Suicide attempts of community adolescents and young adults: An explanatory and predictive epidemiological approach

Inaugural Dissertation

Submitted in partial fulfilment

of the requirements for the degree of

Doctor of Philosophy to the Department of Psychology

of the University of Basel

by

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Basel, 2018

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Basel, September 12, 2018

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Declaration of Authorship

I hereby declare that I have written the submitted doctoral thesis "Suicide attempts of community adolescents and young adults: An explanatory and predictive epidemiological approach" without any assistance from third parties not indicated. Furthermore, I confirm that no other sources have been used in the preparation and writing of this thesis other than those indicated.

Basel, September 12, 2018. Marcel Miché

Acknowledgements

I want to thank Roselind Lieb for her helpful guidance during the entire doctoral period, for her support and trust in giving me the chance to teach students and, most importantly, her friendliness. I want to thank Andrew Gloster for hiring me, for his full and lasting support, and for putting quite a deal of trust in my ability to find solutions to the many (predominantly data) challenges during and after the end of our Daily Symptoms study. In that relatively short period of time, I learned quite a lot, most of which I consider highly relevant, which makes it all the more precious to me. I also want to thank Gunther Meinlschmidt for accepting to be head of the jury of my PhD thesis defense.

I want to thank my wife Konstanze* for being so loving, patient, supportive, in short, for being there. Also I want to thank my son Leonard, age 16, for his support and his understanding. Unfortunately for him, I cannot commute between Basel and Kiel five days a week. I also wish to express my gratitude for the existence of my daughter Clara, age 2 1/2, my "Schätzelein".

Our workplace is a social microcosmos to which I look forward to travel to five days a week. I very much wish to thank Andrea Meyer for his helpful statistical input over the years, Erich Studerus for his important input regarding ML, Hanna Wersebe for her many contributions to get the Daily Symptoms study over the finish line, Catherine Coste, Anita Todd for making me seem to be in control of the English language (she edits our to-be-published papers), our IT-team, and Patrizia Hofer* with whom I work in the same office for how long ? – I forgot, ... probably because she's a perfect office-roommate. Other former and current stars of our microcosmos I also want to thank: Karina Wahl*, Thea Zander-Schellenberg, Isabella Mutschler, Jutta Mata, Cornelia Witthauer, Lavinia Flückiger, Yasemin Meral, Julian Möller, Andrea Spitz, Marcia Rinner, *Jae* Villanueva, Carlotta Heinzel*, Martin Mazanec,

and the many student assistants up here on the 3rd floor. I also thank the master students of the Daily Symptoms project as well as the students in my seminar courses for their efforts and their feedback. After all, teaching actually means intensified learning. I also must not forget to thank the other PhD students from the UPK. I will miss our PhD colloquium (at least sometimes). I want to thank my co-authors, as well as the authors, who invited me to be a co-author. My first association with (co-)authorship is intensive learning (again). That's not the worst first association, as far as I'm concerned.

I want to thank my mother Maren and my sister Jessica who are my beloved family. Well, at least I don't have to think of too many birthdays, right? Their contribution to my life can't be measured with words. Also, my very dear friends I want to thank from my heart: Özgür Güleryüz, Patrick Uzer, and Wolfgang Feller. Your contributions also must remain undescribed.

There are, of course, many other people to whom I owe gratitude, for example all the people with whom I worked for over 11 years in the night shift of a factory, many people associated with my studying psychology in Kiel, and so on.

THANK YOU ALL!

* An additional thanks to you for (bullet-)proofreading of the draft of this PhD thesis.

Abbreviations

AF	Attributable Fraction
APA	American Psychiatric Association
AOO	Age of onset
DIA-X/M-CIDI	Computer-assisted Munich-Composite International Diagnostic Interview
DSM-IV	*Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition
DSM-5	*Diagnostic and Statistical Manual of Mental Disorders*, Fifth Edition
EDSP	Early Developmental Stages of Psychopathology
GLM	Generalized Linear Model
HR	Hazard Ratio
MDD	Major Depressive Disorder
ML	Machine Learning
NSSI	Non-Suicidal Self-Injury
OR	Odds Ratio
PAF	Population Attributable Fraction
PD	Panic Disorder
PTSD	Post-Traumatic Stress Disorder
SA	Suicide Attempt
SI	Suicide Ideation
T	Timepoint
TE	Traumatic Event
WHO	World Health Organization

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Abstract in English

Background: Suicide attempts (SA) among community adolescents and young adults represent a major public health burden. SA rates have remained stable for decades. In order to prevent SAs, risk factors need to be identified, along with their potential for SA prevention. Further, new methodological tools for predicting an individual's SA risk have recently been developed. The pros and cons of these tools need to be empirically evaluated.

Method: In the 10-year longitudinal Early Developmental Stages of Psychopathology (EDSP) study, 3021 community adolescents and young adults were interviewed, using the Munich-Composite International Diagnostic Interview DIA-X/M-CIDI. With the aim of identifying risk factors as well as the potential of SA prevention, we evaluated both a wide range of mental disorders and specific traumatic events (TEs). With the aim of evaluating whether Machine Learning (ML) is a better approach to predict an individual's SA risk, compared to a conventional approach, we empirically compared both approaches.

Results: Except for alcohol abuse/dependence, all of the assessed mental disorders are risk factors for the subsequent first lifetime SA. The TEs physical attack, rape/sexual abuse, serious accident, and witnessing somebody else experiencing a TE are risk factors for a future SA. All of the models we used for individual SA prediction showed comparable results.

Discussion: Specific groups should be targeted when planning to conduct a prevention program, e.g. post-traumatic stress disorder patients or victims of rape/childhood sexual abuse. Our study results do not provide evidence in support of the preferential use of ML in predicting an individual's SA risk. Rather, the preferential use of the conventional prediction model is supported by our data, in combination with considerations of interpretability and practicality.

Abstract in German

Hintergrund: Suizidversuche (SV) von Jugendlichen und jungen Erwachsenen aus der Allgemeinbevölkerung stellen ein schwerwiegendes Problem des öffentlichen Gesundheitswesens dar. Die Rate an SVen ist seit Jahrzehnten konstant geblieben. Um SVe zu verhindern, müssen Risikofaktoren identifiziert und deren Präventionspotential eingeschätzt werden. Zudem sind neue Instrumente zur Vorhersage des individuellen SV-Risikos entwickelt worden. Die Vor- und Nachteile jener Instrumente müssen empirisch überprüft werden.

Methode: In der 10-jährigen Early Developmental Stages of Psychopathology (EDSP) Längsschnittstudie wurden Jugendliche und junge Erwachsene aus der Allgemeinbevölkerung mit dem Munich-Composite International Diagnostic Interview DIA-X/M-CIDI befragt. Um Risikofaktoren für SVe zu identifizieren, sowie deren Präventionspotential, analysierten wir eine breite Anzahl psychischer Störungen sowie traumatische Ereignisse. Um zu untersuchen, ob Machine Learning (ML) einen besseren Ansatz zur Vorhersage des individuellen Suizidrisikos darstellt, verglichen mit einer konventionellen Methode, stellten wir beide Ansätze empirisch einander gegenüber.

Resultate: Bis auf Alkoholmissbrauch/-abhängigkeit zeigten sich alle psychischen Störungen als Risikofaktoren eines künftigen SV, genauso wie die traumatischen Ereignisse körperliche Bedrohung, Vergewaltigung/sexueller Kindesmissbrauch, schwerwiegender Unfall sowie das Bezeugen eines Traumaerlebens von jemand anderem. Die verwendeten Modelle zur Vorhersage des individuellen SV-Risikos zeigten vergleichbare Resultate.

Diskussion: Spezifische Gruppen sollten für Präventionsstudien eingeplant werden, z.B. Personen mit Posttraumatischer Belastungsstörung oder Opfer von Vergewaltigung/sexuellem Kindesmissbrauch. Unsere Studienresultate liefern keine Beweislast,

die ML zur Vorhersage des individuellen SV-Risikos besonders begünstigt. Eher stützen unsere Daten die Bevorzugung des konventionellen Prädiktionsmodells, unter Berücksichtigung von Interpretations- und Praktikabilitätsaspekten.

Introduction

Persistent and intense personal suffering are assumed to play a major role in causing an individual to commit or attempt suicide (Klonsky, May, & Saffer, 2016; WHO, 2014). On the other hand, both committed and attempted suicide also causes suffering in individuals who are indirectly affected by it, e.g. parents (e.g. Chan, Kirkpatrick, & Brasch, 2017; Havârneanu, Burkhardt, & Paran, 2015). Apart from that, there are quantifiable social costs involved. Shepard, Gurewich, Lwin, Reed Jr, and Silverman (2016) report that in 2013 both suicide and SA amounted to a total cost of $93.5 billion (adjusted for underreporting) for the US public. This is one sixth of the estimated costs that the US public paid for cardiovascular disease in 2015 (Khavjou, Phelps, & Leib, 2016), one of the costliest chronic diseases. Suicide and SA costs in other countries are similar, showing that both have a large impact on national public health systems (Shepard et al., 2016). In order to increase awareness for this important issue, the World Health Organization (WHO) published a report on the prevention of suicide in 2014 (WHO, 2014). The aim of the report is to motivate public health officials to either develop or strengthen a national suicide prevention strategy, in order to decrease suicide rates, which on a global level have remained constant for decades (Franklin et al., 2017). Currently, the global suicide rate is 10.7 per 100'000 population (WHO, 2018a). Lifetime prevalence estimates for SA in adults range between 1.9% and 8.7% (Nock et al., 2008), whereas in adolescents they range between 3.1% and 10.9% (Evans, Hawton, Rodham, & Deeks, 2005; Nock et al., 2008).

Many years of research on suicidality have deepened our understanding of it. Most notably, empirical studies have suggested to view the components of suicidality, i.e. completed suicide, SA, suicide plan, and suicide ideation, as distinct phenomena (Kessler, Borges, & Walters, 1999; May & Klonsky, 2016; Wetzler et al., 1996). For

instance, Kessler et al. (1999) reported that only one quarter of suicide ideators go on to make an SA.

It has frequently been shown that a previous SA is highly predictive of both suicide and SA (Franklin et al., 2017; Hawton, Saunders, & O'Connor, 2012; WHO, 2014). Two other notable findings concern age and sex. Compared to other age groups, 15–29 year-olds have the highest risk to die by suicide (WHO, 2014). Regarding sex, males commit suicide almost three times as often as females across countries worldwide (WHO, 2018b), whereas for SA the sex ratio is reversed, i.e. females attempt suicide twice as often as males (Nock et al., 2008). The oddity of the reversed sex ratio might have several reasons, e.g. males using more lethal suicide means than females, or males seeking help for their problems less frequently than females (e.g. Beautrais, 2002).

Attempted suicide is a very complex phenomenon, i.e. many different, possibly interdependent, factors likely contribute to increase its risk. Mental health is considered to be one important factor. Psychological autopsy studies (Cavanagh, Carson, Sharpe, & Lawrie, 2003) and epidemiological community studies both have provided empirical evidence linking mental disorders with SAs, both in adolescents/young adults (e.g. Borges, Benjet, Medina-Mora, Orozco, & Nock, 2008; Nock et al., 2013) and in adults (e.g. Bernal et al., 2007; Nock et al., 2009). However, many of the existing studies have limitations, such as reporting cross-sectional instead of longitudinal associations (e.g. Gould et al., 1998), or reporting associations for mental disorder groups instead of a wide range of specific disorders (e.g. Fergusson, Woodward, & Horwood, 2000). In order to evaluate the possible etiological role that specific mental disorders might play in provoking SAs, such information is pivotal (e.g. Kraemer et al., 1997).

Another thread of research of SA in adolescents and young adults is concerned with traumatic events (TE) as potential risk factors. However, conclusive empirical evidence exists for very few TEs, namely for childhood sexual abuse and physical

abuse (e.g. Brown, Cohen, Johnson, & Smailes, 1999; Fergusson, Horwood, & Lynskey, 1996), and for the number of TEs (e.g. Afifi et al., 2008; Benjet et al., 2017). Empirical evidence is inconclusive for many other TEs (e.g. Castellvi et al., 2017; Liu et al., 2017), and for some TEs it is very rare or not existing. The limitations in the literature are similar to those indicated for mental disorders, i.e. information that brings us closer to the possible etiological role of specific TEs for SAs is scarce (Serafini et al., 2015), and therefore it needs to be complemented.

A recent meta-analysis, spanning the last 50 years of suicide and SA research, showed that our accuracy of predicting an individual's SA is currently only slightly better than chance (Franklin et al., 2017). This meta-analysis recommended to start applying machine learning (ML) algorithms, as opposed to conventional prediction methods, in order to improve our prediction accuracy of SA risk. This thread of research needs to be complemented for several reasons, e.g. in order to accumulate substantive empirical evidence on whether or not ML is indeed a tool that predicts an individual's risk of committing a suicide or SA much more accurately, relative to established methods.

Adolescence and young adulthood is of particular interest when investigating whether mental disorders or TEs elevate the risk of a SA. That is, when it turned out that risk of SAs is elevated in the young, this would strongly argue for national health policies to initialize or intensify prevention efforts in such age groups (Merikangas et al., 2010a).

The content of this dissertation represents the focus of three manuscripts (see Appendices A–C). Their specific aims were derived from current research gaps indicated above. Concerning community adolescents and young adults: In the first manuscript we examined the associations of temporally prior *DSM-IV* mental disorders and the subsequent first lifetime SA, i.e. both analyzing the specific disorders as well as the comorbid number of mental disorders. In the second manuscript we examined the associations of temporally prior traumatic events and

a future SA, i.e. both analyzing specific TEs as well as the number of TEs. In each of the manuscripts one and two we aimed to provide estimations of the potential of SA prevention. In the third manuscript we empirically compared the degree of predictability of an SA across four prediction models, one conventional model and three ML models.

Following this introduction, in the section *Theoretical Background* I will describe the theoretical concepts and previous research on specific factors that have been studied in association with SAs in community adolescents and young adults. In the section *Research Questions*, I will present the research questions, derived from the theoretical background, both within and across the three manuscripts. In the section *Methods*, I will present the design of the study that was used, and I will address the operationalization of the measures that were used to assess the constructs, the methodological approaches of manuscripts number one (see Appendix A (Manuscript 1)) and two (see Appendix B (Manuscript 2)), as opposed to manuscript number three (see Appendix C (Manuscript 3)), and the statistical analyses. In the section *Results*, I will present a brief summary of the results. In the section *Discussion*, I will discuss the implications of the empirical evidence we gathered, both within and across the three manuscripts, the strengths, and the limitations of our studies. The discussion will end with a concluding outlook and recommendations for future research of SAs in the young general community.

Theoretical Background

Suicide Attempt

Suicidality is categorized into completed suicide, SA, suicide plan, and suicide ideation. The focus of this dissertation is SA in community adolescents and young adults.

Mental Disorders

Mental disorders have been shown to be associated with SAs (e.g. Nock et al., 2008). Diagnoses of mental disorders are currently classified according to the 5th edition of the Diagnostic and Statistical Manual of Mental Disorders by the American Psychiatric Association (APA) (*DSM-5*; American Psychiatric Association [APA], 2013). However, the studies presented in this dissertation used the 4th edition of the DSM (*DSM-IV*; APA, 1994), which is why in this dissertation the classification of mental disorders refers to the *DSM-IV*.

The large number of studies that have provided empirical evidence for the association between ill mental health and SAs represent important steps in the pursuit of evaluating a possible causal association. Many previous studies were limited, in that they were crude, selective, or correlative. Crude refers to evidence on aggregated mental disorders (e.g. Fergusson et al., 2000) instead of specific mental disorders. This is a limitation, in that possibly different risk across specific disorders for SA can't be evaluated, which is necessary for future research on possibly different etiological pathways to SAs. Selective refers to evidence on one or on very few specific disorders (e.g. Boden, Fergusson, & Horwood, 2007; Bronisch, Höfler, & Lieb, 2008; Lewinsohn, Rohde, Seeley, & Baldwin, 2001) instead of a wide range of specific disorders. This is a limitation, in that the independent risk for SAs (Kurth & Sonis,

2007) can't be evaluated, i.e. if other mental disorders aren't taken into account, the estimated risk might be biased. Correlative refers to associations between mental disorders and SA, where the temporal order between the two remains unclear (e.g. Gould et al., 1998). Thus, it cannot be inferred whether mental disorders are risk factors for SA or whether SA is a risk factor for mental disorders. All three characteristics, crude, selective, and correlative, have important implications, (a) for gaining further insights into SA, (b) for informing public health institutions, (c) for providing potential targets of SA prevention, and (d) for helping clinical practitioners in their task of assessing the risk of SA in their patients.

In the literature the median age of onset (AOO) is reported for some of the different *DSM-IV* disorder groups. The median AOO for anxiety disorders is 15 years, for mood disorders it is 26 years, and for substance-related disorders it is 21 years (Andrade et al., 2000). These estimates are based on epidemiological community studies from Brazil, Canada, Germany, Mexico, the Netherlands, Turkey, and the USA, conducted between 1990 and 1996. It is important to note the different AOOs, because in samples of adolescents and young adults, some of the individuals might not have reached the critical onset age for a disorder. For such disorders, this might lead to an underestimated risk for SAs, i.e. in studies with adolescents and young adults some participants who confirm a SA might not yet fulfill all diagnostic criteria for a specific mental disorder at the time of the diagnostic interview. Therefore, due to their age, they would be part of the group not exposed to the disorder.

Two studies addressed some of the research gaps prior to our study (see Appendix A (Manuscript 1)) (Borges et al., 2008; Nock et al., 2013). They evaluated whether a wide range of specific mental disorders qualify as risk factors for a subsequent SA, establishing the temporal order via AOO information. However, both studies focused on subjects between 12 and 18 years old, which might have lead to an underestimated risk for SAs because the critical age ranges have not been fully represented, both for SAs (15–29 year-olds) and for some mental disorders.

Traumatic Events

Traumatic events have been shown to be associated with SAs (e.g. Castellvi et al., 2017; Serafini et al., 2015). Conclusive empirical evidence for TEs' association with SAs includes both sexual and physical abuse (e.g. Brown et al., 1999; Fergusson et al., 1996). Additionally, the number of experienced TEs have repeatedly been shown to be associated with SAs (e.g. Afifi et al., 2008; Benjet et al., 2017). However, for most specific TEs, e.g. to experience a serious accident or to witness somebody else experiencing a TE, empirical evidence is either inconclusive, very rare, or not existing (e.g. Castellvi et al., 2017; Liu et al., 2017).

The lifetime prevalence of the experience of at least one TE in adolescents has been reported to be nearly two thirds (McChesney, Adamson, & Shevlin, 2015), and even up to 90% (Elklit & Petersen, 2008). For some TEs, there is evidence that they may occur more frequently in certain age periods, e.g. Breslau, Wilcox, Storr, Lucia, and Anthony (2004) report a peak frequency for experiencing assaultive violence in 16–17 year-olds in their longitudinal epidemiological study of adolescents and young adults. Also, many TEs show sex differences (e.g. McChesney et al., 2015), e.g. rape is experienced more frequently by females, whereas being threatened with a weapon is experienced more often by males. Finally, the AOO has been reported to differ for several TEs (McLaughlin et al., 2013), with being kidnapped, physically abused by a caregiver, and witnessing domestic violence showing the earliest AOO, i.e. 50% of the participants report to have experienced one of these TEs before the age of eight. The high frequency of TEs in the population and their age and sex dependency raise the possibility that the experience of a specific TE increases the risk of a SA, already at an early age. The largely inconclusive or very rare empirical results of most specific TEs in adolescents and young adults makes it all the more important to investigate them, regarding SA.

Miscellaneous Factors

Factors that are reported in the literature to be associated to SAs and that were mentioned so far, are: previous SA, age, sex, mental disorders, and TEs. Due to space limitations, further factors will be listed in table 1. This list is not exhaustive, i.e. only factors will be mentioned which are relevant in this dissertation.

Table 1: Overview of miscellaneous factors used in this dissertation.

Problem-solving
Subjectively perceived coping efficacy across several domains, e.g. finances
Demographics
Socioeconomic class, educational level, living in a rural or urban area
Family history of psychopathology
Parental psychopathology
Temperament
Behavioral inhibition
Psychosis
Subclinical psychotic experiences
External events that require individual adjustment
Any parental separation event, negative life events, daily hassles
Treatment history
Prior psychological help-seeking

Note. The categories are written in italics.

Comorbidity

Comorbidity in epidemiology is defined as *the presence of more than one mental disorder in a person in a defined period of time* (Wittchen, 1996). Comorbidity has several fundamental implications, for theory, for diagnostics, and for therapy. For instance, the comorbidity of pediatric anxiety disorders has been found to negatively impact treatment outcomes (Walczak, Ollendick, Ryan, & Esbjørn, 2017). Empirical findings warrant the use of comorbidity as a separate risk factor for SAs in adolescents and young adults (e.g. Borges, Nock, Medina-Mora, Hwang, & Kessler, 2010; Nock,

Hwang, Sampson, & Kessler, 2010). However, empirical findings so far are not conclusive, with some studies reporting an association between the number of mental disorders and SAs (e.g. Lewinsohn, Rohde, & Seeley, 1995), but not other studies (e.g. Borges et al., 2008). Mixed results also exist, with an increased risk for a subsequent SA in adolescents and young adults in the presence of three disorders, but not two disorders (e.g. Nock et al., 2013).

Risk Factors vs. Risk Algorithms

Due to both the great number of potential risk factors for SAs and the assumed complexity of their associations to SAs, Franklin et al. (2017) suggested to shift the focus away from risk *factors* towards risk *algorithms*, i.e. Machine Learning (ML). ML is deemed to be well suited to investigate complex associations in data. Within the realm of SAs, the overall aim of ML is to accurately predict whether an individual will attempt suicide in the near future, thus providing help to practitioners in deciding whether an individual is at a hightened risk for SA (e.g. Hahn, Nierenberg, & Whitfield-Gabrieli, 2017). Prediction accuracy of SAs is currently only slightly better than chance (Franklin et al., 2017). Improving prediction accuracy of SAs is highly desirable since the suicidal individual, his/her social environment, and the society at large, are strongly affected by this extreme behavior (Shepard et al., 2016).

Due to ML being a relatively new option in analyzing data, and the recency of the recommendation to shift the focus towards this methodological approach in the research field of suicidal behavior, the number of empirical studies that applied ML to SA is relatively low (e.g. Simon et al., 2018; Walsh, Ribeiro, & Franklin, 2018). Currently, none of the published ML-related studies used data from a representative community sample. Furthermore, many ML models are currently considered as black boxes, i.e. interpreting the result of these models is either more difficult than in the generalized linear model (GLM) or even impossible (e.g. Kruppa et al., 2014).

Interpretability is among the most important elements of any scientific endeavor to understand the causal mechanisms of a system, the human psyche being no exception. Therefore, one might argue that in order for ML to become a useful option among clinical practitioners and researchers alike, ML needed to predict an indiviual's SA risk much more accurate than the GLM or the linear regression model (LM), which are the standard options (Steyerberg, van der Ploeg, & Van Calster, 2014a). However, results so far are mixed, with some studies finding ML models to clearly outperform the GLM (e.g. Walsh, Ribeiro, & Franklin, 2017, 2018), whereas in other studies ML models and the LM showed comparable results (e.g. Delgado-Gomez et al., 2011; Delgado-Gomez, Blasco-Fontecilla, Sukno, Ramos-Plasencia, & Baca-Garcia, 2012). Research using data representative of the community and comparing the GLM with ML models, can be regarded as an important contribution to SA research in particular, and to the beginning ML-related debate in psychological research in general (e.g. Hahn et al., 2017; Yarkoni & Westfall, 2017).

Research Questions

Based on the presented theoretical background, the following specific research questions arose, which were answered in the three manuscripts, respectively:

Manuscript 1: *Mental disorders and the risk for the subsequent first suicide attempt: Results of a community study on adolescents and young adults*

1. Which specific mental disorders are associated with the subsequent first lifetime SA?
2. Is the number of mental disorders associated with the subsequent first lifetime SA?
3. What is the proportion of preventable SAs, both in the group exposed to a specific mental disorder and in the overall sample population?

Manuscript 2: *Specific traumatic events elevate the risk of a suicide attempt in a 10-year longitudinal community study on adolescents and young adults*

1. Which specific traumatic events are prospectively associated with an SA?
2. Is the number of traumatic events prospectively associated with an SA?
3. What is the proportion of preventable SAs, both in the group exposed to a specific traumatic event and in the overall sample population?

Manuscript 3: *Suicide attempt prediction in community adolescents and young adults: Comparing a generalized linear model with machine learning models*

1. Is prediction accuracy of a future SA considerably improved when using machine learning algorithms instead of the generalized linear model (GLM)?

2. According to machine learning selection mechanisms, which predictors rank highest, relative to the GLM predictor ranking?

Summarizing the specific research questions, the overall research questions of this dissertation, are:

1. Are there specific mental disorders or TEs that might serve as potentially primary prevention targets for SAs in the young general community?

2. Can ML tools currently be recommended in helping practitioners assess an individual community adolescent's or young adult's SA risk, compared to a conventional prediction model?

Methods

Epidemiological Approach

Epidemiology is a scientific discipline that investigates both, the distribution of health phenomena in defined populations as well as factors that may influence this distribution (Lieb, 2015). The two major subdisciplines are termed descriptive epidemiology, and analytic epidemiology, with the former usually preceding the latter. For instance, using descriptive epidemiology, a researcher might note an apparent different distribution of SAs in two separate groups. By using analytic epidemiology, researchers can determine whether this difference is significant, i.e. whether further investigations into possible reasons for this difference are warranted. Further investigations ultimately aim at the question of whether the investigated factor is a causal risk factor, which requires several consecutive conditions to be met (Kazdin, Kraemer, Kessler, Kupfer, & Offord, 1997; Kraemer et al., 1997). Each condition is stricter than a prior condition. For instance, observing SAs and a mental disorder once in an individual's lifetime excludes the possibility to determine which of the two occurred first. However, assessing SAs and the mental disorder at several times, e.g. once every year, makes the temporal determination possible, as does asking the individual about the age of first onset of both the SA and the mental disorder. Applying the temporal order of two phenomena is a stricter condition than not applying it, therefore the former establishes the status of being a risk factor, whereas the latter is considered a correlate. According to Kraemer et al. (1997) two further questions need to be confirmed before the status of being a causal risk factor can be established. First, can the factor change or be changed? Second, does the manipulation of the the factor change the outcome?

Another important function of epidemiology is to inform national health

systems about particular health phenomena. One way of informing them is by estimating the percentage of preventable cases, e.g. SA cases, in a defined population. This potential for prevention might then be used to select a defined population for a prevention study, testing whether less SA cases are observed in the course of preventing the assumed causal risk factor, either compared to the population itself during the same time period in previous years, or compared to another, very similar, population, during the same time period. If a significant reduction of SA cases was found, a prevention study must provide convincing evidence that the reduction can indeed be attributed to the prevention of the investigated risk factor.

The 'Early Developmental Stages of Psychopathology' Study

Figure 1 shows the 10-year longitudinal design of the 'Early Developmental Stages of Psychopathology' (EDSP) study, adapted to what is relevant in this dissertation, i.e. the EDSP study was more extensive than what is displayed (Lieb, Isensee, von Sydow, & Wittchen, 2000a; Wittchen, Perkonigg, Lachner, & Nelson, 1998b). The EDSP study was conducted with subjects from the greater Munich area in Germany, drawn from the local government registries. Since the focus was the *early* development of psychopathology, compared to 16–21 year-olds, 14–15 year-olds were sampled at twice the probability, whereas 22–24 year-olds were sampled at half the probability. Sampling weights were constructed to account for this sampling scheme. Across the four assessment waves T0–T3 response rates ranged between 70.9% and 88%. At baseline, 3021 subjects between 14 and 24 years old were assessed. At T1 only subjects were assessed that were between ages 14 to 17 at baseline, whereas at T2 and T3 all subjects were invited to the interview. Of the 3021 subjects, 2797 (92.6%) were interviewed at least at one follow-up. Further details are reported elsewhere (Beesdo-Baum et al., 2015).

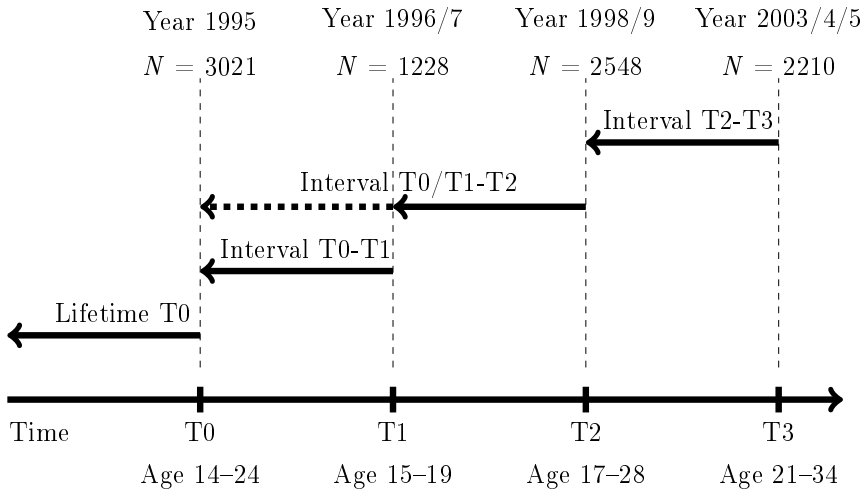

Figure 1: EDSP 10-year longitudinal study design (adapted).

Operationalization of the Construct Measures

In this dissertation, SA is defined as the *engagement in a potentially self-injurious behaviour in which there is at least some intention of dying as a result of the behavior* (O'Connor & Nock, 2014).

Many constructs used in this dissertation, were assessed with the DIA-X/M-CIDI (Wittchen & Pfister, 1997), which is a computer-assisted fully structured clinical interview used to assess symptoms, syndromes, and diagnoses of mental disorders, based on *DSM-IV* (APA, 1994) criteria. The DIA-X/M-CIDI yielded good to excellent reliability and validity (Reed et al., 1998; Wittchen, Lachner, Wunderlich, & Pfister, 1998a). Additionally, the DIA-X/M-CIDI assesses information about onset, duration, and recency of the clinical constructs. Constructs assessed with the DIA-X/M-CIDI were: SAs, mental disorders (see table 2), traumatic events (physical attack, rape, childhood sexual abuse, serious accident, witness to somebody else experiencing a TE, war experience, imprisonment/hostage/kidnapping, and natural disaster), any separation event (defined as parental divorce, death of father or of mother), previous psychological help-seeking, and parental psychopathology (assessed via the offspring; for criterion related validity, see Lieb et al. (2000b)). At baseline

the lifetime version of the DIA-X/M-CIDI was used, whereas at each follow-up the interval version was used (see figure 1), i.e. questions were framed to the time interval since the subject's last interview.

Table 2: Overview of *DSM-IV* diagnoses used in this dissertation.

DSM-IV disorder	*DSM-IV* disorder group
Panic disorder (PD)	Anxiety
Agoraphobia with or without PD	Anxiety
Social phobia	Anxiety
Specific phobia	Anxiety
General anxiety disorder	Anxiety
Post-traumatic stress disorder	Anxiety
Obsessive compulsive disorder	Anxiety
Major depressive disorder (MDD)	Mood
Dysthymia	Mood
Any bipolar disorder	Mood
Nicotine dependence	Substance-related
Alcohol abuse or dependence	Substance-related
Drug abuse or dependence	Substance-related
Pain disorder	Somatoform
Any eating disorder	Eating

Note. *DSM-IV* Diagnostic and Statistical Manual of Mental Disorders (4th edition).

Age, including age cohort (defined as ages 14–17 vs. 18–24 at baseline), sex, education (low, middle, high), and socioeconomic class (low, middle, high), were obtained with the demographic section of the DIA-X/M-CIDI. Table 3 displays further constructs that are relevant in this dissertation, and the instruments they were assessed with.

Number of Risk Factor Categories. The period of time for comorbidity was defined as the subjects' lifetime. Nevertheless, disorders were only considered for comorbidity if their reported AOO was prior to the AOO of the outcome. For instance, if an individual had three lifetime diagnoses but only two of them had an AOO prior to the AOO of the SA, comorbidity for this individual was set to be two

Table 3: Overview of baseline predictors assessed with other instruments than the DIA-X/M-CIDI, used in manuscript 3.

Construct	Definition or example	Assessment instrument
Behavioral inhibition	Tendency to react to social and non-social novelty with behavior characterized by high levels of restraint, withdrawal, and avoidance (Kagan, Reznick, Clarke, Snidman, & Garcia-Coll, 1984).	Retrospective Self-Report of Inhibition (RSRI) (Reznick, Hegeman, Kaufman, Woods, & Jacobs, 1992)
Subclinical psychotic experiences during the previous seven days	Reflection of a graduated continuum from mild social alienation to first-rank symptoms of psychosis.	Symptom-Checklist (SCL)-90-R (Derrogatis, Lipman, & Covi, 1973)
Negative life events in the previous five years across 11 life domains	E.g. hospitalized for a serious illness or accident.	Munich Life Event List (Maier-Diewald, 1983)
Daily hassles in the previous 12 months across several life domains	Frequency of 14 daily stressors, e.g. in school, at work, in social relationships.	Daily Hassles Scale (Perkonigg & Wittchen, 1995a)
Subjectively perceived coping efficacy within the next six months across several life domains	E.g. I am convinced to be able to cope with difficulties and problems concerning my finances.	Scale for Self-Control and Coping Skills (Perkonigg & Wittchen, 1995b)
Rural or urban residency	Inhabitants per square mile: Rural = 553, Urban = 4061.	(Wigman et al., 2012)

diagnoses. The same procedure was applied to determine the number of TEs, except that the referenced time units were the EDSP assessment waves instead of the AOO. Categories of both the number of mental disorders and the number of TEs were zero, one, two, and three or more.

Potential for Prevention. In manuscripts 1 and 2 we estimated the so-called attributable fraction (AF) and the population attributable fraction (PAF). Both estimates represent the potential proportion by which the outcome could have been prevented, given the prevention of the risk factor which is assumed to have causally led to the outcome[1]. The AF differs from the PAF in the referred population, i.e. the AF refers to the group being exposed to the risk factor whereas the PAF refers to the whole sample population.

Temporal Order of Risk Factor and Outcome

According to Kraemer et al. (1997), the temporal order is the criterion for establishing a factor, e.g. a mental disorder, as a risk factor for an outcome. That is, a risk factor must temporally precede the outcome. This is a necessary though not sufficient condition in the evaluation of whether or not a risk factor might be a causal risk factor (Kraemer et al., 1997). In manuscript 1 (see Appendix A (Manuscript 1)), the temporal order was based on the subjects' self-reported AOO for each construct. In manuscript 2 (see Appendix B (Manuscript 2)), the temporal order was based on the four assessment waves, i.e. an incident TE had to be reported at some wave prior to when an SA was reported. Therefore, all cases that reported a SA at baseline, were excluded from the analyses. In manuscript 3 (see Appendix C (Manuscript 3)), the set of predictors were assessed at baseline whereas SA was assessed at one of the three follow-up interviews[2].

[1]The causality assumption is an inseparable component of both the AF and the PAF.
[2]SA assessed at baseline was part of the set of predictors. SA assessed at follow-up was the outcome.

Methodological Approach

In the tradition of analytic epidemiology, both in manuscript 1 and 2 we identified gaps in the literature on a priori specified predictors of SA. The predictors (mental disorders and TEs) were then investigated, while controlling for confounders. In this dissertation this is termed as explanatory epidemiological approach. This approach is characterized by setting the focus on one predictor of particular interest while taking possible confounders into account which are not of primary interest to the researcher. In manuscript 3, on the other hand, variables were not categorized as predictor and confounders. That is, the prediction performance of each model was of particular interest, whereas the importance of any specific predictor, as determined by the prediction models, was not of primary interest. Therefore, in this dissertation this is termed as predictive epidemiological approach.

The distinction between both approaches is important. However, there are overlaps, e.g. in terminology. For instance, explanatory studies also focus on predicting the outcome. Therefore, the term *explanatory*, as opposed to *predictive*, must not be used in general, but exclusively in this context of distinguishing both approaches (e.g. Yarkoni & Westfall, 2017). The central rule in the *predictive* approach is to have two strictly separate datasets. One of them is the training dataset which is used to obtain the prediction estimates. The other one is the test dataset which is used to validate the prediction performance. More detailed differences as well as implications for study design, sample size, research questions, application, etc. can be found elsewhere (Moons, Royston, Vergouwe, Grobbee, & Altman, 2009; Seel, Steyerberg, Malec, Sherer, & Macciocchi, 2012; Shmueli et al., 2010).

Statistical Analyses

All analyses of manuscripts 1–3 were applied in the R statistical software environment (R Core Team, 2017). In manuscripts 1 and 2 we used a time-to-event analysis to estimate the association between a temporally prior predictor (*DSM-IV* mental disorder or TE) and a subsequent SA. The time-to-event analysis we applied is called Cox regression model with time-varying covariates (Therneau & Grambsch, 2013). Time-varying covariates may underestimate the hypothesized causal effect of the predictor on the outcome (Höfler, Brueck, Lieb, & Wittchen, 2005). In order to avoid such an underestimation, in manuscript 1 we constructed the time-varying covariates according to a method suggested by Höfler et al. (2005). The PAF and its confidence intervals were calculated according to a method proposed by Natarajan, Lipsitz, and Rimm (2007). We then extended this approach in calculating the AF and its confidence intervals. In manuscript 3 we applied the generalized linear model (GLM) and Machine Learning (ML) models to the EDSP data, aiming to predict a future SA on the basis of baseline predictor values. Unlike manuscripts 1 and 2, these analyses are not based on the EDSP sampling weights. In manuscript 3 we used the mlr framework for ML experiments (Bischl et al., 2016).

Results

Mental Disorders

All *DSM-IV* mental disorders (see table 2), except for alcohol abuse or dependence, were positively associated with the temporally subsequent first SA. Hazard ratios (HR) obtained from the Cox regression models ranged between 2.4 for drug abuse or dependence and 15.3 for post-traumatic stress disorder (PTSD). The number of temporally prior mental disorders was also positively associated with the subsequent first SA, i.e. relative to no prior mental disorder, one, two, and three or more comorbid disorders increased the risk of the first SA. Furthermore, an overall linear positive association was shown, i.e. relative to the next lower number of prior mental disorders, each increase in number significantly increased the risk of the first SA.

AFs ranged between approximately 58% for drug abuse or dependence and 93% for PTSD. PAFs ranged between 3.3% for any eating disorder and 31.2% for specific phobia. The AF for any *DSM-IV* mental disorder was approximately 82%, whereas the PAF was 63%. For detailed results, see Appendix A (Manuscript 1).

Traumatic Events

The TEs physical attack, rape or childhood sexual abuse, serious accident, and witnessing somebody else experiencing a TE (henceforth trauma witness) were positively associated with a future SA. HRs obtained from the Cox regression models ranged between 2.3 for trauma witness and 9.6 for rape/childhood sexual abuse. The number of temporally prior TEs was also positively associated with a subsequent SA, i.e. relative to no prior TE, one, two, and three or more TEs increased the risk of a future SA. Furthermore, an overall linear positive association was shown, i.e. relative

to the next lower number of prior TEs, each increase in number significantly increased the risk of a future SA.

AFs ranged between 56% for trauma witness and 90% for rape/childhood sexual abuse. PAFs ranged between 6.9% for trauma witness and 23.5% for physical attack. For detailed results, see Appendix B (Manuscript 2).

Prediction Performance Comparison

All four prediction models, i.e. the GLM, the Lasso, the Ridge, and the Random Forest, yielded comparable results. Among the full set of predictors, the most frequently selected one in all prediction models was prior SA. For detailed results, see Appendix C (Manuscript 3).

Results Across Studies

Comparison of manuscripts 1 and 2: While PTSD in manuscript 1 ranked first among all risk estimates, several TEs (a TE being a necessary, though not sufficient criterion for a PTSD diagnosis) also increased the risk for a future SA.

Comparison of manuscripts 1 and 3: The number of *DSM-IV* mental disorders increased the risk for the subsequent first lifetime SA which was confirmed by the selection mechanism of the Lasso regression, by assigning predictive power (β-coefficient > 0) to the baseline number of *DSM-IV* mental disorders.

Comparison of manuscripts 2 and 3: The number of TEs and rape/childhood sexual abuse each increased the risk for a future SA, which was disconfirmed by the selection mechanism of the Lasso regression, by not assigning predictive power (β-coefficient $= 0$) to the baseline number of TEs and rape/childhood sexual abuse, respectively.

Discussion

This dissertation complements the empirical findings concerning suicide attempts among community adolescents and young adults. There are four main contributions to the current literature. First, we showed that a wide range of specific mental disorders are risk factors for the subsequent first lifetime SA in a sample the age range of which covers both the high-risk phase for SA of ages 15–29 years (WHO, 2014) and the first occurrence of anxiety disorders (median AOO 15 years), mood disorders (median AOO 26 years) and substance-related disorders (median AOO 21 years) respectively (Andrade et al., 2000) (manuscript 1). Second, to the best of my knowledge, we showed for the first time that the TEs serious accident as well as trauma witness are risk factors for a future SA (manuscript 2). Third, we showed that a high percentage of SAs might be preventable, both in the exposed groups and in the sample population, depending on the prevention of the risk factor (manuscripts 1 and 2). Fourth, we showed that machine learning per se is not better than a conventional methodological approach in discriminating individuals who will attempt suicide from those who won't (manuscript 3). Additionally, we confirmed that the number of prior mental disorders (comorbidity), and the number of prior TEs both are risk factors for a subsequent SA in a young community sample.

General Implications of the Manuscripts

Almost all of the *DSM-IV* mental disorders we analyzed showed an increased risk for a subsequent SA in the young general population. This finding is largely in accordance with two studies, both of which using a methodological approach very similar to ours (Borges et al., 2008; Nock et al., 2013), even though based on a cross-sectional instead of a longitudinal study design. Any divergent results between

their studies and ours might be explained with differences in the samples' age range (12–18 vs. 14–34 years), or the SA prevalence rates (possible loss of statistical power). Currently, there are no other studies that also investigated a wide range of specific disorders in a young community sample, predicting future SAs. Our findings emphasize that both prevention and intervention efforts in young community members as well as in young patient samples are indicated. In this regard, some mental disorders might be particularly important targets, e.g. PTSD or dysthymia. Yet, according to our findings, not only mental disorders but also TEs indicate the need for preventive health care actions, in particular rape/childhood sexual abuse, which is in accordance with the literature (e.g. Devries et al., 2014; Ng, Yong, Ho, Lim, & Yeo, 2018). Our results warn of underestimating the impact of the TEs serious accident and trauma witness on SA risk.

Answer to Overall Research Question No. 1

Overall research question no. 1 asked: Are there specific mental disorders, or TEs, that might serve as potentially primary prevention targets for SAs in the young general community?

Implications of Mental Disorders for Suicide Attempts

Manuscript 1 suggests that the prevention or early intervention of several mental disorders might reduce SA rates in the young general community. Two recent meta-analyses have shown interventions to decrease the risk of SAs and of non-suicidal self-injury (NSSI) in adolescents (Calati & Courtet, 2016; Ougrin, Tranah, Stahl, Moran, & Asarnow, 2015). However, it is too early to draw firm conclusions, i.e. several limitations have been identified, e.g. heterogeneous outcome measures, short follow-up periods, and lack of independent replications for specific therapeutic interventions. In our study, PTSD showed a highly increased risk for SAs. In a meta-analysis by Morina, Koerssen, and Pollet (2016), psychological interventions have

been shown to reduce PTSD symptoms in children and adolescents, and, to a smaller degree, comorbid depression symptomatology. In our study, all specific anxiety and mood disorders increased the risk of a SA. A meta-analysis by Werner-Seidler, Perry, Calear, Newby, and Christensen (2017) showed that school-based depression and anxiety prevention programs show potential to reduce the mental health burden of these two disorder groups. Effect-sizes were small to medium over short-, medium-, and long-term follow-up. Main limitations in the included studies were publication bias for the depression prevention studies which might have inflated the effect sizes, and the fact that the majority of studies did not exclude participants with significant symptoms, which, however, is typical of universal prevention programs. Overall, promising results exist in terms of prevention and early intervention of specific disorders, e.g. PTSD, in the general young community. The results of our study indicate which specific subgroups, e.g. PTSD, dysthymia, or panic disorder, might be primarily targeted in future SA prevention and intervention studies. The results also suggest for prevention/intervention studies to explicitly include comorbidity as a specific risk factor when evaluating the possible decrease in SA rates.

Implications of Traumatic Events for Suicide Attempts

Manuscript 2 suggests that the prevention or early intervention regarding each of the TEs physical attack, rape or childhood sexual abuse, serious accident, and trauma witness might reduce SA rates in the young general community. These results indicate that it doesn't require the full-blown symptom list of PTSD to increase the risk for SA. The powerful negative impact of TEs on young people's psyche is additionally confirmed by a PTSD prevalence rate of almost 16% among children and adolescents (Alisic et al., 2014), varying strongly, dependent on the type of trauma (interpersonal vs. non-interpersonal) and gender. It's important to note that prevention or early intervention of possible psychological consequences of TEs may directly reduce SA rates, as well as indirectly by preventing the onset of

PTSD. Trauma-Focused Cognitive Behavioral Therapy (TF-CBT) has been shown to effectively decrease symptoms of PTSD across several types of TEs (Cary & McMillen, 2012; Wethington et al., 2008). In particular, victims of rape or sexual childhood abuse were at hightened risk of SA in our study. A meta-analysis by Harvey and Taylor (2010) showed large effect sizes for PTSD/trauma outcomes of psychotherapy with sexually abused children and adolescents. The results of our study indicate which specific subgroups, e.g. victims of rape or childhood sexual abuse, might be primarily targeted in future prevention and intervention studies. Our results also suggest for prevention/intervention studies to explicitly include the category of multiple TEs as a specific risk factor in evaluating the possible decrease in SA rates.

Answer to Overall Research Question No. 2

Overall research question no. 2 asked: Can machine learning tools currently be recommended in helping practitioners assessing an individual's SA risk in community adolescents and young adults?

Based on our results, ML can currently not be recommended as the method of choice, concerning the risk assessment of individuals from the adolescent and young adult general community. Rather, based on our results and on scientific criteria regarding the comparison of two competing methods, the GLM can be considered the better choice. That is, even though the prediction performance was comparable in all four models, the GLM achieves its performance with much less effort (e.g. short computation time), much easier applicability (most default software packages contain the GLM), much better transparency/interpretability (clear functionality of the GLM), and much easier adjustment to different local settings (Steyerberg et al., 2014a; Steyerberg & Vergouwe, 2014b), which is particularly important in SAs, which might strongly vary across regions (Nock et al., 2008).

Possible Causal Mechanisms for Suicide Attempts

The results in this dissertation represent evidence in support of the notion that both specific mental disorders and specific TEs are risk factors for SAs in community adolescents and young adults. Whenever evidence in support of a possible causal association is presented, questions concerning mechanisms arise, by which a causal association might be explained. Our results suggest that there might be specific causal mechanisms, concerning both mental disorders and TEs, since the risk estimates for a SA widely vary. This is in accordance with other studies (Borges et al., 2008; Nock et al., 2013; Nock et al., 2009).

Anxiety disorders are highly prevalent in the general community. Prevalence rates of up to 12% in children and up to 32% in adolescents are reported in the literature (Essau, Lewinsohn, Lim, Moon-ho, & Rohde, 2018). Prevalence rates in adults range between 3.8% and 25% (Remes, Brayne, Van Der Linde, & Lafortune, 2016). In our study, all specific anxiety disorders increased the risk of a future SA. Mathews, Koehn, Abtahi, and Kerns (2016) suggest that domains of emotional competence, e.g. emotion regulation, are driving factors in anxiety disorders. Evidence in support of emotional regulation being a specific characteristic in anxiety disorders is provided by a prospective study by McLaughlin, Hatzenbuehler, Mennin, and Nolen-Hoeksema (2011), where anxiety symptoms, but not depressive symptoms, were prospectively predicted by emotional dysregulation, after controlling for baseline symptoms. Emotional dysregulation has been shown to be associated to SAs (Rajappa, Gallagher, & Miranda, 2012), rendering it one possible causal mechanism. A further specific mechanism concerns the possible causal link between PTSD and SAs as well as between TEs and SAs, namely the concept of entrapment, i.e. the experience of defeat/humiliation from which there is no escape (O'Connor & Portzky, 2018). This concept initially was part of an explanatory model of depression by Gilbert and Allan (1998). Today it is an important component of

the Integrated motivational-volitional model (IMV) (O'Connor, 2011) of suicidal behavior. Entrapment is subdivided into the two dimensions external and internal, the latter dimension pointing to perceptions of being entrapped in one's own thoughts and feelings, which is closely connected to a core symptom of PTSD in the *DSM-IV* and *DSM-5* (APA, 1994, 2013), i.e. *recurrent, involuntary, and intrusive distressing memories of the traumatic event(s)*. Another possible specific causal explanation for the association between PTSD or TE and SA is hyperarousal, also a core symptom of PTSD. It is the PTSD-cluster of hyperarousal which has been found to be especially associated to suicidality in a recent study by Briere, Godbout, and Dias (2015). Furthermore, self-disgust has recently been proposed as an underlying factor for an SA in those exposed to PTSD (Brake, Rojas, Badour, Dutton, & Feldner, 2017). Other possible causal mechanisms that are discussed in the literature on anxiety disorders and SA are not necessarily specific to anxiety disorders, e.g. escape from exacerbated psychological distress induced by the disorder, social isolation, and rummination (Kanwar et al., 2013; Sareen et al., 2005; Thibodeau, Welch, Sareen, & Asmundson, 2013).

The mood disorders MDD, dysthymia, and any bipolar disorder were shown to increase the risk of the subsequent first SA in our study (see Appendix A (Manuscript 1)). Prevalence rates of 14% are reported in the literature for mood disorders in adolescents (Merikangas et al., 2010b), and of approximately 21% in adults (Kessler et al., 2005). A possible causal mechanism between mood disorders and SA might be hopelessness, which is part of the diagnostic criterion *depressed mood*, without which neither MDD, dysthymia, nor any bipolar disorder can be diagnosed (APA, 1994, 2013). Hopelessness is an important component of another contemporary theory of suicidal behavior, i.e. the Three-Step Theory (3-ST) (Klonsky et al., 2016), which in combination with (psychological) pain is thought to develop and sustain suicidal ideation which itself must logically be assumed to precede a SA. Joiner, Brown, and Wingate (2005) hypothesized that, in suicidal people, hopelessness is about feelings

of being a burden on others and of failed belongingness, both these concepts pointing to an interpersonal dimension.

Rape/childhood sexual abuse was particularly pronounced in increasing the risk of a future SA, compared to the other TEs. A possible specific mechanism underlying this association might be maintained suicide ideation (SI). Childhood sexual abuse has been found to predict maintained SI in young male, though not female, high-risk patients of psychosis (Salokangas et al., 2018). This finding might be linked to a study by Miranda, Ortin, Scott, and Shaffer (2014) who found that frequency of SI robustly predicted a future SA in adolescents. If this link held true, this might represent one possible explanation for why we found that males who were raped or sexually abused as a child had a signficantly increased risk of a SA, compared to females. However, this possibility needs to be confirmed by future research. Our own research (see Appendix C (Manuscript 3)) suggests that in our set of 16 baseline predictors neither the number of TEs nor rape/childhood sexual abuse contributes an independent amount of risk for a future SA in community adolescents and young adults (as determined by the Lasso regression algorithm). The possibility of childhood sexual abuse not being an independent risk factor for SAs is suggested by Maniglio (2011) who concludes that childhood sexual abuse should merely be part of multifactorial etiological models of suicidal behavior and ideation.

Generally, many possible mechanisms why people attempt suicide are discussed in the literature, e.g. possible genetic and epigenetic causes are assumed to influence vulnerabilities to SA (e.g. Ludwig, Roy, Wang, Birur, & Dwivedi, 2017), biological causes due to tobacco use (e.g. reduced levels of monoamine oxidase) (e.g. Bohnert et al., 2014; Bronisch et al., 2008; Hughes, 2008; Schneider et al., 2009; Yaworski, Robinson, Sareen, & Bolton, 2011), and psychological causes that pertain to affective processes like anhedonia (e.g. Auerbach, Millner, Stewart, & Esposito, 2015), or to cognitive processes like less specific autobiographical memories (e.g. Arie, Apter, Orbach, Yefet, & Zalzman, 2008).

Strengths of the Manuscripts

- Representativeness: The EDSP sample is representative of the general community.
- Study design: 10-year longitudinal prospective study.
- Sample size: 3021 participants at baseline can be considered as a relatively large sample size for a longitudinal epidemiological study.
- Retention rate: Roughly 71% of the baseline sample has participated at the last follow-up interview; almost 93% of the baseline sample has participated in at least one follow-up interview.
- Assessment instrument: For many constructs, including the ones of main interest, i.e. SA, mental disorders, and TEs, the DIA-X/M-CIDI was used which is a standardized clinical interview, based on *DSM-IV* criteria. The CIDI is widely used, which facilitates comparison with future studies.
- Risk factor evaluation: In all manuscripts, the temporal order of hypothesized risk factor and outcome (SA) was established, therefore allowing us to report risk estimates instead of correlation estimates.
- Range of risk factors: Investigation of a wide range of specific hypothesized risk factors instead of aggregated factor categories.
- Confounding: We adjusted for several important confounders, which is essential in observational studies in order to decrease the likelihood of a false positive finding.

Limitations of the Manuscripts

- Self-report: All analysed data was based on self-report, which is prone to several biases, e.g. recall bias.

- SA assessment: SAs were assessed for all subjects at T2 and T3. At T0 and T1, SA was assessed only if the MDD stem questions had been confirmed. This prevents the determination of SA incidence for all subjects in analyses that are not based on AOO information (manuscripts 2 and 3).

- SA definition: The definition of a SA in this dissertation (see Operationalization of the Construct Measures) is based on the assumption that by asking whether "suicide has been attempted" (German "Suizidversuch"), the criterion of having had at least some intent to die as a result of the SA is fulfilled in all SA cases.

- Factor combination in manuscript 2: Due to a small number of cases, we combined the two separate factors rape and childhood sexual abuse in assessing their risk for a future SA.

- Confounding in manuscript 2: Due to the conditional SA assessment at T0 and T1, we didn't adjust for prior SAs, which might have attenuated our risk estimates.

- Sample size: The EDSP sample size might be considered as small when applying ML algorithms.

- Temporal order: The temporal order of our constructs and the outcome SA doesn't permit further differentiation between short-term (proximal) and long-term (distal) risk.

Overall Conclusion

Starting at early ages, rigorous national efforts to prevent mental disorders and specific traumatic events from occurring are imperative – and possible (D'Arcy & Meng, 2014; Jacka et al., 2013; Magruder, Kassam-Adams, Thoresen, & Olff, 2016). According to the results presented in this dissertation, this might substantially lower SA rates in the young. The fact that suicide and SA rates haven't decreased (Franklin

et al., 2017) despite decades of research might easily be misunderstood as researchers having failed. However, such a conclusion would be unfair. The prevention of mental disorders and specific TEs on the population level has just begun. For instance, recent reviews show that both depression and anxiety can be prevented in children and adolescents using school-based programs or community-based programs (Christensen, Pallister, Smale, Hickie, & Calear, 2010; Hetrick, Cox, Witt, Bir, & Merry, 2016; Neil & Christensen, 2009). Current population-wide prevention programs include the challenge that public health officials and the general public come to realize that prevention and treatment of mental disorders and TEs are of equal worth.

Outlook

Current efforts to prevent (repeated) SAs in adolescents and young adults have shown some potential to succeed (Calati & Courtet, 2016; Singer, O'Brien, & LeCloux, 2017). Overall there are many reasons to continue SA prevention and intervention efforts, by using scientifically gained knowledge (e.g. Brent, 2018) and by improving what has so far been shown to limit further insights into suicidal thoughts and behavior (e.g. Franklin, Huang, Fox, & Ribeiro, 2018; Glenn, Cha, Kleiman, & Nock, 2017; Glenn et al., 2018). One possibility in addition to efforts in preventing mental disorders and TEs, as indicated above, is to offer more training on suicidality to general practitioners, pediatrists, and other health related personnel, in order to increase the likelihood of them screening their clients for SI or SA, and to adequately respond to those clients who confirm these questions (Bommersbach, Chock, Geske, & Bostwick, 2018; Sublette, 2018). Other promising possibilities to act now are to make use of technological advances, e.g. of internet-based interventions and mobile phone apps, that might help to greatly extend the reach of new prevention programs (e.g. Jacka et al., 2013). Also, the internet might be a promising tool to identify and reach those who are at risk of suicide (Chandler, 2018).

Suggested improvements for future research on suicidality include not only methodological advances like ML or Ecological Momentary Assessment (ESM) (e.g. Kleiman & Nock, 2018), which are directly linked to technological advances. Suggested improvements also include the need for conceptual advances. For instance, currently there is no definition of a SA that is unanimously accepted by researchers in the field of suicidality. It is proposed that such a definition ought to include (a) the degree of lethality of the attempt, and (b) the degree of intent to die when making the attempt (Glenn et al., 2017), (c) the degree of premeditation prior to the attempt (enacting a long-term plan vs. acting in a short-term impulsive manner) (Millner, Lee, & Nock, 2017), and (d) the number of previous attempts (single vs. multiple) (e.g. Miranda et al., 2008).

Taken together, we obviously need to much better understand suicidal thoughts and behaviors in adolescents and young adults. Early screening of mental health and TEs might help in referring children, adolescents, or young adults to the psychological health system, enabling prevention and early intervention of declining mental health. The planning of studies on aspects of suicidality ought to especially consider the details of how the outcome is conceptualized and measured, along with providing information on which predictors showed the highest potential to prevent the suicidal outcome. Longitudinal prospective study designs targeting the young general community over several years are rare in SA research and are therefore needed. Using measures that facilitate comparability across studies are highly preferred. An even better solution might be internationally cooperating research teams. Not only because using a homogoneous conceptualization and measure of SA would greatly benefit our insights, but also because a large enough sample size is essential to detect effects, especially when investigating complex models of assumed causal pathways to SA.

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Appendices A–C

Appendix A (Manuscript 1)

Miché, M., Hofer, P. D., Voss, C., Meyer, A. H., Gloster, A. T., Beesdo-Baum, K., & Lieb, R. (2018). Mental disorders and the risk for the subsequent first suicide attempt: Results of a community study on adolescents and young adults. *European Child & Adolescent Psychiatry*, *27*(7), 839–848. doi:10.1007/s00787-017-1060-5

Eur Child Adolesc Psychiatry
DOI 10.1007/s00787-017-1060-5

ORIGINAL CONTRIBUTION

Mental disorders and the risk for the subsequent first suicide attempt: results of a community study on adolescents and young adults

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Received: 13 June 2017 / Accepted: 25 September 2017

Abstract Adolescents and young adults represent the high-risk group for first onset of both DSM-IV mental disorders and lifetime suicide attempt (SA). Yet few studies have evaluated the temporal association of prior mental disorders and subsequent first SA in a young community sample. We examined (a) such associations using a broad range of specific DSM-IV mental disorders, (b) the risk of experiencing the outcome due to prior comorbidity, and (c) the proportion of SAs that could be attributed to prior disorders. During a 10-year prospective study, data were gathered from 3021 community subjects, 14–24 years of age at baseline. DSM-IV disorders and SA were assessed with the Munich-Composite International Diagnostic Interview. Cox models with time-dependent covariates were used to estimate the temporal associations of prior mental disorders with subsequent first SA. Most prior mental disorders showed elevated risk for subsequent first SA. Highest risks were associated with posttraumatic stress disorder (PTSD), dysthymia, and nicotine dependence. Comorbidity elevated the risk for subsequent first SA, and the more disorders a subject had, the higher the risk for first SA. More than 90% of SAs in the exposed group could be attributed to PTSD, and over 30% of SAs in the total sample could be attributed to specific phobia. Several DSM-IV disorders increase the risk for first SA in adolescents and young adults. Several promising early intervention targets were observed, e.g., specific phobia, nicotine dependence, dysthymia, and whether a young person is burdened with comorbid mental disorders.

Keywords First suicide attempt · Adolescents and young adults · Mental disorders · Community sample · Onset · Prospective design

Introduction

Adolescents and young adults are the age group at highest risk for the first onset of commonly occurring mental disorders [1, 2]. This life stage has also been identified as a critical period for the onset of the first suicide attempt (SA) [for reviews, see 3, 4].

Many studies have examined associations between mental disorders and SAs among adolescents and young adults [e.g., 5, 6–11]. Almost all the reported associations, however, are of a cross-sectional nature. As such, they provide no information on the temporal effects.

To date, only a handful of population-based studies have taken the temporal sequence into consideration, that is, whether temporally prior mental disorders increase the risk for subsequent first SA. Using different methodologies, these studies generally [12–17] although not always [18–20] found evidence that mental disorders occurring in adolescence and young adulthood predict the subsequent first onset of SA. Yet most of these studies focused either on disorder groups (e.g., mood, anxiety, or substance use

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Published online: 11 October 2017

disorders; see Fergusson et al. [12]) or on a few individual predictor disorders (for nicotine dependence, see Bronisch et al. [15]; for phobia, general anxiety disorder (GAD), and panic, see Boden et al. [13]; for major depressive disorder, see Lewinsohn et al. [14]). Drawing comparative conclusions is thus difficult because on the one hand, disorder groups do not reveal the contributions of the individual disorders to the reported risk estimates. On the other hand, studies that assessed one or a few individual disorders cannot reveal the risk pattern of a wide range of disorders.

We identified two cross-sectional population-based studies that simultaneously examined for a wide range of mental disorders whether retrospectively assessed prior mental disorders increase the risk for subsequent first onset of SA among youth [16, 17]. Borges et al. [16] used data of the Mexican Adolescent Mental Health Survey (MAMHS), a representative survey of 3005 adolescents aged 12–17 years in Mexico City. For DSM-IV [21] anxiety, mood, and substance use disorders, this group found that with the exception of panic disorder, posttraumatic stress disorder (PTSD), and alcohol abuse, each of the assessed mental disorders (i.e., GAD, specific phobia, social phobia, alcohol dependence, drug abuse) increased the risk for subsequent first SA. In the second study, Nock et al. [17] evaluated associations between prior DSM-IV mental disorders and subsequent first SA on the basis of the U.S. National Comorbidity Survey Replication Adolescent Supplement (NCS-A) in which a total of more than 6000 adolescents 13–18 years of age were assessed. Adjusting for comorbidity, Nock et al. [17] replicated the finding that major depression/dysthymia and any bipolar disorder and in addition any eating disorder predicted subsequent SA. Also consistent with the findings of Borges et al. [16], prior panic disorder and alcohol abuse were not associated with subsequent SA. In contrast to the findings of the Mexican survey, Nock et al.'s [17] findings showed no associations between prior specific phobia, social phobia, or GAD with subsequent SA.

To date, there is almost no information on the proportion of SAs among young people that is attributable to prior mental disorders in the general population. Such information is the basis of any informed prevention effort made on the population level. Only Boden et al.'s [13] longitudinal Christchurch Health and Development Study (CHDS) of over 1000 adolescents and young adults estimated population attributable fractions and found that the presence of any anxiety disorder accounted for 7.5% of the SAs in the cohort. So far, comparable information has never been reported for other mental disorders in the younger general population.

Against this background, we want to extend our own and others' earlier research on the associations between prior mental disorders and subsequent first onset of SA by extending the observed age period to age 34 years and, additionally, estimating for adolescents and young adults fractions of SAs attributable to specific mental disorders.

Using data that were collected prospectively during the 10-year follow-up of the early developmental stages of psychopathology (EDSP) study,

1. we estimated the overall association of a wide range of DSM-IV mental disorders with the risk for subsequent first SA;
2. we evaluated temporal associations between the number of prior mental disorders and subsequent first SA;
3. and we estimated the proportion of first SAs for the specific disorder groups and the total population that could conceivably be prevented by effective prevention in the first three decades of life.

Methods

Design and sample

The EDSP study has a 10-year prospective-longitudinal design. It assesses DSM-IV mental disorders and associated risk factors in a community sample. A sample of 3021 subjects (aged 14–24 years) was first assessed (T0) in 1994, followed by three additional assessments until 2005 (T1, T2, and T3). Subjects were selected from government registries of the greater Munich area, Germany. The focus of the study on the early development of psychopathology is expressed by the sampling scheme: compared to 16- to 21-year-old individuals, those who were 14–15 years old were sampled at twice the probability, whereas 22- to 24-year-old individuals were sampled at half the probability. Subsequent analyses took this scheme into account using sample weights. At baseline, the response (participation) was 70.9% ($N = 3021$). T1's response (range 1.2–2.1 years after baseline) was 88% ($N = 1228$), and only those subjects aged 14–17 years at baseline were assessed. At T2 (range 2.8–4.1 years after baseline) 2548 subjects were interviewed (response 84.3%); at T3 (range 7.3–10.6 years after baseline) 2210 were interviewed (response 73.2%). At baseline, most of the subjects were attending school (51.8%) and were living with their parents (72.7%). The majority were classified as belonging to the middle class (95.9%). More detailed information on methods, design, and sample characteristics has been presented elsewhere [2, 22, 23]. The EDSP project was approved by the Ethics Committee of the Medical Faculty of the Dresden University of Technology. All subjects provided informed consent.

Diagnostic assessment of DSM-IV mental disorders

All DSM-IV mental disorders were assessed by face-to-face interviews, using the computer-assisted Munich-Composite International Diagnostic Interview (DIA-X/M-CIDI) [24]. The DIA-X/M-CIDI was constructed for the standardized assessment of symptoms, syndromes, and diagnoses of DSM-IV disorders, along with information on age of onset (AOO), duration, and severity. Clinical interviewers, who were extensively trained in using the DIA-X/M-CIDI, interviewed the subjects for 2–3 h. At baseline, the DIA-X/M-CIDI lifetime version was used. At each of the three follow-up assessments, the DIA-X/M-CIDI was modified to obtain information about the period between the last and the current assessment. The DSM-IV disorders were obtained using DIA-X/M-CIDI algorithms. Test–retest reliability and validity for the full DIA-X/M-CIDI have been reported elsewhere [25, 26]. Age, sex, and socioeconomic class were assessed in the sociodemographic section of the DIA-X/M-CIDI. Any childhood/adolescence separation event (i.e., death of mother, death of father, separation/divorce of parents) including AOO was assessed in the family history section of the DIA-X/M-CIDI at baseline.

Assessment of SAs

SAs were assessed in the depression section of the DIA-X/M-CIDI with the question "Have you ever attempted suicide?" At baseline and T1, only the individuals who acknowledged having had a period of at least 2 weeks with a continuously depressed mood, low energy, or loss of interest [these are the stem questions for major depressive disorder (MDD)] were asked this question. At T2 and T3, a modification was introduced in the depression section to ensure that all individuals were asked questions regarding suicidality in their lifetime, irrespective of whether the stem questions for MDD were confirmed or denied. All subjects who reported that they had attempted suicide were additionally asked for their age at their first SA.

Data analysis

Data analyses were based on $N = 3021$ subjects. We used the LOCF (last observation carried forward) method, which allowed us to use information from both subjects who dropped out over the study course after baseline and subjects who responded to the follow-up assessments, i.e., for every subject we used the information obtained before dropout, regardless of when it occurred.

Data were weighted by sex, age group, and geographic location at baseline in order to be representative of the original sampling frame. Analyses were performed using R 3.3.3 [27], including the survey [28], survival [29], and ggplot2 [30] packages.

As predictors we used the following DSM-IV diagnoses: panic disorder, agoraphobia with and without panic disorder, social phobia, specific phobia, GAD, PTSD, obsessive compulsive disorder (OCD), major depression, dysthymia, any bipolar disorder, nicotine dependence, alcohol use disorder (alcohol abuse or dependence), drug use disorder (drug abuse or dependence), pain disorder, and any eating disorder. As outcome we used the first SA.

We examined the temporal priority between mental disorders and SAs on the basis of AOO information for both mental disorders and the first SA. Associations between temporally prior mental disorders and temporally subsequent onset of the first SA were estimated using the Cox regression model with person-years as the unit of analysis. Whenever a subject's reported AOO of a respective mental disorder was equal to the AOO of the first SA, the predictor value in the model was set to 0, thereby favoring conservative results. For each disorder, we fitted a separate Cox model. Each model was adjusted for sex, age group, and socioeconomic class, as well as any other mental disorder (yes/no) and any childhood/adolescence separation event (yes/no), respectively, occurring prior to the predictor disorder. Any other mental disorder and any childhood/adolescence separation event were constructed as proposed by Höfler et al. [31]: For subjects with the predictor disorder, we examined whether the covariate occurred prior to the predictor disorder based on reported AOO. For subjects without the predictor disorder, we proceeded in the same way. However, as for these subjects an AOO does not exist, we estimated the AOO by computing the median of the age at which the predictor disorder "typically begins" (based on all data for which AOO was available). The median age of the predictor disorder was thereby computed separately for the age groups 14–15, 16–17, 18–19, 20–21, and 22–24 years at baseline in order to obtain more precise estimates, since median AOO differed among age groups (results available on request). The variables independent of time (sex, age group, and socioeconomic class) were stratified when entered in the Cox model ("stratified Cox regression," [29]).

In an additional survival model, we used the number of mental disorders that occurred prior to the first SA as predictor, adjusting for sex, age cohort, socioeconomic class, and any prior separation event. Next, we computed the attributable fraction (AF) and the population attributable fraction (PAF). Here, the AF denotes the proportion of SAs that can be attributed to the predictor disorder within the exposed group. The PAF denotes the proportion of SAs that can be attributed to the predictor disorder within the total sample population. Therefore, both values represent the proportion of incident SAs that could conceivably be prevented if the

respective mental disorder was prevented or treated effectively early on, among the exposed group (AF) and among the total sample (PAF). Both coefficients are interpreted under the assumption that the mental disorder is the cause of the subsequent SA. Interpretation also strongly depends on whether confounding factors as well as censoring have been taken into account [32]. We estimated the PAF, including its 95% confidence interval (95% CI), using the formula proposed by Natarajan et al. [33]: Pe(HR − 1)/HR, where Pe denotes the cumulative lifetime incidence of the temporally preceding DSM-IV mental disorder at T3 among those who subsequently attempted suicide. Missing AOO information in the presence of a reported disorder led to exclusion. *HR* is the hazard ratio coefficient from the Cox model. The AF formula is almost identical to the PAF formula, except that Pe is not included: (HR − 1)/HR. The 95% CI for the PAFs was computed with the formulae $\left[\mathrm{PE}_L\left(\mathrm{HR}_L-1\right)/\mathrm{HR}_L;\mathrm{PE}_U\left(\mathrm{HR}_U-1\right)/\mathrm{HR}_U\right]$, where *L* and *U* denote the lower and upper bounds of the 97.5% CI, respectively. In computing the 95% CI for the AF, we adapted the formulae in the same way as in estimating the AF, that is, by excluding Pe_L and Pe_U.

Results

Cumulative lifetime incidence and mean age of first onset of SAs

The cumulative lifetime incidence of SA at T3 was 5.5%. Estimates were higher for females (6.6%) than for males (4.4%; OR = 1.5, 95% CI = 1.08–2.18). The mean age at first SA was 16.7 years (95% CI = 15.7–17.6) and was comparable between males and females [$t(167) = 0.67$, $p = 0.51$]. There were 39 subjects who reported an SA but no age at the time of the first attempt. Therefore, these were omitted from any further analyses. For a general overview, see Table 1.

DSM-IV disorders as risk factors for first SAs

Figure 1 displays the hazard ratio for each of the 15 DSM-IV mental disorders included in the analyses. All DSM-IV mental disorders except for any alcohol disorder elevated the risk for a first SA. Among anxiety disorders, PTSD showed the strongest association. Likewise, each of the affective disorders was positively associated with subsequent first SA, with dysthymia ranking first. The results for MDD and any bipolar disorder were similar to one another. Nicotine dependence showed an elevated risk for first SA as did any drug disorder. Finally, pain disorder and any eating disorder were also positively associated with subsequent first SA. The examination of the interactions between sex and prior mental disorders on predicting subjects' first SA revealed no significant interaction effects.

Figure 2 displays the burden of comorbidity with respect to the first onset of SA. Cumulative hazard curves show that the risk for first SA increased with increasing number of DSM-IV mental disorders: Hazard ratios were 2.9, 7.4, and 19.0 for 1 disorder, 2 disorders, and 3 disorders or more, respectively. We estimated that the risk for the subsequent first SA was elevated 8.9-fold on average (95% CI 5.7–13.8) with every unit increase in the comorbidity categories (i.e., 0, 1, 2, and 3 +).

Attributable fractions

The PAF and AF estimates are shown in Table 2. Regarding the AF, within the exposed group, over 90% of first SAs could be attributed to PTSD, and 85% to panic disorder. GAD and OCD present AFs of 79 and 76%, respectively. Other disorders with notably high percentages were dysthymia (87%) and nicotine dependence (73%). Among the disorders that elevated the risk for the subsequent first SA, at a minimum drug abuse/dependence accounted for 57% of the latter. It is noteworthy that 81% of first SAs could be attributed to any DSM-IV disorder within the exposed group. Regarding the PAF, in the total sample, at least 11% of first SAs could be attributed to 7 of the 15 disorders. Highest values were found for specific phobia (31%), followed by nicotine dependence (22%). Further mental disorders with the potential to lower SA incidence by more than 11% were social phobia, dysthymia, PTSD, pain disorder,

Table 1 Cumulative lifetime incidence and mean age of first suicide attempt in the completed 10-year Early Developmental Stages of Psychopathology Study

Sex	*N*	% wt	*N* SA	% wt	95% CI	Mean age (wt)	95% CI
Female	1488	51	106	6.6	5.2–8.0	16.4	15.3–17.4
Male	1533	49	63	4.4	3.2–5.6	17.0	15.4–18.7
Total	3021	100	169	5.5	4.6–6.4	16.7	15.7–17.6

N number of subjects, *wt* weighted, *SA* suicide attempt, *CI* confidence interval

Mean age based on *N* = 130 SA cases with age of first onset information

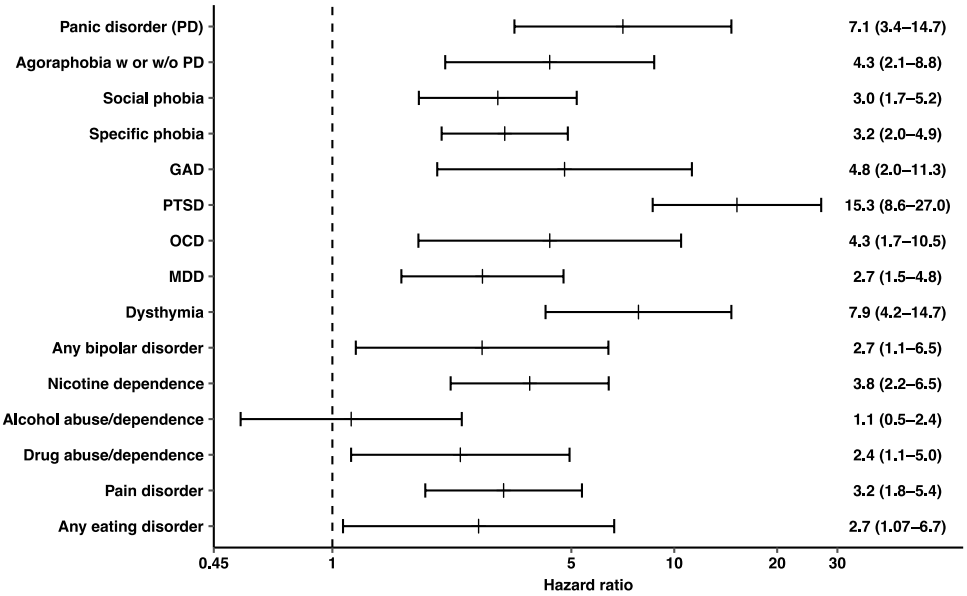

Fig. 1 Temporal associations of prior DSM-IV mental disorder and the subsequent first lifetime suicide attempt, adjusted for sex, age cohort, socioeconomic status, any other prior mental disorder, and any prior separation event. Mean hazard ratios from a Cox regression model with time-dependent covariates are given with 95% confidence intervals in parentheses. The dashed vertical line represents a hazard ratio of 1.0, which means that the risk is elevated whenever the line is not crossed by the lower bound of the confidence interval. Log scaled transformation of horizontal axis. *PD* panic disorder, *GAD* generalized anxiety disorder, *PTSD* posttraumatic stress disorder, *OCD* obsessive–compulsive disorder, *MDD* major depressive disorder

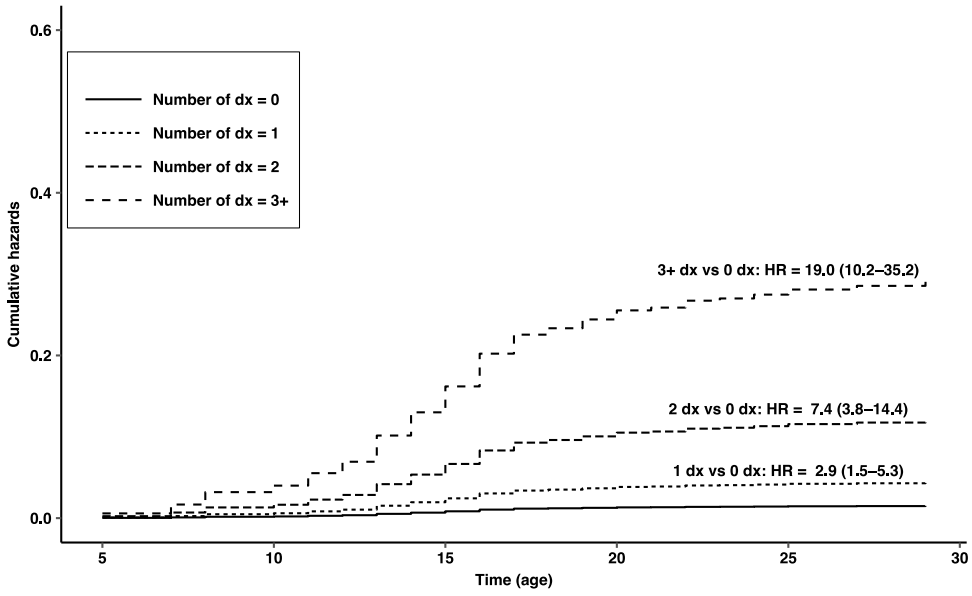

Fig. 2 Cumulative hazard curves by number of DSM-IV mental disorders prior to the first lifetime suicide attempt, based on the reported age of onset and analyzed with the Cox regression model with time-dependent covariates. *Dx* disorders, *HR* hazard ratio; 95% confidence intervals are in parentheses

and MDD. On average, 63% of first SAs could be attributed to any DSM-IV mental disorder in the total sample of adolescents and young adults.

Discussion

Several of our findings deserve to be highlighted: (1) In adjusted analyses, almost all temporally prior DSM-IV mental disorders were positively associated with the subsequent first SA. Highest elevated risks were found for PTSD (> 15-fold), dysthymia and panic disorder (> sevenfold),

Table 2 Population attributable fraction (PAF) and attributable fraction (AF) for the impact of different mental disorders on subsequent first suicide attempt, adjusted for covariates, based on results of the Cox regression model with time-dependent covariates

DSM-IV mental disorder	*N*	AF	95% CI	PAF	95% CI
Panic disorder	2940	85.9	67.4–93.9	7.3	1.1–14.4
Agoraphobia w or w/o PD	2936	76.9	48.2–89.7	8.0	1.8–15.4
Social phobia	2938	67.2	39.7–82.2	14.8	4.9–26.0
Specific phobia	2920	68.7	49.0–80.8	31.2	16.8–45.6
GAD	2938	79.1	44.1–92.2	7.1	0.9–14.5
PTSD	2940	93.4	87.4–96.6	11.9	4.5–19.7
OCD	2938	76.9	36.3–91.6	4.7	0.2–10.5
MDD	2939	63.6	32.0–80.6	11.5	3.0–21.5
Dysthymia	2938	87.3	73.9–93.8	12.4	5.1–20.2
Any bipolar disorder	2940	63.5	3.5–86.3	4.8	−0.1–12.2
Nicotine dependence	2934	73.5	51.3–85.6	22.7	10.4–35.4
Alcohol abuse/ dependence	2932	11.9	−106.4–62.5	1.5	−5.4–13.0
Drug abuse/dependence	2939	57.8	2.0–81.8	4.9	0.0–12.0
Pain disorder	2938	68.4	42.2–82.8	12.4	3.8–22.4
Any eating disorder	2938	62.6	−6.1–86.9	3.3	−0.1–8.9
Any DSM-IV disorder	2940	81.8	68.3–89.6	63.3	46.8–77.3

N number of subjects, *AF* attributable fraction, *PAF* population attributable fraction, *CI* confidence interval, *PD* panic disorder, *GAD* generalized anxiety disorder, *PTSD* posttraumatic stress disorder, *OCD* obsessive–compulsive disorder, *MDD* major depressive disorder

and GAD as well as OCD (each > fourfold). (2) Among the comorbidity categories of no prior mental disorder, 1, 2, and 3 or more prior disorders, on average each increasing unit was positively associated with the subsequent first SA (> eightfold). Risk elevations were threefold for 1 disorder, sevenfold for 2 disorders, and 19-fold for 3 or more disorders. (3) At the minimum, more than 50% of first SAs were preventable in the exposed group if the disorder had been causal and prevented. At the maximum, over 90% of first SAs were preventable in the PTSD group. (4) Half of all DSM-IV disorders each accounted for more than 11% of first SAs in the total sample. Total incidence reductions of first SA by more than 20% and even over 30% were possible, if nicotine dependence or specific phobia had been prevented, respectively.

Our results are best compared to those of the NCS-A study by Nock et al. [17] and the MAMHS study by Borges et al. [16]. They also used a representative sample of adolescents and young adults, included a wide range of specific DSM-IV mental disorders as risk factors for the subsequent first SA, and analyzed data with a discrete-time survival model based on retrospective AOO information. Our 5.5% overall cumulative lifetime incidence of SA is somewhat higher than the prevalence of 4.1% found by Nock et al. [17] and the prevalence of 3.1% found by Borges et al. [16]. A possible explanation for our higher estimate might be that our sample included older individuals up to age 34 and that we used prospective-longitudinal data for the estimation of the prevalence [34]. In good agreement with Nock et al. [17] and Borges et al. [16] as well as with our earlier analyses [10, 18], we observed a higher cumulative incidence of SA in women than in men.

In our study, PTSD strongly elevated the risk for a subsequent first SA. In the NCS-A data [17], PTSD was the only anxiety disorder with an elevated risk, whereas in the MAMHS data [16] PTSD was not predictive. When turning to representative community studies of adults, PTSD is also inconsistently reported to elevate the risk for (first onset) SA [for a review see 35]. In a recent community study of adults in South Africa, prior PTSD was found to be the strongest predictor for the subsequent first SA (adjusted for other DSM-IV mental disorders) [36]. In a cross-national analysis of representative adult samples from 21 countries around the globe, prior PTSD strongly elevated the risk for the subsequent first SA in both developed and developing countries [37], thus suggesting that ours was not a chance finding. Panic disorder was predictive in our study but not in either the NCS-A study [17] or the MAMHS study [16]. Among the anxiety disorders evaluated in the CHDS study [13], panic disorder elevated the risk for an SA in subjects 16–25 years old. Of the three anxiety disorders, it was the only one that remained significant across several sets of confounders, for example, other disorders and life stress. In a review on anxiety disorders and risk for suicide, Sareen [38] concluded that especially PTSD and panic disorder have often been found to be independent risk factors for SA, which is supported by our results for adolescents and young adults.

Among the affective disorders, the risk estimate of dysthymia was relatively large, compared to MDD and any bipolar disorder. In the MAMHS study [16], dysthymia had the highest risk estimate of all disorders analyzed. In the NCS-A data [17], the combined group of MDD/dysthymia elevated the risk for the first SA, yet the compound diagnosis prevents direct comparison to our results. In the CHDS data [12], affective disorders were reported as a compound diagnosis elevating the risk for an SA in 15–21 year olds, also preventing further comparisons to our results.

DSM-IV substance disorders performed relatively weakly in predicting the subsequent first onset of SA. In our study, drug abuse/dependence was predictive, yet alcohol abuse/dependence was not. In the NCS-A study [17], no substance disorder reached the significance level and in the MAMHS study [16] only drug abuse was predictive. However, nicotine dependence yielded a considerable risk estimate in our study, requiring an explanation. Aside from our own

previous results where both non-dependent regular smokers and dependent smokers at baseline were at higher risk for their first future SA [15], we found one other study of young people that took the temporal sequence of tobacco use and SA into account. Using the MAMHS data of 12- to 17-year-old Mexicans, Miller et al. [39] reported elevated risks for the first SA along all different tobacco-related habits [i.e., (irregular) use, weekly use, daily use, dependence] and along all different sets of confounders. In the CHDS study, Boden et al. [40] reported associations between the number of cigarettes per day before the ages 16, 18, and 21 years and the subsequent (not first) SA between these ages. However, the temporal associations pooled over the 3 assessment periods attenuated to non-significance when controlled for non-observed fixed factors, suggesting that even more than 20 cigarettes per day was not an independent risk factor for subsequent SA. This contradiction may be explained by the smaller sample size (between 935 and 983) and the differences in the two data analyses.

Discussing our findings in light of results from adult population samples, all our significant associations have also been observed in adult samples [e.g., 37, 38, 41]. Our results extend these findings insofar as they impressively show that even in a young community sample, empirical evidence of temporal associations exists, adjusting for various confounders.

Several studies [42] have suggested that risk for subsequent SAs seems to be comparable across different mental disorders. Hoertel et al. [41], therefore, investigated in a large population sample whether this observed elevated risk for SA could be due to a general underlying psychopathology dimension. Using structural equation modeling, this group showed that effects of mental disorders on risk of SAs seem to occur through an underlying common general psychopathology dimension. On the other hand, Nock et al. [37], who also found associations between virtually all included mental disorders and subsequent SA in the World Health Organization World Mental Health Survey, demonstrated that the point risk estimates, vary remarkably by type of disorder. Given this variation in estimates, Nock et al. [37] interpreted their findings as arguing against an underlying common psychopathology dimension. Our results are in accordance with Nock et al.'s [37], since our risk estimates also differ remarkably across different disorders. Whether the associations between a variety of prior mental disorders and subsequent SAs are a result of a common psychopathological dimension is beyond the scope of our paper. This surely interesting question should be addressed in future analyses.

We also found that the number of DSM-IV mental disorders was a risk factor for the first SA in our study. Having 1, 2, or 3 or more mental disorders all elevated the risk for a subsequent first SA. This finding is in relatively good agreement with other community surveys [e.g., 43, 44]. Comparable to earlier EDSP analyses based on cross-sectional baseline data [10], our data even support a clear dose–response relationship between number of comorbid mental disorders and the first SA.

AFs have not been estimated so far in studies evaluating the risk of mental disorders for the first SA. It certainly seems impressive that any of the mental disorders that elevated the risk for the subsequent first SA bear the potential of reducing this tragic outcome by at least 57% (drug abuse/dependence) and up to 93% (PTSD). Moreover, anxiety disorders seem to be a very important intervention target in the subpopulation of adolescents and young adults, because not only is the AOO of anxiety disorders earlier compared to other groups of mental disorders but also SA might be prevented to a considerable extent.

PAFs in conjunction with our study characteristics were reported in the CHDS study [13]. Anxiety disorders accounted for 7.5% of SAs in the total birth cohort sample of individuals aged 16–25 years. In our study, PAFs for single anxiety disorders ranged from 4.7 (OCD) to over 30% (specific phobia). Unfortunately, the results of the CHDS study [13] and the results of our study cannot be compared directly due to the use of the disorder group (anxiety) instead of single anxiety disorders in the former. When turning to adult community samples that reported associations between prior mental disorders and the subsequent first SA we found only one study that reported PAFs. Bernal et al. [45] reported that MDD accounted for 28% of first SAs in a sample of more than 21,000 adults (aged 18 years and over) across 6 European countries. GAD accounted for 4% of first SAs. The PAF of 28% is almost 3 times as much as our result of 11.5% for MDD. Most likely this is due to differences in age and other methodological characteristics. In other studies with adult community samples, PAFs were reported not for single disorders but for disorder groups only (e.g., mood disorders, any mental disorder; [46–48]), were based on results that did not take into account the temporal order of risk factor and outcome [49–51], or did not point to the subsequent first SA [41].

Our study points out how essential it is to consider the context of SAs, in terms of age, sex, and psychopathology. When considering SAs or suicidal behavior in general, heuristics do more harm than good; that is, inquiring about suicidal phenomena only if the (young) patient reports depressive symptoms is important, yet not inquiring otherwise might often be fatal. Furthermore, a relatively rare phenomenon such as suicide and all of its cognitive and behavioral derivatives should be approached on the population level with much more determination, as discussed by Knox et al. [52]. The determination to prevent SAs on the population level of course is synonymous with major efforts professionally, politically, and monetarily. Our study might

serve to guide the selection of promising prevention targets for the general population of adolescents and young adults. After all, "it seems likely that earlier identification and earlier symptomatic relief is an important component of the prevention and treatment of youth suicidal behavior" [53].

The present study has several methodological strengths. First, we used a representative community sample of adolescents and young adults with an observation period that fully included the high-risk period of both the first onset of mental disorders and the first SA. Second, our analyses are strengthened by the inclusion of all individuals who reported an SA rather than individuals who received medical attention, and by the inclusion of a comprehensive set of predictor diagnoses that allowed us to evaluate a broad range of mental disorders. Third, we used an interviewer-administered standardized interview.

Our study also has several limitations. First, our analyses were based on self-reported data, which are always prone to recall bias. However, this bias may have been lessened by our longitudinal study design of 3 follow-up assessments over a 5- to 10-year period, which decreased the time frame for retrospective assessments. Second, several disorders known to be associated with suicidal behavior were not analyzed in our study (e.g., schizophrenia, personality disorders), because they were not assessed. Third, the assessment of SA at T0 and T1 was limited to individuals who reported depressive symptoms over at least 2 weeks. Although this might have led to a more conservative prevalence estimate initially, the later follow-up waves assessed lifetime SA in all subjects. Fourth, the AFs and PAFs are preliminary quantitative appraisals of the impact of mental disorders on the risk for onset of a first SA. The preliminary status and the inherent assumption of causality warrant caution in interpreting the results.

These limitations notwithstanding, our study provides valuable new information about mental disorders and SA in adolescence and young adulthood. From a public health perspective, our AFs suggest that the prevention of mental disorders among adolescents and young adults could substantially reduce the incidence of SAs. Our results also clearly demonstrate the importance of considering not only depression but also the full range of mental disorders when evaluating the risk for suicidal behavior. Given the strong associations between comorbidity and SA, clinicians should always conduct a suicide risk assessment among patients presenting with multiple mental disorders. Finally, our results point to the need for future work to increase our understanding of the increased risk for suicidal behaviors during adolescence and of the causal pathways linking mental disorders to suicidal behaviors.

Acknowledgements This work is part of the Early Developmental Stages of Psychopathology (EDSP) Study and is funded by the German Federal Ministry of Education and Research (BMBF) project nos. 01EB9405/6, 01EB 9901/6, EB01016200, 01EB0140, and 01EB0440. Part of the field work and analyses were also additionally supported by grants from the Deutsche Forschungsgemeinschaft (DFG) LA1148/1-1, WI2246/1-1, WI 709/7-1 and WI 709/8-1. Principal investigators are Dr. Hans-Ulrich Wittchen and Dr. Roselind Lieb, who take responsibility for the integrity of the study data. Core staff members of the EDSP group are Dr. Kirsten von Sydow, Dr. Gabriele Lachner, Dr. Axel Perkonigg, Dr. Peter Schuster, Dr. Michael Höfler, Dipl.-Psych. Holger Sonntag, Dr. Tanja Brückl, Dipl.-Psych. Elzbieta Garczynski, Dr. Barbara Isensee, Dr. Agnes Nocon, Dr. Chris Nelson, Dipl.-Inf. Hildegard Pfister, Dr. Victoria Reed, Dipl.-Soz. Barbara Spiegel, Dr. Andrea Schreier, Dr. Ursula Wunderlich, Dr. Petra Zimmermann, Dr. Katja Beesdo-Baum, Dr. Antje Bittner, Dr. Silke Behrendt, and Dr. Susanne Knappe. Scientific advisors are Dr. Jules Angst (Zurich), Dr. Jürgen Margraf (Basel), Dr. Günther Esser (Potsdam), Dr. Kathleen Merikangas (NIMH, Bethesda), Dr. Ron Kessler (Harvard, Boston) and Dr. Jim van Os (Maastricht). Marcel Miché was funded by the Swiss National Science Foundation (SNSF) Grant 100014_149524/1. Katja Beesdo-Baum holds a research professorship funded by the BMBF (01ER1303, 01ER1703).

Compliance with ethical standards

Conflict of interest The authors declare they have no conflict of interests.

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Appendix B (Manuscript 2)

Miché, M., Hofer, P. D., Voss, C., Meyer, A. H., Gloster, A. T., Beesdo-Baum, K., Wittchen, H.-U. & Lieb, R. (2018). *Specific traumatic events elevate the risk of a suicide attempt in a 10-year longitudinal community study on adolescents and young adults.* Manuscript submitted for publication.

Specific traumatic events elevate the risk of a suicide attempt in a 10-year longitudinal community study on adolescents and young adults

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Acknowledgments

This work is part of the Early Developmental Stages of Psychopathology (EDSP) study and is funded by the German Federal Ministry of Education and Research (BMBF) project nos. 01EB9405/6, 01EB9901/6, EB01016200, 01EB0140, and 01EB0440. Part of the field work and analyses were also additionally supported by Deutsche Forschungsgemeinschaft (DFG) grants LA1148/1-1, WI2246/1-1, WI 709/7-1, and WI 709/8-1. Principal investigators are Dr. Hans-Ulrich Wittchen and Dr. Roselind Lieb, who take responsibility for the integrity of the study data. Core staff members of the EDSP group are Dr. Kirsten von Sydow, Dr. Gabriele Lachner, Dr. Axel Perkonigg, Dr. Peter Schuster, Dr. Michael Höfler, Dipl.-Psych. Holger Sonntag, Dr. Tanja Brückl, Dipl.-Psych. Elzbieta Garczynski, Dr. Barbara Isensee, Dr. Agnes Nocon, Dr. Chris Nelson, Dipl.-Inf. Hildegard Pfister, Dr. Victoria Reed, Dipl.-Soz. Barbara Spiegel, Dr. Andrea Schreier, Dr. Ursula Wunderlich, Dr. Petra Zimmermann, Dr. Katja Beesdo-Baum, Dr. Antje Bittner, Dr. Silke Behrendt, and Dr. Susanne Knappe. Scientific advisors are Dr. Jules Angst (Zurich), Dr. Jürgen Margraf (Basel), Dr. Günther Esser (Potsdam), Dr. Kathleen Merikangas (NIMH, Bethesda), Dr. Ron Kessler (Harvard University, Boston), and Dr. Jim van Os (Maastricht University).

Dr. Katja Beesdo-Baum and Catharina Voss are currently funded by the BMBF (project nos. 01ER1303, 01ER1703).

Abstract

Background. Traumatic events (TEs) have been associated with suicide attempts (SAs). However, the empirical status of some TEs is inconclusive. This also concerns community adolescents and young adults, known to be a high-risk group for SAs. We examined associations between (a) a range of prior TEs (physical attack, rape/sexual abuse, serious accident, and witnessing somebody else experiencing a TE) and a subsequent SA, and (b) the number of prior TEs and an SA, and (c) we estimated attributable proportions of SAs, in relation to each TE.

Method. Over a 10-year period the Early Developmental Stages of Psychopathology (EDSP) study prospectively assessed community members, aged 14–24 years at baseline. Starting with 3021 subjects, each individual was assessed up to four times. Assessment was based on the Munich-Composite International Diagnostic Interview. Temporal associations were estimated using the Cox model with time-dependent covariates. Attributable proportions were based on the results of the Cox models.

Results. All four TEs elevated the risk for a subsequent SA, adjusting for confounders. Highest risk was found for the combined TE rape/sexual abuse. Results showed that 56–90% of SAs could be attributed to TEs in the exposed group; on the population level, attributable proportions ranged between 6.9% and 23.5%.

Conclusions. Different TEs have been shown to elevate the risk of an SA in a young community sample. Our results suggest that both health professionals and health policy decision makers consider specific TEs and the number of prior TEs as risk factors for SAs.

Keywords: suicide attempt, adolescents and young adults, traumatic event, community sample, prospective design, attributable fraction

Introduction

Reducing suicide rates has long been an important goal [1]. Unfortunately, despite 50 years of research, that goal is far from being met, as global suicide records indicate [2]. Previous suicide attempts (SAs) have been consistently reported as being "by far" the strongest risk factor for suicide and suicide reattempts [1]. Another consistent finding is that age 15–29 years represents the so-called high-risk period for the first lifetime SA [1]. Therefore, reducing SA rates might help reduce suicide rates, not only but especially in adolescents and young adults. To this end, identifying risk factors for SA in this age group is warranted. Past research has generated a long list of such factors, some more conclusive than others. Traumatic events (TEs) belong to the inconclusive set of purported risk factors (for recent and current reviews and meta-analyses see [3–9]). Possible reasons for the inconclusive results include differences in sample size (insufficient power), sample origin (community vs. selective), study design (cross-sectional vs. longitudinal), and the set of confounders, as well as heterogeneous measurements of both TEs and SAs.

Of all the different TEs it is childhood/adolescent sexual abuse and physical abuse that have most often been reported to increase the risk of an SA (e.g., [10–13]). Also the number of experienced TEs has consistently been reported to increase the risk of an SA among the young (see, e.g., [5, 11, 14, 15]). With respect to two other TEs, serious accidents and witnessed trauma, we have found no study reporting serious accidents as a specific risk factor for SA in a *young* community sample. In a 5-year follow-up prospective study, Nrugham et al. [16] reported on witnessing violent life events in a subsample of adolescents and young adults with low versus high scores on a screening instrument for depression. Also in adult community or patient samples the two TEs have very rarely been reported to be associated with SA (for serious or life-threatening accidents see [17]; for witnessed trauma see [11, 17–19]).

Finally, after searching the literature for associations between specific TEs and SAs

among community adolescents and young adults, we found only five studies and two meta-analyses [4, 10–12, 20–22] that determined attributable fractions on the population level. However, such proportions were derived from so-called interpersonal TEs, for instance, sexual abuse, or from TEs with a broad social background, for instance, community violence. Currently there are no such estimates available for other TEs, such as a serious accident or witnessed trauma. Also, when informing health policies, aside from the population level, there is another important level to consider, namely, the group that is exposed to the risk factor of interest. However, after searching the literature, we were not able to find reports of attributable fractions on the exposed-group level in community samples, irrespective of the life period being covered.

Using data from the 10-year prospective-longitudinal Early Developmental Stages of Psychopathology (EDSP) study, we set out

1. to estimate the longitudinal association of specific TEs and subsequent SAs,
2. to estimate the dose–response relationship between the number of prior TEs and subsequent SAs, and
3. to estimate the proportion of SAs that can be attributed to specific TEs, among both the exposed group and the total population.

Method

The EDSP study prospectively observed adolescents and young adults, 14–24 years old at baseline, for up to 10 years. It included four assessments, starting in 1994 (baseline N = 3021, response = 70.9%) and followed by T1 (N = 1228, response = 88%, range 1.2–2.1 years after baseline), T2 (N = 2548, response = 84.3%, range 2.8–4.1 years after baseline), and T3 (N = 2210, response = 73.2%, range = 7.3–10.6 years after baseline). At baseline, T2, and T3, subjects from the full sample were assessed; at T1 a subsample of those 14–17 years old at baseline was assessed. Subjects were selected from the government registries of the greater Munich area, Germany; 14- to 15-year-olds were sampled at twice the probability of 16- to

21-year-olds, whereas 22- to 24-year-olds were sampled at half the probability. Sample weights were generated to account for this sampling scheme. Further details of the EDSP study methods, design, and sample characteristics have been presented elsewhere [23–25]. The EDSP project was reviewed by the Ethics Committee of the Medical Faculty at the Technische Universität Dresden. All participants provided informed consent.

All assessments were made in face-to-face interviews, using the computer-assisted Munich-Composite International Diagnostic Interview (DIA-X/M-CIDI) [26]. The DIA-X/M-CIDI was constructed for the standardized assessment of symptoms, syndromes, and diagnoses of DSM-IV disorders. At baseline the DIA-X/M-CIDI lifetime version was used. At each of the three follow-up assessments the DIA-X/M-CIDI was modified to obtain information about the period between the previous and the current assessment. TEs were assessed at the beginning of the section covering the DSM-IV criteria for post-traumatic stress disorder (PTSD). In particular, eight specified TEs (war experience, physically attacked, raped, sexually abused as a child, natural disasters, serious accidents, imprisoned/taken hostage/kidnapped, and witnessed somebody else experience a TE) and one open category of TE were assessed. In the current report we used only the eight specified TEs that adhere to the DSM-IV PTSD criterion A1. For more detailed information on how TEs were assessed in the EDSP study, see [27]. The DSM-IV disorders were obtained using DIA-X/M-CIDI algorithms. Psychometric quality criteria such as test–retest reliability and validity for the full DIA-X/M-CIDI have been reported elsewhere [28, 29]. Age and sex were assessed in the sociodemographic section of the M-CIDI. SAs were assessed in the depression section of the DIA-X/M-CIDI with the question “Have you ever attempted suicide?” (lifetime version at baseline) and “Have you attempted suicide?” (interval version at follow-up). At baseline and T1 only the individuals who acknowledged having had a period of at least 2 weeks with a continuously depressed mood, low energy, or loss of interest [these are the stem questions for major depressive disorder (MDD)] were asked this question. At T2 and T3 a modification was

introduced in the depression section to ensure that all individuals were asked questions regarding SA since the last assessment, irrespective of whether the stem questions for MDD were confirmed or denied. Since at baseline and T1 not all individuals were asked about SA, we cannot rule out that in some cases the reported SA at T2 or T3 was not the first lifetime SA.

Data analysis

To analyze longitudinal associations between TEs and SAs, all cases with a baseline SA ($N = 69$) were removed from the overall sample, resulting in $N = 2952$ subjects. Observations were organized according to the four EDSP assessment waves; for example, a subject being assessed for the last time at wave *n* was represented by *n* lines of data. The only exception to that rule was the report of an SA prior to wave *n*, which then reduced the number of lines for that subject accordingly. Thus, TEs being reported after an SA were automatically excluded. TEs were counted when they were reported either prior to or within the same assessment wave as the first reported SA.

Data were weighted by sex, age group, and geographic location at baseline to be representative of the original sampling frame. Analyses were performed using R 3.3.3 [30], including the survey [31] and survival [32] packages. As predictors we used the following TEs: (1) being physically attacked, (2) a variable combining the two TEs rape and sexual abuse as a child, (3) serious accident, and (4) witnessing somebody else experience a TE. Other TEs (war experience, imprisoned/taken hostage/kidnapped, and natural disasters) could not be analyzed separately, due to an insufficient number of cases. However, they were used in analyzing the association between the number of prior TEs and subsequent SAs. Also, each reported TE was counted—that is, multiple occurrences of a single TE category were possible. As outcome we used the dichotomous variable SA. Finally, as both TE and SA prevalence often differ between males and females (for SAs see [33]; for TEs see [34]), in

addition to our main analyses we tested for sex interaction effects.

To analyze the data we used the Cox hazard model with time-dependent covariates. Time units were represented by the assessment waves of the EDSP study. Each subject therefore had a maximum number of four time units, that is, maximally four rows in the long data format. In each Cox model we adjusted for the covariates "any other prior TE" (reported at least one time unit prior to the predictor TE), "any DSM-IV mental disorder" (diagnosed prior to or within the same time unit as the predictor TE), sex, and age cohort (ages 14–17 years vs. 18–24 years at baseline), the latter two covariates being time independent. Using the above-mentioned confounders was suggested both by the literature (e.g., [22]) and by our own previous publications (for sex see [35], and for any DSM-IV mental disorder see [36, 37]).

For the estimation of attributable proportions, we estimated the population attributable fraction (PAF) and the attributable fraction (AF). Both estimates denote the proportion of outcome cases (here: SAs) that would not have occurred if the risk factors (here: TEs) were both causal and had not occurred. The difference between the two estimates is the population they refer to: The PAF refers to the population level, the AF to the group being exposed to the specific risk factor.

For estimating the PAF and its 95% confidence interval (CI) we used a method proposed by Natarjan et al. [38] for complex surveys, which we have used previously and described in an earlier publication [39]. The AF was computed by adapting the method to obtain the PAF, that is, by excluding the multiplier (the cumulative lifetime incidence of TEs among those with an SA) from the formula. To estimate the AF 95% CI we also adapted the PAF method accordingly.

Results

Cumulative lifetime incidence and mean age of first onset of SAs

As already reported in a previous publication [39], the cumulative lifetime incidence

of SA at T3 was 5.5%. Estimates were higher for females (6.6%) than for males (4.4%; odds ratio, OR = 1.5, 95% CI 1.08–2.18).

Cumulated lifetime incidence of specific TEs

Of the 3021 subjects assessed, 513 reported having been physically attacked (16.3%, males 23.8%, females 8.9%, OR = 0.3, 95% CI 0.2–0.4). A total of 139 subjects reported that they had been raped or sexually abused (5.2%, males 0.6%, females 9.6%, OR = 16.8, 95% CI 8.0–35.1). While 399 subjects reported having experienced a serious accident (13.7%, males 17.4%, females 10.0%, OR = 0.5, 95% CI 0.4–0.7), 310 reported having witnessed somebody else experiencing a TE (10.2%, males 14.1%, females 6.3%, OR = 0.4, 95% CI 0.3–0.6). The remaining three TEs, war experience, imprisoned/taken hostage/kidnapped, and natural disasters, were reported by 0.7%, 1.8%, and 0.4%, respectively.

Specific DSM-IV traumatic events as risk factors for an SA

All four TEs we analyzed increased the risk of an SA. As shown in Table 1, rape/sexual abuse had the highest hazard ratio (HR) at 9.6, followed by being physically attacked (HR = 3.8), serious accident (HR = 3.1), and witnessing someone else experiencing a TE (HR = 2.3). Of the four reported TEs there was one significant interaction effect with sex ($HR_{\text{female/male}} = 0.2$, 95% CI 0.04–0.51). Males who reported being raped/sexually abused were at increased risk of a subsequent SA (HR = 69.9, 95% CI 21.8–224.0) compared to females who reported being raped/sexually abused (HR = 5.7, 95% CI 2.8–11.3).

- Table 1 -

Number of DSM-IV traumatic events as a risk factor for an SA

An increase in the number of prior TEs was positively associated with a subsequent SA. Compared to those with no prior TE, one prior TE increased the SA risk by 110% (HR =

2.1, 95% CI 1.2–3.7), two prior TEs led to an increased risk of 120% (HR = 2.2, 95% CI 1.08–4.5), and three or more prior TEs increased the SA risk by 380% (HR = 4.8, 95% CI 2.5–9.2). Overall a linear trend was observed (HR = 2.9, 95% CI 1.8–4.6); that is, on average the risk of a subsequent SA linearly increased with each increasing number of TEs. All analyses were adjusted for sex, age cohort, and any prior or concurrent DSM-IV mental disorder.

Attributable fractions

As can be seen in Table 1, the AF ranged between 89.6% (rape/sexual abuse) and 56% (witnessing someone else experiencing a TE); the PAF ranged between 23.5% (being physically attacked) and 6.9% (witnessing someone else experiencing a TE).

Discussion

We reported on four specific TEs, which all increased the risk of an SA in a community sample of adolescents and young adults. Also, the higher the number of prior TEs the higher the risk of an SA. The analysis of attributable proportions showed that, among subjects exposed to a TE, between 56% and 90% of SAs were attributable to the respective TE. On the population level, between 6.9% and 23.5% were attributable to the respective TE.

Our result regarding the TE of being physically attacked (HR = 3.8) is in line with previous work using large (international) community samples of both adults and adolescents, for example, Afifi et al. [11], Bruffaerts et al. [40], and Gomez et al. [13], who reported adjusted ORs for physical abuse between 2.4 (adults) and 5.8 (adolescents). Equally, our result regarding rape/sexual abuse (HR = 9.6) is in line with previous work, [7, 13, 40] where ORs ranged between 3.8 in adult samples and 9.8 in samples of adolescents/young adults. However, we are not aware of another study reporting an interaction effect between this TE and sex. Fergusson et al. [20] tested an interaction effect, which was not significant, between

childhood sexual abuse and sex for a 30-year longitudinal birth cohort study of over 900 adolescents and young adults. Our interaction effect suggested males are at higher risk of an SA than females if they have experienced rape or sexual abuse. Though speculative, this finding might suggest that males and females cope differently with this highly disturbing experience. Notably, a similar pattern (higher risk estimates and larger CIs in males than in females) can be seen in Molnar et al. [21], who reported risk estimates of rape and sexual molestation prior to age 18 for males and females, separately, due to multiple significant interaction terms in their data.

The findings of many previous studies that the number of prior TEs is a risk factor for a subsequent SA (e.g., [11, 15, 40, 41]) is confirmed by our study, with risk estimates of 2.6 and 5.5 well within the previously reported range of 2.3 to 6.4 (adults) and 2.3 to 5.4 (adolescents). Notably, Borges et al.'s [41] reported risk estimates for exactly one, two, and three or more TEs in a representative sample of 3005 Mexican adolescents are remarkably similar to our results, with exactly one and exactly two TEs being almost identical to one another (2.3 and 2.4 vs. our result of 2.1 and 2.2), and with three or more TEs being higher (5.4 vs. our result of 4.8).

The TE serious accident has never been reported as a specific risk factor for SA in a community sample of adolescents and young adults. Instead, whenever it was assessed, it was part of a composite variable [41] or subsumed in the number of TEs [15]. However, this particular TE might be of considerable importance. In a study of survivors of life-threatening accidents, Grossman et al. [42] reported that 15- to 24-year-olds had the highest accident rate (60%), compared to 25- to 44-year olds (29%) and to those older than 45 years (12%), and traffic accidents, one type of life-threating accident, are the leading cause of death for 15- to 29-year-olds [1]. Together, this suggests that there might be a considerable number of accident survivors in this age group who, if not sufficiently supported after such an event, might attempt suicide some time later. Our results show that survivors of serious accidents

had more than threefold the risk of an SA compared to their counterparts who had not had a serious accident.

As for the TE of having witnessed somebody else experiencing a TE, we found just one study, by Nrugham et al. [16], that followed up on a subsample of 252 "mainly depressed" adolescents and young adults for 5 years. The authors reported no association with a subsequent SA. Again, as with serious accidents, witnessing a TE yielded a significant risk estimate in our study, with adolescents and young adults having a more than twofold risk of an SA compared with the nonexposed group. The Nrugham et al. [16] study cannot be compared to our study, as they are too different, for example, in sample size (252 vs. 3021), sample origin (screened depressive vs. community), and measurement of the TEs (constructed with interviewer's scores vs. direct self-report by study subjects). We found two studies of interest when we turned to adult studies. Afifi et al. [11] reported the witnessing of domestic violence to be a risk factor for SA in women (1.8-fold) yet not in men, using a representative U.S. sample of almost 5700 adults. Other than childhood abuse (sexual and physical), witnessing domestic violence was the only TE reported in the study. Choi et al. [18] found domestic violence not to be a risk factor for SA in an adult U.S. sample, using a case-control design. Our result of a 1.8-fold risk of an SA in adolescents and young adults in the community therefore awaits replication by other studies.

Our estimates of attributable proportions indicate potential prevention effects, that is, prevention of the outcome as a consequence of preventing the causal risk factor beforehand. Of course we cannot infer causality from an observational study. Nonetheless, the two measures, AF and PAF, implicitly assume causality, thereby offering an impression of potential prevention effects, that is, the proportion of SAs that might be prevented if the TE, for example, child sexual abuse [43], sexual assault [44], or child maltreatment [45], was prevented beforehand.

On the level of the target population of our study, we estimated AFs between 6.9%

and 23.5%. The two highest estimates of 23.5% for being physically attacked and 19.7% for rape/sexual abuse are comparable to other PAFs reported in the literature, being between 9% and 25% (e.g., [10, 11, 18, 20, 21]). Our results being at the upper end of the range can be explained both with differing rates of the respective TEs, which influence the PAF result, and with restrictions concerning the life period to which the TE item refers (childhood vs. childhood/adolescence/young adulthood). Our PAF estimate of 14.2% for the TE serious accident is preliminary and awaits replication. The PAF for the TE witnessing someone else experiencing a TE in our study (6.9%) can be compared only indirectly with the results from Afifi et al. [11], who reported a possible 10% reduction in SAs among adult females if witnessing domestic violence had been prevented from ever occurring and it being causal for the SA. The PAF was not reported for adult males, as their risk estimate did not reach significance.

On the level of those being exposed to a specific TE, AFs ranged between 56% and 90%. Although there are no other AFs in the literature to which we could compare our results, we want to emphasize the use of them at this point. This emphasis is also supported by a recent review by Zalsman et al. [46] on suicide prevention strategies, which recommends future suicide prevention research "focus on specific targeted populations," for example, populations that are at increased risk of being exposed to traumatic experiences. The recommendation by Zalsman et al. [46] also stressed "that each specific risk group might need a tailored preventive approach," which might also be true of TEs, in terms of type of event, duration of exposure, age and sex of the trauma victim, and sociocultural background [47].

Taken together, our results support the view that specific TEs should be put on the list of potent risk factors for SA (see also Bruffaerts et al. [48]). Additionally, when considering TEs as risk factors for SA, there is consistent evidence, including from our study, that the number of TEs can be regarded as a risk factor for subsequent SA in its own right.

The present study has the following limitations. First, for some subjects the first

reported SA might not have been the first lifetime SA. Since we do not know the exact number of such subjects, we could not adjust our analyses for a previous SA. Second, we were not able to estimate the effect of three of eight TEs on the risk of SAs, due to an insufficient number of cases, and third, we had to combine the two TEs, rape and sexual abuse, for the same reason. Fourth, the AFs and PAFs are estimates, which inherently contain causal assumptions, which is why they must be interpreted with caution.

The strengths of this study are the following. First, we used data that were prospectively assessed for a period of 10 years, with the vast majority (> 70%) being assessed up to and including the last wave of the study. Second, we adjusted our analyses for sex, age cohort, any other prior TE, and any mental disorder being present either prior to or within the same assessment wave as the incident TE used as predictor. Third, in addition to the two TEs being reported most frequently in the literature (sexual abuse and physical abuse), we reported two TEs that have either never (serious accidents) or just once (witnessed trauma) been reported for community adolescents and young adults. Fourth, we reported PAFs for a young community sample, which are reported rarely for some TEs and which have never been reported for serious accidents. Fifth, to the best of our knowledge, we have been the first to report AFs for a young community sample in the context of specific TEs and SA.

Conflict of Interest

The authors declare they have no conflict of interests.

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Table 1 Risk associations between a prior traumatic event and a subsequent suicide attempt, adjusted for sex, age cohort, any other prior traumatic event, and any prior/concurrent DSM-IV mental disorder. Attributable fraction and population attributable fraction, each with 95% CI

Traumatic Event	**HR**	**95% CI**	**AF**	**95% CI**	**PAF**	**95% CI**
Physically attacked	3.8	(2.3–6.2)	73.5	(53.4–85.0)	23.5	(10.8–37.2)
Rape/sexual abuse	9.6	(4.7–19.3)	89.6	(76.8–95.3)	19.7	(8.8–31.1)
Serious accident	3.1	(1.7–5.7)	67.9	(36.5–83.8)	14.2	(3.7–26.6)
Witnessed trauma	2.3	(1.1–4.5)	56.0	(5.6–79.6)	6.9	(0.2–16.2)

HR Hazard ratio; *CI* confidence interval; *AF* attributable fraction; *PAF* population attributable fraction

Appendix C (Manuscript 3)

Miché, M., Studerus, E., Meyer, A. H., Gloster, A. T., Beesdo-Baum, K., Wittchen, H.-U. & Lieb, R. (2018). *Suicide attempt prediction in community adolescents and young adults: Comparing a generalized linear model with machine learning models.* Manuscript in preparation.

Suicide attempt prediction in community adolescents and young adults: Comparing the generalized linear model with machine learning models

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Acknowledgments

This work is part of the Early Developmental Stages of Psychopathology (EDSP) study and is funded by the German Federal Ministry of Education and Research (BMBF) project nos. 01EB9405/6, 01EB9901/6, EB01016200, 01EB0140, and 01EB0440. Part of the field work and analyses were also additionally supported by Deutsche Forschungsgemeinschaft (DFG) grants LA1148/1-1, WI2246/1-1, WI 709/7-1, and WI 709/8-1. Principal investigators are Dr. Hans-Ulrich Wittchen and Dr. Roselind Lieb, who take responsibility for the integrity of the study data. Core staff members of the EDSP group are Dr. Kirsten von Sydow, Dr. Gabriele Lachner, Dr. Axel Perkonigg, Dr. Peter Schuster, Dr. Michael Höfler, Dipl.-Psych. Holger Sonntag, Dr. Tanja Brückl, Dipl.-Psych. Elzbieta Garczynski, Dr. Barbara Isensee, Dr. Agnes Nocon, Dr. Chris Nelson, Dipl.-Inf. Hildegard Pfister, Dr. Victoria Reed, Dipl.-Soz. Barbara Spiegel, Dr. Andrea Schreier, Dr. Ursula Wunderlich, Dr. Petra Zimmermann, Dr. Katja Beesdo-Baum, Dr. Antje Bittner, Dr. Silke Behrendt, and Dr. Susanne Knappe. Scientific advisors are Dr. Jules Angst (Zurich), Dr. Jürgen Margraf (Basel), Dr. Günther Esser (Potsdam), Dr. Kathleen Merikangas (NIMH, Bethesda), Dr. Ron Kessler (Harvard University, Boston), and Dr. Jim van Os (Maastricht University).

Dr. Katja Beesdo-Baum is currently funded by the BMBF (project nos. 01ER1303, 01ER1703).

Abstract

Background. The use of Machine Learning (ML) algorithms in the research of suicidality has been recommended of late. The aim is to improve the prediction of suicidal outcomes, which currently is poor, as shown in a recent meta-analysis. We compared three ML algorithms, Lasso, Ridge, and Random Forest, and the generalized linear model (GLM), in predicting a future suicide attempt (SA) in a community sample of adolescents and young adults.

Method. The Early Developmental Stages of Psychopathology (EDSP) study prospectively assessed, over the course of 10 years, adolescents and young adults, aged 14–24 years at baseline. Out of a total of 3021 subjects, 2797 subjects were eligible for prospective analyses, because they participated in at least one of the three follow-up assessments. Sixteen baseline predictors, all of which selected a priori according to the literature, were used to predict follow-up SAs. As the main measure of predictive performance we used the area under the curve (AUC).

Results. The AUCs of the four predictive models, GLM, Lasso, Ridge, and Random Forest, were comparable to one another, ranging between 0.818 and 0.833.

Conclusions. All predictive models performed very good in their ability to distinguish between a future SA case and a non-SA case in community adolescents and young adults. Other studies, that apply ML to predict future SAs, using young community samples and a strictly prospective study design, are currently lacking.

Keywords: Machine learning, future suicide attempt, prediction, adolescents and young adults, community sample, prospective design

Introduction

Suicide research has discovered many correlates as well as risk factors for suicide, suicide attempt (SA) and suicide ideation. Nonetheless, according to a recent meta-analysis, our ability to accurately predict SAs is not much better than chance prediction [1]. In an endeavor to increase our ability to predict SAs, machine learning (ML) algorithms have been recommended of late [1–3], as opposed to conventional prediction models, e.g. the generalized linear model (GLM). One argument in support of ML points out that conventional prediction models are (too) simplistic, e.g. they assume nothing but linear associations between predictors and outcome, while in ML there are several models available that can flexibly detect both linear and non-linear relationships in the observed data.

In SA research, some studies have already applied ML, demonstrating that our ability to predict SA indeed can be increased above the heuristic category of "bad" prediction accuracy, as proposed by Šimundić [1, 4] [for SA see [3, 5–11]; for suicidal behavior (suicide and SA combined) see [12]]. Using ML, Walsh et al. [3] achieved very good prediction accuracy for a future SA among adult patients with a claim code of self-injury, using electronic health record (EHR) data. Comparing ML-based with GLM-based prediction accuracy, ML yielded higher results, i.e. ML was better in correctly discriminating SA cases from non-SA cases. Simon et al. [5] also reported very good prediction estimates of future SA cases, using EHR data of almost three million outpatients, aged 13 or older. Results of a conventional regression model were not reported. Barak-Corren et al. [12] reported good prediction, using ML to predict cases of future suicidal behavior (combined SA and suicide) in 1.7 million patients (ages 10 to 90), based on EHR data. Results of a conventional regression model were not reported. Passos et al. [9] applied three ML algorithms in a cross-sectional study of 144 adult patients with mood disorders, achieving prediction accuracies that ranged between sufficient and good. In two further cross-sectional studies, ML-based prediction ranged between sufficient and (very) good, one study using 345 adult

schizophrenia patients to predict a past lifetime SA [10], the other study using 408 patients (ages 14 to 72) with mood, schizophrenia, and personality disorders, predicting either a recent or a remote SA [11]. Results of a conventional regression model were not reported in any of these three studies [9–11]. Another cross-sectional study reported excellent prediction accuracy of SA, applying ML to fMRI data to predict the outcome in 34 participants (17 suicide ideators and 17 controls; mean age 22) [6]. A conventional regression model was not applied, because, according to the authors of that study, such a model cannot capture the multivariate nature of fMRI data. Furthermore, two epidemiologic studies also reported excellent prediction accuracies of SA, with Nock et al. [13] achieving it in a representative sample of almost 30000 US Army soldiers, by using a Cox survival model, and Walsh et al. [14] achieving it in more than 30000 hospitalized adolescents (median age 16 years), using EHR data. While Nock et al. [13] didn't apply ML, Walsh et al. [14] did, reporting that ML clearly outperformed the GLM. Finally, two more cross-sectional studies used ML to predict SA, each using almost 900 adults (primarily inpatients) [7, 8], reporting a measure of prediction accuracy, which cannot directly be compared to the measure either of the recent meta-analysis by Franklin et al. [1], or of any of the above mentioned studies [3, 5, 6, 9–12]. Results of a conventional regression model were presented in addition to the ML results, showing no large differences in either of the two studies [7, 8].

After having reviewed the current literature, we noticed that so far SA prediction accuracy has never been estimated with data from a prospective longitudinal study. Furthermore, none of the samples used so far were representative of the general community. Finally, no study has used ML to predict SAs among adolescents and young adults, who comprise the high-risk group for SA [15], and for whom (15-29 year-olds) suicide is the second leading cause of death [15]. However, all three properties (prospective study design, general community, and young age group) are important, in terms of testing ML approaches to predict future SAs, since, eventually, ML is considered to assist decision makers, e.g.

general practitioners or pediatricians, in assessing the individual risk of a future SA (or suicide) at a time as early as possible in the development of the young individual from the general community.

Therefore, we aimed to empirically assess the prediction accuracy of three ML models and the GLM, using the data of the Early Developmental Stages of Psychopathology (EDSP) study, which prospectively assessed community adolescents and young adults over the course of 10 years. In particular

1. for each model, we estimated several measures, which emphasize different aspects of prediction performance, and
2. for each model, we estimated the relative importance of the single variables, which we used to predict the future SA.

Method

Sample

In the EDSP study, community adolescents and young adults were assessed up to four times between 1995 and 2005. At baseline, participants were between 14 and 24 years of age. The four assessments T0–T3 included an *N* of, respectively, 3021 (T0, response = 70.9%), 1228 (T1, response = 88%, range 1.2–2.1 years after baseline), 2548 (T2, response = 84.3%, range 2.8–4.1 years after baseline), and 2210 (T3, response = 73.2%, range = 7.3–10.6 years after baseline). At baseline, T2, and T3, subjects from the full sample were assessed; at T1 a subsample of those 14–17 years old at baseline was assessed. Subjects were selected from the government registries of the greater Munich area, Germany; 14- to 15-year-olds were sampled at twice the probability of 16- to 21-year-olds, whereas 22- to 24-year-olds were sampled at half the probability. Sample weights were generated to account for this sampling scheme. Further details of the EDSP study methods, design, and sample characteristics have been presented elsewhere [16–18]. The EDSP project was reviewed by the Ethics Committee of the Medical Faculty at the Technische Universität Dresden. All participants provided informed consent.

Selection and assessment of predictors

Based on three considerations, we selected 16 predictors. First, predictors had to be derived a priori from the research literature on suicidality (e.g. 1, 20, 21, 25). Second, predictors had to be selected from the EDSP baseline assessment only, in order to assure the strict temporal order of predictors and the future SA (between T1–T3). Third, in order to obtain robust prediction estimates, we needed to remain close to a ratio of 1:10, i.e. for each predictor to have about 10 outcome cases [22]. Since we observed 137 future SAs, our predictor to outcome ratio was 1:8.

Of the 16 baseline predictors, 10 were assessed with the DIA-X/M-CIDI [23], a fully structured clinical interview for the assessment of syndromes, symptoms, and mental

disorders pertaining to the DSM-IV, along with other various personal information. The DIA-X/M-CIDI has shown good to excellent reliability [24] and validity [25]. The baseline predictors assessed with the DIA-X/M-CIDI, were: Sex, age, education, the number of DSM-IV lifetime mental diagnoses (including panic disorder (PD), agoraphobia with or without PD, social phobia, specific phobia, general anxiety disorder, post-traumatic stress disorder, obsessive compulsive disorder, major depressive disorder (MDD), dysthymia, any bipolar disorder, nicotine dependence, alcohol abuse or dependence, drug abuse or dependence, pain disorder, and any eating disorder), the number of lifetime traumatic events (including war experience, physical attack, natural disaster, serious accident, imprisonment/kept hostage/abduction, witness to someone else experiencing a traumatic event), rape or childhood sexual abuse, parental loss or separation, prior help-seeking for any kind of psychological difficulty, parental psychopathology (assessed via family history information provided by the offspring at baseline; for its criterion related validity, see Lieb et al. [26]. The baseline predictor *prior SA* (lifetime), as well as the outcome *future SA* (follow-up), was assessed in section E of the DIA-X/M-CIDI. At baseline the SA question read: "Have you ever attempted suicide?" At each follow-up (DIA-X/M-CIDI interval versions) it read: "Since our last interview, have you attempted suicide?" At both baseline and T1, only those participants were asked the SA question, if they had confirmed at least one of the MDD stem questions, whereas at both T2 and T3, all participants were asked the SA question.

Further predictors assessed at baseline were: Behavioral inhibition (assessed with the RSRI [27]), subclinical psychotic experiences during the previous seven days (assessed with the SCL-90-R [28]), negative life events in the previous five years (assessed with the Munich Life Event List [29]), daily hassles in the previous 12 months (assessed with the Daily Hassles Scale [30]), whether the participant was living in a rural area (defined as 553 inhabitants per square mile) or in an urban area (defined as 4061 inhabitants per square mile), and subjectively perceived coping efficacy within the next six months (assessed with the German

Scale for Self-Control and Coping Skills [31]; higher scale values denote *lower* perceived coping efficacy).

Data analysis

According to our binary outcome future SA, we chose the GLM as the conventional prediction model, and as ML algorithms, we chose the Lasso regression, the Ridge regression, and the Random Forest model, henceforth being referred to as GLM, Lasso, Ridge, and Random Forest.

All data related procedures were done in R, version 3.3.3 [32]. In the preprocessing of the data we excluded all cases without any follow-up data ($N = 224$), or missing data ($N = 4$), resulting in an N of 2793. The ML models of our choice didn't accept missing data and since there were only four such cases, we didn't see the need to apply imputation methods, assuming that results wouldn't be much different. One of the 16 baseline predictor variables was modified, namely the number of DSM-IV mental disorders, which ranged between zero and nine. After modification, the numeric value 5 represented all participants with five or more baseline diagnoses, because there were relatively few cases that had six or more baseline diagnoses. In our sample there were 137 future SA cases (weighted % = 4.9).

For the application of both the ML algorithms and the conventional GLM, we used the R-package mlr (Machine Learning in R) [33], which is a framework for ML experiments in R. Being a framework, mlr enables researchers to choose among many different ML algorithms, in addition to conventional prediction models like the GLM. This means that once the researcher has learned the logic of the mlr package, he or she won't have to bother with the specific logic of different R-packages, in order to apply the ML algorithm(s), this or that package provides.

R-package mlr and performance measures

The entire procedure up to obtaining the results in mlr consisted of seven steps. First, for our dataset with the binary outcome, future SA, we chose the mlr-category "classification task". Second, we normalized all 16 predictor variables. Third, we selected the performance

measures, according to our study aim of comparing them, i.e. the area under the receiver operating curve (AUC), the Brier-scaled, the true negative rate (TNR), the true positive rate (TPR), and the balanced accuracy (BAC). Akin to presenting several model fit measures in structural equation modeling, performance measures are also best compared, using different measures, each highlighting different aspects of predictive performance. The AUC was our main performance measure. The AUC is a widely used measure of discriminative ability of a predictive model, which summarizes the ratios of the true positive rate (sensitivity) and the false positive rate (1–specificity), across all possible thresholds of predicted probabilities (from 0 to 1), according to which each observed case is assigned to the outcome class of either 0 (non occurrence of the event) or 1 (occurrence of the event). An advantage of the AUC is its insensitivity to imbalanced data, which we deal with whenever the outcome has a very low base rate. The Brier-scaled is a measure of both predictive performance and calibration. Calibration denotes the reliability of a prediction model, which is best described with an example: After having trained a prediction model, an individual x is predicted to attempt a future SA with a probability of, say, 30%. This model is well calibrated, if subsequently in the validation sample SA actually occurred in 30% of people that, in terms of the predictor variables, are similar to the individual x. We used the Brier-scaled instead of the Brier score, because the Brier-scaled is very similar to the Pearson's R^2 statistic [34], i.e. it is much more familiar to the psychologist's immediate understanding. The true negative rate (TNR) is the rate of individuals that were correctly classified as non-outcome cases (no SA), among all who actually were non-outcome cases (TNR = specificity). The true positive rate is the rate of individuals that were correctly classified as outcome cases (SA), among all who actually were outcome cases (TPR = sensitivity). The balanced accuracy (BAC) is the mean of the TNR and the TPR. Therefore, in imbalanced data, the BAC takes into account the often times both low TPR and high TNR. Fourth, for our prediction models we chose the resampling strategy Bootstrapping (with 50 iterations) for the training phase, and 10-fold

repeated cross-validation (each with 10 repetitions), for the validation phase, producing 100 performance estimates for each model. In mlr, this nested resampling procedure, the test phase nested inside the validation phase, shall ensure robust estimates of performance estimates, or, in other words, counteract the possible effect of overfitting (when prediction accuracy in the training data is much better than in the validation data). Fifth, we selected the algorithms for the prediction. Sixth, in the training phase, so-called hyperparmaters (hps) were tuned. In the Lasso and Ridge regression, respectively: The hp "cost" was tuned in the range of 0.05 and 8, in the Random Forest model the hp "mtry" was tuned in the range of 1 and 3; the GLM doesn't have hps. The goal of tuning hps is to improve the prediction performance. However, hps must not be confused with standard model parameters, e.g. the beta coefficients of the GLM. Also, different ML algorithms have neither identical nor equally many hps. The researcher determines for each ML model, both, which hps shall be tuned, and the range of values, within which they shall be tuned. Importantly, the optimal hp value has to be searched and determined anew before each validation phase for each ML model. Finally, the resolution of the tuning space is also determined by the researcher, e.g. a resolution of 10 between the values 0 and 1 is higher/finer grained (0.1, 0.2, …, 1), compared to a resolution of 5 (0.2, 0.4, … 1). We chose a resolution of 10 for our ML models. Seventh, we passed all information of mlr-steps one through six to the mlr-function "benchmark", which estimated the prediction performance for all four models, using the performance measures of our choice (see mlr-step three).

Applied ML algorithms

Both the Lasso and the Ridge regression belong to the family of logistic regression. Apart from the existence of hyperparameters, both the Lasso and the Ridge formula is extended, compared to the GLM formula. This extension determines how predictors with low predictive contribution are penalized. In the Lasso regression, predictors being penalized means that their regression coefficients are set to zero, whereas in the Ridge regression their coefficients

are set to near zero. Random forest models belong to the family of so-called ensemble classifiers. One of its main advantages is its potential to achieve a good predictive performance, compared with other ML algorithms [35]. Each single tree of a random forest model is a hierarchical set of if-then rules, making a single decision tree intuitive and easy to understand for humans. Not relying on the classification result of any such *single* tree, but weighing and then averaging classification over a usually large number of different decision trees, also appeals to human comprehension, as it mimics our tendency not to make a difficult decision based on a single impression, but instead to take different perspectives into account, each perspective with a specific weight attached to it. That way, the overall decision usually is more appropriate, i.e. more likely to be correct [35, 36].

Results

Predictive performance measures

The mean AUC of the GLM, the Lasso, the Ridge, and the Random Forest, respectively, was 0.825, 0.827, 0833, and 0.818. The range of AUCs from the nested resampling procedures for each prediction model can be seen in figure 1. The boxplots of the four prediction models largely overlap one another. The Brier-scaled for the four models, respectively, was 0.186, 0.294, 0.434, and 0.232. The TNR was 0.995, for the three logistic regression models, and 0.997 for the Random Forest. The TPR was 0.216 for the GLM, 0.212 for the Lasso, 0.227 for the Ridge, and 0.171 for the Random Forest. The BAC (mean of TNR and TPR) was 0.606 for the GLM, 0.604 for the Lasso, 0.611 for the Ridge, and 0.584 for the Random Forest. Table 1 shows an overview of all performance measures.

- Figure 1 here -

- Table 1 here -

Variable importance

In the four prediction models, the variable used most often for prediction is prior SA, in the logistic regression models it increases the odds of a future SA by roughly 57% (GLM), 51% (Lasso), and by roughly 47% (Ridge). In the logistic regression models, rank 2 and 3 of the most often used predictors are also equal to one another, education ranking second, with a roughly odds decrease of 50% (GLM), 25% (Lasso), and 28% (Ridge), whereas in the Random Forest model the number of DSM-IV lifetime mental disorders is the second most often used predictor. Prior help-seeking ranks third, with an odds increase of 34% (GLM), 25% (Lasso), and 24% (Ridge). The third rank in the Random Forest is rape/childhood sexual abuse. Overall, in addition to the predictors ranking 1–3, the predictors ranking 4–7 (any

parental mental disorder, parental loss or separation, behavioral inhibition, and number of DSM-IV lifetime diagnoses) among the logistic regression models, GLM, Lasso, and Ridge, are similar to one another in terms of their rank, but they are not similar in rank to the Random Forest. An overview of the predictor importance for each model can be seen in table 2.

- Table 2 here -

Discussion

The three ML models, Lasso, Ridge, and Random Forest, and the GLM all yielded comparable prediction accuracies. When comparing the discriminative ability of our prediction models (AUC ranging between 0.818 and 0.833) with other epidemiological studies, that used ML in the prediction of SA, at face value our results fit into the upper part of the AUC range of 0.65–0.94 across these studies [3, 5, 9–11, 14]. However, we refrain from any further comparisons with these studies, because of the fundamental differences to our study, e.g. in terms of sample type (patients or army soldiers vs. community), sample size, study design (cross-sectional or EHR data vs. prospectively assessed data), and age group (adults vs. adolescents/young adults). Of note, we re-ran the GLM with the same nested resampling setup as our main ML analysis, using only the subset of seven predictors, which were not penalized by the Lasso (β-coefficient = 0), namely, prior SA, education, prior help-seeking, any parental mental disorder, parental loss or separation, behavioral inhibition, and number of lifetime DSM-IV mental disorders. This increased the performance measure AUC from 0.825 to 0.835, i.e. a discriminative performance was achieved, that was not worse than before, despite using less than 50% of the full set of 16 predictors.

Currently there are no other studies that are sufficiently similar to ours, that would allow us to evaluate our results. According to categories of AUC results, our results represent a very good prediction [4]. In terms of Cohen's d, our AUC results can be translated to an effect size of about 1.2 [37]. Unlike the AUC, the Brier-scaled doesn't come with recommended cut-off categories. We can therefore only descriptively note that the Ridge performed best in terms of the Brier-scaled (combination of prediction accuracy and calibration), whereas the other models performed only about three quarters or half as good as the Ridge. Finally, the true negative rate across all models was above 99%, whereas the true positive rate ranged between 17% (Random Forest) and 23% (Ridge). Accordingly, the balanced accuracy (BAC), as the mean of these two rates, is rather low, ranging between 58%

and 61%. This demonstrates the importance of estimating prediction performance with several measures. Although our AUC results are considered a very good prediction [4], on average between 83% (Random Forest) and 77% (Ridge) of those with a future SA were misclassified as non-SA cases, when using the predicted probability threshold of 0.5. However, in suicide or SA risk assessment it is of utmost importance to prevent the type II error, since every false negative risks a (young) human life. Therefore, finding an optimum prediction threshold that might differ from 0.5 is an important issue to consider, when dealing with SA data. When taking the maximum value of the BAC as criterion, our data suggested a threshold between 0.05 and 0.08, thereby increasing the true positive rate (correct classification of SA cases) to a range between 66% and 74%, instead of 17% and 23%. With SA being a very complex phenomenon, it is likely, though, that in other sample types, e.g. patients with anxiety disorders, the optimum prediction threshold might be different than in community samples.

Many ML models are considered to be a black box when it comes to interpreting the importance of the predictors they used most often for prediction. This non-transparency of many ML models is another issue, which needs to be resolved, e.g. by trying to open the black box (e.g. http://mlr-org.github.io/interpretable-machine-learning-iml-and-mlr/). In our study, this issue doesn't concern the logistic regression ML models, Lasso and Ridge, but it concerns the Random Forest model. Nevertheless, it is interesting to note, that prior SA was the most often used predictor across all models, confirming this variable's reputation as supplying the highest predictive power for a subsequent SA [15, 38]. Due to the interpretability issue of the Random Forest model, henceforth we will refer to the logistic regression models only, GLM, Lasso, and Ridge. The second most often used predictor was educational level (see table 2). It confirms the plausibility of this variable as being protective against SA, in that higher educational achievement in adolescence is associated with greater life satisfaction [39]. The third ranking variable, prior psychological help-seeking, is special insofar, as it is not intuitive right away, why it should increase the odds to attempt suicide.

Among several possible reasons for an increased odds, help-seeking can be seen as indicating a greater severity of psychological problem(s) or disorder(s) present at that time [40, 41].

Any scientific field of research by definition is constantly changing. Currently the change in the research of suicidality seems to be particularly pronounced. The recommendation to use ML is part of the newest endeavor to better predict, and hopefully prevent, suicidal behavior. Recommendations, however, are one thing, it's another thing to follow them. On the one hand, recommendations naturally contain (non-statistical) predictions about a better future, as well as enthusiasm to help this future arrive soon. On the other hand, amidst this enthusiasm there are some critical issues, which might easily be overlooked, and which might lead to unexpected disappointments in the future. Therefore, we think that the current phase of change should explicitly be accompanied by the recommendation to not underestimate some critical details, e.g. emphasizing the proper application of ML [22], including ML based predictive modeling, as described by Shmueli [42], into the curriculum of university psychology courses, and stressing that applying ML can make a difference only if data quality is also increased [43], not merely data quantity. Last but not least, it is pivotal for future suicide research to agree upon which (refined) instruments shall be used to measure the hypothesized predictors. After all, high heterogeneity of studies makes it difficult to merge data, in order to benefit from the proclaimed strengths of ML.

We want to mention several strengths of our study. First, to the best of our knowledge it is the first study that used community adolescents and young adults, a group that is known to be the high risk group for the first lifetime SA [15]. Second, to the best of our knowledge we are the first to have applied ML to prospective data, i.e. we used baseline variables to predict a temporally subsequent SA. Third, we adhered to current guidelines of how to apply ML in (psychological) research, e.g. our ratio of the number of predictors and the number of outcome cases of 1:8 is in close agreement with the recommended ratio of 1:10 [22]. The lower this ratio, the more unreliable are the prediction performance estimates. Fourth, we used

predictors that were a priori defined, based on the suicide literature. We assume that this and the EDSP data quality might have lead to the good discriminative ability of the predictive models we applied.

There are also limitations of our study. First, the predictive performance of some ML algorithms depend on the sample size, with larger sample sizes leading to an increased performance result [44]. In that respect our sample size may be considered a weakness. However, other epidemiological studies, that used ML to predict SAs did not report much better results, even though their sample size was up to almost 3 million. Second, despite using prospective data, we cannot differentiate empirically between distal and proximal predictors of the future SA. Third, we used self-reported data, which is critical in terms of several inherent biases.

These limitations notwithstanding, our study has shown that both, ML approaches and the GLM resulted in a very good overall ability to discriminate between individuals who attempt suicide in the future from individuals who don't, in the high-risk sample of community adolescents and young adults. Furthermore, our study contributes to raise awareness, both of the possible benefits of studies that employ ML, and of the many critical challenges in following these recommendations in the research of suicidality.

Conflict of Interest

The authors declare they have no conflict of interests.

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Table 1

Overview of the performance estimates for each prediction model.

Model	AUC	Brier-scaled	BAC	TNR	TPR
GLM	0.825	0.186	0.606	0.995	0.216
LASSO	0.827	0.294	0.604	0.995	0.212
RIDGE	0.833	0.434	0.611	0.995	0.227
RANDOM FOREST	0.818	0.232	0.584	0.997	0.171

Note. AUC Area under the receiver operating curve; BAC Balanced accuracy; TNR True negative rate (specificity); TPR True positive rate (sensitivity).

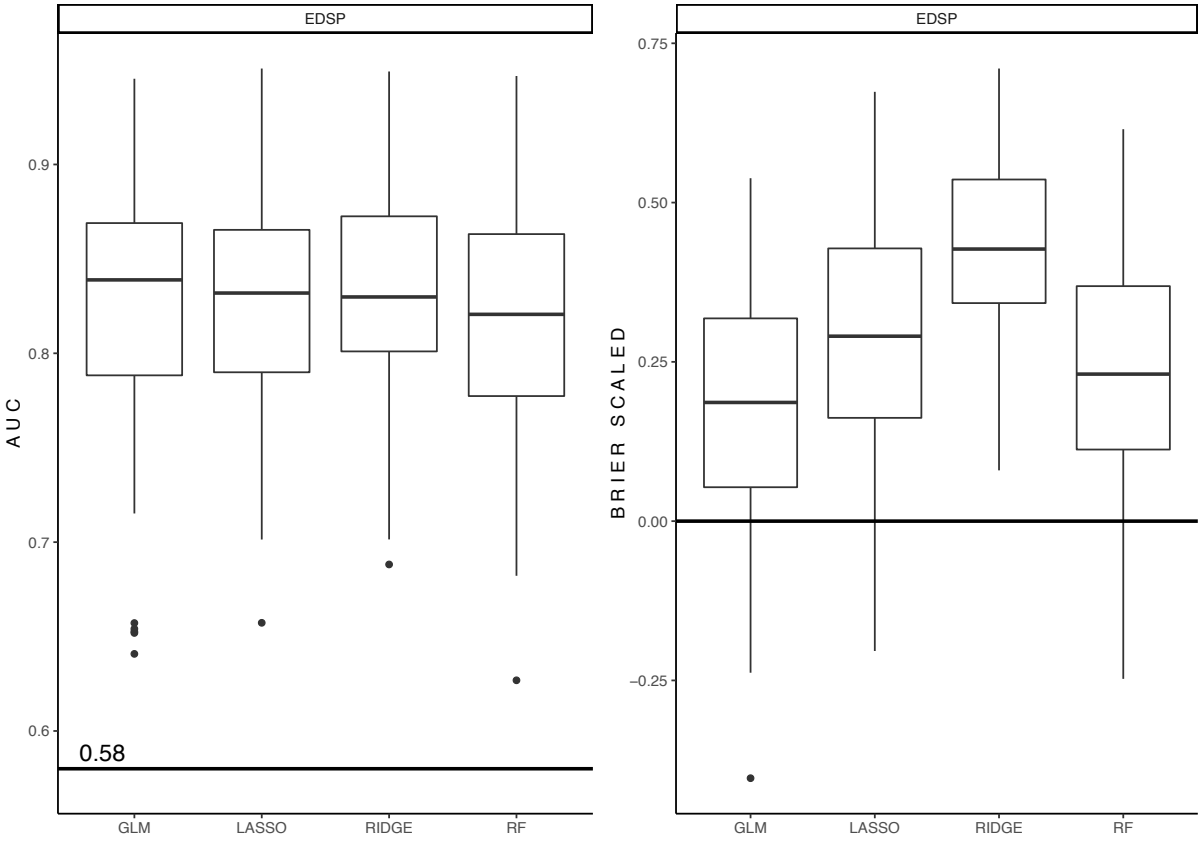

Figure 1. Boxplot of 100 resampling results for each prediction model. GLM Generalized linear model, RF Random Forest model. Left: Area under the curve (AUC), including the AUC of 0.58 as reported in the meta-analysis by Franklin et al. (2017), and right: Brier scaled, with the black horizontal line showing that all values below zero must be truncated.

Table 2

Overview of the decreasing importance of the baseline predictors for each prediction model.

	GLM				LASSO				RIDGE				RANDOM FOREST	
Predictor	**β**	**OR**	**Rank**	**%**	**β**	**OR**	**Rank ***	**%**	**β**	**OR**	**Rank ***	**%**	**Importance**	**Rank ***
Prior SA	0.453	1.57	1	57.3	0.413	1.51	1	51.2	0.388	1.47	1	47.4	8.39	1
Education	-0.405	0.67	2	49.9	-0.227	0.80	2	25.5	-0.247	0.78	2	28.0	0.71	9
Prior help-seeking	0.296	1.34	3	34.4	0.222	1.25	3	24.8	0.212	1.24	3	23.7	0.93	8
Any parental mental dx	0.279	1.32	4	32.1	0.092	1.10	7	9.7	0.142	1.15	5	15.3	-0.14	16
Parental loss or separation	0.245	1.28	5	27.8	0.137	1.15	4	14.7	0.161	1.18	4	17.5	0.13	14
BI	0.224	1.25	6	25.1	0.125	1.13	5	13.3	0.142	1.15	6	15.3	1.24	6
Number of mental dx	0.187	1.21	7	20.6	0.121	1.13	6	12.9	0.131	1.14	7	14.0	2.51	2
DH	-0.172	0.84	8	18.7	0.000	1.00			-0.098	0.91	8	10.3	1.44	4
Number of traumatic events	0.156	1.17	9	16.8	0.000	1.00			0.096	1.10	9	10.0	-0.01	15
Rural	-0.142	0.87	10	15.3	0.000	1.00			-0.090	0.91	10	9.4	0.58	10
Age	-0.139	0.87	11	14.9	0.000	1.00			-0.084	0.92	11	8.8	0.26	12
Sex	0.105	1.11	12	11.0	0.000	1.00			0.062	1.06	13	6.4	0.13	13
PCE	-0.097	0.91	13	10.2	-0.022	0.98	8	2.2	-0.070	0.93	12	7.2	1.37	5
Rape/Childhood sexual abuse	-0.016	0.98	14	1.6	0.000	1.00			-0.002	1.00	16	0.2	1.94	3
NLE	0.015	1.02	15	1.5	0.010	1.01	9	1.0	0.036	1.04	14	3.7	0.27	11
PE	0.001	1.00	16	0.1	0.000	1.00			0.020	1.02	15	2.0	0.97	7

Note. Rank* Order according to the predictor ranking of the GLM; β beta-coefficient of the logistic regression model; OR Odds Ratio; % OR translated to percentage. The original importance values of the Random Forest model have been muliplied by 1000, in order to not having to display too many digits.

Prior SA: Lifetime suicide attempt, reported at baseline; Education 0 = other, 1 = low, 2 = middle, 3 = high; dx Disorder; BI Behavioral inhibition; Number of mental dx: Number of DSM-IV diagnoses 0 = none, 5+ = 5 or more; DH Daily hassles; Rural 0 = Living in an urban area; PCE Perceived coping efficacy (higher PCE values denote lower PCE); NLE Negative life events; PE Psychotic experiences.