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Environmental factors, life events, and trauma in the course of bipolar disorder

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The etiology and clinical course of bipolar disorder are considered to be determined by genetic and environmental factors. Although the kindling hypothesis emphasizes the impact of environmental factors on initial onset, their connection to the outcome and clinical course have been poorly established. Hence, there have been numerous research efforts to investigate the impact of environmental factors on the clinical course of illness. Our aim is to outline recent research on the impact of environmental determinants on the clinical course of bipolar disorder. We carried out a computer-aided search to find publications on an association between environmental factors, life events, and the clinical course of bipolar disorder. Publications in the reference lists of suitable papers have also been taken into consideration. We performed a narrative overview on all eligible publications. The available body of data supports an association between environmental factors and the clinical course of bipolar disorder. These factors comprise prenatal, early-life, and entire lifespan aspects. Given varying sample sizes and several methodological limitations, the reported quality and extent of the association between environmental factors and the clinical course of bipolar disorder should be interpreted with utmost caution. Systematic longitudinal long-term follow-up trials are needed to obtain a clearer and more robust picture.

Key words: bipolar disorder, clinical course, environmental factors, life events, trauma.

BIPOLAR DISORDER IS one of the most common psychiatric illnesses. Its lifetime prevalence is about 3% worldwide.[1–3] Patients with bipolar disorder suffer from instability of mood, cycling between opposing affective states (i.e. between mania and depression). The mean age of onset is set in late adolescence and early adulthood.[4] According to the diagnostic criteria listed in DSM-IV and ICD-10, the core symptoms of depression are depressed mood, loss of energy, inability to experience pleasure, loss of interest in activities, cognitive impairment, changes in sleep and appetite, decreased libido, and suicidal thoughts. Mania, by contrast, is characterized by unusually cheerful and optimistic mood, elevated energy, racing thoughts and accelerated speaking, decreased need for sleep, and unrealistic ideas without considering the consequences. Delusions and hallucinations can occur in both mania and depression. Even in euthymic states, patients with bipolar disorder may suffer from constant neuropsychological impairment, such as mnestic deficits and a reduced psychological capacity,[5] factors that negatively impact on participation in daily life, social integration, and employment status. The etiology and clinical course of bipolar disorder are considered to be determined by genetic and environmental factors.[6–8] Clinicians observe a high diversity of the clinical course and outcome for this

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disease. Kraepelin was one of the first to define the distinct nosology of bipolar disorder and emphasized the importance of the knowledge of the clinical course of illness.[9,10] Based on Post's kindling hypothesis, subsequent episodes have been considered to occur unpredictably and without pattern.[11,12] This also highlights the need to study disease trajectories, in particular given the recent major achievements in psychiatric genetics:[13–20] we now need to learn more about the non-genetic factors and their interaction with genetic underpinnings. A better understanding of the complex interplay between life events and disease course is warranted. Bipolar disorder may serve as a case in point.

Our aim is to summarize and discuss recent research on the impact of environmental factors, trauma, and life events on the clinical course of bipolar disorder in a narrative review.

METHODS

A computer-aided literature search using PubMed was carried out to find articles published between 2005 and January 2016 on the topic of a potential association between environmental factors, life events, and trauma, and the course of bipolar disorder. The keywords 'bipolar disorder', 'manic depressive illness', and 'course' or 'outcome' in combination with 'environmental factors' or 'environmental triggers', 'life events', 'early adversities', 'recurrence', 'life stress', 'climate', 'prenatal infections', 'influenza', 'early adversities', 'maternal smoking', and 'childhood trauma' were used. Publications in the reference list of suitable papers were also taken into consideration.

RESULTS

There is a substantial number of studies investigating factors influencing the course of bipolar disorder. The number of identified studies focusing on specific aspects varied broadly, and so did the sample sizes (see Table 1).[21–89] Categorizing the different aspects has proven to be a non-trivial task as some of the factors may fall within more than one category (see Fig. 1). For example, exposure to maternal smoking during pregnancy can be seen as an environmental trigger, but it is also an early adverse life event and may be considered a trauma to fetal development. Similarly, lack of social support is a traumatic life experience and can also be seen as an adverse life event. Moreover, the amount of social support is an environmental trigger. The complexity and mutual interference of the different categories lead to inconsistent categorization in the literature. Therefore, developing a systematic categorization seems quite infeasible or is at least far beyond the scope of this paper.

Infections

Infections, especially intrauterine infections, are supposed to interfere with fetal and postnatal neurodevelopment. This could lead to impaired neuropsychological health and a higher vulnerability for psychiatric disorders.[28] Canetta *et al.* evaluated whether serologically confirmed maternal exposure to influenza was associated with an increased risk of bipolar disorder.[24] Furthermore, they investigated its impact on psychotic features within bipolar disorder. Their data suggested a fivefold increased risk for bipolar disorder with psychotic symptoms, whereas influenza did not influence bipolar disorder without psychotic symptoms. This could be interpreted as an impact on clinical course as psychotic features stand for a more severe course of illness.[24] Parboosing *et al.* observed a fourfold increased risk for bipolar disorder in general due to gestational influenza infection, regardless of the presence or absence of psychotic symptoms.[23] However, on the other hand, the hypothesis of gestational viral infections increasing susceptibility to bipolar disorder could not be verified by either Pang *et al.*[21] or Mortensen *et al.*[22]

The influence of viral infections during adulthood has been investigated in only a few studies. Okusaga *et al.* evaluated the relation between seropositivity for coronaviruses, influenza A and B viruses, and mood disorders with or without psychotic features and suicide attempts. An infection with any of the three respiratory viruses was associated with major depressive disorder, but not with bipolar disorder. Only influenza B was linked to a history of suicide attempts and psychotic symptoms.[25] It should be pointed out that the sample size was small and that viral infections occur epidemically. Therefore, the results should be considered with caution.

As *Toxoplasma gondii* parasites are supposed to influence dopamine metabolism, toxoplasmosis could possibly influence psychiatric health and impairment, such as bipolar disorder.[90] Only a few studies have investigated *T. gondii* infection in adult

Table 1. Overview of studies and sample sizes

Topic	Author[Ref.]	Year	Sample size	Diagnostic criteria	Country
Infections during pregnancy	Pang *et al.*[21]	2009	3076	ICD-9	UK
	Mortensen *et al.*[22]	2011	127	ICD-10	Denmark
	Parboosing *et al.*[23]	2013	92	DSM-IV	USA
	Canetta *et al.*[24]	2014	85	DSM-IV	USA
Infections in adulthood	Okusaga *et al.*[25]	2011	257	DSM-IV	USA
	Tedla *et al.*[26]	2011	495	CIDI, SCAN	Ethiopia
	Pearce *et al.*[27]	2012	1211	DSM-III	USA
	Hamdani *et al.*[28]	2013	110	—	France
Maternal smoking	Ekblad *et al.*[29]	2010	25 590	ICD-10	Finland
	Talati *et al.*[30]	2013	79	DSM-IV	USA
	Chudal *et al.*[31]	2015	724	ICD-10	Finland
Birth complications	Bain *et al.*[32]	2000	301	ICD-9/-10	Scotland
	Øgendahl *et al.*[33]	2006	196	ICD-8/-10	Denmark
	Nosarti *et al.*[34]	2012	217	ICD-9/-10	Sweden
	Chudal *et al.*[35]	2014	724	ICD-9/-10	Finland
Climate	Volpe *et al.*[36]	2010	5172	ICD-10	Brazil
	Dominiak *et al.*[37]	2015	257	ICD-10	Poland
	Geoffroy *et al.*[38]	2014	Review	—	—
	Young *et al.*[39]	2015	Review	—	—
	Rajkumar *et al.*[40]	2015	357	ICD-10	India
	Hochman *et al.*[41]	2016	148	DSM-IV	Israel
Childhood trauma	Kennedy *et al.*[42]	2002	20	DSM-IV	USA
	Garno *et al.*[43]	2005	100	DSM-IV	USA
	Kauer-Sant'Anna *et al.*[44]	2007	163	DSM-IV	Brazil
	Quarantini *et al.*[45]	2009	140	DSM-IV	Brazil
	Fisher *et al.*[46]	2010	Review	—	—
	Daruy-Filho *et al.*[47]	2011	Review	—	—
	Miller *et al.*[48]	2013	80	DSM-IV	USA
	Aas *et al.*[49]	2014	97	DSM-IV	Norway
	Girshkin *et al.*[50]	2014	Meta-analysis	—	—
	Benedetti *et al.*[51]	2014	136	DSM-IV	Italy
	Sala *et al.*[52]	2014	1600	DSM-IV	USA
	Baumeister *et al.*[53]	2016	Meta-analysis	—	—
	Etain *et al.*[54]	2015	126	DSM-IV	France/Brazil
	Oliveira *et al.*[55]	2015	531	DSM-IV	France
	Benedetti *et al.*[56]	2015	87	DSM-IV	Italy
	Mert *et al.*[57]	2015	91	MINI	Turkey
	Aas *et al.*[58]	2016	Review	—	—
Life events	Ellicott *et al.*[59]	1990	61	DSM-III	USA
	Malkoff-Schwartz *et al.*[60]	1998	39	DSM-IV	USA
	Hlastala *et al.*[61]	2000	64	DSM-IV	USA
	Paykel *et al.*[62]	2003	Review	—	—
	Christensen *et al.*[63]	2003	56	ICD-10	Denmark
	Hillegers *et al.*[64]	2004	140	DSM-IV	Netherlands
	Cohen *et al.*[65]	2004	52	DSM-IV	USA
	Johnson *et al.*[66]	2005	Review	—	—
	Kessing *et al.*[67]	2005	Review	—	—
	Alloy *et al.*[68]	2005	Review	—	—
	Kim *et al.*[69]	2007	38	DSM-IV	USA
	Johnson *et al.*[70]	2008	125	DSM-IV	USA
	Gruber *et al.*[71]	2011	196	DSM-IV	USA

Table 1. (*Continued*)

Topic	Author[Ref.]	Year	Sample size	Diagnostic criteria	Country
	Boland *et al.*[72]	2012	184	DSM-IV	USA
	Hosang *et al.*[73]	2012	512	DSM-IV	UK
	de Dios *et al.*[74]	2012	595	DSM-IV	Spain
	Gershon *et al.*[75]	2013	131	DSM-IV	USA
	Koenders *et al.*[76]	2014	173	DSM-IV	Netherlands
	Simhandl *et al.*[77]	2014	222	ICD-10	Austria
	Kemner *et al.*[78]	2015	51	DSM-IV	Netherlands
	Kemner *et al.*[79]	2015	108	DSM-IV	Netherlands
	Maciukiewicz *et al.*[80]	2016	443	DSM-IV	Poland
Social support	Johnson *et al.*[81]	1999	59	DSM-III	USA
	Johnson *et al.*[82]	2000	31	DSM-III	USA
	Johnson *et al.*[83]	2000	43	DSM-III	USA
	Johnson *et al.*[84]	2003	94	DSM-IV	USA
	Cohen *et al.*[65]	2004	52	DSM-IV	USA
	Miklowitz *et al.*[85]	2005	360	DSM-IV	USA
	Coville *et al.*[86]	2008	44	DSM-IV	USA
	Greenberg *et al.*[87]	2014	Review	—	—
	Ellis *et al.*[88]	2014	95	DSM-IV	USA
	Maciukiewicz *et al.*[80]	2016	443	DSM-IV	Poland
	Owen *et al.*[89]	2015	20	DSM-IV	UK

The colors illustrate the sample sizes. Red: $n \leq 100$; yellow: V = 101–500; green: $n \geq 500$. The numbers in the cells indicate the exact sample size. To provide a better overview on the literature, reviews and meta-analyses are included in the table. CIDI, Composite International Diagnostic Interview; MINI, Mini-International Neuropsychiatric Interview; SCAN, Schedules for Clinical Assessment in Neuropsychiatry.

bipolar patients, but all of them found a higher seroprevalence in bipolar disorder with an odds ratio (OR) between 2.17 and 3;[26–28] however, none of these publications provides information about the influence on the clinical course. Yagmur *et al.* showed a higher seroprevalence in patients who attempted to commit suicide than in controls. The underlying psychiatric diagnoses were not listed.[91]

Maternal smoking

Maternal smoking has been suggested to increase the risk of various mental illnesses, such as attention-deficit and hyperactivity disorder, conduct disorder,[92] and autism spectrum disorder.[93] In a study with a large sample size, Ekblad *et al.* observed an increased risk of psychiatric disorders except for schizophrenia and anorexia nervosa.[29] A respective association with bipolar disorder is poorly investigated and findings are inconsistent. Two studies showed an increased risk of bipolar disorder due to maternal smoking during pregnancy.[29,30] Ekblad

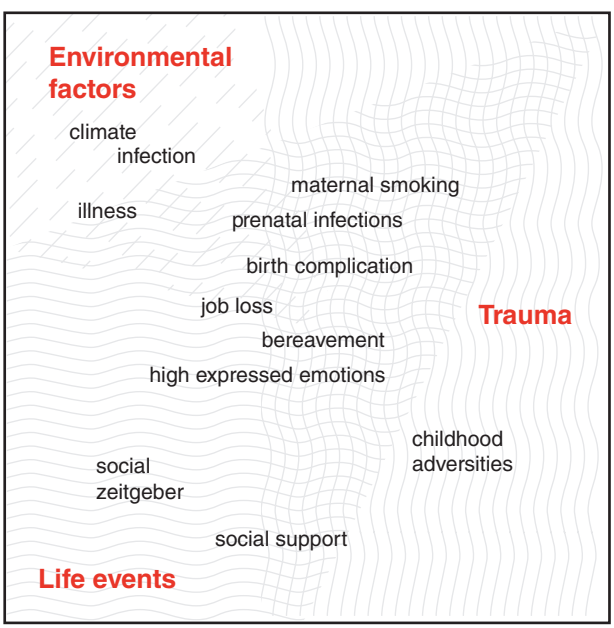

Figure 1. Impact on the course of bipolar disorder.

et al. found a dose relation in the risk of mood disorders, namely less than 10 cigarettes daily with an adjusted OR of 1.65 and more than 10 cigarettes daily with an adjusted OR of 1.93. In this regard, Talati *et al.* observed a twofold greater risk of bipolar disorder. An influence of the quantity of maternal smoking could not be supported.[30] Chudal *et al.* reported a 1.41-fold risk for bipolar disorder with maternal smoking in the past. This increase in risk did not withstand an adjustment for factors such as familial background.[31] Until now, there have not been any systematic research protocols dealing with the impact of maternal smoking during pregnancy on the clinical course of bipolar disorder.

Birth complications

Whether birth complications have an impact on bipolar disorder in general is unclear. There exists only one study that suggests an association with 2.5-fold higher risk of bipolar disorder in offspring delivered by planned cesarean section[35] compared to natural birth. Bain *et al.* could not find such association.[32] There are, anyhow, only a few studies investigating this topic, none of which found an association among birthweight, gestational age, and the risk of bipolar disorder.[32–35] One of these studies found preterm birth to be associated with a higher risk of bipolar disorder.[34] Up to January 2016, there existed no study focusing on a potential impact of birth complications on the clinical course.

Climate

Seasonal effects supposedly influence the regulation of mood, especially in bipolar disorder.[94,95] The first systematic review of this topic concluded that there was a replicable association of seasonal variation and bipolar disorder symptoms.[38] Bipolar patients with seasonal patterns form the minority but suffer from a more severe clinical course. Manic episodes seem to be more frequently linked to seasonality than depressive episodes.[41] Overall mania has its peaks in spring and summer and a third peak in mid-winter, while depression shows high occurrence in winter and spring.[37,38] Furthermore, there are indications that climate factors, such as mean daylight hours, mean daily temperature, and the daily number of sunshine hours, are associated with relapse in bipolar disorder. The shortening of sunlight in particular triggers depressions.[96] The relation between sunlight and mood states is furthermore supported by the positive therapeutic effect of phototherapy in mood disorders. Young *et al.* argue that this fact may lose importance due to the weakening of circadian rhythm in consequence of electric light.[39] It is worth noting that a higher vulnerability to climate and seasonal changes has been reported in females.[38] In contrast, Rajkumar *et al.* observed a greater degree of seasonality in men.[40] In addition to that, these patients suffer more frequently from psychotic features and substance misuse.[36,41]

Childhood trauma

A history of childhood trauma is common in patients with mental disorders, such as bipolar disorder. The prevalence of post-traumatic stress disorder (PTSD) in bipolar disorder ranges from 16% to 39%.[2,97,98] Childhood trauma in the broader sense is considered to be evident in almost 50% of patients with bipolar disorder.[43] There are several bipolar patients who report childhood trauma and do not fulfill the criteria of PTSD. Still, childhood trauma is assumed to impact on the onset and the clinical course of bipolar disorder. So far, there are only four reviews that address childhood trauma. The association between childhood trauma and the onset and course of bipolar disorder has been established quite robustly.[46,47,58,98] The latest review by Aas *et al.* was published in January 2016.[58] The most relevant findings of this review are: Childhood trauma influences the clinical course by leading to an earlier age of onset. It also increases the likelihood of a rapid cycling course, the occurrence of psychotic features, the number of lifetime mood episodes, the risk of suicide ideation and attempts, and substance misuse. Gender issues have been found as well. Females with bipolar disorder reported childhood trauma more frequently and had a stronger association with a more severe clinical course (i.e. rapid cycling, early age of onset, suicide attempts, and more depressive episodes).[58] In contrast to that, Quarantini *et al.* showed that bipolar patients with trauma experienced more severe manic symptoms than depressive symptoms compared to controls.[45] Sala *et al.* investigated dose-response effects of childhood maltreatment and the course of bipolar disorder, including clinical characteristics, probability of treatment, and psychiatric comorbidities.[52] There are different types of trauma, such as physical abuse and neglect, emotional abuse and

neglect, and sexual abuse. Robust data on the epidemiology of trauma types and their impact on the onset and course of bipolar disorder are scarce. Most research into this field concentrated on physical and sexual abuse. But there are indications that emotional abuse and neglect have the highest prevalence among trauma subtypes.[57,99–103] Emotional abuse seems to be disregarded in the literature. One possible explanation is the difficulty to detect emotional abuse in assessment surveys. It is worth noting that bipolar patients gain traumatic experience not only due to childhood trauma, but also as a consequence of their own disruptive behavior during manic episodes.[42]

Aas *et al.* also summarize biological and molecular modifications in bipolar disorder due to childhood trauma.[58] A reduction of brain-derived neurotrophic factor (BDNF)[44,48,49] plus alterations in inflammatory processes[53] and hypothalamic–pituitary–adrenal (HPA) axis functioning have been described.[50] Genetic variations in the following genes have been found as mediating factors in bipolar patients with traumatic experience: *BDNF val66met*,[48] *5-HTTLPR*,[51,54] *TLR2*,[55] *CLOCK*,[56] and SNPs near genes coding for calcium-channel-related proteins.[8] Furthermore, epigenetic modifications of HPA-axis-related genes, stress regulatory genes, and glucocorticoid receptor genes have been implicated. Additionally, reduced telomere length, a marker for biological aging, was found as a mediator of the negative effects of childhood trauma in bipolar disorders.[58]

Life events

The term 'life events' describes any substantial changes in personal surroundings resulting in personal and social consequences. Life events might occur unexpectedly or in an anticipated manner. The social zeitgeber theory has recently gained attention. Social zeitgebers comprise social contact and solitary activities. Changes in social zeitgebers are followed by rhythm disruption in daily life.[71] In consequence, biological circadian rhythms are disrupted and may affect mood stability.[60,72,104] Numerous researchers have shown that certain life events influence the age of onset and the clinical course of bipolar disorder.[7,11,59–62,64,66–68] The types of stressful life events differ in triggering either mania or depression. The literature emphasizes that positive life events and goal attainment are more likely to be followed by mania.[66,68,70,76] Others support the point of view that negative as well as positive life events are able to trigger both depression and mania.[63,65,69,70] Bereavement is assumed to trigger mania, while personal illness more likely causes depression.[67] Interpersonal problems, financial crises, work-related difficulties, failure, and job loss were often found prior to mania.[73] Unemployment at onset is considered to be a risk factor of relapse and psychotic features.[74,80] A poor premorbid social status does not influence the course of bipolar disorder.[80] Gershon *et al.* showed that trauma exposure is related to more severe interpersonal chronic stressors, which causes more severe depressive episodes.[75] There are indications that living in a mixed urban-rural area is associated with a higher risk of relapse.[74] Minor life events have less influence on mood changes than severe life events or several consecutive life events.[72,76] The definition of minor and major life events, respectively, remains uncertain as the perception of burden is highly individual. Overall, the findings are heterogeneous. There exists one prospective study with a considerable sample size of 222 patients by Simhandl *et al.*[77] More than 60% of the patients experienced at least one life event 6 months before a new episode. The risk of a depressive episode was associated with the number of life events, but was independent of the quality of the life event.[77] The quantity of life events has also been investigated. An increased life event load stands for a higher risk of experiencing a first episode plus subsequent episodes.[11,67,78] Whether life events are cause or consequence of mood changes is a topic debated frequently. Life events prior to subsequent episodes were discussed to be caused by the illness itself.[11,67,76] Kemner *et al.* reported that life events in consequence to affective episodes were independent from the psychiatric illness itself.[79] Furthermore, they report a slightly higher impact of life events on onset than on recurrence of bipolar disorder, which underlines Post's kindling hypothesis[78,79] that emphasizes that external triggers, such as life events, have a greater impact on the first episode than on subsequent episodes. Accordingly, recurrent episodes occur more autonomously and independently of life events.[11,105] In terms of life events over the lifespan, the decay model deserves mention. This model describes the fact that earlier life events will no longer have the same impact anymore as time passes. Due to life experience, people gain different coping strategies.[64,78] Thus, the kindling hypothesis is supported from another perspective.

Social support

Social support can be defined as the perception of being loved, cared for, esteemed, valued, and belonging to a network of communication and mutual obligation.[106] As poor social support is considered a long-term psychosocial stress, it has been a research topic in the field of psychiatric diseases. Its influence on bipolar disorder has been investigated as an important impact on clinical course of illness. The reverse influence of the severity of illness on social support should not be neglected. Up to now it has been poorly examined. Greenberg *et al.* published a review concerning social relationships in bipolar disorder. Emerging as the main results of this review is that individuals with bipolar disorder report deficits in many fields of social relationships, such as relationship to parents, family, partner, and friends.[87] The rate of relapse is higher in patients with low social support.[81,82,84,87] Here again, the causality remains unclear. Johnson *et al.* report that patients with incomplete recovery between episodes receive less social support and that vice versa less social support leads to a residual status complicating socialization.[84] Furthermore, the results show that having a partner at onset of illness has a positive effect on the course of illness, especially on the remission between episodes.[84] Furthermore, patients without partners have an increased risk of psychotic features.[80] Owen *et al.* investigated qualitative social factors that prevent or trigger suicidal thoughts and suicide attempts.[89] Overall, controversy surrounds the question of whether low social support influences the recurrence of mania or depression or both.[81,83,84] In addition to social support, family behavior plays an influencing role on the course of bipolar disorder. High expressed emotions and negative affective styles increase the likelihood of a higher risk of relapse.[85,86] High expressed emotions may even influence the prevalence of suicide ideation in young bipolar patients.[88] Miklowitz pointed out that patients who were more distressed by criticisms from their relatives showed more severe symptoms in both depression and mania.[107] Overall, research in this field faces challenges and limitations. Instruments for investigating social support are usually self-rating tools and the evaluation can often be influenced by mood episodes and a possible discrepancy between real and desired social integration. Consequently, the findings are inconsistent and need further investigation.

CONCLUSION

The available body of evidence suggests that environmental factors may either trigger or prevent the development of a psychiatric disorder. Moreover, there is some circumstantial evidence of an association between environmental factors and the clinical course of bipolar disorder.

To conclude, viral infections during pregnancy and adulthood might influence onset and clinical course of bipolar disorder. However, this is only supported by a scarce body of studies. Similarly, the studies concerning maternal smoking show inconsistent findings. Some researchers suggest a strong association between onset and clinical course of bipolar disorder and maternal smoking, and others do not. Likewise, the impact of birth complications on onset and course of bipolar disorder needs further research efforts to allow for robust findings. There is relatively ample data on the influence of climatic factors on bipolar disorder. The occurrence of depressive and manic episodes shows replicable seasonal peaks. Furthermore, there are indications that bipolar patients with seasonality suffer from more severe clinical course.

There are robust findings that childhood trauma triggers onset and especially clinical course. Bipolar patients with trauma history are more likely to show rapid cycling course, psychotic features, higher number of lifetime mood episodes, and greater risk for suicide ideation and attempts, and substance misuse. It seems worthwhile highlighting that emotional abuse has been disregarded in the literature although it is supposed to have the highest prevalence among adverse childhood experiences. Additionally, there are interesting findings in molecular biology, genetics, and epigenetics that need to be vetted in large-scale replication studies. Findings concerning the quality of live events remain inconsistent. As we might assume, social support influences the course of bipolar disorder, with low social support worsening the disease outcome. It is to be noted that live events and social support are influenced by the illness itself. Furthermore, there are national and cultural limitations to be pointed out. These have already been described by Merikangas in context of the World Mental Health Survey Initiative.[4] The countries in which the trials were carried out are listed in Table 1. Nevertheless, there is no detailed information about the participants' ethnicity. The impact of life events, trauma, and social

support on an individual varies across countries and cultures. For example, the actual impact of job loss on one's life will to a large part be determined by the level of social security or public welfare provided. In addition to that, the diagnosis of mental disorders is related to a different degree of stigmatization in different cultures and countries.

Overall, research in this field faces methodological challenges. Therefore, results should be considered cautiously. First, there are fundamental limitations due to different diagnostic definitions. Mostly, the diagnostic interviews are based on the DSM and ICD; still there is a cross-national and cross-cultural variation remaining (for diagnostic criteria see Table 1). In general, apart from environmental factors, trauma, and life events (which influence the clinical course), the differences in the availability of mental health treatment may have an important but often neglected impact on the illness. Most of the studies are retrospective and only a few provide long-term follow-up data. Furthermore, inconsistency of study designs, measures, and analyses lead to partially inconsistent findings. There is an evident problem of how to categorize the influencing factors into further (sub-) groups (see Fig. 1). Creating a standardized consensus categorization would simplify the comparison of research results. One approach has been reached by the International Society for Bipolar Disorders developing consensus nomenclature to describe course and outcome of bipolar disorder.[108] Even if this could be achieved, other challenges remain: we have to consider the critical timing of events and the distinction between general and personal risk factors. The field furthermore needs to reach consensus on the most reliable and valid assessment tools: Structured or at least semi-structured phenotyping tools may be preferred over self-rating questionnaires. Moreover, prospective study designs should be favored over retrospective approaches. Finally, truly large samples sizes are needed. This will require international collaborative networks of peers.

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DISCLOSURE STATEMENT

The authors declare no conflicts of interest.

AUTHOR CONTRIBUTIONS

F.A. and T.G.S. designed the study. F.A. wrote the first draft of the manuscript. Both authors worked on further versions of the manuscript and approved the current version.

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