlations between suicidal behaviour traits i.e., ideation, attempt, self-harm and moderate-to-strong genetic correlations between suicidal behaviour and psychiatric disorders i.e., major depression, bipolar disorder, schizophrenia, PTSD, alcohol use disorder and ADHD. We found that a common factor structure fit the data best for suicidal behaviour traits, major depression, alcohol use disorder and ADHD, suggesting a common genetic pathway to suicidal behaviour through major depression, alcohol use disorder and ADHD. In addition, we identified 2,951 genes and 98 sub-network hub genes associated with the common factor, including pathways associated with developmental biology, signal transduction and RNA degradation. We identified several drug-gene interactions, involving genes in the common or shared genetic pathways that may be worth investigating as potential targets for the prevention and treatment of the common factor.

In Chapter 5 (Study 4), we reported that approximately two-thirds of cases had at least one prior visit to a healthcare facility in the 12 months leading to suicidal behaviour, which suggests opportunities for early intervention. There was no difference between individuals who died by suicide and attempted suicide who accessed healthcare services (~65%) in the year leading to suicidal behaviour.

Table 6.1 Summary of thesis results chapters including methodology and findings

Chapter	Objective	Covariates	Suicidal behaviour	Study design	Methodology	Findings
2	To determine trends in suicide mortality to identify populations at risk in South Africa from 1997 to 2016, and examine other causes of death categories that may include suicide.	Age, sex, method of suicide	Fatal suicide	Surveillance of nationally representative vital registration data	Suicide (X60-X84 and Y87), undetermined intent (Y10-Y34), accidental death and homicide was coded using ICD-10 codes; joint point regression analysis of ASMR and YLL to generate trends.	Suicide mortality was higher in men than women in the 20 years. Hanging and poisoning were the most frequent methods used. There was a significant increase in suicide rates by hanging and poisoning. Suicide rates were substantially underreported. Suicide deaths were potentially misclassified among hanging and poisoning-related deaths.
3	To investigate the association between environmental and occupational OP exposure in the general population and attempted suicide in adults living in Cape Town, South Africa	OP exposure in home & garden, Hazardous drinking Unemployment	Attempted suicide	Hospital-based case-control study	Conditional logistic regression modelling of attempted suicide cases & matched (by age, sex and timing of hospitalisation) non-psychiatric hospital controls	Household pesticide use was common (85%). Attempted suicide was not associated with environmental and occupational OP exposure, but was associated with hazardous drinking and unemployment with no household income while sharing the house with more than three persons was protective.
4	To explore the genetic architecture underlying suicidal behaviour and psychiatric disorders to understand the contribution of genetic factors to the risk of suicidal behaviour using genome-wide summary data	Psychiatric disorders Household income Education years Smoking Drinking frequency	Suicidal ideation Attempted suicide Self-harm Fatal suicide	Genome-wide association study (GWAS)	Linkage disequilibrium Score Regression (LDSC); Genomic structural equation modelling (GenomicSEM)	Strong genetic correlations were observed between suicidal ideation, attempted suicide and self-harm and moderate-to-strong genetic correlations between SB traits and a range of psychiatric disorders, notably MDD. Multivariate analysis revealed a common factor structure for suicidal behaviour traits, MDD, ADHD and alcohol use disorder.
5	To describe healthcare utilisation 12 months before suicidal behaviour among individuals who attempted suicide and who died by suicide, to identify opportunities for suicide prevention strategies in Cape Town, South Africa	Psychiatric diagnoses, chronic illness, HIV	Attempted suicide Fatal suicide	Retrospective analysis of electronic health record linkage study	Kaplan Meier curves were used to compare differences in patterns of healthcare utilisation by psychiatric diagnoses and study groups. Cox proportional hazards model was used to model the relationship between covariates and time from the last facility visit to suicidal behaviour.	Approximately two-thirds of cases accessed healthcare services during the 12 months leading to suicidal behaviour. Fatal suicides had a lower prevalence of psychiatric disorders than attempted suicides. Common reasons for a healthcare visit were chronic illness and assault for fatal suicides; and chronic illness, a psychiatric diagnosis of depression, bipolar or substance use disorders, and HIV care for attempted suicides.

6.2 Discussion of findings and implications for suicide prevention

6.2.1 Surveillance of suicide mortality data and issues in data quality

Suicide prevention is a public health priority. Monitoring the number, rates, and trends of suicide in South Africa is key to understanding the magnitude of the problem, identifying who is at risk, and planning, prioritising and targeting suicide prevention activities. On-going surveillance of national-level suicide data with little lag time can provide up-to-date information essential for an evidence-based response.

An earlier study reported that reliable mortality data were available for less than 30% of the world's population, of which South Africa was considered to have medium-quality mortality data (Bhalla et al., 2010), an improvement from a previous assessment of low-quality (Mathers et al., 2005, Burrows and Laflamme, 2007). In Chapter 2, this study describes a high percentage of missing data for specific variables (ranging from 25% for population group and up to 93% for occupation), a high percentage of ill-defined/unknown causes of death (R99, 11.6%), substantial underreporting of suicide deaths and potential suicide deaths wrongly classified as accidental and undetermined causes of death for hanging and poisoning. These findings point to the poor quality of the mortality data and highlight the urgent need for ongoing training on the cause of death certification and further interventions to improve suicide data quality. Misclassification of suicide deaths is also more likely to occur in the absence of an autopsy. In addition, autopsies often include toxicological testing which is crucial for determining the manner of death for poisoning suicides. Approximately 80% of suicide deaths underwent an autopsy compared to 63% of undetermined intent (Y10-Y34) and 55% of all fatal poisonings. This is confirmed in a cross-national study of 35 European and Asian countries that reported the decline in autopsy rates was associated with a decline in suicide rates (Kapusta et al., 2011), suggesting that autopsy rates directly affected the validity

of suicide data and most likely, the quality of all external causes of death data in general. A surprising finding was despite the high proportion (80%) of fatal hangings that underwent an autopsy, there was a high number of deaths categorised as accidental hanging (n=37,148) and hanging by undetermined intent (n=24,836) compared to the low number of suicide deaths by hanging (n=4,739). This finding suggests that suicide deaths in South Africa are more likely misclassified among deaths categorised as fatal hanging. In addition, errors in death notification forms may also be attributed to the high proportion of suicide and undetermined deaths that occurred outside of the hospital/clinic environment. In these cases, death notification forms are completed by non-medical personnel who would not have been adequately trained and therefore more likely to wrongly assign suicide deaths.

The decrease in undetermined mortality rates (Y10-Y34) suggests an improvement in the quality of vital statistics that may have been due to the introduction of a new death certificate (BI-1663) in 1998, which allowed for selecting an underlying cause of death when more than one cause of death is listed. However, the observed 9% annual increase in deaths from accidental exposure to unspecified factors (X59) over the study period indicates that the drop in undetermined deaths is more likely due to the introduction of ICD-10 coding when deaths by undetermined intent were recategorised to accidental deaths. Recommendations to improve the completeness of the death notification forms and thus the quality of vital registration data should therefore include continued training of doctors and medical personnel in the cause of death certification, improved automated classification of medical entities (ACME) that determines the underlying cause of death at national statistics office, obtaining verbal autopsies for external causes of deaths that occur outside of the hospital environment, revising the death certification forms to include the manner of death from injuries, for example, homicide, suicide and accident and lastly, there should be a mechanism in place for updating Statistics South Africa mortality data once investigations and inquests are complete.

The finding in Chapter 2 of a gender disparity (suicide is more common in men who have a greater YPLL than women) is consistent with previous studies in South Africa (Burrows and Laflamme, 2006, Matzopoulos et al., 2015) and globally (WHO, 2021). This underscores the need to identify and support suicidal men. Interventions that have been shown to successfully improve help-seeking behaviour among men include the use of male role models such as celebrities and soccer players and aims to normalise symptoms and reduce mental health stigma by providing educational material such as brochures to improve mental health literacy and symptom identification (Sagar-Ouriaghli et al., 2019).

One of the main reasons reported for the observed sex difference is the highly lethal methods, such as hanging and firearms, predominantly used by men (Ajdacic-Gross et al., 2008, Denning et al., 2000, Lim et al., 2014, Puzo et al., 2016, Shah and Buckley, 2011, Stenbacka and Jokinen, 2015). In keeping with the literature, we found that hanging was the most common method of suicide in men, accounting for 61% of deaths from 1997 to 2016; while among women, poisoning (40%) and hanging (36%) were the most common methods used. Of concern, we observed an annual increase of 4% and 3% in the suicide rate by hanging for men and women over 20 years, respectively. The increase in the cases of hanging may in part be due to the substitution of means of other methods, suggesting that the increase in hanging could be explained by the decrease in firearm suicides, following the Firearm Control Act of 2000 in South Africa (Matzopoulos et al., 2016). However, the introduction of the Firearm Control Act does not explain the increase (while not significant) in accidental firearm injury and firearm deaths of undetermined intent. This is most likely a reflection of the increase in homicide rates in South Africa, of which 54% of all homicides involved firearms (Groenewald et al., 2003). Further, our results show that firearm-related deaths are more likely to represent wrongly classified homicides rather than firearm suicides. While on the other hand, the increase in suicide by hanging may be explained by easily available means

considering that hanging is a highly lethal method of suicide compared to other means such as poisoning (Gunnell et al., 2005). Strategies for preventing suicide by hanging are challenging because hanging is often carried out privately in the seclusion of the person's own home; individuals use everyday household items such as ropes, clothing lines and belts as ligatures thus making it difficult to restrict access (Biddle et al., 2010) and hang from low suspension points i.e. individuals are sometimes not fully suspended with their feet touching the ground, suggesting relatively minimal neck pressure is required for asphyxiation (Gunnell et al., 2005). More suicide prevention options exist within controlled environments such as psychiatric hospitals and prisons, where high-risk patients and inmates can be screened and placed in safe, ligature-free environments with staff trained in emergency resuscitation techniques (Gunnell et al., 2005).

In contrast with recent findings of a downward trend of suicide by poisoning in both sexes in Australia (Kõlves et al., 2018) and suicide by intentional overdose in men in the USA (Han et al., 2022), this study in South Africa found a 4% increase in suicide by poisoning in men annually, while a 17% increase was observed in women between 1997 and 2005, before stabilising. Restricting access to medication by regulating prescriptions of analgesics to smaller packages has been shown to reduce the number of deaths due to overdose in the UK (Hawton et al., 2001). In addition, healthcare providers can be trained to limit risky prescribing practices by switching to a medication of low lethality and limiting the number of tablets provided in a single prescription (WHO, 2018b). We found that young adults aged 15-29 years are most at risk of suicide (OR=16.7, 95% CI 15.4-18.1), in keeping with 2019 mortality statistics from the World Health Organisation showing that suicide is the fourth leading cause of death among 15-29 years olds worldwide (WHO, 2021). Resources should be allocated towards potential prevention strategies aimed at young adults at high risk for suicide such as promoting peer and family connectedness, improving access to care and

limiting access to lethal means (Brent, 2019). Pesticide poisoning accounts for a third of the world's suicides (Gunnell et al., 2007), and is a prominent method of suicide used in Sub-Saharan Africa (Mars et al., 2014). However, we reported a low prevalence of suicide through pesticide poisoning (2.4%), corresponding with findings from South African mortuary studies (Stark et al., 2010, Patience, 2018). Nevertheless, pesticide poisoning remains an important preventable cause of death in LMICs. Findings from the electronic health record linkage study (Chapter 5, Study 4) showed that 10.3% (9/93) of individuals who died by suicide and underwent a forensic autopsy between 2014 and 2016, died from pesticide poisoning. This is much higher than the reported 2.4% (208/8573) who died by pesticide poisoning from the vital registration data over 20 years. These findings show a significant under counting of suicides and therefore caution is advised when using vital statistics data for external causes of death, particularly for suicide deaths. Further, future studies should consider electronic health record linkage of vital statistics data and mortuary data as a means to assess data quality for ongoing mortality surveillance and to improve the validity of cause-of-death statistics.

Work-related access to means is a risk factor for suicide in specific occupation groups. One theory that has been used to understand suicidal behaviour and has been applied in occupational settings, is the Interpersonal Psychological Theory of Suicidal Behavior. This theory postulates that fatal suicide occurs when an individual has a suicidal desire and capability for suicide (Joiner, 2007). For example, studies have shown that trained military personnel in the US are at increased risk of fatal suicide and the risk was largely driven by access to and familiarity with lethal means compared to the general population (Anestis and Bryan, 2013). Following this point, male veterans in the US were twice as likely to die by suicide and were more likely to use firearms as their method of suicide than non-veterans in the general population (Kaplan et al., 2007). However, these findings could not be

generalised to female military personnel (Chu et al., 2020). Thus, work-related access to and familiarity with lethal means combined with suicide desire may increase the risk of suicide among vulnerable groups. Prevention programs targeting vulnerable occupations and the general population should therefore focus on reducing access to firearms by counselling vulnerable groups, their friends and family members on safe firearm storage practices in the home and outside the home.

Overall, our findings show a changing picture in the direction of temporal suicide trends in South Africa and suggest that analysing suicide trends using national-level mortality data, disaggregated by age, sex and method of suicide would be an important step in improving healthcare. When examining categories other than suicide, our study found that the mortality data was of poor quality. There was a high proportion of ill-defined causes of death (R99), undetermined causes of death (Y10-Y34) and accidental exposure to unknown factors (X59). In addition, this study confirmed our apriori hypothesis that fatal hangings and to a lesser degree fatal poisonings are more likely to contain wrongly assigned suicide deaths, whereas fatal firearm injuries are more likely to include wrongly assigned homicides. These additional cause-of-death categories should therefore be considered when examining suicide deaths. Even with the substantial data quality issues, examining national vital statistics can provide an improved understanding of how the burden of suicide compares by year, age group and sex and provides insight for improving future research for emerging risk groups and where resources need to be allocated for future suicide prevention efforts. However, it is vitally important that mortality data is urgently improved.

6.2.2 Risk factors associated with suicidal behaviour

Many factors lead individuals to try to end their lives. Identifying risk and protective factors for suicidal behaviour is an important component of any prevention strategy and can guide the development of appropriate interventions (WHO, 2014b, Zalsman et al., 2016).

Attempted suicide is more common than fatal suicide and a previous suicide attempt is one of the strongest predictors of subsequent death by suicide (WHO, 2014b). In contrast with previous studies that reported positive associations among agricultural populations (Freire and Koifman, 2013, London et al., 2005, London et al., 2012), our hospital-based case-control study (Chapter 3) found no association between attempted suicide and OP exposure in the general population; and after adjusting for potential misclassification. This negative finding could be explained by the low proportion of participants willing to donate hair (25%) for the measurement of dialkyl phosphates (DAPs) which likely reduced the power of the analysis and the possibility that the pesticides used in the home and garden were likely, not organophosphate-based. Despite this negative finding, this is the first study to examine the association between environmental and occupational OP exposure and attempted suicide in the general population. Future studies should consider culturally acceptable alternatives to hair samples for the assessment of OP exposure, and possibly include multiple measurements over time to assess chronic exposure.

Consistent with previous studies (Darvishi et al., 2015, Conner et al., 2001, Khemiri et al., 2016, Pompili et al., 2010, Vijayakumar et al., 2011), we found that individuals who engage in the harmful use of alcohol, an AUDIT score cut-off of 5 for men and 3 for women, had an increased risk of attempting suicide (Chapter 3). We reported a moderate genetic correlation between suicide attempt and alcohol use disorder (rg=0.54, p=0.0002) (Chapter 4). Findings from the electronic health record linkage study (Chapter 5) showed that individuals were more likely to use health care services in the year before their attempt for the treatment of their substance use disorder (including alcohol use disorder, adjusted HR = 2.19, 95% CI 1.47-3.31). Alcohol is a causal factor of more than 200 diseases and remains a leading risk factor for premature mortality among those aged 15-49 years (Griswold et al., 2018). Further, the harmful use of alcohol caused 1.7 million deaths globally due to non-communicable

diseases, of which 150,000 were due to self-harm (WHO, 2018a). Alcohol also increases inequalities; a modelling study of alcohol-attributable mortality in South Africa found that lower socioeconomic status was associated with an elevated mortality rate from alcohol-attributable causes of death (Probst et al., 2018). Alcohol use disorder is a common comorbid condition among individuals with mental illness (Drake and Mueser, 1996) and common risk factors contribute to both mental illness and alcohol use disorder. The factors that increase the risk of mental illness, such as poverty, unemployment, lack of social cohesiveness, trauma and adverse childhood experiences also increase the risk of substance use (Drake and Wallach, 2000). In addition, it is hypothesised that people with mental illness may start drinking in an attempt to self-medicate which may exacerbate their symptoms and contribute to the progression of their mental illness (Santucci, 2012).

A recent review found that while any acute alcohol use increased the risk of attempted suicide, heavy episodic drinking has been associated with 37 times increased risk of attempted suicide (Borges et al., 2017). This is a major concern as South Africa, in particular, has a high prevalence (59%) of heavy episodic drinking (WHO, 2018a). Harmful use of alcohol is a modifiable risk factor for suicidal behaviour. Given the considerable health, societal and economic harm caused by alcohol, targets to reduce alcohol use and increase treatment intervention by 2030 have been included in the Sustainable Development Goals (SDGs) (WHO, 2016). A recent review of alcohol control policy interventions reported most studies were of low quality and uncertain benefit, and there was a relative absence of studies from LMICs (Siegfried and Parry, 2019). At present, alcohol control strategies in South Africa are limited to increasing the price of alcohol through taxation and limiting the legal minimum drinking age to 18 years (WHO, 2018a). Further work is needed to intensify the availability of counselling and medically assisted treatment for persons struggling with dependence in South Africa.

In this thesis, we examined the socioeconomic determinants of suicide. These measures include education and occupation data from the vital statistics dataset (Chapter 2 - Study 1) education, employment and source of income (Chapter 3 - Study 2) from South African populations and education levels and monthly income from international studies (Chapter 4 - Study 3). In keeping with the literature (Abel and Kruger, 2005), we found an association between fatal suicide and low educational achievement in the bivariate analysis of the national mortality data, despite a large proportion (61%) of missing/unspecified data for education (Chapter 2). We also reported a significant negative genetic correlation between attempted suicide and education attainment ($rg=-0.337$, $p=1.42x10^{-10}$) (Chapter 4), while we found no difference ($p=0.064$) in education levels between attempted suicides and matched controls in the hospital-based case-control study (Chapter 3). Findings from the national South African Stress and Health Study (SASH) confirmed the inverse association between education levels and suicide (Joe et al., 2008). The overall findings of this thesis suggest that higher levels of education levels are associated with improved mental health. We found that approximately 90% of unemployed individuals or those not economically active died by suicide (Chapter 2). It should be noted that unemployment was combined with missing data in the national vital statistics data, meaning that an increase in suicide risk for unemployment may also affect unspecified occupations. Unemployed individuals with no household income were associated with eight-fold odds of attempting suicide (Chapter 3) and we reported an inverse genetic correlation between suicidal behaviour (ideation, self-harm and attempt) and education years (a proxy for socioeconomic status) and household income (Chapter 4). In addition, we found suggestive evidence for the protective effect of genetically predicted higher household income levels on the risk of suicide attempt. Overall, our findings correspond with previous research indicating that low or no household income and unemployment are linked with an increased risk of suicide (Nordt et al., 2015, Bantjes et al.,

2018, Iemmi et al., 2016, Lund et al., 2010). Unemployment increases the risk of suicide by 20–30% (Nordt et al., 2015). Further, periods of economic downturns have also been shown to increase the risk of suicide (Oyesanya et al., 2015), a situation that has become more pronounced by the global recession brought about by the COVID-19 pandemic. Earlier work by Dohrenwend et al. has suggested that the high rate of mental disorders in disadvantaged populations can be explained by the social selection theory, that individuals with mental illness have a predisposition to declining socioeconomic status due to possible genetic factors, hospitalisations related to mental illness, and/or loss of work (Dohrenwend et al., 1992).

Poverty is concentrated in LMICs, where the burden of suicidal behaviour is greatest (WHO, 2021). More than half (55.5%) of the South African population (30.3 million) live below the national poverty line, while a quarter (13.8 million) live in extreme poverty, unable to afford enough food to meet physical needs (World Bank, 2020). Eliminating poverty in South Africa by 2030, as envisaged by the National Development Plan, seems unreachable because of high levels of inequality and income polarisation, and the reversed trajectory of poverty reduction between 2011 and 2015 (Sulla and Zikhali, 2018). However, the introduction of the National Health Insurance (NHI) aimed at universal health coverage is intended to improve the quality and quantity of health services for all individuals, without placing undue financial hardship on individuals and households when accessing healthcare, by offering free healthcare for all (Department of Health, 2017). Despite the steps taken thus far toward universal health coverage, the implementation of the NHI is burdened with many challenges (Michel et al., 2020). However, it remains imperative that mental health services are prioritised in South Africa's ongoing NHI plans (Docrat et al., 2019b), by integrating mental health services in primary care to improve access, improving human resources for mental

health, establish mental health promotion services in communities and addressing violence and trauma as a cross-cutting factor in mental health service provision (Kleintjes et al., 2021).

6.2.3 Healthcare access and suicidal behaviour

A key finding from our study showed that two-thirds of individuals who died by suicide and those who attempted suicide were seen at a health facility in the 12 months before suicidal behaviour. In line with studies from high-income countries, we observed that individuals who died by suicide and those who attempted suicide accessed healthcare services equally (approximately 65%) during the 12 months leading to suicidal behaviour (Luoma et al., 2002, Stene-Larsen and Reneflot, 2017); and primary healthcare visits were more frequent than specialised mental healthcare for both groups (Chapter 4) (Schaffer et al., 2016, Hom et al., 2015). The findings provide new insight into how individuals at risk of suicide use healthcare services in South Africa and suggest that these visits may represent *missed opportunities* for targeted suicide prevention at the primary care level. It further indicates that it may be helpful to integrate suicide prevention strategies into primary healthcare settings in South Africa, as has been suggested in HICs (Ahmedani et al., 2014, Luoma et al., 2002, Stene-Larsen and Reneflot, 2017) and the National Mental Health Policy Framework and Strategic Plan (Department of Health, 2014). Similar arguments have been made regarding interpersonal violence (IPV) and gender-based violence (GBV), to integrate care for GBV survivors within primary healthcare services, as outlined in the National Strategic Plan on Gender-based Violence and Femicide (Department of Women Youth and Persons with Disabilities, 2020). Recommended prevention strategies that have been shown to decrease the risk of suicide ideation, attempts and death, include the education and training of non-psychiatric primary care clinicians and nurses to screen and treat depression (Mann et al., 2021). However, there is insufficient evidence for the benefit of screening for suicide risk among otherwise undetected populations in primary care for reducing the risk of suicide (Zalsman et al., 2016).

In contrast with a previous meta-analysis of 27 studies from high-income countries, where 87% of fatal suicides had a mental health diagnosis (Arsenault-Lapierre et al., 2004), our findings showed that approximately 81% of fatal suicides *did not* have a record of pre-existing mental health conditions. However, as psychiatric disorders are a major risk factor for suicidal behaviour, treating these disorders could contribute substantially to the prevention of suicide (Wasserman et al., 2012). Meta-analyses of randomised control studies have shown that patients on antidepressants if properly monitored, have reduced suicidal behaviour (Mann et al., 2021). In the acute context, ketamine has been shown to decrease suicidal ideation within four hours (Abbar et al., 2022); however, more randomised control trials are needed for further recommendations (Mann et al., 2021). In addition, there is sufficient evidence supporting cognitive and dialectical behaviour therapy for the prevention of repeat self-harm (Mann et al., 2021, Zalsman et al., 2016).

Reasons for using healthcare services in the year before completing suicide were for the management of their chronic conditions (such as cardiovascular disease and diabetes) and the emergency treatment of assault-related injuries; while the major drivers for healthcare use among attempted suicide patients were the management of psychiatric disorders (depression, bipolar and/or substance use disorders), chronic conditions and HIV. South Africa faces a rising quadruple burden of diseases that include HIV and tuberculosis, chronic illness and mental health, injury and violence, and maternal and child mortality (Mayosi et al., 2009, Mayosi et al., 2012, Pillay-Van Wyk et al., 2014). Integrating mental health into chronic care services at the primary healthcare level can lead to improved medication adherence and lower healthcare costs in LMICs (Patel and Thornicroft, 2009). Further, the findings suggest that education and training of non-psychiatric staff should be extended particularly to staff at emergency centres and antiretroviral clinics at primary care facilities.

Overall, we found that linking electronic health records with person-level data for individuals with suicidal behaviour has a high potential to provide retrospective suicide surveillance for individuals with fatal and NFSB. This resource has the potential to benefit clinical care and public health by providing data-driven support for targeted suicide prevention strategies. While our study was limited geographically to Cape Town, future studies should consider linking electronic health records to nationwide cohorts to improve generalisability and enhance the precision of study findings and ultimately, inform a critically-needed national suicide prevention plan in South Africa.

6.2.4 Genetic correlation between suicidal behaviour and psychiatric disorders

We built on existing evidence demonstrating the genetic relationship between suicidal ideation, self-harm and attempted suicide and between suicidal behaviour and psychiatric disorders. In keeping with previous studies (Caspi et al., 2014, Sveticic and De Leo, 2012), we observed strong genetic correlations between suicidal ideation, self-harm and attempted suicide. Our findings support the theory that suicidality may develop over time, along a continuum of less to more severe forms of suicidal behaviour (Kessler et al., 1999, Suominen et al., 2004, Silverman et al., 2007). Understanding the transitions of suicidal behaviour can provide more opportunities for timely interventions. For example, Nock and colleagues found that the recent onset of ideation and self-harm-related behaviours predicted attempted suicide among ideators in the US Army, with fair accuracy (Nock et al., 2018). However, despite 50 years of suicide research, a meta-analysis found no single risk factor was strongly associated with suicide to be clinically useful to predict suicide (Franklin et al., 2017). Nonetheless, a recent review suggested artificial intelligence could be an effective tool to identify patterns in data to generate risk algorithms to determine risk factors for suicide (Lejeune et al., 2022). Since this is still a relatively new field (especially here in South Africa), further research is needed to clarify the value of this technology in suicide prevention.

Our findings from the analyses of international publicly-available genomics GWAS datasets are consistent with previous evidence of shared genetics between suicidal behaviours and major depression (Mullins et al., 2019, Strawbridge et al., 2019, Ruderfer et al., 2019, Levey et al., 2019), ADHD (Ljung et al., 2014, Tistarelli et al., 2020), schizophrenia (Docherty et al., 2020) and alcohol use disorders (Darvishi et al., 2015). Polygenic risk scores (PRS) assess the genetic risk of suicide by summarising the effect of many common variants associated with suicide. While PRS provide promise for stratifying individuals at high risk, recent studies have reported modest predictability of the polygenic risk analysis to suicidal behaviour (Mullins et al., 2019, Ruderfer et al., 2019, Strawbridge et al., 2019, Wray et al., 2018, Levey et al., 2019). At present, genetic risk scores have low specificity and low positive predictive values and while these scores may have future potential clinical utility in psychiatry, these scores have thus far not been able to predict suicide risk that can be translated into a clinical setting (Lopes and McMahon, 2019).

6.3 Limitations

Several limitations should be considered when interpreting the overall findings of this PhD. In this thesis, I utilised multiple sources of suicide data. The data presented in this thesis include South African vital statistics, electronic health records and data from hospital-based studies conducted in Cape Town. Therefore, the study findings from participants with suicidal behaviour recruited in Cape Town may not be generalisable to the rest of the country. While there is no single nationwide surveillance system for suicidal behaviour, the Western Cape Provincial Health Data Centre provides unique individual-level data that contains coverage of administrative systems in all hospitals and clinics in the Western Cape and allowed for electronic health record linkage that would not have been possible in any other province. However, given this present limitation, future work is needed to identify risk

factors and healthcare use in other provinces, particularly, in rural settings. Secondly, there was a lack of available genetic data for suicidal behaviour in South African populations thus limiting the generalisability of the genetics analyses. Due to the low base rate of suicide and the cost implications of obtaining and analysing large-scale genomic data in South Africa, we utilised publicly available summary-level data of suicidal behaviour, psychiatric disorders and socioeconomic-related variables for individuals of European and East Asian ancestry from the northern hemisphere, while the data obtained for the investigation of the burden of suicide and associated risk factors were from the South African population. As such, although perhaps important in contributing to mapping the organic relationships of suicidal behaviour and other psychiatric/behavioural phenotypes, the genetic findings from the individuals of European and East Asian ancestry are not generalisable to South Africa, a population with high levels of genetic diversity (Sengupta et al., 2021). However, this study is exploratory and further research is needed to untangle the biological factors associated with suicidal behaviour in South Africa. Extensive efforts and investment have been undertaken to increase the representation of individuals with African ancestry in genomic research (Bentley et al., 2020, Mulder et al., 2018, Rotimi et al., 2014). However, achieving the desired large-scale sample sizes will require more time and continued efforts. Third, while there are well-studied sex differences reported in the genetic influences of psychiatric disorders (Merikangas and Almasy, 2020) and suicidal behaviour (Kia-Keating et al., 2007, Powers et al., 2020), we could not analyse our data stratified by sex, as sex-specific summary datasets for all datasets were not available. However, as larger, well-powered summary statistics become available, this could be addressed in the future. Fourth, the measurement of OP exposure in hair was meant to account for all routes of exposure but the utility of this measure was limited by the low proportion of participants willing to donate hair which likely reduced the power of the analysis and forced us to rely on self-report measures vulnerable to potential biases. Fifth, the

study findings from the electronic health record linkage study were based on the accuracy and completeness of clinicians/administrators providing appropriate ICD-10 codes for each encounter at health facilities. A large proportion of ICD-10 codes (62%) were missing information on the method of suicide, for non-fatal suicidal behaviour patients. The omission of ICD-10 codes meant that we could not compare suicide methods by suicidal behaviour and healthcare contact.

6.4 Recommendations for future work

Based on the findings from this thesis, there are several possible considerations to be made for future research.

1. Urgency of investigating and improving the completeness and quality of national suicide data in South Africa. Key recommendations to improve the quality of suicide mortality data include:
    - Ongoing training of doctors and medical personnel to complete the death notification forms correctly is urgently needed;
    - Improved automated classification of medical entities (ACME) to determine the underlying cause of death at the national statistics office (Statistics South Africa);
    - Obtaining verbal autopsies for external causes of deaths that occur outside of the hospital environment, in the absence of a suicide note and when deaths are ruled as undetermined intent;
    - Revising the death certification forms to include the manner of death from injuries, for example, homicide, suicide and accident;
    - There should be a system place for updating Statistics South Africa mortality data once investigations and inquests are complete.

- Ongoing surveillance of the vital statistics system, especially suicide mortality data should be used to evaluate measures to improve data quality, monitor changes and trends in mortality rates and facilitate better planning.

2. Increase the number of genetic studies in Africa. A significant gap in the genomic suicide literature is the underrepresentation of people of African ancestry in GWAS. Approximately 88% of findings from GWAS are from populations of European ancestry (Mills and Rahal, 2019), despite being a fraction of the world's population. This disparity implies that individuals of European ancestry are most likely to benefit from genomic research. African populations remain underrepresented in GWAS, despite a reported 2.5% increase in studies with African ancestry (Popejoy and Fullerton, 2016). Factors that perpetuate continued genetic research in well-represented populations include: (i) scientists from low-resource settings and diverse population groups are underrepresented in genetics research (Bentley et al., 2017), (ii) limited community engagement with minority groups creating a lack of trust and leads to low recruitment rates (Tindana et al., 2015), (iii) compared to European ancestry cohorts that are historically well funded, genetic studies in Africa are limited by smaller sample sizes (Bentley et al., 2017), and (iv) the complex genomic diversity within African populations require additional analytical consideration of population structure that is not required for European populations (Bentley et al., 2020). In 2012, the US National Institute of Health (USA) and the Wellcome Trust (UK) funded the Human Hereditary and Health in Africa Consortium (H3Africa), as a means to increase genomics research in Sub-Saharan populations and build capacity in Africa (Rotimi et al., 2014). To date, the H3Africa consortium has recruited over 100,000 participants (https://h3africa.org/; accessed 31 May 2023) and has trained over 500 individuals across the African continent (Mulder et al., 2018). Increasing

diversity in genetic research means that studies may yield results that are meaningfully transferred globally, to improve health outcomes for all.

3. Use new *methodologies* to increase the understanding of suicidal behaviour. Routinely collected data stored as electronic health records in health information systems represent a largely untapped resource and opportunity for improved screening and prevention of suicide. Algorithm-guided electronic health record screening is a promising but relatively underexplored methodology for predicting suicidal behaviour (Barak-Corren et al., 2017, Mann et al., 2021, Tran et al., 2014). This data-driven modelling approach has the added benefit of estimating the cumulative effect of risk factors by using longitudinal electronic health record data and overcomes the problems associated with self-reporting bias.

4. The Provincial Health Data Centre (PHDC) in the Western Cape Province links person-level data across healthcare facilities and provides opportunities for data to improve health services and patient care (Boulle et al., 2019). Therefore, routine data captured by the PHDC makes an ideal case for monitoring attempted suicide for repeated attempts and completion for future studies.

5. Explore culturally feasible biomarkers for OP exposure. While we found no association between OP pesticide exposure and suicide, the low number of participants willing to provide hair samples in this study highlights the need for strategies that promote ethical and sensitive biomarker collection in line with cultural preferences and perspectives, that include education of the study and collection procedures (Heathfield et al., 2017) and explore alternative approaches, other than hair samples, to assess long-term pesticide exposure in our population.

6. Focus on protective factors. Suicide research is mostly focused on risk factors, while much less is known about factors that may exert a protective role. While we reported a

protective relationship between attempted suicide and sharing the house with more than three people, further research is needed to understand the role of close personal relationships in providing social support and suicidal behaviour.

7. We recommend that future suicidal behaviour studies are conducted in other provinces, particularly in rural settings, to determine the applicability of findings from Cape Town.

8. Lastly, we recommend that future genetic studies include both fatal and non-fatal suicidal behaviour data, such as those available from the Suicide Working Group of the Psychiatric Genomics Consortium.

6.5 Conclusions

The key findings of this thesis emphasise that suicide is a serious public health problem and is the result of a complex dynamic interplay between numerous contributing factors. Further, there is an urgent need to improve the quality of mortality data from national vital statistics to enable public health action to reduce the morbidity and mortality of suicidal behaviour in South Africa. Despite this limitation, our findings suggest that monitoring suicide mortality data and linking electronic health records may provide opportunities for suicide surveillance that can help identify where prevention strategies should be allocated for maximum benefits, such as primary healthcare outpatient facilities, emergency treatment centres and antiretroviral clinics. Our knowledge of risk factors is increasing substantially and improved prevention programmes should be an immediate goal in South Africa and other LMICs. Up-to-date empirical data from LMIC settings such as South Africa is critically needed not only to inform targeted suicide prevention strategies but also to elevate suicide prevention onto the political agenda for a national strategy, to close the gap to the 2030 Sustainable Development Goals.

References

Abbar, M., Demattei, C., El-Hage, W., et al. 2022. Ketamine for the acute treatment of severe suicidal ideation: double blind, randomised placebo controlled trial. *BMJ,* 376**,** e067194.

Abel, E. L. & Kruger, M. L. 2005. Educational Attainment and Suicide Rates in the United States. *Psychological Reports,* 97**,** 25-28.

Agerbo, E., Gunnell, D., Bonde, J. P., Mortensen, P. B. & Nordentoft, M. 2007. Suicide and occupation: the impact of socio-economic, demographic and psychiatric differences. *Psychological Medicine,* 37**,** 1131-1140.

Ahmad, O. B., Boschi-Pinto, C., Lopez, A. D., et al. 2001. Age standardization of rates: a new WHO standard. Geneva: World Health Organization.

Ahmedani, B. K., Simon, G. E., Stewart, C., et al. 2014. Health care contacts in the year before suicide death. *Journal of General Internal Medicine,* 29**,** 870-877.

Ajdacic-Gross, V., Weiss, M. G., Ring, M., et al. 2008. Methods of suicide: International suicide patterns derived from the WHO mortality database. *Bulletin of the World Health Organization,* 86**,** 726-732.

Allegrini, A. G., Cheesman, R., Rimfeld, K., et al. 2020. The p factor: genetic analyses support a general dimension of psychopathology in childhood and adolescence. *Journal of Child Psychology and Psychiatry,* 61**,** 30-39.

Anestis, M. D. & Bryan, C. J. 2013. Means and capacity for suicidal behavior: A comparison of the ratio of suicide attempts and deaths by suicide in the US military and general population. *Journal of Affective Disorders,* 148**,** 42-47.

Arsenault-Lapierre, G., Kim, C. & Turecki, G. 2004. Psychiatric diagnoses in 3275 suicides: a meta-analysis. *BMC Psychiatry,* 4**,** 37.

Balme, K. H., Roberts, J. C., Glasstone, M., et al. 2010. Pesticide poisonings at a tertiary children's hospital in South Africa: an increasing problem. *Clinical Toxicology,* 48**,** 928-934.

Bantjes, J. & Kagee, A. 2021. Suicide Prevention in HIV Treatment Centres: Population Attributable Risk Analysis of Treating Common Mental Disorders. *AIDS and Behavior,* 25**,** 1864-1872.

Bantjes, J., Saal, W., Lochner, C., et al. 2020. Inequality and mental healthcare utilisation among first-year university students in South Africa. *International Journal of Mental Health Systems,* 14**,** 1-11.

Bantjes, J., Tomlinson, M., Weiss, R. E., et al. 2018. Non-fatal suicidal behaviour, depression and poverty among young men living in low-resource communities in South Africa. *BMC Public Health,* 18**,** 1195-1195.

Barak-Corren, Y., Castro, V., Javitt, S., et al. 2017. Predicting Suicidal Behavior From Longitudinal Electronic Health Records. *Am J Psychiatry,* 174**,** 154-162.

Barr, D. B., Bravo, R., Weerasekera, G., et al. 2004. Concentrations of dialkyl phosphate metabolites of organophosphorus pesticides in the US population. *Environmental Health Perspectives,* 112**,** 186-200.

Beautrais, A. L. 2001. Suicides and serious suicide attempts: Two populations or one? *Psychological Medicine,* 31**,** 837-845.

Beck, A. T., Kovacs, M. & Weissman, A. 1979. Assessment for suicidal ideation: The Scale for Suicidal Ideation. *Journal of Consulting and Clinical Psychology,* 47**,** 343-352.

Bentley, A. R., Callier, S. & Rotimi, C. N. 2017. Diversity and inclusion in genomic research: why the uneven progress? *J Community Genet,* 8**,** 255-266.

Bentley, A. R., Callier, S. L. & Rotimi, C. N. 2020. Evaluating the promise of inclusion of African ancestry populations in genomics. *NPJ Genomic Medicine,* 5**,** 1-9.

Bernert, R. A., Kim, J. S., Iwata, N. G. & Perlis, M. L. 2015. Sleep disturbances as an evidence-based suicide risk factor. *Current Psychiatry Reports,* 17**,** 554-554.

Bertolote, J. M. 2001. Suicide in the world: an epidemiological overview 1959–2000. *In:* WASSERMAN, D. (ed.) *Suicide: An unnecessary death.* London: Martin Dunitz.

Bertolote, J. M. & Fleischmann, A. 2002. A global perspective in the epidemiology of suicide. *Suicidologi,* 7.

Bertolote, J. M., Fleischmann, A., De Leo, D., et al. 2005. Suicide attempts, plans, and ideation in culturally diverse sites: the WHO SUPRE-MISS community survey. *Psychological Medicine,* 35**,** 1457-65.

Bertolote, J. M., Fleischmann, A., De Leo, D., et al. 2010. Repetition of suicide attempts: data from emergency care settings in five culturally different low- and middle-income countries participating in the WHO SUPRE-MISS Study. *Crisis,* 31**,** 194-201.

Bertolote, J. M., Fleischmann, A., Eddleston, M. & Gunnell, D. 2006. Deaths from Pesticide Poisoning: Are we lacking a global response? *The British Journal of Psychiatry,* 189**,** 201-203.

Beseler, C., Stallones, L., Hoppin, J. A., et al. 2006. Depression and pesticide exposures in female spouses of licensed pesticide applicators in the agricultural health study cohort. *Journal of Occupational and Environmental Medicine,* 48**,** 1005.

Beseler, C. L. & Stallones, L. 2008. A cohort study of pesticide poisoning and depression in Colorado farm residents. *Ann Epidemiol,* 18**,** 768-774.

Beseler, C. L., Stallones, L., Hoppin, J. A., et al. 2008. Depression and pesticide exposures among private pesticide applicators enrolled in the Agricultural Health Study. *Environmental Health Perspectives,* 116**,** 1713.

Bhalla, K., Harrison, J. E., Shahraz, S., Fingerhut, L. A. & Global Burden of Disease Injury Expert, G. 2010. Availability and quality of cause-of-death data for estimating the global burden of injuries. *Bulletin of the World Health Organization,* 88**,** 831-838C.

Biddle, L., Donovan, J., Owen-Smith, A., et al. 2010. Factors influencing the decision to use hanging as a method of suicide: qualitative study. *The British Journal of Psychiatry,* 197**,** 320-325.

Bitton, A., Fifield, J., Ratcliffe, H., et al. 2019. Primary healthcare system performance in low-income and middle-income countries: a scoping review of the evidence from 2010 to 2017. *BMJ Global Health,* 4**,** e001551.

Blanchard, M. & Farber, B. A. 2020. "It is never okay to talk about suicide": Patients' reasons for concealing suicidal ideation in psychotherapy. *Psychotherapy Research,* 30**,** 124-136.

Bondy, B., Buettner, A. & Zill, P. 2006. Genetics of suicide. *Molecular Psychiatry,* 11**,** 336-51.

Border, R., Athanasiadis, G., Buil, A., et al. 2022. Cross-trait assortative mating is widespread and inflates genetic correlation estimates. *Science,* 378**,** 754-761.

Borges, G., Bagge, C. L., Cherpitel, C. J., et al. 2017. A meta-analysis of acute use of alcohol and the risk of suicide attempt. *Psychological Medicine,* 47**,** 949-957.

Borges, G., Nock, M. K., Haro Abad, J. M., et al. 2010. Twelve-month prevalence of and risk factors for suicide attempts in the World Health Organization World Mental Health Surveys. *Journal of Clinical Psychiatry,* 71**,** 1617-1628.

Bostwick, J. M., Pabbati, C., Geske, J. R. & Mckean, A. J. 2016. Suicide attempt as a risk factor for completed suicide: even more lethal than we knew. *Am J Psychiatry,* 173**,** 1094-1100.

Boulle, A., Heekes, A., Tiffin, N., et al. 2019. Data Centre Profile: The Provincial Health Data Centre of the Western Cape Province, South Africa. *International Journal of Population Data Science,* 4.

Bourdon, J. L., Davies, R. A. & Long, E. C. 2020. Four actionable bottlenecks and potential solutions to translating psychiatric genetics research: An expert review. *Public Health Genomics,* 23**,** 171-183.

Bradshaw, D., Pillay-Van Wyk, P., Laubscher, R., et al. 2010. Cause of death statistics for South Africa: Challenges and possibilities for improvement South Africa: Burden of Disease Research Unit, SAMRC.

Brent, D. A. 2019. Master clinician review: Saving Holden Caulfield: Suicide prevention in children and adolescents. *Journal of the American Academy of Child & Adolescent Psychiatry,* 58**,** 25-35.

Brent, D. A. & Mann, J. J. 2005. Family genetic studies, suicide, and suicidal behavior. *Am J Med Genet Part C: Seminars in Medical Genetics,* 133C**,** 13-24.

Brent, D. A. & Melhem, N. 2008. Familial transmission of suicidal behavior. *The Psychiatric Clinics of North America,* 31**,** 157-177.

Bruwer, B., Govender, R., Bishop, M., et al. 2014. Association between childhood adversities and long-term suicidality among South Africans from the results of the South African Stress and Health study: a cross-sectional study. *BMJ Open,* 4**,** e004644.

Bryant, F. B. & Smith, B. D. 2001. Refining the architecture of aggression: A measurement model for the Buss–Perry Aggression Questionnaire. *Journal of Research in Personality,* 35**,** 138-167.

Bulik-Sullivan, B., Finucane, H. K., Anttila, V., et al. 2015. An atlas of genetic correlations across human diseases and traits. *Nature Genetics,* 47**,** 1236-1241.

Bunney, W., Kleinman, A., Pellmar, T. & Goldsmith, S. 2002. *Reducing suicide: A national imperative,* National Academies Press.

Burgess, S. & Small, D. S. 2016. Predicting the Direction of Causal Effect Based on an Instrumental Variable Analysis: A Cautionary Tale. *Journal of Causal Inference,* 4**,** 49-59.

Burrows, S. & Laflamme, L. 2006. Suicide mortality in South Africa. *Social Psychiatry and Psychiatric Epidemiology,* 41**,** 108-114.

Burrows, S. & Laflamme, L. 2007. Assessment of accuracy of suicide mortality surveillance data in South Africa: Investigation in an urban setting. *Crisis,* 28**,** 74-81.

Burrows, S. & Schlebusch, L. 2008. *Priorities and prevention possibilities for reducing suicidal behaviour,* Tygerberg, MRC-UNISA Crime, Violence and Injury Lead Programm.

Caspi, A., Houts, R. M., Belsky, D. W., et al. 2014. The p factor: one general psychopathology factor in the structure of psychiatric disorders? *Clinical Psychological Science,* 2**,** 119-137.

Cavanagh, J. T., Carson, A. J., Sharpe, M. & Lawrie, S. M. 2003. Psychological autopsy studies of suicide: a systematic review. *Psychological Medicine,* 33**,** 395-405.

Centre for Suicide Prevention. 2016. *Straight talk: Youth suicide prevention workshop* [Online]. Available: https://www.suicideinfo.ca/resource/self-harm-and-suicide/ [Accessed 22 April 2022].

Chaiyasong, S., Huckle, T., Mackintosh, A.-M., et al. 2018. Drinking patterns vary by gender, age and country-level income: Cross-country analysis of the International Alcohol Control Study. *Drug and Alcohol Review,* 37 Suppl 2**,** S53-S62.

Chen, Y.-Y., Chien-Chang Wu, K., Yousuf, S. & Yip, P. S. F. 2012. Suicide in Asia: Opportunities and Challenges. *Epidemiologic Reviews,* 34**,** 129-144.

Chimusa, E. R. & Defo, J. 2022. Dissecting Meta-Analysis in GWAS Era: Bayesian Framework for Gene/Subnetwork-Specific Meta-Analysis. *Frontiers in Genetics,* 13**,** 838518.

Chopra, M., Lawn, J. E., Sanders, D., et al. 2009. Achieving the health Millennium Development Goals for South Africa: challenges and priorities. *The Lancet,* 374**,** 1023-1031.

Chu, C., Zuromski, K. L., Bernecker, S. L., et al. 2020. A test of the interpersonal theory of suicide in a large, representative, retrospective and prospective study: Results from the Army Study to Assess Risk and Resilience in Servicemembers (Army STARRS). *Behaviour Research and Therapy,* 132**,** 103688.

Cirillo, E., Parnell, L. D. & Evelo, C. T. 2017. A Review of Pathway-Based Analysis Tools That Visualize Genetic Variants. *Frontiers in Genetics,* 8.

Conner, K. R., Cox, C., Duberstein, P. R., et al. 2001. Violence, Alcohol, and Completed Suicide: A Case-Control Study. *Am J Psychiatry,* 158**,** 1701-1705.

Coon, H., Darlington, T. M., Diblasi, E., et al. 2020. Genome-wide significant regions in 43 Utah high-risk families implicate multiple genes involved in risk for completed suicide. *Molecular Psychiatry,* 25**,** 3077-3090.

Coovadia, H., Jewkes, R., Barron, P., Sanders, D. & Mcintyre, D. 2009. The health and health system of South Africa: historical roots of current public health challenges. *The Lancet,* 374**,** 817-834.

Critchfield, K. L., Levy, K. N. & Clarkin, J. F. 2004. The relationship between impulsivity, aggression, and impulsive-aggression in borderline personality disorder: an empirical analysis of self-report measures. *Journal of Personality Disorders,* 18**,** 555-570.

Cross-Disorder Group of the Psychiatric Genomics Consortium 2019. Genomic Relationships, Novel Loci, and Pleiotropic Mechanisms across Eight Psychiatric Disorders. *Cell,* 179**,** 1469-1482.e11.

Darvishi, N., Farhadi, M., Haghtalab, T. & Poorolajal, J. 2015. Alcohol-Related Risk of Suicidal Ideation, Suicide Attempt, and Completed Suicide: A Meta-Analysis. *PLoS One,* 10**,** e0126870.

Das, S., Suresh, B., Kim, H. & Ramakrishna, S. 2017. RanBPM: a potential therapeutic target for modulating diverse physiological disorders. *Drug Discovery Today,* 22**,** 1816-1824.

Dejong, T. M., Overholser, J. C. & Stockmeier, C. A. 2010. Apples to oranges? A direct comparison between suicide attempters and suicide completers. *Journal of Affective Disorders,* 124**,** 90-97.

Denning, D. G., Conwell, Y., King, D. & Cox, C. 2000. Method choice, intent, and gender in completed suicide. *Suicide and Life-Threatening Behavior,* 30**,** 282-288.

Department of Health 2014. National Mental Health Policy Framework and Strategic Plan 2013-2020.

Department of Health 2017. National Health Insurance for South Africa. Towards Universal Health Coverage. .

Department of Women Youth and Persons with Disabilities 2020. National Strategic Plan on Gender-based Violence & Femicide. Human dignity and healing, safety, freedom & equality in our lifetime.

Diblasi, E., Kang, J. & Docherty, A. R. 2021. Genetic contributions to suicidal thoughts and behaviors. *Psychological Medicine,* 51**,** 2148-2155.

Docherty, A. R., Shabalin, A. A., Diblasi, E., et al. 2020. Genome-Wide Association Study of Suicide Death and Polygenic Prediction of Clinical Antecedents. *Am J Psychiatry,* 177**,** 917-927.

Docrat, S., Besada, D., Cleary, S., Daviaud, E. & Lund, C. 2019a. Mental health system costs, resources and constraints in South Africa: a national survey. *Health Policy and Planning,* 34**,** 706-719.

Docrat, S., Lund, C. & Chisholm, D. 2019b. Sustainable financing options for mental health care in South Africa: findings from a situation analysis and key informant interviews. *International Journal of Mental Health Systems,* 13**,** 4.

Dohrenwend, B. P., Levav, I., Shrout, P. E., et al. 1992. Socioeconomic status and psychiatric disorders: the causation-selection issue. *Science,* 255**,** 946-52.

Doncheva, N. T., Morris, J. H., Gorodkin, J. & Jensen, L. J. 2019. Cytoscape StringApp: Network Analysis and Visualization of Proteomics Data. *J Proteome Res,* 18**,** 623-632.

Dos Santos, J. C. P., Valli, J. B., Sesse, N. S., et al. 2020. Sociodemographic characteristics and exposure patterns of pesticide-related cases reported to a poison service center in Brazil between 2012 and 2016. *Archives of Environmental & Occupational Health***,** 1-10.

Drake, R. & Wallach, M. 2000. Dual Diagnosis: 15 Years of Progress. *Psychiatric Services,* 51**,** 1126-1129.

Drake, R. E. & Mueser, K. T. 1996. Alcohol-Use Disorder and Severe Mental Illness. *Alcohol Health Res World,* 20**,** 87-93.

Dudbridge, F. 2013. Power and predictive accuracy of polygenic risk scores. *PLoS Genetics,* 9**,** e1003348.

Duncan, L. E., Ratanatharathorn, A., Aiello, A. E., et al. 2018. Largest GWAS of PTSD (N=20 070) yields genetic overlap with schizophrenia and sex differences in heritability. *Molecular Psychiatry,* 23**,** 666-673.

Eddleston, M. 2018. Response to Jors et al, Environmental Health Insights. *Environmental Health Insights,* 12**,** 1178630218788554-1178630218788554.

Engelbrecht, C., Blumenthal, R., Morris, N. K. & Saayman, G. 2017. Suicide in Pretoria: A retrospective review, 2007-2010. *South African Medical Journal,* 107**,** 715-718.

Erlangsen, A., Appadurai, V., Wang, Y., et al. 2018. Genetics of suicide attempts in individuals with and without mental disorders: a population-based genome-wide association study. *Molecular Psychiatry***,** 1-12.

Faraone, S. V. & Larsson, H. 2019. Genetics of attention deficit hyperactivity disorder. *Molecular Psychiatry,* 24**,** 562-575.

Fazel, S. & Runeson, B. 2020. Suicide. *New England Journal of Medicine,* 382**,** 266-274.

Fehling, K. B. & Selby, E. A. 2021. Suicide in DSM-5: Current Evidence for the Proposed Suicide Behavior Disorder and Other Possible Improvements. *Frontiers in Psychiatry,* 11.

Flisher, A. J., Liang, H., Laubscher, R. & Lombard, C. F. 2004. Suicide trends in South Africa, 1968-90. *Scandinavian Journal of Public Health,* 32**,** 411-418.

Franklin, J. C., Ribeiro, J. D., Fox, K. R., et al. 2017. Risk factors for suicidal thoughts and behaviors: A meta-analysis of 50 years of research. *Psychological Bulletin,* 143**,** 187.

Freire, C. & Koifman, S. 2013. Pesticides, depression and suicide: A systematic review of the epidemiological evidence. *International Journal of Hygiene and Environmental Health,* 216**,** 445-460.

Freshour, S. L., Kiwala, S., Cotto, K. C., et al. 2020. Integration of the Drug–Gene Interaction Database (DGIdb 4.0) with open crowdsource efforts. *Nucleic Acids Research,* 49**,** D1144-D1151.

Frey, L. M., Hans, J. D. & Cerel, J. 2016. Perceptions of suicide stigma: How do social networks and treatment providers compare? *Crisis,* 37**,** 95.

Fry, A., Littlejohns, T. J., Sudlow, C., et al. 2017. Comparison of Sociodemographic and Health-Related Characteristics of UK Biobank Participants With Those of the General Population. *Am J Epidemiol,* 186**,** 1026-1034.

Fu, Q., Heath, A. C., Bucholz, K. K., et al. 2002. A twin study of genetic and environmental influences on suicidality in men. *Psychological Medicine,* 32**,** 11-24.

Fushimi, M., Sugawara, J. & Saito, S. 2006. Comparison of completed and attempted suicide in Akita, Japan. *Psychiatry and Clinical Neurosciences,* 60**,** 289-295.

Galfalvy, H., Haghighi, F., Hodgkinson, C., et al. 2015. A genome-wide association study of suicidal behavior. *Am J Med Genet Part B: Neuropsychiatric Genetics,* 168**,** 557-563.

Gardner, J. W. & Sanborn, J. S. 1990. Years of potential life lost (YPLL)—what does it measure? *Epidemiology***,** 322-329.

Gaudet, P., Livstone, M. S., Lewis, S. E. & Thomas, P. D. 2011. Phylogenetic-based propagation of functional annotations within the Gene Ontology consortium. *Brief Bioinform,* 12**,** 449-62.

GBD 2019 Adolescent Mortality Collaborators 2021. Global, regional, and national mortality among young people aged 10-24 years, 1950-2019: a systematic analysis for the Global Burden of Disease Study 2019. *The Lancet,* 398**,** 1593-1618.

Gironi, M., Arnò, C., Comi, G., Penton-Rol, G. & Furlan, R. 2016. Chapter 4 - Multiple Sclerosis and Neurodegenerative Diseases. *In:* BORASCHI, D. & PENTON-ROL, G. (eds.) *Immune Rebalancing.* Academic Press.

Giupponi, G., Giordano, G., Maniscalco, I., et al. 2018. Suicide risk in attention-deficit/hyperactivity disorder. *Psychiatria Danubina,* 30**,** 2-10.

Griswold, M. G., Fullman, N., Hawley, C., et al. 2018. Alcohol use and burden for 195 countries and territories, 1990–2016: a systematic analysis for the Global Burden of Disease Study 2016. *The Lancet,* 392**,** 1015-1035.

Groenewald, P., Bradshaw, D., Nojilana, B., et al. 2003. Cape Town mortality 2001, Part 1: cause of death and premature mortality. Cape Town: South African Medical Research Council.

Grotzinger, A. D., Rhemtulla, M., De Vlaming, R., et al. 2019. Genomic structural equation modelling provides insights into the multivariate genetic architecture of complex traits. *Nature Human Behaviour,* 3**,** 513-525.

Gu, Z., Gu, L., Eils, R., Schlesner, M. & Brors, B. 2014. Circlize implements and enhances circular visualization in R. *Bioinformatics,* 30**,** 2811-2812.

Gunnell, D., Bennewith, O., Hawton, K., Simkin, S. & Kapur, N. 2005. The epidemiology and prevention of suicide by hanging: a systematic review. *International Journal of Epidemiology,* 34**,** 433-42.

Gunnell, D., Eddleston, M., Phillips, M. R. & Konradsen, F. 2007. The global distribution of fatal pesticide self-poisoning: systematic review. *BMC Public Health,* 7**,** 1.

Han, B., Compton, W. M., Einstein, E. B., et al. 2022. Intentional Drug Overdose Deaths in the United States. *Am J Psychiatry,* 179**,** 163-165.

Harris, E. C. & Barraclough, B. 1997. Suicide as an outcome for mental disorders. A meta-analysis. *The British Journal of Psychiatry,* 170**,** 205-228.

Hawton, K., Bergen, H., Cooper, J., et al. 2015. Suicide following self-harm: findings from the multicentre study of self-harm in England, 2000–2012. *Journal of Affective Disorders,* 175**,** 147-151.

Hawton, K., Townsend, E., Deeks, J., et al. 2001. Effects of legislation restricting pack sizes of paracetamol and salicylate on self poisoning in the United Kingdom: before and after study. *BMJ,* 322**,** 1203.

Hawton, K. & Van Heeringen, K. 2009. Suicide. *The Lancet,* 373**,** 1372-81.

Heathfield, L. J., Maistry, S., Martin, L. J., Ramesar, R. & De Vries, J. 2017. Ethical considerations in forensic genetics research on tissue samples collected post-mortem in Cape Town, South Africa. *BMC Medical Ethics,* 18**,** 66.

Hedtke, K. A., Ruggiero, K. J., Fitzgerald, M. M., et al. 2008. A longitudinal investigation of interpersonal violence in relation to mental health and substance use. *Journal of Consulting and Clinical Psychology,* 76**,** 633.

Hemani, G., Zheng, J., Elsworth, B., et al. 2018. The MR-Base platform supports systematic causal inference across the human phenome. *eLife,* 7.

Hendin, H., Vijayuakumar, L., Bertolote, J. M., et al. 2008. Epidemiology of suicide in Asia. *Suicide and Suicide Prevention in Asia***,** 7-18.

Herman, A. A., Stein, D., Seedat, S., et al. 2009. The South African Stress and Health (SASH) study: 12 month and lifetime prevelance of common mental disorders. *South African Medical Journal,* 99**,** 339-344.

Hettema, J. M., Verhulst, B., Chatzinakos, C., et al. 2020. Genome-wide association study of shared liability to anxiety disorders in Army STARRS. *Am J Med Genet Part B: Neuropsychiatric Genetics,* 183**,** 197-207.

Hiew, L.-F., Poon, C.-H., You, H.-Z. & Lim, L.-W. 2021. TGF-β/Smad Signalling in Neurogenesis: Implications for Neuropsychiatric Diseases. *Cells,* 10**,** 1382.

Hill, W. D., Hagenaars, S. P., Marioni, R. E., et al. 2016. Molecular genetic contributions to social deprivation and household income in UK Biobank. *Current Biology,* 26**,** 3083-3089.

Hom, M. A., Stanley, I. H. & Joiner, T. E. 2015. Evaluating factors and interventions that influence help-seeking and mental health service utilization among suicidal individuals: A review of the literature. *Clinical Psychology Review,* 40**,** 28-39.

Hosmer Jr, D. W., Lemeshow, S. & Sturdivant, R. X. 2013. *Applied logistic regression,* John Wiley & Sons.

Hosoda, N., Funakoshi, Y., Hirasawa, M., et al. 2011. Anti-proliferative protein Tob negatively regulates CPEB3 target by recruiting Caf1 deadenylase. *The EMBO journal,* 30**,** 1311-1323.

Hottes, T. S., Bogaert, L., Rhodes, A. E., Brennan, D. J. & Gesink, D. 2016. Lifetime Prevalence of Suicide Attempts Among Sexual Minority Adults by Study Sampling Strategies: A Systematic Review and Meta-Analysis. *Am J Public Health,* 106**,** 921-921.

Howard, D. M., Adams, M. J., Clarke, T.-K., et al. 2019. Genome-wide meta-analysis of depression identifies 102 independent variants and highlights the importance of the prefrontal brain regions. *Nature Neuroscience,* 22**,** 343-352.

Hu, X., Zhao, J., Lin, Z., et al. 2022. Mendelian randomization for causal inference accounting for pleiotropy and sample structure using genome-wide summary statistics. *Proceedings of the National Academy of Sciences,* 119**,** e2106858119.

Iemmi, V., Bantjes, J., Coast, E., et al. 2016. Suicide and poverty in low-income and middle-income countries: a systematic review. *The Lancet Psychiatry,* 3**,** 774-783.

IHME. *Self-harm - Level 3 cause 2019* [Online]. Available: https://www.healthdata.org/results/gbd_summaries/2019/self-harm-level-3-cause [Accessed 17 February 2022].

Jack, H., Wagner, R. G., Petersen, I., et al. 2014. Closing the mental health treatment gap in South Africa: a review of costs and cost-effectiveness. *Global Health Action,* 7**,** 23431.

Jaffrey, S. R. & Wilkinson, M. F. 2018. Nonsense-mediated RNA decay in the brain: emerging modulator of neural development and disease. *Nature Reviews Neuroscience,* 19**,** 715-728.

Joe, S., Stein, D. J., Seedat, S., Herman, A. & Williams, D. R. 2008. Non-fatal suicidal behavior among South Africans. *Social Psychiatry and Psychiatric Epidemiology,* 43**,** 454-461.

Johnson, J. A., Lee, A., Vinson, D. & Seale, J. P. 2013. Use of AUDIT-Based Measures to Identify Unhealthy Alcohol Use and Alcohol Dependence in Primary Care: A Validation Study. *Alcoholism: Clinical and Experimental Research,* 37**,** E253-E259.

Joiner, T. 2007. *Why people die by suicide*, Harvard University Press.

Joinpoint Regression Program Version 4.0.4 2013. *Surveillance Research Program.* Statistical Research and Applications Branch, National Cancer Institute.

Joubert, J., Rao, C., Bradshaw, D., Vos, T. & Lopez, A. D. 2013. Evaluating the quality of national mortality statistics from civil registration in South Africa, 1997–2007. *PLoS One,* 8**,** e64592.

Justice, A. E., Winkler, T. W., Feitosa, M. F., et al. 2017. Genome-wide meta-analysis of 241,258 adults accounting for smoking behaviour identifies novel loci for obesity traits. *Nature Communications,* 8**,** 14977.

Kaminer, D., Grimsrud, A., Myer, L., Stein, D. J. & Williams, D. R. 2008. Risk for post-traumatic stress disorder associated with different forms of interpersonal violence in South Africa. *Social Science & Medicine,* 67**,** 1589-95.

Kaplan, M. S., Huguet, N., Mcfarland, B. H. & Newsom, J. T. 2007. Suicide among male veterans: a prospective population-based study. *Journal of Epidemiology & Community Health,* 61**,** 619-624.

Kapoor, M., Wang, J.-C., Wetherill, L., et al. 2014. Genome-wide survival analysis of age at onset of alcohol dependence in extended high-risk COGA families. *Drug and alcohol dependence,* 142**,** 56-62.

Kapusta, N. D., Tran, U. S., Rockett, I. R., et al. 2011. Declining autopsy rates and suicide misclassification: a cross-national analysis of 35 countries. *Archives of General Psychiatry,* 68**,** 1050-1057.

Kavvalakis, M. P. & Tsatsakis, A. M. 2012. The atlas of dialkylphosphates; assessment of cumulative human organophosphorus pesticides' exposure. *Forensic Science International,* 218**,** 111-122.

Kerrien, S., Aranda, B., Breuza, L., et al. 2012. The IntAct molecular interaction database in 2012. *Nucleic Acids Research,* 40**,** D841-D846.

Kessler, R. C., Borges, G. & Walters, E. E. 1999. Prevalence of and risk factors for lifetime suicide attempts in the National Comorbidity Survey. *Archives of General Psychiatry,* 56**,** 617-626.

Khemiri, L., Jokinen, J., Runeson, B. & Jayaram-Lindström, N. 2016. Suicide Risk Associated with Experience of Violence and Impulsivity in Alcohol Dependent Patients. *Scientific Reports,* 6**,** 19373.

Khiari, H., Ouali, U., Zgueb, Y., Mrabet, A. & Nacef, F. 2019. Pathways to mental health care for patients with severe mental illness in Tunisia. *The Pan African Medical Journal,* 34**,** 118-118.

Kia-Keating, B. M., Glatt, S. J. & Tsuang, M. T. 2007. Meta-analyses suggest association between COMT, but not HTR1B, alleles, and suicidal behavior. *Am J Med Genet Part B: Neuropsychiatric Genetics,* 144**,** 1048-1053.

Kim, H. J., Fay, M. P., Feuer, E. J. & Midthune, D. N. 2000. Permutation tests for joinpoint regression with applications to cancer rates. *Stat Med,* 19**,** 335-51.

King, M., Semlyen, J., Tai, S. S., et al. 2008. A systematic review of mental disorder, suicide, and deliberate self harm in lesbian, gay and bisexual people. *BMC Psychiatry,* 8**,** 70.

Kirigia, J. M., Muthuri, R. D. K. & Muthuri, N. G. 2020. The Monetary Value of Human Lives Lost to Suicide in the African Continent: Beating the African War Drums. *Healthcare (Basel),* 8.

Kleintjes, S., Den Hollander, D. H., Pillay, S. R. & Kramers-Olen, A. 2021. Strengthening the National Health Insurance Bill for mental health needs: response from the Psychological Society of South Africa. *South African Journal of Psychology,* 51**,** 134-146.

Klonsky, E. D. & May, A. M. 2015. The three-step theory (3ST): A new theory of suicide rooted in the "ideation-to-action" framework. *International Journal of Cognitive Therapy,* 8**,** 114-129.

Klonsky, E. D., Qiu, T. & Saffer, B. Y. 2017. Recent advances in differentiating suicide attempters from suicide ideators. *Current Opinion in Psychiatry,* 30**,** 15-20.

Knipe, D., Jayasumana, C., Siribaddana, S., et al. 2016. Feasibility of hair sampling to assess levels of organophosphate metabolites in rural areas of Sri Lanka. *Environmental Research,* 147**,** 207-211.

Knipe, D., Williams, A. J., Hannam-Swain, S., et al. 2019. Psychiatric morbidity and suicidal behaviour in low- and middle-income countries: A systematic review and meta-analysis. *PLoS Medicine,* 16**,** e1002905.

Knipe, D. W., Chang, S.-S., Dawson, A., et al. 2017. Suicide prevention through means restriction: impact of the 2008-2011 pesticide restrictions on suicide in Sri Lanka. *PloS One,* 12**,** e0172893.

Kõlves, K., Mcdonough, M., Crompton, D. & De Leo, D. 2018. Choice of a suicide method: Trends and characteristics. *Psychiatry Research,* 260**,** 67-74.

Kruk, M. E., Goldmann, E. & Galea, S. 2009. Borrowing and selling to pay for health care in low-and middle-income countries. *Health Affairs,* 28**,** 1056-1066.

Lam, M., Hill, W. D., Trampush, J. W., et al. 2019. Pleiotropic Meta-Analysis of Cognition, Education, and Schizophrenia Differentiates Roles of Early Neurodevelopmental and Adult Synaptic Pathways. *Am J Hum Genet,* 105**,** 334-350.

Lee, P. H., Anttila, V., Won, H., et al. 2019. Genomic relationships, novel loci, and pleiotropic mechanisms across eight psychiatric disorders. *Cell,* 179**,** 1469-1482. e11.

Lejeune, A., Le Glaz, A., Perron, P.-A., et al. 2022. Artificial intelligence and suicide prevention: a systematic review. *European Psychiatry,* 65**,** 1-22.

Levey, D. F., Polimanti, R., Cheng, Z., et al. 2019. Genetic associations with suicide attempt severity and genetic overlap with major depression. *Translational Psychiatry,* 9**,** 1-12.

Lewis, C. M. & Vassos, E. 2020. Polygenic risk scores: from research tools to clinical instruments. *Genome Medicine,* 12**,** 44.

Lim, M., Lee, S. U. & Park, J.-I. 2014. Difference in suicide methods used between suicide attempters and suicide completers. *International Journal of Mental Health Systems,* 8**,** 54.

Linsley, K. R., Schapira, K. & Kelly, T. 2001. Open verdict v. suicide–importance to research. *The British Journal of Psychiatry,* 178**,** 465-468.

Ljung, T., Chen, Q., Lichtenstein, P. & Larsson, H. 2014. Common Etiological Factors of Attention-Deficit/Hyperactivity Disorder and Suicidal Behavior: A Population-Based Study in Sweden. *JAMA Psychiatry,* 71**,** 958-964.

London, L., Beseler, C., Bouchard, M. F., et al. 2012. Neurobehavioral and neurodevelopmental effects of pesticide exposures. *Neurotoxicology,* 33**,** 887-896.

London, L., Flischer, A. J., Wesseling, C., Mergler, D. & Kromhout, H. 2005. Suicide and exposure to organophosphate insecticides: Cause or effect? *Am J Ind Med,* 47**,** 308-321.

Loos, R. J. F. 2020. 15 years of genome-wide association studies and no signs of slowing down. *Nature Communications,* 11**,** 5900.

Lopes, F. & Mcmahon, F. 2019. The Promise and Limits of Suicide Genetics. *Am J Psychiatry,* 176**,** 600-602.

Lopez, A. D., Abouzahr, C., Shibuya, K. & Gollogly, L. 2007. Keeping count: births, deaths, and causes of death. *The Lancet,* 370**,** 1744-1746.

Lorant, V., Kapadia, D., Perelman, J. & Demetriq Study Group 2021. Socioeconomic disparities in suicide: Causation or confounding? *PloS One,* 16**,** e0243895.

Lund, C., Breen, A., Flisher, A. J., et al. 2010. Poverty and common mental disorders in low and middle income countries: A systematic review. *Social Science & Medicine,* 71**,** 517-528.

Lund, C., Myer, L., Stein, D. J., Williams, D. R. & Flisher, A. J. 2013. Mental illness and lost income among adult South Africans. *Social Psychiatry and Psychiatric Epidemiology,* 48**,** 845-851.

Luoma, J. B., Martin, C. E. & Pearson, J. L. 2002. Contact with mental health and primary care providers before suicide: a review of the evidence. *Am J Psychiatry,* 159**,** 909-16.

Macfarlane, E., Simpson, P., Benke, G. & Sim, M. R. 2011. Suicide in Australian pesticide-exposed workers. *Occupational Medicine,* 61**,** 259-264.

Majara, L., Kalungi, A., Koen, N., et al. 2023. Low and differential polygenic score generalizability among African populations due largely to genetic diversity. *Human Genetics and Genomics Advances,* 4.

Malone, K. M., Haas, G. L., Sweeney, J. A. & Mann, J. J. 1995. Major depression and the risk of attempted suicide. *Journal of Affective Disorders,* 34**,** 173-185.

Mann, J. J., Michel, C. A. & Auerbach, R. P. 2021. Improving suicide prevention through evidence-based strategies: a systematic review. *Am J Psychiatry,* 178**,** 611-624.

Mann, J. J., Waternaux, C., Haas, G. L. & Malone, K. M. 1999. Toward a clinical model of suicidal behavior in psychiatric patients. *Am J Psychiatry,* 156**,** 181-9.

Marais, D. L. & Petersen, I. 2015. Health system governance to support integrated mental health care in South Africa: challenges and opportunities. *International Journal of Mental Health Systems,* 9**,** 1-21.

Mardakheh, F. K., Self, A. & Marshall, C. J. 2016. RHO binding to FAM65A regulates Golgi reorientation during cell migration. *Journal of Cell Science,* 129**,** 4466-4479.

Mars, B., Burrows, S., Hjelmeland, H. & Gunnell, D. 2014. Suicidal behaviour across the African continent: a review of the literature. *BMC Public Health,* 14**,** 606.

Mathers, C. D., Ma Fat, D., Inoue, M., Rao, C. & Lopez, A. D. 2005. Counting the dead and what they died from: an assessment of the global status of cause of death data. *Bulletin of the World Health Organization,* 83**,** 171-177c.

Matzopoulos, R., Groenewald, P., Abrahams, N. & Bradshaw, D. 2016. Where have all the gun deaths gone? *South African Medical Journal,* 106**,** 589-591.

Matzopoulos, R., Norman, R. & Bradshaw, D. 2004. The burden of injury in South Africa: Fatal injury trends and international comparisons. *Tygerberg: Medical Research Council-University of South Africa, Crime, Violence and Injury Lead Programme*.

Matzopoulos, R., Prinsloo, M., Wyk, V. P.-V., et al. 2015. Injury-related mortality in South Africa: a retrospective descriptive study of postmortem investigations. *Bulletin of the World Health Organization,* 93**,** 303-313.

Matzopoulos, R., Simonetti, J., Prinsloo, M., et al. 2018. A retrospective time trend study of firearm and nonfirearm homicide in Cape Town from 1994 to 2013. *South African Medical Journal,* 108**,** 197-204.

Matzopoulos, R. G., Thompson, M. L. & Myers, J. E. 2014. Firearm and nonfirearm homicide in 5 South African cities: a retrospective population-based study. *Am J Public Health,* 104**,** 455-460.

May, A. M. & Klonsky, E. D. 2016. What distinguishes suicide attempters from suicide ideators? A meta-analysis of potential factors. *Clinical Psychology: Science and Practice,* 23**,** 5.

Mayosi, B. M., Flisher, A. J., Lalloo, U. G., et al. 2009. The burden of non-communicable diseases in South Africa. *The Lancet,* 374**,** 934-947.

Mayosi, B. M., Lawn, J. E., Van Niekerk, A., et al. 2012. Health in South Africa: changes and challenges since 2009. *The Lancet,* 380**,** 2029-2043.

Mcgirr, A. & Turecki, G. 2007. The relationship of impulsive aggressiveness to suicidality and other depression-linked behaviors. *Current Psychiatry Reports,* 9**,** 460-466.

Mclean, J., Maxwell, M., Platt, S., Harris, F. M. & Jepson, R. 2008. *Risk and protective factors for suicide and suicidal behaviour: A literature review,* Scottish Government.

Meltzer, H., Griffiths, C., Brock, A., Rooney, C. & Jenkins, R. 2008. Patterns of suicide by occupation in England and Wales: 2001–2005. *The British Journal of Psychiatry,* 193**,** 73-76.

Merikangas, A. K. & Almasy, L. 2020. Using the tools of genetic epidemiology to understand sex differences in neuropsychiatric disorders. *Genes, Brain and Behavior,* 19**,** e12660.

Mew, E. J., Padmanathan, P., Konradsen, F., et al. 2017. The global burden of fatal self-poisoning with pesticides 2006-15: systematic review. *Journal of Affective Disorders,* 219**,** 93-104.

Michel, J., Tediosi, F., Egger, M., et al. 2020. Universal health coverage financing in South Africa: wishes vs reality. *Journal of Global Health Reports,* 4**,** e2020061.

Mills, M. C. & Rahal, C. 2019. A scientometric review of genome-wide association studies. *Communications Biology,* 2**,** 9-9.

Mirkovic, B., Laurent, C., Podlipski, M.-A., et al. 2016. Genetic association studies of suicidal behavior: a review of the past 10 years, progress, limitations, and future directions. *Frontiers in Psychiatry,* 7**,** 158.

Mitterauer, B. 1990. A contribution to the discussion of the role of the genetic factor in suicide, based on five studies in an epidemiologically defined area (Province of Salzburg, Austria). *Comprehensive Psychiatry,* 31**,** 557-565.

Mulder, N., Abimiku, A., Adebamowo, S. N., et al. 2018. H3Africa: current perspectives. *Pharmgenomics Pers Med,* 11**,** 59-66.

Mullins, N., Bigdeli, T. B., Børglum, A. D., et al. 2019. GWAS of suicide attempt in psychiatric disorders and association with major depression polygenic risk scores. *Am J Psychiatry,* 176**,** 651-660.

Mullins, N., Kang, J., Campos, A. I., et al. 2022. Dissecting the Shared Genetic Architecture of Suicide Attempt, Psychiatric Disorders, and Known Risk Factors. *Biological Psychiatry,* 91**,** 313-327.

Mullins, N., Perroud, N., Uher, R., et al. 2014. Genetic relationships between suicide attempts, suicidal ideation and major psychiatric disorders: a genome-wide association and polygenic scoring study. *Am J Med Genet Part B: Neuropsychiatric Genetics,* 165b**,** 428-37.

Naghavi, M. 2019. Global, regional, and national burden of suicide mortality 1990 to 2016: systematic analysis for the Global Burden of Disease Study 2016. *BMJ,* 364**,** l94.

Naidoo, V. & Buckley, C. 2003. *Survey of pesticide wastes in South Africa and review of treatment options,* Water Research Commission Pretoria.

Niculescu, A. B., Le-Niculescu, H., Levey, D. F., et al. 2017. Precision medicine for suicidality: from universality to subtypes and personalization. *Molecular Psychiatry,* 22**,** 1250-1273.

Nock, M. K., Borges, G., Bromet, E. J., et al. 2008. Suicide and suicidal behavior. *Epidemiologic Reviews,* 30**,** 133-154.

Nock, M. K., Green, J. G., Hwang, I., et al. 2013. Prevalence, correlates, and treatment of lifetime suicidal behavior among adolescents: results from the National Comorbidity Survey Replication Adolescent Supplement. *JAMA Psychiatry,* 70**,** 300-310.

Nock, M. K., Hwang, I., Sampson, N., et al. 2009. Cross-National Analysis of the Associations among Mental Disorders and Suicidal Behavior: Findings from the WHO World Mental Health Surveys. *PLoS Medicine,* 6**,** e1000123.

Nock, M. K., Hwang, I., Sampson, N. A. & Kessler, R. C. 2010. Mental disorders, comorbidity and suicidal behavior: results from the National Comorbidity Survey Replication. *Molecular Psychiatry,* 15**,** 868-876.

Nock, M. K., Millner, A. J., Joiner, T. E., et al. 2018. Risk factors for the transition from suicide ideation to suicide attempt: Results from the Army Study to Assess Risk and Resilience in Servicemembers (Army STARRS). *Journal of Abnormal Psychology,* 127**,** 139-149.

Nordsletten, A. E., Larsson, H., Crowley, J. J., et al. 2016. Patterns of Nonrandom Mating Within and Across 11 Major Psychiatric Disorders. *JAMA Psychiatry,* 73**,** 354-61.

Nordt, C., Warnke, I., Seifritz, E. & Kawohl, W. 2015. Modelling suicide and unemployment: a longitudinal analysis covering 63 countries, 2000–11. *The Lancet Psychiatry,* 2**,** 239-245.

Norman, R., Matzopoulos, R., Groenewald, P. & Bradshaw, D. 2007. The high burden of injuries in South Africa. *Bull World Health Organ,* 85**,** 695-702.

Norman, R., Schneider, M., Bradshaw, D., et al. 2010. Interpersonal violence: an important risk factor for disease and injury in South Africa. *Population Health Metrics,* 8**,** 32.

O'carroll, P. W., Berman, A. L., Maris, R. W., et al. 1996. Beyond the Tower of Babel: a nomenclature for suicidology. *Suicide and Life-Threatening Behavior,* 26**,** 237-252.

O'donnell, I. & Farmer, R. 1995. The limitations of official suicide statistics. *The British Journal of Psychiatry,* 166**,** 458-461.

Office for National Statistics. 2022. *Suicides in England and Wales: 2021 registrations* [Online]. Available: https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/deaths/bulletins/suicidesintheunitedkingdom/2021registrations [Accessed 28 April 2023].

Ohberg, A. & Lonnqvist, J. 1998. Suicides hidden among undetermined deaths. *Acta Psychiatr Scand,* 98**,** 214-218.

Okbay, A., Beauchamp, J. P., Fontana, M. A., et al. 2016. Genome-wide association study identifies 74 loci associated with educational attainment. *Nature,* 533**,** 539-542.

Otsuka, I., Akiyama, M., Shirakawa, O., et al. 2019. Genome-wide association studies identify polygenic effects for completed suicide in the Japanese population. *Neuropsychopharmacology,* 44**,** 2119-2124.

Oyesanya, M., Lopez-Morinigo, J. & Dutta, R. 2015. Systematic review of suicide in economic recession. *World Journal of Psychiatry,* 5**,** 243.

Paris, J. 2006. Predicting and preventing suicide: Do we know enough to do either? *Harvard Review of Psychiatry,* 14**,** 233-240.

Patel, V. & Thornicroft, G. 2009. Packages of care for mental, neurological, and substance use disorders in low- and middle-income countries: PLoS Medicine Series. *PLoS Medicine,* 6**,** e1000160-e1000160.

Patience, M. 2018. *Retrospective analysis of suspected pesticide-related fatalities admitted to Salt River Mortuary in the West Metropole of Cape Town, Republic of South Africa.* University of Cape Town.

Patton, J. H., Stanford, M. S. & Barratt, E. S. 1995. Factor structure of Barratt's Impulsiveness Scale. *Journal of Clinical Psychology,* 51**,** 768-774.

Perlis, R. H., Huang, J., Purcell, S., et al. 2010. Genome-wide association study of suicide attempts in mood disorder patients. *Am J Psychiatry,* 167**,** 1499-507.

Peters, D. H., Garg, A., Bloom, G., et al. 2008. Poverty and access to health care in developing countries. *Annals of the New York Academy of Sciences,* 1136**,** 161-171.

Petersen, I., Van Rensburg, A., Kigozi, F., et al. 2019. Scaling up integrated primary mental health in six low-and middle-income countries: obstacles, synergies and implications for systems reform. *BJPsych Open,* 5.

Pillay-Van Wyk, V., Laubscher, R., Msemburi, W., et al. 2014. Second South African National Burden of Disease Study: Data Cleaning, Validation and SA NBD List. Cape Town: Burden of Disease Research Unit, South African Medical Research Council.

Plomin, R., Defries, J. C., Knopik, V. S. & Neiderhiser, J. M. 2016. Top 10 replicated findings from behavioral genetics. *Perspectives on Psychological Science,* 11**,** 3-23.

Polimanti, R., Levey, D. F., Pathak, G. A., et al. 2021. Multi-environment gene interactions linked to the interplay between polysubstance dependence and suicidality. *Translational Psychiatry,* 11**,** 34.

Pompili, M., Serafini, G., Innamorati, M., et al. 2010. Suicidal behavior and alcohol abuse. *International Journal of Environmental Research and Public Health,* 7**,** 1392-1431.

Poorolajal, J. & Darvishi, N. 2016. Smoking and suicide: A meta-analysis. *PloS One,* 11**,** e0156348-e0156348.

Popejoy, A. B. & Fullerton, S. M. 2016. Genomics is failing on diversity. *Nature,* 538**,** 161-164.

Posner, K., Oquendo, M. A., Gould, M., Stanley, B. & Davies, M. 2007. Columbia Classification Algorithm of Suicide Assessment (C-CASA): classification of suicidal events in the FDA's pediatric suicidal risk analysis of antidepressants. *Am J Psychiatry,* 164**,** 1035-1043.

Powers, B., Joyce, C., Kleinman, J. E., et al. 2020. Sex differences in the transcription of glutamate transporters in major depression and suicide. *Journal of Affective Disorders,* 277**,** 244-252.

Prinsloo, M., Bradshaw, D., Joubert, J., Matzopoulos, R. & Groenewald, P. 2017. South Africa's vital statistics are currently not suitable for monitoring progress towards injury and violence Sustainable Development Goals. *South African Medical Journal,* 107**,** 470-471.

Pritchard, C., Iqbal, W. & Dray, R. 2020. Undetermined and accidental mortality rates as possible sources of underreported suicides: population-based study comparing Islamic countries and traditionally religious Western countries. *BJPsych Open,* 6**,** e56.

Probst, C., Parry, C. D., Wittchen, H.-U. & Rehm, J. 2018. The socioeconomic profile of alcohol-attributable mortality in South Africa: a modelling study. *BMC Medicine,* 16**,** 1-11.

Prochaska, J. J., Das, S. & Young-Wolff, K. C. 2017. Smoking, Mental Illness, and Public Health. *Annual Review of Public Health,* 38**,** 165-185.

Puzo, Q., Qin, P. & Mehlum, L. 2016. Long-term trends of suicide by choice of method in Norway: a joinpoint regression analysis of data from 1969 to 2012. *BMC Public Health,* 16**,** 255.

Qin, P., Agerbo, E. & Mortensen, P. B. 2002. Suicide risk in relation to family history of completed suicide and psychiatric disorders: a nested case-control study based on longitudinal registers. *The Lancet,* 360**,** 1126-1130.

Ribeiro, J. D., Franklin, J. C., Fox, K. R., et al. 2016. Self-injurious thoughts and behaviors as risk factors for future suicide ideation, attempts, and death: a meta-analysis of longitudinal studies. *Psychological Medicine,* 46**,** 225-36.

Roomaney, R., Ehrlich, R. & Rother, H.-A. 2012. The acceptability of rat trap use over pesticides for rodent control in two poor urban communities in South Africa. *Environmental Health,* 11**,** 32.

Rotimi, C., Abayomi, A., Abimiku, A., et al. 2014. Research capacity. Enabling the genomic revolution in Africa. *Science,* 344**,** 1346-8.

Rudd, M. D. 2021. Recognizing flawed assumptions in suicide risk assessment research and clinical practice. *Psychological Medicine***,** 1-2.

Ruderfer, D. M., Walsh, C. G., Aguirre, M. W., et al. 2019. Significant shared heritability underlies suicide attempt and clinically predicted probability of attempting suicide. *Molecular Psychiatry***,** 1-9.

Ruffieux, Y., Efthimiou, O., Van Den Heuvel, L. L., et al. 2021. The treatment gap for mental disorders in adults enrolled in HIV treatment programmes in South Africa: a cohort study using linked electronic health records. *Epidemiology and Psychiatric Sciences,* 30.

Runeson, B. & Åsberg, M. 2003. Family history of suicide among suicide victims. *Am J Psychiatry,* 160**,** 1525-1526.

Sagar-Ouriaghli, I., Godfrey, E., Bridge, L., Meade, L. & Brown, J. S. L. 2019. Improving Mental Health Service Utilization Among Men: A Systematic Review and Synthesis of Behavior Change Techniques Within Interventions Targeting Help-Seeking. *American Journal of Men's Health,* 13**,** 1557988319857009.

Salmen, C. 2009. Towards an Anthropology of Organic Health: The Relational Fields of HIV/AIDS Among the Suba of Lake Victoria: Institute of Social and Cultural Anthropology. Oxford University.

Santucci, K. 2012. Psychiatric disease and drug abuse. *Current Opinion in Pediatrics,* 24**,** 233-237.

Saunders, J. B., Aasland, O. G., Babor, T. F., De La Fuente, J. R. & Grant, M. 1993. Development of the alcohol use disorders identification test (AUDIT): WHO collaborative project on early detection of persons with harmful alcohol consumption-II. *Addiction,* 88**,** 791-804.

Schaffer, A., Sinyor, M., Kurdyak, P., et al. 2016. Population-based analysis of health care contacts among suicide decedents: identifying opportunities for more targeted suicide prevention strategies. *World Psychiatry,* 15**,** 135-145.

Schmidtke, A., Bille-Brahe, U., Deleo, D., et al. 1996. Attempted suicide in Europe: rates, trends and sociodemographic characteristics of suicide attempters during the period 1989-1992. Results of the WHO/EURO Multicentre Study on Parasuicide. *Acta Psychiatr Scand,* 93**,** 327-38.

Schosser, A., Butler, A. W., Ising, M., et al. 2011. Genome-wide association scan of suicidal thoughts and behaviour in major depression. *PloS One*.

Scribante, L., Blumenthal, R., Saayman, G. & Roos, J. L. 2004. A retrospective review of 1018 suicide cases from the capital city of South Africa for the period 1997–2000. *American Journal of Forensic Medicine and Pathology,* 25**,** 52-55.

Seedat, S., Williams, D. R., Herman, A. A., et al. 2009. Mental health service use among South Africans for mood, anxiety and substance use disorders. *South African Medical Journal,* 99.

Sengupta, D., Choudhury, A., Fortes-Lima, C., et al. 2021. Genetic substructure and complex demographic history of South African Bantu speakers. *Nature Communications,* 12**,** 2080.

Shah, A. & Buckley, L. 2011. The current status of methods used by the elderly for suicides in England and Wales. *Journal of Injury & Violence Research,* 3**,** 68-73.

Shannon, P., Markiel, A., Ozier, O., et al. 2003. Cytoscape: a software environment for integrated models of biomolecular interaction networks. *Genome research,* 13**,** 2498-2504.

Siegfried, N. & Parry, C. 2019. Do alcohol control policies work? An umbrella review and quality assessment of systematic reviews of alcohol control interventions (2006 – 2017). *PLoS One,* 14**,** e0214865.

Silverman, M. M., Berman, A. L., Sanddal, N. D., O'carroll, P. W. & Joiner, T. E. 2007. Rebuilding the Tower of Babel: A Revised Nomenclature for the Study of Suicide and Suicidal Behaviors. Part 1: Background, Rationale, and Methodology. *Suicide and Life-Threatening Behavior,* 37**,** 248-263.

Silverman, M. M. & Leo, D. D. 2016. Why There Is a Need for an International Nomenclature and Classification System for Suicide. *Crisis,* 37**,** 83-87.

Simpson, S. A., Loh, R. M. & Goans, C. R. 2021. New data on suicide risk assessment in the emergency department reveal the need for new approaches in research and clinical practice. *Psychological Medicine***,** 1-2.

Smith, G. D. & Ebrahim, S. 2004. Mendelian randomization: prospects, potentials, and limitations. *International Journal of Epidemiology,* 33**,** 30-42.

Smoller, J. W., Andreassen, O. A., Edenberg, H. J., et al. 2019. Psychiatric genetics and the structure of psychopathology. *Molecular Psychiatry,* 24**,** 409-420.

Sokero, T. P., Melartin, T. K., Rytsala, H. J., et al. 2003. Suicidal ideation and attempts among psychiatric patients with major depressive disorder. *Journal of Clinical Psychiatry,* 64**,** 1094-100.

Sorenson, S. B. & Rutter, C. M. 1991. Transgenerational patterns of suicide attempt. *Journal of Consulting and Clinical Psychology,* 59**,** 861.

South Africa 1959. Inquest Act No 58 of 1959.

South Africa 1992. Births and Deaths Registration Act. *51.* South Africa.

South Africa 2000. Firearm Control Act 60 of 2000.

Stallones, L. 2006. Suicide and potential occupational exposure to pesticides, Colorado 1990–1999. *Journal of Agromedicine,* 11**,** 107-112.

Stanford, M. S., Mathias, C. W., Dougherty, D. M., et al. 2009. Fifty years of the Barratt Impulsiveness Scale: An update and review. *Personality and Individual Differences,* 47**,** 385-395.

Stark, K., Joubert, G., Struwig, M., et al. 2010. Suicide cases investigated at the state mortuary in Bloemfontein, 2003–2007. *South African Family Practice,* 52.

Statistics South Africa Statistics South Afrca Datasets. Mortality and Causes of Death 1997-2016. *In:* STATISTICS SOUTH AFRICA (ed.). Pretoria.

Statistics South Africa 2018. Mortality and causes of death in South Africa, 2015: Findings from death notification form (P0309.3). Pretoria: Statistics South Africa.

Statistics South Africa 2020. General Household Survey 2020. Pretoria, South Africa: Statistics South Africa.

Stein, D. J., Benjet, C., Gureje, O., et al. 2019. Integrating mental health with other non-communicable diseases. *BMJ,* 364**,** l295.

Stenbacka, M. & Jokinen, J. 2015. Violent and non-violent methods of attempted and completed suicide in Swedish young men: the role of early risk factors. *BMC Psychiatry,* 15**,** 196.

Stene-Larsen, K. & Reneflot, A. 2017. Contact with primary and mental health care prior to suicide: A systematic review of the literature from 2000 to 2017. *Scandinavian Journal of Public Health,* 47**,** 9-17.

Strawbridge, R. J., Ward, J., Ferguson, A., et al. 2019. Identification of novel genome-wide associations for suicidality in UK Biobank, genetic correlation with psychiatric disorders and polygenic association with completed suicide. *EBioMedicine,* 41**,** 517-525.

Sulla, V. & Zikhali, P. 2018. Overcoming poverty and inequality in South Africa: An assessment of drivers, constraints and opportunities. Washington, D.C.: World Bank Group.

Sullivan, P. F., Agrawal, A., Bulik, C. M., et al. 2018. Psychiatric genomics: an update and an agenda. *Am J Psychiatry,* 175**,** 15-27.

Sullivan, P. F., Daly, M. J. & O'donovan, M. 2012. Genetic architectures of psychiatric disorders: the emerging picture and its implications. *Nature Reviews Genetics,* 13**,** 537-551.

Sullivan, P. F., Neale, M. C. & Kendler, K. S. 2000. Genetic epidemiology of major depression: review and meta-analysis. *Am J Psychiatry,* 157**,** 1552-1562.

Suominen, K., Isometsä, E., Suokas, J., et al. 2004. Completed suicide after a suicide attempt: a 37-year follow-up study. *Am J Psychiatry,* 161**,** 562-563.

Sveticic, J. & De Leo, D. 2012. The hypothesis of a continuum in suicidality: a discussion on its validity and practical implications. *Mental illness,* 4**,** e15-e15.

Tindana, P., De Vries, J., Campbell, M., et al. 2015. Community engagement strategies for genomic studies in Africa: a review of the literature. *BMC Medical Ethics,* 16**,** 1-12.

Tistarelli, N., Fagnani, C., Troianiello, M., Stazi, M. A. & Adriani, W. 2020. The nature and nurture of ADHD and its comorbidities: A narrative review on twin studies. *Neuroscience & Biobehavioral Reviews,* 109**,** 63-77.

Tøllefsen, I. M., Helweg-Larsen, K., Thiblin, I., et al. 2015. Are suicide deaths under-reported? Nationwide re-evaluations of 1800 deaths in Scandinavia. *BMJ Open,* 5**,** e009120.

Tøllefsen, I. M., Hem, E. & Ekeberg, Ø. 2012. The reliability of suicide statistics: a systematic review. *BMC Psychiatry,* 12**,** 9.

Tolosana, S., Rother, H.-A. & London, L. 2009. Child's play: Exposure to household pesticide use among children in rural, urban and informal areas of South Africa. *South African Medical Journal,* 99.

Tran, T., Luo, W., Phung, D., et al. 2014. Risk stratification using data from electronic medical records better predicts suicide risks than clinician assessments. *BMC Psychiatry,* 14**,** 1-9.

Trout, D. L. 1980. The role of social isolation in suicide. *Suicide and Life-Threatening Behavior,* 10**,** 10-23.

Tsatsakis, A., Barbounis, M., Kavalakis, M., et al. 2010. Determination of dialkyl phosphates in human hair for the biomonitoring of exposure to organophosphate pesticides. *Journal of Chromatography B,* 878**,** 1246-1252.

Turecki, G. 2001. Suicidal behavior: is there a genetic predisposition? *Bipolar Disorders,* 3**,** 335-349.

Turecki, G. & Brent, D. A. 2016. Suicide and suicidal behaviour. *The Lancet,* 387**,** 1227-1239.

Umubyeyi, A., Mogren, I., Ntaganira, J. & Krantz, G. 2016. Help-seeking behaviours, barriers to care and self-efficacy for seeking mental health care: a population-based study in Rwanda. *Social Psychiatry and Psychiatric Epidemiology,* 51**,** 81-92.

UNAIDS 2018. Country factsheets South Africa 2018.

Van Heeringen, K. 2012. Stress–Diathesis Model of Suicidal Behavior. *In:* DWIVEDI, Y. (ed.) *The Neurobiological Basis of Suicide.* Boca Raton (FL): CRC Press/Taylor & Francis.

Värnik, P., Sisask, M., Värnik, A., et al. 2012. Validity of suicide statistics in Europe in relation to undetermined deaths: developing the 2-20 benchmark. *Injury Prevention,* 18**,** 321-325.

Vendredy, L., Adriaenssens, E. & Timmerman, V. 2020. Small heat shock proteins in neurodegenerative diseases. *Cell Stress Chaperones,* 25**,** 679-699.

Vijayakumar, L., Kumar, M. S. & Vijayakumar, V. 2011. Substance use and suicide. *Current Opinion in Psychiatry,* 24**,** 197-202.

Vijayakumar, L., Nagaraj, K., Pirkis, J. & Whiteford, H. 2005. Suicide in Developing Countries (1) Frequency, Distribution, and Association with Socioeconomic Indicators. *Crisis,* 26**,** 104-111.

Voracek, M. & Loibl, L. M. 2007. Genetics of suicide: a systematic review of twin studies. *Wiener Klinische Wochenschrift,* 119**,** 463-475.

Vos, T., Lim, S. S., Abbafati, C., et al. 2020. Global burden of 369 diseases and injuries in 204 countries and territories, 1990–2019: a systematic analysis for the Global Burden of Disease Study 2019. *The Lancet,* 396**,** 1204-1222.

Walby, F. A., Myhre, M. Ø. & Kildahl, A. T. 2018. Contact With Mental Health Services Prior to Suicide: A Systematic Review and Meta-Analysis. *Psychiatric Services,* 69**,** 751-759.

Wang, K., Li, M. & Hakonarson, H. 2010. ANNOVAR: functional annotation of genetic variants from high-throughput sequencing data. *Nucleic Acids Research,* 38**,** e164-e164.

Wang, L., Jia, P., Wolfinger, R. D., Chen, X. & Zhao, Z. 2011. Gene set analysis of genome-wide association studies: methodological issues and perspectives. *Genomics,* 98**,** 1-8.

Wang, P. S., Aguilar-Gaxiola, S., Alonso, J., et al. 2007. Use of mental health services for anxiety, mood, and substance disorders in 17 countries in the WHO world mental health surveys. *The Lancet,* 370**,** 841-850.

Wasserman, D., Carli, V., Iosue, M., Javed, A. & Herrman, H. 2021. Suicide prevention in psychiatric patients. *Asia Pacific Psychiatry,* 13**,** e12450.

Wasserman, D., Rihmer, Z., Rujescu, D., et al. 2012. The European Psychiatric Association (EPA) guidance on suicide treatment and prevention. *European Psychiatry,* 27**,** 129-141.

Watanabe, K., Taskesen, E., Van Bochoven, A. & Posthuma, D. 2017. Functional mapping and annotation of genetic associations with FUMA. *Nature Communications,* 8**,** 1-11.

Watanuki, T., Funato, H., Uchida, S., et al. 2008. Increased expression of splicing factor SRp20 mRNA in bipolar disorder patients. *Journal of Affective Disorders,* 110**,** 62-69.

Weissman, M. M., Sholomskas, D., Pottenger, M., Prusoff, B. A. & Locke, B. Z. 1977. Assessing depressive symptoms in five psychiatric populations: a validation study. *Am J Epidemiol,* 106**,** 203-214.

Weskamp, K. & Barmada, S. J. 2018. RNA Degradation in Neurodegenerative Disease. *Adv Neurobiol,* 20**,** 103-142.

WHO 2012. Public health action for the prevention of suicide: a framework.

WHO 2013. Comprehensive Mental Health Action Plan 2013-2020. Geneva: World Health Organization.

WHO 2014a. Global status report on violence prevention. Geneva World Health Organisation.

WHO 2014b. Preventing suicide: A global imperative. Geneva, World Health Organisation.

WHO 2016. Sustainable development goals (SDGs): Goal 3. Target 3.4: By 2030, reduce by one third premature mortality from non-communicable diseases through prevention and treatment and promote mental health and well being [poster]. WHO Regional Office for the Western Pacific.

WHO 2018a. Global status report on alcohol and health 2018. Geneva.

WHO 2018b. National suicide prevention strategies: progress, examples and indicators. Geneva: World Health Organisation.

WHO 2021. Suicide worldwide in 2019: Global Health Estimates.

WHO Mortality Database 2023. Geneva: World Health Organization.

Wiederman, M. W., Sansone, R. A. & Sansone, L. A. 1998. History of trauma and attempted suicide among women in a primary care setting. *Violence and Victims,* 13**,** 3.

Williams, D. R., Herman, A. A., Stein, D., et al. 2008. Twelve-month mental disorders in South Africa: prevalence, service use and demographic correlated in the population-based South African Stress and Health study. *Psychological Medicine***,** 211-220.

Williams, S. L., Williams, D. R., Stein, D. J., et al. 2007. Multiple traumatic events and psychological distress: the South Africa stress and health study. *Journal of Traumatic Stress,* 20**,** 845-855.

Willour, V. L., Seifuddin, F., Mahon, P. B., et al. 2012. A genome-wide association study of attempted suicide. *Molecular Psychiatry,* 17**,** 433-444.

Windsor-Shellard, B. & Gunnell, D. 2019. Occupation-specific suicide risk in England: 2011–2015. *The British Journal of Psychiatry,* 215**,** 594-599.

Wootton, R. E., Richmond, R. C., Stuijfzand, B. G., et al. 2020. Evidence for causal effects of lifetime smoking on risk for depression and schizophrenia: a Mendelian randomisation study. *Psychological Medicine,* 50**,** 2435-2443.

World Bank 2020. Poverty & Equity Brief: Sub-Saharan Africa, South Africa. World Bank.

Worthington, R. L. & Moreno, M. V. 2005. Beyond Kinsey and Klein: Measuring Sexual Orientation and Identity. *Division 44 symposium of the 113th Annual Convention of the American Psychological Association.* Washington, DC.

Wray, N. R., Ripke, S., Mattheisen, M., et al. 2018. Genome-wide association analyses identify 44 risk variants and refine the genetic architecture of major depression. *Nature Genetics,* 50**,** 668-681.

Xiong, J., Chen, Y., Wang, W. & Sun, J. 2022. Biological function and molecular mechanism of SRSF3 in cancer and beyond. *Oncology Letters,* 23**,** 1-11.

Xue, H., Shen, X. & Pan, W. 2021. Constrained maximum likelihood-based Mendelian randomization robust to both correlated and uncorrelated pleiotropic effects. *Am J Hum Genet,* 108**,** 1251-1269.

Youssef, M. M. M., Hamada, H. T., Lai, E. S. K., et al. 2022. TOB is an effector of the hippocampus-mediated acute stress response. *Translational Psychiatry,* 12**,** 302.

Zai, C. C., Gonçalves, V. F., Tiwari, A. K., et al. 2015. A genome-wide association study of suicide severity scores in bipolar disorder. *Journal of Psychiatric Research,* 65**,** 23-29.

Zalsman, G., Hawton, K., Wasserman, D., et al. 2016. Suicide prevention strategies revisited: 10-year systematic review. *The Lancet Psychiatry,* 3**,** 646-659.

Zhang, W., Jiang, F. & Ou, J. 2011. Global pesticide consumption and pollution: with China as a focus. *Proceedings of the International Academy of Ecology and Environmental Sciences,* 1**,** 125.

Appendices

Appendix A. Ethics approval documents

UNIVERSITY OF CAPE TOWN
Faculty of Health Sciences
Human Research Ethics Committee

Room G50-46 Old Main Building
Groote Schuur Hospital
Observatory 7925
Telephone [021] 406 6492
Email: hrec-enquiries@uct.ac.za
Website: www.health.uct.ac.za/fhs/research/humanethics/forms

10 January 2020

HREC REF:461/2019

Prof R Ramesar
Division of Human Genetics
Department of Pathology
Falmouth Building-FHS

Dear Prof Ramesar

PROJECT TITLE: GENETIC RISK FACTORS AND EPIDEMIOLOGY OF SUICIDAL BEHAVIOUR IN SOUTH AFRICA (SUB-STUDY LINKED TO 645/2013; 393/2014; 713/2013; 073/2014; 299/2015) (PHD CANDIDATE: DR T KOOTBODIEN)

Thank you for your response letter dated 12 November 2019, addressing the issues raised by the Faculty of Health Sciences Human Research Ethics Committee (HREC).

It is a pleasure to inform you that the HREC has **formally approved** the above-mentioned study.

Please add more details on how the results will be disseminated.

Approval is granted for one year until the 30 January 2021.

Please submit a progress form, using the standardised Annual Report Form if the study continues beyond the approval period. Please submit a Standard Closure form if the study is completed within the approval period.
(Forms can be found on our website: www.health.uct.ac.za/fhs/research/humanethics/forms)

The HREC acknowledge that the student: Dr Tahira Kootbodien will also be involved in this study.

Please quote the HREC REF in all your correspondence.

Please note that the ongoing ethical conduct of the study remains the responsibility of the principal investigator.

Please note that for all studies approved by the HREC, the principal investigator **must** obtain appropriate institutional approval, where necessary, before the research may occur.

Yours sincerely

Signed by candidate

PROFESSOR M BLOCKMAN
CHAIRPERSON, FHS HUMAN RESEARCH ETHICS COMMITTEE

HREC 461/2019sa

UNIVERSITY OF CAPE TOWN

HUMAN RESEARCH ETHICS COMMITTEE
13 JAN 2022
HEALTH SCIENCES FACULTY
UNIVERSITY OF CAPE TOWN

FACULTY OF HEALTH SCIENCES
Human Research Ethics Committee

FHS016: Annual Progress Report / Renewal

HREC office use only (FWA00001637; IRB00001938)			
This serves as notification of annual approval, including any documentation described below.			
☑ Approved	Annual progress report	Approved until/next renewal date	30.01.2023
☐ Not approved	See attached comments		
Signature Chairperson of the HREC/ Designee	Signed by candidate	Date Signed	13/1/22

Note: Please email this form and supporting documents (if applicable) in a combined pdf-file to hrec-enquiries@uct.ac.za.
Please clarify your plan for research-related activities during COVID-19 lockdown.
Please use the latest form found on our website:
http://www.health.uct.ac.za/fhs/research/humanethics/forms

Comments to PI from the HREC
This is an important project, attempting to understand just some of the facets of the complex public health problem of suicides. Dr Kootbodien's project is progressing extremely well towards the finalisation of her PhD. We are grateful for HREC's continued support.

Principal Investigator to complete the following:

1. Protocol information

Date (when submitting this form)	7 December 2021		
HREC REF Number	461/2019	Current Ethics Approval was granted until	30.01.2021
Protocol title	Genetic risk factors and epidemiology of suicidal behaviour in South Africa (sub-study linked to 645/2013; 393/2014; 713/2013; 073/2014; 299/2015)		
Protocol number (if applicable)			
Are there any sub-studies linked to this study?		☐ Yes	X No
If yes, could you please provide the HREC Reference number for all sub-studies? Note: A separate FHS016 must be submitted for each sub-study.	This secondary analysis sub-study is linked to five studies noted above.		
Principal Investigator	Prof Raj Ramesar		

(Note: Please complete the Closure form (FHS010) if the study is completed within the approval period)

Appendix B. WCP DOH Letter of Approval granting access to the PHDC database

Western Cape Government
Health

Chief Directorate: Health Strategy and Support
Reference: Support for Research
Enquiries: Ms Charlene Roderick
Ph: 021-483 9341

Prof L. London

University of Cape Town,
School of Public Health and Family Medicine
Observatory,
South Africa

Project Title: Prior Health Service utilisation by patients attempting suicide in the Western Cape

Dear Prof London

The Western Cape Government Department of Health hereby grants you access to existing database from three study involving patients linked to suicide.

We believe the project will certainly contribute towards the effective management of the suicide problem in the Western Cape Province and possibly the broader South African population.

Kindly ensure that the following are adhered to:

1. Arrangements are made with managers, provided that normal activities at requested facilities/offices are not disrupted;
2. Researchers, in accessing provincial health facilities, patient data and information systems are expressing consent to provide the department with an electronic copy of the final report (Annexure 9) within six months of completion of research. This can be submitted to the Provincial Research Co-ordinator (health.research@pgwc.gov.za);
3. The above reference number should be quoted in all future correspondence.

We look forward hearing from you.

Yours sincerely

Signed by candidate

Dr Anthony Hawkridge
Director: HEALTH IMPACT ASSESSMENT (HIA)
DATE: 27/06/2016

Appendix C. Hospital-based attempted suicide case-control study - Questionnaire

UNIVERSITEIT•STELLENBOSCH•UNIVERSITY
jou kennisvennoot • your knowledge partner

Organophosphate insecticide exposure as a risk factor for attempting suicide

Questionnaire

Study Number	
Hospital name	
Date	
Patient name	
Interviewer name	

Section 1: DEMOGRAPHIC INFORMATION

I would like to ask you a few questions about yourself.

1. Date of birth ____/_____/_____
   DD/ MM/ YY

OR

How old are you? _____years

1.1 What is your highest level of education?

(Interviewer - please place tick ✓to indicate patient's choice)

	Y	N		Y	N		Y	N
Less than one year of school completed			Standard 5/Grade 7			Post matric-complete		
Sub A/Class 1/Grade 1			Standard 6/Grade 8			**Undergraduate qualifications**		
Sub B/Class 2/Grade 2			Standard 7/Grade 9			Degree - incomplete		
Standard 1/Grade 3			Standard 8/Grade 10			Degree - complete		
Standard 2/Grade 4			Standard 9/Grade 11			**Postgraduate qualifications**		
Standard 3/Grade 5			Standard 10/Grade 12			Degree - incomplete		
Standard 4/Grade 6			Post matric - incomplete			Degree - complete		

1.2 What is your home language?

(Interviewer - please first ask what the patient's home language is and allow patient to answer – then say to the patient "please confirm that this is the language you speak most often at home" and place a tick ✓next to the patient's answer in the list provided below.)

	Y	N		Y	N
English			SeTswana		
Afrikaans			SiSwati		
IsiXhosa			TshiVenda		
IsiZulu			Zitsonga		
SeSotho			IsiNdebele		
SePedi					
Other – please specify patient's language					

Section 2: SMOKING HABITS

Interviewer – please place tick ✓to indicate the patient's response

2. Do you smoke?

Yes
No

2.1. If YES please state what you smoke:

	YES	NO
Cigarettes		
Pipe Tobacco		
Dagga		
Other, please describe		

2.2 If NO did you ever smoke and if so what did you smoke?

Yes
No

(If you did smoke before, please state what you smoked)

	YES	NO
Cigarettes		
Pipe Tobacco		
Dagga		

Other, please describe		

Section 3: HOUSEHOLD AND ECONOMIC FACTORS

Next, we would like to ask a few questions about your home and the work that you do. (Mark as '0' if there's no one in relevant category)

3.1 Who of the following live in the same household with you? (Place ✓ followed by the number of people in brackets e.g. ✓(2)

Live alone		Child or Children over 13 years		Father/Male guardian	
Partner		Brother(s) and/or sister(s)		Grandparent(s)	
Child or Children under 13 years		Mother/Female guardian		Other	

3.2 Have you done any paid work in the last 12 months?

YES
NO

3.3 What kind of paid work did you do?

_____

_____

3.4 Please indicate which of the following your sources of income are. **Please answer this question whether or not you are working**.

	Y	**N**		**Y**	**N**		**Y**	**N**
Work			Brother(s) and/or sister(s)			State Old Age Pension		
Spouse/Partner			Children			Disability Grant		
Parents			Child Support Grant			Care Dependency Grant		
Workman's Compensation			Foster Care Grant			Other – please specify		

Section 4: The Alcohol Use Disorders Identification Test (AUDIT)

Instructions for interviewer: *Now we would like to ask you questions about your use of alcohol like beer, wine, brandy, whiskey or vodka during this past year.*

1. How often do you have a drink containing alcohol?

(0) Never (Skip to Qs 9 -10)
(1) Monthly or less
(2) 2 to 4 times a month
(3) 2 to 3 times a week
(4) 4 or more times a week

2. How many drinks containing alcohol do you have on a typical day when you are drinking?

(0) 1 or 2
(1) 3 or 4
(2) 5 or 6
(3) 7, 8 or 9
(4) 10 or more

6. How often during the last year have you needed a first drink in the morning to get yourself going after a heavy drinking session?

(0) Never
(1) Less than monthly
(2) Monthly
(3) Weekly
(4) Daily or almost daily

7. How often during the last year have you had a feeling of guilt or remorse after drinking?

(0) Never
(1) Less than monthly
(2) Monthly
(3) Weekly
(4) Daily or almost daily

3. How often do you have six or more drinks on one occasion? (0) Never (1) Less than monthly (2) Monthly (3) Weekly (4) Daily or almost daily ☐	**8. How often during the last year have you been unable to remember what happened the night before because you had been drinking?** (0) Never (1) Less than monthly (2) Monthly (3) Weekly (4) Daily or almost daily ☐
4. How often during the last year have you found that you were not able to stop drinking once you had started? (0) Never (1) Less than monthly (2) Monthly (3) Weekly (4) Daily or almost daily ☐	**9. Have you or someone else been injured as a result of your drinking?** (0) No (2) Yes, but not in the last year (4) Yes, during the last year ☐
5. How often during the last year have you failed to do what was normally expected from you because of drinking ? (0) Never (1) Less than monthly (2) Monthly (3) Weekly (4) Daily or almost daily ☐	**10. Has a relative or friend or a doctor or another health worker been concerned about your drinking?** (0) No (2) Yes, but not in the last year (4) Yes, during the last year ☐
Record total of specific items ☐	

Section 5: REFINED FOUR FACTOR MEASUREMENT MODEL OF THE AGGRESSION QUESTIONNAIRE

I am going to ask you questions about how you sometimes feel and act. Your answers can range from 1 to 6; 1 being not at all like you and 6 being very much like you.

1	**2**	**3**	**4**	**5**	**6**
Not at all like me					***A lot like me***

Item description	**Score**
1. Given enough provocation, I may hit another person.	
2. There are people who pushed me so far that we came to blows.	
3. There are times when I have threatened people I know.	
4. I often find myself disagreeing with people.	
5. I can't help getting into arguments when people disagree with me.	
6. My friends say that I am somewhat argumentative.	
7. I flare up quickly but get over it quickly.	
8. Sometimes I fly off the handle for no good reason.	
9. I have trouble controlling my temper.	

10. At times I feel I have gotten a raw deal out of life.	
11. I feel that other people always seem to get the breaks.	
12. I wonder why sometimes I feel so bitter about things.	

Section 6: THE CENTRE FOR EPIDEMIOLOGIC STUDIES DEPRESSION SCALE (CESD-D)

Next, I am going to ask you questions about the ways you might have felt or behaved during the past week. I will then offer possible answers and you can choose the one that best describes the way you feel.

1. **Rarely or None of the Time (Less than 1 Day)**
2. **Some or a Little of the Time (1-2 Days)**
3. **Occasionally or a Moderate Amount of Time (3-4 Days)**
4. **Most or All of the Time (5-7 Days)**

During the past week:	**Score**
1. Were you bothered by things that usually don't bother you?	
2. You did not feel like eating; your appetite was poor?	
3. Did you feel that you could not shake off the blues even with help from your family and friends?	
4. Did you feel that you were just as good as other people?	
5. Did you have trouble keeping your mind on what you were doing?	
6. Did you feel depressed?	
7. Did you feel that everything you did was an effort?	
8. Did you feel hopeful about the future?	
9. Did you think that your life had been a failure?	
10. Did you feel fearful?	
11. Was your sleep restless?	
12. Were you happy?	
13. Did you talk less than usual?	
14. Did you feel lonely?	
15. Were people unfriendly?	
16. Did you enjoy life?	
17. Did you have crying spells?	
18. Did you feel sad?	
19. Did you feel that people dislike you?	
20. Did you feel that you could not get 'going'?	

Section 7: SEXUAL ORIENTATION (Sexual Orientation Identity Scale)

Now I am going to ask you questions about your sexual orientation. I am going to read the following definitions while completing the survey items because it is essential that you respond with these definitions in mind. Please tell me which number corresponds to your answer

Interviewer: please insert the number that corresponds with the patient's answer in the table below each item

Sexual arousal refers to the onset and heightening of physical sensations and uncontrollable bodily responses (often accompanied by sexual thoughts and feelings) of a sexual nature from a previously inactive state.

1. To what extent do you experience sexual arousal in response to females? (1 being never and 6 being always)

never					always
1	2	3	4	5	6

2. To what extent do you experience sexual arousal in response to males? (1 being never and 6 being always)

never					always
1	2	3	4	5	6

Sexual attraction refers to intense and recurring sexual feelings or thoughts reflecting sexual interest in another person(s).

3. To what extent do you experience sexual attraction to females? (1 being never and 6 being always)

never					always
1	2	3	4	5	6

4. To what extent do you experience sexual attraction to males? (1 being never and 6 being always)

never					always
1	2	3	4	5	6

Sexual behavior refers to any behavior that a person might engage in that is sexual in nature (e.g., from specific forms of touching to kissing to masturbation to sexual intercourse).

5. To what extent is your sexual behavior associated with females? (1 being never and 6 being always)

never					always
1	2	3	4	5	6

6. To what extent is your sexual behavior associated with males? (1 being never and 6 being always)

never					always
1	2	3	4	5	6

Sexual fantasies are freely envisioned thoughts or mental images of a sexual nature.

7. To what extent are your sexual fantasies associated with females? (1 being never and 6 being always)

never					always
1	2	3	4	5	6

8. To what extent are your sexual fantasies associated with males? (1 being never and 6 being always)

never					always
1	2	3	4	5	6

Romantic relationships refer to dating or courtship relationships that are commonly characterized by feelings of affection, passion, love, sexual attraction and other similar emotions.

9. To what extent do you have romantic relationships with females? (1 being never and 6 being always)

never					always
1	2	3	4	5	6

10. To what extent do you have romantic relationships with males? (1 being never and 6 being always)

never					always
1	2	3	4	5	6

Sexual orientation identification refers to the process of recognizing and identifying with one's inborn tendencies toward same-sex and other-sex sexuality. This ranges from exclusive homosexuality to exclusive heterosexuality and includes various forms of bisexuality. (**Inwardly** meaning how you think about your sexual orientation privately and **outwardly** meaning how you present yourself to society)

11. To what extent do you inwardly identify as heterosexual? (1 being never and 6 being always)

never					always
1	2	3	4	5	6

12. To what extent do you inwardly identify as gay, lesbian, or bisexual? (1 being never and 6 being always)

never					always
1	2	3	4	5	6

13. To what extent are you unsure of your sexual orientation? (1 being never and 6 being always)

never					always
1	2	3	4	5	6

14. To what extent do you outwardly identify as heterosexual? (1 being never and 6 being always)

never					always
1	2	3	4	5	6

15. To what extent do you outwardly identified as gay, lesbian, or bisexual? (1 being never and 6 being always)

never					always
1	2	3	4	5	6

Section 8: BARRAT IMPULSIVENESS SCALE (BIS-II)

Next, I am going to ask you questions that look at the way you act/react in situations on a daily basis. I will then read out some options and you can choose the option that best describes how you react in certain situations.

1. Do you 'squirm' at plays/lectures (in public spaces with other people around/in church, mosque)?

Rarely/Never	
Occasionally	
Often	
Almost Always/Always	

2. Are you restless at the theatre/lectures (in public spaces with other people, church, mosque)?

Rarely/Never	
Occasionally	
Often	
Almost Always/Always	

3. Do you not 'pay attention' (when someone talks to you/during a training session, church, mosque?)

Rarely/Never	
Occasionally	
Often	
Almost Always/Always	

4. Do you concentrate easily (when you have to learn to do something)?

Rarely/Never	
Occasionally	
Often	
Almost Always/Always	

5. Are you a steady thinker?

Rarely/Never	
Occasionally	
Often	
Almost Always/Always	

6. Do you act 'on impulse'?

Rarely/Never	
Occasionally	
Often	
Almost Always/Always	

7. Do you spend or charge ('buy on the book') more than you earn?

Rarely/Never	
Occasionally	
Often	
Almost Always/Always	

8. Do you buy things on impulse?

Rarely/Never	
Occasionally	
Often	
Almost Always/Always	

9. Do you make up your mind quickly (when you have to decide on something)?

Rarely/Never	
Occasionally	
Often	
Almost Always/Always	

10. Do you do things without thinking (of the consequences)?

Rarely/Never	
Occasionally	
Often	
Almost Always/Always	

11. Do you act on the spur of the moment?

Rarely/Never	
Occasionally	
Often	
Almost Always/Always	

12. Are you happy-go-lucky?

Rarely/Never	
Occasionally	
Often	
Almost Always/Always	

13. Are you a careful thinker?

Rarely/Never	
Occasionally	
Often	
Almost Always/Always	

14. Do you plan tasks carefully?

Rarely/Never	
Occasionally	
Often	
Almost Always/Always	

15. Are you self-controlled?

Rarely/Never	
Occasionally	
Often	
Almost Always/Always	

16. Do you plan trips (tasks) well ahead of time?

Rarely/Never	
Occasionally	
Often	
Almost Always/Always	

17. Do you plan for job security (how you will not be replaced in your job/position)?

Rarely/Never	
Occasionally	
Often	
Almost Always/Always	

18. Do you say things without thinking?

Rarely/Never	
Occasionally	
Often	
Almost Always/Always	

19. Do you like to think about complex problems?

Rarely/Never	
Occasionally	
Often	
Almost Always/Always	

20. Do you like puzzles?

Rarely/Never	
Occasionally	
Often	
Almost Always/Always	

21. Do you save regularly?

Rarely/Never	
Occasionally	
Often	
Almost Always/Always	

22. Are you more interested in the present than in the future?

Rarely/Never	
Occasionally	
Often	
Almost Always/Always	

23. Do you get easily bored when solving thought problems (You lose interest quickly when solving problems you have to think about)?

Rarely/Never	
Occasionally	
Often	
Almost Always/Always	

24. Do you change where you stay frequently?

Rarely/Never	
Occasionally	
Often	
Almost Always/Always	

25. Do you change jobs quite frequently?

Rarely/Never	
Occasionally	
Often	

Almost Always/Always	

26. Are you future oriented (plan for the future)?

Rarely/Never	
Occasionally	
Often	
Almost Always/Always	

27. Can you only think about one problem at a time?

Rarely/Never	
Occasionally	
Often	
Almost Always/Always	

28. Do you often have extraneous thoughts when thinking (When thinking/concentrating on a specific thing, do other irrelevant thoughts come into your head?)

Rarely/Never	
Occasionally	
Often	
Almost Always/Always	

29. Do you have 'racing' thoughts?

Rarely/Never	
Occasionally	
Often	
Almost Always/Always	

30. Do you change hobbies?

Rarely/Never	
Occasionally	
Often	
Almost Always/Always	

Section 9: SCALE FOR SUICIDE IDEATION

The following questions are aimed at the way you feel about life and living. I will ask questions and offer options and you can choose the one that best describes the way you feel.

1. How strong is your wish to live?

Moderate to Strong	
Weak	
None	

2. How strong is your wish to die?

None	
Weak	
Moderate to strong	

3. Which is stronger - your reasons for living or for dying?

For living outweigh for dying	

About equal	
For dying outweigh for living	

4. How strong is your desire to make an active suicide attempt?

None	
Weak	
Moderate to strong	

5. How would you describe your desire to commit suicide?

I would take precautions to save life	
I would leave life/death to chance	
I would avoid steps necessary to save or maintain life	

6. When you think about committing suicide, how long do these thoughts last? (Time dimension. Duration of suicide ideation/wish)

Brief, fleeting periods	
Longer periods	
Continuous (chronic) or almost continuous	

7. How often do you think about committing suicide? (Time dimension: Frequency of suicide)

Rarely occasionally	
Intermittent	
Persistently or continuously	

8. How do you feel about your wish to commit suicide? (Attitude towards ideation/wish)

I reject it	
I am ambivalent/indifferent	
I accept it	

9. Do you have any control over your desire to commit suicide?

I have a sense of control	
I am unsure of control	
I have no sense of control	

10. What role would deterrents play in your actively committing/attempting to commit suicide? (Deterrents to active attempt (e.g. family, religion, irreversibility)

I would not attempt because of deterrent	
I have some concern about deterrents	
I have minimal or no concern about deterrents	

11. What is your reason for contemplating an attempt?

To manipulate the environment	
To get attention/revenge	

Combination of 1&2	
To escape, surcease, solve problems	

12. What method will you use to commit suicide? (Method: Specificity/planning of contemplated event)

I have not considered it	
I have considered it, but details not worked out	
I have worked out the details/well formulated	

13. What method will you use to commit suicide? (Specificity/planning of contemplated event)

The method is not available; no opportunity	
The method would take time/effort; opportunity not readily available	
a) The method & opportunity available	
b) Future opportunity/availability of method anticipated	

14. How capable are you of carrying out a suicidal attempt? (Sense of 'capability' to carry out attempt)

I have no courage; too weak; incompetent	
I am unsure of my courage/my competence	
I am sure of my competence/my courage	

15. When will the actual attempt occur? (Expectance/anticipation of actual attempt)

There will be no attempt	
I am uncertain, not sure	
Yes, there will be an attempt	

16. What actual preparation have you made for the contemplated attempt?

No preparation	
Partial (e.g. am starting to collect pills)	
Complete (e.g. have pills etc.)	

17. Have you written a suicide note?

No	
I have started, but not completed, only thought about it	
I have completed it	

18. Have you completed any final acts in anticipation of death? (E.g. insurance with burial policy?)

I have not	
I thought about it or made some arrangements	

I made definite plans or completed arrangements	

19. Have you mentioned your thoughts/plans about the contemplated suicide to anyone? (Deception/Concealment of contemplated suicide)

I have revealed my ideas openly	
I held back on revealing	
I attempted to deceive, conceal, lie	

Section 10: ENVIRONMENTAL EXPOSURE

In this last section I am going to ask you about whether you use any pesticides in your home and garden.

10.1 Do you usually use any pesticides in your garden or in your home?

Yes
No

10.1.1 If Yes, what do you use? _____

10.1.2 If Yes, what do you use it for? _____

10.1.3 If Yes, how long have you been using pesticides at home for?

Months	**Years**

10.1.4 If Yes, how often do you use pesticides at home? (for example, every day, once a week, only in summer)_____

10.2 Do you live near or next to a farm where pesticides are being sprayed?

Yes
No

10.2.1 If YES, can you smell the pesticides when it is being sprayed?

Yes
No

10.2.1.1 When you are sitting inside your home?

Yes
No

10.2.1.2 When you are sitting outside your home?

Yes
No

10.2.1.3 How often during the year can you smell the pesticides while it is being sprayed?

_____

10.3 Have you ever worked on a farm where pesticides are being sprayed?

10.3.1 If YES, were you a sprayer/spray operator?

Yes
No

10.3.2 For how long were you a sprayer?

Months	**Years**

10.4 Were you ever poisoned by pesticides where you felt so sick that you had to stop working?

Yes
No

10.4.1 If YES, did you go to a clinic/day hospital for treatment?

Yes
No

10.4.2 Did you go and see a health care provider (e.g. a nurse/doctor)?

Yes
No

10.4.3 When did this happen? _____

THANK THE PATIENT FOR TAKING PART IN THE STUDY

Appendix D. Mortuary case-series study - Data collection form

WC NO:
DATE OF BIRTH: **AGE:**
RACE: ☐ B ☐ O ☐ A W **SEX:** ☐ M F
PREVIOUS ATTEMPT: ☐ YES ☐ NO If yes, How many times? Methods used :
SUICIDE LETTER: ☐ YES ☐ NO
HISTORY OF: **PSYCHIATRIC ILLNESS:** ☐ YES* ☐ NO *Specify: **MEDICAL PROBLEMS:** ☐ YES* ☐ NO *Specify: **OTHER:** ☐ YES* ☐ NO *Specify:
TREATMENT RECEIVED FOR ANY OF THE ABOVE: ☐ YES* NO *Specify:
FAMILY HISTORY OF: **ANY OF THE ABOVE:** ☐ YES * ☐ NO *Specify:
PRESCRIBED MEDICATION AT TIME OF SUICIDE: ☐ YES* NONE *Specify:
FAMILY HISTORY OF:

COMPLETED SUICIDES: ☐ YES* ☐ NO

*Specify:

FAMILY HISTORY OF:

SUICIDE ATTEMPTS: ☐ YES* ☐ NO

*Specify:

FAMILY AGREED :

- **TO COLLECTION OF BLOOD SAMPLES FROM DECEASED:** ☐ YES ☐ NO
- **USAGE OF SAMPLE IN SUICIDE PROJECT:** ☐ YES ☐ NO
- **STORAGE OF SAMPLE IN DIVISION OF HUMAN GENETICS:** ☐ YES ☐ NO
- **USAGE OF SAMPLE FOR FURTHER RESEARCH PURPOSES IN THE DIVISION OF HUMAN GENETICS:** ☐ YES ☐ NO

Appendix E. Hospital-based attempted suicide case-series study - Data capture form

Deliberate self-harm (DSH) data capture form

Sex:

Male	Female

Age:

Ethnicity:

Black	Asian	Coloured	White	Unknown

Home language:

Afrikaans	isiXhosa	English	Other (Specify)

Nationality:

South African	Other

Religion

Christian	Islam	Hindu	Catholic	Other	Not known

Marital status:

Single	Married	Separated	Divorced	Widowed

Number of dependents (children):

Completed level of education:

Primary schooling	Secondary schooling	Tertiary Education (Under graduate qualification)	Post graduate qualification

Employment status:

Unemployed	Employed

Living circumstances:

Income level (SES):

Method of DSH:

		Quantity:
Prescription medication	Benzodiazepines	
	Barbiturates	
	Tricyclics	
	Anti-psychotics	
	SSRIs	
	Analgesics	
	anti-hypertensives	
	iron tablets	
	antiepileptics,	
	antibiotics	
	oral hypoglycemic agents	
	Unknown	
	Other meds (specify)	

Non-prescription medication	Aspirin	
	Paracetamol	
	Other meds (specify)	
Ingestion or inhalation of poison	Organophosphate	
	Rat poison	
	Corrosive substance (Acid)	
	Bleach	
	Carbon monoxide	
	Other (specify)	
Gun shot		Site of wound(s):
Laceration		Site of wound(s):
Immolation		
Hanging		
Asphyxiation		

Severity of the act:

		Duration of admission
Level of admission	Seen in casualty and discharged	
	Admitted to C13 (short stay medical unit)	
	Admitted to another medical unit	
	Admitted to high care	
	Admitted to ICU	

Level of intervention	None
	Sutured
	Activated charcoal
	Oral medical treatment
	IV medical treatment
	Intubation and ventilation
	Dialysis
	Surgical procedure

GCS on admission	

Stated intention:

To Die	
To regulate the behaviour of someone else	
To regulate emotional state	
To escape a situation	
Implosive act	
To communicate something (eg. distress)	
Mistake	
Not known	
Other (specify)	

Stated reason for the attempt:

Financial concerns	
Marital / romantic relationship issues	
Family conflict	
Medical illness	
Psychiatric illness	
Bereavement	
Academic concerns (exams or performance at school/university)	
Other (specify)	
Not known	

Previous attempts:

Not known	
No previous attempts	
One previous attempt	
Multiple (2 or more) previous attempts	

History of psychiatric illness (Has the patient received a psychiatric Dx prior to this act of DSH?):

Unipolar mood disorder	
Bipolar mood disorder	
Anxiety Disorder	

Personality Disorder	
Psychotic Illness (Schizophrenia)	
Substance dependence	
Post-Traumatic Stress Disorder	
Adjustment disorder	
No psychiatric Dx	
Not known	
Other (specify)	

Current Psychiatric Dx (On assessment following the act of DSH):

Unipolar mood disorder	
Bipolar mood disorder	
Anxiety Disorder	
Personality Disorder	
Psychotic Illness (Schizophrenia)	
Substance dependence	
Post-Traumatic Stress Disorder	
Adjustment disorder	
No psychiatric Dx	
Not known	
Other (specify)	

Receiving psychiatric treatment prior to admission:

Yes	No	Not-known

Receiving psychological treatment (psychotherapy) prior to admission:

Yes	No	Not-known

Medical Dx not related to the incident of DSH:

HIV status:

HV+	HIV-	Not-known

Evidence of alcohol/drug intoxication during the act of DSH:

Yes	Alcohol	
	Cannabis	
	Methaqualone (Mandrax)	
	Cocaine	
	Methamphetamine (Tik)	
	Heroin	
	Solvents	
	Other (specify)	
No		
Not know		

History of substance abuse:

Alcohol abuse	
Cannabis Abuse	
Benzodiazepines	
Methaqualone (Mandrax)	
Cocaine Abuse	
Methamphetamine (Tik) Abuse	
Heroin	
Solvents	
MDMA (Ecstasy)	
Flunitrazipam (Rohypnol)	
Ketamine	
Wellconal (Pinks)	

Psychiatric Plan:

Assessed by psychiatric registrar	Yes	No

Psychotropic meds initiated	No
	Yes (specify)

Psychotropic meds adjusted	No
	Yes (specify)

Input from psychologist	No
	Yes (specify)

Input from social worker	No
	Yes (specify)

Discharged	Discharged without follow up	
	Discharged with follow up at community clinic	
	Discharged follow up at DCAP	
	Discharged with follow-up with drug/alcohol rehab	
	Discharged with follow up in J2	psychiatry
		psychology
	Discharged with referral made to therapeutic unit	G22
		VBH ward 1
		LGH ward 15

Admission	C23 (emergency unity)	voluntary	assisted	involuntary
	G22 (therapeutic unit)	voluntary	assisted	involuntary

Record of follow:

No record of follow up	
Record of follow up	
Not known	

Appendix F. Search strategies for identifying GWAS data

Databases / URL (alphabetical)	Phenotype	Search criteria/keywords
Biobank Japan (BBJ) http://jenger.riken.jp/en/ BBJ PheWeb https://pheweb.jp/ EMBL European Bioinformatics Institute (EMBL-EBI) https://www.ebi.ac.uk/gwas/ FinnGen https://www.finngen.fi/en Gene ATLAS http://geneatlas.roslin.ed.ac.uk/ GIANT Consortium https://portals.broadinstitute.org/collaboration/giant/index.php/GIANT_consortium_data_files GSCAN https://genome.psych.umn.edu/index.php/GSCAN H3 Africa https://catalog.h3africa.org/ IEU open GWAS project https://gwas.mrcieu.ac.uk/ iPSYCH https://ipsych.dk/ Psychiatric Genomics Consortium (PGC) https://www.med.unc.edu/pgc/ PhenoScanner http://www.phenoscanner.medschl.cam.ac.uk/ SSGAC https://thessgac.com/papers/ UK Biobank https://www.ukbiobank.ac.uk/ 2018 UKB Round 2 http://nealelab.is/uk-biobank	Suicidal behaviour	"suicidal behaviour", "suicide", "suicide attempt", "suicide ideation", "suicide behaviour measurement", "suicide ideation measurement", "self-harm", "self-injurious behaviour" or "self-injurious ideation"
	Depression	"depression", "major depressive disorder", "MDD", "major depressive episode", "unipolar depression"
	Schizophrenia	"schizophrenia"
	Bipolar disorder	"bipolar disorder", bipolar mood disorder"
	PTSD	"PTSD", "post-traumatic stress disorder"
	Anorexia nervosa	"anorexia nervosa"
	ADHD	"attention deficit hyperactivity disorder", "ADHD"
	Alcohol use disorder	"alcohol use disorder", "AUD", "alcohol abuse", "alcohol dependence"
	Insomnia	"insomnia", "sleep disorder", "sleep disturbances", "sleep duration"
	Smoking behaviour	"smoking behaviour", "smoking status"
	Alcohol drinking behaviour	"alcohol consumption", "alcohol exposure measurement", "alcohol drinking"
	Body mass index	"body mass index", "BMI"
	Household income	"household income", "household monthly income"
	Education	"educational attainment", "education", "education level"