

EARLY LIFE STRESS: A KEY LINK BETWEEN CHILDHOOD ADVERSITY AND RISK OF ATTEMPTING SUICIDE

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SUMMARY

Introduction: Epidemiology shows that the major risk factors for suicide or attempting suicide are childhood adversities such as sexual and/or physical abuse, neglect, mental illness of caregiver, and family or community violence. Suicide, whether attempted or completed, is a significant social, financial and emotional burden worldwide. Identification of risk factors and antecedents predisposing individuals to increased risk of suicide is hence imperative so as to afford prompt and appropriate monitoring and intervention.

Aim: Using epidemiological data from the Survey of adverse childhood experiences (ACE) among young people in the Republic of Macedonia to examine their association with suicide attempt and to discuss possible mechanisms within the 'stress biology research'.

Subjects and methods: A representative sample consisted of total 1277 students (58.6% female and 41.6%), aged 18 and above in year four of 664 secondary school and 613 first- and second-year university students. The data were obtained using Adverse Childhood Experiences Study Questionnaires (Family Health History Questionnaire) for collecting information on child maltreatment, household dysfunction and other socio-behavioural factors, applying WHO/CDC-recommended methodology. Statistical significance was set up at $p < 0.05$.

Results: Emotional neglect, physical abuse and physical neglect were the most frequent abusive experiences students had. Overall, suicide attempts were reported by 3.1% of respondents (4.7% by females and 0.8% by males). Those respondents who had been emotionally abused were almost three times as likely to attempt suicide, physical abuse almost doubles the chances of attempting suicide, substance abuse in the family increased the chances 2.3 times for attempting suicide, violent treatment of the mother almost quadrupled them for attempted suicide, having a family member who had been in prison increased the odds of almost 3.5 times for attempting suicide. Attempted suicide was found to be 1.5 times more likely as the number of ACEs reaches 3 and 3.4 times more likely as the number of adverse childhood experiences reached four or more.

Conclusions: Identifying and treating children, adolescents and young adults who have been affected by adverse childhood experiences may have substantial value in our evolving efforts to prevent suicide.

Key words: early life stress - childhood adversity - attempted suicide - neurobiology of stress

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INTRODUCTION

In this article the term 'childhood adversity' refers to adverse childhood experiences (ACEs) which is conceptualized as a negative childhood experience associated with increased risk of poorer health (both physical and mental) and social outcomes over the life course (Felitti et al. 1998, Graignic-Philippe et al. 2014). Epidemiological studies have demonstrated that ACEs, such as emotional physical and sexual abuse, neglect, mental illness of caregiver, and family or community violence, predict higher risk of somatic diseases, addictions, depression and premature mortality (Felitti et al. 1998).

From developmental perspective we consider that early life stress and trauma is associated with childhood adversity, which involving relationships (to caregivers, family, community, peers) and other social experiences, interacts with developmental processes (Martikainen et al. 2002).

On the other hand, suicide is an emerging global issue associated with significant morbidity and mortality but also highly preventable. In 2015, there were an estimated 788 000 suicide deaths, translating to an annual global age-standardized suicide rate of 10.7 per 100 000 population and accounting for 1.4% of all deaths (World

Health Organization 2017). It is the second most prevalent cause of death in individuals aged 15-29 years old (World Health Organization 2017). These startling statistics, however, only shed light on a small part of the issue, as suicide attempts are far more prevalent than completions. The Centers for Disease Control and Prevention (CDC) estimated that 1.3 million adults in the United States alone attempted suicide in 2013 (Center for Disease Control and Prevention 2014). Suicide, whether attempted or completed, is a significant social, financial and emotional burden worldwide. Identification of risk factors and antecedents predisposing individuals to increased risk of suicide is hence imperative so as to afford prompt and appropriate monitoring and intervention.

Epidemiology shows that the major risk factors for suicide are sexual and/or physical abuse in childhood and a family history of suicide, together with mental health problems such as borderline personality disorder and post-traumatic stress syndrome. These risk factors are not independent as adolescent male suicide attempters are 5.6 times more likely to suffer from post-traumatic stress syndrome and 3.1 times more likely to suffer from borderline personality disorder if they have been sexually abused as children (Spokas et al. 2009).

Indeed those that have been sexually and/or physically abused when children amount to about 65% of all those who attempt suicide in a study of adolescents in Seattle (Bensley et al. 1999), for a review see (Evans et al. 2005). In this study suicide rates in which the victims injure themselves are five times higher if they have been sexually abused as children than if they have not been abused (Bensley et al. 1999).

Our objective was using epidemiological data from the Survey of adverse childhood experiences (ACE) among young people in the Republic of Macedonia to examine their association with suicide attempt and to discuss possible mechanisms within the 'stress biology research' asking what biological (and psychological) alterations to brain and body can account for the long-term connection between a stressful childhood and ill health that emerges decades later.

SUBJECTS AND METHODS

The study has been conducted in 2010. We examined the relationship of 10 adverse childhood experiences (childhood abuse (emotional, physical and sexual), witnessing domestic violence, parental separation or divorce, and living with substance abusive, mentally ill or criminal household members) to the adolescent risk of suicide attempts in a sample of students in Republic of Macedonia. We also examined the relationship between the number of adverse childhood experiences (ACEs) and suicide attempts during childhood and adolescence.

The Adverse childhood experience study among students in secondary schools and universities in the Republic of Macedonia is collaboration between WHO Department of Violence and Injury Prevention through the WHO Country office in Skopje and University Clinic of Psychiatry, Medical Faculty, Skopje. The overall objective was to assess the impact of numerous ACEs on a variety of health behaviours and outcomes among adolescent population age 18-21. The ACE study was approved by the Ministry of Education and Science of the Republic of Macedonia and its review boards as well as the Ethical Board.

Numerous articles and publications from ACE study have shown a strong graded relationship between the number of ACEs, multiple risk factors for leading causes of death in the US (Felitti et al. 1998) and priority health and social problems such as smoking, sexually transmitted diseases, unwanted pregnancies, and alcohol problems (Felitti et al. 1998, Anda et al. 2001).

The instrument – ACE Questionnaires

The questionnaires that we used in the study were developed by the US Centers for Disease Control and Prevention and Kaiser Permanente in 1997, and include the *Family Health History* and *Physical Health Appraisal questionnaires* for collecting information on childhood maltreatment, household dysfunction and other socio-behavioural factors (CDC 2011). The question-

naires were translated into Macedonian and Albanian and a cognitive testing was done according to the usual procedure.

All the respondents completed a standardized questionnaire - Family Health History (a male and female version). The questionnaire consists of 68 questions examining various types of child maltreatment, childhood adversities rooted in household dysfunctions, and other risk factors. Students' questionnaires were filled out anonymously. Survey procedures were designed to protect student privacy by allowing voluntary and anonymous participation and possibility to withdraw their participation at any time of the research.

Study population

The sample consisted of 664 secondary school students (258 males and 406 females) which represented 2.8% of total student population in fourth grade from general and vocational school, thus obtaining stratified sampling considering different social strata. The university student sample consisted of 613 (343 female and 270 male) students from these four universities, which is 1.9% of the total student population in the first and second year of studies (State Statistical Office 2012).

RESULTS

Table 1 shows the gender and age of respondents.

Table 1. Age and sex of respondents

Sex	N	%	Mean age	St. dev
Female	749	58.6	19.83	2.44
Male	528	41.4	20.14	2.77
Total	1277	100	19.95	2.73

The student response rate was 90.3% (1277 of 1414 students included in the sample). In the 11 secondary school all girls and boys attending selected classrooms, present that day at school were invited to participate in the study. The total number of non-responders in this group was 102 (13.3%). The total number of non-responders in the university group was 35 (5.4%) consisting of 30 male students and 5 female students. The prevalence of each experience and the ACE scores are given in the Table 2. Emotional neglect, physical abuse and physical neglect were the most frequent abusive experiences students had. There was a statistically significant difference between female and male respondents in experiencing sexual abuse, physical neglect (significantly more males) and emotional neglect (significantly more female respondents).

Almost 30% of the respondents reported at least one adverse experience of the 10 categories, 15.5% reported two adverse experiences, 9.8% three such experiences and 9.5% four and more such experiences. Overall, suicide attempts were reported by 3.1% of respondents. There was a statistically significant difference between female and male respondents (for $p < 0.05$), with 4.7%

Table 2. Prevalence of each category of Adverse Childhood Experiences and ACE score by sex

	Female N=749 N (%)	Male N=528 N (%)	Total N=1277 N (%)
Adverse Childhood Experiences			
Emotional abuse	88 (11.7)	51 (9.6)	139 (10.8)
Physical abuse	151 (20.2)	118 (22.3)	269 (21.1)
Sexual abuse	55 (7.3)	110 (20.8)	165 (12.9)
Emotional neglect	266 (35.5)	125 (23.7)	391 (30.6)
Physical neglect	116 (15.5)	139 (26.3)	255 (20.0)
Substance abuse by f.m.	90 (12.0)	81 (15.3)	171 (13.4)
Mental illness by f.m.	31 (5.9)	57 (7.6)	88 (6.9)
Domestic violence	81 (10.8)	48 (9.0)	129 (10.1)
Incarcerated f.m.	34 (4.5)	30 (5.7)	64 (5.0)
Parental separation	33 (4.4)	16 (3.0)	49 (3.8)
ACE score - Number of ACEs			
0	286 (38.2)	173 (32.8)	459 (35.9)
1	213 (28.4)	161 (30.5)	374 (29.3)
2	108 (14.4)	90 (17.0)	198 (15.5)
3	76 (10.1)	49 (9.4)	125 (9.8)
4 and more	66 (8.8)	55 (10.4)	121 (9.5)

**p<0.05; f.m. - family member

Table 3. Characteristics of suicide attempts by adolescents by sex (N=39)

Suicide attempt by adolescents	Female N (%)	Male N (%)	Total N (%)
Suicide attempt	35 (4.7)	4 (0.8)	39 (3.1)
Mean age of the attempt	13.83 years	14.24 years	14.09 years
Suicide attempt resulting in injury	9 (1.2)	2 (0.4)	11 (0.9)
2 or more suicide attempts	11 (1.5)	3 (0.6)	14 (1.2)

for females and 0.8% for males. The age when suicide was first attempted for both sexes was 14. In 1.2% of females and 0.4% of males the attempt(s) resulted in injury, which indicates that the attempt was very serious. More than one attempt was made by 1.5% of females and 0.6% of males (Table 3).

To assess the ACE as risk factors for suicide attempts during childhood and adolescence we examined the association between the type of ACE and suicide attempts. There are statistically significant associations between attempted suicide and all types of abuse for both sexes. For female students there are statistically significant associations between attempted suicide and being physically abused so that one had marks or was injured (Pearson chi-square: 99.9, p<0.01), suicide attempt and emotional abuse (Pearson Chi-square 72.99, p<0.01), between attempted suicide and being physically abused by kicking, grabbing or pushing (Pearson chi-square 12.9 p<0.05), and between attempted suicide and sexual abuse (Pearson chi-square 6.96, p<0.01). For male students there are significant associations between attempted suicide and physical abuse with marks or injury (Pearson chi-square 130.1, p<0.01) and between attempted suicide and physical abuse by being kicked grabbed, pushed (Pearson chi-square 27.9562, p<0.01).

There are significant associations between attempted suicide and household dysfunction, primarily living with

a family member who had attempted suicide (Pearson chi-square 28.1, p<0.01), living with a family member who was mentally ill (Pearson chi-square 23.4, p<0.01) and having an alcoholic family member (Pearson chi-square 17.3, p<0.01) for female respondents only. The relationship between adverse childhood experiences such as all types of abuse during childhood and household dysfunction and later manifestation of health risk behaviours among young people such as suicide attempt, as well as adjusted relative odds of suicide attempt by type of adverse childhood exposure are shown in Table 4.

Table 4. Adjusted relative odds of suicide attempt by type of Adverse Childhood Experience

Adverse Childhood Experiences	Suicide attempt
Emotional abuse	2.354 (1.082-5.119)**
Physical abuse	1.760 (0.872-3.549)
Sexual abuse	2.0 (0.801-4.995)
Emotional neglect	1.064 (0.543-2.084)
Physical neglect	0.717 (0.274-1.871)
Substance abuse by a f.m.	2.229 (1.026-4.845)**
Mental illness by a f.m.	1.979 (0.734-5.269)
Domestic violence	4.082 (1.981-8.411)*
Incarcerated f.m.	3.449 (1.268-9.382)**
Parental separation	0.594 (0.079-4.454)

Odds ratios adjusted for age, sex, SES; **p<0.05; *p<0.01

Table 5. Prevalence and Odds of suicide attempt by number of Adverse Childhood Experiences

Suicide attempt	Number of adverse childhood experiences				
	0 (N=457)	1 (N=374)	2 (N=198)	3 (N=125)	≥4 (N=121)
Prevalence	2.2	2.4	3.0	4.0	7.4
OR (95% CI)	0	0.736 (0.344-1.576)	1.019 (0.418-2.484)	1.533 (1.2070-3.516)*	3.347 (1.525-7.346)**

OR: Odds Ratio; CI: Confidence Interval; Among 749 women; Adjusted for age, sex and SES; *p<0.5; **p<0.05

If a respondent was exposed to one adverse childhood experience, the probability of exposure to any category of health-risk behaviour increased substantially. Those respondents who had been emotionally abused were almost three times as likely to attempt suicide (statistically significant). Physical abuse almost doubles the chances of attempting suicide. Moreover, substance abuse in the family increased the chances 2.3 times for attempting suicide (statistically significant). Violent treatment of the mother, i.e. domestic violence, almost quadrupled them for attempted suicide, (statistically significant). Having a family member who had been in prison increased the odds of almost 3.5 times for attempting suicide (statistically significant). Overall, these results show that being exposed to negative experiences during childhood could result in a number of risky behaviours in adolescence and young adulthood. The general trend indicates that there is a relatively strong graded relationship between health-risk behaviours and number of adverse childhood experiences.

Significantly attempted suicide was found to be 1.5 times more likely (OR=1.533, 95% CI=1.207-3.516) as the number of ACEs reaches 3 and 3.4 times (OR=3.447, 95% CI=1.525-7.346) more likely as the number of adverse childhood experiences reached four or more (see Table 5).

DISCUSSION

Our study confirmed the finding that females significantly more often attempt suicide, significantly more often have more than one attempt, and the attempt(s) more often resulted in injury, thus indicating that the attempt was very serious. During adolescence, girls who are under stress are more likely to suffer from emotional and psychosomatic problems, following the pattern of internalizing psychopathological manifestations (such as anxiety, depression, and somatisation) which at some point might lead to suicidal behaviour. Boys under stress have more behavioural and conduct problems, following the pattern of externalization (Kolip & Schmidt 1999, Raleva 2007). The immediacy of the developmental stress and potential abuse and household dysfunction are experiences not easily elaborated by children and adolescents, as a result of which at certain points suicide may appear to be the only solution. We found that 8 out of 10 adverse childhood experiences increased the risk of attempting suicide during adolescence from 1.5-4 folds. The impact of pain and anxiety caused by emo-

tional, sexual and physical abuse or witnessing domestic violence are experienced in silence and sometimes suicide attempt is perceived as the only way out or an appeal for help. Because the experiences are strongly interrelated and rarely occur in isolation (Finkelhor 1998), it is important to simultaneously consider the impact of multiple experiences. As the number of these experiences increased, the risk of ever attempting suicide, as well as risk of attempting suicide either during childhood/adolescence or adulthood increased dramatically (Dube et al. 2001). A strong graded relationship was reported between the number of adverse experiences in childhood (multiple forms of CAN and household dysfunction) and self-reports of health-risk behaviours during adolescence (such as attempted suicide among others) (Felitti et al. 1998). These findings are supported by studies on abused children and adolescents at high risk of suicidal behaviours (Kaplan et al. 1999).

Information from neurosciences supports the biological plausibility of our findings. Children who experience traumatic events are more likely to have problems with emotional and behavioural self regulation later in life, and are more likely to mutilate themselves and attempt to commit or commit suicide (Brown et al. 1999). Furthermore, the biological processes that occur when children are exposed to adverse events such as recurrent abuse and witnessing domestic violence can disrupt the early development of the central nervous system, which may additionally affect brain functioning later in life (Perry & Pollard 1998, Knudsen et al. 2006, MacMillan et al. 2008, Perry 2009, Shonkoff et al. 2009).

Stress biology findings

The brain

Human brain maturation is a protracted process beginning in fetal life and continuing into early adulthood (Oberlander et al. 2008). Dramatic growth in gray and white matter occurs in the first 2 years of life, when the brain attains 80-90% of its adult volume before continuing to grow at an attenuated rate (Knickmeyer et al. 2008, Deoni et al. 2012). Alongside growth, experience-dependent neural pruning eliminates inactive synapses. Anatomically, the brain matures “from the bottom up,” beginning with primitive brainstem structures and progressing anatomically in anterior-posterior and inferior-superior directions, culminating with the prefrontal cortex (PFC). Investigation has preferentially examined “stress sensitive” areas dense with glucocorticoid recep-

tors, including limbic structures (e.g., hippocampus and amygdala) key to memory, learning, and emotion regulation, as well as the PFC, critical for higher cognition, executive functioning, and “top-down” control of lower regions (McEwen et al. 2016). “Neurotoxicity hypothesis” posits that early elevation of stress mediators, particularly glucocorticoids, kills or impedes growth of neurons in stress-sensitive regions via mechanisms including oxidative damage (Uno et al. 1994). Oxidative stress during early neurodevelopment may also disrupt neural sensitive periods (Do et al. 2015).

Neuroendocrine stress regulation

Childhood adversity impacts stress reactivity as controlled by the hypothalamic-pituitary-adrenal (HPA) and autonomic (sympathetic/parasympathetic) axes. Both axes are under central control by cortico-limbic structures, including the PFC, hippocampus, and amygdala (Danese & McEwen 2012).

In human studies and animal experimentation, childhood adversity consistently predicts HPA dysregulation generally persisting into adulthood, including patterns of hyper-reactivity, suggesting potential acquired resistance to glucocorticoid negative feedback, or hypo-reactivity, suggesting possible attenuated stress sensitivity or exaggerated axis suppression (Lovallo 2013).

An abused child, often had major elevation of her cortisol hormone levels for even young children in an insecure relationship with their parents have such excess elevations following mildly stressful events. Such elevations are known to lead to both emotional and behavioural problems as the child matures. The maturing abused child carries an additional burden due to failure of the negative feedback pathway that dampens down the extent of cortisol release. This leads to high elevation of the hormone in the blood on experiencing mildly stressful events. It does not happen to those that experience occasions of clinical depression who have not been abused as children.

Another hormone that is secreted under stressful conditions, namely ‘corticotropin releasing hormone’ CRH is secreted by the hypothalamus in the brain, and is integral to triggering the release of cortisol from the adrenals. The sensitivity of the gene for this hormone is set early during development to a level that is determined by maternal care: if this decreases, the hormone is found in high levels in the brain at maturity, with consequent higher levels of cortisol in the blood and this is accompanied by fearful behaviour; on the other hand, sustaining maternal care leads in maturity to decreased levels of the hormone and so decreased amounts of cortisol in the blood and reduction in fearful behaviour when faced with a stressful experience.

What is it about the teenage years that makes teenagers vulnerable in a way that most of them do not experience later in life, even if they do have a loving, caring and protective relationship with their parents in childhood? In late childhood and throughout adoles-

cence the gray matter of the cortex declines, some areas more than others, with each area possessing a characteristic time course of decline. By the time youth is over there has been on average a 30% loss of dendrites and synaptic connections compared with that in the gray matter towards the end of childhood. It is likely that this loss of synapses is due to the maturation of neural networks using synaptic connections that are found to be ‘useful’. Their use is determined by the adolescent experiences, with the pruning of those networks and their synapses that prove not to be useful. The cortex requires a very large amount of energy to sustain its activities, about 20% of the entire energy expenditure of the body, so that this sculpting out of neural networks has the effect of reducing the energy demand by a significant amount. But it leaves an adolescent especially vulnerable to the possibility of excessive loss of cortical networks. Sexual or physical abuse as a child introduces a major factor for stripping out excess numbers of synapses during adolescence when mature and stable neural networks are being established, for mildly stressful events leading to elevated levels of cortisol hormone will strip out synapses and the networks they serve. If the number of synaptic connections serving a network falls below about 60% then the network will fail, with all the consequences this has for a normal life both during adolescence and through one’s mature years (Bennett 2013).

Abused girls more often think of committing suicide and actually attempt to do so, than those not abused and this is accompanied by failure of the negative feedback that dampens down cortisol release (de Bellis et al. 1994, Jokinen & Nordstrom 2009). Indeed measures of the extent of this failure provide a good prediction of subsequent suicide behaviour, which has been traced to a decline in the normal function of GR11. In contrast, a loving, caring and protective family environment militates against this decline in function of GR11. The increase in cortisol hormone in the blood that occurs as a consequence of the failure of GR11 is almost certainly responsible for the reduced gray matter in prefrontal cortex that follows major depressive disorder in those that have been sexually abused as children, most likely reflecting a loss of synapses and dendrites in these parts of the brain. It is interesting to note that this is accompanied by an increase in size of the amygdala, reflecting the increased excitability of this part of the brain in such depression. It is crucial to understand how childhood abuse brings about a change in GR11. We should look for understanding in the recently described phenomenon of epigenetics of the GR11. Epigenetics refers to alterations in the function of genes that can be inherited, but are not due to any changes in the sequence of nucleotides that make up DNA, the normal basis for changes in the function of genes. It is now known that children who have been sexually or physically abused and are victims of suicide possess epigenetic changes in the gene for GR11 that lead to its down-regulation. Genes possess promoters that are regions which when

activated, for example by proteins delivered to the cell nucleus, can regulate expression of the gene. If these promoters are blocked such expression ceases. Such a block is affected by a process called methylation which is instigated in children through a cascade of chemical events triggered by abuse. Examination of the gene promoter for GR11 in suicide victims who have suffered from childhood abuse shows extensive methylation compared with suicide victims with no history of such abuse or of subjects that have not committed suicide. DNA methylation makes DNA less accessible and thus reduces gene activity (McGowan et al. 2009).

Childhood sexual and physical abuse, in particular, have been associated with suicide attempts (Beautrais et al. 1996, Finkelhor 1998, Kaplan et al. 1999, Wagner 1997). In the last decades research in the neurobiology of suicide suggests that there is a strong epigenetic relationship between multiple childhood trauma, such as abuse, witnessing domestic violence, and other forms of household dysfunction and the risk for suicide attempt (Moffitt 2013). Childhood adversity can have long-term epigenetic consequences which may be inherited by subsequent generations.

The findings of the present study provide strong grounds for funding public policy planning and health interventions to support victims of childhood adversity. Areas for future research should include preventive and treatment strategies and factors promoting resilience following childhood adversity. Early identification, close follow-up and rendering therapy to these at risk individuals may potentially avoid the catastrophic outcome of suicide.

This study has several limitations that should be discussed. First, the retrospective nature of adverse childhood experiences self-reporting may be prone to recall bias or imperfections in human memory. Second, the generalizability of our findings is limited by the fact that this study, however, only shed light on a small part of the issue, as suicide attempts are far more prevalent than completions. Third, most studies focused on female suicidality with little attention paid to male victims of adverse childhood experiences. This is an important area for future research.

CONCLUSIONS

We have found that adverse childhood experiences increase the risk of attempting suicide. Thus, recognition that adverse childhood experiences are common and frequently happen as multiple events may be the first step in preventing their occurrence. Strengthening response and support for child victims of childhood adversities, through out the lifecycles is extremely important. It is therefore imperative for health providers and researchers to identify and treat children, adolescents and young adults who have been affected by such experiences. And, equally important is to respond to the problem of suicide prevention by incorporating suicide informed strategies with the populations they serve.

Adverse childhood experience surveys offer a rapid mechanism to encourage investment in early interventions, by identifying the scale of family problems and the potential health and social benefits of addressing such problems.

Acknowledgements:

This study was implemented by support from WHO Regional Office for Europe - Copenhagen.

Conflict of interest: None to declare.

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