Amelioration of inflammation in young men with cardiovascular risks participating pedometer-based walking programme

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ABSTRACT

Introduction: Inflammation plays a central role in the pathogenesis of cardiovascular events. The lack of exercise among Malaysians and the increasing cardiovascular diseases among young men are of concern. The aim of this study was to evaluate the reducing of inflammation by measuring C-Reactive protein (CRP), interleukin-6 (IL-6) and tumour necrosis factor-alpha (TNF-α).

Materials and Methods: A total of 70 young men (20 - 40 years) who were sedentary, achieving less than 5,000 steps/day in casual walking with 2 or more cardiovascular risk factors were recruited in Institute of Vocational Skills for Youth (IKBN Hulu Langat). Subjects were randomly assigned to a control group (CG) (n=34; no change in walking) and pedometer group (PG) (n=36; minimum target: 8,000 steps/day). All parameter was measured at baseline, at 6 weeks and after 12 weeks.

Results: At post intervention, the CG step counts were similar (4983 ± 366vs 5697 ± 407steps/day). The PG significant increased step count from 4996 ± 805 to 10,128 ±511 steps/day (p<0.001). The PG showed significant improvement in anthropometric variables and lipid (time and group effect p<0.001). After intervention, CRP, IL-6 and TNF-α were significantly reduced for time and group effect (p<0.001). However, no changes were seen in CG.

Conclusion: The pedometer-based walking programme improved health status in terms of improving inflammation and arterial stiffness.

KEYWORDS:
Pedometer based walking programme, inflammation, young men, cardiovascular risks.

INTRODUCTION

Cardiovascular diseases (CVD) are the leading cause of mortality and disability that challenges humankind in both health and wealth in developing countries including Malaysia and the prevalence of CVD is still rising.[1] Among the CVD, more than 50% were due to ischemic heart disease (IHD). Twenty-three per cent of these patients were reported to be less than 50 years old. Most of the Acute Coronary Syndrome (ACS) cases involved men.[2] The increased in the prevalence of IHD may be due to increase in CVD risk factors such as lack of physical activity, smoking, hypertension, dyslipidaemia, obesity, and diabetes mellitus.[3] Atherosclerosis may develop with the presence of cardiovascular risk factor. Atherosclerosis is a chronic and progressive inflammatory disease of the artery which develops in the intima layer of the artery. Atherosclerotic plaques contain various cells (inflammatory, endothelial and smooth muscle cells), connective tissue and fat.[4] The initial steps involved in the formation of fatty streak which consist of foam cells, which are actually macrophages that engulf fat.

Atherosclerosis will develop if a diet high in cholesterol mainly low-density lipoprotein (LDL) is taken. LDL in the blood would enter the intima layer of the arterial wall and with the presence of free radicals it will become oxidized LDL. Oxidized LDL will stimulate release of phospholipids and further activate the expression of vascular cell adhesion molecule–1 (VCAM-1) and intercellular cell adhesion molecule-1 (ICAM-1) in the endothelial cells. VCAM-1 and ICAM-1 on the surface of endothelial cells may attract leucocytes in the blood to bind with endothelial cells and enter the intima layer. These leucocytes will release a lot of cytokines that enhance inflammation in this area. Oxidized LDL will be taken by macrophages via scavenger receptors and produce foam cells that make macrophage less mobile and start to accumulate in this region. Foam cells are still active and can produce inflammatory cytokines such as macrophage chemoattractant protein-1 (MCP-1).[5] These activities will enhance the inflammatory process and produce various inflammatory mediators such as tumour TNF-α, Monocyte Colony Stimulating factor (MCSF), MMP-1 and Interleukin-18. These mediators further stimulate release of IL-6 and this mediator will enter the bloodstream and stimulate the liver secretion of CRP. CRP will enhance more inflammatory mediators release by macrophages and worsen the inflammation in that area. CRP may also impair

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bioavailability of nitrous oxide (NO) in the arterial wall and lead to vasoconstriction.[6]

Overcoming the sedentary lifestyle by engaging in sustainable daily physical activity (PA) is a practical approach in reducing the risk of developing CVD. The National Institute for Health and Clinical Excellence (NICE), 2006[12] guidelines highlights the contribution of regular physical activity in promoting to the health of communities. It is recommended that every adult accumulates the recommended 30 minutes of moderate physical activity on five days of the week or to accumulate 150 minutes per week in at least bouts of ten minutes of sustained physical activity. Besides, the Centers for Disease Control and Prevention (CDC) and the American College of Sports Medicine (ACSM) also recommends adults to walk 10,000 steps/day on most days of the week . These recommendations have been shown to promote and maintain health and significantly reduce the risk for CAD.[13]

Walking is a form of exercise that is very acceptable to many people and may be integrated easily into daily routine. However, NICE indicates that there is currently insufficient evidence to recommend the promotion of organised walking schemes, and that the effects of low levels of exercise are poorly documented.

Thus, the aim of the present study was to determine the effects of pedometer-based walking programme at workplace on reducing reducing of inflammation by measuring CRP, IL-6 and TNF-α. Up to now, there are only a few reports of adherence within unsupervised walking programme in reducing cardiovascular risks.[14,15] Furthermore, there are gaps in evidences in relation to the effects of varying doses of exercise using pedometers as an adjunct to other interventions. In addition, pedometer-based health promotion is gaining in popularity but data on its role in intervention for health is lacking.

MATERIALS AND METHODS

Subjects

This prospective randomized controlled trial study was conducted in the Institute of Vocational Skills for Youth (IKBN) Hulu Langat, Selangor, Malaysia. The inclusion criteria were young men aged 20-40 years old, sedentary lifestyles with less than 5000 steps per day and have 2 or more cardiovascular risk factors such as hypertension, dyslipidemia, abdominal obesity, smoking, and family history (FH) of CVD. Exclusion criteria were those with diabetes mellitus (DM) and other chronic disease such as CVD, peripheral vascular disease, lung disease, liver disease, and inflammatory disease. Adults above 40 years old were excluded to prevent bias since the body changes may differ either between men and women or young and adults people. DM was excluded since this disease is equivalent to coronary artery disease (CAD), and subjects may have advanced vascular properties compared to other CV risk factors.[16] Criteria for young Malaysian males for various CV risk factors was observed as per reference given with each of the following: 1) Hypertension: systolic blood pressure ≥140 and/or diastolic ≥90 or on antihypertensive medication. 2) Diabetes mellitus: fasting plasma glucose ≥7mmol/L.[17] 3) Smokers: a habit of daily smoking continued at the time of recruitment for study. 4) Abdominal obesity: waist circumference >90 cm. 5) Family history (FH) of premature CAD: when parents had CAD at <55 (father) or <65 (mother) age. 6) Dyslipidemia: when TC >6.2mmol/L, TG >1.7mmol/L, LDL >4.2mmol/L, or HDL <1.04mmol/L.[18] In this study, a total of eligible 70 young men (20 - 40 years) who were sedentary, achieving less than 5,000 steps/day in casual walking with 2 or more cardiovascular risk factors were recruited.

Pedometer-based walking programme

The research design was approved by the Research and Ethics Committee of Universiti Kebangsaan Malaysia (FF-2019-139). The protocol as well as the potential risks and benefits of participating in this programme were explained to each subject before he gave written consent. Once enrolled in the program, subjects underwent a complete medical history and physical examinations to ensure that they were fit for the exercise intervention. During the trial phase, each subject was exposed to the self-monitoring pedometer programme which needed full commitment from each subject. The subjects were informed that the programme involved a self-monitoring-based pedometer intervention, and they were expected to give full commitment and must be mentally and physically prepared to go through the next phases. In the trial week, the subjects were instructed to assess their average number of daily steps with a pedometer for five days including four working and one non-working day. The average number of daily steps was used as the baseline for the further step goals. Subjects with less than 5000 steps per day were recruited in this programme. In this 4-week trial, subjects are required to gradually increase their walking by 1000 steps/day over 4 weeks. At the end of the trial phase, they were to achieve a mean daily step count of 3000 steps/day on at least 5 days of the week, so that a total minimum number of 8000 steps/day is needed before the start of the actual intervention phase. The most important goal was the improvements above the baseline values. No instructions were given regarding nutritional intake or dietary habits.

Then, subjects were randomly assigned to either a control or pedometer group. Seventy random numbers obtained through Microsoft Excel 2007. Each random number representing the two groups, either pedometer or control group. Each subject was required to select a random number without knowing which group represented the number. The subjects were divided into groups according to a random number assigned either a CG or PG. Those subjects assigned to the PG were followed a 12-week pedometer-based walking programme using pedometers (Yamax Digi-Walker SW-200)[19] for monitor the number of steps initiated by them from wake-up to bed time every day (five days per week) and the numbers of step were keyed in into diary book. Flow of chart of the study is summarized in Figure 1.

Subjects assigned to the CG were maintained their habitual lifestyle and not to change their activity throughout this programme. There were three sessions of cardiovascular markers assessments: at baseline, at 6-weeks intervention (short-term effects) and at 12-weeks intervention (post intervention).

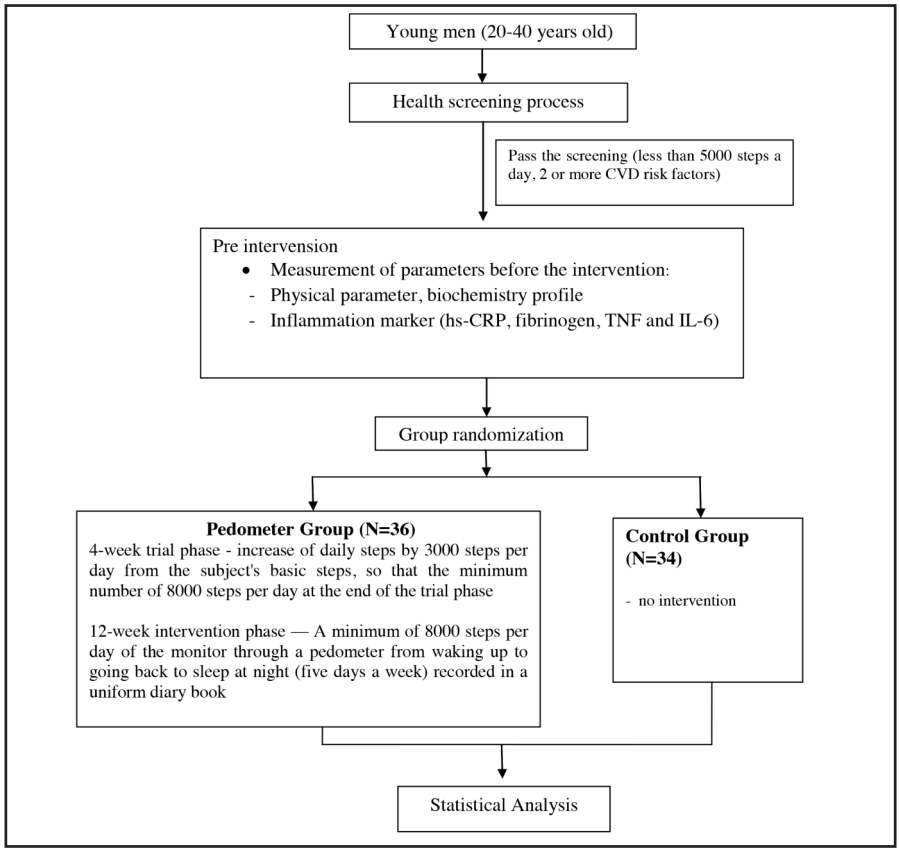

Fig. 1: Flow chart of the study.

Measurement of Physical parameters.
Heights of subjects was measured by a wall-mounted stadiometer (SECA, Hamburg, Germany) and weight was measured by using a digital scale (SECA, Hamburg, Germany). Body mass index was then calculated as weight (kg)/height (m2). Waist circumference was measured by a measuring tape on the horizontal plane, midway between the anterior superior iliac spine and lower rib after normal expiration.[18]

Measurement of blood parameters.
About 5 ml of blood was withdrawn from the antecubital vein after fasting for a minimum of 8 hours. Blood samples were then sent to Gribbles pathology laboratory (Petaling Jaya, Selangor, Malaysia) for further analysis of lipid profiles, CRP, and glucose. This laboratory obtained International Organization of Standardization (ISO: MS ISO 15189) in compliance with the standard quality. The serum TG, HDL cholesterol, and TC were measured using enzymatic methods (Advia 2400 Chemistry Analyzer, Siemens, Tokyo, Japan). The blood glucose was measured by enzymatic method using hexokinase and glucose-6-phosphate dehydrogenase enzymes (Advia 2400 Chemistry Analyzer, Siemens, Tokyo, Japan). For lipids profile, the inter-assay coefficient of variant (CV) ranged from 1.4-3.5%. The inter-assay CV for CRP ranged between 2-2.4%, and CV for glucose ranged from 1.6-1.7%. The TNF-α & IL-6 were conducted using enzyme immunoassay (ELISA) method.

Statistical analysis
Visual inspection of the histogram (plotted as the distribution frequencies) and acceptable level of skewness (-1 to 1) and kurtosis (-1 to 1) were used to determine the normality of the data. All the data were normally distributed except for CRP, TNF-α & IL-6 which were skewed. The values of CRP were logarithmically transformed to improve the skewness and were used in data analysis. All the data were in mean (95% CI) except for CRP, TNF-α & IL-6 which was in median [inter quartile range (IQR)]. The levels of cardiovascular parameters between groups were compared by general linear model (GLM) repeated measures. The significant results were accepted as $p<0.05$. All the data were analyzed using the Statistical Package for Social Sciences Version 20 (SPSS Inc., Chicago, IL, USA).

RESULTS

The characteristics of the subjects for the whole and each groups is summarized in Table I. They were young males (n=70), with mean BP, WC, lipid profile, blood sugar and PWV within normal range. The CRP level was considered to be in the average risk. The prevalence of hypertension was 4.0%, abdominal obesity 51%, dyslipidemia 67 %, smoker 74 %, and FH of CAD 10%. None of them had DM or prediabetes (6.1 mmol/L, <FBS <7mmol/L).

In following intervention, the number of steps for PG significant increase for time and group effect ($p<0.05$).

Table I: Subject`s characteristics

Parameter	Pedometer Group(N=36)	Control Group(N=34)	p value
Age (years)	26.17 ± 6.68	26.62 ± 7.393	0.937
Weight (kg)	73.32 ±18.47	68.94 ± 14.15	0.271
Height (m)	1.67± 0. 056	1.68 ± 0. 056	0.818
BMI (kg/m2)	26.13± 5.99	24.49± 4.54	0.202
Waist circumference (cm)	86.56± 15.09	83.75±14.01	0.422
SBP rest (mmHG)	120.22± 8.97	122.12±8.23	0.361
DBP rest (mmHG)	64.70± 8.84	67.52± 8.31	0.172
HR rest (bpm)	70.81±12.09	70.32± 14.20	0.879
Cholesterol level (mmol/L)	5.01± 0.80	5.10 ± 1.26	0.732
Triglyceride level (TG) (mmol/L)	1.81 ± 0.90	1.82±1.24	0.939
HDL level(mmol/L)	1.17± 0.17	1.18± 0.19	0.718
LDL level(mmol/L)	3.07±0.76	3.28± 1.04	0.314
Fasting Blood Glucose(mmol/L)	4.94± 0.85	4.77± 0.42	0.293
CRP (mg/L)	2.23 ± 2.32	2.49 ± 2.25	0.729
TNF-α (pg/ml)	22.00± 7.75	21.50 ± 8.00	0.520
IL-6 (pg/ml)	12.50 ± 10.47	11.25 ± 6.96	0.590

Data is presented as mean± SD, except for hs-CRP, TNF-α & IL-6 data are presented as median± interquartile range (IQR)
*p< 0.05 is considered significant

Table II: Number of steps per day

	Pedometer group(N=36)		Control Group(N=34)	
	Week 1	Week 12	Week 1	Week 12
STEPS/DAY	4996 ± 805	10128 ± 511**#	4983 ± 366	5697 ± 407 NS

*p< 0.05 (time interaction*group) ** p< 0.01 (time interaction*group) # p<0.05(time effect)

Table III: Changes characteristics of the subjects

	Pedometer group(N=36)			Control Group(N=34)		
	Week 1	Week 6	Week 12	Week 1	Week 6	Week 12
Weight (kg)	73.32± 18.47	72.62± 18.37**	71.35± 16.47**#	68.94± 14.15	69.71± 13.47	69.69± 13.69
BMI (kg/m2)	26.13± 5.99	25.88± 5.93**	25.43± 5.27**#	24.49± 4.54	24.56± 4.51	24.54± 4.57
Waist circumference (cm)	86.56± 15.09	84.87± 13.94**	83.62± 13.53**#	83.75±14.01	84.46±13.79	84.01± 13.11
SBP rest (mmHG)	120.22± 8.97	116.39± 9.71*	116.33± 9.62**#	122.12±8.23	118.62±10.57	118.71± 10.63
DBP rest (mmHG)	64.70± 8.84	63.89± 8.83	63.83± 8.73*	67.52± 8.31	67.44± 9.69	67.82± 6.68
HR rest (bpm)	70.81±12.09	67.92± 12.50	66.89±10.83*	70.32± 14.20	71.18±14.33	71.23± 12.87
Total cholesterol	5.01± 0.80	4.92 ±1.02	4.62± 1.08*	5.10 ± 1.26	5.17± 1.11	5.29± 1.08
TG	1.81 ± 0.90	1.31± 0.91*	1.16± 0.59**#	1.82±1.24	1.75± 0.69	1.77± 1.31
HDL	1.17± 0.17	1.24± 0.21*	1.29± 0.24**#	1.18± 0.19	1.17± 0.16	1.16 ± 0.16
LDL	3.07±0.76	3.05±0.82	2.87± 0.85*	3.28± 1.04	3.35±0.82	3.6± 1.35
FBS	4.94± 0.85	4.99± 0.98	4.84 ± 0.83	4.77± 0.42	4.61±0.34	4.68± 0.53

*p< 0.05 (time interaction*group) ** p< 0.01 (time interaction*group) # p<0.05(time effect)

Table IV: Changes of inflammation markers

	Pedometer group(N=36)			Control Group(N=34)		
	Week 1	Week 6	Week 12	Week 1	Week 6	Week 12
CRP(mg/L)	2.23 ± 2.32	1.44 ± 2.13*#	0.95 ± 1.58*#	2.49 ± 2.25	2.55 ± 2.15	2.99 ± 3.40
TNF-α (pg/ml)	22.00± 7.75	20.00 ± 7.00*#	14.00±16.50**#	21.50 ± 8.00	22.00± 10.50	23.35 ± 9.75
IL-6 (pg/ml)	12.50±10.47	7.37± 7.33*#	5.25± 3.47**#	11.25 ± 6.96	11.55 ± 6.79	11.56 ±7.13

*p< 0.05 (time interaction*group) ** p< 0.01 (time interaction*group) # p<0.05(time effect)

However no change seen in CG (Table II). In term of physical parameter , after pedometer-based interventions for 12 weeks, the body weight and waist circumference were significant decreased for PG (time and group effect, $p<0.05$) and significant improved for lipid profiles in PG (Table III).

The median CRP changes significantly decreased in PG for time and group interaction, $p<0.05$ (Table IV) as well as significant reduced noted for TNF-α & IL-6 (time and group effect, $p<0.05$). No change seen in CG (Table IV).

DISCUSSION

The pedometer is a validated instrument to measure steps, and it encourages increased physical activity effecting health-related quality of life.[21] Pedometers allow ambulatory populations to track their steps, which influences motivation through goal-setting. The current study noted better compliance and more accumulated steps in the subjects treated with pedometers and a daily step-recording log.

The results of our study suggest exercise interventions decrease body weight, BMI, WC, total cholesterol, increase high-density lipoproteins (HDL), decrease low-density lipoproteins (LDL) and lower blood pressure . The current study did not produce significant changes in fasting blood glucose (FBG). The lack of changes in FBG in this study may have been attributed due to baseline value was in normal range. The blood lipid results from our study compliment prior studies that have shown that physical activity effectively increases HDL and decreases both LDL and total cholesterol. Leon and colleagues (2000) reported that 20 weeks (5 months) of supervised exercise significantly improved HDL.[22] Our study showed an increase in HDL for PG in 12 weeks duration. The increased HDL increase in this study, may be attributed to: the 5 days exercise vs. 3 times per week in the Leon et al. study, to the self-selected exercise intensity in the current study, higher self-selected volume of exercise, or to a random effect of our smaller sample size, gender, or ethnicity. Walking exercise training programs can result in modest decreases in body weight and fat stores, blood pressure (particularly in persons with elevated resting blood pressure), serum triglycerides, and low-density lipoprotein cholesterol, and increases in the "protective" high density lipoprotein cholesterol.

Both SBP and DBP were found to be reduced in the first 6 weeks and maintained over the second six weeks. The physical conditioning achieved by regular walking exercise decreases the heart rate and blood pressure at rest and at given level of exercise.[23] Consequently, the workload on the heart is reduced and angina symptoms may be alleviated. Regular exercise also improves muscle function and increases the cardiac ability of the patients to take in and use oxygen. This is commonly referred to as the maximal oxygen consumption or aerobic capacity. As the ability of the body to transport and deliver oxygen improves, the patient has added energy and less fatigue. This benefit is important for patients with cardiovascular risk whose aerobic fitness is typically less than that of healthy adults of similar age. Moreover, moderate exercise on overall cardiovascular risk, when combined with other lifestyle modifications (such as proper nutrition, cessation of smoking, and medication use), can be dramatic.

Inflammatory markers in cardiovascular risks

The study showed a significant reduction in CRP, TNF-α and IL-6 in the pedometer group after the intervention, and no significant change for the control group.[24,25] There are significant differences and the interaction effects between the two groups pedometer and control. A reading of fibrinogen, TNF-α and IL-6 in both groups respectively but still within the normal range in the direction of the border beyond the normal. However, the pedometer group showed a significant decrease in the pattern of TNF-α and IL-6 at the end of the intervention. CRP readings for the two groups are in a moderate risk range of between 1 to 3 mg / L. For the pedometer, the overall decline of 0.65 mg / L is equivalent to 57% is a very large and so makes reading Hs-CRP less risky belongs to a group at the end of the intervention. According to a study conducted by[26] as much as 16-41% decrease in CRP after undergoing regular physical activity can reduce the risk of heart disease.

As stated previously, the production of CRP is stimulated by IL-6 and also of IL-1 and TNF-α. Hiperinsulin factors contributing to obesity and increased production of inflammatory markers. Inflammatory process that occurs starting from adipose tissue leads to obesity due to excessive adipocyte cell hypertrophy and infiltration of macrophages.[27] The increased number of fat cells that trigger an inflammatory response. Production of proinflammatory cytokines trigger inflammation in the arterial wall. Primary cytokines (interleukin- 1 [IL-1], tumour necrosis factor - α [TNF-α]) mediates attraction and migration of inflammatory cells into the vascular tissue. It is also encouraging intermediary other cytokines such as interleukin- 6 (IL-6), which is released into the systemic circulation, causing the liver to increase the production of acute phase reactants, such as CRP. IL-6 is a cytokine primary procoagulant. It can increase the plasma concentration of fibrinogen and CRP that strengthens the inflammatory response and procoagulant.[28]

Thus, through physical activity such as walking in this study can reduce the mass of adipose tissue and indirectly reduce inflammation or inflammation. This study is in line with another by Mayer et al. (1998)[29] that has shown that physical activity lowers the level of IL-6, TNF-α and CRP reduction in line with the reduction of obesity and insulin sensitivity. Physical activity also reduces inflammation through repair of endothelial function. As is well known endothelial cells secrete IL-1 and IL-6, and activated endothelial cells will increase the production of interleukins and adhesion molecules that promote inflammation. Therefore, constant physical activity lowers peripheral inflammatory markers associated with endothelial dysfunction, for example, intracellular and vascular adhesion molecules and MCP-1.[30] In addition, moderate-intensity physical activity such as walking continued this can improve endothelial function by maintaining or increasing nitric oxide and increase anti-oxidant defence through up-regulation of anti-oxidant enzymes. Furthermore, the anti-oxidant effect of physical activity can reduce LDL other than

their more oxidized, which in turn can help prevent endothelial dysfunction and inflammation. In summary, this continuous physical activity can reduce CRP directly through cytokine reduction in fat, muscle and mononuclear cells and indirectly through increased insulin sensitivity, repair of endothelial function and weight reduction.

CONCLUSION

A pedometer-based walking programme may be an effective strategy for promoting increased daily physical activity which reduces inflammatory processes and improving arterial stiffness which can be seen as early as 6 weeks and normalized after 12 weeks and thus improve cardiovascular health. Findings from this study will provide future direction for community based physical activity. Physical health and work performance of the employee are directly related. Healthy work environment will help in improving his productivity. It helps in giving job satisfaction to the employees and to motivate the employees to work better and in safer manner such as work hard and play safe.

AUTHOR CONTRIBUTIONS

Conceptualization, N.O and M.S.M.S.; data curation, N.O.; investigation, N.O.; methodology, N.O., AA., and K.C.; original draft preparation, N.O.; writing—review and editing, N.O., R.Z., M.S.M.S., A.A., and K.C. All authors have read and agreed to the published version of the manuscript.

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CONFLICTS OF INTEREST

The authors declare no conflict of interest.

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