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Relationships between body mass index, lifestyle habits, and locomotive syndrome in young- and middle-aged adults: A cross-sectional survey of workers in Japan

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Abstract

Objectives: Although many studies have examined locomotive syndrome (LS) among elderly people, few studies have examined LS in young- and middle-aged adults. This study aimed to provide basic data on the epidemiological characteristics of LS, including in young- and middle-aged adults.

Method: We conducted a cross-sectional survey of a nonrandom sample of 852 adults aged 18–64 (678 males, 174 females) working in five companies in Japan, between December 2015 and February 2018. LS stage was determined using the criteria proposed by the Japanese Orthopaedic Association (JOA). LS stage 0 was defined as No-LS, and stages 1 and 2 were defined as LS. Multiple logistic regression analysis was used to investigate the independent relationship between LS and sociodemographic, smoking, alcohol drinking (AD), frequency of breakfast consumption (FBC), dietary variety score (DVS), and the University of California Los Angeles (UCLA) activity score after adjusting for age and sex.

Results: We found that 23.1% of participants were evaluated as LS, including 21.5% of males and 29.3% of females ($P < 0.05$). Participants aged ≥45 years exhibited higher rates of LS (males: 23.1%, females: 43.6%) compared with those aged <45 years ($P < 0.05$). Logistic regression analysis revealed that age, body mass index (BMI), AD, UCLA activity score, and FBC were also related to LS.

Conclusion: Education initiatives about LS should be targeted not only to elderly populations but also to young- and middle-aged adults in the workplace.

KEYWORDS

a cross-sectional survey, body mass index, lifestyle habits, locomotive syndrome, young- and middle-aged adults

1 | INTRODUCTION

In 2015, the average life expectancy in Japan was 80.8 years for men and 87.0 years for women, and both are predicted to rise in the future. Moreover, people >65 years of age comprised 27.3% of the entire Japanese population in 2016, and this proportion is expected to increase to 38.4% by 2065. No country has previously experienced such a long life expectancy, and it is clear that Japan is a rapidly aging society.[1]

Locomotion difficulties affect activities of daily living in older people. In 2007, the Japanese Orthopaedic Association (JOA) proposed the concept of locomotive syndrome (LS) to refer to the risk of elderly individuals becoming bedridden because of reduced function of the locomotive organs (eg, muscles, bones, and joints). LS is caused by reduced muscle strength and balance associated with aging and locomotive pathologies such as osteoporosis, osteoarthritis (OA), and sarcopenia.[2-4]

In 2013, the JOA proposed using the following three tests for assessing the risk of LS: the two-step test, the stand-up test, and the 25-question Geriatric Locomotive Function Scale (GLFS-25).[5] The JOA determined the clinical decision limits of these three indices for assessing the risk of LS in 2015, and Yoshimura et al[6] reported that all of these indices could significantly and independently predict a decline in mobility and, according to general population data, high scores on these indices may exponentially increase the risk of immobility.

The following factors have been proposed as causes of LS: lack of regular exercise, excessive exercise and injury, being underweight or overweight, and reduced physical activity.[7] All of these factors are closely related to lifestyle, dietary, and exercise habits acquired from a young age. Therefore, it is important for individuals, and for Japanese society as a whole, to effectively cope with the expected restrictions in walking ability that become present after middle age. Although some studies investigating physical function and degenerative disorders, such as lumbar canal stenosis and OA, have reported evidence of an improvement in LS in older adults,[8-10] little is known about the actual state of LS in young- and middle-aged adults. Thus, differences in LS status among different age groups are important to understand. We have just reported the prevalence of LS and the LS level among young- and middle-aged adult workers.[11] However, the relationships between lifestyle habits such as dietary habits and LS are unknown.

The current study sought to provide basic data on the epidemiological features of LS in young- and middle-aged adults, including lifestyle habits such as dietary habits and physical activity. These data can provide a scientific basis for preventing and treating LS.

2 | METHODS

A cross-sectional study was conducted with the employees of five companies, who were recruited by the public health department of Mie Prefecture, Japan, between December 2015 and February 2018. These companies consisted of various white-collar (74.6%) and blue-collar (25.4%) departments at two drug companies (Company A, 250 day shift employees; Company B, 124 day shift employees), a chemical company (Company C, 275 day shift employees), an office equipment manufacturer (Company D, 258 day shift employees), and an electronics company (Company E, 215 day shift employees). The participants were not eligible to participate in the survey if they: (a) could not walk without instruments (T-cane, crutch, wheelchair, etc.); (b) had some sort of injury so as to hinder exercise at the time of the survey and (c) were not able to participate in all activities to evaluate LS. Each company notified its employees about the eligibility for participation in advance and only collected voluntary participants. All participants were provided written informed consent prior to participating in the study, which was approved by the Institutional Review Board of Suzuka University of Medical Science (approval no. 241). This study was conducted in accordance with the principles of the Declaration of Helsinki.

Body weight was measured using Inner Scan® 50V (BC-622; TANITA Co., Tokyo, Japan). Body mass index (BMI) was calculated as follows: weight (kg)/height (m)^2. Data on LS stage, demographic factors, socioeconomic status, lifestyle habits, and physical activity were collected using LS scales or paper-based questionnaires. The independent variables included age (<45 or ≥45), BMI (<18.5 or 18.5-24.9 or ≥25.0), sex (male or female), education (<13 years or ≥13 years), occupation (white collar or blue collar), income (<5 million yen/year or ≥5 million yen/year), smoking (none, past smoker, current smoker), alcohol drinking (AD; none, a few times/month, a few times/week, daily), the University of California Los Angeles (UCLA) activity score (<5 points or ≥5 points),[12] frequency of breakfast consumption (FBC) (<6 days/week or ≥6 days/week), and the dietary variety score (DVS) (<3 points or 3-5 points or ≥6 points).[13]

Physical activity was assessed using UCLA activity score,[12] which is a simple scale that ranges from 1 to 10. Participants indicated their most appropriate activity level, with 1 defined as "no physical activity, dependent on others" and 10 defined as "regular participation in impact sports."

Dietary variety was assessed using the DVS developed by Kumagai et al.[13] DVS is a food-based composite score that is calculated using the consumption frequencies of 10 food items (fish and shellfish, meats, eggs, milk and dairy products, soybeans and soybean products, green and yellow vegetables,

TABLE 1 Sociodemographic characteristics and lifestyle habit, diet habit, and physical activity of all participants

Variables	Total (n = 852)	%
Age (years)	44.3 ± 10.2	
Sex		
Male	655	76.9
Female	197	23.1
BMI	23.7 ± 3.3	
Occupation		
White collar	634	74.4
Blue collar	218	25.6
Income		
<5 million yen	154	18.1
≥5 million yen	698	81.9
Smoking		
None	515	60.4
Past smoker	124	14.6
Current smoker	213	25.0
AD		
None	280	32.9
A few times/month	144	16.9
A few times/week	228	26.8
Daily	200	23.5
UCLA activity score	5.1 ± 2.4	
FBC	6.1 ± 2.0	
DVS	2.8 ± 1.8	

BMI, body mass index; AD, alcohol drinking; UCLA, University of California Los Angeles; FBC, frequency of breakfast consumption; DVS, dietary variety score.

seaweed, potatoes, fruits, and fats and oils) in the week before the questionnaire was administered. To reflect differences in consumption patterns and to simplify scoring, a score of 1 was given if a food item was consumed every day; otherwise the score was zero. Therefore, dietary variety improves as DVS approaches 10. Four weeks before physical measurements were obtained and LS stage was determined; questionnaires were distributed to all day shift employees at each company.

To evaluate LS, we used the two-step test,[14] stand-up test,[14] and GLFS-25.[15] In the two-step test, participants start in a standing posture, then move two steps forward with maximum stride, while being careful not to lose balance. The stand-up test is performed with stools that are 10, 20, 30, and 40 cm in height. Subjects are requested to stand up from each stool, using one leg or two legs. GLFS-25 is a self-reported comprehensive measure, consisting of 25 questions referring to the preceding month. The scale includes four questions regarding pain, 16 questions regarding activities of daily living, three questions regarding social functioning, and two questions regarding mental health status. We determined the risk of LS as follows: if the two-step score was <1.3, LS risk is 1; if the two-step score was <1.1, LS risk is 2; if the participant could not stand up from a height of 40 cm on either leg, LS risk was 1; if the participant could not stand up from a height of 20 cm on both legs, LS risk was 2; if the participant received ≥7 points on GLFS-25, LS risk was 1; if the participant received ≥16 points on GLFS-25, LS risk was 2. We used the highest risk level among these three LS evaluation tests. For example, if LS risk of the two-step test was 0, LS risk of the stand-up test was 2 and LS risk of GLFS-25 was 1, the stand-up test of LS risk 2 was adopted. These LS risk scores were evaluated according to the "How to determine your risk level" section of the official JOA website for LS.[7]

Participants were classified as No-LS (LS risk stage 0) or LS (LS risk stage 1 or 2), and the independent variables were compared between groups. Differences in continuous variables between the No-LS and the LS groups were evaluated using t-tests, and chi-square tests were used to evaluate categorical variables.

Multiple logistic regression analysis was used to investigate the relationship between dietary habits, lifestyle and physical activity, and LS, after adjusting for age and sex. The independent variables included sex, age, BMI, occupation, income, smoking, AD, UCLA activity score, FBC, and DVS. Adjusted odds ratios (OR) and 95% confidence intervals (CI) were calculated. All statistical analyses were conducted using JMP 9.0.2 (SAS Institute Inc., Cary, NC).

3 | RESULTS

In total, 852 participants responded to the questionnaire and had their physical attributes measured (678 males and 174 females) (mean age ± standard deviation = 44.4 ± 10.2 years; range = 18-64 years) (Table 1), and the response rate was 75.9% (852 of 1122 eligible employees). The response rate of Company A was 74.8% (187 of 250 eligible employees), that of Company B was 80.6% (100 of 124 eligible employees), that of Company C was 84.0% (231 of 275 eligible employees), that of Company D was 76.4% (197 of 258 eligible employees), and that of Company E was 63.7% (137 of 215 eligible employees).

Sociodemographic characteristics and lifestyle habit, diet habit, and physical activity of all participants are shown in Table 1. The mean BMI was 23.7 ± 3.3. With regard to occupation and income, 634 (74.4%) were white collar, and 698 (81.9%) had a salary of ≥5 million yen. Of the 852 employees, nonsmokers and non-AD were 515 (60.4%) and 280 (32.9%), respectively. The mean UCLA activity score, FBC, and DVS were each 5.1 ± 2.4, 6.1 ± 2.0, and 2.8 ± 1.8.

Table 2 shows the age-stratified prevalence of LS stages 1 and 2 and the corresponding indices in the Short Test Battery

TABLE 2 Prevalence of indices of the short test battery for locomotive syndrome in the different LS stage groups

Age strata (years)	Number	Age (years)	Two-step test score < 1.3 (%)	Difficulty with one-leg standing from 40-cm-high seat (either leg) (%)	GLFS-25 score ≥ 7 (%)	LS-1 or 2 (%)
All						
<30	83	24.2 ± 3.0	2.4	4.8	14.6	21.8
30-39	164	35.2 ± 2.8	0.0	8.5	18.3	26.8
40-49	313	44.5 ± 2.8	0.6	5.1	16.7	22.4
50-59	257	54.2 ± 2.7	0.8	10.5	20.6	31.9
60-65	35	62.0 ± 1.7	0.0	14.7	25.7	40.4
Total	852	44.4 ± 10.2	0.1	7.8	18.3	26.2
Male						
<30	58	24.4 ± 3.0	3.4	5.2	19.0	27.6
30-39	133	35.3 ± 2.8	0.0	6.8	17.3	24.1
40-49	240	44.6 ± 2.8	0.4	3.8	12.9	23.1
50-59	217	54.3 ± 2.8	0.9	8.3	18.9	28.1
60-65	30	62.1 ± 1.8	0.0	17.2	23.3	40.5
Total	678	44.9 ± 10.2	0.1	6.5	16.6	23.2
Female						
<30	25	23.9 ± 2.9	0.0	4.0	4.2	8.2
30-39	31	34.8 ± 2.9	0.0	16.1	22.6	38.7
40-49	73	44.1 ± 2.6	1.4	9.6	29.2	40.2
50-59	40	53.6 ± 2.4	0.0	22.5	30.0	52.5
60-65	5	61.6 ± 1.1	0.0	0.0	40.0	40.0
Total	174	42.3 ± 10.4	0.1	12.6	25.0	37.7

GLFS-25, 25-question geriatric locomotive function scale; LS-1, locomotive syndrome stage 1; LS-2, locomotive syndrome stage 2.

TABLE 3 Age and sex distributions of the No-LS and LS groups

	All		Male		Female	
Age, years	No-LS	LS	No-LS	LS	No-LS	LS
<45	325 (49.6)	77 (39.1)	246 (46.2)	60 (41.1)	79 (64.2)	17 (33.3)
≥45	330 (50.4)	120 (60.9)	286 (53.8)	86 (58.9)	44 (35.8)	34 (66.6)
Total	655 (76.9)	197 (23.1)	532 (78.5)	146 (21.5)	123 (70.7)	51 (29.3)

The number in parentheses indicates the percentage in each age category.
LS, locomotive syndrome; No-LS, no locomotive syndrome.

for LS. LS stage 1 or 2 was present for both males and females in all the age-stratified groups (Table 2). The percentage of LS in females gradually increased with age excluding 60-65.

Table 3 shows the two age group prevalence of LS that was determined using the criteria proposed by JOA. Of all participants, 23.1% were evaluated as LS (21.5% of males and 29.3% of females; $P < 0.05$). Participants aged ≥45 years showed significantly higher percentages of LS (male: 23.1%, female: 43.6%) compared with those aged <45 years (male: 19.6%, female: 17.7%). Participants aged ≥45 years in the female's group showed significantly higher percentages of LS compared with aged <45 (aged <45: 33.3%, aged ≥45: 66.7%; $P < 0.001$), while there were no significant differences between the male groups (aged <45: 41.1%, aged ≥45: 58.9%; $P = 0.27$).

The distributions of the participant characteristics in the No-LS and LS groups are shown in Table 4. Age, sex, AD, UCLA activity score, and FBC significantly differed between groups, whereas BMI, occupation, income, smoking, and DVS did not significantly differ between groups.

Table 5 shows the results of logistic regression analysis of associated factors for LS in all participants. The odds ratio of

TABLE 4 Characteristics of the No-LS and LS groups

Characteristics	Total	No-LS	LS	*P*-value
Age				
<45	402 (47.2)	325 (49.6)	77 (39.1)	
≥45	450 (52.8)	330 (50.4)	120 (60.9)	0.001
Sex				
Male	655 (76.9)	532 (81.2)	146 (74.1)	
Female	197 (23.1)	123 (18.8)	51 (25.9)	0.029

Data were expressed as n (%).
LS, locomotive syndrome; No-LS, no locomotive syndrome.

LS was 0.50 (95% Cl 0.35-0.71) for UCLA activity score (≥5 points) compared with UCLA activity score (<5 points), 0.41 (0.24-0.69) for AD (a few times/month) or 0.44 (0.26-0.72) for AD (a few times/week) or 0.64 (0.43-0.96) for AD (daily) compared with AD (none), and 0.52 (0.35-0.78) for FBC (≥6 days / week) compared with FBC (<6 days/week). In contrast, the odds ratio of LS was 1.53 (1.11-2.13) for participants ≥45 years old compared with those <45 years old, and 1.43 (1.00-2.02) for BMI (≥25.0) compared with BMI (18.5-24.9).

4 | DISCUSSION

The current study investigated the relationships between LS in young- and middle-aged adults and demographic, socioeconomic status, lifestyle habits, dietary habits, and physical activity. The results revealed that age, BMI, AD, UCLA activity score, and FBC were significantly associated with LS. Overall, this cross-sectional observational study of lifestyle habits, dietary habits, and physical activity in young- and middle-aged adults in Japan revealed that moderate alcohol consumption, better physical activity, and higher FBC were significantly associated with lower levels of LS. To the best of our knowledge, this is the first report to demonstrate a relationship between lifestyle habits, dietary habits, and physical activity and the classification of LS proposed by the JOA to assess the risk of the disorder in young- and middle-aged adults.

The decay of locomotive function typically starts from the late 40s. Functional decline of movement often progresses without detection, particularly in modern societies with widespread motorized transportation.[16] Regarding the prevalence of the indices in LS risk stages 1 and 2, we found that they exist in all of the age groups and indicated that LS risk was increased in participants over the age of 45. Our data indicated a gradual increase with advancing age as with our previous report.[11] Moreover, there were no significant differences between the male groups, while participants aged ≥45 years in the female's group showed significantly higher percentages of LS compared with aged <45. As one of the causes of sex difference, the effect of testosterone which has protein anabolism and promotes muscle mass development is known. It has been reported that males have more muscle mass than females as testosterone rises since puberty, and muscle mass reduction rate increases with decreasing testosterone after middle age. There is also a report suggesting that female muscle mass reduction is related to the female hormone.[17,18] In any case, it is clear that there is a gender difference in muscle mass and age change, and it is necessary to examine both males and females when examining muscle mass. In general, females have more diseases of locomotive organs such as knee osteoarthritis (KOA) than males.[19,20] Therefore, it is considered that there are many LS which are highly related to diseases of locomotive organs.

Several previous reports have indicated that BMI is positively correlated with KOA which is a potential cause of LS.[21,22] Jiang et al[23] concluded that obesity is a risk factor for KOA after systematically analyzing the correlation between BMI and KOA in 21 independent reports. Moreover, Liu et al[24] also reported that populations with high BMI showed a significantly increased risk of KOA. Obesity is a risk factor for these disorders because the pressure exerted on the articular cartilage is increased, accelerating degeneration. In contrast, Nakamura et al[25] reported that BMI, particularly BMI ≥ 23.5 kg/m^2, was significantly associated with LS in Japanese women over 60 years of age, and that BMI was an important measure for the detection of LS. In this study, BMI of LS group is significantly higher than that of No-LS group in multivariate analysis. This result may indicate that high BMI is a useful screening tool for LS prevention in young- and middle-aged adults in Japan.

Patel et al[26] reported that the amount of physical activity performed in middle age is associated with mobility in older adulthood. Moreover, several studies reported that sports participation and a high level of total physical activity were associated with reduced decline in physical function, indicating that a higher level of physical activity may protect against impairments in activities of daily living.[27,28] In Japan, Akune et al[29] reported that exercise habits during middle age were associated with a lower prevalence of sarcopenia, which is one of the main causes of LS. Furthermore, Nishimura

TABLE 5 Logistic regression analysis of factors associated with LS

Variable	No-LS group (n = 655)	LS group (n = 197)	OR	95% CI Lower	95% CI Upper	*P*-value
Age						
<45	325	77	Ref			
≥45	330	120	1.53	1.11	2.13	0.009
Sex						
Male	532	146	Ref			
Female	123	51	1.47	0.92	2.34	0.107
BMI						
18.5-24.9	448	119	Ref			
<18.5	19	6	1.09	0.38	2.70	0.866
≥25.0	188	72	1.43	1.00	2.02	0.043
Occupation						
White collar	495	139	Ref			
Blue collar	160	58	1.25	0.87	1.81	0.225
Income						
<5 million yen	112	42	Ref			
≥5 million yen	543	155	0.73	0.49	1.12	0.147
Smoking						
None	404	111	Ref			
Past smoker	95	29	1.35	0.81	2.23	0.252
Current smoker	156	57	1.36	0.89	2.06	0.154
AD						
None	192	88	Ref			
A few times/month	121	23	0.41	0.24	0.69	0.001
A few times/week	194	34	0.44	0.26	0.72	0.001
Daily	148	52	0.64	0.43	0.96	0.032
UCLA activity score						
<5 points	377	146	Ref			
≥5 points	278	51	0.50	0.35	0.71	0.001
FBC						
<6 days/week	115	50	Ref			
≥6 days/week	540	147	0.52	0.35	0.78	0.002
DVS						
<3 points	336	109	Ref			
3-5 points	258	75	0.86	0.61	1.21	0.379
≥6 points	61	13	0.59	0.30	1.10	0.099

BMI, body mass index; AD, alcohol drinking; UCLA, University of California Los Angeles; FBC, frequency of breakfast consumption; DVS, dietary variety score; CI, confidence interval; LS, locomotive syndrome; OR, odds ratio; ref, reference.

et al[30] recently reported that exercise habits during middle age contribute to preventing LS in old age. The current results revealed that UCLA scores in the No-LS group were significantly greater than those in the LS group, suggesting that lower levels of physical activity can contribute to LS, even in young- and middle-aged adults.

The LS group had a significantly lower FBC compared with the No-LS group. Some previous studies suggested that skipping breakfast is associated with lower levels of physical activity. For example, individuals who skip breakfast have been observed to participate in less exercise and exhibit lower levels of physical activity than those who eat breakfast.[31,32]

Moreover, Sukurai et al[33] reported that a higher frequency of skipping breakfast was associated with a higher likelihood of current smoking and a lower likelihood of habitual exercise. However, we did not collect comprehensive data on these variables, which is a limitation of the current study. However, some lifestyle factors closely associated with skipping breakfast may also affect the onset of LS. Therefore, it is important to encourage people who skip breakfast to change their lifestyle to form reliable breakfast eating habits.

Several previous studies have suggested a dose-response relationship between alcohol consumption and levels of physical activity,[34-36] indicating that as drinking increases, so does physical activity level. According to a review by Piazza-Gardner et al[37] examining the association between alcohol consumption and levels of physical activity, alcohol consumers of all ages were more physically active than their nondrinking peers. However, alcohol consumption is reported to be associated with osteoporosis which is a potential cause of LS. Importantly, moderate alcohol consumption has been shown to have a protective effect against osteoporosis, while heavy alcohol intake is conversely associated with an increased risk of osteoporosis.[38] Akahane et al[39] reported that alcohol consumption a few times/month or a few times/week was inversely related to the presence of LS in a cross-sectional study using an Internet panel survey. The current results indicated a similar tendency. However, regarding the association between alcohol consumption and LS, we may have only observed the effect of alcohol consumption on a healthy worker. In general, it is known that alcohol consumption has a complex association with health and some studies link its consumption to acute and chronic diseases.[40-42] Other research suggests that low levels of alcohol consumption can have a protective effect on ischemic heart disease, diabetes, and several other outcomes.[43-45] However, it is possible that those who drink too much and impair their locomotive function could not work effectively and could not participate in our study.

This study involved several limitations that should be considered. First, the study design was occupational field based, not population based. Moreover, because the participants in this study were workers and the ratio of males and females varied widely between companies, we pooled the data for all companies for analysis. Therefore, caution should be exercised when generalizing these results to the general population of the same generation. Second, in this study, employees who were hindered from exercising at the time of the survey in advance were excluded for safety considerations. Moreover, because the current examination was not compulsory, but voluntary, it is possible that people with LS were less likely to participate in the experiment, since many locomotive organ diseases, such as OA and spinal canal stenosis, are associated with pain and limited movement. This could represent a potential bias. Furthermore, convenience sampling may have contributed to selection bias, with most of the sample being the healthy voluntary participants, the white collar and relatively high-income levels. A replication of the study with a random sample of diverse employees (eg, employees who had diverse injury or illness history, poorer socioeconomic backgrounds, more variety of occupations) is recommended to improve the generalizability of results. Finally, female employees were more difficult to recruit for this study. Future research should be conducted using a larger and more diverse sample group, including all genders.

In conclusion, we conducted a cross-sectional study to investigate the relationship between LS and demographic factors, socioeconomic status, lifestyle habits, dietary habits and physical activity of young- and middle-aged adults in five local companies. We found that age, gender, BMI, alcohol consumption, physical activity, and frequency of breakfast consumption were significantly associated with LS. Health education factors, including lifestyle habit, dietary habit, and physical activity in the workplace, are important for reducing the risk of LS. Therefore, education initiatives about LS should be targeted not only to elderly populations but also to young- and middle-aged adults in the workplace. However, since this study was a cross-sectional study, causal relationships cannot be determined. In the future, we have to examine whether lifestyle habit, dietary habits, and physical activity are the results of LS or the cause of LS.

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DISCLOSURE

Approval of the research protocol: This study was approved by the Institutional Review Board of Suzuka University of Medical Science (approval no. 241). This study was conducted in accordance with the principles of the Declaration of Helsinki. *Informed Consent:* All participants provided written informed consent prior to participating in the study. *Registry and the Registration No. of the study/Trial:* N/A. *Animal Studies:* N/A. Conflict of Interest: All author report no conflict of interest related to our manuscript.

AUTHOR CONTRIBUTION

M.O., A.N., T.K., S.S., and A.S. contributed to the conception and design of the study. M.O., in cooperation with T.S. and H.O., was responsible for subject recruitment and data collection. M.O., A.N., and T.K. participated in the statistical analysis. M.O., A.N., T.K., S.S., T.S., H.O., R.N-N., and A.S. participated in the interpretation of the data. M.O drafted the manuscript. A.N., T.K., S.S., T.S., H.O., R.N-N., and A.S. critically commented on the manuscript. A.N. and T.K. obtained funding.

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