The Effect of Stressful Life Events and Schizophrenia Polygenic Risk on Suicide in Schizophrenia

by

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Institute of Medical Science
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Abstract

Suicidal ideation and suicide attempts are prevalent in individuals with schizophrenia. Recent stressful life events are associated with suicidal ideation, and early-life stressful events and polygenic risk score for schizophrenia are implicated in suicide attempt. My thesis aimed to determine if recent stressful life events are associated with emergent suicidal ideation, and whether specific domains of stressful events are involved. It also aimed to determine whether traumatic and non-traumatic early-life stressful events and the polygenic risk score for schizophrenia predict lifetime suicide attempt status. Logistic regression, classification trees, and random forest models were used. Recent stress total scores were not significantly associated with emergent suicidal ideation, but health-related stress was. Greater early-life stressful events were significantly predictive of suicide attempt. In modestly-sensitive models, sexual molestation and mental illness in early life were, overall, the most important predictors. The genome-wide schizophrenia polygenic risk scores were not significantly predictive.
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Contributions

Samia Tasmim wrote the thesis and completed all the analyses fully or in part. There were contributions by other individuals which are formally and inclusively acknowledged:

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List of Abbreviations (alphabetical order)

Alcohol Use Disorders Identification Test (AUDIT)
American Psychiatric Association (APA)
Area Under Curve (AUC)
Beck Hopelessness Scale (BHS)
Beck Scale for Suicide Ideation (BSS)
Brief Psychiatric Rating Scale (BPRS)
Calgary Depression Scale for Schizophrenia (CDS)
Centre for Addiction and Mental Health (CAMH)
Chlorpromazine equivalents (CPZe)
Columbia Classification Algorithm of Suicide Assessment (C-CASA)
Composite International Diagnostic Interview (CIDI)
Drug Abuse Screening Test (DAST)
Diagnostic and Statistical Manual of Mental Disorders (DSM)
Emergent suicidal ideation group (SI)
European Parasuicide Study Interview-schedule (EPSIS)
Fagerström Test for Nicotine Dependence (FTND)
Family Interview for Genetic Studies (FIGS)
Genome-wide Association Studies (GWAS)
International Schizophrenia Consortium (ISC)
International Statistical Classification of Diseases and Related Health Problems (ICD)
Life Events Inventory (LEI-2)
Life Change Unit (LCU)
Mean Allele Frequency (MAF)
Mini Mental State Examination (MMSE)
Non-emergent suicidal ideation group (Non-SI)
Non-suicide attempter group (Non-SA)
Positive and Negative Symptom Scale (PANSS)
Psychiatric Genomics Consortium (PGC)
Receiver Operating Characteristic (ROC)
Schedule for Assessment of Insight (SAI)
Schizophrenia Working Group (SWG)
Single nucleotide polymorphism (SNP)
Specialized Computing Cluster (SCC)
Structured Clinical Interview for the Diagnostic and Statistical Manual of Mental Disorders (SCID)
Suicide attempter group (SA)
World Health Organization (WHO)
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Chapter 1

1 Literature Review

Every 40 seconds, one person dies by suicide (WHO, 2017b). Although the global rate of suicide is on a steady decline, in the Americas, suicide rates have risen from 8.3 per 100,000 in the year 2000, up to 9.8 per 100,000 in 2016 (WHO, 2018).

Suicide rates are highest in individuals with psychiatric diagnoses. Bertolote and colleagues (2004) reported that fourteen percent of suicide deaths occur in individuals with schizophrenia. More recently, a study from Ontario reported that 11.7% of suicide deaths occur in individuals with schizophrenia spectrum disorders (Zaheer et al., 2018).

Despite these alarming statistics and notwithstanding the determined efforts aiming to prevent suicide, there remains a large gap in our understanding of suicide, both of the genetic and environmental factors. Especially in the vulnerable group of individuals with schizophrenia, our limited understanding has led to a lack of effective preventive measures.

In the following literature review, I highlight the work that has been done on two key factors associated with suicide in schizophrenia: stressful life events and genetics, and thereby lay the foundation for the analyses done in my thesis that aim to address these factors.
1.1 Schizophrenia

Schizophrenia is a psychiatric disorder that often leads to patients losing their grasp over reality.
In the following section, I provide a description of this disorder, covering the relevant genetic and non-genetic factors.

1.1.1 Overview, epidemiology, and clinical features

Starting as early as the mid-1800s, European psychiatrists were observing cases they were unable to attribute causes to, cases that were affecting mainly the younger populace (Jablensky, 2010). These cases were particularly frustrating as their progression invariably led to chronic deterioration. These disorders were termed “démence précoce” in France by Morel, and were subsequently described by German psychiatrists Kahlbaum and Hecker as catatonic syndrome and hebephrenia, respectively. But the most influential observations made in the 19th century were in 1899 by the German Scientist Emil Kraepelin, who first described schizophrenia-like symptoms in his book as “dementia praecox”. Kraepelin’s seminal work integrated the different descriptions of symptoms of unknown causes that were causing progressive deterioration especially in young people.

The term “schizophrenia” was eventually coined by Eugen Bleuler, who modified Kraepelin’s description to include the “obligatory” and “supplementary” symptoms of schizophrenia (Jablensky, 2010). Symptoms of schizophrenia include both positive and negative symptoms (Liddle, 1987), as well as cognitive disabilities that were first described by Kraepelin in 1919, and reviewed by others (Harvey & Keefe, 1997). Examples of the positive symptoms are
hallucinations and delusions, while negative symptoms include blunted affect, alogia, and social withdrawal (Gogtay et al., 2011).

The positive symptoms are often regarded to be the defining characteristics of the disorder. Nevertheless, the positive symptoms tend to relapse and remit, and are therefore not chronic. The negative symptoms (such as avolition, social withdrawal, and reduction in spontaneous speech) and the cognitive decline are chronic, however, and lead to major social and functional incapacities for individuals with schizophrenia (Owen et al., 2016).

1.1.2 Diagnosis

Clinical diagnoses are made based on the Diagnostic and Statistical Manual of Mental Disorders (DSM) criteria or the World Health Organization’s International Statistical Classification of Diseases and Related Health Problems (ICD) criteria. In research studies in North America, a diagnosis of schizophrenia is primarily made using the Structured Clinical Interview for the DSM (SCID). The most recent DSM is the 5th version, where the diagnosis of schizophrenia is done in the continuum of “Schizophrenia Spectrum and Other Psychotic Disorders” (American Psychiatric Association, APA, 2013). The DSM-V requires the presence of one of the following symptoms in the past 6 months: delusions, hallucinations, and disorganized speech, as well as an additional symptom from the 3 mentioned, or one of negative symptoms or grossly disorganized or catatonic behaviour (APA, 2013). The symptoms must have been present during most of the past 1 month (APA, 2013). Additionally, schizophrenia is also diagnosed using the ICD. The latest version of the ICD is the 11th edition, revised in 2018, classifying schizophrenia in the spectrum of “Schizophrenia spectrum and other primary psychotic disorders”. Both the ICD and DSM work groups have worked to harmonize the two systems such that the most recent versions
have fairly small differences in the psychotic disorder chapters, with differences mainly existing with regards to the time and duration criteria (Biedermann et al., 2016).

Studies on schizophrenia populations often include individuals with schizoaffective disorders (Schizophrenia Working Group of the Psychiatric Genomics Consortium (SWG of the PGC) et al., 2014). This is relevant in the large-scale studies of schizophrenia discussed in the following sections, the most significant of which includes the samples of the large Psychiatric Genomics Consortium.

Schizophrenia is usually detected in late adolescence to early adulthood (APA, 2013). Nevertheless, as with other aspects of schizophrenia, there exists some heterogeneity in the age at onset, such that, as noted in the review of the literature by Rajji et al. (2009), a range is possible: the age at onset in men is usually between 10-25 years, while in women, the age of onset is usually between 25-35 years (Buchanan & Carpenter, 2005). Moreover, 23% of women have a peak of the age at onset at around 40 years of age (Harris et al., 1988). Some rare instances of onset (1 per 10,000 in children and 1-2 per 1,000 in adolescents) very early in childhood also occur, mainly in males after 5 years of age (McClenann, 2005). Some instances also occur after the age of 60 as very-late-onset schizophrenia-like psychosis (Howard et al., 2000).

Rates of schizophrenia were traditionally thought to be similar between males and females. However, more recent studies suggest that there might be some differences. In particular, a pivotal meta-analysis found that although schizophrenia prevalence is similar in males and females, incidence of schizophrenia has been found to be greater in men compared to women, with a 1.4:1 ratio of affected males: females (McGrath et al., 2008). Similarly, contrary to earlier
beliefs, rates of schizophrenia are affected by various epidemiological aspects. Indeed, the
disease itself presents with significant heterogeneity in prevalence and incidence, rates of illness
in different countries or in urban versus rural environments, and migration status and month of
birth (McGrath et al., 2006). For example, the rates of schizophrenia are higher in migrants
versus non-migrants, and in people living in urban areas compared to rural areas (McGrath et al.,
2008). The incidence rate for schizophrenia is 15.2 per 100,000 and the lifetime morbid risk is
around 7.2 per 1,000. The median prevalence rates per 1,000 are 4.6, 3.3, and 4.0, for point,
period, and lifetime, respectively.

1.1.3 Genetics of schizophrenia

The genetic model of schizophrenia has been a matter of discourse since the early 20th century,
with models including monogenic inheritance being proposed (Henriksen et al., 2017). The
genetics of schizophrenia has been studied via candidate gene studies, linkage studies, and
genome-wide association studies (Chen et al., 2015; Henriksen et al., 2017). Overall, both rare
and common variants affect the risk for schizophrenia, and these include both single nucleotide
variants and copy number variants.

1.1.3.1 Family studies of schizophrenia

Family studies have revealed that a greater polygenic risk for schizophrenia is found in family
members of individuals with schizophrenia compared to individuals with no family history of
schizophrenia (Bigdeli et al., 2016). The heritability of schizophrenia is estimated between 81%
(Sullivan et al., 2003) and 64% (Lichtenstein et al., 2009). Adoption studies have revealed that
the heritability of schizophrenia is indeed rooted in genetics, as some schizophrenia-associated
SNPs were associated specifically with a family history of schizophrenia, including some SNPs.
that were not even nominally significant in the 2014 GWAS by the SWG of the PGC (Bigdeli et al., 2016).

1.1.3.2 Genome-wide association studies (GWAS)

Linkage and candidate gene analyses that were done on schizophrenia did not provide replicable and consistent results (Chen et al., 2015). Hence, the next course of action was focusing on GWAS, which offer the advantage of not requiring any a-priori knowledge of the variants. The GWAS technique is based on the common gene-common variant technique, with common genes defined as those with a Minor Allele Frequency (MAF) of greater than 1% (Chen et al., 2015). Common schizophrenia loci explain up to 50% of the variance in liability to schizophrenia (Ripke et al., 2013), although the common loci individually explain only a very small portion. Recent analyses have included an extensive usage of the polygenic risk score analysis, to account for these small effect sizes.

The GWAS technique has been used frequently in the analyses of many disorders, including many psychiatric disorders. In contrast, although suicidal behaviours are a major cause of concern in individuals with psychiatric disorders, a recent review highlighted the paucity of studies on GWAS of suicidal behaviours in schizophrenia and psychotic disorders (Mirkovic et al., 2016). Indeed, our group (Bani-Fatemi et al., 2016) completed a GWAS on a sample of 121 schizophrenia patients (n = 53 with suicide attempt lifetime) and found a SNP associated with suicidal behaviours (OR = 3.91) and another SNP with an interaction effect with early-life trauma (OR = 1.13), although none of these associations remained significant after multiple-test correction. However, no further studies have been completed in a larger cohort of suicidal individuals with schizophrenia.
1.1.3.2.1 Polygenic risk

Common genetic variants can include both single nucleotide variants and copy number variants (Chen et al., 2015). The effect of the genetic risk loci across the genome may be quantified as a polygenic risk score, described as a quantified sum of an individual’s genetic risk (Hettige et al., 2016). A polygenic model for schizophrenia was originally proposed in the 20th century by Gottesman and colleagues (1967). The International Schizophrenia Consortium (ISC; 2009) then provided a convincing demonstration that there was a polygenic component associated with schizophrenia, as they found common SNPs that were individually associated with a small effect but together explained at least 33% of the variation. Later, in a landmark study in 2014, a genome-wide association study (GWAS) by the SWG of the PGC with 36,989 cases and 113,075 controls discovered 128 genetic variants (associated with 128 index SNPs) associated with schizophrenia risk, in 108 distinct loci, at the genome-wide significance level of $p=10^{-8}$ (SWG of the PGC et al., 2014). These loci together conferred genome-wide polygenic risk for schizophrenia and while these loci individually had a small effect, their combined effect was much greater. In particular, the genome-wide risk loci explained 3.4% of the schizophrenia liability.

The schizophrenia risk loci have been able to explain some of the schizophrenia phenotypes and symptom dimensions (Domenici, 2017). The studied factors include cognitive dysfunction (Lencz et al., 2014), neurocognition and social cognition (Germine et al., 2016), sensorimotor gating (Roussos et al., 2016), and first-episode psychosis (Sengupta et al., 2016). As another avenue, the schizophrenia polygenic risk can be mapped into other disorders to get estimates of vulnerability (Domenici, 2017).
The small effect sizes of the schizophrenia variants in turn highlight the importance of large collaborative efforts such as the PGC. Rees and colleagues (2015), in their comprehensive review of schizophrenia genetics, reiterated the genetic overlap between schizophrenia and disorders including major depressive disorder, autism spectrum disorders, and bipolar disorder. This follows from the exciting work by the Cross-Disorder Group of the PGC (2013a, 2013b). The polygenic risk for schizophrenia was also associated with suicide attempt in a target sample (Sokolowski et al., 2016a). Thus, my thesis chapter on the effect of the genome-wide significant schizophrenia polygenic risk score on lifetime suicide attempt status in schizophrenia aims to utilize this important characteristic.

1.1.3.2.2 Schizophrenia genetic model

Individuals with schizophrenia have both common and rare genetic variants, although, as their names suggest, the relative proportions of the variants differ. Currently, a polygenic liability threshold model suggests that the polygenic risk from common genetic variants with a small effect and the risk from rare variants including copy-number variants with a stronger effect both affect the liability to schizophrenia (Tansey et al., 2016).

1.1.3.2.3 Rare genetic variants and de novo mutations

The common genetic variants only explain a part of the heritability and genetic risk for schizophrenia, which brings up the possibility of rare variants being a big modulator (Chen et al, 2015). Schizophrenia is affected by rare genetic variants that include single nucleotide variants and insertion/deletion variants and rare copy number variants, as well as de novo mutations including copy number variants and single nucleotide variants and insertion/deletion variants.
The de novo mutations are mainly of the single nucleotide variants (Chen et al., 2015). As will be discussed further in my thesis, and as highlighted in the review by Chen et al. (2015), the uncommonness of these rare variants makes them difficult to observe in studies employing small cohorts, and demonstrates the necessity of collaborative efforts between scientists, similar to those seen in the PGC. Moreover, there are hundreds of variants involved, and the degree of overlap between schizophrenia patients may vary, leading to the difficulty in obtaining more comprehensive treatments for schizophrenia.

1.1.4 Schizophrenia treatment and comorbidity

Although newer discoveries about schizophrenia continue to be made, the exact biological mechanisms remain unclear. Nevertheless, schizophrenia is thought to have both neurodevelopmental and neurodegenerative aspects (Larson et al., 2010). A diagnosis of schizophrenia can be disruptive for those afflicted and their families, as the illness is chronic, treatment is not fully effective, and many individuals lose the ability to live independently. However, as discussed in a recent systematic review and meta-analysis (Van Eck et al., 2018) the illness trajectory in schizophrenia is heterogeneous, meaning there is room for remission and possible symptom improvement.

Schizophrenia is currently treated with a combination of antipsychotic and other symptom-specific drug treatments, as well as routine monitoring by a psychiatrist, as applicable. Although antipsychotic treatment in schizophrenia is effective, approximately 30% of individuals with schizophrenia are treatment resistant (Meltzer, 1997), such that three or more periods of treatment with at least two different antipsychotics used in the correct dosage for at least six
weeks are deemed ineffective as moderate to severe symptoms and poor social and functional prognosis persist. Clozapine is introduced in such cases and is usually met with a better prognosis for the affected individual, including regaining the ability to live in the community (Taylor, 2017).

Antipsychotics used for schizophrenia treatment almost always have the side effect of weight gain (De Hert et al., 2011). Cardiovascular problems are a major concern (as reviewed by Bushe et al., 2010). In fact, up to 66% of the excess mortality in schizophrenia has been attributed to natural causes, most prominent of which are cardiovascular problems and cancer. A recent review (Nguyen et al., 2018) even argued that systemic biomarkers of aging are present in individuals with schizophrenia.

Suicidal ideation is highly prevalent in individuals with schizophrenia (Hor et al., 2010) and suicide is a major cause of death. Thus, studies have aimed to determine if the antipsychotics are able to relay an anti-suicidal effect. Interestingly, Pompili and colleagues (2007) noted that clozapine is strongly associated with an anti-suicidal effect. Recently, another review found that there was preliminary evidence suggesting the association of other atypical antipsychotics with reduced suicidality in patients with schizophrenia (Pompili et al., 2016). Nevertheless, much more research needs to be undertaken in this regard, and suicidality remains a major cause of concern in the population of individuals with schizophrenia.

1.2 Suicide

Suicide is a major cause of death and suffering worldwide. Suicide attempts and suicidal ideation are even more common and amount to significant disability. Deaths from suicide are
preventable, and a lot of research continues to be done with the aim of suicide prevention. However, there remains a lot of progress to be made in the field, as the predictive ability of suicide risk factors has not increased sufficiently in the past 50 years (Franklin et al., 2017).

The following sections outline the state of suicide research, including the facts and figures, definitions of important terms and the prominent models of suicidal behaviours.

1.2.1 Overview, epidemiology, and risk factors

According to the World Health Organization, suicide was the cause of 1.4% of the total deaths worldwide (WHO, 2017b) in 2015, leading to a total of 788,000 lives being lost (WHO, 2017a), that is, 10.7 deaths per 100,000 people. An even higher suicide rate of 12.0 suicides per 100,000 people was reported in Canada (Statistics Canada, 2017). Almost twice as many males commit suicide as females; the rate of male: female suicide completion was estimated at 1.7:1 (WHO, 2017a).

The WHO defines suicide as “the act of deliberately killing oneself” (WHO, 2014). The Columbia Classification Algorithm of Suicide Assessment (C-CASA) definition of the more explicit “completed suicide” is as follows: “A self-injurious behavior that resulted in fatality and was associated with at least some intent to die as a result of the act” (Posner et al., 2007). Both of these definitions highlight a key feature of suicide, that the act must have been associated with an intention to die, regardless of the severity of the intent.

Suicide is a complex phenomenon, affected by different factors. Psychopathological, psychosocial, personality, and demographic factors have been associated with suicide. A recent review by Franklin et al. (2017) emphasized the lack of specificity of the risk factors associated
with suicidal thoughts and behaviours, citing the array of literature findings supporting a multitude of factors without a specific focus on any one factor. They found that mental illnesses, serious or chronic physical illness, life stress, special population status, and access to lethal means were most associated.

A psychiatric diagnosis is observed in almost 9 out of 10 suicide cases (Arsenault-Lapierre et al., 2004). Psychopathological characteristics that are consistently associated with suicide include depression, hopelessness, psychotic symptoms, and drug or alcohol abuse or dependence. A large study (DeVylder et al., 2015) in adults experiencing psychotic episodes (n = 11,716) revealed that delusions and/or hallucinations in a 12-month period are a risk factor concurrently affecting both suicidal ideation and suicide attempt, adjusting for demographic variables and co-occurring depressive symptoms and anxiety and alcohol or drug use. Particularly, the psychotic episodes were found more frequently in individuals reporting severe suicide attempts, but suicidal ideation was no longer significantly associated when considered separately from suicide attempt.

A review by Zai et al. (2012) suggested that several personality traits including impulsive aggression, neuroticism (depression facet), extraversion, and hopelessness are associated with suicidal thoughts and behaviours. Moreover, impaired problem-solving, learning and decision-making functioning were associated with suicide attempts.

In terms of psychosocial factors, although multiple studies have reported various factors to be associated with suicide, a recent comprehensive review found strong evidence for the association with poorer cognitive abilities, poorer socio-economic status, and mental illness/psychological distress (Batty et al., 2018).
Demographic factors such as male gender, older age, and lower socio-economic status have been associated with suicide (Choi et al., 2018). Interestingly, a recent meta-analysis (of studies until the end of 2014), found that the demographic factors confer different effects for suicide completion, attempt, and ideation (Huang et al., 2017). What was a common theme throughout, however, is that these factors had a low odds ratio (OR<1.5) in each case, with the notable exception of the effect of socio-economic status on suicide completion (OR=2.65; p<0.001).

The different factors affecting suicidal ideation and suicide attempt are discussed in greater detail in the following sections.

1.2.2 Suicidal ideation

Suicidal ideation is defined as the “Passive thoughts about wanting to be dead or active thoughts about killing oneself, not accompanied by preparatory behavior” (Posner et al., 2007). Suicidal ideation can be passive, when there are thoughts that the person would be better off dead. Conversely, when there are plans and intent to commit suicide, this is known as active suicidal ideation (May et al., 2015). Both of these types of ideation are important in suicide risk evaluation. Suicidal ideation, and specifically, frequent and sustained suicidal ideation is associated with an increased risk of suicide in the future (Simon et al., 2017). Moreover, endorsing suicidal intent or intent with plans (i.e., ratings of 4 or 5 in the 5-point Columbia-Suicide Severity Rating Scale), as opposed to thoughts and ideas alone, is associated with an increased risk of suicide attempt (Posner et al., 2011).

Any suicidal ideation is associated with a negative outlook on life and may warrant counselling and a requirement for increased support from friends and family. But the emergence (worsening) of suicidal ideation should not be overlooked as any change in the person’s life that leads to
emergent suicidal ideation need to be addressed. Indeed, a recent study reported that frequent suicidal ideation and worsening suicidal ideation assessed at a healthcare visit between two visits 3 months apart were most strongly associated with suicide attempt or completed suicide (Simon et al., 2017). A reduction in reported suicidal ideation was conversely associated with reduced risk.

1.2.2.1 Factors affecting suicidal ideation

As alluded to in the prior section, suicidal ideation is affected by a multitude of factors. Franklin et al. (2017) in their large-scale meta-analysis on the factors associated with suicidal thoughts and behaviours found the top five predictors of suicidal ideation (with the weighted odds ratios): prior suicidal ideation (3.55); hopelessness (3.28); diagnosis of depression (2.45); any kind of abuse history (1.93); diagnosis of anxiety (1.79). Additionally, positive symptoms of psychosis were also suggested as risk factors for suicidal ideation (Huang et al., 2018).

On the other hand, demographic factors were statistically significantly associated, but they had very weak predictive effects due to their overall odds ratio being 1.25, and thus they were deemed to be not clinically significant (Huang et al., 2017). The significant factors were sex, family types, employment status, and marital status, but none of the factors were deemed to be particularly strong.

There are certain factors that may be associated with suicidal ideation in schizophrenia in particular, bearing in mind the heterogeneity of the disorder and the specific features associated with its diagnosis. The factors associated with suicidal ideation in schizophrenia in a recent review (Cassidy et al., 2017) were: greater depressive symptoms; greater Positive and Negative Symptom Scale (PANSS) general score; and a higher number of psychiatric hospitalizations. The
diagnosis of depression or the presence of depressive symptoms appears to be an important factor for suicidal ideation.

1.2.2.2 Emergent suicidal ideation

Studies of suicidal ideation have provided insight into the workings of the suicidal brain. Nevertheless, emergent suicidal ideation merits special attention in its own right, as fluctuations (and in particular, re-emergence) of suicidal ideation were associated with suicide attempt in a longitudinal study of adolescents (Prinstein et al., 2008). However, in contrast to suicidal ideation, factors associated with emergent suicidal ideation have not been discussed in great detail, precluding the conduction of any large meta-analyses. With changes in factors likely causing the worsening of suicidal ideation that may be different from those leading to the suicidal ideation at a steady stable state, emergent suicidal ideation should be handled separately.

1.2.3 Suicide attempt

Suicide attempts are a sign of distress, and they are one of the most robust predictors of future suicide death. For every completed suicide, there are 20 more attempts (WHO, 2017b). Approximately 60% of suicide deaths occur in the index suicide attempt, while the percentage of deaths exceeds 80% when including the deaths in the first year from this initial attempt (Bostwick et al., 2016).

A suicide attempt, according to the Columbia Classification Algorithm of Suicide Assessment (C-CASA) is defined as: “A potentially self-injurious behavior, associated with at least some intent to die as a result of the act. Evidence that the individual intended to kill him/herself, at least to some degree, can be explicit or inferred from the behavior or circumstance. A suicide
attempt may or may not result in actual injury.” (Posner et al., 2007). Regardless of the outcome of the suicide attempt, it is a very complex behaviour involving multiple factors. These are discussed in the next section.

1.2.3.1 Factors affecting suicide attempt

Suicide attempts arise from the complex interplay of a myriad of factors, and suicide involves going against the basic human instinct of survival. The exact cause and possible predictors for suicide attempts thus remain elusive.

As such, many studies have been conducted to better understand the causes and predictive factors associated with suicidal behaviours. Despite the number and breadth of studies that have been conducted so far, it has not yet been possible to pin point factors that are definitive predictors of suicide attempt. Unfortunately, a recent meta-analysis (Franklin et al., 2017) concluded that the past 50 years of research have not resulted in a significant increase in our predictive ability of suicide risk, with even longitudinal studies unable to lead to better prediction. The top 5 factors associated with suicide attempt were prior non-suicidal self-injury (4.15), prior suicide attempt (3.41), screening instruments (mainly consisting of questions about prior suicidal thoughts and behaviours; 2.51), an axis II diagnosis of any kind (2.35), prior psychiatric hospitalization (2.32), with the overall weighted odds ratios amounting to 1.51. Factors with very small (odds ratios of around 1) but significant associations with suicide attempts have included demographic variables like age, sex, race/ethnicity, family types, education levels and socio-economic status (Huang et al., 2017). High religiosity is a factor inversely associated with the risk of suicide attempt, albeit with a weak effect as the aforementioned demographic factors.
Suicide attempts occur at much higher rates in individuals with psychiatric diagnoses than in individuals without any diagnoses. A recent meta-analysis of suicide in schizophrenia (Cassidy et al., 2017) identified a history of alcohol/drug/tobacco use; a family history of psychiatric illness or suicide; a history of depression; depressive symptoms; physical comorbidity; and being white as the most consistent variables to be associated with suicide attempts in schizophrenia.

1.2.4 Genetics of suicide

Suicidal behaviour has a familial transmission that is not directly associated with a psychiatric diagnosis (Brent & Mann, 2005). Adoption and twin studies of suicide indicate, nonetheless, that the familial transmission is attributable to genetic factors (Tidemalm et al., 2011).

There have been numerous studies on suicide genetics, focusing on candidate-gene association studies, family-based association studies, and GWAS (Mirkovic et al., 2016). The serotonergic and dopaminergic systems are implicated, as well as the catecholamines epinephrine and norepinephrine and the brain-derived neurotrophic factors (Mirkovic et al., 2016; Wang et al., 2017). According to a recent review, the candidate genes with the strongest association include TPH1-rs1800532, SLC6A4-5-HTTLPR, COMT-rs4680 or BDNF-rs6265 (Mirkovic et al., 2016). The studies, however, focused on different psychiatric disorders, so if they did not include a proper control group, the associations reported may have been more associated with the psychiatric disorder than suicide. These studies have nonetheless allowed us to learn about important genes and pathways.

GWAS generally employ much larger sample sizes and use more stringent p-value thresholds. Nonetheless, GWAS have failed to demonstrate replicable genome-wide significant results, and have mostly reported no association or only marginally-significant associations (Mirkovic et al.,
2016). This is likely suggesting a small effect of the genetic variants, which can be observed in studies with larger sample sizes (Wang et al., 2017). Forming large consortia can be useful in this regard, perhaps similar to those seen for the psychiatric disorders in the form of the PGC. A recent review of the GWAS studies in suicide found that only 2 studies reported genome-wide significant associations (Mirkovic et al., 2016). Moreover, the review revealed that most studies were done on individuals with major depressive disorder or bipolar disorders, while there were a few studies that assessed mixed populations including individuals with schizophrenia. The GWAS findings, moreover, were highly discordant between studies, with very little to no overlap between the top hits (Galfalvy et al., 2014). This is likely due to the studies being underpowered to detect the effect sizes of small magnitude that are commonly observed in these studies (e.g., below odds ratios of 2). Nevertheless, the lack of genome-wide associations in suicidal behaviours signals the presence of loci of smaller effect that are genome-wide non-significant effect, and also hints toward gene-gene and gene-environment interactions.

1.2.5 Models of suicidal behaviour

Suicide deaths are potentially preventable phenomena. The help-seeking behavior of future attempters, and thereby the window for implementation of possible preventive measures, can be demonstrated by the finding that almost all of suicide attempters seek out healthcare facilities a year before diagnosis, 64% seek help in the past month, while almost 40% access healthcare facilities one week prior to their suicide attempt (Ahmedani et al., 2015). Particularly, 25% of suicide attempters made a visit with a mental health diagnosis one week prior to the attempt, while 43.9% made the visit one month prior.
As such, prediction models for suicide have been suggested in the past and are frequently being updated and utilized. A vital factor, to ensure the predictive model for suicide is feasible, is to ensure the validity of the model itself. Models and theories of suicide have been around at least since the late 19th century, with Durkheim’s (Durkheim, 1897/1951) sociological model of suicide (Franklin et al., 2017). Psychological, biological, and many different models of suicide have been suggested. A recent review by Barzilay et al. (2014) highlighted a dozen psychological models. Of the suggested models, a common factor in many models is the influence of stress in triggering suicidal behaviours (Ludwig et al., 2017). However, since even severe stress is unable to elicit a suicidal response in some individuals, it is evident that there must be more factors leading to the complex phenomenon of suicide, as opposed to stress by itself. This led to the conceptualization of the stress-diathesis model of suicidal behaviour (Mann et al., 1999). Other models include the interpersonal model (Joiner, 2005), and a modified version of the model called the lifespan model (Ludwig et al. 2017).

1.2.5.1 Stress-diathesis model of suicidal behaviour

Stress is routinely attributed to be a factor associated with poor functioning. However, it is difficult to find an operational definition of stress. A recent review conceptually defined stress as a force or pressure that is perceived to be overwhelming by a person, and leads to a measurable response from the person (Goodnite, 2014). A relevant example is the stress sensitization model of depression (Hammen et al., 2000) based on the stress-diathesis model, and it posits that individuals with early-life adversities are sensitized to later life stress, making them more prone to depression.
Diatheses on the other hand are innate, and are widely-considered to be latent (Ingram & Luxton, 2005) predisposing factors that are at the root of the disordered state making individuals vulnerable to developing this state (van Heeringen, 2012). Diatheses usually constitute the genetic factors that cause a biological trait, but social and cognitive factors that may predispose to disorders like depression are also included. Thus, as discussed in Zuckerman’s work on vulnerability to psychopathology (1999), the predisposition to stress is, in fact, also a diathetic attribute (van Heeringen, 2012). Diathesis can also be defined as the “vulnerability” that can be a fixed factor such as the genetic predisposition in individuals, or something more mutable and amenable to change such as learning through experiences (as dysfunctional learning is thought to be at the core of the vulnerability) (Ingram & Luxton, 2005). The nature of the interaction between the stress and diathesis is also subject to different interpretations in the different models. For instance, in the model of additivity, an additive effect is described such that the genetic predisposition in any individuals and the life stress can additively lead to psychopathologies. On the other hand, ipsative models are described as stress and diathesis adding up such that when one factor is increased, the other is reduced. Mega models suggest that both the stress and diathesis factors need to be heightened to lead to psychopathologies.

The stress-diathesis model posits that owing to the differences in diatheses for disorders in different individuals, different amounts of stress can lead to the disorders in different individuals (van Heeringen, 2012). For some individuals with a strong diathesis, minor stress may be able to trigger disorder. Diathesis may be constituted by a single factor or multiple factors, as evidenced by an interpersonal cognitive theory or a polygenic basis of many disorders. The polygenic basis also allows for varying amounts of both the levels of stress and the amount of the diathesis leading to variations in a disorder.
The stress-diathesis model of suicidal behaviour has been studied extensively and has many different versions, with updates based on newer findings. This influential model has been validated by neurobiological (Jollant et al., 2008), cognitive psychological (Williams & Pollock, 2001), and the clinical (Mann et al., 1999) models (van Heeringhen, 2012). These are discussed in the following sections.

1.2.5.1.1 Clinical stress-diathesis model

Mann and colleagues in 1999 laid the framework for future work on suicide research with their influential clinical “Stress-diathesis model” model for suicide. In this model, stress has been suggested to play a major role in leading to suicidal behaviours (Mann et al., 1999). There are both state and trait-dependent factors of suicidal behaviour. Suicide attempts have been associated with greater subjective feelings of depression, suicidal ideation, aggression, impulsivity and fewer reasons for living. Moreover, comorbid borderline personality disorder, smoking, past substance use disorder or alcoholism, family history of suicidal acts, head injury, and childhood abuse history have also been associated with suicide attempts.

Indeed, studies on the factors associated with suicide have revealed that prior stressful life events were found in many of the cases of suicide. However, the models of suicidal behaviours are very complex, and thus, along with the progress in our understanding of the effect of stress on suicide, the models have also been progressing, with updates and modifications based on the newest research.
1.2.5.1.2 Cognitive psychological stress-diathesis model

The cognitive psychological stress-diathesis model of suicidal behaviour by Williams and Pollock (2001) is based on a “cry of pain” model. The model refers to a three-part response to stimuli, including a heightened response to a “loser” status due to attentional biases, as determined from an emotional Stroop task (Williams & Pollock, 2001). In other words, individuals with suicidal behaviours are very sensitive to perceptions of defeat. However, in the review by van Heeringen and colleagues (2003) it was mentioned that these attentional biases are more robustly associated with suicidal ideation, rather than suicidal behaviour. Moreover, these individuals believe they have no way to escape from their life stressors, due to what is known as “perception of no possible escape”, which is based on the limited ability for problem-solving and strategizing, which are in turn related to deficits of autobiographical memory (Williams & Pollock, 2001). Finally, there is the perception of “no possible rescue”, which relates to hopelessness and desperation that the future holds nothing.

Taken together, these three responses are associated with biases in attention, memory, and fluency (van Heeringen & Marušić, 2003). These are also associated with neurobiological mechanisms of both cortical and subcortical structures. As seen in the following section, the neurobiological factors suggested by Jollant et al. (2008) line up with the aspects of this model.

1.2.5.1.3 Neurobiological stress-diathesis model

The neurobiological stress-diathesis model was validated by using functional neuroimaging to study the neural activity of a group of euthymic young males with a history of depression, when they were exposed to happy, angry, and neutral faces (Jollant et al., 2008). When viewing
prototypical angry versus neutral faces, suicide attempters showed greater activity in the right lateral orbitofrontal cortex (Brodmann area 47) compared to the non-attempters. In contrast, the non-attempters showed greater activity in the right superior frontal gyrus (area 6). Next, when viewing mild happy versus neutral faces, the suicide attempters showed greater activity in the right anterior cingulate gyrus (area 32 extending to area 10). Finally, when viewing mild angry versus neutral faces, suicide attempters showed greater activity in the right cerebellum. The authors suggested that these differences in neural activity delineate the differences in sensitivity in suicide attempters versus non-attempters, such that the suicide attempters tend to focus on negative things like disapproval from others. They also tend to act on their own negative emotions, and pay less attention to stimuli that can be deemed mildly positive. These factors tie in with the “cry of pain” model where the individuals tend to get affixed on the “loser” status and then are trapped by a sense of hopelessness and feel that they have no way out (Williams et al., 2001).

1.2.5.2 Interpersonal model of suicidal behaviour

Joiner (2005) suggested that people do not commit suicide until they have both the desire and the ability for the act, and the ability may need to be acquired over time. He provided the idea for the “Interpersonal” model of suicide with thwarted belongingness and perceived burdensomeness as predecessors to suicidal behaviour, and the acquired ability to commit suicide as the precipitator. The theory was further developed by Van Orden and colleagues (2010). The updated definitions and factors are discussed below, as are the hypotheses related to passive and active suicidal ideation, suicidal intent, lethal and near lethal suicide attempts.
In this model, the construct of thwarted belongingness is associated with loneliness and the absence of reciprocally-caring relationships (Van Orden et al., 2010). The construct of perceived burdensomeness is associated with self-hate, and the feeling that their loved ones will be better off without them. Finally, the acquired capacity for suicide is associated with a lowered fear of death and a heightened pain tolerance potential. Passive suicidal ideation is caused by thwarted belongingness and perceived burdensomeness, and when these two factors are deemed to be stable and unchanging, it leads to active suicidal ideation. Suicidal desire is then converted into suicidal intent when the fear of death is reduced, and on top of all these factors, when there is also an elevated pain tolerance, there is the culmination into lethal or near lethal suicide attempts.

1.2.5.3 Lifespan model of suicidal behaviour

Ludwig et al. (2017) suggested a model that unifies the stress-diathesis model with the interpersonal model suggested by Joiner (2005). This is the “Lifespan Model”, a three-part model whereby the stress and trauma (associated with the epigenome) as well as the diathesis (associated with the genome) are associated with the acquired capability for suicide. This acquired capability then interacts with the thwarted belongingness and the perceived burdensomeness, and all these lead to the act of suicide.

1.2.5.4 Relevance of models to our analyses

The discussion of the models may facilitate the understanding of the results of our study. As such, it may be possible that certain aspects of some models are able to better explain our results.
1.2.6 Examples of stressful life events

Very negative stressful events have been suggested as precipitators of disease, even in the absence of any biological or psychological symptoms (van Heeringen, 2012). A recent systematic review by Liu and Miller (2014) aggregated the findings of studies that assessed stressful life events and suicidality, and concluded that the occurrence of life events is associated with suicidality, either directly or indirectly. Most studies, however, were done in community samples rather than clinical samples. When the studies were classified according to the type of suicidal behaviours, suicide attempts were found in most cases to be associated with life events, and the few non-significant or negative findings were better explained by an inadequate sample size or faulty study design. These shortcomings were also suggested to be the main reason for the lack of association observed in a few studies between stressful life events and suicidal ideation and plan.

Multiple studies have found that recent stressful events are predictive of suicidal behaviours (Delgado-Gomez et al., 2012; Priya et al., 2016), including in first-episode psychosis (Fedyszyn et al., 2012) and schizophrenia (Funahashi et al., 2000). Both proximal (recent) and distal (early) stressful life events affect suicidal behaviours.

The literature supports the overall effect of early-life stress in leading to suicidal behaviour. In terms of the stress sensitization model by Hammen et al. (2000), a version of the stress-diathesis model, this indicates that individuals with a history of early-life adversities are more vulnerable to stress as they are sensitized to it (Heim et al., 2008). Indeed, this was demonstrated by a recent study by Miller et al. (2017) where a greater risk of suicidal ideation and suicidal behaviour was observed in individuals with a history of physical and sexual abuse who had also recently
undergone stressors. A recent systematic review and meta-analysis reported that physical abuse, emotional abuse, and neglect in childhood are associated with suicide attempts and suicidal behaviour (Norman et al., 2012). A history of abuse in particular predicts a worse reaction to a future exposure to stress and depression, and thus is more likely to lead to suicidal ideation and behaviour (Miller et al., 2017).

1.2.6.1 Recent stressful life events

Suicidal ideation is significantly affected by recent stressful events in adults (Cupina, 2009), adolescents (Grover et al., 2009), and college students (You et al., 2014). Interestingly, a stronger cortisol response was associated with brief suicidal ideation, as opposed to chronic suicidal ideation (Rizk et al., 2018). A prospective study on adolescents and young adults revealed that recent life loss events were significantly associated with emergent suicidal ideation even after accounting for psychopathological and other factors (Daniel et al., 2017). Only in a model where depression was also included, the recent loss events were also associated with suicide attempt. This study also found that loss events were associated with suicidal thoughts and suicide attempt only when baseline levels of depression, hopelessness, and anxiety were low.

1.2.6.2 Earli-life stressful life events

Even at the prenatal period, the effect of stress on pregnant mothers is transmitted to their children via their hormonal changes. Buss et al. (2012) found that changes in cortisol levels in the mother affect the child, as the fetal brain is exposed to maternal cortisol. Greater levels of maternal cortisol are associated with greater amygdala volume in the offspring. This is associated
with higher amygdala connectivity and greater internalizing activity in the children. Females appear to be more vulnerable to this effect of cortisol.

Stressful life events can leave an imprint on affected individuals, especially if these experiences are in early life, before the onset of adulthood. Indeed, such life events have been associated with psychiatric disorders. Mouse models have suggested that early life stress in youth increases the susceptibility to stress and depression (Peña et al., 2017). In fact, the more “hits” of stress in early life, the greater the susceptibility in later life. Caregiver neglect in particular is associated with greater psychopathologies later in life (Bick et al., 2015). Altered epigenetic signatures are associated with the different methylation patterns seen in individuals with childhood maltreatment (Lutz & Turecki, 2014).

Any abuse or dysfunction in the household in childhood has also been associated with later life mortality in individuals (Felitti et al., 1998). This brings to the fore the neurodevelopmental consequences of a violation of a “species-expectant experience” (McLaughlin et al., 2017). Early-life stress is a risk factor for suicide attempt later in life (Labonté & Turecki, 2010). Moreover, such early life stressful events also indirectly affect lifetime suicide attempt by leading to an increased risk of psychiatric disorders, which are in turn associated with a greater risk of lifetime suicide attempt. Studies have found an association between sexual abuse in early life and suicidal behaviour in later life. In fact, physical, sexual, or emotional abuse, and emotional or physical neglect in childhood has been associated with suicide attempt in individuals with schizophrenia (Roy, 2005).
1.3 Suicide in schizophrenia: some important considerations

1.3.1 Epidemiology

As previously discussed, a diagnosis of schizophrenia significantly increases mortality (Bushe et al., 2010). Individuals with schizophrenia have a shorter lifespan than individuals without schizophrenia. A review by Hennekens et al. (2005) revealed that these individuals have a lifespan that is 20% shorter than the average lifespan of 76 years (average of 72 years for males and 80 years for females). Their lifespan is an average of 61, 57 and 65 years in males and females respectively. It is estimated that 20-40% of these individuals attempt suicide (Pompili et al., 2007) and 5% commit suicide (Palmer et al., 2005).

1.3.2 Genetics of suicide in schizophrenia

Schizophrenia and suicide attempt both have high genetic propensity (Gejman et al., 2010; Tidemalm et al., 2011). Neurodevelopmental genes are implicated in suicide attempt in schizophrenia (Sokolowski et al., 2016a; 2016b), and schizophrenia polygenic risk has also been associated (Sokolowski et al., 2016a). Sokolowski et al. (2016a) analyzed 660 family trios with offspring who had a confirmed suicide attempt, including 62 individuals with schizophrenia or schizoaffective disorder, and found that the polygenic risk for schizophrenia was significantly associated with suicide attempt in these individuals. Approximately 37% of the variance was explained in the suicide attempters with schizophrenia, and 4.5% of the variance in people without schizophrenia.
1.4 Machine learning model in suicide attempt prediction

Suicidal ideation and suicide attempts are associated with significant mortality and morbidity, making it imperative to predict and prevent the occurrence of suicidal behaviour. Unfortunately, accurate prediction of suicidal behaviour is yet not possible, and the effectiveness of treatment is inadequate, even in cases with high suicide risk. Indeed, despite the amount of research and effort on finding reliable predictors of suicide and suicidal behaviours, the overall predictive ability of the risk factors for suicidal behaviors has been limited. As of now, many risk factors have been associated with suicidal ideation and suicide attempt, and owing to the large number of predictors associated with suicidal behaviour, a machine learning model is a plausible solution. Machine learning models are recently being used in psychiatry to detect illness prognosis, in keeping with the advancement of the field of computational psychiatry (Huys, et al., 2016). A recent meta-analysis of the past 50 years of suicide research (Franklin et al., 2017) suggested a machine learning approach as the way forward in research focusing on suicide prevention.

1.5 Study Objectives and Hypotheses

Stressful life events and genetic factors influence suicidal ideation and suicide attempt in schizophrenia. However, emergent suicidal ideation in schizophrenia has not been assessed previously. Moreover, studies on early-life stress have mainly focused on traumatic events. Furthermore, genetic factors capable of potentially improving the predictive ability of the model have not yielded consistent results.
Bearing in mind the aforementioned factors, my thesis is divided into 3 broad rationales with specific aims and hypotheses, addressed in 3 chapters: Chapter 2, Chapter 3, and Chapter 4.

**Chapter 2**

**Rationale:** Recent stressful life events are associated with suicidal ideation, suicide attempt, and completed suicide. Emergent suicidal ideation is a cause for concern, both due to its direct debilitating effect, as well as its influence on future suicide attempt. However, it remains unknown whether total recent stress is associated with emergent suicidal ideation, and whether any specific domains of stressful events—interpersonal, work, finance, legal, and health—are most highly associated. Knowledge of these associations may open up avenues for intervention and subsequent prevention of emergent suicidal ideation.

**Specific Aims:**

1. Determine whether recent stressful life events are associated with emergent suicidal ideation.
2. Determine whether specific domains of stressful life events are associated with emergent suicidal ideation.

**Hypothesis:** Recent stressful life events will be associated with emergent suicidal ideation, such that there will be a greater stress load in the individuals with emergent suicidal ideation. To test this hypothesis, we assessed the association of the total score for recent stressful life events with emergent suicidal ideation in a logistic regression model. We also assessed the association of stressful events in the domains of interpersonal, work, finance, legal, and health.

**Chapter 3**
**Rationale:** Early-life stress, and in particular, traumatic events such as childhood physical, emotional, and sexual abuse, have been implicated in suicide attempt. However, studies have not focused on “non-traumatic” stressful events. Based on the effect of early-life events on shaping brain development, these events may be important in assessing suicide risk.

**Specific Aims:**

1. Determine whether early-life stressful events are predictive of suicide attempt.
2. Determine whether specific types of early-life stressful events predict suicide attempt.

**Hypothesis:** Early-life stressful events will be predictive of suicide attempt, such that there will be a greater stress load in the suicide attempters. To test this hypothesis, we assessed the total number of early-life stressful events and used the total score as a predictor of suicide attempt.

The specific stressful early-life events will be important predictors of suicide attempt. To test this hypothesis, we assessed specific stressful events including both traumatic and non-traumatic stressful events and used them as predictors of suicide attempt.

**Chapter 4**

**Rationale:** Schizophrenia has a substantial genetic component with up to 50% of the genetic risk being indexed by common variants. Moreover, the polygenic risk score for the genome-wide significant variants is a prominent contributor to the genetic risk for schizophrenia. Individuals with schizophrenia have up to 40% chance of attempting suicide in their lifetime. It is plausible to assume that some of the increased risk of suicide attempt may be associated with the genetic risk for schizophrenia. However, previous results have not been conclusive.
Specific Aims:

1. Determine whether the polygenic risk score for schizophrenia calculated from the genome-wide significant variants predicts suicide attempt.
2. Determine whether the genome-wide significant variants predict suicide attempt.

Hypothesis: Schizophrenia polygenic risk score will be predictive of suicide attempt such that greater scores will increase risk for suicide attempt. To test this hypothesis, we used schizophrenia polygenic risk score as a predictor of suicide attempt.

The genome-wide significant variants for schizophrenia will be predictive of suicide attempt. To test this hypothesis, we used the genome-wide significant variants as predictors of suicide attempt.
Chapter 2

2 Effect of recent stressful life events on emergent suicidal ideation in schizophrenia

2.1 Abstract

Introduction: In individuals with schizophrenia, suicide accounts for 5% of deaths. Suicidal ideation is common, and emergent suicidal ideation is a particular cause for concern. Usually, stressful life events precede suicidal ideation, but studies on emergent suicidal ideation and stressful life events are lacking. Thus, we analyzed the effect of recent stressful life events on emergent suicidal ideation in schizophrenia.

Methods: We assessed 136 individuals with schizophrenia spectrum and other psychotic disorders at study entry and three-month follow-up. Suicidal ideation was assessed by the Columbia-Suicide Severity Rating Scale (C-SSRS). Subjects with a positive difference in the C-SSRS between the two appointments were considered as having emergent suicidal ideation. At follow-up, we administered the modified Social Readjustment Rating Scale (SRRS) to assess recent stressful life events. We calculated the SRRS total score and domain scores for interpersonal, finance, legal, work, and health domains. Demographic and clinical variables were assessed. Logistic regression was used to determine the effect of variables on emergent suicidal ideation.

Results: Of the 136 individuals, 15 developed emergent suicidal ideation (11%). Individuals with emergent suicidal ideation were mainly female (OR= 4.37; 95% CI=1.40, 13.66; p=0.011). Higher scores in the health domain were significantly associated with emergent suicidal ideation (OR=1.29, 95%CI=1.12, 1.50, p<0.001).
**Discussion/Conclusion:** Health problems are associated with a modest increase in the risk for emergent suicidal ideation, especially in females. Thus, incorporating a holistic healthcare assessment, including at the visits for mental health assessments, can be valuable. Larger studies incorporating more predictors are warranted.
2.2 Introduction

Suicidal ideation – the thoughts, ideas and plans of suicide – has a lifetime global prevalence rate of 9.2% (Nock et al., 2008) and a 12-month prevalence rate of 2% (Borges et al, 2010). It is often a precursor to suicide attempts (Funahashi et al., 2000; Klonsky et al., 2016; Nock et al., 2008). Suicidal ideation is highly prevalent in schizophrenia (Hor et al., 2010), with suicide accounting for an estimated 5% of deaths (Palmer et al., 2005). Emergent (worsening) suicidal ideation is a particular cause for concern, and in a prospective study on adolescents and young adults, emergent suicidal ideation was preceded by recent life loss events (Daniel et al., 2017).

The majority of studies have focused on the effect of recent stress on completed suicide or suicide attempts. Suicide attempts were predicted by stressful events in the past year and in the past month (Priya et al., 2016), while completed suicide was predicted by at least one adverse life event in the recent past, as revealed by a synthesis of data from psychological autopsy studies (Foster., 2011). Interpersonal conflicts or loss were among the most notable life event associated with suicide completion, although somatic problems in the past three months were also found to be associated. In summary, suicidal behaviour in the short term may be precipitated by different types of stressful life events such as interpersonal or relationship problems, financial, work and legal problems, and somatic illnesses (Beautrais et al., 1997). Suicidal individuals with schizophrenia experienced more life events in the year preceding suicide, primarily related to work/school, injury/illness to self or family, and severe interpersonal problems, compared to non-suicidal individuals (Funahashi et al., 2000).

Many of the studies assessing suicide or suicidal ideation used a cross-sectional approach, thus they only assessed suicidal ideation at a certain time point. In other studies that had a
longitudinal component, the follow-up date was much later than the original baseline assessment. Studies assessing emergent suicidal ideation have mostly assessed this phenotype from a pharmacological perspective (i.e., treatment-emergent suicidal ideation), including a recent study that reported a 6% incidence of treatment-emergent suicidal ideation in first-episode psychosis (Madsen et al., 2016). Overall, very few studies have focused on the suicidal ideation phenotype in individuals with schizophrenia, and none of these studies have been on the effect of recent stressors on emergent suicidal ideation.

Thus, we aimed to analyze the effect of recent stressful life events on emergent suicidal ideation. We hypothesized that higher total scores and domain scores for the stressful life events would be associated with emergent suicidal ideation. To test our hypothesis, we determined the association of total scores and domain scores for recent stressful life events on emergent suicidal ideation.

2.3 Methods

2.3.1.1 Study Sample

Individuals were recruited from the Centre for Addiction and Mental Health (CAMH) in Toronto, Ontario. The inclusion criteria were the ascertainment of schizophrenia spectrum and other psychotic disorders by the Mini International Neuropsychiatric Interview (M.I.N.I.; Sheehan et al., 1998) or the Structured Clinical Interview for the Diagnostic and Statistical Manual of Mental Disorders (SCID DSM-IV or DSM-V; First et al., 2015) or the patient’s medical charts (if required). The personality profiles were assessed using the NEO-FFI (Costa et al., 1992). The age range was set between 18-75 years old, and the participants needed to have the capability to provide written consent. Exclusion criteria were a history of head trauma with a
loss of consciousness, or an organic cause of psychosis (including drug-induced psychosis) and intellectual disabilities.

2.3.1.2 Clinical assessments

The participants were assessed for symptom severity and mental health status at study entry and three-month follow-up visits. Assessments were done by trained graduate students and research assistants such that high inter-rater reliability was maintained.

The Columbia-Suicide Severity Rating Scale (C-SSRS) was administered at both visits. The C-SSRS has been consistently used in research studies as a valid, reliable, and internally consistent measure of suicide attempt and suicidal ideation (Posner et al., 2011). The scale allows for the assessment of suicidal ideation severity and intensity in the past month. The ideation severity is a categorical scale ranging from 0 “absence of suicidal or death thoughts” to 5 “Active Suicidal Ideation with Specific Plan and Intent”. The intensity of ideation scale consists of 5 questions, assessing the frequency, duration, controllability, deterrents, and reasons for ideation, each scored from 1 to 5. This allows for the intensity score to range from 0 (for someone with no ideation) to up to 25 (for someone who scores a 5, the maximum score, for each of the questions). Emergent suicidal ideation was the outcome measure of interest, defined as a higher score at the three-month follow-up visit compared to study entry visit for either suicidal ideation severity or intensity.

The Social Readjustment Rating Scale (SRRS) (Holmes & Rahe, 1967), modified for assessing stressful life events in the past 3 months, is a self-report scale administered at the three-month follow-up visit. The SRRS assesses a series of stressful life events, some of which fall in the domains of finance, health, relationship/interpersonal, work and legal. The SRRS focuses on
stress due to any readjustment, and each of the 43 stressful life events carries a different weight, as determined by the “Life Change Unit (LCU)” associated with it, ranging from 11 to 100. The weighted items, as well as the items arranged by domain, are summarized as follows:

There were 13 interpersonal items and the “death of spouse” had the highest weight (100), while “trouble with in laws” had the lowest weight (29). There were 5 items related to health, and “personal injury or illness” had the highest weight (53) while “change in eating habits” had the lowest weight (15). There were 2 legal items: “jail term” (63) and a “minor violation of the law” (11). There were 7 work-related items and “fired at work” had the highest weight (47), while “change in work hours or conditions” had the lowest weight (20). There were 4 finance items and “change in financial state” had the highest weight (38), while “mortgage or loan less than $20,000” had the lowest weight (17).

For our analyses, the total stress score was the sum score for all 43 of the SRRS items that were experienced by the participant in the past three months, while the domain score was the sum score for specific items in the interpersonal, finance, legal, work, and health domains, with the domains consisting of items as defined above. The SRRS is a reliable and valid scale (Holmes & Rahe, 1967; Noone, 2017; Scully et al., 2000) and is used widely, including in studies on stress and suicide (Blasco-Fontecilla et al., 2012; Delgado-Gomez et al., 2012).

Basic demographic and clinical factors such as age, sex, age at onset of psychotic symptoms, and the presence of an affective psychosis as the primary diagnosis (e.g., schizoaffective disorder, mood disorder with psychotic features) were assessed. The duration of illness (calculated as age at onset subtracted from current age), the presence of a family history of suicide attempt, and
ethnicity were also assessed. The medication dosages at the baseline visit were standardized as chlorpromazine equivalents (CPZe), based on the work by Gardner and colleagues (2010).

In addition, based on the literature, a number of relevant psychopathological factors were assessed at the baseline and three-month visits. The Brief Psychiatric Rating Scale (BPRS; Overall et al., 1962) and the Calgary Depression Scale for Schizophrenia (CDS; Addington et al., 1990) were administered to assess changes in psychosis and depression, respectively. For the BPRS, the sub scores for the domains of disorganization, anxiety and depression, negative symptoms, and reality distortion, were also analyzed separately. Hopelessness was assessed by the Beck Hopelessness Scale (BHS; Beck & Steer, 1989). Current nicotine dependence, drug use, and alcohol use were assessed using the Fagerström Test for Nicotine Dependence (FTND; Fagerström, 1978), the Alcohol Use Disorders Identification Test (AUDIT; Saunders et al., 1993) and the Drug Abuse Screening Test (DAST; Skinner, 1982), respectively. Any change in cognitive functioning was assessed using the Mini Mental State Examination (MMSE; Folstein et al., 1975), and insight was assessed by the Schedule for Assessment of Insight (SAI; David, 1990; Sanz et al., 1998).

2.3.1.3 Statistical analysis

The change in psychopathological characteristics in the three-month period was assessed by subtracting the scores for the baseline visit from the three-month visit. The variables (demographic/clinical and baseline and change in psychopathology scores) were inputted into logistic regression models to assess their effect on emergent suicidal ideation.
The mean stressful life events scores (total and domain) were calculated. The total stress score and the domain scores for the financial, health, interpersonal, work, and legal life events, were each rescaled (by dividing the scores by 10).

Logistic regression was used to determine the effect of total stress scores and domain scores on emergent suicidal ideation. Two models were used: a basic model with only the stress score (total and domain) by themselves, and an advanced model with the stress score (total and domain) and significant factors from the logistic regression analysis of demographics/clinical and baseline and change in psychopathology scores.

The logistic regression coefficients and their 95% confidence intervals were exponentiated to get odds-ratios and their confidence intervals. All analyses were carried out in the statistical software SPSS, version 24. Due to the nature of analyses conducted, a conservative p-value of 0.005, as suggested by Ioannidis (2018), was considered statistically significant. A p-value of 0.05 was the threshold for nominal significance. Power calculation for the effect sizes observed was done using G*Power version 3 (Faul et al., 2007).

2.4 Results

2.4.1 Demographic and clinical variables

The basic demographic characteristics of the sample are summarized in Table 1. Fifteen out of the total 136 individuals (~11%) developed emergent suicidal ideation during the three-month follow-up. Note that in the following tables and figures, SI and Non-SI refer to the groups with emergent suicidal ideation and non-emergent suicidal ideation, respectively.
Table 2-1 Basic demographic characteristics of the participants (n=136)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Participant statistic (% or Mean ± SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender (Female)</td>
<td>35.3</td>
</tr>
<tr>
<td>Age</td>
<td>41.8 ± 13.9</td>
</tr>
<tr>
<td>Duration of illness</td>
<td>19.4 ± 13.6</td>
</tr>
<tr>
<td>Affective psychosis</td>
<td>46.3</td>
</tr>
</tbody>
</table>

Demographic and baseline clinical variables for the SI and Non-SI participants are summarized in Table 2. Being female was predictive of developing emergent suicidal ideation, such that 67% of the individuals with emergent suicidal ideation were female (OR= 4.37; 95% CI=1.40, 13.7; p=0.011). The presence of an affective psychosis was predictive of emergent suicidal ideation (OR=3.65; 95% CI=1.10, 12.1; p=0.034).

Table 2-2 Characteristics and distal factors of SI and non-SI participants

<table>
<thead>
<tr>
<th>Demographic/Clinical characteristics</th>
<th>SI (% or Mean ± SD)</th>
<th>Non-SI (% or Mean ± SD)</th>
<th>SE</th>
<th>OR (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender (Female)</td>
<td>66.7%</td>
<td>31.4%</td>
<td>0.582</td>
<td>4.368 (1.397, 13.660)</td>
<td>0.011</td>
</tr>
<tr>
<td>Affective psychosis</td>
<td>73.3%</td>
<td>43.0%</td>
<td>0.612</td>
<td>3.649 (1.099, 12.111)</td>
<td>0.034</td>
</tr>
<tr>
<td>Age</td>
<td>40.9 ± 13.3</td>
<td>41.9 ± 14.0</td>
<td>0.020</td>
<td>0.995 (0.957, 1.035)</td>
<td>0.804</td>
</tr>
<tr>
<td>Age at Onset</td>
<td>22.2 ± 13.0</td>
<td>22.1 ± 7.66</td>
<td>0.033</td>
<td>1.002 (0.940, 1.068)</td>
<td>0.951</td>
</tr>
<tr>
<td>Duration of illness</td>
<td>18.7 ± 12.2</td>
<td>19.5 ± 13.8</td>
<td>0.020</td>
<td>0.996 (0.957, 1.037)</td>
<td>0.846</td>
</tr>
<tr>
<td>Ethnicity (non-white)</td>
<td>40.0%</td>
<td>56.7%</td>
<td>0.558</td>
<td>0.510 (0.171, 1.523)</td>
<td>0.228</td>
</tr>
<tr>
<td>No family history of suicide</td>
<td>93.3%</td>
<td>75.0%</td>
<td>1.057</td>
<td>4.667 (0.588, 37.050)</td>
<td>0.145</td>
</tr>
<tr>
<td>CPZe</td>
<td>252 ± 324</td>
<td>151 ± 211</td>
<td>0.001</td>
<td>1.002 (0.999, 1.004)</td>
<td>0.163</td>
</tr>
<tr>
<td>NEO Neuroticism</td>
<td>39.0 ± 10.8</td>
<td>34.6 ± 8.36</td>
<td>0.032</td>
<td>1.059 (0.996, 1.127)</td>
<td>0.068</td>
</tr>
<tr>
<td>NEO Extraversion</td>
<td>37.2 ± 7.98</td>
<td>37.9 ± 7.44</td>
<td>0.037</td>
<td>0.987 (0.919, 1.061)</td>
<td>0.731</td>
</tr>
<tr>
<td>NEO Openness</td>
<td>39.5 ± 8.59</td>
<td>39.8 ± 6.15</td>
<td>0.043</td>
<td>0.995 (0.915, 1.082)</td>
<td>0.904</td>
</tr>
<tr>
<td>NEO Agreeableness</td>
<td>39.6 ± 3.40</td>
<td>40.7 ± 4.61</td>
<td>0.062</td>
<td>0.945 (0.837, 1.067)</td>
<td>0.364</td>
</tr>
<tr>
<td>NEO Conscientiousness</td>
<td>44.7 ± 8.17</td>
<td>43.0 ± 7.71</td>
<td>0.036</td>
<td>1.029 (0.959, 1.105)</td>
<td>0.426</td>
</tr>
</tbody>
</table>

Greater depressive symptoms (OR=1.203; 95% CI= 1.049, 1.38; p= 0.008) and hopelessness (OR= 1.12; 95% CI= 1.01, 1.243; p= 0.03) at the baseline were predictive of emergent suicidal ideation (outlined in Table 3).
In terms of the change scores (Table 4), an increase in alcohol use in the past three months was associated with emergent suicidal ideation at the nominal significance level (OR= 1.208; 95% CI= 1.02, 1.43; p= 0.029).

### Table 2-3 Proximal psychopathological factors at baseline

<table>
<thead>
<tr>
<th>Clinical characteristics</th>
<th>SI (Mean ± SD)</th>
<th>Non-SI (Mean ± SD)</th>
<th>SE</th>
<th>OR (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>BPRS Total</td>
<td>31.0 ± 7.61</td>
<td>29.3 ± 7.59</td>
<td>0.034</td>
<td>1.029 (0.962, 1.100)</td>
<td>0.410</td>
</tr>
<tr>
<td>BPRS Reality Distortion</td>
<td>6.93 ± 2.60</td>
<td>7.34 ± 3.89</td>
<td>0.078</td>
<td>0.970 (0.832, 1.103)</td>
<td>0.693</td>
</tr>
<tr>
<td>BPRS Negative Symptoms</td>
<td>4.80 ± 1.82</td>
<td>4.62 ± 2.12</td>
<td>0.126</td>
<td>1.041 (0.813, 1.332)</td>
<td>0.751</td>
</tr>
<tr>
<td>BPRS Disorganization</td>
<td>3.67 ± 1.11</td>
<td>3.79 ± 1.42</td>
<td>0.215</td>
<td>0.931 (0.611, 1.418)</td>
<td>0.738</td>
</tr>
<tr>
<td>BPRS Anxiety Depression</td>
<td>7.73 ± 4.01</td>
<td>6.32 ± 2.97</td>
<td>0.084</td>
<td>1.146 (0.973, 1.351)</td>
<td>0.104</td>
</tr>
<tr>
<td>CDS</td>
<td>5.67 ± 4.61</td>
<td>3.00 ± 3.14</td>
<td>0.07</td>
<td>1.203 (1.049, 1.38)</td>
<td>0.008</td>
</tr>
<tr>
<td>SAI</td>
<td>10.3 ± 4.45</td>
<td>11.0 ± 3.31</td>
<td>0.074</td>
<td>0.946 (0.818, 1.094)</td>
<td>0.458</td>
</tr>
<tr>
<td>FTND</td>
<td>0.27 ± 0.80</td>
<td>1.98 ± 2.81</td>
<td>0.260</td>
<td>0.615 (0.369, 1.024)</td>
<td>0.062</td>
</tr>
<tr>
<td>MMSE</td>
<td>26.0 ± 2.30</td>
<td>26.4 ± 3.59</td>
<td>0.075</td>
<td>0.969 (0.836, 1.122)</td>
<td>0.670</td>
</tr>
<tr>
<td>BHS</td>
<td>7.00 ± 5.41</td>
<td>4.21 ± 4.36</td>
<td>0.053</td>
<td>1.120 (1.010, 1.243)</td>
<td>0.031</td>
</tr>
<tr>
<td>AUDIT</td>
<td>1.60 ± 2.53</td>
<td>2.80 ± 4.07</td>
<td>0.103</td>
<td>0.894 (0.730, 1.094)</td>
<td>0.277</td>
</tr>
<tr>
<td>DAST</td>
<td>3.73 ± 4.35</td>
<td>4.04 ± 5.66</td>
<td>0.052</td>
<td>0.989 (0.893, 1.096)</td>
<td>0.837</td>
</tr>
</tbody>
</table>

### Table 2-4 Change in proximal psychopathological factors

<table>
<thead>
<tr>
<th>Clinical characteristics</th>
<th>SI (Mean ± SD)</th>
<th>Non-SI (Mean ± SD)</th>
<th>SE</th>
<th>OR (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>BPRS Total</td>
<td>3.53 ± 9.21</td>
<td>1.87 ± 7.30</td>
<td>0.035</td>
<td>1.029 (0.960, 1.102)</td>
<td>0.419</td>
</tr>
<tr>
<td>BPRS Reality Distortion</td>
<td>0.67 ± 3.20</td>
<td>0.44 ± 3.47</td>
<td>0.080</td>
<td>1.019 (0.872, 1.192)</td>
<td>0.810</td>
</tr>
<tr>
<td>BPRS Negative Symptoms</td>
<td>1.20 ± 3.30</td>
<td>0.74 ± 2.73</td>
<td>0.096</td>
<td>1.059 (0.877, 1.280)</td>
<td>0.549</td>
</tr>
<tr>
<td>BPRS Disorganization</td>
<td>-0.20 ± 0.86</td>
<td>-0.04 ± 1.38</td>
<td>0.206</td>
<td>0.914 (0.610, 1.369)</td>
<td>0.663</td>
</tr>
<tr>
<td>BPRS Anxiety Depression</td>
<td>1.60 ± 4.40</td>
<td>0.19 ± 2.81</td>
<td>0.084</td>
<td>1.151 (0.977, 1.357)</td>
<td>0.093</td>
</tr>
<tr>
<td>CDS</td>
<td>1.33 ± 5.86</td>
<td>0.36 ± 3.21</td>
<td>0.072</td>
<td>1.075 (0.933, 1.238)</td>
<td>0.318</td>
</tr>
<tr>
<td>SAI</td>
<td>-0.87 ± 3.66</td>
<td>-0.33 ± 3.07</td>
<td>0.088</td>
<td>0.946 (0.796, 1.125)</td>
<td>0.530</td>
</tr>
<tr>
<td>FTND</td>
<td>0.47 ± 1.51</td>
<td>0.08 ± 1.66</td>
<td>0.156</td>
<td>1.144 (0.843, 1.553)</td>
<td>0.386</td>
</tr>
<tr>
<td>MMSE</td>
<td>-0.20 ± 2.51</td>
<td>0.48 ± 2.42</td>
<td>0.122</td>
<td>0.881 (0.694, 1.119)</td>
<td>0.301</td>
</tr>
<tr>
<td>BHS</td>
<td>0.53 ± 4.39</td>
<td>0.02 ± 3.65</td>
<td>0.073</td>
<td>1.038 (0.899, 1.199)</td>
<td>0.613</td>
</tr>
<tr>
<td>AUDIT</td>
<td>2.33 ± 6.53</td>
<td>-0.70 ± 3.37</td>
<td>0.086</td>
<td>1.208 (1.020, 1.430)</td>
<td>0.029</td>
</tr>
<tr>
<td>DAST</td>
<td>0.33 ± 2.47</td>
<td>-0.95 ± 4.71</td>
<td>0.077</td>
<td>1.085 (0.932, 1.263)</td>
<td>0.291</td>
</tr>
</tbody>
</table>
2.4.2 Stressful life events in emergent suicidal ideation

The number of subjects experiencing specific stressful life events in each group is presented in Table 5. As

### Table 2-5 Count of individuals experiencing stressful life events in each group

<table>
<thead>
<tr>
<th>Stress Item</th>
<th>SI (n=13)</th>
<th>Non-SI (n=119)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death of spouse</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Divorce</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Marital Separation</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Death of close family member</td>
<td>3</td>
<td>21</td>
</tr>
<tr>
<td>Marriage</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>Marital reconciliation</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Change in health of family member</td>
<td>3</td>
<td>18</td>
</tr>
<tr>
<td>Gain of a new family member</td>
<td>2</td>
<td>10</td>
</tr>
<tr>
<td>Death of a close friend</td>
<td>1</td>
<td>13</td>
</tr>
<tr>
<td>Change in number of arguments with spouse</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Change in number of family get-togethers</td>
<td>2</td>
<td>26</td>
</tr>
<tr>
<td>Son or daughter leaving home</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Trouble with in laws</td>
<td>0</td>
<td>5</td>
</tr>
<tr>
<td>Jail Term</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>Minor violation of the law</td>
<td>2</td>
<td>5</td>
</tr>
<tr>
<td>Personal injury or illness</td>
<td>6</td>
<td>18</td>
</tr>
<tr>
<td>Pregnancy</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Sex difficulties</td>
<td>6</td>
<td>16</td>
</tr>
<tr>
<td>Change in sleeping habits</td>
<td>8</td>
<td>39</td>
</tr>
<tr>
<td>Change in eating habits</td>
<td>3</td>
<td>40</td>
</tr>
<tr>
<td>Fired at work</td>
<td>1</td>
<td>5</td>
</tr>
<tr>
<td>Retirement</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Business readjustment</td>
<td>0</td>
<td>16</td>
</tr>
<tr>
<td>Change to a different line of work</td>
<td>2</td>
<td>21</td>
</tr>
<tr>
<td>Change in responsibilities at work</td>
<td>1</td>
<td>15</td>
</tr>
<tr>
<td>Trouble with boss</td>
<td>1</td>
<td>7</td>
</tr>
<tr>
<td>Change in work hours or conditions</td>
<td>4</td>
<td>20</td>
</tr>
<tr>
<td>Change in financial state</td>
<td>2</td>
<td>26</td>
</tr>
<tr>
<td>Mortgage over $20,000</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Foreclosure of mortgage or loan</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Mortgage or loan less than $20,000</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>
there were few individuals experiencing each item, specific analyses were not performed.

2.4.3 Total and domain stress basic logistic regression models

Table 6 reveals the basic logistic regression scores for the total stress and stress domains. The mean weighted total stress scores were 202 in the emergent suicidal ideation group and 139 in the non-emergent suicidal ideation group. Although the group with emergent suicidal ideation

<table>
<thead>
<tr>
<th>Stress</th>
<th>SI</th>
<th>Non-SI</th>
<th>S.E.</th>
<th>OR (95%CI)*</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>202 ± 153</td>
<td>139 ± 147</td>
<td>0.016</td>
<td>1.024 (0.991, 1.057)*</td>
<td>0.156</td>
</tr>
<tr>
<td>Health</td>
<td>61.9 ± 44.2</td>
<td>23.9 ± 31.1</td>
<td>0.076</td>
<td>1.293 (1.115, 1.500)*</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Interpersonal</td>
<td>57.9 ± 65.9</td>
<td>35.9 ± 67.9</td>
<td>0.034</td>
<td>1.038 (0.971, 1.109)*</td>
<td>0.277</td>
</tr>
<tr>
<td>Finance</td>
<td>7.15 ± 17.8</td>
<td>8.97 ± 17.8</td>
<td>0.181</td>
<td>0.939 (0.659, 1.337)*</td>
<td>0.726</td>
</tr>
<tr>
<td>Legal</td>
<td>1.69 ± 4.13</td>
<td>2.05 ± 10.7</td>
<td>0.317</td>
<td>0.963 (0.517, 1.791)*</td>
<td>0.904</td>
</tr>
<tr>
<td>Work</td>
<td>22.8 ± 33.9</td>
<td>22.7 ± 38.4</td>
<td>0.077</td>
<td>1.001 (0.860, 1.164)*</td>
<td>0.995</td>
</tr>
</tbody>
</table>

*Note that the logistic regression model used scaled stressors

had a higher mean total stress score, the basic logistic regression revealed low odds of the total stress in associating with emergent suicidal ideation that was not significant (OR=1.024; 95% CI=0.991, 1.057; p=0.156). The domain scores were not significantly associated with emergent suicidal ideation with the exception of the health stressors (p<0.001).

2.4.4 Total and domain stress adjusted logistic regression models

The total stress was not significantly associated with emergent suicidal ideation in the adjusted model with the covariates (Table 7), but higher scores in the health domain were associated with emergent suicidal ideation (Table 8; OR=1.323, 95% CI= 1.075, 1.629, p=0.008). None of the other stressors (Table 9 - Table 12) were significantly associated with emergent suicidal
ideation, but increase in alcohol use, the presence of affective psychosis in diagnoses, and female
gender were associated with emergent suicidal ideation.

Table 2-7 Total stress and emergent suicidal ideation in an adjusted model

<table>
<thead>
<tr>
<th>Variable</th>
<th>S.E.</th>
<th>OR (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total stress</td>
<td>0.022</td>
<td>1.037 (0.992, 1.083)</td>
<td>0.106</td>
</tr>
<tr>
<td>CDS</td>
<td>0.113</td>
<td>1.182 (0.948, 1.475)</td>
<td>0.137</td>
</tr>
<tr>
<td>BHS</td>
<td>0.073</td>
<td>1.092 (0.946, 1.261)</td>
<td>0.230</td>
</tr>
<tr>
<td>AUDIT change</td>
<td>0.127</td>
<td>1.303 (1.016, 1.672)</td>
<td>0.037</td>
</tr>
<tr>
<td>Affective psychosis</td>
<td>0.832</td>
<td>5.395 (1.056, 27.569)</td>
<td>0.043</td>
</tr>
<tr>
<td>Female gender</td>
<td>0.807</td>
<td>6.081 (1.249, 29.595)</td>
<td>0.025</td>
</tr>
</tbody>
</table>

Table 2-8 Health stress and emergent suicidal ideation in an adjusted model

<table>
<thead>
<tr>
<th>Variable</th>
<th>S.E.</th>
<th>OR (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Health stress</td>
<td>0.106</td>
<td>1.323 (1.075, 1.629)</td>
<td>0.008</td>
</tr>
<tr>
<td>CDS</td>
<td>0.115</td>
<td>1.157 (0.923, 1.450)</td>
<td>0.207</td>
</tr>
<tr>
<td>BHS</td>
<td>0.076</td>
<td>1.067 (0.920, 1.238)</td>
<td>0.393</td>
</tr>
<tr>
<td>AUDIT change</td>
<td>0.132</td>
<td>1.227 (0.947, 1.588)</td>
<td>0.121</td>
</tr>
<tr>
<td>Affective psychosis</td>
<td>0.886</td>
<td>6.002 (1.056, 34.104)</td>
<td>0.043</td>
</tr>
<tr>
<td>Female gender</td>
<td>0.922</td>
<td>9.854 (1.618, 60.011)</td>
<td>0.013</td>
</tr>
</tbody>
</table>

Table 2-9 Interpersonal stress and emergent suicidal ideation in an adjusted model

<table>
<thead>
<tr>
<th>Variable</th>
<th>S.E.</th>
<th>OR (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Interpersonal</td>
<td>0.045</td>
<td>1.064 (0.974, 1.162)</td>
<td>0.166</td>
</tr>
<tr>
<td>CDS</td>
<td>0.113</td>
<td>1.176 (0.943, 1.466)</td>
<td>0.151</td>
</tr>
<tr>
<td>BHS</td>
<td>0.074</td>
<td>1.100 (0.951, 1.272)</td>
<td>0.201</td>
</tr>
<tr>
<td>AUDIT change</td>
<td>0.128</td>
<td>1.328 (1.033, 1.709)</td>
<td>0.027</td>
</tr>
<tr>
<td>Affective psychosis</td>
<td>0.819</td>
<td>4.948 (0.994, 24.617)</td>
<td>0.051</td>
</tr>
<tr>
<td>Female gender</td>
<td>0.798</td>
<td>4.971 (1.039, 23.774)</td>
<td>0.045</td>
</tr>
</tbody>
</table>
### Table 2-10 Financial stress and emergent suicidal ideation in an adjusted model

<table>
<thead>
<tr>
<th>Variable</th>
<th>S.E.</th>
<th>OR (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Finance</td>
<td>0.277</td>
<td>0.879 (0.511, 1.511)</td>
<td>0.640</td>
</tr>
<tr>
<td>CDS</td>
<td>0.109</td>
<td>1.138 (0.919, 1.409)</td>
<td>0.236</td>
</tr>
<tr>
<td>BHS</td>
<td>0.072</td>
<td>1.083 (0.940, 1.248)</td>
<td>0.269</td>
</tr>
<tr>
<td>AUDIT change</td>
<td>0.127</td>
<td>1.343 (1.047, 1.721)</td>
<td>0.020</td>
</tr>
<tr>
<td>Affective psychosis</td>
<td>0.816</td>
<td>5.053 (1.020, 25.034)</td>
<td>0.047</td>
</tr>
<tr>
<td>Female gender</td>
<td>0.793</td>
<td>5.443 (1.150, 25.754)</td>
<td>0.033</td>
</tr>
</tbody>
</table>

### Table 2-11 Legal stress and emergent suicidal ideation in an adjusted model

<table>
<thead>
<tr>
<th>Variable</th>
<th>S.E.</th>
<th>OR (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Legal</td>
<td>0.378</td>
<td>0.956 (0.456, 2.007)</td>
<td>0.906</td>
</tr>
<tr>
<td>CDS</td>
<td>0.109</td>
<td>1.144 (0.925, 1.415)</td>
<td>0.215</td>
</tr>
<tr>
<td>BHS</td>
<td>0.074</td>
<td>1.083 (0.937, 1.251)</td>
<td>0.282</td>
</tr>
<tr>
<td>AUDIT change</td>
<td>0.122</td>
<td>1.324 (1.042, 1.682)</td>
<td>0.022</td>
</tr>
<tr>
<td>Affective psychosis</td>
<td>0.810</td>
<td>4.727 (0.966, 23.128)</td>
<td>0.055</td>
</tr>
<tr>
<td>Female gender</td>
<td>0.789</td>
<td>5.827 (1.241, 27.371)</td>
<td>0.026</td>
</tr>
</tbody>
</table>

### Table 2-12 Work stress and emergent suicidal ideation in an adjusted model

<table>
<thead>
<tr>
<th>Variable</th>
<th>S.E.</th>
<th>OR (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Work</td>
<td>0.084</td>
<td>1.050 (0.890, 1.239)</td>
<td>0.565</td>
</tr>
<tr>
<td>CDS</td>
<td>0.109</td>
<td>1.159 (0.936, 1.435)</td>
<td>0.176</td>
</tr>
<tr>
<td>BHS</td>
<td>0.072</td>
<td>1.080 (0.938, 1.243)</td>
<td>0.285</td>
</tr>
<tr>
<td>AUDIT change</td>
<td>0.122</td>
<td>1.325 (1.042, 1.684)</td>
<td>0.022</td>
</tr>
<tr>
<td>Affective psychosis</td>
<td>0.804</td>
<td>4.642 (0.961, 22.423)</td>
<td>0.056</td>
</tr>
<tr>
<td>Female gender</td>
<td>0.793</td>
<td>6.005 (1.270, 28.405)</td>
<td>0.024</td>
</tr>
</tbody>
</table>
For the health stress (Figure 1), the Area Under Curve (AUC) was 0.913, and the adjusted model revealed that health-related stress was significantly associated with emergent suicidal ideation (p<0.001), with the 95% CI of the AUC between 0.846 to 0.980. The model characteristics are also displayed in the confusion matrix (Figure 2).

**Figure 2-1** Receiver Operating Characteristic (ROC) curve showing ability of the adjusted model with health stress to significantly predict emergent suicidal ideation.
Figure 2-2 Confusion matrix for adjusted health stress and emergent suicidal ideation (SI) showing the numbers of predicted and observed individuals with (SI) and without (non-SI) emergent suicidal ideation.
2.4.5 Power analysis

Assuming an odds ratio of 1.3 and the emergent suicidal ideation rate of 11% and sample size of 136, and a two-tailed alpha of 0.05, our analyses had 8% power. It had 1% power at the alpha of 0.005.

2.5 Discussion

In our sample, emergent suicidal ideation was significantly associated with being female, which is concordant with the findings of Wei et al. (2018) who studied adults with suicide attempt. We found that higher baseline depression and hopelessness were associated with emergent suicidal ideation, highlighting the importance of including these symptoms in any models of suicidal ideation. Moreover, a diagnosis of an affective psychosis, including a diagnosis of schizoaffective disorder, was associated with emergent suicidal ideation at the nominal p-value significance. Psychopathological factors including depression, hopelessness, and psychosis have been consistently associated with suicidal ideation (Bornheimer & Jaccard, 2017; Cassidy et al., 2017; DeVylder et al., 2015). Emergent suicidal ideation was associated with the increase in the alcohol use at the nominal significance level. This is also concordant with findings from studies on suicidal behaviour. However, changes in the other psychopathological factors were not associated with emergent suicidal ideation. As our analysis is on the emergent suicidal ideation phenotype as opposed to suicidal ideation as a whole, very few studies have been conducted for specifically assessing this phenotype and thus well-powered studies can help solidify our findings and determine whether the change in any other psychopathologies are significantly affecting emergent suicidal ideation.
Our hypothesis that the total stress score would be associated with emergent suicidal ideation was not supported, as both the basic and adjusted models had low odds of prediction, and at a significance level greater than the nominal p-value of p<0.05. In a study on adult psychiatric outpatients consisting mostly of male veterans (May et al., 2015), suicidal ideation in the past three months was significantly associated with specific stressors. Particularly, recent hospitalizations for severe medical problems were marginally significant (p=0.05), but total stressful events experienced were not, similar to our findings.

Our hypothesis that domain scores would be associated with emergent suicidal ideation was partially supported, as the health domain scores were indeed associated with emergent suicidal ideation status, both in the basic and the adjusted models. The health domain score was calculated from the scores for 5 items:

1. Personal injury or illness,
2. Pregnancy,
3. Sex difficulties,
4. Change in sleeping habits,
5. Change in eating habits.

Physical problems in the past three months were previously associated with cases of suicide (Heikkinen et al., 1992). Additionally, moderate to high somatic problems were more common in individuals with suicidal ideation compared to those without suicidal ideation (Gradus et al., 2017). Health-related concerns are amenable to treatment and counselling and thus a possible means of reducing the incidence of emergent suicidal ideation can be by providing individuals
with counselling or treatment options and referrals to general practitioners that are able to assist in alleviating some of their symptoms.

We did not see an association between recent loss of a job and emergent suicidal ideation, or the other factors reported by others including financial, legal, interpersonal, or legal problems. Blasco-Fontecilla et al. (2012) found interpersonal problems between spouses to be the most important factor associated with suicide attempt, followed by personal injury or illness. It is important to note that we were unable to conduct specific analyses on each type of stressor due to our small sample size for each item. Moreover, we focused on patients with schizophrenia, while most of the earlier studies were not restricted to a specific psychiatric diagnosis. Many of the individuals in our study rely on government support or allowances or tend not to work in very stressful environments, hence they may be less likely to face work-related stressors. Even when they are reported, they may not be very stressful compared to the other stressors they face, including their health-related problems, and therefore, are not predictive of emergent suicidal ideation. A similar argument may hold for legal and financial problems.

To the best of our knowledge, our study is the first to analyze the effect of recent stressful life events on emergent suicidal ideation in the population of individuals with schizophrenia spectrum and other psychotic disorders. The strength of our study is that we assess the effect of stressful life events in emergent suicidal ideation, a phenotype associated with a higher possibility of suicide attempt in the near future (Simon et al., 2017), in a vulnerable population of schizophrenia patients. Previous studies have focused on mainly non-psychiatric populations. Another strength is using the SRRS as it can shorten assessment time as it involves simply going through a checklist of questions, and this is especially relevant in a population of individuals with schizophrenia who may be unwilling or unable to go through a rigorous detailed interview.
Additionally, as we assess the events in the past 3 months as opposed to using longer timelines, it is possible that our participants were able to recall these recent events and correctly identify them. Indeed, the literature suggests that the major advantage of a three-month timeline is its usefulness in ensuring more of the recent events are remembered and have been used previously in studies on completed suicide (Cooper et al., 2002; Heikkinen et al., 1992; Heikkinen et al., 1995) and suicidal behaviours (Fedyszyn et al., 2012). Moreover, we have well-characterized case and control groups of emergent and non-emergent suicidal ideation, compared to studies on completed suicide (Heikkinen et al., 1992).

It is important to acknowledge that our results must be interpreted in the light of some limitations. Due to our modest sample size for the emergent suicidal ideation group we were unable to use machine learning models with cross-validation. We were also unable to run specific analyses. The SRRS is easy to administer and use, but suffers from having broad categories of items, that may incorporate large and small magnitude items, as opposed to more specific items administered in a longer and more detailed interview, that perhaps could be better able to delineate the factors affecting emergent suicidal ideation (Dohrenwend, 2005). Another concern is that the events like change in eating and sleeping habits are symptoms or indicators of social functioning problems due to psychiatric disorder. In our population of interest, health-related problems in general may be common and thus it would be useful to pinpoint the exact health-related stress that leads to emergent suicidal ideation.

Although we have found a significant association between health stress and emergent suicidal ideation, the odds ratios from our study, as well as from other studies, are modest, which points to the confounding effect of other factors (Dohrenwend, 2005). Larger sample sizes through collaborations and large consortia could provide an opportunity to assess more of these factors.
and determine their effect. Nevertheless, it is also important to bear in mind that the clinical utility of the test is a separate construct from the statistical significance.

Furthermore, in our analyses, the emergent suicidal ideation phenotype was determined from the C-SSRS suicidal ideation severity or frequency increase, and although the C-SSRS is widely-used for suicidal ideation and suicide attempt determination, the determination of emergent suicidal ideation may be subject to spontaneous changes in suicidal ideation status reporting by the participant in the interview, possibly due to reluctance in disclosing their mental health status or because they are a poor historian. As we defined emergent suicidal ideation as any increase of suicidal ideation from baseline to the three-month visit, any increase in the severity or intensity of ideation as determined by the C-SSRS would be considered emergent suicidal ideation. However, it is possible that the emergent suicidal ideation phenotype can be mainly assessed for severe changes. For example, a score of 4 (suicidal intent) or 5 (suicidal intent with plan) severity in the C-SSRS has been predictive of suicide attempt. Thus, the change of the C-SSRS severity from 3 (suicidal thoughts with methods) to 4 (suicidal intent), for example, may be more severe than the change from 1 (wish to be dead) to 2 (nonspecific active suicidal thoughts). Future studies may benefit from delineating the emergent suicidal ideation group more stringently and including individuals whose suicidal ideation is at 4 or 5 at the follow-up visit.

2.6 Conclusion

Overall, our analyses suggest that females with an affective psychosis who recently experience health problems are at a greater risk of developing emergent suicidal ideation. Thus, incorporating a holistic healthcare assessment as part of psychiatric assessments in individuals with schizophrenia and other psychoses is warranted.
Better-powered studies need to include a larger group with emergent suicidal ideation and incorporate a cross-validated machine learning model or a model with separate training and testing data so as to determine the best model with the most useful predictors. These studies on the effects of stressors on individuals with schizophrenia can help determine the specific types of stressors associated with emergent suicidal ideation, and thereby let us know of the groups with most vulnerability. Moreover, studies that assess daily stressors can be useful so as to devise patient tailored plan to tackle the day-to-day stressors that affect suicidal ideation.
Chapter 3

3 Early-life stressful events and suicide attempt in schizophrenia

3.1 Abstract

**Introduction:** Up to 40% of individuals with schizophrenia attempt suicide. Early-life stressful events are known precursors to suicide attempt in individuals with schizophrenia. However, studies focusing on both traumatic and non-traumatic early-life stressful events leading to suicide attempt in schizophrenics remain scarce. Thus, we aimed to assess the effect of early-life stressful events in schizophrenia. Our hypothesis was that a greater load of early-life stressful events will be predictive of suicide attempt, and specific stressful events will be important predictors.

**Methods:** Lifetime suicide attempt status in individuals with schizophrenia spectrum and other psychotic disorders was assessed using the Columbia-Suicide Severity Rating Scale (C-SSRS). Early-life stressful events were assessed using the Life Events Inventory (LEI-2). The number of total life events, and specific life events with 10-fold cross-validated logistic regression, classification tree, and random forest models were used as predictors of lifetime suicide attempt.

**Results:** The analysis included 189 individuals, including 72 with a lifetime suicide attempt (38%). Greater load of early-life stressful events was predictive of suicide attempt (OR=1.26; 95% CI=1.13, 1.41; p<0.001). The models had modest-moderate accuracy (63% - 69%), low sensitivity, and high specificity. Specific models placed the highest importance on sexual molestation and suffering from mental illness in early life in triggering suicide attempt. Other traumatic and non-traumatic events were also implicated.
Conclusion: Our analyses reiterate the importance of traumatic events in predicting suicide attempt, and make the case for considering non-traumatic events and carefully-selected variables when building a better predictive model. Larger studies with well-defined testing and training datasets are warranted.
3.2 Introduction

Every year, more than 700,000 lives are lost to suicide (WHO, 2017a). For every act of committed suicide, there are reportedly as many as 20 suicide attempts (WHO, 2017b). The rates of suicide are particularly high in individuals with mental health problems. A recent study in a Canadian population estimated that 11.7% of suicide deaths occur in individuals with schizophrenia spectrum disorders (Zaheer et al., 2018), while the rate of suicide attempt is estimated between 20-40% (Pompili et al., 2007).

Previous studies have found multiple risk factors associated with suicide attempt. For example, abuse or household dysfunction in childhood were found to be associated with causes of adult death (Felitti et al., 1998) and in particular, neglect from caregivers is associated with greater psychopathologies later in life (Bick et al., 2015). In individuals with schizophrenia, any physical, emotional, or sexual abuse, or emotional or physical neglect, experienced as a child, have been associated with suicide attempt (Roy, 2005). A further study replicated the associations reported by Roy (2005) with the exception of physical neglect (Hassan et al., 2016). Studies in individuals with schizophrenia spectrum disorders have, nonetheless, primarily focused on a narrow range of traumatic events, and studies on other types of events are scarce. However, owing to the critical influence of childhood events in shaping the neural development of an individual, events that are classified as non-traumatic could potentially be associated with disorders later in the lifetime.

Franklin et al. (2017), in a comprehensive meta-analysis on suicide with special emphasis on suicide risk factors, found a wide range of factors that are associated with suicide, which they suggested analyzing using a machine learning approach. A machine learning model has been
previously applied (Hettige et al., 2017), whereby sociocultural and clinical features were used to classify suicide attempters in a reasonably predictive model. However, although the analysis included factors assessing abuse and neglect, other early life stressful events were not included in the analysis, including many factors considered to be non-traumatic.

Thus, we aimed to analyze the effect of early-life stressful events on suicide attempt. Our hypothesis was that a greater load of early-life stressful events (comprising of both traumatic and non-traumatic events) will be predictive of suicide attempt. We tested this hypothesis in two parts: we used the total number of stressful life events as a predictor of suicide attempt in a logistic regression model. We then used the specific stressful life events as predictors of suicide attempt using cross-validated models of logistic regression, classification tree, and random forest, to determine the specific stressful events that are the most important predictors.

3.3 Methods

3.3.1 Participant Characteristics

Participants were recruited from the Centre for Addiction and Mental Health. The psychiatric diagnosis was confirmed using the Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders (SCID DSM-IV or DSM-V) (First et al., 2015), or the Mini-International Neuropsychiatric Interview (MINI) (Sheehan et al., 1998), and participants’ medical charts (if required). The inclusion criteria were the assessment of schizophrenia spectrum and other psychotic disorders (e.g., schizophrenia, schizoaffective disorder, psychotic disorder NOS), aged between 18-75 years of age, and having the capability to provide written
consent. Exclusion criteria were a history of head trauma with a loss of consciousness, or an organic cause of psychosis (including drug-induced psychosis and intellectual disabilities).

3.3.2 Demographic and Clinical variables

Demographic information such as age, sex, and ethnicity were assessed. Further, the presence of a family history of suicide was assessed, as well as information on whether the individual engaged in any non-suicidal self-injury in their lifetime and the number of psychiatric hospitalizations they had. Additionally, the lifetime abuse or dependence on drugs or alcohol was assessed.

Individuals were assessed for lifetime suicide attempt status using the Columbia-Suicide Severity Rating Scale (C-SSRS; Posner et al., 2011). The C-SSRS is consistently used in research studies as a valid, reliable, and internally consistent measure of suicide attempt. An advantage of using the C-SSRS is it allows to clearly differentiate between an actual suicide attempt and an aborted or interrupted attempt. This is important, given the heterogeneity associated with suicide. For our analysis, a suicide attempter was defined as anyone who has attempted suicide at least once in their lifetime, as assessed by the C-SSRS. Participants were then grouped into suicide attempter and non-attempter.

The Life Event Inventory (LEI-2; Wasserman et al., 2006) was used to assess the life events occurring in early-life, i.e., those events happening before 18 years of age. The LEI-2 was created using questions from the Post Traumatic Stress Disorder (PTSD) section of the Composite International Diagnostic Interview (CIDI; WHO, 1997) and the Life Events section of the European Parasuicide Study Interview-schedule (EPSIS; Kerkhof et al., 1989). The LEI-2 includes questions on any adverse events faced in an individual’s lifetime. The questions have a
yes/no component, and if individuals answer “yes” to the questions, they are asked follow-up questions regarding when they experienced the event. Individuals then can indicate whether they experienced the adverse event after 18 years of age, before 18 years of age, or in both these stages of life. We coded a “yes” response when participants confirmed any event that had occurred before 18 years of age, or both before and after. The events only occurring in adulthood were, however, coded as “no”. Questions 1-23 were included in our analyses. Each “yes” response was coded by 1 and “no” was coded by 0.

The responses were also summed to yield the total load of early-life stressful events.

The questions relevant to our analysis are outlined below:

1. Did you ever have direct combat experience in a war?
2. Were you ever involved in a life-threatening accident?
3. Were you ever involved in a fire, flood or natural disaster?
4. Did you ever witness someone being badly injured or killed?
5. Were you ever raped?
6. Were you ever sexually molested?
7. Were you ever seriously physically attacked or assaulted?
8. Have you ever been threatened with a weapon (being robbed for instance), held captive or kidnapped?
9. Have you ever been tortured or the victim of terrorists?
10. Did you ever experience severe poverty?

11. Did you ever experience severe difficulties in finding a suitable place to live?

12. Did you ever have severe difficulties with your work, studies or other tasks assigned to you?

13. Have you ever been convicted of a criminal offense?

14. Were you ever subjected to bullying, harassment?

15. Did you experience periods when you were lonely, having no one to confide in?

16. Did you ever suffer from any physical illness, harm or incapacity leading to medical treatment?

17. Did you ever suffer from mental ill-health?

18. Did you or persons close to you ever feel dissatisfied with your appearance/stature?

19. Did you ever have a long-lasting controversy/conflict with someone?

20. Did someone you cared much about ever harm her/himself with the intent to end her/his life?

21. Did you "lose" someone you cared much about by reasons of death?

22. Did you "lose" someone you cared much about by some circumstances as indicated by the key-word (not death)? Associative key-words: Someone like close family member, Partner or close friends, Lost love, By divorce/separation, Someone close moving far away, Someone close making a fool of you, or bullying you, in an unforgiveable way, Someone close deceiving you

23. Have you ever been sentenced to jail or any other correctional institution?
3.3.3 Statistical Analyses

Due to the nature of analyses conducted, a conservative p-value of 0.005, as suggested by Ioannidis (2018), was considered statistically significant. A p-value of 0.05 was the threshold for nominal significance.

3.3.3.1 Participant and model characteristics

The student’s t-test and chi-square test were conducted with the demographic and clinical factors as variables. Additionally, the numbers of individuals in each group experiencing the different stressful early-life events were assessed by a chi-square test or fisher’s exact test, as appropriate. Analyses were done on SPSS (version 24). The demographic and clinical variables were inputted into logistic regression models to determine their odds of predicting suicide attempt.

A correlation analysis using a correlation plot to determine multicollinearity was first done to determine any variables that have high correlation (defined in this case as correlation > 0.5), and exclude them from the model. The package “corrplot” (Wei & Simko, 2017) on R was used for the correlation analysis.

3.3.3.2 Predictive analyses

A basic logistic regression model in SPSS (version 24) was used to assess the ability of the total load of stressful early-life events to predict suicide attempt. The analysis was also replicated in R with 10-fold cross-validation. Additionally, an adjusted model using the total stress load and significant (p<0.05) predictors from the demographic and clinical characteristics from Section 3.3.3.1 was used.
The specific types of early-life stressors were also inputted into 10-fold cross-validated models for prediction of suicide attempt. The 3 models for analysis of the specific stressful events were logistic regression, classification tree, and random forest. The cross-validated analyses were done in R (version 3.5.0) through RStudio (RStudio Team, 2016). The packages used were “caret” (Kuhn, 2018), “rpart” (Therneau et al., 2018), and “randomForest” (Liaw & Wiener, 2002).

In each case, the model was cross-validated with 10-fold cross-validation, and the confusion matrices and the variables of highest importance in the models were determined. Important variable determination for logistic regression was based on the absolute value of the t-statistic, while for the classification tree and random forest it was based on the accuracy of classification. In addition, the model characteristics of accuracy, sensitivity, specificity, and positive and negative predictive values were calculated.

3.4 Results

3.4.1 Overview and model characteristics

The basic participant characteristics are outlined in Table 1. In the following tables and figures, SA refers to suicide attempters and non-SA refers to non-attempters.

<table>
<thead>
<tr>
<th>Table 3-1 Basic characteristics of the participants (n=189)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Characteristic</strong></td>
</tr>
<tr>
<td>Gender (% M)</td>
</tr>
<tr>
<td>Age</td>
</tr>
<tr>
<td><strong>Primary diagnosis</strong></td>
</tr>
<tr>
<td>Schizophrenia</td>
</tr>
<tr>
<td>Schizoaffective</td>
</tr>
<tr>
<td>Other psychotic disorders</td>
</tr>
</tbody>
</table>
The final model consisted of 189 individuals, including 72 suicide attempters (38%). The characteristics are outlined in Table 2. The suicide attempter group had a higher mean number of self-reported psychiatric hospitalizations (6.38 versus 3.07; p=<0.001). A higher percentage of individuals in the suicide attempter group engaged in non-suicidal self-injury: 18.1% versus 6.00% (p=0.012). The other demographic and clinical factors were not significantly different between individuals with or without suicide attempts.

<table>
<thead>
<tr>
<th>Table 3-2 Characteristics of SA and non-SA participants</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demographic/Clinical characteristics</td>
</tr>
<tr>
<td>---------------------------------------------------------</td>
</tr>
<tr>
<td>Gender (%Male)</td>
</tr>
<tr>
<td>Mean Age ± SD</td>
</tr>
<tr>
<td>Mean number of psychiatric hospitalizations ± SD</td>
</tr>
<tr>
<td>Ethnicity (%not white European)</td>
</tr>
<tr>
<td>Lifetime alcohol abuse/dependence (%)</td>
</tr>
<tr>
<td>Lifetime substance abuse/dependence (%)</td>
</tr>
<tr>
<td>Non-suicidal self-injury (%)</td>
</tr>
<tr>
<td>No Family history of suicide attempt/completion (%)</td>
</tr>
</tbody>
</table>

The percentage of individuals in each group experiencing each type of event is outlined in Table 3. The chi-square analysis of the number of each types of event between the two groups revealed that the suicide attempters were more likely to have been sexually molested (25.0% versus...
8.50%; p = 0.002), to have suffered from mental ill-health in their early life (47.2% versus 25.6%; p = 0.002), to have experienced fire/flood/natural disasters (15.3% versus 3.40%; p = 0.003), and to have been dissatisfied with their appearance (37.5% versus 17.9%, p = 0.003).

Table 3-3 Percentage of individuals experiencing stressful life events in each group

<table>
<thead>
<tr>
<th>Stress Item</th>
<th>SA (n=72)</th>
<th>Non-SA(n=117)</th>
<th>Sig. (2-tailed)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Did you ever have direct combat experience in a war?</td>
<td>1.4%*</td>
<td>1.7%*</td>
<td>1.000*</td>
</tr>
<tr>
<td>2. Were you ever involved in a life-threatening accident?</td>
<td>13.9%</td>
<td>9.4%</td>
<td>0.340</td>
</tr>
<tr>
<td>3. Were you ever involved in a fire, flood or natural disaster?</td>
<td>15.3%</td>
<td>3.4%</td>
<td><strong>0.003</strong></td>
</tr>
<tr>
<td>4. Did you ever witness someone being badly injured or killed?</td>
<td>16.7%</td>
<td>12.8%</td>
<td>0.463</td>
</tr>
<tr>
<td>5. Were you ever raped?</td>
<td>20.8%</td>
<td>7.7%</td>
<td><strong>0.008</strong></td>
</tr>
<tr>
<td><strong>6. Were you ever sexually molested?</strong></td>
<td><strong>25.0%</strong></td>
<td><strong>8.5%</strong></td>
<td><strong>0.002</strong></td>
</tr>
<tr>
<td>7. Were you ever seriously physically attacked or assaulted?</td>
<td>19.4%</td>
<td>18.8%</td>
<td>0.913</td>
</tr>
<tr>
<td>8. Have you ever been threatened with a weapon (being robbed for instance), held captive or kidnapped?</td>
<td>9.7%</td>
<td>7.7%</td>
<td>0.626</td>
</tr>
<tr>
<td>9. Have you ever been tortured or the victim of terrorists?</td>
<td>1.4%*</td>
<td>0.9%*</td>
<td>1.000*</td>
</tr>
<tr>
<td>10. Did you ever experience severe poverty?</td>
<td>22.2%</td>
<td>17.1%</td>
<td>0.383</td>
</tr>
<tr>
<td>11. Did you ever experience severe difficulties in finding a suitable place to live?</td>
<td>13.9%</td>
<td>12.8%</td>
<td>0.833</td>
</tr>
<tr>
<td>12. Did you ever have severe difficulties with your work, studies or other tasks assigned to you?</td>
<td>37.5%</td>
<td>35.0%</td>
<td>0.732</td>
</tr>
<tr>
<td>13. Have you ever been convicted of a criminal offense?</td>
<td>11.1%</td>
<td>7.7%</td>
<td>0.425</td>
</tr>
<tr>
<td>14. Were you ever subjected to bullying, harassment?</td>
<td>45.8%</td>
<td>35.0%</td>
<td>0.140</td>
</tr>
<tr>
<td>15. Did you experience periods when you were lonely, having no one to confide in?</td>
<td>48.6%</td>
<td>32.5%</td>
<td><strong>0.027</strong></td>
</tr>
<tr>
<td>16. Did you ever suffer from any physical illness, harm or incapacity leading to medical treatment?</td>
<td>33.3%</td>
<td>18.8%</td>
<td><strong>0.024</strong></td>
</tr>
<tr>
<td><strong>17. Did you ever suffer from mental ill-health?</strong></td>
<td><strong>47.2%</strong></td>
<td><strong>25.6%</strong></td>
<td><strong>0.002</strong></td>
</tr>
</tbody>
</table>
18. Did you or persons close to you ever feel dissatisfied with your appearance/stature? | 37.5% | 17.9% | 0.003
19. Did you ever have a long-lasting controversy/conflict with someone? | 26.4% | 12.8% | 0.018
20. Did someone you cared much about ever harm her/himself with the intent to end her/his life? | 13.9% | 4.3% | 0.018
21. Did you "lose" someone you cared much about by reasons of death? | 30.6% | 29.9% | 0.926
22. Did you "lose" someone you cared much about by some circumstances (not death)? | 33.3% | 16.2% | 0.006
23. Have you ever been sentenced to jail or any other correctional institution? | 11.1% | 5.1% | 0.127

*Fisher’s exact test.

3.4.2 Machine learning models

From the correlation plot analysis (Figure 1) it was found that items 13 and 23 (0.69), and items 10 and 11 (0.53) were highly correlated. Thus, in the specific analyses, one item of each pair (items 11 and 23) were removed.
3.4.2.1 Overall logistic regression model

The overall basic logistic regression analysis (Figure 2) assessing the prediction of suicide attempts by total load of early-life stressful events was significant (OR=1.261; 95% CI=1.127,
1.411; p<0.0001). The model had 68% accuracy of prediction. The sensitivity was 31% and the specificity was 91%. The positive predictive value was 67%, while the negative predictive value was 68%. The model using the cross-validation provided similar results: 67% accuracy and odds of 1.232 (for replication; results not displayed).

<table>
<thead>
<tr>
<th>Observed</th>
<th>Predicted</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Non-SA</td>
</tr>
<tr>
<td>Non-SA</td>
<td>106</td>
</tr>
<tr>
<td>SA</td>
<td>50</td>
</tr>
</tbody>
</table>

**Figure 3-2** Basic Confusion Matrix for total stress score showing the numbers of predicted and observed suicide attempters (SA) and non-attempters (non-SA).
In an adjusted model (Figure 3 and Table 4) accounting for mean number of psychiatric hospitalizations and non-suicidal self-injury, the model was nominally-significant at p<0.05, but better at accurately identifying attempters.

![Adjusted Confusion Matrix](image)

**Figure 3-3** Adjusted Confusion Matrix for total stress score showing the numbers of predicted and observed suicide attempters.

**Table 3-4** Adjusted model for total stress predicting suicide attempt

<table>
<thead>
<tr>
<th>Variable</th>
<th>S.E.</th>
<th>OR (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total stress</td>
<td>0.058</td>
<td>1.160 (1.034, 1.301)</td>
<td>0.011</td>
</tr>
<tr>
<td>Non-suicidal self-injury</td>
<td>0.547</td>
<td>0.415 (0.142, 1.212)</td>
<td>0.108</td>
</tr>
<tr>
<td>Number of psychiatric hospitalizations</td>
<td>0.049</td>
<td>1.182 (1.074, 1.300)</td>
<td>0.001</td>
</tr>
</tbody>
</table>
3.4.2.2 Models for specific items

3.4.2.2.1 Logistic regression

The logistic regression analysis with the cross-validation (Figure 4) revealed the model had overall accuracy of 62%, with the 95% CI between 55%-69%; sensitivity of 38%, and specificity of 77%. The positive predictive value was 50%, while the negative predictive value was 67%.

![Confusion Matrix for the logistic regression model showing the numbers of predicted and observed suicide attempters.](image-url)

**Figure 3-4** Confusion Matrix for the logistic regression model showing the numbers of predicted and observed suicide attempters.
The top 20 items in this model ordered by importance are also displayed in Table 5; the top 5 items are Item 6, Item 3 and Item 17, 5, and 7.

<table>
<thead>
<tr>
<th>Item</th>
<th>Importance %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Item 6</td>
<td>100</td>
</tr>
<tr>
<td>Item 3</td>
<td>92.0</td>
</tr>
<tr>
<td>Item 17</td>
<td>87.7</td>
</tr>
<tr>
<td>Item 5</td>
<td>77.8</td>
</tr>
<tr>
<td>Item 7</td>
<td>70.4</td>
</tr>
<tr>
<td>Item 19</td>
<td>68.5</td>
</tr>
<tr>
<td>Item 20</td>
<td>62.8</td>
</tr>
<tr>
<td>Item 22</td>
<td>58.5</td>
</tr>
<tr>
<td>Item 18</td>
<td>52.3</td>
</tr>
<tr>
<td>Item 12</td>
<td>34.5</td>
</tr>
<tr>
<td>Item 8</td>
<td>34.5</td>
</tr>
<tr>
<td>Item 4</td>
<td>23.8</td>
</tr>
<tr>
<td>Item 15</td>
<td>16.2</td>
</tr>
<tr>
<td>Item 16</td>
<td>10.9</td>
</tr>
<tr>
<td>Item 21</td>
<td>9.7</td>
</tr>
<tr>
<td>Item 9</td>
<td>8.4</td>
</tr>
<tr>
<td>Item 14</td>
<td>7.1</td>
</tr>
<tr>
<td>Item 10</td>
<td>5.5</td>
</tr>
</tbody>
</table>
3.4.2.2.2 Classification tree

The classification tree (Figure 5) revealed overall accuracy of 69% with the 95% CI of 62%-75%; sensitivity 36% and specificity of 89%. The positive predictive value in this case was 67%, and negative predictive value was 69%.

![Confusion matrix](image)

**Figure 3-5** Confusion matrix for the classification tree showing the numbers of predicted and observed suicide attempters

The important predictor analysis revealed that there were 6 items used in this model (Table 6). The other items were given an importance of 0. The top 5 items were Items 3, 22, and 18, 17, and 6.
Table 3-6 Classification tree important predictors

<table>
<thead>
<tr>
<th>Item</th>
<th>Importance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Item 3</td>
<td>100</td>
</tr>
<tr>
<td>Item 22</td>
<td>92.8</td>
</tr>
<tr>
<td>Item 18</td>
<td>90.4</td>
</tr>
<tr>
<td>Item 17</td>
<td>88.8</td>
</tr>
<tr>
<td>Item 6</td>
<td>58.8</td>
</tr>
<tr>
<td>Item 16</td>
<td>42.2</td>
</tr>
</tbody>
</table>

3.4.2.3 Random forest

The Random Forest confusion matrix (Figure 6) had an accuracy of 63%, sensitivity of 15%, and specificity of 93%. The positive predictive value was 58%, and the negative predictive value was 64%. Additionally, the model revealed a high rate of error for the classification of suicide attempters (85%) compared to the non-attempters (15%).

![Confusion Matrix](image)

**Figure 3-6** Confusion matrix for the random forest model showing the numbers of predicted and observed suicide attempters.
The 20 items arranged by importance are shown in the table (Table 7). The top 5 items are Items 17, 6, and 18, 15, and 16.

<table>
<thead>
<tr>
<th>Item</th>
<th>Importance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Item 17</td>
<td>100</td>
</tr>
<tr>
<td>Item 6</td>
<td>95.6</td>
</tr>
<tr>
<td>Item 18</td>
<td>89.7</td>
</tr>
<tr>
<td>Item 15</td>
<td>83.5</td>
</tr>
<tr>
<td>Item 16</td>
<td>81.3</td>
</tr>
<tr>
<td>Item 22</td>
<td>80.6</td>
</tr>
<tr>
<td>Item 19</td>
<td>64.9</td>
</tr>
<tr>
<td>Item 3</td>
<td>64.5</td>
</tr>
<tr>
<td>Item 5</td>
<td>55.7</td>
</tr>
<tr>
<td>Item 20</td>
<td>52.8</td>
</tr>
<tr>
<td>Item 14</td>
<td>51.7</td>
</tr>
<tr>
<td>Item 12</td>
<td>50.0</td>
</tr>
<tr>
<td>Item 10</td>
<td>48.8</td>
</tr>
<tr>
<td>Item 7</td>
<td>45.1</td>
</tr>
<tr>
<td>Item 4</td>
<td>43.0</td>
</tr>
<tr>
<td>Item 21</td>
<td>42.3</td>
</tr>
<tr>
<td>Item 13</td>
<td>35.7</td>
</tr>
<tr>
<td>Item 2</td>
<td>35.3</td>
</tr>
</tbody>
</table>
### 3.5 Power analysis

At the alpha of 0.05 and the odds ratio of 1.2 for our sample size of 189 with 38% suicide attempters, our analysis had 9% power. The power was 1% at the alpha of 0.005.

### 3.6 Discussion

Previous studies have found the number of psychiatric hospitalizations to be strongly associated with suicide attempt (Hettige et al., 2017), and this trend was also observed in our analyses. Moreover, non-suicidal self-injury may be the signalling of “the acquired capability for suicide”, as defined by the Interpersonal Theory of suicide (Joiner, 2005; Van Orden et al., 2010), thus it would be expected to be greater in the suicide attempters.

Our analyses demonstrate the predictive ability of early-life stress in suicide attempt in schizophrenia. Particularly, the basic model was significantly predictive at the significance level of 0.005. Thus, the hypothesis that greater stressful life events in the early life increase the risk for attempting suicide at least once in the lifetime was supported by this model, and in an adjusted model at the nominal significance level of 0.05.

For the specific analyses, the most important predictors were determined. Our logistic regression model had accuracy of 62%, while our classification tree model had an accuracy of 69%, and the random forest model had an accuracy of 63%. The accuracy for the prediction of suicide attempt
and completion has historically been modest, as apparent from the meta-analysis by Franklin et al. (2017) that reported studies had accuracies slightly above chance. Similarly, the sensitivity and specificity achieved in our analyses resembles those achieved in the meta-analysis as well—the values reported were 26% and 75%, respectively (Franklin et al., 2017). The top 5 items in the 3 models were:

Items 17, 6, and 18, 15, and 16.

Item 6, Item 3 and Item 17, 5, and 7

Items 3, 22, and 18, 17, and 6.

Both traumatic and non-traumatic event types were important predictors in our models. Items 6 (sexual molestation) and 17 (suffer from any mental illness) can be suggested to be the most important items overall, as they were rated in the top 5 important items for all three cross-validated models. Item 6 is the item regarding sexual molestation, and it is related to item 5 (being a victim of rape), which was also an important predictor.

Any physical assault experienced by individuals was also important, as evident from the importance placed on Item 7 (being physically attacked or assaulted. Item 3 (involvement in a fire, flood or natural disaster), was also important. All these items underscore the effect of traumatic early life events in predicting suicide attempts.

The importance of “non-traumatic” stressful life events in early life in predicting suicide attempt in later life can be inferred from the high importance placed on item 17(individual suffered from mental ill-health in their early life), 15 (loneliness), 16 (suffering from any physical illness, harm or incapacity leading to medical treatment), 18 (dissatisfaction with appearance/stature), and 22
(losing someone close by means other than death), which round up the other items in the top 5 lists of all the 3 models.

Similar to our findings, the literature supports the influence of any physical, emotional, or sexual abuse, or emotional or physical neglect experienced as a child on suicide attempt (Roy, 2005).

The strength of our analysis is the assessment of both traumatic and non-traumatic early-life events. However, our analyses must be interpreted in the light of inherent limitations. As our study consisted of a retrospective assessment, this may have resulted in underreporting of childhood events due to recall bias. Indeed, a follow-up study of individuals who experienced physical and sexual abuse in childhood revealed that these individuals underreported the abuse they had experienced (Widom & Shepard 1996; Widom & Shepard 1997). Males tended to underreport more than females, and this might be significant in our analyses as our sample consists of approximately 60% males.

Moreover, our data consisted of only one set which was divided into training and testing sets by the machine learning models. Such cross-validation techniques are very useful in cases where a separate training and testing set are not available, but it must be noted that since the cross-validation involves the random assignment and splitting of the data, the values obtained here are subject to some minor inconsistencies if the model is run again. For example, the exact importance of the items in the models and the model characteristics (accuracy, sensitivity, etc.) are subject to some minor discrepancies because every time the data is split in a random manner and thus the model characteristics are affected by the split. As such, it is helpful to ensure studies have a separate cohort of individuals as the training cohort to train the model, while another cohort can serve as the testing cohort. Although this might be difficult owing to the difficulty of
obtaining large sample sizes for studies on suicide, it again signals toward the need for large consortia for suicide studies so that large datasets can be used.

Due to the complexity of suicide and the advent of machine learning models, it is tempting to try to input any and all factors into the model assuming they can increase the model’s predictive accuracy. Nevertheless, too many unimportant variables in the model can lead to the model being over-fitted and thus, performing worse when tested on another dataset. Our study and previous studies demonstrate modest odds for stressful events, thus other variables are undoubtedly playing a role in suicide attempt. Our current study was under-powered, but studies with larger samples can accommodate more predictors, and further models (accounting for useful predictors) are warranted. In this regard, future studies can focus on building a machine-learning model that is able to select the most relevant predictors to create the predictive model (Franklin et al., 2017).

3.7 Conclusion

This study provides support to the notion of both traumatic and non-traumatic early-life events as being important in predicting suicide attempt in later life. However, owing to the limitations of our study, the accuracy and sensitivity were modest, and larger studies suitable for better implementation of the requirements of a machine learning model are required. Incorporating both the stress variables as well an individual’s demographics and other characteristics, as suggested by Franklin and colleagues (2017) may be helpful to create a more accurate predictive algorithm for predicting suicide attempt in the individual level. Future studies can benefit from creating a holistic model with sufficient sample sizes whereby they can be tested with more accuracy. These studies, coupled with genetic and imaging data, can be the next step in suicide prevention.
4 Effect of schizophrenia polygenic risk score on lifetime suicide attempt

4.1 Abstract

**Introduction:** Up to 40% of individuals with schizophrenia attempt suicide. Schizophrenia has a sizable genetic component, and the burden of suicide is also attributed to a genetic component. Thus, it is plausible to hypothesize that some of the genetic risk for schizophrenia may be attributable to the genetic risk for suicide. Recently, the Schizophrenia Working Group of the Psychiatric Genomics Consortium successfully discovered common risk loci, including genome-wide significant variants at 108 loci that account for up to 3.4% of the risk for schizophrenia. We aimed to determine whether the genome-wide significant risk loci are associated with an increased risk for suicide attempt.

**Methods:** Individuals with schizophrenia spectrum or other psychotic disorders were recruited, and their blood was collected. Logistic regression (in the genome analysis toolkit PLINK) was used to determine the ability of the polygenic risk score from the genome-wide significant schizophrenia variants, as well as the variants themselves, to predict suicide attempt lifetime. Lifetime suicide attempt was assessed using the Columbia-Suicide Severity Rating Scale.

**Results:** There were 224 individuals in the analysis, 93 with suicide attempt lifetime. Suicide attempt was not significantly predicted by the polygenic risk score for 105 variants, but there were nominally significant associations in the variant analysis.

**Conclusion:** In our analysis using a modest sample size, suicide attempt does not appear to be predicted by the polygenic risk score of the genome-wide significant schizophrenia risk loci.
Larger discovery sample studies, and target studies including copy-number variants and rare genetic risk loci, may be the way forward.
4.2 Introduction

Suicide accounts for 5% of the deaths in schizophrenia (Palmer et al., 2005). Individuals with schizophrenia have a higher risk of suicide attempt, which in turn is a predictor of completed suicide. A recent Canadian study found that, after accounting for other factors, individuals with schizophrenia were 6 times more likely to attempt suicide than individuals without schizophrenia (Fuller-Thomson & Hollister, 2016).

Schizophrenia is a complex genetic disorder, which means that a large portion of the heritability is attributable to different genetic variants (Gejman et al., 2010). A polygenic component is associated with schizophrenia, and a number of common alleles with small effects are involved (Purcell et al., 2009). In effect, genome-wide variants with individually non-significant effects are associated with the heritability of schizophrenia (Bigdeli et al., 2016). Polygenic risk score calculation is a viable method of assessment for such cases of risk prediction based on multiple variants (Wray et al., 2007; Dudbridge, 2013). Genetic factors determine a large proportion of the risk for schizophrenia (Gejman et al., 2010), with up to 81% heritability being suggested (Sullivan et al., 2003).

On a similar note, cases of suicide usually occur in families with a history of suicide completion, with adoption and twin studies indicating that the familial transmission can be attributed to genetic factors (Tidemalm et al., 2011). Genetic studies on schizophrenia have been steadily accumulating evidence for the association of multiple loci, and the most significant milestone was the large study conducted by the Schizophrenia Working Group (SWG) of the Psychiatric Genomics Consortium (PGC) and colleagues (2014). In this genome-wide association study with 36,989 cases and 113,075 controls, 108 genome-wide significant schizophrenia risk loci were found, which, when calculated as a polygenic risk score, explained 3.4% of the genetic liability.
for schizophrenia. Moreover, expanding to less stringent p-value thresholds, the overall polygenic score estimated 7% of the genetic liability for schizophrenia (SWG of the PGC et al., 2014).

The polygenic risk score for schizophrenia has been associated with many other traits, and they have also been used in predictive models. Based on the prevalence of suicidal behaviour in schizophrenics, an association analysis was done using the polygenic risk score from the discovery sample by the SWG (2014) for detecting suicide attempt in a target sample (Sokolowski et al., 2016a). The suicide attempters in this study were high lethality suicide attempters. The results were promising, hinting that there exists a pleiotropy between the genetic variants for schizophrenia and suicide attempt. Particularly, the study included suicide attempter family trios (n=660), and found that the polygenic risk for schizophrenia was significantly associated with suicide attempt both in individuals with schizophrenia (about 37% variance explained) and perhaps surprisingly, even in those without schizophrenia (4.5% variance explained).

Thus, we aimed to analyze the effect of the polygenic risk scores calculated from the variants of the genome-wide significant loci, on suicide attempt. Owing to the excess mortality associated with schizophrenia, and the high genetic susceptibility, we hypothesized that a greater polygenic risk (indicating a high genetic burden for schizophrenia) would be predictive of lifetime suicide attempt status. Specifically, we would observe lower polygenic risk scores for individuals without any lifetime suicide attempt, and higher scores for individuals with a lifetime suicide attempt. Moreover, we hypothesized that the schizophrenia variants associated with the genome-wide significant loci would be predictive of suicide attempt.
4.3 Methods

4.3.1 Participant Characteristics

Participants were recruited from the Centre for Addiction and Mental Health. The inclusion criteria were the assessment of schizophrenia spectrum and other psychotic disorders, 18-75 years of age, and the capability to provide written consent. Exclusion criteria were a history of head trauma with a loss of consciousness, or an organic cause of psychosis. All participants were from a white European background.

4.3.2 Demographic and clinical variables

The psychiatric diagnosis was confirmed using the Structured Clinical Interview for the Diagnostic and Statistical Manual of Mental Disorders, version IV (SCID DSM-IV; First et al., 2015) or the Mini-International Neuropsychiatric Interview (MINI; Sheehan et al., 1998), and the participants’ medical charts (if required). Demographic and clinical information such as age at the interview, sex, and age at onset of psychotic symptoms were assessed. Duration of illness was calculated by subtracting the age at onset of psychotic symptoms from the age at the interview. Family history of suicide attempt/completion was assessed using the Family Interview for Genetic Studies (FIGS; Nurnberger et al., 1994).

Individuals were assessed for lifetime suicide attempt status using the Columbia-Suicide Severity Rating Scale (C-SSRS; Posner et al., 2011), or the Beck Scale for Suicide Ideation (BSS; Beck & Steer, 1991). A suicide attempter was defined as anyone who has attempted suicide at least once in their lifetime, according to the C-SSRS, which allows to clearly differentiate between actual and aborted or interrupted suicide attempts.
4.3.3 Genotyping

Venous blood was obtained from participants. Genomic DNA was extracted from the white blood cells using the QIAamp DNA Blood Maxi Kit (QIAGEN Inc., Valencia, CA, USA). DNA samples were Genotyped using the Illumina Infinium® Omni2.5. Imputation was performed using IMPUTE2/2.3.2 for imputing missing genotypes (Howie et al. 2009). The reference genome was the 1,000 Genomes haplotypes Phase 3 (integrated variant set release in NCBI build 37 (hg19) coordinates). The CAMH Specialized Computing Cluster (SCC) was used for the computationally intensive analyses.

4.3.4 Polygenic Risk Analysis of genome-wide significant loci

We aimed to analyse the 108 genome-wide significant loci (for the threshold of $5 \times 10^{-8}$). The 108 variants associated with these loci, selected based on the highest effect sizes at each locus, were analyzed from the initial list of 128 genome-wide significant SNPs found by the Psychiatric Genomics Consortium. Risk loci effect sizes were available for download from the Psychiatric Genomics Consortium (PGC) Website. The polygenic risk score was calculated by combining the 108 SNPs genotyped in our sample. The genetic analysis toolkit PLINK (Purcell et al., 2007) was used for our calculations. Two different polygenic risk score calculations were applied: unweighted and weighted. For the unweighted polygenic risk score, at each locus, when one risk allele was present, the genotype was given a value of 1; the presence of two risk alleles was given a value of 2; and a value of 0 was given when no risk allele was present (Hettige et al., 2016). For the weighted polygenic risk score: the weighted score at each locus was obtained by multiplying the allele count by the risk allele effect size (beta score) as observed in the PGC2
schizophrenia GWAS (Ripke et al., 2014). The weighted score thus obtained for each individual was standardized by multiplying with the total allele count and dividing by the total effect size.

4.3.4.1 Locus analyses for the genome-wide significant SNPs

The association of each of the genome-wide significant SNPs with suicide attempter status was calculated using PLINK (Purcell et al., 2007).

4.3.5 Statistical Analyses

The mean and standard deviation or the associated percentages for the demographic and clinical variables were assessed. The mean polygenic risk score was calculated for suicide attempters and non-attempters. The polygenic risk scores were used in a logistic regression model in SPSS to predict suicide attempt. The basic logistic regression model used the variables (outlined in the demographic and clinical variables section, 4.3.2) or the polygenic risk score by itself to predict suicide attempt. The advanced model used the polygenic risk score and the significant predictors obtained in the basic model. Manhattan plots were created to demonstrate the effect of each SNP on suicide attempter status. A conservative statistical significance level was chosen: p-values lower than 0.005 (as described by Ioannidis, 2018). The nominal significance level was set to p-values lower than 0.05. For the locus analysis, the corrected significance level was p-values lower than 0.00005 after a Bonferroni correction.

4.4 Results

4.4.1 Demographics and clinical variables

Basic demographic characteristics are outlined in Table 1.
Table 4-1 Basic demographic characteristics of the participants (n=224)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Percentage (%) or Mean ± SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender (%F)</td>
<td>30.8</td>
</tr>
<tr>
<td>Age</td>
<td>44.5 ± 13.1</td>
</tr>
<tr>
<td>Duration of illness</td>
<td>21.9 ± 13.5</td>
</tr>
</tbody>
</table>

The sample consisted predominantly of males, with a similar number of males and females in both groups. Suicide attempters were older than non-attempters at the time of the interview. The average age of suicide attempters was 47 years while that of non-attempters was 43 years (p=0.012). The suicide attempters also had a longer duration of illness (26 years versus 19 years; p= 0.00037). More individuals who attempted suicide also reported a family history of suicide (33% versus 20%; p=0.036). Table 2 provides the characteristics for the participants.

Table 4-2 Characteristics of SA and non-SA participants

<table>
<thead>
<tr>
<th>Demographic/Clinical characteristics</th>
<th>SA (n=93)</th>
<th>Non-SA (n=131)</th>
<th>SE</th>
<th>OR (95% CI)</th>
<th>Sig.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender (M/F) (n)</td>
<td>65 / 28</td>
<td>90 / 41</td>
<td>0.294</td>
<td>0.946 (0.531, 1.683)</td>
<td>0.849</td>
</tr>
<tr>
<td>Family history of suicide attempt/completion (% no)</td>
<td>67.4%</td>
<td>80.0%</td>
<td>0.315</td>
<td>0.517 (0.279, 0.959)</td>
<td>0.036</td>
</tr>
<tr>
<td>*Age at interview</td>
<td>47.1± 11.8</td>
<td>42.6± 13.7</td>
<td>0.011</td>
<td>1.027 (1.006, 1.049)</td>
<td>0.012</td>
</tr>
<tr>
<td>Age at Onset (Mean±SD)</td>
<td>21.3 ± 7.2</td>
<td>23.3 ± 8.0</td>
<td>0.019</td>
<td>0.966 (0.931, 1.002)</td>
<td>0.063</td>
</tr>
<tr>
<td>*Duration of Illness (Mean±SD)</td>
<td>25.8 ± 13.1</td>
<td>19.1 ± 13.2</td>
<td>0.011</td>
<td>1.038 (1.017, 1.060)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

*Note: variables highly correlated (Pearson’s correlation coefficient= 0.8; p<0.001).

In the following tables and figures, SA refers to suicide attempters and Non-SA refers to non-attempters.

4.4.2 Polygenic risk score of genome-wide significant loci

Our analyses were done on 105 genome-wide significant variants, as imputation failed for 3 variants. The mean unweighted (p= 0.849) and standardized weighted (p= 0.880) polygenic risk
scores were not significantly predictive of suicide attempt in the basic model (Table 3; Figure 1; Figure 2), or the adjusted models. The adjusted models consisted of the logistic regression with the family history of suicide and the duration of illness as independent variables along with the unweighted score (Table 4), and the weighted score (Table 5), in the respective models.

**Table 4-3 Basic model of unweighted and weighted scores**

<table>
<thead>
<tr>
<th>Variable</th>
<th>SA (Mean ± SD)</th>
<th>Non-SA (Mean ± SD)</th>
<th>S.E.</th>
<th>Sig.</th>
<th>OR</th>
<th>Lower 95% CI</th>
<th>Upper 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unweighted score</td>
<td>95 ± 6.5</td>
<td>95 ± 6.6</td>
<td>0.021</td>
<td>0.849</td>
<td>0.996</td>
<td>0.957</td>
<td>1.037</td>
</tr>
<tr>
<td>Weighted score</td>
<td>0.9 ± 0.05</td>
<td>0.9 ± 0.05</td>
<td>2.762</td>
<td>0.880</td>
<td>1.516</td>
<td>0.007</td>
<td>339.925</td>
</tr>
</tbody>
</table>

**Figure 4-1** Similar mean unweighted polygenic risk score observed in suicide attempters (SA) and non-attempters (Non-SA). Error bars represent standard deviation from mean.
**Figure 4-2** Similar mean weighted polygenic risk score observed suicide attempters (SA) and non-attempters (Non-SA). Error bars represent standard deviation from mean.

**Table 4-4** Adjusted model of unweighted scores

<table>
<thead>
<tr>
<th>Variable</th>
<th>S.E.</th>
<th>Sig.</th>
<th>OR</th>
<th>Lower 95% CI</th>
<th>Upper 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unweighted score</td>
<td>0.022</td>
<td>0.768</td>
<td>0.994</td>
<td>0.952</td>
<td>1.037</td>
</tr>
<tr>
<td>Duration of illness</td>
<td>0.011</td>
<td><strong>0.001</strong></td>
<td>1.038</td>
<td>1.016</td>
<td>1.060</td>
</tr>
<tr>
<td>Family history of suicide</td>
<td>0.325</td>
<td>0.056</td>
<td>0.537</td>
<td>0.284</td>
<td>1.015</td>
</tr>
</tbody>
</table>

**Table 4-5** Adjusted model of weighted scores

<table>
<thead>
<tr>
<th>Variable</th>
<th>S.E.</th>
<th>Sig.</th>
<th>OR</th>
<th>Lower 95% CI</th>
<th>Upper 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weighted score</td>
<td>2.917</td>
<td>0.904</td>
<td>0.703</td>
<td>0.002</td>
<td>213.9</td>
</tr>
<tr>
<td>Duration of illness</td>
<td>0.011</td>
<td><strong>0.001</strong></td>
<td>1.038</td>
<td>1.016</td>
<td>1.060</td>
</tr>
<tr>
<td>Family history of suicide</td>
<td>0.326</td>
<td>0.057</td>
<td>0.537</td>
<td>0.283</td>
<td>1.018</td>
</tr>
</tbody>
</table>
4.4.3 Genome-wide significant locus Analysis

The analysis for the 105 variants revealed that none of the variants were significantly predictive of suicide attempt status. Nevertheless, there were some associations at the nominally significant level of $p<0.05$ (Table 6). The most significant association was with rs6466055, followed by rs140505938, rs12845396, and rs950169.

Table 4-6 Top 10 genome-wide significant variants logistic regression results

<table>
<thead>
<tr>
<th>CHR</th>
<th>SNP</th>
<th>A1</th>
<th>OR</th>
<th>SE</th>
<th>L95</th>
<th>U95</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>7</td>
<td>rs6466055</td>
<td>A</td>
<td>0.614</td>
<td>0.210</td>
<td>0.407</td>
<td>0.927</td>
<td><strong>0.020</strong></td>
</tr>
<tr>
<td>1</td>
<td>rs140505938</td>
<td>T</td>
<td>0.486</td>
<td>0.319</td>
<td>0.260</td>
<td>0.907</td>
<td><strong>0.023</strong></td>
</tr>
<tr>
<td>X</td>
<td>rs12845396</td>
<td>T</td>
<td>0.702</td>
<td>0.164</td>
<td>0.508</td>
<td>0.968</td>
<td><strong>0.031</strong></td>
</tr>
<tr>
<td>15</td>
<td>rs950169</td>
<td>T</td>
<td>0.649</td>
<td>0.220</td>
<td>0.422</td>
<td>0.999</td>
<td><strong>0.050</strong></td>
</tr>
<tr>
<td>2</td>
<td>rs6704768</td>
<td>G</td>
<td>0.686</td>
<td>0.200</td>
<td>0.464</td>
<td>1.015</td>
<td>0.059</td>
</tr>
<tr>
<td>1</td>
<td>rs12129573</td>
<td>A</td>
<td>0.687</td>
<td>0.199</td>
<td>0.465</td>
<td>1.015</td>
<td>0.059</td>
</tr>
<tr>
<td>5</td>
<td>rs4388249</td>
<td>T</td>
<td>1.574</td>
<td>0.241</td>
<td>0.981</td>
<td>2.525</td>
<td>0.060</td>
</tr>
<tr>
<td>X</td>
<td>rs5937157</td>
<td>G</td>
<td>0.725</td>
<td>0.182</td>
<td>0.507</td>
<td>1.036</td>
<td>0.078</td>
</tr>
<tr>
<td>5</td>
<td>rs79212538</td>
<td>T</td>
<td>2.33</td>
<td>0.480</td>
<td>0.910</td>
<td>5.971</td>
<td>0.078</td>
</tr>
<tr>
<td>6</td>
<td>rs117074560</td>
<td>T</td>
<td>2.974</td>
<td>0.630</td>
<td>0.866</td>
<td>10.2</td>
<td>0.083</td>
</tr>
</tbody>
</table>

The associations of the 105 variants are displayed in a Manhattan plot (Figure 3).

Figure 4-3 Manhattan plot showing the variants associated with suicide attempt. None of the variants were significantly predictive of suicide attempt.
4.5 Discussion

We found a longer duration of illness to be predictive of suicide attempt. However, we also found individuals with suicide attempt were older, so the older age could mean that as the individuals had lived longer, they also had a longer time to try to attempt suicide. An authoritative review by Hor and colleagues (2010) found that duration of illness has been associated with suicide, albeit with inconsistencies.

Suicide attempters more frequently reported a family history of suicide attempt or completion, and this is in line with these findings (Hor et al., 2010). A recent study by Laursen and colleagues (2017) also found that a family history of mental disorders was significantly associated with 2 or more suicide attempts in schizophrenia.

Contrary to our hypothesis, the genome-wide significant polygenic risk score was not predictive of lifetime suicide attempter status. In a recent review, Bogdan et al. (2018) summarized different studies using the polygenic risk score method but were careful to emphasize the lack of clinical utility using the polygenic risk assessment, at least as of now, due to the current discovery GWAS sizes that possibly are not large enough. Interestingly, the recent Danish population-based study by Laursen and colleagues (2017) with 1780 cases with schizophrenia and 1768 controls found the schizophrenia polygenic risk score was only weakly associated with suicide attempt in a basic-adjusted model, and this association did not remain in an adjusted model. However, the study found the polygenic risk score had odds of 1.18 (p≤0.0021) in the full sample for individuals with more than 2 suicide attempts. Nevertheless, the classification into two groups, schizophrenia and control, demonstrated that the schizophrenia polygenic risk was in fact more predictive of suicide attempt in the control group. This is in contrast to the work of
Sokolowski et al. (2016a), who found an association between the schizophrenia polygenic risk and suicide attempter status, both in individuals with schizophrenia and schizoaffective disorders. They observed 37% predictive ability in the individuals with diagnoses, and 4% predictive ability in suicide attempters with no diagnosis of psychiatric disorders. The main differences were that the Sokolowski sample size was small, but all subjects who were enrolled were diagnosed with a severe suicide attempt defined by a score of 2 or higher on the Medical Damage Rating Scale. In contrast, the Laursen et al. (2017) sample consisted of people with any suicide attempt. This is similar to our study, as we did not stratify according to suicide attempt lethality due to our modest sample size. Nevertheless, the Laursen et al. (2017) study had further assessed suicide mortality but did not find an association with the polygenic risk.

On a related note, copy-number variants (CNVs) may be important to consider in schizophrenic suicide attempters, based on findings from Sokolowski and colleagues (2016b). In the individuals whose suicide attempt was associated with schizophrenia CNVs, the polygenic risk was conversely associated with a lower risk of suicide attempt, and vice-versa. Exploring these CNVs in addition to the polygenic risk might be a relevant avenue for future research (Lewis & Vassos, 2017).

Our hypothesis of the genome-wide significant schizophrenia risk variants predicting suicide attempt status was not supported. However, four SNPs demonstrated significance at the nominal p-value of 0.05, and three of these SNPs were also implicated in the work by Sokolowski and colleagues (2016a). The speculated protein-coding genes associations with rs6466055 are MLL5, PUS7, and SRPK2; with rs140505938 are ANP32E, APH1A, C1orf51, C1orf54, CA14, OTUD7B, PLEKHO1, VPS45, with rs12845396 is NLGN4X, and with rs950169 are ADAMTSL3, GOLGA6L4, ZSCAN2 (SWG of the PGC et al., 2014).
There are certain limitations with our analyses. Firstly, our sample size was modest, consisting of 224 individuals, with 93 suicide attempters in the final sample, thus it was not feasible to complete a high-lethality suicide attempter group polygenic risk ascertainment. Moreover, our polygenic score calculation was on the genome-wide significant variants, and further analyses with more relaxed significance threshold can provide a stronger overview of the association.

4.6 Conclusion

Individuals with schizophrenia with a longer duration of illness (or older age) and a family history of suicide attempt or completion may be at an elevated risk for suicide attempts. Polygenic risk scores offer a reliable biological assessment for schizophrenia by summing up the cumulative effects of variants with small effects. However, the polygenic risk, at least for the common genome-wide significant schizophrenia variants, by itself may not be sufficient as a tool to detect association with suicide risk.

Further studies need to be well-powered, perhaps making use of the data available from the SWG, but they also need to assess the polygenic risk scores for higher p-value thresholds. Studies can also assess different ethnicities as the main focus of the previous studies has been on white European populations. Moreover, it is worthwhile to analyse genetic data from other psychiatric consortia, including depression, bipolar disorder, and a control group with no disorder. Well-powered studies on high lethality attempters versus individuals without any suicide attempt or ideation may help determine the veracity of this notion.
Chapter 5

5 General discussion

5.1 Discussion

Every year thousands of lives are lost due to suicide. Individuals with mental illnesses like schizophrenia are more predisposed to suicidal ideation and suicide attempt, with almost 5% of individuals with schizophrenia committing suicide (Palmer et al., 2005). Suicide attempters are a heterogeneous group (Pompili et al., 2011), and schizophrenia itself is associated with significant heterogeneity (McGrath et al., 2006). Thus, assessing suicide risk in schizophrenia is a challenging task, and there remains a scarcity of studies focusing on suicide attempt and suicidal ideation in individuals with schizophrenia spectrum disorders.

My thesis aimed to determine the effect of recent stressful life events on emergent suicidal ideation in schizophrenia, and early-life stressful events on suicide attempt. My thesis also incorporated an analysis of the polygenic risk score for schizophrenia in suicide attempt.

5.1.1 Recent stressful life events affecting emergent suicidal ideation

We hypothesized that greater recent stress would be associated with emergent suicidal ideation. In particular, we hypothesized that greater total stress scores and domain scores would be associated. Although we did not find the total recent stress scores to be associated, we found an increased risk of emergent suicidal ideation in individuals with schizophrenia spectrum disorders who recently experienced any health problems (OR=1.3; p=0.008). In particular, females were more predisposed to this risk. Similar to our findings, there has been other evidence of greater
suicidal ideation in females compared to males (Dutta et al., 2017). It is worth noting that the gender effect on suicidal ideation is subject to discrepancies within studies. For example, one study found no differences between rates of treatment-emergent suicidal ideation in males and females (Menke et al. 2012). However, another study on adolescent suicide attempters reported a higher prevalence of sustained suicidal ideation in males (Soler et al., 2016). Nevertheless, evidence from animal models suggests that early life stress has a different effect in the molecular level on males and females (Peña et al., 2017). Thus, it is important to appreciate gender differences, as well as the biological effects of sex differences.

Similar to our findings regarding association of health-related stress, specific types of stressors, but not total stress, in the past 3 months were associated with suicidal ideation (May et al., 2015). In another study, life events involving recent health problems were found to be independently associated with suicidal ideation in a sample of suicide attempters, but other negative life events were not associated, further highlighting the importance of health-related stressors (Laglaoui Bakhiyi et al., 2017). The literature suggests that many different types of stressful life events can lead to emergent suicidal ideation and subsequent suicide attempts, but the finding of health-related problems have been replicated in a lot of studies. Our study builds on these studies by focusing on schizophrenia spectrum disorders, as well as highlighting the emergent suicidal ideation phenotype that has not been the focus of other studies to date. Our findings suggest that it is worthwhile for psychiatrists to enquire about any health stressors that may be affecting patients. Larger, well-powered studies, making use of pooled data from different groups or consortia on health-related factors, can help further solidify the importance of specific health-related issues that require the most immediate attention with regards to emergent suicidal ideation.
In our sample, baseline hopelessness and depression, the presence of an affective psychosis, and increased use of alcohol at the three-month visit were nominally-associated with emergent suicidal ideation. The literature supports the role of hopelessness, depression, and substance abuse in leading to suicidal ideation. Nevertheless, the modest effect sizes in our study point toward the underlying effect of more factors, including genetic and epigenetic factors. As discussed in the following sections, a model able to account for relevant clinical/demographic factors, stressful life events, and genetic factors is a future direction warranting our attention.

5.1.2 Early-life stressful events affecting lifetime suicide attempt

We hypothesized that early-life stressful events will be predictive of suicide attempt, such that there will be a greater stress load in the suicide attempters. We further hypothesized that specific types of early-life stressful events will be predictive of suicide attempt.

Accordingly, we found that experiencing a higher number of stressful life events before 18 years of age was significantly associated with a lifetime attempt of suicide, although the finding was only nominally-significant in our adjusted model. In this model, the number of psychiatric hospitalizations was significantly predictive of suicide attempt, concordant with literature suggesting a linkage between admission or discharge from hospitals and a higher risk of suicide attempt (Qin & Nordentoft, 2005).

Previous studies have reported higher suicide rates in individuals with more exposure to stressful early-life events. In particular, the analysis of the specific stressful early-life events supported the pivotal effect of traumatic events including sexual molestation on predicting suicide attempt, and also revealed the role for factors that may be deemed “non-traumatic”, such as mental health problems in early life. Our findings suggest that both traumatic and non-traumatic events
potentially can affect suicidal behavior. This is not surprising given neurodevelopmental changes are mediated by early-life events, and the brain is very receptive to experiences in early life. Although a major limitation from our analysis is our small sample size and subsequent modest sensitivity and accuracy which precludes us from making firm conclusions, our study provides impetus for pursuing further analyses using both traumatic and non-traumatic events to achieve a better predictive model of suicide attempt.

5.1.3 Schizophrenia polygenic risk score affecting lifetime suicide attempt

Our hypotheses were not supported as we were unable to find an association between the polygenic risk score for the genome-wide significant schizophrenia risk variants and suicide attempt status. We were also unable to find an association between the genome-wide significant variants themselves and suicide attempt status, finding only a nominal association. Sokolowski and colleagues (2016b) reported that the polygenic risk SNPs for schizophrenia were pleiotropic with suicide attempt (Mullins et al., 2014; Sokolowski et al., 2016a). However, a more recent study with a larger sample found no association between the polygenic risk score for schizophrenia and mortality (Laursen et al., 2017). Furthermore, the association they saw between the polygenic risk score and more than two suicide attempts was only apparent in a basic model rather than the adjusted model. Thus, studies with individuals with no psychiatric disorder but with lifetime suicide attempts, and those with other disorders and lifetime suicide attempts, are warranted.

On a related note, the study by Mullins and colleagues (2014) reported an inverse association of the schizophrenia polygenic risk with suicide attempt, such that attempters had a lower polygenic risk for schizophrenia compared to the non-attempters. This indicates a lower polygenic risk for
schizophrenia may be in fact associating with suicide attempt. However, a limitation of the study was that it did not include any individuals with schizophrenia, as it focused on patients with major depressive disorder and bipolar disorder.

It is plausible that our analyses were underpowered to detect any differences between the two groups, as our sample size was modest, with 224 individuals in total and 93 suicide attempters. Future studies can benefit from including participants with a confirmed high-lethality suicide attempt and a family history of schizophrenia, and non-attempters with no family history of schizophrenia and no suicide attempt. Although it is possible that the heterogeneity of suicide attempts is in part responsible for the apparent lack of genetic influence, it is also plausible that the schizophrenia risk locus SNPs, based on our current panel of alleles, are not associated with suicide attempt.

5.2 Limitations

There are some limitations associated with our analyses.

Suicide attempts are affected by both proximal and distal factors, but due to the nature of suicide attempts and the difficulty of obtaining a sample of participants with a recent suicide attempt, it was not feasible for us to complete an integrated analysis of suicide attempters with information regarding both their early life stressful events (distal factors) and proximal stress factors immediately prior to the suicide attempt.

In the emergent suicidal ideation and recent stress study, the assessment of emergent suicidal ideation is subject to bias, as participants may be less inclined to disclose their suicidal thoughts, and sometimes may not disclose their thoughts fully due to the perceived stigma that is attached
to suicidal ideation. Compared with the suicide attempt status in the lifetime which we double-checked with medical records if needed, the emergent suicidal ideation suffers from this bias. Moreover, the sensitivity of the model to capture a slight worsening ideation may be insufficient. Finally, we were unable to use a machine learning model with fold-validation and test-train sub-samples in our study as the sample size of the emergent suicidal ideation was low, so the two groups of emergent suicidal ideation and non-emergent suicidal ideation were mismatched. We used the logistic regression model without any fold validation, and hence the accuracy of this model is inflated. Independent sample sets to train and test the model, or a larger sample size with a higher proportion of individuals with emergent suicidal ideation to allow fold-validation, could help create a better model.

In terms of the stressful life events faced in early life, we defined early life as ages below 18 years. However, there are some sensitive periods of life when the effects of stressful events may be most effective in leading to changes in the brain. As our analysis includes individuals facing stressful events at any age until 18, some of our stressful events may be more or less associated with the suicide attempt outcome, irrespective of the type of event faced. Moreover, as the events may have happened at any time before the suicide attempt, events occurring closer to the time of the attempt may carry more importance.

In the lifetime suicide attempt analyses, as we analyze any suicide attempts in the individuals’ lifetime, we are unable to assess the factors right at the time of the suicide attempt. This is relevant because both early-life and recent events affect suicide attempt and thus analyses that can take into consideration the overall situation may be a better way forward in suicide research. As we also use the machine learning approach for our suicide attempt prediction, it is worthwhile
to also note such models are prone to over-fitting, especially when using a large number of variables as predictors. This limits the generalizability of any data obtained.

Overall, we considered the objective experience of stressful life events, as we aimed to determine the types of life events that affect suicidal ideation and attempt. An aspect that was not accounted for is the perception of stress, as different stressors may be perceived differently by people. This may in turn affect the association of life events with suicide. Suicidal ideation, in particular, is associated with the subjective rating of depression, and any reduction in the rating is associated with a decline in suicidal ideation (Keilp et al., 2018). Excess of subjective distress over clinician rating is defined as pessimism, and it is associated with a familial transmission of suicidal behaviour, adding another layer of heterogeneity to the analyses. Yet, a problem with the subjective stress scales and any complex scales in general would be the possible misunderstanding/reluctance to answer some questions due to participants getting frustrated or bored. We observed in our analyses of emergent suicidal ideation that baseline hopelessness and depression were both associated with the emergent suicidal ideation. Nevertheless, our model with the health-stressors was significant with the covariates included.

Furthermore, our sample size was modest for detection of a polygenic risk analysis. Sample sizes of up to tens of thousands may be most desirable for such analyses, but recent studies like those by the International Schizophrenia Consortium using training and testing data sets of large sizes are also useful in attaining sufficiently powerful sample sizes (Dudbridge, 2013). Studies have suggested that there may be additional interaction effects between genes, as well as effect of many copy-number variants and any rare variants that we did not include in our analyses.
As suicide is a complex phenomenon, certain factors remained that we were not able to control for. Factors such as the presence of any autoimmune disorders and even the general physical health of individuals can affect the prognosis of suicide. In particular, the immune system has been implicated in suicidal behaviour in schizophrenia (Steiner et al., 2009). Some other possible confounders include lifestyle choices including the amount of lithium in drinking water (Helbich et al., 2015), omega-3 fatty acids in the diet (Hibbeln, 2009), and exercise (Davidson et al., 2013). Intensity and stability of positive affect are also important factors that may modulate risk for suicidal ideation (Tian et al., 2017).

To conclude, several factors affect suicidal behaviour, and stressful life events themselves precede many psychopathologies, and can affect multiple pathways. Thus, our understanding of stress and suicide should also include an awareness of this, and the fact that a direct relationship between stress and suicide is not the only possible pathway.

5.3 Conclusion

Recent health stress was the stressor most associated with emergent suicidal ideation. Although total stress was higher in the group with emergent suicidal ideation, the most significant association was with recent health-related stressful events, followed by the diagnosis of an affective psychosis, depressive symptoms, hopelessness, and female gender.

Total early-life stressful events, comprising of both traumatic and non-traumatic events, was predictive of suicide attempt. Sexual molestation and suffering from mental illness in early life were the most important predictors.
The polygenic risk score calculated from the genome-wide significant schizophrenia variants was not predictive of suicide attempt, and neither were the individual variants.

An important finding from both my emergent suicidal ideation analyses and suicide attempt analyses is the influence of health stressors in leading to suicidality. Both proximal and distal studies point toward the association of health-related stressful events with suicide attempt in individuals with schizophrenia spectrum disorders. Coupled with the fact that over 50% of the individuals among this population who commit suicide access some form of mental health care in the 30 days prior to death (Zaheer et al., 2018), it is important to emphasize the need to enquire about health-related stressful events in these individuals.

Due to the complexity of the workings of the human brain, and the integration with the environment and genetics, suicide research requires a collective effort from researchers and clinicians, a field with steady progress. The advent of large psychiatric consortia makes it feasible to carry out analyses on suicide in schizophrenia, with studies that are sufficiently powered. As most of these consortia include genetic data, using both the psychiatric assessment data and genomics data together can be invaluable. Our analyses can be considered preliminary analyses that demonstrate the need for increased homogeneity in research on suicide. Classifying suicide attempters based on family history, suicide attempt lethality, and number of attempts, can allow us to make more conclusive claims regarding the predictors of suicide. Consortia for suicide research make it possible to be mindful of these classifications while simultaneously not compromise on sample size.
5.4 Future studies

Suicide risk assessment in real-time (Kleiman & Nock., 2018) can be an avenue of future research. Individuals assessed to be at a heightened risk of suicide attempt can be assessed in real time, thereby providing means for possible suicide intervention. Similarly, individuals with a risk for emergent suicidal ideation can also be monitored.

5.4.1 Generalizability to other populations, other disorders

Our research focus has been on the Canadian population, and a majority of our participants are white European. Moreover, most research on suicide has had a focus on European/American populations, although the burden of suicide falls heavily on African and Asian peoples as well. There are reports of differences in different populations, and thus it is imperative to use the machine learning model in other populations. Moreover, the model may be used in predicting suicide in other psychiatric disorders (and also in individuals without any psychiatric disorders), in line with recent research suggesting common genetic pathways between the different psychiatric disorders.

5.4.2 Clearly differentiating the extreme suicide phenotypes

Recent work has shed light on the heterogeneity of the suicide attempt status itself. Certain traits like depression and hopelessness (Mann et al., 2016) are associated with a familial transmission of suicidal behavior. Moreover, a review identified impulsive aggression, neuroticism, and deficient working memory and executive functioning to be associated with familial suicidal behavior (Brent & Melhem, 2008). Studying the relatives of suicide attempters is an interesting
avenue for future studies, so as to differentiate between the suicide attempter and non-attempter relatives.

Future studies should aim to clearly identify the severity of suicide attempt and the familial history of suicide in their samples so as to remove this heterogeneity in their analyses. A similar suggestion has been made earlier (Hettige, 2016). However, it is admittedly difficult to obtain a large sample size with a homogenous sample. Consortia created for suicide prevention studies, can help ease some of these difficulties. On a related note, there is some debate regarding the veracity of distinctions between disorders like schizophrenia and bipolar disorder. Due to advancements like recent genetic studies demonstrating multiple shared genetic pathways, a classification based on genetic and neurophysiological factors seems reasonable. The DSM-5, with diagnoses that are “phenomenological and largely arbitrary” (Weinberger, 2015), could perhaps get some upgrades based on the Research Domain Criteria (RDOC).

5.4.3 Interaction studies

Analyses of stress*gene interaction in suicidal ideation and suicide attempt can be carried out in a much larger scale. We have some pilot data on stress*gene interactions in suicidal ideation. A preliminary analysis of 23 individuals revealed that the marker in chromosome 11, rs61126341, is associated with the risk of emergent suicidal ideation (nominal significance, p=0.04), although an interaction effect was not observed.

Moreover, further studies delineating the interaction of early-life stressful events and recent stressful events on suicide attempt, especially in first-time suicide attempters (Pompili et al., 2011). Since suicide attempt lethality was found to be associated with neurodevelopmental genes (Sokolowski et al., 2016a; 2016b), these genes could potentially be altered by early life stressors,
providing a possible biological mechanism underpinning the interaction of early life stressful events and polygenic risk for schizophrenia in affecting suicide attempt.

Indeed, a study on the interaction of stressful life events and polygenic risk for bipolar disorder found that there was a trend for association of the polygenic risk alone with the suicide attempt, while the interaction analysis revealed significant association of the stress*bipolar polygenic risk interaction with suicide attempt (Wilcox et al., 2017). One cautionary tale in this case is the lack of an interactive effect found between the recent life stress (in the past 2 years) and polygenic risk for major depressive disorder in a cohort of adults aged 50 years or older (Musliner et al., 2015), which brings into question the nature of the interactive effect we should be aiming to observe in schizophrenia suicide attempters as well. The study did find an additive effect, however. This is especially relevant since studies of schizophrenia usually incorporate individuals with schizoaffective disorders, and often may also include individuals with any other comorbid affective or mood disorders.

5.4.4 Neuroimaging genetics

Future studies could focus on the growing field of neuroimaging genetics, creating machine learning algorithms using all available clinical and psychopathological factors to assess individuals at a higher risk of emergent suicidal ideation and suicide attempt. Considering translation into clinical practice as a predictive instrument, an issue might be the costs associated with imaging techniques, but it is an avenue which has been gathering a lot of traction in the recent years and soon could be possible to image at much lower costs than we have now. The genetics, neurobiology, and the behavioral aspects of suicide can thus be integrated.
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