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ORIGINAL ARTICLE

Impulsive and aggressive traits and increased peripheral inflammatory status as psychobiological substrates of homicide behavior in schizophrenia

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Abstract
Background and objectives: An association between inflammation and psychopathological domains of psychotic disorders is widely acknowledged; however, the involvement of inflammatory processes in the underlying pathophysiology of violent behavior in schizophrenia is yet to be elucidated. In this study, we aimed to address the differences in impulsive and aggressive traits as well as C-reactive protein (CRP) to albumin ratio (CAR) as a marker of inflammation between schizophrenia patients with a history of homicide and those without any history of interpersonal violence or criminal background.
Methods: The study population consisted of 80 male DSM-5 schizophrenia patients who were classified into two groups: homicidal (n=40) and non-violent (n=40). Impulsive and aggressive traits were evaluated with Barratt Impulsivity Scale-11 (BIS-11), and the Buss-Warren Aggression Questionnaire (BWAQ), respectively. For the calculation of CAR, the CRP and albumin levels were obtained from the file records of routine blood screenings performed in the month before the patients were included in the study.
Results: When adjusted for age, all subscale scores of the BIS-11 as well as BWAQ Total, Physical and Hostility scores were significantly higher in the homicidal group than in the control group. CRP and CAR were significantly higher, and albumin was significantly lower in the homicidal patients than the controls when adjusted for age, body-mass index and smoking status. Univariate and stepwise multivariate regression models indicated that BIS-11 Non-planning, BWAQ Total, BWAQ Hostility and CAR were independent predictors of belonging to the homicidal patient group, after stepwise adjustment for all potential confounders.

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Conclusions: Our findings suggest that certain impulsive and aggressive traits as well as CAR, as a proxy marker of peripheral inflammation, may contribute towards homicidal tendencies and may predict a specific predisposition towards lethal violence in schizophrenia. The study highlights inflammation as a potential biological correlate of a specific behavioral phenotype (homicide) in schizophrenia.

Introduction

The majority of individuals with schizophrenia are not considered to be dangerous to society, and their contribution to the overall homicide rate is small. However, an association between schizophrenia and homicide has not only been established in the public mind and law, but has also been demonstrated in epidemiological research.[1–5] This association appears to be complex and is largely mediated by factors distinct from the diagnosis itself. Numerous attempts with different methodologies have been employed to characterize patients who commit homicide. However, the question of why schizophrenia is associated with an elevated homicide risk remains unanswered, and available data, the majority of which address a broader framework of psychosis-violence nexus, explains only some of the variance observed.[6] Retrospective studies have identified certain sociodemographic characteristics that are related to elevated homicide risk among individuals with schizophrenia, including living alone, being unemployed, alcohol and substance misuse, history of trauma, easy access to weapons, the severity of symptoms, longer duration of untreated illness, and non-adherence to medication.[3,7,8] However, studies that focus on behavioral traits and biological substrates that may predispose to homicidal behavior in schizophrenia are currently lacking.

Impulsiveness is a multidimensional behavioral trait encompassing spontaneous, poorly planned, and situationally inappropriate behaviors as reactions to internal or external stimuli, and usually leads to negative consequences for oneself or others.[9] Aggression is another behavioral trait that is defined by behavior directed toward another individual with an intent to cause harm. Aggression, however, is a multi-faceted concept that is construed as a unitary trait capturing personal and stable tendencies involving emotional, cognitive, and behavioral processes.[10] Previous studies have reported that high impulsiveness in schizophrenia, evaluated with either self-report or behavioral tasks, is associated with increased risk of suicidal and violent behavior,[11] while increased aggression in schizophrenia, regardless of the instrument used, was predictive of violent behavior.[12] However, to date, the relationship between impulsive/aggressive traits and homicidal behavior among schizophrenia patients has not been examined.

Inflammation can have a complex central neuromodulatory role in the occurrence of aggression in humans through its effects on neurotransmitters. Additionally, increased levels of circulating proinflammatory mediators such as tumor necrosis factor (TNF)-α and C-reactive protein (CRP) were shown to be associated with aggression, hostility, and anger in healthy individuals.[13,14]Although peripheral indicators of inflammation have been suggested to reflect both the pathogenesis and behavioral phenotype in schizophrenia, the facilitatory role of immuno-inflammatory mechanisms in aggressive and violent behavior in schizophrenia is yet to be understood.[15,16] CRP is a well-documented circulating marker for systemic inflammation.[17] Albumin is a negative acute-phase protein, serum levels of which are down-regulated in response to an inflammatory state.[18] Increased plasma CRP,[19] and decreased serum albumin levels[20] have been shown in patients with schizophrenia and the CRP to albumin ratio (CAR) was reported to be a trait marker that was increased in schizophrenia.[21] In one study, elevated CRP was associated with an increased probability of aggressive behavior in schizophrenia patients.[16] However, CAR, which has been suggested to be a better indicator of an inflammatory response than CRP or albumin alone,[22] has not yet been studied for its association with aggressive and violent behavior in schizophrenia. Indeed, there is a paucity of research that examines the association between peripheral inflammatory status and history of lethal violence in schizophrenia; such an association may be of importance to comprehend a specific biological predisposition towards severe violence in this population.

In the current study, we aimed to address the differences in impulsive and aggressive traits between homicidal and non-violent schizophrenia patients. We examined CAR as a proxy marker of inflammation between two patient groups. We hypothesized that after controlling for confounding factors, total and motor impulsiveness, total, physical and hostile aggression, as well as CAR, can be predictive of enhanced homicidal tendencies among patients with schizophrenia.

Methods

Participants, study design and procedure

In this cross-sectional comparative study, a total number of 80 male participants (range of age 18-65 years) with a DSM-5 diagnosis of schizophrenia were divided into two groups. One group (n=40) consisted of consecutively recruited patients admitted to the forensic psychiatry unit at the Bakirkoy Prof Mazhar Osman Training and Research Hospital for Psychiatry, Neurology, and Neurosurgery (Istanbul, Turkey), between January 2019 – July 2020. This group of patients, referred to as the homicidal group, had pleaded guilty as charged with at least one act of an intentional killing before admission and were either detained for assessment or under compulsory treatment through a court order prescribed by the Turkish Criminal (Penal) Code (TCC, Law No. 5237). The other group, referred to as the non-violent group (n=40), included age-matched schizophrenia patients

who had neither a history of interpersonal violence nor criminal background and were recruited from other units of the same hospital.

Patients were excluded from the study if they met one or more of the following criteria: illiteracy, uncooperativeness to psychometric instruments, poor intellectual ability, and presence of a comorbid neurological disorder. Other exclusion criteria included the presence of a systemic disease that may influence inflammatory statuses such as diabetes mellitus, hepatic or renal failure, hypertension, acute infection, acute or chronic immunologic or inflammatory disease or pregnancy; use of anti-inflammatory or immunosuppressive medication, steroids, and antibiotics due to their modifying effects on CRP and albumin levels; documented laboratory findings of liver or renal pathology; nutritional deficiency of vitamin B12 or folate and iron-deficiency anemia; lack of any laboratory screening within the last month before the study was conducted. The study sample was composed only of males because the number of homicidal female patients in the forensic unit during the study period was low; this precluded the acquisition of statistically meaningful and comparable data. Another reason for including only male subjects was to rule out female-specific hormonal alterations related to the menstrual cycle, which have a complex influence on inflammatory processes. Ten male patients from the homicidal group and nineteen patients from the non-violent group were initially excluded because they met the exclusion criteria, before recruiting the final 80 patients as the study population.

CRP and albumin levels were obtained from the file records of routine blood screenings performed in the last month before the patients were included in the study. After recording these parameters, the CRP to albumin ratio was calculated. According to our hospital's blood sampling protocol, samples are drawn at the outpatient or inpatient units in the morning at around 8—10 a.m. from a forearm vein at the end of an overnight fasting period of at least 8 hours. Albumin was measured with a spectrophotometer (Cobas 8000 series c702 modular analyzer). CRP level was determined using the immunoturbidimetric method (Wako Chemicals, Osaka, Japan) on a Hitachi 7600 chemistry analyzer (Hitachi, Tokyo, Japan).

The study was approved by the local Ethics Committee [IRB: 10.01.2019—2019/5483], and written informed consent was obtained from all participants and, if any, their legal representatives/guardians following a thorough explanation of the study procedure. A semi-structured data form that included sociodemographic, historical, clinical, and forensic background, was applied to the participants using multiple sources of information. Body-mass index (BMI) was calculated from height and weight measurements. Trait impulsiveness was measured with the Barratt Impulsiveness Scale (BIS-11). BIS-11 is a self-reported scale that was developed by Barratt[23] and is used to assess trait impulsiveness. The scale is structured to assess long-term patterns of behavior, and its factorial structure was established in 1995 by Patton et al.[24] It consists of a 4-point Likert type scale with 30 items and has three subscales: attention (inattention, cognitive dysregulation), motor (motor impulsiveness, impatience) and non-planning (inability to control, intolerance to cognitive confusion). The higher the total BIS-11 score, the higher the patient's level of impulsiveness. Trait aggressiveness was evaluated with the Buss-Warren Aggression Questionnaire (BWAQ), which evaluates various types of aggressive behavior and was developed by Buss and Warren.[25] This self-reported scale consists of 34 items with 5 different sub-dimensions of aggression including physical aggression, verbal aggression, anger, hostility, and indirect aggression. Each of the questions is evaluated on a 5-point Likert-type scale. The total score of the scale indicates the total aggression level. The Positive and Negative Syndrome Scale (PANSS) was used to evaluate the severity of current symptoms related to schizophrenia.

Statistical analysis

The data were analyzed using the Statistical Package for Social Sciences for Mac OS, Version 25.0 software (Armonk, NY: IBM Corp.). The significance level was accepted as $p<0.05$. After a comparative analysis of the descriptive data between homicidal and non-violent groups, total and subscale scores of BIS-11 and BWAQ were adjusted for age and compared between groups using analysis of covariance (ANCOVA). ANCOVA was also performed to compare the groups for the levels of CRP and albumin and the CAR, after adjustment for age, BMI, and smoking status. Univariate and stepwise multivariate logistic regression analyses of potential BIS-11 and BWAQ domains, CRP, albumin, and CAR were used to determine predictors of being in the homicidal schizophrenia group.

Results

The descriptive characteristics of the study sample are presented in Table 1. All participants were male and their mean age was 43.98±11.22 years for the homicidal group and 43.28±9.75 years for the non-violent group. Education level in years was significantly lower in the homicidal group ($t=2.127$, $p=0.037$). A history of alcohol use disorder ($\chi 2=11.815$, $p=0.001$) was significantly more frequent in the homicidal patients. These patients also had a higher age at illness onset compared to non-violent counterparts ($t=2.395$, $p=0.019$). The current PANSS Total score was higher in homicidal patients ($t=7.054$, $p<0.001$). The median age at the first offense was 31 years for the homicidal group; 12.5% (n=5) of these patients had a criminal record prior to the index homicide. 10 % (n=4) of the homicidal patients killed multiple victims on a single occasion, while another 10 % (n=4) recidivated with a homicide. The most common homicidal method was the use of sharp instruments (67.5%); additionally, 92.5% of the incidents were accompanied or driven by psychotic symptoms.

When adjusted for age, Total ($F=25.564$, $p<0.001$), Attention ($F=20.055$, $p<0.001$), Motor ($F=12.101$, $p=0.001$), and Non-planning ($F=25.696$, $p<0.001$) scores of the BIS-11, and Total ($F=11.892$ $p=0.001$), Physical ($F=13.591$, $p<0.001$), and Hostility ($F=41.826$, $p<0.001$) scores of BWAQ were significantly higher in the homicidal group compared to the control group. Based on ANCOVA, CRP levels ($F=7.185$, $p=0.009$) and CAR ($F=9.273$, $p=0.003$) were significantly higher while albumin levels ($F=8.072$, $p=0.006$) were significantly lower in homicidal patients when adjusted for age, BMI, and smoking status (Table 2).

Table 1 Background characteristics of homicidal and non-violent groups.

	Total Sample (N=80)			
	Homicidal (n=40) Mean±SD / n (%)	Non-violent (n=40) Mean±SD n (%)	t/ χ2	*p*
Age	43.98±11.22	43.28±9.75	0.298	0.796
Education (years)	7.88±3.90	9.78±4.08	2.127	**0.037**
Marital status (not married)	30 (75)	29 (72.5)	0.065	0.799
Employment (No/irregular)	33 (82.5)	26 (65)	3.164	0.075
Suicide attempt	13 (32.5)	11 (27.5)	0.238	0.626
Lifetime AUD	14 (35)	1 (2.5)	11.815	**0.001**
Lifetime SUD	9 (22.5)	3 (7.5)	3.529	0.060
Age at illness onset	26.75±9.65	22.52±6.98	2.395	**0.019**
Duration of illness	17.02±10.54	20.83±11.16	-1.570	0.120
Current AP dose (CED mg)	634.76±299.45	572.62±273.35	0.969	0.335
Current PANSS Total	60.13±13.09	43.48±7.16	7.054	**<0.001**
Body-mass index	26.38±3.33	28.16±4.45	-2.028	**0.046**
Smoking (yes)	31 (77.5%)	21 (52.5%)	5.495	**0.019**

	Homicidal (n=40) Median (min-max) / n (%)
Age at the first offense	31 (14-57)
Total no. of offenses	1 (1-13)
Reoffending	13 (32.5)
Prior offense	5 (12.5)
Imprisonment	29 (70.7)
Total duration of imprisonment (arrested/convicted) (months)	12 (1-126)
Recidivated with homicide	4 (10)
Multiple homicide	4 (10)
Treatment non-adherence at the time of the index homicide	36 (90.0)
Stranger victim	3 (7.5)
Homicide with sharp instrument	27 (67.5)
Private indoor as place of homicide	26 (65)
Homicide with psychotic motivation	39 (95)
Delusions	37 (92.5)
Hallucinations	12 (30)
Homicide predominantly impulsive	24 (60)
Intoxication at the time of the homicide	6 (15)

Abbreviation: SD, Standard deviation; AUD, Alcohol use disorder; SUD, Non-alcohol substance use disorder; AP, Antipsychotic; CED, Chlorpromazine equivalent dose; PANSS, Positive and Negative Syndrome Scale; BIS-11, Barratt Impulsiveness Scale-11; BWAQ, Buss-Warren Aggression Questionairre
p<0.05 statistically significant (bold values).

Logistic regression analyses were performed using potential BIS-11 and BWAQ domains as well as CRP, albumin and CAR. In the first step, univariate regression analyses indicated that BIS-11 Total, BIS-11 Attention, BIS-11 Motor, BIS-11 Non-planning, BWAQ Total, BWAQ Physical, BWAQ Hostility, CRP, albumin, and CAR were significant predictors of being in the homicidal group among patients with schizophrenia. In the second step, stepwise multivariate regression analyses were performed to test the effect of the covariates in the presence of homicide in schizophrenia. The model was statistically significant (χ^2(55.966) = 54.937, p<0.001) with a Nagelkerke R^2 value of 0.67. BIS-11 Non-planning (β=0.21, p=0.012), BWAQ Total (β=-0.06, p=0.032), BWAQ Hostility (β=0.34, p=0.001), and CAR (β=1.18, p=0.014) were found to be independent predictors of belonging to the homicidal group, after stepwise controlling for all confounders including age (β=0.174, p=0.677), body-mass index (β=2.122, p=0.145), smoking status (β=0.61, p=0.448), none of which contributed statistically significantly to the model (Table 3).

Discussion

To our knowledge, this study is the first to examine the role of impulsive and aggressive traits as well as levels of circulating plasma proteins as a marker of increased systemic inflammation as possible substrates of homicidal behavior in schizophrenia. The data as a whole indicated that the higher level of certain dimensions of impulsiveness and aggression

Table 2 Comparison of BIS-11, BWAQ and inflammatory markers between groups.

	Total Sample (N=80)			
	Homicidal (n=40) Mean±SE	Non-violent (n=40) Mean±SE	F	*p*
BIS-11 Total[a]	78.05±2.05	63.42±2.05	25.564	**<0.001**
Attention[a]	20.31±0.66	16.09±0.66	20.055	**<0.001**
Motor[a]	25.12±0.90	20.68±0.90	12.101	**0.001**
Non-planning[a]	32.63±0.83	26.65±0.83	25.696	**<0.001**
BWAQ Total[a]	90.83±3.62	73.17±3.62	11.892	**0.001**
Physical[a]	22.35±1.21	16.05±1.21	13.591	**<0.001**
Verbal[a]	12.80±0.67	11.72±0.67	1.311	0.256
Anger[a]	15.04±0.98	14.71±0.98	0.058	0.810
Hostility[a]	28.99±0.97	20.15±0.96	41.826	**<0.001**
Indirect[a]	11.64±0.62	10.54±0.62	1.572	0.214
CRP[b]	5.61±0.61	3.25±0.61	7.185	**0.009**
Albumin[b]	4.14±0.05	4.37±0.05	8.072	**0.006**
CAR[b]	1.39±0.15	0.74±0.15	9.273	**0.003**

Abbreviation: SE, Standard error; BIS-11, Barratt Impulsiveness Scale-11; BWAQ, Buss-Warren Aggression Questionairre; CRP, C-reactive protein; CAR, C-reactive protein-to-albumin ratio.
p<0.05 statistically significant (bold values).
[a] adjusted for age with ANCOVA.
[b] adjusted for age, body-mass index and smoking status with ANCOVA.

along with increased peripheral inflammation may discriminate homicidal patients diagnosed with schizophrenia from non-violent schizophrenia patients.

All dimensions of trait impulsiveness were found to be significantly higher in homicidal patients than the non-violent subjects in the current study. Similarly, previous studies which employed neuropsychological assessments have reported that total and motor impulsiveness was associated with a history of lethal and non-lethal violence in schizophrenia patients.[26–29] Pathways underlying the psychosis-impulsiveness-violence nexus are best attributable to impaired executive functioning and disrupted top-down control in schizophrenia leading to inadequate behavioral control.[30–32] In our study, total, physical, and hostility scores of aggression were found to be higher in the homicidal group. There is a lack of research on the involvement of aggressive traits in the occurrence of lethal violence in schizophrenia. On the other hand, El-Hadidy reported that recent physical, verbal, anger, hostility, and total aggression scores were higher in homicidal schizophrenia patients compared to non-criminal counterpart patients,[33] which is in line with our findings. Of note, after controlling for age, non-planning impulsiveness and aggressive hostility were found in the current study to be independent significant

Table 3 Univariate and stepwise multivariate regression analyses of potential BIS-11 and BWAQ domains, CRP, albumin and CRP-to-albumin ratio for prediction of being in the group of homicidal schizophrenia patients.

	Univariate			Multivariate[a]		
	β	Sig.	Exp (B) [%95 CI]	β	Sig.	Exp (B) [%95 CI]
BIS-11 Total	0.08	**<0.001**	**1.085** [1.042 – 1.130]		E	
BIS-11 Attention	0.22	**<0.001**	**1.251** [1.109 – 1.412]		E	
BIS-11 Motor	0.14	**0.002**	**1.148** [1.052 – 1.254]		E	
BIS-11 Non-planning	0.20	**<0.001**	**1.223** [1.108 – 1.350]	0.21	**0.012**	**1.228** [1.046 – 1.440]
BWAQ Total	0.03	**0.002**	**1.033** [1.012 – 1.054]	-0.06	**0.032**	**0.930** [0.886 – 0.995]
BWAQ Physical	0.10	**0.001**	**1.109** [1.041 – 1.181]		E	
BWAQ Hostility	0.21	**<0.001**	**1.234** [1.124 – 1.355]	0.34	**0.001**	**1.410** [1.142 – 1.742]
CRP	0.18	**0.012**	**1.194** [1.039 – 1.374]		E	
Albumin	-2.23	**0.002**	**0.108** [0.026 – 1.350]	-1.59	0.106	0.205 [0.030 – 1.402]
CRP-to-albumin ratio	0.87	**0.005**	**2.393** [1.308 – 4.378]	1.18	**0.014**	**3.245** [1.267 – 8.309]

Abbreviation: E, excluded by the model; BIS-11, Barratt Impulsiveness Scale-11; BWAQ, Buss-Warren Aggression Questionairre; CRP, C-reactive protein.
p<0.05 statistically significant (bold values).
[a] Results from forward stepwise logistic regression, Model summary; $\chi^2(55.966) = 54.937$, p<0.001, Percent correct classification 83% with R^2 of 0.67, Confounder covariates: age (β=0.174, p=0.677), body-mass index (β=2.122, p=0.145), smoking status (β=0.61, p=0.448).

predictors of being in the homicidal group among patients with schizophrenia, which is a novel finding.

In the current study, homicidal patients had higher CRP and CAR, and lower albumin levels compared to non-violent subjects. Higher levels of peripheral inflammatory markers including serum pro-inflammatory cytokines have been reported in schizophrenia patients showing increased agitation and violence.[34,35] Several studies conducted in non-psychotic populations have demonstrated that peripheral inflammatory markers are increased in subjects with violent and explosive behaviors.[36–38] In four previous studies investigating the relationship between CRP and aggressive behavior in schizophrenia, it has been shown that high plasma CRP levels are associated with aggressive behavior.[16,39–41] The relationship between increased peripheral inflammatory status and predisposition to severe violent behavior in schizophrenia might be ascribed to compromised tryptophan-kynurenine pathway in the presence of higher levels of proinflammatory cytokines. These cytokines, which are correlated with plasma CRP levels,[38] inhibit indoleamine 2,3,-dioxygenase (IDO), the rate-limiting enzyme that converts tryptophan to kynurenine and leads to a decrease in serotonin synthesis, which may precipitate violence,[42] In addition, enhanced synthesis of quinurenic acid and quinolinic acid, in the presence of a hypofunctional IDO, can also cause cognitive and behavioral changes including violent behavior, by disrupting glutamatergic function.[43] Increased inflammatory signaling can also disrupt the HPA-axis, which cannot regulate the stress response appropriately; an impaired stress response may, in turn, lead to testosterone/cortisol imbalance that can enhance the inclination to violent and aggressive behavior.[44] These postulations may explain the significant difference in the levels of peripheral inflammatory markers between homicidal and non-violent groups in our study. Of note, previous research has suggested that adjunct therapy with anti-inflammatory drugs provided significant improvement in symptoms of patients with schizophrenia.[45] Furthermore, second-generation antipsychotics have been reported to demonstrate anti-inflammatory properties by modulating several intra- and intercellular inflammatory pathways.[46,47] Eicosapentaenoic acid and docosahexaenoic acid, which are fatty acids recognized to have anti-inflammatory effects, were reported to reduce violent behavior among schizophrenia patients compared to the placebo in a recent study.[48] Nevertheless, the data currently available is insufficient to answer the question "Does alleviating inflammation reduce the risk of aggressive and violent behavior in schizophrenia?". Therefore, it seems pivotal to consider the effect of anti-inflammatory treatment on violent behavior in schizophrenia independent of the effects of these drugs on psychopathology. Our findings implicate CAR as a biomarker of inflammation with behavioral implications for homicide among schizophrenia patients. Further investigations are needed to establish the possibility that anti-inflammatory medication or antipsychotics may decrease the risk of violence by reducing inflammatory biomarkers such as CRP and CAR, through complex alterations in neurotransmitter-mediated signaling.

The results of the current study should be evaluated by considering some limitations. The sample size was rather small. Furthermore, any self-report measure like BIS-11 and BWAQ must be interpreted with caution, particularly in forensic settings. We could not include any female subjects due to availability of insufficient data and possible hormonal fluctuations in female patients that may influence inflammatory markers. The cross-sectional nature of the study design also precluded access to laboratory data just after the homicidal incident. Despite these limitations, data from the current study suggest that peripheral inflammatory markers can be used as bona fide trait markers.

Conclusion

The current study ascertained that certain impulsive and aggressive traits may possess a tendency towards lethal violence in schizophrenia. Furthermore, CAR, as a proxy marker of the peripheral inflammatory state, may reflect a predisposition towards homicidal behavior through complex biological mechanisms. Future investigations are needed to elaborate the psychological and biological underpinnings of substrates of homicidal behavior. Such studies are warranted to develop early detection and intervention strategies for the risk of lethal violence in schizophrenia patients in both clinical and forensic psychiatric settings.

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Ethical statement

The study was approved by the local ethics committee [IRB: 10.01.2019—2019/5483]. Written informed consent was obtained from all participants and, if any, their legal representatives/guardians following a thorough explanation of the study procedure.

Conflict of interest

The authors declare no potential conflicts of interest concerning to the research, authorship, and/or publication of this article.

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