Acta Cardiol Sin 2019;35:534–541
Original Article
doi: 10.6515/ACS.201909_35(5).20190126A

Epidemiology

InVestiGation of the Association of Physical Activity and Sedentary Behavior with tHe Occurrence of Future Cardiovascular Disease and Long Term Outcome in General Population Using the HEALTHCARE Database (*VGH-HEALTHCARE*)

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Background: Current evidence supports the beneficial effect of physical activity in reducing adverse events, however studies on Asian populations are limited and have reported inconsistent findings. The aim of this study was to investigate the association between physical activity and the development of cardiovascular disease, diabetes, hypertension and malignancy in a large Asian cohort. We also investigated interactions between the intensity of physical activity, environmental exposure and biochemical markers.

Methods: Subjects who received annual checkups at Taipei Veterans General Hospital were invited to join this study. Information on physical activity was evaluated using the International Physical Activity Questionnaire Short Form (IPAQ-SF). Associations between the occurrence of clinical events including cardiovascular events, diabetes and malignancies and the intensity of physical activity, biochemical markers, imaging findings, personality trait evaluations and nutrition were evaluated.

Results: In the initial stage of this study, a total of 1010 patients enrolled, 626 (62%) were male, 74 (7.4%) had diabetes, 183 (18.3%) had hypertension, and 220 (21.8%) were smokers. The total cholesterol was 202.1 ± 36.2 mg/dL and low-density lipoprotein-cholesterol was 125.7 ± 32.9 mg/dL, including 49.3 ± 13.1 mg/dL for serum high-density lipoprotein-cholesterol and 120.7 ± 70.7 mg/dL for triglycerides. The fasting glucose level was 93.8 ± 21.9 mg/dL, and HbA1c was 5.7 ± 0.7%. All information collected will be incorporated with future events to analyze the relationship between biochemical parameters, physical activity and future adverse events.

Conclusions: These findings will contribute to the understanding of the value of physical activity in determining future cardiovascular and non-cardiovascular events in Asian populations.

Key Words: Physical activity • Prognosis • Sedentary behavior

INTRODUCTION

Low physical activity and a sedentary lifestyle are considered to be leading causes of chronic diseases such as cardiovascular disease,[1] diabetes[2] and cancer.[3,4] Therefore, current guidelines suggest physical activity for at least 30 minutes of moderate to intense exercise on preferably all days of the week to maintain good

Received: November 24, 2018 Accepted: January 26, 2019
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health.[5,6] Physical activity can lead to a reduction in body weight,[7,8] lower blood pressure,[9] improved lipid profile[10] and a lower incidence of cardiovascular (CV) events.[11] Although studies have investigated the risk factors associated with the occurrence of acute coronary syndrome in Taiwan,[12] few studies have evaluated associations between the intensity of physical activity and the occurrence of chronic diseases using a prospective cohort design in an Asian population. Moreover, interactions between nutritional intake, environmental exposure, personality traits and biochemical profiles remain relatively unexplored.

We therefore conducted this study to investigate the role of physical activity or a sedentary lifestyle on the occurrence of chronic diseases including CV disease, diabetes, hypertension and malignancies in a large cohort with detailed data on biochemical parameters, imaging studies, tumor markers, personality trait evaluations and nutritional intake. Although many factors related to adverse CV outcomes have been reported, few studies have investigated these factors in Taiwanese subjects, and local data are needed because of the different environmental exposure in Taiwanese subjects compared with other populations. Using detailed assessments, the impact of physical activity either independently or concomitantly contributing to the occurrence of adverse events and the interactions between physical activity and related biochemical markers were evaluated. In addition, all baseline biochemical profiles were analyzed simultaneously to assess the associations between baseline risk factors. Furthermore, the long-term outcome follow-up allowed for the identification of independent predictors for CV disease in Taiwanese subjects.

METHODS

Study subjects

VGH-HEALTHCARE is a prospective cohort study conducted to evaluate the impact of physical activity and sedentary behavior on long-term outcomes. The study design is shown in Figure 1. Subjects aged > 20

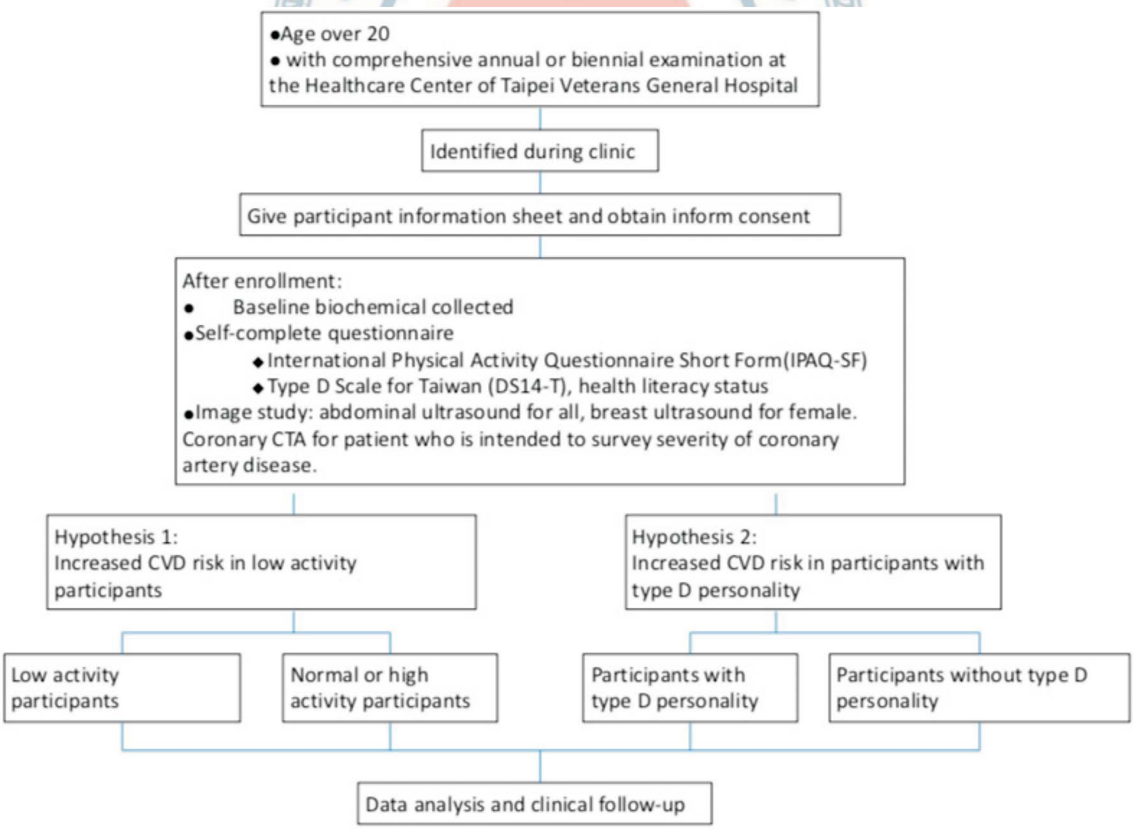

Figure 1. *Study flow.*

years who received a comprehensive annual or biennial examination at the Healthcare Center of Taipei Veterans General Hospital were invited to join this cohort study. Information on physical activity and sedentary behavior was collected after enrollment. This study followed the Declaration of Helsinki and was approved by the Internal Research Board of Taipei Veterans General Hospital. All information was obtained after receiving informed consent from the study subjects.

Personal and clinical profiles at enrollment

After enrollment, specially trained study nurses prospectively collected all data where feasible. Baseline information and medical history such as hypertension, diabetes, surgery, and smoking status were collected. Dietary information and data on daily food intake were also collected using standardized, self-administered food frequency questionnaires as previously described and validated in Taiwan.[13,14] In addition, the health literacy of the study subjects was evaluated using the short-form Mandarin Health Literacy Scale as previously validated.[15,16]

Physical activity and sedentary behavior

Physical activity levels and sedentary status were assessed using the validated Chinese version of the International Physical Activity Questionnaire Short Form (IPAQ-SF).[17,18] The IPAQ-SF includes the number of days and duration of vigorous, moderate, and walking activities during the previous week.[19,20] In addition, the IPAQ-SF enables the calculation of metabolic equivalents (MET-minutes per week), derived by assigning standardized MET values of 3.3, 4, and 8 for walking, moderate intensity, and vigorous intensity, respectively. These data were quantified, and an estimated metabolic equivalent of task for each individual was classified as being high, moderate or low physical activity according to the IPAQ-SF score.[19,20] This method has been used to measure physical activity in Asian populations and has been published previously.[21]

Biochemical parameters

Biochemical parameters including glucose, hemoglobin A1C (HbA1C), uric acid, total cholesterol, triglycerides, low-density lipoprotein-cholesterol (LDL-C), high-density lipoprotein-cholesterol (HDL-C), aspartate aminotransferase (AST), alanine aminotransferase (ALT), bilirubin and high sensitivity C-reactive protein (hsCRP) were measured after an overnight fasting period. In addition, tumor makers including α-fetal protein (AFP), carcinogen embryonic antigen (CEA) and prostate specific antigen (PSA)/CA-125 were also measured at the same time (Table 1).

Imaging and endoscopy studies

Imaging studies including abdominal ultrasound for all of the enrolled subjects, prostate ultrasound for the male subjects, and breast ultrasound for the female subjects were performed. Coronary computed tomography (CT) angiography was also performed in some cases to evaluate the coronary calcium score and severity of coronary artery stenosis. In addition to the imaging studies, nearly all of the subjects received endoscopy to evaluate the upper gastrointestinal tract and colonoscopy to evaluate the lower gastrointestinal tract.

Personality assessment

In addition to recording the baseline biochemical and physical activity data, we used the type D personality Scale for Taiwan (DS14-T) to evaluate whether the

Table 1. Data collection outlined below

- Characteristic demography
- Co-morbidities (review of primary care medical record or by self-report)
- Life style behavior – smoking, alcohol intake
- Clinical examination – blood pressure, weight, height, waist circumference
- Blood test – including glucose, HbA1C, uric acid, total cholesterol, triglycerides, LDL-C, HDL-C, AST, ALT, bilirubin and high sensitivity C-reactive protein were measured after an overnight fasting period. In addition, tumor makers including α-fetal protein, carcinogen embryonic antigen and prostate specific antigen/CA-125 were also measured at the same time

ALT, alanine aminotransferase; AST, aspartate aminotransferase; HbA1C, hemoglobin A1C; HDL-C, high-density lipoprotein-cholesterol; LDL-C, low-density lipoprotein-cholesterol.

presence of type D personality would cause adverse future CV events. The DS14-T was translated from the original DS14 scale and has been validated for the Taiwanese population.[22] This version has adequate construct validity and can be considered equivalent to the English version.[22] In short, this instrument measures negative affectivity (NA, the tendency to experience negative emotions) (e.g., "I often make a fuss about unimportant things," and, "I have a gloomy view of things") and social inhibition (SI, the tendency to inhibit the expression of emotions) (e.g., "I make contact easily when I meet people," and, "I find it hard to start a conversation"). The scale has seven five-point items that are rated on a Likert scale ranging from 0 (false) to 4 (true) for each subscale. The DS14-T is regarded to be the current standard for identifying type D patterns.[23] Using a standardized cut-off score of > 10, patients scoring high on both subscales were classified as having a type D personality.[22] We recently elucidated the connection between poor outcomes of type D personality in patients with coronary artery disease after percutaneous coronary interventions (PCIs).[24] In this study, we investigated type D personality further and other risk factors in the general population.

Clinical follow-up for CV and non-CV adverse events

Each study subject was prospectively and regularly followed up. The occurrence of adverse CV events was recorded, including all-cause mortality, CV death, nonfatal myocardial infarction, nonfatal stroke, unplanned revascularization procedures, unplanned hospitalization for refractory or unstable angina, and other causes including stroke, transient ischemic attack, heart failure, or peripheral arterial occlusive disease. Myocardial infarction was confirmed if ischemic symptoms were noted, including elevated serum cardiac enzyme levels and/or characteristic electrocardiogram changes. Coronary revascularization procedures with either PCIs or coronary artery bypass graft surgery were confirmed by a medical record review. Stroke was confirmed by a new neurological deficit lasting for at least 24 hours with definite imaging evidence of a cerebrovascular accident either in magnetic resonance imaging or CT. The follow-up protocol for CV events was similar to that reported in our previous studies.[25-27] In addition to CV events, non-CV-related events including the occurrence of malignancy, diabetes, renal failure, and non-CV death were also recorded during the follow-up period. Furthermore, to allow for long-term follow-up, the assessment of clinical events was also conducted using the national health insurance database if the patients agreed. These are outlined in Table 2. Furthermore, all cross-sectional and longitudinal information collected were analyzed to evaluate the relationships between these data obtained from routine physical checkups to provide future advice for subjects receiving routine checkups.

Statistics

Quantitative variables with normal or median distribution are expressed as mean and standard deviation, and those with an asymmetric distribution as interquartile range. The statistical analysis was performed as follows. First, for the baseline data, a cross-sectional design was used to explore the relationships between quantified physical activity and different outcomes. Multivariate analysis including factor analysis, principal component analysis, and dimension-reduction stratified sampling analysis was then used to investigate patterns in the quantified data, followed by multivariate linear regression (for linear outcomes) or logistic regression (for categorical outcomes) to interpret the relationships between physical activity and sedentary status and future adverse events. Second, we conduct a prospective study to investigate the relationships between the amount of physical activity, different patterns of exercise, and the risk of various diseases. Subjects with and without newly developed adverse events during the follow-up period were compared. Survival curves for the different levels of physical activity were assessed using Kaplan-Meier analysis, and the strength of each relationship was presented with hazard ratio and 95% confidence interval. Multivariate Cox proportional hazards models were used

Table 2. Out-come outlined below

- CV event – all cause mortality, cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, unplanned revascularization procedures, unplanned hospitalization for refractory or unstable angina, heart failure, peripheral arterial occlusive disease
- Non-CV-related event – malignancy, diabetes, renal failure, and non-CV death

to adjust for confounders and estimate the risk of chronic diseases in groups with different patterns of physical activity and in those with a sedentary lifestyle. We also controlled for confounding factors by performing semi-randomization with propensity score matching to analyze relationships between different exercise patterns and chronic diseases. In all of the tests, a two-tailed alpha significance level of 0.05 was used to represent statistical significance.

RESULTS

According to statistics published by the Health Promotion Administration, the CV mortality rate in Taiwan is 5.7%, and the incidence of hypertension in an adult is 25.7%, with an odds ratio (OR) of 2.0-2.5. G power software was used to calculate the sample size needed (α = 0.05, power = 0.8, and OR = 2.0) for the logistic regression model, which showed that at least 1081 cases would be needed. We have already collected 1010 participants in this study. Because the study is still ongoing, we are continuing to enroll cases and follow the outcomes prospectively.

Baseline data of the initial 1010 patients enrolled

Among the 1010 patients enrolled so far, 626 (62%) were male, 74 (7.4%) had diabetes, 183 (18.3%) had hypertension, and 220 (21.8%) were smokers. The baseline characteristics of the overall population are provided in Table 3. The total cholesterol level was 202.1 ± 36.2 mg/dL and LDL-C was 125.7 ± 32.9 mg/dL, including 49.3 ± 13.1 mg/dL for serum HDL-C and 120.7 ± 70.7 mg/dL for triglycerides. The fasting glucose level was 93.8 ± 21.9 mg/dL, and HbA1c was 5.7 ± 0.7%. Physical activity status as evaluated using the IPAQ-SF showed low, moderate, and high levels of 41.4%, 42.1% and 16.5%, respectively. The average daily sitting time was 6.6 ± 3.1 hours/day.

DISCUSSION

Low physical activity and sedentary behavior have been associated with the development of chronic diseases including obesity, hypertension, diabetes, CV disease, mortality and even certain malignancies.[1-4] Although these diseases can be treated pharmacologically, more needs to be done to reduce their risk through lifestyle modifications such as a healthy diet, not smoking and exercise. However, few studies have evaluated associations between the degree of physical activity and the

Table 3. Baseline characteristics of study subjects (n = 1010)

Age, years	51.0 ± 11.3
Male, n (%)	626 (62.0)
HTN, history n (%)	183 (18.3)
Diabetes, n (%)	47 (4.7)
Height, cm	166.4 ± 8.2
Weight, kg	66.7 ± 12.3
BMI, kg/m^2	24.0 ± 3.4
WC, cm	85.1 ± 9.3
SBP, mmHg	120.6 ± 17.9
DBP, mmHg	76.1 ± 11.3
Smoking, n (%)	220 (21.8)
Drinking, n (%)	329 (32.6)
Cholesterol, mg/dL	202.1 ± 36.2
Triglyceride, mg/dL	120.7 ± 70.7
Uric acid, mg/dL	6.4 ± 1.6
HDL-C, mg/dL	49.3 ± 13.1
LDL-C, mg/dL	125.7 ± 32.9
HbA1c, (%)	5.7 ± 0.7
Fasting glucose, mg/dL	93.8 ± 21.9
ALT, IU/L	27.5 ± 20.4
Total bilirubin, mg/dL	1.1 ± 0.5
Creatinine, mg/dL	0.9 ± 0.2
Sitting time, hours/day	6.6 ± 3.1
IPAQ level	
Low, n (%)	418 (41.4)
Moderate, n (%)	425 (42.1)
High, n (%)	167 (16.5)
MET-min/wk	1,674.7 ± 2,003.5
Framingham score (BMI)	11.8 ± 9.6
Framingham score (lipid)	11.5 ± 9.3
Pulmonary function test	
FVC, l	3.5 ± 0.8
FEV1, l	2.9 ± 0.7
FEV1/FVC, %	83.0 ± 6.8

Data are mean ± SD or n (%).
ALT, alanine aminotransferease; BMI, body mass index; DBP, diastolic blood pressure; FEV1, forced expiratory volume in one second; FVC, forced vital capacity; HbA1c, hemoglobin A1c; HDL, high-density lipoprotein; IPAQ, International Physical Activity Questionnaire; LDL, low-density lipoprotein; SBP, systolic blood pressure; TG, triglyceride; WC, waist circumference.

occurrence of chronic diseases using a prospective cohort design in an Asian population. Therefore, in this study, we obtained detailed information on sedentary lifestyles and biochemical parameters in an Asian cohort, and investigated the impact of physical activity on the occurrence of adverse events. We hope that these findings can help with the development of strategies for primary and secondary preventions of diseases in the general population.

A recent epidemiologic study in Taiwan reported that the prevalence of obesity [body mass index (BMI) ≥ 27 kg/m^2] increased from 11.8% in 2013 to 22.0% in 2014.[28] In addition, these obese subjects tended to have lower physical activity, suggesting that avoiding a sedentary lifestyle could be beneficial in maintaining good health. It has also been reported that the risk of adverse effects can be reduced by 30% to 50% with regular physical activity.[29,30] The benefits of physical activity may come from improvements in CV and muscular endurance.[31] In addition, regular activity has been shown to prevent depression and improve cognitive function.[32,33] Furthermore, exercise can reduce body weight, blood pressure and improve cardiometabolic biomarkers. Taken together, all of these factors may contribute to better clinical outcomes.

Although increased physical activity and maintaining a normal weight are recommended for the general population, inconsistent benefits have been observed in patients with different diseases. For example, a recent study focusing on congestive heart failure demonstrated that increased physical activity was only beneficial among patients with preserved left ventricular ejection fraction (LVEF), but not in those with a reduced LVEF, suggesting that physical activity or exercise guidelines may only be applicable to specific subgroups.[34] In addition, in another report focusing on patients after cardiac surgery, the patients that were overweight/mildly obese paradoxically had the lowest risk of future adverse event.[35] The apparent benefit of being overweight has also been observed in patients undergoing dialysis.[36] However, Pandey recently reported strong, dose-dependent associations between physical activity levels, BMI, and the risk of overall heart failure, indicating that higher levels of physical activity and a lower BMI are still recommended for patients with CV disease.[37] In the current study, we investigated the relationship between biochemical parameters and physical activity at baseline and the association between the risk of developing a chronic disease and a sedentary lifestyle.

Study limitations

There are several limitations to this study. First, the included subjects were recruited from those who received annual checkups at our hospital, and selection bias arising from educational background and personal income could not be excluded. Second, this is a hospital-based study not a community-based study, and there may be geographic variations such as environmental exposure to risk factors for chronic diseases. Furthermore, we used the IPAQ-SF to evaluate the physical activity status of the participants, because all of the subjects received detailed biochemical marker evaluations (e.g., blood routine, lipid profiles, liver function, nutrition, electrolytes, and renal function), as well as X-rays, abdomen sonograms, endoscope studies, questionnaires to evaluate type D personality and IPAQ-SF, and even coronary CT in some subjects. Due to the number of assessments, the participants did not undergo cardiopulmonary fitness evaluations. Finally, it is difficult to know the ratio of non-symptoms to symptoms related to CV disease. Because all study subjects were enrolled during a checkup and not at the cardiology clinic, it is reasonable to assume that most subjects did not have CV symptoms. In addition, all of the participants were invited to complete all questionnaires and sign informed consent forms after explanation. Enrollment of subjects with symptoms was avoided.

CONCLUSIONS

In conclusion, the VGH-HEALTHCARE study is a prospective cohort study aiming to provide detailed information about a sedentary lifestyle and biochemical parameters in an Asian population. We hope that this information will be used to assess the future risk of developing chronic diseases in Asian populations. In addition, the analysis of interactions between biochemical markers, personality traits and environment factors may lead to a better understanding of the complexity of diseases and improve treatment strategies for the general population.

ACKNOWLEDGEMENTS

We would like to thank Prof. Weng for agreement for utilization of type D questionnaire in Taiwan.

DECLARATION OF CONFLICT OF INTEREST

All the authors declare no conflict of interest.

FUNDING

This trial is funded by the Taipei Veterans General Hospital (V106C-142).

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