REVIEW

New threats for pediatric respiratory health: beware of vaping

Maria **Di Cicco** [1, 2, *], Alessandra **Beni** [1, 2], Vincenzo **Ragazzo** [3], Diego G. **Peroni** [1, 2]

[*] **Correspondence to:**
maria.dicicco@unipi.it/ORCID: https://orcid.org/0000-0002-7027-6817

ABSTRACT

Electronic cigarette (EC) was proposed on the market about 15 years ago as a harmless alternative to traditional combustion cigarettes (CC). Since then, EC and other electronic devices that deliver nicotine by simulating traditional smoking without combustion have achieved unexpected success, with around 80 million users worldwide by 2023. Such devices are commonly felt to be safer than CC, especially among adolescents, who are also the main target for aggressive marketing from the tobacco industry. Increasing evidence shows that e-liquids and vape contain toxicants and irritants and that acute and chronic vaping causes airway inflammation and bronchoconstriction and reduces responses to infections. Moreover, some studies have shown that second- and third-hand smoke, as well as in utero exposure, may cause detrimental effects to the airways and to health in general. Notably, the recent E-cigarette or Vaping use-Associated Lung Injury (EVALI) epidemic in the USA has shown that EC has higher acute toxicity than CC, while long-term effects are still not known. Since adolescents and children are often completely unaware of the health risks associated with vaping or of the potential presence of nicotine in e-liquids, pediatricians play a crucial role in educating them, in order to prevent vaping, as well as smoking. Pediatricians should always consider the possibility of vaping as the cause of unusual respiratory diseases, especially in adolescents. This narrative review paper briefly outlines the most recent data on EC and their effects on the airways, focusing on childhood and adolescence.

IMPACT STATEMENT

The worldwide vaping epidemic among adolescents represents a serious threat to health and a new challenge for healthcare professionals. Pediatricians should screen and educate patients and parents on vaping.

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[1] Pediatrics Unit, Pisa University Hospital, Pisa, Italy
[2] Department of Clinical and Experimental Medicine, University of Pisa, Pisa, Italy
[3] Pediatrics and Neonatology Division, Women's and Children's Health Department, Versilia Hospital, Lido di Camaiore, Italy

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ABBREVIATIONS

ARDS: Acute Respiratory Distress Syndrome; CC: Combustion Cigarette; EC: Electronic Cigarette; EU: European Union; ENDS: Electronic Nicotine Delivery Systems; EVALI: E-cigarette or Vaping use-Associated Lung Injury; FDA: Food and Drug Administration; HTTP: Heated Tobacco Products; PG: Propylene Glycol; US/USA: United States of America; VG: Vegetable Glycerin; WHO: World Health Organization.

KEY WORDS

Adolescents; e-cigarette; nicotine; smoke; vape.

INTRODUCTION

In 2003, the Chinese pharmacist Hon Lik proposed the first modern model of electronic cigarette (EC) on the Chinese market as a harmless alternative to traditional combustion cigarettes (CC). About three years later, EC reached the European and American markets achieving unexpected success, with an exponential growth in sales and estimates referring to around 80 million users worldwide by 2023 (1). In the European Union, 1 citizen out of 7 (41% of 2020 EU citizens) had tried EC at least once, while only around 1 in 20 (6%) had tried heated tobacco products (HTP) in 2020 (2). In Italy, according to recent data from the National Institute of Health, there are 12.4 million current smokers (24.2% of the population) and 1.2 million habitual or occasional EC users (2.4% of the population) (3). EC and other electronic devices that deliver nicotine by simulating traditional smoking without combustion (Electronic Nicotine Delivery Systems - ENDS) (see Glossary, **Table 1**) will soon overtake CC in the market for several reasons: first of all, they were introduced as non-harmful alternatives to CC, which release more than 7000 compounds during combustion (at least 70 carcinogens), and so they are commonly felt to be safer (4). Secondly, due to the increasing restrictions on the sale of tobacco worldwide, together with people prematurely dying from smoking, the industry is using aggressive marketing to target youths, especially on social media, in order to recruit new long-lasting customers, taking advantage of the fact that restrictions on ENDS sales are lacking or patchily distributed (5). Last but not least, EC use is easily conceivable, the colorful packaging is captivating, and the availability of many sweet flavors attracts many customers. Unsurprisingly, the available data clearly show that vaping is spreading especially among the very young, who start vaping mostly because they are driven by curiosity and the desire to imitate their peers and are often completely unaware of the health risks associated with vaping or of the potential presence of nicotine in e-liquids (6, 7). In 2018, the US Surgeon General declared youth EC use as an epidemic in the USA, where these devices have become the most used tobacco product among adolescents since 2014. According to data from the National Youth Tobacco Survey in the US, 19.6% of high school students (3.02 million) and 4.7% of middle school students (550.000) reported current (within the preceding 30 days) EC use in 2020 (8). In Italy, 1.7% of adolescents already habitually use EC and 41.5% have tried EC at least once (9). Such data are particularly worrying considering that a recent systematic review including 9 prospective longitudinal studies on adolescents who never smoked tobacco CC with follow-up periods between 4 and 24 months, showed that EC use increases the risk of becoming a current CC smoker by 4-fold, serving as a gateway to cigarette smoking (10).

Finally, recently the phenomenon of stealth vaping (*i.e.*, the act of vaping in a discreet manner by using small quantities of vape or smaller devices or devices resembling different types of electronic devices) started to spread among adolescents, making it even more difficult to detect the addiction inside the family or school environment (11).

This narrative review paper briefly outlines the most recent data on EC and their potential detrimental effects on the airways, focusing on childhood and adolescence. For the purpose of this review, we will refer only to EC, while we will not include evidence on devices with different aerosolization mechanisms such as HTP.

E-CIGARETTES, E-LIQUIDS AND VAPE: WHAT ARE VAPERS INHALING?

The aerosol produced by EC and other ENDS is generally called *"vape"* and appears denser than that produced by CC. EC have undergone numerous evolutions over the years, but they are all basically equipped with three main components: 1) a power source (usually a rechargeable lithium battery); 2) an atomizer, equipped with a resistance that heats up as the current passes through it, allowing the solution (e-liquid) to be vaporized by heating it to high temperatures; 3) a liquid storage unit (12). EC may be activated by the user's inhalation or by manual activation through a button. The most modern devices allow the user to set the resistance and power, thus varying the temperature of the aerosol: with higher

Cloud-chasing	Vaping technique with the goal to create different types of aerosol plume, emerging as competition among adolescents.
Dabbing	The term refers to vaping marijuana by heating concentrated cannabis oil ("dabs").
Dripping	Vaping technique in which dense vape is generated manually by dripping e-liquids directly onto the device's heating coils.
Dual user	User of both EC and traditional combustible cigarettes.
E-Cigarette	Strictly speaking, "electronic cigarettes" are portable battery-powered electronic devices that simulate the act of smoking a traditional cigarette without burning tobacco, by delivering an inhalable liquid-based aerosol.
ENDS	"Electronic Nicotine Delivery Systems" (ENDS) is a generic term used to identify all the currently available electronic devices used to deliver nicotine by inhalation without tobacco combustion. ENDS include EC, e-pipes, e-cigars, e-hookahs, vape pens, personal vaporizers, and so on.
EVALI	This acronym was introduced in 2019 and stands for "E-*cigarette or Vaping use-Associated Lung Injury*". EVALI is a diagnosis of exclusion in patients presenting with respiratory distress and a recent history of vaping, abnormal chest CT, absence of signs of pulmonary infection or any other alternative plausible diagnoses. Some Authors recently proposed introducing also the term EVALD (*"E-cigarette or Vaping use-Associated Lung Disease"*) to underline that vaping may cause different types of lung disease and not only acute injury.
Heat-not-burn devices/Heated tobacco products	Electronic devices generating aerosol by heating up tobacco, without burning it.
Pod-mods	Miniaturized ENDS usually resembling a USB flash drive and delivering high concentration of nicotine by using nicotine salts which do not cause a sensation of harshness or irritation on the airways during inhalation.
Puff	The term refers to disposable, cheap and highly concealable EC resembling pod-mods, the use of which is spreading among adolescents.
Stealth Vaping	The act of vaping in a discreet manner by using small quantities of vape or particularly small devices. ENDS resembling other devices such as car keys, teapots, credit card holders, asthma inhalers and so on are also available on the web.
Smoker	Combustible cigarette user.
Vape	The aerosol produced by ENDS, which usually appears denser than that produced by traditional cigarettes. The act of inhaling and exhaling the vapor produced by ENDS is known as "vaping".
Vaper	Electronic cigarette user.

Table 1. *Vaping glossary.*

temperatures, a stronger "hit" (sensation felt in the throat during inhalation) is generated (13, 14). As for e-liquids, they consist of a solution mostly composed (80-95%) of solvents such as propylene glycol (PG) or vegetable glycerin (VG, also known as glycerol); the remaining components are represented by one or more flavoring additives which make it possible to obtain a vapor with a distinctive flavor, and by nicotine which may be absent in EC but, when present, can reach high concentrations, up to more than 50 mg/mL (in the EU a limit has been set at 20 mg/mL). There are more than 15,000 different types of EC flavors on the market, ranging from the aroma of tobacco to food (fruit, sweets, candies) or stimulating drinks (coffee, alcohol). All these compounds are generally recognized as safe by the Food and Drug Administration (FDA) as they are widely used in the food and cosmetic industries, but it should be noted that their effects when chronically inhaled are still only partially known. Moreover, the e-liquid composition declared by manufacturing companies is not always truthful, both regarding the levels of nicotine (15, 16) and the

presence of other substances, including toxic and/or irritative ones, such as tobacco alkaloids and nitrosamines, volatile organic compounds, ethanol, metals, formaldehyde, acetaldehyde and acrolein, which have been found in e-liquids and vape, at different concentrations depending on the temperatures to which the liquid had been heated (17-19). In general, vapers probably inhale fewer toxic substances than CC smokers, but it is not easy to elucidate this issue because research studies are performed on precise quantities of vape produced and inhaled under standardized conditions, while in real life the exposure depends on the methods of EC use (voltage, heat of the liquid) and on the habits of the vaper (20).

Notably, among the currently available four generations of EC, the devices belonging to the fourth are those that give rise to more concern: such devices are the so-called "pod-mods" which look like USB pens and are very popular among teenagers because it is easy to hide their use (21). Pod-mods are particularly dangerous as they use a formulation of nicotine derived from nicotine salts with benzoic acid, delivering high concentrations without causing a sensation of harshness or irritation on the airways, thus increasing the amount consumed in a short time (22). Recently, disposable, and cheaper EC have become available and have gained immediate success, with an increase in sales from 2019 to 2020 in the US of 1000% in high school users and 400% in middle school users (8, 23).

EFFECTS OF VAPING ON RESPIRATORY HEALTH

The first case report describing respiratory distress caused by vaping dates back to 2012 (24), and since then, the number of published papers on the subject has increased exponentially (25). Increasingly available evidence shows that vaping exerts negative effects on airway biology and, consequently, on respiratory health, and this was largely expected, as there were previous reports of respiratory symptoms caused by inhalation of substances later found in e-liquids and vape. Apart from the detrimental effects of inhalation of toxicants and irritants, it has been reported that inhalation of PG and VG causes acute dry cough and wheezing and long-term respiratory impairment in theater and cinema workers exposed to stage fog produced by heating these solvents, which have hygroscopic properties that cause hyperosmotic stress and the subsequent release of inflammation mediators, ciliary function alteration and bronchoconstriction (26). Furthermore, the inhalation of diacetyl (2,3-butanedione), one of the most used chemical compounds in e-liquids, and especially in buttery or sweet aromas, has been shown to cause bronchiolitis obliterans in microwave popcorn factory workers ("*The Popcorn Worker's Lung*") (27-29). Moreover, some flavors contain known allergens such as cinnamaldehyde, eugenol and benzaldehyde (30-31).

To date, the effects of vaping reported both in vitro and in vivo on the respiratory system can be summarized in: a) pro-inflammatory effect, b) stimulation of bronchial hyperreactivity and c) increased susceptibility to infections (32-34) (**Figure 1**).

In 2022, an analysis of longitudinal data from the US PATH (Population Assessment of Tobacco and Health) study clearly demonstrated that vaping is an independent risk factor for the development of respiratory symptoms, such as cough and wheezing in otherwise healthy young adults, including those who have never smoked CC (35). A recent review and meta-analysis of epidemiological studies, both cross-sectional and longitudinal, has shown a significant association of EC use with asthma (pooled adjusted odds ratio 1.39 (95% CI 1.28-1.51)) and COPD (pooled adjusted odds ratio 1.49 (95% CI 1.36-1.65)), controlling for cigarette smoking and other covariates. Among the 15 selected studies on asthma, 11 included adolescents and were school-based data collections, mainly on high school students, of which 6 were carried out in the US, 4 in Asia and 1 in Canada (36). Nevertheless, evidence on vaping effects in childhood and adolescence, and also in asthmatics, is still scarce and mainly based on cross-sectional studies on adolescents, showing that EC use increases by about 2-fold the risk of developing self-reported symptoms attributable to chronic bronchitis and/or asthma, such as chronic cough, phlegm, dyspnea (37). It should be noted that adolescents with asthma smoke as much as their non-asthmatic peers and seem to use EC more than their peers due to the belief that vaping is safer than CC (38-41).

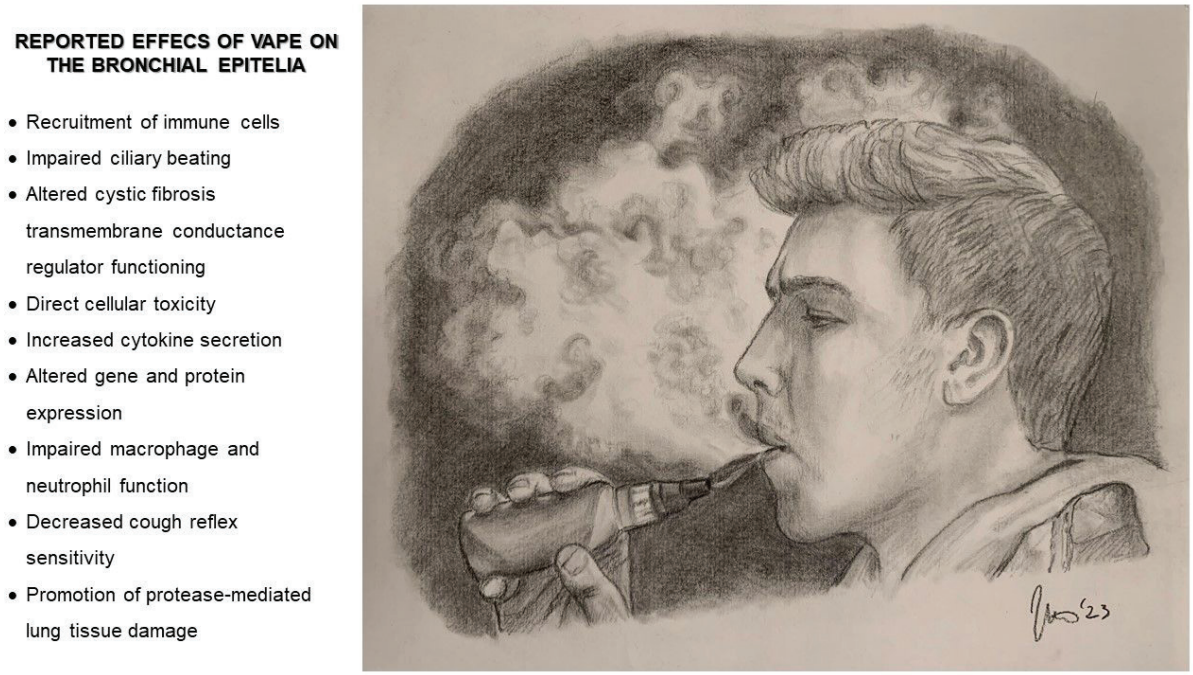

Figure 1. *Main effects of vaping on the airways. The picture summarizes the currently reported effects of vape exposure both in vitro and in vivo on the airway's mucosa.*

Finally, the EVALI (*E-cigarette or Vaping use-Associated Lung Injury*) epidemic that occurred in the US in 2019 demonstrated that vaping is associated with severe acute lung toxicity patterns which have never been described in CC smokers (42). This condition has been linked to the use of e-liquids containing tetrahydrocannabinol and/or vitamin E acetate and affects mainly young adults and adolescents showing respiratory symptoms such as shortness of breath, cough and chest pain, sometimes evolving into ARDS with the need for mechanical ventilation, and gastrointestinal symptoms (nausea, vomiting, diarrhea, abdominal pain) (43-44). All patients also show one or more constitutional symptoms (mostly fever) and CT scans of the thorax typically demonstrate ground-glass opacities with perilobular and peribronchial distribution and subpleural sparing, consistent with an organizing pneumonia pattern of lung injury resulting from toxic inhalation (45-46). In these patients, systemic glucocorticosteroid treatment seems to be effective while antibiotics do not improve lung function (47-48). To date, a few EVALI cases have been reported in other countries, including a recent ARDS case report in a 15-year-old girl in Italy (49).

It should be noted that while vitamin E acetate is safe as food supplementation or in cosmetics, it interacts with phosphatidylcholine when inhaled, thus altering the surfactant, which is no longer able to warrant the surface tension and the related normal functioning of the alveoli, subsequently giving rise to inflammation (50-51). As far as the long-term consequences of vaping are concerned, the presence of known carcinogens in vape and e-liquids suggests caution, but as yet no studies are available in this regard except for some studies on mice reporting an increased risk of lung adenocarcinoma (52). As regards second-hand smoke, in 2022 Islam et al. showed for the first time an association between exposure to passive smoke from EC containing nicotine and an increased risk of developing respiratory symptoms such as wheezing or bronchitis in more than 2,000 adolescents and young adults (53). This finding is not surprising, since the presence of toxic compounds in the indoor air of EC users' houses, such as $PM_{2.5}$ PM_{10}, nicotine and volatile organic compounds, had already been reported. This evidence advises against using EC indoors, especially in the presence of children and adolescents. There is currently no available data on third-hand va-

ping exposure, but traces of nicotine and particulate matter have been detected on surfaces exposed to vaping (54-56). With respect to pregnancy, data relating to the birth of low-birth-weight newborns from mothers who had vaped during pregnancy are starting to emerge (57, 58): as a result, the World Health Organization (WHO) has declared the use of ENDS to be unsafe in pregnancy (59).

THE ROLE OF PEDIATRICIANS

Pediatricians play a crucial role in fighting smoking, as more than half of current smokers started smoking before the age of 18. In such a scenario, the vaping epidemic represents both a new challenge for healthcare providers and an insidious threat for young people, and adolescents in particular, whose brain is particularly at risk of becoming nicotine addicted. Since adolescents who begin vaping or smoking early are less likely to stop using tobacco products (60-63), they represent the main target of advertising campaigns by EC brands, who are continuously trying to recruit new customers to replace those quitting or prematurely dying from smoking. Therefore, pediatricians should be updated on the subject and on health effects of vaping, in order to adequately educate and warn their patients and their parents, including all the possible ways of exposure (64) (**Figure 2**). Their commitment and involvement are particularly important when considering that knowledge of EC is usually inadequate in both adolescents and parents, as shown in a recent single-site prospective questionnaire analysis of 300 adolescents and their parents (65). The education of parents should also be targeted to their smoking and vaping habits since, similarly to what happens with CC, parents using ENDS predicts a higher probability of their children using them, even after controlling for parent past month CC use (66). The same is true regarding exposure to vaping imagery in television or film, which was found to be associated with a significantly increased risk of vaping uptake among young people (67). Last but not least, pediatricians should warn families about the risks of device exposure causing burns and wounds (68-70), as well as of an increasing number of reports on poisoning due to accidental or intentional ingestion of e-liquid in childhood and adolescence (71).

In the last few years, several scientific societies have become aware of the tremendous implications of vaping epidemic in adolescence as well as vape's potential health effects throughout life (72) and started to take a position, recommending that environments where children and adolescents live should be free of ENDS and other tobacco products. In 2015, The American Academy of Pediatrics have released recommendations on vaping, suggesting universal screening and prevention counseling on tobacco use and other substance use in adolescence, including EC, both for parents and children (63). In 2018 the Forum of International Respiratory Societies (FIRS) released a position statement including, among other recommendations, that i) EC be regulated as tobacco products and included in smoke-free policies, ii) sale of EC to youths should be banned worldwide, iii) advertising accessible by youths and young adults should be banned, and iv) flavoring should be prohibited in EC (73). The European Respiratory Society (ERS) Tobacco Control Committee in 2021 warned about the potential toxicity of prolonged exposure to vape, until proved otherwise (74). The European Academy of Paediatrics (EAP) recently released ten recommendations regarding EC, underlining that since there is incontrovertible evidence that the acute toxicity of EC is greater than that of CC and even if the chronic toxicity of EC is still unknown, it cannot be assumed that EC are safer than CC (75).

Lastly, it should be noted that EC are currently not recognized as smoking cessation aids by both the FDA and WHO due to inconclusive evidence, with some studies demonstrating their effectiveness (76-77) and others showing that they may perpetuate addiction or even encourage dual use (78). Both these institutions have produced educational material warning against potential health effects of ENDS, especially in children, adolescents, and young adults, which is freely available on the Internet (79-80).

CONCLUSIONS

It is staggering how the use of ENDS is rapidly spreading among youth and adolescents and represents a worrisome source of new threats to respiratory health and to health in general in the short and probably also

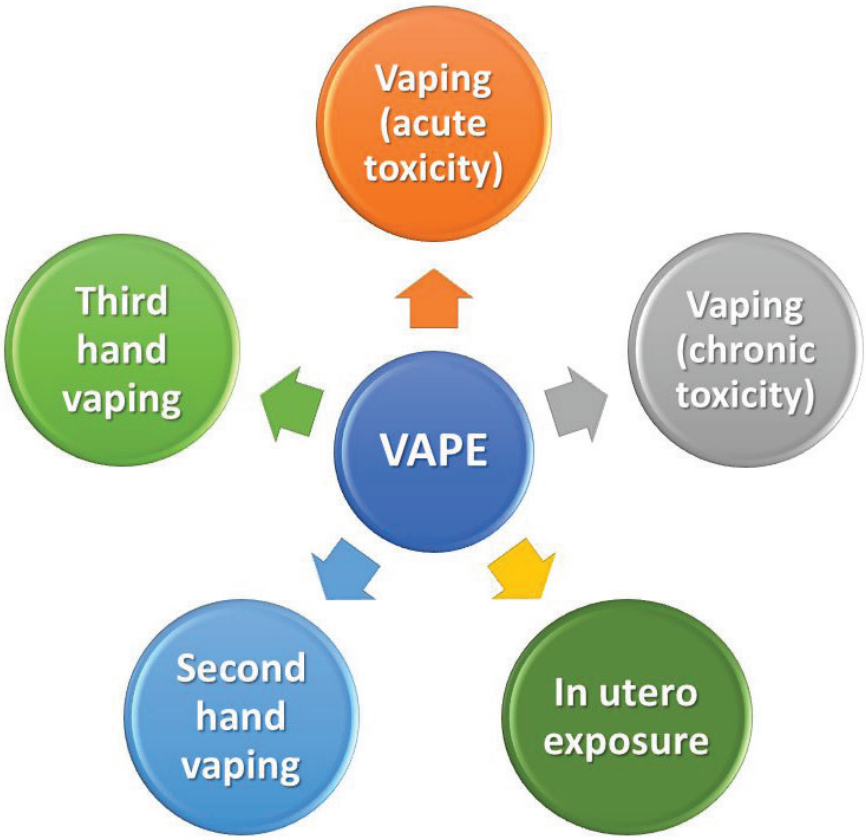

Figure 2. *Harmful routes of vaping exposure. Available evidence shows that vaping exerts detrimental effects both in the short and long term in first-hand vapers, but data are becoming available on second and third-hand vaping as well as on in utero exposure.*

in the long term. Data on the detrimental effects of different ways of vaping exposure, including in utero, are rapidly becoming available.

COMPLIANCE WITH ETHICAL STANDARDS

Conflict of interests

The Authors have declared no conflict of interests.

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Authorship

Drs. Maria Di Cicco, Alessandra Beni, Vincenzo Ragazzo, Diego G. Peroni.

Author contributions

MDC and AB: conceptualized the study, drafted the initial manuscript, reviewed the literature and critically revised the final manuscript. MS, VR, DP: contributed to the review of the literature and data collection. They also actively participated in manuscript drafting, critically reviewing it. VR: performed the artwork, too. All Authors read and approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

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N/A.

Animal studies

N/A.

Data sharing and data accessibility

The data underlying this article are available in the article.

Publication ethics

Plagiarism

N/A.

Data falsification and fabrication

All the data correspond to the real.

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