ORIGINAL RESEARCH

Childhood trauma and negative memory bias as shared risk factors for psychopathology and comorbidity in a naturalistic psychiatric patient sample

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Abstract  
Background: Both childhood trauma and negative memory bias are associated with the onset and severity level of several psychiatric disorders, such as depression and anxiety disorders. Studies on these risk factors, however, generally use homogeneous noncomorbid samples. Hence, studies in naturalistic psychiatric samples are lacking. Moreover, we know little about the quantitative relationship between the frequency of traumatic childhood events, strength of memory bias and number of comorbid psychiatric disorders; the latter being an index of severity. The current study examined the association of childhood trauma and negative memory bias with psychopathology in a large naturalistic psychiatric patient sample.  
Methods: Frequency of traumatic childhood events (emotional neglect, psychological-, physical- and sexual abuse) was assessed using a questionnaire in a sample of 252 adult psychiatric patients with no psychotic or bipolar-I disorder and no cognitive disorder as main diagnosis. Patients were diagnosed for DSM-IV Axis-I and Axis-II disorders using a structured clinical interview. This allowed for the assessment of comorbidity between disorders. Negative memory bias for verbal stimuli was measured using a computer task.  
Results: Linear regression models revealed that the frequency of childhood trauma as well as negative memory bias was positively associated with psychiatric comorbidity, separately and above and beyond each other (all \( p < .01 \)).  
Conclusions: The results indicate that childhood trauma and negative memory bias may be of importance for a broader spectrum of psychiatric diagnoses, besides the frequently studied affective disorders. Importantly, frequently experiencing traumatic events during childhood increases the risk of comorbid psychiatric disorders.

KEYWORDS  
childhood trauma, cognitive bias, comorbidity, memory bias, psychiatry

Shared first authorship.
The lifetime prevalence of DSM-IV (American Psychiatric Association, 1994) Axis-I disorders is 46% (Kessler et al., 2005). Evidence-based guidelines have been developed to address treatment for single Axis-I and Axis-II disorders, however, comorbidity of psychiatric disorders is highly frequent (Zimmerman, McGlinchey, Chelminski, & Young, 2008). For example, studies show that 17%–21% of psychiatric patients met the criteria for three or more psychiatric disorders (Andres, Slade, & Issakidis, 2002; Kessler et al., 2005). Not only the co-occurrence of DSM-I Axis-I disorders, but also between Axis-I and personality (Axis-II) disorders is common (Links & Eynan, 2013). The high level of comorbidity suggests that similar pathogenic factors play a role in different psychiatric disorders. More knowledge about factors that influence the development, maintenance, recurrence, and co-occurrence of psychiatric disorders can increase our understanding of psychiatric pathogenesis and might help in developing better diagnostic instruments, treatment options, and (relapse) prevention interventions.

Cognitive models have provided a solid framework to understand how the experience of adverse events, especially interpersonal trauma, during childhood contributes to the development psychopathology (Beck, 1967, 2008; Beck & Bredemeier, 2016). The experience of adverse or even traumatic events during childhood may result in dysfunctional basic assumptions about the self and the world. Information is processed in accordance with these assumptions, setting the stage for cognitive biases and increasing the risk for the development of psychiatric problems such as depression. The association between highly impactful negative childhood events, cognitive biases, and depression has been confirmed (Beck & Bredemeier, 2016; Scher, Ingram, & Segal, 2005), but childhood adversity is also an important and prevalent risk factor for psychiatric disorders other than depression, such as anxiety disorders, eating disorders, addiction, and sleep disorders (Chen et al., 2010; Hovens, Wiersma, Gitlay, & van Oppen, 2010; Kessler, Davis, & Kendler, 1997; Spinhoven et al., 2010). The risk effect of impactful negative childhood events might thus be based on similar cognitive schemas across psychiatric disorders. Frequent occurrence of childhood trauma and a greater range of different types of childhood traumas increases the risk of the development of psychiatric disorders (Hovens et al., 2010). Hence it is important to take both the type of childhood trauma and the frequency of the events into account when studying psychopathology.

As said, the experience of childhood trauma may foster dysfunctional basic assumptions, which can result in negative cognitive biases (Beck, 2008). Negative cognitive bias is defined as preferential processing of negative material and has been found in different cognitive domains and in several psychiatric disorders (Arntz, Weertman, & Salet, 2011; Brooks, Prince, Stahl, Campbell, & Treasure, 2011; Mathews & MacLeod, 2005). Biased processing of emotional material in memory has frequently been studied and appears to be a robust cognitive emotional process, especially in depression (Gotlib & Joormann, 2010; Matt, Vazquez, & Campbell, 1992). Negative memory bias entails that negative material is more accessible in memory, resulting in more frequent and effective recall (Gotlib & Joormann, 2010).

Negative memory bias is a risk factor for the development, maintenance, and recurrence of depression (De Raedt & Koster, 2010; Gotlib & Joormann, 2010). In anxiety disorders, however, the evidence for memory bias is mixed (Mathews & MacLeod, 2005; Mitte, 2008). Furthermore, some recent studies found evidence for memory bias in disorders other than depression and anxiety, e.g., borderline personality disorder (Winter, Elzinga, & Schmahl, 2014), eating disorders (Nikendeli et al., 2008), and schizophrenia (Peters, Hauschildt, Moritz, & Jelinek, 2013). The association between memory bias and psychiatric comorbidity is unclear at this point, but negative emotions are a key aspect of not only depression and anxiety, but of many psychiatric disorders (American Psychiatric Association, 1994). Therefore, we expect that the impact of childhood trauma on memory bias might in turn effects the level of comorbidity of psychiatric disorders (Zimmerman et al., 2008). We expect negative memory bias to be relevant for a broad spectrum of psychiatric disorders as well as the level of comorbidity between disorders. The latter might be driven by the specific comorbidity between depression and/or anxiety disorders with other disorders. This is however difficult to disentangle in a naturalistic psychiatric sample.

That childhood trauma and memory bias have mostly been studied in well-defined depressed or anxious samples is in sharp contrast with psychiatric practice, where comorbidity between Axis-I disorders, as well as between Axis-I and Axis-II disorders is high (Andrews et al., 2002; Links & Eynan, 2013; Winter et al., 2014). In order to gain the understanding of the global nature of these risk factors as well as their contribution to comorbidity, they need to be examined together in a large heterogeneous naturalistic psychiatric patient sample. It is currently unknown if the frequency and diversity of childhood trauma has a cumulative effect on the development of psychiatric comorbidity. Not do we know if the strength of negative memory bias is related to the frequency and diversity of traumatic childhood events and the number of current psychiatric comorbidity as an index of the complexity and severity of the psychiatric problems. Hence, the aim of the current study was to explore the association of the frequency and diversity of childhood trauma and negative memory bias with a broad range of psychiatric disorders, as well as comorbidity between disorders. We expect more psychiatric diagnoses in patients with a higher frequency and diversity of childhood trauma, see studies showing a possible dose-response relationship childhood trauma and psychiatric comorbidity (Hovens et al., 2010; Spinhoven et al., 2010). Furthermore, also negatively biased memory was expected to be associated with childhood trauma and the number of psychiatric diagnoses (Dozois & Dobson, 2001; Lemout & Joormann, 2012). Moreover, in line with the cognitive models, the association between childhood trauma and comorbidity was expected to be mediated by negative memory bias. Taken together, the results of the study will provide an indication of influencing factors of psychiatric disorders and comorbidity in a naturalistic sample.
2 | Method

2.1 | Participants

This study is part of the MATCH Cohort Study (see Koekkoek, Manders, Tendolkar, Hutschemaekers, & Tiemens, 2016). The MATCH Cohort study is initiated by Research Group Social Psychiatry & Mental Health Nursing at the HAN University of Applied Sciences in Nijmegen, the Netherlands. A total of 285 psychiatric patients participated in the study. They were recruited at three large Dutch mental health institutes in the east of The Netherlands. Psychiatric patients were eligible if they met the criteria of a main psychiatric disorder according to the DSM-IV, but had no psychotic or bipolar-I disorder and no cognitive disorder as the main diagnosis. Patients with these main diagnoses were not invited because the psychiatric problems making the performance of the questionnaires and tasks too difficult. Participants were between 18 and 65 years of age and showed sufficient comprehension of the Dutch language. All eligible patients were invited for the study by means of an invitation letter. If a patient was willing to participate, a first appointment was made to obtain informed consent and collect the baseline data. Memory bias data of ten patients were missing. Subjects who did not recall any words were excluded from the analyses, because bias could not be measured (n = 10). The DSM-IV diagnoses were not available for one participant; a further eleven participants did not fill out the NEMESIS-childhood trauma questionnaire, and one participant did not complete the sociodemographic questionnaire, resulting in a final sample of 252 participants for analyses. Participants were rewarded a gift certificate for their participation. All procedures contributing to this work comply 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 study was approved by the local Medical Ethical Committee ("Commissie Mensgebonden Onderzoek regio Arnhem-Nijmegen").

2.2 | Materials and apparatus

2.2.1 | Sociodemographics

Participant's gender, age in years and the highest level of education were assessed by means of an interview.

2.2.2 | Structured clinical interviews

The Mini International Neuropsychiatric Interview Plus (MINI Plus; Sheehan et al., 1997, 1998) is a validated structured diagnostic psychiatric interview. It was used by trained assessors to classify the DSM-IV Axis-I disorders within the following clusters: mood disorders, anxiety disorders, substance abuse, manic disorders, psychotic disorders, eating disorders, somatoform disorders, and ADHD. Because we were interested in comorbidity across disorders, we clustered specific disorders based on the main categories. For example, a patient with social phobia was classified as having "an anxiety disorder" without further specification of the type of anxiety disorder.

If a patient scored above the cut-off on the Standardized Assessment of Personality-Abbreviated Scale (Germans, Van Heck, & Hodiamont, 2012), the Structured Interview for DSM Personality Disorders (Pfohl, Blum, & Zimmerman, 1995) was used to classify the Axis-II DSM-IV personality disorders. The following personality disorders were assessed: schizoid, schizotypal, antisocial, borderline, histrionic, narcissistic, avoiding, dependent, and obsessive-compulsive personality disorders.

2.2.3 | Childhood trauma

In line with Hovens et al. (2010) and Wiersma et al. (2009), childhood trauma was assessed retrospectively by a semi-structured interview, previously used in the Netherlands Mental Health Survey and Incidence Study (NEMESIS; De Graaf, Bijl, Ten Have, Beekman, & Vollebergh, 2004; De Graaf, Ten Have, & van Dorsselaer, 2010; Van Nierop et al., 2014). The NEMESIS-childhood trauma questionnaire was used to identify stressful events endured by the subjects before the age of sixteen. Administration of the questionnaire took approximately 10 min and was done by a trained assessor. The questionnaire allows for the identifications of four meaningful types of traumatic childhood events within the family: emotional neglect, psychological abuse, physical abuse, and sexual abuse. The frequency of each type of childhood trauma was scored on a five-point Likert scale, ranging from "0" (not) to "5" (very often). In accordance with the previous work on childhood trauma (Hovens et al., 2010), the outcomes of the frequencies of each type of traumatic childhood event were divided into three frequency scores: 0 represented "not," 1 represented "once/sometimes" and 2 represented "regular/often/very often" occurrence of this type of traumatic childhood event. The "childhood trauma index" (Hovens et al., 2010) was calculated by taking the sum of the frequency scores of the four types of traumatic events and represented a combination of frequency and diversity of traumatic events. This index is highly correlated with the severity of psychopathology and the duration of depressive symptoms (see Hovens et al., 2010; Wiersma et al., 2009). This indicates that the childhood trauma index is a strong variable for examining the association between childhood trauma and psychopathology.

2.2.4 | Memory bias

The computerized Self Referent Encoding Task (SRET; Derry & Kuiper, 1981) was used to measure the memory bias. Memory bias is especially strong for self-relevant information such as self-descriptive adjectives (Matt et al., 1992; Symons & Johnson, 1997). The SRET is a reliable and stable tool for assessing the memory bias (Derry & Kuiper, 1981; Dobson & Shaw, 1987). During the encoding phase, 24 adjectives (twelve positively and twelve negatively valenced words) were sequentially presented in fixed random order on a computer screen with the restriction that not more than two words of the same valence would be presented sequentially. The participant was instructed to press the “j” (“ja” being Dutch for “yes”) key on the keyboard if the word described him/her and the “n” key if the word was not
self-descriptive. After a brief distraction, the participant was asked to type in as many words as he/she could remember from the previous task (i.e., the encoding phase) within 3 min. Spelling errors were permitted. The first two and the last two words were not included in the test results to reduce praxic and recency effects on the memory bias index. A negative memory bias index was calculated by dividing the number of endorsed and correctly recalled negative words by the total number of words endorsed and recalled (Gotlib et al., 2004).

2.3 Statistical analyses

Two variables representing the level of comorbidity were created: one indicating if comorbidity between psychiatric disorders was present (no disorder, 1 disorders diagnosed, 2 or more disorders diagnosed). The other comorbidity variable represented the total number of current psychiatric disorders. This variable was created by taking the sum of the main Axis-I and personality (Axis-II) disorders. Groups of overly treated patients without a current diagnosis are common in psychiatric care (Druss et al., 2007; Lawrence, Rasinski, Yoon, & Curlin, 2015; PLOS Medicine Editors, 2013), and were hence not excluded from the analyses in this naturalistic sample. Patients with and without traumatic childhood events, as well as patients with and without a current DSM-IV diagnosis were compared on gender, age, and educational level using chi-square analyses (categorical variables) and t tests. Age, gender, and education level were included as covariates, because they are associated with childhood events, psychopathology, and memory performance (Bjelland et al., 2008; Kendler, Kuhn, & Prescott, 2004). Direct linear associations between childhood trauma, negative memory bias, and comorbidity, as well as mediation by negative memory bias mediation were tested using the PROCESS tool for SPSS (Hayes, 2013). PROCESS bootstraps (1,000 samples) the indirect effect and outputs a 95% confidence interval. Note that if zero is not in the interval then the indirect effect is statistically significant at the .05 level.

3 RESULTS

3.1 Sample descriptives

The sample descriptives can be found in Table 1. Patients with and patients without childhood trauma, as well as patients with and patients without a current psychiatric diagnosis did not differ on gender, age, or level of education: all p > .12. Because of the frequent co-occurrence of DSM-IV Axis-I and Axis-II personality disorder diagnoses in our naturalistic sample (i.e., 30.2% of participants), we did not examine the unique contribution of these types of disorders separately. Table 2 presents details on childhood trauma and psychiatric disorders in the sample.

3.2 Mediation model for the presence of comorbidity

A higher childhood trauma index score was significantly associated with the presence of comorbidity. The model is presented in Figure 1.

More frequent and diverse childhood trauma was also significantly associated with more negatively biased memory, and negative memory bias was in turn significantly positively associated with the presence of comorbidity. Moreover, evidence for mediation was found: the relationship between childhood trauma and the presence of comorbidity was mediated by negative memory bias. The standardized indirect effect “ab” was .02. The ratio of the indirect effect to the direct effect was .19 (referred to as P_M). The P_M value provides an indication of the effect size. The bootstrapped unstandardized indirect effect 95% confidence interval ranged from .006 to .03, indicating a significant indirect effect.

### TABLE 1 Sociodemographic characteristics of the sample. Absolute numbers and means (SD) with standard deviations, or percentages of gender, age, and education level

<table>
<thead>
<tr>
<th>Variable</th>
<th>Absolute number (N = 252)</th>
<th>Means (SD) or percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender, female</td>
<td>179</td>
<td>71.0%</td>
</tr>
<tr>
<td>Age, years</td>
<td>—</td>
<td>38.2 (11.6)</td>
</tr>
<tr>
<td>Level of education^a</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lower education</td>
<td>9</td>
<td>3.6%</td>
</tr>
<tr>
<td>Lower vocational education</td>
<td>18</td>
<td>7.1%</td>
</tr>
<tr>
<td>Secondary general education</td>
<td>32</td>
<td>12.7%</td>
</tr>
<tr>
<td>Secondary vocational education</td>
<td>72</td>
<td>28.6%</td>
</tr>
<tr>
<td>High school</td>
<td>43</td>
<td>17.1%</td>
</tr>
<tr>
<td>Higher vocational education</td>
<td>49</td>
<td>19.4%</td>
</tr>
<tr>
<td>University</td>
<td>29</td>
<td>11.5%</td>
</tr>
</tbody>
</table>

^aHighest educational level finished with a diploma.

### TABLE 2 Mean (SD), range, and absolute numbers (percentages) of participants who experienced childhood trauma, and of patients diagnosed with one or two or more current DSM-IV disorders specified for Axis-I disorders, Axis-II disorders, and any psychiatric disorders (Axis-I and/or-II)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Mean (SD)</th>
<th>Range</th>
<th>n (% of total)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Childhood trauma</td>
<td>3.1 (2.3)</td>
<td>0–8</td>
<td>201 (79.7%)</td>
</tr>
<tr>
<td>Negative memory bias</td>
<td>0.8 (0.4)</td>
<td>0–1</td>
<td>—</td>
</tr>
<tr>
<td>Current Axis-I diagnosis</td>
<td>1.3 (1.1)</td>
<td>0–6</td>
<td>83 (32.9%)</td>
</tr>
<tr>
<td>One</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Two or more</td>
<td>—</td>
<td>—</td>
<td>102 (41.7%)</td>
</tr>
<tr>
<td>Current personality disorders diagnosis (Axis-II)</td>
<td>0.7 (1.2)</td>
<td>0–6</td>
<td>—</td>
</tr>
<tr>
<td>One</td>
<td>—</td>
<td>—</td>
<td>37 (14.7%)</td>
</tr>
<tr>
<td>Two or more</td>
<td>—</td>
<td>—</td>
<td>45 (18.3%)</td>
</tr>
<tr>
<td>Current psychiatric diagnosis (Axis-I and/or Axis-II)</td>
<td>1.9 (1.9)</td>
<td>1–11</td>
<td>—</td>
</tr>
<tr>
<td>One</td>
<td>—</td>
<td>—</td>
<td>62 (24.6%)</td>
</tr>
<tr>
<td>Two or more</td>
<td>—</td>
<td>—</td>
<td>133 (52.8%)</td>
</tr>
</tbody>
</table>
3.3 | Diversity and frequency of childhood trauma

Post hoc analyses were conducted to explore whether diversity or frequency of childhood trauma drove the associations with negative memory bias and the presence of comorbidity. Two new childhood trauma variables were calculated: the diversity variable was the sum of the types of childhood trauma (range 0–4) an individual experienced and the frequency variable represented the total frequency rating across types of childhood trauma (range 0–20). Diversity of childhood trauma was significantly associated with both negative memory bias (a = 0.04, p < .05) and the presence of comorbidity (c = 0.16, p < .001). The latter association remained significant when negative memory bias was included in the model (c’ = 0.18, p < .001). As presented above and in Figure 1, negative memory bias and the presence of comorbidity were significantly associated. The standardized indirect effect “ab” was .03, \( b = 0.70^* \), and the confidence interval ranged from .002 to .06, indicating mediation of the association between diversity of childhood trauma and the presence of comorbidity by negative memory bias. Evidence for mediation was also found when including the frequency of childhood trauma variable in the model. Frequency of trauma was significantly associated with both negative memory bias (a = 0.01, p < .05) and the presence of comorbidity (c = 0.04, p < .001, c’ = 0.05, p < .001). The standardized indirect effect “ab” was .01, \( b = 1.16^* \), and the confidence interval ranged from 0.003 to 0.02. Comparing the coefficients and \( P_M \)-values (as indication of effect size) between the model using the childhood trauma diversity and model using the frequency variable, indicates that the mediation of negative memory bias may be stronger for frequency of childhood trauma.

3.4 | Associations between childhood trauma, negative memory bias, and number of psychiatric disorders diagnosed

More frequent/diverse childhood trauma was significantly associated with current higher total number of Axis-I and Axis-II psychiatric disorders diagnosed (i.e., indicating level of comorbidity). This model is presented in Figure 2. The first mediation model already showed that the childhood trauma index was significantly positively associated with negative memory bias. More negative memory bias was also significantly associated with a higher number of diagnoses. The relationship between childhood trauma and number of current psychiatric disorders diagnosed was mediated by negative memory bias with a standardized indirect effect “ab” of .03, and a \( P_M \) value of .11. The bootstrapped unstandardized indirect effect 95% confidence interval ranged from .01 to .06. Thus, the indirect effect was statistically significant.¹

4 | DISCUSSION

In the current study, we substantiate and elaborate on first recent evidence on the relevance of memory bias in psychiatric disorders other than depression and anxiety (Nikendei et al., 2008; Winter et al., 2014). Our results reveal that both childhood trauma and negative memory bias are associated with comorbidity between psychiatric disorders. The current results once more highlight the detrimental effects of traumatic childhood events on psychiatric morbidity in adult life, as childhood trauma may have a cumulative effect on developing (comorbid) psychiatric disorders. Moreover, the high prevalence of childhood trauma in this naturalistic psychiatric patient sample (almost 80%) underscores its key role in psychological development. For comparison, in an independent sample 52% of depressed individuals experienced childhood trauma (measured with the same tool; De Graaf et al., 2004). Also the role of distorted cognitive processes in

¹Negative memory bias still mediated the association between childhood trauma and number of current psychiatric disorders diagnosed when excluding subjects with a current (comorbid) depression diagnosis (n = 77). All direct associations were significant at the p < .05 level. The standardized indirect effect “ab” was still .03 and the \( P_M \) value was .13. The bootstrapped unstandardized indirect effect 95% confidence interval ranged from .002 to .06, indicating a statistically significant indirect effect.

FIGURE 1 | Standardized regression coefficients for the relationship between childhood trauma and the presence of comorbidity as mediated by negative memory bias. The standardized regression coefficient c’ between childhood trauma and comorbidity controlling for negative memory bias is in parentheses. *Significant at p < .05 level.

FIGURE 2 | Standardized regression coefficients for the relationship between childhood trauma and number of psychiatric disorders diagnosed as mediated by negative memory bias. The standardized regression coefficient c’ between childhood trauma and number of diagnoses controlling for negative memory bias is in parentheses. *Significant at p < .05 level.
the association between childhood trauma and mental problems is indicated by the significant mediation effect.

Our results again indicate childhood trauma as risk factor for a broad spectrum of psychiatric disorders. Research has shown that depressed patients who experienced childhood trauma respond differently to treatment than patients without the experience of aggression or abuse during childhood (Nemeroff et al., 2003). They are more likely to have a recurrent or even chronic course of depression (Nanni, Uher, & Danese, 2012). It has been suggested that the neurobiological consequences of early trauma may lead to brain changes underlying cognitive factors causing and maintaining depression. Animal studies have demonstrated that chronic repeated stress evokes excitotoxicity changes in the hippocampus (McEwen, 2001) and smaller hippocampi has been linked to an increase in memory bias (Gerritsen et al., 2011), which in turn is thought to be a vulnerability factor for depression. Also, the impact of childhood trauma on changes in prefrontal and limbic brain structures can be found in various disorders (McCrory, De Brito, & Viding, 2012). This may explain the difference in course of psychiatric problems as well as in treatment responses.

Our findings in a naturalistic sample may have broader implications for diagnostics and clinical evaluations. The current findings support the idea that a higher frequency and diversity of traumatic childhood events may be a risk factor for a chronic course of multiple psychiatric disorders, as well as for diminishing responsiveness to treatment of disorders other than depression. Future studies will have to investigate whether such a frequency and diversity variable may be used as a semi-quantitative vulnerability factor in clinical staging. Based on the positive association between the frequency and diversity of childhood trauma and negative memory bias, the latter may also serve as a valid biomarker in clinical staging. In the current study, memory bias was also associated with psychiatric comorbidity, even when patients with a current (comorbid) depression were excluded.1 Up to now, only a few studies investigated an association between negative memory bias and psychiatric disorders other than depression, or with psychiatric comorbidity (Dozois & Dobson, 2001; Lemoult & Joormann, 2012). These studies support the current results indicating that cognitive bias may be considered not only as a risk factor for the onset, maintenance, and recurrence of a disorder, but—if substantiated—also for comorbidity between psychiatric disorders (Links & Eynan, 2013). Importantly, the current study provides evidence for this association between risk factors in a naturalistic sample of psychiatric patients, and hence takes a step closer to the clinical practice where comorbidity is common.

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CONFLICT OF INTEREST

There are no conflicts of interest to report.

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