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(REVIEW ARTICLE)

The association of gut microbiome with central precocious puberty in female adolescent: A Systematic Review

Deandra Maharani Widiatmaja [1, 2, *], Thania Lathifatunnisa Putri Agusti [3] and Dini Cynthia Dewi Tanuwijaya [4]

[1] *Kalabahi Regional General Hospital, Alor, East Nusa Tenggara, Indonesia.*
[2] *Faculty of Medicine, Universitas Airlangga, Surabaya, East Java, Indonesia.*
[3] *Department of Obstetrics and Gynecology, Faculty of Medicine, Universitas Indonesia, Jakarta, Indonesia.*
[4] *Borong Regional General Hospital, East Manggarai, East Nusa Tenggara, Indonesia.*

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Abstract

Background: Central precocious puberty (CPP) involves the early onset of puberty, leading to accelerated growth and bone maturation. The incidence of CPP is rising worldwide, presenting various challenges. The causes of CPP are complex, including genetic, environmental, and metabolic factors. Recent research suggests that the gut microbiome (GM) may influence endocrine function and hormonal regulation. This systematic review aims to investigate the association between GM composition and the onset of CPP in female adolescent, exploring the potential of specific microbial profiles as predictors of this condition.

Method: We evaluated all studies assessing GM diversity in female adolescents diagnosed with CPP. We included observational study designs and restricted the review to English-language articles. A systematic literature search was conducted using specific keywords and terms in the PubMed, Scopus, ProQuest, and Web of Science databases.

Results: Sixty-four suitable studies were assessed in this review. Two observational studies met the inclusion criteria, encompassing a total sample of 198. The studies reported differing findings: one study found that the genera *Blautia*, *Streptococcus*, and *Ruminococcus* were more enriched in CPP patients compared to healthy controls, while the other study identified an enrichment of *Ruminococcus*, *Gemmiger*, and *Clostridia*. These genera were associated with increased nitric oxide and the production of short-chain fatty acids, which may promote the pulsatile release of Gonadotropin-Releasing Hormone (GnRH), potentially inducing CPP.

Conclusion: Several gut microbes were correlated with CPP and may serve as novel predictors and prevention of the condition.

Keywords: Central Precocious Puberty; Female; Adolescent; Gut Microbiome

1. Introduction

Precocious puberty is defined as the occurrence of secondary sexual development before the age of 8 in girls and before the age of 9 in boys. Central precocious puberty, also known as GnRH-dependent precocious puberty, is triggered by the early activation of the hypothalamic-pituitary gonadal axis (HPGA). The etiology of this condition remains idiopathic; however, a genetic factor is a potential contributor. Furthermore, central-type precocious puberty in other cases is attributed to lesions in the central nervous system [1], [2], [3]. Central precocious puberty (CPP) is significantly more common in girls than in boys, with rates ranging from 29 per 100,000 girls in the USA to 92 per 100,000 girls in Denmark. A recent epidemiological study on South Korean children, spanning from 2008 to 2014, revealed a notably

* Corresponding author: Deandra Maharani Widiatmaja

high incidence of 263 cases of CPP per 100,000 girls [4]. One of the primary concerns associated with precocious puberty is the eventual attainment of a short stature in adulthood, attributed to the premature fusion of growth plates. This condition also carries notable psychosocial implications and subsequent health complications, such as obesity, type 2 diabetes, coronary artery disease, hypertension, stroke, and hormone-dependent cancers as a result of heightened exposure to estrogen [5].

Several studies have identified risk factors for CPP, including genetic, female gender, reduced exercise, frequent intake of nutritional supplements and high-protein food, increased BMI, early maternal menarche, long-term use of electronic devices, vitamin D deficiency, and inadequate sleep. These factors are strongly linked to precocious puberty in children [2], [3], [6], [7]. The gut microbiota (GM) has a critical role in metabolizing nutrients, breaking down dietary fibers and undigested proteins to produce beneficial metabolites such as γ-aminobutyric acid (GABA), norepinephrine, dopamine, histamine, and serotonin. These bioactive compounds have a discernible impact on modulating the gut-brain axis. The interconnection of the gut-brain axis is established through bidirectional neural, endocrine, and immune communication, allowing alterations in one organ to exert influence on the other [3], [8].

Recent findings indicate that the GM may significantly influence the timing of puberty through metabolic and hormonal mechanisms. Nevertheless, the relationship between GM and CPP has not been thoroughly examined. Therefore, our goal is to systematically analyze the correlation between the GM and CPP in female adolescents.

2. Material and methods

2.1. Study Design

This study was a systematic review analyzing the association of gut microbiome and central precocious puberty (CPP) in adolescent female. As it was a review of published literature, institutional review board approval was not required.

2.2. Protocol and Registration

The present study adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines 2020 [9].

2.3. Eligibility Criteria

The inclusion criteria were structured in accordance with the Participants, Exposure, Comparison, Outcomes, and Study Design (PECOS) model. We evaluated all the studies assessing gut microbiome composition and diversity among CPP girls compare to healthy girls We included only observational study designs. There is no restriction on the year of publication. The selection for included studies was restricted to the English language and only articles with full text available.

2.4. Search Strategy

We conducted systematic literature searches of PubMed, Scopus, ProQuest, and Web of Science databases to identify all relevant studies from the inception to July, 31st 2024. The search was conducted adopting the following keywords and MESH terms: (((Female Adolescent) OR (female young adult) OR girl* OR (teenage girl) OR (young woman) OR (adolescent female)) AND ((gut microbiome) OR (gut flora) OR (intestinal microbiota)) AND ((precocious puberty) OR (early puberty) OR (premature puberty) OR (early menarche))).

2.5. Study Selection

Two reviewers (TLPA, DCDT) independently screened the titles and abstracts for eligible studies. Duplication was removed manually and using Rayyan online software. The results were then compared and any disagreements were resolved by discussion among the reviewers and if required, with the involvement of the most experienced authors (DMW).

2.6. Data Extraction

Included studies were extracted independently by two reviewers (TLPA, DCDT). The following data were extracted from each included study: (1) first author's last name and publication year; (2) country of study; (3) sample size and age ; (4) study design; (5) study results. Disagreements were resolved by discussion among the reviewers and if required, with the involvement of the most experienced authors (DMW).

2.7. Risk of Bias and Quality Assessment

The quality of the included studies was assessed using the Newcastle–Ottawa Scale (NOS) for observational studies. The NOS is a validated, easy-to-use scale of 8 items in three domains, selection, comparability, and outcome. The NOS was used to assess the quality of the included studies. Studies are graded one point each for all items except comparability which has the potential to score up to two points, with the maximum possible score being nine. Studies are rated from 0–9, with those studies rating 0–2 (poor quality), 3–5 (fair quality), and 6–9 (good/high quality) [10].

3. Results

3.1. Study selection, characteristics of the participants, and risk of bias within studies

The electronic search resulted in the initial identification of references. After removal of duplicates and an initial shift for relevance, there are only 29 publications left. We screened titles and abstracts of all 29 references, resulting in 2 potentially eligible articles. We obtained the full texts of all studies and assessed them for eligibility. Two observational studies met the inclusion criteria. In addition, we hand-searched the references of all the studies for which the full text was retrieved. However, we identified no additional studies that could provide data to answer the research question. A study flow diagram is shown in Figure 1, according to the template described in the PRISMA statement. The total population of all studies was 198 patients, with 116 girls diagnosed with CPP anfd 82 healthy non-CPP girls as the control.

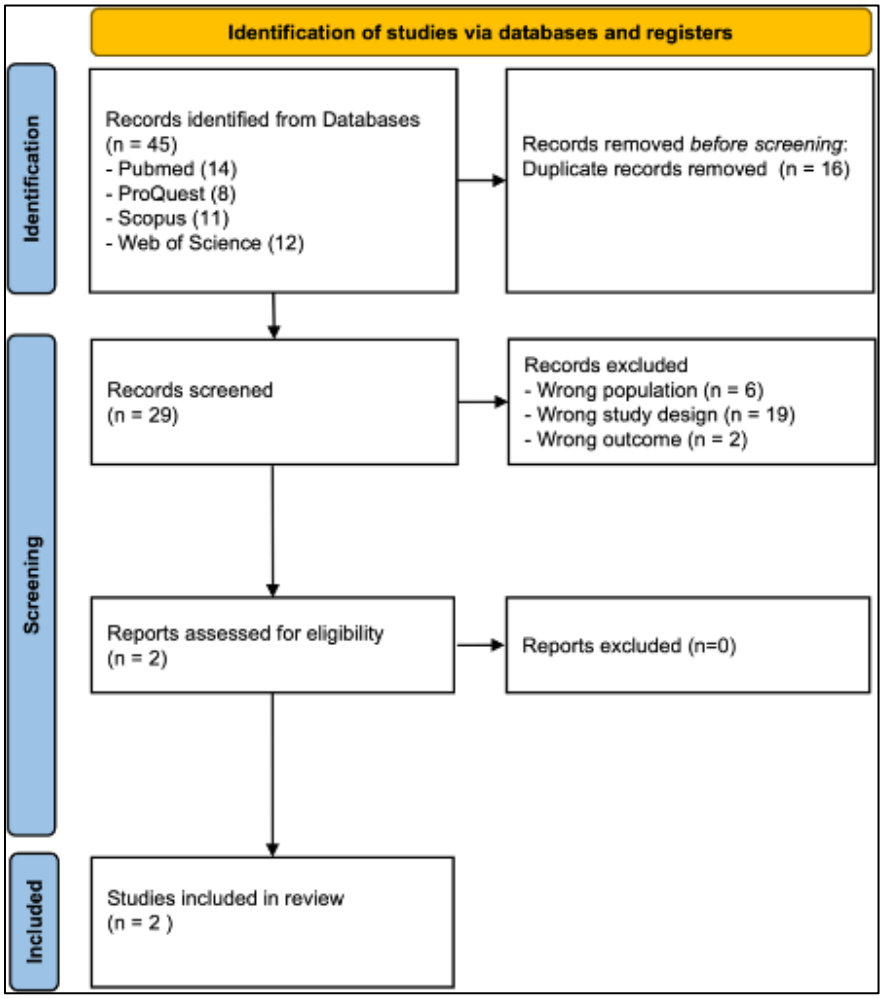

Figure 1 PRISMA flow chart diagram

3.2. Study Finding

3.2.1. Enriched GM in Female Adolescent Diagnosed with CPP

In study conducted by Dong et al. (2020) it was known that in the CPP group, 13 genera were enriched, with the highest relative abundances observed for genus *Ruminococcus*, *Gemmiger*, and *Roseburia* (each >1%). A total of 16 species differed significantly between the two groups (FDR < 0.05). Among these, 15 species were enriched in the CPP group, while *Bacteroides plebeius, Bacteroides coprocola, Gemmiger formicilis, Ruminococcus bromii*, and *Roseburia inulinivorans* showed the highest relative abundance (>1%) in the control group. Notably, all genera enriched in the CPP group exhibited relative abundances of less than 1% in the control group. In contrast, *Bacteroides plebeius, Bacteroides coprocola, and Ruminococcus gnavus* were the most abundant species in the control group (>1%), with *Ruminococcus gnavus* being the only species significantly enriched in the control group [2].

Furthermore, a study by Huang et al. (2023) mentioned that in the CPP group, *Ruminococcus*, *Blautia*, and *Streptococcus* were reported as enriched genera. However, this study did not provide information on the relative abundances of these genera in either group, nor was the gut microbiota composition of the control group described

3.2.2. Association of GM with Several Clinical Indicators in Sexual Development

Study by Dong et al. (2020) showed a positive correlation of Follicle-stimulating hormone (FSH) with Fusobacterium, while luteinizing hormone (LH) was positively correlated with *Gemmiger* and negatively correlated with Romboutsia. Functional analysis indicated that LH-associated *Gemmiger* was positively correlated with pathways related to environmental adaptation but negatively correlated with energy metabolism and signaling molecules and interaction. In addition, insulin resistance (IR) was positively correlated with *Gemmiger*, *Ruminococcus*, *Megamonas*, and *Ruminococcus*, and IR-associated *Ruminococcus* was further found to be positively correlated with environmental adaptation and cell motility [2].

3.2.3. Association of GM with Several Clinical Indicators in Sexual Development

Interestingly, a molecular analysis conducted by Huang et al. showed that several gut microbiota groups were correlated with increased levels of certain metabolites known to play molecular roles in the development of CPP. It showed that *Ruminococcus* was positively correlated with M149T215 (bisphenol B) and M431T154 (α-tocopherol, vitamin E). In addition, *Blautia*, *Streptococcus*, and *Ruminococcus*, which exhibited higher abundances in the CPP group, were positively associated with M430T323 (tubacin). Furthermore, *Blautia* and *Ruminococcus* showed positive correlations with M247T196 (tryptophan betaine) [3].

Table 1 Characteristic of study and main finding

Author, year	Origin	Type of study	Population				GM Composition					
			Subject (n)	Age (mean ± SD, year)								
				CPP group	Control group	*p*-value	CPP group			Control group		
							GM	Relative abundance	sig.	GM	Relative abundance	sig.
Dong *et al.*, 2020	China	Cross-sectional study	Total: 48 CPP: 25 Control: 23	7.045 ± 1.08	8.462 ± 2.288	0.024	Genus-level					
							Gemmiger□ *Roseburia* *Ruminococcus*□	>1%	FDR <0.05*	*Acinetobacter* *Barnesiella* *Clostridium sensustricto* *Clostridium XlVb* *Coprococcus* *Holdemania* *Oscillibacter* *Roseburia*	<1%	NS
							Acinetobacter *Barnesiella* *Clostridium sensu stricto* *Clostridium XlVb* *Coprobacter* *Coprococcus* *Holdemania* *Oscillibacter* *Pseudomonas* *Psychrobacter*	<1%				
										Anaerostipes◦ *Bacteroides*◦ *Ruminococcus*◦ *Blautia*◦ *Clostridium XlVa*◦ *Faecalibacterium*◦ *Fusobacterium*◦ *Lachnospiracea incertaesedis*◦ *Megamonas*◦ *Parabacteroides*◦	NA	
							Bacteroides□ *Ruminococcus*□ *Blautia*□ *Fusicatenibacter*□ *Megamonas*□ *Parabacteroides*□ *Prevotella*□	NA	NS			
										Coprobacter *Psychrobacter*	NS	

Table 1 (continued)

Author, year	Origin	Type of study	Population				GM Composition					
			Subject (n)	Age (mean ± SD, year)								
				CPP group	Control group	*p*-value	CPP group			Control group		
							GM	Relative abundance	sig.	GM	Relative abundance	sig.
							Species-level					
							Bacteroides coprocola□ *Bacteroides plebeius*□ *Gemmiger formicilis*□ *Roseburia inulinivorans* *Ruminococcus bromii*	>1%	FDR <0.05*	*Bacteroides uniformis*◦	2.477 ± 5.606 %	FDR = 0.019+
										Barnesiella intestinihominis *Clostridium disporicum*	>1%	NS
							Barnesiella intestinihominis *Clostridium disporicum* *Clostridium lactatifermentans* *Clostridium leptum* *Clostridium sporosphaeroides* *Coprobacter fastidiosus* *Coprococcus eutactus* *Eubacterium coprostanoligenes* *Psychrobacter fulvigenes*	NA		*Clostridium lactatifermentans* *Clostridium leptum* *Clostridium sporosphaeroides* *Coprococcus eutactus* *Eubacterium coprostanoligenes* *Faecalibacterium prausnitzii*◦ *Gemmiger formicilis* *Megamonas funiformis*◦ *Roseburia inulinivorans* *Ruminococcus bromii*	NS	

							Ruminococcus callidus			*Ruminococcus callidus* *Coprobacter fastidiosus* *Psychrobacter fulvigenes* *Clostridium lactatifermentans* *Clostridium leptum*		
							Ruminococcus gnavus *Bacteroides ovatus* *Bacteroides uniformis* *Faecalibacterium prausnitzii* *Megamonas funiformis*	NA	NS	*Clostridium sporosphaeroides* *Coprococcus eutactus*	NS	

Table 1 (continued)

Author, year	**Origin**	**Type of study**	**Population**				**GM Composition**					
			Subject (n)	Age (mean ± SD, year)								
				CPP group	Control group	*p*-value	CPP group			Control group		
							GM	Relative abundance	sig.	GM	Relative abundance	sig.
Huang *et al.*, 2023	China	Cross-sectional study	Total: 150 CPP: 91 Control: 59	NA	NA	NA	Genera-level					
							Ruminococcus *Blautia*	NA	$p \leq 1.0E^{-4}$*	NA		
							Streptococcus	NA	$p \leq 0.001$			
							Bacteroides *Faecalibacterium* *Prevotella 9* *Dialister* *Escherichia-shigella* *Roseburia* *Subdoligranulum*	NA	NS			
							Species-level					
							NA			NA		

CPP, central precoccious puberty; FDR, false discovery rate; GM, gut microbiome; NA, not available; ND, not detected; NS, not significant (FDR>0.05 or p>0.05); SD, standard deviation; ♂ top 10 in CPP group ; ♀ top 10 in control group; * significantly encriched in CPP group compared to control group (FDR<0.05 or p<0.05); ⁺ significantly encriched in control group compared to CPP group (FDR<0.05 or p<0.05)

Table 2 Association of GM with several clinical indicators

Author, year	**GM genera**	**Clinical Indicator**					
		FSH		LH		IR	
		r	*P*-value	r	*P*-value	r	*P*-value
Dong *et al.*, 2020	*Fusobacterium*	0.633	0.004*	NA	NA	NA	NA
	Gemmiger	NA	NA	0.0633	0.004*	>0.400	<0.100
	Rombutsia	NA	NA	-0.465	0.045*	NA	NA
	Ruminococcus	NA	NA	NA	NA	>0.400	<0.100
	Megamonas	NA	NA	NA	NA	>0.400	<0.100
	Ruminococcus	NA	NA	NA	NA	>0.400	<0.100

FSH, follicle stimulating hormone; GM, gut microbiome; IR, insulin resistance; LH, luteinizing homrone; NA, not available; r, correlation coefficient; *significant correlation between GM and clinical indicator (P<0.05)

Table 3 Association of GM with several metabolites related to sexual development

Author, year	GM genera	Findings
Huang *et al.*, 2023	*Streptococcus*	Positively correlated with M430T323 (Tubacin)
	Ruminococcus	Positively correlated with M149T215 (Bisphenol b), M431T154 (alpha-Tocopherol (Vitamin E)), M430T323 (Tubacin), and M247T196 (Tryptophan betaine)
	Blautia	Positively correlated with M430T323 (Tubacin) and M247T196 (Tryptophan betaine)

GM, gut microbiome

4. Discussion

This study results identified that enrichment of gut microbiome could play a role in the development of CPP. There are several mechanisms that can explain these findings. Huang et al. (2023) found a significant enrichment of nitric oxide–related gut–brain modules in female children with CPP. As mentioned in their study, *Ruminococcus*, *Blautia*, and *Streptococcus* were reported as enriched genera in CPP group. Functional prediction analysis showed that microbial genera such as Bacillus, Paenisporosarcina, Rhodococcus, *Ruminococcus*, *Streptococcus*, and *Blautia* contributed to pathways involved in NO synthesis [3]. Nitric oxide is a known neuromodulator that facilitates hypothalamic signaling and plays a key role in activating reproductive neuroendocrine pathways, thereby linking gut microbial metabolism to pubertal initiation. Microbiome-derived NO and neuroactive metabolites are closely linked to stimulation of gonadotropin-releasing hormone (GnRH). Correlation analyses revealed that *Ruminococcus*, *Streptococcus*, and *Blautia* were positively associated with metabolites known to activate NO signaling, which in turn promotes GnRH neuron activation. This provides a mechanistic link between gut microbiota dysbiosis and premature activation of the hypothalamic–pituitary–gonadal (HPG) axis ([2], [3], [8], [11], [12]).

The study by Huang et al. (2023) demonstrated increased microbial functional pathways related to short-chain fatty acid (SCFA) metabolism, including propionic acid and isovaleric acid synthesis, in CPP patients. Enriched taxa such as *Blautia* and *Ruminococcus*, which are established SCFA-producing bacteria, were associated with altered microbial fermentation activity. Dong et al. (2020) also highlighted that increased SCFA, particularly acetate and propionate, are known microbial metabolites that influence host energy metabolism and endocrine signaling. These SCFAs are important mediators of gut–brain communication and may influence neuroendocrine regulation that can modulate metabolic and hormonal pathways relevant to pubertal timing. Like the role of NO, SCFAs as microbiota-derived metabolites also contribute to activation of gonadotropin-releasing hormone (GnRH) neurons [2], [3] [12] [13], [14], [15].

Through enhanced GnRH secretion, microbiome alterations indirectly contribute to increased of gonadotropin (FSH and LH) levels, characteristic of CPP. In addition, microbial changes affecting SCFA production, lipid metabolism, and bile acid pathways may promote metabolic environment that induce earlier and stronger activation of the hypothalamic–pituitary–gonadal (HPG) axis, resulting in elevated gonadotropin levels [3]. Dong et al. (2020) emphasized the association of gut microbiota dysbiosis with increase of obesity-related metabolic changes and IR, which are all factors known to accelerate pubertal onset. Girls with CPP exhibited a distinct gut microbiota composition enriched in bacteria associated with enhanced energy harvest and metabolic activity. These microbial shifts were associated with higher body mass index (BMI), altered glucose metabolism, and increased IR, conditions known to accelerate pubertal development. Inflammation state and IR are mechanistically important because hyperinsulinemia can enhance HPG axis sensitivity, amplifying GnRH-driven secretion of FSH and LH [2] [16].

Molecular analysis conducted by Huang et al. (2023) showed that several gut microbiota groups were positively correlated with increased levels of Bisphenol B, Vitamin E, tubacin, and tryptophan betaine, which known ti have a link with CPP development. Bisphenol B has been reported to alter the uterine immune environment in mouse models [17]. In addition, vitamin E has been shown to play a critical role in the hypothalamic regulation of luteinizing hormone–releasing hormone (LHRH) and ascorbic acid (AA) secretion by modulating NO release in mice karanth. Tubacin has been demonstrated to markedly upregulate endothelial NO synthase expression, while NO is a well-established stimulator of gonadotropin-releasing hormone (GnRH) secretion [18], [19]. Moreover, tryptophan betaine has been identified as a strong indicator of vitamin D status, and accumulating evidence suggests that vitamin D levels may be linked to the risk of central precocious puberty (CPP), potentially through a threshold-dependent effect [10], [20]

This study has several limitations that should be acknowledged. First, only two observational studies met the inclusion criteria, resulting in a relatively small total sample size, which limits the generalizability and strength of the conclusions. Second, both included studies employed cross-sectional designs, preventing the establishment of causal relationships between gut microbiome alterations and the development of central precocious puberty (CPP). Third, gut microbiome profiling in the included studies was primarily based on 16S rRNA gene sequencing, which provides limited taxonomic and functional resolution and does not allow direct assessment of microbial metabolic activity. In addition, heterogeneity in study populations, microbiome analysis methods, and reported outcomes limited direct comparison between studies and precluded quantitative meta-analysis. Potential confounding factors such as diet, obesity status, environmental exposures, and lifestyle variables were not consistently controlled across studies. Finally, the review was restricted to English-language publications, which may have introduced publication and language bias. Therefore, the findings should be interpreted with caution, and further well-designed longitudinal and mechanistic studies are needed to clarify the role of gut microbiota in CPP.

5. Conclusion

This systematic review suggests that alterations in gut microbiome composition are associated with central precocious puberty in female adolescents. Specific bacterial genera, including *Ruminococcus*, *Blautia*, *Streptococcus*, *Ruminococcus*, and *Gemmiger*, were consistently enriched in girls with CPP and were linked to metabolites and pathways involved in nitric oxide signaling, short-chain fatty acid production, metabolic regulation, and activation of the hypothalamic–pituitary–gonadal axis. These findings indicate that gut microbiota dysbiosis may contribute to the premature initiation of pubertal processes through neuroendocrine and metabolic mechanisms. Although current evidence is limited, gut microbiome profiling holds potential as a novel predictive and preventive approach for CPP. Future large-scale, longitudinal, and functional studies integrating microbiome, metabolomic, and clinical data are required to validate these associations and to explore therapeutic strategies targeting the gut microbiome in CPP management. Overall, the alterations of metabolites associated with microbiota dysbiosis provided new insights for the diagnosis and treatment of CPP.

Compliance with ethical standards

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Disclosure of conflict of interest

The authors state there's no conflict of interest associated with this publication, and there has been no significant financial support for this work that could have influenced its outcome. The manuscript has been read and approved for submission by all the named authors.

Statement of ethical approval

This study is an empirical study using public data and does not involve ethical review issues.

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