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Metabolic Syndrome Prevention: Effects of Behavioural Change and Communication on Lifestyle Habits and Behaviours among Secondary school Adolescents in Addis Ababa, Ethiopia

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Abstract

Background: Prevalence of metabolic syndrome is rapidly increasing and adolescents' lifestyle including dietary; smoking, alcohol consumption, physical inactivity and sedentary habits are major risk factors for developing metabolic syndrome and cardiovascular diseases. The study aimed to investigate the effects of behavioural change and communication on lifestyle behaviours on metabolic syndrome.

Methods: Multistage, school-based randomised control trial was done among secondary school adolescents in Addis Ababa, Ethiopia. The intervention lasted for six months and data was collected using a modified WHO STEP wise approach for Non-communicable Diseases Surveillance and analysed using SPSS version 24. Descriptive statistics were used to organise and describe the findings, Mc Nemar test was used to determine the effect of the intervention on adolescent's lifestyle, self-efficacy and outcome expectations of behavioural change. P-value<0.05 was considered statistically significant.

Results: There were 413 and 411 adolescents in the control and interventional groups respectively. After six months of intervention prevalence of metabolic syndrome declined from 12.4% to 9.95%; sedentary life of ≥ 2 hr/day declined from 89.8% to 60.6%, alcohol intake declined from 22.6% to 14.8% and smoking declined from 9.7% to 8.5% in the interventional group. The changes were significant p-value<0.001. Adolescents who were involved in moderate or vigorous physical activities significantly increased from 55.2% to 58.6% in the interventional group but remained the same in the control group. Self-efficacy and all outcome expectations significantly improved (P<0.05) in the interventional group. Overweight, triglycerides and total cholesterol levels significantly declined in both groups P-value<0.05 and fasting blood glucose significantly increased in the control group but significantly declined in the intervention group p-value<0.001).

Conclusion: Behavioural change and communication intervention had significant impact on modification of the adolescents' lifestyle behaviour and is effective in reducing metabolic syndrome in adolescents.

Keywords: Adolescents; Lifestyle; Metabolic syndrome; Behavioural change; Communication intervention

Abbreviations BMI: Body Mass Index; cm: Centimetre; HDL-C: High Density Lipoprotein Concentration; Kg: Kilo gram; mmHg: Millimetre Mercury; SD: Standard Deviation; SPSS: Statistical Package for Social Sciences Software; WHO: World Health Organization

Introduction

Hypertension, dyslipidaemia, obesity and disordered glucose metabolism are factors associated with increased risk of developing cardiovascular diseases [1]. The combination of these factors have a strong association with increased prevalence of obesity [2,3] and it is hypothesised that these factors constituted a syndrome of metabolic disorder currently referred to as metabolic syndrome. Metabolic syndrome is a cluster of cardiovascular risk factors secondary to an inflammatory and insulin resistance state that increases the risk of cardiovascular disease and type 2 diabetes mellitus in adulthood [4,5].

The diagnosis of metabolic syndrome include fasting blood glucose ≥ 100 mg/dl or patient receiving medicine for hyperglycaemia; raised blood pressure ≥ 130/85 mm Hg or receiving antihypertensive medicines; raised blood triglycerides ≥ 150 mg/dl or receiving medication for hyper-triglycerides; reduced HDL-C ≤ 40 mg/dl or ≤ 50 mg/dl in men and women respectively or receiving treatment for reduced HDL-C and high waist circumference ≥ 94 cm or ≥ 80 cm in men and women respectively [6].

Metabolic syndrome is becoming a global epidemiological challenge because of increasing prevalence of obesity and sedentary life habits [7-9]. Recent studies have indicated that adolescent's lifestyle habits including dietary, smoking, alcohol consumption, physical inactivity and sedentary life are major contributors of chronic non-communicable diseases and metabolic syndrome at adulthood [10,11].

A study in Iceland showed that 89% of secondary school students consumed one or more types of alcohol; another 21.4% and 20.3% were current smokers and had sedentary lifestyle respectively [12]. The clinical management of metabolic syndrome is complex, costly and

challenging, therefore preventive action and in particular lifestyle and behaviour modification and communication have shown to be most powerful and effective tools that motivate adolescents through improving their awareness on the benefit of positive health behaviours, improving self-efficacy and confidence to maintain lifelong positive health behaviour [13,14].

Over 65% of the population in Ethiopia is aged below 25 years and recently the country's Federal Ministry of Health [15] reported poor community awareness and misconceptions about the burden and consequences of chronic non-communicable diseases. Currently Ethiopia is undergoing major economic transformation from an agricultural based to an industrial based economy. This has resulted in proliferation of food and beverages processing companies that promote alcohol drinking, cigarette smoking, eating refined food, food with high levels of salt, sugar and saturated fat targeting adolescents and young people.

There is need for the country to develop comprehensive guidelines that target at reducing adolescent's risk of developing metabolic syndrome and other non-communicable diseases. This study aimed to assess the effects of lifestyle behavioural change and communication intervention on reducing metabolic syndrome and promoting good health behaviour among adolescents in Ethiopia.

Research Methodology

Study area

The study was carried out among secondary school adolescents in Addis Ababa City, Ethiopia in 2016/2017. According to the 2007 census, the population in Addis Ababa City was 3.65 million, of which, 1.89 million is females and 1.76 million is male. The city is divided into 10 sub-cities and 99 kebeles (villages). The city has 76 public secondary schools.

Study design and population

School-based randomised control trial was carried out to determine the effect of behavioural change and communication intervention on lifestyle behaviours and metabolic syndrome among secondary school adolescents. The sample frame included all secondary school students in the city enrolled in the 2016/2017 academic year. Both male and female aged between 100-19 years, willing to participate in the study and those below 18 years have parental or guardian consent and assent were eligible for inclusion in the study. All students whose ages were ≤ 10 and ≥ 19 years, pregnant and disabled were excluded from the study.

Sampling technique and sample size

Multistage sampling technique was used to determine the sample. There are 10 sub-cities with a total of 76 secondary schools in Addis Ababa city. The first stage of sampling involved assigning numbers to the 10 sub-cities from which, three sub-cities were randomly selected. There were eight secondary schools in the three randomly selected sub-cities. In the second stage of randomisation the unit of randomisation were the schools, therefore four schools were randomly assigned to the control group and four schools were assigned to the interventional group.

The sample size was determined by the assumption that 50% of the adolescents had metabolic syndrome with 5% marginal error and 95% CI and multiplying by design effect 2 due to the multi stage nature of the sampling technique and adding none response rate of 10%. Using the formula for single population proportion the estimated sample size was 844. In the third randomisation, the unit of randomisation were adolescents.

This stage involved identification of all eligible adolescents based on age and voluntariness to participate in the study. Random numbers were allocated to the adolescents from whom 422 were randomly assigned to each of the control and case group. Data collectors were blinded in the allocation of interventional and control groups and during data collection and processing.

Intervention procedures

The intervention protocol was developed by reviewing several behavioural guidelines previously used [16,17] focusing on improving adolescents' lifestyle behaviours. The intervention lasted for six months and was conducted under the supervision of the first author with the assistance of trained research assistants. In summary, leaflets and posters containing information on the risk factors, clinical manifestations and preventive measures for Metabolic syndrome were prepared by the first author, distributed to the interventional group and were used as training guides and counselling materials.

The key messages were on metabolic syndrome and risk factors, lifestyles, dietary habits, physical activities, avoidance of smoking and alcohol consumption. Research assistants were trained for one week on collection of key messages and preparation and distribution of leaflet and brochure with key messages were circulated once every month.

Discussion on the relationship of metabolic syndrome and lifestyles were carried out every month. The control group was followed for a period of six months and students were allowed to proceed with their normal routine activities and had no access to the materials used in the intervention group. In both groups data was collected at the beginning of the study (baseline data) and after six month.

Data collection

The outcome measures were obtained at baseline and six months into the study in both control and intervention group. Quantitative data was collected using a modified WHO STEP wise approach for Non-Communicable Diseases Surveillance [18]. The questionnaire consisted of four parts: Part I-the socio-demographic characteristics; Part II- included questions on behaviour and habits (dietary, physical activity, alcohol consumption and smoking); Part III-focused on physiological measurements (height, weight, waist circumference and blood pressure) and Part IV-was on biochemical measurements (fasting blood glucose, serum total cholesterol, serum triglyceride, and serum high-density lipoprotein). Data for Part III and IV were collected before (baseline) and post intervention.

Height was measured in the standing position using a Stadiometer with 0.1 cm resolution and weight was measured in the standing position, barefooted and wearing light clothes using beam balance with 0.1 Kg resolution. While sitting upright with his/her right upper arm positioned at the level of the heart with both feet flat on the floor, waist circumference was measured from midpoint between the last rib and iliac crest using measuring tape of 0.1 cm resolution.

Systolic and diastolic blood pressure were measured in the sitting position using a stethoscope and a mercury sphygmomanometer after 5 minutes rest and repeated measures were taken after 2 minutes of

additional rest. The mean of the two measurements was recorded as the blood pressure.

Blood sample was collected by trained nurses blood glucose level was measured directly by using Sensocard Plus blood glucose meter and sensor card. Blood samples for measurement of the lipid profile was stored at 2-8°C in iceboxes and transported to the Afenicho ber Health Center Laboratory for analysis within 6 hours of collection. The lipid profile (total cholesterol, triglyceride, high-density lipoprotein) was analysed using Biosystem A 25 Automotive Chemistry machine.

Data quality assurance

The questionnaire was pre-tested on 42 (5% of the sample size) adolescents who were not involved in the main study. Anthropometric and laboratory measurement equipment were checked and calibrated daily and before new measurements were made. The data collectors were trained and supervised throughout the data collection period and the questionnaire was checked every day for completeness.

Data management and analysis

Data were checked for completeness and consistency, captured and analysed using Statistical Package for Social Sciences software (SPSS) version 24.0. Descriptive statistics were used to present the findings and Mc Nemar test was used to determine the effects of behavioural change and communication intervention on adolescent's lifestyle, self-efficacy and outcome expectations. Chi-square test and bivariate analysis were used to describe the association of factors (variables) with metabolic abnormalities. P-value<0.05 was considered statistically significant.

Results

Demographic characteristics

Participant's demographic characteristics are presented in Table 1. Out of the 844 participants, 9 and 11 from the control and interventional group respectively, for various reasons including defaulting did not complete the study. Therefore, 824 (97.6%) secondary school adolescents completed the study of which 413 and 411 were from the control and interventional group respectively.

More than half 421 (51.1%) were female and age ranged between 13 and 19 years, mean age of the adolescents was 16.59 ± 1.36 SD. Majority 769 (93.3%) were in the age group of 15-19 years and 789 (95.8%) were single whereas 10 (1.2%) were married.

Regarding educational status, 321 (39.0%) grade 9 216 (26.2%) and 10, 130 (15.8%) were grade 10 and 11 respectively. The rest were grade 12. Three hundred sixty five (44.3%) of the adolescents' parent were privately employed, 233 (27.1%) government employees and 85 (10.3%) were employed by non-governmental organisations.

Variables	Number	%
Sex		
Male	403	48.9
Female	421	51.1
Age in years		
10-14	55	6.7
15-19	769	93.3
Marital status		
Single	789	95.8
Divorcee	25	3
Married	10	1.2
Education status		
Grade 9	321	39
Grade 10	216	26.2
Grade 11	130	15.8
Grade 12	157	19
Parent occupation		
Private workers	365	44.3
Government employed	223	27.1
Unemployed	151	18.3
Non-governmental organisation employed	85	10.3

Table 1: Demographic characteristics of the secondary school adolescents in Addis Ababa, Ethiopia (N=824).

The effects of intervention on adolescents' lifestyle behaviours

Table 2 shows the effects of the intervention on adolescent's lifestyle behaviours. The proportion of adolescent smokers declined from 9.4% to 8.5% in the intervention groups but remained similar in the control group. The proportion of alcohol intake also declined from 22.6% to 14.8% in the intervention groups. Vigorous or moderate activities remained unchanged in the control group but increased from 41.4% to 44.8% in the intervention group. Sedentary of ≥ 2 hours/day declined from 89.8% to 60.6% in the intervention group.

Lifestyle and habits	Baseline assessment		End line assessment	
	Control N (%)	Intervention N (%)	Control N (%)	Intervention N (%)
Smoking				
Yes	28 (6.8)	40 (9.7)	27 (6.5)	35 (8.5)
No	385 (93.2)	371 (90.3)	386 (93.5)	376 (91.5)

Alcohol intake				
Yes	91 (22.0)	93 (22.6)	85 (20.6)	61 (14.8)
No	322 (78.0)	318 (77.4)	328 (79.4)	350 (85.2)
Vigorous or moderate physical activity				
Yes	195 (47.2)	170 (41.4)	195 (47.2)	184 (44.8)
No	218 (52.8)	241 (58.6)	218 (52.8)	227 (55.2)
Sedentary activity				
<2 hour/day	103 (24.9)	42 (10.2)	103 (24.9)	162 (39.4)
≥ 2 hour/day	310 (75.1)	369 (89.8)	310 (75.1)	249 (60.6)
Eating fruits or vegetables				
Yes	203 (49.2)	138 (33.6)	203 (49.2)	175 (42.6)
No	210 (50.8)	273 (66.4)	210 (50.8)	236 (57.4)

Table 2: The effect of the intervention on lifestyle behaviours among secondary school adolescents in Addis Ababa, Ethiopia

Effects of intervention on cognitive aspects

Table 3 shows that the intervention given to adolescents had a significant impact on modification of the adolescents' lifestyle behaviour, self-efficacy, outcome expectation and attitude. Self-confidence (self-efficacy) among the intervention group significantly changed (P=0.014) after the intervention period compared to insignificant change (P=0.401) in the control group. All outcome expectations significantly changed in the intervention group of the adolescents compared to only significant changed were observed in eating and smoking habits in the control group.

	Control (N=413)		**P=valve**	**Case (N=411)**		**P-value**
Variables	**Baseline (%)**	**Post (%)**	**Baseline (%)**	**Post (%)**		
Self-efficacy						
Low self-confidence	226 (54.7)	219(53.0)	0.401	197 (47.9)	180(43.8)	0.014
High self-confidence	187 (45.3)	194(47.0)		214 (52.1)	231(56.2)	
Improve eating habit outcome expectation						
Low outcome expectation	293 (70.9)	234(56.7)	0.00	282 (68.6)	96 (23.4)	0.00
High outcome expectation	120 (29.1)	179(43.3)		129 (31.4)	315(76.6)	
Stop alcohol intake outcome expectation						
Low outcome expectation	297 (71.9)	252(61.0)	0.00	295 (71.8)	161(39.2)	0.00
High outcome expectation	116 (28.1)	161(39.0)		116 (28.2)	250(60.8)	
Physical exercise outcome expectation						
Low outcome expectation	225 (54.5)	217(52.5)	0.268	219 953.3)	181(44.0)	0.00
High outcome expectation	188 (45.5)	196(47.5)		192 (46.7)	230(56.0)	
Stop/avoid smoking outcome expectation						
Low outcome expectation	223 (54.0)	221(53.5)	0.896	189 (46.0)	163(39.7)	0.00
High outcome expectation	190 (46.0)	192(46.5)		222 (54.0)	248(60.3)	
Nutritional habit change attitude						

Negative attitude	276 (66.8)	274(66.3)	0.88	238 (57.9)	190(46.2)	0.00
Positive attitude	137 (33.2)	139(33.7)		173 (42.1)	221(53.8)	
Physical activity attitude						
Negative attitude	194 (47.0)	190(46.0)	0.541	192 (46.7)	174(42.3)	0.00
Positive attitude	219 (53.0)	223(54.0)		219 (53.3)	237(57.7)	
Stop/avoid smoking or alcohol intake attitude						
Negative attitude	212 (51.3)	205(49.6)	0.551	232 (56.4)	108(26.3)	0.00
Positive attitude	201(48.7)	208(50.4)		179 (43.6)	303(73.7)	

Table 3: Effects of intervention on self-efficacy and outcome expectations among secondary school adolescents in Addis Ababa, Ethiopia.

Effects of intervention on metabolic syndrome and individual components

Table 4 presents effects of intervention on the prevalence of metabolic syndrome and individual components. The overall prevalence of metabolic syndrome slightly increased from 13.1% to 13.8% (p=0.690) in the non-intervention group but significantly decreased from 11.7% to 6.1% in the intervention group (p-value<0.001). The prevalence of high waist circumference and high blood pressure insignificantly decreased from 40.7% to 39.0% (p-value>0.05) and from 10.9% to 10.4% (p>0.05) in the non-interventional group respectively. In the intervention group, high waist circumference declined significantly from 23.6% to 19.0% (P-value<0.001) and high blood pressure had a significant decline from 6.1% to 4.4% (P-value=0.016). The prevalence of high fasting blood glucose level increased significantly from 56.9% to 63.7% (P-value<0.001) in non-interventional group whereas it decreased significantly in the interventional group from 58.6% to 38.7% (P-value<0.001). Other metabolic abnormalities decreased significantly in both interventional and non-interventional groups.

Variables	**Control (N=413)**		**P-value**	**Cases (N=411)**		P-value
	Baseline (%)	**Post (%)**	**Baseline (%)**	Post (%)		
Metabolic syndrome						
Yes	54 (13.1)	57 (13.8)	0.69	48 (11.7)	25 (6.1)	0
No	359 (86.9)	356(86.2)		363 (88.3)	386 93.9)	
High blood pressure						
<130/85 mmHg	368 (89.1)	370(89.6)	0.688	386 (93.9)	393(95.6)	0.016
≥ 130/85 mmHg	45 (10.9)	43 (10.4)		25 (6.1)	18 (4.4)	
Waist circumference						
<90th percentile	245 (59.3)	252(61.0)	0.065	314 (76.4)	333(81.0)	0.00
≥ 90th percentile	168 (40.7)	161(39.0)		97 (23.6)	78 (19.0)	
Fasting blood glucose level						
<100mg/dl	178 (43.1)	150(36.3)	0.00	170 (41.4)	252(61.3)	0.00
≥ 100mg/dl	235 (56.9)	263(63.7)		241 (58.6)	159 38.7)	
Total cholesterol						
<200 mg/dl	371 (89.8)	377(91.3)	0.031	358 (87.1)	377(91.7)	0.00
≥200 mg/dl	42 (10.2)	36 (8.7)		53 (12.9)	34 (8.3)	
Triglyceride level						
<150 mg/dl	312 (75.5)	324(78.5)	0.002	296 (72.0)	349(84.9)	0.00

≥ 150 mg/dl	101 (24.5)	89 (21.5)		115 (28.0)	62 (15.1)	
High density lipoprotein level						
≤ 40 mg/dl	80 (19.4)	72 (17.4)	0.021	90 (21.9)	53(12.9)	0.00
>40 mg/dl	333 (80.6)	341(82.6)		321 (78.1)	358(87.1)	
BMI						
Normal	342 (82.8)	351(85.0)	0.025	373 (90.8)	380(92.5)	0.046
Overweight	62 (15.0)	53 (12.8)		35 (8.5)	28 (6.8)	
Obesity	9 (2.2)	9 (2.2)		3 (0.7)	3 (0.7)	

Table 4: Effects of intervention on the prevalence of metabolic syndrome and its individual components among secondary school adolescents in Addis Ababa, Ethiopia.

Discussion

Studies among individual metabolic abnormalities in children have reported increased cardiovascular risk [19] and can be traced from childhood to adulthood which leads one to suspect that metabolic syndrome might also track into adulthood [20]. In fact childhood obesity predicts the development of metabolic syndrome in adulthood [21]. Adolescents with metabolic syndrome have lower exercise capacity than obese and normal-weight controls [22] and obesity alone increases the risk of hypertension, cholecystitis, and slipped capital femoral epiphysis and is associated with psychosocial symptoms in children [23].

Presently, there is strong evidence that children with metabolic syndrome are at an increased risk of cardiovascular diseases and type 2 diabetes mellitus [24]. The increase in the prevalence of metabolic syndrome among adolescents is posing public health challenge in many countries and routine screening among adolescents has been recommended to prevent future complications. Literature on this global agenda is still scarce among adolescents in Ethiopia.

Lifestyle interventions help to reduce risky behaviours including sedentary behaviours, physical inactivity and dietary habits that increase the risk of developing metabolic syndrome or individual metabolic abnormalities [25]. The study in California among Latino population showed that sedentary behaviour decreased by 38% and moderate physical activity increased by 29% in the guided imagery intervention group when compared to digital storytelling intervention group [26].

Similarly, in a school-based intervention study among adolescents in Mexico, BMI decreased by 0.3% in the interventional group whereas increased by 0.2% in the non-interventional group. In addition, the waist circumference of the interventional group remained the same in the baseline assessment and end line assessment but it increased by 1.7 cm in the non-interventional group in the end line assessment. Sedentary lifestyle was reduced in the interventional group by 0.4hour per day whereas it increased by 0.2 hour per day in the non-interventional group [27].

In this study, behavioural change and communication intervention focusing on social cognitive theory constructs was given to the intervention group for six months while the control group performed their usual activities without any manipulation by the researcher. The results show a significant reduction in the prevalence of metabolic syndrome in the intervention group compared to the control group.

Our findings are in support of a study in Brazil which reported that after 16 weeks of intervention the number of overweight adolescents decreased from 43 to 38 and insignificantly increased from 36 to 37 in the intervention and control group respectively. Similarly the intervention reduced metabolic syndrome risks including waist circumference, blood triglyceride level, blood HDL-C level, fasting blood glucose level and blood pressure [28].

Our study also found among the intervention group a reduction in the risk factors for metabolic syndrome including alcohol consumption, sedentary life (inactivity) and smoking; the proportion of adolescents who participated in moderate or vigorous physical activities increased from 41.4% to 44.8% and adolescents who spent more than 2 hour per day on sedentary activities declined from significantly at the end of six months of intervention.

These findings are in contrast with the findings of a school-based interventional study in Mexico which reported that the time spent for sedentary activities was not reduced in the interventional group [27] and the difference could be attributed to methodological and cultural factors which need further studies. The findings in our study indicate that sustaining effective communication on lifestyle and behavioural change to adolescents is likely to result in healthier lifestyles as the adolescents enter into adulthood.

We also found that the intervention given to adolescents had a significant impact on modification of the adolescents' lifestyle behaviour, self-efficacy, outcome expectation and attitude. The intervention had motivational effects in building confidence and improved perceptions on the major outcome expectations. However, there were no statistical difference in the BMI, cholesterol, HDL-C and triglycerides between the two groups. Some previous reports have also shown similar results of no difference in BMI between the intervention and control groups [29,30].

Since these factors are highly associated with obesity, one possible explanation to the finding is the phenomenon of stagnation of BMI among children as they grow [31,32] indicating that in fact the phenomenon had effects on both resulting in no statistical difference between the groups. The other possible explanation is that, this study was carried out in the capital city of Ethiopia where media campaigns against obesity through radio, television and health education has like

in many developing countries become common. The characteristic of the study population is likely to be a limitation if the results are to be generalised.

The prevalence of metabolic syndrome and its individual components were in this study higher than some of the reports in Europe [17,33]. As the economy of Ethiopia is rapidly growing access to fast foods with high energy and fats has become easy; and coupled with increased sedentary life may partly explain this growing trend of metabolic syndrome among adolescents in Ethiopia.

Because children spend long hours at school, school environment plays important roles in contributing to risk factors for overweight and obesity. For example, most food prepared by schools is more dense energy and the snacks are in most cases fried [34] increasing risks for developing metabolic syndrome. Healthier food options should be available to school children and school administration and the government should take roles in enforcing accessible healthier foods on campuses. Schools should enhance regular physical education in their curricula because physical activities enhance insulin sensitivity and leads to a reduction in diastolic blood pressure [35,36].

Conclusion

In conclusion, this study has shown that behavioural change and communication intervention results in a reduction of metabolic syndrome and its components. Concerted efforts involving school administration, the government, parent and the community should engage with adolescents on the adverse effects of the risk factors for metabolic syndrome. The media and other communication strategies should be co-opted in the campaign.

Declarations

The authors have declared that all the sources that used or quoted have been indicated and acknowledged by means of complete references. We also declared that we respected all ethical principles throughout the research process and the participants were informed about the publication of the research at the time of data collection.

Ethical Considerations

Ethical clearance was obtained from University of South Africa Ethics Review Board and the Addis Ababa Health Bureau Institutional Review Board. Permission to carry the study at the schools was obtained from the Regional Education Authorities and from the secondary schools' management in Addis Ababa, Ethiopia. Written consent was also obtained from the parents and the students to conduct the study.

Conflict of Interest

The authors have declared no competing conflict of interest.

Author's Contributions

G.E. B conceived the topic, development of data extraction tool, interpretation of research findings and writing the manuscript. G.T. and Y.M. were involved in mentoring and finalising the research protocol, data extraction tool, interpretation of research findings and writing the manuscript. All authors have read and revised the manuscript and agreed to submit for publication.

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Availability of Data and Materials

The original data used in the analysis of this study is available at the hand of corresponding author.

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