Consumed by a forbidden emotion: anger and aggression in patients with psychiatric disorders

Bles, N.J. de

Consumed by a forbidden emotion

Anger and aggression in patients with psychiatric disorders

Nienke J. de Bles

Consumed by a forbidden emotion

Anger and aggression in patients with psychiatric disorders

Nienke J. de Bles

Consumed by a forbidden emotion:
Anger and aggression in patients with psychiatric disorders.

Author: Nienke de Bles
PhD thesis, Leiden University Medical Center, the Netherlands, 2023

Provided by thesis specialist Ridderprint, ridderprint.nl
Printing: Ridderprint
Cover design: D.M. de Bles
Layout and internal design: Timo Wolf Kamp, persoonlijkproefschrift.nl

Consumed by a forbidden emotion

Anger and aggression in patients with psychiatric disorders

Proefschrift

ter verkrijging van
de graad van doctor aan de Universiteit Leiden,
op gezag van rector magnificus prof. dr. ir. H. Bijl,
volgens besluit van het college voor promoties
te verdedigen op woensdag 26 april 2023
klokke 16.15 uur

door

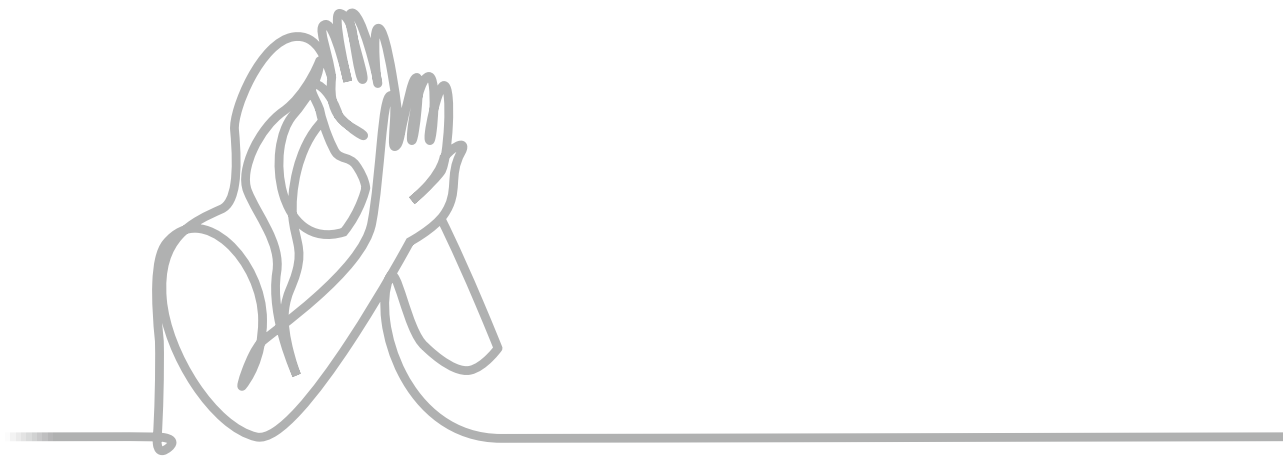
Nienke Jolande de Bles
geboren te Alkmaar
in 1992

Promotor
Prof. dr. A.M. van Hemert

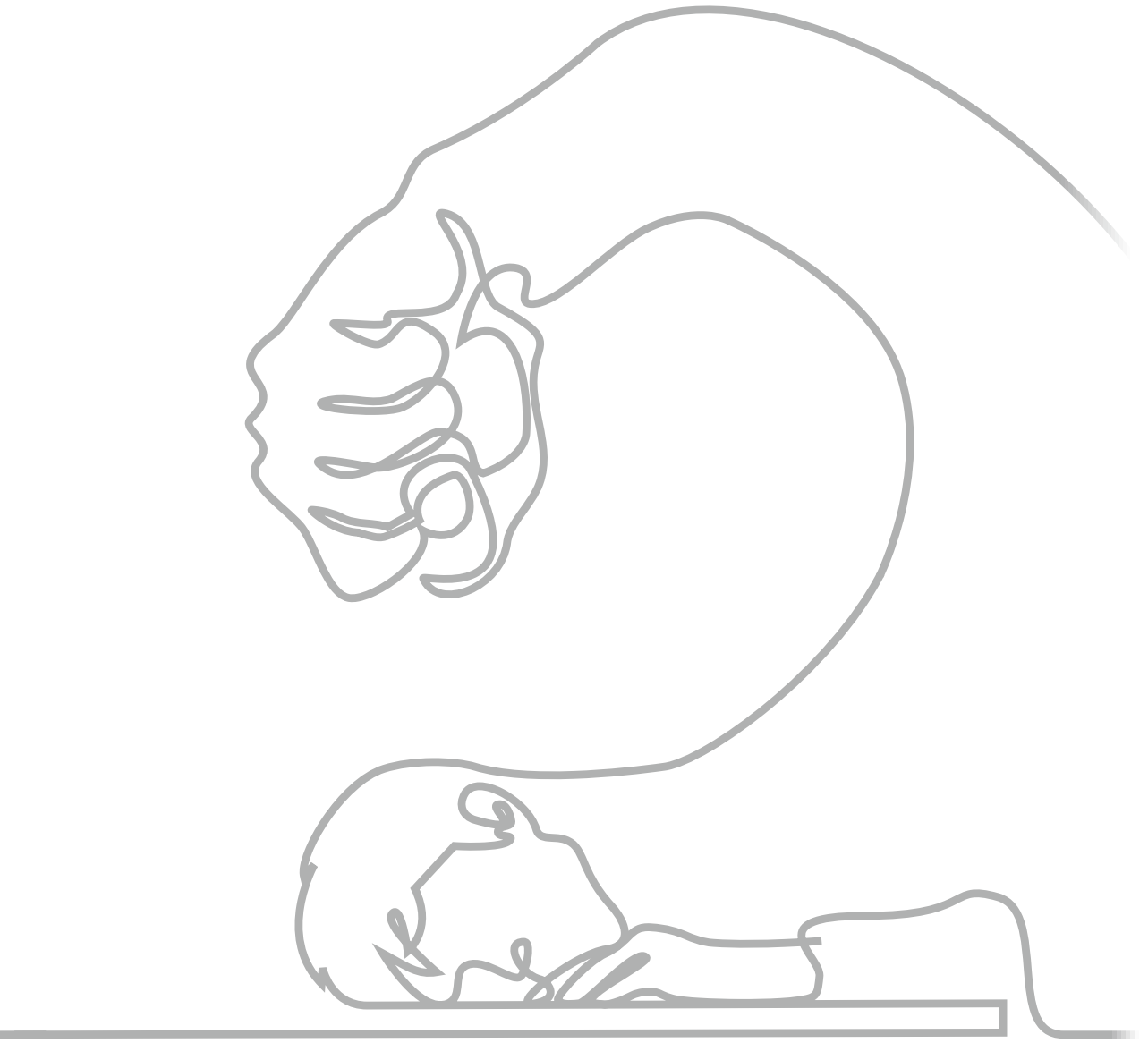
Co-promotoren
Dr. E.J. Giltay
Dr. N. Rius Ottenheim

Promotiecommissie
Prof. dr. J.C. Kiefte-de Jong
Prof. dr. B.M. Elzinga (Universiteit Leiden)
Prof. dr. J.M. Geleijnse (Wageningen University & Research)
Prof. dr. M. Morrens (Universiteit Antwerpen)

Table of contents



1 General introduction and outline of the thesis



Background

> *Anybody can become angry, that is easy; but to be angry with the right person, and to the right degree, and at the right time, for the right purpose, and in the right way, that is not within everybody's power and is not easy.*
>
> – Aristotle (384 BC – 322 BC)

Emotions are a universal part of the human condition. Like sadness and fear, anger is one of the negative emotions and is experienced regularly across cultures. When someone becomes angry, it is easy to recognize the emotion: frowning eyebrows, protruding nostrils, pursed lips. In appropriate (and usually mild) forms, anger has teleologic (evolutionary) advantages, as it ensures that we can set our boundaries and protect ourselves or loved ones in threatening situations. More accurately stated, in our evolutionary ancestry, this defence mechanism may have generated reproductive advantages for our genes, resulting in more replications of the multiple genes that determine the many facets of anger. However, anger becomes problematic if it occurs regularly or is very intense, especially in our current 'civilized' societies, where it is related to numerous negative (health) outcomes and poorer quality of life [1-4]. Although not always, anger can also trigger aggression and violent behaviour [5], including self-directed violence [6]. Despite these substantial effects of anger on individuals, relatives, and society, anger has long been overlooked in both research and clinical practice.

Anger

Since ancient times philosophers like Aristotle, Marcus Aurelius, and Nietzsche have pondered the definition of anger. One of the first modern definitions of anger was given by Spielberger,[7] and was described as follows:

> 'Anger is an emotional state that comprises feelings that vary in intensity from mild annoyance and aggravation to fury and rage, and that is accompanied by arousal of the autonomic nervous system'.

Although important aspects of anger are covered, the definition also has some limitations. First, it is limited to subjective feelings, and does not include cognitive or

behavioural components. Second, the definition states that annoyance and rage are synonyms of anger, rather than other related concepts. Third, it is a mere descriptive definition that does not encompass the purpose or goals of the emotional state. Consequently, Kennedy [8] described anger as:

> 'An affective state experienced as the motivation to act in ways that warn, intimidate, or attack those who are perceived as challenging or threatening. Anger is coupled to and is inseparable from a sensitivity to the perception of challenges or a heightened awareness of threats (irritability). This affective motivation and sensitivity can be experienced even if no external action occurs'.

An important aspect of Kennedy's definition is that it includes the motivational aspect of anger. More recently, these and other existing definitions have been integrated in the following broader definition:

> 'Anger is a subjectively experienced emotional state with high sympathetic autonomic arousal. It is initially elicited by a perception of a threat (to one's physical well-being, property, present or future resources, self-image, social status or projected image to one's group, maintenance of social rules that regulate daily life, or comfort), although it may persist even after the threat has passed. Anger is associated with attributional, informational, and evaluative cognitions that emphasize the misdeeds of others and motivate a response of antagonism to thwart, drive off, retaliate against, or attack the source of the perceived threat. Anger is communicated through facial or postural gestures or vocal inflections, aversive verbalizations, and aggressive behaviour. One's choice of strategies to communicate anger varies with social roles, learning history, and environmental contingencies' [9].

Yet, these given definitions are all characterized by their focus on anger as a state. However, Spielberger [7] stresses the importance of the distinction between states and traits of emotions. State anger is defined as an emotional–physiological condition that occurs in response to an immediate stressor or threat. If severe, such a state can develop into an anger attack: sudden spells of anger accompanied by symptoms of autonomic activation such as tachycardia, sweating, hot flashes, or tightness of the chest [10]. Trait anger, on the other hand, refers to individual differences in anger proneness as a personality trait. Trait anger is related to state anger as it is assumed

that high trait anger individuals experience more frequent state anger [7, 11]. Another important distinction that is often made, is between the experience and the expression of anger. Making a distinction between individuals who are often feeling angry but never express these feelings, and individuals who are expressing anger every time they are feeling angry is of clinical importance. The same is true for individuals with an angry disposition as a constant factor embedded in personality, and individuals who respond angrily to an immediate situation. In conclusion, the definition of anger and related concepts remains subject to semantic discussion; definitions differ. To identify individuals most prone to anger, it is important to be aware of what is and what is not considered anger.

Aggression

Aggression is a behaviour that ranges from mild acts, such as swearing, to more severe acts, such as physical assaults [12, 13]. Although aggression shows a robust relationship with anger, they serve as distinct outcomes of interest, as anger does not always lead to aggression, nor is aggression necessarily motivated by anger [14]. Due to the variety of forms and contexts, it is not always clear to define what is, and what is not aggression. Aggression has been defined as:

> 'Any behaviour directed toward another individual that is carried out with the proximate (immediate) intent to cause harm. In addition, the perpetrator must believe that the behaviour will harm the target, and that the target is motivated to avoid the behaviour' [15].

This operational definition comprises four characteristics of aggression that need nuancing. First, aggression relates to behaviour, and does not include an emotion or cognition. Second, aggression is intentional, though sometimes unconscious. Third, aggressive behaviour comprises another individual, meaning that aggression towards objects does not fall under the definition unless it is intended to harm another individual. And last, the target is motivated to avoid the behaviour. The latter characteristic excludes suicide-related behaviour from the realm of aggression, which could be relevant in the context of monitoring aggression amongst psychiatric patients. The necessity of intention to commit aggressive behaviour is still subject to debate [16]. Unintentional aggression is especially common among psychiatric patients, as aggressive acts could be a consequence of a psychotic state. Therefore, several measures of

aggression, such as the Staff Observation Aggression Scale – Revised (SOAS-R) monitor a broader range of aggressive behaviours, including self-mutilation and aggressive acts in the context of a psychosis. The underlying definition for the SOAS-R described aggression as 'any verbal, non-verbal or physical behaviour that was threatening or physical behaviour that actually did harm (to self, others or property)' [17].

Anger and aggression among psychiatric patients

Currently, there is only one disorder described in the fifth edition of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-5) with a primary focus on anger and aggression among adults, which is the Intermittent Explosive Disorder (IED) [18]. However, anger and related concepts such as irritability are mentioned as a diagnostic criterion for some other disorders, including Post-Traumatic Stress Disorder (PTSD) and Borderline Personality Disorder (BPD). Nevertheless, even without anger or aggression being mentioned as a diagnostic criterion, it is suggested that pathological anger is common across different psychiatric disorders [19]. Research has shown that half of psychiatric outpatients reported moderate to severe anger [20]. Furthermore, aggression is highly prevalent among psychiatric inpatients, as aggressive behaviour regularly was the triggering event that led to a referral to inpatient care. Thus, anger and aggression play a prominent role beyond anger-related disorders as mentioned by the DSM-5, and could have a substantial influence on the development and treatment of psychiatric disorders [19]. However, despite its presumed meaningfulness, anger is often described as "forgotten emotion", as it is much less studied in the literature compared to emotions such as sadness (depression), fear (anxiety), and even happiness (mania). The term "psychiatry" in combination with "depression" (141,661 results), "anxiety" (68,366 results), or "mania" (7,179 results) revealed much more results compared to "psychiatry AND anger" (4,251 results) on PubMed. These findings might reflect the forbidden aspect of anger, as there is a strong social disapproval of being angry. The expression of anger might lead to harmful events, including events which are prohibited by law, leading to a tendency to suppress the feeling of being angry in a social context. Given the dearth of knowledge with respect to anger in research literature, which has led to a scarcity of anger instruments, and psychological and pharmacological treatment options, there is a serious need to identify individuals most prone to anger and to establish the mechanisms by which anger presents itself, to better initiate effective treatment.

Affective disorders

Strong relationships were found between anger on the one hand, and a range of mood and anxiety disorders on the other hand - even after adjusting for demographics and comorbidity [21-23]. Originally, psychoanalysts like Abraham [24] and Freud (1917) presumed depression to be a result of anger turned inward. In their view, excess anger towards the self may cause feelings of guilt, worthlessness and self-criticism [25]. More recently, another theory assumed that failure to handle anger potentially leads to helplessness, with a depressive disorder as a potential consequence [9]. As both hypotheses assume a prominent role of anger in the onset and course of depression, it is of importance to identify individuals most prone to high levels of anger. Previous studies have shown high levels of irritability among almost half of patients with major depressive disorder (MDD) [26, 27]. Also, elevated levels of hostility, anger, and difficulties with anger expression are often reported in depressed patients [28-31]. The prevalence of anger attacks ranged from 26% to 49% in individuals with MDD [32-38], and from 28% to 53% in patients with dysthymia [2, 38]. Furthermore, two longitudinal studies reported a three times increased risk of violent offending in individuals with depression compared to the general population [39].

Likewise, anger is common across anxiety disorders, with anger attacks being reported by one-third of the patients [40]. However, different patterns of anger experience and anger expression have been suggested for each of the different anxiety disorders [22]. Generalized Anxiety Disorder (GAD) is the only anxiety disorder for which an anger related concept, namely irritability, is mentioned as a diagnostic criterion in the DSM-5 [41]. Indeed, multiple dimensions of anger, including aggressive behaviour, were shown to be related to GAD [20, 22, 42, 43]. Similarly, patients suffering from panic disorder (PD) reported significantly elevated levels of anger compared to controls [22, 44]. Also, patients with obsessive compulsive disorder (OCD) have shown difficulties with the expression of anger, among which anger attacks and anger toward the self [45, 46]. In contrast, although the experience of anger was also elevated among patients with social phobia (SP), these patients were more likely to suppress their anger, resulting in a low prevalence of verbal aggression and anger attacks [22, 40, 43, 44]. Thus, anger and aggression among patients with anxiety disorders seems disorder dependent, which makes it important to study the strength of the relationship with anger separately according to the specific diagnosis.

Bipolar Disorder (BD), which is characterized by both manic and depressive episodes, was found to be most robustly correlated with symptoms of anger compared to depressive- and anxiety disorders [43]. Evidence suggests that the relationship

between anger and BD was largely independent from the mood (i.e., manic or depressive) episodes, and anger was also found to be common during prodromal phases [47]. Furthermore, anger attacks were reported twice as often (62%) among depressed bipolar patients compared to unipolar depressed counterparts (26%) [33]. Prevalence rates of anger attacks did not differ between bipolar I versus bipolar II subtypes [48], which was in line with a longitudinal study that reported higher scores on self-reported anger and aggression among individuals with either bipolar I or bipolar II disorder compared to nonbipolar psychiatric controls and healthy controls across 4-year follow-up [49]. Aggression among patients with BD comprises mainly impulsive aggression and occurs during the manic phase [50, 51].

Personality disorders

Personality disorders are characterized as enduring, cognitive, behavioural, or emotional disturbances in more than one domain of function. The development of personality disorders is a complex interaction between genes and environmental factors, including childhood trauma [52]. Core dimensions in – especially cluster B – personality include affective instability and impulsive aggression amongst others. Personality disorders were found to be associated with elevated levels of subjective anger and a threefold increase in the odds of aggressive behaviour compared with the general population, with cluster B personality disorders (i.e., antisocial, borderline, histrionic, and narcissistic personality disorder) making a unique contribution to these outcomes [20, 23, 53]. This is particularly the case for Borderline Personality Disorder (BPD), being one of the few disorders for which intense anger or difficulty controlling anger, and emotional instability including irritability is listed as a diagnostic DSM-5 criterion [41]. In addition, being easily provoked or aggressive is a diagnostic criterion for Antisocial Personality Disorder (ASPD) [41]. Therefore, existing literature regarding anger and aggression among personality disorders most often refers to BPD and ASPD. These studies found higher scores on trait anger, state anger, and lifetime aggression, including against themselves, among patients with BPD compared to controls [54-56]. Among inpatients diagnosed with BPD anger was reported by almost 90% [57], and 73% engaged in violence over the course of one year [58]. These high percentages could be explained by comorbid ASPD amongst others [58, 59]. Consistently, individuals diagnosed with ASPD had an almost thirteenfold increase in violent outcomes compared to the general population [53]. Despite the high prevalence of anger and aggression, evidence for the efficacy of psychotherapy [60, 61] and psychopharmacology [62, 63] among personality disorders is limited.

Schizophrenia spectrum disorders

Schizophrenia and related psychoses have also been associated with aggression, although the mechanisms through which people with a psychotic illness progress to actual acts of violence has been understudied [64, 65]. It is suggested that the direct relationship between the experience of anger and aggressive behaviour which is often seen in the general population is different in the context of psychotic illness. Among the latter, the experience and expression of anger and aggression could be a product of paranoid delusions and perceptual distortions [65, 66]. This was in line with studies that found heightened levels of trait anger to be associated with delusional pathology, paranoia, and impulsivity among individuals with schizophrenia [67, 68]. Among inpatients with psychotic illness, angry feelings were particularly problematic, as they were related to self-harming behaviours and attentional demands towards the staff [69]. Furthermore, aggressive behaviours were found among approximately one third of the people with schizophrenia worldwide [70], with the risk of aggression being 51.5% among inpatients versus 15.2% among schizophrenic outpatients [71]. These aggressive behaviours are related to numerous negative outcomes for patients themselves, including coercion and involuntary hospitalization [72]. In addition, involuntary patients have been found to be more aggressive during hospitalization, which may lead to distress and may be traumatic for other patients and staff [13, 73]. Aggression reduction already has a high priority in psychiatric inpatient care (e.g., de-escalating programs, adequate pharmacotherapy), but more effective and innovative methods to prevent aggression are needed [74].

Substance use disorders

Individuals with psychiatric disorders often have cooccurring substance use disorders (SUDs) and vice versa [75]. SUDs have been shows to be associated with elevated anger [43], including state and trait anger and difficulties controlling anger [76-78], leading to aggressive behaviour. Aggressive behaviour was observed either as a direct result of the substance consumed, or during substance withdrawal. Aggression might be a result of disinhibitory effects of alcohol intoxication [79], while on the contrary, cannabis intoxication might reduce aggression in the first place, but increases during withdrawal [80, 81]. A meta-analysis showed that the risk of aggressive behaviour among patients with schizophrenia spectrum disorders with substance abuse is similar to that for patients with substance abuse without psychosis [64]. In sum, it could be hypothesized that elevated anger and aggression among psychiatric patients could be explained by

(comorbid) SUDs rather than the mental illness itself, which might be of interest for aggression reduction strategies.

Neurobiological correlates of anger and aggression

From the reviewed literature, anger and aggression seem prevalent among diverse psychiatric patients. Yet, it does not apply to all psychiatric patients. Therefore, to develop effective interventions for those who are at risk, it is also important to better understand the underlying neurobiological processes, besides the social, psychological, and psychiatric causes, underlying both anger and aggression. One of these suggested approaches that could be of transdiagnostic relevance comprises the identification of biological markers. However, one must notice that mental disorders might not be explained by monocausal frameworks, but rather by a network approach point of view, where symptoms may cohere as syndromes because of mutually reinforcing symptoms [82].

Serotonin

One of the best-studied neurotransmitters related to aggression is 5-hydroxytryptamine (5-HT), commonly known as serotonin. Extensive research showed that serotonin seems to be inversely related to aggression [83]. Selective serotonin reuptake inhibitors (SSRI) including fluoxetine have shown anti-aggressive effects in randomised trials among psychiatric patients [84-86]. There are also indications that the deprivation of the amino acid tryptophan, the dietary precursor of serotonin, can induce aggressiveness, although effects are small [83]. In addition, the serotonergic system seems to be involved in brain regions including the amygdala and prefrontal regions, specifically when processing angry faces [87-89]. In sum, evidence leads to the hypothesis that serotonin does not act as a unitary system but rather is involved in complex parallel circuits.

Hypothalamic–pituitary–adrenal (HPA)-axis

The contributing role of the hypothalamic-pituitary-adrenal (HPA)-axis is another focus of research in unravelling aggressive behaviour. The HPA-axis is central in stress-regulating mechanisms and is often assessed using measures of its most important end-product cortisol. Cortisol only has an effect after binding to one of two related transcription factors: the glucocorticoid receptor (GR) and mineralocorticoid receptor (MR). Whereas MR is important in maintaining basal conditions, GR plays an

important role in the stress response via a negative feedback loop regulating HPA-axis activity. Severe stress in early life could induce long-lasting alterations of the HPA axis [90]. For example, a decrease of GR activation was seen after lower maternal care, leading to hypoactivity of the HPA-axis due to an impaired feedback loop [91]. It has been hypothesized that a heightened HPA axis response to stress might be linked to reactive aggression [92]. As a result of the latter, individuals with decreased basal levels of cortisol may be more sensitive to provocation and react more aggressively compared to others [93].

Immune system

In the past few decades, an important link has been found between the immune system, cytokines, and aggression [16, 94]. The immune system is composed of innate and adaptive immune responses, with the intracellular parasite *Toxoplasma gondii (T. gondii)* provoking one of the most potent pro-inflammatory responses [95]. Inflammatory cytokine levels might contribute to sickness behaviour and other psychological effects, including irritability and aggression [94, 96, 97]. Elevated inflammatory cytokine levels including interleukin-6 (IL-6), tumor necrosis factor-α (TNF-α), and C-reactive protein (CRP) have been found to be linked to high aggression traits among healthy individuals [98]. Studies among psychiatric patients confirmed these findings. A chronic inflammatory state was linked to aggressive BD patients both towards themselves as well as towards others [99]. In addition, a positive relationship was found between cerebrospinal fluid soluble interleukin-1 Receptor II (sIL-1RII) and aggression in individuals with a personality disorder [100]. Increased levels of pro-inflammatory markers including IL-6, TNF-α, IL-1β, and IL-RA have also been found among schizophrenic patients [101]. However, meta-analyses found inconsistent results which could be explained by differences in antipsychotic treatment amongst others [101].

Nutritional psychiatry

An important role in biological processes including the synthesis of neurotransmitters and inflammation, is the supply of essential nutrients, such as lipids, amino acids, vitamins, and minerals, with the gut-brain axis as a potential mediating pathway [102-106]. Deficiencies of these essential nutrients are consequently thought to deteriorate the brain's structure and functioning. For example, vitamin B6, vitamin B12 and folate are crucial in the formation of neurotransmitters such as epinephrine, norepinephrine, γ-amino butyric acid, and serotonin [102]. In particular, a deficiency in serotonin seems

to play a key role in depressed mood, considering that selective serotonin reuptake inhibitors (SSRIs) are generally accepted in the recovery from mental illness [107], and the deprivation of the amino acid tryptophan, the dietary precursor of serotonin, can induce a lowered mood [108]. As a consequence, diet is suggested to be a modifiable factor affecting mood and behaviour [105, 109-111], giving rise to the field that is often called 'nutritional psychiatry' [112].

Nutritional supplementation and mental illness

Mounting evidence suggests that micronutrient supplementation may have a beneficial effect among people with mental illnesses. Strongest evidence was found for polyunsaturated fatty acids (PUFA), with several meta-analyses that reported the efficacy of PUFA on depressive symptoms in major depressive disorder (MDD) [113]. However, the quality of these studies was being questioned, and small-to-modest positive effects of n-3PUFAs were not clinically beneficial on depressive symptomology [114]. Mixed results were also found among people with schizophrenia. Meta-analyses reported a lack of significant benefits [115, 116], although a recent review found n-3PUFAs to be effective in reducing psychotic symptom severity in the prodromal phase of schizophrenia on [117]. The relationship between other vitamins (such as vitamin E, C or D) and mental illness have scarcely been studied [118], especially among long-stay psychiatric inpatients [111]. Such inpatients are likely to have a poorer nutritional status than the general population, due to the consumption of more energy-dense and nutrient-poor diets, insufficient outdoor activities (lowering vitamin D status), as well as potential detrimental effect of psychotropics (e.g., antipsychotics) on appetite, gastrointestinal function, the microbiome, and (energy and micronutrient) metabolism [119-121]. Studies have found that participants with the lowest nutrient concentrations seemed to have benefited the most from nutritional supplementation [117, 122]. It can therefore be hypothesized that psychiatric inpatients are liable to deficiencies and may benefit from supplementation with essential nutrients.

Nutritional supplementation and aggressive behaviour

Previous literature has explored the effectiveness of nutritional supplementation in the reduction of aggressive behaviour. These studies focused on young male prisoners [122-125] and children with behavioural problems [126-128], some of whom were diagnosed with autism spectrum disorder (ASD) [129], attention deficit hyperactivity disorder (ADHD) [130], conduct disorder (CD), and oppositional defiant disorder (ODD) [131]. These randomized controlled trials showed reductions in aggression, with 26% to 47% less

aggression-related incidents in the group receiving nutritional supplements compared to those receiving a placebo [122-126]. In addition, trials that assessed subjective feelings of aggression as an outcome showed findings that were in line with these studies that assessed actual aggressive behaviour [127-131]. However, in these previous trials, patients with psychosis were often excluded [127, 128, 130, 131] or no information on the use of psychotropic medication was given [123, 126]. Therefore, the effectiveness of nutritional supplements in reducing aggressive incidents needs to be confirmed in a sample of long-stay psychiatric inpatients among whom aggressive incidents are common.

Data

The Netherlands Study of Depression and Anxiety (NESDA)

The first part of this thesis is based on data from the Netherlands Study of Depression and Anxiety (NESDA). NESDA is an ongoing longitudinal, multisite, naturalistic cohort study and was designed to examine the long-term course and consequences of depressive and anxiety disorders. At baseline, a total of 2981 participants (18–65 years) were recruited from community care (19%), primary care (54%), and specialized mental health care (27%) in the Netherlands. This population was composed of participants with current or remitted depressive and anxiety disorders, and comorbid depressive and anxiety disorders. The control group consisted of participants without lifetime psychiatric disorders. Exclusion criteria were (1) the presence of other psychiatric disorders (e.g., psychotic, obsessive–compulsive, bipolar, or severe addiction disorder) and (2) not being fluent in Dutch. Assessments included a face-to-face interview, written questionnaires, and biological measurements. These assessments started in 2004 and since then have been repeated six times over a period of 9 years. Data on anger, including trait anger and anger attacks, were gathered at the 4th wave at 4-year follow up between August 2008 and May 2011. Participants who completed this wave totalled 2402 (80.6% of the original cohort). A more detailed description of NESDA is given elsewhere [132].

Diet and Aggression

The second part of this thesis comprises data from the Diet and Aggression trial, which was registered in the Clinical Trials Register (NCT02498106). This pragmatic, multicentre, randomized, double-blind, placebo-controlled, intervention trial aimed to assess whether multivitamin, mineral, and n-3 PUFA supplementation would reduce aggressive incidents among long-stay psychiatric inpatients. The trial was coordinated

in the department of psychiatry at the Leiden University Medical Centre (LUMC). Participants were recruited between 25 July 2016 through 29 October 2019 from 8 local sites for mental healthcare in the Netherlands and Belgium. Data collection took place at the ward where the participants resided. Inclusion criteria were (1) being 18 years or older and (2) expected to reside at a facility for long-term psychiatric inpatient care for at least 6 months, irrespective of their specific psychiatric disorder. Exclusion criteria were (1) pregnancy, (2) breastfeeding, (3) contra-indication for nutritional supplements, (4) expected discharge or transfer within eight weeks, (5) restrictions against the consumption of pork gelatine, and (6) continuous use of other nutritional supplements (within the preceding eight weeks), exceptions included vitamin B1 and D, which are mostly prescribed to prevent complications of alcoholism or to treat low vitamin D plasma levels in Northern countries, respectively, and which entailed no health risks in combination with this study's supplements. We assessed 1,121 patients for eligibility and excluded 945. In total, 176 participants were randomised into the trial (supplements, *n* = 87; placebo, *n* = 89). Most included patients suffered from a psychotic disorder (60.8%).

Aims and outline of this thesis

Aims

This thesis aims to unravel the occurrence, potential determinants, and treatment of anger and aggression among both psychiatric outpatients and psychiatric inpatients. The main objectives of this thesis are:

1. To examine whether and to what extent anger and aggression are associated with psychiatric disorders (Chapter 2, 3 and 6).
2. To deepen our understanding of some aspects of the pathophysiology of anger manifestations (Chapter 4 and 5).
3. To investigate the effectiveness of nutritional supplementation to reduce aggressive incidents among psychiatric inpatients (Chapter 7 and 8).

Outline

In this thesis, we discuss several studies that were undertaken to describe the prevalence and potential pathways of anger and aggression. Chapters 2 and 3 comprise research on the relationship between different anger measures and depressive-, anxiety- and bipolar disorder. In **Chapter 2**, we examined to what extent depressive and anxiety disorders, relevant clinical correlates, and sociodemographics determined the

level of trait anger and the prevalence of recent anger attacks. Thereafter, in **Chapter 3**, we investigated whether patients who converted to BD showed more feelings of anger, including borderline and antisocial personality traits, than people with unipolar depression. Additionally, the predictive role of aggression reactivity in conversion to BD was determined. Chapters 4 and 5 address the pathophysiology of anger among psychiatric outpatients. **Chapter 4** describes the associations of childhood trauma and anger constructs in adulthood. We also address which types of childhood trauma predominate in the prediction of anger. In **Chapter 5**, the associations between *T. gondii* infection and affective disorders, as well as with aggression reactivity and suicidal thoughts were examined. Chapters 6, 7 and 8 focus on aggression among long-stay psychiatric inpatients. In **Chapter 6,** an estimation is given on the overall incidence of aggression and the weighted average financial costs thereof in long-term psychiatric inpatient care. In **Chapter 7**, we describe the results from an RCT which assessed whether multivitamin, mineral and n-3 PUFA supplementation was effective in reducing the number of aggressive incidents among long-term psychiatric inpatients. Lessons learned from the RCT described in Chapter 7, in combination with a comparable RCT, are presented in **Chapter 8.** Finally, in **Chapter 9**, our main findings are summarized and considered within the current perspective. Suggestions are made for future research.

References

1. Chida Y, Steptoe A. The association of anger and hostility with future coronary heart disease: a meta-analytic review of prospective evidence. *Journal of the American College of Cardiology*. 2009;53(11):936-46.
2. Painuly N, Grover S, Gupta N, Mattoo SK. Prevalence of anger attacks in depressive and anxiety disorders: implications for their construct? *Psychiatry and clinical neurosciences*. 2011;65(2):165-74.
3. Mostofsky E, Penner EA, Mittleman MA. Outbursts of anger as a trigger of acute cardiovascular events: a systematic review and meta-analysis. *Eur Heart J*. 2014;35(21):1404-10.
4. Pouwer F, Kupper N, Adriaanse MC. Does emotional stress cause type 2 diabetes mellitus? A review from the European Depression in Diabetes (EDID) Research Consortium. *Discov Med*. 2010;9(45):112-8.
5. Chereji SV, Pintea S, David D. The relationship of anger and cognitive distortions with violence in violent offender's population: A meta-analytic review. *European Journal of Psychology Applied to Legal Context*. 2012;4(1).
6. Orri M, Perret LC, Turecki G, Geoffroy MC. Association between irritability and suicide-related outcomes across the life-course. Systematic review of both community and clinical studies. *Journal of affective disorders*. 2018;239:220-33.
7. Spielberger CD, Krasner SS, Solomon EP. The Experience, Expression, and Control of Anger. In: Janisse MP, editor. Individual Differences, Stress, and Health Psychology. New York, NY: Springer New York; 1988. p. 89-108.
8. Kennedy HG. Anger and irritability. *The British journal of psychiatry : the journal of mental science*. 1992;161:145-53.
9. DiGiuseppe R, Tafrate RC. Understanding anger disorders: Oxford University Press; 2007.
10. Fava M, Anderson K, Rosenbaum JF. "Anger attacks": possible variants of panic and major depressive disorders. *The American journal of psychiatry*. 1990;147(7):867-70.
11. Spielberger CD, Gorsuch RL, Lushene RE, Vagg PR, Jacobs GA. Manual for the State-Trait Anxiety Inventory. Palo Alto, CA: Consulting Psychologists Press; 1983.
12. Frueh BC, Knapp RG, Cusack KJ, Grubaugh AL, Sauvageot JA, Cousins VC, et al. Patients' reports of traumatic or harmful experiences within the psychiatric setting. *Psychiatric services (Washington, DC)*. 2005;56(9):1123-33.
13. Nijman HLI, Bowers L, Oud N, Jansen G. Psychiatric nurses' experiences with inpatient aggression. *Aggressive behavior*. 2005;31(3):217-27.
14. Lee AH, DiGiuseppe R. Anger and aggression treatments: a review of meta-analyses. *Current Opinion in Psychology*. 2018;19:65-74.
15. Anderson CA, Bushman BJ. Human aggression. *Annual review of psychology*. 2002;53.
16. Manchia M, Comai S, Pinna M, Pinna F, Fanos V, Denovan-Wright E, et al. Biomarkers in aggression. *Adv Clin Chem*. 2019;93:169-237.
17. Morrison EF. Violent psychiatric inpatients in a public hospital. *Scholarly inquiry for nursing practice*. 1990;4(1):65-82; discussion 3-6.
18. Association AP. Diagnostic and statistical manual of mental disorders (DSM-5®): American Psychiatric Pub; 2013.
19. Cassiello-Robbins C, Barlow DH. Anger: The Unrecognized Emotion in Emotional Disorders. *Clinical Psychology: Science and Practice*. 2016;23(1):66-85.

20. Posternak MA, Zimmerman M. Anger and aggression in psychiatric outpatients. *The Journal of clinical psychiatry*. 2002;63(8):665-72.
21. Barrett EM, KL; Teesson, M. Mental health correlates of anger in the general population: Findings from the 2007 National Survey of Mental Health and Wellbeing. *Australian & New Zealand Journal of Psychiatry*. 2013;47(5):470-6.
22. Hawkins KA, Cougle JR. Anger problems across the anxiety disorders: findings from a population-based study. *Depression and anxiety*. 2011;28(2):145-52.
23. Genovese T, Dalrymple K, Chelminski I, Zimmerman M. Subjective anger and overt aggression in psychiatric outpatients. *Compr Psychiatry*. 2017;73:23-30.
24. Abraham K. Notes on the psycho-analytical investigation and treatment of manic-depressie insanity and allied conditions. . 1927 ed: Hogarth Press; 1911.
25. Busch FN. Anger and depression. *Advances in Psychiatric Treatment*. 2009;15(4):271-8.
26. Fava M, Hwang I, Rush AJ, Sampson N, Walters EE, Kessler RC. The importance of irritability as a symptom of major depressive disorder: results from the National Comorbidity Survey Replication. *Molecular psychiatry*. 2010;15(8):856-67.
27. Verhoeven FE, Booij L, Van der Wee NJ, Penninx BW, Van der Does AJ. Clinical and physiological correlates of irritability in depression: results from the Netherlands study of depression and anxiety. *Depression research and treatment*. 2011;2011:126895.
28. Riley WT, Treiber FA, Woods MG. Anger and hostility in depression. *The Journal of nervous and mental disease*. 1989;177(11):668-74.
29. Judd LL, Schettler PJ, Coryell W, Akiskal HS, Fiedorowicz JG. Overt irritability/anger in unipolar major depressive episodes: past and current characteristics and implications for long-term course. *JAMA psychiatry*. 2013;70(11):1171-80.
30. Fisher LB, Fava M, Doros GD, Alpert JE, Henry M, Huz I, et al. The Role of Anger/Hostility in Treatment-Resistant Depression: A Secondary Analysis From the ADAPT-A Study. *The Journal of nervous and mental disease*. 2015;203(10):762-8.
31. Pasquini M, Picardi A, Biondi M, Gaetano P, Morosini P. Relevance of Anger and Irritability in Outpatients with Major Depressive Disorder. *Psychopathology*. 2004;37(4):155-60.
32. Winkler D, Pjrek E, Kasper S. Anger attacks in depression--evidence for a male depressive syndrome. *Psychotherapy and psychosomatics*. 2005;74(5):303-7.
33. Perlis RH, Smoller JW, Fava M, Rosenbaum JF, Nierenberg AA, Sachs GS. The prevalence and clinical correlates of anger attacks during depressive episodes in bipolar disorder. *Journal of affective disorders*. 2004;79(1-3):291-5.
34. Sayar K, Guzelhan Y, Solmaz M, Ozer OA, Ozturk M, Acar B, et al. Anger attacks in depressed Turkish outpatients. *Annals of clinical psychiatry : official journal of the American Academy of Clinical Psychiatrists*. 2000;12(4):213-8.
35. Winkler D, Pjrek E, Kindler J, Heiden A, Kasper S. Validation of a simplified definition of anger attacks. *Psychotherapy and psychosomatics*. 2006;75(2):103-6.
36. Fava M, Rosenbaum JF, Pava JA, McCarthy MK, Steingard RJ, Bouffides E. Anger attacks in unipolar depression, Part 1: Clinical correlates and response to fluoxetine treatment. *The American journal of psychiatry*. 1993;150(8):1158-63.

37. Fava M, Alpert J, Nierenberg AA, Ghaemi N, O'Sullivan R, Tedlow J, et al. Fluoxetine treatment of anger attacks: a replication study. *Annals of clinical psychiatry : official journal of the American Academy of Clinical Psychiatrists*. 1996;8(1):7-10.
38. Fava M, Nierenberg AA, Quitkin FM, Zisook S, Pearlstein T, Stone A, et al. A preliminary study on the efficacy of sertraline and imipramine on anger attacks in atypical depression and dysthymia. *Psychopharmacology bulletin*. 1997;33(1):101-3.
39. Fazel S, Wolf A, Chang Z, Larsson H, Goodwin GM, Lichtenstein P. Depression and violence: a Swedish population study. *The Lancet Psychiatry*. 2015;2(3):224-32.
40. Gould RA, Ball S, Kaspi SP, Otto MW, Pollack MH, Shekhar A, et al. Prevalence and correlates of anger attacks: a two site study. *Journal of affective disorders*. 1996;39(1):31-8.
41. APA. Diagnostic and Statistical Manual of Mental Disorders, 5th ed. Washington, DC: American Psychiatric Association; 2013.
42. Deschenes SS, Dugas MJ, Fracalanza K, Koerner N. The role of anger in generalized anxiety disorder. *Cogn Behav Ther*. 2012;41(3):261-71.
43. Barrett EL, Mills KL, Teesson M. Mental health correlates of anger in the general population: Findings from the 2007 National Survey of Mental Health and Wellbeing. *Australian & New Zealand Journal of Psychiatry*. 2013;47(5):470-6.
44. Moscovitch DA, McCabe RE, Antony MM, Rocca L, Swinson RP. Anger experience and expression across the anxiety disorders. *Depression and anxiety*. 2008;25(2):107-13.
45. Painuly N, Grover S, Mattoo SK, Gupta N. Anger attacks in obsessive compulsive disorder. *Industrial psychiatry journal*. 2011;20(2):115-9.
46. Whiteside SP, Abramowitz JS. Obsessive-Compulsive Symptoms and the Expression of Anger. *Cognitive Therapy and Research*. 2004;28(2):259-68.
47. Skjelstad DV, Malt UF, Holte A. Symptoms and signs of the initial prodrome of bipolar disorder: A systematic review. *Journal of affective disorders*. 2010;126(1-2):1-13.
48. Mammen OK, Pilkonis PA, Chengappa KN, Kupfer DJ. Anger attacks in bipolar depression: predictors and response to citalopram added to mood stabilizers. *The Journal of clinical psychiatry*. 2004;65(5):627-33.
49. Ballester J, Goldstein B, Goldstein TR, Yu H, Axelson D, Monk K, et al. Prospective longitudinal course of aggression among adults with bipolar disorder. *Bipolar disorders*. 2014;16(3):262-9.
50. Látalová K. Bipolar disorder and aggression. *International Journal of Clinical Practice*. 2009;63(6):889-99.
51. Volavka J. Violence in schizophrenia and bipolar disorder. *Psychiatr Danub*. 2013;25(1):24-33.
52. Goodman M, New A, Siever L. Trauma, genes, and the neurobiology of personality disorders. *Ann N Y Acad Sci*. 2004;1032:104-16.
53. Yu R, Geddes JR, Fazel S. Personality disorders, violence, and antisocial behavior: a systematic review and meta-regression analysis. *J Pers Disord*. 2012;26(5):775-92.
54. Prada P, Hasler R, Baud P, Bednarz G, Ardu S, Krejci I, et al. Distinguishing borderline personality disorder from adult attention deficit/hyperactivity disorder: a clinical and dimensional perspective. *Psychiatry research*. 2014;217(1-2):107-14.
55. Lampe K, Konrad K, Kroener S, Fast K, Kunert HJ, Herpertz SC. Neuropsychological and behavioural disinhibition in adult ADHD compared to borderline personality disorder. *Psychological medicine*. 2007;37(12):1717-29.

56. Joyce PR, Mulder RT, Luty SE, McKenzie JM, Sullivan PF, Cloninger RC. Borderline personality disorder in major depression: symptomatology, temperament, character, differential drug response, and 6-month outcome. *Compr Psychiatry*. 2003;44(1):35-43.
57. Mary C. Zanarini ED, Frances R. Frankenburg MD, D. Bradford Reich MD, Kenneth R. Silk MD, James I. Hudson MD, Sc.D. ,, Lauren B. McSweeney BA. The Subsyndromal Phenomenology of Borderline Personality Disorder: A 10-Year Follow-Up Study. *American Journal of Psychiatry*. 2007;164(6):929-35.
58. Newhill CE, Eack SM, Mulvey EP. Violent behavior in borderline personality. *J Pers Disord*. 2009;23(6):541-54.
59. Allen A, Links PS. Aggression in borderline personality disorder: evidence for increased risk and clinical predictors. *Curr Psychiatry Rep*. 2012;14(1):62-9.
60. Rameckers SA, Verhoef REJ, Grasman R, Cox WR, van Emmerik AAP, Engelmoer IM, et al. Effectiveness of Psychological Treatments for Borderline Personality Disorder and Predictors of Treatment Outcomes: A Multivariate Multilevel Meta-Analysis of Data from All Design Types. *J Clin Med*. 2021;10(23).
61. Gibbon S, Khalifa NR, Cheung N-Y, Völlm BA, McCarthy L. Psychological interventions for antisocial personality disorder. *Cochrane Database of Systematic Reviews*. 2020(9).
62. Khalifa NR, Gibbon S, Völlm BA, Cheung NH, McCarthy L. Pharmacological interventions for antisocial personality disorder. *Cochrane Database Syst Rev*. 2020;9(9):Cd007667.
63. Gartlehner G, Crotty K, Kennedy S, Edlund MJ, Ali R, Siddiqui M, et al. Pharmacological Treatments for Borderline Personality Disorder: A Systematic Review and Meta-Analysis. *CNS drugs*. 2021;35(10):1053-67.
64. Fazel S, Gulati G, Linsell L, Geddes JR, Grann M. Schizophrenia and violence: systematic review and meta-analysis. *PLoS Med*. 2009;6(8):e1000120.
65. Reagu S, Jones R, Kumari V, Taylor PJ. Angry affect and violence in the context of a psychotic illness: a systematic review and meta-analysis of the literature. *Schizophr Res*. 2013;146(1-3):46-52.
66. Darrell-Berry H, Berry K, Bucci S. The relationship between paranoia and aggression in psychosis: A systematic review. *Schizophrenia Research*. 2016;172(1):169-76.
67. Gadea M, Herrero N, Picó A, Espert R, Salvador A, Sanjuán J. Psychobiological response to an anger induction task in schizophrenia: The key role of anxiety. *Psychiatry research*. 2019;271:541-7.
68. Darrell-Berry H, Bucci S, Palmier-Claus J, Emsley R, Drake R, Berry K. Predictors and mediators of trait anger across the psychosis continuum: The role of attachment style, paranoia and social cognition. *Psychiatry research*. 2017;249:132-8.
69. Fassino S, Amianto F, Gastaldo L, Leombruni P. Anger and functioning amongst inpatients with schizophrenia or schizoaffective disorder living in a therapeutic community. *Psychiatry and clinical neurosciences*. 2009;63(2):186-94.
70. Li W, Yang Y, Hong L, An FR, Ungvari GS, Ng CH, et al. Prevalence of aggression in patients with schizophrenia: A systematic review and meta-analysis of observational studies. *Asian journal of psychiatry*. 2019;47:101846.
71. Ose SO, Lilleeng S, Pettersen I, Ruud T, van Weeghel J. Risk of violence among patients in psychiatric treatment: results from a national census. *Nord J Psychiatry*. 2017;71(8):551-60.

72. Canova Mosele PH, Chervenski Figueira G, Antonio Bertuol Filho A, Ferreira de Lima JAR, Calegaro VC. Involuntary psychiatric hospitalization and its relationship to psychopathology and aggression. *Psychiatry research*. 2018;265:13-8.
73. Bowers L, Stewart D, Papadopoulos C, Dack C, Ross J, Khanom H, et al. Inpatient violence and aggression: a literature review. 2011.
74. Health NCCfM, editor Violence and Aggression: short-term management in mental health, health and community settings: updated edition2015: British Psychological Society.
75. Robinson ZD, Riggs PD. Cooccurring Psychiatric and Substance Use Disorders. *Child and adolescent psychiatric clinics of North America*. 2016;25(4):713-22.
76. Aharonovich E, Nguyen HT, Nunes EV. Anger and depressive states among treatment-seeking drug abusers: testing the psychopharmacological specificity hypothesis. *Am J Addict*. 2001;10(4):327-34.
77. Fernandez E, Scott S. Anger treatment in chemically-dependent inpatients: evaluation of phase effects and gender. *Behav Cogn Psychother*. 2009;37(4):431-47.
78. Lin WF, Mack D, Enright RD, Krahn D, Baskin TW. Effects of forgiveness therapy on anger, mood, and vulnerability to substance use among inpatient substance-dependent clients. *Journal of consulting and clinical psychology*. 2004;72(6):1114-21.
79. McCloskey MS, Berman ME, Echevarria DJ, Coccaro EF. Effects of acute alcohol intoxication and paroxetine on aggression in men. *Alcoholism, clinical and experimental research*. 2009;33(4):581-90.
80. Budney AJ, Moore BA, Vandrey RG, Hughes JR. The time course and significance of cannabis withdrawal. *J Abnorm Psychol*. 2003;112(3):393-402.
81. Kouri EM, Pope HG, Jr., Lukas SE. Changes in aggressive behavior during withdrawal from long-term marijuana use. *Psychopharmacology (Berl)*. 1999;143(3):302-8.
82. Robinaugh DJ, Hoekstra RHA, Toner ER, Borsboom D. The network approach to psychopathology: a review of the literature 2008-2018 and an agenda for future research. *Psychological medicine*. 2020;50(3):353-66.
83. Duke AA, Bègue L, Bell R, Eisenlohr-Moul T. Revisiting the serotonin-aggression relation in humans: a meta-analysis. *Psychol Bull*. 2013;139(5):1148-72.
84. Coccaro EF, Lee RJ, Kavoussi RJ. A double-blind, randomized, placebo-controlled trial of fluoxetine in patients with intermittent explosive disorder. *The Journal of clinical psychiatry*. 2009;70(5):653-62.
85. George DT, Phillips MJ, Lifshitz M, Lionetti TA, Spero DE, Ghassemzedeh N, et al. Fluoxetine treatment of alcoholic perpetrators of domestic violence: a 12-week, double-blind, randomized, placebo-controlled intervention study. *The Journal of clinical psychiatry*. 2011;72(1):60-5.
86. Silva H, Iturra P, Solari A, Villarroel J, Jerez S, Jiménez M, et al. Fluoxetine response in impulsive-aggressive behavior and serotonin transporter polymorphism in personality disorder. *Psychiatr Genet*. 2010;20(1):25-30.
87. Rosell DR, Siever LJ. The neurobiology of aggression and violence. *CNS spectrums*. 2015;20(3):254-79.
88. Grady CL, Siebner HR, Hornboll B, Macoveanu J, Paulson OB, Knudsen GM. Acute pharmacologically induced shifts in serotonin availability abolish emotion-selective responses to negative face emotions in distinct brain networks. *European Neuropsychopharmacology*. 2013;23(5):368-78.

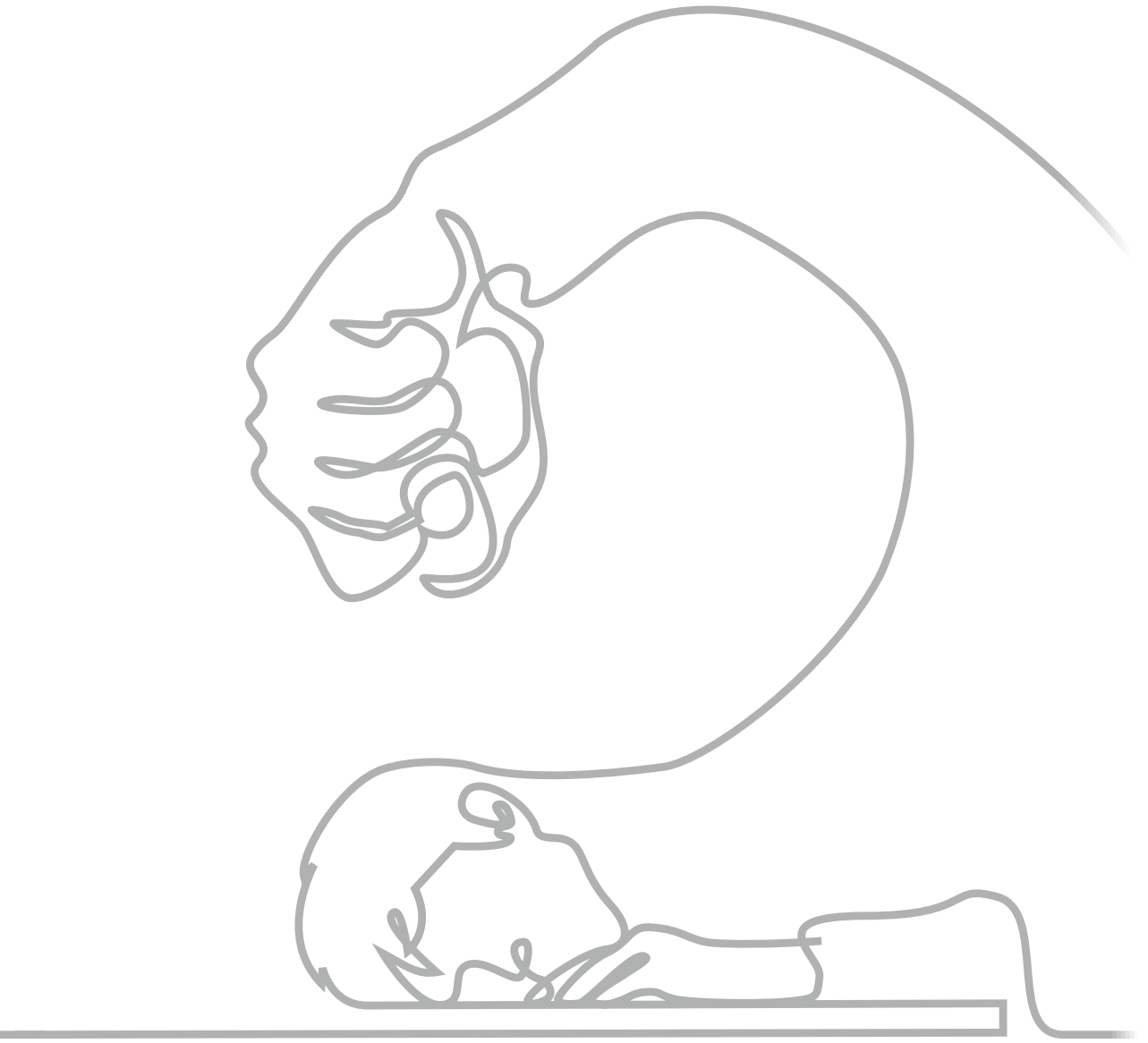
89. Passamonti L, Crockett MJ, Apergis-Schoute AM, Clark L, Rowe JB, Calder AJ, et al. Effects of acute tryptophan depletion on prefrontal-amygdala connectivity while viewing facial signals of aggression. *Biological psychiatry*. 2012;71(1):36-43.
90. van Bodegom M, Homberg JR, Henckens MJAG. Modulation of the Hypothalamic-Pituitary-Adrenal Axis by Early Life Stress Exposure. *Frontiers in Cellular Neuroscience*. 2017;11(87).
91. Weaver ICG, Cervoni N, Champagne FA, D'Alessio AC, Sharma S, Seckl JR, et al. Epigenetic programming by maternal behavior. *Nature Neuroscience*. 2004;7(8):847-54.
92. Lopez-Duran NL, Olson SL, Hajal NJ, Felt BT, Vazquez DM. Hypothalamic pituitary adrenal axis functioning in reactive and proactive aggression in children. *Journal of abnormal child psychology*. 2009;37(2):169-82.
93. Böhnke R, Bertsch K, Kruk MR, Naumann E. The relationship between basal and acute HPA axis activity and aggressive behavior in adults. *Journal of neural transmission (Vienna, Austria : 1996)*. 2010;117(5):629-37.
94. Zalcman SS, Siegel A. The neurobiology of aggression and rage: role of cytokines. *Brain Behav Immun*. 2006;20(6):507-14.
95. Miller CM, Boulter NR, Ikin RJ, Smith NC. The immunobiology of the innate response to Toxoplasma gondii. *International journal for parasitology*. 2009;39(1):23-39.
96. Dantzer R, O'Connor JC, Freund GG, Johnson RW, Kelley KW. From inflammation to sickness and depression: when the immune system subjugates the brain. *Nature reviews Neuroscience*. 2008;9(1):46-56.
97. van Eeden WA, van Hemert AM, Carlier IVE, Penninx B, Lamers F, Fried EI, et al. Basal and LPS-stimulated inflammatory markers and the course of individual symptoms of depression. *Translational psychiatry*. 2020;10(1):235.
98. Takahashi A, Flanigan ME, McEwen BS, Russo SJ. Aggression, Social Stress, and the Immune System in Humans and Animal Models. *Front Behav Neurosci*. 2018;12:56.
99. Fico G, Anmella G, Pacchiarotti I, Verdolini N, Sagué-Vilavella M, Corponi F, et al. The biology of aggressive behavior in bipolar disorder: A systematic review. *Neuroscience and biobehavioral reviews*. 2020;119:9-20.
100. Coccaro EF, Lee R, Coussons-Read M. Cerebrospinal fluid inflammatory cytokines and aggression in personality disordered subjects. *Int J Neuropsychopharmacol*. 2015;18(7):pyv001-pyv.
101. Momtazmanesh S, Zare-Shahabadi A, Rezaei N. Cytokine Alterations in Schizophrenia: An Updated Review. *Front Psychiatry*. 2019;10:892.
102. Parletta N, Milte CM, Meyer BJ. Nutritional modulation of cognitive function and mental health. *The Journal of nutritional biochemistry*. 2013;24(5):725-43.
103. Haag M. Essential fatty acids and the brain. *Canadian journal of psychiatry Revue canadienne de psychiatrie*. 2003;48(3):195-203.
104. Scapagnini G, Davinelli S, Drago F, De Lorenzo A, Oriani G. Antioxidants as antidepressants: fact or fiction? *CNS drugs*. 2012;26(6):477-90.
105. Mörkl S, Wagner-Skacel J, Lahousen T, Lackner S, Holasek SJ, Bengesser SA, et al. The Role of Nutrition and the Gut-Brain Axis in Psychiatry: A Review of the Literature. *Neuropsychobiology*. 2020;79(1-2):80-8.

106. Calderón-Ospina CA, Nava-Mesa MO. B Vitamins in the nervous system: Current knowledge of the biochemical modes of action and synergies of thiamine, pyridoxine, and cobalamin. *CNS neuroscience & therapeutics*. 2020;26(1):5-13.
107. Vaswani M, Linda FK, Ramesh S. Role of selective serotonin reuptake inhibitors in psychiatric disorders: a comprehensive review. *Prog Neuropsychopharmacol Biol Psychiatry*. 2003;27(1):85-102.
108. Neumeister A, Hu X-Z, Luckenbaugh DA, Schwarz M, Nugent AC, Bonne O, et al. Differential Effects of 5-HTTLPR Genotypes on the Behavioral and Neural Responses to Tryptophan Depletion in Patients With Major Depression and Controls. *Archives of general psychiatry*. 2006;63(9):978-86.
109. Benton D. The impact of diet on anti-social, violent and criminal behaviour. *Neuroscience and biobehavioral reviews*. 2007;31(5):752-74.
110. Adan RAH, van der Beek EM, Buitelaar JK, Cryan JF, Hebebrand J, Higgs S, et al. Nutritional psychiatry: Towards improving mental health by what you eat. *European neuropsychopharmacology : the journal of the European College of Neuropsychopharmacology*. 2019.
111. Marx W, Moseley G, Berk M, Jacka F. Nutritional psychiatry: the present state of the evidence. *The Proceedings of the Nutrition Society*. 2017;76(4):427-36.
112. Sarris J, Logan AC, Akbaraly TN, Amminger GP, Balanza-Martinez V, Freeman MP, et al. Nutritional medicine as mainstream in psychiatry. *The lancet Psychiatry*. 2015;2(3):271-4.
113. Mocking RJ, Harmsen I, Assies J, Koeter MW, Ruhé HG, Schene AH. Meta-analysis and meta-regression of omega-3 polyunsaturated fatty acid supplementation for major depressive disorder. *Translational psychiatry*. 2016;6(3):e756.
114. Appleton KM, Sallis HM, Perry R, Ness AR, Churchill R. Omega-3 fatty acids for depression in adults. *Cochrane Database Syst Rev*. 2015;2015(11):Cd004692.
115. Grosso G, Pajak A, Marventano S, Castellano S, Galvano F, Bucolo C, et al. Role of omega-3 fatty acids in the treatment of depressive disorders: a comprehensive meta-analysis of randomized clinical trials. *PloS one*. 2014;9(5):e96905.
116. Fusar-Poli P, Solmi M, Brondino N, Davies C, Chae C, Politi P, et al. Transdiagnostic psychiatry: a systematic review. *World psychiatry : official journal of the World Psychiatric Association (WPA)*. 2019;18(2):192-207.
117. Hsu MC, Huang YS, Ouyang WC. Beneficial effects of omega-3 fatty acid supplementation in schizophrenia: possible mechanisms. *Lipids Health Dis*. 2020;19(1):159.
118. Firth J, Teasdale SB, Allott K, Siskind D, Marx W, Cotter J, et al. The efficacy and safety of nutrient supplements in the treatment of mental disorders: a meta-review of meta-analyses of randomized controlled trials. *World psychiatry : official journal of the World Psychiatric Association (WPA)*. 2019;18(3):308-24.
119. Gezmen-Karadag M, Celik E, Kadayifci FZ, Yesildemir O, Ozturk YE, Agagunduz D. Role of fooddrug interactions in neurological and psychological diseases. *Acta neurobiologiae experimentalis*. 2018;78(3):187-97.
120. Sloane PD, Ivey J, Helton M, Barrick AL, Cerna A. Nutritional issues in long-term care. *Journal of the American Medical Directors Association*. 2008;9(7):476-85.
121. Maier L, Pruteanu M, Kuhn M, Zeller G, Telzerow A, Anderson EE, et al. Extensive impact of non-antibiotic drugs on human gut bacteria. *Nature*. 2018;555(7698):623-8.

122. Schoenthaler S, Amos S, Doraz W, Kelly M-A, Muedeking G, Jr JW. The Effect of Randomized Vitamin-Mineral Supplementation on Violent and Non-violent Antisocial Behavior Among Incarcerated Juveniles. *Journal of Nutritional & Environmental Medicine*. 1997;7(4):343-52.
123. Zaalberg A, Nijman H, Bulten E, Stroosma L, van der Staak C. Effects of nutritional supplements on aggression, rule-breaking, and psychopathology among young adult prisoners. *Aggressive behavior*. 2010;36(2):117-26.
124. Gesch CB, Hammond SM, Hampson SE, Eves A, Crowder MJ. Influence of supplementary vitamins, minerals and essential fatty acids on the antisocial behaviour of young adult prisoners. Randomised, placebo-controlled trial. *The British journal of psychiatry : the journal of mental science*. 2002;181:22-8.
125. Schoenthaler S, Gast D, Giltay EJ, Amos S. The Effects of Vitamin-Mineral Supplements on Serious Rule Violations in Correctional Facilities for Young Adult Male Inmates: A Randomized Controlled Trial. *Crime & Delinquency*. 2021:0011128721989073.
126. Schoenthaler SJ, Bier ID. The effect of vitamin-mineral supplementation on juvenile delinquency among American schoolchildren: a randomized, double-blind placebo-controlled trial. *Journal of alternative and complementary medicine (New York, NY)*. 2000;6(1):7-17.
127. Long SJ, Benton D. A double-blind trial of the effect of docosahexaenoic acid and vitamin and mineral supplementation on aggression, impulsivity, and stress. *Human psychopharmacology*. 2013;28(3):238-47.
128. Tammam JD, Steinsaltz D, Bester DW, Semb-Andenaes T, Stein JF. A randomised double-blind placebo-controlled trial investigating the behavioural effects of vitamin, mineral and n-3 fatty acid supplementation in typically developing adolescent schoolchildren. *The British journal of nutrition*. 2016;115(2):361-73.
129. Adams JB, Audhya T, McDonough-Means S, Rubin RA, Quig D, Geis E, et al. Effect of a vitamin/mineral supplement on children and adults with autism. *BMC pediatrics*. 2011;11:111.
130. Rucklidge JJ, Eggleston MJF, Johnstone JM, Darling K, Frampton CM. Vitamin-mineral treatment improves aggression and emotional regulation in children with ADHD: a fully blinded, randomized, placebo-controlled trial. *Journal of child psychology and psychiatry, and allied disciplines*. 2018;59(3):232-46.
131. Raine A, Cheney RA, Ho R, Portnoy J, Liu J, Soyfer L, et al. Nutritional supplementation to reduce child aggression: a randomized, stratified, single-blind, factorial trial. *Journal of child psychology and psychiatry, and allied disciplines*. 2016;57(9):1038-46.
132. Penninx BWJH, Beekman ATF, Smit JH, Zitman FG, Nolen WA, Spinhoven P, et al. The Netherlands Study of Depression and Anxiety (NESDA): rationale, objectives and methods. *International Journal of Methods in Psychiatric Research*. 2008;17(3):121-40.

Published as: de Bles, N. J., Rius-Ottenheim, N., van Hemert, A. M., Pütz, L. E. H., van der Does, A. J. W., Penninx, B. W. J. H., & Giltay, E. J. (2019). Trait anger and anger attacks in relation to depressive and anxiety disorders. *Journal of Affective Disorders*, *259*, 259-265.

2 Trait anger and anger attacks in relation to depressive and anxiety disorders



Abstract

Background: Patients with various psychiatric disorders may suffer from feelings of anger, sometimes leading to maladaptive (e.g., aggressive) behaviours. We examined to what extent depressive and anxiety disorders, relevant clinical correlates, and sociodemographics determined the level of trait anger and the prevalence of recent anger attacks.

Methods: In the Netherlands Study of Depression and Anxiety (NESDA), the Spielberger Trait Anger Subscale and the Anger Attacks Questionnaire were analysed in patients with depressive (n = 204), anxiety (n = 288), comorbid (n = 222), and remitted disorders (n = 1107), as well as in healthy controls (n = 470) based on DSM-IV criteria.

Results: On average, participants were 46.2 years old (SD = 13.1) and 66.3% were female. Trait anger and anger attacks were most prevalent in the comorbid group (M = 18.5, SD = 5.9, and prevalence 22.1%), followed by anxiety disorder, depressive disorder, remitted disorder, and controls (M = 12.7; SD = 2.9, and prevalence 1.3%). Major depressive disorder, social phobia, panic disorder, and generalized anxiety disorder were most strongly associated to trait anger and anger attacks.

Limitations: Due to a cross-sectional design, it was not possible to provide evidence for temporal or causal relationships between anger and depressive and anxiety disorders.

Conclusions: Trait anger and anger attacks are linked to depressive and anxiety disorders, although the strength of the relationship differed among both anger constructs.

Introduction

Anger is a common emotion and ranges from mild irritation to fury. In mild forms, anger can be functional in threatening situations but becomes problematic if it occurs regularly or is very intense. High levels of anger may be associated with maladaptive behaviours, resulting in adverse health outcomes and poorer quality of life [1-5]. Anger can also trigger aggression and violent behaviour [6, 7], and is related to lifetime suicidality [8]. Given the serious consequences for individuals and society, it is of importance to identify individuals most prone to high levels of anger.

To identify predictors of anger, we made the distinction between "trait anger" and "state anger." Trait anger connotes an angry disposition: a proneness to experience feelings of anger. State anger refers to an emotional–physiological condition that occurs in response to an immediate stressor or threat [9, 10]. If severe, such a state can develop into an anger attack: sudden spells of anger accompanied by symptoms of autonomic activation such as tachycardia, sweating, hot flashes, or tightness of the chest [11].

Several psychological constructs are closely linked to anger. Almost half of patients with major depressive disorder (MDD) have shown high levels of irritability [12, 13]. Also, elevated levels of anger and hostility are often reported in depressed patients [14, 15]. The prevalence of anger attacks ranged from 26% to 49% in individuals with MDD [16-20] and from 28% to 53% in patients with dysthymia [4, 21].

Patients with anxiety disorders also showed increased levels of anger; 29–32% experience anger attacks [22]. Similarly, patients with generalized anxiety disorder (GAD), obsessive–compulsive disorder (OCD), social phobia (SP), and panic disorder (PD) experience higher levels of hostility and anger compared to controls [23-25].

To summarize, the available literature on this topic indicates that anger is more prevalent in individuals with depression or anxiety. Yet, most previous studies used insufficiently validated instruments or used only a single item to measure irritability. To date, two large-scale population-based cohort studies have been conducted, including 5692 [26] and 8841 participants [27] and a patient-based study included 3800 psychiatric outpatients [28]. All three studies reported strong relationships with depressive and anxiety disorders-even after adjusting for demographics and comorbidity. However, anger was assessed through two [28] and four items [27] that were compiled from larger questionnaires (i.e., Schedule for Affective Disorders and Schizophrenia and the International Personality Disorder Examination respectively). Those items were originally part of a questionnaire measuring another construct. Hence, their

validity to measure anger is unknown. In addition, existing research has not provided for a clear distinction between trait and state anger. Given that anger research is scarce, it is important to examine the construct and broader context of anger in order to understand this heterogeneous construct. While research suggests different patterns for anger experience and anger expression in relation to anxiety disorders [26], the same can be thought of for state and trait anger. Making a distinction between patients with an angry disposition as a constant factor embedded in personality, and patients that respond angrily to an immediate situation, is of clinical importance. This may enable patients and clinicians to more effectively target anger-related problems.

We aimed to investigate the prevalence of anger and its sociodemographic and clinical associations using validated trait anger and anger attack measures in a cohort that included patients without lifetime psychiatric disorders ("control subjects"), with current or remitted depressive and anxiety disorders, or comorbid depressive and anxiety disorders.

Methods

Participants

Participants stemmed from the Netherlands Study of Depression and Anxiety (NESDA), an ongoing longitudinal, multisite, naturalistic cohort study. At baseline, 2981 participants (18–65 years) were recruited from community care (19%), primary care (54%), and specialized mental health care (27%) in the Netherlands. The study included individuals without lifetime psychiatric disorders ("control subjects"), with current or remitted depressive and anxiety disorders, or comorbid depressive and anxiety disorders. Exclusion criteria included not speaking Dutch and having another primary clinical diagnosis (e.g., psychotic, obsessive–compulsive, bipolar, or severe addictive disorders). All participants gave written informed consent before enrolment, and the ethical committees of participating universities (VU University Medical Centre, Leiden University Medical Centre, and University Medical Centre Groningen) granted ethical approval. For a detailed description of NESDA [29].

Data on anger were gathered at the 4th wave at 4-year follow up between August 2008 and May 2011. Participants who completed this wave totalled 2402 (80.6%). Participants with missing data on one or both anger questionnaires ($n = 111$) were excluded, yielding 2291 participants for the current analyses. Participants with missing data at the 4-year follow-up had more severe depressive ($p < 0.001$) and anxiety (p's < 0.05) symptoms compared to the sample included in this paper.

Measurements

Trait anger

We assessed trait anger using the Dutch adaptation of the Spielberger State–Trait Anger Scale (STAS; [30, 31], which consists of two self-report questionnaires that measure state and trait anger. In the current study, we only administered the subscale for trait anger that measured individual differences in anger proneness as a personality trait. The trait anger scale consists of 10 items and is further divided into two sub scores: temperament (i.e., a general disposition for experiencing anger and eventually expressing it; Items 1, 2, 3, 5, and 6) and reaction (i.e., a general disposition for expressing anger, especially after provocation; Items 7, 8, and 10). Participants score each item on a 4-point Likert scale, ranging from 1 (*almost never*) to 4 (*almost always*), and total sum score ranges from 10 to 40. Items 4 and 9 ("I get annoyed quickly," "I am quickly irritated," respectively) measure the immediacy of an anger response [32]. Psychometric research showed good item correlations and high test–retest reliability [31]. The internal consistency (i.e., Cronbach's alpha) in our sample was 0.89.

Anger attacks

The Anger Attacks Questionnaire is a self-rating scale developed to assess the presence of distinct forms of anger attacks during the past 6 months [33]. Anger attacks are sudden spells of anger accompanied by symptoms of autonomic activation and are uncharacteristic actions that are inappropriate for a situation [11]. To identify a patient who is experiencing anger attacks, all of the following criteria needed to be met during the past 6 months: (1) irritability, (2) overreaction to minor annoyances, (3) inappropriate anger and rage directed at others, (4) incidence of at least one anger attack within the past month, and (5) occurrence of at least four out of the following 13 autonomic and/or behavioural features in at least one of the attacks: tachycardia, hot flashes, tightness of the chest, paraesthesia, dizziness, shortness of breath, sweating, trembling, panic, feeling out of control, feeling like attacking others, attacking physically or verbally, and throwing or destroying objects [34].

Depressive and anxiety disorders

The Composite International Diagnostic Interview (CIDI; WHO version 2.1), a comprehensive, fully standardized diagnostic interview, was used to screen for depressive (i.e., MDD, dysthymia) and anxiety disorders (i.e., PD, SP, GAD, agoraphobia [AP]) based on criteria of the fourth edition of the Diagnostic and Statistical Manual of Mental

Disorders (DSM-IV [35]). Upon completing the CIDI, participants were categorized into one of five psychopathology groups: (1) healthy participants with no current or past history of psychiatric dis- orders (*n* = 470); (2) participants with a lifetime history of a depressive or anxiety disorder, but not in the preceding 6 months (*n* = 1262); (3) patients with a depressive (*n* = 141) or (4) anxiety disorder (*n* = 263) within their last 6 months; and (5) patients with comorbid depressive and anxiety disorders within their last 6 months (*n* = 155).

Symptom severity

Depression. The 30-item Inventory of Depressive Symptomatology (self-report version; IDS-SR) was used to measure severity of depressive symptoms during the last 7 days [36, 37]. Patients scored items on a 4-point Likert scale (0–3), ranging from 0 to 84 points (only 28 of the 30 items are rated). A higher overall score on the IDS indicates more severe depression symptoms.

Anxiety. Anxiety was assessed using three severity scales. The self-report, 21-item Beck Anxiety Inventory (BAI) focuses on somatic symptoms of anxiety during the past week [38]. Patients rated items on a 4-point Likert scale with total scores ranging from 0 to 63 points. The self-report, 15-item Fear Questionnaire (FQ; [39]) assesses level of distress and avoidance of situations (i.e., AP, SP, and blood-injury phobia) using a 9-point Likert scale, with total scores ranging from 0 to 120. The 16-item, self-report Penn State Worry Questionnaire (PSWQ; [40]) assesses pathological worry and general anxiety on a 5-point Likert scale. Although the original PSWQ includes 11 positively worded items and 5 negatively worded items, NESDA used the abbreviated 11-item version due to significantly stronger correlations and a higher internal consistency, with a Cronbach's alpha of 0.94 compared to a Cronbach's alpha of 0.90 for the original version [41]. The total score ranges from 11 to 55 points.

Covariates

Sociodemographic covariates were self-reported age, gender, level of education (in years), and any use of drugs in the past month. Body Mass Index (BMI) was calculated based on measured height and weight, and smoking status (current/not current) and lifetime DSM IV-based alcohol dependency and abuse were assessed using the CIDI.

Statistical analyses

Sociodemographic and clinical characteristics were summarized within the five groups of psychopathologies using descriptive statistics. Categorical variables were presented

as proportions and continuous variables as means with standard deviations (*SD*). An analysis of variance (ANOVA) compared the mean levels of the continuous variable trait anger, and chi-squared tests were used to compare the prevalence of the dichotomous variable anger attacks among psychopathology groups. In our study, we repeated the analyses and adjusted for sex, age, level of education, BMI, smoking, alcohol dependence/abuse, and drug use using analysis of covariance (ANCOVA) and multivariable logistic regression analyses. We used (stacked) bar plots to examine differences in prevalence rates among psychopathology groups. Therefore, we divided the total score of trait anger into high and low scores based on the 75th percentile scores of the total group—a score higher than P_{75} represented high trait anger.

We also performed multivariable linear and logistic regression analyses to examine the associations of trait anger and anger attacks, respectively, according to demographic characteristics and psychiatric disorders. These associations were first tested in an unadjusted model. Subsequently, we adjusted the full model according to sex, age, level of education, BMI, smoking status, alcohol dependency/abuse, drug use, dysthymia, MDD, SP, PD, AP, and GAD.

Four symptom severity scales (i.e., depression, anxiety, fear, and worry) were measured to explore which symptom was more strongly associated with trait anger and anger attacks. We plotted fully adjusted mean scores of these anger scores for the four severity scales. All statistical tests were based on continuous scores of severity scales. A two- tailed significance level of $p < 0.05$ was considered statistically significant. Analyses were performed using IBM SPSS statistical software (version 23, IBM Corp).

Results

Sample characteristics

The mean age of the participants ($N = 2291$) was 46.2 years ($SD = 13.1$), and 66.3% were female. As shown in Table 1, participants with a remitted or current disorder had significantly fewer years of education and a higher BMI, were more often smokers, and more often suffered from alcohol dependency/abuse than healthy controls. These participants also scored higher on depression and anxiety severity scales and used more psychotropic medication compared to healthy controls.

Prevalence of trait anger and anger attacks

Between-group differences were present for all anger measures (all p values < 0.001; see Table 2) that persisted in the adjusted models, ($F(4, 2113) = 70.15$, $p < 0.001$ for trait

anger and $\chi^2(11) = 122.12$, $p < 0.001$ for anger attacks). Similarly, (adjusted) subscale scores of trait anger (i.e., "Temperament" and "Reaction") differed significantly among the five groups. The adjusted odds of anger attacks were 21.4 times higher for patients with current comorbid anxiety and depression than for healthy controls.

Fig. 1 shows the differences in prevalence rates among psychopathology groups in (stacked) bar plots. Controls had the lowest prevalence of high trait anger (5.1%), whereas patients with comorbid disorders had the highest prevalence (43.7%). A significant trend was found for anger attacks over psychopathology groups; controls showed the lowest prevalence (1.3%) and patients with comorbid disorders showed the highest prevalence (22.1%). The distribution of having anger attacks and trait anger scores are presented in Fig. 1 of the Supplementary material.

Correlates of trait anger and anger attacks

Table 3 shows the result of linear regression analyses for trait anger according to demographic characteristics and psychiatric disorders. In the fully adjusted model, being male, ($\beta = -0.060$, $p = 0.004$), completing fewer years of education ($\beta = -0.047$, $p = 0.03$), depending on or abusing alcohol ($\beta = 0.090$, $p < 0.001$), and drug use ($\beta = 0.045$, $p = 0.04$) remained independently associated with trait anger. All psychiatric disorders were associated with higher trait anger scores in the (adjusted) model; MDD, SP, and GAD showed the strongest independent associations (β's > 0.1, $p < 0.001$).

For results of logistic regression analyses for anger attacks see Table 4. Younger age, fewer years of education, alcohol dependency/ abuse, drug use, depressive and anxiety disorders related significantly to anger attacks in the crude models. In the fully adjusted model, significance remained only for age (*OR* = 0.81), drug use (*OR* = 2.41), MDD (*OR* = 1.62), and anxiety disorders (i.e., SP *OR* = 1.70, PD *OR* = 2.08, GAD *OR* = 3.61), but not AP.

The adjusted mean values and *OR*s of trait anger and anger attacks in relation to symptom severity (i.e., IDS, PSWQ, BAI, and FQ) are presented in Fig. 2 of the Supplementary material. The mean values indicated a general pattern of linear associations (Supp. Fig. 2A, 2C, 2E, 2G). Adjusted *OR*s with 95% confidence intervals (CI) show that all severity scores had linear associations with trait anger and anger attacks, though of different strengths (Supp. Fig. 2B, 2D, 2F, 2H). The IDS and PSWQ showed the strongest associations for both trait anger and anger attacks.

Table 1. Baseline characteristics of the study sample (*N* = 2291) according to psychopathology groups

	Controls (*n* = 470)	Remitted anxiety and/or depressive disorder† (*n* = 1107)	Current depressive disorder† (*n* = 204)	Current anxiety disorder† (*n* = 288)	Current comorbid anxiety and depressive disorder† (*n* = 222)
Sociodemographics:					
Male sex, no. (%)	193 (41.1%)	361 (32.6%)	54 (26.5%)	85 (29.5%)	80 (36.0%)
Age in years, mean (*SD*)	45.9 (14.6)	46.0 (12.9)	48.0 (12.3)	45.8 (12.9)	46.4 (11.9)
Education in years, mean (*SD*)	13.4 (3.3)	12.9 (3.2)	12.7 (3.4)	12.4 (3.5)	11.7 (3.3)
BMI, kg/m2, mean (*SD*)	25.6 (4.8)	26.3 (4.8)	26.3 (5.1)	25.8 (4.8)	27.1 (6.2)
Smoking, no. (%)	97 (20.6%)	347 (31.3%)	67 (32.8%)	92 (32.1%)	88 (39.6%)
Lifetime alcohol dependency/abuse, no. (%)	17 (3.6%)	60 (5.4%)	22 (10.8%)	23 (8.0%)	32 (14.4%)
Any use of drug in past month, no (%)	19 (4.0%)	57 (5.1%)	8 (3.9%)	19 (6.6%)	13 (5.9%)
Clinical characteristics:					
Severity measures					
IDS-SR total score, mean (*SD*)	6.0 (5.0)	12.6 (8.4)	25.2 (11.6)	19.9 (10.0)	33.8 (11.8)
BAI total score, mean (*SD*)	2.7 (3.5)	6.2 (5.8)	11.2 (7.9)	12.9 (9.2)	19.7 (10.7)
PSWQ total score, mean (*SD*)	16.7 (6.8)	24.5 (9.6)	33.0 (10.1)	31.7 (10.0)	38.2 (9.1)
FQ total score, mean (*SD*)	7.7 (9.1)	14.1 (13.1)	23.3 (17.9)	30.2 (18.1)	39.7 (21.6)
Medication use					
Benzodiazepines, no. (%)	7 (1.5%)	88 (7.9%)	42 (20.6%)	48 (16.7%)	69 (31.1%)
SSRI, no. (%)	3 (0.6%)	157 (14.2%)	41 (20.1%)	54 (18.8%)	40 (18.0%)
TCA, no. (%)	1 (0.2%)	29 (2.6%)	10 (4.9%)	6 (2.1%)	13 (5.9%)
Other AD, no. (%)	2 (0.4%)	46 (4.2%)	21 (10.3%)	21 (7.3%)	34 (15.3%)

Note. BMI = Body Mass Index; IDS-SR = Inventory of Depressive Symptomatology, self-report; BAI = Beck Anxiety Inventory; PSWQ = Penn State Worry Questionnaire; FQ = Fear Questionnaire; SSRI = Selective Serotonin Reuptake Inhibitor; TCA = Tricyclic Antidepressant. Chi-square values have been computed for categorical variables, ANOVA for interval variables.
† Based on 6 months.

Table 2. Prevalence of trait anger and anger attacks according to psychopathology groups

	Controls (n = 470)	Remitted anxiety and/or depressive disorder† (n = 1107)	Current depressive disorder† (n = 204)	Current anxiety disorder† (n = 288)	Current comorbid anxiety and depressive disorder† (n = 222)	Test statistic	p value
Trait Anger							
Total score, crude	12.70 (0.13)[a]	15.13 (0.13)[b]	16.48 (0.35)[c]	16.72 (0.30)[c]	18.51 (0.39)[d]	$F(4, 641) = 99.44$	< 0.001
Total score, adjusted‡	12.72 (0.21)[a]	15.08 (0.14)[b]	16.39 (0.31)[c]	16.67 (0.26)[c]	18.21 (0.30)[d]	$F(4, 2113) = 70.15$	< 0.001
Temperament subscale[1]	5.56 (0.06)[a]	6.42 (0.07)[b]	7.00 (0.18)[c]	6.94 (0.15)[c]	7.91 (0.21)[d]	$F(4, 633) = 60.10$	< 0.001
Temperament subscale[1], adjusted‡	5.55 (0.11)[a]	6.38 (0.07)[b]	6.94 (0.16)[c]	6.87 (0.13)[c]	7.80 (0.15)[d]	$F(4, 2102) = 41.56$	< 0.001
Reaction subscale[2]	4.17 (0.06)[a]	5.07 (0.05)[b]	5.38 (0.13)[c]	5.66 (0.12)[c]	6.05 (0.14)[d]	$F(4, 644) = 66.89$	< 0.001
Reaction subscale[2], adjusted‡	4.21 (0.08)[a]	5.06 (0.05)[b]	5.33 (0.12)[c]	5.67 (0.10)[d]	5.90 (0.12)[d]	$F(4, 2107) = 48.66$	< 0.001
Anger Attacks							
Total prevalence of anger attacks (%):	6 (1.3%)[a]	52 (4.7%)[b]	10 (4.9%)[b]	33 (11.5%)[c]	49 (22.1%)[d]	$\chi^2(4) = 127.23$	< 0.001
Crude odds ratio (*OR*)	Ref.[a]	3.81 (1.63–8.94)[b]	3.99 (1.43–11.12)[b]	10.01 (4.14–24.20)[c]	21.90 (9.22–52.05)[d]	$\chi^2(4) = 104.75$	< 0.001
Adjusted odds ratio (*OR*)‡	Ref.[a]	3.83 (1.62–9.03)[b]	3.36 (1.14–9.92)[b]	9.32 (3.79–22.88)[b]	21.44 (8.88–51.76)[b]	$\chi^2(11) = 122.12$	< 0.001

Note. Data are (adjusted) means (with standard errors in parentheses) or number of participants (with percentages in parentheses). Values in the same row with different superscript letters are significantly different, $p < 0.05$ (in post hoc comparisons).

[1]Subscale consisting of items 1, 2, 3, 5, and 6.

[2]Subscale consisting of items 7, 8, and 10.

† Based on 6 months.

‡ Adjusted for sex, age, level of education, BMI, smoking, alcohol dependency/abuse, drug use.

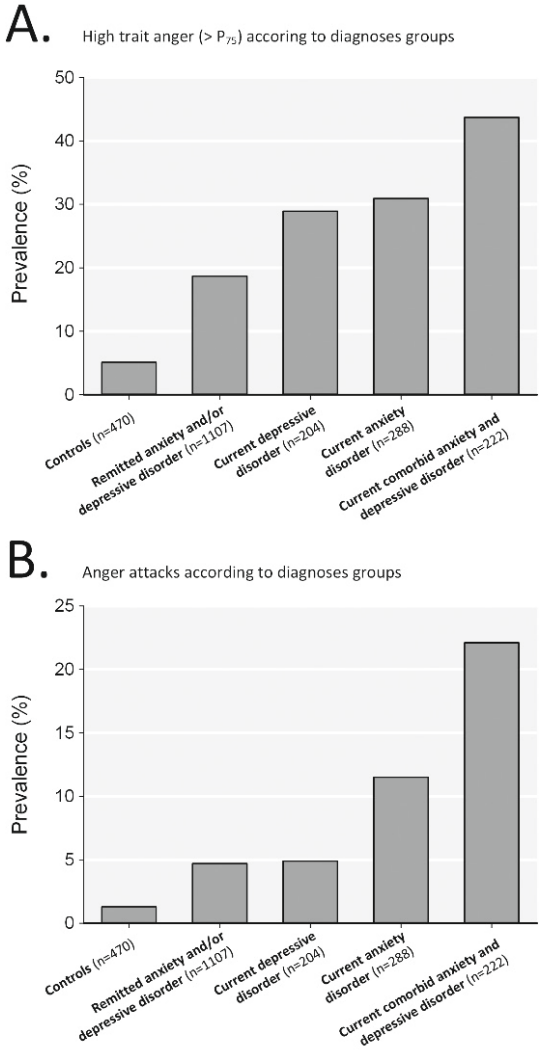


Fig. 1. Prevalence of trait anger and anger attacks according to psychopathology groups

Table 3. Linear regression analyses predicting trait anger according to demographic characteristics and psychiatric disorders ($N = 2291$)

	Univariable		Full model†	
	β	***p* value**	*β*	***p* value**
Sociodemographics:				
Female sex	−0.083	**< 0.001**	−0.060	**0.004**
Age, in *SD* (standardized)	0.010	0.63	0.007	0.73
Education in *SD* (standardized)	−0.085	**< 0.001**	−0.047	**0.03**
BMI, in *SD* (standardized)	0.043	**0.046**	0.012	0.57
Smoking	0.060	**0.004**	0.006	0.77
Alcohol dependency/abuse	0.138	**< 0.001**	0.090	**< 0.001**
Any use of drug in past month	0.074	**< 0.001**	0.045	**0.04**
Mood disorders (6-month diagnoses)				
Dysthymia	0.190	**< 0.001**	0.053	**0.02**
MDD	0.206	**< 0.001**	0.111	**< 0.001**
Anxiety disorders (6-month diagnoses)				
Social Phobia	0.197	**< 0.001**	0.113	**< 0.001**
Panic Disorder	0.131	**< 0.001**	0.073	**0.001**
Agoraphobia	0.088	**< 0.001**	0.051	**0.015**
Generalized Anxiety Disorder	0.196	**< 0.001**	0.109	**< 0.001**

Note. Standardized beta-coefficients and accompanying *p* values by linear regression analyses.
†Model that includes all the independent variables in one multivariable regression model.

Discussion

In our study, trait anger and anger attacks were prevalent and associated with several depression and anxiety disorders. Our findings indicate that anger was most prevalent in participants with comorbid depressive and anxiety disorders—followed by anxiety-, depressive-, and remitted disorder—and that these participants exhibited a higher prevalence of anger than healthy controls.

Our finding that patients with a current disorder reported higher trait anger than controls supports prior population-based cohort studies [26, 27] and one cohort of psychiatric outpatients [28]. Likewise, recent anger attacks were more common in participants with a current disorder than healthy controls, which supports findings from two previous studies [4, 42].

Participants with a remitted disorder still exhibited elevated levels of trait anger and recent anger attacks. This mirrors findings where recovered depressed

Table 4. Logistic regression analyses predicting anger attacks according to demographic characteristics and psychiatric disorders (*N* = 2291)

	Crude		Full model†	
	***OR* (95% CI)**	***p* value**	***OR* (95% CI)**	***p* value**
Sociodemographics				
Female sex	0.80 (0.57–1.12)	0.19	0.92 (0.63–1.35)	0.67
Age, in *SD* (standardized)	0.85 (0.72–1.00)	**0.046**	0.81 (0.67–0.98)	**0.03**
Education, in *SD* (standardized)	0.79 (0.67–0.94)	**0.006**	0.84 (0.70–1.02)	0.09
BMI, in *SD* (standardized)	1.14 (0.98–1.34)	0.10	1.08 (0.91–1.27)	0.39
Smoking	1.00 (0.70–1.44)	0.99	0.72 (0.47–1.10)	0.13
Alcohol dependency/abuse	2.62 (1.61–4.25)	**< 0.001**	1.43 (0.80–2.57)	0.23
Any use of drug in past month	2.24 (1.27–3.97)	**0.005**	2.41 (1.24–4.69)	**0.01**
Mood disorders (6-month diagnoses)				
Dysthymia	4.01 (2.55–6.29)	**< 0.001**	1.41 (0.80–2.50)	0.24
MDD	2.90 (2.03–4.14)	**< 0.001**	1.62 (1.04–2.51)	**0.03**
Anxiety disorders (6-month diagnoses)				
Social Phobia	3.06 (2.06–4.55)	**< 0.001**	1.70 (1.06–2.72)	**0.03**
Panic Disorder	3.16 (2.01–4.96)	**< 0.001**	2.08 (1.23–3.53)	**0.01**
Agoraphobia	2.20 (1.24–3.88)	**0.007**	1.60 (0.84–3.06)	0.15
Generalized Anxiety Disorder	7.13 (4.66–10.91)	**< 0.001**	3.61 (2.19–5.95)	**< 0.001**

Note. Odds ratios (*OR*), 95% confidence interval (CI), and accompanying *p* values by logistic regression analyses.
†Model that includes all the independent variables in one multivariable logistic regression model.

participants were more likely to report fear of anger expression and having experienced anger attacks compared to controls [43], which may be the result of residual symptoms or psychiatric disorders that were not assessed in this study. Higher levels of anger, however, may also indicate vulnerability to depressive and anxiety disorders.

We found the largest effect sizes in patients with comorbid de- pression and anxiety, which coincides with earlier findings in samples from the general population [4, 44]. Considering specific disorders, MDD, SP, PD, and GAD most strongly associated with both trait anger and recent anger attacks. The strong association between anger and MDD and anxiety disorders supports previous research [26-28].

In summary, our findings confirm that anger is highly prevalent in patients with MDD, SP, and GAD. Yet, trait anger and anger attacks may be easily overlooked or ignored by clinicians and patients themselves because they are not part of the core DSM-IV symptoms, and insight and self-consciousness of feelings of anger may be hampered. Addressing anger in therapy, however, might help clinicians to reduce

conflicts or resistance to therapy [26]. Even so, management of anger is a major public safety concern due to the relationship between anger and aggression [45]. In recent years, research has increased regarding the treatment of anger in a clinical context (involving aggression–anticipation in psychiatric hospitals; [46] and in the effectiveness of therapies targeting anger. Cognitive behavioural therapy [47, 48] and psychopharmacological therapy like fluoxetine have received empirical support for reducing anger [49-51].

Interestingly, men reported higher levels of trait anger, which might be explained through neuroendocrine effects of testosterone and other androgens [52]; however, previous large-scale studies [27, 28] found higher levels of anger in women. Similar to other studies, we found that individuals who were younger, who completed fewer years of education, who were dependent on or abused alcohol, and who used drugs the past month also reported higher levels of trait anger [27, 28, 53, 54].

Regarding symptom severity measures, we found that depressive and worry symptoms most strongly associated with trait anger and recent anger attacks, which is supported by previous studies [24, 55]. These associations with anger might be explained by a common underlying factor, such as emotion dysregulation [56-58]. A key neural region involved in emotion regulation is the amygdala, which is part of the limbic system. Research has shown that the amygdala is hyperactive in anxious and depressed patients, as well as in individuals with heightened anger [59, 60].

We conducted our study within a large cohort study. In anger research, the use of two different anger measures is fairly unique; many previous studies reported on a single-item to a five-item measure of anger [12, 28, 61] or used single instruments to measure anger [32, 44, 62]. Furthermore, the state of anger that can be studied in the form of anger expression (e.g., recent anger attacks) was not taken into account in one of the three previous cohort studies [27]. The other cohort study took anger expression into account, but focused on the link with anxiety disorders [26].

Limitations of our study, however, must be addressed. First, our analyses had a cross-sectional design, so we cannot provide evidence for temporal or causal relationships between anger and depressive and anxiety disorders. Second, anger is a subjective measure based on self-report data, while there are some observation-based assessment tools for aggressive incidents, such as the Modified Overt Aggression Scale (MOAS; [63, 64] and the Staff Observation Aggression Scale-revised (SOAS-R; [65]. Also, our sample was recruited in only one country while cultural differences might play a role in the expression of anger, making it less generalizable to other cultures [66]. Lastly, according to the newest version of the DSM (DSM-V [67]), there are several disorders in

which anger is a central feature, but that were either not included or not assessed in our study. One such example in which anger is a diagnostic criterion is post-traumatic stress disorder (PTSD) [68], which patients were not included in NESDA. Several studies found high associations between PTSD and anger [69, 70]. The intermittent explosive disorder (IED), a disorder that is characterized by impulsivity and aggression, was not assessed in NESDA. Previous studies found that patients with depression are at increased risk of IED [67, 71, 72] and that patients with Cluster B and C (especially borderline) personality disorder show higher levels of anger [28, 73, 74]. Although anger attacks could be part of an IED, we define anger attacks by their internal affective and physical attributes rather than defining it by their external characteristics, which may result in smashing things or (threatening to) hitting someone.

In summary, the level of trait anger and the prevalence of recent anger attacks is higher in patients suffering from depressive and anxiety disorders than in healthy controls. Participants with a remitted disorder still had higher scores for both trait anger and anger attacks. Because anger is an adverse mood state related to numerous negative outcomes for patients, relatives, and society, it is important that clinicians enquire about feelings and attacks of anger and address this in their therapy of emotion regulation [62, 75]. Temporal and causal relationships between anger and psychiatric dis- orders must be investigated further using longitudinal designs, which may have consequences for (psychotherapeutic) interventions targeting anger.

Funding

The funding source had no role in the design of this study, it's execution, analyses, interpretation of the data, or decision to submit results.

CRediT authorship contribution statement

Nienke J. de Bles: Writing - original draft. Nathaly Rius Ottenheim: Supervision, Writing - review & editing. Albert M. van Hemert: Writing - review & editing. Laura E.H. Pütz: Writing - original draft. A.J. Willem van der Does: Writing - review & editing. Brenda W.J.H. Penninx: Writing - review & editing. Erik J. Giltay: Supervision, Writing - review & editing.

Data for reference

An a priori analysis plan for this study was approved by the principal investigator of NESDA and the NESDA board. Because of ethical and legal restrictions, data involving clinical participants are not included in the manuscript or made available in a public repository. However, subject to approval, data are available upon request from the NESDA Data Access Committee (nesda@ggzingeest.nl).

Declaration of Competing interest

A.J.W.D reports personal fees from Mitsubishi Tanabe Pharma Europe, outside the submitted work. All other authors declare that they have no conflicts of interest.

Acknowledgments

The infrastructure for the NESDA study (www.nesda.nl) is funded through the Geestkracht program of the Netherlands Organization for Health Research and Development (ZonMw, grant number 10-000- 1002) and financial contributions by participating universities and mental health care organizations (VU University Medical Center, GGZ inGeest, Leiden University Medical Center, Leiden University, GGZ Rivierduinen, University Medical Center Groningen, University of Groningen, Lentis, GGZ Friesland, GGZ Drenthe, Rob Giel Onderzoekscentrum).

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jad.2019.08.023.

References

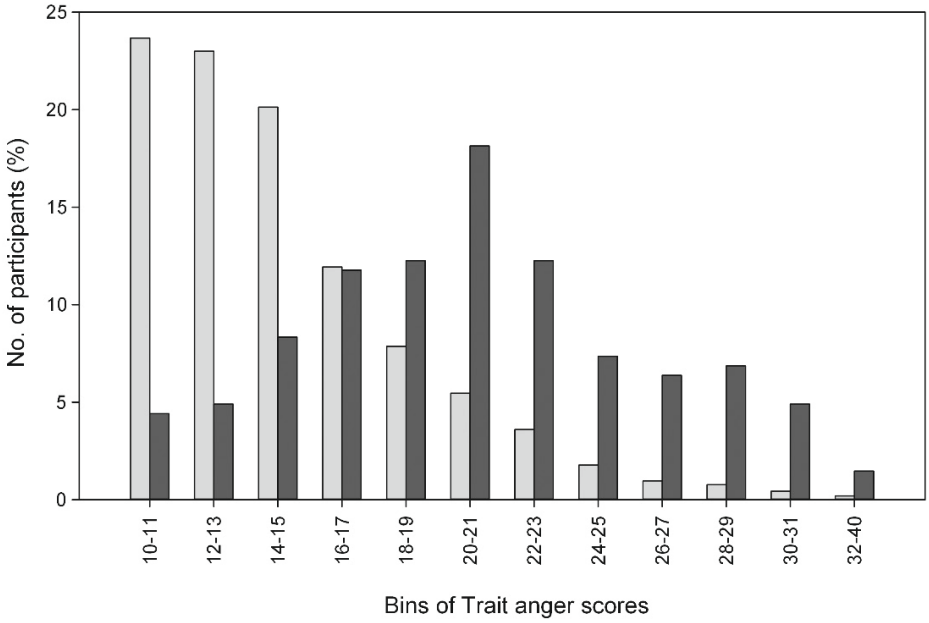
1. Abraham S, Shah NG, Diez Roux A, Hill-Briggs F, Seeman T, Szklo M, et al. Trait anger but not anxiety predicts incident type 2 diabetes: The Multi-Ethnic Study of Atherosclerosis (MESA). *Psychoneuroendocrinology*. 2015;60:105-13.
2. Chida Y, Steptoe A. The association of anger and hostility with future coronary heart disease: a meta-analytic review of prospective evidence. *Journal of the American College of Cardiology*. 2009;53(11):936-46.
3. Fraguas R, Iosifescu DV, Bankier B, Perlis R, Clementi-Craven N, Alpert J, et al. Major depressive disorder with anger attacks and cardiovascular risk factors. *International journal of psychiatry in medicine*. 2007;37(1):99-111.
4. Painuly N, Grover S, Gupta N, Mattoo SK. Prevalence of anger attacks in depressive and anxiety disorders: implications for their construct? *Psychiatry and clinical neurosciences*. 2011;65(2):165-74.
5. Painuly N, Sharan P, Mattoo SK. Antecedents, concomitants and consequences of anger attacks in depression. *Psychiatry research*. 2007;153(1):39-45.
6. McDermut W, Fuller JR, DiGiuseppe R, Chelminski I, Zimmerman M. Trait Anger and Axis I Disorders: Implications for REBT. *Journal of Rational-Emotive & Cognitive-Behavior Therapy*. 2009;27(2):121-35.
7. Owen JM. Transdiagnostic cognitive processes in high trait anger. *Clinical psychology review*. 2011;31(2):193-202.
8. Hawkins KA, Cougle JR. A test of the unique and interactive roles of anger experience and expression in suicidality: findings from a population-based study. *The Journal of nervous and mental disease*. 2013;201(11):959-63.
9. Deffenbacher JL, Oetting ER, Thwaites GA, Lynch RS, Baker DA, Stark RS, et al. State–trait anger theory and the utility of the trait anger scale. *J Couns Psychol*. 1996;43(2):131.
10. Spielberger CD, Krasner SS, Solomon EP. The Experience, Expression, and Control of Anger. In: Janisse MP, editor. Individual Differences, Stress, and Health Psychology. New York, NY: Springer New York; 1988. p. 89-108.
11. Fava M, Anderson K, Rosenbaum JF. "Anger attacks": possible variants of panic and major depressive disorders. *The American journal of psychiatry*. 1990;147(7):867-70.
12. Verhoeven FE, Booij L, Van der Wee NJ, Penninx BW, Van der Does AJ. Clinical and physiological correlates of irritability in depression: results from the Netherlands study of depression and anxiety. *Depression research and treatment*. 2011;2011:126895.
13. Fava M, Hwang I, Rush AJ, Sampson N, Walters EE, Kessler RC. The importance of irritability as a symptom of major depressive disorder: results from the National Comorbidity Survey Replication. *Molecular psychiatry*. 2010;15(8):856-67.
14. Fisher LB, Fava M, Doros GD, Alpert JE, Henry M, Huz I, et al. The Role of Anger/Hostility in Treatment-Resistant Depression: A Secondary Analysis From the ADAPT-A Study. *The Journal of nervous and mental disease*. 2015;203(10):762-8.
15. Riley WT, Treiber FA, Woods MG. Anger and hostility in depression. *The Journal of nervous and mental disease*. 1989;177(11):668-74.
16. Perlis RH, Smoller JW, Fava M, Rosenbaum JF, Nierenberg AA, Sachs GS. The prevalence and clinical correlates of anger attacks during depressive episodes in bipolar disorder. *Journal of affective disorders*. 2004;79(1-3):291-5.

17. Sayar K, Guzelhan Y, Solmaz M, Ozer OA, Ozturk M, Acar B, et al. Anger attacks in depressed Turkish outpatients. *Annals of clinical psychiatry : official journal of the American Academy of Clinical Psychiatrists*. 2000;12(4):213-8.
18. Winkler D, Pjrek E, Kasper S. Anger attacks in depression--evidence for a male depressive syndrome. *Psychotherapy and psychosomatics*. 2005;74(5):303-7.
19. Winkler D, Pjrek E, Kindler J, Heiden A, Kasper S. Validation of a simplified definition of anger attacks. *Psychotherapy and psychosomatics*. 2006;75(2):103-6.
20. Fava M, Alpert J, Nierenberg AA, Ghaemi N, O'Sullivan R, Tedlow J, et al. Fluoxetine treatment of anger attacks: a replication study. *Annals of clinical psychiatry : official journal of the American Academy of Clinical Psychiatrists*. 1996;8(1):7-10.
21. Fava M, Nierenberg AA, Quitkin FM, Zisook S, Pearlstein T, Stone A, et al. A preliminary study on the efficacy of sertraline and imipramine on anger attacks in atypical depression and dysthymia. *Psychopharmacology bulletin*. 1997;33(1):101-3.
22. Gould RA, Ball S, Kaspi SP, Otto MW, Pollack MH, Shekhar A, et al. Prevalence and correlates of anger attacks: a two site study. *Journal of affective disorders*. 1996;39(1):31-8.
23. Deschenes SS, Dugas MJ, Fracalanza K, Koerner N. The role of anger in generalized anxiety disorder. *Cogn Behav Ther*. 2012;41(3):261-71.
24. Moscovitch DA, McCabe RE, Antony MM, Rocca L, Swinson RP. Anger experience and expression across the anxiety disorders. *Depression and anxiety*. 2008;25(2):107-13.
25. Fava GA, Grandi S, Rafanelli C, Saviotti FM, Ballin M, Pesarin F. Hostility and irritable mood in panic disorder with agoraphobia. *Journal of affective disorders*. 1993;29(4):213-7.
26. Hawkins KA, Cougle JR. Anger problems across the anxiety disorders: findings from a population-based study. *Depression and anxiety*. 2011;28(2):145-52.
27. Barrett EL, Mills KL, Teesson M. Mental health correlates of anger in the general population: Findings from the 2007 National Survey of Mental Health and Wellbeing. *Australian & New Zealand Journal of Psychiatry*. 2013;47(5):470-6.
28. Genovese T, Dalrymple K, Chelminski I, Zimmerman M. Subjective anger and overt aggression in psychiatric outpatients. *Compr Psychiatry*. 2017;73:23-30.
29. Penninx BWJH, Beekman ATF, Smit JH, Zitman FG, Nolen WA, Spinhoven P, et al. The Netherlands Study of Depression and Anxiety (NESDA): rationale, objectives and methods. *International Journal of Methods in Psychiatric Research*. 2008;17(3):121-40.
30. Spielberger CD. Preliminary Manual for the State-Trait Anger Scale (STAS). 1980.
31. Van der Ploeg HM, Defares PB, Spielberger CD. Handleiding bij de zelf-analyse vragenlijst ZAV. Een vragenlijst voor het meten van boosheid en woede, als toestand en als dispositie. Manual for the self-analysis questionnaire, a Dutch adaptation of the Spielberger State-Trait Anger Scale. Lisse: Swets & Zeitlinger; 1982.
32. Lubke GH, Ouwens KG, de Moor MH, Trull TJ, Boomsma DI. Population heterogeneity of trait anger and differential associations of trait anger facets with borderline personality features, neuroticism, depression, Attention Deficit Hyperactivity Disorder (ADHD), and alcohol problems. *Psychiatry research*. 2015;230(2):553-60.
33. Fava M, Rosenbaum JF, McCarthy M, Pava J, Steingard R, Bless E. Anger attacks in depressed outpatients and their response to fluoxetine. *Psychopharmacology bulletin*. 1991;27(3):275-9.

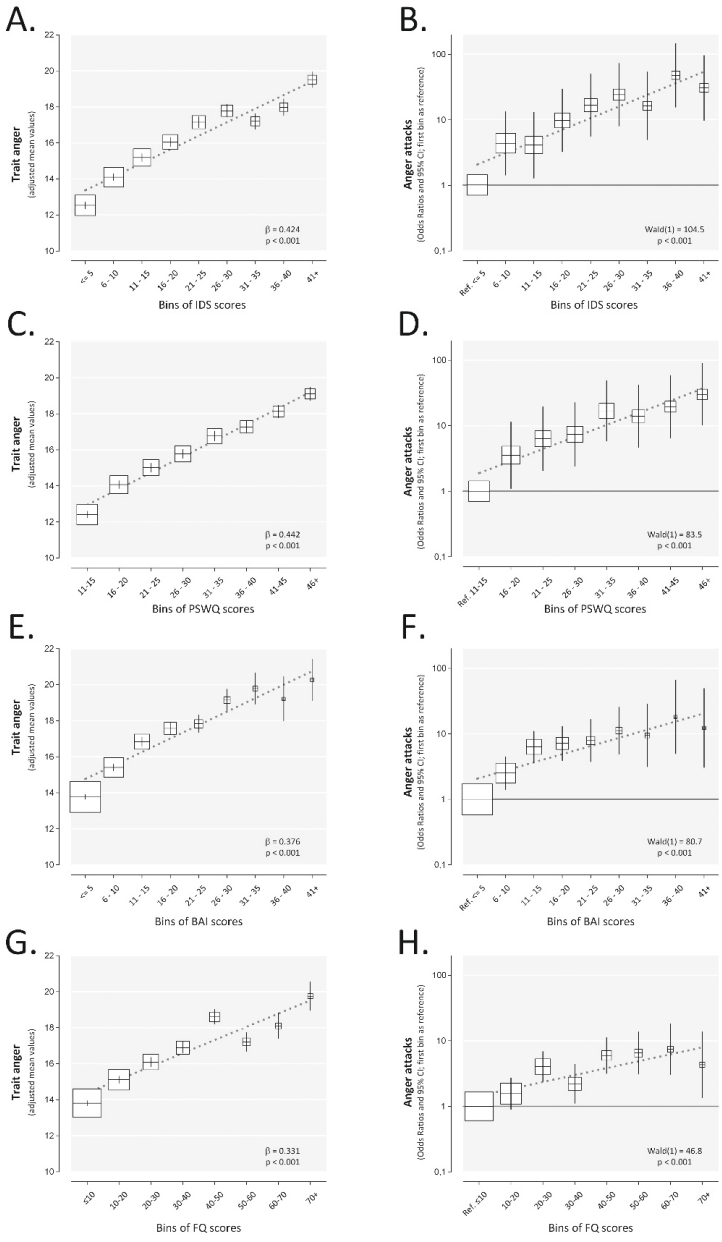
34. Fava MR, JF. Anger Attacks in Patients with Depression. *The Journal of clinical psychiatry*. 1999;60:21-4.
35. APA. Diagnostic and Statistical manual of mental disorders 4th edition (DSM-IV). *Washington, DC: British Library Cataloguing in Publication Data*. 1994.
36. Rush AG, CM; Basco, MR; Jarrett, RB; Trivedi, MH. The Inventory of Depressive Symptomatology (IDS): psychometric properties. *Psychological medicine*. 1996;26(3):477-86.
37. Rush AJ, Giles DE, Schlesser MA, Fulton CL, Weissenburger J, Burns C. The Inventory for Depressive Symptomatology (IDS): preliminary findings. *Psychiatry research*. 1986;18(1):65-87.
38. Beck AT, Epstein N, Brown G, Steer RA. An inventory for measuring clinical anxiety: psychometric properties. *Journal of consulting and clinical psychology*. 1988;56(6):893-7.
39. Marks IM, Mathews AM. Brief standard self-rating for phobic patients. *Behaviour research and therapy*. 1979;17(3):263-7.
40. Meyer TJ, Miller ML, Metzger RL, Borkovec TD. Development and validation of the penn state worry questionnaire. *Behaviour research and therapy*. 1990;28(6):487-95.
41. Fresco DM, Mennin DS, Heimberg RG, Turk CL. Using the Penn State Worry Questionnaire to identify individuals with generalized anxiety disorder: a receiver operating characteristic analysis. *Journal of behavior therapy and experimental psychiatry*. 2003;34(3-4):283-91.
42. Fava M, Rosenbaum JF, Pava JA, McCarthy MK, Steingard RJ, Bouffides E. Anger attacks in unipolar depression, Part 1: Clinical correlates and response to fluoxetine treatment. *The American journal of psychiatry*. 1993;150(8):1158-63.
43. Brody CL, Haaga DA, Kirk L, Solomon A. Experiences of anger in people who have recovered from depression and never-depressed people. *The Journal of nervous and mental disease*. 1999;187(7):400-5.
44. Judd LL, Schettler PJ, Coryell W, Akiskal HS, Fiedorowicz JG. Overt irritability/anger in unipolar major depressive episodes: past and current characteristics and implications for long-term course. *JAMA psychiatry*. 2013;70(11):1171-80.
45. Lee AH, DiGiuseppe R. Anger and aggression treatments: a review of meta-analyses. *Current Opinion in Psychology*. 2018;19:65-74.
46. Bowers L, Stewart D, Papadopoulos C, Dack C, Ross J, Khanom H, et al. Inpatient violence and aggression: a literature review. 2011.
47. Milkman HB, Wanberg KW. Cognitive-Behavioral Treatment: A review and discussion for corrections professionals.: Washington, DC: National Institute of Corrections; 2007.
48. Trupin EW, Stewart DG, Beach B, Boesky L. Effectiveness of a Dialectical Behaviour Therapy Program for Incarcerated Female Juvenile Offenders. *Child and Adolescent Mental Health*. 2002;7(3):121-7.
49. Capitao LP, Chapman R, Murphy SE, Harvey CJ, James A, Cowen PJ, et al. A single dose of fluoxetine reduces neural limbic responses to anger in depressed adolescents. *Translational psychiatry*. 2019;9(1):30.
50. Choi-Kwon S, Han SW, Kwon SU, Kang DW, Choi JM, Kim JS. Fluoxetine treatment in poststroke depression, emotional incontinence, and anger proneness: a double-blind, placebo-controlled study. *Stroke*. 2006;37(1):156-61.

51. Coccaro EF, Lee RJ, Kavoussi RJ. A double-blind, randomized, placebo-controlled trial of fluoxetine in patients with intermittent explosive disorder. *The Journal of clinical psychiatry*. 2009;70(5):653-62.
52. Batrinos ML. Testosterone and Aggressive Behavior in Man. *International Journal of Endocrinology and Metabolism*. 2012;10(3):563-8.
53. Giancola PR, Saucier DA, Gussler-Burkhardt NL. The effects of affective, behavioral, and cognitive components of trait anger on the alcohol-aggression relation. *Alcoholism, clinical and experimental research*. 2003;27(12):1944-54.
54. Sadikaj G, Moskowitz DS. Alcohol Consumption and Trait Anger Strengthen the Association Between Perceived Quarrelsomeness and Quarrelsome Behavior via Feeling Angry. *Alcoholism, clinical and experimental research*. 2018.
55. Fracalanza K, Koerner N, Deschênes SS, Dugas MJ. Intolerance of Uncertainty Mediates the Relation Between Generalized Anxiety Disorder Symptoms and Anger. *Cognitive Behaviour Therapy*. 2014;43(2):122-32.
56. Baker R, Holloway J, Thomas PW, Thomas S, Owens M. Emotional processing and panic. *Behaviour research and therapy*. 2004;42(11):1271-87.
57. Hawkins KA, Macatee RJ, Guthrie W, Cougle JR. Concurrent and Prospective Relations Between Distress Tolerance, Life Stressors, and Anger. *Cognitive Therapy and Research*. 2013;37(3):434-45.
58. Salters-Pedneault K, Roemer L, Tull MT, Rucker L, Mennin DS. Evidence of Broad Deficits in Emotion Regulation Associated with Chronic Worry and Generalized Anxiety Disorder. *Cognitive Therapy and Research*. 2006;30(4):469-80.
59. Sheline YI, Barch DM, Donnelly JM, Ollinger JM, Snyder AZ, Mintun MA. Increased amygdala response to masked emotional faces in depressed subjects resolves with antidepressant treatment: an fMRI study. *Biological psychiatry*. 2001;50(9):651-8.
60. Stein MB, Goldin PR, Sareen J, Zorrilla LTE, Brown GG. Increased Amygdala Activation to Angry and Contemptuous Faces in Generalized Social Phobia. *JAMA psychiatry*. 2002;59(11):1027-34.
61. Posternak MA, Zimmerman M. Anger and aggression in psychiatric outpatients. *The Journal of clinical psychiatry*. 2002;63(8):665-72.
62. Newman JL, Fuqua DR, Gray EA, Simpson DB. Gender Differences in the Relationship of Anger and Depression in a Clinical Sample. *Journal of Counseling & Development*. 2006;84(2):157-62.
63. Kay SR, Wolkenfeld F, Murrill LM. Profiles of aggression among psychiatric patients. I. Nature and prevalence. *The Journal of nervous and mental disease*. 1988;176(9):539-46.
64. Yudofsky SC, Silver JM, Jackson W, Endicott J, Williams D. The Overt Aggression Scale for the objective rating of verbal and physical aggression. *The American journal of psychiatry*. 1986;143(1):35-9.
65. Nijman HLI, Muris P, Merckelbach HLGJ, Palmstierna T, Wistedt B, Vos AM, et al. The staff observation aggression scale–revised (SOAS-R). *Aggressive behavior*. 1999;25(3):197-209.
66. Matsumoto D, Yoo SH, Chung J. The Expression of Anger Across Cultures. In: Potegal M, Stemmler G, Spielberger C, editors. International Handbook of Anger: Constituent and Concomitant Biological, Psychological, and Social Processes. New York, NY: Springer New York; 2010. p. 125-37.
67. APA. Diagnostic and Statistical Manual of Mental Disorders, 5th ed. Washington, DC: American Psychiatric Association; 2013.

68. Friedman MJ. Finalizing PTSD in DSM-5: getting here from there and where to go next. *Journal of traumatic stress*. 2013;26(5):548-56.
69. Orth U, Wieland E. Anger, hostility, and posttraumatic stress disorder in trauma-exposed adults: a meta-analysis. *Journal of consulting and clinical psychology*. 2006;74(4):698-706.
70. Taft CT, Creech SK, Murphy CM. Anger and aggression in PTSD. *Curr Opin Psychol*. 2017;14:67-71.
71. Coccaro EF. Intermittent explosive disorder as a disorder of impulsive aggression for DSM-5. *The American journal of psychiatry*. 2012;169(6):577-88.
72. Medeiros GC, Seger L, Grant JE, Tavares H. Major depressive disorder and depressive symptoms in intermittent explosive disorder. *Psychiatry research*. 2018;262:209-12.
73. Bertsch K, Krauch M, Roelofs K, Cackowski S, Herpertz SC, Volman I. Out of control? Acting out anger is associated with deficient prefrontal emotional action control in male patients with borderline personality disorder. *Neuropharmacology*. 2018:107463.
74. Mancke F, Herpertz SC, Bertsch K. Correlates of Aggression in Personality Disorders: an Update. *Current Psychiatry Reports*. 2018;20(8):53.
75. Weissman MM, Klerman GL, Paykel ES. Clinical evaluation of hostility in depression. *The American journal of psychiatry*. 1971;128(3):261-6.



Supplementary Fig. 1. Distribution of having anger attacks according to trait anger scores

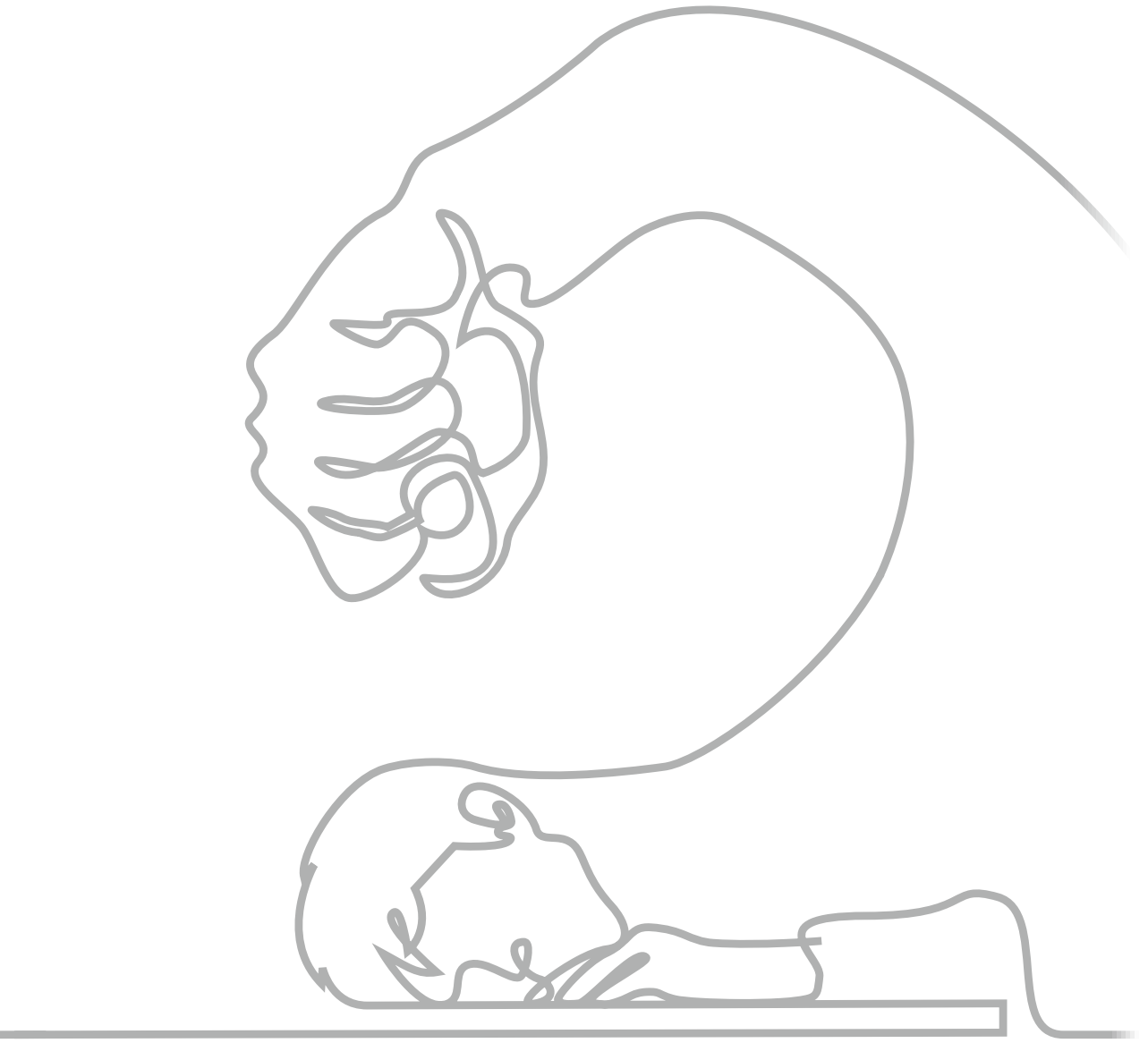


Supplementary Fig. 2. Adjusted associations between trait anger and anger attacks and bins of the IDS (A and B), PSWQ (C and D), BAI (E and F), and FQ (G and H) scores in the overall sample. The size of each square is proportional to the number of participants in each bin. Error bars indicate standard errors. Standardized beta-coefficients, adjusted for sex, age, level of education, BMI, smoking, alcohol dependency/abuse, with their accompanying p values are given.

Note: IDS = Inventory of Depressive Symptomatology; PSWQ = Penn State Worry Questionnaire; BAI = Beck Anxiety Inventory; FQ = Fear Questionnaire.

Published as: Mesbah, R., de Bles, N. J., Rius-Ottenheim, N., van der Does, A. J. W., Penninx, B. W. J. H., van Hemert, A. M., de Leeuw, M., Giltay, E. J., & Koenders, M. (2021). Anger and cluster B personality traits and the conversion from unipolar depression to bipolar disorder. *Depression and Anxiety, 38*(6), 671-681.

3 Anger and cluster B personality traits and the conversion from unipolar depression to bipolar disorder



Abstract

Introduction: Feelings of anger and irritability are prominent symptoms of bipolar disorder (BD) that may occur during hypomanic, depressive and, especially, during mixed mood states. We aimed to determine whether such constructs are associated with the conversion to BD in subjects with a history of unipolar depression.

Methods: Data were derived from the depressed participants of Netherlands Study of Depression and Anxiety with 9 years of follow-up. Hypomania was ascertained using the Composite International Diagnostic Interview at 2-, 4-, 6-, and 9-years follow-up. Cross-sectionally, we studied the association between prevalent hypomania and anger related constructs with the "Spielberger Trait Anger subscale," the "Anger Attacks" questionnaire, the cluster B personality traits part of the "Personality Disorder Questionnaire," and "aggression reactivity." Prospectively, we studied whether aggression reactivity predicted incident hypomania using Cox regression analyses.

Results: Cross-sectionally, the bipolar conversion group (n = 77) had significantly higher scores of trait anger and aggression reactivity, as well as a higher prevalence on "anger attacks," "antisocial traits," and "borderline traits" compared to current (n = 349) as well as remitted (n = 1159) depressive patients. In prospective analyses in 1744 participants, aggression reactivity predicted incident hypomania (n = 28), with a multivariate-adjusted hazard ratio of 1.4 (95% confidence interval: 1.02–1.93; p = .037).

Conclusion: Anger is a risk factor for conversion from unipolar depression to BD. In addition, patients who converted to BD showed on average more anger, agitation, and irritability than people with a history of unipolar depression who had not converted.

Introduction

Bipolar disorder (BD) is a severe and debilitating mood disorder, characterized by hypomanic and depressive episodes [1]. Most patients with BD have experienced one or more episodes of depression before the onset of hypomania [2, 3], and as a consequence are initially diagnosed with a unipolar depression. Since the treatment for unipolar depression is different from BD and may instigate hypomania [4], earlier detection of a vulnerability to BD would benefit these patients. Moreover, risk factors for the conversion to BD may yield anchor points for psychological interventions, for early recognition and appropriate treatment.

Previous studies showed that a parental history of BD, more severe depression, comorbid psychotic symptoms, childhood trauma and atypical symptoms of depression were risk factors for a conversion from unipolar to BD [2, 5, 6]. Irritability and anger in unipolar depression appeared to be a robust clinical marker of undiagnosed or subthreshold BD, or so-called bipolar spectrum illness [7, 8]. It is important to examine the association between anger and BD, because of its impact on the patient and family and loved ones. Knowing there is an association can help us to target treatment. It is also important to properly investigate whether experiencing irritability/anger would have predictive value in the development of BD.

Anger can be divided into feelings and expressions. The feeling of anger involves different constructs, encompassing trait- and state anger [9, 10]. Trait anger is defined by the constant tendency to experience anger upon the slightest provocation. It is a chronic condition that is intertwined in one's personality. A high level of anger can be a personality trait [11]. State anger is defined as the temporary psychological, emotional feeling at a particular time and situation that can vary in intensity from mild irritation to intense fury and rage. These angry feelings could lead to the expression of anger including anger attacks and aggression. Attacks are spells of anger of a sudden surge of autonomic arousal with symptoms, such as tachycardia, sweating, flushing, and a feeling of being out of control. They are experienced as uncharacteristic and may occur in inappropriate situations [12]. Anger attacks are associated with verbal and physical aggression, which in turn can cause social avoidance to prevent a future anger attack and has certainly a negative impact on interpersonal relations [13]. All emotional states of anger, agitation and irritability will be referred to as anger in the current paper.

Anger might be part of emotion regulation problems and it has been hypothesized that heightened emotionality is an enduring characteristic of BD [14]. This suggests that people with BD experience more intense and more frequently fluctuating negative

and positive emotions (apart from their mood episodes). This might increase their risk of developing mood episodes. Most previous studies found cross-sectional associations between anger and bipolarity [15-19]. In one prospective study (255 BD, 85 non-BP psychopathology and 84 healthy controls) BD patients reported persistently higher scores on self-report questionnaires on anger and feelings of aggression compared to psychiatric and healthy controls across a four-year follow-up [20]. There are indications that people with BD show stronger emotional reactivity compared to healthy controls on self-report questionnaires [21], or specifically report more anger and frustration during euthymic states [22, 23], but contradictory findings have been reported as well [24].

Emotional instability in BD is often mistaken for comorbid personality disorder since this is such a core characteristic of especially cluster B personality disorders. Ecological momentary assessments (EMA) studies have shown that BD patients in remission report more overall negative affect [25, 26] and more fluctuations in both negative and positive emotionality compared to healthy controls [27]. Earlier cross-sectional studies have found that some of the symptoms of BD (e.g., irritability, anger, and emotional instability) overlap with personality disorders, such as borderline personality disorder and antisocial personality disorder [28, 29]. In total, 44% of patients diagnosed with borderline personality disorder were found to meet strict diagnostic criteria for BD [30]. Moreover, 55% of newly diagnosed BD patients (without comorbid personality disorder) showed signs of juvenile antisocial behaviour in a retrospective study [31]. These findings suggest that borderline and antisocial personality disorders have construct overlap with BD. Especially affective instability and impulsivity were traits that may link BD to personality disorders [32].

In sum, the majority of the studies have shown a relation between BD and emotional instability, and specifically of anger, also in stable periods. In the current study, we investigated whether patients who converted to BD showed more feelings of anger, irritability, and antisocial and borderline personality traits than people with a history of unipolar depression who did not convert. Second, we aimed to determine whether increased aggression reactivity increases the risk of conversion from depression to BD.

Methods

Study sample

Data were derived from the Netherlands Study of Depression and Anxiety (NESDA) with measurement points at baseline and at the 2-, 4-, 6-, and 9-year follow-up. NESDA is an ongoing longitudinal cohort study, consisting of 2981 participants (18–65 years).

Participants were recruited at baseline from community care (19%), primary care (54%), and specialized mental health care (27%) in the Netherlands. Individuals included in the NESDA study were participants with current or remitted depressive disorders and/or comorbid anxiety. The control group consisted of participants without lifetime psychiatric disorders. Exclusion criteria included (1) the presence of other psychiatric disorders (e.g., psychotic, obsessive–compulsive, bipolar, or severe addiction disorder) and (2) not being fluent in Dutch. Participants gave written informed consent before enrolment, and ethical approval was granted by all ethical committees of participating universities (VU University Medical Centre, Leiden University Medical Centre, and University Medical Centre Groningen). A detailed description of NESDA is given elsewhere [33].

Specially trained research staff administered the diagnostic interviews using the Composite International Diagnostic Interview (CIDI; version 2.1) to assess remitted or current depressive disorders and incidents of hypomania which is indicative for BD. In the current study, we analysed data cross-sectionally and prospectively with survival analysis.

Cross-sectional analysis sample: data on anger related questionnaires (i.e., trait anger, aggression reactivity, anger attacks, and personality traits associated with more anger) were gathered only at the fourth wave at 4-year follow-up. Therefore, we selected participants who completed the fourth wave (n = 2402; 80.6%) to examine the construct of anger cross-sectionally. Participants suffering from a remitted and current depressive disorder and BD patients who converted between baseline and 4 years of follow-up were included. In a previous NESDA study [34], healthy controls showed significantly less trait anger and had lowest prevalence of anger attacks compared with groups of depression with or without comorbid anxiety disorder. For this reason, healthy controls were excluded in the current study. Participants with missing data on questionnaires regarding (hypo)manic episodes, or on one of the anger-related questionnaires were excluded, resulting in a total sample of 1585 (53.2%) of the 2981 participants for the cross-sectional analyses (see Flowchart in Figure 1).

Prospective analysis sample: aggression reactivity questionnaire was the only measured anger related instrument at baseline. Therefore, aggression reactivity was used as the predictor for incident (hypo)mania during the 9 years of follow-ups. We included 1744 (58.5%) of 2981 participants, with remitted or current depressive disorder with at least one follow-up assessment (Figure 1).

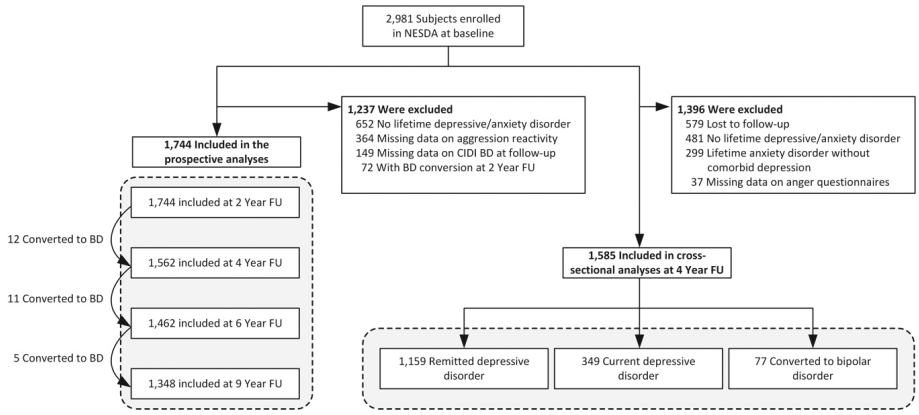


Fig. 1. Flowchart of included participants in prospective and cross-sectional analyses. BD, bipolar disorder; FU, follow up; NESDA, Netherlands Study of Depression and Anxiety

Measures

Aggression reactivity

This questionnaire was used in prospective analysis as predictor and in cross-sectional as one of the anger-related constructs. It was measured with the aggression reactivity subscale of the Leiden index of depression sensitivity–revised (LEIDS-R; [35, 36]). The LEIDS-R contains 34 items with six subscales. Aggression reactivity is one of these subscales and has six items (e.g., "In a sad mood, I do more things that I will later regret"; "When I feel bad, I feel like more breaking things"; "In a sad mood I'm more bothered by aggressive thoughts"; "When I feel down, I more easily become cynical or sarcastic"; "When I feel sad, I do more risky things"; "When feel down, I lose my temper more easily"). These items measure how people react in a sad mood. Items are answered on a five-point Likert scale from 0 to 4, with total scores ranging from 0 to 24. The internal consistency (Cronbach's alpha) for the aggression reactivity subscale was 0.80 in the current NESDA sample.

CIDI hypomanic episodes

The CIDI (WHO version 2.1) is a comprehensive, fully standardized diagnostic interview to screen for mental disorders based on diagnostic and statistical manual of mental disorder-fourth edition (DSM-IV) criteria. The CIDI was used to assess remitted or current depressive disorders in the preceding 6 months. Incident cases of hypomanic episodes, which were indicative of BD, were ascertained using the CIDI "bipolar" section. The CIDI has high interrater reliability, (BDI: $\kappa = 0.92$, BDII: $\kappa = 0.94$ [37]) and is

a valid instrument (diagnosis of a lifetime BD sensitivity 0.87 and specificity 0.89 [38]) for yielding DSM-IV diagnoses.

Trait anger

Trait anger was assessed via the Dutch adaption of the Spielberger state–trait anger scale (STAS [39, 40]) and was gathered at the fourth wave at 4-year follow-up. The STAS is divided into two subscales for state and trait anger, whereby only the latter was administered in the current study. Trait anger is described as anger proneness as a personality trait [41]). The trait anger scale is a 10-item, self-report questionnaire. Participants score items on a four-point Likert scale from 1 to 4. The total sum score ranges from 10 to 40. Psychometric properties have shown good item correlations, high test-retest reliability, and high internal consistency values with Cronbach's alphas ranging from 0.75 to 0.91 [39, 40]. The internal consistency (i.e., Cronbach's alpha) in our sample was 0.89.

Anger attacks

The anger attacks questionnaire [13] is a self-rated instrument used to measure the presence or absence of anger attacks during the previous 6 months. It was measured at the fourth wave at 4-year follow-up. Anger attacks are sudden spells of anger inappropriate to the situation, accompanied by irritability, a sense of being out of control, and autonomic arousal symptoms [13]. To define who was experiencing anger attacks, the following criteria had to be met the previous 6 months: (1) irritability, (2) overreaction to minor annoyances, (3) inappropriate anger and rage directed at others, (4) incidence of at least one anger attack within the past month, and (5) presence of at least four or more of the following symptoms in at least one of the attacks: tachycardia, hot flashes, tightness of the chest, paraesthesia, dizziness, shortness of breath, sweating, trembling, panic, feeling out of control, feeling like attacking others, attacking physically or verbally, and throwing or destroying objects.

Cluster B personality traits

Antisocial behaviour was assessed with the Dutch adaptation of the personality disorder questionnaire (PDQ-4 [42]) and data was gathered at the fourth wave at 4-year follow-up. It was used to identify the key features or possible presence of a personality disorder. Items included in the PDQ-4 were adapted from the diagnostic criteria for personality disorders of the DSM-IV [43]. In the current study, a shortened version of the PDQ-4 with 37 dichotomous ("true"/"false") was assessed. Items were divided into

three subcategories; borderline personality disorder (15 items; e.g., "I have difficulty controlling my anger or temper"); antisocial personality disorder (eight items; e.g., "I don't care if others get hurt so long as I get what I want") and antisocial behaviour before the age of fifteen (14 items; e.g. "I was considered a bully"). Based on items of the subscales for borderline and antisocial personality traits the presence or absence of these symptomatology and characteristics was assessed. The PDQ-4 has a high sensitivity and moderate specificity (Cronbach's alpha = 0.97 [44]), and a test–retest reliability of 0.67 [45].

Covariates

Sociodemographic covariates were self-reported age, gender, and level of education in years. Lifetime DSM IV-based alcohol dependency and abuse and drug use were assessed using the CIDI. In addition, the severity of depression during the past week was assessed with the 30-item self-report inventory of depressive symptomatology (IDS [46]). Items were scored on a four-point Likert scale (0–3) with total sum score ranges from 0 to 84 (only 28 of the 30 items are rated) The IDS had good internal reliability (Cronbach's alpha = 0.85). This is a 21-item self-report inventory with an internal consistency (Cronbach's alpha) of 0.92 [47]. Comorbid current anxiety use was assessed with CIDI.

Statistical analyses

Sociodemographic and clinical characteristics were summarized according to CIDI using descriptive statistics. Missing values of BMI and smoking status were imputed with the respective values from the previous wave.

Cross-sectional analyses

The CIDI was used to assess remitted or current depressive disorders and incident hypomanic episodes in the previous two years for cross- sectional analysis at the fourth wave at 4-year follow-up. Upon completing the CIDI, participants were categorized into one of the following two psychopathology groups: remitted- and current depression. In these two groups a number of participants had experienced a hypomanic episode between baseline and 4-year follow-up, thus being classified in the BD converted group. We used analysis of variance to compare the mean levels of the continuous variables trait anger and aggression reactivity, and chi-squared tests were used to compare the prevalence of the dichotomous variables anger attacks, antisocial and borderline personality traits among the three psychopathology groups (i.e., remitted depression,

current depression, converted BD group). Furthermore, analyses were repeated for marginal means, resulting from adjustment for gender, age, level of education, alcohol and drugs use, severity of depressive symptoms and comorbid anxiety disorder using analysis of covariance (ANCOVA) and multivariable logistic regression analyses, when appropriate. The results of these analyses were presented in forest plots.

Moreover, multivariate linear regression analysis was used to analyse all the individual items of all the anger constructs (i.e., trait anger, aggression reactivity, anger attacks, and personality traits associated with more anger). Individual items estimated betas (with error bars representing 95% confidence interval [CI]) were summarized and presented in supplementary forest plots. These were sorted by the size of each estimated beta for each construct separately.

Prospective analyses

At baseline, patients with a self-reported or with a professionally reported primary clinical diagnosis of BD were excluded. As the BD section of the CIDI was not conducted at baseline, we applied a lag- time analysis of 2 years, excluding all incident cases of hypomanic cases based on the CIDI between baseline and 2-year follow-up. In 1744 participants, 28 experienced CIDI-confirmed incident hypomania during follow-up (between 2 and 9 years). Kaplan–Meier analysis was used to examine the relationship between baseline aggression reactivity and conversion to BD. Hazard ratios (HR) with 95% CI of conversion to BD were estimated by Cox proportional hazards models. The date of inclusion into the cohort was considered the baseline for each patient in the survival analysis. The primary endpoint consisted of all incident cases during the follow-up period, the survival time, and the diagnoses at each time point based on the CIDI. All follow-up losses as well as patients who did not experience a hypomanic episode were censored. We estimated three models: (a) a crude model that did not include any covariates, (b) an adjusted model that included gender, age, and level of education, and (c) a fully adjusted model that also included alcohol dependency, severity of depression symptoms and comorbid anxiety disorder. We tested for a linear trend across tertiles of incidents of hypomania.

Multivariable logistic and Cox regression analyses and ANCOVA were performed using IBM SPSS statistical software (version 25; IBM Corp.). The analyses regarding individual items and forest plots were computed using the R statistical software, version 3.4.1 (R Foundation for Statistical Computing, Vienna, Austria, 2016. URL: https://www.R-project.org/). A two-sided *p* value was considered statistically significant at the 0.05 level.

Table 1. Baseline characteristics of the study sample

	Baseline characteristics (*N* = 1744)	**4 year (wave 4) characteristics (*N* = 1585)**		
		Remitted depressive disorder (*n* = 1159)	Current depressive disorder (*n* = 349)	Converted group bipolar disorder (*n* = 77)
All Sociodemographic:				
Female sex, no. (%)	1,290 (68.3%)	796 (68.7%)	253 (72.5%)	41 (53.2%)
Age in years, mean (SD)	42.5 (12.6)	46.2 (12.7)	47.0 (12.3)	44.8 (11.2)
Education, in years, mean (SD)	12.1 (3.3)	12.7 (3.3)	12.2 (3.3)	12.2 (3.3)
Body mass index (BMI), in kg/m^2, mean (SD)	25.7 (5.1)	26.3 (5.0)	26.4 (5.5)	26.9 (5.7)
Smoking, no. (%)	737 (39.0%)	371 (32.0%)	129 (37.0%)	34 (44.2%)
Alcohol dependency, no. (%)	549 (29.1%)	75 (6.5%)	42 (12.0%)	11 (14.3%)
Clinical characteristics:				
Severity depression IDS-SR total score, mean (SD)	33.03 (2.45)	14.95 (9.79)	29.45 (12.63)	24.70 (13.55)
Medication use, no. (%)				
Benzodiazepines	335 (17.7%)	124 (10.7%)	86 (24.6%)	20 (26.0%)
Selective serotonin reuptake inhibitors	411 (21.8%)	186 (16.0%)	65 (18.6%)	17 (22.1%)
Tricyclic antidepressants	63 (3.3%)	30 (2.6%)	17 (2.9%)	5 (6.5%)
Other antidepressants	129 (6.8%)	64 (5.5%)	46 (13.2%)	8 (10.4%)
Antipsychotic	35 (1.5%)	11 (0.9%)	12 (3.4%)	9 (11.7%)
Mood stabilizers	54 (3.1%)	21 (1.8%)	19 (5.4%)	8 (10.4%)

Data are means (with standard errors in parentheses) or number of participants (with percentages in parentheses).
IDS-SR = Inventory of Depressive Symptomatology, self-report.

Results

Cross-sectional results

Demographic and clinical characteristics on (hypo)manic episodes of wave 4 (at 4 years follow-up) are shown in Table 1. Participants (N = 1585) were on average 46.3 years old (SD = 12.6) and 68.8% were female. There were 77 (4.9%) patients who had converted from unipolar depression to BD based on CIDI during the two through four-year waves (Table 1). There were no notable differences found in the sociodemographic between the groups. Patients with current depressive disorder showed more severe symptoms of depression compared with the other two groups. The group of converted patients smoked more often and suffered more from alcohol dependency than the two other groups. These patients also used more benzodiazepines, selective serotonin reuptake inhibitors, and psychotropic medication compared to other groups.

Significant differences were present in the crude model for all anger constructs among the three groups (all p's < .001). The between differences persisted the adjusted models in continuous variables (see forest plot in Figure 2) with (F (2, 1582) = 8.20, p < .001 for trait anger; F (2, 1456) = 5.61, p = .004 for aggression reactivity. In the adjusted models, patients who were converted had the highest marginal mean levels on trait anger and aggression reactivity in comparison with remitted patients with a mean difference; (MD = 1.87, SE = 0.6, p = .001) for trait anger, and (MD = 1.76, SE = 0.5, p = .001) for aggression reactivity and current depressed patients (MD = 2.35, SE = 0.6, p < .001) for trait anger, (MD = 1.71, SE = 0.6, p = .002) for aggression reactivity.

Results of adjusted analysis in categorical variables (see forest plot in Figure 3) were also significant with χ^2 (2) = 4.55, p = .041 for anger attacks; χ2 (2) = 5.12, p = .02 for antisocial personality traits; and χ^2 (2) = 10.41, p = .001 for borderline personality traits. Furthermore, the converted group also had the highest prevalence of anger attacks (22.1%), antisocial personality traits (9.1%) and borderline personality traits (36.4%) compared to those with remitted and current depression.

Results of the individual items of constructs (Figures S1–S5) with estimated betas and 95% CI show that anger attack items measuring physical sensation and anger items were most strongly associated with hypomania. Moreover, almost all the items of PDQ borderline personality disorder-subscale were statistically significantly associated with hypomania and were more prominently associated than the other anger constructs. It was also notable that specifically the items that measure impulsiveness were strongly associated, rather than items that measure anti-sociability, such as bullying or harming other people.

CIDI diagnosis groups	n	Crude mean (95%CI)	Test (crude)	Adjusted mean (95%CI)	Test (adjusted)
Trait anger					
• Remitted depressive disorder	1159	15.57 (15.31-15.84)	F(2, 1582) = 30.5; P < .001	16.12 (15.84-16.39)	F(2, 1582) = 8.20; P < .001
• Current depressive disorder	349	17.19 (16.62-17.76)		15.63 (15.10-16.17)	
• Converted group BD	77	19.15 (17.68-20.62)		18.03 (17.00-19.03)	
Aggression reactivity					
• Remitted depressive disorder	1078	4.92 (4.67-5.17)	F(2, 1466) = 24.39; P < .001	5.26 (5.00-5.51)	F(2, 1456) = 5.61; P = .004
• Current depressive disorder	324	6.24 (5.72-6.75)		5.30 (4.80-5.80)	
• Converted group BD	67	7.92 (6.81-9.03)		7.01 (6.01-8.01)	

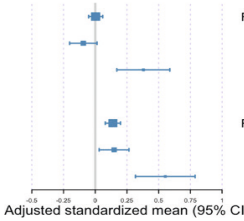


Fig. 2. Forest plot showing the estimated marginal means (with 95% confidence interval [CI]) of trait anger and aggression reactivity according to three diagnoses groups. The adjusted analyses were adjusted for gender, age, level of education, alcohol dependency, drugs use, severity of depressive symptoms, and comorbid anxiety disorder

CIDI diagnosis groups	n (%)	Crude OR (95%CI)	Test (crude)	Adjusted OR (95%CI)	Test (adjusted)
Anger attacks					
• Remitted depressive disorder	99 (8.5%)	1.0 (ref)	χ2 (2) = 26.3, P < 0.001	1.0 (ref)	χ2 (2) = 4.55, P = 0.041
• Current depressive disorder	59 (16.9%)	2.18 (1.54-3.08)		1.55 (0,85-2,83)	
• Converted group BD	17 (22.1%)	3.03 (1.70-5.40)		1.98 (1.03-3.79)	
Antisocial personality traits					
• Remitted depressive disorder	15 (1.3%)	1.0 (ref)	χ2 (2) = 19.1, P < 0.001	1.0 (ref)	χ2 (2) = 5.12, P = 0.02
• Current depressive disorder	14 (4.0%)	3.19 (1.52-6.67)		1.82 (0.72-4.5)	
• Converted group BD	7 (9.1%)	7.63 (3.01-19.31)		3.5 (1.22-10.04)	
Borderline personality traits					
• Remitted depressive disorder	106 (9.1%)	1.0 (ref)	χ2 (2) = 87.5, P < 0.001	1.0 (ref)	χ2 (2) = 10.41, P = 0.001
• Current depressive disorder	93 (26.6%)	3.61 (2.65-4.92)		1.61 (0.93-2.78)	
• Converted group BD	28 (36.4%)	5.68 (3.42-9.41)		3.02 (1.65-5.53)	

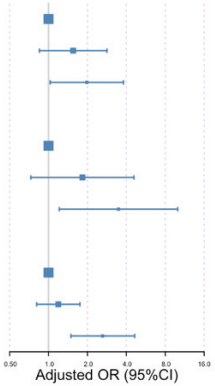


Fig. 3. Forest plot showing (adjusted) odds ratios (OR) of anger attacks, antisocial and borderline personality traits according to three diagnoses groups. The adjusted analyses were adjusted for gender, age, level of education, alcohol dependency, drugs use, severity of depressive symptoms, and comorbid anxiety disorder. CI, confidence interval

Prospective results

Baseline characteristics are summarized in Table 1. The subjects at baseline (n = 1744) were on average 42.5 years of age (SD = 12.6) and were predominantly female (68.3%). The sample consisted of 560 (29.7%) patients with remitted depressive and/or anxiety disorder and 1.328 (70.3%) patients with a current depressive and/or anxiety disorder. Based on CIDI 28 cases of hypomanic episodes were identified, signalling conversion to BD, from 2 to 9 years of follow-up. Relatively smaller number of incident cases of (hypo)mania in prospective analysis compared with cross-sectional analysis (28 vs. 77) is due to the exclusion of all the cases between baseline and 2 years of follow-up in prospective analysis to exclude all prevalent cases from the prospective analysis.

Kaplan–Meier analysis of survival with the incident hypomanic episode as outcome showed that patients with higher levels of aggression reactivity had higher conversion rates compared to patients with lower levels of aggression reactivity (Figure 4). This association is also displayed in Table 2; showing that, compared to patients in the lower tertile of aggression reactivity (low is reference with HRs of 1 and intermediate with HRs of 1.34), those in the top tertile had a higher rate (HRs of 4.63) of incident cases of hypomania. In the fully adjusted model, aggression reactivity was a significant predictor, with an HRs 1.4 (95% CI, 1.02–1.93; p = .037) per 1-SD increase in aggression reactivity.

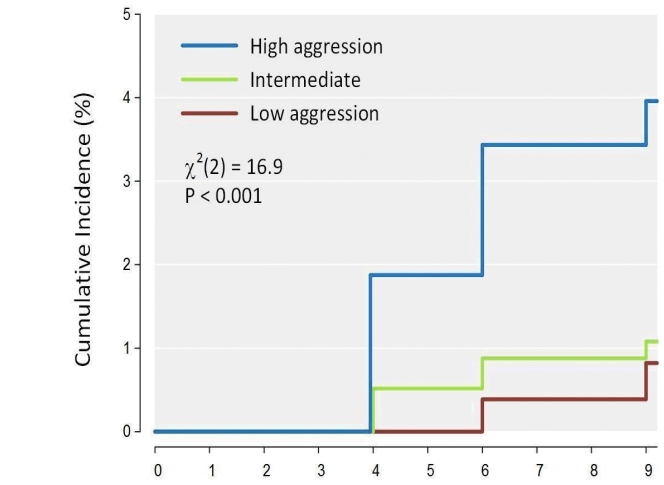


Fig. 4. Kaplan–Meier curves of incident (hypo)mania according to tertiles of aggression reactivity. P value by log-rank (Mantel–Cox) test

Table 2. Tertiles of aggression reactivity as a predictor of incident of (hypo)mania in sample of patients with depression and/or anxiety disorder

	Tertiles of aggression reactivity			
	Lower scores	**Intermediate scores**	**Higher scores**	**P-value for Trend#**
Participants, No.	590	623	525	
Cases, NO. (%)	4 (0.7%)	6 (1.0%)	18 (3.4%)	
Hazard ratio (95% confidence interval):				
Crude	1.0 (ref)	1.41 (0.40-4.99)	5.27 (1.79-15.6)	< 0.001
Adjusted*	1.0 (ref)	1.37 (0.39-4.88)	4.87 (1.63-14.6)	< 0.001
Fully adjusted model**	1.0 (ref)	1.34 (0.37-4.69)	4.63 (1.54-13.9)	0.037
	Continuous aggression reactivity (z-value)			**P-value**
Hazard ratio (95% confidence interval):				
Crude	1.84 (1.41-2.41)			< 0.001
Adjusted*	1.78 (1.36-2.35)			< 0.001
Fully adjusted model**	1.4 (1.02-1.93)			0.037

Data obtained by an analysis of variance for trend, linear term.
*Adjusted for gender, age, level of education.
** Additionally adjusted for alcohol dependence and severity of depression symptoms (IDS).

Discussion

The purpose of this study was first to examine the association of different constructs of anger with BD; and second to determine the predictive role of aggression reactivity in conversion to BD. Our study demonstrated a strong and consistent finding in the prospective as well as in the cross-sectional analyses. We found that higher levels of anger in all its variants were consistently associated with bipolarity versus those with a history of unipolar depression. Second, we found that aggression reactivity was predictive of conversion to BD.

Cross-sectionally, all the different constructs of anger and affective instability (i.e., trait anger, aggression reactivity, anger attacks, and personality traits associated with more anger) showed consistent associations, with the strongest association and highest prevalence in the converted group in comparison to the remitted and current depression groups. These results were in line with previous findings showing that BD patients scored higher on anger-related measures [18, 22] in comparison to unipolar depressed groups.

Regarding our prospective findings, we found that aggression reactivity was a risk factor for the conversion to BD in persons with a history of unipolar depression. Although two earlier prospective studies [20, 22] showed that feelings of anger were more frequent during the follow-up waves in BD patients in comparison with subjects with other psychiatric disorders and healthy controls, we are not aware of previous studies that examined the predictive value of an anger construct in relation to conversion to BD.

Affective instability and dysregulation in general seem to be distinctive factors for BD compared to unipolar depression in the current sample, since our results show that both antisocial- and borderline personality traits were more prevalent in the BD conversion group than in the currently depressed and remitted unipolar depression group. Results were most striking for the borderline traits, which is in line with previous findings showing that emotional instability is a core characteristic in both BD and borderline personality disorder. Deltito et al. (2001) suggest that the current classification may fail to differentiate between the two disorders considering the complexity and heterogeneity within these patient groups and that perhaps borderline and bipolar might be the two extremes of the same spectrum [30]. Additionally, a longitudinal study showed that comorbid borderline and antisocial personality traits predicted the risk of aggression in BD, while controlling for potential confounding factors [48].

Whether emotion regulation problems are more characteristic for BD than unipolar depression is unclear, since the few studies into this topic had contradicting results [49, 50]. We might carefully conclude, based on the current and previous findings, that especially anger and aggression dysregulation are the most distinct affective characteristics for BD when compared to unipolar depression. One important explanation for this finding might be the occurrence of mixed mood states. Although results are not fully conclusive, agitated depression or mixed depression (i.e., depressed episodes with the simultaneous presence of several manic symptoms, like irritability) in unipolar depression might be one of the early signs of conversion to BD since mixed episodes are more prevalent in BD [51]. However, it is unclear to what extent the current and previous findings are associated with the increased occurrence of mixed mood states in BD patients.

Another potential explanation for the more distinct problems in regulation of anger in BD patients compared to unipolar depression patients might reside in differences in emotion regulation styles. Although most dysfunctional emotion regulation styles are comparable between BD and unipolar depression patients (e.g., rumination and catastrophizing) [52, 53] there are indications for important differences. Both on the

cognitive and behavioural levels, BD patients seem to have the tendency to upregulate activated mood states. For instance, Kelly, Mansell [54] showed that positive appraisal about activated states predicted BD (in a sample with BD, unipolar depression, and healthy controls). BD patients also seem to have more extreme positive self-relevant appraisals of the feelings of activation than healthy controls and unipolar depressed patients [55, 56]. Additionally, at least a subgroup of the bipolar patients is more likely to engage in stimulating and activating behaviour that potentially induces a hypomanic episodes [57]. Although previous studies focused specifically on activated states, such as happiness or euphoria, anger can also be considered as an activated mood state as well.

Feelings of anger might be an important target for early recognition of illness and intervention in BD. Increased feelings of anger in unipolar patients in combination with some other known clinical characteristics, such as multiple brief depressed episodes, a lack of response to antidepressants, a family history of BD [58] might help to signal an upcoming conversion to BD. In addition, agitated affective states in BD patients deserve attention for its own sake, as these may have negative consequences for their quality of life and that of their loved ones [59]. Since BD patients experience extensive emotional instability even during euthymic states [14] and seem to use maladaptive strategies [60], it is important that they learn to regulate such feelings in an appropriate way. Psychotherapy, social therapy, and group-oriented approaches can help BD patients to prevent decompensation and to develop healthier social relationships. Other treatment strategies that may especially be apt to improve emotion regulation are dialectical behaviour therapy and systems training for emotional predictability and problem-solving program, which is based on cognitive behavioural therapy combined with emotional management skill training [61, 62].

One of the strengths of this study is its longitudinal design and the inclusion of a large group of participants that oversampled patients with (preceding) depression. This is the first study that investigated prospectively the predictive value of feelings of anger in conversion to BD. In addition, this is the first study that examined five different constructs of anger in relation to BD, with strong and consistent findings. There are also limitations that need to be addressed. First, the primary focus of this prospective cohort study on unipolar rather than bipolar depression resulted in a relatively small sample of patients who experienced a hypomanic episode during follow-up. Second, even though we adjusted for potential confounders, a family history of BD was not assessed and could not be included as cofounder. Third, the current use of antipsychotic medication and mood stabilizers might have had a dampening effect on anger and

aggression, leading to an underestimation rather than an overestimation of our results [63]. However, the group taking these medications was fairly small. Finally, participants who dropped out or missed scales at follow-ups had probably higher risk of anger or irritability. Exclusion of this specific group might have led to underestimation of our results.

We can conclude that aggression reactivity is a robust risk factor for the conversion from unipolar to BD. In addition, patients who had experienced hypomania and thus had converted to BD showed more feelings of anger in comparison with unipolar depressive patients. Identifying the potential risk factors for the development of BD might have clinical value in earlier recognition, prevention of conversion into mania, and better targeted interventions.

Acknowledgments

The infrastructure for the NESDA study (www.nesda.nl) is funded through the Geestkracht program of the Netherlands Organization for Health Research and Development (ZonMw, grant number 10-000-1002) and financial contributions by participating universities and mental health care organizations (VU University Medical Center, GGZ inGeest, Leiden University Medical Center, Leiden University, GGZ Rivierduinen, University Medical Center Groningen, University of Groningen, Lentis, GGZ Friesland, GGZ Drenthe, Rob Giel Onderzoekscentrum).

Conflict of interests

The authors declare that there is no conflict of interests.

Data availability statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Supporting information

Additional supporting information may be found online in the Supporting Information section.

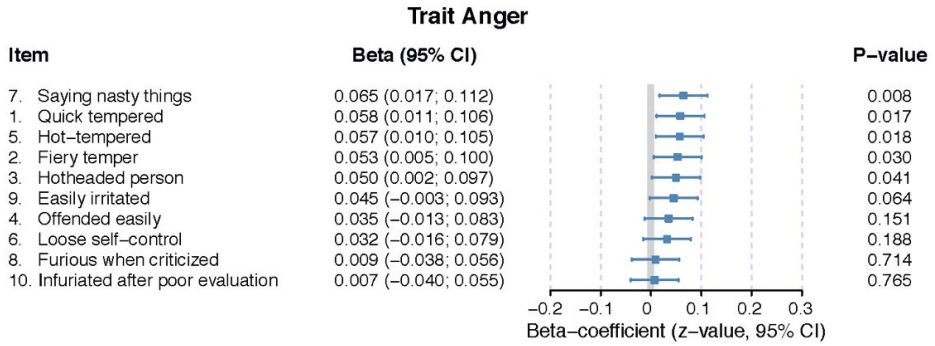
References

1. Judd LL, Akiskal HS, Schettler PJ, Coryell W, Maser J, Rice JA, et al. The comparative clinical phenotype and long term longitudinal episode course of bipolar I and II: a clinical spectrum or distinct disorders? *Journal of affective disorders*. 2003;73(1-2):19-32.
2. Gilman SE, Dupuy JM, Perlis RH. Risks for the transition from major depressive disorder to bipolar disorder in the National Epidemiologic Survey on Alcohol and Related Conditions. *The Journal of clinical psychiatry*. 2012;73(6):829-36.
3. Perlis RH, Delbello MP, Miyahara S, Wisniewski SR, Sachs GS, Nierenberg AA. Revisiting depressive-prone bipolar disorder: polarity of initial mood episode and disease course among bipolar I systematic treatment enhancement program for bipolar disorder participants. *Biological psychiatry*. 2005;58(7):549-53.
4. Bowden CL. A different depression: clinical distinctions between bipolar and unipolar depression. *Journal of affective disorders*. 2005;84(2-3):117-25.
5. Perlis RH, Brown E, Baker RW, Nierenberg AA. Clinical features of bipolar depression versus major depressive disorder in large multicenter trials. *The American journal of psychiatry*. 2006;163(2):225-31.
6. Dom G, Moggi F. Co-occurring addictive and psychiatric disorders: Springer; 2016.
7. Benazzi F. Possible bipolar nature of irritability in major depressive disorder. *The Journal of clinical psychiatry*. 2005;66(8):1072; author reply 3.
8. Benazzi F, Akiskal H. Irritable-hostile depression: further validation as a bipolar depressive mixed state. *Journal of affective disorders*. 2005;84(2-3):197-207.
9. Deffenbacher JL, Oetting ER, Thwaites GA, Lynch RS, Baker DA, Stark RS, et al. State–trait anger theory and the utility of the trait anger scale. *J Couns Psychol*. 1996;43(2):131.
10. Spielberger CD, Reheiser EC, Sydeman SJ. Measuring the experience, expression, and control of anger. *Issues Compr Pediatr Nurs*. 1995;18(3):207-32.
11. Williams R. Anger as a Basic Emotion and Its Role in Personality Building and Pathological Growth: The Neuroscientific, Developmental and Clinical Perspectives. *Front Psychol*. 2017;8:1950.
12. Fava M, Anderson K, Rosenbaum JF. "Anger attacks": possible variants of panic and major depressive disorders. *The American journal of psychiatry*. 1990;147(7):867-70.
13. Fava M, Rosenbaum JF, Pava JA, McCarthy MK, Steingard RJ, Bouffides E. Anger attacks in unipolar depression, Part 1: Clinical correlates and response to fluoxetine treatment. *The American journal of psychiatry*. 1993;150(8):1158-63.
14. Henry C, Van den Bulke D, Bellivier F, Roy I, Swendsen J, M'Baïlara K, et al. Affective lability and affect intensity as core dimensions of bipolar disorders during euthymic period. *Psychiatry research*. 2008;159(1-2):1-6.
15. Ballester J, Goldstein T, Goldstein B, Obreja M, Axelson D, Monk K, et al. Is bipolar disorder specifically associated with aggression? *Bipolar Disorders*. 2012;14(3):283-90.
16. Benazzi F, Akiskal HS. Psychometric delineation of the most discriminant symptoms of depressive mixed states. *Psychiatry research*. 2006;141(1):81-8.

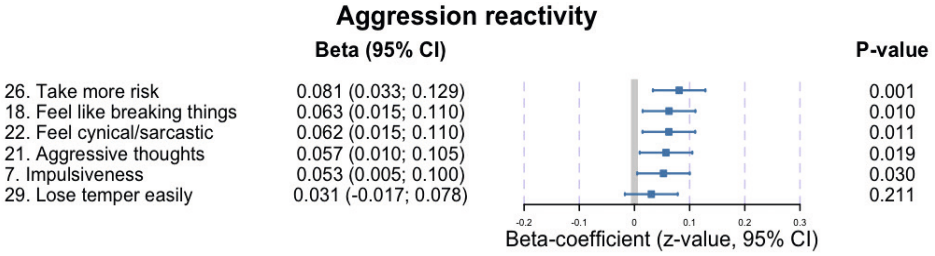
17. Mammen OK, Pilkonis PA, Chengappa KN, Kupfer DJ. Anger attacks in bipolar depression: predictors and response to citalopram added to mood stabilizers. *The Journal of clinical psychiatry*. 2004;65(5):627-33.
18. Perlis RH, Smoller JW, Fava M, Rosenbaum JF, Nierenberg AA, Sachs GS. The prevalence and clinical correlates of anger attacks during depressive episodes in bipolar disorder. *Journal of affective disorders*. 2004;79(1-3):291-5.
19. Abrams R, Taylor MA. A comparison of unipolar and bipolar depressive illness. *The American journal of psychiatry*. 1980;137(9):1084-7.
20. Ballester J, Goldstein B, Goldstein TR, Yu H, Axelson D, Monk K, et al. Prospective longitudinal course of aggression among adults with bipolar disorder. *Bipolar disorders*. 2014;16(3):262-9.
21. Aas M, Pedersen G, Henry C, Bjella T, Bellivier F, Leboyer M, et al. Psychometric properties of the Affective Lability Scale (54 and 18-item version) in patients with bipolar disorder, first-degree relatives, and healthy controls. *Journal of affective disorders*. 2015;172:375-80.
22. Dutra SJ, Reeves EJ, Mauss IB, Gruber J. Boiling at a different degree: an investigation of trait and state anger in remitted bipolar I disorder. *Journal of affective disorders*. 2014;168:37-43.
23. Johnson SL, Carver CS. Emotion-relevant impulsivity predicts sustained anger and aggression after remission in bipolar I disorder. *Journal of affective disorders*. 2016;189:169-75.
24. Edge MD, Miller CJ, Muhtadie L, Johnson SL, Carver CS, Marquinez N, et al. People with bipolar I disorder report avoiding rewarding activities and dampening positive emotion. *Journal of affective disorders*. 2013;146(3):407-13.
25. Havermans R, Nicolson NA, Berkhof J, deVries MW. Mood reactivity to daily events in patients with remitted bipolar disorder. *Psychiatry research*. 2010;179(1):47-52.
26. Gruber J, Kogan A, Mennin D, Murray G. Real-world emotion? An experience-sampling approach to emotion experience and regulation in bipolar I disorder. *J Abnorm Psychol*. 2013;122(4):971-83.
27. Knowles R, Tai S, Jones SH, Highfield J, Morriss R, Bentall RP. Stability of self-esteem in bipolar disorder: comparisons among remitted bipolar patients, remitted unipolar patients and healthy controls. *Bipolar Disord*. 2007;9(5):490-5.
28. Bauer M, Pfennig A. Epidemiology of bipolar disorders. *Epilepsia*. 2005;46:8-13.
29. Kolla NJ, Meyer JH, Bagby RM, Brijmohan A. Trait Anger, Physical Aggression, and Violent Offending in Antisocial and Borderline Personality Disorders. *J Forensic Sci*. 2017;62(1):137-41.
30. Deltito J, Martin L, Riefkohl J, Austria B, Kissilenko A, Corless CMP. Do patients with borderline personality disorder belong to the bipolar spectrum? *Journal of affective disorders*. 2001;67(1-3):221-8.
31. Barzman DH, DelBello MP, Fleck DE, Lehmkuhl H, Strakowski SM. Rates, types, and psychosocial correlates of legal charges in adolescents with newly diagnosed bipolar disorder. *Bipolar Disord*. 2007;9(4):339-44.
32. Renaud S, Corbalan F, Beaulieu S. Differential diagnosis of bipolar affective disorder type II and borderline personality disorder: analysis of the affective dimension. *Compr Psychiatry*. 2012;53(7):952-61.
33. Penninx BWJH, Beekman ATF, Smit JH, Zitman FG, Nolen WA, Spinhoven P, et al. The Netherlands Study of Depression and Anxiety (NESDA): rationale, objectives and methods. *International Journal of Methods in Psychiatric Research*. 2008;17(3):121-40.

34. de Bles NJ, Rius Ottenheim N, van Hemert AM, Putz LEH, van der Does AJW, Penninx B, et al. Trait anger and anger attacks in relation to depressive and anxiety disorders. *Journal of affective disorders*. 2019;259:259-65.
35. Van der Does W. Thought suppression and cognitive vulnerability to depression. *Br J Clin Psychol*. 2005;44(Pt 1):1-14.
36. Van der Does W. Different types of experimentally induced sad mood? *Behav Ther*. 2002;33(4):551-61.
37. Wittchen HU, Robins LN, Cottler LB, Sartorius N, Burke JD, Regier D. Cross-cultural feasibility, reliability and sources of variance of the Composite International Diagnostic Interview (CIDI). The Multicentre WHO/ADAMHA Field Trials. *The British journal of psychiatry : the journal of mental science*. 1991;159:645-53, 58.
38. Lecrubier Y, Sheehan DV, Weiller E, Amorim P, Bonora I, Sheehan KH, et al. The Mini International Neuropsychiatric Interview (MINI). A short diagnostic structured interview: reliability and validity according to the CIDI. *European psychiatry*. 1997;12(5):224-31.
39. Van der Ploeg HM, Defares PB, Spielberger CD. Handleiding bij de zelf-analyse vragenlijst ZAV. Een vragenlijst voor het meten van boosheid en woede, als toestand en als dispositie. Manual for the self-analysis questionnaire, a Dutch adaptation of the Spielberger State-Trait Anger Scale. Lisse: Swets & Zeitlinger; 1982.
40. Spielberger CD. Preliminary Manual for the State-Trait Anger Scale (STAS). 1980.
41. Spielberger CD, Krasner SS, Solomon EP. The Experience, Expression, and Control of Anger. In: Janisse MP, editor. Individual Differences, Stress, and Health Psychology. New York, NY: Springer New York; 1988. p. 89-108.
42. Hyler SE, Rieder RO, Williams JB, Spitzer RL, Hendler J, Lyons M. The Personality Diagnostic Questionnaire: development and preliminary results. *Journal of Personality Disorders*. 1988;2(3):229.
43. APA. Diagnostic and Statistical manual of mental disorders 4th edition (DSM-IV). *Washington, DC: British Library Cataloguing in Publication Data*. 1994.
44. Stringer B, van Meijel B, Eikelenboom M, Koekkoek B, Licht CM, Kerkhof AJ, et al. Recurrent suicide attempts in patients with depressive and anxiety disorders: the role of borderline personality traits. *Journal of affective disorders*. 2013;151(1):23-30.
45. Furnham A, Milner R, Akhtar R, De Fruyt F. A review of the measures designed to assess DSM-5 personality disorders. *Psychology*. 2014;5(14):1646.
46. Rush AJ, Gullion CM, Basco MR, Jarrett RB, Trivedi MH. The Inventory of Depressive Symptomatology (IDS): psychometric properties. *Psychological medicine*. 1996;26(3):477-86.
47. Beck AT, Epstein N, Brown G, Steer RA. An inventory for measuring clinical anxiety: psychometric properties. *Journal of consulting and clinical psychology*. 1988;56(6):893-7.
48. Garno JL, Gunawardane N, Goldberg JF. Predictors of trait aggression in bipolar disorder. *Bipolar Disord*. 2008;10(2):285-92.
49. Becerra R, Cruise K, Harms C, Allan A, Bassett D, Hood S, et al. Emotion regulation and residual depression predict psychosocial functioning in bipolar disorder: Preliminary study. *Universitas Psychologica*. 2015;14(3):855-64.
50. Rive MM, Mocking RJ, Koeter MW, van Wingen G, de Wit SJ, van den Heuvel OA, et al. State-Dependent Differences in Emotion Regulation Between Unmedicated Bipolar Disorder and Major Depressive Disorder. *JAMA psychiatry*. 2015;72(7):687-96.

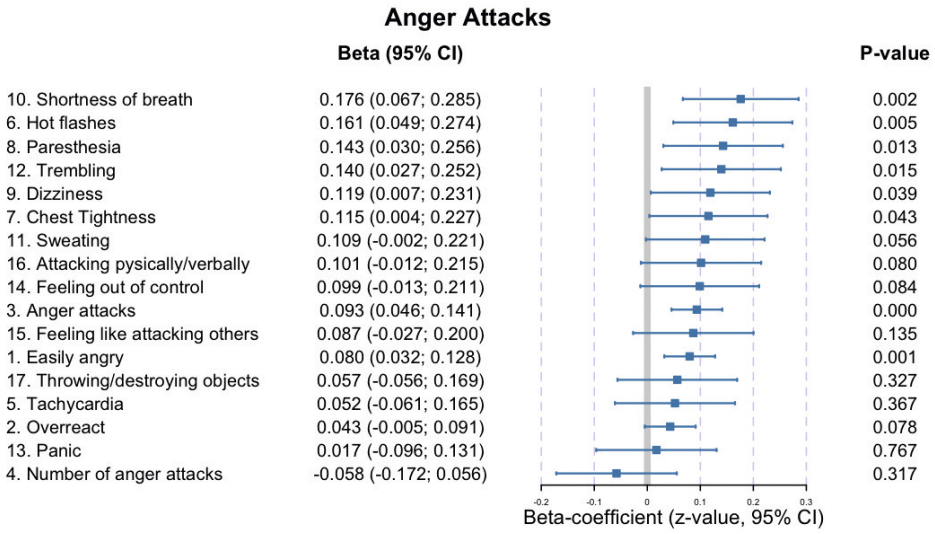
51. Vázquez GH, Lolich M, Cabrera C, Jokic R, Kolar D, Tondo L, et al. Mixed symptoms in major depressive and bipolar disorders: A systematic review. *Journal of affective disorders*. 2018;225:756-60.
52. Fletcher K, Parker G, Manicavasagar V. Behavioral Activation System (BAS) differences in bipolar I and II disorder. *Journal of affective disorders*. 2013;151(1):121-8.
53. Fuhr K, Hautzinger M, Meyer TD. Implicit motives and cognitive variables: specific links to vulnerability for unipolar or bipolar disorder. *Psychiatry research*. 2014;215(1):61-8.
54. Kelly RE, Mansell W, Wood AM, Alatiq Y, Dodd A, Searson R. Extreme positive and negative appraisals of activated states interact to discriminate bipolar disorder from unipolar depression and non-clinical controls. *Journal of affective disorders*. 2011;134(1-3):438-43.
55. Mansell W, Paszek G, Seal K, Pedley R, Jones S, Thomas N, et al. Extreme appraisals of internal states in bipolar I disorder: A multiple control group study. *Cognitive Therapy and Research*. 2011;35(1):87-97.
56. Tosun A, Maçkali Z, Çağin Tosun Ö, Kapucu Eryar A, Mansell W. Extreme Appraisals of Internal States and Duration of Remission in Remitted Bipolar Patients. *Noro Psikiyatr Ars*. 2015;52(4):406-11.
57. Lee R, Lam D, Mansell W, Farmer A. Sense of hyper-positive self, goal-attainment beliefs and coping strategies in bipolar I disorder. *Psychological medicine*. 2010;40(6):967-75.
58. Ghaemi SN, Boiman EE, Goodwin FK. Diagnosing bipolar disorder and the effect of antidepressants: a naturalistic study. *The Journal of clinical psychiatry*. 2000;61(10):804-8; quiz 9.
59. Lee Mortensen G, Vinberg M, Lee Mortensen S, Balslev Jørgensen M, Eberhard J. Bipolar patients' quality of life in mixed states: a preliminary qualitative study. *Psychopathology*. 2015;48(3):192-201.
60. Dodd A, Lockwood E, Mansell W, Palmier-Claus J. Emotion regulation strategies in bipolar disorder: A systematic and critical review. *Journal of affective disorders*. 2019;246:262-84.
61. Eisner L, Eddie D, Harley R, Jacobo M, Nierenberg AA, Deckersbach T. Dialectical Behavior Therapy Group Skills Training for Bipolar Disorder. *Behav Ther*. 2017;48(4):557-66.
62. Van Dijk S, Jeffrey J, Katz MR. A randomized, controlled, pilot study of dialectical behavior therapy skills in a psychoeducational group for individuals with bipolar disorder. *Journal of affective disorders*. 2013;145(3):386-93.
63. Correll CU, Yu X, Xiang Y, Kane JM, Masand P. Biological treatment of acute agitation or aggression with schizophrenia or bipolar disorder in the inpatient setting. *Annals of clinical psychiatry : official journal of the American Academy of Clinical Psychiatrists*. 2017;29(2):92-107.



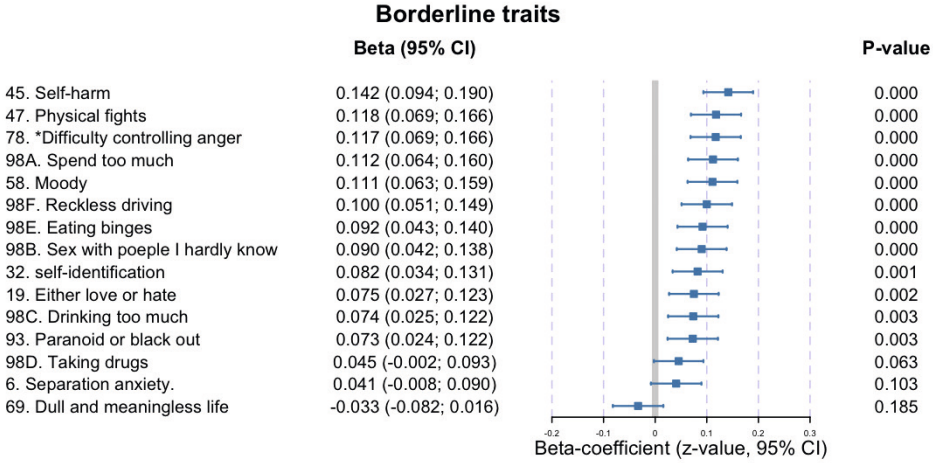
Supplementary Fig. 1. Associations of individual items of trait anger estimated beta with 95% CI (represented by error bars of those converting to BD versus those with remitted unipolar depression). Analyses were adjusted for gender, age and level of education.



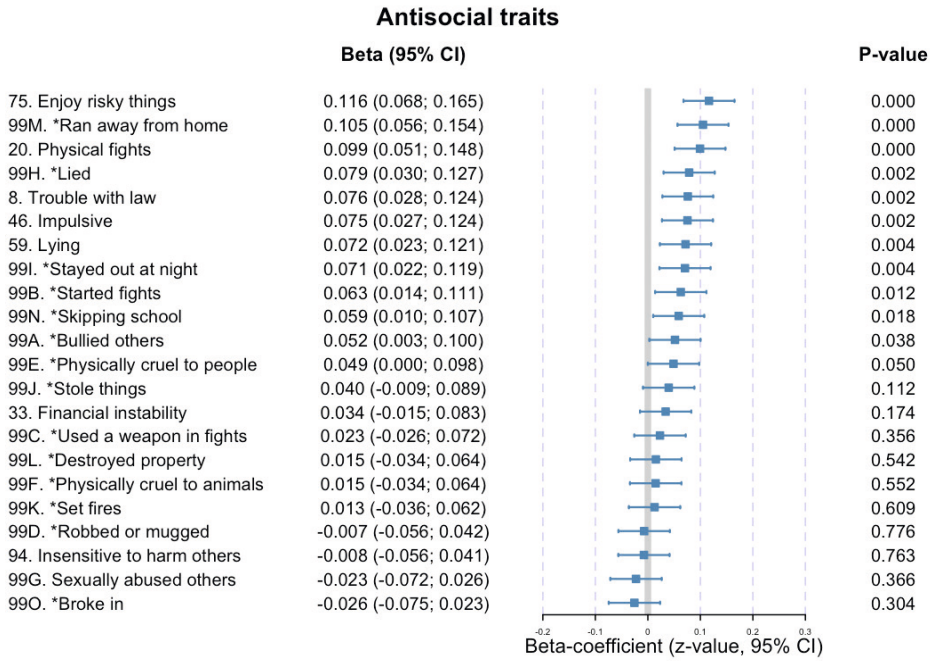
Supplementary Fig. 2. Associations of individual items of aggression reactivity estimated beta with 95% CI (represented by error bars of those converting to BD versus those with remitted unipolar depression). Analyses were adjusted for gender, age and level of education.



Supplementary Fig. 3. Associations of individual items of anger attack estimated beta with 95% CI (represented by error bars of those converting to BD versus those with remitted unipolar depression). Analyses were adjusted for gender, age and level of education.



Supplementary Fig. 4. Associations of individual items of borderline personality traits estimated beta with 95% CI (represented by error bars of those converting to BD versus those with remitted unipolar depression). Analyses were adjusted for gender, age and level of education.

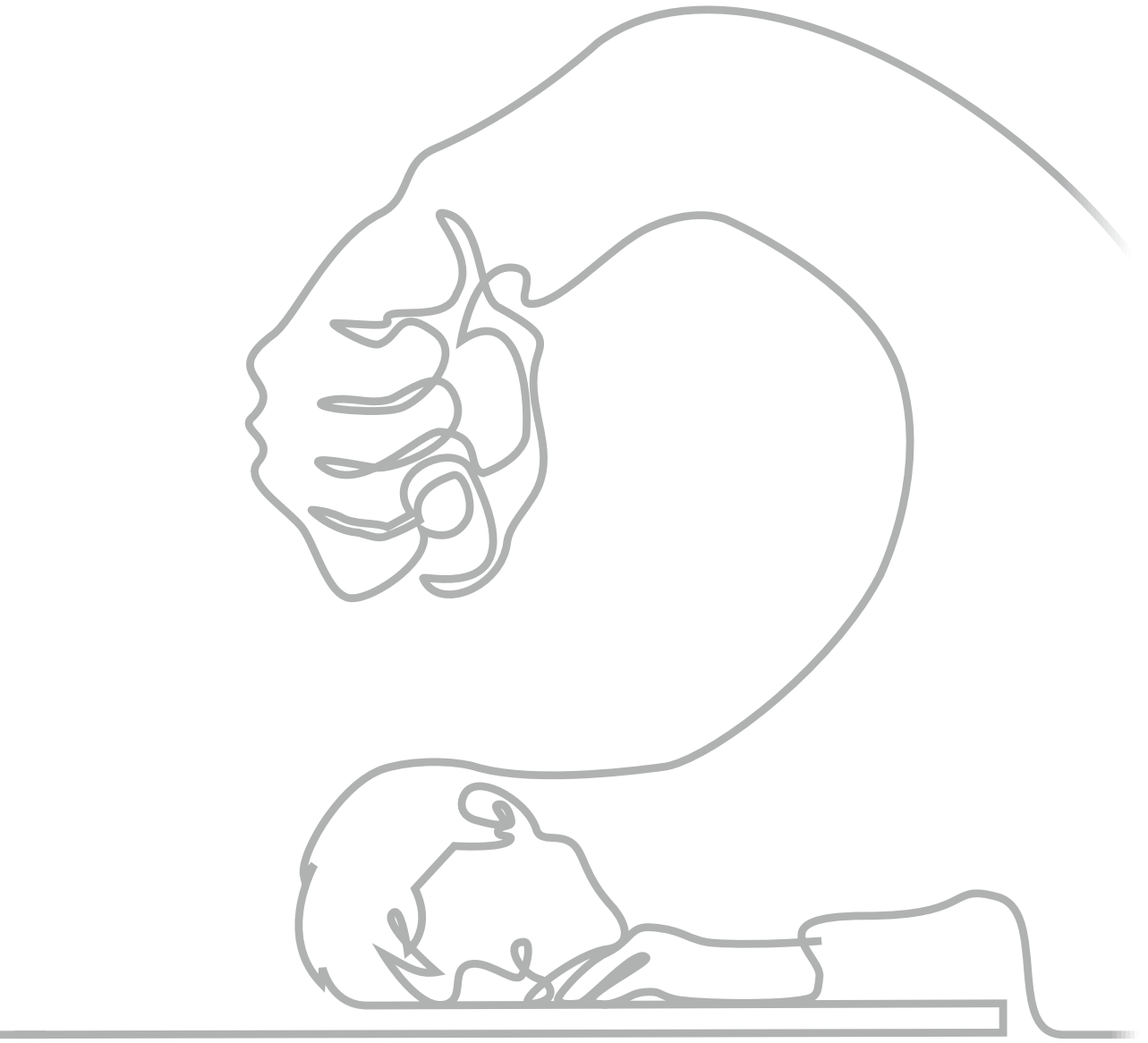


Supplementary Fig. 5. Associations of individual items of antisocial personality traits estimated beta with 95% CI (represented by error bars of those converting to BD versus those with remitted unipolar depression). Analyses were adjusted for gender, age and level of education.
*Childhood antisocial personality traits.

Submitted as: de Bles, N. J.*, Pütz, L. E. H.*, Rius Ottenheim, N., van Hemert, A. M., Elzinga, B. M., Penninx, B. W. J. H., & Giltay, E. J. (2023). Childhood trauma and anger in adults with and without depressive and anxiety disorders

*Joint first author

4 Childhood trauma and anger in adults with and without depressive and anxiety disorders



Abstract

Background: Childhood trauma is associated with severe sequelae, including stress-related mental health disorders that can perpetuate long into adulthood. A key mechanism in this relationship seems to be emotion regulation. We aimed to investigate (1) whether childhood trauma is associated with anger in adulthood, and, if so, (2) to explore which types of childhood trauma predominate in the prediction of anger in a cohort that included participants with and without lifetime affective disorders.

Methods: In the Netherlands Study of Depression and Anxiety (NESDA), childhood trauma was assessed with a semi-structured Childhood Trauma Interview (CTI) at baseline, and analysed in relation to anger as measured at 4-year follow-up with the Spielberger Trait Anger Subscale (STAS), the Anger Attacks Questionnaire, and cluster B personality traits (i.e., borderline, antisocial) of the Personality Disorder Questionnaire 4 (PDQ-4), using analysis of covariance (ANCOVA) and multivariable logistic regression analyses. Post-hoc analyses comprised cross-sectional regression analyses, using the Childhood Trauma Questionnaire – Short Form (CTQ-SF) also obtained at 4-year follow-up.

Results: Participants (n = 2271) were on average 42.1 years (SD = 13.1), and 66.2% were female. Childhood trauma showed a dose-response association with all anger constructs. All types of childhood trauma were significantly associated with borderline personality traits, independently of depression and anxiety. Additionally, all types of childhood trauma except for sexual abuse were associated with higher levels of trait anger, and a higher prevalence of anger attacks and antisocial personality traits in adulthood. Cross-sectionally, the effect sizes were larger compared to the analyses with the childhood trauma measured four years prior to the anger measures.

Conclusions: Childhood trauma is linked with anger in adulthood, which could be of particular interest in the context of psychopathology. Focus on childhood traumatic experiences and adulthood anger may help to enhance the effectiveness of treatment for patients with depressive and anxiety disorders. Trauma-focused interventions should be implemented when appropriate.

Introduction

Childhood trauma (CT) is associated with severe mental health consequences that can perpetuate long into adulthood [1]. CT, as stated by the World Health Organization (WHO), is defined as "all forms of physical and/or emotional ill-treatment, sexual abuse, neglect or negligent treatment or commercial or other exploitation, resulting in actual or potential harm to the child's health, survival, development or dignity in the context of a relationship of responsibility, trust or power" [2]. In the Netherlands, up to 1 out of 4 children reported ever having endured some form of maltreatment [3], although the prevalence of CT is likely to be an underestimation as a result of underreporting due to fear, secrecy, and stigma [4].

The substantial impact of CT is reflected by its association with the high prevalence of depressive and anxiety disorders in adulthood, including increased comorbidity and chronicity [5]. Although there are multiple potential mechanisms for psychopathology in the context of CT, emotion regulation arises as a key mechanism [6]. Poor emotion regulation can be a consequence of parents lacking sensitiveness and responsiveness to their children's emotional states or a poor parental self-regulation, learning children to be very attentive and ready to brace themselves for a possible emotional outburst of a parent [7]. This heightened sense of awareness of the emotional state of a parent can lead to a faster perception of threat in later life and to a defense system more 'ready' to respond lowering the threshold to experience anger [8]. Furthermore, by being exposed to the uncontrolled anger of primary caregivers, maltreated children are at higher risk of becoming perpetrators themselves by modelling [9, 10].

Cross-sectional studies that took into account a broad spectrum of childhood adversities found significant associations between CT, on the one hand, and anger in adulthood, on the other hand, including a dose-response relationship [11-14]. Male delinquents with a history of emotional or sexual abuse were nearly twice more likely to have high trait anger than those without emotional or sexual abuse [11], and a history of physical abuse was found to be associated with a 27% increase in trait anger in the general population [15]. Only a few cross-sectional studies focused on other anger constructs than trait anger, such as anger expression–outwards, anger expression–inwards, and anger control, although these studies found low correlations [16] or no correlations with CT at all [17]. Longitudinal studies, in contrast, showed that childhood maltreatment was predictive of anger in adulthood [18, 19]. Thus, the evidence suggests that CT is related to anger in adulthood, although the relationship has not been studied extensively among patients with affective disorders.

The link between CT and anger among adult patients with an affective disorder could be of importance, as anger is very prevalent among such disorders [20] and may even serve as a mediator of the relationship between CT and subsequent adulthood psychopathology [21]. Additionally, previous studies have shown that high levels of anger may lead to treatment dropout and poorer treatment outcomes in adults [22, 23]. Continuing on this, anger remains elevated in remitted patients compared to healthy controls [20], and both residual symptoms and the experience of childhood trauma are risk factors for relapse [24]. Thus, the link between CT and anger may yield anchor points for better and enduring effects of treatment for affective disorders.

The aims of the present study were (1) to investigate the association between CT and anger in adulthood, including trait anger, anger attacks, and borderline- and antisocial personality traits as constructs of anger and (2) to explore which types of CT predominate in the prediction of anger in a cohort that included participants without lifetime psychiatric disorders, with current or remitted depressive and anxiety disorders, or comorbid depressive and anxiety disorders.

Methods

Participants

Data stemmed from the Netherlands Study of Depression and Anxiety (NESDA), an ongoing, multisite, prospective cohort study. The study included participants with current or remitted depressive and anxiety disorders, comorbid depressive and anxiety disorders, and individuals without lifetime psychiatric disorders ("healthy controls"). In total, NESDA recruited 2981 participants at baseline ranging from 18-65 years old, as described in detail elsewhere [25]. The exclusion criteria were (1) suffering from another primary diagnosis (e.g., psychotic disorder, severe substance abuse disorder, bipolar or obsessive-compulsive disorder) and (2) insufficient mastery of the Dutch language. Baseline data collection took place between 2004 and 2007 and the 4-year follow-up between 2008 and 2011 in which wave anger was assessed. NESDA recruited participants from community care, primary care, and specialized outpatient mental health care from areas around Amsterdam, Groningen, and Leiden. The study was approved by the ethical committees of participating universities (VU University Medical Center, University Medical Center Groningen, and Leiden University Medical Center). All participants provided written informed consent.

Eleven participants with missing data on CT at baseline, 573 participants who dropped out between baseline and 4-year follow-up, and 126 participants with missing

data on CT or anger questionnaires at 4-year follow-up were excluded, resulting in a remaining sample of 2271 (76.2%) included in the main analyses (Fig. 1). The excluded 710 participants had a lower level of education ($p < 0.001$), a higher Body Mass Index (BMI) ($p = 0.040$), were more often current smokers ($p < 0.001$), alcohol dependent or alcohol abusers ($p = 0.004$), had less severe worry symptoms (p's < 0.001), and had more severe depressive and anxiety symptoms (p's < 0.001) at baseline compared to the 2271 included participants.

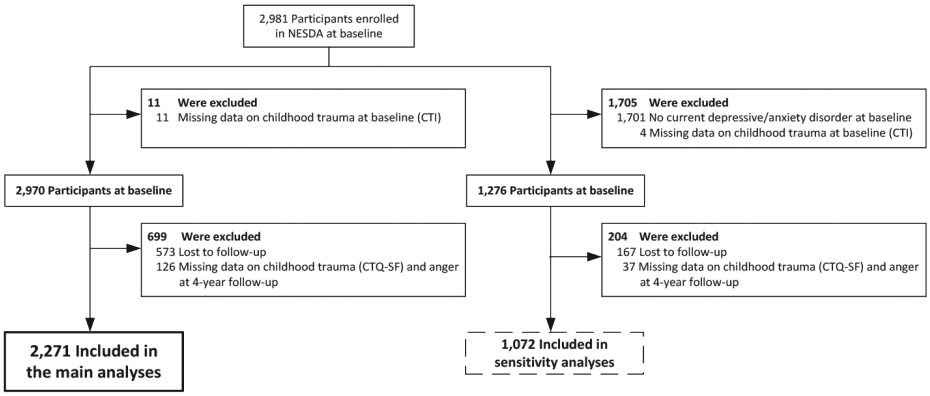


Fig. 1. Flowchart of included participants in the main and sensitivity analyses
Note. NESDA = Netherlands Study of Depression and Anxiety; CTI = Childhood Trauma Interview; CTQ-SF = Childhood Trauma Questionnaire – Short Form.

Measurements

CT and life events

Exposure to CT in NESDA was assessed twice: at the baseline using the structured Childhood Trauma Interview (CTI) [26], and at a 4-year follow-up using the self-reported Childhood Trauma Questionnaire-Short Form (CTQ-SF) [27].

The CTI comprised two sections. The first section of the interview consists of several questions on childhood life events before the age of 16: parental loss, divorce of parents, or being placed in care (i.e., child home, juvenile prison, foster family). Each event was scored as 0 (*did not happen*) or 1 (*did happen*). The childhood life event index ranged from 0–2 (0, no childhood life events; 1, one childhood life event; 2, two or more childhood life events [28]).

The second section contains four yes or no questions on experienced emotional neglect, psychological, physical, or sexual abuse before the age of sixteen. Participants

were asked the following questions: (1) Were you emotionally neglected, meaning nobody ever listened to you at home, your problems and experiences were ignored, and you felt that there was no attention or support from your parents? (2) Were you psychologically abused, meaning being yelled at, falsely punished, subordinated to your siblings, or being blackmailed? (3) Were you being abused physically, meaning being hit, kicked, beaten up or other types of physical abuse? (4) Were you sexually abused, meaning being touched or having to touch someone in a sexual way against your will? [26]. Subsequently, if answered yes, participants were asked to score the frequency on a 5-point Likert-scale ranging from 1 (*once*) to 5 (*very often*) and were asked for the perpetrator. Scores for each question were categorized to calculate a frequency score ranging from 0–2 (0, never happened; 1, once or sometimes; 2, regularly/very often). These scores combined into the childhood trauma index. This is the sum score of the four questions ranging from 0–8, where a higher number corresponds with a higher frequency and more types of CT [28, 29].

At 4-year follow-up, the CTQ-SF was assessed, which is a 28-item self-report instrument. It retrospectively assesses the same four CT categories of the CTI, with the addition of physical neglect [27]. Convergent validity was found to be fair as indicated by moderate correlations between analogous subscales of the CTQ-SF and the CTI (i.e., childhood trauma index): emotional neglect ($\rho = .60$), emotional abuse ($\rho = .57$), physical abuse ($\rho = .61$), and sexual abuse ($\rho = .57$) [30]. These associations were not attenuated by disorder status.

Trait Anger

Trait anger is described as a person's proneness to experience feelings of anger and was measured using a Dutch adaptation of the trait anger subscale of the Spielberger State-Trait-Anger Scale (STAS) [31, 32]. The STAS is a self-report measure that also includes a measure of state anger, not used in this study. The trait anger subscale contains 10 items to which participants answer on a 4-point Likert scale ranging from 1 (*almost never*) to 4 (*almost always*), leading to a sum score ranging from 10 to 40. The scale is subdivided in two scores, namely 'temperament' (i.e., the disposition to experience anger; Items 1, 2, 3, 5, and 6) and 'reaction', (i.e., the disposition to express anger especially upon provocation; Items 7, 8, and 10). Psychometric properties have shown high test-retest reliability (rtt = 0.78) and good item-total correlations (> 0.40) [31]. The Cronbach's alpha in our sample was 0.89, showing good internal consistency.

Anger Attacks

The anger attacks questionnaire [33] is a self-rated instrument used to measure the presence or absence of anger attacks during the previous 6 months. Anger attacks are described as sudden spells of anger accompanied by autonomic activation and are experienced as uncharacteristic and inappropriate for the situation [34]. In order to establish the presence of anger attacks in a dichotomous matter, all the criteria of the questionnaire need to be met over a period of the past 6 months: (1) irritability, (2) overreaction to minor annoyances, (3) inappropriate anger and rage directed at others, (4) incidence of one or more anger attacks within in the past month, (5) occurrence of at least four out of the thirteen following autonomic and/or behavioral features in at least one of the attacks: tachycardia, hot flashes, tightness of the chest, paresthesia, dizziness, shortness of breath, sweating, trembling, panic, feeling out of control, feeling like attacking others, attacking physically or verbally, and throwing or destroying objects [35].

Cluster B personality traits

A shortened 37-item version of the Dutch adaptation of the Personality Disorder Questionnaire (PDQ-4) was used to screen for the presence or absence of characteristics of antisocial and borderline personality traits, based upon the criteria of the fourth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) for these personality disorders [36, 37]. The questionnaire consists of dichotomous ('true'/'false') items, of which 8 items correspond with borderline personality disorders traits (e.g., "I have difficulty controlling my anger or temper"), and one additional item (the 9th item) measuring the impulsivity (e.g. "I have done things on impulse that could have gotten me into trouble") comprising 6 sub-items (e.g. "Reckless driving"). Seven items correspond with antisocial personality disorder traits (e.g. "I don't care if others get hurt as long as I get what I want") and the remaining 15 items correspond with antisocial behavior before the age of 15 (e.g. "I was considered a bully"). Borderline personality disorder traits ($\alpha = 0.75$) and antisocial personality disorders traits ($\alpha = 0.57$) were used in the current analyses, with a cut-off for the presence of these traits being ≥ 5 and ≥ 3 respectively. Test-retest reliability over three different time periods were on average 0.67 [38].

Symptom severity

The severity of depressive symptoms in the last seven days was measured using the self-report 30-item Inventory of Depressive Symptomatology (IDS-SR) [39]. Answers are

given on a 4-point Likert scale (0–3), with a sum score ranging from 0 to 84, due to a calculation of only 28 out of 30 items. The Beck Anxiety Inventory (BAI) is a self-report measure consisting of 21 items answered on a 4-point Likert scale (0–3). The answers result in a sum score ranging from 0 to 63 [40]. The BAI gives an impression of the somatic manifestation of anxiety over the last week. The Fear Questionnaire (FQ), a 15-item self-report measure, uses a 9-point Likert scale (0–8), with a sum score ranging from 0 to 120 [41]. This measure assesses distress and avoidance instead of fear of particular situations. The abbreviated 11-item version of the Penn State Worry Questionnaire (PSWQ) was used to assess pathological worry and general anxiety [42]. Answers to this questionnaire were given on a 5-point Likert scale (1–5), with a sum score ranging from 11 to 55 points.

Covariates

Sociodemographic and clinical covariates used for the analyses were self-reported sex, age, level of education (in years), BMI, smoking status (current/not current), and lifetime DSM IV-based alcohol dependency or abuse as measured using the Composite International Diagnostic Interview (CIDI; WHO version 2.1). The CIDI, which is a diagnostic interview based on the criteria of the DSM-IV, was also used to diagnose depressive (i.e., major depressive disorder and dysthymia) and anxiety disorders (i.e., panic disorder, social phobia, generalized anxiety disorder and agoraphobia). The CIDI was used to assess remitted or current disorders in the preceding 6 months at both baseline and 4-year follow-up. The CIDI shows high interrater reliability [43] and high test-retest reliability [44].

Statistical analyses

The main analyses used the CTI indices to reduce the chance of reverse causation. Baseline sociodemographic and clinical characteristics were summarized across the childhood trauma index (i.e., score 0, 1–3 and 4–8), using analysis of variance (ANOVA) for continuous variables and chi-squared tests for categorical variables.

ANOVA was used to compare the mean levels of the continuous variable trait anger, and chi-squared tests were used to compare the prevalence of the dichotomous variables anger attacks, borderline personality traits, and antisocial personality traits across the childhood trauma index. These analyses were repeated and adjusted for sex, age, level of education, BMI, smoking, alcohol dependency or abuse, and disorder status using analysis of covariance (ANCOVA) and multivariable logistic regression analyses.

We used a table and forest plot to show the results from the effects of the CTI (i.e., presence of childhood life events and the four CT types [i.e., emotional neglect, psychological, physical, or sexual abuse]) on the different anger measures, through logistic regression analysis (with 95% CI). The total trait anger score was dichotomized using the 75th percentile as a cut-off, representing a high trait anger score (cutoff ≥ 18). Logistic regression analyses were performed to examine the associations between the presence of childhood life events with a childhood life events index > 1 and different types of CT (i.e., emotional neglect, psychological abuse, physical abuse, and sexual abuse) measured at baseline, and the outcome anger measures obtained at 4-year follow-up. The analyses were repeated adjusting for sex, age, level of education, BMI, smoking, alcohol dependency or abuse, and disorder status (i.e., current depressive disorder and current anxiety disorder) using multivariable logistic regression.

A correlation analysis was performed establishing the correlation coefficients between the childhood life event index, childhood trauma index, CTQ-SF, anger measures (i.e., trait anger, anger attacks, borderline personality traits, and antisocial personality traits), and symptom severity measures (i.e., IDS-SR, BAI, PSWQ, FQ). To present the correlations in an intuitive manner, the data was visualized as a heat plot.

Regression analyses were repeated cross-sectionally, using the CTQ-SF. The CTQ-SF total score was categorized into three severity groups. The associations between the CTQ-SF and outcome anger measures were first tested in an unadjusted model using ANOVA and chi-squared tests. Subsequently, ANCOVA and multivariable logistic regression analyses were performed adjusting for the previously mentioned covariates.

As negative affect may enhance the recollection of negative experiences [45], we also performed sensitivity analyses. We repeated the main analyses using the childhood trauma index at baseline and the anger measures at 4-year follow-up excluding participants with a current depressive and/or anxiety disorder at baseline (Fig. 1). A two-tailed $p < 0.05$ was considered statistically significant. Analyses were performed using IBM SPSS statistical software (version 25, IBM Corp) and the R statistical software, version 4.0.3 (R Foundation for Statistical Computing, Vienna, Austria 2016. URL: https://www.R-project.org/).

Results

Sample characteristics

The mean age of the participants (*N* = 2271) was 42.1 years, and 66.2% were female. Table 1 shows the sample characteristics categorized according to the childhood trauma index. As shown here, participants with a higher childhood trauma score were significantly more often female, older, had less years of education, a higher BMI, were more often smokers, and more often suffered from alcohol dependency or abuse compared to participants with low childhood trauma scores. A higher childhood trauma score was associated with a current diagnosis of depression, both with and without a comorbid anxiety disorder, but the childhood trauma score was not associated with pure anxiety disorder. Furthermore, a higher childhood trauma score was associated with higher scores on depression and anxiety severity scales, and the use of benzodiazepines and antidepressants.

Table 1. Characteristics of the study sample (*N* = 2271) at baseline according to childhood trauma index

	Childhood trauma score			
	0 (*n* = 1216)	1–3 (*n* = 600)	4–8 (*n* = 455)	*P*-value for trend
Sociodemographics				
Female sex, no. (%)	743 (61.1)	433 (72.2)	328 (72.1)	< 0.001
Age in years, mean (*SD*)	40.6 (13.7)	42.5 (12.5)	45.6 (11.4)	< 0.001
Education in years, mean (*SD*)	12.5 (3.2)	12.7 (3.3)	11.7 (3.3)	< 0.001
BMI, kg/m^2, mean (*SD*)	25.2 (4.7)	25.3 (5.0)	26.6 (5.6)	< 0.001
Smoking, no. (%)	406 (33.4)	206 (34.3)	182 (40.0)	0.019
Lifetime alcohol dependency/abuse, no. (%)	286 (23.5)	166 (27.7)	137 (30.1)	0.003
Clinical characteristics				
Disorder status				
Current depressive disorder, no. (%)	129 (10.6)	81 (13.5)	79 (17.4)	< 0.001
Current anxiety disorder, no. (%)	203 (16.7)	117 (19.5)	89 (19.6)	0.11
Current comorbid disorder, no. (%)	188 (15.5)	153 (25.5)	160 (35.2)	< 0.001
Severity measures				
IDS-SR total score, mean (*SD*)	15.7 (12.5)	21.7 (13.3)	28.2 (13.3)	< 0.001
BAI total score, mean (*SD*)	8.68 (9.2)	11.7 (9.3)	15.6 (10.6)	< 0.001
FQ total score, mean (*SD*)	18.9 (16.4)	25.1 (19.0)	31.4 (21.4)	< 0.001
PSWQ total score, mean (*SD*)	25.7 (13.1)	29.5 (13.9)	31.9 (14.7)	< 0.001
Medication use				
Benzodiazepines, no. (%)	121 (10.0)	103 (17.2)	91 (20.0)	< 0.001
Antidepressants, no. (%)	219 (18.0)	156 (26.0)	160 (35.2)	< 0.001

Note. BMI = Body Mass Index; IDS-SR = Inventory of Depressive Symptomatology, self-report; BAI = Beck Anxiety Inventory; FQ = Fear Questionnaire; PSWQ = Penn State Worry Questionnaire. Data are number (percentage) or mean (SD), when appropriate. *P*-values by ANOVA linear term or Chi square tests (for linear association). Significant at $p < 0.05$.

Anger according to trauma groups

Between-group differences according to childhood trauma index are shown in table 2. A higher childhood trauma score was associated with a higher trait anger score ($p < 0.001$). Additionally, the prevalence of anger attacks ($p < 0.001$), borderline personality traits ($p < 0.001$), and antisocial personality traits ($p = 0.002$) was significantly higher in participants having suffered from childhood trauma compared to those reporting no history of childhood trauma. All associations remained statistically significant in the adjusted models.

Type of childhood trauma associated with anger

Figure 2 shows the (adjusted) odds ratios of different anger measures according to childhood life events and different types of childhood trauma. Childhood life events and all types of CT except sexual abuse were independently associated with trait anger, showing the strongest association with emotional neglect ($OR = 1.42$, $p < 0.001$). Furthermore, emotional neglect ($OR = 1.35$, $p = 0.004$), psychological abuse ($OR = 1.31$, $p = 0.024$) and physical abuse ($OR = 1.48$, $p = 0.004$) were independently associated with anger attacks. All types of CT, but not the childhood life event index, were significantly associated with borderline personality traits, with high ORs regarding emotional neglect ($OR = 1.76$, $p < 0.001$) and psychological abuse ($OR = 1.77$, $p < 0.001$). Last, all trauma measures except for sexual abuse were significantly associated with antisocial personality traits, with the highest OR for physical abuse ($OR = 1.98$, $p = 0.002$). However, it must be noted that only a few ($n = 40$; 1.8%) participants were categorized as having antisocial personality traits.

Correlations between outcomes

Figure 3 shows a heat plot of the correlations between trauma, anger and different severity measures of depression and anxiety. The childhood trauma index and CTQ-SF were strongly correlated ($\rho = 0.686$, $p < 0.001$), but both measures showed only a weak correlation with the childhood life event index. All three trauma measures showed significant but only rather weak correlations with anger outcomes, with a moderately strong correlation between the CTQ-SF and borderline personality traits ($\rho = 0.329$, $p < 0.001$). Childhood life events showed a weak correlation with the BAI (ρ's 0.046, $p = 0.028$), but non-significant correlations with other severity measures (i.e., IDS-SR, FQ, PSWQ). In contrast, the childhood trauma index and the CTQ-SF correlated with all symptom severity measures, with low to moderate correlations.

	n	Unadjusted OR (95% CI)	*P*-value	Adjusted OR (95% CI)	*P*-value
Childhood Life Event Index					
Trait anger	472	1.58 (1.40–1.78)	<0.001	1.41 (1.16–1.72)	0.001
Anger attacks	149	1.25 (0.92–1.70)	0.15	1.20 (0.88–1.64)	0.26
PDQ–4 Borderline	241	1.36 (1.07–1.74)	0.012	1.29 (0.99–1.67)	0.06
PDQ–4 Antisocial	40	2.06 (1.29–3.29)	0.002	1.91 (1.18–3.08)	0.008
Emotional neglect					
Trait anger	472	1.61 (1.44–1.80)	<0.001	1.42 (1.25–1.62)	<0.001
Anger attacks	149	1.54 (1.27–1.87)	<0.001	1.35 (1.10–1.66)	0.004
PDQ–4 Borderline	241	2.05 (1.76–2.39)	<0.001	1.76 (1.49–2.09)	<0.001
PDQ–4 Antisocial	40	2.03 (1.42–2.89)	<0.001	1.88 (1.29–2.74)	0.001
Psychological abuse					
Trait anger	472	1.45 (1.25–1.67)	<0.001	1.28 (1.10–1.49)	.002
Anger attacks	149	1.52 (1.22–1.89)	<0.001	1.31 (1.04–1.65)	0.024
PDQ–4 Borderline	241	2.11 (1.78–2.49)	<0.001	1.77 (1.47–2.13)	<0.001
PDQ–4 Antisocial	40	1.88 (1.29–2.74)	0.001	1.69 (1.13–2.52)	0.011
Physical abuse					
Trait anger	472	1.65 (1.40–1.95)	<0.001	1.37 (1.16–1.62)	<0.001
Anger attacks	149	1.72 (1.36–2.18)	<0.001	1.48 (1.15–1.89)	0.004
PDQ–4 Borderline	241	2.10 (1.74–2.53)	<0.001	1.71 (1.39–2.09)	<0.001
PDQ–4 Antisocial	40	2.20 (1.50–3.23)	<0.001	1.98 (1.32–2.95)	0.002
Sexual abuse					
Trait anger	472	1.16 (1.00–1.35)	0.052	1.20 (1.04–1.38)	0.15
Anger attacks	149	1.20 (0.95–1.52)	0.13	1.15 (0.89–1.48)	0.36
PDQ–4 Borderline	241	1.45 (1.21–1.73)	<0.001	1.33 (1.09–1.62)	0.011
PDQ–4 Antisocial	40	1.13 (0.71–1.79)	0.61	1.21 (0.74–1.99)	0.54

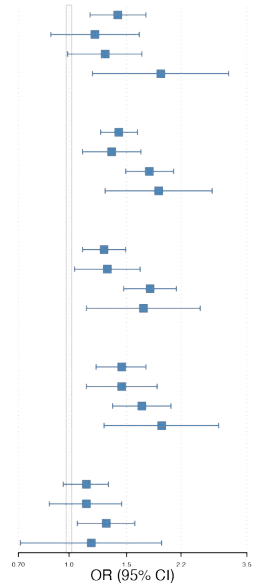


Fig. 2. The (adjusted) odds ratios of different anger measures according to childhood life events and different types of childhood trauma. Model 1 shows the crude (unadjusted) model. Model 2 adjusted for sex, age, level of education, BMI, smoking, alcohol dependency/abuse, disorder status at baseline.

Post-hoc analyses

Supplementary Table 1 shows the cross-sectional between-group differences according to the CTQ-SF. The associations between CT and anger measures remained in the cross-sectional analyses, with a higher score on the CTQ-SF corresponding to a higher trait anger score ($p < 0.001$). A higher prevalence of anger attacks ($p < 0.001$), borderline personality traits ($p < 0.001$), and antisocial personality traits ($p < 0.001$) was found in participants having suffered from CT compared to those reporting no history of CT. Cross-sectionally, the effect sizes were larger compared to the analyses with the CT measured four years prior to the anger measures.

In sensitivity analyses, we excluded participants with a current depressive and/or anxiety disorder at baseline to check for reporting bias (Table 3). A higher score on the childhood trauma index was associated with a higher trait anger score ($p < 0.001$) and a higher prevalence of borderline personality traits ($p < 0.001$). Childhood trauma score was not associated with anger attacks ($X^2 = 2.47$, $p = 0.12$) and antisocial personality

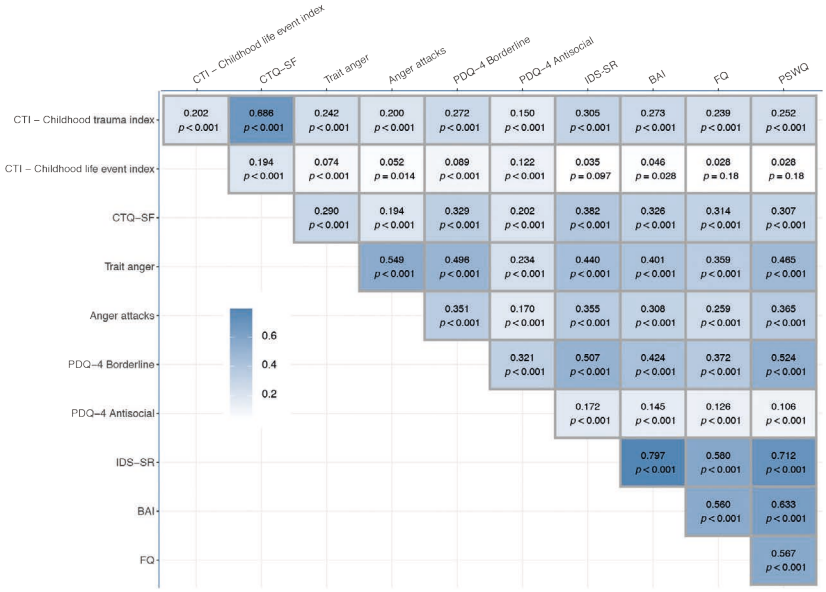


Fig. 3. Heat plot of correlations between childhood trauma (i.e., CTI - Childhood trauma index; CTQ-SF), childhood life events, anger measures (i.e., Trait anger, Anger attacks, PDQ-4 Borderline, PDQ-4 Antisocial), and symptom severity measures (i.e., IDS-SR, BAI, FQ, PSWQ). We used a sum score for the dichotomous variables anger attacks, PDQ-4 Borderline, and PDQ-4 Antisocial using the 5, 9, and 7 items respectively. The darker the color, the stronger the correlation. Non-significant correlations are shown in white. Correlations are presented in Spearman's *ρ*. CTI = Childhood Trauma Interview; CTQ-SF = Childhood Trauma Questionnaire – Short Form; PDQ-4. = Personality Disorder Questionnaire 4; IDS-SR = Inventory of Depressive Symptomatology, self-report; BAI = Beck Anxiety Inventory; FQ = Fear Questionnaire; PSWQ = Penn State Worry Questionnaire.

traits ($X^2 = 1.64$, $p = 0.20$). Due to the exclusion of participants with a current depressive and/or anxiety disorder, only 30 and 6 participants remained with anger attacks and antisocial personality traits respectively and therefore limited the statistical power of the current analysis.

Table 2. Anger outcomes at 4 years according to childhood trauma index at baseline

	Childhood trauma score				
	0 (*n* = 1216)	**1-3 (*n* = 600)**	**4-8 (*n* = 455)**	**Test statistic for trend**	***P*-value for trend**
Trait anger					
Unadjusted means (*SE*)	14.37 (0.12)[a]	15.92 (0.19)[b]	16.85 (0.24)[c]	F(1,2270) = 107.73	< 0.001
Adjusted means (*SE*)	14.56 (0.13)[a]	15.85 (0.18)[b]	16.43 (0.22)[c]	F(1,2270) = 60.64	< 0.001
Anger attacks					
Prevalence of anger attacks (%)	57 (4.7)	42 (7.0)	49 (10.8)	X^2 (1) = 20.05	< 0.001
Unadjusted odds ratio (*OR, 95%CI*)	1.0, Ref.[a]	1.53 (1.01-2.31)[b]	2.45 (1.65-3.65)[c]	Wald(1) = 19.42	< 0.001
Adjusted odds ratio (*OR, 95%CI*)	1.0, Ref.[a]	1.34 (0.87-2.05)[a]	1.92 (1.24-2.95)[b]	Wald(1) = 8.64	0.003
Borderline personality traits					
Prevalence (%)	65 (5.3)	77 (12.8)	99 (21.8)	X^2 (1) = 98.00	< 0.001
Unadjusted odds ratio (*OR, 95%CI*)	1.0, Ref.[a]	2.61 (1.84-3.68)[b]	4.92 (3.52-6.88)[c]	Wald (1) = 89.65	< 0.001
Adjusted odds ratio (*OR, 95%CI*)	1.0, Ref.[a]	2.31 (1.60-3.33)[b]	3.66 (2.54-5.29)[c]	Wald (1) = 49.16	< 0.001
Antisocial personality traits					
Prevalence (%)	14 (1.2)	9 (1.5)	16 (3.5)	X^2 (1) = 9.50	0.002
Unadjusted odds ratio (*OR, 95%CI*)	1.0, Ref.[a]	1.31 (0.56-3.04)[a]	3.13 (1.51-6.46)[b]	Wald (1) = 8.95	0.003
Adjusted odds ratio (*OR, 95%CI*)	1.0, Ref.[a]	1.35 (0.56-3.22)[a]	2.92 (1.33-6.44)[b]	Wald (1) = 6.78	0.009

Note. Data are (adjusted) means (with standard errors in parentheses) or number of participants (with percentages in parentheses). Values in the same row with different superscript letters are significantly different, $p < 0.05$ (in post hoc comparisons). Adjusted for sex, age, level of education, BMI, smoking, alcohol dependency/abuse, disorder status at baseline.

Table 3. Sensitivity analyses of anger outcomes according to childhood trauma score at baseline

	Childhood trauma score				
	0 (*n* = 696)	**1-3 (*n* = 249)**	**4-8 (*n* = 127)**	**Test statistic for trend**	***P*-value for trend**
Trait anger					
Unadjusted means (*SE*)	13.39 (0.13)[a]	15.08 (0.27)[b]	15.47 (0.40)[b]	F(1,1071) = 50.68	< 0.001
Adjusted means (*SE*)	13.38 (0.15)[a]	15.09 (0.25)[b]	15.49 (0.35)[b]	F(1,1071) = 49.28	< 0.001
Anger attacks					
Prevalence of anger attacks (%)	14 (2.0)	12 (4.8)	4 (3.1)	X^2 (1) = 2.47	0.12
Unadjusted odds ratio (*OR, 95%CI*)	1.0, Ref.[a]	2.47 (1.12-5.41)[b]	1.58 (0.51-4.89)[b]	Wald(1) = 2.42	0.12
Adjusted odds ratio (*OR, 95%CI*)	1.0, Ref.[a]	2.62 (1.17-5.87)[b]	1.75 (0.54-5.66)[b]	Wald(1) = 2.87	0.09
Borderline personality traits					
Prevalence (%)	7 (1.0)	17 (6.8)	8 (6.3)	X^2 (1) = 21.42	< 0.001
Unadjusted odds ratio (*OR, 95%CI*)	1.0, Ref.[a]	7.21 (2.95-17.61)[b]	6.62 (2.36-18.59)[c]	Wald (1) = 18.57	< 0.001
Adjusted odds ratio (*OR, 95%CI*)	1.0, Ref.[a]	8.33 (3.32-20.90)[b]	8.94 (2.93-27.30)[c]	Wald (1) = 20.64	< 0.001
Antisocial personality traits					
Prevalence (%)	3 (0.4)	1 (0.4)	2 (1.6)	X^2 (1) = 1.64	0.20
Unadjusted odds ratio (*OR, 95%CI*)	1.0, Ref.[a]	0.93 (0.10-9.00)[a]	3.70 (0.61-22.34)[a]	Wald (1) = 1.54	0.21
Adjusted odds ratio (*OR, 95%CI*)	1.0, Ref.[a]	1.15 (0.11-11.46)[a]	5.02 (0.67-37.70)[a]	Wald (1) = 1.97	0.16

Note. Data are (adjusted) means (with standard errors in parentheses) or number of participants (with percentages in parentheses). Values in the same row with different superscript letters are significantly different, $p < 0.05$ (in post hoc comparisons). Adjusted for sex, age, level of education, BMI, smoking, alcohol dependency/abuse, disorder status at baseline.

Discussion

This study aimed to examine the association between CT and several anger outcomes. Our findings indicate that a history of CT is associated with higher levels of trait anger, and a higher prevalence of anger attacks, borderline-, and antisocial personality traits in adulthood. All types of CT except for sexual abuse were associated with trait anger, anger attacks and antisocial personality traits, independently of depression and anxiety. Additionally, all types of CT were significantly associated with borderline personality traits.

Our findings support prior cross-sectional and longitudinal studies that found an association between CT and different anger outcomes in adulthood [11-14, 18, 19], including a dose-response relationship between CT and anger. A higher score for CT, both due to a higher frequency or more types of CT, are associated with higher anger scores [12-14]. However, most of these studies included non-clinical volunteers or adults without a history of psychopathology who had been placed in residential care as a child [17-19]. A recent study conducted among participants with psychopathology found trait anger to be an important mediator between CT and later psychopathology [21], though it did not consider other anger outcomes than trait anger. The potential relationship with other anger outcomes like anger attacks, in particular in the context of psychopathology, has received much less attention, yet it has been suggested that different forms of CT may affect the development of anger and aggression differently [46].

In that light, our study elaborates on previous research that found distinct effects of subtypes of abuse on emotion regulation difficulties in adulthood [47, 48]. The current findings show that emotional neglect predominates in the prediction of both trait anger and borderline personality traits, whereas physical abuse predominates in the prediction of anger attacks and antisocial personality traits. Neglect occurs in case a caregiver is not sensitive to the emotions of a child, causing a lack of emotional validation and emotional interactions. Hence, neglect may lead to disorganized attachment, rejection sensitivity, and impaired emotion regulation [49], which is linked to symptoms of borderline personality disorder (BPD), amongst others [50]. The negative impact of emotional abuse and neglect on anger was also found in previous studies [11-13, 19]. While neglect may result in difficulties in the regulation of emotions, physical abuse may result in hypervigilance to threat. Hypervigilance to threat could be an adaptation to the exposure of physical abuse, learning children to be attentive to threat-related signals. This was confirmed by children with a history of physical abuse who displayed a response bias for angry facial expressions [51]. The heightened sense of awareness of

the emotional state of a parent can lead to an earlier perception of threat in later life and to a defense system more 'ready' to respond lowering the threshold to experience anger [8]. Additionally, children who are exposed to physical abuse are at higher risk of becoming perpetrators themselves by modelling [9]. It should be noted though that perpetrators of physical abuse and physical and emotional neglect are often the parents of those afflicted, whereas most studies, including the current one, cannot differentiate between the effects of environmental and hereditary factors. Interestingly, the current study found sexual abuse to be only associated with borderline personality traits, but not with other anger outcomes. These findings could be explained in the light of previous studies which demonstrated that survivors of childhood sexual abuse had a heightened sense of interpersonal rejection sensitivity [52]. This may lead to the suppression of anger, as expressing anger might drive others away from the individual. Thus, the current results highlight the importance of considering different childhood trauma subtypes and their long-term effects on emotion regulation, more specifically the regulation of anger.

Our findings may yield anchor points for appropriate treatment. In clinical practice, it is important to explain and validate the relationship between childhood trauma and anger in adulthood, as psychoeducation is an essential constituent of the approaches to reduce symptoms of anger [53]. Unfortunately, emotion regulation difficulties and impulsive behavior are often viewed upon as limiting factors in trauma-focused therapy, thinking it may worsen these symptoms. As a result, it could be that patients are prevented from receiving a beneficial additive treatment. A meta-analysis that included those that had experienced childhood trauma did not find symptom complexity to be a contraindication for trauma-focused psychological interventions [54]. Moreover, trauma-focused treatments including eye movement desensitization and reprocessing (EMDR) have been found to be effective in the reduction of anger in patients suffering from PTSD [55]. As for pharmacotherapy, antidepressants were found to be effective in the treatment of anger [56], although some studies indicate that pharmacotherapy is less efficacious in depressive patients with a history of childhood trauma compared to their counterparts having no history of childhood trauma [57, 58]. On the contrary, a recent meta-analysis in patients with major depressive disorder found symptom improvement after pharmacotherapy regardless of their exposure to childhood trauma, yet did not take into account residual symptoms including anger [59]. To sum up, we believe that optimal and long-lasting treatment effects should include the exploration of childhood traumatic experiences and anger in adulthood.

One of the strengths of the current study is the inclusion of a large number of participants that oversampled patients with (preceding) depressive and anxiety disorders. Furthermore, all domains of CT and childhood life events were assessed using a structured interview. Even though retrospective and subjective data collection of CT is sensitive for recall bias, a structured interview is considered the 'gold standard' [60]. In addition, four anger outcomes were included, which differentiate between individuals with an angry disposition (embedded in personality) and individuals responding angrily to an immediate situation. In our main analyses, trauma and anger data were assessed four years apart, to reduce the chance of reverse causation as current anger may influence the appraisal of childhood experiences. Limitations, however, include that anger outcomes were only assessed once. As we also could not differentiate between environmental and hereditary effects, it was not possible to draw firm conclusions about the causality of CT in the onset and development of anger in adulthood. Second, only a few participants showed self-report evidence of antisocial personality traits, which limited the statistical power for this outcome. Third, the current study did not take into account certain psychiatric disorders that often display anger as a part of the disorder symptoms, with PTSD being of particular importance [61]. Although the prevalence of PTSD was high in the current sample [62], we did not adjust for PTSD due to the risk of overadjustment. Fourth, participants with a current disorder could have a different recollection of CT, yet previous research did not find such a relationship [63].

In summary, our findings confirm that those who have experienced CT are at increased risk of emotions of anger. In order to stop the cycle of abuse [64, 65], it is important that clinicians are aware of this relationship, explore adverse childhood experiences and start trauma-focused therapeutic interventions when appropriate. Twin and adoption studies may help to disentangle the complex effects of genetic vulnerability and traumatic childhood experiences on the development of the complex psychological constructs and behaviors associated with anger.

Acknowledgments

The infrastructure for the NESDA study (www.nesda.nl) is funded through the Geestkracht program of the Netherlands Organization for Health Research and Development (ZonMw, grant number 10-0001002) and financial contributions by participating universities and mental health care organizations (VU University Medical Center, GGZ inGeest, Leiden University Medical Center, Leiden University, GGZ Rivierduinen, University Medical Center Groningen, University of Groningen, Lentis, GGZ Friesland, GGZ Drenthe, Dimence, Rob Giel Onderzoekscentrum).

References

1. McKay MT, Cannon M, Chambers D, Conroy RM, Coughlan H, Dodd P, et al. Childhood trauma and adult mental disorder: A systematic review and meta-analysis of longitudinal cohort studies. *Acta psychiatrica Scandinavica.* 2021;143(3):189-205.
2. World Health Organization. Report of the consultation on child abuse prevention, 29-31 March 1999, WHO, Geneva. World Health Organization; 1999.
3. Schellingerhout R, Ramakers, C. Scholierenonderzoek Kindermishandeling 2016. Nijmegen: ITS, Radboud Universiteit Nijmegen; 2017.
4. Pinheiro PS. World report on violence against children. 2006.
5. Kuzminskaite E, Penninx BWJH, van Harmelen A-L, Elzinga BM, Hovens JGFM, Vinkers CH. Childhood Trauma in Adult Depressive and Anxiety Disorders: An Integrated Review on Psychological and Biological Mechanisms in the NESDA Cohort. *Journal of affective disorders.* 2021;283:179-91.
6. Panagou C, MacBeth A. Deconstructing pathways to resilience: A systematic review of associations between psychosocial mechanisms and transdiagnostic adult mental health outcomes in the context of adverse childhood experiences. *Clinical psychology & psychotherapy.* 2022;29(5):1626-54.
7. Wang X, Zhao F, Yang J, Gao L, Li B, Lei L, et al. Childhood Maltreatment and Bullying Perpetration among Chinese Adolescents: A Moderated Mediation Model of Moral Disengagement and Trait Anger. *Child abuse & neglect.* 2020;106:104507.
8. Zhu W, Chen Y, Xia L. Childhood maltreatment and aggression: The mediating roles of hostile attribution bias and anger rumination. *Personality and Individual Differences.* 2020;162:110007.
9. Ryan G. Preventing Violence and Trauma in the Next Generation. *Journal of Interpersonal Violence.* 2005;20(1):132-41.
10. Anderson CA, Bushman BJ. Human Aggression. Annual Review of Psychology. 2002;53(1):27-51.
11. Tang LN, Ye XZ, Yan QG, Chang HJ, Ma YQ, Liu DB, et al. Factors associated with trait anger level of juvenile offenders in Hubei province: A binary logistic regression analysis. *J Huazhong Univ Sci Technolog Med Sci.* 2017;37(1):20-4.
12. Sudbrack R, Manfro PH, Kuhn IM, de Carvalho HW, Lara DR. What doesn't kill you makes you stronger and weaker: how childhood trauma relates to temperament traits. *Journal of psychiatric research.* 2015;62:123-9.
13. Teicher MH, Samson JA, Polcari A, McGreenery CE. Sticks, stones, and hurtful words: relative effects of various forms of childhood maltreatment. *The American journal of psychiatry.* 2006;163(6):993-1000.
14. Adler AB, LeardMann CA, Roenfeldt KA, Jacobson IG, Forbes D. Magnitude of problematic anger and its predictors in the Millennium Cohort. *BMC Public Health.* 2020;20(1):1168.
15. Springer KW, Sheridan J, Kuo D, Carnes M. Long-term physical and mental health consequences of childhood physical abuse: results from a large population-based sample of men and women. *Child Abuse Negl.* 2007;31(5):517-30.
16. Cowell W, Taing L, Askowitz T, Bosquet Enlow M, Hacker MR, Wright RJ. Associations of Maternal Trait Anger Expression and Lifetime Traumatic and Non-traumatic Experiences with Preterm Birth. *Matern Child Health J.* 2021;25(4):635-44.

17. Glück TM, Knefel M, Lueger-Schuster B. A network analysis of anger, shame, proposed ICD-11 post-traumatic stress disorder, and different types of childhood trauma in foster care settings in a sample of adult survivors. *Eur J Psychotraumatol.* 2017;8(sup3):1372543.
18. Herrenkohl TI, Klika JB, Herrenkohl RC, Russo MJ, Dee T. A prospective investigation of the relationship between child maltreatment and indicators of adult psychological well-being. *Violence Vict.* 2012;27(5):764-76.
19. van Vugt E, Lanctôt N, Paquette G, Collin-Vézina D, Lemieux A. Girls in residential care: from child maltreatment to trauma-related symptoms in emerging adulthood. *Child Abuse Negl.* 2014;38(1):114-22.
20. de Bles NJ, Rius Ottenheim N, van Hemert AM, Putz LEH, van der Does AJW, Penninx B, et al. Trait anger and anger attacks in relation to depressive and anxiety disorders. *J Affect Disord.* 2019;259:259-65.
21. Win E, Zainal NH, Newman MG. Trait anger expression mediates childhood trauma predicting for adulthood anxiety, depressive, and alcohol use disorders. *Journal of affective disorders.* 2021;288:114-21.
22. Newman CF. When Clients' Morbid Avoidance and Chronic Anger Impede Their Response to Cognitive-Behavioral Therapy for Depression. *Cogn Behav Pract.* 2011;18(3):350-61.
23. Erwin BA, Heimberg RG, Schneier FR, Liebowitz MR. Anger experience and expression in social anxiety disorder: Pretreatment profile and predictors of attrition and response to cognitive-behavioral treatment. *Behavior Therapy.* 2003;34(3):331-50.
24. Buckman JEJ, Underwood A, Clarke K, Saunders R, Hollon SD, Fearon P, et al. Risk factors for relapse and recurrence of depression in adults and how they operate: A four-phase systematic review and meta-synthesis. *Clinical psychology review.* 2018;64:13-38.
25. Penninx B, Eikelenboom M, Giltay EJ, van Hemert AM, Riese H, Schoevers RA, et al. Cohort profile of the longitudinal Netherlands Study of Depression and Anxiety (NESDA) on etiology, course and consequences of depressive and anxiety disorders. *Journal of affective disorders.* 2021;287:69-77.
26. de Graaf R, Bijl RV, Ten Have M, Beekman AT, Vollebergh WA. Pathways to comorbidity: the transition of pure mood, anxiety and substance use disorders into comorbid conditions in a longitudinal population-based study. *Journal of affective disorders.* 2004;82(3):461-7.
27. Bernstein DP, Stein JA, Newcomb MD, Walker E, Pogge D, Ahluvalia T, et al. Development and validation of a brief screening version of the Childhood Trauma Questionnaire. *Child Abuse Negl.* 2003;27(2):169-90.
28. Hovens JG, Wiersma JE, Giltay EJ, van Oppen P, Spinhoven P, Penninx BW, et al. Childhood life events and childhood trauma in adult patients with depressive, anxiety and comorbid disorders vs. controls. *Acta Psychiatr Scand.* 2010;122(1):66-74.
29. Wiersma JE, Hovens JG, van Oppen P, Giltay EJ, van Schaik DJ, Beekman AT, et al. The importance of childhood trauma and childhood life events for chronicity of depression in adults. *J Clin Psychiatry.* 2009;70(7):983-9.
30. Spinhoven P, Penninx BW, Hickendorff M, van Hemert AM, Bernstein DP, Elzinga BM. Childhood Trauma Questionnaire: factor structure, measurement invariance, and validity across emotional disorders. *Psychol Assess.* 2014;26(3):717-29.

31. Van der Ploeg HM, Defares P.B., Spielberger C.D. Handleiding bij de Zelf-Analyse Vragenlijst ZAV. Een vragenlijst voor het meten van boosheid en woede als toestand en als dispositie. Manual for the Self-Analysis questionnaire, a Dutch adaptation of the Spielberger State-Trait Anger Scale. Lisse: Swets & Zeitlinger; 1982.
32. Spielberger CD. Preliminary Manual for the State-Trait Anger Scale (STAS). 1980.
33. Fava M, Rosenbaum JF, McCarthy M, Pava J, Steingard R, Bless E. Anger attacks in depressed outpatients and their response to fluoxetine. *Psychopharmacology bulletin.* 1991;27(3):275-9.
34. Fava M, Anderson K, Rosenbaum JF. "Anger attacks": possible variants of panic and major depressive disorders. *The American journal of psychiatry.* 1990;147(7):867-70.
35. Fava M, Rosenbaum JF. Anger attacks in patients with depression. *J Clin Psychiatry.* 1999;60 Suppl 15:21-4.
36. Hyler SE, Rieder R.O., Williams J.B.W. Spitzer, R.L. Hendler, J. & Lyons M. . The Personality Diagnostic Questionnaire: Development and Preliminary Results. *Journal of Personality Disorders.* 1988;2(3):229–37.
37. APA. Diagnostic and Statistical Manual of Mental Disorders 4th Edition (DSM-IV). Washington D.C.1994.
38. Okada M, Oltmanns TF. Comparison of Three Self-Report Measures of Personality Pathology. *J Psychopathol Behav Assess.* 2009;31(4):358-67.
39. Rush AJ, Gullion CM, Basco MR, Jarrett RB, Trivedi MH. The Inventory of Depressive Symptomatology (IDS): psychometric properties. *Psychol Med.* 1996;26(3):477-86.
40. Beck AT, Epstein N, Brown G, Steer RA. An inventory for measuring clinical anxiety: psychometric properties. *Journal of consulting and clinical psychology.* 1988;56(6):893-7.
41. Marks IM, Mathews AM. Brief standard self-rating for phobic patients. Behav Res Ther. 1979;17(3):263-7.
42. Meyer TJ, Miller ML, Metzger RL, Borkovec TD. Development and validation of the Penn State Worry Questionnaire. *Behav Res Ther.* 1990;28(6):487-95.
43. Wittchen HU, Robins LN, Cottler LB, Sartorius N, Burke JD, Regier D. Cross-cultural feasibility, reliability and sources of variance of the Composite International Diagnostic Interview (CIDI). The Multicentre WHO/ADAMHA Field Trials. *The British journal of psychiatry : the journal of mental science.* 1991;159:645-53, 58.
44. Wacker HR, Battegay, R., Mullejans, R., & Schlosser, C. . Using the CIDI-C in the general population. In: C. N. Stefanis ADR, & C. R. Soldatos, editor. Psychiatry: A world perspective. Amsterdam: Elsevier Science Publishers; 2006. p. 138-43.
45. Marsh C, Hammond MD, Crawford MT. Thinking about negative life events as a mediator between depression and fading affect bias. *PloS one.* 2019;14(1):e0211147-e.
46. Lee V, Hoaken PN. Cognition, emotion, and neurobiological development: mediating the relation between maltreatment and aggression. *Child Maltreat.* 2007;12(3):281-98.
47. Zhou X, Zhen R. How do physical and emotional abuse affect depression and problematic behaviors in adolescents? The roles of emotional regulation and anger. *Child Abuse Negl.* 2022;129:105641.
48. Cheng P, Langevin R. Unpacking the effects of child maltreatment subtypes on emotional competence in emerging adults. *Psychol Trauma.* 2022.
49. De Wolf M. Psychoanalytische theorievorming en de DSM-5. Ontwikkeling en. 2015.

50. Linehan MM. Cognitive-behavioral treatment of borderline personality disorder. New York, NY, US: Guilford Press; 1993. xvii, 558-xvii, p.
51. Pollak SD, Cicchetti D, Hornung K, Reed A. Recognizing emotion in faces: developmental effects of child abuse and neglect. *Developmental psychology.* 2000;36(5):679-88.
52. Luterek JA, Harb GC, Heimberg RG, Marx BP. Interpersonal rejection sensitivity in childhood sexual abuse survivors: mediator of depressive symptoms and anger suppression. *J Interpers Violence.* 2004;19(1):90-107.
53. Coon DW, Thompson L, Steffen A, Sorocco K, Gallagher-Thompson D. Anger and depression management: psychoeducational skill training interventions for women caregivers of a relative with dementia. *The Gerontologist.* 2003;43(5):678-89.
54. Ehring T, Welboren R, Morina N, Wicherts JM, Freitag J, Emmelkamp PM. Meta-analysis of psychological treatments for posttraumatic stress disorder in adult survivors of childhood abuse. *Clinical psychology review.* 2014;34(8):645-57.
55. Stapleton JA, Taylor S, Asmundson GJ. Effects of three PTSD treatments on anger and guilt: exposure therapy, eye movement desensitization and reprocessing, and relaxation training. *Journal of traumatic stress.* 2006;19(1):19-28.
56. Bond AJ. Antidepressant treatments and human aggression. *Eur J Pharmacol.* 2005;526(1-3):218-25.
57. Nelson J, Klumparendt A, Doebler P, Ehring T. Childhood maltreatment and characteristics of adult depression: Meta-analysis. *The British Journal of Psychiatry.* 2017;210(2):96-104.
58. Nanni V, Uher R, Danese A. Childhood Maltreatment Predicts Unfavorable Course of Illness and Treatment Outcome in Depression: A Meta-Analysis. *American Journal of Psychiatry.* 2012;169(2):141-51.
59. Kuzminskaite E, Gathier AW, Cuijpers P, Penninx BWJH, Ammerman RT, Brakemeier E-L, et al. Treatment efficacy and effectiveness in adults with major depressive disorder and childhood trauma history: a systematic review and meta-analysis. *The Lancet Psychiatry.* 2022;9(11):860-73.
60. Paivio SC. Stability of retrospective self-reports of child abuse and neglect before and after therapy for child abuse issues. *Child Abuse Negl.* 2001;25(8):1053-68.
61. APA. Diagnostic and Statistical Manual of Mental Disorders, 5th ed. Washington, DC: American Psychiatric Association; 2013.
62. van den Berg LJM, Tollenaar MS, Spinhoven P, Penninx B, Elzinga BM. A new perspective on PTSD symptoms after traumatic vs stressful life events and the role of gender. *Eur J Psychotraumatol.* 2017;8(1):1380470.
63. Hardt J, Rutter M. Validity of adult retrospective reports of adverse childhood experiences: review of the evidence. *Journal of child psychology and psychiatry, and allied disciplines.* 2004;45(2):260-73.
64. Mielke EL, Neukel C, Fuchs A, Hillmann K, Zietlow AL, Bertsch K, et al. The Cycle of Abuse: Emotional Availability in Resilient and Non-Resilient Mothers with Early Life Maltreatment. *Psychopathology.* 2020;53(5):298-305.
65. Widom CS. The Cycle of Violence. *Science.* 1989;244(4901):160-6.

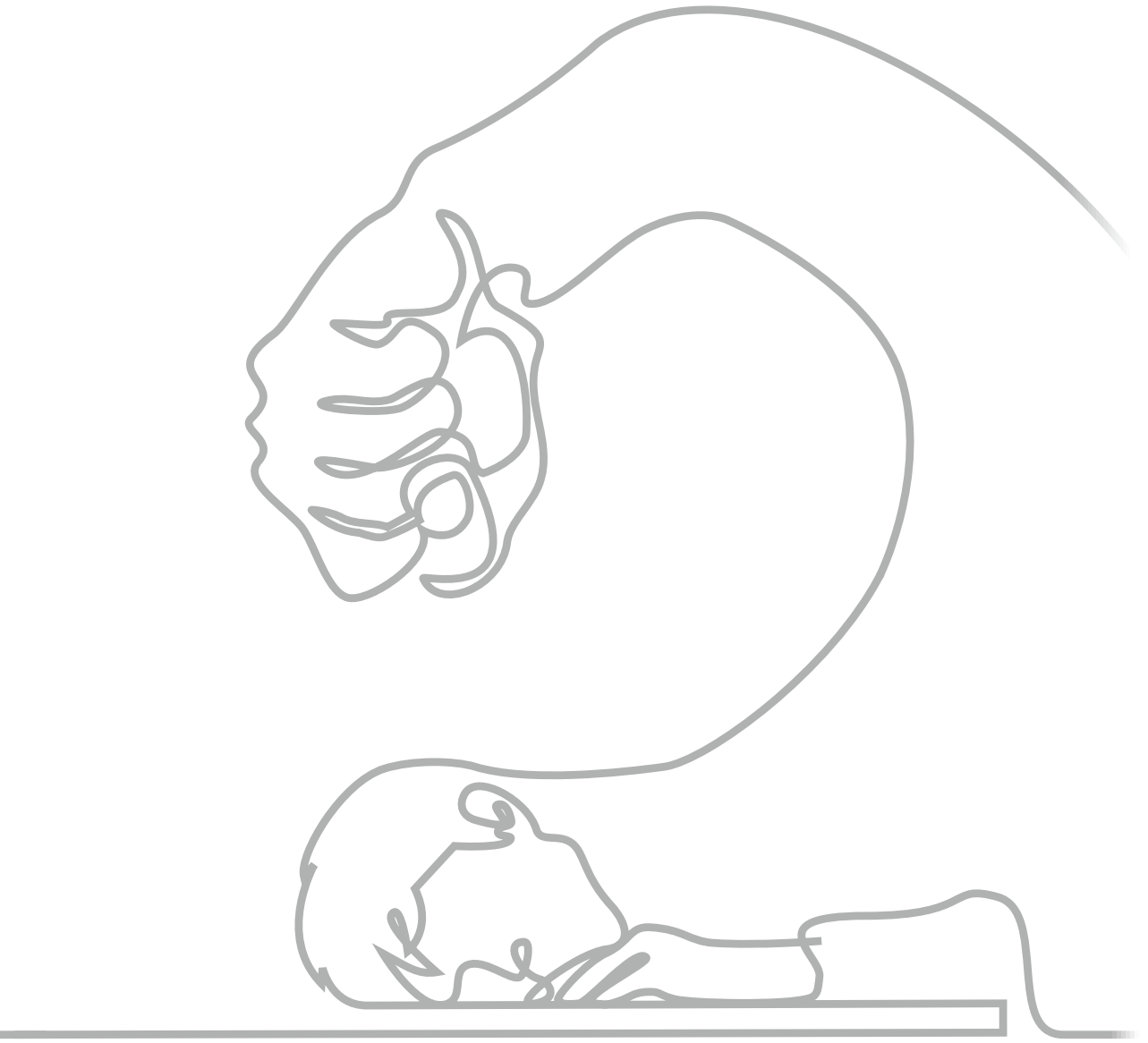
Supplementary Table 1. Cross-sectional anger outcomes according to CTQ-SF at 4-year follow-up

	Childhood trauma score				
	0 (*n* = 783)	**1-3 (*n* = 762)**	**4-8 (*n* = 726)**	**Test statistic for trend**	***P*-value for trend**
Trait anger					
Unadjusted means (*SE*)	13.86 (0.14)[a]	15.17 (0.17)[b]	16.92 (0.19)[c]	F(1,2270) = 165.94	< 0.001
Adjusted means (*SE*)	14.13 (0.16)[a]	15.20 (0.16)[b]	16.59 (0.17)[c]	F(1,2270) = 104.66	< 0.001
Anger attacks					
Prevalence of anger attacks (%)	26 (3.3)	51 (6.7)	71 (9.8)	X^2 (1) = 25.83	< 0.001
Unadjusted odds ratio (*OR, 95%CI*)	1.0, Ref.[a]	2.09 (1.29-3.39)[b]	3.16 (1.99-5.01)[c]	Wald(1) = 24.75	< 0.001
Adjusted odds ratio (*OR, 95%CI*)	1.0, Ref.[a]	1.86 (1.14-3.05)[b]	2.43 (1.50-3.94)[c]	Wald(1) = 12.78	< 0.001
Borderline personality traits					
Prevalence (%)	24 (3.1)	59 (7.7)	158 (21.8)	X^2 (1) = 137.09	< 0.001
Unadjusted odds ratio (*OR, 95%CI*)	1.0, Ref.[a]	2.65 (1.63-4.31)[b]	8.80 (5.65-13.70)[c]	Wald (1) = 117.34	< 0.001
Adjusted odds ratio (*OR, 95%CI*)	1.0, Ref.[a]	2.26 (1.37-3.73)[b]	6.77 (4.26-10.77)[c]	Wald (1) = 80.62	< 0.001
Antisocial personality traits					
Prevalence (%)	7 (0.9)	4 (0.5)	28 (3.9)	X^2 (1) = 18.98	< 0.001
Unadjusted odds ratio (*OR, 95%CI*)	1.0, Ref.[a]	0.58 (0.17-2.01)[a]	4.45 (1.93-10.24)[b]	Wald (1) = 16.44	< 0.001
Adjusted odds ratio (*OR, 95%CI*)	1.0, Ref.[a]	0.46 (0.13-1.61)[a]	3.54 (1.46-8.60)[b]	Wald (1) = 12.08	0.001

Note. Data are (adjusted) means (with standard errors in parentheses) or number of participants (with percentages in parentheses). Values in the same row with different superscript letters are significantly different, $p < 0.05$ (in post hoc comparisons). Adjusted for sex, age, level of education, BMI, smoking, alcohol dependency/abuse, disorder status at baseline.

Published as: de Bles, N. J., van der Does, J. E. H., Kortbeek, L. M., Hofhuis, A., van Grootheest, G., Vollaard, A. M., Schoevers, R. A., van Hemert, A. M., Penninx, B. W. J. H., Rius-Ottenheim, N., & Giltay, E. J. (2021). Toxoplasma gondii seropositivity in patients with depressive and anxiety disorders. *Brain, behavior, & immunity – health*, *11*, 100197.

5 Toxoplasma gondii seropositivity in patients with depressive and anxiety disorders



Abstract

Introduction: *Toxoplasma gondii* (*T. gondii*) is an obligate intracellular parasite that is estimated to be carried by one-third of the world population. Latent *T. gondii* infection has been linked to several neuropsychiatric mood disorders and behaviours. The aim of the present study was to examine whether *T. gondii* seropositivity is associated with affective disorders, as well as with aggression reactivity and suicidal thoughts.

Methods: In the Netherlands Study of Depression and Anxiety (NESDA), *T. gondii* antibodies were assessed in patients with current depressive (*n* = 133), anxiety (*n* = 188), comorbid depressive and anxiety (*n* = 148), and remitted disorders (*n* = 889), as well as in healthy controls (*n* = 373) based on DSM-IV criteria. Seropositivity was analysed in relation to disorder status, aggression reactivity and suicidal thoughts using multivariate analyses of covariance and regression analyses.

Results: Participants were on average 51.2 years (*SD* = 13.2), and 64.4% were female. Seropositivity was found in 673 participants (38.9%). A strong positive association between *T. gondii* seropositivity and age was observed. No significant associations were found between *T. gondii* seropositivity and disorder status, aggression reactivity and suicidal thoughts. The adjusted odds ratio (OR) for any remitted disorder versus controls was 1.13 (95% CI: 0.87-1.49), and for any current disorder versus controls was 0.94 (95% CI: 0.69-1.28).

Conclusions: No evidence was found for a relationship between affective disorders and *T. gondii* infection in the current sample.

Introduction

Toxoplasma gondii (*T. gondii*) is an obligate intracellular parasite estimated to be carried by one-third of the world's population, making it one of the most successful human parasites [1, 2]. It can infect mammals and many other warm-blooded animals, with cats and other felidae as its definitive hosts for sexual reproduction and the only mammals known to shed *T. gondii* oocysts with their faeces [3]. In the intermediate host, the parasite can lead to a lifelong, latent infection in various tissues, including muscles, the eye, and the central nervous system, where it forms persistent cysts. Humans are infected by swallowing *T. gondii* tissue cysts in contaminated food (undercooked infected meat) or oocysts in water, or through environmental exposure (e.g., through gardening).

While an acute infection is commonly asymptomatic or presenting with nonspecific symptoms like fatigue or lymphadenopathy, it can in some cases lead to toxoplasmic encephalitis. In case of a congenital toxoplasmosis, most lesions will be seen in the eyes and in the brain (e.g., intracranial calcifications, hydrocephalus). The parasite will not be cleared, and, after an acute symptomatic phase, the parasite will be present as a latent infection that is commonly thought to be asymptomatic [4]. However, there are indications of more subtle behavioural or psychological consequences. Evidence is also accumulating for an association between *T. gondii* infection and schizophrenia [5]. Additionally, an increase in *T. gondii* immunoglobulin G (IgG) titers, but not in immunoglobulin M (IgM), was found among patients with schizophrenia [6, 7]. This may implicate a latent *T. gondii* infection rather than an acute infection where both IgG and IgM titers would have increased. Increased IgG titers are thought to represent reactivation with release of tachyzoites, which may lead to psychopathology [8]. The interest in the possible link between *T. gondii* and depression was sparked by a case report [9], describing a depressed patient who possibly remitted after antibiotic treatment of his latent *T. gondii* infection. Subsequent studies investigated the possible link between *T. gondii* infection and depression, yet provided no clear consensus on this association. Several studies found positive associations between depressive symptoms and *T. gondii* seropositivity [10-12]. Additionally, two studies found a dose-response relationship, with higher IgG titers associated with higher depressive symptoms [13, 14]. However, a negative association between diagnoses of depression and *T. gondii* seropositivity in women was observed in a cross-sectional study of 1486 subjects [15]. Taking both genders together in one analysis, however, the association with *T. gondii* seropositivity did not longer persist. In concordance, a systematic review including

ten studies with data on major depressive disorder (MDD), found no support for a significant association between *T. gondii* infection and depression, with an odds ratio (OR) of only 1.21 (95% confidence interval [CI]: 0.86-1.70) [16], which is in line with recent cross-sectional studies on MDD and *T. gondii* infection [17-19].

Besides depression, anxiety disorders have also been studied in relation to *T. gondii* infection. An association between *T. gondii* seropositivity and generalized anxiety disorder (GAD) has been reported, with ORs ranging from 2.05 to 2.25 [11, 14, 18], with an even higher OR of 4.17 among children [20]. On the other hand, a large population-based cross-sectional study of 1846 participants [17] reported no significant associations between *T. gondii* infection and GAD or panic disorder (PD).

Furthermore, latent *T. gondii* infection has been linked to behavioural changes such as increased feelings of aggression and anger [12, 21, 22] and self-directed violence (e.g., suicide attempts, completed suicide, and self-directed violence) [10, 23-27]. A study of 1000 participants without any psychiatric diagnoses showed an association between *T. gondii* seropositivity and trait reactive aggression among women [22], which was in line with a smaller study among 70 female veterans showing a relationship between *T. gondii* seropositivity and higher anger scores [12]. Another previous study on *T. gondii* seropositivity and anger included both healthy participants and psychiatric patients. This cross-sectional study of 358 adults found an association between *T. gondii* seropositivity and higher aggression and impulsivity. Additionally, seropositivity was highest in subjects with intermittent explosive disorder (21.8% of n = 110), compared to healthy controls (9.1% of n = 110), and other psychiatric patients (16.7% of n = 138) [21]. Several studies on self-harm have also been conducted. Cross-sectional and case-control studies focusing on suicide attempts and *T. gondii* infection found evidence for a relationship with seropositivity, with ORs ranging from 1.57 to 7.12 [10, 25, 28], and antibody titers, meaning that higher IgG titers were associated with suicide attempts [23-25, 28]. In a large register-based prospective cohort study among 45,788 women after childbirth, *T. gondii*–infected mothers had a relative risk of self-directed violence of 1.53 (95% CI, 1.27-1.85) versus non-infected counterparts [26]. Thus, there seems to be an association between *T. gondii* latent infection on the one hand and (self-directed) aggression and suicidality on the other hand.

We aimed to further examine the link between *T. gondii* infection and (comorbid) depressive and anxiety disorders in a large cohort study. Based on existing literature, we hypothesized [1] that *T. gondii* seropositivity is associated with the presence and severity of depressive and anxiety disorders, and [2] that *T. gondii* seropositivity is associated with aggression reactivity and suicidal thoughts.

Methods

Participants

Participants were selected from the Netherlands Study of Depression and Anxiety (NESDA), an ongoing multisite, naturalistic, longitudinal cohort study. NESDA was designed to examine the long-term course and consequences of depressive and anxiety disorders. A total of 2981 participants (18–65 years) were enrolled at baseline. This population was composed of participants with current or remitted depressive and anxiety disorders, and comorbid depressive and anxiety disorders. The control group consisted of participants without lifetime psychiatric disorders. Participants were recruited from the community, primary care, and specialized (mental) health care in the vicinity of the clinical sites (i.e., Amsterdam [Northwest], Leiden [Southwest], Groningen [Northeast]). Exclusion criteria were (1) the presence of other psychiatric disorders (e.g., psychotic, obsessive–compulsive, bipolar, or severe addiction disorder): and (2) not being fluent in Dutch. All participants gave written informed consent before enrolment, and the ethical committees of participating universities (VU University Medical Centre, Leiden University Medical Centre, and University Medical Centre Groningen) granted ethical approval. A more detailed description of NESDA is given elsewhere [29].

For the current cross-sectional study, data was gathered at the 6th wave at 9-year follow-up between 2014 and 2017. Participants who completed the 6th wave totalled 2069 (69.4%), of whom 1731 titers were obtained and used for the current analyses. Excluded participants were younger ($p = 0.004$), more often women ($p < 0.001$) and had more fear symptoms ($p < 0.001$) compared to the sample included in the current study.

Measurements

Toxoplasma gondii IgG antibodies

Citrated plasma samples were kept frozen at −80 °C until essayed for *T. gondii* IgG antibodies. In response to the parasite*, T. gondii* IgG antibodies are produced within the first two to three weeks after infection, peaks at 3 months and, although it can decrease slowly, remains detectable over the individual's lifetime. IgG antibody levels were assayed in duplicate in plasma using a sandwich Enzyme Linked Immunosorbent Assay (ELISA) with a plasma dilution of 1:20 (adapted from a previously described method [30]). Detection of IgG antibodies in citrated plasma was first validated in a subpopulation of 100 participants, by comparing *T. gondii* seropositivity in citrated

plasma from the 6th wave with serum samples from the 5th wave. The agreement for IgG antibodies in serum and citrated plasma was 100% (Suppl. Fig. 1). The time span between blood collection at these waves ranged from 28 to 56 months. The sensitivity and specificity of the ELISA were 99–100% and 90–99% respectively. The antigen is derived from a crude extract of a *Toxoplasma* RH strain, the conjugate is a peroxidase-labelled anti-human IgG conjugate (Dako, Denmark). A cut-off serum was used, and its optical density (OD) value was allowed to vary between 0.10 and 0.30. The extinction value of the tested sample and the cut-off serum was used to calculate a ratio. A subject with a ratio of at least 1.0 was considered to be seropositive for *T. gondii* [31].

Depressive and anxiety disorders

Diagnoses of depression (i.e., MDD, dysthymia) and anxiety disorders (i.e., social phobia [SP], PD, GAD, agoraphobia [AP]) were established with the Composite International Diagnostic Interview (CIDI; WHO version 2.1). The CIDI is a fully structured clinical interview based on criteria of the fourth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV [32]). Based on the CIDI information, all 1731 NESDA participants were divided into the following psychopathology groups: [1] healthy participants who have no current and past history of psychiatric disorders (n = 373); [2] participants with a lifetime history of a depressive or anxiety disorder, but not in the last 6 months (n = 889); [3] patients with a current depressive (n = 133) or [4] anxiety disorder (n = 188); and [5] patients with current comorbid depressive and anxiety disorders (n = 148). The CIDI was established at the same day of blood collection.

Symptom severity

The severity of depressive symptoms was assessed with the Inventory of Depressive Symptomatology (self-report version; IDS-SR) [33, 34]. The IDS-SR is a 30-item questionnaire scored on a 4-point Likert scale (0–3), with sum scores ranging from 0 to 84 (28 out of 30 items are rated). The internal consistency (i.e., Cronbach's alpha) of the IDS-SR in our sample was 0.89. The Beck Anxiety Inventory (BAI) is a 21-item self-report questionnaire for measuring the somatic symptoms of anxiety [35]. It uses a 4-point Likert scale (0–3), with total scores ranging from 0 to 63. The current sample showed an internal consistency (i.e., Cronbach's alpha) of 0.92. Additionally, the 15-item self-rating Fear Questionnaire (FQ) was obtained to measure phobias and, particularly, related avoidance [36], on a 9-point Likert scale (0–8), with total scores ranging from 0 to 120 and a Cronbach's alpha of 0.89 in the current sample. The abbreviated 11-item version

of the Penn State Worry Questionnaire (PSWQ) was assessed to measure pathological worry and general anxiety [37]. Items are scored on a 5-point Likert scale (1–5), with sum score ranging from 11 to 55. Our sample presented an internal consistency (i.e., Cronbach's alpha) of 0.96.

Cognitive reactivity

The revised Leiden Index of Depression Sensitivity (LEIDS-R) is a 34-item self-report questionnaire developed to measure cognitive reactivity to sad mood [38, 39]. Items are divided into six reactivity subscales, of which the subscales aggression and hopelessness/suicidality were used in the current wave. Items are filled out on a 5-point Likert scale ranging from 0 to 4. The aggression subscale constitutes of 6 items (e.g., 'In a sad mood, I am bothered more by aggressive thoughts'), with a maximum score of 24. The hopelessness/suicidality subscale constitutes of 5 items (e.g., 'When I feel sad, more thoughts of dying or harming myself go through my mind'), with a maximum score of 20. The internal consistency (i.e., Cronbach's alpha) of the LEIDS-R subscales in our sample were 0.83 and 0.87, respectively.

Covariates

Sociodemographic covariates consisted of sex, age, education (in years), North European ancestry (yes/no), and clinical site location (i.e., Amsterdam, Leiden, Groningen). Age was divided into four age groups (i.e., 40 and younger; 41–50; 51–60; 61 and older). Body Mass Index (BMI) was calculated based on measured weight and height.

Statistical analyses

Sociodemographic characteristics were described within the *T. gondii* seronegative and seropositive groups using chi-squared tests for categorical variables and t-tests (ANOVA) for continuous variables. We also performed multivariable logistic regression analyses to examine the associations of *T. gondii* seropositivity according to demographic characteristics.

Chi-squared tests for independent samples were conducted to compare the prevalence of seropositivity among psychiatric disorders. Using multivariable logistic regression, these comparisons were repeated, adjusting for sex, age, level of education, North European ancestry, BMI, and clinical site location. Subsequently, we adjusted the full model according to previous mentioned sociodemographic variables and healthy controls, remitted depression and/or anxiety, and current dysthymia,

MDD, SP, PD, AP, and GAD. A forest plot was used to examine the OR (with 95% CI) of seropositivity among psychiatric diagnoses. In addition to testing for dichotomous seropositivity, sensitivity analyses were performed using multivariable linear regression for the continuous level of *T. gondii* IgG antibodies expressed as the ratio of OD values. The level of *T. gondii* IgG antibodies was naturally log transformed in order for its distribution to approach normality.

We also performed t-tests for independent samples to examine the association of symptom severity measures and cognitive reactivity (i.e., aggression and suicidality) with seropositivity. Using analysis of covariance (ANCOVA), analyses were repeated adjusting for sex, age, level of education, North European ancestry, BMI, and clinical site location. A second forest plot was used to examine the association of seropositivity with symptom severity and cognitive reactivity. Subsequently, sensitivity analyses were performed for the transformed level of *T. gondii* IgG antibodies in multivariable linear regression. A two-tailed significance level of $p < 0.05$ was considered statistically significant for all analyses. The Benjamini-Hochberg (B–H) correction was performed in order to correct for a false discovery rate (FDR) in multiple comparisons [40]. Analyses were performed using IBM SPSS statistical software (version 25, IBM Corp.).

Results

The mean age of the participants ($N = 1731$) was 51.2 years ($SD = 13.2$), and 64.4% were female. As shown in Fig. 1, 673 participants (38.9%) were seropositive for *T. gondii* antibodies. The odds of being seropositive for *T. gondii* increased strongly with age. *T. gondii* seroprevalence differed per clinical site location, ranging from 30.0% in Groningen (Northeast), 41.9% in Amsterdam (Northwest), to 44.6% in Leiden (Southwest). The area remained independently associated with *T. gondii* infection after adjustment for demographic characteristics. However, this was only true for Groningen compared to Amsterdam and Leiden, but not for Amsterdam and Leiden compared to each other.

Fig. 2 shows the adjusted odds of being seropositive for depressive and anxiety disorders. Healthy controls were taken as the reference group in Model 1. No associations were found between seropositivity and depressive and anxiety diagnoses after adjusting for sociodemographic variables. The odds ratio (OR) for any remitted disorder versus controls was 1.13 (95% CI: 0.87-1.49), and for any current disorder versus controls was 0.94 (95% CI: 0.69-1.28). The fully adjusted model only showed a significant negative association between *T. gondii* seropositivity and SP ($OR = 0.62$;

95% CI: 0.39-0.96). However, after B–H correction, the result was no longer deemed statistically significant. When these analyses were repeated for *T. gondii* IgG antibodies, no significant associations were found in the models adjusting for sociodemographic variables. The fully adjusted model resulted in a significant negative association with *T. gondii* and MDD ($\beta = -0.09$; $p = 0.008$), and with *T. gondii* and SP ($\beta = -0.06$; $p = 0.03$; Suppl. Table 2). Again, these associations were no longer deemed statistically significant after B–H correction.

As shown in Fig. 3, no mean differences were found between seropositive and seronegative subjects on symptom severity measures (i.e., IDS-SR, BAI, FQ, and PSWQ), aggression reactivity and suicidal thoughts. These associations remained non-significant after adjustment for sociodemographic variables. All severity measures were also tested for seropositivity in diagnostic strata (i.e., controls, remitted, and current psychopathology), in which no important differences in effect sizes among the groups were found, and none of the comparisons were statistically significant (data not shown). Analyses for a crude and adjusted model were repeated for antibody levels and also found no significant relationships (Suppl. Table 2).

Sociodemographics	IgG seronegative (*n*=1 058)	IgG seropositive (*n*=673)	*P* value	Adjusted OR (95% CI)	Adjusted *P* value
Female sex, no. (%)	695 (65.7%)	419 (62.3%)	0.146	0.93 (0.75-1.15)	0.52
Age in years, mean (SD)	47.9 (13.0)	56.5 (11.7)	< 0.001		
Age categories:					
≤ 40 years, no. (%)	367 (34.7%)	84 (12.5%)	< 0.001	1.00 (Ref.)	
41-50 years, no. (%)	219 (20.7%)	99 (14.7%)	0.002	1.78 (1.26-2.52)	0.001
51-60 years, no. (%)	244 (23.1%)	181 (26.9%)	0.071	2.87 (2.09-3.94)	< 0.001
≥ 61 years, no. (%)	228 (21.6%)	309 (45.9%)	< 0.001	5.05 (3.65-7.04)	< 0.001
Education in years, mean (SD)	13.3 (3.1)	12.5 (3.5)	< 0.001	0.84 (0.72-0.99)	0.04
North European ancestry, no. (%)	1 012 (95.7%)	651 (96.7%)	0.26	1.56 (0.91-2.68)	0.11
BMI, kg/m2, mean (SD)	26.1 (5.0)	26.9 (4.7)	0.003	1.02 (0.92-1.14)	0.67
Clinical site location:					
Amsterdam, no. (%)	350 (33.1%)	252 (37.4%)	0.063	1.00 (Ref.)	
Leiden, no. (%)	312 (29.5%)	251 (37.3%)	0.001	0.99 (0.77-1.27)	0.93
Groningen, no. (%)	396 (37.4%)	170 (25.3%)	< 0.001	0.73 (0.56-0.95)	0.02

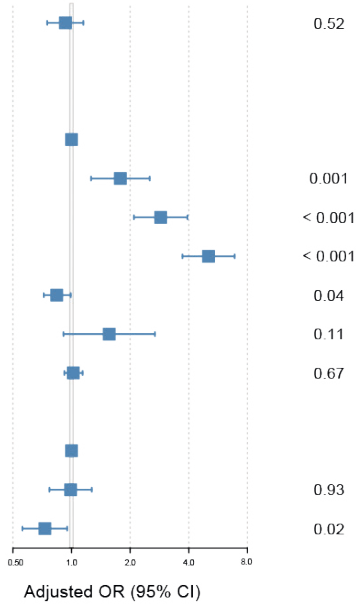


Fig 1. Characteristics of the study sample (*N* = 1731) according *T. gondii* seropositivity and the adjusted odds ratios for all independent variables in one multivariable logistic regression model.
Note. BMI = Body Mass Index; Chi-square values have been computed for categorical variables, ANOVA for interval variables; Education in years and BMI were studied per 5 units (i.e., 5 kg/m^2) increase.

Diagnosis groups	IgG seronegative (*n*=1 058)	IgG seropositive (*n*=673)	Model 1 (OR, 95% CI)	*P* value Model 1	Model 2 (OR, 95% CI)	*P* value Model 2
Healthy controls	233 (62.5%)	140 (37.5%)	1.00 (ref)		0.80 (0.50-1.29)	0.37
Remitted depression and/or anxiety	526 (59.2%)	363 (40.8%)	1.13 (0.87-1.49)	0.36	0.91 (0.58-1.41)	0.67
Any current depression and/or anxiety disorder	299 (63.8%)	170 (36.2%)	0.94 (0.69-1.28)	0.68		
Current Dysthymia	49 (58.3%)	35 (41.7%)	0.99 (0.58-1.68)	0.96	1.21 (0.72-2.05)	0.47
Current Major Depressive Disorder	171 (66.8%)	85 (33.2%)	0.84 (0.58-1.21)	0.34	0.70 (0.46-1.07)	0.10
Current Social Phobia	107 (70.9%)	44 (29.1%)	0.71 (0.45-1.10)	0.12	0.62 (0.39-0.96)	0.03
Current Panic Disorder	83 (65.4%)	44 (34.6%)	0.92 (0.58-1.46)	0.71	0.80 (0.50-1.28)	0.36
Current Agoraphobia	82 (56.6%)	63 (43.4%)	1.22 (0.79-1.88)	0.38	1.36 (0.87-2.13)	0.18
Current Generalized Anxiety Disorder	50 (66.7%)	25 (33.3%)	0.96 (0.54-1.71)	0.90	0.98 (0.55-1.72)	0.94

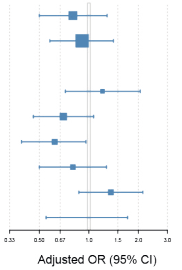


Fig. 2. The (adjusted) odds ratios of seropositivity for depressive and anxiety disorders. Model 1 adjusted for sex, age, level of education, North European ancestry, BMI, and clinical site location with healthy controls taken as the reference group. Model 2 adjusted for the beforementioned sociodemographic variables, healthy controls, remitted depression and/or anxiety, and current dysthymia, MDD, SP, PD, AP, and GAD.

Severity measure	IgG seronegative (*n*=1 058)	IgG seropositive (*n*=673)	Mean difference (*SE*)	*P* value	Adjusted mean difference (*SE*)	Adjusted *P* value
Depression:						
IDS-SR	14.73 ± 0.37	14.91 ± 0.44	0.18 ± 0.58	0.75	-0.74 ± 0.60	0.22
Anxiety:						
BAI	7.47 ± 0.26	7.72 ± 0.32	0.25 ± 0.41	0.54	-0.08 ± 0.42	0.86
FQ	15.42 ± 0.51	15.15 ± 0.67	-0.26 ± 0.83	0.75	-0.58 ± 0.87	0.50
PSWQ	25.92 ± 0.36	25.39 ± 0.43	-0.53 ± 0.56	0.34	-0.20 ± 0.60	0.74
Cognitive reactivity (LEIDS-R):						
Aggression	3.33 ± 0.11	3.03 ± 0.14	-0.30 ± 0.17	0.08	-0.02 ± 0.18	0.92
Hopelessness / suicidality	3.15 ± 0.11	3.01 ± 0.15	-0.14 ± 0.18	0.44	-0.14 ± 0.19	0.47

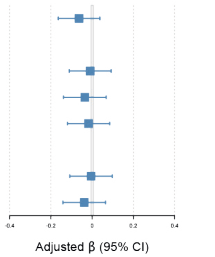


Fig. 3. Mean differences (with standard errors in parentheses) between IgG seronegative and seropositive subjects on symptom severity measures (i.e., IDS-SR, BAI, FQ, and PSWQ), aggression reactivity and suicidal thoughts. Adjusted for sex, age, level of education, North European ancestry, BMI, and clinical site location.
Note: IDS-SR = Inventory of Depressive Symptomatology – self-report; BAI = Beck Anxiety Inventory; FQ = Fear Questionnaire; PSWQ = Penn State Worry Questionnaire; LEIDS-R = Leiden Index of Depression Sensitivity – Revised.

Discussion

This study aimed to examine the link between *T. gondii* specific IgG antibodies and disorder status, aggression reactivity and suicidal thoughts. No significant association was found for *T. gondii* seropositivity in relation to disorder status. Similarly, no significant associations were found for *T. gondii* seropositivity in relation to aggression reactivity or suicidal thoughts. *T. gondii* seropositivity was strongly associated with older age.

Our findings of a lack of the association between *T. gondii* seropositivity and depression diagnosis is in line with the before-mentioned meta-analysis [16] and several population-based cross-sectional studies [17-19]. We extended their findings by showing that there was no association neither with self-reported depressive symptoms nor with observer-rated depression diagnoses through standardized diagnostic psychiatric interviews. Although, some significant associations between seroprevalence and depressive symptoms were found in some studies, these findings were done in studies with smaller sample sizes of at most 51 seropositive subjects, increasing the risk of chance findings [10-12]. A dose-response relationship, with higher antibody titers being associated with an increase in depressive symptoms, was reported in two studies [13, 14]. The majority of studies, however, did not find any associations [11, 17, 18], which was in line with our findings. Previous inconsistencies could be explained neither by differences in age distribution nor by the strain hypothesis which states that strains of *T. gondii* differ in virulence and in ability to influence human behaviour [41-43]. Hence, the current study bolsters the rejection of the hypothesis that *T. gondii* seropositivity is associated with the presence and severity of major depression.

In line with our findings on depressive status, we did not find associations between *T. gondii* seropositivity and anxiety disorders. This was concordant with population-based studies of 1846 and 7712 participants respectively that did not find an association between *T. gondii* and GAD or PD [17], and between *T. gondii* and PD, AP, or SP [14], as established with the CIDI. The latter study only found a significant relationship between *T. gondii* seropositivity and GAD, yet no corrections for multiple comparisons were used [14]. Two other large population-based studies reported a significant relationship between *T. gondii* seropositivity and GAD as established with a telephone survey [18], and general anxiety based on a screening tool [11]. These results contradict animal studies that suggest reduced anxiety-like behaviour in *T. gondii* infected rodents [44, 45].

The association of seropositivity with aggression reactivity was inconsistent with previously reported studies on self-reported anger and aggressive behaviour [12, 21, 22]. However, those studies used other but related constructs (i.e., anger mood, aggressive tendencies as a personality trait, and a history of actual aggressive behaviour), although one study also measured aggression reactivity [22]. The latter study found significant results only among women. Importantly, aggressive reactivity measures thoughts rather than actual behaviour like the history of aggression. The current study also took into account self-directed aggression by measuring suicidal thoughts. No differences were found between seropositive and seronegative subjects, which contradicts the previous studies that found an association between *T. gondii* infection and suicidality [10, 23-26, 28]. However, some of these studies reported inconsistent findings, with a significant relationship of suicide attempts with seropositivity but not with antibody levels [10], or the inverse [23, 24]. Furthermore, the significant associations that were reported in Okusaga et al. (2011) were only found among patients under 38, while no association for seropositivity or antibody levels was found among older patients. In addition, as most of these studies had a cross-sectional design, there remains the possibility of reverse causation, meaning that disorder status or behavioural traits may have affected the risk of *T. gondii* infection [18, 22, 27].

The seroprevalence of *T. gondii* strongly increased with age, which is a result of cumulative seropositivity and is in line with previous studies [2, 31, 46]. Although some studies found differences between males and females [15, 22], others, including ours, did not [18]. Our finding that seroprevalence was independently associated with geographical regions was concordant with previous results from the Netherlands [31]. These previous results indicated highest seroprevalence rates in the Northwest (43%) and Southwest (37%) regions, compared to other provinces in the Netherlands. They also found a steepest rise in seroprevalence in the age group 15–49 years. Importantly, the current sample had a mean age of 51.2 years. Furthermore, a substantial part of the sample was recruited in Western regions. These two factors may explain our relatively high seroprevalence rate of 38.9%.

This study has several strengths. We investigated seroprevalence in a large cohort that included patients without lifetime psychiatric disorders (“control subjects”), with (current and remitted) depressive and anxiety disorders, or comorbid depressive and anxiety disorders. Diagnoses were established with the CIDI (WHO version 2.1), a comprehensive observer-rated instrument with high interrater reliability [47], high test–retest reliability [48] and high validity for depressive and anxiety disorders [49, 50]. Moreover, we not only stratified participants according to their diagnosis, but also

studied symptom severity levels. Furthermore, blood samples were assayed according to a reliable standardized in-house ELISA protocol of the RIVM, with a sensitivity and specificity of 99–100% and 90–99% respectively. The methods, antigens and controls have not altered over the past 35 years, making the results of the different studies comparable.

Limitations of the current study must also be mentioned. The cross-sectional design of the current study hampers inferences of causation, therefore prospective studies are still needed. A second limitation is that the difference between strains (i.e., Types I, II, III, and atypical or recombinant strains) which causes chronic infection is not accounted for. Since we assume that infections with distinct strains all result in increased titers, seropositivity itself cannot be used to differentiate between strains or help to unravel differences in (neuro)virulence between strains. We also did not exclude other infections and immune system diseases. Some studies suggest that *T. gondii* antibodies may only be an indicator of previous contacts with cats, with these cats carrying other pathogens such as *Bartonella henselae* affecting mental health [51-53]. A last limitation is that we did not study actual suicidal and aggressive behaviours.

In conclusion, the current study does not support the hypothesis that *T. gondii* seropositivity is associated with depressive or anxiety disorders, or with aggressive and suicidal thoughts. In light of previous studies and our new findings, it seems unlikely that *T. gondii* seropositivity plays a major role in the risk of affective disorders, suicidality and aggressive thoughts.

Data availability statement

An a priori analysis plan for this study was approved by the principal investigator of NESDA and the NESDA board. Because of ethical and legal restrictions, data involving clinical participants are not included in the manuscript or made available in a public repository. However, subject to approval, data are available upon request from the NESDA Data Access Committee (nesda@ggzingeest.nl).

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

We would like to thank Manal el Ameri and Denise Hoek-van Deursen for their highly appreciated work in the lab. The infrastructure for the NESDA study (www.nesda.nl) is funded through the Geestkracht program of the Netherlands Organisation for Health Research and Development (ZonMw, grant number 10-000-1002) and financial contributions by participating universities and mental health care organizations (VU University Medical Center, GGZ inGeest, Leiden University Medical Center, Leiden University, GGZ Rivierduinen, University Medical Center Groningen, University of Groningen, Lentis, GGZ Friesland, GGZ Drenthe, Rob Giel Onderzoekscentrum.

Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bbih.2020.100197.

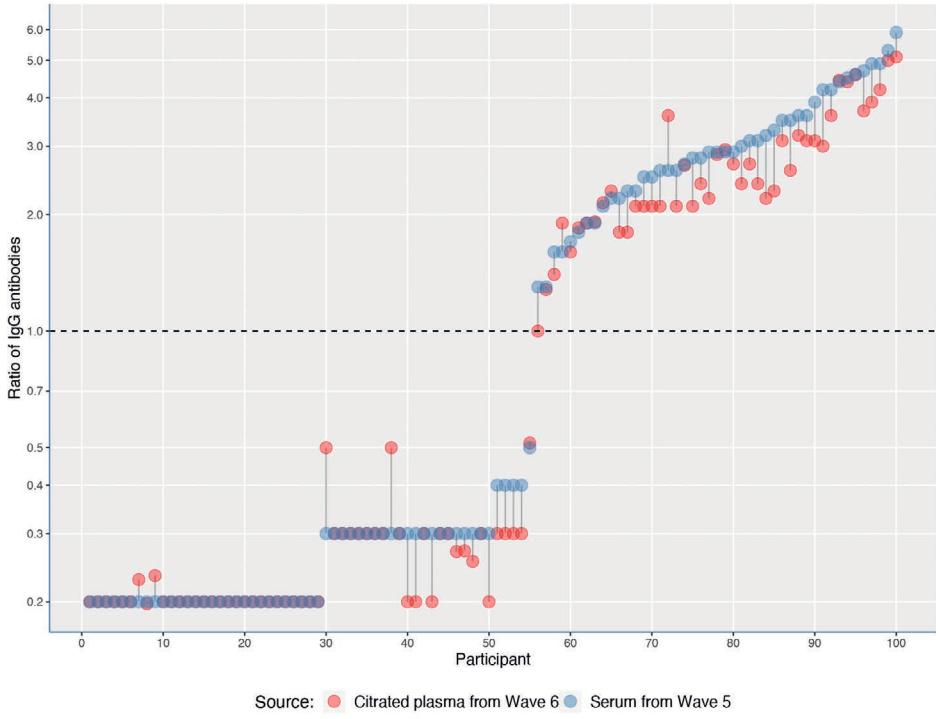
References

1. Halonen SK, Weiss LM. Toxoplasmosis. *Handb Clin Neurol*. 2013;114:125-45.
2. Montoya JG, Liesenfeld O. Toxoplasmosis. *The Lancet*. 2004;363(9425):1965-76.
3. Miller CM, Boulter NR, Ikin RJ, Smith NC. The immunobiology of the innate response to Toxoplasma gondii. *International journal for parasitology*. 2009;39(1):23-39.
4. Saadatnia G, Golkar M. A review on human toxoplasmosis. *Scandinavian Journal of Infectious Diseases*. 2012;44(11):805-14.
5. Fuglewicz AJ, Piotrowski P, Stodolak A. Relationship between toxoplasmosis and schizophrenia: A review. *Adv Clin Exp Med*. 2017;26(6):1031-6.
6. Ibrahim Ali M, Abdel Gawad Mousa Ismail M, Abd-Elftah Abd-Allah G, Abdel-Latif M, Mohamed Shaapan R, Salah H, et al. Toxoplasmosis in Schizophrenic Patients: Immune-diagnosis and Serum Dopamine Level. *Pak J Biol Sci*. 2020;23(9):1131-7.
7. Leweke FM, Gerth CW, Koethe D, Klosterkötter J, Ruslanova I, Krivogorsky B, et al. Antibodies to infectious agents in individuals with recent onset schizophrenia. *European archives of psychiatry and clinical neuroscience*. 2004;254(1):4-8.
8. Hester J, Mullins J, Sa Q, Payne L, Mercier C, Cesbron-Delauw M-F, et al. Toxoplasma gondii antigens recognized by IgG antibodies differ between mice with and without active proliferation of tachyzoites in the brain during the chronic stage of infection. *Infection and immunity*. 2012;80(10):3611-20.
9. Kar N, Misra B. Toxoplasma seropositivity and depression: a case report. *BMC Psychiatry*. 2004;4:1.
10. Bak J, Shim SH, Kwon YJ, Lee HY, Kim JS, Yoon H, et al. The Association between Suicide Attempts and Toxoplasma gondii Infection. *Clin Psychopharmacol Neurosci*. 2018;16(1):95-102.
11. Bay-Richter C, Buttenschon HN, Mors O, Eskelund A, Budac D, Kaerlev L, et al. Latent toxoplasmosis and psychiatric symptoms - A role of tryptophan metabolism? *Journal of psychiatric research*. 2019;110:45-50.
12. Duffy AB, TM; Brenner, LA; Beckstead, JW; Seyfang, A; Postolache, TT; Groer, MW. Relationship between Toxoplasma gondii and mood disturbance in women veterans. *Mil Med*. 2015;180(6):621-5.
13. Groer MW, Yolken RH, Xiao JC, Beckstead JW, Fuchs D, Mohapatra SS, et al. Prenatal depression and anxiety in Toxoplasma gondii-positive women. *Am J Obstet Gynecol*. 2011;204(5):433 e1-7.
14. Suvisaari J, Torniainen-Holm M, Lindgren M, Harkanen T, Yolken RH. Toxoplasma gondii infection and common mental disorders in the Finnish general population. *Journal of affective disorders*. 2017;223:20-5.
15. Flegr J, Escudero DQ. Impaired health status and increased incidence of diseases in Toxoplasma-seropositive subjects – an explorative cross-sectional study. *Parasitology*. 2016;143(14):1974-89.
16. Sutterland AL, Fond G, Kuin A, Koeter MW, Lutter R, van Gool T, et al. Beyond the association. Toxoplasma gondii in schizophrenia, bipolar disorder, and addiction: systematic review and meta-analysis. *Acta psychiatrica Scandinavica*. 2015;132(3):161-79.

17. Gale SB, BL; Berrett, A; Erickson, LD; Hedges, DW. Association between latent toxoplasmosis and major depression, generalised anxiety disorder and panic disorder in human adults. *Folia Parasitologica*. 2014;61(4):285-92.
18. Markovitz AA, Simanek AM, Yolken RH, Galea S, Koenen KC, Chen S, et al. Toxoplasma gondii and anxiety disorders in a community-based sample. *Brain, Behavior, and Immunity*. 2015;43:192-7.
19. Sugden KM, TE; Pinto, L; Poulton, R; Williams, RS; Caspi, A. Is Toxoplasma Gondii Infection Related to Brain and Behavior Impairments in Humans? *PloS one*. 2016;11(2):e0148435.
20. Akaltun I, Kara SS, Kara T. The relationship between Toxoplasma gondii IgG antibodies and generalized anxiety disorder and obsessive-compulsive disorder in children and adolescents: a new approach. *Nord J Psychiatry*. 2018;72(1):57-62.
21. Coccaro EL, R; Groer, MW; Can, A; Coussons-Read, M; Postolache, TT. Toxoplasma gondii infection: relationship with aggression in psychiatric subjects. *The Journal of clinical psychiatry*. 2016;77(3):334-41.
22. Cook TB, LA; Cloninger, CR; Langenberg, P; et al. "Latent" infection with Toxoplasma gondii: Association with trait aggression and impulsivity in healthy adults. *Journal of psychiatric research*. 2015;60:87-94.
23. Alvarado-Esquivel C, Sánchez-Anguiano LF, Arnaud-Gil CA, López-Longoria JC, Molina-Espinoza LF, Estrada-Martínez S, et al. Toxoplasma gondii infection and suicide attempts: a case-control study in psychiatric outpatients. *The Journal of nervous and mental disease*. 2013;201(11):948-52.
24. Arling TA, Yolken RH, Lapidus M, Langenberg P, Dickerson FB, Zimmerman SA, et al. Toxoplasma gondii antibody titers and history of suicide attempts in patients with recurrent mood disorders. *The Journal of nervous and mental disease*. 2009;197(12):905-8.
25. Okusaga O, Langenberg P, Sleemi A, Vaswani D, Giegling I, Hartmann AM, et al. Toxoplasma gondii antibody titers and history of suicide attempts in patients with schizophrenia. *Schizophrenia research*. 2011;133(1-3):150-5.
26. Pedersen MG, Mortensen PB, Norgaard-Pedersen B, Postolache TT. Toxoplasma gondii infection and self-directed violence in mothers. *Archives of general psychiatry*. 2012;69(11):1123-30.
27. Sutterland AL, Kuin A, Kuiper B, van Gool T, Leboyer M, Fond G, et al. Driving us mad: the association of Toxoplasma gondii with suicide attempts and traffic accidents - a systematic review and meta-analysis. *Psychological medicine*. 2019;49(10):1608-23.
28. Zhang Y, Traskman-Bendz L, Janelidze S, Langenberg P, Saleh A, Constantine N, et al. Toxoplasma gondii immunoglobulin G antibodies and nonfatal suicidal self-directed violence. *The Journal of clinical psychiatry*. 2012;73(8):1069-76.
29. Penninx BWJH, Beekman ATF, Smit JH, Zitman FG, Nolen WA, Spinhoven P, et al. The Netherlands Study of Depression and Anxiety (NESDA): rationale, objectives and methods. *International Journal of Methods in Psychiatric Research*. 2008;17(3):121-40.
30. Ruitenberg EJ, van Knapen F. The Enzyme-Linked Immunosorbent Assay and Its Application to Parasitic Infections. *The Journal of Infectious Diseases*. 1977;136(Supplement_2):S267-S73.

31. Hofhuis AvP, W; van Duynhoven, YT; Nijhuis, CD; Mollema, L; van der Klis, FR; Havelaar, AH; Kortbeek, LM. Decreased prevalence and age-specific risk factors for Toxoplasma gondii IgG antibodies in The Netherlands between 1995/1996 and 2006/2007. *Epidemiol Infect*. 2011;139(4):530-8.
32. APA. Diagnostic and Statistical manual of mental disorders 4th edition (DSM-IV). *Washington, DC: British Library Cataloguing in Publication Data*. 1994.
33. Rush AG, CM; Basco, MR; Jarrett, RB; Trivedi, MH. The Inventory of Depressive Symptomatology (IDS): psychometric properties. *Psychological medicine*. 1996;26(3):477-86.
34. Rush AJ, Giles DE, Schlesser MA, Fulton CL, Weissenburger J, Burns C. The Inventory for Depressive Symptomatology (IDS): preliminary findings. *Psychiatry research*. 1986;18(1):65-87.
35. Beck AT, Epstein N, Brown G, Steer RA. An inventory for measuring clinical anxiety: psychometric properties. *Journal of consulting and clinical psychology*. 1988;56(6):893-7.
36. Marks IM, Mathews AM. Brief standard self-rating for phobic patients. *Behaviour research and therapy*. 1979;17(3):263-7.
37. Meyer TJ, Miller ML, Metzger RL, Borkovec TD. Development and validation of the penn state worry questionnaire. *Behaviour research and therapy*. 1990;28(6):487-95.
38. Van der Does A, Williams JJLU. Leiden index of depression sensitivity-revised (LEIDS-R). 2003.
39. Van der Does W. Cognitive reactivity to sad mood: structure and validity of a new measure. *Behaviour research and therapy*. 2002;40(1):105-20.
40. Benjamini Y, Hochberg Y. Controlling the false discovery rate: a practical and powerful approach to multiple testing. 1995;57(1):289-300.
41. Abdoli A. Toxoplasma gondii and neuropsychiatric diseases: strain hypothesis. *Neurol Sci*. 2013;2013(34):1697-8.
42. Xiao JB, SL; Cannon, TD; Suzuki, Y; Viscidi, RP; Torrey, EF; Yolken, RH. Serological pattern consistent with infection with type I toxoplasma gondii in mothers and risk of psychosis among adult offspring. *Microbes Infect*. 2009;11(13):1011-8.
43. Xiao JJ-B, L; Talbot, CC Jr; Yolken, RH. Differential effects of three canonical Toxoplasma strains on gene expression in human neuroepithelial cells. *Infect Immun*. 2011;79(3):1363-73.
44. Berdoy MW, JP; MacDonald, DW. Fatal Attraction in Rats Infected with Toxoplasma gondii. *Proc Biol Sci*. 2000;267(1452):1591-4.
45. Vyas AS-K, K; Giacomini, N; Boothroyd, JC; Sapolsku, RM. Behavioural changes induced by Toxoplasma infection in rodents are highly specific to aversion of cat odours. *Proc Nat Acad Sci USA*. 2007a;104:6442-7.
46. Kortbeek LdM, HE; Veldhuijzen, IK; Conynvan Spaendonck, MA. Population-based Toxoplasma seroprevalence study in The Netherlands. *Epidemiol Infect*. 2004;132(839-845).
47. Wittchen HU, Robins LN, Cottler LB, Sartorius N, Burke JD, Regier D. Cross-cultural feasibility, reliability and sources of variance of the Composite International Diagnostic Interview (CIDI). The Multicentre WHO/ADAMHA Field Trials. *The British journal of psychiatry : the journal of mental science*. 1991;159:645-53, 58.
48. Wacker H, Battegay R, Mullejans R, Schlosser C. Using the CIDI-C in the general population. *Psychiatry: A world perspective*. 1990;1:138-43.
49. Wittchen HU. Reliability and validity studies of the WHO-Composite International Diagnostic Interview (CIDI): A critical review. *Journal of psychiatric research*. 1994;28(1):57-84.

50. Wittchen HU, Burke JD, Semler G, Pfister H, Von Cranach M, Zaudig M. Recall and dating of psychiatric symptoms: test-retest reliability of time-related symptom questions in a standardized psychiatric interview. *Archives of general psychiatry*. 1989;46(5):437-43.
51. Flegr J, Hodny Z. Cat scratches, not bites, are associated with unipolar depression--cross-sectional study. *Parasit Vectors*. 2016;9:8.
52. Flegr JP, M; Balátová, P. Depressiveness and Neuroticism in Bartonella Seropositive and Seronegative Subjects - Preregistered Case-Controls Study. *Frontiers in Psychiatry*. 2018;9(314):1-14.
53. Yuksel Pea. The role of latent toxoplasmosis in the aetiopathogenesis of schizophrenia: the risk factor or an indication of a contact with cat? *Folia Parasitologica*. 2010;57(2):121-8.



Supplementary Fig. 1. Ratio of T. gondii IgG antibodies (on a log scale) in serum and citrated plasma in a subpopulation of 100 participants
† Adjusted for sex, age, level of education, North European ancestry, BMI, and clinical site location.

Supplementary Table 1. *T. gondii* IgG antibody levels according to diagnosis groups

Diagnosis groups	Model 1[†]		Model 2[±]	
	β	***P* value**	*β*	***P* value**
Healthy controls	1.00 (ref)		-0.06	0.15
Remitted depression and/or anxiety	0.03	0.50	-0.06	0.25
Any current depression and/or anxiety disorder	0.09	0.11		
Current Dysthymia	0.03	0.76	0.02	0.38
Current Major Depressive Disorder	-0.008	0.91	-0.09	0.008
Current Social Phobia	0.05	0.54	-0.06	0.03
Current Panic Disorder	0.12	0.13	-0.01	0.58
Current Agoraphobia	0.08	0.30	0.03	0.36
Current Generalized Anxiety Disorder	0.05	0.52	-0.004	0.87

[†] Adjusted for sex, age, level of education, North European ancestry, BMI, and clinical site location.
[±] Adjusted for the beforementioned sociodemographic variables, healthy controls, remitted depression and/or anxiety, and current dysthymia, MDD, SP, PD, AP, and GAD.

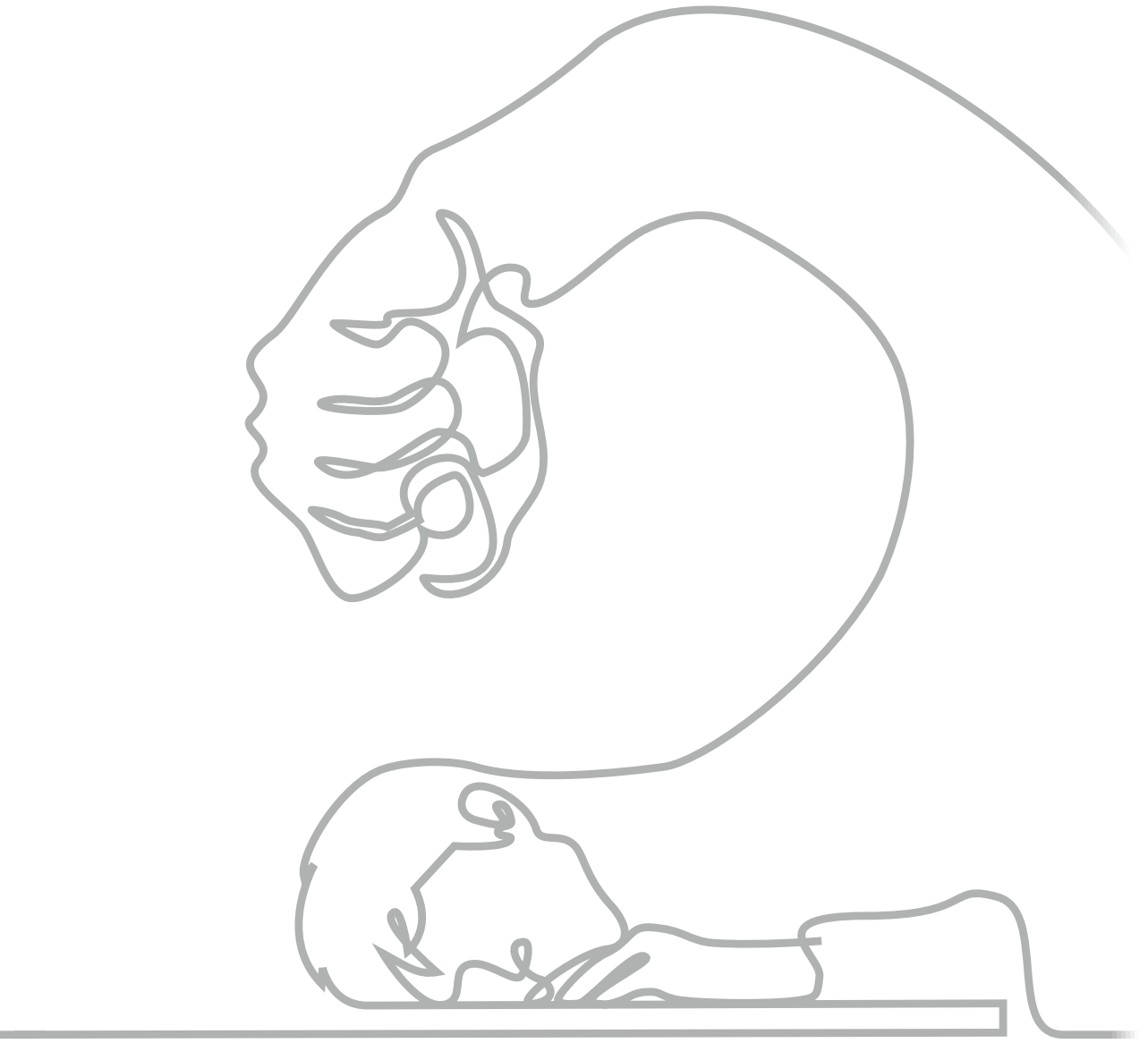
Supplementary Table 2. *T. gondii* IgG antibody levels according to severity measures

Severity measure	Crude		Adjusted Model[†]	
	β	***P* value**	*β*	**Adjusted *P* value**
Depression:				
IDS-SR	0.002	0.93	-0.03	0.21
Anxiety:				
BAI	0.02	0.40	0.004	0.88
FQ	-0.008	0.74	-0.02	0.47
PSWQ	-0.03	0.24	-0.02	0.49
Cognitive reactivity (LEIDS-R):				
Aggression	-0.04	0.08	-0.01	0.75
Hopelessness / suicidality	-0.01	0.63	-0.01	0.65

[†] Adjusted for sex, age, level of education, North European ancestry, BMI, and clinical site location.

Published as: de Bles, N. J., Hazewinkel, A. W., Bogers, J. P., van den Hout, W. B., Mouton, C., van Hemert, A. M., Rius-Ottenheim, N., & Giltay, E. J. (2021). The incidence and economic impact of aggression in closed long-stay psychiatric wards. *International Journal of Psychiatry in Clinical Practice*, *25*(4), 430-436.

6 The incidence and economic impact of aggression in closed long-stay psychiatric wards



Abstract

Objective: Aggressive behaviour is highly prevalent in long-term psychiatric inpatient care. We aimed to estimate the overall incidence of aggression, the time staff took to handle aggression incidents, and the weighted average financial costs thereof.

Methods: A random sampling procedure was conducted at long-term psychiatric inpatient care facilities. Nurses were asked to recall all incidents (i.e., verbal, physical towards objects, self, or others) of their shift. For the time spent on each type of incident, staff were monitored in real-time. Estimated costs were calculated by the time spent multiplied by hourly wages in addition to material-related costs.

Results: Incidence rates were 90 incidents per patient year. The average time spent per incident was 125 min but differed for each type of incident. Almost 80% of this time was consumed by nursing staff. The average cost per aggression incident was €78; extrapolated per patient year, the total costs were approximately €7000.

Conclusions: The current study found a high rate of aggression incidents in closed long-stay psychiatric wards. Reports of aggression on these types of wards are scarce. Nevertheless, aggression seems to have a severe impact on invested time and related costs, which suggests a need for aggression-prevention and de-escalating programs.

Key points

- Aggression incidents are highly prevalent and are accompanied by high costs.
- The effect of aggression incidents on the workload for staff members is high, especially for nursing staff.
- Studies across countries on the incidence and the costs of aggression among psychiatric inpatients are needed to help model the effects of (new) strategies for aggression reduction.

Introduction

Despite the increased awareness and efforts to reduce violence in clinical care among healthcare workers [1, 2] and policy-makers [3], aggression incidents remain prevalent in psychiatric inpatient facilities [4]. Aggression is expressed either verbally or physically or both, and can be directed at objects, patients themselves, other patients, and staff members. Consequences of aggression incidents are diverse and occasion- ally substantial. For instance, incidents may have physical consequences, may cause distress, and may be traumatic for patients and staff [4, 5]. Last year the highest percentages reported by mental health workers were for verbal aggression. For physical abuse, percentages between73% and 80% were reported [5, 6]. These latter forms of aggression sometimes lead to severe injury (e.g., broken bones, loss of teeth), which was reported by 16% of psychiatric nurses. The exposure to aggression may also lead to acute stress disorder, and post-traumatic stress disorder (PTSD) in severe cases (14–17% of exposed staff members), but more frequently, it leads to subclinical symptoms which may include hyperarousal [7, 8]. Besides violence directed at staff members, a survey among psychiatric inpatients revealed that 54% had been exposed to threats and aggression from other patients and 31% had been physically assaulted [9].

Furthermore, aggression incidents have substantial financial consequences relating to, for example, damaged property, higher drug use, and more time spent by staff due to an increased work burden [10], also relating to staff sick-leave due to the physical and psychological consequences that might follow a critical incident [5, 11, 12]. As far as we know, only two studies contain information on the costs of aggression in psychiatric inpatients. Annual economic costs of aggression incidents were substantial in both Spain [13] and the United Kingdom [14]. Furthermore, these estimates may underestimate the actual costs because indirect costs were not taken into account. High indirect costs include lost staff workdays, which range between 38 and 85 days per injured staff member [5, 11, 15]; longer hospital admissions; and more readmissions [10].

Incidence rates for aggression in psychiatry vary, ranging from less than 1 to 60 incidents per patient year in two systematic reviews [4, 16]. The wide range of estimates may be explained by the fact that incidents are less often documented officially, compared to what is actually experienced by staff members, according to self-reported questionnaires and videos, particularly with regard to verbal aggression [17-19]. Furthermore, there are large variations in study design (e.g., prospective versus retrospective data collection), differences in how the studies' authors defined aggression (e.g., including

or excluding verbal aggression and self-harm), and emphases on different patient populations (e.g., these included acute or long stay wards; open or closed wards; and forensic, mixed, or psychiatric wards). While incidence estimates have often been based on data collected from (acute) admission wards [14, 20, 21] and (forensic) hospitals [11, 13, 15], data from long-stay facilities for psychiatric care is much more scarce. Yet, aggressive behaviour regularly leads to a referral to a long-term inpatient care [22]. The severely ill and more complex patients residing in these facilities may show different patterns of aggressive behaviour than patients in acute-admission wards.

In this study, we aimed (i) to estimate the incidence rates of different types of aggression in closed long-stay psychiatric wards in the Netherlands, (ii) to estimate the time spent by staff members per aggression incident, and (iii) to estimate the direct costs associated with aggression in long-stay psychiatric wards.

Methods

Participants

The study was conducted in closed psychiatric long-stay wards belonging to three regional mental healthcare centres in urbanised areas of the Netherlands: Rivierduinen Psychiatric Centre in Oegstgeest, Parnassia Psychiatric Institute in The Hague, and Inforsa in Amsterdam. All three institutes provide long-term inpatient care. The psychiatric clinical capacity for long-stay (defined as an admission duration of more than 1 year) in the Netherlands in 2017 was 6250 beds, of which 23% (or about 1438 beds) are in a closed setting [23]. Although patients can be admitted or discharged during the year, the total number of admitted patients at any time stays close to 1438 – a rather high occupancy rate for long-stay clinical psychiatry. In all three centres, about two-thirds of the patients were male and had been diagnosed predominantly with psychosis spectrum disorders or severe personality disorders, with approximately 80% of patients meeting diagnostic criteria for either one of these disorders. Patients were mainly admitted involuntarily. The Medical Ethical Committee of Leiden University Medical Centre granted permission for this study. Considering the mostly descriptive nature of the current study, no sample size calculation was performed beforehand. Moreover, no recent reliable data were available for the proportion of interest from previous studies in the group of patients from long-stay wards, which is necessary for its calculation.

Definition of aggression incidents

We categorised aggression incidents into four categories, based on the Overt Aggression Scale (OAS) [24]. First, we defined 'verbal aggression' as yelling, shouting, using obscenities or swearwords, sexual remarks, and threatening others (with or without a threatening posture). Second, we defined 'physical aggression towards an object' as kicking, hitting, throwing objects (e.g., chairs, dishes, or cups), and slamming doors. Third, we defined 'self-harm' as any act of physical aggression towards the self, such as hitting, cutting, burning, strangulation, overdosing on medication, and jumping from heights (with or without suicidal intent). Fourth, we defined 'physical aggression towards others' as a physical assault on another person by means of hitting, pushing, pulling, holding, scratching, kicking, biting, spitting, touching inappropriately, strangulating, and/or attacking someone with an object (e.g., a chair or a knife). We did not categorise incidents based on severity. Case vignettes illustrating each of the categories are presented in Supplement 1.

Aggression incidence

To estimate the incidence of aggression across the four categories, we applied a random sampling procedure, which included 21 nursing shifts over a 6-month period (February–July 2014) at all three facilities (Figure 1). All weekdays (Monday–Sunday) and shift types (day, evening, and night) were covered. At the end of each shift, one of the psychiatric nurses was interviewed via telephone; we asked him/her to recall all incidents during the preceding 8 h. If one patient caused several incidents, or if an incident escalated to a graver category, only the most severe incident was recorded for that shift. Using a random number generator, participating staff members were randomly selected from the total available ward staff per shift. The number of patients observed per shift was used to calculate the total number of observed patient years. This total, along with the observed incidents, was then used to calculate incidence rates per patient year. The ratio of the occurrence of the four types of aggression was used as a weight factor to calculate the time spent and the total cost of all aggression incidents.

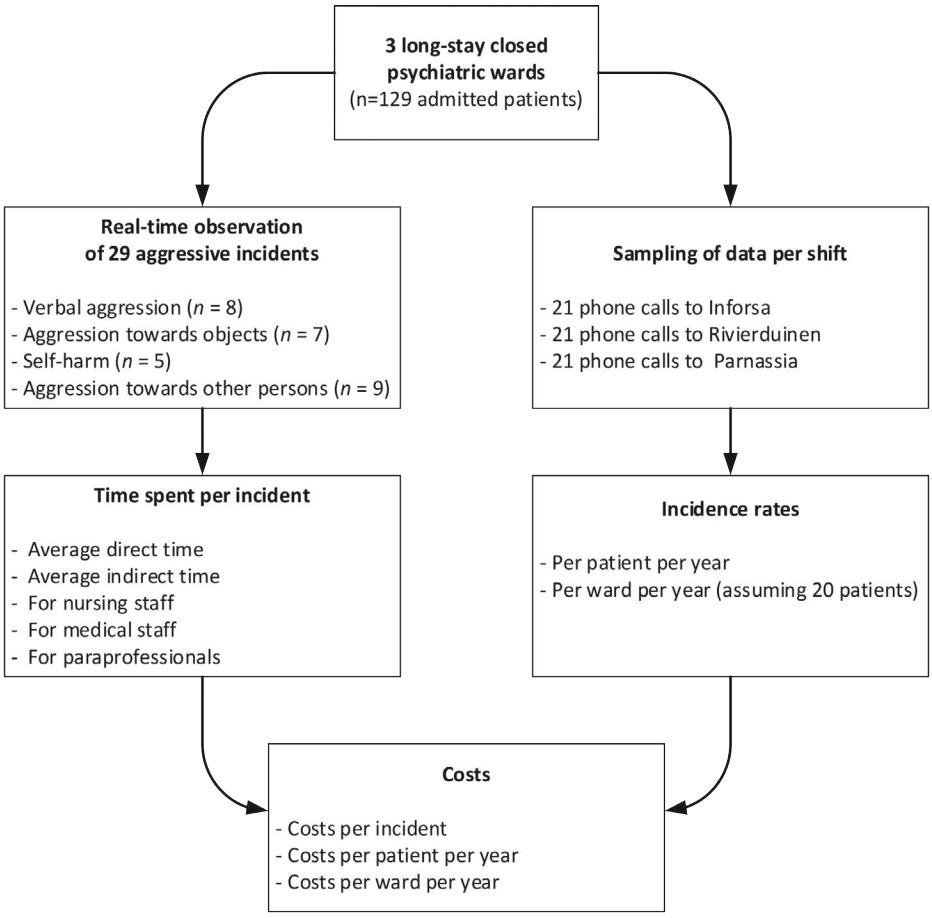


Fig. 1. Flowchart displaying data collection

Time spent on aggression

The time spent on each type of incident by staff members was monitored in real-time by a researcher who was present during day shifts and evening shifts over a period of one week at each of the three facilities. The researcher followed all incidents from start to finish to record all the activities by all staff members who handled the incident. Just as for the calculation of the incidence, if an incident escalated to a graver category, only the most severe incident, as experienced by nursing staff, was assigned to one of the four categories. These activities were collapsed into two categories: direct time (i.e., de-escalating conversation, restraining patients, checking up on isolated patients, administering medication, and tending to medical needs) and indirect time

(i.e., administrative activities, discussing and evaluating the incident, information transfer, consultation, and transport).

Costs of aggression incidence

To estimate costs for each type of aggression incident from an institutional perspective, staff wages and material costs of both damaged property and immediate medical care were taken into account. We defined 'nursing staff' in a psychiatric ward as licenced nurses and psychiatric social workers whose responsibilities include the day-to-day care for patients. We labelled other assistive personnel as 'paraprofessionals', which included patient supporters, activity supervisors, and specially trained security personnel who support nursing staff during aggression incidents. Average yearly wages were derived from the Collective Labour Agreement for the Mental Health Sector (2017–2019) [25]. Consistent with the guidelines of the Dutch Healthcare Authority, these wages were adjusted incrementally with the mandatory insurances provided by the employer. The same Collective Labour Agreement also provides the yearly number of available work hours per staff member, taking into account average days of sick leave and annual leave. Yearly salary costs were divided by the total available work hours, resulting in hourly wages for each staff category (Supplement 2). To account for the incidents occurring outside the standard 40-h working week, hourly wages were increased with a percentage surcharge for irregular shifts in proportion to the number of incidents taking place during evening and night shifts and during the weekend. Finally, staff costs were calculated by multiplying appropriate hourly wages with the average amount of time spent by each type of professional per incident type.

Material-related costs consisted of property damages caused by the patient (e.g., broken furniture or windows) and immediate medical expenses at the ward (e.g., costs of administering medication or necessary medical treatment of injured patients or members of staff as a direct consequence of the incident). The costs of non-immediate medical treatment or sick leave taken by staff members as a result of the incident could not be included, as it was impossible to link these to individual aggression incidents.

Adding the average personnel and material costs for each type of incident allowed us to calculate the average costs per incident for each of the four incident categories. Using the previously estimated number of incidents per patient year, we inferred the annual costs (i) per patient and (ii) per ward (assuming 20 patients per ward).

Results

Ward characteristics

Table 1 shows the characteristics of the psychiatric wards; the psychiatric centre Inforsa in Amsterdam has the highest number of nurses and psychiatrists per patient. The average number of patients per ward was 23, and the average number of patients per nurse across all shifts was five. The proportion of patients admitted involuntarily was above 85% for all wards.

Table 1. Characteristics of the three included closed psychiatric wards

Name of psychiatric centre	**Psychiatric center Inforsa**	**Psychiatric center Rivierduinen**	**Parnassia psychiatric institute**
City	Amsterdam	Oegstgeest	the Hague
Number of admitted patients (all wards)	45	36	48
Number of admitted patients per ward	9	36	24
Number of nurses per ward per shift[a]	3	6	4
Average number of patients per nurse	3	6	6
Average number of psychiatrists (Fte; fulltime-equivalent)	1.7	1.0	1.0
Proportion of patients involuntarily admitted[b]	100%	89%	85%

[a] Occupancy during day and evening shifts; night shifts usually have about half the daytime occupancy.
[b] According to the Dutch law BOPZ, concerning involuntary admittance in psychiatric hospitals.

Incidence rate of aggression

Data on aggression incidents for the three wards together are shown in Table 2. In total, 81 incidents occurred. The data were extrapolated to yield incidence rates per patient year, leading to an average of 90 incidents per patient per year. The incidence rates per patient year for the different categories were 63 for verbal aggression, 8 for physical aggression towards objects, 7 for self-harm, and 12 for physical aggression towards others. Eighty-eight percent of incidents occurred during the day and evening (7:00–23:00). Incidents were roughly evenly divided among week- days and weekends (31% occurred on the weekend).

Time spent on aggression

While we measured personnel costs of time spent by members of staff dealing with aggression, we directly observed 29 incidents during three consecutive one-week observation periods (verbal aggression *n* = 8, physical aggression towards an object *n* = 7, self-harm *n* = 5, physical aggression towards others *n* = 9). In total, 5324 min were spent on the 29 incidents that we observed. Table 2 shows that the average time spent on aggression incidents varied among the types of incidents. Of this time, 77% was spent by nursing staff, 6% by medical doctors, and 18% by paraprofessionals. For all aggression incidents, average total time spent was 125 min; 44% of that time (i.e., 55 min) was spent in contact with the patient during and after the incident, and 56% (i.e., 70 min) of that time was spent on 'indirect' consequences such as information transfer among staff, administrative activities, and care for involved personnel. Assuming a staff occupancy of five patients per nurse and 96 min per incident spent on nursing time, nurses spend 39 min on average per shift dealing with aggression.

Costs of aggression

The average hourly gross personnel costs for nursing staff are €26 (ranging between €17 and €29). At the psychiatric centre Rivierduinen, a security guard trained for healthcare receives an hourly wage of €33. Hourly costs for medical staff are €46 for doctors and €74 for psychiatrists. Average direct costs per incident are shown in Table 2. The average direct cost per incident was €78. Material costs were on average €3 per incident, with the highest direct costs in the category of physical aggression towards an object (€27). With 90 incidents per patient year, direct costs per patient amount to about €7000 annually. In a typical closed ward setting that supports 20 patients for long-term psychiatric care, the annual direct cost would amount to €140,000 annually.

Table 2. Characteristics and time- and material-related costs of four types of aggression incidents

	Verbal aggression (*n* = 57)	**Aggression towards objects** (*n* = 7)	**Self-harm** (*n* = 6)	**Aggression towards other persons** (*n* = 11)	**All aggression incidents**[a] (*n* = 81)
Incidence rate per patient per year[b]	63 (49–80)	8 (4–15)	7 (3–14)	12 (7–20)	90 (73–110)
Incidence rate per ward per year (assuming 20 patients)[b]	1261 (1193–1332)	155 (132–181)	133 (112–157)	243 (214–275)	1792 (1711–1876)
Average total time (min)[b]:	80 (34–126)	77 (52–103)	223 (126–320)	336 (121–551)	125 (65–185)
direct time (min)[b]	39 (11–67)	30 (11–50)	111 (65–158)	124 (46–202)	55 (31–79)
indirect time (min)[b]	42 (22–61)	47 (34–60)	112 (43–181)	212 (8–417)	70 (22–119)
for nursing staff (min)[b]	52 (25–78)	72 (48–97)	185 (136–235)	292 (103–480)	96 (44–147)
for medical staff (min)[b]	2 (0–5)	0 (0–0)	31 (0–86)	21 (0–44)	7 (0–15)
for paraprofessionals (min)[b]	26 (0–53)	5 (0–12)	7 (0–13)	24 (7–41)	23 (10–35)
Material-related costs per incident (*SD*)[c]	€1 ± €2 (€0–€6)	€27 ± €39 (€0–€101)	€1 ± €1 (€0–€3)	€1 ± €4 (€0–€11)	€3 ± €14 (€0–€101)
Costs per incident (*SD*)[c]	€50 ± €44 (€10–€116)	€89 ± €74 (€20–€234)	€120 ± €73 (€54–€241)	€196 ± €195 (€45–€649)	€78 ± €100 (€10–€649)
Annual costs per patient	€3200	€700	€800	€2400	€7000
Annual costs per ward (assuming 20 patients)	€64000	€14000	€16000	€48000	€140000

[a] Incidence weighted averages are given.
[b] Data between brackets are the 95% confidence intervals.
[c] Data between brackets are the ranges.

Discussion

We found an incidence rate of 90 incidents per patient year, amounting to five incidents per day in an average ward with 20 inpatients. The average time spent was 125 min per incident, which indicates that (given average staff occupancy) each individual nurse spent more than half an hour per shift dealing with aggression. These direct costs related to incidents amounted to approximately €78 per incident. Based on our incidence rate, this would result in an estimate of €7000 per patient per year. The maximum cost for a psychiatric nursing day was €328.43 in 2018 [26], implying that 6% of the total budget was earmarked for aggression.

The incidence rates we found for aggressive behaviour were higher than those reported in earlier studies (which range from less than 1 to 60 incidents per patient year), mostly in acute and forensic settings [4, 16]. These differences exist partly because these studies used retrospective data collection or data from officially reported incidents only [4]. Such designs have a risk of selective recall and underreporting for milder incidents. Furthermore, the varying incidence rates could be due to differences in how the aggression incidents and ward types were defined and which sampling methods were used. The current study used a broad definition that included verbal aggression; most previous studies did not include these incidents. Verbal aggression is the most common form of aggression [27, 28], and can have a strong mental impact on other patients and staff, but it is often overlooked when reporting all types of aggressive behaviour. In line with existing literature, we found that verbal aggression occurred most often and aggression relating to self- harm occurred the least often [28, 29].

Interestingly, the current study found that time spent indirectly lasted longer than time spent in direct contact with patients (on average 55 versus 70 min). Around 85% of indirect time consisted of the transfer of information and consulting. Much of this indirect time was used for interpersonal support among colleagues and the venting of emotions by staff members, which reflect the emotional impact of aggression on the staff. Moreover, the time (and cost) spent on aggression cannot be invested in therapeutic and social activities. Among the different disciplines, nursing staff spent the majority of time (and cost) dealing with aggression. This confirms previous research, which states that nurses working in inpatient psychiatric wards are at high risk for experiencing aggression at work [5, 30].

The largest contributors to total cost were verbal aggression (due to its highest incidence rate) and physical aggression towards others (due to the large amount of time needed to intervene in these incidents). That verbal aggression was expensive in

absolute terms was also found in acute psychiatric wards [14]. Further, staff members are often the target of both verbal aggression and aggression towards others; this could increase burnout and sick leave [5, 31], meaning our estimated costs were likely conservative. Likewise, an incident sometimes took place during multiple shifts (and even days) and may have incurred costs long after the initial incident happened. Aggressive patients are more often secluded and consume higher doses of medication [10]. Like most other studies that focused on healthcare costs [13, 14], we did not include costs that were indirectly caused by aggression (e.g., staff absence, re-admissions, and assistance of police or ambulance). Training courses for staff, special designs of wards that reduces the risks of violence, and interventions to reduce aggression are costly. Interventions comprise medication and psychotherapy [32-34], and aggression management courses for staff [12]. One such programme is the Safewards model, providing 10 interrelated interventions [35, 36]. Although several studies on Safewards showed significant reductions in conflict events, no cost-effective studies were performed [37-40]. Depending on the available staff capacity, costs in terms of money and budget may be smaller or larger than the costs we estimated in this analysis. When staff capacity is sufficient, a change in aggression level need not affect the budget but would be compensated by the time that is available for therapeutic and social activities. In that case the costs are intangible, in terms of reduced quality of care. But when personnel capacity is insufficient, aggression may require a full additional staff member in the ward. In that case the budget impact could be considerably larger than estimated.

To date, studies providing information on costs of aggression are scarce. Recently, a systematic review was conducted on health-service use and costs associated with aggressiveness and agitation in psychiatric care [10]. In the review, nine out of ten studies analysed the impact on care such as longer stay and more frequent re-admissions, but they did not quantify the costs. Only one study estimated the cost of conflict-related behaviour using a bottom-up approach similar to ours. They converted time involved in conflicts to a monetary amount using national unit cost data and found annual costs to be €182,616 per ward. Estimated costs per aggression incident ranged from £23 (€27) to £200 (€236) per incident [14, 41], compared to an average of €78 per incident in the present study. However, due to differences in the organisation of mental health- care between countries, it remains difficult to compare studies across countries [42, 43]. To better estimate the costs of aggression, future studies in different settings and countries are needed.

To our knowledge, our study is the first that prospectively estimates aggression in closed long-stay psychiatric wards and suggests a methodology that can be employed

in different settings. Real-time observation of incidents enabled us to make accurate assessments of the time invested by staff. Additionally, we sampled from three different centres, which moderated some of the differences between each location.

An important limitation of the current study is that we sampled a relatively small group of patients within a short amount of time. Studies show considerable variation in the prevalence of aggression between patients; a small number of patients is often responsible for a large proportion of aggression [5, 27]. Likewise, we did not observe patients during all seasons, and studies have indicated that this could affect the incidence rate of aggression [44]. Therefore, future studies should collect more data on incidents from more diverse wards and countries, and preferably use validated tools such as the Staff Observation Aggression Scale- revised (SOAS-R [45]). The SOAS-R quantifies the frequency and severity of aggression incidents, making it easier to compare the scarce studies on aggression. Furthermore, interviewing nurses at the end of their shift may have led to underreporting. We posit, however, that our method of asking specifically for all types of aggression that occurred over a recently completed 8- h shift may be more accurate than retrospective data collected over much longer time intervals. Another contributor to underreporting may be that only the most severe incident was registered even when a patient caused several incidents. However, we may have also overestimated the related costs. It is possible that mild incidents, which consumed no time, were included in calculating the incidence rate but were not taken into account in the time measurement, which would result in an overestimation of the time spent as well as the costs for aggression.

Conclusions

Incidence rates of aggression, the workload for staff members, and the associated direct costs in closed long-stay psychiatric wards are high. Aside from the financial perspective, reduction of aggression is highly valuable for both patients and staff. Aggression reduction already has a high priority in long-term psychiatric inpatient care (e.g., de-escalating programs, adequate pharmacotherapy), but more effective and innovative methods to prevent aggression are needed.

Acknowledgements

The authors thank all nurses who contributed to the current study.

Disclosure statement

No potential conflict of interest was reported by the author(s).

Funding

This work was supported by ZonMw (The Netherlands Organisation for Health Research and Development) under Grant [number 836031016].

Data availability statement

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

References

1. McDermott BE, Holoyda BJ. Assessment of aggression in inpatient settings. *CNS spectrums*. 2014;19(5):425-31.
2. Spelten E, Thomas B, O'Meara PF, Maguire BJ, FitzGerald D, Begg SJ. Organisational interventions for preventing and minimising aggression directed towards healthcare workers by patients and patient advocates. *Cochrane Database Syst Rev*. 2020;4.
3. Volksgezondheid WeS, Koninkrijksrelaties BZe, Justitie Ve, al. e. Actieplan Veilig werken in de zorg. 2012.
4. Bowers L, Stewart D, Papadopoulos C, Dack C, Ross J, Khanom H, et al. Inpatient violence and aggression: a literature review. 2011.
5. Nijman HLI, Bowers L, Oud N, Jansen G. Psychiatric nurses' experiences with inpatient aggression. *Aggressive behavior*. 2005;31(3):217-27.
6. Edward KL, Stephenson J, Ousey K, Lui S, Warelow P, Giandinoto JA. A systematic review and meta-analysis of factors that relate to aggression perpetrated against nurses by patients/relatives or staff. *Journal of Clinical Nursing*. 2016;25(3-4):289-99.
7. Richter D, Berger K. Post-traumatic stress disorder following patient assaults among staff members of mental health hospitals: a prospective longitudinal study. *BMC Psychiatry*. 2006;6:15.
8. Lee J, Daffern M, Ogloff JR, Martin T. Towards a model for understanding the development of post-traumatic stress and general distress in mental health nurses. *International journal of mental health nursing*. 2015;24(1):49-58.
9. Frueh BC, Knapp RG, Cusack KJ, Grubaugh AL, Sauvageot JA, Cousins VC, et al. Patients' reports of traumatic or harmful experiences within the psychiatric setting. *Psychiatric services (Washington, DC)*. 2005;56(9):1123-33.
10. Rubio-Valera M, Luciano JV, Ortiz JM, Salvador-Carulla L, Gracia A, Serrano-Blanco A. Health service use and costs associated with aggressiveness or agitation and containment in adult psychiatric care: a systematic review of the evidence. *BMC Psychiatry*. 2015;15:35.
11. Hillbrand M, Foster HG, Spitz RT. Characteristics and cost of staff injuries in a forensic hospital. *Psychiatric services (Washington, DC)*. 1996;47(10):1123-5.
12. Farrell G, Cubit K. Nurses under threat: a comparison of content of 28 aggression management programs. *International journal of mental health nursing*. 2005;14(1):44-53.
13. Serrano-Blanco A, Rubio-Valera M, Aznar-Lou I, Baladon Higuera L, Gibert K, Gracia Canales A, et al. In-patient costs of agitation and containment in a mental health catchment area. *BMC Psychiatry*. 2017;17(1):212.
14. Flood C, Bowers L, Parkin D. Estimating the costs of conflict and containment on adult acute inpatient psychiatric wards. *Nursing economics*. 2008;26(5):325-30, 4.
15. Hunter M, Carmel H. The cost of staff injuries from inpatient violence. *Psychiatric Services*. 1992;43(6):586-8.
16. Nijman HLI, Palmstierna T, Almvik R, Stolker JJ. Fifteen years of research with the Staff Observation Aggression Scale: a review. *Acta psychiatrica Scandinavica*. 2005;111(1):12-21.
17. Ferns T. Under-reporting of violent incidents against nursing staff. *Nurs Stand*. 2006;20(40):41-5.
18. Nolan KA, Citrome L. Reducing inpatient aggression: does paying attention pay off? *The Psychiatric quarterly*. 2008;79(2):91-5.

19. Archer S, Thibaut BI, Dewa LH, Ramtale C, D'Lima D, Simpson A, et al. Barriers and facilitators to incident reporting in mental healthcare settings: A qualitative study. *Journal of psychiatric and mental health nursing*. 2019;n/a(n/a).
20. Nijman HLI, Merckelbach HL, Allertz WF, a Campo JM. Prevention of aggressive incidents on a closed psychiatric ward. *Psychiatric services (Washington, DC)*. 1997;48(5):694-8.
21. Hankin CS, Bronstone A, Koran LM. Agitation in the inpatient psychiatric setting: a review of clinical presentation, burden, and treatment. *Journal of psychiatric practice*. 2011;17(3):170-85.
22. Daffern M, Howells K. Psychiatric inpatient aggression: A review of structural and functional assessment approaches. *Aggression and Violent Behavior*. 2002;7(5):477-97.
23. Kroon H, Michon H, Knispel A, Hulschbosch L, de Lange A, Boumans J, et al. Landelijke monitor ambulantisering en hervorming langdurige GGZ. Utrecht: Trimbos instituut; 2018.
24. Yudofsky SC, Silver JM, Jackson W, Endicott J, Williams D. The Overt Aggression Scale for the objective rating of verbal and physical aggression. *The American journal of psychiatry*. 1986;143(1):35-9.
25. Nederland G. Collectieve arbeidsovereenkomst GGZ 2017 - 2019. Amersfoort: GGZ Nederland; 2017.
26. Zorgautoriteit DN. Tariefbeschikking Generalistische basis-ggz - TB/REG-18608-01 2017 [cited 2020 February 3].
27. Foster C, Bowers L, Nijman H. Aggressive behaviour on acute psychiatric wards: prevalence, severity and management. *Journal of advanced nursing*. 2007;58(2):140-9.
28. Stone T, McMillan M, Hazelton M, Clayton EH. Wounding words: swearing and verbal aggression in an inpatient setting. *Perspectives in psychiatric care*. 2011;47(4):194-203.
29. Li W, Yang Y, Hong L, An FR, Ungvari GS, Ng CH, et al. Prevalence of aggression in patients with schizophrenia: A systematic review and meta-analysis of observational studies. *Asian journal of psychiatry*. 2019;47:101846.
30. Campbell JC, Messing JT, Kub J, Agnew J, Fitzgerald S, Fowler B, et al. Workplace violence: prevalence and risk factors in the safe at work study. *Journal of occupational and environmental medicine*. 2011;53(1):82-9.
31. Bowers L, Allan T, Simpson A, Jones J, Van Der Merwe M, Jeffery D. Identifying key factors associated with aggression on acute inpatient psychiatric wards. *Issues in mental health nursing*. 2009;30(4):260-71.
32. Alpert JE, Spillmann MK. Psychotherapeutic approaches to aggressive and violent patients. *Psychiatr Clin North Am*. 1997;20(2):453-72.
33. Jones RM, Arlidge J, Gillham R, Reagu S, van den Bree M, Taylor PJ. Efficacy of mood stabilisers in the treatment of impulsive or repetitive aggression: systematic review and meta-analysis. *The British journal of psychiatry : the journal of mental science*. 2011;198(2):93-8.
34. Correll CU, Yu X, Xiang Y, Kane JM, Masand P. Biological treatment of acute agitation or aggression with schizophrenia or bipolar disorder in the inpatient setting. *Annals of clinical psychiatry : official journal of the American Academy of Clinical Psychiatrists*. 2017;29(2):92-107.
35. Bowers L. Safewards: a new model of conflict and containment on psychiatric wards. *Journal of psychiatric and mental health nursing*. 2014;21(6):499-508.
36. Bowers L, Alexander J, Bilgin H, Botha M, Dack C, James K, et al. Safewards: the empirical basis of the model and a critical appraisal. *Journal of psychiatric and mental health nursing*. 2014;21(4):354-64.

37. Bowers L, James K, Quirk A, Simpson A, Stewart D, Hodsoll J. Reducing conflict and containment rates on acute psychiatric wards: The Safewards cluster randomised controlled trial. *International journal of nursing studies*. 2015;52(9):1412-22.
38. Fletcher J, Spittal M, Brophy L, Tibble H, Kinner S, Elsom S, et al. Outcomes of the Victorian Safewards trial in 13 wards: Impact on seclusion rates and fidelity measurement. *International journal of mental health nursing*. 2017;26(5):461-71.
39. Maguire T, Ryan J, Fullam R, McKenna B. Evaluating the Introduction of the Safewards Model to a Medium- to Long-Term Forensic Mental Health Ward. *J Forensic Nurs*. 2018;14(4):214-22.
40. Baumgardt J, Jäckel D, Helber-Böhlen H, Stiehm N, Morgenstern K, Voigt A, et al. Preventing and Reducing Coercive Measures-An Evaluation of the Implementation of the Safewards Model in Two Locked Wards in Germany. *Front Psychiatry*. 2019;10:340.
41. Bank EC. http://www.ecb.europa.eu/stats/exchange/eurofxref/html/index.en.html 2020 [cited 2020 03 February].
42. Raboch J, Kalisova L, Nawka A, Kitzlerova E, Onchev G, Karastergiou A, et al. Use of coercive measures during involuntary hospitalization: findings from ten European countries. *Psychiatric services (Washington, DC)*. 2010;61(10):1012-7.
43. Kalisova L, Raboch J, Nawka A, Sampogna G, Cihal L, Kallert TW, et al. Do patient and ward-related characteristics influence the use of coercive measures? Results from the EUNOMIA international study. *Social psychiatry and psychiatric epidemiology*. 2014;49(10):1619-29.
44. Bader S, Evans SE, Welsh E. Aggression Among Psychiatric Inpatients: The Relationship Between Time, Place, Victims, and Severity Ratings. *Journal of the American Psychiatric Nurses Association*. 2014;20(3):179-86.
45. Nijman HLI, Muris P, Merckelbach HLGJ, Palmstierna T, Wistedt B, Vos AM, et al. The staff observation aggression scale–revised (SOAS-R). *Aggressive behavior*. 1999;25(3):197-209.

Supplementary Table 1. Case vignettes for each of the four aggression categories

	Verbal aggression	Aggression towards objects	Self-harm	Aggression towards other persons
Description	Patient yells at nurse, saying his therapists are criminals and that his medication makes him ill. Also yells at another patient.	Patient was throwing things throughout her room, unprovoked. Staff member approached her, patient yells and keeps throwing. Also broke chair and door.	Patient was found in room with rope around neck. Vital functions intact. Given intramuscular medication.	Patient is restless and yells at staff, acts paranoid. Is offered medication. Kicks door of medication room, hitting doctor. Kicks staff member in the crotch. Is isolated by multiple staff members and given intramuscular medication.
Gender	male	female	female	male
Age	54	25	24	23
Diagnosis	schizophrenia	borderline personality disorder	schizophrenia	schizophrenia
Provocation	none	none	psychotic symptoms	psychotic symptoms
Intervention	de-escalating conversation	de-escalating conversation	medication	medication and isolation
Time spent on				
Managing incident (min)	11	55	60	420
Transfer of information (min)	35	64	75	100
Reporting (min)	5	5	25	40
Total costs	€ 30.18	€ 234.19	€ 82.02	€ 342.23

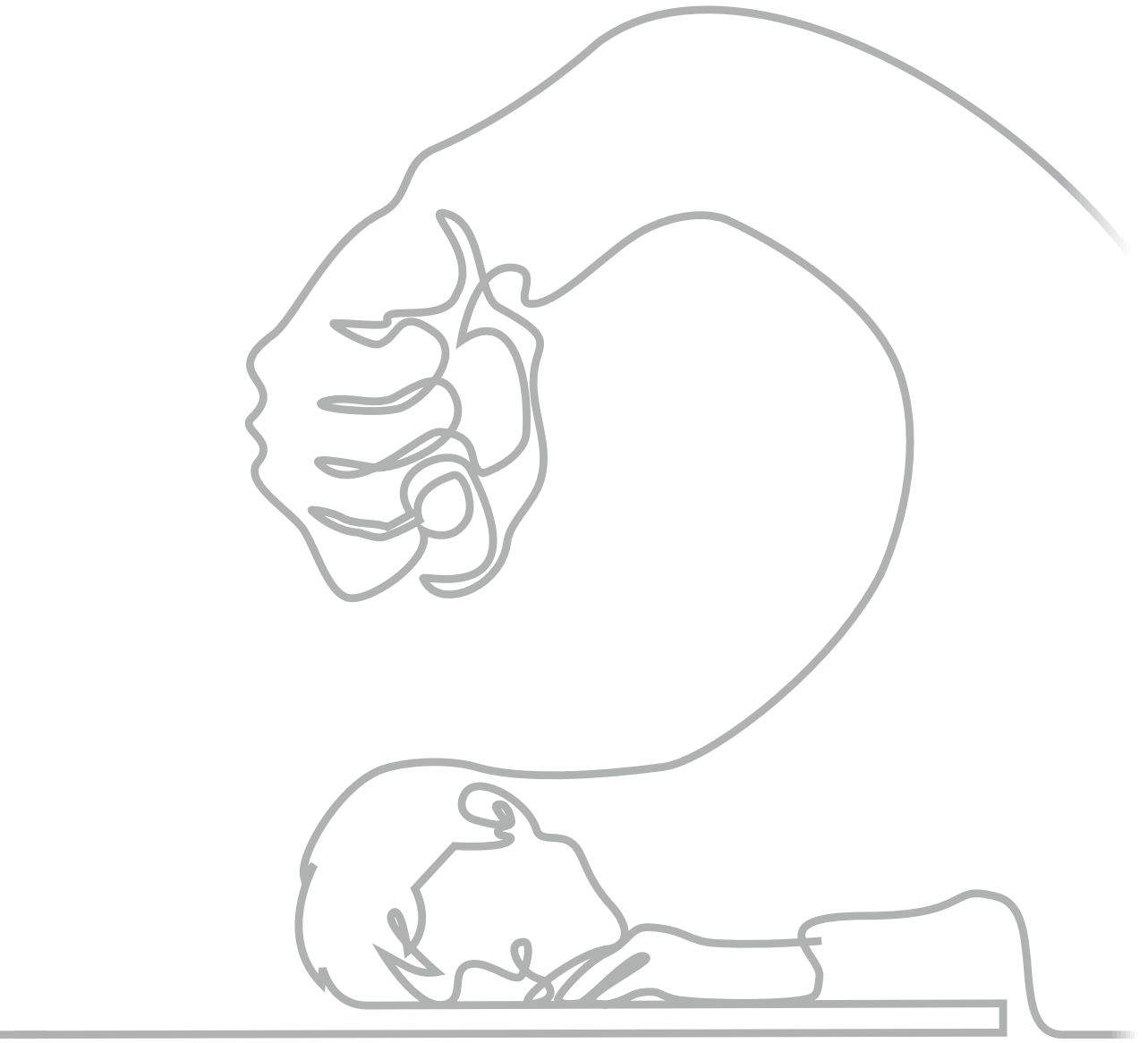
Supplementary Table 2. Hourly wages for each staff category

	Monthly salary	Hourly wages
Student nurse	€ 1,570	€ 17[1]
Nurse (MBO qualified)	€ 2,578	€ 28[1]
Nurse (HBO qualified)	€ 2,724	€ 29[1]
Social worker	€ 2,724	€ 29[1]
Groupworker	€ 2,724	€ 29[1]
Client supporter	€ 2,188	€ 24[1]
Activity supervisor	€ 2,380	€ 26[1]
Security guard		€ 33[1]
Physician	€ 4,305	€ 46[2]
Psychiatrist	€ 6,887	€ 74[2]

Note. Wages were derived from the Collective Labour Agreement for the Mental Health Sector (2017–2019).
[1] +22% Monday till Friday (06.00-07.00 and 20.00-22.00); +38% Saturdays (06.00-08.00 and 12.00-22.00); +44% nights (22.00-06.00); +49% Saturday nights (22.00-06.00); +60% Sundays and holidays (00.00-24.00).
[2] +75% Saturdays (06.00-08.00 and 12.00-22.00); +50% nights (22.00-06.00); +100% Saturday nights (22.00-06.00); +100% Sundays and holidays (00.00-24.00)

Published as: De Bles, N. J., Rius-Ottenheim, N., Geleijnse, J. M., Van De Rest, O., Bogers, J. P., Schat, A., Nijman, H. L. I., van den Berg, D., Joos, L., van Strater, A., de Ridder, T., Stolker, J. J., van den Hout, W. B., van Hemert, A. M., & Giltay, E. J. (2022). Effects of multivitamin, mineral and n-3 polyunsaturated fatty acid supplementation on aggression among long-stay psychiatric in-patients: randomised clinical trial. *BJPsych open, 8*(2).

7 Effects of multivitamin, mineral and n-3 polyunsaturated fatty acid supplementation on aggression among long-stay psychiatric in-patients: randomised clinical trial



Abstract

Background: Aggression and violent incidents are a major concern in psychiatric in-patient care. Nutritional supplementation has been found to reduce aggressive incidents and rule violations in forensic populations and children with behavioural problems.

Aims: To assess whether multivitamin, mineral and n-3 polyunsaturated fatty acid supplementation would reduce the number of aggressive incidents among long-stay psychiatric in-patients.

Method: The trial was a pragmatic, multicentre, randomised, double-blind placebo-controlled study. Data were collected from 25 July 2016 to 29 October 2019, at eight local sites for mental healthcare in The Netherlands and Belgium. Participants were randomised (1:1) to receive 6-month treatment with either three supplements containing multivitamins, minerals and n-3 polyunsaturated fatty acid, or placebo. The primary outcome was the number of aggressive incidents, determined by the Staff Observation Aggression Scale – Revised (SOAS-R). Secondary outcomes were patient quality of life, affective symptoms, and adverse events.

Results: In total, 176 participants were randomised (supplements, $n = 87$; placebo, $n = 89$). Participants were on average 49.3 years old ($SD = 14.5$) and 64.2% were male. Most patients had a psychotic disorder (60.8%). The primary outcome of SOAS-R incidents was similar in supplement (1.03 incidents per month, 95% CI 0.74–1.37) and placebo groups (0.90 incidents per month, 95% CI 0.65–1.19), with a rate ratio of 1.08 (95% CI 0.67–1.74, $p = 0.75$). Differential effects were not found in sensitivity analyses on the SOAS-R or on secondary outcomes.

Conclusions: Six months of nutritional supplementation did not reduce aggressive incidents among long-stay psychiatric in-patients.

Introduction

Aggression and violent incidents are highly prevalent in psychiatric in-patient care, varying from nine to 90 incidents per patient per year, depending on the type of ward [1-3]. Although pharmacotherapy and psychotherapy may help to mitigate feelings of irritability, anger or overt aggression [4], clinical guidelines emphasise the need for additional treatment options [5].

Nutritional psychiatry

Research is increasingly suggesting diet to be a modifiable factor affecting mood and behaviour, giving rise to the field of nutritional psychiatry [6]. Essential nutrients, including lipids, amino acids, vitamins, and minerals, play an important role in biological processes such as inflammation, oxidative stress, neuroplasticity, neurogenesis, and synthesis of neurotransmitters, with the gut–brain axis acting as a potential mediating pathway [7, 8]. For example, vitamin B6, vitamin B12 and folate are crucial in the formation of neurotransmitters such as epinephrine, norepinephrine, γ-amino butyric acid, and serotonin [7]. In particular, a deficiency in serotonin seems to play a key role in aggressive behaviour [9, 10], considering that the deprivation of the amino acid tryptophan, the dietary precursor of serotonin, can induce aggressiveness [11], and the selective serotonin reuptake inhibitor fluoxetine has shown anti-aggressive effects in randomised trials among psychiatric patients [12, 13]. However, as essential nutrients act in synergistic combinations, broad-spectrum micronutrients are recommended in trials among psychiatric populations, rather than focusing on a single nutrient [14].

Previous findings

Previous literature has explored whether multivitamin, mineral and n-3 polyunsaturated fatty acid (PUFA) supplementation may help to reduce aggressive behaviour. Hitherto, researchers in this field have studied young male prisoners [15-18] and children with behavioural problems [19-21], some of whom were diagnosed with autism spectrum disorder [22], attention-deficit hyperactivity disorder [23], conduct disorder and oppositional defiant disorder [24]. In total, five out of six randomised controlled trials showed reductions in aggression, and there were 26–47% fewer aggressive-related incidents in the group receiving nutritional supplements compared with those receiving a placebo [15-19]. In addition, one of these studies demonstrated that participants with the lowest nutrient concentrations seemed to have benefited the most from nutritional supplementation [17]. Reductions in aggressive behaviour based on the number of

disciplinary incidents were not found in a study among school-aged children [21]. In the same study, however, an observer-rated scale was also included that did show a significant reduction in these behaviours in the intervention compared with the control group. Trials that assessed subjective feelings of aggression as an outcome showed consistent findings [20, 22-24]. Thus, nutritional supplementation may help to reduce aggression, but this needs to be confirmed in a sample of long-stay psychiatric in-patients.

Long-stay psychiatric in-patients are more at risk for nutrient deficiencies compared with the general population, because of the consumption of more energy-dense and nutrient-poor diets, insufficient outdoor activities and the potential detrimental effect of psychotropics (e.g. antipsychotics) on appetite, gastrointestinal function, the microbiome and (energy and micronutrient) metabolism [25, 26]. The overall poor quality dietary intake was also confirmed in a pilot study in a group of 21 patients from the target population (Supplementary Appendices 1 and 2 available at https://doi.org/10.1192/bjo.2022.8). Hence, it can therefore be hypothesised that psychiatric in-patients may likely benefit from nutritional supplementation.

Aim and hypothesis

A randomised, double-blind placebo-controlled trial was initiated to determine the effectiveness of nutritional supplements in reducing aggressive incidents among long-stay psychiatric in-patients. We hypothesised that nutritional supplementation would reduce aggressive incidents, feelings of aggression and affective symptoms, and would increase patient quality of life.

Method

Design

This pragmatic, multicentre, randomised, double-blind, placebo-controlled intervention trial was coordinated in the Department of Psychiatry at the Leiden University Medical Centre (LUMC). Participants were recruited between 25 July 2016 and 29 October 2019, from eight local sites for mental healthcare in The Netherlands and Belgium. Data collection took place at the ward where the participants resided. Participants received a small financial compensation (€2.50) for completing each assessment. Written informed consent was obtained from all participants, in some cases from a relative or legal representative, where appropriate. All procedures contributing to this work complied with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of

1975, as revised in 2008. The trial protocol (Supplementary Appendix 3) was approved by the Medical Ethical Committee of the LUMC, under reference number P14.332, and the study followed the Consolidated Standards of Reporting Trials (CONSORT) reporting guideline. The trial was registered at ClinicalTrials.gov (identifier NCT02498106).

Participants

Inclusion criteria were age ≥ 18 years and expected to reside at a facility for long-term psychiatric in-patient care for at least 6 months, irrespective of their specific psychiatric disorder. Exclusion criteria were pregnancy, breastfeeding, contraindication for nutritional supplements, expected discharge or transfer within 8 weeks, restrictions against the consumption of pork gelatine and continuous use of other nutritional supplements within the preceding 8 weeks (exceptions included vitamin B1 and vitamin D, which are mostly prescribed to prevent complications of alcoholism or to treat low vitamin D plasma levels in Northern countries, respectively, and which entailed no health risks in combination with this study's supplements).

Intervention

A 2-week placebo run-in phase was followed by a 6-month nutritional intervention, during which participants received a daily dose of two capsules containing multivitamins and minerals and one capsule containing n-3 PUFA (i.e. eicosapentaenoic acid and docosahexaenoic acid [27]; Supplementary Appendix 4). The control group received three placebo capsules per day, containing the neutral n-9 oleic acid. The n-3 PUFA content of both nutritional supplements and placebo capsules was checked during follow-up and showed no noticeable decay. Intervention costs were estimated at €393 per patient year, of which 80% was for the supplements and 20% was for distribution (assuming 30 s of nursing staff time per patient per day, at €26 per hour; Supplementary Appendix 5).

Randomisation

Participants were randomised in a 1:1 ratio, using blocks of 12 participants, and were stratified by gender and ward type (open or closed). At the end of the study, participants and nurses were asked whether they thought the participant had received supplements or placebo, to check whether blinding had been successful.

Measurements

Primary outcome variable

The primary outcome in this study was the number of aggressive incidents registered, as determined by the Staff Observation Aggression Scale – Revised (SOAS-R), created originally for use in in-patient psychiatric wards [28]. The SOAS-R is a quick and easy-to-use tool, which comprises five columns recording provocation, means used, the target, consequences and measures taken to stop aggression. Each time an aggressive incident occurred, nursing staff were expected to complete the SOAS-R. Aggression was defined as 'any verbal, nonverbal, or physical behaviour that was threatening (to self, others, or property) or [any] physical behaviour that actually did harm (to self, others, or property)' [28, 29]. The SOAS-R total severity score ranges from 0 to 22 points, with scores of 0–7 indicating mild, 8–15 indicating moderate and 16–22 indicating severe severity [30]. Severity of an incident was also judged on a 100-mm visual analogue scale, ranging from 0 (not severe at all) to 100 (extremely severe). Results on the psychometric properties of the SOAS-R indicate fair to good interrater reliability, with an intraclass correlation of 0.96 [31], reported Cohen's kappas of between 0.61 and 0.74 [32-34] and a Pearson's product-moment *r* between independent raters of 0.87 [32]. The SOAS-R severity scores indicate significant concurrent validity [1].

Secondary outcome variables

The 11-item Social Dysfunction and Aggression Scale (SDAS) [35] was completed by nurses at baseline and after 2 weeks, 2 months and 6 months. In our sample, the intraclass correlation was 0.76, suggesting moderate stability over time. It is recommended to use the SDAS in conjunction with the SOAS-R, as the former is more sensitive to measure more subtle aggression incidents [36]. Additionally, patients were asked to complete several questionnaires at baseline, 2 months and 6 months: A Dutch version of the shortened 12-item Aggression Questionnaire [37, 38], the 26-item World Health Organization Quality of Life [39, 40] and the abbreviated 25-item version of the Comprehensive Psychopathological Rating Scale (CPRS) [41, 42]. The CPRS included the ten-item Montgomery–Åsberg Depression Rating Scale [43], the ten-item Brief Anxiety Scale [44] and a five-item inhibition subscale.

Other variables

Non-fasting blood samples were collected to determine nutritional status and to monitor adherence in those who consented to blood collection (in 82.6% of participants in

The Netherlands). Belgian institutions did not collect blood because of pragmatic reasons, as samples were transported through the regular postal service. Blood samples were collected only if a participant agreed to a venipuncture. Two tubes were collected (one serum separator and one ethylenediaminetetraacetic acid (EDTA) tube) before and after the trial, by competent nurses appointed in each institution. Subsequently, blood samples were sent to the LUMC within 24 h, through the regular postal service. The samples were stored at −80°C until analysis. Samples were analysed for vitamins A (retinoids), E (tocopherol), B12 (cobalamin) and D (calciferol), folic acid and iron in blood serum. Vitamin B1 (thiamine), vitamin B6 (pyridoxine) and a fatty acid spectrum to yield n-3 fatty acid levels (alpha-linolenic acid, eicosapentaenoic acid, and docosahexaenoic acid) were analysed in EDTA blood samples. Blood level assessments are described in detail in the Supplementary Material.

Sociodemographic covariates were age, gender, level of education (categorised into low (primary education, lower secondary education), medium (upper secondary education, post-secondary non-tertiary education) and high (tertiary education, Bachelor's, Master's, doctoral)), marital status (never married, ever married (married, widow/widower or divorced)), ancestry (European, non-European ancestry), smoking (yes, no), any use of recreational drugs (never, ever, current (past month)) and use of alcohol (>14 units per week). Body mass index was calculated based on measured height and weight. Ward type (open, closed), primary diagnosis and medication use were obtained from the treating psychiatrist.

Statistical analyses

The sample size was based on results of previous literature [15-17, 19, 45, 46]. We assumed a conservative delta of 26% reduction in the number of incidents, whereby incidents are modelled according to a Poisson distributed random variable [47]. Assuming 80% power, $\alpha = 0.05$ and an overall rate of 4, a final total sample size of 132 was required to be able to reject the null hypothesis. Assuming a drop-out rate of 25%, we aimed to include at least 166 patients.

Sociodemographic and clinical characteristics were summarized per allocation, using independent samples t-test and χ^2-test. Micronutrient status was assessed with linear mixed models. The frequency of aggressive incidents was presented as the back-transformed geometric mean number of incidents per month. Negative binomial regression analyses were performed to analyse the number of aggressive incidents, as overdispersion was anticipated. An offset was used to take the log number of days that a patient participated in the trial into account. We applied triple masking, which

ensured that the treatment was unknown to the participants and to the nurses and physicians, as well as the epidemiologist (J.M.G.) who analysed the effect on the primary outcome but was not part of the coordinating centre.

To investigate the trend of the incidence rate ratio, a negative binomial regression was performed for each month separately, plotted over time. Incidents were studied in total and individually, according to their level of severity and type. Sensitivity analyses were performed in subgroups excluding patients with an extreme number of incidents (i.e., either zero incidents per month or more than ten incidents per month), adjusting for baseline SDAS. Post hoc subgroup analyses were performed for sociodemographic and clinical variables. Differences between the randomised groups on the secondary outcomes were performed following intention-to-treat (ITT) analysis, using multilevel regression (mixed) models. In the case of missing data, we used last observation carried forward for the ITT analyses. χ^2-Tests were performed to check whether participants and nurses gave the correct answer more often than expected by chance, excluding the ones who gave the answer 'I do not know'. χ^2-Tests were also performed to compare the number of side-effects among the randomised groups. A two-tailed significance level of $p < 0.05$ was considered statistically significant. Negative binomial regression analyses were performed with R software within RStudio (R version 3.6.0 for macOS; R Foundation for Statistical Computing, Vienna, Austria, 2016; https://www.R-project.org/) and the main package MASS (version 7.3). All other analyses were performed with IBM SPSS statistical software (version 25, IBM Corp, 2017, IBM SPSS Statistics for Windows).

Results

We assessed 1121 patients for eligibility and excluded 945 (Fig. 1). The high number of excluded patients could be explained by the fact that treating psychiatrists regularly did not give permission to contact certain patients because it might disturb their treatment plan or therapeutic relationship ($n = 358$). In total, 176 participants were randomised into the trial (supplements, $n = 87$; placebo, $n = 89$), most of whom had a psychotic disorder (60.8%). The mean age of the participants was 49.3 years (s.d. 14.5), and 64.2% were male. No significant demographic or clinical group differences were observed at baseline (Table 1).

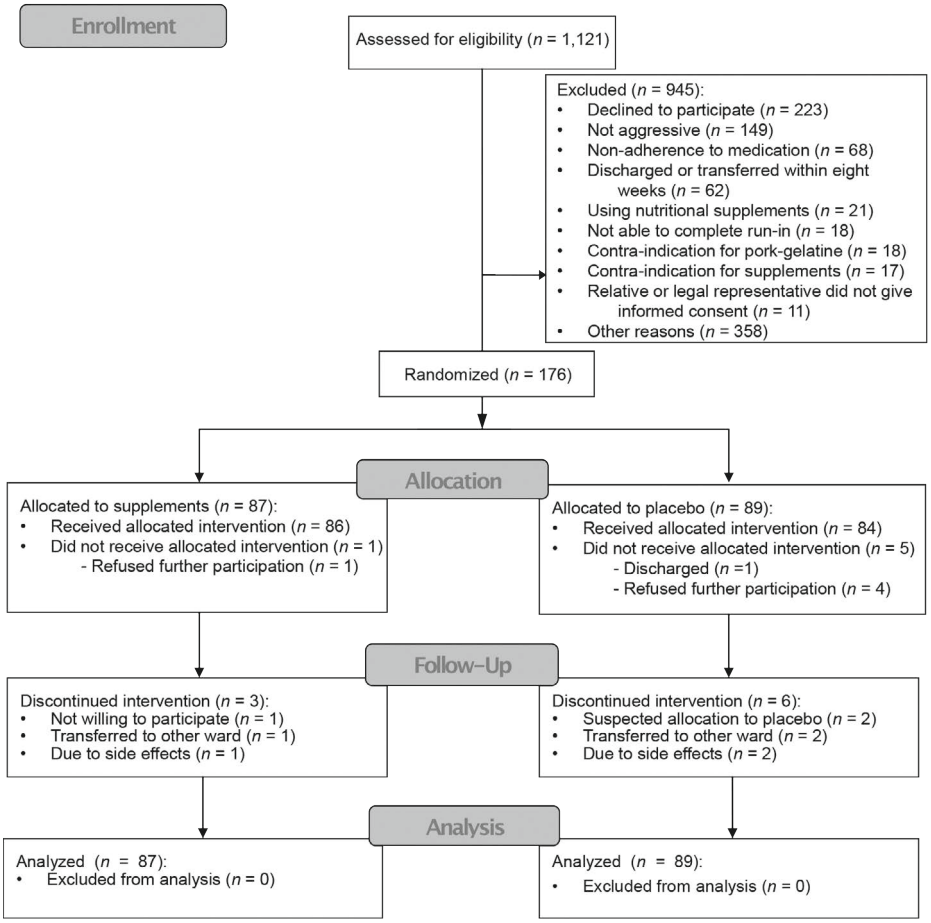


Fig. 1. Consolidated Standards of Reporting Trials flow diagram of participants through the study

Protocol adherence

In total, 114 participants agreed to blood sampling (82.6% of 138 participants from The Netherlands) at baseline, endpoint or both. Expected increases were found in the intervention compared with placebo groups, which were statistically significant for vitamin B6 ($p = 0.005$), folic acid ($p < 0.001$), vitamin B12 ($p = 0.04$), vitamin E ($p = 0.02$), eicosapentaenoic acid ($p < 0.001$) and docosahexaenoic acid ($p < 0.001$; Supplementary Appendix 6).

Table 1. Baseline characteristics of study participants (*N* = 176)

	Supplements (*n* = 87)	Placebo (*n* = 89)	*p* value
Demographics			
Male gender, no (%)	54 (62.1%)	59 (66.3%)	0.56
Age in years, mean (*SD*)	49.1 (14.2)	49.4 (14.8)	0.88
BMI (kg/m^2), mean (*SD*)	28.9 (6.0)	28.5 (7.9)	0.73
Closed ward, no (%)	56 (64.4%)	55 (61.8%)	0.72
Never married, no (%)	63/82 (76.8%)	69/85 (81.2%)	0.49
Education low, no (%)	49/79 (62%)	47/79 (59.5%)	0.74
European ancestry, no (%)	71 (81.6%)	70 (78.7%)	0.62
Current smoker[a], no (%)	61/86 (70.9%)	64/86 (74.4%)	0.61
Alcohol ≥ 14 U/wk[a], no (%)	9/76 (11.8%)	7/82 (8.5%)	0.49
Recreational drugs[b], no (%)	46/85 (54.1%)	48/85 (56.5%)	0.76
Clinical data			
Primary diagnosis, no (%)			0.97
Psychotic disorder	52 (59.8%)	55 (61.8%)	
Mood disorder	8 (9.2%)	9 (10.1%)	
Personality disorder	9 (10.3%)	9 (10.1%)	
Other	18 (20.7%)	16 (18.0%)	
Medication use			
Antipsychotics	76/80 (95.0%)	70/80 (87.5%)	0.09
FGA	42/80 (52.5%)	33/80 (41.3%)	0.15
SGA	60/80 (75.0%)	54/80 (67.5%)	0.29
Antidepressants	31/80 (38.8%)	31/80 (38.8%)	1.00
Benzodiazepines	61/80 (76.3%)	67/80 (83.8%)	0.24
Mood stabilizers	38/80 (47.5%)	35/80 (43.8%)	0.63

Note. Data are number of participants (with percentages in parentheses) or means (with standard errors in parentheses). BMI=Body Mass Index; First Generation Antipsychotics=FGA; Second Generation Antipsychotics=SGA.
[a] Based on last month.
[b] Ever used.

Primary outcome measures

Figure 2 presents the main outcomes. The primary outcome of SOAS-R incidents was similar in those assigned to supplements (1.03 incidents per month, 95% CI 0.74–1.37) and placebo (0.90 incidents per month, 95% CI 0.65–1.19), with a rate ratio of 1.08 (95% CI 0.67–1.74, $p = 0.75$). Also, no significant effects were found according to the severity or type of aggressive incidents. Sensitivity analyses in subgroups according

to the number of incidents (i.e., either zero or more than ten incidents per month) did not influence these results, which also applies to the analysis adjusting for baseline SDAS score. Supplementary Appendix 7 shows the incidence rate ratio per month during the 6-month intervention period. The geometrical mean number of incidents in a curve showed that during the first 2 months after the start of the intervention, patients in the intervention group had a slightly higher (but not significant) rate of aggressive incidents compared with those receiving placebo. As shown in Supplementary Appendix 8, subgroup analyses showed no evidence for effect modification by other variables, except for antipsychotic use. In the small subgroup of participants not using antipsychotics (n = 14), supplements showed a beneficial effect compared with placebo (p = 0.004).

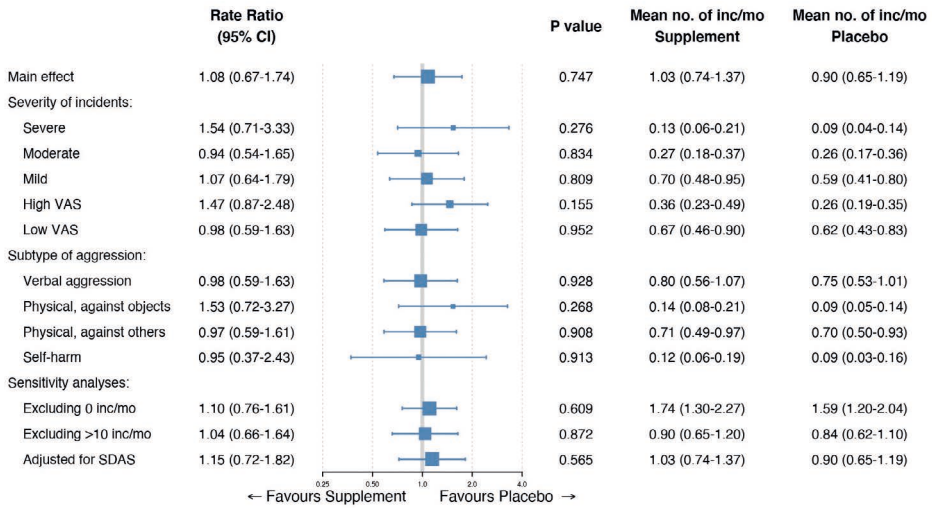


Fig. 2. Effectiveness analyses on primary outcome. The mean is the geometrical mean number of incidents per month. Severe: 16 – 22; Moderate: 8 – 15; Mild: 0 – 7; High VAS: ≥ 5; Low VAS: < 5. SDAS, Social Dysfunction and Aggression Scale; VAS, visual analogue scale.

Secondary outcome measures

As seen in Table 2, an ITT approach showed that nutritional supplementation did not significantly affect any of the secondary outcomes. In detail, no differential effects for supplements versus placebo were found for either self- and observer-rated aggression, quality of life, depression severity, anxiety severity or inhibition.

Table 2. Intention to treat analyses of the effectiveness on secondary outcomes

		n	Baseline	2 weeks	2 months	6 months	Interaction: score * time	
							Test	*P*
SDAS	Supplements	84	9.2 (0.9)	8.2 (0.9)	7.9 (0.8)	7.7 (0.8)	*F*(df. 1)=0.016	0.90
	Placebo	84	9.6 (0.9)	8.0 (0.7)	8.4 (0.8)	7.8 (0.7)		
AQ	Supplements	84	30.4 (1.2)	–	28.7 (1.2)	30.1 (1.2)	*F*(df. 1)=0.576	0.45
	Placebo	84	32.0 (1.1)	–	30.9 (1.0)	30.8 (1.0)		
Anger	Supplements	82	7.5 (0.4)	–	7.0 (0.4)	7.2 (0.4)	*F*(df. 1)=0.006	0.94
	Placebo	84	8.2 (0.4)	–	7.8 (0.4)	7.9 (0.3)		
Hostility	Supplements	84	9.0 (0.4)	–	8.6 (0.4)	8.8 (0.4)	*F*(df. 1)=0.319	0.57
	Placebo	82	9.5 (0.4)	–	9.6 (0.4)	9.0 (0.4)		
Physical aggression	Supplements	82	7.3 (0.4)	–	6.8 (0.4)	7.0 (0.4)	*F*(df. 1)=0.052	0.82
	Placebo	83	7.1 (0.4)	–	6.8 (0.3)	6.8 (0.4)		
Verbal aggression	Supplements	81	6.4 (0.4)	–	6.4 (0.4)	6.8 (0.4)	*F* (df. 1)=0.958	0.33
	Placebo	82	7.4 (0.3)	–	7.0 (0.3)	7.4 (0.3)		
WHO-QOL	Supplements	77	87.4 (2.0)	–	85.2 (2.1)	85.8 (2.0)	*F*(df. 1)=0.596	0.44
	Placebo	79	83.5 (1.9)	–	83.6 (1.8)	84.0 (1.8)		
Physical health	Supplements	78	13.2 (0.4)	–	13.0 (0.4)	13.2 (0.4)	*F*(df. 1)=0.001	0.98
	Placebo	78	12.6 (0.4)	–	12.7 (0.3)	12.8 (0.3)		
Psychological health	Supplements	78	12.6 (0.4)	–	12.7 (0.4)	12.4 (0.4)	*F*(df. 1)=0.952	0.33
	Placebo	77	12.4 (0.4)	–	12.4 (0.3)	12.7 (0.4)		
Social relationships	Supplements	78	12.9 (0.4)	–	12.6 (0.4)	12.6 (0.5)	*F*(df. 1)=0.687	0.41
	Placebo	74	12.6 (0.4)	–	12.5 (0.4)	12.9 (0.4)		
Environment	Supplements	78	14.4 (0.3)	–	13.8 (0.4)	14.1 (0.3)	*F*(df. 1)=0.105	0.75
	Placebo	79	13.7 (0.3)	–	13.8 (0.3)	13.5 (0.3)		
MADRS	Supplements	69	13.0 (1.3)	–	12.2 (1.3)	12.5 (1.2)	*F*(df. 1)=0.021	0.89
	Placebo	71	13.3 (1.3)	–	13.0 (1.3)	13.2 (1.2)		
BAS	Supplements	69	12.0 (1.0)	–	10.7 (0.9)	11.5 (0.9)	*F*(df. 1)=0.033	0.86
	Placebo	68	11.8 (0.9)	–	11.6 (0.8)	11.6 (0.8)		
Inhibition Scale	Supplements	70	4.7 (0.5)	–	4.0 (0.5)	4.1 (0.4)	*F*(df. 1)=0.462	0.50
	Placebo	71	4.7 (0.5)	–	4.6 (0.5)	4.6 (0.5)		

Note. Data are means (with standard errors in parentheses). SDAS=Social Dysfunction and Aggression Scale, observer rated; AQ=Aggression Questionnaire; WHO-QOL=World Health Organization Quality of Life; MADRS=Montgomery-Åsberg Depression Rating Scale; BAS=Brief Anxiety Scale.

Blinding

Blinding was successful among participants, who guessed correctly whether they had been taking the supplements or placebo no more frequently than incorrectly ($p = 0.44$). Nurses who distributed the supplements, however, more frequently guessed

the randomised condition of the participants correctly (n = 38 out of 55; 69.1% correct; p = 0.005). Still, the majority of both participants (n = 48 out of 116; 41.4%) and nurses (n = 75 out of 130; 57.7%) answered with 'I do not know'.

Adverse effects

At least one side-effect was reported by 15 out of 73 patients in the control group (20.5%) and 17 out of 74 patients in the intervention group (23.0%; p = 0.72; see Supplementary Appendix 9). Burping (p = 0.049) and rash (p = 0.04) were significantly more frequently reported by participants in the intervention group compared with the control group, with burping being the most frequently reported (11.1 v. 2.8%). In total, two participants died during the trial (supplements, n = 1; placebo, n = 1). The age of these participants was 55 and 83 years. Reasons of death were respiratory disease and cardiac arrest, respectively. This was confirmed by their physicians, who all judged that there were no causal relationships with the supplements.

Discussion

Our findings provided no support for the effectiveness of multivitamin, mineral and n-3 PUFA supplementation in reducing the number of aggressive incidents among psychiatric in-patients during a 6-month intervention. *Post hoc* analyses according to the severity or type of aggressive incidents corroborated this conclusion. No differences were found between the randomized groups regarding the secondary outcomes, including self- and observer-rated aggression, quality of life and affective symptom severity.

The current study is the first to investigate the effect of nutritional supplements in in-patients suffering from chronic psychiatric disorders. These patients are often not included in clinical trials, leading to a lack of evidence for effective care and treatment [48]. In previous trials that investigated the effect of nutritional supplements on aggressive incidents, patients with psychosis were often excluded [20, 21, 23, 24] or no information on the use of psychotropic medication was given [15, 19]. Our sample included participants with psychotic disorders (60.8%), a vast majority of whom were using antipsychotics (91.2%). The extensive use of antipsychotics in our population may have led to a ceiling effect, as antipsychotics are prescribed to mitigate agitation and aggression [49], creating a situation in which no additional effect of a nutritional intervention could be found. Additionally, adverse effects of antipsychotics comprise gastrointestinal and metabolic side-effects, which may result in dysbiosis [26, 50], the disruption of the

bacterial species of the gut microbiota, which could potentially adversely affect mood and behaviour through the gut–brain axis [8]. Note that an exploratory analysis of the subsample of patients with psychosis who did not use antipsychotic agents in the current study did suggest a reduction of incidents among the patients with psychosis who had taken the nutritional supplements. Furthermore, an exploratory trial including acute patients with schizophrenia treated with antipsychotic medication found no effect of n-3 PUFA supplementation on hostility compared with the control group [51]. In addition, the incidents of the patients with psychosis in the current study may comprise different forms of aggression than those expressed by participants in previous trials, such as aggression resulting from the nature of their psychiatric disorders, like paranoid delusions [52]. Moreover, aggressive behaviours in psychiatric patients may be masked by the complex interaction of different causal factors.

Besides the different study populations, there may be several other explanations for the discrepant findings of the current study with previous trials showing beneficial effects [15-19]. The current study was the first to investigate the intervention among older patients, with a mean age of 49.3 years, whereas the mean age of participants from earlier forensic and youth trials ranged from 5 to 25 years. This is important as supplementation may have different effects across the lifespan, depending on the stages of brain development [53]. Second, although some studies used a similar combination of multivitamins, minerals and n-3 PUFA [15, 16, 20, 21, 24], many others did not include n-3 PUFA in their active treatment arm [17-19, 22, 23]; n-3 PUFA is known to be involved in brain structure and function [7]. Dosages in prior studies varied in their recommended daily allowance (RDA), but two studies used substantially higher dosages [23]. One of these two studies was a recently published three-arm trial that demonstrated that participants in the RDA group showed significantly less serious rule violations, whereas the participants in the higher-dose supplement group did not, compared with the placebo group [18]. In our trial, we used relatively high dosages of B vitamins because a meta-analysis showed increased beneficial effects on perceived stress and hostility in the trials that used higher doses of B vitamins [54]. Furthermore, the duration of the exposure in our trial was relatively long (6 months) compared with previous trials, which had a median intervention period of 3 months (ranging from 70 to 142 days). The longer exposure used in our study ensured the minimal duration of supplementation to establish equilibration of n-3 PUFA into different organs, including the brain [55]. Our sample size of 176 participants was comparable to earlier trials, with a median number of randomised participants of 209 (ranging from 62 to 468).

In line with our primary outcome, we found no evidence for improvements on self- and observer-rated aggression questionnaires. However, previous trials that found significant aggression reductions also did not observe improvements on self- and observer-rated aggression questionnaires. This suggests that supplements affect objectively observed aggressive incidents more than subjectively perceived aggressive feelings and behaviour [15, 18, 20, 24].

Some limitations need to be discussed. First, we were obliged to be explicit toward potential participants about our aim to reduce aggressive incidents. As a consequence, patients, especially the more aggressive ones, were often not willing to participate [56]. Second, nurses had to complete the SOAS-R in addition to writing up a description of the event in the patient records. Because of the high workload in psychiatric care, some (milder) incidents could have been missed. However, this phenomenon likely occurred in equal proportions in both randomised groups, and no beneficial effect was found for severe incidents, which were unlikely to be missed. In addition, using two different instruments (i.e., the incident-based SOAS-R and the SDAS based on the preceding week) simultaneously in the recording of aggressive behaviour gave us more complete information on the effects of the intervention [36]. Third, although blinding was effective in participants, retrospectively, nurses often guessed the participant condition correctly. Fourth, as included participants were diagnosed with diverse psychiatric disorders, we cannot exclude the possibility that nutritional supplements would be beneficial within one specific kind of psychiatric disorder. Yet, subgroup analyses performed according to the diagnosis (i.e., psychotic disorder versus other) showed no evidence for effect modification. Fifth, participants from Belgium could not provide blood samples because of logistical reasons. Finally, no information was gathered about dietary habits, as most of our participants suffered from mental disorders characterised by disruptions in thought processes and were therefore less likely to complete food frequency questionnaires accurately.

In summary, this is the first randomised controlled trial that studied the effect of nutritional supplementation among long-stay psychiatric in-patients. Despite some promising effects of nutritional supplementation on aggressive incidents found in previous studies, we found no evidence of effect in chronically ill psychiatric in-patients.

Acknowledgments

We would like to thank all members of the Diet and Aggression study for their highly appreciated work. A full list of study members can be found in the Supplementary Material.

Supplementary material

Supplementary material is available online at https://doi.org/10.1192/bjo.2022.8

Author contributions

A.S. and E.J.G. designed the study and wrote the grant application. N.J.d.B., N.R.-O. and E.J.G. coordinated the study, processed the data, performed the analyses, drafted the manuscript, and designed the figures. N.R.-O., A.M.v.H. and E.J.G. supervised the work. J.M.G. and O.v.d.R. aided in interpreting the results in the light of previous research on nutrition. W.B.v.d.H. performed the cost-effectiveness analysis. J.P.A.M.B., H.L.I.N., D.v.d.B., L.J., A.v.S., J.J.S. and T.d.R. provided access to participants in in-patient care and aided with recruitment and data collection. All authors discussed the results and commented on the manuscript.

Funding

This work was supported by ZonMw (The Netherlands Organisation for Health Research and Development) under grant number 836031016.

Declaration of interest

None.

Data availability

The data that support the findings of this study are available from the corresponding author, N.J.B., upon reasonable request.

References

1. Nijman HLI, Palmstierna T, Almvik R, Stolker JJ. Fifteen years of research with the Staff Observation Aggression Scale: a review. *Acta psychiatrica Scandinavica*. 2005;111(1):12-21.
2. Bowers L, Stewart D, Papadopoulos C, Dack C, Ross J, Khanom H, et al. Inpatient violence and aggression: a literature review. 2011.
3. de Bles NJ, Hazewinkel AWP, Bogers JPAM, van den Hout WB, Mouton C, van Hemert AM, et al. The incidence and economic impact of aggression in closed long-stay psychiatric wards. *International journal of psychiatry in clinical practice*. 2020:1-7.
4. Jones RM, Arlidge J, Gillham R, Reagu S, van den Bree M, Taylor PJ. Efficacy of mood stabilisers in the treatment of impulsive or repetitive aggression: systematic review and meta-analysis. *The British journal of psychiatry : the journal of mental science*. 2011;198(2):93-8.
5. Health NCCfM, editor Violence and Aggression: short-term management in mental health, health and community settings: updated edition2015: British Psychological Society.
6. Sarris J, Logan AC, Akbaraly TN, Amminger GP, Balanza-Martinez V, Freeman MP, et al. Nutritional medicine as mainstream in psychiatry. *The lancet Psychiatry*. 2015;2(3):271-4.
7. Parletta N, Milte CM, Meyer BJ. Nutritional modulation of cognitive function and mental health. *The Journal of nutritional biochemistry*. 2013;24(5):725-43.
8. Mörkl S, Wagner-Skacel J, Lahousen T, Lackner S, Holasek SJ, Bengesser SA, et al. The Role of Nutrition and the Gut-Brain Axis in Psychiatry: A Review of the Literature. *Neuropsychobiology*. 2020;79(1-2):80-8.
9. Popova NK. From gene to aggressive behavior: The role of brain serotonin. *Neuroscience and Behavioral Physiology*. 2008;38(5):471-5.
10. Crockett MJ, Clark L, Hauser MD, Robbins TW. Serotonin selectively influences moral judgment and behavior through effects on harm aversion. *Proceedings of the National Academy of Sciences*. 2010;107(40):17433-8.
11. Bjork JM, Dougherty DM, Moeller FG, Cherek DR, Swann AC. The effects of tryptophan depletion and loading on laboratory aggression in men: time course and a food-restricted control. *Psychopharmacology (Berl)*. 1999;142(1):24-30.
12. Coccaro EF, Kavoussi RJ. Fluoxetine and impulsive aggressive behavior in personality-disordered subjects. *Archives of general psychiatry*. 1997;54(12):1081-8.
13. Coccaro EF, Lee RJ, Kavoussi RJ. A double-blind, randomized, placebo-controlled trial of fluoxetine in patients with intermittent explosive disorder. *The Journal of clinical psychiatry*. 2009;70(5):653-62.
14. Rucklidge JJ, Kaplan BJ. Broad-spectrum micronutrient formulas for the treatment of psychiatric symptoms: a systematic review. *Expert Review of Neurotherapeutics*. 2013;13(1):49-73.
15. Zaalberg A, Nijman H, Bulten E, Stroosma L, van der Staak C. Effects of nutritional supplements on aggression, rule-breaking, and psychopathology among young adult prisoners. *Aggressive behavior*. 2010;36(2):117-26.

16. Gesch CB, Hammond SM, Hampson SE, Eves A, Crowder MJ. Influence of supplementary vitamins, minerals and essential fatty acids on the antisocial behaviour of young adult prisoners. Randomised, placebo-controlled trial. *The British journal of psychiatry : the journal of mental science*. 2002;181:22-8.
17. Schoenthaler S, Amos S, Doraz W, Kelly M-A, Muedeking G, Jr JW. The Effect of Randomized Vitamin-Mineral Supplementation on Violent and Non-violent Antisocial Behavior Among Incarcerated Juveniles. *Journal of Nutritional & Environmental Medicine*. 1997;7(4):343-52.
18. Schoenthaler S, Gast D, Giltay EJ, Amos S. The Effects of Vitamin-Mineral Supplements on Serious Rule Violations in Correctional Facilities for Young Adult Male Inmates: A Randomized Controlled Trial. *Crime & Delinquency*. 2021:0011128721989073.
19. Schoenthaler SJ, Bier ID. The effect of vitamin-mineral supplementation on juvenile delinquency among American schoolchildren: a randomized, double-blind placebo-controlled trial. *Journal of alternative and complementary medicine (New York, NY)*. 2000;6(1):7-17.
20. Long SJ, Benton D. A double-blind trial of the effect of docosahexaenoic acid and vitamin and mineral supplementation on aggression, impulsivity, and stress. *Human psychopharmacology*. 2013;28(3):238-47.
21. Tammam JD, Steinsaltz D, Bester DW, Semb-Andenaes T, Stein JF. A randomised double-blind placebo-controlled trial investigating the behavioural effects of vitamin, mineral and n-3 fatty acid supplementation in typically developing adolescent schoolchildren. *The British journal of nutrition*. 2016;115(2):361-73.
22. Adams JB, Audhya T, McDonough-Means S, Rubin RA, Quig D, Geis E, et al. Effect of a vitamin/mineral supplement on children and adults with autism. *BMC pediatrics*. 2011;11:111.
23. Rucklidge JJ, Eggleston MJF, Johnstone JM, Darling K, Frampton CM. Vitamin-mineral treatment improves aggression and emotional regulation in children with ADHD: a fully blinded, randomized, placebo-controlled trial. *Journal of child psychology and psychiatry, and allied disciplines*. 2018;59(3):232-46.
24. Raine A, Cheney RA, Ho R, Portnoy J, Liu J, Soyfer L, et al. Nutritional supplementation to reduce child aggression: a randomized, stratified, single-blind, factorial trial. *Journal of child psychology and psychiatry, and allied disciplines*. 2016;57(9):1038-46.
25. Sloane PD, Ivey J, Helton M, Barrick AL, Cerna A. Nutritional issues in long-term care. *Journal of the American Medical Directors Association*. 2008;9(7):476-85.
26. Maier L, Pruteanu M, Kuhn M, Zeller G, Telzerow A, Anderson EE, et al. Extensive impact of non-antibiotic drugs on human gut bacteria. *Nature*. 2018;555(7698):623-8.
27. Melnyk BM, Kelly SA, Stephens J, Dhakal K, McGovern C, Tucker S, et al. Interventions to Improve Mental Health, Well-Being, Physical Health, and Lifestyle Behaviors in Physicians and Nurses: A Systematic Review. *American Journal of Health Promotion*. 2020;34(8):929-41.
28. Nijman HLI, Muris P, Merckelbach HLGJ, Palmstierna T, Wistedt B, Vos AM, et al. The staff observation aggression scale–revised (SOAS-R). *Aggressive behavior*. 1999;25(3):197-209.
29. Morrison EF. Violent psychiatric inpatients in a public hospital. *Scholarly inquiry for nursing practice*. 1990;4(1):65-82; discussion 3-6.

30. Heinze C. Aggression und Gewalt bei psychiatrischen Patienten-eine Untersuchung mit der Staff Observation Aggression Scale-Revised (SOAS-R) an zwei Berliner Krankenhäusern: Diplomarbeit zur Erlangung des Grades einer Diplompflegepädagogin des …; 2000.
31. Palmstierna T, Wistedt B. Staff observation aggression scale, SOAS: presentation and evaluation. *Acta psychiatrica Scandinavica*. 1987;76(6):657-63.
32. Nijman H, Allertz W, Merckelbach H, Campo J, Ravelli D. Aggressive behaviour on an acute psychiatric admission ward. *European Legacy-toward New Paradigms*. 1997;11:106-14.
33. Steinert T, Woelfle M, Gebhardt RP. No correlation of serum cholesterol levels with measures of violence in patients with schizophrenia and non-psychotic disorders. *Eur Psychiatry*. 1999;14(6):346-8.
34. Steinert T, Wölfle M, Gebhardt RP. Measurement of violence during in-patient treatment and association with psychopathology. *Acta psychiatrica Scandinavica*. 2000;102(2):107-12.
35. Wistedt B, Rasmussen A, Pedersen L, Malm U, Traskman-Bendz L, Wakelin J, et al. The development of an observer-scale for measuring social dysfunction and aggression. *Pharmacopsychiatry*. 1990;23(6):249-52.
36. Kobes MH, Nijman HH, Bulten EB. Assessing aggressive behavior in forensic psychiatric patients: validity and clinical utility of combining two instruments. *Archives of psychiatric nursing*. 2012;26(6):487-94.
37. Buss AH, Perry M. The aggression questionnaire. *J Pers Soc Psychol*. 1992;63(3):452-9.
38. Hornsveld RHJ, Muris P, Kraaimaat FW, Meesters C. The Aggression Questionnaire in Dutch violent forensic psychiatric patients and secondary vocational students. *Assessment*. 2009;16:181-92.
39. De Vries J, Van Heck G. De Nederlandse versie van de WHOQOL-Bref.[The Dutch version of the WHOQOL-Bref]. Tilburg: Tilburg University; 1996.
40. Group W. Development of the World Health Organization WHOQOL-BREF quality of life assessment. *J Psychological medicine*. 1998;28(3):551-8.
41. Goekoop JG, Knoppert-Van der Klein EA, Hoeksema T, Klinkhamer RA, Van Gaalen HA, Van der Velde EA. The interrater reliability of a Dutch version of the Comprehensive Psychopathological Rating Scale. *Acta psychiatrica Scandinavica*. 1991;83(3):202-5.
42. Åsberg M, Montgomery S, Perris C, Schalling D, Sedvall GJAps. A comprehensive psychopathological rating scale. 1978;57(S271):5-27.
43. Montgomery SA, Asberg M. A new depression scale designed to be sensitive to change. *The British journal of psychiatry : the journal of mental science*. 1979;134:382-9.
44. Tyrer P, Owen R, Cicchetti D. The Brief Scale for Anxiety: A subdivision of the Comprehensive Psychopathological Rating Scale. *Journal of neurology, neurosurgery, and psychiatry*. 1984;47:970-5.
45. Benton D. The impact of diet on anti-social, violent and criminal behaviour. *Neuroscience and biobehavioral reviews*. 2007;31(5):752-74.
46. Legare N, Brosseau E, Joyal CC. Omega-3 and violence in schizophrenia. *Schizophr Res*. 2007;96(1-3):269.
47. Signorini, DAVID F. Sample size for Poisson regression. *Biometrika*. 1991;78(2):446-50.
48. Shepherd V. An under-represented and underserved population in trials: methodological, structural, and systemic barriers to the inclusion of adults lacking capacity to consent. *Trials*. 2020;21(1):445.

49. Correll CU, Yu X, Xiang Y, Kane JM, Masand P. Biological treatment of acute agitation or aggression with schizophrenia or bipolar disorder in the inpatient setting. *Annals of clinical psychiatry : official journal of the American Academy of Clinical Psychiatrists*. 2017;29(2):92-107.
50. Dinan TG, Cryan JF. Schizophrenia and the microbiome: Time to focus on the impact of antipsychotic treatment on the gut microbiota. *The World Journal of Biological Psychiatry*. 2018;19(8):568-70.
51. Qiao Y, Liu CP, Han HQ, Liu FJ, Shao Y, Xie B. No Impact of Omega-3 Fatty Acid Supplementation on Symptoms or Hostility Among Patients With Schizophrenia. *Frontiers in psychiatry*. 2020;11:312-.
52. Darrell-Berry H, Berry K, Bucci S. The relationship between paranoia and aggression in psychosis: A systematic review. *Schizophrenia Research*. 2016;172(1):169-76.
53. Georgieff MK, Ramel SE, Cusick SE. Nutritional influences on brain development. 2018;107(8):1310-21.
54. Long SJ, Benton D. Effects of vitamin and mineral supplementation on stress, mild psychiatric symptoms, and mood in nonclinical samples: a meta-analysis. *Psychosomatic medicine*. 2013;75(2):144-53.
55. Browning LM, Walker CG, Mander AP, West AL, Madden J, Gambell JM, et al. Incorporation of eicosapentaenoic and docosahexaenoic acids into lipid pools when given as supplements providing doses equivalent to typical intakes of oily fish. *The American journal of clinical nutrition*. 2012;96(4):748-58.
56. Steinert T, Hamann K. External validity of studies on aggressive behavior in patients with schizophrenia: systematic review. *Clin Pract Epidemiol Ment Health*. 2012;8:74-80.

Supplementary Material 1. Characteristics of psychiatric inpatients versus controls

	Psychiatric inpatients (n=21)	Controls (n=38)	*P* value[a]
Age in years, mean (*SD*)	40.0 (13.1)	46.7 (16.3)	0.11
Male gender, no (%)	14 (66.7%)	18 (47.4%)	0.12
Higher education, no (%)	5 (23.8%)	30 (78.9%)	< 0.001
BMI (kg/m^2), mean (*SD*)	26.9 (7.8)	24.4 (3.6)	0.11
Dutch Nationality, no (%)	14 (66.7%)	38 (100%)	< 0.001
Alcohol ≥ 14 U/wk, no (%)	1 (4.8%)	12 (31.6%)	0.02
Current smoker, no (%)	21 (100%)	15 (39.5%)	< 0.001
Recreational drugs, no (%)	8 (38.1%)	0 (0%)	< 0.001
Unmarried, no (%)	21 (100.0%)	10 (26.3%)	< 0.001
Physically active, no (%)	5 (23.8%)	18 (47.4%)	0.07
Psychotropic use, no (%)	21 (100.0%)	0 (0.0%)	< 0.001

Note. Data are number of participants (with percentages in parentheses) or means (with standard errors in parentheses). BMI=Body Mass Index.

[a] Chi-square values have been computed for categorical variables, t-test for independent samples for interval variables.

Supplementary Material 2. Comparison of dietary intake of food groups and micro(nutrients) in psychiatric inpatients versus controls

	Psychiatric inpatients (n=21)	Controls (n=38)	Adjusted Mean difference	*P* value[a]
Total caloric intake[b]	1700 (120.8)	2016 (90.7)	−316 (−620; −13)	< 0.001
Total protein, g	69.0 (2.9)	72.6 (2.1)	−3.71 (−11.4; 3.96)	0.34
Vegetable protein, g	31.9 (1.7)	30.9 (1.2)	1.00 (−3.34; 5.34)	0.65
Animal protein, g	37.1 (3.0)	41.7 (2.2)	−4.65 (−12.6; 3.27)	0.24
Total fat, g	62.3 (2.6)	63.7 (1.9)	−1.32 (−8.09; 5.45)	0.70
Saturated fatty acids, g	23.6 (1.2)	23.8 (0.8)	−0.19 (−3.23; 2.84)	0.90
Monounsaturated fatty acids, g	20.7 (1.1)	22.4 (0.8)	−1.71 (−4.57; 1.15)	0.24
Poly unsaturated fatty acids, g	12.1 (0.9)	11.2 (0.7)	0.90 (−1.55; 3.36)	0.47
Trans fatty acids, g	1.22 (0.1)	1.48 (0.1)	−0.26 (−0.49; −0.03)	0.03
a-Linolenic acid (ALA, mg)	0.98 (0.1)	0.94 (0.01)	0.04 (−0.13; 0.20)	0.68
Eicosapentaenoic acid (EPA, mg)	0.02 (0.02)	0.06 (0.01)	−0.04 (−0.08; 0.001)	0.056
Docosahexaenoic acid (DHA, mg)	0.04 (0.02)	0.10 (0.02)	−0.06 (−0.12; -0.004)	0.035
Cholesterol, mg	140 (12)	200 (8.6)	−60.8 (−92.2; −29.5)	< 0.001
Total carbohydrates, g	262 (7.9)	224 (5.6)	38.1 (17.6; 58.7)	< 0.001
Total mono and disaccharides, g	149 (6.8)	105 (4.8)	44.1 (26.4; 61.7)	< 0.001
Total polysaccharides, g	112 (6.0)	119 (4.3)	−6.32 (−21.9; 9.31)	0.42
Total dietary fibre, g	20.7 (1.3)	23.2 (0.9)	−2.53 (−6.00; 0.92)	0.15
Calcium (mg)	919 (78.5)	857 (56.1)	62.2 (−143; 267)	0.55
Iron (mg)	11.2 (0.5)	11.7 (0.3)	−0.50 (−1.71; 0.72)	0.41
Zinc (mg)	7.8 (0.4)	9.0 (0.3)	−1.17 (−2.21; −0.12)	0.03
Copper (mg)	2.6 (0.3)	1.3 (0.2)	1.25 (0.58; 1.92)	< 0.001
Magnesium (mg)	327 (13.6)	336 (9.7)	−9.18 (−44.7; 26.3)	0.61
Selenium (µg)	34.1 (1.9)	43.2 (1.4)	−9.15 (−14.2; −4.06)	0.001
Iodine (µg)	27.0 (3.2)	46.1 (2.3)	−19.1 (−27.5; −10.7)	< 0.001
Vitamin A (retinol, mg)	305 (136.3)	624 (97.4)	−319 (−675; 37.5)	0.08
Beta carotene (g)	2.50 (0.2)	2.03 (0.2)	0.47 (−0.14; 1.08)	0.13
Thiamin (vitamin B1,mg)	1.03 (0.1)	1.14 (0.0)	−0.11 (−0.25; 0.03)	0.12
Riboflavin (vitamin B2,mg)	1.41 (0.1)	1.30 (0.1)	0.11 (−0.15; 0.36)	0.40
Niacin (Vitamin B3, mg)	15.4 (0.9)	18.4 (0.7)	−2.97 (−5.35; −0.59)	0.02
Pyridoxine (vitamin B6, mg)	1.35 (0.1)	1.70 (0.0)	−0.36 (−0.54; −0.18)	< 0.001
Folates naturally occurring,(µg)	198 (11.6)	201 (8.3)	−2.89 (−33.2; 27.4)	0.85
Cobalamin (vitamin B12, µg)	3.18 (0.5)	4.23 (0.4)	−1.05 (−2.42; 0.33)	0.13
Vitamin C (mg)	106 (9.1)	97.8 (6.5)	8.36 (−15.4; 32.1)	0.48
Vitamin D (µg)	1.74 (0.3)	2.57 (0.2)	−0.83 (−1.49; −0.16)	0.02
Vitamin E (mg)	9.45 (0.7)	9.35 (0.5)	0.10 (−1.75; 1.95)	0.91

Data are (adjusted) means (with standard errors in parentheses) and adjusted mean differences (with 95% confidence intervals in parentheses). Adjusted values were calculated with analysis of variance adjusted for gender, age, BMI, and total caloric intake.

Supplementary Material 4. Doses of previous studies including the current study

	Previous studies									
	Schoenthaler 1997	Schoenthaler 2000	Gesch 2002	Zaalberg 2010	Adams[a] 2011	Long 2013	Tammam 2016	Raine 2016	Rucklidge[b] 2018	PSYVA
Minerals										
Potassium (mg)			4	4	50	40		40	192	
Calcium (mg)	122	200	100	100	100	162		162	1056	
Manganese (mg)	3	1	3	3	3	2	2	2	7.7	**5**
Iron (mg)	18	9	12	12		5	12	7.2	10.8	**8**
Zinc (mg)	15	8	15	15	12	5	15	8.3	38.4	**7.5**
Copper (mg)	2	1	2	2		0.5	1	0.9	5.8	**0.5**
Magnesium (mg)	59	80	30	100	100	100	94	20	480	
Molybdenum (µg)	250	120	250	250	150	50			120	**13**
Selenium (µg)	100	50	50	50	22	30	55		168	**75**
Chromium (µg)	100	50	200	200	70	40	50		504	**13**
Iodine (µg)	150	75	140	140	100	100	130	160	163	**150**
Lithium (µg)					500					
Sulfur (mg)					500					
Phosphorus (mg)						125			672	
Chloride (mg)						36.3				
Vitamins										
A (Retinol, mg)	1.5	0.75	0.75	0.75	0.6	0.8	0.4	0.8	1.4	
A (Beta carotene, mg)		–	–	0.13						**6**
B1 (Thiamin, mg)	4.5	0.75	1.2	1.2	20	1.4	6	1.4	48	**15**
B2 (Riboflavin, mg)	5.1	0.9	1.6	1.6	20	1.75	3	1.75	14.4	**15**
B3 (Niacinamide, mg)	60	10	18	18	25	20	18	20	72	**20**
B5 (Pantothenic acid, mg)	30	5	4	4	15	7.5	6	7.5	24	**15**
B6 (Pyridoxine, mg)	30	1	2	2	40	2	8	2	56	**5**
Folic acid / B11 (µg)	400	200	400	400	100	200	400	200	640	**400**
B12 (Canocobalamin, µg)	18	3	3	3	500	2.5	15	2.5	720	**25**
Biotin (µg)		150	100	100	150	62.5	75		864	**25**
C (Ascorbic acid, mg)	120	40	60	60	600	100	80	100	480	**100**
D3 (Cholecalciferol, µg)	5	5	10	5	7.5	5	20	5	60	**25**
E (D-alpha-tocopherol, mg)	80	10	10	10	270	15	8	15	200	**53**
K (µg)	50	50				30		30	96	
Other										
Inositol (mg)	40				100				144	
Benzoic acid (mg)	50									
Choline (mg)	40				250				*432*	
Fatty acids										
Linoleic acid (mg)			1260			10		400		
***γ*-Linolenic acid (mg)**			160	100						
EPA (mg)			80	400			165	200		**329**
DHA (mg)			44	400		673	116	300		**219**

[a] Dosage was adjusted based on baseline measured body weight up to a maximum of 100 lbs. The dosage shown is for a 60 lbs child.

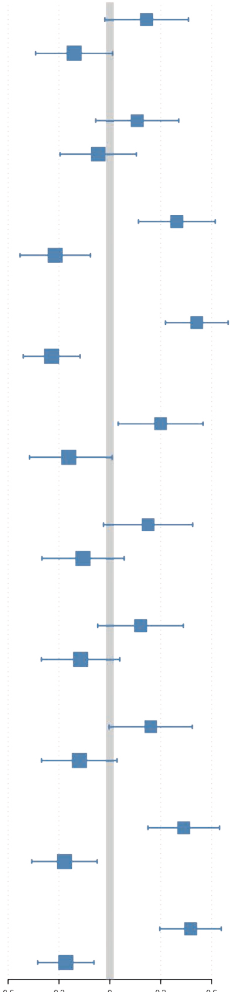
[b] Target dose was based on the response rates.

Supplementary Material 5. Average costs (in €) per patient year, by randomization group

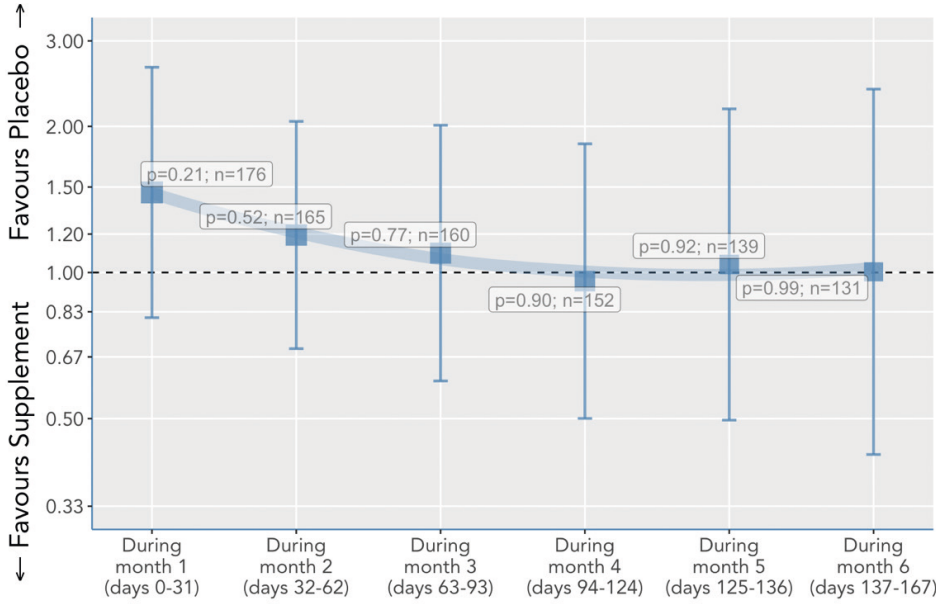
	Supplementation		**Placebo**		**Difference**	
	Frequency	Costs	Frequency	Costs	Costs	*p* value
Supplements[a]		314		0	314	-
Distribution		79		0	79	-
Total intervention costs		**393**		**0**	**393**	-
Verbal incidents	3.9	197	2.3	114	83	0.16
Physical against objects	1.4	122	0.9	76	46	0.20
Physical self-harm	1.9	223	1.9	224	-1	0.99
Physical against others	15.2	2,985	16.5	3,241	-256	0.79
Total aggression costs	**22.4**	**3,526**	**21.5**	**3,655**	**-128**	0.90
Total healthcare costs		**3,919**		**3,655**	**264**	**0.81**

[a] Reported costs are for the supplements used in the study. Less expensive supplements are available for €69 per patient year

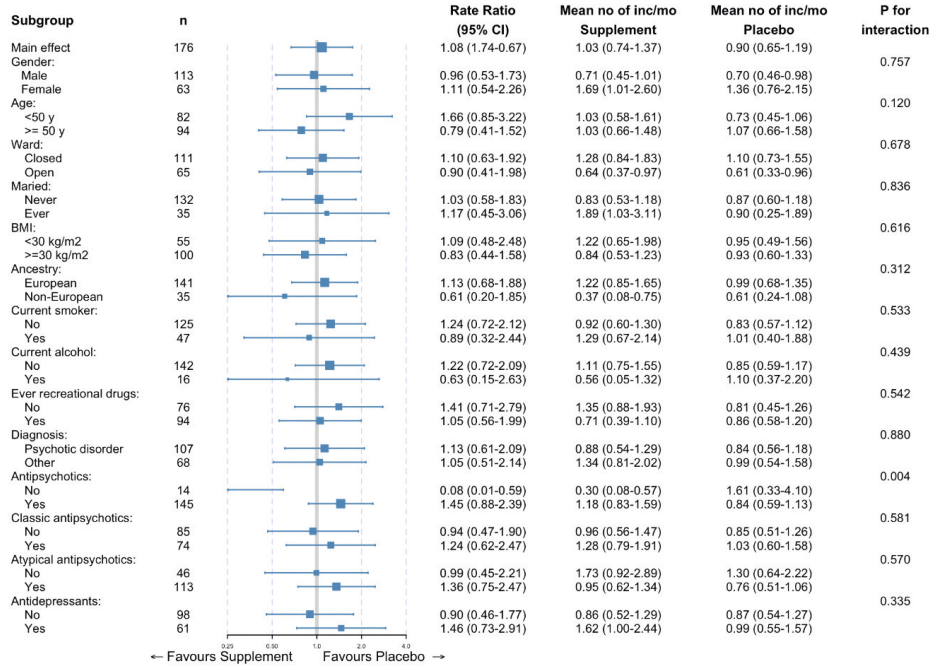
Micronutrient	n	Baseline (mean ± SE)	n	Follow-up (mean ± SE)	Test for interaction (time * group)
Vitamin A (µmol/L):					
Supplement	45	2.45 ± 0.10	33	2.68 ± 0.12	F(df. 1) = 3.68; P = 0.06
Placebo	52	2.26 ± 0.10	44	2.21 ± 0.10	
Vitamin B1 (nmol/L):					
Supplement	44	13.2 ± 1.7	32	19.3 ± 2.0	F(df. 1) = 2.74; P = 0.10
Placebo	49	13.2 ± 1.6	41	14.1 ± 1.7	
Vitamin B6 (nmol/L):					
Supplement	45	86.7 ± 9.89	33	129.0 ± 11.5	F(df. 1) = 7.97; P = 0.005
Placebo	51	59.6 ± 9.29	43	51.8 ± 10.1	
Folic Acid (nmol/L):					
Supplement	44	10.4 ± 1.1	33	26.8 ± 1.2	F(df. 1) = 53.40; P < 0.001
Placebo	52	10.3 ± 1.0	44	10.5 ± 1.1	
Vitamin B12 (pmol/L):					
Supplement	44	439 ± 28.2	33	547 ± 30.9	F(df. 1) = 4.22; P = 0.04
Placebo	52	367 ± 26.0	44	397 ± 27.4	
Vitamin D3 (nmol/L):					
Supplement	44	98.5 ± 6.0	33	112.0 ± 6.5	F(df. 1) = 2.86; P = 0.09
Placebo	52	88.0 ± 5.6	44	89.7 ± 5.8	
Vitamin E (µmol/L):					
Supplement	45	27.9 ± 1.2	33	32.5 ± 1.3	F(df. 1) = 5.17; P = 0.02
Placebo	52	27.0 ± 1.1	44	27.5 ± 1.2	
Iron (µmol/L):					
Supplement	44	16.2 ± 0.9	33	17.5 ± 1.0	F(df. 1) = 2.34; P = 0.13
Placebo	52	14.8 ± 0.8	44	13.9 ± 0.9	
EPA (mass%):					
Supplement	45	0.80 ± 0.08	33	1.64 ± 0.09	F(df. 1) = 20.85; P < 0.001
Placebo	52	0.65 ± 0.07	44	0.92 ± 0.07	
DHA (mass%):					
Supplement	45	2.85 ± 0.15	33	5.20 ± 0.17	F(df. 1) = 24.09; P < 0.001
Placebo	52	2.42 ± 0.14	44	3.56 ± 0.15	



Supplementary Material 6. Changes in micronutrient levels between supplementation and placebo
Note. Reference values as used by the LUMC: Vitamin A=0.7 – 2.6; Vitamin B1=78 – 143; Vitamin B6=51 – 183; Folic acid=8.8 – 60.8; Vitamin B12=150 – 700; Vitamin D=50 – 250; Vitamin E=16.0 – 41.0; Iron=♂ 14 – 35; Iron = ♀ 10 – 25.



Supplementary Material 7. Effect on aggressive incidents over time during 6 months of supplementation



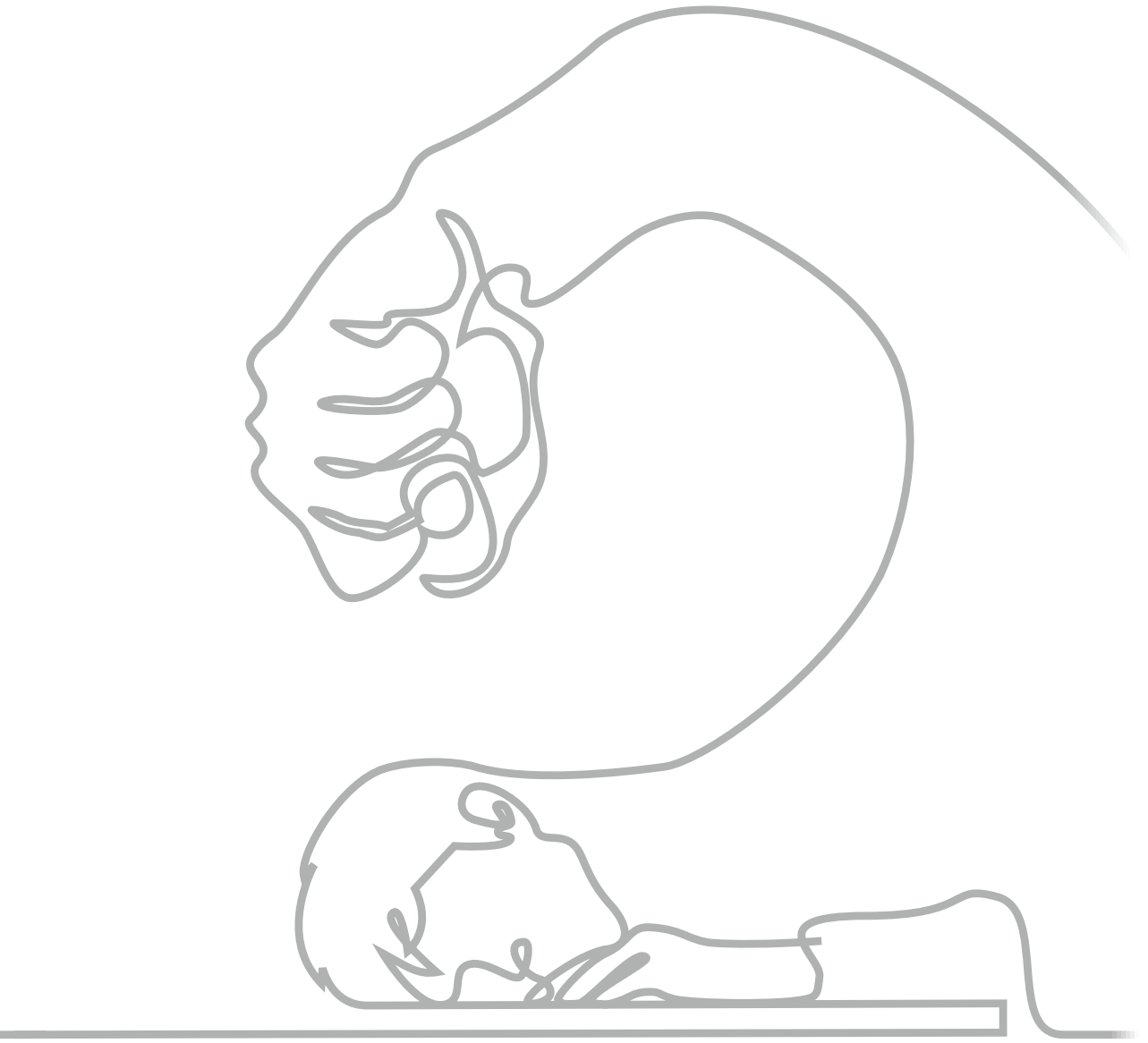
Supplementary Material 8. Subgroup analyses of the effect of supplementation on aggressive incidents according to demographic and clinical data

Supplementary Material 9. Adverse effects in both groups

Side effect	Placebo	Supplements	*p* value
Any side effect, no (%)	15 (20.5%)	17 (23.0%)	0.72
Nauseous, no (%)	4 (5.6%)	2 (2.7%)	0.39
Diarrhea, no (%)	3 (4.2%)	6 (8.2%)	0.31
Burping, no (%)	2 (2.8%)	8 (11.1%)	0.049
Tiredness, no (%)	3 (4.2%)	4 (5.5%)	0.71
Rash, no (%)	0 (0.0%)	4 (5.5%)	0.04
Headache, no (%)	3 (4.2%)	3 (4.1%)	0.99
Sleep problems, no (%)	2 (2.8%)	3 (4.1%)	0.66
Weight gain, no (%)	2 (2.8%)	2 (2.7%)	0.99
Weight loss, no (%)	3 (4.2%)	1 (1.4%)	0.30
Other, no (%)	5 (6.9%)	3 (4.1%)	0.44

Published as: de Bles, N. J.*, Gast, D. A.*, van der Slot, A. J., Didden, R., van Hemert, A. M., Rius-Ottenheim, N., & Giltay, E. J. (2022). Lessons learned from two clinical trials on nutritional supplements to reduce aggressive behaviour. *Journal of evaluation in clinical practice.*
* Joint first author.

8 Lessons learned from two clinical trials on nutritional supplements to reduce aggressive behaviour



Abstract

Background: Setting up and conducting a randomised controlled trial (RCT) has many challenges—particularly trials that include vulnerable individuals with behavioural problems or who reside in facilities that focus on care as opposed to research. These populations are underrepresented in RCTs.

Approach: In our paper, we describe the challenges and practical lessons learned from two RCTs in two care settings involving long-stay psychiatric inpatients and people with intellectual disabilities. We describe five main difficulties and how these were overcome: (1) multisite setting, (2) inclusion of vulnerable participants, (3) nutritional supplements and placebos, (4) assessment of behavioural outcomes, and (5) collecting bio samples.

Conclusions: By sharing these practical experiences, we hope to inform other researchers how to optimally design their trials, while avoiding and minimising the difficulties that we encountered, and to facilitate the implementation of a trial. Both trials were registered in the Clinical Trials Register (RCT A: NCT02498106; RCT B: NCT03212092).

Introduction

Conducting clinical trials presents many challenges. We performed two pragmatic randomised clinical trials (RCTs) to determine the effectiveness of nutritional supplements to reduce aggression among two populations: (1) psychiatric patients who resided at long-stay wards within mental health care organisations (RCT A) and (2) people who received care for their intellectual disabilities (IDs; RCT B). We hope that by sharing the difficulties that we encountered and the ways in which we dealt with these challenges, we may help future researchers who want to set up similar trials.

RCTs are considered to provide evidence for the effectiveness of a particular treatment [1]. Unfortunately, vulnerable individuals with behavioural problems are underrepresented in RCTs, resulting in a lack of evidence-based care for these groups [2]. For example, the prescription of antipsychotics as behavioural medication among people with IDs is widespread. However, the evidence for the efficacy of this policy is meagre and has been extrapolated from research on other populations [3, 4]. Another example is the guidelines for treatment of aggression among patients with schizophrenia; these guidelines are based on RCTs whose generalisability is questionable [5]. Because treatments for aggressive behaviour are used on vulnerable populations within long-term care, the RCTs should also take place within these populations and settings [6].

Aggressive behaviour frequently occurs among psychiatric patients [7] and people with IDs [8]. A substantial number of individuals admitted to long-term facilities (e.g., psychiatric patients or people with IDs) may express aggressive behaviours not only as the reason for admission but also as a consequence thereof. Aggressive acts range from mild verbal incidents, such as screaming or swearing, to more severe incidents, such as physical violence and self-harm [9-11]. The burden of these incidents lies not only with care professionals, often causing distress and sick leave, but also with other admitted individuals and perpetrators themselves [12-14]. There is a need for evidence-based treatment options to reduce aggression among these populations.

To address this need, we designed two RCTs involving long-stay psychiatric inpatients and people with IDs. Facilities where these individuals reside, however, generally focus on care rather than research and often have no existing infrastructure to enable clinical research. While conducting the two studies, we encountered many challenges and arranged these into five main topics: (1) multisite setting, (2) inclusion of vulnerable participants, (3) nutritional supplements and placebos, (4) assessment

of behavioural outcomes, and (5) collecting bio samples. In this study, we describe the challenges we encountered and how these challenges were overcome.

Multisite setting

RCT A and RCT B were set up as multisite randomised double-blind placebo-controlled pragmatic intervention studies, which aimed to include 200 participants each. The multisite setting of both trials was necessary to meet their sample size requirement. In addition, a multisite setting features better external validity, which may result in findings that are more generalisable across different settings and circumstances [15, 16]. Despite the advantages, multisite studies tend to be more complicated to conduct compared to single-site studies. It is necessary to take these complexities into account from the start of the design of a trial.

Challenges and lessons learned

Most sites highly valued both their involvement and our research goals; however, we encountered several barriers, including the recruitment of sites and their internal coordination of the study.

Although it is often hard to recruit participants in regular trials, it can be just as hard (or even harder) to recruit sites [17]. First, most sites had no research infrastructure. Thus, some personnel were somewhat reluctant to participate because of the anticipated extra workload. Additionally, the reluctance to participate was sometimes caused by reorganisations within some of the sites. As a consequence, we had to approach far more organisations than we had initially anticipated. In our experience, the time it took from our first contact with the organisation to the time the first participants could be included from that site was 1 year (or more). This lengthy process was due to the formal paperwork we needed to obtain the approval by management and the research committees.

Once our sites were recruited, an additional challenge was to involve a coordinator from the institution to help us run the study from the inside. To help us reach our goals, it was important that the inside coordinators had a coordinating function but (more important) that they were also helpful, approachable, and motivated to support the execution of the study—a research champion. A previous study (partially) reimbursed the hours local coordinators spent on the trial [18]. In RCT B, we did this by paying a fixed amount to a few selected sites for every completed data(set) but doing so did not always lead to higher motivation in local personnel. Another way in which

we promoted the engagement of local coordinators was by offering co-authorship when a certain number of participants per site were successfully included. Of course, co-authorship was only possible in cases were the co-author also made significant scientific contributions to the final manuscript. Unfortunately, this arrangement did not seem to result in a faster or higher recruitment rate.

During the study, we found that consistent personal contact with the care professionals at the sites was essential to maintain motivation. To this end, the RCT A team travelled to the locations every week, and the RCT B team maintained high-frequency contacts via telephone and e-mail.

There were three main lessons that we learned from our experiences with the multisite settings. First, recruiting multiple sites is time-consuming [17], which should be taken into account in the time-management plan of the trial. Second, it is crucial to invest in local coordinators who are intrinsically motivated—often called 'champions' [18-22]. And third, frequent (preferably face-to-face) contact with the champions and with the other care professionals is important to keep the sites engaged.

Inclusion of vulnerable participants

The inclusion of participants with aggressive behavioural problems poses additional difficulties [23]. Such individuals tend to be less cooperative and are less likely to be included in clinical trials.5 Thus, vulnerable individuals with chronic behavioural problems are often neither willing nor able to give informed consent. We aimed to include participants with psychiatric diagnosis, or ID, who had behavioural problems. Moreover, we also included minors in RCT B, which resulted in extra challenges. In general, individuals who lack the capacity to provide autonomous consent to participate in a study have often been excluded from clinical trials [2]. Yet, the topic deserves our attention because of the effects on the well-being of patients themselves, their potential victims, society at large, and the economic costs [7, 24, 25].

According to the European Guideline for Good Clinical Practice, researchers are required to give the potential participant a declaration of consent (or 'informed consent'), which must comply with strict requirements. For instance, the declaration must stipulate the research involved and what the participant is giving permission for (https://english.ccmo.nl/human-subjects/informed-consent). Thus, we had to state the goals of both trials in a manner that suited individuals' level of intellectual ability. For individuals who were (at that moment) incapable of giving consent, a legally authorised representative had to provide consent.

Challenges and lessons learned

During the recruitment, we encountered challenges in recruiting people with aggressive behaviour and in gaining their informed consent.

First, we used the words 'aggressive behaviour' in the title of the study and in the information leaflets; as a direct result, many potential participants refused to participate because they did not associate themselves with aggression. To counteract this negative association, we selected a broader and less stigmatising term 'challenging behaviour' instead of 'aggression' when communicating with the sites in RCT B.

Second, it is important to realise that recruiting vulnerable participants is time-consuming.2 A systematic review of 33 studies on aggressive behaviour in schizophrenia reported a recruitment period of 3 years on average, with a mean sample size of 93 [5]. A main reason is that individuals with aggressive or challenging behaviour generally seem less willing to participate in trials. As a consequence, less aggressive participants were more often included in RCT A than their more aggressive counterparts, leading to a large proportion of participants showing less than three aggression incidents during the trial (46%). Unlike the RCT A trial, participants in the RCT B study were screened for their aggression levels in the run-in phase of the study and were excluded for randomisation if they did not show an aggression frequency above a certain threshold.

A third challenge was the process of informed consent and how to transfer knowledge to the potential participants, whose cognitive abilities were often poor. For RCT B, we designed an animation (https://www.youtube.com/watch?v=49wDsOYIxsY) to explain the aim of the study in a way that was understandable to participants with mild IDs and borderline intellectual functioning (IQ 50–85). Even so, not all participants had the capacity to provide written informed consent. In RCT A, the treating psychiatrist assessed a patient's capacity. In cases where a participant was unable to give informed consent, a relative or legal representative was needed to give consent (https://english.ccmo.nl/investigators/legal-framework-for-medical-scientific-research/wmo-protection-human-subjects-central/consent). In RCT B, a relative or legal representative had to provide written informed consent in most cases. All procedures complied with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008. Both trial protocols were approved by the Medical Ethical Committee of the Leiden University Medical Centre (LUMC).

Three main lessons can be learned from our experiences with recruiting vulnerable participants. First, we recommend avoiding the use of potentially stigmatising

terms, such as 'aggression' or 'violence', in the study's description or communication. Researchers in a study on interpersonal violence recommended framing the research question in a nonstigmatizing way (i.e., using a nonthreatening and positive theme) [26]. Second, we advise researchers to screen participants for entry level of the outcome variable to avoid recruiting participants who show little to no aggression; be aware that the recruitment of more aggressive participants is time consuming. Third, researchers should compose information materials tailored to participants with IDs and should including patient representatives and local care professionals during the design phase.

Nutritional supplements and placebos

Nutritional supplements are a special type of intervention for RCTs. RCTs require successful blinding, and the choice of the placebo is not as straightforward as it may seem [27]. To achieve its purpose, a placebo needs to match the sensory characteristics of the active supplements. This includes visual aspects of the capsules (i.e., shape, size, colour, and texture) as well as their weight, taste, and odour. Any sensory differences between the two capsules may impede the blinding [28]. To address this issue, we used placebo and verum that were made using the same procedures in the same factory (MCO Health for RCT A; Bonusan for RCT B). This resulted in a placebo that was largely indistinguishable from the verum in terms of appearance.

Another aspect in the selection of a nutritional supplement and its placebo concerns the characteristics of the supplements, such as size and shape (swallowability), which can cause participants to drop out of the study [29]. Therefore, we used soft gel capsules to deliver the supplements in RCT A; gel capsules are known to be relatively easy to swallow and may help to mask unpleasant tastes and odours [30]. In RCT B, the multivitamin and mineral capsules from the factory were large, and during the preparation of the trial, they proved difficult to swallow for some participants. To increase swallowability, we crushed the tablets and filled the content of a single tablet into two opal-coloured placebo capsules (Size 0). The 2-week run-in phase before randomisation (using placebo capsules) helped us to select participants who were willing and able to swallow the supplements.

Challenges and lessons learned

We encountered several challenges before achieving successful blinding and a low dropout rate.

First, both trials aimed to use indistinguishable supplements, but this was only partly possible. We succeeded in designing similar supplements regarding the visual characteristics (texture and weight); however, the odour and taste of some of the active ingredients proved difficult to mask [31]. To match the odour of the placebo with the active supplements in RCT B, we added vanilla-scented silica gel sachets to all of the jars.

A second challenge was that the active ingredients could have caused physical changes in participants, which could have hampered the blinding. One of the most common and unpleasant sensations in trials with omega-3 is dysgeusia due to the fishy taste [32]. This could explain why a relatively high percent of participants were able to guess their randomisation group in many previous studies on the effects of fish oil [33, 34]. Furthermore, vitamin B2 (riboflavin) may give urine a typical dark yellow/orange colour [35]. Odour and urine discoloration can be simulated by adding a small amount of riboflavin to the placebo [36]. Therefore, the RCT B multivitamin placebo contained 10% (0.8 mg) of the riboflavin dose of an active capsule. At the end of RCT B, the participants and care professionals were not able to guess the group assignment above chance level. In RCT A, we did not take these precautions to improve the blinding. As a result, burping was slightly (though significantly) more often reported by participants in the intervention group compared to the placebo group, but the majority of participants and nurses could not guess the condition to which the participants had been assigned.

A third problem concerned swallowability. Problems in swallowing the supplements, combined with characteristics such as odour and taste, could cause participants to drop out from the study [37]. The dropout rate among children in a previous fish-oil study ranged from 0% to 58% [29]. We used a 2-week run-in phase to lower such initial dropout rates due to swallowing problems. In addition, we reminded participants in the protocol that the supplements should be taken with meals, which reduced the chance of a fishy aftertaste [38]. We noticed during the trial that some participants had difficulty taking the supplements daily. During the trial, however, we could not change the intervention. We therefore recommend a feasibility study to test how best to administer the supplement for the specific target population. There are several options besides capsules, such as liquids [39], chewable tablets with a tasty flavour [40], or food products containing the active ingredients (e.g., drinks, margarine, and eggs), which are also called 'functional foods' [41].

Problems concerning blinding methodology and selective dropout are common in diet-related research [42]. Based on our experiences, there were three main methods to tackle these problems. First, adding vanilla-scented silica gel sachets to the jars containing the supplements helped to mask the odour. Second, researchers should select the appropriate supplement form to aid the administration to the target population. Third, researchers should advise participants to take the capsules during their meals. An option that we could have considered was to offer participants a swallowing course [43].

Assessment of behavioural outcomes

The main objective of both trials was to assess whether nutritional supplementation could reduce aggression incidents. There are different ways to measure aggression, and it is important that the measurement tools are valid and reliable. Both studies defined aggression as 'any verbal, nonverbal, or physical behaviour that was threatening (to self, others, or property) or physical behaviour that actually did harm (to self, others or property)' [44]. Aggression can be assessed through self- and observer-rated scales. Most of our participants suffered from limited intellectual and self-reflective capacities and were therefore less capable of completing self-report scales accurately. Thus, as a primary outcome, we chose observer-rated scales, which is the preferred method to investigate state aggression [45]. In RCT A, we assessed the number of aggression incidents using the Staff Observation Aggression Scale-Revised (SOAS-R) [46]. The SOAS-R is a quick and easy-to-use tool and is used in psychiatric settings worldwide [47]. In RCT B, we assessed aggression using the Modified Overt Aggression Scale (MOAS) [48], which is used to monitor different types of aggressive behaviours in studies among adults with IDs [49].

Challenges and lessons learned

There were three main challenges regarding the assessment of behavioural outcomes, including the operational observation of aggression, unreported incidents, and the high turnover of staff.

First, although both trials specified the definition of aggression, care professionals are regularly exposed to aggressive behaviour and may be desensitised to more subtle aggression. It may not be apparent to a seasoned care professional to consider an incident a form of aggression. A problem with measuring aggression in RCT B was that care professionals looked at the objective behaviour as well as the intention of

the behaviour. They believed that behaviour without intention to cause harm should not be considered aggression. However, intentions are not always clear among participants with IDs, and some behaviour could be a way of seeking attention instead of harming someone (e.g., throwing crockery). During the pretraining, we emphasised that care professionals had to report the objective behaviour, not their interpretation of the behaviour.

Second, we noticed that a worrisome amount of aggression incidents was not documented. We posit two main reasons why these incidents were underreported. First, care professionals may have become hardened by the frequent occurrence of mild to moderate incidents and thus were less likely to report them. Second, care professionals indicated that when their workload increased, sometimes as a consequence of aggression, reporting incidents could be given a lower priority [50]. These unreported incidents were difficult to monitor in RCT A due to the use of the incident-based SOAS-R. When no incidents were recorded during a certain time interval, we could not assess whether this was because no incidents had taken place or because nothing had been reported. In RCT B, we used the time-based MOAS scale, which allowed us to monitor whether all time intervals were reported [51]. To reduce underreporting in each trial, research assistants performed weekly monitoring by visiting the local site (RCT A) or by contacting the site via phone or email (RCT B). Because the risk of underreporting is highest for mild-to-moderate verbal aggression [52], we asked care professionals specifically whether these incidents had occurred since our last contact. If the answer was yes, care professionals were asked to fill in the SOAS-R or MOAS for that incident.

Last, the high turnover of care professionals was a problem [53] because information acquired through an observational scale is based on the capacities, experiences, and opinions of care professionals and thus vulnerable to subjectivity and measurement error. To ensure validity and accuracy, we provided (new) care professionals in each study with an interactive SOAS-R or MOAS training module before the start of the trial to improve accuracy and precision. In RCT B, we even created an e-learning platform to provide new personnel with a standard form of training.

There are three main lessons to be learned from our experiences regarding the assessment of behavioural outcomes. First, researchers should use a scale that can easily monitor aggressive behaviour and that is validated to assess the outcome in the specific study population. Second, setting up a monitoring plan at regular intervals can help researchers to detect and to reduce underreporting of incidents. Third, we encourage researchers to train (new) care professionals continuously throughout the trial phase to calibrate the assessments of the care professionals [54].

Collecting bio samples

In both studies, we collected a series of bio samples. In RCT A, we collected blood samples to determine compliance. In RCT B, we collected faecal samples to assess the effects on participants' microbiomes.

Biomarkers are more reliable than self-reports in measuring compliance [55]. In RCT A, we collected blood samples to measure the concentration of vitamins, minerals, and a fatty acid spectrum, which yielded participants' n-3 FA levels. We collected two tubes (1 serum separator [SST] and 1 ethylenediaminetetraacetic acid [EDTA] tube) before and after the trial. The blood samples were taken by trained care professionals from the local laboratory appointed to each institution. Most sites had a fixed morning once a week during which blood was collected. In RCT A, the blood samples were sent to the laboratory via regular mail within 24 h. Mailing blood samples offered a cost-effective approach, which we found to be true in a previous study from our group [56]. During the two studies in question, we reliably found the essential n-3 PUFAs in EDTA plasma after next-working-day mail delivery. Indeed, vitamins have been shown to be stable after delayed whole-blood processing among various temperatures and storage time [57,58].

In RCT B, we took faecal samples before and after the trial to measure the effect of nutritional supplements on the microbiome and to assess whether the changes of the microbiome mediated the effect of nutritional supplements on aggressive behaviour. For the collection of the faecal samples, we developed a sample manual with simple text and images (see Supplementary Material 1). The samples were frozen on site (–20°C), after which the researcher used a small portable freezer to transfer the samples to a –80°C freezer at the LUMC, where they were stored until analysis. Sequencing the 16s rRNA gene is still the most widely used method for gut microbiome analysis because the financial costs are lower than that of whole-genome metagenomic analysis [59]. The disadvantage is that the cheaper method provides less information regarding the level of genus, species, and strains, but only of the higher taxa such as family, order, class, and phyla.

Challenges and lessons learned

For biomarkers, there were several challenges regarding the sampling procedure and the transport of the samples. Separate consent was required for the collection of bio samples, but participants who did not consent to donating bio-samples were still eligible to participate.

First, the blood samples did not always arrive at our laboratory on time, which was due to several reasons. Because of the high turnover of care professionals, the envelope with blood samples (RCT A) was regularly forgotten by care professionals. To reduce this error, it was important to contact care professionals from the site where the participant resided and to communicate directly with the local laboratory. Furthermore, it was important that blood was collected Monday through Thursday because samples needed to be processed on working days. When the baseline samples did not arrive on time, the participant had to postpone the start of the trial and wait for the next opportunity. Belgian institutions could not participate in blood collection because the mail delivery from Belgium took more than 24 h to reach the laboratory.

Second, freezing faeces (RCT B) directly at −20°C regularly resulted in practical challenges because the participants resided at 69 different locations (far more than we had anticipated), and each participant had to produce two samples. Using portable freezers to reach every location was not feasible, so we had to use freezers that were available on site, which was often difficult to arrange. So, even with proper preparation, the logistics of faecal-sample collection can be complex and time consuming. Therefore, we advise researchers to opt for methods that are straightforward.

Based on our experiences, there were three main lessons in collecting biomarker outcomes. Investing in strong collaboration with the local laboratory and care professionals is important when taking blood samples. When collecting faecal samples, it is essential to distribute a manual that the target group can understand. And when choosing a specific bio sample, it is important to consider the feasibility of the necessary logistics.

Conclusions

Conducting a successful RCT among vulnerable populations presents unique challenges, which we have discussed in detail. These trials were conducted in long-term wards for psychiatric inpatients and people with IDs. Such studies are essential to help develop new evidence-based treatment options. Facilities where these individuals reside, however, generally focus on care rather than research and often have no existing infrastructure to enable clinical research. Yet, both RCT A and RCT B successfully recruited participants to determine the effectiveness of nutritional supplements to reduce aggression among two different populations. We stumbled upon numerous difficulties and found ways to modify our practices successfully regarding the following aspects: (1) multisite setting, (2) inclusion of vulnerable participants, (3) nutritional supplements and placebos, (4) assessment of behavioural outcomes, and (5) collecting bio samples—all of which were essential for the success of both projects (Table 1). We hope that by sharing our practical experiences, we may enable future researchers to more effectively conduct clinical trials in these populations who could still gain much from improved clinical care.

Table 1. Practical recommendations for future research

Topic	Recommendation
1. Multisite setting	• Take the recruitment of sites into account in the time-management plan.
	• Choose a key contact within the organization based not only on that person's function but also someone who is helpful, approachable, and motivated to support the execution of the study.
	• Invest time at each site (once a week or more), preferably face to face. Develop a remote consent and enrollment process for situations where face-to-face contact is not possible.
2. Recruitment of vulnerable participants	• Use subtle terminology. Instead of "aggression," use "challenging behavior" and other words and phrases with more neutral connotations.
	• Screen participants for at least some level of aggression to avoid recruiting participants who show little to no aggression
	• Tailor information materials to participants according to their intellectual abilities and include patient representatives and local care professionals.
3. Nutritional supplements and placebos	• Add vanilla-scented sachets to the jars of supplements.
	• Choose an appropriate form of the supplements to aid administration to the target population.
	• Advise participants to take the capsules during the meal.
4. Assessment of behavioral outcomes	• Use a scale that can easily monitor aggressive behavior and that is validated to assess the study population.
	• Set up a plan to monitor participants at regular intervals in order to reduce underreporting of incidents.
	• Train (new) care professionals continuously throughout the trial phase.
5. Collecting bio samples	• Invest in strong collaboration with the local laboratory.
	• Develop a simple and illustrated manual that can be understood by the participants.
	• If possible, choose a bio-sample that can be transported reliably and easily to a central laboratory.

Acknowledgments

The authors would like to acknowledge all participants and care professionals for giving generously of their time and effort on this study. This study was supported by ZonMw (The Netherlands Organisation for Health Research and Development) under Grant [number 836031016], and the Healthcare Insurance Fund, The Netherlands (Het Innovatiefonds Zorgverzekeraars) under Grant [number 3326]. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Conflict of interests

The authors declare that there are no conflict of interests.

Data availability statement

The datasets used and/or analysed during this study are available from the corresponding author on reasonable request.

Supporting information

Additional supporting information may be found in the online version of the article at the publisher's website.

References

1. Hariton E, Locascio JJ. Randomised controlled trials - the gold standard for effectiveness research: Study design: randomised controlled trials. *BJOG*. 2018;125(13):1716-.
2. Shepherd V. An under-represented and underserved population in trials: methodological, structural, and systemic barriers to the inclusion of adults lacking capacity to consent. *Trials*. 2020;21(1):445.
3. Scheifes A, Egberts TCG, Stolker JJ, Nijman HLI, Heerdink ER. Structured Medication Review to Improve Pharmacotherapy in People with Intellectual Disability and Behavioural Problems. 2016;29(4):346-55.
4. Sheehan R, Hassiotis A. Digital mental health and intellectual disabilities: state of the evidence and future directions. *Evidence-based mental health*. 2017;20(4):107-11.
5. Steinert T, Hamann K. External validity of studies on aggressive behavior in patients with schizophrenia: systematic review. *Clin Pract Epidemiol Ment Health*. 2012;8:74-80.
6. Daffern M, Howells K. Psychiatric inpatient aggression: A review of structural and functional assessment approaches. *Aggression and Violent Behavior*. 2002;7(5):477-97.
7. Bowers L, Stewart D, Papadopoulos C, Dack C, Ross J, Khanom H, et al. Inpatient violence and aggression: a literature review. 2011.
8. Didden R, Lindsay W, Lang R, Sigafoos J, Deb S, Wiersma J. Handbook of Evidence-Based Practices for Individuals with Intellectual and Developmental Disabilities. 2016.
9. Dack C, Ross J, Papadopoulos C, Stewart D, Bowers L. A review and meta-analysis of the patient factors associated with psychiatric in-patient aggression. 2013;127(4):255-68.
10. Ose SO, Lilleeng S, Pettersen I, Ruud T, van Weeghel J. Risk of violence among patients in psychiatric treatment: results from a national census. *Nordic Journal of Psychiatry*. 2017;71(8):551-60.
11. Robertson J, Emerson E, Pinkney L, Caesar E, Felce D, Meek A, et al. Quality and costs of community-based residential supports for people with mental retardation and challenging behavior. *American journal of mental retardation : AJMR*. 2004;109(4):332-44.
12. Edward K-L, Ousey K, Warelow P, Lui S. Nursing and aggression in the workplace: A systematic review. *British journal of nursing (Mark Allen Publishing)*. 2014;23:653-9.
13. Frueh BC, Knapp RG, Cusack KJ, Grubaugh AL, Sauvageot JA, Cousins VC, et al. Patients' reports of traumatic or harmful experiences within the psychiatric setting. *Psychiatric services (Washington, DC)*. 2005;56(9):1123-33.
14. Nijman HLI, Bowers L, Oud N, Jansen G. Psychiatric nurses' experiences with inpatient aggression. *Aggressive behavior*. 2005;31(3):217-27.
15. Glasgow RE, Riley WT. Pragmatic measures: what they are and why we need them. *Am J Prev Med*. 2013;45(2):237-43.
16. Smith L, Tan A, Stephens JD, Hibler D, Duffy SA. Overcoming Challenges in Multisite Trials. *Nursing research*. 2019;68(3):227-36.
17. Wüsthoff LE, Waal H, Gråwe RW. When research meets reality-lessons learned from a pragmatic multisite group-randomized clinical trial on psychosocial interventions in the psychiatric and addiction field. *Subst Abuse*. 2012;6:95-106.

18. Friese CR, Mendelsohn-Victor K, Ginex P, McMahon CM, Fauer AJ, McCullagh MC. Lessons Learned From a Practice-Based, Multisite Intervention Study With Nurse Participants. *J Nurs Scholarsh*. 2017;49(2):194-201.
19. DeVon HA, Patmon FL, Rosenfeld AG, Fennessy MM, Francis D. Implementing clinical research in the high acuity setting of the emergency department. *J Emerg Nurs*. 2013;39(1):6-12.
20. Empey PE, Stevenson JM, Tuteja S, Weitzel KW, Angiolillo DJ, Beitelshees AL, et al. Multisite Investigation of Strategies for the Implementation of CYP2C19 Genotype-Guided Antiplatelet Therapy. *Clin Pharmacol Ther*. 2018;104(4):664-74.
21. Manojlovich M, Bedard L, Griggs JJ, McBratnie M, Mendelsohn-Victor K, Friese CR. Facilitators and Barriers to Recruiting Ambulatory Oncology Practices Into a Large Multisite Study: Mixed Methods Study. *JMIR Cancer*. 2020;6(1):e14476.
22. Ploeg J, Davies B, Edwards N, Gifford W, Miller PE. Factors influencing best-practice guideline implementation: lessons learned from administrators, nursing staff, and project leaders. *Worldviews on evidence-based nursing*. 2007;4(4):210-9.
23. Hodgins S, Müller-Isberner R. Preventing crime by people with schizophrenic disorders: the role of psychiatric services. *The British journal of psychiatry : the journal of mental science*. 2004;185:245-50.
24. de Bles NJ, Hazewinkel AWP, Bogers JPAM, van den Hout WB, Mouton C, van Hemert AM, et al. The incidence and economic impact of aggression in closed long-stay psychiatric wards. *International journal of psychiatry in clinical practice*. 2020:1-7.
25. Lloyd BP, Kennedy CH. Assessment and treatment of challenging behaviour for individuals with intellectual disability: a research review. *J Appl Res Intellect Disabil*. 2014;27(3):187-99.
26. Hardesty JL, Haselschwerdt ML, Crossman KA. Qualitative Research on Interpersonal Violence: Guidance for Early Career Scholars. *Journal of Interpersonal Violence*. 2019;34(23-24):4794-816.
27. Fergusson D, Glass KC, Waring D, Shapiro S. Turning a blind eye: the success of blinding reported in a random sample of randomised, placebo controlled trials. *Bmj*. 2004;328(7437):432.
28. Mocking RJ, Harmsen I, Assies J, Koeter MW, Ruhé HG, Schene AH. Meta-analysis and meta-regression of omega-3 polyunsaturated fatty acid supplementation for major depressive disorder. *Translational psychiatry*. 2016;6(3):e756.
29. van der Wurff ISM, Meyer BJ, de Groot RHM. A Review of Recruitment, Adherence and Drop-Out Rates in Omega-3 Polyunsaturated Fatty Acid Supplementation Trials in Children and Adolescents. *Nutrients*. 2017;9(5).
30. Benza HI, Munyendo WLJIJPSRR. A review of progress and challenges in soft gelatin capsules formulations for oral administration. 2011;10:20-4.
31. Delompré T, Guichard E, Briand L, Salles C. Taste Perception of Nutrients Found in Nutritional Supplements: A Review. *Nutrients*. 2019;11(9).
32. Chang CH, Tseng PT, Chen NY, Lin PC, Lin PY, Chang JP, et al. Safety and tolerability of prescription omega-3 fatty acids: A systematic review and meta-analysis of randomized controlled trials. *Prostaglandins Leukot Essent Fatty Acids*. 2018;129:1-12.
33. Tammam JD, Steinsaltz D, Bester DW, Semb-Andenaes T, Stein JF. A randomised double-blind placebo-controlled trial investigating the behavioural effects of vitamin, mineral and n-3 fatty acid supplementation in typically developing adolescent schoolchildren. *The British journal of nutrition*. 2016;115(2):361-73.

34. Zaalberg A, Nijman H, Bulten E, Stroosma L, van der Staak C. Effects of nutritional supplements on aggression, rule-breaking, and psychopathology among young adult prisoners. *Aggressive behavior*. 2010;36(2):117-26.
35. Moriyama Y. Riboflavin transporter is finally identified. *J Biochem*. 2011;150(4):341-3.
36. Rucklidge JJ, Frampton CM, Gorman B, Boggis A. Vitamin-mineral treatment of attention-deficit hyperactivity disorder in adults: double-blind randomised placebo-controlled trial. *The British journal of psychiatry : the journal of mental science*. 2014;204:306-15.
37. Kaplan BJ, Steiger RA, Pope J, Marsh A, Sharp M, Crawford SG. Successful treatment of pill-swallowing difficulties with head posture practice. *Paediatr Child Health*. 2010;15(5):e1-5.
38. Lee JH, O'Keefe JH, Lavie CJ, Marchioli R, Harris WS. Omega-3 fatty acids for cardioprotection. *Mayo Clin Proc*. 2008;83(3):324-32.
39. Adams JB, Audhya T, McDonough-Means S, Rubin RA, Quig D, Geis E, et al. Effect of a vitamin/mineral supplement on children and adults with autism. *BMC pediatrics*. 2011;11:111.
40. Raine A, Cheney RA, Ho R, Portnoy J, Liu J, Soyfer L, et al. Nutritional supplementation to reduce child aggression: a randomized, stratified, single-blind, factorial trial. *Journal of child psychology and psychiatry, and allied disciplines*. 2016;57(9):1038-46.
41. Wu Q, Zhou T, Ma L, Yuan D, Peng Y. Protective effects of dietary supplementation with natural ω-3 polyunsaturated fatty acids on the visual acuity of school-age children with lower IQ or attention-deficit hyperactivity disorder. *Nutrition*. 2015;31(7-8):935-40.
42. Hébert JR, Frongillo EA, Adams SA, Turner-McGrievy GM, Hurley TG, Miller DR, et al. Perspective: Randomized Controlled Trials Are Not a Panacea for Diet-Related Research. *Adv Nutr*. 2016;7(3):423-32.
43. Forough AS, Lau ET, Steadman KJ, Cichero JA, Kyle GJ, Serrano Santos JM, et al. A spoonful of sugar helps the medicine go down? A review of strategies for making pills easier to swallow. *Patient preference and adherence*. 2018;12:1337-46.
44. Morrison EF. Violent psychiatric inpatients in a public hospital. *Scholarly inquiry for nursing practice*. 1990;4(1):65-82; discussion 3-6.
45. Suris A, Lind L, Emmett G, Borman PD, Kashner M, Barratt ES. Measures of aggressive behavior: overview of clinical and research instruments. *Aggression and Violent Behavior*. 2004;9(2):165-227.
46. Nijman HLI, Muris P, Merckelbach HLGJ, Palmstierna T, Wistedt B, Vos AM, et al. The staff observation aggression scale–revised (SOAS-R). *Aggressive behavior*. 1999;25(3):197-209.
47. Nijman HLI, Palmstierna T, Almvik R, Stolker JJ. Fifteen years of research with the Staff Observation Aggression Scale: a review. *Acta psychiatrica Scandinavica*. 2005;111(1):12-21.
48. Kay SR, Wolkenfeld F, Murrill LM. Profiles of aggression among psychiatric patients. I. Nature and prevalence. *The Journal of nervous and mental disease*. 1988;176(9):539-46.
49. Oliver PC, Crawford MJ, Rao B, Reece B, Tyrer P. Modified Overt Aggression Scale (MOAS) for People with Intellectual Disability and Aggressive Challenging Behaviour: A Reliability Study. *Journal of Applied Research in Intellectual Disabilities*. 2007;20(4):368-72.
50. Ferns T. Under-reporting of violent incidents against nursing staff. *Nurs Stand*. 2006;20(40):41-5.

51. Drieschner KH, Marrozos I, Regenboog M. Prevalence and risk factors of inpatient aggression by adults with intellectual disabilities and severe challenging behaviour: a long-term prospective study in two Dutch treatment facilities. *Research in developmental disabilities*. 2013;34(8):2407-18.
52. Volavka J. Neurobiology of violence: American Psychiatric Pub; 2008.
53. Sahs JA, Nicasio AV, Storey JE, Guarnaccia PJ, Lewis-Fernández R. Developing Research Collaborations in an Academic Clinical Setting: Challenges and Lessons Learned. *Community Ment Health J*. 2017;53(6):647-60.
54. Willard-Grace R, Knox M, Huang B, Hammer H, Kivlahan C, Grumbach K. Burnout and Health Care Workforce Turnover. *Annals of family medicine*. 2019;17(1):36-41.
55. Leyse-Wallace R. Nutrition and mental health: CRC Press; 2013.
56. Giltay EJ, Geleijnse JM, Schouten EG, Katan MB, Kromhout D. High stability of markers of cardiovascular risk in blood samples. *Clin Chem*. 2003;49(4):652-5.
57. Albahrani AA, Rotarou V, Roche PJ, Greaves RF. Analyte stability during the total testing process: studies of vitamins A, D and E by LC-MS/MS. *Clin Chem Lab Med*. 2016;54(10):1609-18.
58. Drammeh BS, Schleicher RL, Pfeiffer CM, Jain RB, Zhang M, Nguyen PH. Effects of delayed sample processing and freezing on serum concentrations of selected nutritional indicators. *Clin Chem*. 2008;54(11):1883-91.
59. Panek M, Čipčić Paljetak H, Barešić A, Perić M, Matijašić M, Lojkić I, et al. Methodology challenges in studying human gut microbiota – effects of collection, storage, DNA extraction and next generation sequencing technologies. *Scientific Reports*. 2018;8(1):5143.

Supplementary Material 1. Manual for the collection of faecal samples

Verzamelen van ontlasting

Hartelijk dank dat je mee wilt werken met het verzamelen van ontlasting.
In deze instructie lees je stap voor stap hoe dat gaat.

1 In het pakket zit een papieren fecesvanger
Vraag aan een begeleider of die de papieren fecesvanger op de wc-bril plakt.
De gebruiksaanwijzingen staan op de fecesvanger.
Een plaatje van de fecesvanger zie je hiernaast.


1
Hier voorzichtig in de richting van de pijl losmaken.
Gebruiksaanwijzing voor de Fecesvanger
Gaatjes gebruiker.
De Fecesvanger vergemakkelijkt het nemen van een monster van de ontlasting. Het werkt eenvoudig en hygiënisch.
Voor een betrouwbaar resultaat zonder kans op vervuiling van het monster. Reinigingsmiddelen en toiletverfrissers kunnen de uitslag van het onderzoek beïnvloeden.
U gebruikt de Fecesvanger als volgt:
1. Open de Fecesvanger door het papier voorzichtig in de richting van de pijlen te openen.
2. Plak de Fecesvanger adhesief de WC bril, zoals in het plaatje is aangegeven.
3. Voorkom dat het papier in aanraking komt met water.
4. Neem na het ontlasten het monster zoals in de gebruiksaanwijzing is aangegeven.
Hier voorzichtig in de richting van de pijl losmaken

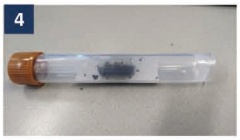
2 Doe je behoefte op de fecesvanger die boven de wc hangt.


2

3 In het pakket zitten ook 2 buisjes.
Draai de buisjes open.
Je ziet dat aan het dopje van een buisje een klein schepje zit.
Je haalt een schepje uit het midden van de ontlasting.
Dit doe je voor allebei de buisjes


3

4 Dan doe je het schepje weer in het buisje en draait de dop dicht


4

5 In het pakket zit ook een zwart plastic zakje
Je doet de 2 buisjes in het zwarte zakje en klinkt het zakje dicht.


5

6 In het pakket zit ook een safetybag.
Je doet het zwarte zakje met de buisjes in de safetybag en maakt die dicht.

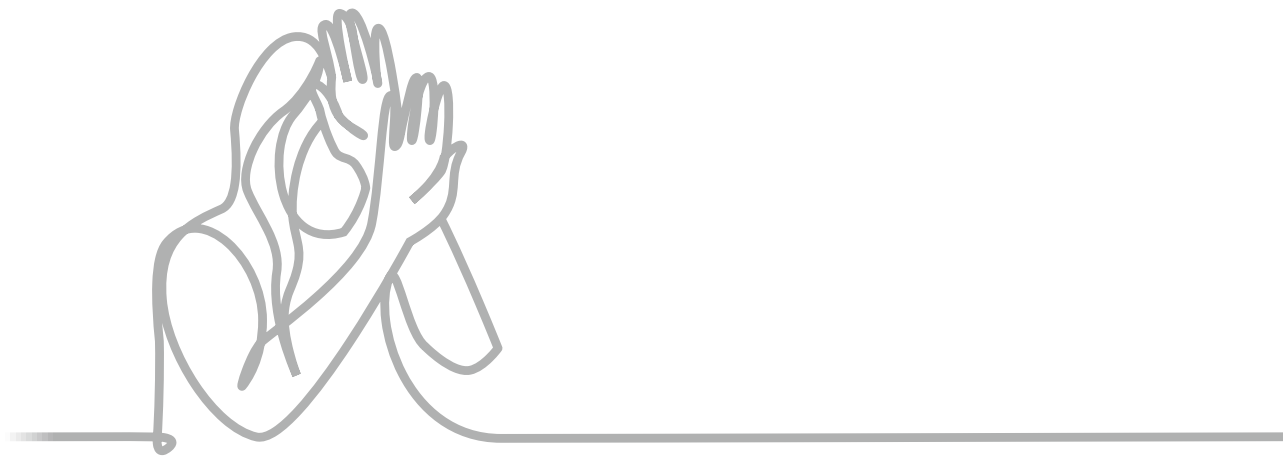

6

7 Op de achterkant van dit papier staan vragen.
Vul de vragen in.
Als je het niet weet kan de begeleider je helpen.

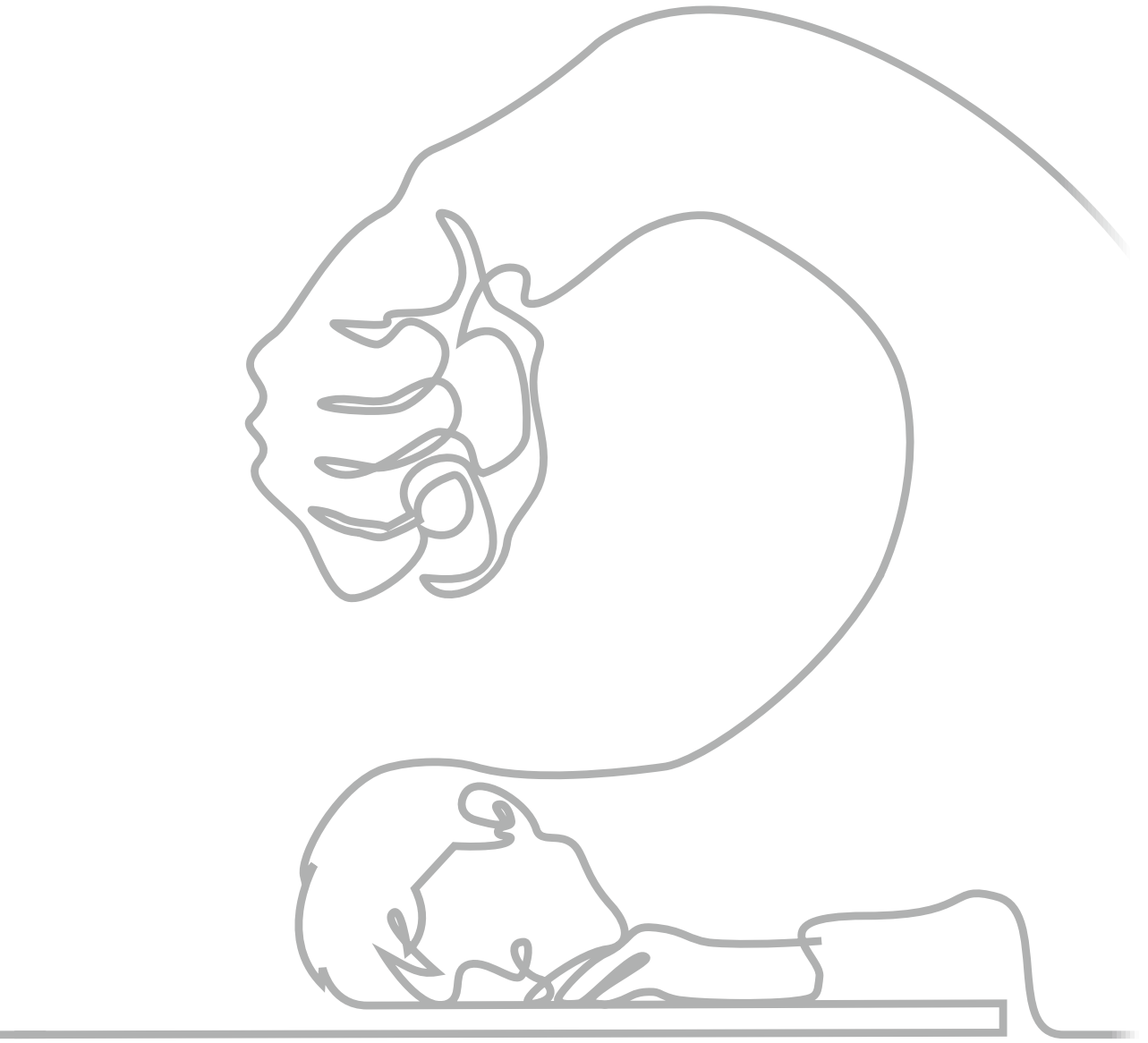
8 Geef de safetybag met de ingevulde vragenlijst aan de begeleider.
De begeleider zorgt ervoor dat de safetybag binnen 8 uur wordt ingevroren.
De vragenlijst wordt aan de onderzoeker meegegeven.

Hebt u vragen over het verzamelen van ontlasting? Neemt u dan gerust contact op met ons op.
Op werkdagen van 08:00 uur – 17:00 uur bereikbaar via 071 – 526 1517.
Of email: agressievermindering@lumc.nl

Agressievermindering door supplementen



9 Summary and General Discussion



The overall purpose of this thesis was threefold: (1) To examine whether and to what extent anger and aggression are associated with psychiatric disorders; (2) to deepen our understanding of some aspects of the pathophysiology of anger manifestations; and (3) to investigate the effectiveness of nutritional supplementation to reduce aggressive incidents among psychiatric inpatients. The first and second part of this thesis were based on data from the Netherlands Study of Depression and Anxiety (NESDA), which recruited individuals from community care, primary care, and specialized outpatient mental health care. The third part of this thesis comprised data from the Diet and Aggression trial, which randomized individuals who resided at facilities for long-term psychiatric inpatient care.

In this last chapter, the main findings of this thesis will be summarized and discussed in the context of current research. Subsequently, implications for clinical practice and public health will be outlined. In addition, suggestions for future research to prevent anger and aggression among psychiatric patients are proposed and discussed.

Summary of findings

Part I: Anger measures and psychiatric outpatients

The first part of this thesis, *Chapters 2* and *3*, examined the relationship between different anger measures and depressive-, anxiety- and bipolar disorder among psychiatric outpatients.

Chapter 2: Trait anger and anger attacks in relation to depressive and anxiety disorders

Depressive and anxiety disorders are closely linked to anger. Yet, most previous studies conducted in patients with depressive- and anxiety disorders used insufficiently validated instruments or used only a single item to measure solely an aspect of anger such as irritability. Therefore, we investigated the prevalence of anger using a validated 10-item Spielberger Trait Anger Scale and the 19-item Anger Attacks Questionnaire in 2402 participants from the Netherlands Study of Depression and Anxiety (NESDA). Anger was most prevalent in participants with comorbid depressive and anxiety disorders—followed by anxiety-, depressive-, and remitted disorder—and these participants exhibited a higher prevalence of anger than healthy controls. Our findings showed robust evidence of a relationship between anger and psychopathology, although the strength differed across both anger constructs.

Chapter 3: Anger and cluster B personality traits and the conversion from unipolar depression to bipolar disorder

Patients with bipolar disorder (BD) have often experienced one or more episodes of depression before the onset of (hypo)mania, and consequently are frequently initially diagnosed with a unipolar depression. Identifying risk factors for the conversion to BD may yield anchor points for early recognition and appropriate treatment. We examined whether patients who converted to BD showed more feelings of anger, irritability, and antisocial and borderline personality traits than people with a history of unipolar depression who did not convert using the data from NESDA. Furthermore, we prospectively examined whether higher aggression reactivity could predict conversion from unipolar depression to BD later on. Different constructs of anger and affective instability (i.e., trait anger, aggression reactivity, anger attacks, and cluster B personality traits) showed consistent associations, with the strongest association and highest prevalence in the 77 participants who converted in comparison to the 1159 with a remitted and 349 with a current depression. Furthermore, aggression reactivity was a predictor for the conversion to BD in persons with a history of unipolar depression. These results suggest that assessment of anger might have clinical value in earlier recognition of conversion into (hypo)mania.

Part II: Pathophysiology of anger manifestations

The second part of this thesis addressed the pathophysiology of anger among psychiatric outpatients. The aim was to unravel the associations between childhood trauma, *Chapter 4*, and *T. gondii* infection, *Chapter 5*, with anger manifestations.

Chapter 4: Childhood trauma and anger in adults with and without depressive and anxiety disorders

Stress in early life could induce long-lasting alterations of the HPA axis, which is associated with severe sequelae that can perpetuate long into adulthood. We investigated (1) whether childhood trauma is associated with anger in adulthood and, if so, (2) to explore which types of childhood trauma predominate in the prediction of anger in a cohort that included participants with and without lifetime affective disorders. Therefore, the associations between childhood trauma and anger in adulthood, including trait anger, anger attacks, and borderline- and antisocial personality traits as constructs of anger, were examined in 2276 participants from NESDA. The results showed that all types of childhood trauma were significantly associated with borderline personality traits, independently of depression and anxiety. Additionally, all types

of childhood trauma except for sexual abuse were associated with higher levels of trait anger, and a higher prevalence of anger attacks and antisocial personality traits in adulthood, which may suggest that multiple anger manifestations are potentially the result of childhood trauma.

Chapter 5: Toxoplasma gondii seropositivity in patients with depressive and anxiety disorders

We also need to better understand the neurobiology of aggression. Latent Toxoplasma gondii (T. gondii) infection has been linked to several neuropsychiatric mood disorders and behaviours, yet studies provided no clear consensus on these associations. We hypothesized (1) that *T. gondii* seropositivity would be associated with the presence and severity of depressive and anxiety disorders, and (2) that *T. gondii* seropositivity would be associated with aggression reactivity and suicidal thoughts. In our study, a total of 1731 titers were obtained from participants from NESDA, of which 673 participants (38.9%) were seropositive for T. gondii antibodies, with a higher age associated with a higher risk. However, no significant associations were found between T. gondii seropositivity and disorder status, aggression reactivity and suicidal thoughts. Considering previous studies and our new findings, it seems unlikely that T. gondii seropositivity plays a major role in the risk of affective disorders, suicidality, and aggressive thoughts.

Part III: Aggression and psychiatric inpatients

The last part of this thesis focused on aggression among long-stay psychiatric inpatients. In *Chapter 6* and *7*, we examined the incidence and economic impact of aggressive incidents and determined the effectiveness of nutritional supplementation to reduce these incidents. Finally, in *Chapter 8*, we described the challenges and practical lessons learned from setting up and conducting a randomized controlled trial involving long-stay psychiatric inpatients.

Chapter 6: The incidence and economic impact of aggression in closed long-stay psychiatric wards

Aggressive behaviour is highly prevalent in psychiatric inpatient care, with substantial physical, mental, and economic consequences. However, estimates have often been based on data collected from (acute) admission wards and (forensic) hospitals, while data from long-stay facilities for psychiatric care are much scarcer. We hypothesized that the incidence rates of aggression, the workload for staff members, and the associated direct costs in closed long-stay psychiatric wards would be high. We found an

incidence rate of 90 incidents per patient year in closed psychiatric long-stay wards belonging to three regional mental healthcare centres. The incidence amounted to five incidents per day in an average ward with 20 inpatients. The average time spent was 125 min per incident, which indicates that each individual nurse spent more than half an hour per shift dealing with aggression. The direct costs related to incidents amounted to approximately €78 per incident. Based on our incidence rate, this would result in an estimate of €7000 per patient per year. These costs are likely to be an underestimation, as we did not include costs that were indirectly caused by aggression (e.g., staff absence, re-admissions, and assistance of police or ambulance). Aside from the financial perspective, reduction of aggression is highly valuable for both patients and staff. A positive change in aggression level need not affect the budget directly but would be compensated by the time that is available for therapeutic and social activities, as a result of which quality of care will likely improve.

Chapter 7: Multivitamin, mineral, and n-3 PUFA supplementation to reduce aggression among long-stay psychiatric inpatients: a randomized clinical trial

Previous studies found nutritional supplementation to be effective in reducing aggressive incidents and rule violations among forensic populations and children with behavioural problems. Yet, this had never been confirmed in a sample of long-stay psychiatric inpatients. We hypothesized that nutritional supplementation would reduce aggressive incidents, feelings of aggression, and affective symptoms and would increase the patients' quality of life. We therefore assessed the effectiveness of multivitamin, mineral, and n-3 PUFA supplementation in reducing aggressive incidents among 176 long-stay psychiatric inpatients. Our findings provided no support for the effectiveness of the current intervention in reducing the number of incidents during a 6-month intervention. Zooming in on the severity or type of aggressive incidents corroborated this conclusion. Our results suggest that the promising effects of nutritional supplementation on aggressive incidents found in previous studies cannot be replicated in these psychiatric inpatients. Although healthy diets should be stimulated for reasons of well-being and general health issues, there is yet no role for supplements in order to reduce aggression.

Chapter 8: Lessons learned from two clinical trials on nutritional supplements to reduce aggressive behaviour

Randomized controlled trials (RCTs) are considered to provide evidence for the effectiveness of a particular treatment. Setting up and conducting an RCT required

continuous decision making and has many challenges—particularly trials that include vulnerable individuals with behavioural problems or who reside in facilities that focus on care and not on research. As a consequence, vulnerable individuals with behavioural problems are underrepresented in RCTs, resulting in a lack of evidence-based care for these groups. We described the challenges and practical lessons learned from two RCTs in two care settings involving long-stay psychiatric inpatients and people with intellectual disabilities. We described five main difficulties and how these were overcome: (1) multisite setting, (2) inclusion of vulnerable participants, (3) nutritional supplements and placebos, (4) assessment of behavioural outcomes, and (5) collecting bio samples.

Clinical perspectives

Assessment of anger and aggression

Anger and aggression are both multifaceted constructs that are difficult to differentiate in clinical practice. Therefore, it is relevant to distinguish the subjective experience and the (physical) expression of anger and aggression [1]. Another distinction is that between state versus trait anger and aggression, which is of importance to determine whether a construct is rather constant or fluctuates over time within a person (4). For example, The Anger Attacks Questionnaire [2] aims to assess a certain mental state, whereas the Aggression Questionnaire [3] aims to assess trait aspects of aggression. The State-Trait Anger Expression Inventory-II (STAXI-2) is a self-report questionnaire that distinguishes trait and state anger, but also distinguishes between the expression and regulation of anger [4, 5]. To identify individuals most prone to anger, aggression, and related constructs, it is important to be aware of the aspect that someone aims to measure.

Another important consideration involves the choice of method for data collection. Although the instruments mentioned before are all self-report questionnaires, a more fundamental disadvantage of these constructs is that many people tend to give socially desirable answers [6]. In addition, psychiatric inpatients might suffer from limited intellectual and self-reflective capacities and consequently be less capable of completing self-report scales accurately. Hence, observer-rated scales are also a preferred method to investigate state aggression [7]. These scales include the Social Dysfunction and Aggression Scale [8], the Staff Observation Aggression Scale – Revised [9], and the Modified Overt Aggression Scale [10], amongst others. A downside of these scales is that observers, often care professionals, are regularly exposed to aggressive

behaviour, and may be desensitized to the more subtle forms of aggression, leading to underreporting and a lack of interobserver reliability. The latter could be compensated by training observers to calibrate assessments [11].

Additional issues that could influence the validity of an instrument are the characteristics of the study population and the instrument itself. Various study populations including the general population and psychiatric patients have been studied in the development of self-report questionnaires like the Aggression Questionnaire and the STAXI-2. More specifically, the SOAS-R has been validated among psychiatric populations and has been used in psychiatric settings worldwide [12]. Anger and aggression are often assessed through the measurement of a subscale as part of a larger questionnaire. Examples are the aggression subscales of the revised Leiden Index of Depression Sensitivity (LEIDS-R) [13, 14] and the SQ-48 [15]. Hence, the validity of these subscales for actual measured anger or aggression is unknown and may rather reflect irritability than aggression.

Thus, there are various instruments to assess the many different facets of aggression, and the choice of which to use depends on the aims of clinicians and researchers. These aims comprise identifying individuals prone to anger and aggressive behaviour, measuring change after an intervention, or predicting the potential of aggression in the future. Considerations that are of importance in selecting an instrument include the conceptualization of anger, aggression, and related concepts like irritability, as well as the method of data collection, study population, and instrument characteristics.

Outpatient settings

The current thesis demonstrated a high occurrence of anger and aggression among psychiatric patients. These results were in line with those from large population-based cohort studies as well as a patient-based study of psychiatric outpatients [1, 16, 17]. Chapter 2 showed that 30% of the patients with a depressive or anxiety disorder reported high trait anger scores. Anger attacks were reported by 4.9% and 11.5% of the patients with a depressive or anxiety disorder, respectively. Patients with comorbid depressive and anxiety disorders had the highest prevalence for both trait anger (43.7%) and anger attacks (22.1%). These patients showed the same level of trait anger and prevalence of anger attacks as patients with a bipolar disorder, which we found and reported in Chapter 3. Due to the observational and cross-sectional nature of our study design, it remains unknown whether anger and aggression are the result of (residual) affective symptoms or that the presence of anger and aggression may increase the vulnerability to psychopathology. Yet, in the prospective study of

Chapter 3, we found that anger predicted for the conversion of a (history of) unipolar into a bipolar disorder (BD) independent of depression severity and comorbid anxiety disorders. Thus, we demonstrated that anger could be a potential risk factor for the conversion to BD.

Our findings have several clinical implications. It means that anger symptoms are important to inquire about for the diagnosis, treatment, and prognosis of each patient with an affective disorder. Although common, anger may be easily overlooked or ignored by clinicians and patients themselves because they are not part of the core DSM-5 symptoms, and insight and self-consciousness of feelings of anger may be hampered. Moreover, this emotional state is also prone to conscious or unconscious denial as a taboo subject, and therefore needs a balanced approach to address. Yet, addressing anger in therapy may help clinicians to reduce conflicts or resistance to therapy [18].

As a first step, interventions aimed at better self-recognition and self-control may be helpful. Frequently, anger will be externalized or attributed to the psychiatric condition. It is therefore important to support patients in taking control over their harmful behaviour. These interventions comprise cognitive behavioural therapies, which are the most studied type for anger treatment, but also relaxation, social skills and cognitive therapies, or a combination of these approaches [19]. Meta-analyses comparing these interventions show that effects are comparable and moderately effective [20-22].

In the light of effective therapy, it is urgent to understand mechanisms underlying anger in adulthood. Prior cross-sectional and longitudinal studies found associations between childhood trauma and anger outcomes in adulthood. However, most studies focused on trait anger, while different forms of childhood trauma may affect the development of different aspects of anger and aggression [23]. This is line with findings described in Chapter 4, stating that childhood trauma is most strongly linked with trait anger and borderline personality traits, but physical abuse was the strongest predictor for anger attacks and antisocial personality traits. A complicating layer to these relationships is that experienced trauma and neglect by parents and hereditary factors interact in complex ways. In clinical practice, it is important to explain and validate the relationship between childhood trauma and anger in adulthood. Unfortunately, symptom complexity such as emotion regulation difficulties and impulsive behaviour is often viewed upon as a limiting factor in trauma-focused therapy, thinking it may worsen these symptoms. As a result, it could be that patients are prevented from receiving a beneficial additive treatment. A meta-analysis that included those that

had experienced childhood trauma did not find symptom complexity to be a contraindication for trauma-focused psychological interventions [24]. So, in addition to anger control, trauma-focused treatments might lead to reductions in anger. To inform future treatments, it remains important to further personalize treatments, and to identify which components work for which individuals.

Inpatient settings

Aggression and violent incidents are highly prevalent in psychiatric inpatient care, as aggressive behaviour is often the triggering event that leads to a referral to these settings [25]. In addition, patients have been found to be more aggressive during hospitalization [26]. So, a substantial number of individuals admitted to inpatient settings express aggressive behaviours not only as the reason for admission but also as a consequence thereof. However, exact estimates of the prevalence and incidence are mixed, which may be explained by large variations in types of patients, settings, the types of aggression that is measured (e.g., including or excluding verbal aggression and self-harm), and the fact that incidents are less often reported officially, compared to what is actually experienced by staff members [27, 28]. In addition, incidence estimates have often been based on data collected from (acute) admission wards [29, 30] and (forensic) hospitals [31, 32]. As a consequence, a wide range of incidence rates have been reported varying from less than 1 to 60 incidents per patient year, mostly in acute and forensic settings [12, 33], and up to 90 incidents in closed long-stay wards as described in Chapter 6 of the current thesis.

The main treatment approaches to reduce aggression comprise psychotherapy, including behavioural interventions, and psychopharmacological therapy [34, 35]. However, evidence for the efficacy of these interventions is not conclusive [36-39]. RCTs are often underpowered and long-term outcomes are lacking [34]. In addition, only 30% of the patients displaying aggression would be eligible to participate in RCTs investigating pharmacological interventions targeting aggression, which may decrease the generalizability to clinical practice [40]. Consequently, clinical guidelines emphasise the need for additional and innovative treatment options [41]. Despite some promising effects of multivitamin, mineral and n-3 polyunsaturated fatty acid (PUFA) supplementation on aggressive incidents found in previous studies [42-51], we found no evidence of a beneficial effect in chronically ill psychiatric in-patients.

Aggressive behaviour and the management thereof do not only focus on patient factors, but also concentrate on other variables including the physical environment and staff factors. Thus, interventions include aggression management courses for

staff, such as the Safewards model, providing ten interrelated interventions [52, 53]. Despite the increased awareness and efforts to reduce aggression in clinical care, it remains important to establish robust evidence to improve the experience of safety in inpatient settings for both patients and staff [54, 55].

Public health impact

Anger and aggression have substantial public health implications, both for individuals, mental healthcare organizations, and society. Implications may comprise primarily anger reactions in a social context, especially the people described as loved ones by these individuals [56]. Additionally, high levels of anger might trigger self-directed aggression [57] and aggression towards others. In case aggressive behaviour is a risk to patients or their environment, it could result in the use of coercive measures, such as involuntary admissions to psychiatric wards, which patients often describe as traumatic [58, 59]. Among the different disciplines of these wards, nursing staff is particularly at risk, with psychiatric nurses having a three times increased risk of physical aggression from patients compared to nonpsychiatric nurses [60]. These incidents sometimes lead to serious injuries (e.g., fractures, eye injuries and permanent disability), which was reported by 26% of psychiatric nurses [61]. The exposure to aggression may also lead to acute stress disorder, and post-traumatic stress disorder (PTSD) in severe cases (14–17% of exposed staff members), but more frequently, it leads to subclinical burnout-related symptoms [62, 63]. A review on workplace violence towards healthcare staff employed in psychiatric wards reported that 7.5 to 33% of the victims developed symptoms including anxiety, depression, and avoidance behaviour after the occurrence of an incident [64].

Mental health sequalae among healthcare staff have substantial consequences on an organizational level as well; the exposure to aggression seems to be related to job dissatisfaction [65], burnout [66], and absenteeism [67]. These symptoms are concerning, as it may result in lower standards of care [68] and increased intent to leave the organization [69]. In addition, lost staff work-days due to the physical and psychological consequences that might follow critical incidents are accounted by high costs, even long after the initial incident happened. Other costs include the time spent on aggression by staff, damaged property, higher use of psychotropic medication, and longer hospital admissions [70]. As a result, the few studies that provided information on the costs of aggression showed an enormous economic burden on the organizations budget yet are thought to be conservative estimates as indirect costs are often not or not completely taken into account.

In the long-term, aggression towards professionals might also have an impact on society, not only limited to the psychiatric population as the aggressor, but also other individuals from the general population. As a consequence, aggression is not only experienced by mental healthcare professionals, but also by other healthcare professionals, police officers, firefighters and traffic controllers [71]. It is disputed whether there is a stagnation in the scope of aggression, due to increased reporting and broader aggression definitions. Nevertheless, the exposure to aggression is experienced as high, which became even more evident in recent years during the COVID-19 pandemic and the accompanying restrictions [72, 73]. A recent report among 11,092 respondents found that three quarters of healthcare professionals in the Netherlands have been exposed to aggression or unwarranted behaviour from patients or clients at least once during the past year. These incidents ranged from verbal or physical aggression to sexual or other harassment or threat, causing 4% of the respondents thinking about leaving the sector [72]. Interventions to reduce these behaviours include adequate registration, the development of specific protocols, and training. However, these approaches do not focus on the role of aggressive individuals within the general population, for example through campaigns or education. In addition, most interventions have not been evaluated for their effectiveness. As these professions, including healthcare professionals, police officers, firefighters, and traffic controllers, are essential to ensure the continuity and resilience of our society, it is of utmost importance that aggression receives high priority among public health interventions.

Future directions

This thesis adds and broadens robust evidence confirming the relationship between anger and aggression, and psychopathology, as well as expanding upon some aspects of the pathophysiology of these relationships. However, this thesis also raises some key issues for future studies.

Dynamic interplay between the context,
anger, and other symptoms psychiatric disorders

Our research implies that participants with a remitted psychiatric disorder still exhibited higher levels of trait anger and recent anger attacks compared to controls, which may be the result of residual symptoms or psychiatric disorders that were not assessed in our study. A common residual symptom that is often mentioned is irritability [74]. Furthermore, symptomatically remitted patients with schizophrenia or

bipolar disorder remain impaired in the recognition of facial expressions depicting anger [75]. Interestingly, while studies show irritability and the identification of anger as residual symptoms, the experience and expression of anger among remitted patients often remains neglected in the literature. The question whether anger is a residual symptom could be of importance as residual symptoms are relevant clinical predictors for the recurrence of depression. Recurrence of depression is especially high in specialized mental health care with a percentage of up to 85% after 15 years [76]. Thus, the identification of residual symptoms might lead to an improvement of therapy and the course of mental illness to prevent relapse.

Higher levels of anger, however, may also indicate vulnerability to psychopathology. Despite the connection between anger and psychopathology, anger is often overlooked as it may come and go during the course of psychopathology. According to the DSM-5, only Intermittent Explosive Disorder (IED) has a primary focus on anger and aggression among adults [77]. Nevertheless, the research in the current thesis seems to confirm that pathological anger is common across different psychiatric disorders, as described in Chapter 2 and 3, and it could have a substantial influence on the development and treatment of these disorders [78]. Underlying this relationship, it is suggested that an angry disposition embedded in personality leads to expressed anger, resulting in conflicts and difficulties in interpersonal relationships, which may in turn lead to psychopathology [79-81]. Additionally, there is increasing evidence that childhood trauma is linked to psychopathology in adulthood [82], with trait anger as possible mediating pathway [83]. Among individuals who experienced childhood trauma it is seen that the amygdala becomes overactive, in order to facilitate the rapid detection of potential threats [84]. This results in heightened emotional reactivity and emotional dysregulation [84-88] across the life course, including heightened anger symptoms in adulthood as described in Chapter 4. Elevated emotional reactivity, emotional dysregulation, and alterations in amygdala have all been shown to mediate the link between childhood trauma exposure and transdiagnostic psychopathology later in life [89-93].

A longitudinal cohort study may help to disentangle the temporal and causal relationships between anger and transdiagnostic psychopathology, using both self- and observer-rated anger measures and incorporating the exposure to childhood trauma. More idiographic study approaches, in which time series of symptoms including anger as assessed sequentially may help to increase the insight of precursors of aggression for the individual patient [94]. Such designs may have beneficial consequences for (psychotherapeutic) interventions targeting anger and the development of psychopathology.

Include long-term inpatients to provide evidence for the effectiveness of a particular treatment.

A large share of healthcare costs is spent on long-term care, with aggression being a relevant component of these costs [70, 95, 96]. As described in Chapter 7, the promising effects of nutritional supplementation on aggressive incidents found in previous studies were not replicated in psychiatric inpatients, indicating that we should be careful to generalize previous results to (long-term) psychiatric inpatients or others with severe mental illness (SMI).

The gap that is present between eligible patients and real-world patients became recently evident in a review that found that almost 80% of patients with schizophrenia spectrum disorders were ineligible for RCTs on the efficacy of antipsychotics, due to strict exclusion criteria [97]. The most frequent reasons for ineligibility were concomitant use of mood stabilizers or antidepressants and serious somatic comorbidities, while precisely these patients have moderately higher risks of admission. Moreover, individuals with SMI including schizophrenia and related psychotic disorders have a higher prevalence of comorbid chronic somatic disorders, predominantly cardiovascular and metabolic diseases [98-100]. This translates to shortened life expectancy of over 10 years as compared to the general population [101-103]. Consequently, clinical trials that do include individuals with SMI in an inpatient setting, most often focus on both mental and physical health, for example by using motivation techniques to reduce cardiometabolic risk factors [104, 105].

In sum, it is important for both individual and public health in general that future researchers conduct pragmatic trials and well-designed observational studies to investigate treatment strategies among underrepresented subgroups such as long-stay psychiatric inpatients who could still gain much from improved clinical care.

Investigate nonpharmacological interventions to improve mental and physical health.

A vast majority of the participants recruited for the Diet and Aggression trial were using antipsychotics during the intervention (91.2%). A novel hypothesis is that antipsychotics may cause undesirable mental and physical effects that could be mediated by their deleterious effects on the microbiome; the genes and genomes found in the microbiota inducing dysbiosis [106, 107].

Intestinal microbiota and diet are suggested to play a role in the gut-brain axis, with diet as an important factor to influence the gut microbiome rapidly [108]. The gut-brain axis connects the enteric nervous system to the central nervous system [109].

This way, the intestine and the brain are thought to communicate bidirectionally. The disruption of bacterial species of the gut microbiota, dysbiosis, seems to be related to several mental disorders as well as obesity and type 2 diabetes [110]. For example, research in germ-free mice has shown that gut microbiota is required for normal brain development and consequential healthy social and exploratory behaviours [111-114]. Preclinical rodent studies revealed that probiotics (i.e., supplements with beneficial viable gut microbes) had an antidepressant effect, indicating that probiotics may intervene serotonin metabolism [115].

Knowledge is increasing on the relation between the gut microbiota and brain function, but less is known about the effects of modification of the gut microbiota on affective and anger symptoms in humans. Adverse effects of antipsychotics may be highest in case of chronic antipsychotic use [107, 116, 117] and long periods of hospitalization, which is associated with more physical inactivity. Therefore, it is important to investigate interventions that target the gut microbiota to improve both mental and physical health among long-stay psychiatric inpatients to provide effective care, treatment, and prevention for this population.

Concluding remarks

This thesis leads to empirical insights in the relationship between anger and aggression, on the one hand, and psychopathology, on the other hand, using robust study designs and a broad spectrum of anger manifestations. In the previous Chapters, it became clear that the occurrence of anger and aggression are common among both psychiatric outpatients, including individuals with depressive-, anxiety-, and bipolar disorders, and psychiatric inpatients, including individuals with psychotic- and personality disorders. Therefore, we emphasize on the importance to address anger in patient interviews and (psycho)therapy. This way, it might be possible to break the taboo of feeling angry. Addressing this might help clinicians to reduce conflicts or resistance to therapy. Even so, management of anger is a major public health and safety concern due to the strong link between anger and aggression.

Aggressive behaviour regularly leads to a referral to long-stay inpatient care. As supported by this thesis, the costs of aggression within long-stay wards are high, although these estimates are most likely underestimated. The societal relevance to reduce aggression was also recognized by policymakers, resulting in a grant from ZonMw (The Netherlands Organisation for Health Research and Development) under grant number 836031016. However, despite the increased awareness and efforts to

reduce violence in clinical care among healthcare workers and policymakers, aggression incidents remain highly prevalent in psychiatric inpatient facilities. Research suggests diet to be a modifiable factor affecting mood and behaviour. However, the promising effects of nutritional supplementation on aggressive incidents found in previous studies were not replicated in psychiatric inpatients. These results strengthen the need for study of additional preventative and treatment options. Furthermore, our results underline the importance of including vulnerable populations, who are often underrepresented in RCTs, to provide evidence-based care for these groups. An important characteristic of psychiatric inpatients is the extensive use of antipsychotic medication amongst others.

In conclusion, early recognition and appropriate treatment of anger and aggression could enormously influence the ultimate functioning of care professionals, society, and, most important, patients themselves. It is in the interest of all of us that patients are able to verbalise their feelings of anger, but to no longer being consumed by anger.

References

1. Hawkins KA, Cougle JR. Anger problems across the anxiety disorders: findings from a population-based study. *Depression and anxiety*. 2011;28(2):145-52.
2. Fava M, Rosenbaum JF. Anger attacks in patients with depression. *The Journal of clinical psychiatry*. 1999;60 Suppl 15:21-4.
3. Hornsveld RHJ, Muris P, Kraaimaat FW, Meesters C. The Aggression Questionnaire in Dutch violent forensic psychiatric patients and secondary vocational students. *Assessment*. 2009;16:181-92.
4. Hovens J, Lievaart M, Rodenburg J. STAXI-2: Vragenlijst over boosheid. *Amsterdam: Hogrefe*. 2014.
5. Spielberger CD. Staxi-2: state-trait anger expression inventory-2; professional manual: PAR, Psychological Assessment Resources; 1999.
6. Fisher RJ, Katz JE. Social-desirability bias and the validity of self-reported values. *Psychology & marketing*. 2000;17(2):105-20.
7. Suris A, Lind L, Emmett G, Borman PD, Kashner M, Barratt ES. Measures of aggressive behavior: overview of clinical and research instruments. *Aggression and Violent Behavior*. 2004;9(2):165-227.
8. Wistedt B, Rasmussen A, Pedersen L, Malm U, Traskman-Bendz L, Wakelin J, et al. The development of an observer-scale for measuring social dysfunction and aggression. *Pharmacopsychiatry*. 1990;23(6):249-52.
9. Nijman HLI, Muris P, Merckelbach HLGJ, Palmstierna T, Wistedt B, Vos AM, et al. The staff observation aggression scale–revised (SOAS-R). *Aggressive behavior*. 1999;25(3):197-209.
10. Kay SR, Wolkenfeld F, Murrill LM. Profiles of aggression among psychiatric patients. I. Nature and prevalence. *The Journal of nervous and mental disease*. 1988;176(9):539-46.
11. de Bles NJ, Gast DAA, van der Slot AJC, Didden R, van Hemert AM, Rius-Ottenheim N, et al. Lessons learned from two clinical trials on nutritional supplements to reduce aggressive behaviour. *Journal of Evaluation in Clinical Practice*.n/a(n/a).
12. Nijman HLI, Palmstierna T, Almvik R, Stolker JJ. Fifteen years of research with the Staff Observation Aggression Scale: a review. *Acta psychiatrica Scandinavica*. 2005;111(1):12-21.
13. Van der Does A, Williams JJLU. Leiden index of depression sensitivity-revised (LEIDS-R). 2003.
14. Van der Does W. Cognitive reactivity to sad mood: structure and validity of a new measure. *Behaviour research and therapy*. 2002;40(1):105-20.
15. Carlier I, Schulte-Van Maaren Y, Wardenaar K, Giltay E, Van Noorden M, Vergeer P, et al. Development and validation of the 48-item Symptom Questionnaire (SQ-48) in patients with depressive, anxiety and somatoform disorders. *Psychiatry research*. 2012;200(2-3):904-10.
16. Barrett EL, Mills KL, Teesson M. Mental health correlates of anger in the general population: Findings from the 2007 National Survey of Mental Health and Wellbeing. *Australian & New Zealand Journal of Psychiatry*. 2013;47(5):470-6.
17. Genovese T, Dalrymple K, Chelminski I, Zimmerman M. Subjective anger and overt aggression in psychiatric outpatients. *Compr Psychiatry*. 2017;73:23-30.
18. Beutler LE, Harwood TM. Prescriptive psychotherapy: A practical guide to systematic treatment selection. New York, NY, US: Oxford University Press; 2000. viii, 198-viii, p.
19. Lee AH, DiGiuseppe R. Anger and aggression treatments: a review of meta-analyses. *Current Opinion in Psychology*. 2018;19:65-74.

20. Bowman Edmondson C, Cohen Conger J. A review of treatment efficacy for individuals with anger problems: conceptual, assessment, and methodological issues. *Clinical psychology review*. 1996;16(3):251-75.
21. Del Vecchio T, O'Leary KD. Effectiveness of anger treatments for specific anger problems: A meta-analytic review. *Clinical psychology review*. 2004;24(1):15-34.
22. Saini M. A Meta-analysis of the Psychological Treatment of Anger: Developing Guidelines for Evidence-Based Practice. *Journal of the American Academy of Psychiatry and the Law Online*. 2009;37(4):473-88.
23. Lee V, Hoaken PN. Cognition, emotion, and neurobiological development: mediating the relation between maltreatment and aggression. *Child Maltreat*. 2007;12(3):281-98.
24. Ehring T, Welboren R, Morina N, Wicherts JM, Freitag J, Emmelkamp PM. Meta-analysis of psychological treatments for posttraumatic stress disorder in adult survivors of childhood abuse. *Clinical psychology review*. 2014;34(8):645-57.
25. Daffern M, Howells K. Psychiatric inpatient aggression: A review of structural and functional assessment approaches. *Aggression and Violent Behavior*. 2002;7(5):477-97.
26. Canova Mosele PH, Chervenski Figueira G, Antonio Bertuol Filho A, Ferreira de Lima JAR, Calegaro VC. Involuntary psychiatric hospitalization and its relationship to psychopathology and aggression. *Psychiatry research*. 2018;265:13-8.
27. Arnetz JE, Hamblin L, Ager J, Luborsky M, Upfal MJ, Russell J, et al. Underreporting of Workplace Violence: Comparison of Self-Report and Actual Documentation of Hospital Incidents. *Workplace health & safety*. 2015;63(5):200-10.
28. Flannery RB, Wyshak G, Flannery GJ. Characteristics of International Staff Victims of Psychiatric Patient Assaults: Review of Published Findings, 2013–2017. *Psychiatric Quarterly*. 2018;89(2):285-92.
29. Foster C, Bowers L, Nijman H. Aggressive behaviour on acute psychiatric wards: prevalence, severity and management. *Journal of advanced nursing*. 2007;58(2):140-9.
30. Carr VJ, Lewin TJ, Sly KA, Conrad AM, Tirupati S, Cohen M, et al. Adverse incidents in acute psychiatric inpatient units: rates, correlates and pressures. *The Australian and New Zealand journal of psychiatry*. 2008;42(4):267-82.
31. Eisele F, Flammer E, Steinert T. Incidents of aggression in German psychiatric hospitals: Is there an increase? *PloS one*. 2021;16(1):e0245090.
32. Nicholls TL, Brink J, Greaves C, Lussier P, Verdun-Jones S. Forensic psychiatric inpatients and aggression: an exploration of incidence, prevalence, severity, and interventions by gender. *International journal of law and psychiatry*. 2009;32(1):23-30.
33. Bowers L, Stewart D, Papadopoulos C, Dack C, Ross J, Khanom H, et al. Inpatient violence and aggression: a literature review. 2011.
34. Rampling J, Furtado V, Winsper C, Marwaha S, Lucca G, Livanou M, et al. Non-pharmacological interventions for reducing aggression and violence in serious mental illness: A systematic review and narrative synthesis. *Eur Psychiatry*. 2016;34:17-28.
35. Goedhard LE, Stolker JJ, Heerdink ER, Nijman HL, Olivier B, Egberts TC. Pharmacotherapy for the treatment of aggressive behavior in general adult psychiatry: A systematic review. *The Journal of clinical psychiatry*. 2006;67(7):1013-24.

36. Rameckers SA, Verhoef REJ, Grasman R, Cox WR, van Emmerik AAP, Engelmoer IM, et al. Effectiveness of Psychological Treatments for Borderline Personality Disorder and Predictors of Treatment Outcomes: A Multivariate Multilevel Meta-Analysis of Data from All Design Types. *J Clin Med*. 2021;10(23).
37. Gibbon S, Khalifa NR, Cheung N-Y, Völlm BA, McCarthy L. Psychological interventions for antisocial personality disorder. *Cochrane Database of Systematic Reviews*. 2020(9).
38. Khalifa NR, Gibbon S, Völlm BA, Cheung NH, McCarthy L. Pharmacological interventions for antisocial personality disorder. *Cochrane Database Syst Rev*. 2020;9(9):Cd007667.
39. Gartlehner G, Crotty K, Kennedy S, Edlund MJ, Ali R, Siddiqui M, et al. Pharmacological Treatments for Borderline Personality Disorder: A Systematic Review and Meta-Analysis. *CNS drugs*. 2021;35(10):1053-67.
40. Goedhard LE, Stolker JJ, Nijman HL, Egberts TC, Heerdink ER. Trials assessing parmacotherapeutic management of aggression in psychiatric patients: comparability with clinical practice. *Pharmacopsychiatry*. 2010;43(6):205-9.
41. Health NCCfM, editor Violence and Aggression: short-term management in mental health, health and community settings: updated edition2015: British Psychological Society.
42. Schoenthaler S, Amos S, Doraz W, Kelly M-A, Muedeking G, Jr JW. The Effect of Randomized Vitamin-Mineral Supplementation on Violent and Non-violent Antisocial Behavior Among Incarcerated Juveniles. *Journal of Nutritional & Environmental Medicine*. 1997;7(4):343-52.
43. Schoenthaler S, Gast D, Giltay EJ, Amos S. The Effects of Vitamin-Mineral Supplements on Serious Rule Violations in Correctional Facilities for Young Adult Male Inmates: A Randomized Controlled Trial. *Crime & Delinquency*. 2021:0011128721989073.
44. Schoenthaler SJ, Bier ID. The effect of vitamin-mineral supplementation on juvenile delinquency among American schoolchildren: a randomized, double-blind placebo-controlled trial. *Journal of alternative and complementary medicine (New York, NY)*. 2000;6(1):7-17.
45. Gesch CB, Hammond SM, Hampson SE, Eves A, Crowder MJ. Influence of supplementary vitamins, minerals and essential fatty acids on the antisocial behaviour of young adult prisoners. Randomised, placebo-controlled trial. *The British journal of psychiatry : the journal of mental science*. 2002;181:22-8.
46. Zaalberg A, Nijman H, Bulten E, Stroosma L, van der Staak C. Effects of nutritional supplements on aggression, rule-breaking, and psychopathology among young adult prisoners. *Aggressive behavior*. 2010;36(2):117-26.
47. Long SJ, Benton D. A double-blind trial of the effect of docosahexaenoic acid and vitamin and mineral supplementation on aggression, impulsivity, and stress. *Human psychopharmacology*. 2013;28(3):238-47.
48. Tammam JD, Steinsaltz D, Bester DW, Semb-Andenaes T, Stein JF. A randomised double-blind placebo-controlled trial investigating the behavioural effects of vitamin, mineral and n-3 fatty acid supplementation in typically developing adolescent schoolchildren. *The British journal of nutrition*. 2016;115(2):361-73.

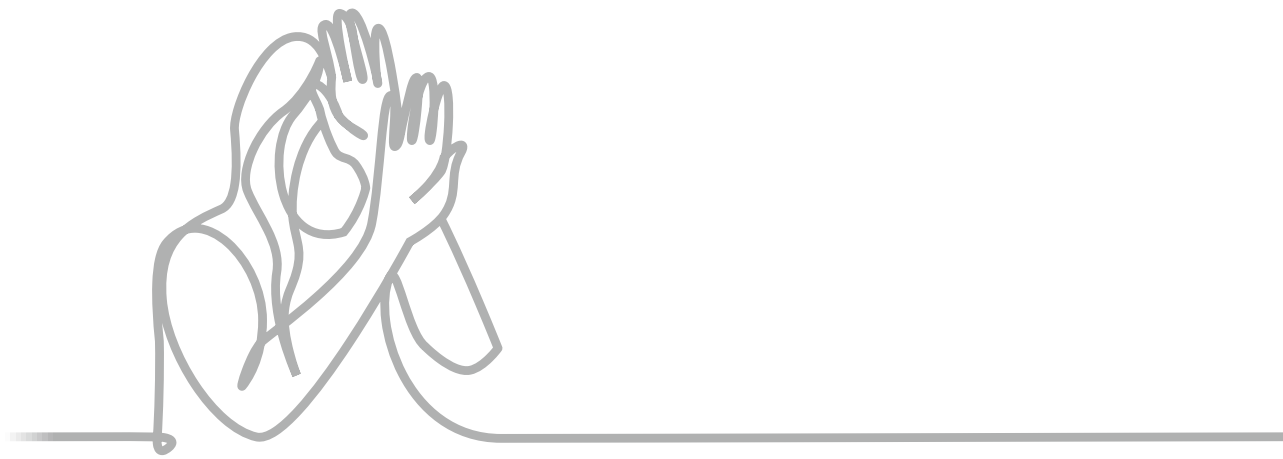
49. Raine A, Cheney RA, Ho R, Portnoy J, Liu J, Soyfer L, et al. Nutritional supplementation to reduce child aggression: a randomized, stratified, single-blind, factorial trial. *Journal of child psychology and psychiatry, and allied disciplines*. 2016;57(9):1038-46.
50. Rucklidge JJ, Eggleston MJF, Johnstone JM, Darling K, Frampton CM. Vitamin-mineral treatment improves aggression and emotional regulation in children with ADHD: a fully blinded, randomized, placebo-controlled trial. *Journal of child psychology and psychiatry, and allied disciplines*. 2018;59(3):232-46.
51. Adams JB, Audhya T, McDonough-Means S, Rubin RA, Quig D, Geis E, et al. Effect of a vitamin/mineral supplement on children and adults with autism. *BMC pediatrics*. 2011;11:111.
52. Bowers L. Safewards: a new model of conflict and containment on psychiatric wards. *Journal of psychiatric and mental health nursing*. 2014;21(6):499-508.
53. Bowers L, Alexander J, Bilgin H, Botha M, Dack C, James K, et al. Safewards: the empirical basis of the model and a critical appraisal. *Journal of psychiatric and mental health nursing*. 2014;21(4):354-64.
54. Finch K, Lawrence D, Williams MO, Thompson AR, Hartwright C. A Systematic Review of the Effectiveness of Safewards: Has Enthusiasm Exceeded Evidence? *Issues in mental health nursing*. 2022;43(2):119-36.
55. Ward-Stockham K, Kapp S, Jarden R, Gerdtz M, Daniel C. Effect of Safewards on reducing conflict and containment and the experiences of staff and consumers: A mixed-methods systematic review. *International journal of mental health nursing*. 2022;31(1):199-221.
56. Tafrate RC, Kassinove H, Dundin L. Anger episodes in high- and low-trait-anger community adults. 2002;58(12):1573-90.
57. Orri M, Perret LC, Turecki G, Geoffroy MC. Association between irritability and suicide-related outcomes across the life-course. Systematic review of both community and clinical studies. *Journal of affective disorders*. 2018;239:220-33.
58. Olofsson B, Jacobsson L. A plea for respect: involuntarily hospitalized psychiatric patients' narratives about being subjected to coercion. *Journal of psychiatric and mental health nursing*. 2001;8(4):357-66.
59. Allikmets S, Marshall C, Murad O, Gupta K. Seclusion: A Patient Perspective. *Issues in mental health nursing*. 2020;41(8):723-35.
60. Edward KL, Stephenson J, Ousey K, Lui S, Warelow P, Giandinoto JA. A systematic review and meta-analysis of factors that relate to aggression perpetrated against nurses by patients/relatives or staff. *Journal of Clinical Nursing*. 2016;25(3-4):289-99.
61. Moylan L, Cullinan MJJop, nursing mh. Frequency of assault and severity of injury of psychiatric nurses in relation to the nurses' decision to restrain. 2011;18(6):526-34.
62. Richter D, Berger K. Post-traumatic stress disorder following patient assaults among staff members of mental health hospitals: a prospective longitudinal study. *BMC Psychiatry*. 2006;6:15.
63. Lee J, Daffern M, Ogloff JR, Martin T. Towards a model for understanding the development of post-traumatic stress and general distress in mental health nurses. *International journal of mental health nursing*. 2015;24(1):49-58.
64. d'Ettorre G, Pellicani V. Workplace Violence Toward Mental Healthcare Workers Employed in Psychiatric Wards. *Saf Health Work*. 2017;8(4):337-42.

65. Zhao SH, Shi Y, Sun ZN, Xie FZ, Wang JH, Zhang SE, et al. Impact of workplace violence against nurses' thriving at work, job satisfaction and turnover intention: A cross-sectional study. *J Clin Nurs*. 2018;27(13-14):2620-32.
66. López-López IM, Gómez-Urquiza JL, Cañadas GR, De la Fuente EI, Albendín-García L, Cañadas-De la Fuente GA. Prevalence of burnout in mental health nurses and related factors: a systematic review and meta-analysis. *International journal of mental health nursing*. 2019;28(5):1032-41.
67. Nijman HLI, Bowers L, Oud N, Jansen G. Psychiatric nurses' experiences with inpatient aggression. *Aggressive behavior*. 2005;31(3):217-27.
68. Arnetz JE, Arnetz BB. Violence towards health care staff and possible effects on the quality of patient care. *Soc Sci Med*. 2001;52(3):417-27.
69. Sofield L, Salmond SW. Workplace violence. A focus on verbal abuse and intent to leave the organization. *Orthop Nurs*. 2003;22(4):274-83.
70. Rubio-Valera M, Luciano JV, Ortiz JM, Salvador-Carulla L, Gracia A, Serrano-Blanco A. Health service use and costs associated with aggressiveness or agitation and containment in adult psychiatric care: a systematic review of the evidence. *BMC Psychiatry*. 2015;15:35.
71. Aarten P, Hudepohl M, Lakerveld Jv, Matthys J, Buiskool B-J. Agressie en geweld in het veiligheidsveld. 2020.
72. Agressie en ongewenst gedrag op de werkvloer. Ipsos; 2021.
73. Abraham M, Soomeren Pv. Buitengewoon veilig. 2020.
74. Pede VB, Jaiswal SV, Sawant VA. Study of prodromal and residual symptoms of depression. *Industrial psychiatry journal*. 2017;26(2):121-7.
75. Hoertnagl CM, Yalcin-Siedentopf N, Baumgartner S, Biedermann F, Deisenhammer EA, Hausmann A, et al. Affective prosody perception in symptomatically remitted patients with schizophrenia and bipolar disorder. *Schizophrenia Research*. 2014;158(1):100-4.
76. Hardeveld F, Spijker J, De Graaf R, Nolen WA, Beekman ATF. Prevalence and predictors of recurrence of major depressive disorder in the adult population. *Acta psychiatrica Scandinavica*. 2010;122(3):184-91.
77. Association AP. Diagnostic and statistical manual of mental disorders (DSM-5®): American Psychiatric Pub; 2013.
78. Cassiello-Robbins C, Barlow DH. Anger: The Unrecognized Emotion in Emotional Disorders. *Clinical Psychology: Science and Practice*. 2016;23(1):66-85.
79. Nabi H, Singh-Manoux A, Ferrie JE, Marmot MG, Melchior M, Kivimäki M. Hostility and depressive mood: results from the Whitehall II prospective cohort study. *Psychological medicine*. 2010;40(3):405-13.
80. Miller TQ, Markides KS, Chiriboga DA, Ray LA. A Test of the Psychosocial Vulnerability and Health Behavior Models of Hostility: Results From an 11-Year Follow-Up Study of Mexican Americans. *Psychosomatic medicine*. 1995;57(6).
81. Smith TW. Hostility and health: current status of a psychosomatic hypothesis. *Health Psychol*. 1992;11(3):139-50.
82. McKay MT, Cannon M, Chambers D, Conroy RM, Coughlan H, Dodd P, et al. Childhood trauma and adult mental disorder: A systematic review and meta-analysis of longitudinal cohort studies. *Acta psychiatrica Scandinavica*. 2021;143(3):189-205.
83. Win E, Zainal NH, Newman MG. Trait anger expression mediates childhood trauma predicting for adulthood anxiety, depressive, and alcohol use disorders. *Journal of affective disorders*. 2021;288:114-21.

84. McLaughlin KA, Lambert HK. Child trauma exposure and psychopathology: mechanisms of risk and resilience. *Current Opinion in Psychology*. 2017;14:29-34.
85. McLaughlin KA. Future Directions in Childhood Adversity and Youth Psychopathology. *J Clin Child Adolesc Psychol*. 2016;45(3):361-82.
86. McLaughlin KA, Peverill M, Gold AL, Alves S, Sheridan MA. Child Maltreatment and Neural Systems Underlying Emotion Regulation. *J Am Acad Child Adolesc Psychiatry*. 2015;54(9):753-62.
87. McLaughlin KA, Weissman D, Bitrán D. Childhood Adversity and Neural Development: A Systematic Review. *Annu Rev Dev Psychol*. 2019;1:277-312.
88. Viding E, Sebastian CL, Dadds MR, Lockwood PL, Cecil CA, De Brito SA, et al. Amygdala response to preattentive masked fear in children with conduct problems: the role of callous-unemotional traits. *The American journal of psychiatry*. 2012;169(10):1109-16.
89. Weissman DG, Bitran D, Miller AB, Schaefer JD, Sheridan MA, McLaughlin KA. Difficulties with emotion regulation as a transdiagnostic mechanism linking child maltreatment with the emergence of psychopathology. *Development and psychopathology*. 2019;31(3):899-915.
90. Heleniak C, Jenness JL, Stoep AV, McCauley E, McLaughlin KA. Childhood Maltreatment Exposure and Disruptions in Emotion Regulation: A Transdiagnostic Pathway to Adolescent Internalizing and Externalizing Psychopathology. *Cognit Ther Res*. 2016;40(3):394-415.
91. McLaughlin KA, Kubzansky LD, Dunn EC, Waldinger R, Vaillant G, Koenen KC. Childhood social environment, emotional reactivity to stress, and mood and anxiety disorders across the life course. *Depression and anxiety*. 2010;27(12):1087-94.
92. Herringa RJ, Birn RM, Ruttle PL, Burghy CA, Stodola DE, Davidson RJ, et al. Childhood maltreatment is associated with altered fear circuitry and increased internalizing symptoms by late adolescence. *Proc Natl Acad Sci U S A*. 2013;110(47):19119-24.
93. Kim-Spoon J, Cicchetti D, Rogosch FA. A longitudinal study of emotion regulation, emotion lability-negativity, and internalizing symptomatology in maltreated and nonmaltreated children. *Child Dev*. 2013;84(2):512-27.
94. van der Maas HL, Molenaar PC. Stagewise cognitive development: an application of catastrophe theory. *Psychological review*. 1992;99(3):395-417.
95. de Bles NJ, Hazewinkel AWP, Bogers JPAM, van den Hout WB, Mouton C, van Hemert AM, et al. The incidence and economic impact of aggression in closed long-stay psychiatric wards. *International journal of psychiatry in clinical practice*. 2020:1-7.
96. Meerding WJ, Bonneux L, Polder JJ, Koopmanschap MA, van der Maas PJ. Demographic and epidemiological determinants of healthcare costs in Netherlands: cost of illness study. *Bmj*. 1998;317(7151):111-5.
97. Taipale H, Schneider-Thoma J, Pinzón-Espinosa J, Radua J, Efthimiou O, Vinkers CH, et al. Representation and Outcomes of Individuals With Schizophrenia Seen in Everyday Practice Who Are Ineligible for Randomized Clinical Trials. *JAMA psychiatry*. 2022;79(3):210-8.
98. Osby U, Correia N, Brandt L, Ekbom A, Sparén P. Mortality and causes of death in schizophrenia in Stockholm county, Sweden. *Schizophr Res*. 2000;45(1-2):21-8.
99. Walker ER, McGee RE, Druss BG. Mortality in Mental Disorders and Global Disease Burden Implications: A Systematic Review and Meta-analysis. *JAMA psychiatry*. 2015;72(4):334-41.

100. Correll CU, Solmi M, Veronese N, Bortolato B, Rosson S, Santonastaso P, et al. Prevalence, incidence and mortality from cardiovascular disease in patients with pooled and specific severe mental illness: a large-scale meta-analysis of 3,211,768 patients and 113,383,368 controls. 2017;16(2):163-80.
101. Tiihonen J, Lönnqvist J, Wahlbeck K, Klaukka T, Niskanen L, Tanskanen A, et al. 11-year follow-up of mortality in patients with schizophrenia: a population-based cohort study (FIN11 study). *Lancet*. 2009;374(9690):620-7.
102. Lawrence D, Hancock KJ, Kisely S. The gap in life expectancy from preventable physical illness in psychiatric patients in Western Australia: retrospective analysis of population based registers. 2013;346:f2539.
103. Oakley P, Kisely S, Baxter A, Harris M, Desoe J, Dziouba A, et al. Increased mortality among people with schizophrenia and other non-affective psychotic disorders in the community: A systematic review and meta-analysis. *Journal of psychiatric research*. 2018;102:245-53.
104. Ringen PA, Falk RS, Antonsen B, Faerden A, Mamen A, Rognli EB, et al. Using motivational techniques to reduce cardiometabolic risk factors in long term psychiatric inpatients: a naturalistic interventional study. *BMC Psychiatry*. 2018;18(1):255.
105. Hjorth P, Davidsen AS, Kilian R, Pilgaard Eriksen S, Jensen SO, Sørensen H, et al. Improving the physical health of long-term psychiatric inpatients. *The Australian and New Zealand journal of psychiatry*. 2014;48(9):861-70.
106. Maier L, Pruteanu M, Kuhn M, Zeller G, Telzerow A, Anderson EE, et al. Extensive impact of non-antibiotic drugs on human gut bacteria. *Nature*. 2018;555(7698):623-8.
107. Dinan TG, Cryan JF. Schizophrenia and the microbiome: Time to focus on the impact of antipsychotic treatment on the gut microbiota. *The World Journal of Biological Psychiatry*. 2018;19(8):568-70.
108. David LA, Maurice CF, Carmody RN, Gootenberg DB, Button JE, Wolfe BE, et al. Diet rapidly and reproducibly alters the human gut microbiome. *Nature*. 2014;505(7484):559-63.
109. Cryan JF, O'Mahony SM. The microbiome-gut-brain axis: from bowel to behavior. *Neurogastroenterol Motil*. 2011;23(3):187-92.
110. Wiley NC, Cryan JF, Dinan TG, Ross RP, Stanton C. Production of Psychoactive Metabolites by Gut Bacteria. *Mod Trends Psychiatry*. 2021;32:74-99.
111. Luczynski P, Whelan SO, O'Sullivan C, Clarke G, Shanahan F, Dinan TG, et al. Adult microbiota-deficient mice have distinct dendritic morphological changes: differential effects in the amygdala and hippocampus. *Eur J Neurosci*. 2016;44(9):2654-66.
112. Mayer EA, Knight R, Mazmanian SK, Cryan JF, Tillisch K. Gut microbes and the brain: paradigm shift in neuroscience. *J Neurosci*. 2014;34(46):15490-6.
113. Sommer F, Backhed F. The gut microbiota--masters of host development and physiology. *Nat Rev Microbiol*. 2013;11(4):227-38.
114. Stilling RM, Dinan TG, Cryan JF. Microbial genes, brain & behaviour - epigenetic regulation of the gut-brain axis. *Genes Brain Behav*. 2014;13(1):69-86.
115. Evrensel A, Ceylan ME. The Gut-Brain Axis: The Missing Link in Depression. *Clin Psychopharmacol Neurosci*. 2015;13(3):239-44.
116. Bretler T, Weisberg H, Koren O, Neuman H. The effects of antipsychotic medications on microbiome and weight gain in children and adolescents. *BMC Med*. 2019;17(1):112.

117. Flowers SA, Evans SJ, Ward KM, McInnis MG, Ellingrod VL. Interaction Between Atypical Antipsychotics and the Gut Microbiome in a Bipolar Disease Cohort. *Pharmacotherapy*. 2017;37(3):261-7.



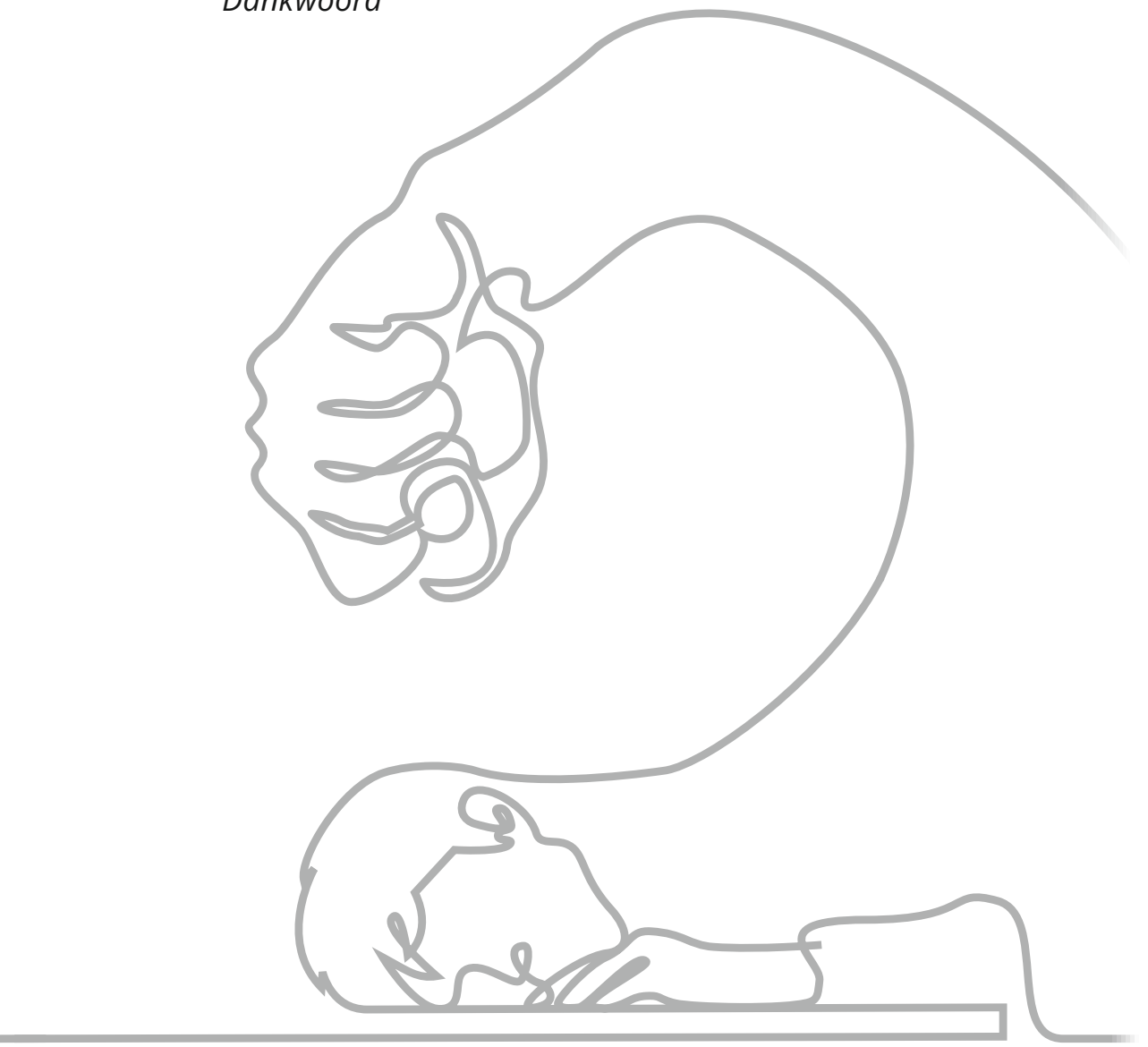
Addendum

Nederlandse samenvatting

List of publications

Curriculum vitae

Dankwoord



Nederlandse samenvatting

Boosheid is een universele emotie die, net als verdriet en angst, regelmatig wordt ervaren in verschillende culturen. Boosheid kan echter ook problematisch worden wanneer iemand zich veelvuldig en overmatig boos voelt. Het uiten van boosheid kan leiden tot schadelijke gebeurtenissen, waaronder gebeurtenissen die bij wet verboden zijn. In onze huidige "beschaafde" samenleving is er dan ook een sterke sociale afkeur om boos te zijn. Boosheid lijkt hierdoor een verboden emotie te zijn geworden, wat is terug te zien in het feit dat het lang genegeerd is in wetenschappelijk onderzoek en in de klinische praktijk. Dit heeft geleid tot een schaarste aan meetinstrumenten en psychologische en medicamenteuze behandelingsopties, terwijl er een grote behoefte is om te identificeren wie het meest kwetsbaar is voor onaangepaste boosheid en om de mechanismen die hiermee gemoeid zijn vast te stellen om zo effectieve interventies te kunnen initiëren.

Het doel van dit proefschrift is om de prevalentie, determinanten en behandeling van boosheid en agressie bij psychiatrische patiënten te ontrafelen. De doelstellingen waren drieledig: (1) onderzoeken of en in welke mate boosheid en agressie geassocieerd zijn met psychiatrische stoornissen; (2) ons begrip vergroten van mechanismen die kunnen leiden tot boosheid dan wel agressie; en (3) om te onderzoeken of het toedienen van voedingssupplementen helpt in het verminderen van agressie bij psychiatrische patiënten.

Het eerste en tweede deel van dit proefschrift zijn gebaseerd op gegevens van de Nederlandse Studie naar Depressie en Angst (NESDA). Binnen NESDA werden deelnemers mét en zónder klachten van angst en/of depressie geworven via huisartspraktijken en GGZ-instellingen in de regio Amsterdam, Leiden, en de provincies Groningen, Drenthe en Friesland. Het derde deel van dit proefschrift maakt gebruik van de Voeding en Agressie-studie, een gerandomiseerde klinische studie waarin deelnemers werden geworven die in instellingen voor langdurige psychiatrische zorg verbleven. In de volgende paragrafen worden de belangrijkste resultaten van deze studies besproken in de context van bestaand onderzoek.

Deel I: Boosheid bij poliklinische psychiatrische patiënten

In **Hoofdstuk 2** onderzochten we de prevalentie van boosheid als karaktertrek en in de vorm van woedeaanvallen bij patiënten met stemmings- en/of angststoornissen en gezonde controles. Dit borduurt voort op eerdere studies. Echter, eerdere onderzoeken gebruikten onvoldoende gevalideerde instrumenten of zelfs slechts één item om een deelaspect, zoals prikkelbaarheid, te meten. Het maken van een onderscheid tussen een toestandsbeeld versus een karaktereigenschap is van belang om te bepalen of een construct constant is of fluctueert over de tijd. Onze bevindingen lieten zien dat boosheid meer voorkomt bij patiënten met stemmings- en angststoornissen ten opzichte van gezonde controles. Met name was dit het geval bij de patiënten met een gecombineerde stemmings- en angststoornis, gevolgd door patiënten met enkel een angststoornis, stemmingsstoornis, en patiënten bij wie deze stoornis in remissie was. Meer dan 40% van de patiënten met een gecombineerde diagnose rapporteerde een verhoogde aanleg om boos te worden en ruim 20% rapporteerde woedeaanvallen, ten opzichte van slechts 5% en 1% bij de groep gezonde controles. Concluderend vinden wij een robuust bewijs voor de relatie tussen boosheid en bepaalde vormen van psychopathologie.

De relatie tussen boosheid en psychopathologie hebben we nader bestudeerd bij een specifieke groep van patiënten met stemmingsklachten. Een deel van de patiënten met stemmingsklachten wordt namelijk aanvankelijk gediagnosticeerd met een depressieve stoornis, maar later blijkt dat er sprake is van een bipolaire stoornis. Dit komt doordat patiënten met een bipolaire stoornis vaak een of meer depressieve episoden doormaken voor het begin van hun eerste (hypo)manische episode. Omdat de behandeling voor een bipolaire stoornis anders is dan voor een depressie, is het van belangrijk om risicofactoren van het ontwikkelen van een bipolaire stoornis te identificeren. In **Hoofdstuk 3** van dit proefschrift keken we naar de relatie tussen verschillende aspecten van boosheid aan de ene kant, en het ontwikkelen van een bipolaire stoornis aan de andere kant. We onderzochten of patiënten met een bipolaire stoornis meer boosheid, woedeaanvallen en antisociale- en borderline persoonlijkheidskenmerken rapporteerden dan patiënten met een (voorgeschiedenis van een) depressie. Daarnaast is prospectief gekeken of een hogere rapportage op een maat voor agressiereactiviteit het ontwikkelen van een bipolaire stoornis kan voorspellen. De verschillende aspecten van boosheid werden inderdaad vaker gerapporteerd door patiënten met een bipolaire stoornis ten opzichte van patiënten met een (voorgeschiedenis van een) unipolaire depressie. Bovendien was agressiereactiviteit een voorspeller voor de conversie naar bipolaire stoornis bij personen met een voorgeschiedenis

van unipolaire depressie. Deze resultaten suggereren dat het uitvragen van boosheid klinisch relevant kan zijn in het kader van vroege herkenning van een (hypo)manie en de eventuele preventieve behandeling daarvan.

Deel II: De pathofysiologie van boosheid en agressie

Het tweede deel van dit proefschrift richt zich op de pathofysiologie van boosheid en agressie. Hoewel we een robuuste relatie vinden tussen boosheid en agressie aan de ene kant, en psychopathologie aan de andere kant, geldt deze relatie niet voor iedere individuele psychiatrische patiënt. Om effectieve behandelingen te ontwikkelen is het van belang om meer te weten te komen over onderliggende processen. Een benadering die over diagnosen heen van belang kan zijn is het identificeren van neurobiologische processen. Hierbij lijken onder andere het serotonerge systeem, de werking van de hypothalamus-hypofyse-bijnier (HPA)-as, en het immuunsysteem van belang te zijn. Veranderingen van de HPA-as kunnen onder andere veroorzaakt worden door de blootstelling aan stress in de kindertijd. Deze veranderingen kunnen gepaard gaan met ernstige gevolgen die tot ver in de volwassenheid kunnen voortduren. Ook is in de afgelopen decennia een belangrijke link gevonden tussen de activatie van het immuunsysteem (met verhoogde cytokines) en agressie. Het immuunsysteem bestaat uit de aangeboren en adaptieve immuunrespons, waarbij bijvoorbeeld een infectie met de intracellulaire parasiet *Toxoplasma gondii* (*T. gondii*) een krachtige pro-inflammatoire reactie kan uitlokken. Bij mensen die eenmaal geïnfecteerd zijn met *T. gondii* is de parasiet als latente infectie levenslang aanwezig.

In **Hoofdstuk 4** is de relatie tussen jeugdtrauma en boosheid als volwassene onderzocht. Hierbij is ook gekeken welk type jeugdtrauma een relatie heeft met verschillende aspecten van boosheid, en of deze relatie onafhankelijk is van psychopathologie. Wij vonden een dosis-responsrelatie tussen het mee hebben gemaakt van jeugdtrauma en het op latere leeftijd ervaren van boosheid. Dit betekent dat hoe ernstiger en/of frequenter het jeugdtrauma, hoe hoger er werd gescoord op de verschillende boosheidsaspecten. Bovendien werden verschillende types jeugdtrauma, behalve seksueel misbruik, in verband gebracht met boosheid als karaktertrek, woedeaanvallen, en cluster B persoonlijkheidskenmerken. Dit verband bleek onafhankelijk te zijn van de gemeten psychopathologie. Deze resultaten wijzen erop dat boosheid tijdens de volwassenheid mogelijk een laat gevolg kan zijn van jeugdtrauma. Om de cyclus van misbruik te doorbreken, is het belangrijk dat clinici zich bewust zijn van deze relatie en waar nodig traumagerichte behandeling starten ter voorkoming van zowel psychopathologie als boosheid.

In **Hoofdstuk 5** is de relatie tussen *T. gondii* seropositiviteit in relatie tot de aanwezigheid en ernst van depressie en angststoornissen onderzocht. Daarnaast onderzochten we de relatie tussen *T. gondii* seropositiviteit met zowel agressieve en suïcidale gedachten. Om dit te onderzoeken maakten we gebruik van 1731 bloedmonsters verkregen van NESDA deelnemers, waarvan 673 deelnemers (38,9%) seropositief waren voor *T. gondii*-antilichamen. Wij vonden hierbij geen relatie tussen *T. gondii* seropositiviteit en psychopathologie, agressieve- of suïcidale gedachten. In het licht van onze bevindingen, in combinatie met eerdere studies waarbij geen duidelijke consensus over deze relatie werd gevonden, lijkt het onwaarschijnlijk dat seropositiviteit van *T. gondii* een belangrijke rol speelt in het risico op affectieve stoornissen, agressieve- en suïcidale gedachten.

Deel III: Agressie bij langdurig opgenomen psychiatrische patiënten

Het laatste deel van dit proefschrift gaat over agressie bij langdurig opgenomen psychiatrische patiënten. Agressie komt veel voor in de intramurale zorg, mede ook omdat agressief gedrag vaak een reden is voor een doorverwijzing naar deze vorm van zorg. Dit betekent dan ook dat een aanzienlijk aantal opgenomen patiënten agressief gedrag vertoont, wat niet alleen een reden is voor opname, maar mogelijk ook een gevolg ervan.

In **Hoofdstuk 6** onderzochten we de incidentie van agressie op gesloten opname afdelingen. Op basis van een telling van de frequentie van agressief gedrag (incidentie) onderzochten we vervolgens de tijds- en geldinvestering die hiermee gepaard gaat. We vonden een incidentie van 90 incidenten per patiëntjaar op gesloten opname afdelingen van drie regionale GGZ-centra. Omgerekend betekent dit dat er gemiddeld 5 incidenten per dag voorkomen op een afdeling waar 20 patiënten verblijven. De gemiddelde tijdsbesteding per incident was 125 minuten, wat bekent dat elke individuele verpleegkundige, gegeven de gemiddelde personeelsbezetting, meer dan een half uur per dienst bezig was met een incident. De directe kosten gerelateerd aan incidenten bedroegen circa € 78 per incident. Op basis van onze incidentie zou dit resulteren in een schatting van € 7000 per patiënt per jaar. Deze kosten zijn een onderschatting, omdat we geen kosten hebben opgenomen die indirect worden veroorzaakt door agressie (bijvoorbeeld door afwezigheid van personeel, heropnames en hulp van politie of ambulance). Afgezien van het financiële perspectief, is het verminderen van agressie van groot belang voor zowel patiënten als personeel. Een positieve verandering in het agressieniveau hoeft niet direct van invloed te zijn op het budget,

maar wordt gecompenseerd door de beschikbare tijd voor therapeutische en sociale activiteiten, waardoor de kwaliteit van de zorg kan verbeteren.

Eerdere studies bij forensische populaties en kinderen met gedragsproblemen lieten aanwijzingen zien dat voedingssuppletie effectief kan zijn in het verminderen van agressie-incidenten en overtredingen. Dit effect is echter nooit aangetoond bij langdurig opgenomen psychiatrische patiënten. In **Hoofdstuk 7** onderzochten we de effectiviteit van suppletie met multivitaminen, mineralen en n-3 PUFA in het verminderen van agressie-incidenten bij 176 langdurig opgenomen psychiatrische patiënten. Wij onderzochten ook of voedingssuppletie gevoelens van agressie en affectieve symptomen kan verminderen en de kwaliteit van leven kan verbeteren. Onze bevindingen bieden helaas geen ondersteuning voor de effectiviteit van deze interventie in het verminderen van agressie na een interventie van 6 maanden. Ook wanneer werd ingezoomd op de ernst of het type incidenten werd geen effectiviteit aangetoond. Hoewel gezonde voeding gestimuleerd moet worden vanwege welzijns- en algemene gezondheidsproblemen, is er vooralsnog geen rol weggelegd voor voedingssupplementen om agressie te verminderen.

Zoals beschreven in hoofdstuk 7, hebben wij de veelbelovende effecten van voedingssuppletie op agressie-incidenten, die in eerdere studies werden gevonden, niet kunnen bevestigen bij opgenomen psychiatrische patiënten. Dit gegeven benadrukt dat we voorzichtig moeten zijn met het generaliseren van eerdere resultaten naar (langdurig) opgenomen psychiatrische patiënten of anderen met een ernstige psychiatrische aandoening (EPA). Helaas is deze doelgroep ondervertegenwoordigd in interventiestudies, wat resulteert in een gebrek aan bewezen effectieve zorg voor deze groep. Het opzetten en uitvoeren van een interventiestudie vereiste continue besluitvorming en kent veel uitdagingen, met name bij een kwetsbare doelgroep met gedragsproblemen. In **Hoofdstuk 8** reflecteren we op de uitdagingen en beschrijven we de lessen die zijn getrokken uit twee interventiestudies, de een bij langdurig opgenomen psychiatrische patiënten, en de ander bij mensen met een verstandelijke beperking. We beschreven vijf thema's die het onderzoek bemoeilijken: (1) onderzoek op meerdere locaties, (2) inclusie van kwetsbare deelnemers, (3) voedingssupplementen en placebo's, (4) agressie als uitkomstmaat en (5) verzamelen van bio-monsters. Door deze ervaringen te delen, hopen we andere onderzoekers op weg te helpen in het opzetten van interventiestudies, waarbij zij de problemen waar wij tegenaan liepen hopelijk kunnen minimaliseren om zo de implementatie van interventiestudies te vergemakkelijken.

Samenvattend is mijn conclusie dat vroegtijdige herkenning en een passende behandeling van boosheid en agressie een enorme invloed kan hebben op het uiteindelijke functioneren van zorgprofessionals, de samenleving, en bovenal de patiënten zelf. Het is in het belang van ons allemaal dat we boosheid aan de orde stellen tijdens intake en (psycho)therapie. Dit kan er aan bijdragen om het taboe rond boosheid te doorbreken, zodat patiënten hierin niet langer alleen staan en door boosheid worden verslonden.

List of publications

De Bles, N. J., Rius Ottenheim, N., Geleijnse, J. M., Van De Rest, O., Bogers, J. P., Schat, A., Nijman, H. L. I., van den Berg, D., Joos, L., van Strater, A., de Ridder, T., Stolker, J. J., van den Hout, W. B., van Hemert, A. M., & Giltay, E. J. (2022). Effects of multivitamin, mineral and n-3 polyunsaturated fatty acid supplementation on aggression among long-stay psychiatric in-patients: randomised clinical trial. *BJPsych open*, *8*(2).

De Bles, N. J., Gast, D. A., van der Slot, A. J., Didden, R., van Hemert, A. M., Rius-Ottenheim, N., & Giltay, E. J. (2022). Lessons learned from two clinical trials on nutritional supplements to reduce aggressive behaviour. *Journal of evaluation in clinical practice*.

De Bles, N. (2021). Breng boosheid tijdig in kaart! *GZ-Psychologie*, *13*(2), 26-29.

Mesbah, R., **de Bles, N.J.**, Rius-Ottenheim, N., van der Does, A. J. W., Penninx, B. W. J. H., van Hemert, A. M., de Leeuw, M., Giltay, E. J., & Koenders, M. (2021). Anger and cluster B personality traits and the conversion from unipolar depression to bipolar disorder. *Depression and anxiety*, *38*(6), 671-681.

De Bles, N. J., van der Does, J. E. H., Kortbeek, L. M., Hofhuis, A., van Grootheest, G., Vollaard, A. M., Schoevers, R. A., van Hemert, A. M., Penninx, B. W. J. H., Rius Ottenheim, N., & Giltay, E. J. (2021). Toxoplasma gondii seropositivity in patients with depressive and anxiety disorders. *Brain, behavior, & immunity-health*, *11*, 100197.

De Bles, N. J., Hazewinkel, A. W. P., Bogers, J. P. A. M., van den Hout, W. B., Mouton, C., van Hemert, A. M., Rius Ottenheim, N., Giltay, E. J. (2020). The incidence and economic impact of aggression in closed long-stay psychiatric wards. *International Journal of Psychiatry in Clinical Practice, 25*(4), 430-436.

De Bles, N. J., Rius Ottenheim, N., van Hemert, A. M., Putz, L. E. H., van der Does, A. J. W., Penninx, B. W. J. H., & Giltay, E. J. (2019). Trait anger and anger attacks in relation to depressive and anxiety disorders. *Journal of Affective Disorders*, 259-265.

Jakob, L., Bojanić, L., Tsvetanova, D. D., Buabang, E. K., **De Bles, N. J.**, Sarafoglou, A., Dijkzeul, A., Del Pino, R. (2016). Study Protocol on Cognitive Performance across Europe: The Normacog Brief Battery. *Frontiers in Psychology*, 1658.

Ruggeri, K., Lind Andersen, T., Robbins, T. W., Folke, T. E. N., Schei, T. S., Matz, S. C., Müller, S. R., Van Bokhorst, L. G., Marenco, P., Buabang, E. K., Tsvetanova, D. D., Egervári, A., Wingen, T., Hubená, B., **De Bles, N. J.,** Szebeni, Z. K., Carbajal, G. V., Thomson, D. T., Čermak, N., Bojanić, L., Tomić, D., Estal Muñoz, V., Wicher, P., Jakob, L., Haastrup, L., Van Geert, E., Knapová, L., Orhon, A., Bursalıoğlu, A., Jarke, H., Gjorgijovska, J., Lecuona, O., Janssens, M., & Zupan, Z. (2016). *Insights for Impact.* University of Cambridge., ISBN: 2398-8932.

Curriculum Vitae

Nienke Jolande de Bles was born on February 10th, 1992, in Alkmaar, The Netherlands. She graduated from high school in 2010 at the Murmellius Gymnasium in Alkmaar. That same year, she moved to Leiden to study Psychology. In 2016, she received her Master of Science in Clinical Neuropsychology (cum laude) at Leiden University. During her master's she conducted her thesis internship at the Generation R study, at the Erasmus MC. This longitudinal cohort study stimulated her enthusiasm about research, which is why she applied for the Junior Researcher Programme; an initiative supported by the department of Psychology at the University of Cambridge. This programme started as a summer school and resulted in a European research project on neurocognitive testing. To complete the Junior Researcher Programme, she co-authored an article during her month as a visiting researcher at the Policy Research Group in Cambridge. In March 2017 she began her doctoral research as described in this thesis at the department of Psychiatry of the Leiden University Medical Centre (LUMC). This research was conducted under the supervision of prof. dr. A. M. van Hemert, dr. E. J. Giltay and dr. N. Rius Ottenheim. During her PhD, she followed several courses and attended and presented at national and international congresses in Maastricht, Nice, Dublin, and Warsaw. In 2020, she was project coordinator of a successful ZonMw grant application for the implementation of the Stress Buddy, which was part of the psychosocial support programme of LUMC during the COVID-19 pandemic. Nienke aims to combine research with clinical work, which is why, in June 2021, she started working as a psychologist at the Fit op Weg Poli of GGZ Delfland while finishing her PhD.

Dankwoord

Mijn promotietraject was leerzaam, maar heb ik bovenal met veel plezier beleefd! In de eerste plaats wil ik daarom mijn promotor, Prof. Dr. Bert van Hemert, en copromotoren, Dr. Erik Giltay en Dr. Nathaly Rius Ottenheim, bedanken. Bert, dankjewel voor alle mogelijkheden de afgelopen jaren om mij te blijven ontwikkelen. Jouw manier van feedback geven heeft me met alle manuscripten geholpen en neem ik de rest van mijn (wetenschappelijke) carrière mee. Erik en Nathaly, jullie stuurden bij waar nodig, maar gaven me tegelijkertijd veel vrijheid. Erik, ik denk dat iedereen wetenschap leuk vindt zodra ze met jou samenwerken. Jouw efficiënte manier van werken zonder passie voor het vak te verliezen is bewonderenswaardig! Nathaly, of het nu ging om de grote lijn of juist om details, jouw aanvullingen waren altijd van grote toegevoegde waarde. Je hebt een scherp oog voor interpersoonlijke vraagstukken en het voelde vertrouwd om hierover bij jou terecht te kunnen.

Dit onderzoek had ik uiteraard niet kunnen uitvoeren zonder iedereen die heeft deelgenomen aan NESDA en PSYVA. Met name voor PSYVA, dat als rode draad door mijn PhD liep, wil ik alle zorgmedewerkers bedanken die hebben geholpen met inclusie, het uitzetten van supplementen en het registreren van incidenten.

Manoek en Simone, door jullie voelde werken op de afdeling meteen aan als een warm bad. Ik ben blij dat we elkaar onder het genot van een glas wijn nog regelmatig spreken. Ook dank ik onderzoeksassistenten en stagiaires voor alle hulp bij de dataverzameling; Elise, Kim, Jantine, Niki, Isabelle, Annemarie, Xanthe, Jos, Lisanne, Juliette, Naomi, Yvonne, Marlijn, Sanne en Jan. Met een koffer vol pillen naar België, op een GGZ terrein staan met een lege accu van de huurauto, in de zomer een ijsje eten samen met een patiënt terwijl je een vragenlijst afneemt; mooie momenten die ik zal blijven koesteren.

Ook bedank ik alle collega's van de afdeling Psychiatrie. Martijn, dankjewel voor het bieden van een platform waar ik werd uitgedaagd om een artikel om te zetten in lekentaal. Rita, wat fijn dat ik met jou heb kunnen meekijken op de afdeling en zo mijn eerste CGT-technieken in de praktijk heb kunnen brengen. Ingrid, dankjewel voor jouw begeleiding rondom de digitalisering van de ROM. Eric, Manon, Nic, dank voor jullie waardevolle input om Stressbuddy uit te rollen. Gea, Mirjam, Petra, zonder jullie (mentale) steun rondom regels en wetten voor het doen van onderzoek was het niet

gelukt! Alice, dankjewel voor de fijne ondersteuning. Zelfs in corona-tijden zorgde jij voor eenheid binnen de afdeling.

Rahele, je bent een geweldig lieve collega en ondanks weinig overlap op de kantoortuin weten we elkaar altijd te vinden. Hoe leuk toen onze onderwerpen samen kwamen in het schrijven van een artikel! Ook Wessel, Stephanie, David, Ericka, Floor, Erwin, Ikrame, Eline, Elvira dank jullie wel voor de tijd in de kantoortuin en daarbuiten. Door jullie heb ik veel geleerd buiten mijn eigen onderzoeksveld: Van psychedelica tot bipolaire patiënten en mensen met een verstandelijke beperking. Ik kijk terug op mooie discussies, borrels en congressen!

Collega's van de Fit op Weg-poli, wat ben ik blij dat ik me twee jaar geleden bij dit mooie team heb kunnen aansluiten. In het bijzonder wil ik mijn werkbegeleiders Suzanne en Janneke bedanken. Jullie kennis en ervaring motiveren me om ook op klinisch vlak te blijven leren.

Lieve Leidse vrienden en vriendinnen, dank jullie allen voor de support, maar bovenal de vele leuke afleidingen. Lieve Emilie, dankjewel voor jouw warme vriendschap vanaf ons allereerste college. Lisa, met jou wonen was een feestje (niet alleen vanwege jouw bakkunsten). Ik bewonder jouw passie voor wetenschap! Sjoerd, dank voor jouw luisterend oor, altijd. Op nog vele NS-wandelingen. An, Ed, Room, Claire, Val en Tess, onze weekendjes bleken genoeg voer voor het maken van spellen! Tess, dankjewel voor jouw duizend voorstellen om te wandelen, musea te bezoeken of een filmpje te pakken. Het is fijn om zo'n vriendin te hebben!

Lieve (schoon)familie, bedankt voor jullie support, etentjes en spelletjesavonden. Oma de Bles, bedankt voor het laten zien blij te zijn met het kleine. Opa & oma Lodder, jullie motto dat ieder succes gevierd moeten worden heb ik de afgelopen jaren ter harte genomen.

Lieve Han en Janny, bedankt voor jullie grenzeloze belangstelling. Ik voel me altijd welkom bij jullie.

Jasper, ik bewonder de manier waarop jij contact legt met mensen over de hele wereld. Wouter, het is heerlijk om jouw ontwikkeling van student naar werkend man te zien. Doortje, ik geniet als wij samen zijn en hou van je creativiteit! Papa en mama, jullie hebben de wereld voor ons over! Van een luisterend oor tot aan uitjes samen. Weet hoe waardevol dat is!

Lieve David, met veel plezier fiets ik naar werk, maar met nog veel meer plezier fiets ik terug naar jou! Ik kijk uit naar alles wat komen gaat.

Life can be compared to a piece of embroidered material of which, every-one in the first half of his time, comes to see the top side, but in the second half, the reverse side. The latter is not so beautiful, but it is more instructive because it enables one to see how the threads are connected together.

— **Irvin D. Yalom**