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Sudden cardiac death associated to substances of abuse and psychotropic drugs consumed by young people: A population study based on forensic autopsies

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ABSTRACT

Background: Toxic substances are one of the main risk factors for sudden cardiac death (SCD) in young people. However, there is limited information about this matter based on clinical research. The aim of this study was to analyze the use of substances of abuse (legal and illicit) and prescribed psychotropic drugs in young people who died by SCD.

Methods: A population-based study performed in 15–35-year-olds who died by SCD in Biscay (Basque-Country) between 1991 and 2016. Cases were analyzed prospectively by a complete autopsy, toxicological and histopathological studies. A case was considered positive for exposure to cardiotoxic substances if smoking status was diagnosed or if toxicological analysis detected any drug associated with increased risk of SCD.

Results: There were 204 SCD; 98 (48%) were exposed to a cardiotoxic substance, including smoking status (n = 72) and/or positive toxicology (n = 58). Illicit drugs (n = 29, mainly cannabis and cocaine), ethanol (n = 25), and prescribed psychotropic drugs (n = 11) were detected. Positive cases were more frequent in males than in females (54% vs. 19%). They were also more common in subjects who died by acute (86%) and chronic (71%) ischemic heart disease than in myocardial diseases (33%) and sudden arrhythmic death syndrome (36%). All positive cases of illicit drugs were males. Smoking status was very high in deaths due to acute ischemic heart disease.

Conclusions: The proportion of users of substances of abuse was unexpectedly high, even more prevalent than other cardiovascular risk factors. Toxic substances could play an important role as triggers of SCD in young people.

1. Introduction

Sudden cardiac death (SCD) is an important public health issue. In adolescents and young people, although infrequent, it is a devastating event for the family and the community. The incidence is about 1.5 cases/100,000 persons/year (Bagnall et al., 2016). The main causes are ischemic heart disease (IHD), cardiomyopathies or channelopathies (Bagnall et al., 2016). Several cardiovascular risk factors for SCD have been observed in developed countries, including abuse of both illicit drugs (mainly cocaine) and legal substances (ethanol and tobacco). Additionally, several prescribed psychotropic drugs (even in therapeutic postmortem concentrations), such as some antipsychotics, antidepressants and methadone, can modify the QT interval, increasing the risk of SCD (Chugh et al., 2008; Ray et al., 2009; Fischbach, 2017; Morentin et al., 2018).

It has been suggested that cardiotoxic substances may interact with the anatomical substrate responsible for SCD through transient functional alterations, triggering a lethal arrhythmia. In addition, these substances can also induce chronic structural alterations in the heart, which also increase the risk of SCD (reviewed in Morentin et al., 2018).

Smoking has been identified as the single factor most strongly associated with heart diseases, and specifically with IHD, among young individuals (Khan et al., 2015). Exposure to tobacco develops thrombosis (Barua and Ambrose, 2013); even in young populations, it can

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impair endothelium (Messner and Bernhard, 2014). The proarrhythmogenic action of alcohol may also be responsible for some forms of SCD (Day et al., 1993; Fischbach, 2017; Morentin et al., 2018).

The risk for cardiovascular complications related to cannabis use is considered low in healthy subjects. In contrast, in patients at high risk for coronary events, the acute effects of cannabis may increase the risk of myocardial infarction by up to 5 times (Jouanjus et al., 2017). Cocaine increases heart rate, blood pressure, left ventricular contractility and myocardial oxygen demand. Cocaine may also increase ventricular irritability and lower the threshold for fibrillation. Furthermore, it has been related to coronary vasoconstriction and thrombus formation. Additionally, chronic use could accelerate atherosclerosis and cause left ventricular hypertrophy and myocardial fibrosis.

Although toxic substances can play an important role in the genesis of SCD, very few articles based on forensic autopsies have been published concerning SCD due to drug effects (Lucena et al., 2010; Morentin et al., 2014; Bjune et al., 2018). Population studies based on forensic autopsies could be of interest in order to improve the epidemiological and pathophysiological knowledge about this phenomenon. Moreover, these studies offer pathological and toxicological data and allow a clinical-pathological correlation.

The main objective of this forensic research was to analyze the consumption of cardiotoxic substances (abuse [legal and illicit] and psychotropic drugs associated with an increased risk of SCD) in a well-defined population of young people aged 15–35 years who died due to SCD. As a secondary objective of the study, we examined if demographic and clinical characteristics as well as causes of death were different in the group of SCD positive for cardiotoxic substances and in the negative group.

2. Materials and methods

2.1. Data source

The study was performed in Biscay, an industrial province of the Basque Country (South Europe) with a total population of 1,150,040 inhabitants (15–35 years population = 268,545) (www.ine.es).

Sudden death is defined as an unexpected non-violent (natural) phenomenon in which death occurs instantaneously or within one hour of the onset of symptoms or collapse, in non-hospitalized individuals participating in their regular activities until the final event (Basso et al., 2017). Biscay Forensic Pathology Service is the only institution in charge of the investigation of sudden deaths in the province of Biscay. Since 1991 a Register of Sudden Deaths in subjects ≤ 35 years old has been used in this Service.

Cases are studied prospectively (Morentin et al., 2003). A forensic autopsy is always required in sudden unexpected deaths of young people. Forensic autopsy reports are coded according to the underlying cause of death following the International Classification of Diseases (ICD-10).

2.2. Selection of subjects

All SCD of persons between 15 and 35 years old from 1 January 1991 to 31 December 2016 were included.

2.3. Autopsy procedure

In all the subjects a complete autopsy, as well as toxicological and histopathological studies, were carried out. Clinical data and the circumstances surrounding the death were also reviewed. This information was obtained from physicians' and forensic doctors' reports and interviews with the family. All the organs were examined, weighed, and photographed. Heart study included: myocardial structure, measures of wall thickness and ventricular chamber size, examination of the valves, and the origin, course, and patency of the coronary arteries. Samples for histology were taken from both ventricles, ventricular septum and epicardial coronary arteries. These sections were stained with hematoxylin and eosin and with Masson trichrome stain. Sections from brain tissue, lungs, liver, spleen, kidneys, thyroids and suprarenal glands were also obtained.

2.4. Toxicological study

Blood, vitreous fluid and urine samples were collected for toxicological analyses. They were performed at the Laboratory Service of the Basque Institute of Legal Medicine and at the National Institute of Toxicology and Forensic Sciences in Madrid. Enzyme immunoassay, high-performance liquid chromatography and gas chromatography/mass-spectrometry were used for the detection of therapeutic drugs, illicit drugs and ethanol.

Toxicology results for prescribed psychotropic drugs, other therapeutic drugs, illicit drugs and alcohol were recorded. A blood alcohol concentration of 0.5 g/l was used as cut-off. Drugs administered during resuscitation attempts were not included.

2.5. Variables analyzed

Demographic, clinical and toxicological data, cardiovascular risk factors, as well as cause of death were analyzed.

The cause of death was established considering together clinical history, autopsy findings and the results of all ancillary examinations. Cases with lethal blood-levels of one substance or with toxic levels of more than one depressant drug of the central nervous system (Winek et al., 2001; Musshoff et al., 2004; Jönsson et al., 2014) were excluded because they were diagnosed as toxic deaths. Four groups of structural cardiac pathology were established: myocardial diseases (primary cardiomyopathies and myocarditis); acute IHD (acute myocardial infarction and/or coronary thrombosis); chronic IHD (ischemic scar and/or atherosclerotic plaque with coronary luminal stenosis > 75% or anomalous origin of coronary artery); and others. This fifth group is composed of cases with structurally normal heart (apparently arrhythmic deaths in which the autopsy did not discover any organic or toxic cause of death and where there was not a clinical history that could explain the death as asthma, epilepsy, etc.). Nowadays, these deaths are classified as sudden unexplained deaths or sudden arrhythmic death syndrome (SADS) (Morentin et al., 2003; Bagnall et al., 2016).

2.6. Exposure to cardiotoxic substances

According to the presence or not of toxic substances associated with an increased risk of SCD, two groups were established. A case was included in the positive group if smoking status was diagnosed or if the toxicological analysis detected alcohol, illegal drugs (cannabis, cocaine or amphetamine or their metabolites) or prescribed drugs (or their metabolites) associated with QT prolongation in blood. The time of detection of the majority of psychotropic drugs is usually less than 24–48 h, except for cannabis (which is longer). Otherwise, the case was classified as negative. The number of cardiotoxic substances detected in each case was also recorded.

Smoking status was considered positive if medical antecedents existed and/or if the histopathological study detected respiratory bronchiolitis-associated interstitial lung disease (characteristic finding of heavy smokers) in absence of other medical cause that can produce this finding (Morentin et al., 2014).

All the procedures were performed in compliance with policies of research and ethical boards for postmortem forensic studies.

2.7. Data analysis

The distribution of data is presented as median or mean ± SEM of

Table 1
Clinical characteristics of the subjects and causes of sudden cardiac death (N = 204).

	TOTAL	Presence of substances related to SCD		
	(N = 204)	Yes (N = 98)	No (N = 106)	Statistical analysis (p)
	n (%)	n (%)	n (%)	
Demographical data				
Gender				χ^2 15.3 (< 0.001)
Male	167	91 (93)	76 (72)	
Female	37	7 (7)	30 (28)	
Age				
median	29.5	32	27	M-W (< 0.001)
mean (SD)	28.1 (6.1)	30.2 (5)	26.2 (6.4)	
Personal antecedents				
Cardiac diseases				χ^2 1.6 (0.9)
Diagnosis of cardiac disease before death	18 (9)	9 (9)	9 (9)	
Cardiovascular symptoms	57 (28)	26 (27)	31 (29)	
No	128 (63)	62 (64)	66 (62)	
Psychiatric or neurological diseases	23 (11)	14 (14)	9 (9)	χ^2 1.7 (0.26)
Cardiovascular risk factors (except smoking)	46 (22)	26 (26)	20 (19)	χ^2 1.7 (0.24)
History of toxic habits and drug abuse	30 (15)	29 (31)	1 (1)	χ^2 33.6 (< 0.001)
Pathological data				
Cause of sudden cardiac death				χ^2 31.4 (< 0.001)
Myocardial diseases	60 (29)	20 (20)	40 (38)	
Sudden arrhythmic death syndrome	58 (28)	21 (21)	37 (35)	
Chronic ischemic heart disease	31 (15)	22 (22)	9 (8)	
Acute ischemic heart disease	28 (14)	24 (25)	4 (4)	
Other structural causes	27 (13)	11 (11)	16 (15)	

Differences between groups were compared using χ^2 test for categorical variables; and Mann-Whitney (M–W) for continuous variables.

individual values or as a percentage. Differences between groups were compared using χ^2 test for categorical variables and Mann-Whitney or Kruskal Wallis for continuous variables. Only variables with a frequency > 10% were analyzed. A p value < 0.05 was regarded as statistically significant.

3. Results

During the 26 years analyzed, 204 SCD of 15–35 years old persons were investigated in Biscay. They were 82% men. The median age was 29.5 years (percentile 25 and 75: 24 and 33). Clinical antecedents of cardiac, psychiatric and neurological diseases, cardiovascular risk factors and toxic habits are described in Table 1. The main psychiatric and neurological diseases found were schizophrenia (n = 7), mental retardation (n = 5) and depression (n = 3). Cardiovascular risk factors, except smoking, were present in 46 cases (22%): obesity (n = 33), hyperlipemia (n = 13), diabetes mellitus (n = 4) and high blood pressure (n = 3) were all found. History of drug abuse was recorded in 30 persons (15%): illicit drugs (n = 17), excessive alcohol consumption (n = 10) and both (n = 3). The main causes of SCD were myocardial diseases and SADS followed by chronic and acute IHD (Table 1).

The positive group for exposure to a cardiotoxic substance included 98 subjects (48% of the total sample). Positive toxicology for drugs related to increased risk for SCD was found in 58 subjects, and 72 were smokers. Alcohol was present in 12% (range 0.5–2.00) and illicit drugs, mainly cannabis and cocaine, in 14% of the subjects (Table 2). In 11 cases (5%), prescribed drugs associated with QT prolongation were detected, and 5 presented two different substances. All drugs detected were in concentrations that were evaluated not to have caused the death. The number of cardiotoxic substances found in each person is shown in Table 2. The median substances by person was 0, and the grouped median was 0.58.

Table 2
Presence of toxic substances associated with an increased risk of sudden cardiac death (SCD) (N = 204).

Toxic substance	n (%)
Tobacco	**72 (35)**
Ethanol	**25 (12)**
Illicit drugs	**29 (14)**
Cannabis	20
Cocaine	15
Amphetamine	5
Prescribed Psychotropic drugs	**11 (5)**
Second generation antipsychotics	6
Antidepressants	5
First generation antipsychotics	3
Methadone	2
Number of toxic substances related to SCD found by subject	
0	106 (51)
1	61 (30)
2	24 (12)
3	6 (3)
4	5 (2)
5	1
6	1

The negative group included 106 subjects. In 28 of them, toxicological analysis detected prescribed drugs not related to SCD. In 11 cases of the positive group, prescribed drugs not related to SCD were also detected. The most common drugs found not related to SCD were nonsteroidal anti-inflammatory drugs [n = 26] and benzodiazepines [n = 14].

3.1. Comparison between positive and negative groups for exposure to a cardiotoxic substance

The frequency of males was higher among positive than negative cases (93% vs. 72% p < 0.001). Positive cases were significantly older than negative cases (Mann-Whitney; p < 0.001). Clinical antecedents were similar between both groups. History of toxic habits was much higher among positive cases (Table 1).

The distribution of causes of SCD was different for positive and negative cases. Myocardial diseases and SADS were predominant in the negative group (75%), whilst IHD (acute and chronic) had a low frequency (12%). On the contrary, IHD had a higher frequency in the positive group (46%), and that of MD and SADS was lower (41%) (Table 1).

3.2. Cardiotoxic substances in relation to gender and causes of SCD

The median cardiotoxic substances by subject was higher for males (1; grouped median 0.69) than for females (0; grouped median 0.20) (M-W: U 1961; P < 0.001). The median and grouped median were also higher for subjects who died by acute IHD (1 and 1.33) or chronic IHD (1 and 1.05) than for those who died by SAD (0 and 0.42) or MD (0 and 0.37) (K-W: χ2 32.06; P < 0.001).

The proportion of subjects exposed to smoking (41% vs. 11%; χ2 11.86; P < 0.001) or use of illicit drugs (17% vs. 0%; χ2 7.49; P = 0.003) was significantly higher among males than females.

Regarding the frequency of cardiotoxic substances in relation to cause of SCD, smoking status was very high (82%) in acute IHD and high (61%) in chronic IHD (Fig. 1). Recent use of illicit drugs, mainly cocaine (Fig. 1), was higher in subjects who died by acute IHD (25%). It must be noted that four of the five positive cases for amphetamine died

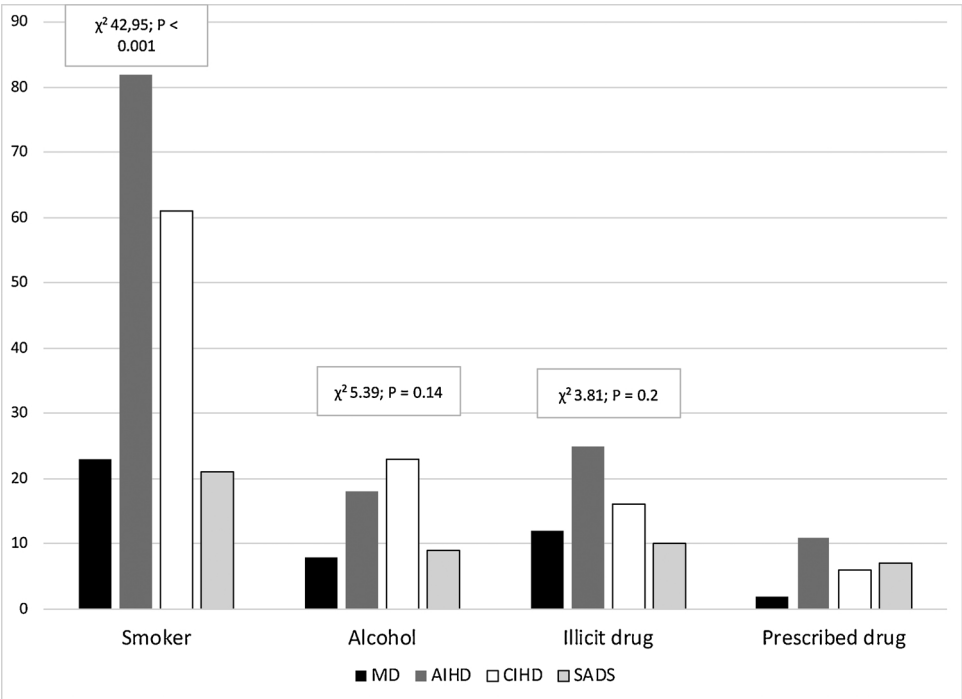

Fig. 1. Representation of the percentage of toxic substances associated with an increased risk of sudden cardiac death by cause of death.
AIHD: acute ischemic heart disease; CIHD: chronic IHD; MD: myocardial diseases; SADS: sudden arrhythmic death syndrome. Other causes of death were excluded from statistical analysis.

by acute IHD.

4. Discussion

The data about prevalence of use of legal and illicit drugs of abuse in the general population of the Basque Country aged 15–34 years (Observatorio Vasco de Drogodependencias, 2013) indicates that the risk of SCD is very low for the people that use these substances. However, the results of the present research show that the prevalence of use of cardiotoxic substances in young people who died by SCD is very high. This fact suggests that strategies to control smoking, alcohol and drug use in young people may be useful for primary prevention of SCD. According to our study, the risk increase for SCD related to cardiotoxic substances consumed in young people is much higher than that of other classical cardiovascular risk factors or the diagnosis of a cardiovascular disease in life.

4.1. Comparison with other studies

Few studies based on forensic autopsies have analyzed the association between SCD and the use of potential cardiotoxic substances, focused mainly on cocaine. In Seville (Spain), 668 sudden deaths were evaluated; 21 of them were associated with recent use of cocaine (Lucena et al., 2010). In a previous case-control study conducted by our research team, 311 SCD of people between 15 and 49 years were also examined. This study showed that the main risk factor for SCD was recent use of cocaine (increased risk by four) followed by smoking (increased risk by two) (Morentin et al., 2014).

We have only found one other population-based forensic study in the medical literature similar to ours. Bjune et al. (2018) performed an investigation about this problem in Denmark during 2000-09 in persons aged 1–49 years. Our global data are in consonance with it; both show the important role of drugs in SCD. In the Danish study, 477 SCD cases with toxicological analysis were examined, and 57% of them had a positive toxicology profile (also including drugs not related to SCD). In our study this percentage was slightly lower.

There are other differences between both studies, such as the frequency of drugs detected in toxicological analysis, the frequency of causes of death, and the frequency of drugs detected with respect to the cause of death. In the Danish study, the frequency of a positive toxicological profile was statistically significantly higher in SADS than in explained SCD. Conversely, in our investigation the prevalence of cardiotoxic substances use was higher in explained SCD than in SADS.

Although both studies were performed in European populations and based on forensic autopsies, the results are difficult to compare due to methodological differences including diagnostic criteria for SADS.

The interpretation of some causes of death and results of toxicology may be difficult in forensic pathology (Basso et al., 2017). This happens mainly in autopsies with no structural changes that could explain sudden death and with positive toxicology for some drugs in non-lethal concentrations. In these cases, the degree of certainty to establish the cause of death is low. Some forensic pathologists may diagnose these deaths as SADS and others as drug-related deaths or deaths due to adverse drug reaction. The difficulty in interpretation is increased by the complexity of postmortem toxicology and the overlap between therapeutic and toxic concentrations for many substances.

4.2. Use of abuse substances with respect to gender

As could be expected considering general population data (Observatorio Vasco de Drogodependencias, 2013), the frequency of males was higher in the positive group for exposure to a cardiotoxic substance. Similarly, the median of cardiotoxic substances by person was 3 times higher among males than among females. It is also remarkable that the 29 cases of illicit drugs use occurred in males. These data suggest that the toxic factor could be one of the causes of the higher prevalence of SCD in males.

4.3. Use of abuse substances with respect to cause of death

A recent study of SCD in young people (subjects aged 5–34 years old) observed, as did ours, an unexpectedly high overall prevalence of

tobacco consumption (Jayaraman et al., 2017). One of the main findings of our work is the significant association between smoking habits and acute IHD (81% of acute IHD were smokers). This is in consonance with other articles that have concluded that smoking is a major risk factor for acute coronary thrombosis, responsible for myocardial infarction and SCD (Burke et al., 1997).

In our study, recent alcohol use had a frequency of 12%. This figure is lower than that observed in a study from Northern Finland, in which it was observed that almost 4 of 10 out of the victims of unexpected SCD had evidence of alcohol intake before the fatal event (Perkiömäki et al., 2016).

Illicit drugs (especially cocaine) have acute and chronic effects on the cardiovascular system. In the present research, the most frequent illicit drugs were cannabis (n = 20) and cocaine (n = 15). In the general population of the Basque Country, the prevalence of cannabis use is higher than cocaine use (Observatorio Vasco de Drogodependencias, 2013). Moreover, cannabis has a much longer half-life, suggesting that the effect of cocaine as a trigger for SCD is more important than that of cannabis (Morentin et al., 2014).

Cocaine has been related to several cardiovascular complications including SCD (Fischbach, 2017; Morentin et al., 2018). In our research, the frequency of recent cocaine use was highest in acute IHD (21% vs. 3–6% on the other 3 groups). This finding seems to indicate that in the SCD of young people, coronary thrombosis is the most harmful effect of cocaine use. In other series, myocardial ischemia has also been the most frequent morphological substrate of SCD associated with recent cocaine use (Lucena et al., 2010).

In our study, the percentage of young people with psychiatric diseases and the frequency of cases with positive toxicology for drugs associated with QT seem to be high for an unselected general population. These findings agree with previous reports, which have established that patients with mental illnesses have a higher incidence of SCD (Koponen et al., 2008), probably due to the cardiovascular side-effects of medical treatment. Unlike other works that have associated this complication mainly with SADS (Bjune et al., 2018), we observed a similar frequency of drugs associated with altered QT between SADS and explained SCD.

Half of our cases had more than one drug associated with QT prolongation. The prevention of drug-associated SCD may require monitoring potential drug-induced cardiovascular abnormalities, minimizing synergistic interactions and, in particular, avoiding exposure by choosing drugs with a higher safety profile, mainly in cases with greater susceptibility. Genetic factors play a role in the individual response to some medications, and gene–drug interaction should be considered, especially with QT interval-acting drugs (Basso et al., 2017).

4.4. Limitations and strengths

The present study did not evaluate the long-term complications of life time drugs use but the role of them as an acute trigger for SCD. Therefore, only the relationship between SCD and recent drugs use was analyzed. Hair analysis could have been interesting to measure the chronic use of illicit drugs, but it was not performed.

The study is observational (without control group) and does not prove causation nor assess the absolute risk for SCD. We analyzed the association between SCD and substances that can increase the risk of SCD, but we do not conclude that these substances are causative of SCD.

The data of smoking status cannot be assessed through a structured uniform questionnaire in forensic samples, such as ours, because in some patients it could be difficult or impossible to obtain such data in the familiar interview. Thus, we decided to use pathological data in addition to the clinic antecedents to evaluate the existence of smoking status.

On the other hand, the methodology of our investigation has several strengths: a) an unselected population of a whole province was studied for a long period of time; b) the cases were investigated prospectively according to a complete protocol; c) in all cases histopathological and toxicological analysis were conducted; and d) it is a forensic sample which brings additional evidence to clinical studies.

5. Conclusions

The proportion of legal or illicit drugs abuse in young people who died by SCD was unexpectedly high and even more prevalent than other cardiovascular risk factors. In this sense, cardiotoxic substances could play an important role as triggers of SCD in young males. The influence of illicit drugs (mainly cocaine) and tobacco is principally important in IHD and particularly in acute IHD.

The use of toxic substances should be considered in cases of acute cardiovascular diseases in young people, mainly in males. In all SCD cases, both explained and unexplained (SADS) deaths, the possibility that an illicit or prescribed drug may have triggered the death, acting as an additional factor to the anatomical or genetical substrates, should be carefully considered.

These data provide a good approach to develop useful prevention strategies. Educational campaigns about the potential cardiovascular risks of smoking or drugs consuming should be promoted to reduce the mortality associated.

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Contributors

Both authors took part in all stages of the research: conceptualization, design, retrieval and treatment of data, and drafting of the manuscript and have approved of the final version of the manuscript.

Conflict of interest

No conflict declared.

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