Effect of long-term *Helicobacter pylori* infection on growth of children: a cohort study

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Original article

Background: **The effects of *Helicobacter pylori* (*H. pylori*) infection on growth are a controversial issue. We investigated the effects of long-term *H. pylori* infection on height and weight in children.**

Methods: **A total of 200 children of 7-18 years old suffering from dyspeptic complaints were classified into two groups: *H. pylori* positive and negative groups, respectively. Whether the infection was impoved was followed up while performing urea breath test, and according to exposure time to the infection, the children were further divided into group 1 (≤1.5 months), group 2 (>1.5-≤6 months) and group 3 (>6 months). Antropometric measurements were obtained and repeated every six months.**

Results: **Mean growth velocity scores in the *H. pylori* positive and negative groups were 0.49±3.85 [95% confidence interval (CI): -0.21-1.18] and 1.98±4.42 (95% CI: 1-2.96), respectively. The difference between both groups was statistically significant (*P*=0.012). Mean growth velocity scores in groups 1, 2 and 3 were 0.96±3.84, 0.16±4.51 and -0.85±3.09, respectively. Mean growth velocity scores of group 3 were significantly lower than those of groups 0 and 1 (*P*=0.005 and *P*=0.041). The mean weight scores in group 3 were similar to those in group 2, but the scores in group 3 were significantly lower than those in group 1 (-1.75±1.05, -1.21±1.37 and -0.88±1.49, respectively).**

Conclusion: **As the duration of exposure is prolonged in children with *H. pylori* infection, the negative effect of the infection on both height and weight is evident.**

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Introduction

Helicobacter pylori (*H. pylori*) infection plays a role in the development of chronic digestive diseases.[1] *H. pylori* infection is witnessed in nearly 50% of the world's population. *H. pylori* is mostly acquired in the period of childhood, and its prevalence is higher in children from the lower socio-economic strata.[2,3] However, the consequences of infection encountered in children remain controversial. In a longitudinal study performed in 347 healthy children with *H. pylori* negativity, Mera et al[4] determined within the follow-up that 105 children were infected with *H. pylori*, and reported that growth delay became more pronounced in the first four months, continued decreasingly during the following eighth month, and no height catch-up was observed by the end of follow-up period. Dehghani et al[5] investigated 113 children aged 4-18 years, and found that there was no significant association between *H. pylori* infection and growth parameters.

Three different approaches elucidating the pathophysiology of such a negative effect have been suggested. First, malabsorption developing secondary to the suppression of gastric acid secretion leads to gastrointestinal infection and diarrhoea.[6] Second, a decreased appetite and malabsorption caused by *H. pylori* infection results in failure to thrive.[7,8] Finally, iron deficiency anemia due to *H. pylori* infection is also considered to impair growth.[9,10] Also, studies suggesting an association between *H. pylori* infection and level of plasma ghrelin have recently been published.[11] However, some studies[12,13] suggested that *H. pylori* infection plays no direct role in growth, and that the lower socio-economic strata leads to an increase in the prevalance of *H. pylori* infection as well as failure to thrive.

The effect of *H. pylori* infection on height and

weight has not yet been clarified. The present study was undertaken to investigate whether a transient or permanent *H. pylori* infection has an effect on the height and weight of children.

Methods

In this study, the children aged between 8 and 18 years came from lower to medium socio-economic strata in Turkey. They had no chronic diseases and their parents mostly did blue-collar jobs. Included were the children who exposed to ^{14}C-urea breath test in the Department of Nuclear Medicine in order to determine *H. pylori* infection after the admission because of dyspeptic complaints. Those with a history of *H. pylori* infection were excluded, and a total of 243 patients, 131 with *H. pylori* infection (positive group) and 112 without *H. pylori* infection (negative group), were determined. Twelve patients in the *H. pylori* positive group and 18 in the *H. pylori* negative group were excluded because of the incompliance with the follow-up or therapy, and 13 patients were excluded becuase of *H. pylori* infection in a later period.

Written consent was obtained from the parents of the patients, and the parents were asked to fill in a questionnaire including such items as properties, number of family members, educational status of parents, and gross level of income per month.

Anthropometric variables were measured thrice for all patients, first on admission and then every 6 months during one-year follow-up using a Seca 284 electronic measuring station (Seca, Hamburg, Germany). Personnel performing anthropometric measurements were masked for the results of breath test. Height and weight *Z*-scores were calculated with respect to reference values for Turkish children.[14] Body weight was measured with the patients wearing only underwear to the nearest 100 g using a weighing scale. Height was measured to the nearest 0.1 cm as standing with a height meter.

A 2-week concurrent thriple treatment regimen of proton pump inhibitors, clarithromycin and amoxicillin was given to all patients in the *H. pylori* positive group, and ^{14}C-urea breath test was performed every 1.5-3 months. Treatment regimen was repeated until the results of the test were negative. In the study, the exposure time was described as the duration from the date of the first positive breath test to that of the next negative breath test. Based on exposure time to the infection, patients with *H. pylori* infection were categorized into group 1 (≤1.5 months), group 2 (>1.5-≤6 months) and group 3 (>6 months). However, those without *H. pylori* infection served as group 0.

Statistical analysis was performed using the SPSS for Windows (Chicago, IL, USA). Whether the distributions of data were normal or not was assessed by the Kolmogorov-Smirnov test. Analysis of data was based on non-parametric statistical methods because of the small size of samples and abnormal distribution of variables. For paired comparisons, the Mann-Whitney *U* test was used for subgroup analysis. On the other hand, data that were determined to be normally distributed after the Kolmogorov-Smirnov test were evaluated using the independent samples *t* test. A *P* value less than 0.05 was considered statistically significant. This study was approved by the Ethics Committee of the Meram Medical School of Necmettin Erbakan University.

Results

Of total 200 patients, median age was 14.3 years [inter-quartile range (IQR): 12.1-16.2 years], and sex distribution was 64.7% female and 35.3% male in 119 children with *H. pylori* infection, while median age was 13.7 years (IQR: 11.8-16.4 years), and sex distribution was 70.4% female and 29.6% male in 81 children without *H. pylori* infection.

Table 1. Social-economical variables of the *H. pylori* positive and negative groups

Variables	*H. pylori* (+), *n*=119	*H. pylori* (–), *n*=81	*P* value
No. of family members	5 (IQR: 4-5)	5 (IQR: 4-5.5)	>0.05
Educational status of mothers (%)			
Elementary school	87.4	76.5	
High school	10.1	22.2	
College	2.5	1.3	
Educational status of fathers (%)			
Elementary school	70.6	65.4	
High school	24.4	26.0	
College	5.0	8.6	
Income ($/mon)	400 (IQR: 350-500)	425 (IQR: 350-700)	>0.05

H. pylori: *Helicobacter pylori*; $: US dollar; IQR: inter-quartile range.

In both *H. pylori* positive and negative groups, the number of family members, educational status of parents, and gross income level per month were similar (Table 1). Height and weight scores of children in the *H. pylori* positive and negative groups at enrollment, and months 6 and 12 were similar (Table 2). The lowest scores were observed in group 3 but there was no difference between both average percentiles of height and weight, and between average heigth and weight *Z*-scores of the groups at enrollment, and months 6 and 12 (Figs. 1-4).

Average exposure time of the *H. pylori* positive

Table 2. Average height, weight and growth velocity scores of the *H. pylori* positive and negative groups at enrollment, and months 6 and 12

	Variables	Entry	Mon 6	Mon 12
H. pylori positive (*n*=119)	Height (cm)	152 (140-160)	153 (142-160)	155 (145-162)
	Weight (kg)	43 (33-52)	46 (34-52.5)	48 (36-54)
	GV SDS	Male (*n*=42)		-1.43 (-3.19-1.12)
		Female (*n*=77)		0.52 (-1.72-3.08)
H. pylori negative (*n*=81)	Height (cm)	154 (140-162)	156 (144-162.5)	158 (145-165)
	Weight (kg)	42 (32-53)	43 (34.5-55)	46 (36.5-57.5)
	GV SDS	Male (*n*=24)		0.85 (-1.97-3.62)
		Female (*n*=57)		1.62 (-0.14-5.32)

Results were presented as median (inter-quartile range). *H. pylori*: *Helicobacter pylori*; GV SDS: growth velosity standard deviation score.

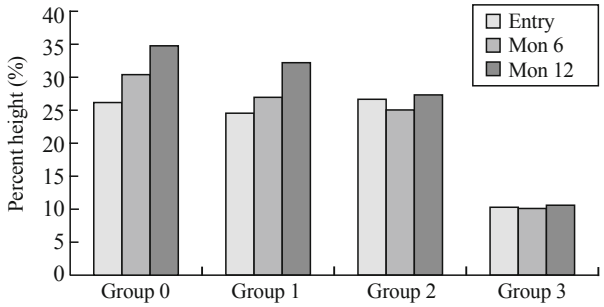

Fig. 1. Mean height percentile values of groups 0, 1, 2 and 3 at the enrollment, 6th and 12th mon. 95% confidence interval (CI) for group 0: enrollment, 19.7-32.2, mon 6, 23.5-37.1, mon 12, 27.2-41.9; 95% CI for group 1: enrollment, 18.7-30.2, mon 6, 20.8-33.1, mon 12, 24.9-39.3; 95% CI for group 2: enrollment, 13.4-39.7, mon 6, 11.7-38.2, mon 12, 14.5-39.9; 95% CI for group 3: enrollment, 5.1-15.3, mon 6, 4.6-15.6, mon 12, 4.5-16.7.

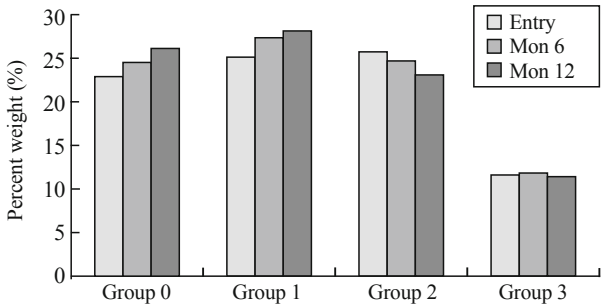

Fig. 2. Mean weight percentile values of groups 0, 1, 2 and 3 at the enrollment, 6th and 12th mon. 95% confidence interval (CI) for group 0: enrollment, 16.7-29.1, mon 6, 17.9-31, mon 12, 19.2-32.7; 95% CI for group 1: enrollment, 18.6-31.4, mon 6, 20.4-33.7, mon 12, 21.2-34.8; 95% CI for group 2: enrollment, 11.2-39.8, mon 6, 9.9-39.1, mon 12, 8.6-37.6; 95% CI for group 3: enrollment, 3.3-20.4, mon 6, 3.6-20.2, mon 12, 3.6-19.6.

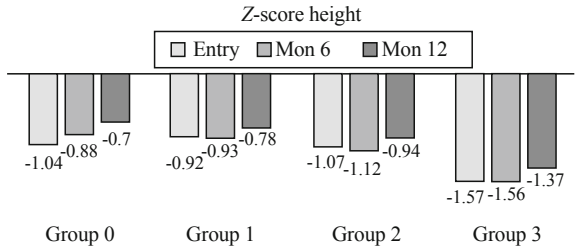

Fig. 3. Mean *Z*-score height values of groups 0, 1, 2 and 3 at the enrollment, 6th and 12th mon. 95% confidence interval (CI) for group 0: enrollment, -1.33(-)-0.76, mon 6, -1.19(-)-0.57, mon 12, -1.05(-)-0.35; 95% CI for group 1: enrollment, -1.19(-)-0.65, mon 6, -1.21(-)-0.65, mon 12, -1.06(-)-0.5; 95% CI for group 2: enrollment, -1.72(-)-0.42, mon 6, -1.75(-)-0.47, mon 12, -1.53(-)-0.35; 95% CI for group 3: enrollment, -1.91(-)-1.23, mon 6, -1.99(-)-1.13, mon 12, -1.95(-)-0.78.

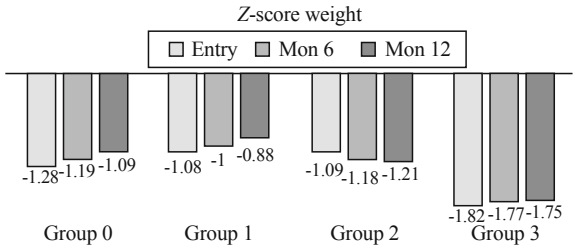

Fig. 4. Mean *Z*-score weight values of groups 0, 1, 2 and 3 at the enrollment, 6th and 12th mon. 95% confidence interval (CI) for group 0: enrollment, -1.6(-)-0.96, mon 6, -1.53(-)-0.86, mon 12, -1.42(-)-0.76; 95% CI for group 1: enrollment, -1.38(-)-0.78, mon 6, -1.31(-)-0.69, mon 12, -1.2(-)-0.55; 95% CI for group 2: enrollment, -1.78(-)-0.4, mon 6, -1.88(-)-0.49, mon 12, -1.9(-)-0.53; 95% CI for group 3: enrollment, -2.31(-)-1.33, mon 6, -2.25(-)-1.3, mon 12, -2.20(-)-1.3.

Table 3. Growth scores of *H. pylori* positive group according to exposure time and of *H. pylori* negative group

	Variables	Group 0 [*H. pylori* (-)], *n*=81	Group 1 (≤1.5 mon), *n*=78	Group 2 (>1.5-≤6 mon), *n*=18	Group 3 (>6 mon), *n*=23
Entry	Percent height	26.0±28.4	24.4±25.3	26.6±26.5	10.2±11.7
	Percent weight	22.9±28.0	25.0±28.3	25.5±28.8	11.8±19.8
	Z-score height	-1.04±1.30	-0.92±1.20	-1.07±1.31	-1.57±0.79
	Z-score weight	-1.28±1.45	-1.08±1.33	-1.09±1.39	-1.82±1.14
Mon 6	Percent height	30.3±30.8	26.9±27.4	24.9±26.6	10.1±12.8
	Percent weight	24.4±29.6	27.1±29.3	24.5±29.4	11.9±19.2
	Z-score height	-0.88±1.42	-0.93±1.25	-1.12±1.28	-1.56±1.00
	Z-score weight	-1.19±1.50	-1.00±1.38	-1.18±1.40	-1.77±1.10
Mon 12	Percent height	34.6±33.4	32.1±32.1	27.2±25.6	10.6±14.2
	Percent weight	25.9±30.5	28.0±30.1	23.1±29.1	11.6±18.5
	Z-score height	-0.70±1.57	-0.78±1.23	-0.94±1.19	-1.37±1.34
	Z-score weight	-1.09±1.49	-0.88±1.49	-1.21±1.37	-1.75±1.05
	GV SDS	1.98±4.42	0.96±3.84	0.16±4.51	-0.85±3.09

Results were presented as mean±standard deviation. *H. pylori*: *Helicobacter pylori*; GV SDS: growth velosity standard deviation score.

group to the infection was 3.4±3.4 months (min: 1.5, max: 12). Based on categorized exposure time, the average height and weight percentile, *Z*-score values, and growth velocity standard deviation scores (GV SDS) found at enrollment, and months 6 and 12 are summarized in Table 3.

At enrollment, no difference was detected between the average height percentile and height *Z*-scores, and between the weight percentile and weight *Z*-scores of groups 0, 1 and 2. Meanwhile, no difference was observed between the height percentile scores of groups 3 and 0, and the height percentile score of group 3 was significantly lower than those of groups 1 and 2 (P=0.011 and P=0.038). The fact that mean height *Z*-score of group 3 was significantly lower than those of groups 1 and 2 supported this finding (P=0.006 and P=0.038). Moreover, the weight percentile scores of groups 3 and 1 were significantly different (P=0.015), but no difference was seen between the weight percentile scores of groups 3, 0 and 2. The fact that the mean weight *Z*-score of group 3 was lower than that in group 1 supported this finding (P=0.016).

At the 6th month, no difference was observed between height and weight scores of groups 0, 1 and 2. The average height percentile and height *Z*-scores of group 3 were lower than those of groups 0 (P=0.016, P=0.032) and 1 (P=0.008, P=0.014). However, the average weight percentile and weight *Z*-scores of group 3 were lower than those of group 1 (P=0.012, P=0.013).

At the 12th month, no difference was found between the average height and weight scores of groups 0, 1 and 2. The average height percentile and height *Z*-scores of group 3 were lower than those of groups 0 (P=0.006, P=0.033) and 1 (P=0.002, P=0.011). However, the average weight percentile and weight *Z*-scores of group 3 were lower than those of groups 0 (P=0.49, P=0.045) and 1 (P=0.005, P=0.004). The differences in the height and weight scores were more evident than those at the 6th month.

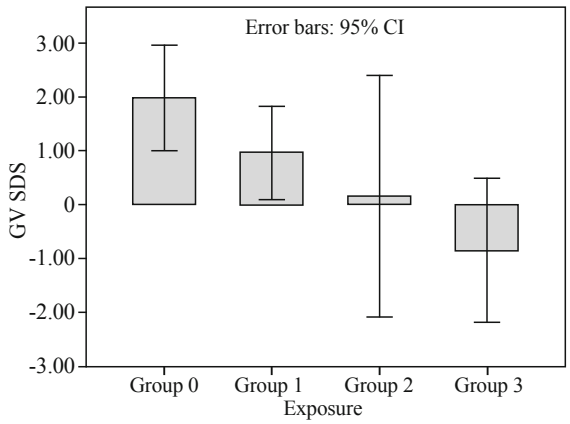

Fig. 5. Mean growth velocity standard deviation score (GV SDS) of groups 0, 1, 2 and 3 at the enrollment, months 6 and 12. CI: confidence interval.

The mean GV SDSs in *H. pylori* positive and negative groups were 0.49±3.85 (min: -7.13; max: 12.15; 95% CI: -0.21-1.18) and 1.98±4.42 (min: -5.73; max: 19.17; 95% CI: 1-2.96), respectively, and the difference between both groups was statistically significant (P=0.012). The mean GV SDSs in groups 0, 1, 2 and 3 were 1.98±4.42, 0.96±3.84, 0.16±4.51 and 0.85±3.09, respectively (Fig. 5). However, no difference was found between the mean GV SDSs of groups 0, 1 and 2, and between the mean GV SDSs of groups 2 and 3. The mean GV SDSs of groups 0 and 1 were significantly different from those of group 3 (P=0.005, P=0.041).

There was no difference between *H. pylori* positive and negative groups in a mixed model formed with height as a dependent variable, and age, gender and exposure time as independent variables (P=0.14). The effect of time on height gain was different between both groups (P=0.002) and lower in patients with *H. pylori* infection. Although there was no difference in the measurements performed at enrollment and month 6 (P=0.326, P=0.073), significant difference was seen between the two groups at month 12 (P=0.048). Between groups 1 and 2 at enrollment, and months 6 and 12, no difference was found in a mixed model formed with height as a dependent variable, and age, gender and categorized exposure time as independent variables. However, there was no difference between groups 3 and 1 at enrollment, but a difference was seen between these groups at months 6 and 12 (P=0.031, P=0.008).

No difference was found in a mixed model formed with weight as a dependent variable and age, gender and exposure time as independent variables between *H. pylori* positive and negative groups (P=0.516). The effect of exposure time was not significant in a mixed model formed with weight as a dependent variable and age, gender and categorized exposure time as independent variables (P=0.104).

In our study, a negative correlation was found between GV SDS and exposure time, although it was not statistically significant (P=0.093, r =-0.155).

Discussion

Growth is a multifactorial process affected by a number of environmental and genetic factors.[2] So, it is unlikely to evaluate merely a single factor by ignoring others. Investigating the effect of *H. pylori* infection on growth in a homogenous society as to socioeconomic strata and ethnicity could reveal more reliable outcomes.[13] The

fact that such factors as the number of family members, educational status of parents and level of monthly income were similar in *H. pylori* positive and negative groups, and our participants were from the same ethnic group demonstrated that our study group was rather homogenous. We consider that the homogenity presents a convenient opportunity to analyze other exogenous factors such as *H. pylori* infection in the development of failure to thrive.

The relation of *H. pylori* infection to failure to thrive remains controversial, and there are many reports on the presence[2,4,5,10,12,15] and absence[9,13,16,17] of such an association. Dehghani et al[5] reported that no effect of symptomatic *H. pylori* infection on linear growth of children was observed. Sood et al[13] also reported that children with *H. pylori* infection were shorter and with less weight, but such a difference disappeared when their socioeconomic status and ethnic division were changed. However, the two studies were cross-sectional. But our study was a longitudinal one with a larger cohort. In the above-mentioned studies, no difference was found between height percentile and height *Z*-scores of the *H. pylori* positive and negative groups at enrollment whereas the mean GV SDS was lower in the *H. pylori* positive group. Additionally, at months 6 and 12, the average height percentile, height *Z*-scores and mean GV SDS of group 3 patients suffering from infection were significantly lower during a 12-month follow-up than those in groups 0 and 1. We considered that the difference between average height scores was due to the negative effect of *H. pylori* on growth, rather than socioeconomic strata and ethnic factors. Additionally, the difference in average height scores between groups 3 and 0 and between groups 3 and 1 was more significant at month 12. This finding also indicated that the more the exposure time was prolonged, the more the effect on height got increased.

Passaro et al[3] found a decrease in weight gain shortly after the exposure to *H. pylori* infection, but this effect could be determined in height gain. The average height scores of group 3 exposed to the infection were similar to those in groups 0, 1 and 2 at enrollment in our study, but the average weight scores of group 3 were significantly lower than those of group 1. This finding suggested that weight is influenced by *H. pylori* infection in an earlier period, compared to height. At month 6, however, both average height and weight scores differed significantly between groups 3 and 1, suggesting that height gain is also influenced by *H. pylori* infection, as exposure time is lengthened. In addition, the difference in average weight scores between groups 3 and 1 was more evident at month 12. The difference of weight between groups 3 and 0 at enrollment and month 6 was also statistically significant at month 12, and this also indicated that as exposure time elongates, the effect on weight increases.

In their study on pre-school children, Mera et al[4] found that the effect of *H. pylori* infection on height gain was more marked within the first 4 months after exposure to the infection and decreased gradually until the 8th month. In contrast to these findings, we found that average height scores of groups 0, 1 and 2 were similar at enrollment and months 6 and 12, and average height scores of group 3 at monts 6 and 12 were lower than those of groups 0 and 1. The difference was defined with time. We considered that shorter exposure time exerts no effect on height gain, and as the time elongates the effect becomes more prominent. However, such a difference could have arisen from our patients older than those in the study by Mera et al.[4]

In their study conducted in 12- to 60-month-old children, Bravo et al[2] found that if the exposure time continues more than six months, newly-diagnosed *H. pylori* infection has a persistant and untolerable effect on height gain. We also found that *H. pylori* infection has a negative effect on height gain, which is evident at month 6. Bravo et al found a decrease in growth rate at month 1 or 2 after *H. pylori* infection, whereas our study demonstrated that weight was affected by infection at an earlier period, and height later. Being younger than our children, those in the study by Bravo et al[2] might have been affected earlier by *H. pylori* infection.

To our knowledge, studies on the effect of *H. pylori* infection on growth of children in pre-pubertal and pubertal periods with overt growth spurt are too limited. While finding no negative association between height gain and *H. pylori* infection in children between the age of 3.3 to 8.5 years, Perri et al[17] found that this association was remarkable in 8.5 to 14-year-old children, and they elucidated the condition by relating children at older age with longer-term exposure time. Fialho et al[12] reported that *H. pylori* infection has a negative effect especially on children at the age of 8-14 years. In our study, the average height, weight scores and mean GV SDS of patients in group 3 were significantly lower than those in group 1, suggesting that the negative effect on growth is more pronounced as the exposure time elongates.

In a study on school children in Colombia, Mera et al[18] found that the mean height gain in *H. pylori* negative group was 21.5 cm, in the group becoming positive later on while being negative first as 20.1 cm, in the group becoming negative while being positive first as 21.3 cm, and in the group remaining positive during the follow-up as 19.8 cm. They also found that the mean height gain of the group remaining *H. pylori* positive was significantly lower than that of

both *H. pylori* negative group and the one becoming negative later while being positive first. The findings in their study were consistent with those of our study, suggesting that the growth scores of children remaining positive during a 12-month follow-up were significantly lower than those of other groups.

One limitation of our study is the small number of participants. The other is that it is unlikely to determine exactly when the participants are infected with *H. pylori*.

In conclusion, our study indicates that long-term infection of *H. pylori* has a negative effect on height and weight gain in children, and that children with failure to thrive should be investigated for *H. pylori* infection by healthcare providers. Although it is unlikely to determine exactly when the children are infected by *H. pylori*, failure to thrive in infected children can be prevented through the diagnosis and treatment of *H. pylori* infection as early as possible.

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Contributors: KC and OA contributed to the conception and design. KC, CM and SES contributed to the acquisition, analysis and interpretation of the data. KC drafted the article. KC and OA revised critically the article for important intellectual content. All authors listed here approved the final version of the article.

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