Association of Amoxicillin Use During Early Childhood With Developmental Tooth Enamel Defects

Liang Hong, DDS, MS, PhD; Steven M. Levy, DDS, MPH; John J. Warren, DDS, MS; Deborah V. Dawson, PhD; George R. Bergus, MD, MA; James S. Wefel, PhD

Background: It has been speculated that amoxicillin use could be associated with dental enamel defects.

Objective: To assess the association between dental fluorosis, one of the most common developmental tooth enamel defects, and amoxicillin use during early childhood.

Design, Setting, and Participants: As participants in the Iowa Fluoride Study, subjects were followed up from birth to 32 months using questionnaires every 3 to 4 months to gather information on fluoride intake and amoxicillin use.

Methods: Early-erupting permanent teeth of 579 subjects were assessed for fluorosis using the Fluorosis Risk Index at approximately the age of 9 years. Relationships between fluorosis and amoxicillin use were assessed using relative risk (RR), Mantel-Haenszel stratified analyses, and multivariable logistic regression.

Results: Amoxicillin use was reported by 75% of subjects by 12 months and 91% by 32 months. Overall, 24% had fluorosis on both maxillary central incisors. Amoxicillin use from 3 to 6 months significantly increased the risk of fluorosis on the maxillary central incisors (RR = 2.04; 95% confidence interval [CI], 1.49-2.78). After adjusting for fluoride intake and otitis media, the risk of fluorosis on the maxillary central incisors from amoxicillin use during 3 to 6 months (Mantel-Haenszel RR = 1.85; 95% CI, 1.20-2.78) was still statistically significant. Multivariable logistic regression analyses confirmed the increased risk of fluorosis from amoxicillin use during 3 to 6 months (odds ratio = 2.50; 95% CI, 1.21-5.15); fluoride intake was also statistically significant.

Conclusion: The findings from this study suggest a link between amoxicillin use during infancy and developmental enamel defects of permanent teeth; however, further research is needed.

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Many antibiotics have been introduced and are commonly prescribed for childhood infections. Some antibiotics, such as tetracyclines, clearly influence the development of the tooth. However, little is known regarding the effects of most drugs in this therapeutic class. Amoxicillin is one of the most common antibiotics used among pediatric patients, mainly for the treatment of otitis media, and even a small effect on dental enamel could have a significant effect on the public's dental health because of its widespread use.

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Dental enamel is the hardest, most mineralized tissue in the human body and its formation is a complex, highly concerted, and well-programmed biominer-
METHODS

Data were collected as part of the Iowa Fluoride Study, a prospective study investigating fluoride exposures, biological and behavioral factors, and children’s dental health.\(^5,14-18\) Using institutional review board–approved informed consent procedures, 1390 subjects were successfully recruited at birth from 8 Iowa hospitals from March 4, 1992, to February 2, 1995, and subjects were excluded if they were too ill to participate. Variable numbers of participants responded to each questionnaire. Although this cohort was not randomly selected, the participants were generally representative of children in Iowa. There were 698 subjects who received dental examinations of the primary dentition, and 579 who received examinations of the early-erupting permanent teeth and amoxicillin use during the first 32 months of life.

![Figure 1. Teeth showing definitive, mild fluorosis of the incisal zones, typical of Fluorosis Risk Index score 2.](Image)

particularly diffuse opacities. These diffuse opacities, possibly due to enamel hypomineralization, appear clinically similar to dental fluorosis, but are different from tetracycline staining. Using data collected in the Iowa Fluoride Study, we reported the association between primary tooth fluorosis and amoxicillin use during the first year of life.\(^14\) A significant risk for primary tooth fluorosis from amoxicillin use during early infancy was detected only in bivariate, not multivariable, analyses, and the evidence was not conclusive.\(^14\) However, the period of enamel development for primary teeth is largely prenatal, while intake of a high level of fluoride could occur postnatally. Also, the sample size was small and the number of fluorosis cases available for primary tooth analyses was few. Therefore, the purpose of this article is to report on the association between dental fluorosis of early-erupting permanent teeth and amoxicillin use during the first 32 months of life.

Data were collected as part of the Iowa Fluoride Study, a prospective study investigating fluoride exposures, biological and behavioral factors, and children’s dental health.\(^5,14-18\) Using institutional review board–approved informed consent procedures, 1390 subjects were successfully recruited at birth from 8 Iowa hospitals from March 4, 1992, to February 2, 1995, and subjects were excluded if they were too ill to participate. Variable numbers of participants responded to each questionnaire. Although this cohort was not randomly selected, the participants were generally representative of children in Iowa. There were 698 subjects who received dental examinations of the primary dentition, and 579 who received examinations of the early-erupting permanent teeth. Therefore, among the 1390 at 6 months of age, the mean annual attrition rate was 6.3%. Demographic characteristics at baseline were described in detail previously.\(^5,14,15\) Briefly, this cohort is preponderantly white (about 98% vs 91% for dropouts), were more educated (45% vs 46% of mothers having completed 4 years of college); 44% were female, and from families of relatively high socioeconomic status (71% having family income of ≥$30,000 and 46% of mothers having completed 4 years of college); 44% were first children, 32% had breast fed for at least 6 months, only 4% had low birth weight, and 3% had developmental disorders. Subjects who continued participation in the study and completed the mixed dentition examination were more often white (98% vs 91% for dropouts), were more educated (43% of mothers with college degrees vs 26%), had higher family incomes (33% >$50,000 vs 18%), and had older parents (mean age of mothers, 30 vs 26 years; mean age of fathers, 32 vs 30 years). Questionnaires were sent to parents at 3- and 4-month intervals, from the child’s birth to 32 months of life, assessing fluoride intake from various sources, antibiotic use, children’s illnesses, and breastfeeding patterns. Data collection details have been described previously.\(^5,14-16\) Fluoride intake in milligrams per kg body weight per day was estimated from water, beverages, and selected food; dietary fluoride supplement; and fluoride dentifrice based on responses to a series of detailed questions.\(^14\) Parents were asked to identify specific antibiotics that were prescribed and given to the child by selecting from a list of commonly used antibiotics.\(^14\) Parents reported whether antibiotics were administered systemically, orally, or topically, the number of episodes of illnesses for which antibiotics were used, and the numbers of days of any antibiotic use during a reporting period. If more than one antibiotic was used during a reporting period, the numbers of days of amoxicillin use were estimated by adjustment for the use of other concomitant antibiotics.\(^14\) Topical antibiotics were excluded from the analyses. Parents were also asked to report the occurrence of selected illnesses for which antibiotics were prescribed during the previous reporting period,\(^5,14\) using a list of illnesses provided.\(^14\)

Traditionally, diffuse opacities of tooth surfaces have been called “dental fluorosis” since excessive fluoride ingestion is the most common cause. The original, primary purpose of the Iowa Fluoride Study has been to study fluoride intake/exposure and dental fluorosis, and, thus, we follow the tradition of using the term dental fluorosis for the condition of diffuse opacities on tooth surfaces. We assessed them in a manner similar to previous epidemiological studies, using visual examinations only, without using questionnaire data and history to define cases. The Fluorosis Risk Index (FRI) was chosen to assess this condition because of its advantages in the analytical epidemiological studies of dental fluorosis.\(^19\) Children (N=579; 297 females and 282 males) were examined for dental fluorosis on early-erupting permanent teeth (incisors and first molars) at about 8 through 10 years of age (mean age, 9.2 years) by 2 trained and calibrated examiners (J.J.W. and another examiner) using the FRI. The examiners were blind to questionnaire information on fluoride intake, childhood infections, and antibiotic use.\(^19\) All 12 early-erupting permanent teeth were examined for each subject: 4 mandibular incisors, 4 maxillary incisors, and 4 first molars. A mouth mirror and examination light were used, and teeth were dried slightly with gauze. Fluorosis was differentiated from nonfluorosis opacities based on Russell’s criteria\(^20\) and from “white spot” carious lesions based on color, texture, demarcation, and relationship to the gingival margin.\(^18\) Using the FRI, 3 zones (incisal edge, incisal third, and middle third) of facial surfaces were assessed separately for these early-erupting permanent teeth, with FRI scoring criteria differentiating no fluorosis, questionable fluorosis (≥30% of zone with white striations), definitive fluorosis (>30% of zone with white striations, Figure 1), and severe fluorosis (zone displays pitting, staining, and/or deformity, Figure 2).\(^18\) Analyses were conducted defining cases vs noncases, both limited to incisal edges of maxillary central incisors only (FRI zone I) and separately using 3 zones of maxillary central incisors. Person level interexaminer reliability was 85.7% agreement (κ=0.72) for permanent incisors and 88.2% (κ=0.60) for permanent first molars.

A dental fluorosis case was defined as having FRI definitive to severe fluorosis on both maxillary central incisors; control subjects had fluorosis on neither of these incisors. All other subjects with any FRI questionable fluorosis were excluded as well as subjects whose relevant zones could not be scored because of reasons such as incomplete eruption. Subjects with only one maxillary central incisor having fluorosis were also excluded. In this way, these analyses included only individuals with de-
fluent or severe fluorosis and those without fluorosis with a high degree of certainty of the diagnosis.

Exposure to amoxicillin therapy was first categorized into “yes” or “no” groups for individual and cumulative periods. Also, its use was categorized into mutually exclusive groups for the first year of life, including those who never used amoxicillin during the first year, sole use during birth to 3 months, sole use during 3 to 6 months, sole use during 6 to 9 months, sole use during 9 to 12 months, and multiple period use during the first year. The estimated daily average fluoride intake was categorized into tertiles (low, middle, and high fluoride intakes) based on the frequency distribution of average fluoride intake for each period.

The associations between fluorosis on both maxillary central incisors and amoxicillin use were first assessed using χ² tests and then Mantel-Haenszel stratified analyses controlling for fluoride intake and otitis media. Relative risks (RRs) and 95% confidence intervals (CIs) were calculated. Breslow-Day tests assessed the homogeneity of the RRs of amoxicillin use across the strata. The association between fluorosis on both maxillary central incisors and fluoride intake was also assessed.

Use of other antibiotics (cephalosporins, penicillins, sulfas, erythromycins, and a combination of erythromycin ethylsulinate and sulfisoxazole acetyl [Pediacet; Ross Laboratories, Division of Abbott Laboratories, Columbus, Ohio]) and other factors, including sex, family income at baseline ($<20,000, $20,000-$39,999, $40,000), mother’s age at birth of child, mother’s educational level at baseline (up to high school, some college, college graduate or higher), birth weight (<2.5 kg or ≥2.5 kg), illness during the first year (yes/no), developmental disorders (yes/no), and breastfeeding (<6 vs ≥6 months), were also assessed for individual association with fluorosis by χ² tests. Variables with P < .10 in bivariate analyses were selected for multivariable logistic regression, and the main effects and 2-way interactions between them were assessed and odds ratios (ORs) were obtained. Adjusted RRs were computed using an analogous multivariable log-binomial regression model using the PROC GENMOD procedure of SAS (SAS Institute Inc, Cary, NC). Sensitivity analyses were conducted to assess the effects of the subjects with questionable fluorosis. The statistically significant level was α = .05. Data were analyzed with SAS statistical software for Windows version 9.1.2 (SAS Institute Inc).

RESULTS

Considering 3 zones on the maxillary central incisors, 139 subjects (24%) (only 3 subjects had severe fluorosis) had fluorosis on both maxillary central incisors, 45 (8%) had fluorosis on 1 maxillary central incisor, 214 (37%) were questionable fluorosis cases, and 181 (31%) had no fluorosis. Considering only incisal edges (FRI zone I), the corresponding numbers are 115 (20%), 42 (7%), 130 (22%), and 292 (51%), respectively. Subsequent analyses focus primarily on the 407 subjects having either fluorosis on incisal edges of 2 maxillary central incisors or no fluorosis on either of 2 maxillary central incisors.

Period-specific amoxicillin exposure was substantial in this cohort of 407 subjects, increasing from 18.6% (0-3 months) to 41.0% (12-16 months), before declining to 21.2% (28-32 months). Cumulatively, 43.6% had amoxicillin use from birth to 6 months, 74.5% by 12 months, 86.5% by 20 months, and 91.8% by 32 months.

From bivariate analyses, amoxicillin use during 3 to 6 months (RR = 2.04; 95% CI, 1.49-2.78) and cumulatively birth to 6 months (RR = 1.92; 95% CI, 1.35-2.70) and birth to 9 months (RR = 1.75; 95% CI, 1.15-2.70) were significantly associated with fluorosis. In addition, analyses using the mutually exclusive amoxicillin-use groups showed that sole use from 3 to 6 months (RR = 1.53; 95% CI, 1.44-4.41) and multiple periods of amoxicillin use in the first year of life (RR = 1.20; 95% CI, 1.03-4.38) significantly increased the risk of fluorosis on both maxillary central incisors when compared with those who never used amoxicillin during the first year of life. Parallel results using all 3 zones found similar results (3-6 months RR = 1.72; 95% CI, 1.33-2.51; cumulatively 0-6 months RR = 1.69; 95% CI, 1.27-2.17; and 0-9 months RR = 1.43; 95% CI, 1.03-2.00). Most individual periods and almost all cumulative periods of fluoride intake were significantly associated with fluorosis on the maxillary central incisors.

Otitis media accounted for 60% to 82% of childhood illnesses, depending on the reporting period. Also, amoxicillin use was strongly related to the treatment of otitis media, accounting for 73% to 84% of antibiotics prescribed for the treatment of otitis media during the first year of life. Otitis media during 3 to 6 months (RR = 1.78; 95% CI, 1.30-2.43) and cumulatively from birth to 6 months (RR = 1.54; 95% CI, 1.10-2.17) were significantly associated with fluorosis on the maxillary central incisors (data not shown).

Using Mantel-Haenszel stratified analyses, the effect of amoxicillin use on fluorosis of the maxillary central incisors was assessed jointly controlling for fluoride intake and otitis media (Table 1). The risks of fluorosis on incisal edges of both maxillary central incisors for amoxicillin use during 3 to 6 months (RR = 1.85; 95% CI, 1.20-2.78) and cumulatively birth to 6 months (RR = 1.85; 95% CI, 1.25-2.70) and birth to 9 months (RR = 1.79; 95% CI, 1.10-2.94) remained significant after stratification. Breslow-Day test results consistently showed homogeneity of the RRs for amoxicillin use across levels of daily fluoride intake and otitis media, indicating no significant 3-way interactions among amoxicillin use, fluoride intake, and otitis media. Relative risks for amoxicillin use were generally higher among those without otitis media than those with otitis media across different levels of fluoride intake. Parallel analyses using all 3 zones found generally similar results (3-6 months RR = 1.92; 95% CI, 1.32-2.78; cumulatively 0-6 months RR = 1.72; 95% CI, 1.18-2.56).
The other classes of antibiotics were not found to be significantly associated with fluorosis on both maxillary central incisors at \( \alpha = .05 \). Other factors were as follows: female (RR = 1.02, \( P = .90 \)); family income at baseline (low vs others, RR = 1.18, \( P = .47 \)); mother’s age at birth of child (\( > 30 \) vs others, RR = 0.88, \( P = .10 \)); mother’s educational level at baseline (up to high school vs others, RR = 1.07, \( P = .58 \)); low birth weight (RR = 1.34, \( P = .31 \)); illness during the first year of life (RR = 1.32, \( P = .37 \)); developmental disorders (RR = 1.00, \( P = .99 \)); and breastfeeding fewer than 6 months (RR = 1.39, \( P = .07 \)).

Individual variables with \( P < .10 \) in the bivariate assessment were chosen for multivariable logistic regression analyses: amoxicillin use during 3 to 6 months (yes/no), otitis media during 3 to 6 months (yes/no), breastfeeding during the first year of life (<6 months vs \( \geq 6 \) months), and daily average fluoride intake during the first year of life (low, middle, and high levels). Table 2 gives logistic regression analysis with fluorosis on both incisal edges and these 4 explanatory variables. Amoxicillin use during 3 to 6 months (OR = 2.50, 95% CI, 1.21–5.15) was significantly associated with fluorosis on the maxillary central incisors after controlling for other risk factors. A high level of fluoride intake during the first 12 months was also significantly related to fluorosis on maxillary central incisors (OR = 6.00; 95% CI, 2.58–13.99), but other factors were not statistically significant. No significant 2-way interactions were detected. Adjusted RR for amoxicillin use during 3 to 6 months computed using a multivariable log-binomial regression model was 1.78 (95% CI, 1.04–3.06).

In sensitivity analyses using multivariable logistic regression controlling for other potential factors (fluoride intake, otitis media, and breast-feeding), the OR for amoxicillin use was 2.08 (95% CI, 1.09–3.94) when questionable fluorosis cases were considered nonfluorosis and 2.14 (95% CI, 1.24–3.63) when questionable was considered as a case. The corresponding adjusted RRs were 1.65 (95% CI, 1.09–2.97) and 1.45 (95% CI, 1.10–1.92), respectively.

Similar results were obtained from the assessment of the association between fluorosis on 2 or more first molars and amoxicillin use. Briefly, amoxicillin use from birth to 6 months was significantly associated with first molar fluorosis (Mantel-Haenszel adjusted RR = 2.08; 95% CI, 1.27–3.45 after controlling for fluoride intake and otitis media; OR = 3.10; 95% CI, 1.55–6.17 in multivariable logistic regression; and adjusted RR = 1.82; 95% CI, 1.04–3.18 in the multivariable log-binomial regression model).

The primary purpose of this study was to assess the possible relationship between early-erupting permanent tooth...
fluorosis and amoxicillin use during early childhood. The results show that amoxicillin use during early infancy seems to be linked to dental fluorosis on both permanent first molars and maxillary central incisors. Duration of amoxicillin use was related to the number of early-erupting permanent teeth with fluorosis. The significantly elevated risk for dental fluorosis associated with amoxicillin use during early infancy was found at all levels of statistical analyses, even after controlling for other potential risk factors, such as fluoride intake, otitis media infections, and breast feeding. The significance of amoxicillin use as a risk factor was supported by both the analysis on the basis of logistic regression model using the OR, and by analyses on the basis of the log-binomial regression model using the RR. Regardless of which of the 2 modeling approaches was used, the same conclusions were drawn regarding the significance (and nonsignificance) of the potential explanatory variables.

The assessment of confounding and interactions at different levels consistently indicated that the effects of amoxicillin use were independent of other risk factors, such as fluoride intake and otitis media. This was consistent with the findings from our analyses concerning primary teeth and might suggest that the effects of amoxicillin use during early infancy tended to have higher fluoride intake than those of otitis media. However, because of the design of this study, only the illnesses with antibiotic treatment were reported by parents and used for analyses. Information about other illnesses that did not require antibiotics, such as isolated fevers or colds, was not gathered; therefore, their effects were unknown. In addition, because otitis media could have gone undiagnosed or, after diagnosis, prescriptions for treatment of otitis media might not have been filled, results could have underestimated any possible association between otitis media and fluorosis.

The period of amoxicillin use important to fluorosis on early-erupting permanent teeth was found to be within the first year of life, particularly the first 6 months. Therefore, the window of opportunity for amoxicillin use to affect enamel formation of maxillary central incisors seems to be quite narrow. Amelogenesis is one of the most remarkable examples of biomineralization, and consists broadly of 3 stages: proliferation and differentiation of enamel-forming cells (ameloblasts), secretion of the extracellular matrix, and mineralization of the extracellular matrix. Developing enamel distinguishes itself from other biological mineralizing systems, such as bone and dentin, in that most organic matrix proteins are removed during the maturation stages of amelogenesis. The enamel matrix proteins provide the framework for mineralization and play a significant role in nucleation, crystal orientation, and crystal growth. Our results showed that amoxicillin use early during the first year of life seems to be linked to fluorosis-like enamel defects on maxillary central incisors. Considering the developmental stages of enamel formation of maxillary central incisors, we speculate that the critical stages for the effects of amoxicillin could be the secretory stages. For example, amoxicillin use could reduce gene expression of matrix proteins (such as amelogenins) or decrease the activity of proteinases that hydrolyze matrix proteins. However, the delineation of the exact mechanisms requires further study. Furthermore, the cause of developmental enamel defects, such as dental fluorosis, might be complex and many other factors, such as malnutrition, could contribute to the development of this type of enamel anomaly.

Although this was a well-designed, longitudinal epidemiological study, limitations must be acknowledged, including use of a convenience sample, relatively high socioeconomic status, and use of self-administered questionnaires without direct verification. There were few complete nonusers of amoxicillin, restricting assessment among mutually exclusive groups of amoxicillin use and making it difficult to control for the cumulative effects of amoxicillin use from previous periods, possibly compromising detection of the importance of individual periods. Although the analyses indicated an independent effect from amoxicillin use, children who took amoxicillin during infancy tended to have higher fluoride intake. However, our analyses suggested that this association was not due to socioeconomic status, such as family income and parents’ educational levels, and thus the underlying reasons were unclear. As mentioned, illnesses were reported only if they were associated with antibiotic use and, thus, could underestimate their occurrence. Information on fevers and fever-reducing medication was not collected. In addition, there were incomplete (missing) questionnaire data for many indi-

Table 2. Logistic Regression Analyses for Fluorosis* and 4 Predictor Variables (N = 332)†

<table>
<thead>
<tr>
<th>Variable</th>
<th>Risk Group</th>
<th>OR (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amoxicillin use from 3-6 mo</td>
<td>Yes</td>
<td>2.50 (1.21-5.15)</td>
<td>.01</td>
</tr>
<tr>
<td>Otitis media infection during 3-6 mo</td>
<td>Yes</td>
<td>1.18 (0.57-2.44)</td>
<td>.65</td>
</tr>
<tr>
<td>Breastfeeding during first year</td>
<td>&lt;6 mo</td>
<td>1.72 (0.82-3.57)</td>
<td>.15</td>
</tr>
<tr>
<td>Average daily fluoride intake during first 12 mo§</td>
<td>High level</td>
<td>6.00 (2.58-13.99)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td></td>
<td>Middle level</td>
<td>1.35 (0.75-2.45)</td>
<td>.35</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; OR, odds ratio.
*Fluorosis case defined as fluorosis present on incisal edges (Fluorosis Risk Index zone I) of both maxillary central incisors.
†Analyses were conducted on the 407 subjects either having fluorosis on incisal edges of both maxillary central incisors or no fluorosis on either of the 2 maxillary central incisors. The numbers of subjects who did not return questionnaires varied at each period.
‡No significant 2-way interactions were found. §Fluoride intake was categorized using tertiles of the frequency distribution based on daily combined average fluoride intake in milligrams of fluoride per kilograms of birth weight per day from drinking water, beverages, and selected foods; dietary fluoride supplements; and fluoride dentifrice ingestion during the first year of life.
individuals during some reporting periods, which is unavoidable in longitudinal studies. Some individuals left the study, so that the results could be different if all children had remained in the study. Therefore, our results suggest a link between amoxicillin use and fluorosis-like enamel defects, but the findings are not conclusive because of the substantial limitations of the study. There is a need for further research, such as animal studies, histopathologic studies, and well-designed cohort studies.

The findings suggest that amoxicillin use in infancy could carry some heretofore undocumented risk to the developing teeth. Fluorosis or fluorosis-like opacities of the permanent teeth are typically much less esthetically objectionable than tetracycline staining, and most mild fluorosis is not a concern. However, several recent studies have shown that lay people readily notice tooth surfaces affected by mild fluorosis.27,28 Clearly, additional laboratory and clinical studies, such as controlled animal studies with specified amoxicillin dosages, chemical analysis and histological examination of affected teeth, and additional well-designed epidemiological studies, are needed to confirm the results. While the results of this one study do not warrant recommendations to cease use of amoxicillin early in life, they do further highlight the need to use antibiotics judiciously, particularly during infancy. Moreover, new guidelines for management of acute otitis media stress that 80% of children's ear infections resolve without antibiotics with no increased risk for serious infections,29 so that the decision for antibiotic therapy often is not justified. Further, injudicious use of antibiotics could increase risk of antibiotic resistance, and antibiotic use was recently linked to atopic disorders such as asthma30 and, although not verified, also to breast cancer in one report.31 Therefore, antibiotic use needs special caution and justification among infants and young children because they are in the critical stages of development and growth.

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Correspondence: Steven M. Levy, DDS, MPH, Department of Preventive and Community Dentistry, University of Iowa College of Dentistry, Iowa City, IA 52242-1010 (steven-levy@uiowa.edu).
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Additional Information: The corresponding author has full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analyses, and has final responsibility for the decision to submit for publication.
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REFERENCES